DATA-BASED RADIATION ONCOLOGY – DESIGN OF CLINICAL TRIALS

EDITED BY : Kerstin A. Kessel, Anne W. Lee, Søren M. Bentzen, Bhadrasain Vikram, Fridtjof Nuesslin and Stephanie E. Combs
PUBLISHED IN : Frontiers in Oncology

frontiers Research Topics

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.

Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.

By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

DATA-BASED RADIATION ONCOLOGY – DESIGN OF CLINICAL TRIALS

Topic Editors:

Kerstin A. Kessel, Klinikum rechts der Isar, Technische Universität München, Helmholtz Zentrum München, Germany
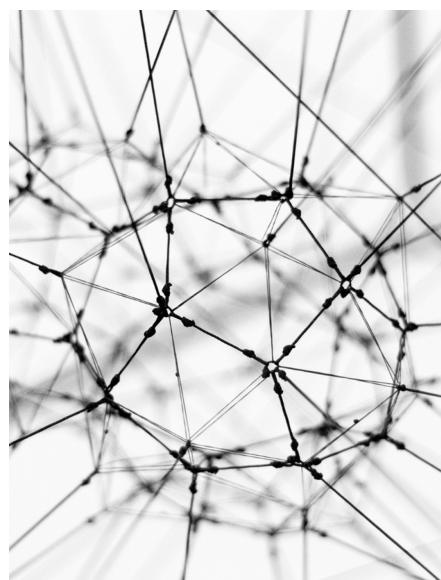
Anne W. Lee, The University of Hong Kong Shenzhen Hospital, China

Søren M. Bentzen, University of Maryland, United States

Bhadrasain Vikram, National Cancer Institute (NIH), United States

Fridtjof Nuesslin, Klinikum rechts der Isar, Technische Universität München, Germany

Stephanie E. Combs, Klinikum rechts der Isar, Technische Universität München, Helmholtz Zentrum München, Germany

San Francisco Museum of Modern Art, San Francisco, United States.

Image: Jason Leung/Unsplash.com

Table of Contents

Editorial: Data Based Radiation Oncology—Design of Clinical Trials

Kerstin Anne Kessel[1,2]*, Anne W. M. Lee[3], Søren M. Bentzen[4], Bhadrasain Vikram[5], Fridtjof Nüsslin[1] and Stephanie E. Combs[1,2]

[1] *Department of Radiation Oncology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany,* [2] *Institute for Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Munich, Germany,* [3] *Department of Clinical Oncology, The University of Hong Kong Shenzhen Hospital, Shenzhen, China,* [4] *Division of Biostatistics and Bioinformatics, Department of Epidemiology and Public Health, The Greenebaum Cancer Center, School of Medicine, University of Maryland, Baltimore, MD, United States,* [5] *National Cancer Institute (NIH), Rockville, MD, United States*

Keywords: clinical trials, data collection, radiation oncology, clinical study design, study management

Editorial on the Research Topic

Data Based Radiation Oncology—Design of Clinical Trials

In radiation oncology as in many other specialties, clinical trials are essential to investigate new therapeutic approaches. Usually, preparation for a prospective clinical trial is time-consuming until ethics approval is obtained. To test a new treatment many years pass before it can be implemented in the routine care. During that time, already new interventions emerge, new drugs appear on the market, technical and physical innovations are being implemented, novel biology-driven concepts are translated into clinical approaches while we are still investigating the ones from years ago.

Another problem is associated with molecular diagnostics and the growing amount of tumor-specific biomarkers which allow for better stratification of patient subgroups. On the other side, this may result in a much longer time for patient recruiting and consequently in larger multicenter trials. Moreover, all of the relevant data must be readily available for treatment decision making, treatment as well as follow-up, and ultimately for trial evaluation. This challenges even more for agreed standards in data acquisition, quality, and management.

How could we change the way currently clinical trials are performed in a way they are safe and ethically justifiable and speed up the initiation process so that we can provide new and better treatments faster for our patients?

Furthermore, while we rely on various quantitative information handling distributed, large heterogeneous amounts of data efficiently is very important. Thus, data management becomes a strong focus. A good infrastructure helps to plan, tailor and conduct clinical trials in a way they are easy and quickly analyzable.

In this research topic, we want to discuss new ideas for intelligent trial designs and concepts for data management.

AUTHOR CONTRIBUTIONS

All authors wrote and revised the editorial.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Big Data in Designing Clinical Trials: Opportunities and Challenges

Charles S. Mayo*, Martha M. Matuszak, Matthew J. Schipper, Shruti Jolly, James A. Hayman and Randall K. Ten Haken

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Emergence of big data analytics resource systems (BDARSs) as a part of routine practice in Radiation Oncology is on the horizon. Gradually, individual researchers, vendors, and professional societies are leading initiatives to create and demonstrate use of automated systems. What are the implications for design of clinical trials, as these systems emerge? Gold standard, randomized controlled trials (RCTs) have high internal validity for the patients and settings fitting constraints of the trial, but also have limitations including: reproducibility, generalizability to routine practice, infrequent external validation, selection bias, characterization of confounding factors, ethics, and use for rare events. BDARS present opportunities to augment and extend RCTs. Preliminary modeling using single- and muti-institutional BDARS may lead to better design and less cost. Standardizations in data elements, clinical processes, and nomenclatures used to decrease variability and increase veracity needed for automation and multi-institutional data pooling in BDARS also support ability to add clinical validation phases to clinical trial design and increase participation. However, volume and variety in BDARS present other technical, policy, and conceptual challenges including applicable statistical concepts, cloud-based technologies. In this summary, we will examine both the opportunities and the challenges for use of big data in design of clinical trials.

Keywords: big data, trial design, randomized controlled trials, informatics, analytics

INTRODUCTION

A primary objective of clinical research is gaining knowledge from studying a subset of patients which can then be applied to a much wider group of patients to improve care. In routine practice, patient care is delivered within a rich background of intrinsic and endemic confounding factors and biases associated with practices and patients. Clinical research methodologies are challenged to accurately delineate specific relationships and be relevant to routine practice.

Optimal trial design methodologies have a long history of debate within the medical field (1–15). Recently, there has been substantial growth in the number of academic groups investing in development of big data analytics resource systems (BDARSs) to support practice quality improvement (PQI) and translational research (TR) applications in radiation oncology (16, 17). BDARSs aggregate clinical data from multiple systems including electronic health records (EHRs), Radiation Oncology information systems (ROISs), treatment planning systems (TPSs), and others into common location designed to support analyzing this data to improve patient care. Our objective in this presentation is to explore how these big data efforts might intersect with trial design methodologies to augment or extend these approaches.

RANDOMIZED CLINICAL TRIALS

Randomized controlled trials (RCTs) provide the highest ranked level of evidence for delineation of causal relationships between treatment results and outcomes. Using a design methodology that meticulously minimizes and controls variation encountered in routine practice, RCTs are designed for statistical rigor. They have high internal validity for selected constraints and treatment delivery conditions specified in the trial design. RCTs are well incorporated into clinical and research systems. Systems for funding, management, and infrastructure supporting collaborative trials research are oriented to RCTs. However, RCT's also have challenges including: reproducibility, generalizability, cost, external validation, and delay (1, 2, 14). Meta-analysis of individual patient data addresses some of these challenges of any single trial. In particular, results of a meta-analysis of multiple clinical trials will generally be more reproducible, generalizable, and have greater external validity. However, they also have greater delay and cost than any single trial. Additionally, they are still based on the population of patients who actually enroll in clinical trials which may not be fully representative of a broader patient population.

Reproducibility

Multiple, independent measurements demonstrating reproducibility of results are strong evidence for the validity of the result. Difficulty in reproducing results for RCTs is a concern in the community and for the National Institutes of Health (3). Observational studies are ranked lower than RCTs in level of evidence, but frequently utilize larger number of patients. Some researchers have demonstrated greater consistency among observational studies than findings consistent with RCTs (2, 4, 5). In an analysis comparing results of independent RCTs (45) to independent, well-designed observational studies (44) spanning five clinical research topics, Concato demonstrated more inconsistency in RCT, and much tighter confidence intervals for the observational studies which included larger number of subjects (2). In an early meta-analysis Horwitz examined 200 RCTs spanning 36 topics in cardiology and gastroenterology highlighting conflicting results. He found that complex design and inconsistencies in clinical execution and therapeutic evaluation undermined reproducibility (4). In radiation oncology, complex single institution trials may require significant redesign to reduce complexity, such as in the case of translating the University of Michigan's PET adaptive lung cancer trial to a cooperative group trial run through RTOG (18, 19). Additionally, compared with pharmacologic interventions, technique-based interventions in Radiation Oncology as in Surgery, introduce added complexities sensitive to skill of individual practitioners, and evolution of technique over the period of the trial as experience is acquired.

Cost

Effort required for collection and aggregation of data frequently falls outside the range of routine clinical practice. Interfaces to EHRs, ROISs, and TPSs typically require manual inspection of all to synthesize, extract, and report required trial data.

Generalizability

Complexity and cost of implementing trials work against recruitment of large numbers of patients and introduces selection bias for patient cohorts with geographic, insurance, and medical history profiles commensurate with treatment at medical centers that also have sufficient resources to participate in trials. This selection bias can become dangerous when the RCT result is applied to an underrepresented group of patients that were not well represented in trial enrollment and whose disease may not respond to the experimental treatment. In addition, RCTs are typically designed to test a drug or specific intervention in a patient cohort with strict eligibility criteria. In many cases, RCTs are testing these interventions in a small subset of patients in larger disease sites. So, even after a positive trial, the number of patients that the results of an RCT may apply to, could be relatively small. However, this does not prevent the community from applying the intervention to a larger cohort of patients, making future observation studies potentially washed out or negative due to inappropriate use of the trial results.

As more data on genomic variations across patients and tumors becomes available, it is also possible that the results of certain positive trials could be driven by strong positive result in a previously unknown subset of the population. Without further study and patient classification by BDR, the ability to further analyze these trials is lost.

Infrequent External Validation

If an objective of funding RCTs is to improve care for a broader segment of the population, then demonstrations of external validation are needed. Due to a variety of factors, RCTs suffer from low rates of external validation. Larger RCT series with multiple studies testing similar regimes, such as accelerated whole breast irradiation (6, 7) are the exceptional case where RCTs can lead to sweeping practice changes and updated national guidelines. However, smaller RCTs, especially those run in a single institution setting, are rarely validated in an external cohort due to complex design, cost, and loss of equipoise after the initial trial is published.

One reason for this may be that testing a trial concept for extensibility to and validity in the "real world" of routine clinical practice is rarely a priority in trial design. Therefore, RCTs continue to include a much, much smaller number of patients and less variable clinical practices than represented by the majority of patients treated.

As more and more biomarker and image driven treatment selection is incorporated into trials, this lack of external validation will only become worse. Not only will the validation studies not be possible due to the lack of knowledge and resources to run the trial, but specific nuances of image analysis and bio-specimen testing/handling, may be unavailable or irreproducible. National clinical trial resources and core facilities will assist in this area for larger cooperative group studies, but this remains an issue for single institution studies.

Delay

Clinical trial infrastructure, both at individual institutions and cooperative groups, is organized in such a way that trials go

through a number of steps to ensure that trials are of sufficient potential benefit to the patient or population, are able to be funded appropriately, and are designed properly. While these steps are essential, it also means that the initiation of a trial is delayed by even years before starting.

Almost one-fifth clinical trials even at large centers are "slow-accruing" (14). Thus, once a trial opens, the study question may no longer be as relevant as it was when the concept was first initiated. Expense of tests and staff to carry out the RCT may limit resources needed for accrual into the trial. Use of manual rather than standardized electronic means at point of care—point of data entry impede aggregation from multiple institutions. Managing logistics of clinical process flows and mechanisms for data aggregation for RCTs that differ from those used for the majority of off-protocol patients add to cost and slow accrual.

SYNERGIES IN CONSTRUCTING BIG DATA SYSTEMS AND SUPPORTING CLINICAL TRIALS

Rather than replacing RCTs, we posit that BDARSs will present resources and methodologies that can be incorporated into design of RCTs to augment and extend them to address the issues outlined above. Assuring that data elements needed for BDARSs are routinely aggregated using methodologies that assure accurate electronic extraction is also synergistic with objectives for clinical trials and observational studies. Construction of effective BDARSs includes development and use of standardizations that can be practically fitted into clinical practice. Coordination with multi-disciplinary groups to clean point of care—point of data entry processes to support BDARSs is extensible to these groups for entry of data elements necessary for clinical trials. Standardizations in designation of key data elements, nomenclatures supporting exchange, and clinical processes improving accurate are vital to these efforts.

EHR Templates

For example, our BDARS, the University of Michigan Radiation Oncology Analytics Resource (M-ROAR), requires accurate data on provider reported toxicities, recurrence, performance status, etc. (18). Examining the work flows of care providers, the most consistent point of entry is provider notes in the electronic health record (EHR). Our EHR, EPIC, does not provide quantified fields for these key data elements. However, with development of M-ROAR to enable use of the full text of encounter notes, options for standardizing text entry to enable accurate, automated electronic extraction became viable solutions.

The EHR does provide means create templates that regularize text entry of information. In that EHR system, these are known as Smart List and Smart Phrase objects. Smart List objects allow defining a tab activated drop down list of serializable options to be inserted in the text field of a clinical note. Smart phrases are used to assemble sets of smart lists embedded with other standardized text.

We developed a standardized schema for representation of key data elements in text fields utilizing these smart objects to regularize data entry across providers. With this schema

standardization, software tools known as regular expressions can be used to accurately extract key data elements from the text of clinical encounter notes. This is carried out in high volume for all patients.

The schema developed demarking key data elements are illustrated below. Highlighted text indicates characters with specific interpretations. Italicized text indicates place holders for specific information types.

|>*Key Data Element* = *Value* (*qualifying information*) | *supplemental element* = *value*<|

Figure 1 illustrates creation of smart list objects using this schema. The |> and <| character combinations delineate the beginning and the end of a key data element. The text to the left of the = sign following |> is a standardized name for the key data element; the text to the right indicates the value assigned to the data element. Parenthesis characters, (), are used to delineate optional commentary information. The bar symbols, |, demark entry of optional supplemental item/value pairs related to the key data element. Four examples of schema valid text fields are listed below.

|>Xerostomia = 1<|
|>Dysphagia = 2 (Symptomatic, altered eating swallowing) | Attribution = related to treatment<|
|>Recurrence = Local<|
|>Performance:KPS = 90<|
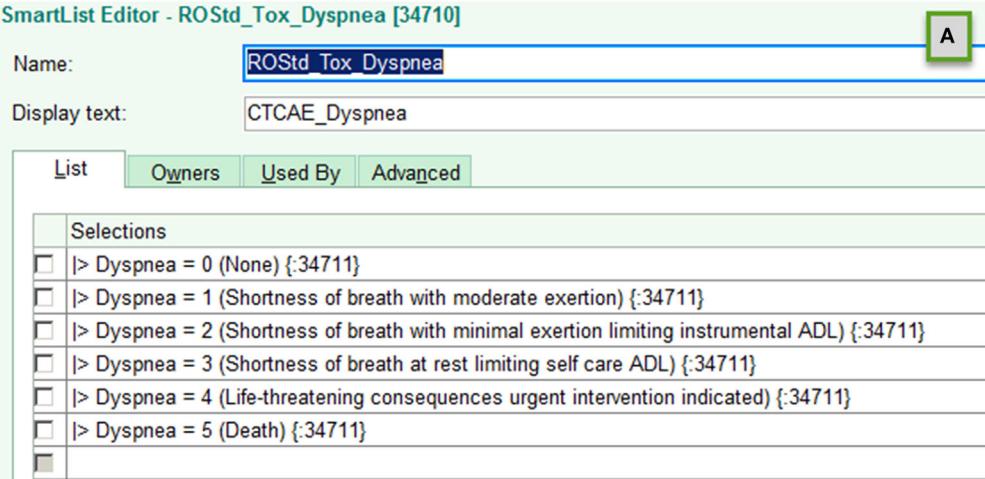
The standardized schema assures accurate identification of key data elements and component information elements. Together with definition of a standardized data dictionary of key elements, supplemental information items and allowed values, the standardized schema provides a flexible but fully defined means to accurately and electronically extract information needed for BDARSs.

When a clinical trial is implemented, additional key data elements may be needed. If the EHR is the optimal point of care-point of data entry mechanism, then the data dictionary is extended, and new smart list/smart phrase objects are constructed using the standardized schema developed to support extractions for the BDARS.

Note that while access to TPS and ROIS data is routine in most Radiation Oncology clinics, access to EHR data varies widely among institutions. Considerable cooperation between the EHR vendor and the institutional IT groups controlling access with end users is required. Introduction of standardizations, like that defined above, increases the value of the enterprise data stores for both vendors and IT groups as well as for end users. However, these standardizations only arise and become incorporated into routine practice if end users are enabled to access and use the data. This is especially important for community clinics, where the majority of patients are treated.

Optimized Clinical Process Flow Using Existing Systems

For several key data element categories, ROISs or TPSs may be optimal point of care-point of data entry systems. Optimizing

FIGURE 1 | Examples of using template objects in electronic health records to implement data entry standardizations that support accurate automated electronic extraction are shown for **(A)** smart list and **(B)** smart phrase objects in an EPIC environment.

clinical process to assure availability of these elements for all patients supporting the BDARSs also eliminates extra efforts to acquire these elements when needed for clinical trials.

For example, by modifying clinical process flows to implement a standardized approach for entry of diagnosis and staging information along with explicit linkages to treatment course, both the BDARS and clinical trials are supported. In another example supporting the BDARS, we modified our clinical process to assure routine creation of as treated plan sums to enable automated extraction of course cumulative dose volume histogram (DVH) curves reflecting cumulative doses for the plans and actual number fractions treated. In addition, the standardized nomenclature recommendations of AAPM TG-263 for targets and normal structures were adopted to assure correct identification of structures in extract, transform, and loads (ETLs) of DVH curves.

Patient reported outcomes aggregation required modification of clinical process flows and staffing as well as collection technology. With subsequent completion of the informatics circle to ETL PRO data into M-ROAR, the PRO data became available for large volume analysis. With that step, the mechanisms used for gathering PROs for M-ROAR, could plausibly be extended to support gathering analogous information for patients on RCTs.

Multiple Institutions

Ability to aggregate key data elements, including survival, recurrence, and toxicity, is challenged when patients do not return for follow-up or shift away from the academic center delivering specialized care back to their local community hospital for ER and continuing care visits. Fully understanding therapeutic outcomes requires longitudinal follow-up data over many years. Scalable, automated solutions are technically feasible, but requisite contractual relationships and PHI protection compliance mechanisms are not. Health care policy efforts to improve continuity of care will in the long run benefit both BDRs and RCTs.

The regulatory and institutional compliance office constraints arising from the Health Insurance Portability and Accountability Act (HIPAA) are important for protecting sensitive, personal information of patients from misuse. However, HIPAA can be a double edged sword. Ability to utilize information gained from prior patients from multiple institutions to improve treatments of future patients is a desirable use. Current views of how to implement the intent of HIPAA often prevent reaching this potential. Finding a middle ground that affords needed protections, while also enabling the benefits of multi-institutional datasets is a vital area of collaboration between patient advocacy groups, legislators, regulatory groups, and researchers.

USING BIG DATA TO AUGMENT TRIAL DESIGN

As BDARSs emerge, are integrated with EHRs, ROISs, and TPSs and applied to all patients treated, they present resources for improving trial design. Successfully carrying out this integration requires navigating multi-disciplinary, multi-stakeholder clinical processes needed to achieve access, and implement standardizations (20, 21). Building standardizations and automations into systems reduces the amount of manual effort required to enter and extract data, lowering cost. In addition, wider adoption of standardizations and templates and applications supporting BDARSs lowers resource thresholds for participation in RCTs. This should translate to increasing participation in RCTs.

By proactively identifying and incorporating BDARS supporting standardizations, researchers designing trials can improve curation and reproducibility. Standardizations reduce complexity introduced by variability and increase reliability of consistency checks on inputs and outputs. Use of these standards in routine clinical care and in RCTs makes possible development of sharable automated curation algorithms to flag outliers or longitudinal variation in data entry that may signal errors.

For example, AAPM's Task group 263 on Standardization of Nomenclature for Radiation Therapy defined standards for naming of target and normal structures as well as defining a schema for representing DVH metrics. The task group of 57 members representing, a broad range of roles (e.g., physician, physicist, vendor), professional societies (e.g., AAPM, ASTRO, ESTRO), clinic types (e.g., academic, community practice), and specialty groups (e.g., IHE-RO, DICOM, NRG) to meet common needs of RCTs and routine practice (22). This standard has been adopted by NRG in designing new trials (23). By adopting this standardization into routine practice, effort to prepare data for RCT trial aggregation sites or use in local PQI and TR is reduced.

By designing trials to utilize BDARSs as the optimal aggregation system rather than manual one-by-one extraction from EHRs, ROISs, and TPSs, ability to extend trial results to routine practice and later to carry out validation studies is improved. With this approach, by utilizing BDARS aggregations up front when there are resources for introducing the RCT, then the infrastructure for follow-on efforts is largely in place. In addition, by identifying and fixing "pinch points" in clinical processes to support the BDARS, highlighting practice sensitive data elements

affecting RCTs and ability to design trials with intent to incorporate external validation is improved.

Further, with automated aggregation of multiple data elements the range of confounding factors that can be tested in the trial increases. In addition, standardization and automation extended across multiple centers increases ability aggregate enough patients to examine rare events.

CONSIDERATIONS IN OBSERVATIONAL STUDIES

One of the main challenges to learning from BDARSs is the potential for confounding. In RCTs, the randomization ensures that patients receiving each of the randomized treatments will, on average, be similar with respect to any baseline variable. In observational datasets, there often exist selection biases such that patients receiving two different treatments have different distributions of a variable that may be related to an outcome of interest.

There are a number of statistical approaches to assessing and accounting for confounders. A simple approach is to use multivariable regression models in which potential confounders are included as covariates in addition to treatment. A generally preferable approach is to use propensity scores as weights (inverse probability of treatment), strata, or matching variables (24). Using propensity scores as weights creates a "synthetic" population of outcomes in which both treatment groups have similar distributions of any measured confounders. In this sense, it mirrors an RCT. Both multivariable regression models and propensity methods account only for measured confounders. In some settings, there may be unmeasured confounders.

Instrumental variable analysis (IVA) (25) represents an approach which can provide valid treatment effect estimates in the presence of unmeasured confounding if certain assumptions are met. IVA analyses rely on the selection of an "instrumental" variable that is correlated with treatment and meets other conditions. Importantly, these conditions cannot be verified empirically from the data so that selection of an instrument must be based on subject-matter knowledge.

USING BIG DATA TO EXTEND TRIAL DESIGN

Increase in availability of BDARS also presents several opportunities to extending clinical trial design methodologies or to generate RCT hypothesis fueled by large, preliminary observational studies. BDARS make distributions for a wide range of treatment and diagnostic parameters readily available. These distributions can be utilized to carry out "virtual design trials" ahead of designing the RCT (**Figure 2**).

For example, in designing a trial aimed at investigating the co-dependence of a chemotherapy regime used in conjunction with an SBRT dose escalation strategy for lung cancer patients, historic data could be used to examine distributions, and cross-correlations of demographic, radiation, and chemo therapy treatment parameters, dosimetric, and laboratory values, survival, recurrence, provider reported toxicities, and patient reported outcomes. With the distributions and inter-relationships
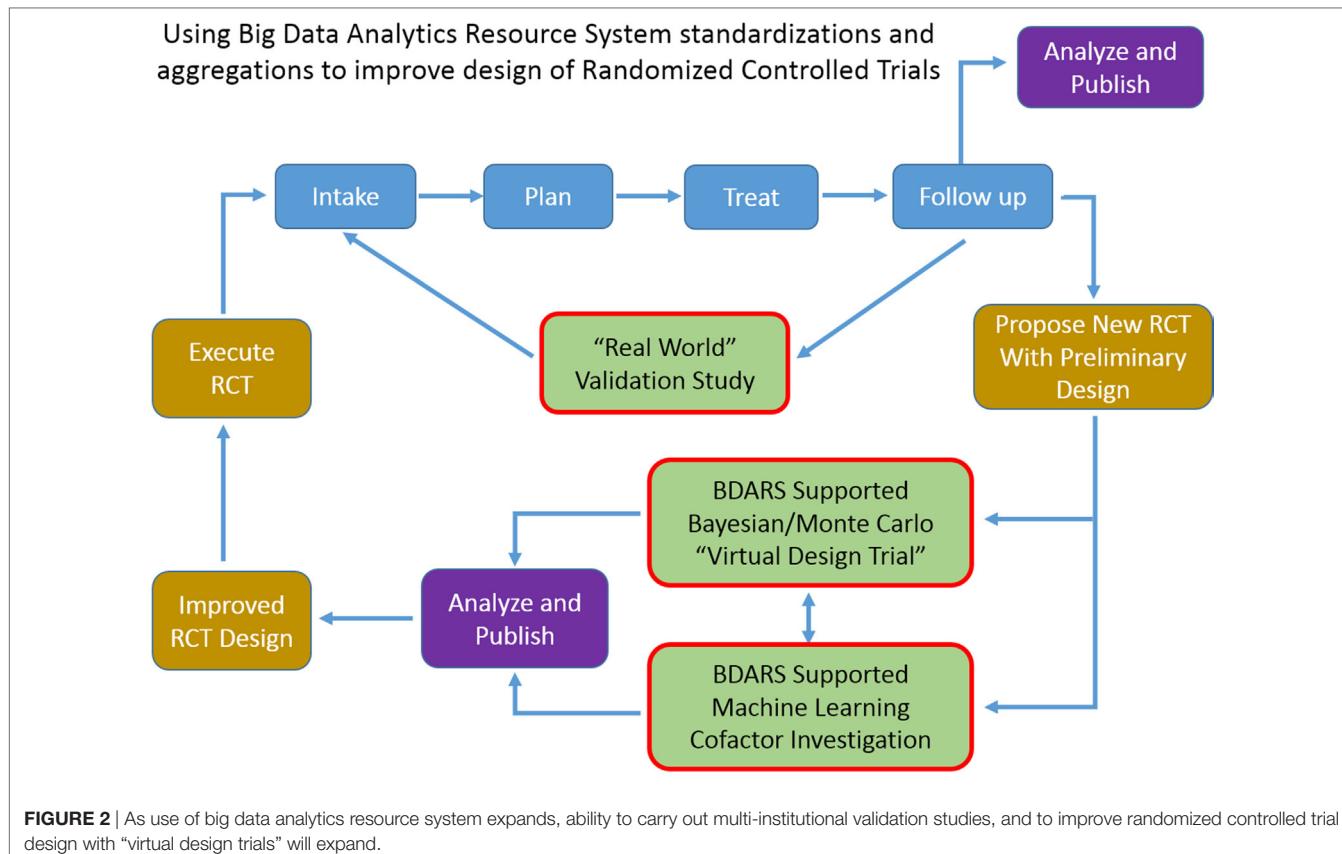
FIGURE 2 | As use of big data analytics resource system expands, ability to carry out multi-institutional validation studies, and to improve randomized controlled trial design with "virtual design trials" will expand.

characterized, variations as anticipated from the proposed trial can be simulated with Monte Carlo and Bayesian methods to better anticipate confounding interactions and to optimize design decisions. Machine learning approaches can be used to leverage the wide range of data element categories contained in BDARS to identify unanticipated interactions and dependencies that should be considered in the RCT design. When the BDARS contains data on charges and procedure codes, ability to improve projecting budgets for the trial is improved. This approach puts examination of the confidence intervals of key parameters and implications for the study up front using actual data rather using hypothetical projections and having to adjust the RCT after it is started.

Prior to conducting an RCT, investigators could utilize BDARSs to more precisely understand characteristics of patients with a particular type of cancer or of patients being treated with a certain treatment. This knowledge could then be translated into the design of the RCT to ensure that the patients enrolled on the RCT are reflective of the intended population. This could mean, for example, that enrollment would be stratified by subgroups. A key step in designing RCTs is selection of sample size. Key drivers of sample size include effect size estimates as well as estimates of variance. There is much room for improvement in how these parameters are selected in the design stage and BDARSs could be utilized to estimate them more precisely and accurately. BDARSs could also be used to accurately estimate the number of eligible patients and hence likelihood of completing accrual within a timely fashion.

After an RCT is completed, BDARSs could be utilized to assess uptake of the "winning" treatment and importantly whether the results in actual clinical practice are similar to those observed in the RCT. One reason for discrepancy has to do with how the treatments are implemented. Treatments such as IMRT are complex and can vary substantially in important details such as normal tissue constraints. If these variables are captured as part of the BDAR, then the source of discrepant results can be sought in discrepant implementations.

In addition, ability for a site proposing an RCT to carry out this analysis demonstrating the potential of the proposed RCT, either as a single- or multi-institutional effort, provides a low cost means of testing the potential value of the RCT and focuses funding on efforts with significant likelihood of success. Publication of these virtual trial results ahead of implementing the actual RCT would place specific and focused discussion of the trial design and potential weaknesses ahead of implementation.

CONCLUSION

The recent surge in big data initiatives in health care is expected to have a positive impact on clinical trials. Increased standardization of common data elements and nomenclature should assist in streamlined trial design and exchange of data. Standardize between trials and will allow easier multi-study analysis. Standardization and quality improvement efforts go hand in

hand with a maturing big data infrastructure providing collateral benefits to data curation for RCTs (24, 26).

The quality and power of observational studies will increase tremendously as use of BDARS increases. Addition of standard outcomes measurements and patient reported outcomes to clinical databases will widen the range for which observational studies are deemed high quality evidence. While BDARS-based observational studies will not eliminate need for RCTs, they can be anticipated to raise expectations for level of evidence thresholds required from RCTs and prompt more frequent validation studies.

Granting agencies may note dividends from BDARS supporting standardizations and ETLs for lowering cost and improving

RCT design. Funding for virtual design trials using Bayesian and Machine Learning methodologies will promote standardizations and growth of BDARS that will ultimately support and improve the quality of RCTs.

AUTHOR CONTRIBUTIONS

The authors have participated in discussion of concepts presented in the manuscript, writing, and/or review of the manuscript.

FUNDING

REFERENCES

1. McLeod RS, Wright JG, Solomon MJ, Bao M, Hu X, Walter BC, et al. Randomized controlled trials in surgery: issues and problems. *Surgery* (1996) 119(5):483–6. doi:10.1016/S0039-6060(96)80254-6

2. Concato J, Sha N, Horwitz RI. Randomized, controlled trials, observational studies and the hierarch of research designs. *N Engl J Med* (2010) 342(25):1887–92. doi:10.1056/NEJM200006223422507

3. Collins FS, Tabak LA. NIH plans to enhance reproducibility. *Nature* (2014) 505(7485):612–3. doi:10.1038/505612a

4. Horwitz RI. Complexity and contradiction in clinical trial research. *Am J Med* (1987) 82(3):498–510. doi:10.1016/0002-9343(87)90450-5

5. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev* (2014) 4:MR000034. doi:10.1002/14651858.MR000034.pub2

6. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* (2010) 362:513–20. doi:10.1056/NEJMoa0906260

7. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumor excision: long-term results of a randomised trial. *Lancet Oncol* (2006) 7:467–71. doi:10.1016/S1470-2045(06)70699-4

8. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* (2013) 14:1086–94. doi:10.1016/S1470-2045(13)70386-3

9. Hahn OM, Schilsky RL. Randomized controlled trials and comparative effectiveness research. *J Clin Oncol* (2012) 30:4194–201. doi:10.1200/JCO.2012.42.2352

10. Kaplan RM, Chambers DA, Glasgow RE. Big data and large sample size: a cautionary note on the potential for bias. *Clin Transl Sci* (2010) 7(4):342–6. doi:10.1111/cts.12178

11. Hudis CA. Big data: are large prospective randomized trials obsolete in the future. *Breast* (2015) 24(2):S15–8. doi:10.1016/S0960-9776(15)70007-X

12. Angus DC. Fusing randomized trials with big data: the key to self-learning health care systems? *JAMA* (2015) 314(8):767–8. doi:10.1001/jama.2015.7762

13. Kessel KA, Combs SE. Review of developments in electronic, clinical data collection, and documentation systems over the last decade—are we ready for big data in routine health care? *Front Oncol* (2016) 6:75–80. doi:10.3389/fonc.2016.00075

14. Tang C, Sherman SI, Price M, Weng J, Davis SE, Hong DS, et al. Clinical trial characteristics and barriers to participant accrual: the MD Anderson cancer center experience over 30 years, a historical foundation for trial improvement. *Clin Cancer Res* (2017) 23(6):1414–21. doi:10.1158/1078-0432.CCR-16-2439

15. Aliving B, Brady L, Tavel J, et al. *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary 2010 National Academy of Sciences ISBN-13: 978-0-309-15332-4.* (2010). Available from: https://www.ncbi.nlm.nih.gov/books/NBK50888/

16. Mayo CS, Kessler ML, Eisbruch A, Weyburne G, Feng M, Hayman JA, et al. The big data effort in radiation oncology: data mining or data farming? *Adv Radiat Oncol* (2016) 1(4):260–71. doi:10.1016/j.adro.2016.10.001

17. Janke AT, Overbeek DL, Kocher KE, Levy PD. Exploring the potential of predictive analytics and big data in emergency care. *Ann Emerg Med* (2016) 67(2):227–36. doi:10.1016/j.annemergmed.2015.06.024

18. Kong FM, Ten Haken RK, Schipper M, Hayman J, Ramnath N, Hassan K, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non–small-cell lung cancer: a phase 2 clinical trial. *JAMA Oncol* (2017). doi:10.1001/jamaoncol.2017.0982

19. RTOG1106. (2016). Available from: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106

20. Mayo CS, Deasy JO, Chera BS, Freymann J, Kirby JS, Hardenberg PH. How can we effect culture change toward data-driven medicine? *Int J Radiat Oncol Biol Phys* (2016) 95(3):916–21. doi:10.1016/j.ijrobp.2015.12.355

21. Sloan JA, Halyard M, El Naqa I, Mayo C. Lessons from large-scale collection of patient-reported outcomes: implications for big data aggregation and analytics. *Int J Radiat Oncol Biol Phys* (2016) 95(3):922–9. doi:10.1016/j.ijrobp.2016.04.002

22. Mayo C, Moran JM, Xiao Y, Bosch WR, Matuszak MM, Marks LB, et al. AAPM taskgroup 263: tackling standardization of nomenclature for radiation therapy. *Int J Radiat Oncol Biol Phys* (2015) 93(3):E383–4. doi:10.1016/j.ijrobp.2015.07.1525

23. Yu J, Straube W, Mayo C, Giaddui T, Bosch W, Ulin K, et al. Radiation therapy digital data submission process for national clinical trials network Int. *J Radiat Oncol Biol Phys* (2014) 90(2):466–7. doi:10.1016/j.ijrobp.2014.05.2672

24. D'Agostino RB. Tutorial in biostatistics propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group statistics in medicine. *Stat Med* (1998) 17:2265–81. doi:10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B

25. Johnston KM, Gustafson P, Levy AR, Grootendorst P. Use of instrumental variables in the analysis of generalized linear models in the presence of unmeasured confounding with applications to epidemiological research. *Stat Med* (2008) 27:1539–56. doi:10.1002/sim.3036

26. Jagsi R, Griffith KA, Heimburger D, Walker EM, Grills IS, Boike T, et al. Choosing wisely? Patterns and correlates of the use of hypofractionated whole-breast radiation therapy in the state of Michigan. *Int J Radiat Oncol Biol Phys* (2014) 90:1010–6. doi:10.1016/j.ijrobp.2014.09.027

Check for updates

mHealth and Application Technology Supporting Clinical Trials: Today's Limitations and Future Perspective of smartRCTs

Marco M. E. Vogel[1,2]*, Stephanie E. Combs[1,2] and Kerstin A. Kessel[1,2]

[1] Department of Radiation Oncology, Technische Universität München (TUM), Munich, Germany, [2] Institute for Innovative Radiotherapy, Helmholtz Zentrum München, Neuherberg, Germany

Nowadays, applications (apps) for smartphones and tablets have become indispensable especially for young generations. The estimated number of mobile devices will exceed 2.16 billion in 2016. Over 2.2 million apps are available in the Google Play store®, and about 1.8 million apps are available in the Apple App Store®. Google and Apple distribute nearly 70,000 apps each in the category Health and Fitness, and about 33,000 and 46,000 each in medical apps. It seems like the willingness to use mHealth apps is high and the intention to share data for health research is existing. This leads to one conclusion: the time for app-accompanied clinical trials (smartRCTs) has come. In this perspective article, we would like to point out the stones put in the way while trying to implement apps in clinical research. Further, we try to offer a glimpse of what the future of smartRCT research may hold.

Keywords: clinical trials, app, smartRCT, eHealth, mHealth

INTRODUCTION

In the twenty-first century, digitalization in day-to-day life is ubiquitous, and besides conventional computers, laptops, and mobile phones, the use of smartphones is continuously increasing and far beyond writing messages or phone calls. Applications (apps) for smartphones and tablets have become indispensable, especially for young generations; however, increasing use of apps in the middle-aged and elderly population is observed, thus arguing for a common use across generation borders (1). The estimated number of mobile devices will exceed 2.16 billion in 2016 (2). Over 2.2 million apps are available in the Google Play store®, and about 1.8 million apps are available in the Apple App Store®. Google and Apple distribute nearly 70,000 apps each in the category Health and Fitness, and about 33,000 and 46,000 each in medical apps (3, 4). The WHO defines these tools under the label "mHealth" or "eHealth" as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" (5). The willingness to use mHealth apps or devices seems high. In a current study, Chen et al. (6) showed a great acceptance (77%) to share data for health research, which leads to the natural conclusion: the time for app-accompanied clinical trials has come. In addition, we are living in the era of Big Data, where lots of data are generated and analyzing strategies need to be found. Big Data is defined as "high volume, high velocity, and/or high variety information assets that require new forms of processing to enable enhanced decision making, insight discovery, and process optimization." (7)

Currently, the medical field shows an evolving trend in developing apps used as tools for behavior change therapy or lifestyle intervention, such as diabetes, weight loss, or exercise performance (8–10). But to date, only a few researchers like Volkova et al. (11) use mobile apps as supporting tools in trials. In their research, they launched the app-based Food Label Trial investigating the impact of labels on consumer behavior. They created the very apt term "smartRCTs" (app-accompanied randomized controlled trials).

In this perspective article, we would like to investigate the rocky path while attempting to implement apps in clinical research. Further, we try to offer a glimpse of what the future of smartRCT research may hold.

LIMITATIONS AND BARRIERS OF smartRCTs

Legal Limitations—Do Researchers Need a Law Degree?

When implementing apps in clinical research, one of the highest barriers to overcome is the legal limitations. The requirements differ in each country. We describe the situation in Germany, as it has one of the strictest data privacy regulations [place 7 in Privacy and Human Rights Report 2007 (12)], and we are experienced with the legal situation. Clinical trials need to be approved by the ethics committee (preventing unethical practice) and the data protection officer (enforcing data privacy laws). Usually, the ethics commission supports smartRCTs, if all the data privacy regulations are met (13). However, it is difficult to meet the requirements of the data privacy officer. Informal consent by patients must be obtained before entering the trial. This means, besides the usual trial information, patients have to be educated about the app technology, secure data transfer (anonymous or pseudonymous), data storage, time of storage, and the possibility to delete data if they discontinue the study. When recruiting patients prospectively during treatment this is less problematic, but gaining patient consent by phone or letter is difficult and time consuming.

The type of data transfer needs to be chosen carefully: anonymous data transfer (no patient-related data are transferred) will not conflict with data privacy regulations. Whereas pseudonymous data transfer (patient data are tagged with a pseudonym) requires proper planning. Pseudonyms must be generated to be untraceable and securely stored. The best approach is to set up two different servers: on server A, patients' data are stored, while server B contains the pseudonym and identifier. Both servers are not connected, hence, only authorized trial personal, who has access to both servers, is able to retrieve sensitive data (14).

Further, it is important to be in full control of patient data, as the right to informational self-determination is fundamental. Data deletion based on patient's wish needs to be possible. However, services from third-party providers often store data on remote servers outside the respective law system. Complete deletion of data is impossible and, therefore, such services do not comply with the law. Furthermore, secure data storage must be ensured for at least 10 years, which might lead to data overload (described below). It is important to stay—already in the phase of trial planning—in close contact with the ethics commission and the data privacy officer to meet all regulations and adapt the study protocol, if necessary. It would be beneficial if the German data privacy regulations and laws would get adjusted to the new technology to reduce bureaucracy and allow for high-tech research.

Medical apps demand a different quality standard. It is crucial that apps in smartRCTs need to meet standardized criteria, as they are involved in patient care. In Germany, apps that are considered as medical products need to comply with the Medizinproduktegesetz (Law for Medical Products) and thus must meet stricter criteria as common apps. Medical products need clinical testing and certification. Further, compliance with the Telemedizingesetz (Law for Telemedicine) needs to be ensured. The U.S. Food and Drug Administration published similar guidelines (15). Hence, it is viable to ensure the legal status of the app before starting the programming phase.

Patients—An App a Day Keeps the Doctor Away?

Limitations of smartRCTs are set by the patients themselves. In earlier publications, we investigated the attitude toward apps for therapeutic and scientific purposes. We saw a dependency on age and gender. Men and participants <60 years are more likely to use an app (16). The reluctance of female patients needs to be further evaluated. The age appears to be a limiting factor in app use. In 2014, only 18% of elderly people (>65 years) owned smartphones or tablets. Seventy-seven percent of the elderlies would request help when learning to use this new technology (17). Consequentially, this may lead to a lack of compliance when using apps in smartRCTs. In contrast, Smith et al. (18) showed a growing trend in smartphone use by people >65 years in 2015: already 27% in the U.S. owned smartphones, which means older citizens increasingly adapt to the new technology. Either way, smartRCTs must be planned considering involved patient cohort. Trials with elderly participants need careful selection of the mobile tools and possibly intense pretrial participant teaching. After all, Denis et al. showed that patient using mHeatlh apps feel closer to their treating doctor due to better communication (19).

Another problem could be that patients do not always own an adequate mobile device. Although in industrial countries like Germany (60%) or the United States (72%) a majority of the citizens is in possession of a mobile device (20), the variety of devices and operating systems is huge. Certainly, participation in smartRCTs can be predicated by adding smartphone possession (maybe even with certain operating systems) to the inclusion criteria, but this leads to preselection and therefore to biased results. One approach is to hand out a mobile device with a specified operating system to the participants while taking part in the trial. This reduces the costs for developing apps for different operating systems and ensures non-biased samples, however, requires funding to purchase devices. In summary, patients might be a limiting factor when launching a smartRCT, but proper preparation and careful planning can lead to an exceptional trial compliance.

Staff—An Important Cog in the Wheel?

As in the case with patients, the age of clinicians and principal investigators is an obstacle when implementing smartRCTs. In an earlier series, we investigated the attitude of health-care professionals toward app use of patients during treatment and aftercare. The idea of implementing apps was supported by 84.3%; 64.8% even preferred to be alerted if patients enter severe side effects, which require action. The majority (93.5%) supports scientific evaluation of the collected data. The named arguments against app use were legal uncertainty regarding medical responsibility; wish for sole personal contact between health-care professionals and patient; missing technical skills; and lack of time (14).

Legal uncertainty should be minimal within smartRCTs, as the study protocol describes precise treatment algorithms, which are audited by the ethics commission. Principal investigators and staff need to be technically trained. Without proper skills, they are not able to work with the used tools, as well as teach patients. Certainly, the fear of additional work exists. However, Denis et al. (19) showed that treating doctors needed less than 15 min per week for data analysis and phone calls within the entire cohort of 42 patients. With the appropriate development of automated data analyses, the staffs' work time can be minimized. Time-consuming clinical visits might be reduced, as some are replaced by app-based follow-ups. The delegation of tasks to specifically trained medical support staff like study nurses could reduce high workloads for principal investigators.

As always when introducing new technologies, there are supporters and critics within the medical profession. However, a smartRCT can only be successful if all principal investigators and the participating staff are technically educated and ready to support the project. Otherwise, failure is unavoidable.

Technical Realization—Let Us Start Programming in the Garage?

When overcoming all barriers, technical realization of smartRCTs is a minor obstacle. Programming from scratch needs qualified staff, which increases the costs of trials. Projects with apps require also medical computer scientists who not only provide technical skills but also understand how medical trials are conducted and have basal knowledge of the physicians' daily work and patients' needs. However, there are open source development kits offered by providers (e.g., Apple Researchkit® and Google Study kit®) to compose an app based on the respective operating system. For instance, Bot et al. (21) use the Apple Researchkit® in his "mPower" Parkinson trial.

As stated above, it is important to match the legal requirements for data transfer, security, and privacy when developing apps. Data transfer to a cloud or server needs to be encrypted to ensure the best possible protection of highly sensitive patient information. He et al. (22) showed that few Android mHealth apps match these criteria, although technical capabilities are already established: Thilakanathan et al. (23) developed a secure protocol for sharing patient data in clouds, and Silva et al. (24) presented the DE4MHA algorithm for secure encryption. Moreover, data storage needs to be encrypted to protect patient data from unauthorized access. A long-term storage on secure servers in favor of transparency

and plausibility of trial data is needed. This may lead to higher costs and data overload. Today, public health studies need already data storage capacity of 10 trillion bytes (10 TB) and more. This would equal tens of millions of floppy disks (25). Eventually, this is a future challenge for data transfer, storage, and management systems, which is no insurmountable problem.

FUTURE PERSPECTIVE OF smartRCTs

Apps Supporting Clinical Trials—Time Is Money

Besides all the barriers, smartRCTs hold numerous benefits in supporting trials. Khan et al. (26) observed the work time of three individual clinical trial managers and showed that tasks such as documentation (24%), administrative work (20%), and recruitment (16%) are time consuming. Moreover, activities, such as filling out case report forms (12%), data entry (10%), and recruiting eligible patients (9%), are exhausting. The most commonly used tool was paper (24%). Data collection with apps can reduce all those tasks and thus duration. Neuer et al. (27) suggest a 30% decrease in duration by using electronic data capture. Therefore, data analyses can be achieved faster, and results are quicker implemented into clinical routine (28).

The whole process of documentation could be simplified by asking patients to document trial parameters, quality of life scores, or other information *via* an app. Consequentially, a new dimension of information is added to the usual trial data: the patients' view. Going even a step further, mHealth devices such as activity trackers, blood pressure monitors, blood glucose meters, or personal scales can be connected with apps. Hence, the completeness and timeliness of the data are increased, because the course of the disease is monitored longitudinally and not only cross-sectional as it is the case with classical periodical visits. Highly compliant patients could even enter blood test or imaging results made by other physicians (see **Figure 1**).

Needless to say, it is possible to develop apps to be used two sided, and physicians or study nurses could also enter data into the app. Standardized entry is guaranteed, and paperwork is diminished. Reduced paperwork protects the environment and leads to a more secure archiving of patient data. Subsequent changes of data are more difficult; hence, data transparency is improved. Errors during processing and digitizing data are prevented. Dependencies can be used to check entries for plausibility, and automated algorithms can verify inputs already before storing.

The time-consuming recruitment process can be simplified by using apps. It is difficult to find eligible patients for trials using the traditional form of recruitment. With mHealth tools, a wide range of people can be approached, and, therefore, it is easier, faster, and more cost-effective. Laws et al. (29) showed that online recruitment compared to a practitioner and face-to-face recruitment is the quickest and cheapest form with average costs of AUD$ 14 per participant.

With all named benefits a higher cost-effectiveness can be achieved. Sertkaya et al. (30) applied a media data study and showed total costs of $78.6 million for phase 1–4 trials investigating drugs in oncology. Administrative staff costs (phase 3:
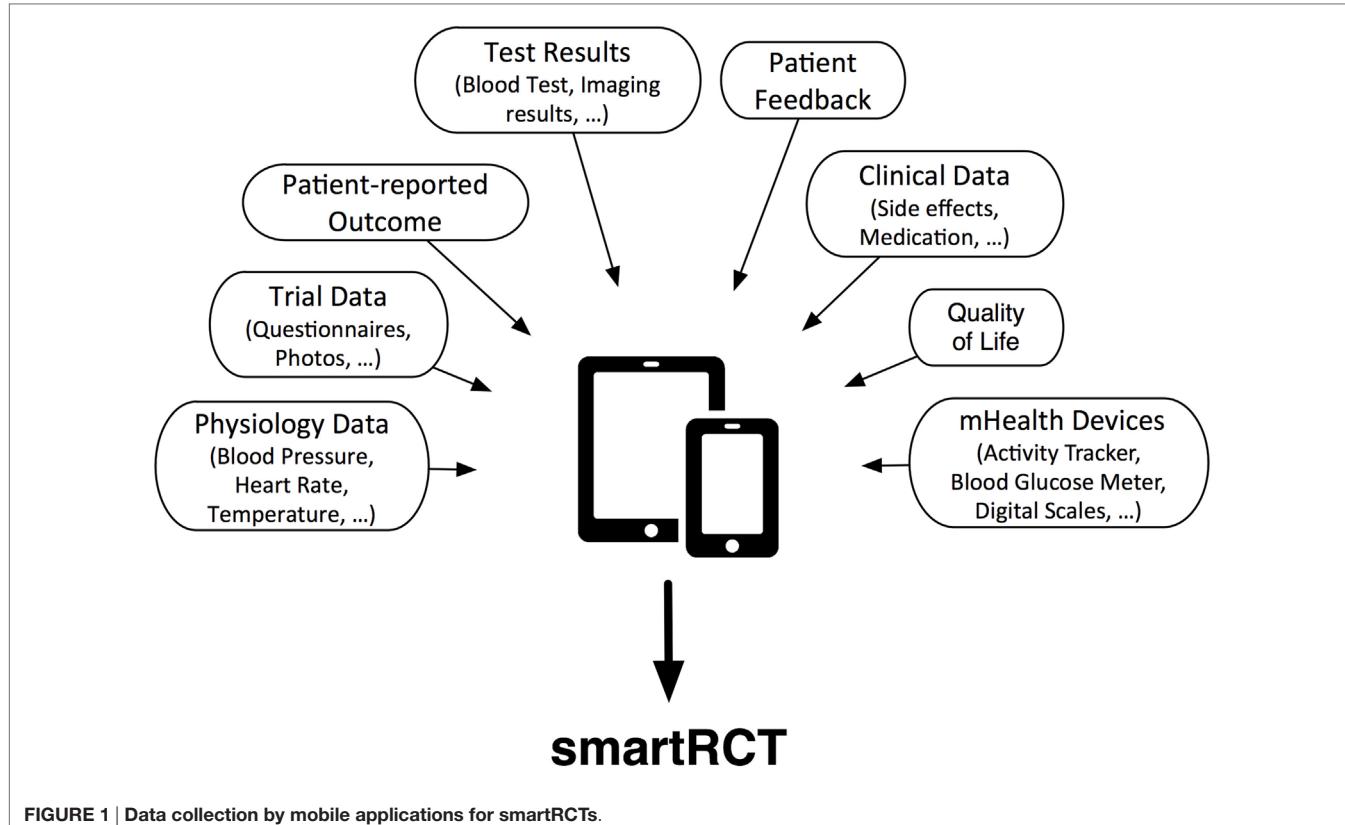
FIGURE 1 | **Data collection by mobile applications for smartRCTs.**

20.40%), physician costs (phase 3: 7.08%), source data verification costs (phase 3: 3.52%), patient recruitment costs (phase 3: 2.71%), and data management costs (phase 3: 0.34%) (30) can be reduced by using app technology where appropriate. The prerequisite is that apps operate as safe and without patient discomfort as humans. Sertkaya et al. suggest a total cost reduction of 7.91% (=$6.2 million) if mobile technology is used. Eisenstein et al. (31) calculated a reduction of 9.8% by using electronic data capture.

A huge problem within trials is the inevitable subjectivity of research personnel. Various studies of Hróbjartsson et al. (32–34) showed an occurring bias, especially if blinding is not feasible. App-based data collection is objective as well as standardized, for example, pre-validated questionnaires can be used. Furthermore, smartRCTs simplify multicenter trials as data transfer is easier and all investigators are closely connected. It is possible to centralize the data storage and prevent data loss (28). Moreover, app-based study procedures are equal and objective within all centers.

The mentioned advantages can be of great scientific value in radiation oncology as it is a highly technical discipline. In contrast to classical clinical visits, apps can be used for trial documentation of side effects caused by radiotherapy or concomitant radiochemotherapy. Trial compliance is enhanced as apps can be used to remind patients of radiation dates or drug intake. Continuous aftercare over years plays an important role in radiation oncology. App-based research could enhance documentation and therefore simplify trials on long-term toxicity. The implementation of

smartRTCTs would be of great benefit as it marks the departure into the new era of radiation oncology 4.0 (35).

Apps and Big Data—I Have a Dream …

smartRCTs and app-based research generate a huge amount of data—Big Data. Only a fraction of collected trial data are used and published. The data could, however, be utilized to perform sub-studies or can be merged to acquire new insights for clinical day-to-day life. Epidemiological researchers could identify patterns, causes, and effects of diseases without high costs and workload. In return, it is important to improve the level of technical skills within epidemiological studies (36).

Moreover, Big Data can be used to perform clinical trials *in silico*, which means computer simulations are run instead of classical studies (37). Less animal testing and patient recruitment in pharmaceutical or other trials would be needed (38). Especially, research in the area of highly rare conditions would benefit. Instead of using the hard road of recruiting a huge number of patients to gather valid results, computer simulation can accompany trials in rare tumor or diseases. Furthermore, Big Data shows potential in the evolving genomics research. A variety of recently published studies used electronic health data to show relationships between genetic variations and clinical conditions (39–41). Bowton et al. (42) showed this approach to be cost-effective and quick. The Omics movement led to further research disciplines: pharmacogenomics investigates effects of genetics on the individuals' drug response. Omics can be used to

predict disease probability, a great tool for preventive medicine (43). Hence, Big Data and Omics will be a major step toward personalized and precise medicine.

CONCLUSION

smartRCTs and app-based studies are the future of medical research—radiation oncology in particular. While there are certain barriers—especially the data privacy laws—the advantages outweigh the limitations. It would be desirable if politicians and lawmakers establish better opportunities and adjust the regulations to the new technology. This is possible without undermining the right to informational self-determination and data privacy. Further, all parties involved—data privacy officers,

ethical commission, patients, and researchers—need to support an aspired smartRCT. Necessarily, apps for research need to meet certain criteria concerning patient safety and good clinical practice; therefore, generally accepted standards for trial apps need to be established. If so, apps can reduce trial costs, study duration, and subjectivity bias as well as collect a wider range of data. One thing is clear: smartRCT is not a question of whether or not, but of when and how.

AUTHOR CONTRIBUTIONS

MV wrote the manuscript. SC advised and edited this manuscript. KK advised and edited the manuscript and proposed the initial concept. All authors approved the manuscript.

REFERENCES

1. Ehlers DK, Huberty J, Buman M, Hooker S, Todd M, de Vreede GJ. A novel inexpensive use of smartphone technology for ecological momentary assessment in middle-aged women. *J Phys Act Health* (2016) 13(3):262–8. doi:10.1123/jpah.2015-0059

2. eMarketer. *2 Billion Consumers Worldwide to Get Smart (Phones) by 2016.* (2014). Available from: http://www.emarketer.com/Article/2-Billion-Consumers-Worldwide-Smartphones-by-2016/1011694 (Archived by WebCite® at http://www.webcitation.org/6jGNrtCR8)

3. Jordan J. *App Store Metrics.* (2016). Available from: http://www.pocketgamer.biz/metrics/app-store/ (Archived by WebCite® at http://www.webcitation.org/6jGO48VjD)

4. Maurer U, Vogelzang M. *Android Statistics.* (2016). Available from: http://www.appbrain.com/stats (Archived by WebCite® at http://www.webcitation.org/6jGO1n8c5)

5. World Health Organization (WHO). *mHealth: New Horizons for Health Through Mobile Technologies: Second Global Survey on eHealth.* Geneva (2011).

6. Chen J, Bauman A, Allman-Farinelli M. A study to determine the most popular lifestyle smartphone applications and willingness of the public to share their personal data for health research. *Telemed J E Health* (2016) 22:655–65. doi:10.1089/tmj.2015.0159

7. Beyer MA, Laney D. *The Importance of 'Big Data': A Definition.* Stamford, CT: Gartner (2012). p. 2014–8.

8. Gimenez-Perez G, Recasens A, Simo O, Aguas T, Suarez A, Vila M, et al. Use of communication technologies by people with type 1 diabetes in the social networking era. A chance for improvement. *Prim Care Diabetes* (2016) 10(2):121–8. doi:10.1016/j.pcd.2015.09.002

9. Stephens JD, Yager AM, Allen J. Smartphone technology and text messaging for weight loss in young adults: a randomized controlled trial. *J Cardiovasc Nurs* (2017) 32(1):39–46. doi:10.1097/JCN.0000000000000307

10. Fong SS, Ng SS, Cheng YT, Zhang J, Chung LM, Chow GC, et al. Comparison between smartphone pedometer applications and traditional pedometers for improving physical activity and body mass index in community-dwelling older adults. *J Phys Ther Sci* (2016) 28(5):1651–6. doi:10.1589/jpts.28.1651

11. Volkova E, Li N, Dunford E, Eyles H, Crino M, Michie J, et al. "Smart" RCTs: development of a smartphone app for fully automated nutrition-labeling intervention trials. *JMIR Mhealth Uhealth* (2016) 4(1):e23. doi:10.2196/mhealth.5219

12. *Privacy and Human Rights 2006: An International Survey of Privacy Laws and Developments.* Washington, DC: Electronic Privacy Information Center & Privacy International (2007).

13. McCann M. The smartphones study: an analysis of disciplinary differences in research ethics committee responses to phone app-based automated data collection. *Eur J Public Health* (2016) 26(Suppl):1. doi:10.1093/eurpub/ckw164.002

14. Kessel KA, Vogel MM, Schmidt-Graf F, Combs SE. Mobile apps in oncology: a survey on health care professionals' attitude toward telemedicine, mHealth,

and oncological apps. *J Med Internet Res* (2016) 18(11):e312. doi:10.2196/jmir.6399

15. *Mobile Medical Applications – Guidance for Industry and Food and Drug Administration Staff: Food and Drug Administration.* (2015). Available from: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf (Archived by WebCite® at http://www.webcitation.org/6mtiwpLTZ)

16. Kessel KA, Vogel MM, Combs SE. Mobile applications as part of the oncological therapy – a survey on evaluating the acceptance in a German Oncology Center. *Strahlenther Onkol* (2016) 192(1):143. doi:10.1007/s00066-016-0974-z

17. Smith A. *Older Adults and Technology Use: Pew Research Center.* (2014). Available from: http://www.pewinternet.org/2014/04/03/older-adults-and-technology-use/ (Archived by WebCite® at http://www.webcitation.org/6mqbkRuIu)

18. Smith A. *U.S. Smartphone Use in 2015: Pew Research Center.* (2015). Available from: http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/ (Archived by WebCite® at http://www.webcitation.org/6nF7QSBT7)

19. Denis F, Viger L, Charron A, Voog E, Dupuis O, Pointreau Y, et al. Detection of lung cancer relapse using self-reported symptoms transmitted via an internet web-application: pilot study of the sentinel follow-up. *Support Care Cancer* (2014) 22(6):1467–73. doi:10.1007/s00520-013-1954-9

20. Poushter J. *Smartphone Ownership and Internet Usage Continues to Climb in Emerging Economies: Pew Research Center.* (2016). Available from: http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/ (Archived by WebCite® at http://www.webcitation.org/6mquZnvXU)

21. Bot BM, Suver C, Neto EC, Kellen M, Klein A, Bare C, et al. The mPower study, Parkinson disease mobile data collected using ResearchKit. *Sci Data* (2016) 3:160011. doi:10.1038/sdata.2016.11

22. He D, Naveed M, Gunter CA, Nahrstedt K. Security concerns in android mHealth apps. *AMIA Annu Symp Proc* (2014) 2014:645–54.

23. Thilakanathan D, Calvo RA, Chen S, Nepal S, Glozier N. Facilitating secure sharing of personal health data in the cloud. *JMIR Med Inform* (2016) 4:e15. doi:10.2196/medinform.4756

24. Silva BM, Rodrigues JJPC, Canelo F, Lopes IC, Zhou L. A data encryption solution for mobile health apps in cooperation environments. *J Med Internet Res* (2013) 15:e66. doi:10.2196/jmir.2498

25. Schnabel J. *Big Data – Overload: The Quest for Knowledge in an Era Flooded with Information.* Baltimore: Johns Hopkins Public Health (2012). p. 20–4.

26. Khan SA, Payne PRO, Johnson SB, Bigger JT, Kukafka R. Modeling clinical trials workflow in community practice settings. *AMIA Annu Symp Proc* (2006) 2006:419–23.

27. Neuer A, Slezinger E, Warnock N. *The Upfront Cost Hurdle of EDC: Applied Clinical Trials.* (2010). Available from: http://www.appliedclinicaltrialsonline.com/upfront-cost-hurdle-edc (Archived by WebCite® at http://www.webcitation.org/6mvSo6yeO)

28. Kessel KA, Bohn C, Engelmann U, Oetzel D, Bougatf N, Bendl R, et al. Five-year experience with setup and implementation of an integrated database system for clinical documentation and research. *Comput Methods Programs Biomed* (2014) 114(2):206–17. doi:10.1016/j.cmpb.2014.02.002

29. Laws AR, Litterbach EK, Denney-Wilson AE, Russell GC, Taki S, Ong KL, et al. A comparison of recruitment methods for an mHealth intervention targeting mothers: lessons from the growing healthy program. *J Med Internet Res* (2016) 18(9):e248. doi:10.2196/jmir.5691

30. Sertkaya A, Birkenbach A, Berlind A, Eyraud J. *Examination of Clinical Trial Costs and Barriers for Drug Development Eastern Research Group/ U.S. Department of Health and Human Services*. (2014). Available from: https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development (Archived by WebCite® at http://www.webcitation.org/6mvPwSwvm)

31. Eisenstein EL, Collins R, Cracknell BS, Podesta O, Reid ED, Sandercock P, et al. Sensible approaches for reducing clinical trial costs. *Clin Trials* (2008) 5(1):75–84. doi:10.1177/1740774507087551

32. Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ* (2012) 344:e1119. doi:10.1136/bmj.e1119

33. Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *CMAJ* (2013) 185(4):E201–11. doi:10.1503/cmaj.120744

34. Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Rasmussen JV, Hilden J, et al. Observer bias in randomized clinical trials with time-to-event outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *Int J Epidemiol* (2014) 43(3):937–48. doi:10.1093/ije/dyt270

35. Zimmermann D. *On the Cusp of Medicine 4.0*. (2015). Available from: http://www.healthcare-in-europe.com/en/article/15539-on-the-cusp-of-medicine-4-0.html (Archived by WebCite® at http://www.webcitation.org/6oC1sKhZX)

36. Mooney SJ, Westreich DJ, El-Sayed AM. Epidemiology in the era of big data. *Epidemiology* (2015) 26(3):390–4. doi:10.1097/EDE.0000000000000274

37. The power of big data must be harnessed for medical progress. *Nature* (2016) 539(7630):467–8. doi:10.1038/539467b

38. Viceconti M, Henney A, Morley-Fletcher E. In silico clinical trials: how computer simulation will transform the biomedical industry. *Int J Clin Trials* (2016) 3(2):37–46. doi:10.18203/2349-3259.ijct20161408

39. Denny JC, Ritchie MD, Crawford DC, Schildcrout JS, Ramirez AH, Pulley JM, et al. Identification of genomic predictors of atrioventricular conduction: using electronic medical records as a tool for genome science. *Circulation* (2010) 122(20):2016–21. doi:10.1161/CIRCULATIONAHA.110.948828

40. Kullo IJ, Ding K, Jouni H, Smith CY, Chute CG. A genome-wide association study of red blood cell traits using the electronic medical record. *PLoS One* (2010) 5(9):e13011. doi:10.1371/journal.pone.0013011

41. Ritchie MD, Denny JC, Crawford DC, Ramirez AH, Weiner JB, Pulley JM, et al. Robust replication of genotype-phenotype associations across multiple diseases in an electronic medical record. *Am J Hum Genet* (2010) 86(4):560–72. doi:10.1016/j.ajhg.2010.03.003

42. Bowton E, Field JR, Wang S, Schildcrout JS, Van Driest SL, Delaney JT, et al. Biobanks and electronic medical records: enabling cost-effective research. *Sci Transl Med* (2014) 6(234):234cm3. doi:10.1126/scitranslmed.3008604

43. Chen R, Snyder M. Promise of personalized omics to precision medicine. *Wiley Interdiscip Rev Syst Biol Med* (2013) 5(1):73–82. doi:10.1002/wsbm.1198

Which Obstacles Prevent Us from Recruiting into Clinical Trials: A Survey about the Environment for Clinical Studies at a German University Hospital in a Comprehensive Cancer Center

Christoph Straube[1,2,3]*, Peter Herschbach[2,3,4] and Stephanie E. Combs[1,2,3,5]

[1]Department of Radiation Oncology, Klinikum rechts der Isar, Technische Universität München (TUM), Munich, Germany, [2]Deutsches Konsortium für Translationale Krebsforschung (DKTK) – Partner Site München, Munich, Germany, [3]Roman Herzog Comprehensive Cancer Center (RHCCC), Munich, Germany, [4]Klinik für psychosomatische Medizin und Psychotherapie, Klinikum rechts der Isar, Technische Universität München (TUM), Munich, Germany, [5]Department of Radiation Sciences (DRS), Institute for Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Oberschleißheim, Germany

Background: Prospective clinical studies are the most important tool in modern medicine. The standard in good clinical practice in clinical trials has constantly improved leading to more sophisticated protocols. Moreover, translational questions are increasingly addressed in clinical trials. Such trials must follow elaborate rules and regulations. This is accompanied by a significant increase in documentation issues which require substantial manpower. Furthermore, university-based clinical centers are interested in increasing the amount of patients treated within clinical trials, and this number has evolved to be a key quality criterion. The present study was initiated to elucidate the obstacles that limit clinical scientists in screening and recruiting for clinical trials.

Methods: A specific questionnaire with 28 questions was developed focusing on all aspects of clinical trial design as well as trial management. This included questions on organizational issues, medical topics as well as potential patients' preferences and physician's goals. The questionnaire was established to collect data anonymously on a web-based platform. The survey was conducted within the Klinikum rechts der Isar, Faculty of Medicine, Technical University of Munich; physicians of all levels (Department Chairs, attending physicians, residents, as well as study nurses, and other study-related staff) were addressed. The answers were analyzed using the Survio analyzing tool (http://www.survio.com/de/).

Results: We collected 42 complete sets of answers; in total 28 physicians, 11 study nurses, and 3 persons with positions in administration answered our survey. The study centers reported to participate in a range of 3–160 clinical trials with a recruitment rate of 1–80%. Main obstacles were determined: 31/42 (74%) complained about limited human resources and 22/42 (52%) reported to have a lack on technical

resources, too. 30/42 (71%) consented to the answer, that the documentation effort of clinical trials is too large. A possible increase of the patients' study participation rate up to over 20% was deemed to be possible if the described limitations could be overcome.

Discussion: The increasing documentation effort in clinical trials has led to a strong increase in the work load of scientific personnel. Recruiting of patients into clinical trials therefore is not only limited by patient issues, but also by the infrastructure of the centers. Especially the lack of study nurses is likely to be a major limitation. Furthermore, technical resources for time efficient and safe documentation within clinical routine as well as in clinical trials are required. By optimization of these factors, a significant increase in the amount of patients treated in clinical trials seems to be possible.

Keywords: barriers to participation, clinical trials as topic, survey, physicians, management

INTRODUCTION

Prospective clinical trials, especially randomized controlled trials, are accepted as the most important source of evidence in most subdisciplines of modern medicine; data from clinical trials do constantly shape our guidelines for clinical practice and thus contribute essentially to up-to-date patient care (1, 2). However, gaining this evidence is often hampered by low patient accrual-rates that subsequently can lead to a failure of important trials because they do not reach the preplanned sample sizes in adequate time intervals (3). Many studies have been conducted to investigate the role of patients in this recruitment dilemma. It has been shown that, besides other factors, patients' concerns about the possibility to be randomized to a placebo treatment or to the standard treatment arm can lead to the hesitation to give informed consent to participate in a trial (4). Also the consent process itself has been identified as one barrier for patients as well as for clinicians to participate in clinical trials (5).

Focusing only on the unwillingness of patients to participate in clinical trials, however, might be an oversimplification of this problem. Trial recruitment depends on several factors, which can also be organizational, financial, or related to other factors relevant to trial management. Therefore, mainly focusing on the patient itself may underestimate the difficulties. Surprisingly, these factors have only been studied marginally so far, although time shortenings and lack of study staff have been blamed as barriers for clinical trials (5, 6).

In order to optimize the recruitment of patients into clinical trials in our hospital, we conducted informative interviews, generated and conducted a quantitative survey, and discussed the results at an open conference at our center. We hypothesized, that recruitment into clinical trials is also limited by infrastructural shortenings. This was confirmed by the responses to our questionnaire. The quantitative results of this survey gave us strong arguments to ease financial resources and to force changes in the administrative framework. We hereby present the results from our survey as similar obstacles might be present in other clinical trial centers, too.

MATERIALS AND METHODS

Questionnaire Development

After a series of informative interviews with department chairs and leading senior professionals from 17 departments of the University Hospital Klinikum rechts der Isar, Technical University of Munich (TUM), Germany, a specific questionnaire was developed, focusing on all aspects of clinical trial design as well as trial management. The questionnaire included 28 questions. We included demographic questions, namely two multiple choice questions about the position in the clinic and the predominant medical field (i.e., medical vs. surgical treatments), two dichotomous questions about the sex of the participant and whether the participant belongs to the TUM and seven open-ended questions asking for the age of the participant, the years of experience in clinical trials, the number of clinical trials and study nurses within the clinical center, and the amount of patients that are treated within different subtypes of clinical trials. Subsequently, 16 rating-scale questions asked whether patient relate complaints, trial factors, structural aspects, and complaints or administrative obstacles had an influence onto the rate of patients recruited to clinical trials (**Table 1**). Lastly, an open-ended questions asked to which extent the amount of patients within clinical trials could be increased if the obstacles stated in the rating-part would be eliminated. Additionally, the responders had the possibility to leave comments at the end of the survey.

Furthermore, questions on the medical background and the organizational structure of the participant's centers were included. The questionnaire was piloted within a small cohort of physicians. Participants of the pilot run were instructed not to participate in the final run of the survey, however, as we performed an anonymous web-based survey it cannot been ruled out that some participants from the pilot run also answered the final questionnaire.

The questionnaire was established to collect data anonymously on a web-based platform (the entire questionnaire in German language can be found within Table S1 in Supplementary Material). The survey was conducted within the Klinikum rechts

der Isar, Faculty of Medicine, TUM; clinical scientists of all levels (Departments Chairs, attending physicians, residents, as well as study nurses, and other study-related staff) were addressed. The questionnaire was performed within the quality assurance program of the Comprehensive Cancer Center of our hospital and was therefore in line with the institutional guidelines of the local Ethic's committee. The answers were analyzed using the web-based Survio analyzing tool (http://www.survio.com/de/) and Microsoft© Excel 2016. The frequency of the answers given by physicians and study nurses were compared with each other using the χ^2-test function of SPSS v. 18 (IBM).

RESULTS

The web-based survey counted 120 visits resulting in 44 completed questionnaires (37%). Twenty-nine physicians, most of them senior physicians (20), 12 study nurses, and 3 persons with administrative areas of responsibility completed the questionnaire. Eighteen physicians were from non-surgical and medical specialties, eight physicians had a surgical background, and three physicians had a surgical as well as a medical background. All physicians reported to have long-term experiences in conducting prospective medical trials (median 10 years, range 4–27 years).

Study nurses were employed in surgical disciplines in one (8%) case, in medical disciplines (e.g., internal medicine or radiation oncology) in seven cases (58%), and in subjects with medical and surgical treatments in four cases (33%). The level of experience was comparable with the group of physicians (median 10 years, range 1–15 years). Based on the composition of this cohort, the sample has to be considered as a random sample, as especially department chairs and residents are underrepresented.

The participants did also answer questions about their study centers. Overall, the centers reported to have 0–160 active trials (median 15 trials). Compared with the large number of trials, centers employed only a relative small number of study nurses (median 3, range 0–6), indicating that this might limit the maximum number of patients recruited into clinical trials; in average, every study nurse cared for 10.5 clinical trials. 32 of 44 persons (73%, 7 totally agreed, 25 agreed mostly, **Table 1**) consented to the answer, that the documentation effort of clinical trials is to large (10 of 12 study nurses, 20 of 29 physicians). Focusing on the clinical routine, 14 physicians (48%) affirmed the statement, that a large burden of documentation is an important obstacle in recruiting patients to clinical trials. Deficits in information technology resources were described by 52% of the responders.

Consistent to this findings, limited human resources were complained by 31 persons (70%; 19 agreed totally, 12 agreed mostly). Additionally, eight responders highlighted this topic within the free-text answers. Limited resources in information technology were also reported by the participants, although by a smaller number (23 of 44 answers, 52%).

Trial-related factors as well as patient-related factors were deemed to have less influence on the recruitment rates, only two physicians (7%) answered, that there are not enough trials

TABLE 1 | Questions and results from the questionnaire (translated from German language).

	"I do agree totally" or "[…] mostly"			p-Values
	All	**Physicians**	**Study nurses**	
Trial related				
There are currently no trials available for our patient cohort	2 (4%)	2 (7%)	0	0.351
Important trials could not be established at our center	13 (29%)	12 (41%)	1 (8%)	0.039
The inclusion and exclusion criteria are to exclusive	4 (9%)	3 (10%)	1 (8%)	0.843
Concerning the conduction of clinical trials, I am discouraged by legal regulations (German medical law, German medical technology law, German law for radiation protection, etc.)	10 (23%)	10 (34%)	0	0.019
We offer several trials with almost identical inclusion and exclusion criteria (that do compete to each other)	11 (25%)	8 (28%)	3 (25%)	0.865
Patient related				
Most patients do refuse to participate in clinical trials	4 (9%)	1 (3%)	2 (17%)	0.139
I want to protect my patient from additional stress that could be caused by participating in clinical trials	0	0	0	n/a
Organization related				
The documentation effort of clinical trials is to large	32 (73%)	20 (69%)	10 (83%)	0.345
The documentation effort within the daily clinical routine hampers me to recruit patients to clinical trials	22 (50%)	14 (48%)	7 (58%)	0.558
There are not enough human resources to conduct (more) clinical trials	31 (70%)	20 (69%)	8 (67%)	0.886
Technical resources or software solutions for the conduction of clinical trials are lacking	23 (52%)	15 (52%)	7 (58%)	0.699
Structural shortcomings (technical and/or human resources) already resulted in a refusal from sponsors to initiate a trial at our center	5 (11%)	4 (14%)	1 (8%)	0.627
Within the last years, trials could not be initiated due to administrative hurdles	10 (23%)	7 (24%)	2 (17%)	0.599
We do not have enough collaborators to conduct clinical trials	5 (11%)	4 (14%)	0	0.176
Conflicts within our center do negatively interfere with our recruiting activity	6 (14%)	3 (10%)	2 (17%)	0.574
I am not experienced enough yet to conduct clinical trials	2 (4%)	1 (3%)	1 (8%)	0.509

The results represent the complete or predominant agreement to the given statements. The frequency of the answers from physicians and study nurses were compared with the χ^2 test.

available for patients treated at their department. Also refusal from patients to participate in prospective clinical trials seems to be a minor issue in our center (one physician agreed mostly onto that statement).

Altogether, obstacles in infrastructure as well as limitation of human resources were deemed to limit the number of recruited patients by all but six participants. Vice versa, the participants expected to be able to substantially increase the recruitment of patients to clinical trials in 39 cases (89%) if the obstacle would be improved.

We grouped the answers of the responders according to their job type (e.g., physicians vs. study nurses) and compared the frequency of the answers. There were no significant differences in the frequency of affirmations to questions asking for patient- or organization-related factors. However, physicians agreed significantly more to the statements "Important trials could not be established at our center" ($p = 0.039$) and "Concerning the conduction of clinical trials, I am discouraged by legal regulations […]" ($p = 0.019$).

DISCUSSION

In the present analysis, we sought to determine major obstacles for prospective clinical trials. In a detailed questionnaire, we identified documentation tasks as a key factor, as well as the difficulty to recruit well trained staff. Limited personnel resources may be a main obstacle for effective conduction of clinical trials. Furthermore, the majority of participants suspected an increased efficacy in patient recruiting if these obstacles would be eased.

Clinical trials are the most important sources for valuable evidence in modern medicine. Unfortunately, a large proportion of trials undergo early closure due to poor accrual. While patient-related obstacles for the recruitment into clinical trials have already been studied, literature on institutional obstacles for trial recruitment is scarce. A large documentation due to rising quality claims and increasing legal regulations are reasons for the growing documentation effort in clinical trials that leads to an increase of workload for the scientific personnel in university hospitals (6–8). Besides there is no evidence that this continuous increase in regulation efforts does really improves the quality of scientific results, conduction of clinical trials is increasingly complex. Consequently, the vast majority of our participants did agree to the statement, that the documentation effort of clinical trials is to large. As many responders complained about large documentation efforts within the routine treatment of patients and about deficits in the information technology infrastructure, one could summarize that infrastructural shortenings do currently limit time of physicians and study nurses to an extent that precludes the recruitment of more patients. While this already seems to be a significant problem at a German university hospital, centers within the developing world do suffer even more from this development (6, 7). Therefore, the discussion of this topic should be continued although the recently updated GCP guidelines do allow "more efficient approaches to clinical trial design […], recording […and] reporting" (9). It is within the responsibility of future sponsors and investigators to optimize their protocols

to consequently reduce the requested information to the least necessary amount.

Current trials, however, still suffer from the large burden of necessary documentation which only can be handled by the help of an adequate number of supportive personal (5). This was confirmed by one key-finding from our survey: a shortening of human resources is one of the most important obstacles for increasing the rate of patients recruited to clinical trials. This was also reported within a survey by Kaanoi et al., who reported that 22 of 27 oncologists in Hawaii did not have enough support staff to recruit more patients to clinical trials; he explained, that the low number of study nurses limited the amount of patients in clinical trials for which all quality claims for clinical trials could be fulfilled (10). Furthermore, a systematic review by Fisher and colleagues summarized, that a lack of time for the screening, treatment, and follow up of clinical trials is a major barrier for oncologists to participate in clinical trials (5). Notably, the increasing documentation duties within the clinical routine leads to a further increase of this barrier, a finding that was already described in the early 1990s in the United Kingdom (11). While especially investigator initiated trials are often underfinanced, a political debate on the necessity of supportive scientific personnel in clinical centers is needed. Furthermore, the additional personnel effort should be taken into consideration when contracts for company initiated trials are made. Concerted lists for the costs of study personal as well as medial measures, as already common for the pharmacists in dispensaries in Germany, could become an important tool for the planning, contracting, and the conduction of clinical trials.

The results of our survey cannot be generalized to the level of individuals of our center, as especially department chairs, and residents are underrepresented. However, the survey was answered mostly by experienced physicians involved in the conception of clinical trials as well as in the management of the scientific centers. The second largest group consisted of the supportive scientific staff. These two large groups are likely to give valuable information about their centers since they are the two main groups in charge of day-to-day issues in clinical trial management. Therefore, the obstacles reported by the participants are likely to represent the most important institutional barriers for patient recruitment to clinical trial at our center. Whether the results of our survey can be generalized to other centers can hardly be answered, as key values needed for a comparison, i.e., the number of study nurses or the number of active trials, are not available for other centers. However, since at least within Germany University Hospitals are characterized by similar organizational structures most arguments most likely hold true for other sites. Further investigations about an ideal balance between the number and complexity of clinical trials at one center, the number of study nurses and the number of patients within clinical trials are therefore highly recommended.

Until that, a continuous review of the study process on all levels of a scientific clinical center seems to be a sufficient tool to identify barriers for the conduction of clinical trials. Of importance, patient related as well as structural factors need to be analyzed to improve the process of clinical trials. Results of

quantitative surveys can help to hierarchical sort the importance of administrative hurtles and can serve as arguments for easing financial of personnel resources for their solution. Coming back to our experiences, the results from the interviews as well as from the survey allowed us to build an interdisciplinary consent about the most important issues, and some of the most important issues have already been solved. Additionally, clinical scientists should take the personal limitations of clinical centers into account when new protocols for clinical trials are generated. A lower burden of documentation, partially by focusing onto the main objectives of the trial, can help to increase the efficacy of the trial centers which subsequently can handle more patients within clinical trials.

REFERENCES

1. Breast E, Trialists C, Group C. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* (2015) 6736:1–12. doi:10.1016/S0140-6736(15)61074-1
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* (2005) 352:987–96. doi:10.1056/NEJMoa043330
3. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technol Assess* (2007) 11:iii, ix–105. doi:10.3310/hta11480
4. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol* (2006) 7:141–8. doi:10.1016/S1470-2045(06)70576-9
5. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* (1999) 52:1143–56. doi:10.1016/S0895-4356(99)00141-9
6. Vischer N, Pfeiffer C, Limacher M, Burri C. "You can save time if…" – a qualitative study on internal factors slowing down clinical trials in Sub-Saharan Africa. *PLoS One* (2017) 12:e0173796. doi:10.1371/journal.pone.0173796
7. Lang T, Cheah PY, White NJ. Clinical research: time for sensible global guidelines. *Lancet* (2011) 377:1153–555. doi:10.1016/S0140-6736(10)62052-1
8. McMahon AD, Conway DI, MacDonald TM, McInnes GT. The unintended consequences of clinical trials regulations. *PLoS Med* (2009) 6:e1000131. doi:10.1371/journal.pmed.1000131
9. ICH Harmonized Guideline. *Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Available from: http://www.ich.org
10. Kaanoi M, Braun KL, Gotay CC, Abrigo L. Oncologists' knowledge, attitudes and practices related to cancer treatment clinical trials. *Hawaii Med J* (2002) 61:91–5. doi:10.3816/CLM.2009.n.003.Novel
11. Smyth JF, Mossman J, Hall R, Hepburn S, Pinkerton R, Richards M. Conducting clinical research in the new NHS: the model of cancer. UK Coordinating Committee on Cancer Research. *BMJ* (1994) 309:457–61. doi:10.1136/bmj.309.6952.457

AUTHOR CONTRIBUTIONS

CS drafted and designed the survey, approved the survey, analyzed the results, and wrote the manuscript. PH and SC designed the survey, approved the survey, critically discussed the results, gave important intellectual input, and wrote the manuscript. All authors approved the final version for the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fonc.2017.00181/full#supplementary-material.

Use of Multicenter Data in a Large Cancer Registry for Evaluation of Outcome and Implementation of Novel Concepts

Gabriele Schubert-Fritschle[1]*, Stephanie E. Combs[2,3,4,5], Thomas Kirchner[2,5,6], Volkmar Nüssler[2] and Jutta Engel[1,2]

[1] Munich Cancer Registry (MCR) of the Munich Tumour Centre (TZM), Institute for Medical Information Processing, Biometry and Epidemiology (IBE), University Hospital of Munich, Ludwig-Maximilians-University (LMU), Munich, Germany, [2] Munich Tumour Centre (TZM), Medical Faculties, Ludwig-Maximilians-University (LMU) and the Technical University of Munich (TUM), Munich, Germany, [3] Department of Radiation Oncology, Technische Universität Munich (TUM), Klinikum rechts der Isar, Munich, Germany, [4] Department of Radiation Sciences (DRS), Institute for Innovative Radiotherapy (iRT), Helmholtz Zentrum Munich, Oberschleißheim, Germany, [5] Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Site Munich, Munich, Germany, [6] Institute for Pathology, Ludwig-Maximilians-University (LMU), Munich, Germany

Large clinical cancer registries (CCRs) in Germany shall be strengthened by the German Social Code Book V (SGB V) and implemented until the end of 2017. There are currently several large cancer registries that support clinical data for outcome analysis and knowledge acquisition. The various examples of the Munich Cancer Registry outlined in this paper present many-sided possibilities using and analyzing registry data. The main objective of population-based cancer registration within a defined area and the performance of outcomes research is to provide feedback regarding the results to the broad public, the reporting doctors, and the scientific community. These tasks determine principles of operation and data usage by CCRs. Each clinical department delivers its own findings and applied therapy. The compilation of these data in CCRs provides information on patient progress through the regional network of medical care and delivers meaningful information on the course of oncological diseases. Successful implementation of CCRs allows for presenting the statistical outcomes of health-care delivery, improving the quality of care within the region, accelerating the process of implementing innovative therapies, and generating new hypotheses as a stimulus for research activities.

Keywords: cancer incidence, cancer mortality, survival, trends, data analysis, quality assurance, comparative effectiveness research

REGIONAL CCRs—INSTRUMENTS FOR CLINICAL AND EPIDEMIOLOGICAL RESEARCH

According to the 1995 German law regarding the regulating of cancer registration (Cancer registry law, Krebsregistergesetz—KRG 1995), German states were required to establish cancer registries until January 1999. All German states complied with this regulation and generated comprehensive epidemiological cancer registrations. Over time, there has been increasing precision in the

estimation of cancer incidence and mortality by the German Society for Epidemiological Cancer Registries in Germany (GEKID) (1) and the Centre for Cancer Registry Data (ZFKD) at the Robert Koch-Institute (RKI) (2). In addition, data from nine German regions are currently published in the WHO publication Cancer Incidence in Five Continents, Vol. X (3), and 23% of EUROCARE-5 (4) data originate from Germany.

Population-based cancer registries are important instruments for epidemiological reference. Epidemiology involves the analysis of health and illness or, more generally, the dynamics, causes, and consequences of the health status of a defined population (5). Cancer will affect more than 40% of all people globally. In Germany alone, approximately 477,000 persons per year are diagnosed with cancer, and 221,000 persons die each year from cancer (6).

The few indices, however, that may be estimated by epidemiological cancer registries are not sufficient to describe the complex structures, care, and outcomes of cancer diseases. Therefore, it is necessary to obtain evidence on cancer subtypes, various outcomes of cancer care, clinical experiences, and knowledge origination, all of which require population-based clinical data collected by way of CCRs and then analyzed and published by the registries in cooperation with their clinical partners.

Therefore a national law, the Krebsfrüherkennungs- und -registergesetz (KFRG), which generated basic conditions for population-based CCRs in all regions of Germany (SGB V §65c), was enacted in April 2013. The KFRG requires that cancer data be recorded in CCRs countrywide, but in small regions (federal state or parts of it), in accordance with standardized definitions [see common German oncological basic dataset and its supplementary organ-specific modules edited by ADT (Arbeitsgemeinschaft Deutscher Tumorzentren, working group of German cancer centers) and GEKID]. Data acquisition must be completed relative to cases with defined ICD-10 codes and items of ADT-oncological data sets within a defined region. Each federal state has to legislate specific details (e.g., data protection) by its own.

Clinical cancer registries may provide useful data on cancer diseases and cancer care if all doctors and hospitals within a defined region and within defined fields, such as surgery, pathology, radiotherapy, and systemic oncology, prepare and submit all independent and cross-sectoral findings and therapies from the primary diagnosis through the course of the disease. Data are checked, coded, and compiled in CCRs, and data management is completed using follow-up information, including date and cause of death. Based on this structure, feedback may be realized in the manner postulated by law.

THE MUNICH CANCER REGISTRY (MCR)—ORGANIZATION AND STRUCTURE OF A MULTICENTER DATA POOL

The MCR is the population-based clinical cancer registry of Upper Bavaria and one region of Lower Bavaria (Southern Germany) (7). Since 1978, the registry's catchment area has been enlarged twice. In 2002, it was increased to 2.3 million inhabitants, and in 2007, it was increased to 4.5 million inhabitants. It currently includes more than 4.8 million inhabitants (**Figure 1**).

Pathology reports of solid tumors from all pathology laboratories in this catchment area are available. From these reports, the total number of cancer patients in the region is systematically assessed and the main prognostic factors were ascertained. In parallel, clinicians complete standardized forms concerning patients' domicile, age, primary disease characteristics such as TNM-stage, histology, grade, as well as therapies or deliver these data online to the MCR.

The life status of patients diagnosed with cancer is maintained by clinicians and is systematically updated by the MCR through death certificates. **Figure 2** displays the interdisciplinary and cross-sectoral documentation of course of cancer disease.

All data and clinical findings during the course of the disease (e.g., local or regional recurrence, metastases, and death) are coded according to the guidelines of the International Agency for

MCR
Foundation in 1978
> 620,000 patients registered
Population-based since 1998
Region and catchment area with about:
    4.8 million inhabitants
    22 institutes of pathology
    21 institutes of radiotherapy
    73 hospitals
    350 departments
    23 public health offices

FIGURE 1 | The Munich Cancer Registry (MCR)—catchment area and key data (7).
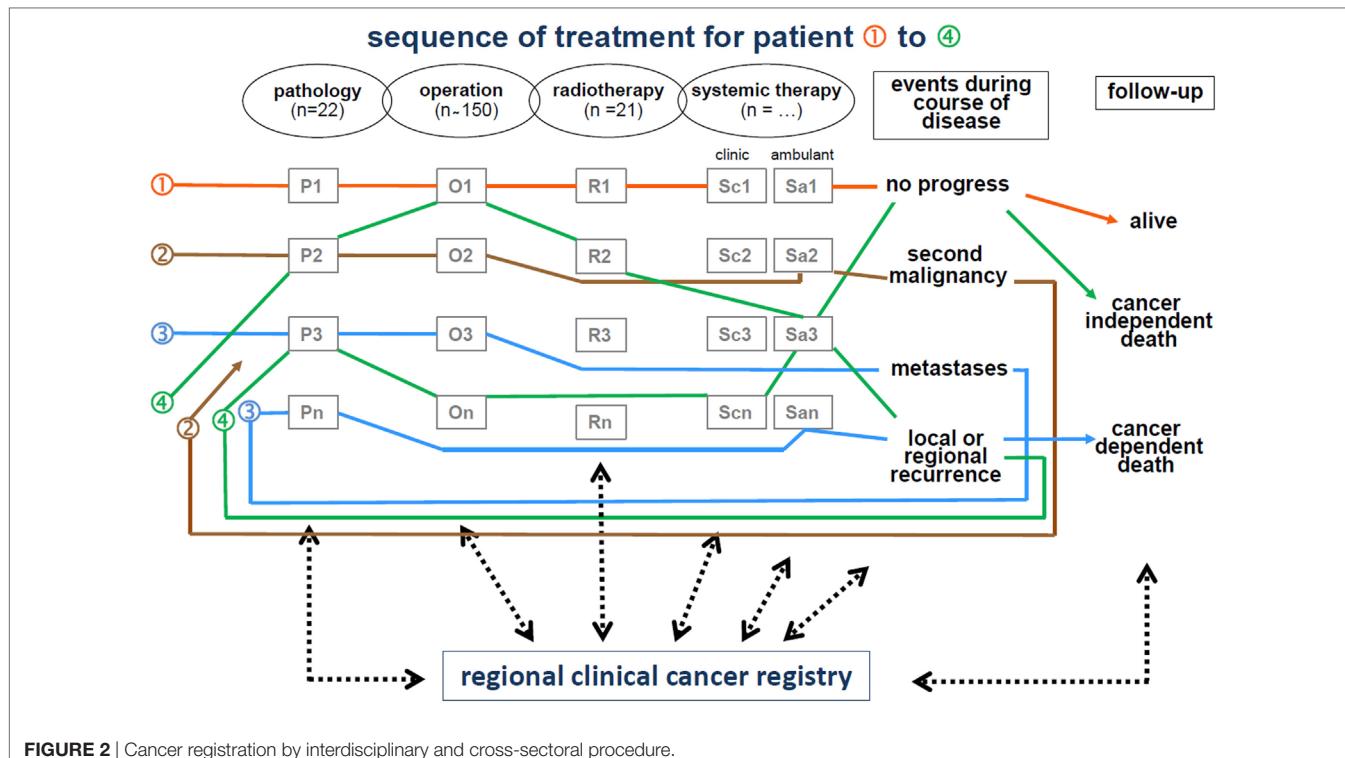
FIGURE 2 | Cancer registration by interdisciplinary and cross-sectoral procedure.

TABLE 1 | Malignancies by year of diagnosis from 1998 to 2015 defined by KFRG.

ICD10-diagnosis	C00-C97 without C44 and C77-C79	D00-D09 without D04	D32-D33 D35.2-4	D39.1 D41.4 D42-D43 D44.3-5 D45-D46 D47.1/3-5	Total	Portion death certificate-only (DCO)		Portion children	
Year	n	n	n	n	n	n	%	n	%
1998	10,682	564	37	79	11,362	1,355	10.6	69	0.6
1999	10,744	611	44	90	11,489	1,281	10.0	64	0.6
2000	10,619	638	94	101	11,452	1,446	11.2	62	0.5
2001	11,075	650	204	100	12,029	1,458	10.8	57	0.5
2002	18,336	1,009	297	176	19,818	3,253	14.0	94	0.5
2003	18,371	1,143	292	167	19,973	2,729	12.0	109	0.5
2004	18,751	1,489	268	181	20,689	2,556	10.9	121	0.6
2005	19,066	1,592	298	211	21,167	2,287	9.7	146	0.7
2006	19,485	1,630	307	237	21,659	1,995	8.4	116	0.5
2007	22,407	1,928	398	322	25,055	2,406	8.7	154	0.6
2008	22,943	2,086	376	329	25,734	2,233	7.9	156	0.6
2009	22,787	2,170	383	363	25,703	2,085	7.5	118	0.5
2010	22,520	2,376	256	348	25,500	2,158	7.8	145	0.6
2011	22,743	2,561	397	359	26,060	2,069	7.3	149	0.6
2012	22,734	2,480	374	294	25,882	2,008	7.2	168	0.6
2013*	21,737	2,660	207	294	24,898	1,991	7.4	136	0.5
2014*	17,681	2,126	174	203	20,184	2,003	9.0	63	0.3
2015*	14,218	1,656	29	120	16,023	1,610	9.1	20	0.1
Total	326,899	29,369	4,435	3,974	364,677	36,923	9.2	1947	0.5
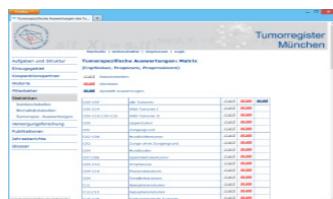
Without DCO-cases (portion from sum of columns total, DCO and children).
Without children <18 years (portion from sum of columns total + children).
Without non-melanotic skin cancer (C44, D04), secondary malignancies (C77-C79).

Research on Cancer. Tumors are classified in compliance with the staging criteria of the TNM Classification of Malignant Tumors (8). There are approximately 350 departments in approximately 70 hospitals in the cooperating network of the MCR. Currently, more than 25,000 new cases are registered each year. Within the smaller catchment area, there were approximately 11,000 new cases reported annually in 1998, which increased to approximately 25,000 annually by 2015. Accordingly, there were more than 360,000 cancer cases registered in the MCR from 1998 to 2015 (**Table 1**).
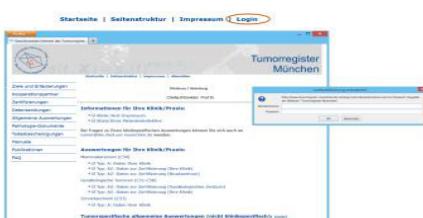
www.tumorregister-muenchen.de/en/index.php
basic statistics and survival analyses
①
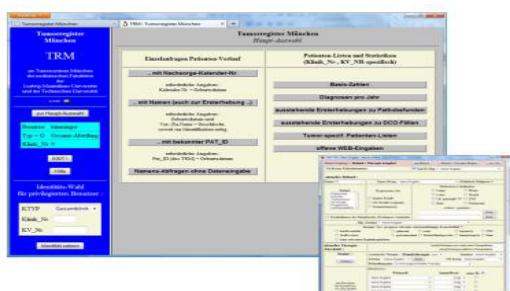
www.tumorregister-muenchen.de/en/index.php/login
detailed cancer specific analyses
②

www.tumorregister-muenchen.de/en/index.php/login
detailed cancer specific
and clinic specific analyses
③

online access:
access to case histories,
queries,
online documentation
④

FIGURE 3 | Four levels of feedback *via* the Internet.

All patients are followed actively and prospectively to make the database as complete as possible. Over time, approximately 50% of the patients have deceased. The course of the disease in the other 50% is continuously being adjusted by including information regarding disease progression and life status. Furthermore, the percentage of death certificate-only cases decreased from 10 to 7% from 1998 to 2015.

The diagnoses of cancers with high incidence rates, such as breast or colorectal cancer, range from 3,500 to 4,000 per year. While the catchment area is large, only a small number of patients with rare cancers, such as vulvar cancer or Hodgkin's lymphoma, is expected. This quantity structure must be considered in the data analysis and study design. Nonetheless, even given the cooperation of several institutions and the aggregation of time periods, there remain an insufficient number of

patients with rare cancers to conclude reliable survival analyses or to conduct multivariate statistical methods.

FEEDBACK REGARDING RESULTS

One of the elementary tasks of CCRs is to provide information regarding patients' cancers to the cooperating partners, doctors, hospitals, public, and most especially, to the patients and their relatives. The MCR developed four levels of data presentation, all of which can be accessed *via* the Internet (**Figure 3**).

Level 1 provides open access information on age distribution, incidence, mortality, and survival as ordered by ICD-10 (C- and D-diagnoses) for all interested persons (9). Access to level 2 information is restricted by password to cooperators and authorized persons. Level 2 provides special analyses of the whole catchment

area and is limited to the main ICD-10 cancer diagnoses. The statistics and results presented in level 3 are restricted to the cohort of patients of a single hospital and may be accessed using a unique hospital password. Level 1 to level 3 presents aggregated statistics with a varying degree of detail. Finally, doctors with special personal identification are allowed online access to the MCR database in level 4. Basic queries may be performed on single patients or patient groups with defined characteristics, and it is possible to perform online documentation of cancer patients.

USE OF MULTICENTER DATA TO EVALUATE OUTCOMES AND IMPLEMENT NOVEL CONCEPTS

Cancer registry data may be used in various clinical and scientific applications. Clinicians must have access to case histories for daily patient care or for evaluation of the course of disease for single patients. A precondition for clinical QA measures is to ensure data correction and completion of documents that gather information such as disease parameters and types of therapies. Certain questions are intended for patient cohorts with comparable diagnostics or treatments. The demands on an individual level are described in the upper portion of **Figure 4**.

Descriptive and analytical statistics are essential for certain scientific applications. For example, the analyses of hospital variations are useful for benchmarking, providing information feedback required for QA and reproducing published results using epidemiological data from the CCR for CER. These and other examples are outlined in the lower portion of **Figure 4**. The duties and responsibilities of CCRs can be defined through comparisons of hospitals, analyses of certification audits, comparisons

to cancer-specific guidelines, assessments of regional and time trends, and individual benchmark results of clinical study outcomes.
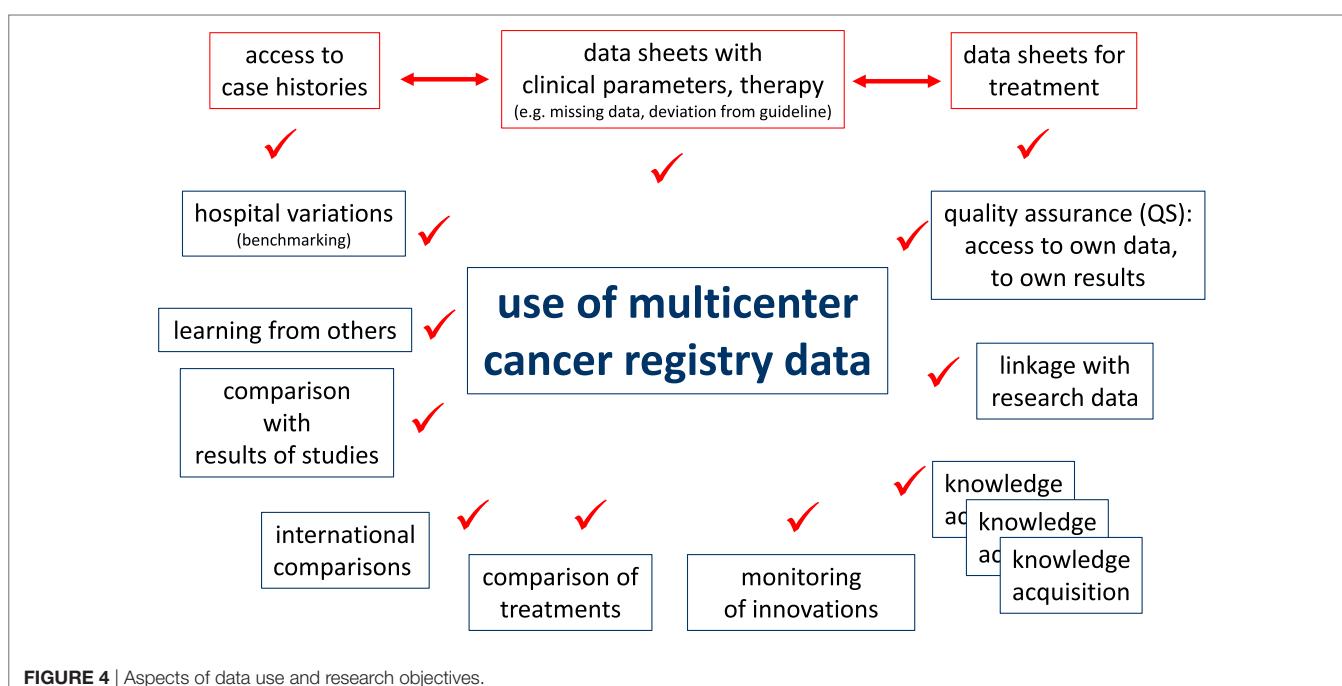
Caution should be taken when interpreting the results, as data from single cooperating hospitals have various types of bias and lack representation. Thus, for proper comparisons, CCRs should provide statistics that include averages of epidemiological results from general clinical data and data on the course of the disease that are aggregated by different characteristics. In this way, comparisons can be made and single hospital results can be appropriately interpreted.

OUTCOME EVALUATION

Additional clinical data are required for QA and CER in oncology to increase the explanatory power attained by representing a defined population. With relevant positive and negative deviations found through multivariate data analyses, the following examples illustrate the various uses of CCR data to evaluate outcomes.

Estimation of Prognosis

A cancer prognosis is important not only for evaluating outcomes but also for the patients' information. The main criterion of prognosis is survival, which is calculated as overall survival (OS), which includes all deceased individuals, and relative survival (RS). RS is the ratio of the observed survival rate to the expected survival rate. RS may be interpreted as cancer survival after correcting for other causes of death; therefore, it is used to estimate cancer-specific survival. The expected survival time of age-matched individuals is calculated according to the Ederer II method using life tables of the German population (10).

FIGURE 4 | Aspects of data use and research objectives.

There is a good prognosis for people with prostate cancer, a disease in older men with a median age of 69 years, especially in the T1 and T2 categories. **Figure 5** shows OS (**Figure 5A**) and RS (**Figure 5B**) as estimator of cancer-specific survival. The survival rate (>100%) for patients with T2 tumors during the first 7 years after diagnosis is better than the mean survival rate of the German male population. The relative 5-year survival rates are 101.1 and 95.1% for the T2 and T1 categories, respectively, primarily due to incidental carcinomas. **Figure 5** shows the effect of calculating RS, which accounts for the mean life expectancy of the German male population.

The morphological verification of tumors delivers important information for treatment planning and prognosis estimation. **Figure 6** presents the spectrum of morphology and the frequency
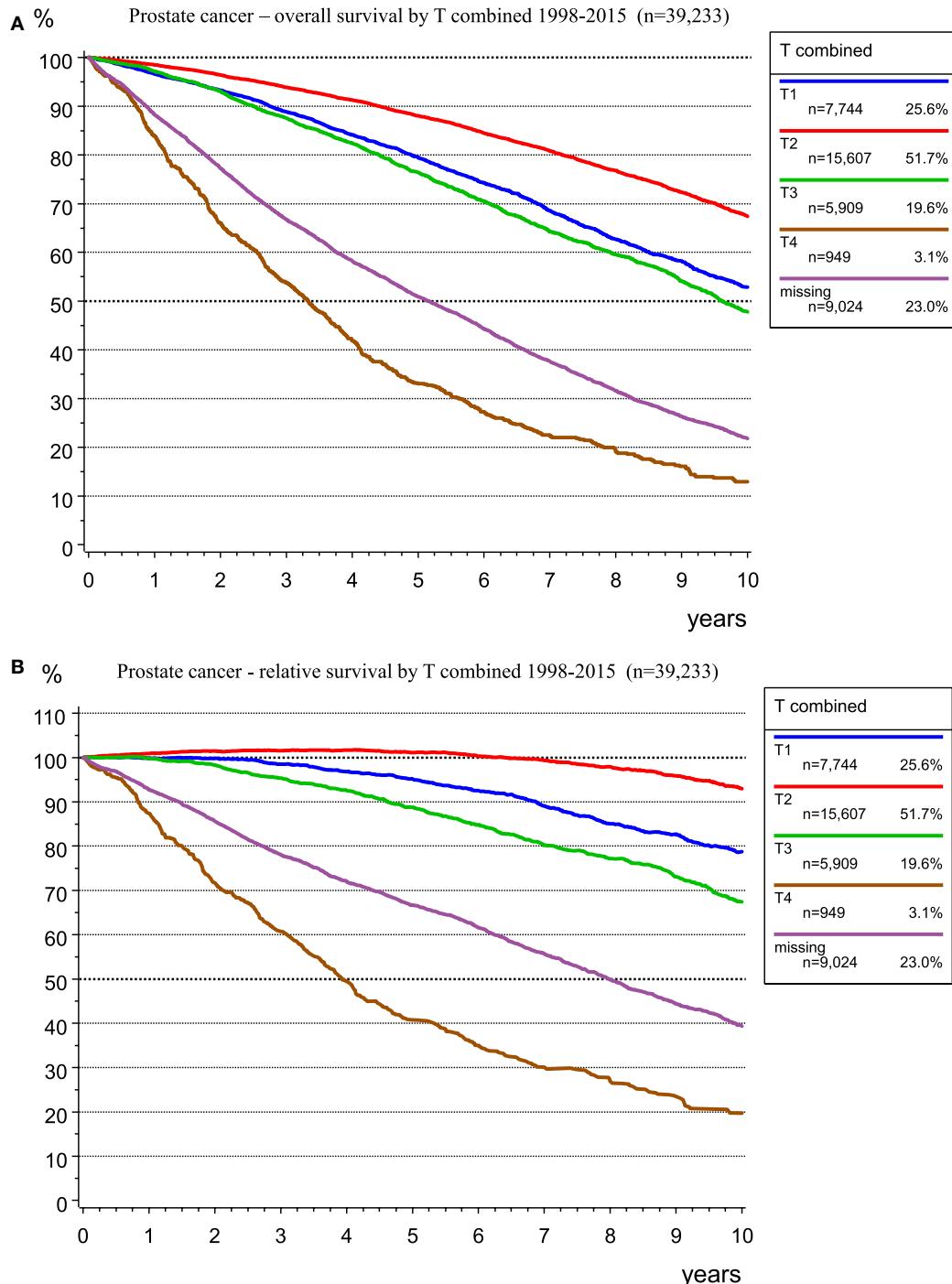
FIGURE 5 | Observed overall **(A)** and relative **(B)** survival for prostate cancer by T-categories for 39,233 patients (1998–2015).
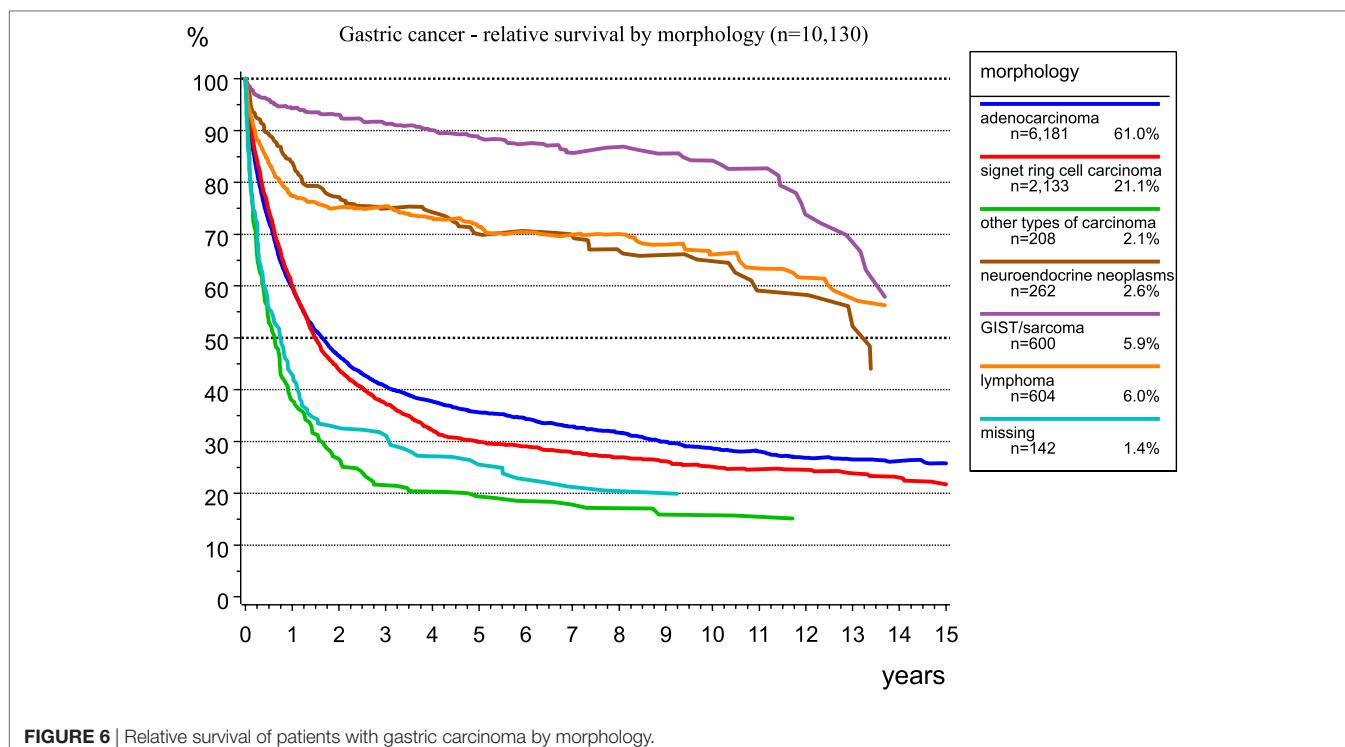
FIGURE 6 | Relative survival of patients with gastric carcinoma by morphology.

of morphological types of gastric cancer. As RS largely depends on morphology, there are better results for GIST and neuroendocrine neoplasms. The relative 5-year survival rates for patients with stomach adenocarcinoma, signet ring cell carcinoma, and GIST/sarcoma are 35.6, 29.9, and 88.6%, respectively.

Benchmarking

There may be selection bias within single hospitals that influences outcomes. Therefore, the results of single institutions must be compared to each other using measures based on summary population-based data. Accordingly, these results may be interpreted as the mean epidemiological values.

Figure 7 presents two diagrams of the percentages of UICC stage III and IV colorectal cancer, where one red bar indicates one co-operating hospital. For UICC stage III colorectal cancer, the upper diagram reveals a variation between 20.9 and 36.7%, with an epidemiological mean of 29.2%. For UICC stage IV colorectal cancer, the lower diagram shows a variation between 12.0 and 34.7%, with an epidemiological mean of 23.5%.

This example of clinic-specific variation emphasizes the use of multivariate statistical methods, such as proportional hazard models, to adjust not only for multiple prognostic parameters but also for clinical variations.

IMPLEMENTATION OF NOVEL CONCEPTS

The implementation of novel concepts in cancer care is a continuous process that relies on the presumption of results from research and randomized clinical studies as well as reliable evidence from observational data (e.g., provided by population-based CCRs). Oncological guidelines compile and periodically actualize the state of the art of diagnostics and treatment. CER proves the degree of implementation and the effectiveness of the applied measures.

Breast Cancer

Since 2008, the German S3 guideline for breast cancer has recommended a sentinel lymph node biopsy (SLNB) (11). **Figure 8** reveals the implementation of the SLNB parallel to the trends of other axilla operations within the catchment area of the MCR. When the guideline was published in 2008, SLNBs were being practiced in more than 50% of all axilla operations. In 2015, SLNBs were performed in 74.8% of all axilla operations.

From 1998 to 2015, lymphadenectomies during the observation period decreased from 88.5 to 4.5%, respectively.

Additionally, during this time, adjuvant and neoadjuvant therapy was refined and intensified. Accordingly, the RS rate for breast cancer patients within the MCR region increased from 1998 to 2015 (**Figure 9**).

Vulva Carcinoma

An article published about a less invasive local lymph node surgery for squamous cell vulvar carcinoma (12) reported that in an analysis of 1,133 patients diagnosed between 1998 and 2013, there were significant decreases in complete vulvectomies and inguinal lymph node surgeries. Moreover, the change in therapy to less radical procedures did not negatively affect the time to local and lymph node recurrence, OS, or RS.

This publication is an example of the limits of evidence-based medicine, but it also indicates that population-based CCRs with a large catchment area of about five million inhabitants and a multicenter cooperation structure such as the MCR still deliver
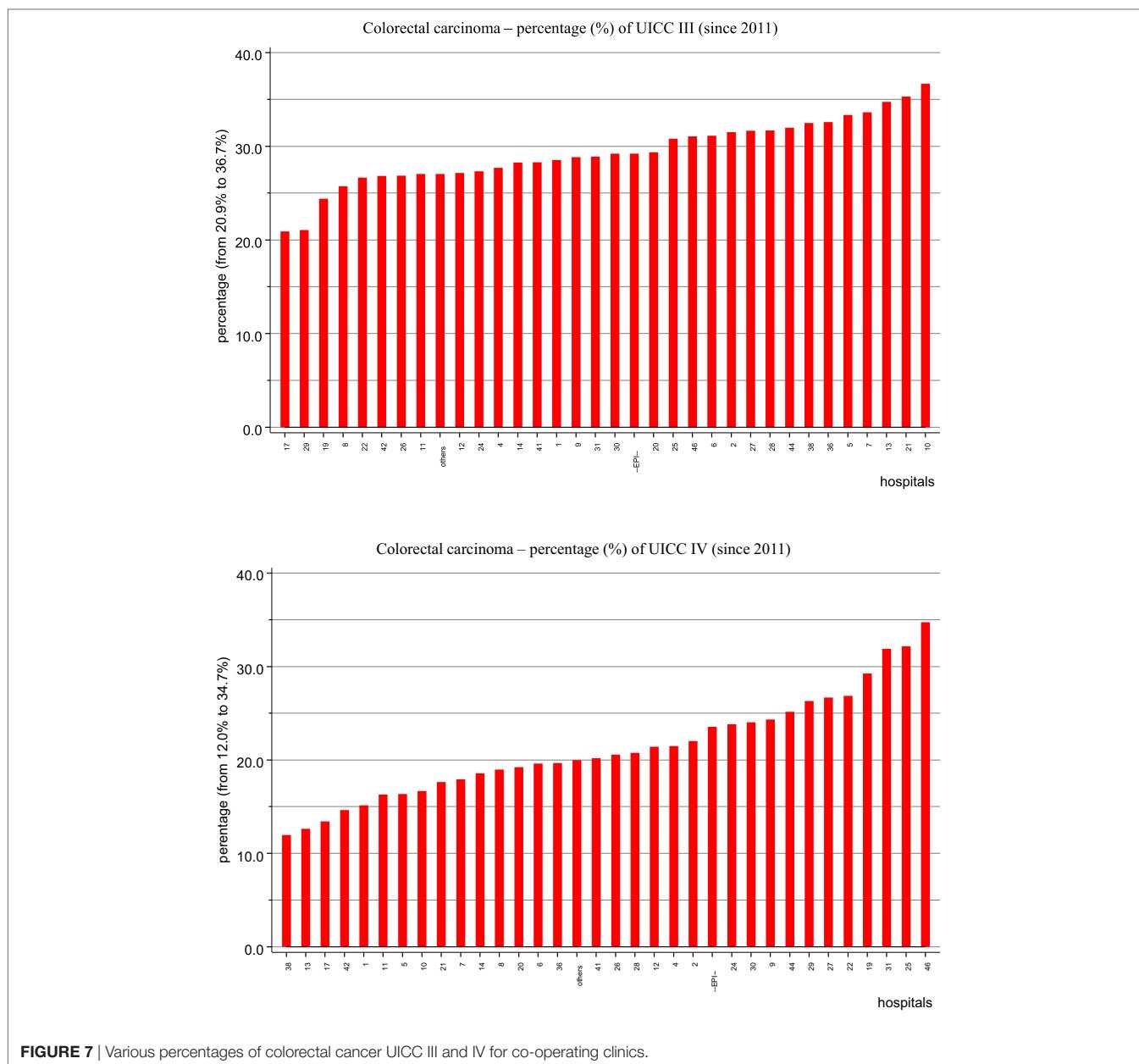
FIGURE 7 | Various percentages of colorectal cancer UICC III and IV for co-operating clinics.

for small cohorts of rare cancers such as vulvar carcinoma. An important advantage of larger CCRs is its possibility to deal with rare cancers.

Lung Cancer

The implementation of new therapeutic concepts in patient care requires the evaluation of their effects on outcomes. For therapy planning and predicting the prognosis of UICC stage IV non-small cell lung cancer (NSCLC), the role of the EGFR mutation (EGFR mutated) was examined in 536 patients of the MCR (**Figure 10**) because the mutation of EGFR is a good predictor of the effectiveness of tyrosine kinase inhibitors (13).
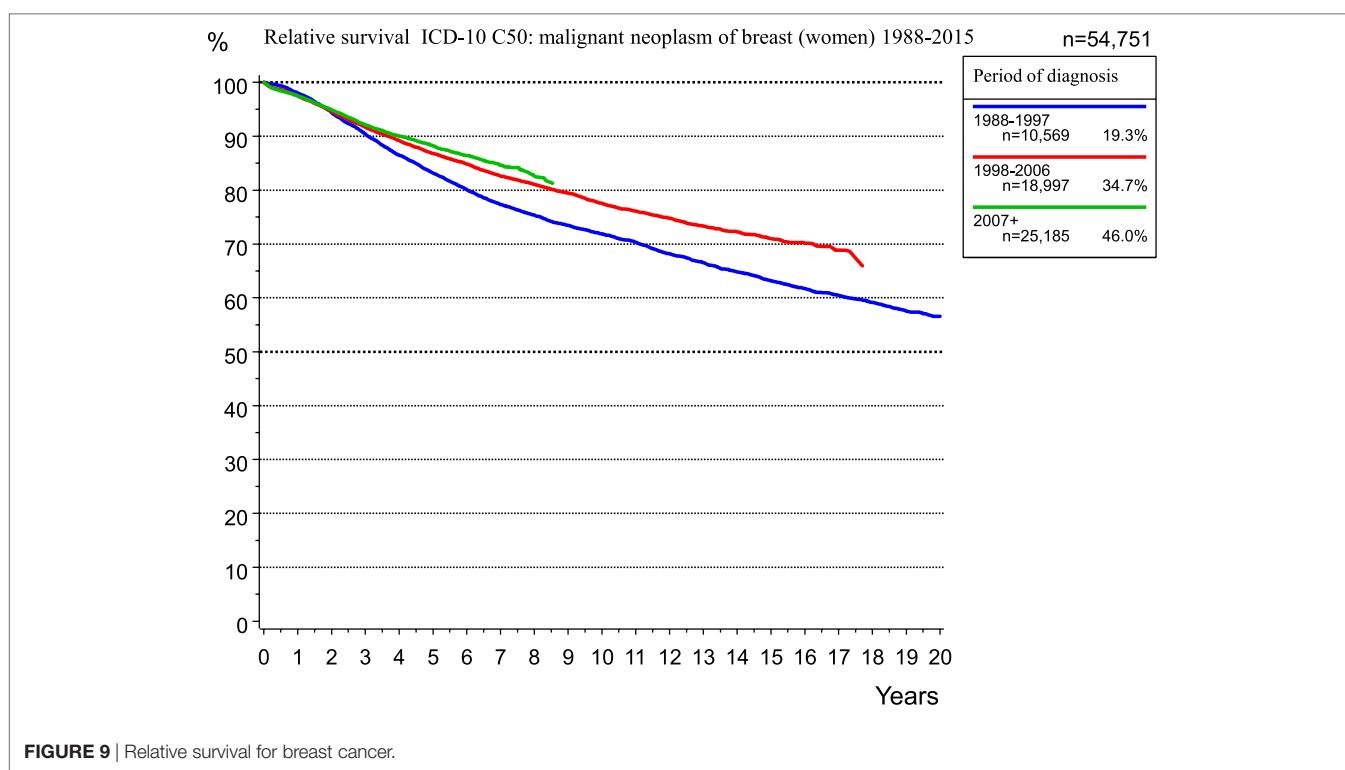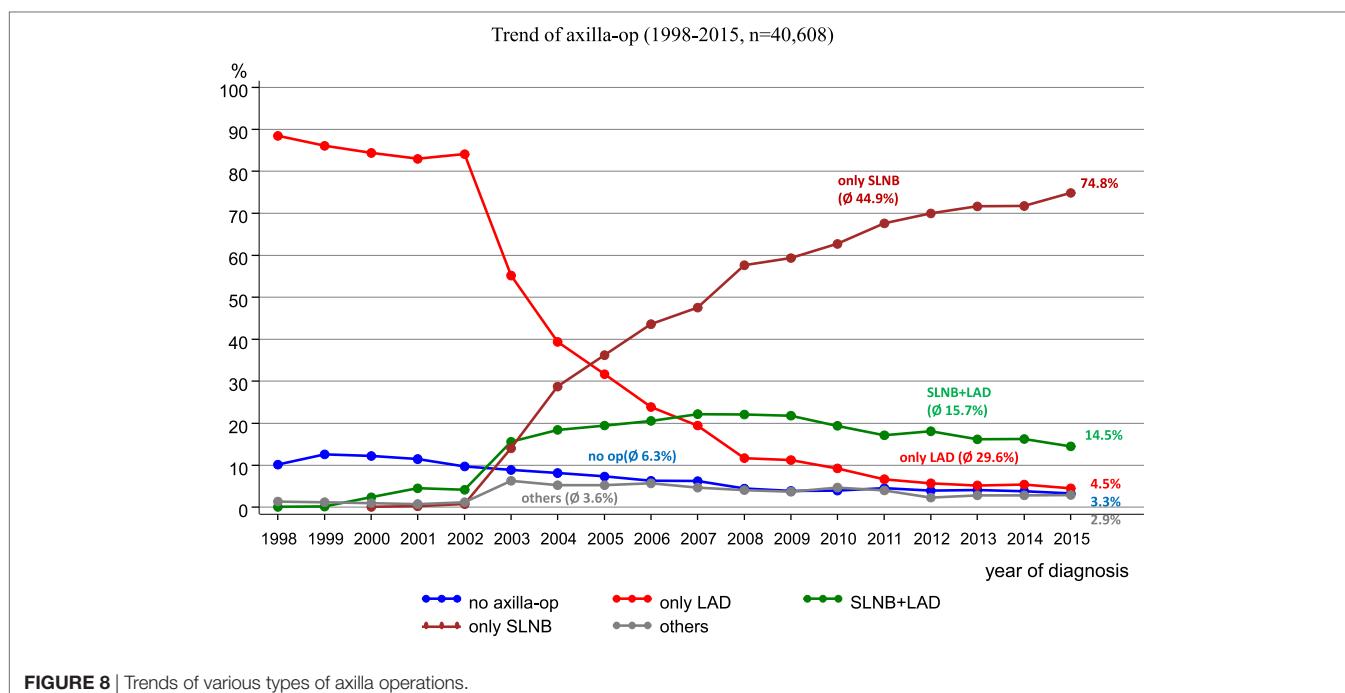
While there is no validation of the type of therapy applied, the median RS for patients with EGFR mutation is 23.5 month,

which is more than twice that (11.2 months) for patients without EGFR mutation, that is, EGFR wild type.

Rectal Cancer

The therapy for rectal cancer has changed within the past 30 years as it concerns surgery, radiotherapy, and systemic therapy.

In the last decades, there has been a population-based implementation of total mesorectal excision of rectal cancer, along with a quality assessment using the MERCURY classification, as well as initially the implementation of adjuvant radiotherapy and subsequent of neoadjuvant radio-chemotherapy for UICC-stages II and III. Effectiveness of therapeutic innovations may be attested by data from population-based CCRs, as presented in **Figure 11**, for rectal carcinoma treated within the catchment area of the MCR.

FIGURE 8 | Trends of various types of axilla operations.

FIGURE 9 | Relative survival for breast cancer.

KNOWLEDGE ACQUISITION

Incidence of Second Malignancies

The incidence of second malignancies is not well known. The network of different medical departments for different tumor entities within a cancer registry enables gathering all malignancies. Thus, multiple malignomas can be compiled, which is difficult for a single department of a particular discipline. In addition, results of risk estimations depend on the calculation method. Whereas the probability calculated using the Kaplan–Meier method
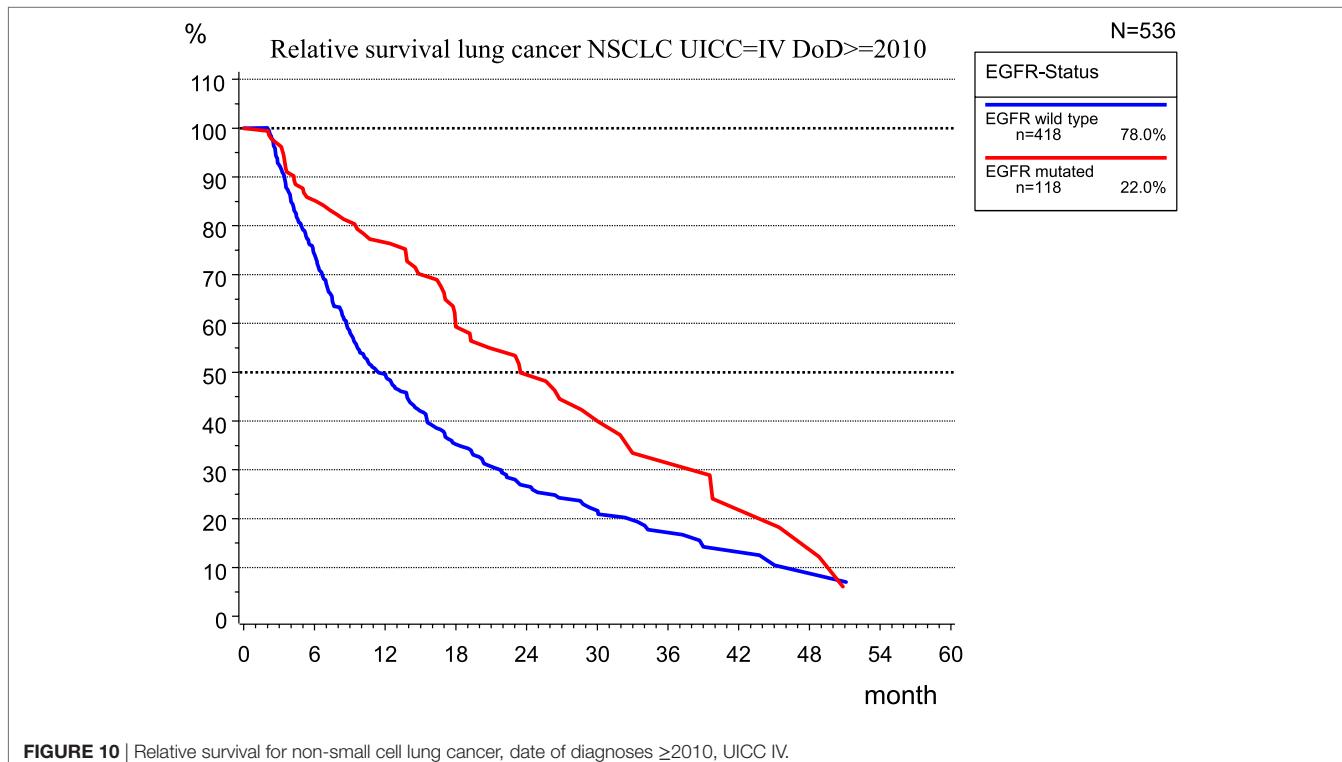
FIGURE 10 | Relative survival for non-small cell lung cancer, date of diagnoses ≥2010, UICC IV.
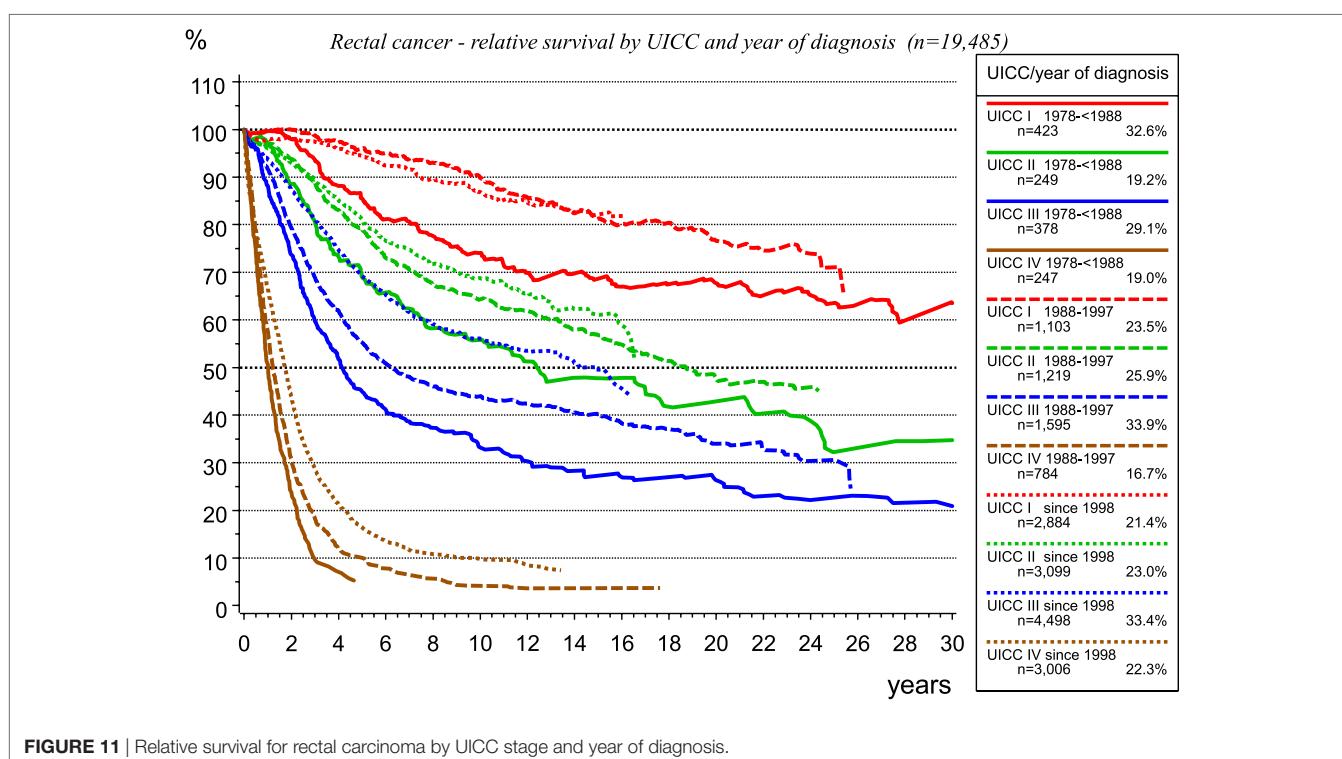
FIGURE 11 | Relative survival for rectal carcinoma by UICC stage and year of diagnosis.

considers the cases lost to follow-up due to censoring, the inverse rate (1-KM) quantifies the percentage of secondary primaries occurring per year and cumulated over years (**Figure 12**, upper diagram).

The calculation of the cumulative incidence function (CI) considering competing risks (14), e.g., the risk of dying before a second malignancy is diagnosed, leads to lower probabilities of the occurrence of second malignancies (**Figure 12**, lower diagram).
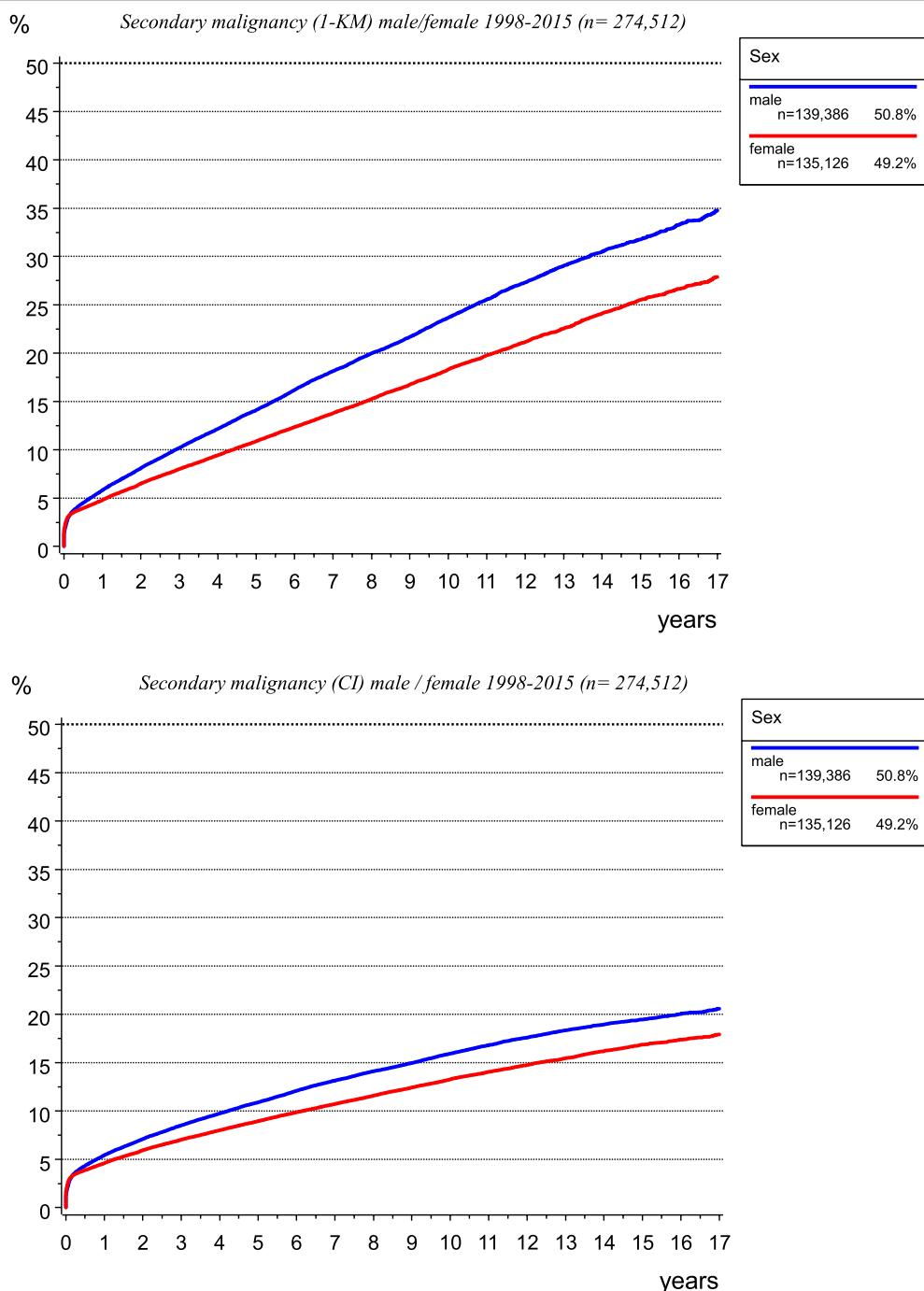
FIGURE 12 | Risk of secondary malignancy as calculated using the Kaplan–Meier method (left) and cumulative incidence function when accounting for competing risks (right).

Translational Research

Translational medicine describes the effort, in which research results are transformed into routine patient care. One aspect in this field is the investigation of molecular characteristics and the functioning of cancer cells and its metabolites. The cooperation

of the MCR with pathological institutes has led to a series of publications (15–23). Moreover, the connection between *in vitro* results and clinical data from CCRs validates laboratory insights regarding the course of the disease, the quality of life, and the prognoses.

Hypothesis: Lymph Nodes do not Metastasize

The influence of positive lymph nodes on the process of metastasization is not finally clear and is one subject of research at the MCR. Although the presence of positive lymph nodes is a key prognostic factor, there is little evidence as to whether tumor cells in positive lymph nodes infiltrate other lymph nodes or distant organs. Moreover, while there is no evidence in the registry data of increased survival resulting from lymph node dissection. The success of the sentinel lymph node concept for some solid tumors and the fact that lymph node recurrence is rare in the course of disease of many solid tumors support the hypothesis, that "positive lymph nodes do not metastasize" (24).

LIMITATIONS AND CHANCES

Clinical cancer registries with their network for information processing and feedback provide a powerful infrastructure for optimizing patient care and initiating research projects. Though there are promising activities in the use of CCRs, the data are observational and thus contain various types of bias that must be considered in statistical analyses. Furthermore, the results should be interpreted with caution and knowledge of the state of the art, and the limitations and risks associated with using observational data must be evaluated separately according to the specific application.

Clinical cancer registries meet the demands of a defined catchment area, including population-based data attained due to the thoroughness of the registration and the appropriateness of the form and content of the incoming documents. Involvement of clinicians and scientists into cancer registries is necessary to keep registries in a current state and to support analysis of open questions. Therefore, catchment area for a population-based CCR should not cover far more than five million residents. Thus, it is highly likely that meaningful cancer data will be gathered and available for analyses by clinicians, scientists, and epidemiologists.

The main issue with respect to oncology and public health is the creation of transparency in patient care, developing state of the art updates in diagnostics and therapy, quantifying the outcome of procedures subject to the guidelines and, if necessary, defining starting points for improvement. The results from CCRs may be compared with those of other hospitals, with the results of randomized controlled trials, and with the results published in the national and international literatures. Positive and negative deviations must be noticeable and considered for drawing relevant conclusions. All this aspects until now are handled only partly or only in some regions but not for Germany in total. So, it will be a main task for CCRs to create an infrastructure and the valid database to deal with these questions on a regional, but comparable way.

While, in the past, many centers build up single databases without network and communication, such effects as described in the present manuscript offer significant short- and long-term benefit for all participants, generate large and multicenter data, and provide a comprehensive platform for scientific work as well as quality-related evaluations (25, 26).

The current work discusses only some of the applications and multiple aspects of the use of CCRs. The legislative and financial support provided by the KFRG should be used for further activities in health-care delivery research. Cancer control and patient care may benefit. In the future, such data will become even more important and will be an indispensable key element of all cancer centers.

AUTHOR CONTRIBUTIONS

GS-F: conception and design, collection and assembly of data, data analysis, and interpretation, manuscript writing, final approval of manuscript. SC and TK: conception and design, collection and assembly of data, final approval of manuscript. VN: collection and assembly of data, final approval of manuscript. JE: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

ACKNOWLEDGMENTS

FUNDING

REFERENCES

1. *Krebs in Deutschland 2011/2012*. 10. Ausgabe ed. Berlin: Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg) (2015).

2. *Gesellschaft der epidemiologischen Krebsregister in Deutschland: Atlas der Krebsinzidenz und –mortalität in Deutschland (GEKID-Atlas), Datenstand 2013*. (2016). Available from: http://www.gekid.de

3. Robert Koch Institut: Zentrum für Krebsregisterdaten. (2017). Available from: http://www.krebsdaten.de/Krebs/DE/Content/ZfKD/zfkd_node.html

4. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Pineros M, et al., editors. *Cancer Incidence in Five Continents, Vol. X. IARC Scientific Publication No.164*. Lyon: International Agency for Research on Cancer(2014).

5. Hölzel D, Schubert-Fritschle G, Schmidt M, Eckel R, Engel J. Klinisch-epidemiologische Krebsregistrierung in Deutschland. *Der Onkologe* (2016) 22:61–78. doi:10.1007/s00761-015-3058-2

6. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. *Lancet Oncol* (2014) 15:23–34. doi:10.1016/S1470-2045(13)70546-1

7. Munich Cancer Registry. *Catchment Area of MCR*. (2017). Available from: http://www.tumorregister-muenchen.de/en/area.php

8. Wittekind CH, Meyer H-J. *TNM Klassifikation maligner Tumoren*. 7. Aufl. ed. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA (2012). 4. korr. Nachdruck.

9. *Munich Cancer Registry*. (2017). Available from: http://www.tumorregister-muenchen.de/en/facts/specific_analysis.php

10. Ederer F, Heise H. *Instructions to IBM 650 Programmers in Processing Survival Computations. Methodological Note No. 10. End Results Evaluation Section.* Bethesda: National Cancer Institute (1959).

11. Kreienberg R, Kopp I, Albert U, et al. *Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. 1. Aktualisierung.* München: Zuckschwerdt Verlag (2008).

12. Rottmann M, Beck T, Burges A, Dannecker C, Kiechle M, Mayr D, et al. Trends in surgery and outcomes of squamous cell vulvar cancer patients over a 16-year period (1998-2013): a population-based analysis. *J Cancer Res Clin Oncol* (2016) 142(6):1331–41. doi:10.1007/s00432-016-2135-2

13. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* (2011) 29(21):2866–74. doi:10.1200/JCO.2010.33.4235

14. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data.* New York: John Wiley (1980).

15. Woischke C, Blay C, Schmidt M, Lamprecht S, Engel J, Hermeking H, et al. CYB5R1 links epithelial-mesenchymal transition and poor prognosis in colorectal cancer. *Oncotarget* (2016) 7(21):31350–60. doi:10.18632/oncotarget.8912

16. Hermans C, Anz D, Engel J, Kirchner T, Endres S, Mayr D. Analysis of FoxP3+ T-regulatory cells and CD8+T-cells in ovarian carcinoma: location and tumor infiltration patterns are key prognostic markers. *PLoS One* (2014) 9(11):e111757. doi:10.1371/journal.pone.0111757

17. Heublein S, Grasse K, Hessel H, Burges A, Lenhard M, Engel J, et al. KRAS, BRAF genotyping reveals genetic heterogeneity of ovarian borderline tumors and associated implants. *BMC* (2013) 13:483. doi:10.1186/1471-2407-13-483

18. Neumann J, Wehweck L, Maatz S, Engel J, Kirchner T, Jung A. Alterations in the EGFR pathway coincide in colorectal cancer and impact on prognosis. *Virchows Arch* (2013) 463:509–23. doi:10.1007/s00428-013-1450-0

19. Engelstaedter V, Schiffers J, Kahlert S, Mainka P, Engel J, Kirchner T, et al. Her-2/neu and topoisomerase IIα in advanced breast cancer: a comparative FISH analysis of 245 cases. *Diagn Mol Pathol* (2012) 21:77–83. doi:10.1097/PDM.0b013e31823b6e43

20. Engelstaedter V, Boda J, Völklein C, Engel J, Jeschke U, Kirchner T, et al. Lack of prognostic relevance of Her-2/neu, topoisomerase IIα and EGFR in advanced ovarian carcinoma. *Exp Ther Med* (2012) 3:825–34. doi:10.3892/etm.2012.481

21. Neumann J, Horst D, Kriegl L, Maatz S, Engel J, Jung A, et al. A simple immunhistochemical algorithm predicts the risk of distant metastases in right-sided colon cancer. *Histopathology* (2012) 60:416–26. doi:10.1111/j.1365-2559.2011.04126.x

22. Beji A, Horst D, Engel J, Kirchner T, Ullrich A. Towards the prognostic significance and therapeutic potential of HER3 receptor tyrosine kinase in human colon cancer. *Clin Cancer Res* (2012) 18(4):956–68. doi:10.1158/1078-0432.CCR-11-1186

23. Vogler T, Kriegl L, Horst D, Engel J, Sagebiel S, Schäffauer AJ, et al. The expression pattern of aldehyde dehydrogenase 1 (ALDH1) is an independent prognostic marker for low survival in colorectal tumors. *Exp Mol Pathol* (2012) 92(1):111–7. doi:10.1016/j.yexmp.2011.10.010

24. Engel J, Emeny RT, Hölzel D. Positive lymph nodes do not metastasize. *Cancer Metastasis Rev* (2012) 31:235–46. doi:10.1007/s10555-011-9343-7

25. Kessel KA, Bohn C, Engelmann U, Oetzel D, Bougatf N, Bendl R, et al. Five-year experience with setup and implementation of an integrated database system for clinical documentation and research. *Comput Methods Programs Biomed* (2014) 114(2):206–17. doi:10.1016/j.cmpb.2014.02.002

26. Kessel KA, Combs SE. Review of developments in electronic, clinical data collection, and documentation systems over the last decade – are we ready for big data in routine health care? *Front Oncol* (2016) 6:75. doi:10.3389/fonc.2016.00075

Data-Based Radiation Oncology: Design of Clinical Trials in the Toxicity Biomarkers Era

David Azria[1]*[†], Ariane Lapierre[1†], Sophie Gourgou[1], Dirk De Ruysscher[2,3],
Jacques Colinge[1], Philippe Lambin[2], Muriel Brengues[1], Tim Ward[4], Søren M. Bentzen[5],
Hubert Thierens[6], Tiziana Rancati[7], Christopher J. Talbot[8], Ana Vega[9], Sarah L. Kerns[10],
Christian Nicolaj Andreassen[11], Jenny Chang-Claude[12,13], Catharine M. L. West[14],
Corey M. Gill[15,16] and Barry S. Rosenstein[15,16]

[1]Department of Radiation Oncology, Radiobiology Unit, Biometric and Bio-informatic Divisions, Montpellier Cancer Institute (ICM), IRCM, INSERM U1194, Montpellier, France, [2]Department of Radiation Oncology, Maastricht University Medical Centre, MAASTRO Clinic, Maastricht, Netherlands, [3]Radiation Oncology, KU Leuven, Leuven, Belgium, [4]Patient Advocate, Manchester, UK, [5]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA, [6]Department of Basic Medical Sciences, Ghent University, Ghent, Belgium, [7]Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [8]Department of Genetics, University of Leicester, Leicester, UK, [9]Fundacion Publica Galega de Medicina Xenomica-SERGAS, Grupo de Medicina Xenomica-USC, IDIS, CIBERER, Santiago de Compostela, Spain, [10]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY, USA, [11]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [12]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [13]University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [14]Division of Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, Christie Hospital NHS Trust, Manchester, UK, [15]Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [16]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

The ability to stratify patients using a set of biomarkers, which predict that toxicity risk would allow for radiotherapy (RT) modulation and serve as a valuable tool for precision medicine and personalized RT. For patients presenting with tumors with a low risk of recurrence, modifying RT schedules to avoid toxicity would be clinically advantageous. Indeed, for the patient at low risk of developing radiation-associated toxicity, use of a hypofractionated protocol could be proposed leading to treatment time reduction and a cost–utility advantage. Conversely, for patients predicted to be at high risk for toxicity, either a more conformal form or a new technique of RT, or a multidisciplinary approach employing surgery could be included in the trial design to avoid or mitigate RT when the potential toxicity risk may be higher than the risk of disease recurrence. In addition, for patients at high risk of recurrence and low risk of toxicity, dose escalation, such as a greater boost dose, or irradiation field extensions could be considered to improve local control without severe toxicities, providing enhanced clinical benefit. In cases of high risk of toxicity, tumor control should be prioritized. In this review, toxicity biomarkers with sufficient evidence for clinical testing are presented. In addition, clinical trial designs and predictive models are described for different clinical situations.

Keywords: trial design, patient selection, biomarkers, radiotherapy, toxicity tests

INTRODUCTION

Radiotherapy (RT) is one of the leading treatment modalities in oncology, and over 50% of patients diagnosed with cancer undergo RT during their course of treatment. Although RT is primarily a local treatment, patients are exposed to a risk of toxicities in the treatment field and surrounding tissues, which may develop acutely and late. Early toxicities are defined as side effects occurring during treatment or in the first 3 months after treatment completion. Late toxicities are defined as those occurring more than 3 months following RT and could increase over time for a period of many months to years. Late toxicities often persist and can have a significant negative impact on quality of life among cancer survivors. A sequential effect between early and late toxicity is often reported.

A total of 5–10% of patients will eventually develop severe side effects with a significant impact on treatment outcome or quality of life. Based on this observation and dependent upon the prognosis that reflects the type of tumor and its stage at time of treatment, dose–volume constraints to organs-at-risk are usually chosen in order to keep the risk of developing grade 3 or higher side effects below 5% (1, 2). Due to considerable progress in cancer management in recent decades, the number of cancer survivors has dramatically increased, raising new challenges in the various phases of survivorship. Thus, posttreatment morbidity and quality of life have become a critical concern in the growing patient population (3). However, there is large patient-to-patient variability for the development of adverse outcomes following RT, in terms of both prevalence and severity. While most patients will develop toxicities within the normal range, some patients demonstrate a hypersensitive phenotype and develop severe toxicities even at standard radiotherapeutic doses.

The first example of individual variation in degree of response was described by Holthusen in 1936 (4). Numerous normal tissue complication probability (NTCP) models have since been developed, and variation in normal tissue response has been shown to follow a normal distribution with 5% of patients considered as radiosensitive (5). Identification of these patients beforehand is critical to avoid morbidity because severe toxicities in a minority of patients limit the dose that can be safely delivered to the majority of patients (6). In addition, individualized risk estimation for even mild or moderate effects would provide patients with information as to their risk for complications following treatment and could be used to select patients for interventions designed to prevent or mitigate toxicities. Thus, understanding individual variation is crucial to individualization of RT treatment planning and increased therapeutic outcomes (7).

While early toxicities might compromise treatment completion, they can usually be managed with adequate care. In contrast, late toxicities can significantly affect quality of life in survivors and may require extensive treatments to alleviate symptoms. However, acute radiation reactions are not necessarily an indicator of a predisposition for late toxicity (8). Therefore, there is a need to measure individual radiosensitivity and predict the risk of toxicity before treatment. Even though many external factors such as age, concomitant medications, or recent surgery impact on the risk of toxicity, the main determinant seems to

be genetic factors (i.e., intrinsic radiosensitivity). However, it is unlikely that intrinsic radiosensitivity is the product of a single genetic alteration, and as such, it should be regarded as a complex polygenic trait (7). If a link can be found between underlying genetic variation and normal tissue susceptibility to developing toxicity, then patients could benefit from genomically guided, therapeutic individualization of their treatment: early identification of patients predicted to be at high risk for radiation-induced toxicities may benefit from either RT dose reduction or hyperfractionation. Conversely, identification of patients who are at low risk of toxicity could allow for (i) hypofractionation of the treatment plan, thereby shortening treatment time or (ii) dose escalation, which could improve tumor control (9).

Several observations support the hypothesis that clinical normal tissue radiosensitivity is influenced by genomics. However, very little is known about the genetic architecture of radiosensitivity or the specific genomic variants underlying interindividual differences in normal tissue reactions to RT in unselected cancer patients. It is considered that intrinsic radiosensitivity of a patient should be regarded as a complex trait depending on the combined effect of multiple genomic alterations (9). However, factors other than intrinsic radiosensitivity (i.e., genetically determined) will influence the risk of toxicity (e.g., radiation dose, age, and comorbidities), which highlights the need to collect and include multiple variables in studies.

Several genes involved in response to radiation injury were identified because homozygous mutations resulted in unusually severe reactions to RT (e.g., ATM). Other genes studied were known to be involved in the DNA damage response to ionizing radiation or the development of fibrosis. Most studies to date investigated single nucleotide polymorphisms (SNPs) because of their high prevalence in a population. With the rise of next-generation sequencing and genome-wide assays, genomic studies have been immensely facilitated (10). SNPs associated with radiation injury have been identified using high-throughput genotyping, in genome-wide association studies (GWASs) as well as candidate gene studies (11, 12). However, SNP discovery through GWAS requires a large number of patients to reach statistical significance, and the number of patients who exhibit severe toxicity is relatively low in clinical studies (6). In addition, careful clinical consideration is required when designing radiogenomic studies. While radiation dose is the main factor influencing toxicity, additional factors, including genomic alterations (e.g., SNP) and treatment volume, may be effect modifiers of the dose–toxicity relationship. Other clinical factors such as age, smoking habits (13, 14), or preexisting conditions (autoimmune diseases such as collagen vascular diseases) (15) may influence toxicity independently of genetic background, and so it is important that risk prediction models are not restricted to only genetic or only non-genetic factors.

It is also important to consider the future development of a test for clinical application. Rigorous methodology in choice of hypothesis, methods, and result reporting is required to allow generalization of the results (16) (see also Cancer Research UK predictive biomarker roadmap: http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@fre/@fun/

documents/generalcontent/cr_027486.pdf). In addition, the methodology developed for reporting tumor markers could be used for evaluating the level of evidence of prognostic normal tissue radiosensitivity markers (17–20). Based on these works, our consortium developed an 18-item checklist for reporting radiogenomic studies called STROGAR (**Table 1**), which should stand as reference for any new predictive biomarker development (21).

This study aims to review currently available radiogenomic assays based on level of evidence and clinical relevancy and to

TABLE 1 | STROGAR 18-item checklist for reporting radiogenomic studies from Kerns et al. (21).

	Item number	Recommendations
Title and abstract		
Title and abstract	1	Include the primary outcome(s) and type of study [whether genome-wide association studies (GWASs) or gene-specific]; provide an informative summary of the study including study design, whether discovery or validation, sample size, main end points, and major results.
Introduction		
Background/rationale	2	Note if the study is a GWAS or a candidate gene/SNP study and, if candidate gene study, rationale for choice of genes/SNPs; give a general description of the study setting.
Objectives	3	Define the primary/main outcome(s) of interest; describe the overall/long-term goal of the study; note if it is a discovery, validation, or multistage study. Use terminology and definitions from National Cancer Institute biomarker study guidelines (22), where applicable.
Methods		
Study design	4	Specify the study design (case–control, cohort); whether data were collected under a controlled trial setting; whether data were collected retrospectively or prospectively. Report power and sample size considerations.
Patient population	5	Specify the source(s) of the patients and, if multiple sources, whether they are pooled or treated as separate cohorts; define inclusion/exclusion criteria; report whether comorbidities and medications were assessed by self-report or medical records; define methods/system used for tumor staging; describe the larger patient population from which the study sample was drawn; define how major changes in treatment protocol were handled in the analysis.
Radiation exposure	6	Specify details of radiation treatment parameters including: organ(s)-at-risk, dose–time fractionation; dose rate, target volume selection (e.g., breast + boost), dose to critical substructures, dose–volume metric used, the type of treatment and treatment setting, radiation modality (e.g., external beam vs. brachytherapy), whether single or combined treatment modalities were used, whether primary treatment or salvage therapy, imaging and planning details, ICRU recommendations followed and note relaxation of criteria, note any changes in dose or treatment protocol over the time course of enrollment and whether there were any interruptions in treatment.
Phenotype(s)	7	Specify how intrapatient or pretreatment assessment was made and whether it is accounted for in defining phenotype(s); note whether patient-reported outcomes or physician-assessed outcomes are being used to define phenotype(s); note which toxicity scoring system was used (if using a common/standard system); define the grading scales used and whether the phenotype(s) is/are defined as continuous, dichotomous or categorical; describe frequency of follow-up scheduling and diagnostic intensity; define the posttreatment time frame for assessment of toxicity outcomes; describe whether outcome(s) is/are based on a single time point or the maximum/worst time point out of a series of follow-up assessments; note if/how competing risks were handled (such as non-radiation-related manifestation of the phenotype); note any medical intervention that may influence study outcome(s).
Genotyping strategy and quality control (QC)	8	Specify DNA source and isolation methods; note the methods/platform used for genotyping; specify whether genotyping was done in one stage or multiple stages; note whether genotyping was done in more than one lab or batch, and if so, how batch effects were handled; describe methods for genotype calling and cite the algorithm used; note whether genotype calling was done for the whole study sample together or in batches; describe QC methods including concordance between duplicates, control samples, and checks for cryptic relatedness; describe methods for assessing population structure; describe SNP/CNP filtering methods including filtering on per-sample call rate, per-SNP call rate, minor allele frequency, and Hardy–Weinberg equilibrium; note whether imputation was used and, if so, describe methods.
Data analysis and statistical methods	9	Define the statistical methods and models used for association testing; cite the software and settings used; describe how censoring was handled; define model selection methods used for multivariable models; describe whether all samples are analyzed together or sequentially if the study involves multiple cohorts; for multistage studies, define methods for selecting variants to follow-up in subsequent stages; describe how missing data were handled; if multiple cohorts were included, describe data harmonization methods; note whether gene–gene interaction or gene–environment interaction was investigated; describe methods used to adjust for population structure; describe methods used to correct for multiple comparisons and/or control for risk of false-positive findings.

(Continued)

TABLE 1 | Continued

	Item number	Recommendations
Results		
Patient characteristics	10	Report number of individuals at each stage of the study (e.g., numbers examined for eligibility, numbers confirmed eligible, included in study, completed follow-up, successfully genotyped and analyzed). Give reasons for non-participation at each stage. Give description of the included patient sample regarding demographic (e.g., age at start of therapy, sex, race/ethnicity) and clinical characteristics (e.g., site and stage of primary tumor, chemotherapy, hormone therapy), details of radiation exposure, where appropriate (e.g., type, dose, boost) and potential confounders and effect modifiers (e.g., lifestyle-related factors, comorbidities, and medications), including missing data; report length of follow-up and number of events and number of patients at risk at various follow-up times, e.g., yearly. It is recommended to include a flow diagram of patients included/excluded from the study, as proposed by the CONSORT statement.
Phenotype(s)	11	Report baseline function (if relevant); report numbers of responders and non-responders for dichotomous outcomes, descriptive statistics for quantitative outcome(s), or distributions for categorical outcomes.
Genotypes	12	Report call rates; numbers of samples and numbers of SNPs excluded on the basis of QC filters; if imputation was used, note which variants are imputed and which are genotyped directly; report genetically determined racial/ethnic groups or other population clusters; report genomic inflation factor as well as corrected genomic inflation factor after controlling for population structure.
Primary associations	13	For each SNP/CNP, report: common identifier (such as dbSNP rs number), minor allele identity and frequency, phenotype by genotype category, effect size (with 95% confidence interval) and p-value; genetic inheritance model(s) used; for multivariable analyses, report unadjusted and adjusted estimate and note which covariates were included in the model(s).
Secondary analyses	14	Report subgroup analyses and/or secondary outcomes of interest.
Discussion		
Key results	15	Summarize key results in the context of the study objectives given in Section "Introduction."
Limitations	16	Discuss limitations of the study in the context of bias (noting both direction and size), confounding, sample size and power, and representativeness of study population.
Interpretation	17	Provide an overall interpretation of the findings in the context of previous clinical studies, genetic association studies, and biological studies of radiation response.
Generalizability and clinical utility	18	Comment on the potential clinical utility of the findings in the context of the patient populations to which the results may apply.

evaluate potential ways in which these assays might be implemented in routine clinical practice.

AVAILABLE RADIOGENOMIC BIOMARKERS AND THEIR RESPECTIVE LEVELS OF EVIDENCE

SNP Association Studies

The initial research performed in radiogenomics involved candidate gene studies, which focused on genes encoding proteins with known associations with pathways involved in responses to radiation, such as DNA repair processes and cell cycle checkpoint control. Although a number of positive associations were reported, these studies often did not adequately correct for multiple hypothesis testing and generally were not validated in subsequent studies, with several notable exceptions described below. More recent advances in radiogenomics research have been achieved through use of SNP microarrays and the performance of GWASs in which large numbers of SNPs across the genome have been evaluated. Using both of these approaches, several large studies have been accomplished involving a rigorous analysis for association between particular SNPs and toxicity outcomes that

follow the STROGAR guidelines for reporting radiogenomic studies (**Table 1**) (21).

The most progress has probably been made in identifying specific SNPs associated with late toxicity following RT for prostate cancer. The first radiogenomics GWASs performed aimed to identify SNPs associated with erectile dysfunction in African-American men treated with RT for prostate cancer (23). Through this study, a SNP (rs2268363) in the FSHR gene, which encodes follicle-stimulating hormone, was identified (unadjusted p-value $= 5.46 \times 10^{-8}$; Bonferroni p-value $= 0.028$). In another prostate cancer study, a three-stage GWAS was conducted using discovery and replication cohorts that included the use of Standardized Total Average Toxicity (STAT) score (24) as a measure of overall toxicity, combining urinary and rectal end points. A locus encompassing the TANC1 gene was associated with STAT score for overall late toxicity (25) with an odds ratio (OR) of ~6 (combined p-value $= 4.64 \times 10^{-11}$). More recently, a GWAS meta-analysis was performed using data from four cohorts of men treated for prostate cancer for whom toxicity was measured at 2-year post-RT (26). Two SNPs were identified in this study that met genome-wide significance. One was rs17599026, which resides on chromosome 5q31.2 and associated with urinary frequency and characterized by an OR of 3.1 (95% confidence

interval 2.1–4.7, $p = 4.2 \times 10^{-8}$). rs7720298, which is situated on chromosome 5p15.2, was associated with decreased urine stream with an OR of 2.7 (95% CI 1.9–3.9, p-value $= 3.2 \times 10^{-8}$). This SNP is located in an intronic region downstream of DNAH5 exon 30. Using a candidate gene approach, a study of more than 5,000 patients who underwent RT for either prostate or breast cancer reported an association between overall toxicity and rs1801516 in the ATM gene with ORs of 1.5 for acute and 1.2 for late toxicity (27).

Several other studies have been successful in identification of SNPs associated with the development of adverse normal tissue outcomes following RT for breast cancer. For example, a study comprising four SNPs related to the TGFβ pathway reported associations with several outcomes, including breast induration, telangiectasia, and overall toxicity (28). Significant and replicated associations with adverse outcomes following breast RT were reported for the TNF SNP rs1800629 and rs2857595, which is located 25.7 kb from rs1800629 and resides in the intergenic region between NCR3 and AIF1. Another validated study of breast cancer patients identified SNP rs1139793 in TXNRD2 associated with subcutaneous fibrosis following RT (29). A separate study used a two-stage design to investigate associations between SNPs in genes whose products are involved with responses to oxidative stress with toxicities following radiation treatment of women diagnosed with breast cancer. The rs2682585 SNP in XRCC1 (30) was found to be associated with reduced risk for skin toxicities (OR 0.77, 95% CI 0.61–0.96, $p = 0.02$) and decreased STAT scores (−0.08, 95% CI −0.15 to −0.02, $p = 0.016$).

Several candidate gene SNP studies have successfully identified and validated SNPs associated with late RT toxicity in lung cancer. It was reported in studies of patients treated with RT for non-small-cell lung cancer (NSCLC) that the HSPB1 rs2868371 SNP was associated with grade 3 or greater radiation pneumonitis (31) in both the training ($p = 0.031$) and validation sets ($p = 0.025$) and that this SNP was also associated with the development of grade 3 or greater radiation-induced esophagitis (32) in both the training ($p = 0.045$) and validation cohorts ($p = 0.031$). In addition, it was reported that the TGFB1 rs1800469 SNP was associated with a higher risk of radiation esophagitis in both the training ($p = 0.045$) and validation (0.023) sets of NSCLC patients (32).

While much work remains to be done in order to identify the many radiosensitivity SNPs that likely remain undiscovered, the studies published to date represent an important step toward development of polygenic risk models. Furthermore, the GWASs have contributed to uncovering novel radiation biology genes and pathways. Functional studies of these genes will provide important information for development of pharmacological interventions to prevent or mitigate the toxic effects of radiation on normal tissues.

Fibroblast-Based Assays

Fibroblasts have traditionally been the gold-standard considered to be the best model of normal tissue for RT studies, given the importance of fibrosis in late effects and that these cells play a large role in the supporting cellular networks that surround tumors outside of the central nervous system. The first study of this model was conducted by Burnet et al. in 1992 (33). Since then, several studies suggested that fibroblast radiosensitivity *in vitro* could predict early toxicity risk. This association was studied in the clinical setting, in breast and head and neck cancer, where fibroblast clonogenic survival after irradiation was associated with radiation-induced toxicity in patients (34). However, to date, no prospective study has been able to demonstrate a significant association between fibroblast radiosensitivity and radiation-induced toxicity in patients (35, 36).

Radiation-Induced Lymphocyte Apoptosis (RILA) Assay

In response to the limited success of fibroblast-based tests, lymphocyte-based assays were developed in their stead. While clonogenic assays showed promise in a prospective setting and in multivariable analysis (37), the 2-week assay time was considered a barrier to clinical implementation. Therefore, Ozsahin et al. developed an assay based on CD8+ T-lymphocyte apoptosis after *in vitro* irradiation with a single 8-Gy dose (38). While no association between lymphocyte apoptosis and early toxicities was found in multivariate analyses, CD8+ T-lymphocyte apoptosis was significantly associated with late effects in various cancers in a single-center prospective trial (39) and recently confirmed in a prospective multicenter study for late breast fibrosis (40). Furthermore, this assay has been shown to be reproducible between laboratories, making it a robust test to assess individual radiosensitivity (39, 41). As such, several prospective trials are currently assessing the clinical validity of the RILA assay in different cancer settings, such as prostate or lung cancer (42).

Other Lymphocyte-Based Assays

As lymphocytes are a convenient model for radiation response, several other lymphocyte-based assays have been used to assess individual radiosensitivity. Of these, the most common is the γ-H2AX residual foci assay. H2AX is a protein phosphorylated upon double-strand breaks formation and is one of the earliest events that can be detected after cell irradiation. The number of γ-H2AX foci after cell damage has been extensively used to evaluate response to chemotherapy and RT (43–45). However, the association between the number of residual foci and clinical response to radiation on the patient level (either measured by toxicity or tumor response) has failed to be prospectively validated.

G2 metaphase and G0 micronuclei assays were initially used to assess chromosomal radiosensitivity and predisposition to breast cancer. Along with the γ-H2AX assay, many studies have sought to find an association between G2 metaphase and G0 micronuclei assays and radiation-induced toxicity (46). However, the G2 metaphase assay has exhibited low reproducibility. As new techniques have improved this assay, its use warrants prospective validation (47, 48). Similarly, the G0 micronuclei assay has been compared to other lymphocyte-based assays, but failed to be prospectively validated for prediction of either early or late radiation-associated toxicity (49–51).

Table 2 rates these tests according to their respective level of evidence, based on the STROGAR items and adapted from the levels of evidence proposed by Simon et al. (19).

TABLE 2 | Available assays for radiosensitivity assessment with their respective level of evidence adapted from Simon et al. (19).

Assay	Available studies	Level of evidence
rs17599026 and rs7720298 SNPs for prostate cancer	Meta-analysis for radiation-induced toxicity (26)	I
SNPs for breast cancer	Observational studies (28, 29)	II
SNPs for lung cancer	Observational studies (31, 32)	II
RILA	Prospective multicenter study for breast cancer (40)	I
Fibroblast-based assay	Retrospective studies only (34)	IV
G2 metaphase	Retrospective studies only (47, 48)	IV
G0 micronuclei	Retrospective studies only (50)	IV
Residual γ-H2AX foci	No validation studies available (45)	IV

SNP, single nucleotide polymorphism; RILA, radiation-induced lymphocyte apoptosis. Level of evidence based on REMARK guidelines (19).

CLINICAL IMPLEMENTATION

For a radiosensitivity test to have utility in the clinic, a valid alternative treatment option that permits modification of the proposed treatment based on the results of a test must be available. These interventions could be dose or fractionation alterations, addition or omission of concomitant treatments (such as chemotherapy or RT mitigators), or complete exclusion of RT in hypersensitive patients if the predicted risk of toxicity exceeds the expected benefit of RT. For these individuals, treatment with either surgery and/or chemotherapy may be considered. Overall, these interventions can be divided into four situations, based on a patient's tumor control probability (TCP) and NTCP.

High TCP, Low NTCP

A low risk of tumor recurrence and a low risk of radiation-induced toxicity are the ideal clinical presentation. In this situation, quality of life improvement during radiation treatment should be the main goal of any intervention.

There is no need to increase total tumor dose since local control is high with standard treatment. However, alternate fractionation, such as hypofractionation, could offer a shorter treatment course with a substantial increase in quality of life. Hypofractionation has been shown to be a valid alternative for early breast cancer radiation, with schedules decreasing from 33 to 15–16 and finally 5 fractions yielding similar results in well-selected patients (52–54). In this case, hypofractionation could cut the treatment duration by half and have a significant impact on quality of life and treatment cost (55). Furthermore, a combined analysis of the START trials for breast cancer suggests that overall treatment time might be a significant determinant of local cancer control after adjuvant whole breast RT with a lower relapse rate in the accelerated arms (56).

Similarly, several hypofractionated schedules have shown promising results in prostate cancer (most recently the CHHip and HYPRO trials), with only moderate increase in rectal toxicities (57, 58). Furthermore, when analyzed from a medico-economic point of view, hypofractionated regimens could result in improved health gains at lower cost (59).

High TCP, High NTCP

In this case, the patient would be at increased risk for developing severe toxicity following RT, but at a low risk of tumor recurrence.

This scenario is when alternate treatment plans may be most appropriate, such as a strictly surgical treatment. For example, in low-risk prostate cancer, treatment with either surgery or RT, or even active surveillance in appropriately selected patients has demonstrated similar survival outcomes (60). However, toxicity profiles differ significantly; there is a higher risk for urinary toxicity and erectile dysfunction after surgery, but a greater incidence of rectal bleeding and fecal incontinence after RT (61). Therefore, these treatment options could be offered to the patient, who could take all of these factors into careful consideration when deciding upon the type of treatment. In addition, focal therapies could be considered for appropriately selected patients.

In the case of postoperative prostate cancer, adjuvant RT has been shown to reduce the risk of biochemical failure but without overall survival improvement (62). Thus, in highly radiosensitive patients, RT could be postponed until disease recurrence or omitted altogether.

Considering early breast cancer, postoperative RT has been shown to decrease the risk of local recurrence by 15% (63). However, mastectomy with immediate reconstructive surgery could be an alternative to breast-conserving surgery plus RT for patients at high risk for development of radiation-induced toxicity (64, 65). Of course, in this case, as in any treatment change, patient's opinion should be taken into account in the decision-making process, as a more invasive surgery might be proposed.

Alternatively, in low risk breast cancer and elderly patients, cosmetic results could be improved by reducing radiation treatment volumes with intraoperative RT or partial breast irradiation (66, 67), while maintaining excellent tumor control (68, 69).

Low TCP, Low NTCP

Increasing total treatment dose would be the easiest intervention for a high risk of tumor recurrence in a patient with low risk of radiation-induced toxicity.

Dose escalation has been shown to improve local control in several tumor types, such as prostate or rectal cancer, where an increase in total dose could yield a higher rate of pathological complete response after surgery (70). Several dose escalation trials (in prostate, rectum, cervix or lung cancer for example) are currently recruiting, and these patients could be ideal candidates for radiogenomic trials.

Alternatively, chemotherapy or radiosensitizers could be used to increase radiation efficacy without increasing the physical dose or overall treatment time. In head and neck cancers, for example, the hypoxic modifier nimorazole could be added to the treatment regimen to overcome tumor hypoxia in patients with low risk of radiation-induced toxicity (71, 72). Gemcitabine use in locally advanced bladder cancers also has radiosensitizer effects (73).

Low TCP, High NTCP

This presentation is the worst-case scenario with a highly radiosensitive patient and a high risk of tumor recurrence or progression.

Since the main goal of RT is to ensure tumor control, dose deescalation cannot be offered to these patients since the need for tumor control exceeds the risk of radiation-induced toxicity.

In this case, alternate fractionation could be considered, such as a hyperfractionated regimen, which may maintain the same therapeutic ratio with decreased risk of toxicity (74). When available, stereotactic body radiation therapy could also offer a decreased risk of normal tissue complications with excellent tumor control rates (75). The use of proton or carbon ion RT could also be considered if these modalities are available. Prediction models including clinical and dosimetric parameters are currently under development (76). Individual radiosensitivity measured using the aforementioned tests should be incorporated into these predictive models (77).

When alternate fractionation schedules are not applicable, radioprotectors may reduce the risk of normal tissue toxicity while maintaining comparable tumor control rates (78). Amifostine is the only Federal Drug Administration (FDA)-approved radio-protector (79). However, severe side effects (nausea, hypotension) limit its widespread clinical use. However, patients predicted to be high risk for development of adverse outcomes following RT

could be good candidates for this treatment, whose pharmacologic side effects might prove more easily manageable than severe radiation-induced toxicity.

Table 3 summarizes the different clinical situations stratified by type of cancer and the suggested interventions.

STUDY DESIGN AND MEDICO-ECONOMIC CONSIDERATIONS

Randomized prospective clinical trials are the gold standard for interventional studies (19). There are 10 theoretical possible designs for testing clinical utility of radiogenomics models (80). However, of these, four are most applicable to randomized trials: randomize-all, interaction or risk factor-stratified design, targeted or selection design, and the individual profile design (81).

Randomize-all is the simplest design, with patients randomized for both treatments, regardless of their prognostic group and those being studied subsequently in each treatment arm. It is the most robust design to assess an intervention, regardless of patient profile. The risk factor-stratified design enables hierarchical

TABLE 3 | Suggested treatment adaptations based on TCP and NTCP.

Cancer type	Suggested treatment adaptations			
	High NTCP **Low TCP**	**High NTCP** **High TCP**	**Low NTCP** **Low TCP**	**Low NTCP** **High TCP**
Breast	• Consider the risk of recurrence first • If possible, discussion of a mastectomy ± reconstructive surgery without adjuvant RT	• Consider no adjuvant RT if elderly • Limit large RT fields (consider partial breast RT or IORT)	• Increase treatment fields (IMC, axilla) • Consider hypofractionation	• Consider no adjuvant RT or IORT if elderly • Consider hypofractionation and accelerated RT ± partial breast RT or IORT
Prostate	• Discuss possibility of surgery • RT with rectal spacer • RT with transponders • Discuss indication of pelvic RT • Discuss interest of proton therapy	• Active surveillance • Focal therapy • Brachytherapy • RT with rectal spacer • RT with transponders with reduced margins	• Dose escalation (boost brachytherapy if indicated) • Pelvic RT if indicated	• Active surveillance • Hypofractionation • SBRT
Lung	• Surgery if possible • Discuss hyperfractionation if large volumes	• Surgery • Very limited SBRT in case of non-operable lesions	• Dose escalation • Increase nodal volume (ENI) if indicated	• SBRT
Rectum Esophagus	• Consider the risk of recurrence first • Reduce the volume of fields if possible discuss interest of proton therapy	• Involved field RT • Discuss the need of RT	• Dose escalation if boost indicated	• Involved field RT • Contact therapy
Head and neck	• Consider the risk of recurrence first • Reduce the volume of fields if possible discuss interest of proton therapy	• Involved field RT	• Dose escalation • Discuss the use of radiosensitizers (e.g., nimorazole)	• Involved field RT • Hypofractionation
Gynecological tumors	• Consider the risk of recurrence first • Reduce the volume of fields if possible discuss interest of proton therapy	• Involved field RT • No adjuvant RT in adjuvant setting	• Dose escalation	• Involved field RT • Hypofractionation
CNS	• Consider the risk of recurrence first • Proton therapy is mandatory	• Involved field RT • No adjuvant RT	• Dose escalation	• Involved field RT • Hypofractionation • SBRT

TCP, tumor control probability; NTCP, normal tissue complication probability; IORT, intraoperative radiotherapy; RT, radiotherapy; IMC, internal mammary chain; SBRT, stereotactic body radiation therapy; ENI, elective nodal irradiation; CNS, central nervous system.

statistical tests, by stratifying patients according to their risk level before intervention. In the targeted design, only subjects identified as high-risk patients are randomized for intervention. This model allows studies to target a specific population with a higher statistical power, even if the accuracy of the model is low. Finally, the individual profile design enables parallel therapeutic strategies to be tested in various patient profiles with patients randomized between standard treatment and a risk profile-based strategy (81).

Nevertheless, trials of radiogenomics models should carefully follow appropriate reporting guidelines, such as STROGAR, CONSORT and REMARK in order to make large-scale validation of the results easier (18, 21, 82). Development of these tests for clinical implementation should theoretically follow region-specific guidelines, such as FDA or European Medicines Agency (16). However, not all tests can comply with every item in these guidelines, such as availability of randomized interventional studies. We consider retrospective and large prospective multicenter cohorts to be a required minimum in these cases.

As normal tissue response to radiation is a polygenic trait also affected by clinical, demographic and health behavior factors, multiparametric models should be the gold standard for predictive assays. Furthermore, given that radiosensitivity assays are predictive factors, they cannot be interpreted in an independent manner (83). For example, the RILA assay has been shown to be biased by numerous factors in breast fibrosis prediction, such as smoking habits or hormone therapy (41). A nomogram has thus been developed to incorporate effect modifiers and confounding parameters when predicting risk of radiation-induced breast fibrosis. Similar considerations apply to SNP-based predictive assays. For example, the SNP tagging the TANC1 risk locus for late toxicity in prostate cancer was shown to interact with radiation dose (25). There are likely other gene-by-environment interactions that remain to be uncovered, and inclusion of interaction terms is expected to improve performance of predictive models.

From a health-economic perspective, identification of hypersensitive patients could significantly decrease the cost of radiation-associated toxicity treatments, or even the cost of treatment in low NTCP high TCP patients eligible for accelerated regimen. There are approximately 15.5 million cancer survivors in the US, and there may be substantial costs to clinically manage the toxicities that could result from treatment of their disease (84). Cardiac complications that can develop after RT to the chest area (in breast cancer or lung cancer), for example, can be substantial. Costs associated with adverse outcomes following RT are often hard to specify, because they represent a small part of a complex disease management protocol (85). However, decreasing the rate of late toxicities will undeniably lower long-term costs of cancer survivorship.

In order to clearly quantify the economic gain from radiogenomics tests, several factors need to be considered. First, the cost of the actual test needs to be taken into account. For instance, the costs of the RILA assay or targeted SNP genotyping or gene sequencing for a limited panel are generally less than 2,000€, and the price for clinical whole genome sequencing continues to drop. Treatment costs must also be considered. In this case, treatment

adaptation to the NTCP of the patient could result in significant savings: total health-care expenditures for breast cancer can be decreased by 10% with hypofractionated RT (86). The cost–utility of intervention must be assessed by comparing these costs to Quality-Assessed Life Years, in all patient groups.

Once a test has shown sufficient clinical validity, it can be used to create medical companies, such as Novagray® for the RILA assay, to promote and market the test.

CONCLUSION AND PERSPECTIVES

A large number of tests for radiosensitivity have been investigated over the last three decades, and some have proven their validity in multicenter prospective settings. Of the many tests developed over the years, only several SNP assays and the RILA assay have shown replicated performance in the development phase.

The next step that should be undertaken is the large-scale study of these models to implement clinical use and assess cost–utility. This is being carried out in Europe through the ongoing REQUITE project, using the RILA assay, as well as other validated biomarkers (42). The RILA assay incorporated in a nomogram with the other independent factors has already proven its validity in a multicenter study on breast cancer and is currently under evaluation for other cancer types (40).

Similarly, the Radiogenomics Consortium has developed the TAILORED project to validate the concept of stratification to identify cancer patients with increased individual radiosensitivity and provide cost-effective therapeutic interventions to reduce the side effects of RT for cancer. This would allow for a personalized risk-adapted approach to provide more effective treatments.

AUTHOR CONTRIBUTIONS

DA participated in the design of the trial, wrote the manuscript, and coordinated the corrections of all the consortium participants. AL participated in the design of the trial, wrote the manuscript, and coordinated the corrections of all the consortium participants. SG, DD, JC, PL, MB, TW, SB, HT, TR, CT, AV, SK, CA, JC-C, CW, CG, and BR participated in writing the manuscript.

FUNDING

REFERENCES

1. Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* (1991) 21:109–22. doi:10.1016/0360-3016(91)90171-Y

2. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* (2010) 76:S3–9. doi:10.1016/j.ijrobp.2009.09.040

3. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* (2012) 62:220–41. doi:10.3322/caac.21149

4. Holthusen H. Erfahrungen über die verträglichkeitsgrenze für röntgenstrahlen und deren nutzanwendung zur verhütung von schäden. *Strahlentherapie* (1936) 57:254–69.

5. Burnet NG, Johansen J, Turesson I, Nyman J, Peacock JH. Describing patients' normal tissue reactions: concerning the possibility of individualising radiotherapy dose prescriptions based on potential predictive assays of normal tissue radiosensitivity. *Int J Cancer* (1998) 79:606–13. doi:10.1002/(SICI)1097-0215(19981218)79:6<606:AID-IJC9>3.0.CO;2-Y

6. Barnett GC, West CML, Dunning AM, Elliott RM, Coles CE, Pharoah PDP, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer* (2009) 9:134. doi:10.1038/nrc2587

7. Andreassen CN, Alsner J, Overgaard J. Does variability in normal tissue reactions after radiotherapy have a genetic basis – where and how to look for it? *Radiother Oncol* (2002) 64:131–40. doi:10.1016/S0167-8140(02)00154-8

8. Bentzen SM, Overgaard M. Relationship between early and late normal-tissue injury after postmastectomy radiotherapy. *Radiother Oncol* (1991) 20:159–65. doi:10.1016/0167-8140(91)90092-U

9. Burnet NG, Elliott RM, Dunning A, West CML. Radiosensitivity, radiogenomics and rapper. *Clin Oncol* (2006) 18:525–8. doi:10.1016/j.clon.2006.05.007

10. Simon R. Roadmap for developing and validating therapeutically relevant genomic classifiers. *J Clin Oncol* (2005) 23:7332–41. doi:10.1200/JCO.2005.02.8712

11. Kerns SL, Ostrer H, Rosenstein BS. Radiogenomics: using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. *Cancer Discov* (2014) 4:155–65. doi:10.1158/2159-8290.CD-13-0197

12. Kerns SL, West CML, Andreassen CN, Barnett GC, Bentzen SM, Burnet NG, et al. Radiogenomics: the search for genetic predictors of radiotherapy response. *Future Oncol* (2014) 10:2391–406. doi:10.2217/fon.14.173

13. Lilla C, Ambrosone CB, Kropp S, Helmbold I, Schmezer P, von Fournier D, et al. Predictive factors for late normal tissue complications following radiotherapy for breast cancer. *Breast Cancer Res Treat* (2007) 106:143–50. doi:10.1007/s10549-006-9480-9

14. Solanki AA, Liauw SL. Tobacco use and external beam radiation therapy for prostate cancer: influence on biochemical control and late toxicity. *Cancer* (2013) 119:2807–14. doi:10.1002/cncr.28128

15. Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. *Cancer* (2008) 113:648–53. doi:10.1002/cncr.23591

16. Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials, Board on Health Care Services, Board on Health Sciences Policy, Institute of Medicine. In: Micheel CM, Nass SJ, Omenn GS, editors. *Evolution of Translational Omics: Lessons Learned and the Path Forward.* Washington, DC: National Academies Press (US) (2012). Available from: http://www.ncbi.nlm.nih.gov/books/NBK202168/

17. Hayes DF, Bast RC, Desch CE, Fritsche H, Kemeny NE, Jessup JM, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst* (1996) 88:1456–66. doi:10.1093/jnci/88.20.1456

18. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Diagnostics for the SS of the N-EWG on C. Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* (2005) 97:1180–4. doi:10.1093/jnci/dji237

19. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* (2009) 101:1446–52. doi:10.1093/jnci/djp335

20. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *PLoS Med* (2012) 9(5):e1001216. doi:10.1371/journal.pmed.1001216

21. Kerns SL, de Ruysscher D, Andreassen CN, Azria D, Barnett GC, Chang-Claude J, et al. STROGAR – Strengthening the reporting of genetic association studies in radiogenomics. *Radiother Oncol* (2014) 110:182–8. doi:10.1016/j.radonc.2013.07.011

22. Dancey JE, Dobbin KK, Groshen S, Jessup JM, Hruszkewycz AH, Koehler M, et al. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res* (2010) 16:1745–55. doi:10.1158/1078-0432.CCR-09-2167

23. Kerns SL, Ostrer H, Stock R, Li W, Moore J, Pearlman A, et al. Genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) 78:1292–300. doi:10.1016/j.ijrobp.2010.07.036

24. Barnett GC, West CML, Coles CE, Pharoah PDP, Talbot CJ, Elliott RM, et al. Standardized total average toxicity score: a scale- and grade-independent measure of late radiotherapy toxicity to facilitate pooling of data from different studies. *Int J Radiat Oncol Biol Phys* (2012) 82:1065–74. doi:10.1016/j.ijrobp.2011.03.015

25. Fachal L, Gómez-Caamaño A, Barnett GC, Peleteiro P, Carballo AM, Calvo-Crespo P, et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. *Nat Genet* (2014) 46:891–4. doi:10.1038/ng.3020

26. Kerns SL, Dorling L, Fachal L, Bentzen S, Pharoah PDP, Barnes DR, et al. Meta-analysis of genome wide association studies identifies genetic markers of late toxicity following radiotherapy for prostate cancer. *EBioMedicine* (2016) 10:150–63. doi:10.1016/j.ebiom.2016.07.022

27. Andreassen CN, Rosenstein BS, Kerns SL, Ostrer H, De Ruysscher D, Cesaretti JA, et al. Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. *Radiother Oncol* (2016) 121(3):431–9. doi:10.1016/j.radonc.2016.06.017

28. Talbot CJ, Tanteles GA, Barnett GC, Burnet NG, Chang-Claude J, Coles CE, et al. A replicated association between polymorphisms near TNFα and risk for adverse reactions to radiotherapy. *Br J Cancer* (2012) 107:748–53. doi:10.1038/bjc.2012.290

29. Edvardsen H, Landmark-Høyvik H, Reinertsen KV, Zhao X, Grenaker-Alnaes GI, Nebdal D, et al. SNP in TXNRD2 associated with radiation-induced fibrosis: a study of genetic variation in reactive oxygen species metabolism and signaling. *Int J Radiat Oncol Biol Phys* (2013) 86:791–9. doi:10.1016/j.ijrobp.2013.02.025

30. Seibold P, Behrens S, Schmezer P, Helmbold I, Barnett G, Coles C, et al. XRCC1 polymorphism associated with late toxicity after radiation therapy in breast cancer patients. *Int J Radiat Oncol Biol Phys* (2015) 92:1084–92. doi:10.1016/j.ijrobp.2015.04.011

31. Pang Q, Wei Q, Xu T, Yuan X, Lopez Guerra JL, Levy LB, et al. Functional promoter variant rs2868371 of HSPB1 is associated with risk of radiation pneumonitis after chemoradiation for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2013) 85:1332–9. doi:10.1016/j.ijrobp.2012.10.011

32. Guerra JLL, Gomez D, Wei Q, Liu Z, Wang L-E, Yuan X, et al. Association between single nucleotide polymorphisms of the transforming growth factor β1 gene and the risk of severe radiation esophagitis in patients with lung cancer. *Radiother Oncol* (2012) 105:299–304. doi:10.1016/j.radonc.2012.08.014

33. Burnet NG, Wurm R, Yarnold JR, Peacock JH, Nyman J, Turesson I. Prediction of normal-tissue tolerance to radiotherapy from in-vitro cellular radiation sensitivity. *Lancet* (1992) 339:1570–1. doi:10.1016/0140-6736(92)91833-T

34. Geara FB, Peters LJ, Kian Ang K, Wike JL, Brock WA. Prospective comparison of in vitro normal cell radiosensitivity and normal tissue reactions in radiotherapy patients. *Int J Radiat Oncol Biol Phys* (1993) 27:1173–9. doi:10.1016/0360-3016(93)90540-C

35. Peacock J, Ashton A, Bliss J, Bush C, Eady J, Jackson C, et al. Cellular radiosensitivity and complication risk after curative radiotherapy. *Radiother Oncol* (2000) 55:173–8. doi:10.1016/S0167-8140(00)00173-0

36. Somaiah N, Chua MLK, Bourne S, Daley F, A' Hern R, Nuta O, et al. Correlation between DNA damage responses of skin to a test dose of radiation

and late adverse effects of earlier breast radiotherapy. *Radiother Oncol* (2016) 119:244–9. doi:10.1016/j.radonc.2016.04.012

37. West CM, Davidson SE, Elyan SA, Valentine H, Roberts SA, Swindell R, et al. Lymphocyte radiosensitivity is a significant prognostic factor for morbidity in carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* (2001) 51:10–5. doi:10.1016/S0360-3016(01)01575-9

38. Ozsahin M, Ozsahin H, Shi Y, Larsson B, Würgler FE, Crompton NE. Rapid assay of intrinsic radiosensitivity based on apoptosis in human CD4 and CD8 T-lymphocytes. *Int J Radiat Oncol Biol Phys* (1997) 38:429–40. doi:10.1016/S0360-3016(97)00038-2

39. Mirjolet C, Merlin JL, Dalban C, Maingon P, Azria D. Correlation between radio-induced lymphocyte apoptosis measurements obtained from two French centres. *Cancer Radiother* (2016) 20:391–4. doi:10.1016/j.canrad.2016.03.007

40. Azria D, Riou O, Castan F, Nguyen TD, Peignaux K, Lemanski C, et al. Radiation-induced CD8 T-lymphocyte apoptosis as a predictor of breast fibrosis after radiotherapy: results of the prospective multicenter french trial. *EBioMedicine* (2015) 2:1965–73. doi:10.1016/j.ebiom.2015.10.024

41. Brengues M, Lapierre A, Bourgier C, Pèlegrin A, Özsahin M, Azria D. T lymphocytes to predict radiation-induced late effects in normal tissues. *Expert Rev Mol Diagn* (2017) 17(2):119–27. doi:10.1080/14737159.2017.1271715

42. West C, Azria D, Chang-Claude J, Davidson S, Lambin P, Rosenstein B, et al. The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality of life in cancer survivors. *Clin Oncol (R Coll Radiol)* (2014) 26:739–42. doi:10.1016/j.clon.2014.09.008

43. Olive PL, Banáth JP, Keyes M. Residual γH2AX after irradiation of human lymphocytes and monocytes in vitro and its relation to late effects after prostate brachytherapy. *Radiother Oncol* (2008) 86:336–46. doi:10.1016/j.radonc.2007.09.002

44. Ivashkevich A, Redon CE, Nakamura AJ, Martin RF, Martin OA. Use of the γ-H2AX assay to monitor DNA damage and repair in translational cancer research. *Cancer Lett* (2012) 327:123–33. doi:10.1016/j.canlet.2011.12.025

45. Pinkawa M, Brzozowska K, Kriehuber R, Eble MJ, Schmitz S. Prediction of radiation-induced toxicity by in vitro radiosensitivity of lymphocytes in prostate cancer patients. *Future Oncol* (2016) 12:617–24. doi:10.2217/fon.15.334

46. Dorling L, Barnett GC, Michailidou K, Coles CE, Burnet NG, Yarnold J, et al. Patients with a high polygenic risk of breast cancer do not have an increased risk of radiotherapy toxicity. *Clin Cancer Res* (2016) 22:1413–20. doi:10.1158/1078-0432.CCR-15-1080

47. Hoeller U, Borgmann K, Bonacker M, Kuhlmey A, Bajrovic A, Jung H, et al. Individual radiosensitivity measured with lymphocytes may be used to predict the risk of fibrosis after radiotherapy for breast cancer. *Radiother Oncol* (2003) 69:137–44. doi:10.1016/j.radonc.2003.10.001

48. Terzoudi GI, Hatzi VI, Barszczewska K, Manola KN, Stavropoulou C, Angelakis P, et al. G2-checkpoint abrogation in irradiated lymphocytes: a new cytogenetic approach to assess individual radiosensitivity and predisposition to cancer. *Int J Oncol* (2009) 35:1223–30. doi:10.3892/ijo-00000439

49. Scott D, Barber JB, Spreadborough AR, Burrill W, Roberts SA. Increased chromosomal radiosensitivity in breast cancer patients: a comparison of two assays. *Int J Radiat Biol* (1999) 75:1–10. doi:10.1080/095530099140744

50. Barber JBP, Burrill W, Spreadborough AR, Levine E, Warren C, Kiltie AE, et al. Relationship between in vitro chromosomal radiosensitivity of peripheral blood lymphocytes and the expression of normal tissue damage following radiotherapy for breast cancer. *Radiother Oncol* (2000) 55:179–86. doi:10.1016/S0167-8140(99)00158-9

51. Padjas A, Kedzierawski P, Florek A, Kukolowicz P, Kuszewski T, Góźdz S, et al. Comparative analysis of three functional predictive assays in lymphocytes of patients with breast and gynaecological cancer treated by radiotherapy. *J Contemp Brachytherapy* (2012) 4:219–26. doi:10.5114/jcb.2012.32556

52. FAST Trialists group, Agrawal RK, Alhasso A, Barrett-Lee PJ, Bliss JM, Bliss P, et al. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiother Oncol* (2011) 100:93–100. doi:10.1016/j.radonc.2011.06.026

53. Fisher CM, Rabinovitch R. Frontiers in radiotherapy for early-stage invasive breast cancer. *J Clin Oncol* (2014) 32:2894–901. doi:10.1200/JCO.2014.55.1184

54. Zhou Z-R, Mei X, Chen X-X, Yang Z-Z, Hou J, Zhang L, et al. Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer. *Surg Oncol* (2015) 24:200–11. doi:10.1016/j.suronc.2015.06.005

55. Min C, Connolly E, Chen T, Jozsef G, Formenti SC. Hypofractionated radiation therapy for early stage breast cancer: outcomes, toxicities, and cost analysis. *Breast J* (2014) 20:267–73. doi:10.1111/tbj.12254

56. Haviland JS, Bentzen SM, Bliss JM, Yarnold JR; START Trial Management Group. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: an analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. *Radiother Oncol* (2016) 121:420–3. doi:10.1016/j.radonc.2016.08.027

57. Aluwini S, Pos F, Schimmel E, van Lin E, Krol S, van der Toorn PP, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol* (2015) 16:274–83. doi:10.1016/S1470-2045(14)70482-6

58. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* (2016) 17(8):1047–60. doi:10.1016/S1470-2045(16)30102-4

59. Zemplényi AT, Kaló Z, Kovács G, Farkas R, Beöthe T, Bányai D, et al. Cost-effectiveness analysis of intensity-modulated radiation therapy with normal and hypofractionated schemes for the treatment of localised prostate cancer. *Eur J Cancer Care (Engl)* (2016). doi:10.1111/ecc.12430

60. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* (2016) 375:1415–24. doi:10.1056/NEJMoa1606220

61. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* (2016) 375:1425–37. doi:10.1056/NEJMoa1606221

62. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) 380:2018–27. doi:10.1016/S0140-6736(12)61253-7

63. EBCTCG. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet* (2011) 378:1707–16. doi:10.1016/S0140-6736(11)61629-2

64. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* (2005) 366:2087–106. doi:10.1016/S0140-6736(05)67887-7

65. Litière S, Werutsky G, Fentiman IS, Rutgers E, Christiaens M-R, Van Limbergen E, et al. Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol* (2012) 13:412–9. doi:10.1016/S1470-2045(12)70042-6

66. Lemanski C, Azria D, Gourgou-Bourgade S, Ailleres N, Pastant A, Rouanet P, et al. Electrons for intraoperative radiotherapy in selected breast-cancer patients: late results of the Montpellier phase II trial. *Radiat Oncol* (2013) 8:191. doi:10.1186/1748-717X-8-191

67. Keshtgar MRS, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS, et al. Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial. *Breast Cancer Res Treat* (2013) 140:519–25. doi:10.1007/s10549-013-2641-8

68. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* (2013) 14:1269–77. doi:10.1016/S1470-2045(13)70497-2

69. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT – a randomised trial. *Lancet* (2014) 383:603–13. doi:10.1016/S0140-6736(13)61950-9

70. Hall MD, Schultheiss TE, Smith DD, Fakih MG, Wong JYC, Chen Y-J. Effect of increasing radiation dose on pathologic complete response in rectal cancer patients treated with neoadjuvant chemoradiation therapy. *Acta Oncol* (2016) 55:1392–9. doi:10.1080/0284186X.2016.1235797

71. Henk JM, Bishop K, Shepherd SF. Treatment of head and neck cancer with CHART and nimorazole: phase II study. *Radiother Oncol* (2003) 66:65–70. doi:10.1016/S0167-8140(02)00284-0

72. Bentzen J, Toustrup K, Eriksen JG, Primdahl H, Andersen LJ, Overgaard J. Locally advanced head and neck cancer treated with accelerated radiotherapy, the hypoxic modifier nimorazole and weekly cisplatin. Results from the DAHANCA 18 phase II study. *Acta Oncol* (2015) 54:1001–7. doi:10.3109/0284186X.2014.992547

73. Caffo O, Thompson C, De Santis M, Kragelj B, Hamstra DA, Azria D, et al. Concurrent gemcitabine and radiotherapy for the treatment of muscle-invasive bladder cancer: a pooled individual data analysis of eight phase I-II trials. *Radiother Oncol* (2016) 121:193–8. doi:10.1016/j.radonc.2016.09.006

74. Thames HD, Peters LT, Withers HR, Fletcher GH. Accelerated fractionation vs hyperfractionation: rationales for several treatments per day. *Int J Radiat Oncol Biol Phys* (1983) 9:127–38. doi:10.1016/0360-3016(83)90089-5

75. Milano MT, Constine LS, Okunieff P. Normal tissue toxicity after small field hypofractionated stereotactic body radiation. *Radiat Oncol* (2008) 3:36. doi:10.1186/1748-717X-3-36

76. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol* (2013) 107:267–73. doi:10.1016/j.radonc.2013.05.007

77. Rosenstein BS, West CM, Bentzen SM, Alsner J, Andreassen CN, Azria D, et al. Radiogenomics: radiobiology enters the era of big data and team science. *Int J Radiat Oncol Biol Phys* (2014) 89:709–13. doi:10.1016/j.ijrobp.2014.03.009

78. Kamran MZ, Ranjan A, Kaur N, Sur S, Tandon V. Radioprotective agents: strategies and translational advances. *Med Res Rev* (2016) 36:461–93. doi:10.1002/med.21386

79. Kouvaris JR, Kouloulias VE, Vlahos LJ. Amifostine: the first selective-target and broad-spectrum radioprotector. *Oncologist* (2007) 12:738–47. doi:10.1634/theoncologist.12-6-738

80. Kraft P, Cox DG. Study designs for genome-wide association studies. *Adv Genet* (2008) 60:465–504. doi:10.1016/S0065-2660(07)00417-8

81. De Ruysscher D, Defraene G, Ramaekers BLT, Lambin P, Briers E, Stobart H, et al. Optimal design and patient selection for interventional trials using radiogenomic biomarkers: a REQUITE and radiogenomics

82. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* (2008) 5:e20. doi:10.1371/journal.pmed.0050020

83. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "Optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* (1994) 86:829–35. doi:10.1093/jnci/86.11.829

84. Rim SH, Guy GP, Yabroff KR, McGraw KA, Ekwueme DU. The impact of chronic conditions on the economic burden of cancer survivorship: a systematic review. *Expert Rev Pharmacoecon Outcomes Res* (2016) 16:579–89. doi:10.1080/14737167.2016.1239533

85. Yabroff KR, Warren JL, Brown ML. Costs of cancer care in the USA: a descriptive review. *Nat Rev Clin Oncol* (2007) 4:643–56. doi:10.1038/ncponc0978

86. Bekelman JE, Sylwestrzak G, Barron J, Liu J, Epstein AJ, Freedman G, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA* (2014) 312:2542–50. doi:10.1001/jama.2014.16616

consortium statement. *Radiother Oncol* (2016) 121(3):440–6. doi:10.1016/j.radonc.2016.11.003

frontiers
in Oncology

Challenges for Quality Assurance of Target Volume Delineation in Clinical Trials

Amy Tien Yee Chang[1,2]*, Li Tee Tan[3], Simon Duke[3] and Wai-Tong Ng[1]

[1] Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, Hong Kong, [2] Department of Clinical Oncology, University of Hong Kong, Hong Kong, [3] Department of Oncology, Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom

In recent years, new radiotherapy techniques have emerged that aim to improve treatment outcome and reduce toxicity. The standard method of evaluating such techniques is to conduct large scale multicenter clinical trials, often across continents. A major challenge for such trials is quality assurance to ensure consistency of treatment across all participating centers. Analyses from previous studies have shown that poor compliance and protocol violation have a significant adverse effect on treatment outcomes. The results of the clinical trials may, therefore, be confounded by poor quality radiotherapy. Target volume delineation (TVD) is one of the most critical steps in the radiotherapy process. Many studies have shown large inter-observer variations in contouring, both within and outside of clinical trials. High precision techniques, such as intensity-modulated radiotherapy, image-guided brachytherapy, and stereotactic radiotherapy have steep dose gradients, and errors in contouring may lead to inadequate dose to the tumor and consequently, reduce the chance of cure. Similarly, variation in organ at risk delineation will make it difficult to evaluate dose response for toxicity. This article reviews the literature on TVD variability and its impact on dosimetry and clinical outcomes. The implications for quality assurance in clinical trials are discussed.

Keywords: target volume delineation variability, contouring guidelines, peer review, education program, clinical trial

INTRODUCTION

The last 20 years has seen the emergence of novel anticancer treatments which have the potential to improve clinical outcomes for patients. The standard method of evaluating such treatments is to conduct large scale multicenter clinical trials, often across continents. Radiotherapy is indicated for more than 50% of all cancer patients (1). Many oncology clinical trials, therefore, include radiotherapy within their treatment protocol even if the radiotherapy technique itself is not the subject of evaluation. Poor radiotherapy technique has been shown to be associated with inferior overall survival in many clinical trials; the benefit of any intervention in a clinical trial may, therefore, be compromised by suboptimal radiotherapy.

The radiotherapy quality assurance (RTQA) program was introduced to standardize radiotherapy across participating centers within a clinical trial. The RTQA program covers all aspects of the radiotherapy process including volume delineation, planning and delivery as well as infrastructure, equipment, personnel, and procedures. Several trial groups have reported that the implementation

of RTQA procedures has enhanced protocol compliance and improved clinical trial outcome (2). However, the RTQA procedures in different clinical trials vary considerably making analysis and inter-trial comparisons to identify the most effective procedures difficult. Moreover, the cost of running a trial RTQA program is substantial, even more so with the introduction of advanced radiotherapy techniques.

Advanced radiotherapy techniques improve local tumor control and reduce treatment toxicity by delivering higher radiation doses to tumors while sparing adjacent normal tissue. Examples include intensity-modulated radiotherapy (IMRT), which allows the radiotherapy dose to be conformed to the target volume while sparing nearby organs at risk (OAR), and image-guided radiotherapy, which improves the precision of treatment delivery and allows smaller margins to be added to the target volume for delivery uncertainty (3). The benefit of these and other high precision techniques is critically dependent on optimal target volume delineation (TVD) by radiation oncologists as the steep dose gradients and reduced margins leave little room for error. There are numerous reports in the literature of suboptimal TVD, which can lead to fatal marginal recurrences due to geographical miss (4–8).

This article reviews the literature on TVD variability and its impact on dosimetry and clinical outcomes. The current methods for reducing TVD variability within and outside clinical trials and their limitations are discussed.

MAGNITUDE OF TVD VARIABILITY

The delivery of radiotherapy treatment has long been subject to careful measurement and evaluation of the causes and magnitude of systematic and random errors. As a result, evidence-based strategies have been developed and universally adopted which have enabled radiotherapy delivery to approach millimeter precision.

In contrast, variability in TVD has not been evaluated with the same rigor. In 2016, Vinod et al. (9) published a systematic review of publications on uncertainties in TVD in radiation oncology. They identified 119 papers on TVD variability published between 2000 and 2014 covering the following clinical topics—breast, bladder, prostate, lung, esophagus, stomach, pancreas, liver, rectum, head and neck, brain, cervix, uterus, lymphoma, sarcoma, palliative radiotherapy, and OAR contouring. A number of studies focused on specific advanced radiotherapy techniques including image-guided brachytherapy (IGBT) for cervical cancer, stereotactic ablative body radiotherapy for lung cancer, and stereotactic radiosurgery for brain metastases.

All the studies showed considerable TVD variability between observers, often measured in centimeters. TVD variability was evident in all the volumes pertinent to radiotherapy planning as specified in ICRU Report 50 (10) published in 1978, i.e., the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV).

Target volume delineation variability was seen among experienced radiation oncologists as well as trainees. There were also differences between different specialists [diagnostic radiologists, positron emission tomography (PET) physicians, neurosurgeons, orthopedic surgeons, gynecology oncologists, medical oncologists, hematologists, respiratory physicians] and disciplines (medical physicists and radiation therapists/radiographers). In one highly cited French study of GTV delineation in lung cancer (11), nine radiologists and eight radiation oncologists working in five different centers, classified as either "junior" or "senior" according to their professional experience, were asked to delineate the primary tumor and involved lymph nodes on the computed tomography (CT) images of 10 patients. The study showed that compared to radiation oncologists, radiologists tended to delineate smaller volumes and encountered fewer difficulties to delineate "difficult" cases. Junior doctors also tended to delineate smaller and more homogeneous volumes than their senior colleagues, regardless of their specialty, especially for "difficult" cases.

CAUSES OF TVD VARIABILITY

Despite the numerous papers on TVD variability within and outside clinical trials, very few have attempted to evaluate the causes of TVD variability in a systematic fashion.

Several studies have reported the impact of imaging modality on TVD variability. For example, a number of studies (12–14) showed that more consistent definition of the GTV in lung cancer can be obtained if the CT images were co-registered with 2-[18F]-fluoro-2-deoxy-D-glucose PET images. Similarly, there are studies showing more consistent definition of GTV and CTV of brain tumors on CT images co-registered with magnetic resonance images (MRI) (15). Image co-registration is now standard practice for both these tumor sites.

It is important to appreciate that reduced TVD variability seen on one imaging modality does not necessarily equate to this being a superior imaging modality. In a study on IGBT for cervical cancer (16), 23 gynecologic radiation oncology experts were asked to delineate the CTV on CT and MRI. There was a higher level of agreement of contours on CT despite MRI being universally recognized as the superior imaging modality. This probably reflects clinician unfamiliarity of MRI image interpretation for IGBT cervix planning where post-radiation changes can be a confounding factor.

It is commonly assumed that the major cause of intra-observer TVD variability is suboptimal image interpretation (17). However, other factors such as conceptual understanding of patterns of tumor spread and organ motion are equally important. In a study on definitive radiotherapy for cervical carcinoma (18), five radiation oncologists and two gynecologists independently contoured the CTVs for three patients. The study showed good consistency in outlined anatomical structures suggesting that image interpretation was not an issue. However, there was large inter-observer variability in CTV delineation with the ratio between largest and smallest volumes ranging between 3.6 and 4.9 for all observers. The ratio of common volumes to encompassing volumes ranged between 0.11 and 0.13 for the radiation oncologists, and between 0.30 and 0.57 for the gynecologists.

The TVD variability between gynecologists and radiation oncologists probably reflects different conceptual understanding of areas at risk of microscopic disease between the two specialties. The core skill for gynecologists is to remove the tumor with a

small margin (usually 5 mm) with minimal disruption of surrounding tissue. In contrast, radiation oncologists irradiate large volumes of tissue to a relatively homogenous dose to minimize the risk of in-field and edge recurrences. The concepts of microscopic disease for these two specialties are, therefore, likely to be very different. This explanation could also account for the TVD variability between radiologists and radiation oncologists in the lung cancer study. Cancer radiologists are required to accurately define the tumor (avoiding both under and over estimation) to predict surgical resectability whereas the prime concern of radiation oncologists is to avoid missing the tumor. It is, therefore, easy to see why in difficult cases, some radiation oncologists would err on the side of caution and include areas of uncertainty in the GTV. Similarly, it is well recognized that junior doctors are less able to appreciate uncertainties than their senior colleagues, a phenomenon known as the Dunning Kruger effect based on Charles Darwin's quote that "Ignorance more frequently begets confidence than does knowledge."

Consistency and clarity of conceptual understanding is particularly important when new concepts are introduced. An example is the internal target volume (ITV), a concept first introduced in ICRU Report 62 published in 1999 (19). The ITV is defined as the CTV plus a margin taking into account uncertainties in size, shape, and position of the CTV within the patient. The margin for the ITV (called the internal margin) is distinct from the setup margin used for the PTV. However, in a survey of 50 radiation oncologists at a pelvic IMRT workshop (unpublished), 38% did not use the concept of the ITV in their daily practice, 30% incorporated the internal margin into the CTV, 26% incorporated the internal margin into the PTV, and only 8% contoured the ITV as a separate structure.

ASSESSMENT OF TVD VARIABILITY

The Vinod et al. review (9) reported that the number of imaging datasets in the studies on TVD variability varied from 1 to 132 with a median of 9, while the number of participants contouring ranged from 3 to 50 with a median of 7. There are no studies which have systematically analyzed the impact of number of imaging datasets or number of participants on TVD variability unlike the literature on setup accuracy. In those studies, where more than one case was used, the magnitude and direction of TVD variability varied considerably between cases reflecting the variation in patient anatomy and tumor topography.

There was also a wide range of methods used to assess TVD variability. A volume metric (volume measurements, volume ratios) was most consistently reported across most studies. Measures of overlap (concordance index, discordance index, dice similarity coefficient) were also frequently reported. Comparisons were usually measured against a reference contour. The definition of a reference contour varied from the contour of a recognized expert to a consensus contour with multiple observers or a Simultaneous Truth and Performance Level Estimation (STAPLE) contour (20) (STAPLE is the probabilistic estimate of the "true" volume generated from all observers). All these methods have an inherent deficiency in that they do not provide any information on the location of any discrepancies or their clinical significance.

DOSIMETRIC IMPACT OF TVD VARIABILITY

Vinod identified only 25 (21%) studies which evaluated the impact of variability in target and OAR contouring on dosimetry (9). Thirteen studies evaluated the dosimetric impact of target volume variability; it was interesting that three of these studies found no significant impact on PTV dose coverage. Ten studies also evaluated the impact of target volume variability on OAR doses; of these, eight studies found a significant impact on OAR dose–volume histograms (DVH). Twelve studies examined the impact of variability in OAR volume delineation; eight of these studies found statistically significant differences in OAR doses.

Vinod classified the analysis of the dosimetric impact of TVD variability into three broad methods. The first method involved a reference plan (usually the treatment plan or a plan optimized to a reference or expert contour) being applied to the volumes of many observers. This technique was used by Hellebust et al. (4) to study the dosimetric impact of contouring variations on a group of patients treated with IGBT for cervix cancer. They found that that the dose to the GTV and high-risk CTV (HR-CTV) had the smallest variation compared to the dose to the intermediate risk CTV (IR-CTV). This is perhaps not surprising as the IR-CTV is a new and complex concept, first introduced in 2005, which requires the clinician to integrate the CTV at the time of brachytherapy (BT) with the GTV at diagnosis. For OAR, the dose effect was largest for the sigmoid colon which again illustrates the greater uncertainty in defining this organ compared to the rectum and bladder. Overall, TVD variability resulted in a deviation of up to 5 Gy to the HR-CTV and up to 3 Gy for OAR.

The same method was used by Loo et al. (5) to investigate the dosimetric impact of variability in OAR contouring for head and neck IMRT. Four radiation oncologists and three radiologists delineated the parotid gland on the CT datasets of 10 patients with oropharyngeal carcinoma treated with parotid-sparing IMRT. The DVH for each study contour was calculated using the IMRT plan actually delivered for that patient and was compared with the original DVH obtained when the plan was used clinically. The mean parotid dose achieved during actual treatment was within 10% of 24 Gy for all patients. However, using the study contours, the mean parotid dose was within 10% of 24 Gy for only 53% of volumes by radiation oncologists and 55% of volumes by radiologists. The parotid DVH of 46% of the study contours were sufficiently different from the clinical DVH, such that a different IMRT plan would have been produced.

The second method as identified by Vinod is the converse of method one. In this method, the plans generated from many observer volumes are assessed for resultant dosimetry on a reference volume. This method was used in the INTERLACE study on IMRT for cervix cancer (6). No plan generated from the observer volumes was found to achieve the optimal gold standard PTV (GS-PTV) coverage; on average, the resultant dose (V95%, D95%) was 10–20% lower. The GS-PTV volume outside the 95% isodose ranged from 83 to 458 cc. A qualitative assessment showed the most common anatomical areas not covered by the 95% isodose were vagina, obturator, and nodal regions such as external iliac nodes.

In the first two methods, there is an assumption that the reference plan is "correct" and based on a "gold standard" volume which is again correct. If the reference plan is based on a volume that is an outlier compared to the contours being analyzed, the systematic differences measured may be amplified. In contrast, the third method involves a comparison of all plans applied to all contours without a reference. A plan is optimized to a particular delineated volume and then applied to all other volumes to assess dosimetry. This is then repeated for each observer's volume. This allows for the most in-depth comparison of dosimetry relating to TVD variability but is also the most resource-intensive.

The third method was used in a lung cancer study by Van de Steene et al. (21) in which five clinicians were asked to define the GTV (tumor and lymph node) on the planning CT scans of eight patients. For each volume, a standard conformal treatment plan comprising two pairs of opposed antero-posterior and lateral beams were created. The study reported inter-observer variation in the dimensions of the primary tumor of up to 4.2 (transverse), 7.9 (cranio-caudal), and 5.4 cm (antero-posterior). The variation in the extreme extensions of the GTV (tumor and lymph nodes) ranged from 2.8 to 7.3 cm. After common review, only 63% of involved lymph node regions were delineated by the clinicians (i.e., 37% were false negative). The probability (in the population of all conformal plans) of irradiating at least 95% of the GTV with at least 95% of the nominal treatment dose decreased from 96% for a matched plan (i.e., a plan created for that GTV volume) to 88% for an unmatched plan.

The authors suggested four possible causes for the large inter-observer variation—problems with methodology including definitions and concepts (e.g., definition of GTV to exclude atelectasis, definition of involved lymph nodes based on size, contouring of individual lymph nodes, or lymph node regions), difficulty differentiating between tumor and benign pathology (e.g., atelectasis), difficulty differentiating between tumor and normal structures, and lack of knowledge of anatomy. Interestingly, they also concluded that only the minority of the issues could be resolved objectively.

CLINICAL IMPACT OF TVD VARIABILITY

There are no studies which have assessed the direct impact of TVD variability on clinical outcome.

Peters et al. (8) retrospectively analyzed 780 patients in the Trans-Tasman Radiation Oncology Group 02.02 (TROG 02.02) HeadSTART trial in head and neck cancer and found that patients whose radiotherapy plans failed trial quality assurance (12% overall) had poorer survival and loco-regional control compared to the those with protocol-compliant plans [2-year overall survival (OS) 50 vs. 70%, $p < 0.001$, 2-year loco-regional control 54 vs. 78%, $p < 0.001$]. However, incorrect volume delineation was a feature in only 25% (24/97) non-compliant plans.

A number of studies have modeled the potential impact of TVD variability. Van de Steene et al (11) estimated the impact of GTV delineation variability on tumor cure probability (TCP). Across all plans, the mean TCP decreased from 51% for a matched plan (i.e., a plan created for that GTV volume) to 42% for an unmatched plan (i.e., a plan created for another GTV),

a difference of 9%. The mean range in TCP across the eight patients was 2% (maximum range 5%) for matched plans compared to 14% (maximum 31%) for unmatched plans. They also estimated the normal tissue complication probabilities for different OAR but this analysis was of limited value as the plans used were 4-field boxes which would not have been used clinically.

Jameson et al. (7) also modeled the impact of GTV delineation variability on TCP and equivalent uniform dose (EUD) in lung cancer. Three radiation oncologists contoured the GTV on the planning CT, the diagnostic PET–CT and the radiotherapy planning PET–CT for seven patients. An optimized plan with 3–5 conformal beams was created for each volume. The SD of the volumes across all seven patients ranged from 39 to 419 cc. However, the SD of the EUD was ≤1 Gy in four of the seven patients (range 0.09–21.2 Gy). Similarly, the SD of the TCP was negligible (0–1%) in four of the seven patients (range 0–22%). Contouring variations in the lateral dimensions had the greatest impact on EUD and TCP.

MINIMIZING TVD VARIABILITY IN ROUTINE PRACTICE

Several interventions have been developed to reduce inter-observer TVD variability. These have been reviewed in another publication by Vinod et al. (21).

Contouring Guidelines and Atlases

The most common method for reducing TVD variability within and outside clinical trials is probably the use of consensus contouring guidelines and/or atlases (22, 23). Lobefalo et al. (24) evaluated the benefit of a contouring guideline on consistency of TVD in a study of rectal cancer. Four radiation oncologists contoured the CTV on 10 patients before and after the introduction of a shared guidelines. The Agreement Index improved from 0.57 (pre-guideline) to 0.69 (post-guideline). The unmatched PTV coverage improved from 93.7 ± 9.2 to 96.6 ± 4.9% for 3D conformal radiotherapy and 86.5 ± 13.8 to 94.5 ± 7.5% for a volumetric modulated arc radiotherapy (VMAT) technique. This suggests that the dosimetric impact of inter-observer variation is more pronounced for advanced radiotherapy techniques.

Eminowicz et al. (22) from the INTERLACE trial reported the reduction of inter-observer contouring variation and increased protocol adherence after introduction of an atlas. They analyzed seven key guidelines for target volume contouring in cervical cancer and identified 11 common areas of variation. A pictorial atlas was then derived to illustrate a consistent delineation method for these areas. The average proportion of outlines (of 4; primary CTV, nodal CTV, bladder, rectum) complying to the protocol improved from 1.8/4 to 2.7/4 with atlas use.

While contouring guidelines are undoubtedly invaluable in making TVD more consistent, they can also be a source of variability if different groups produce conflicting guidelines for the same tumor site or anatomical region. For example, the GYN consortium consensus guidelines for CTV delineation for IMRT for cervix cancer defines the lateral border of the parametrium as the medial edge of internal obturator muscle/ischial ramus

(i.e., lateral to the pelvic vessels) whereas the EMBRACE-II guidelines define this border as the medial edge of internal iliac and obturator vessels. Similarly, the inferior border of the pre-sacral nodes has been defined as S2 in gynecological guidelines (23, 25), S3 in prostate guidelines (26, 27) and bottom of the coccyx in anal guidelines (28, 29). It is easy to see how a clinician used to contouring in a particular way will continue to do so in a clinical trial regardless of the protocol specification.

Multi-Modality Imaging

Improved imaging, e.g., use of intravenous contrast, optimal window settings, and multi-modality imaging, is an intuitive way to improve TVD consistency. In the Vinod et al. review (9), there were more published studies using this method than all other methods combined. However, results have been mixed and 9 of the 31 studies reviewed did not demonstrate a statistically significant reduction in TVD variability. It appears that interpretation of the additional imaging modality and image co-registration are sources of error in themselves.

Auto-Contour Provision

A few studies have reported improved TVD consistency from clinicians editing an auto-contour compared to manual delineation (21). However, if the auto-contour contains an error, then this is more likely to be transmitted through the manual editing process as a systematic error. The majority of auto-contouring software in clinical use utilize atlas-based segmentation which always requires manual review and adjustment due to the wide variation in normal and post-treatment anatomy. Machine learning techniques hold promise for increasing accuracy and reducing the burden of user editing as discussed in a review by Sharp et al. (30).

Contouring Workshops and Educational Programs

Several publications have reported the benefit of contouring workshops on reducing TVD variability. An example is an International Atomic Energy Agency study over a 1-year period involving 11 pairs of clinicians comprising a radiation oncologist and a nuclear medicine physician (31). Training consisted of lectures, contouring practice, and group and individualized feedback. Following the first training, overall concordance indices for three repeated cases increased from 0.57 ± 0.07 to 0.66 ± 0.07. After further training, overall concordance indices for another three repeated cases further increased from 0.64 ± 0.06 to 0.80 ± 0.05 ($p = 0.01$).

Contouring workshops are a popular method for teaching TVD but they have several limitations. In most cases, improvement is measured by re-contouring on the same cases and it is difficult to ascertain whether learning is transferred to different cases with different patient anatomy and tumor topography. The number of participants is limited by logistics and cost.

Recent advances in technology such as web-enabled video conferencing and interactive software have enabled both live and offline educational interventions to reach across geographical boundaries. An example is the FALCON program (Fellowship in Anatomic delineation and Contouring), offered by the European Society for Radiotherapy & Oncology (32). However, online workshops will face the same pedagogical issues as live ones.

A few contouring tools have been developed to support self-learning TVD programs. These tools offer delineation practice often with provision of a reference volume and/or automated feedback. These programs are in their infancy and their utility remains to be established. Issues include difficulty in defining a reference volume given the extent of disagreement in TVD among experts, challenges for user engagement and outdated internet access particularly in hospitals.

Peer Review

Peer review involves the review of aspects of radiotherapy treatment by two or more radiation oncologists, or another specialist such as a radiologist. It may cover indications for treatment, treatment approach, volume delineation, planning directives, evaluation of plan quality and/or treatment verification. The American Society for Radiation Oncology has identified TVD as the first priority for peer review due to the heterogeneity in contouring and its impact on the rest of the radiotherapy process (33).

Multiple audits of peer review have identified that a proportion of radiotherapy treatments require significant alteration. In an early study (34), 3,052 cases were reviewed over 8 years of which 4.1% were "not approved." More recently, Mackenzie et al. (35) presented a prospective audit of peer review meetings in breast, head and neck, and lung cancer. Overall 9% of treatments required alteration before the first or next fraction of radiotherapy, although this varied significantly across the tumor sites (1–16%). A study by Dimigen et al. (36) reported that involving a radiologist in weekly QA meetings resulted in a significant change in management in 6% of cases.

Multiple professional organizations now advocate peer review as an important component of safe and effective radiotherapy. However, there are significant barriers to its implementation including a lack of personnel, dedicated time and facilities, and a reluctance of clinicians to invite scrutiny, especially across institutions. Given its cost and resource implications, rigorous research to evaluate its benefit is urgently needed. Technologies which allow large scale remote assessment of contours would be hugely advantageous.

MINIMIZING TVD VARIABILITY IN CLINICAL TRIALS

The process for RTQA of TVD in clinical trials may involve one or more of the following (37):

- A benchmark case—the participating institution is asked to delineate radiotherapy volumes on one or more standardized cases according to the protocol.
- A dummy run—the institution uploads the datasets of one or more of their patients treated locally for central review.
- Individual case review—during the course of the trial, some or all of the patients' radiotherapy datasets will be requested for prospective or retrospective central review.

Most of the reports on RTQA for TVD have used benchmark cases. An example is the INTERLACE study on IMRT for cervix cancer. The principal investigators (PIs) of participating centers

were asked to contour the CTV on two cases with different FIGO stages. 21 outlines were compared for case 1 and 22 for case 2. The delineated volumes ranged from 340 to 676 cc for case 1 and 458 to 806 cc for case 2. The direction of the maximum variation was different in the two cases.

The EMBRACE-I study on IGBT for cervix cancer is an example of RTQA based on a dummy run (38). Each center was asked to upload a "good response" case and a "poor response" case for central review. The review was qualitative with one physician reviewing all the external beam radiotherapy (EBRT) contours and three other physicians reviewing the BT contours. Out of 30 submitting centers, 13 had major inconsistencies in BT contouring while 11 had major inconsistencies in EBRT contouring. Centers with experience in IGBT (>30 cases) performed better than those with limited experience.

Retrospective individual case review was reported by the SCALOP trial in pancreatic cancer (39). The chief investigator and a radiologist contoured the GTV on the 60 of 74 patients who received radiotherapy in the study (12 patients had planning CTs which were deemed to be of insufficient quality for re-contouring) and compared their gold standard contours with the treating clinicians' contours using the Jaccard conformity index and geographical miss index. The median geometric indices for GTV and PTV seen in on-trial patients were better than the pre-trial benchmark case, suggesting that overall, quality of tumor delineation was acceptable and that the pre-trial RTQA may have enhanced the quality of tumor delineation within the main trial. However, tumor was completely missed in one patient, and ≥50% of the tumor was missed in three cases. The authors reported that patients with Jaccard conformity index for GTV ≥ 0.7 had 7.12 (95% CIs: 1.83–27.67, $p = 0.005$) higher odds of progressing by 9 months in multivariate analysis, which is counter-intuitive.

DISCUSSION

Our review has found that although there are numerous publications reporting considerable TVD variability within and outside clinical trials, there are very few which have investigated the causes of the variability or its impact on actual clinical outcomes. The limited data on outcomes are conflicting with modeling papers suggesting different impact on TCP in different patterns which is perhaps not surprising. The one paper which correlated TVD variability with outcomes showed that higher concordance with the gold standard contours actually worsens outcome. All the data to date suggest that the relationship between TVD variability and outcome is not straightforward and further research is required. Similarly, several educational strategies have been put forward to minimize TVD variability but there is little systematic research into the effectiveness of the strategies and more importantly, whether learning is retained.

The problem is particularly acute for clinical trials due to the requirement to assess clinicians from many participating centers, in dispersed locations. The logistics are such that most clinical trials limit their RTQA process to the PIs who are probably the most likely to contour correctly. Similarly, most RTQA is based on 1 or 2 carefully chosen benchmark cases which does not take into account patient anatomy and difficult topography. The assessment process is usually subjective and there may be a conflict of interest for the central review team to "pass" centers in order to increase trial recruitment.

In 2010, the Global Clinical Trials RTQA Harmonization Group (GHG) (40) was established to

- collate, homogenize and distribute information regarding the RTQA standards of clinical trial groups,
- provide a platform for prospective discussions on new RTQA procedures, software tools, guidelines and policies of trial groups,
- provide a framework to endorse existing and future RTQA procedures and guidelines across various trial groups.

The aim is to increase cooperation between trial groups internationally and facilitate the exchange and interpretation of RTQA data.

Perhaps a neglected opportunity in clinical trials is the potential to use RTQA content for systematic education. This strategy has been adopted in the EMBRACE-II study of IMRT and IGBT in cervix cancer (www.embracestudy.dk). In addition to workshops and annual update meetings, the study has set up an online continuous education program for all study participants. The program includes a number of educational resources not commonly available in clinical trials such as training contouring cases and quizzes. The quizzes in particular have been popular with participants and have identified gaps in knowledge and participant comprehension of the protocol. This has enabled the trial management group to develop targeted learning resources which should hopefully improve protocol compliance. The aim is to eventually make these resources available to non-trial participants as well.

CONCLUSION

Target volume delineation variability is a significant problem in radiotherapy both within and outside clinical trials. More research is required to evaluate the causes of variability and its impact on dosimetry and clinical outcome.

AUTHOR CONTRIBUTIONS

AC: draft outline and final manuscript. LT and SD: revision of some sections of the manuscript and organization of references. W-TN: revision and review of the manuscript.

REFERENCES

1. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment. *Cancer* (2005) 104:1129–37. doi:10.1002/cncr.21324

2. Ohri N, Shen X, Dicker AP, Doyle LA, Harrison AS, Showalter TN. Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials. *J Natl Cancer Inst* (2013) 105:387–93. doi:10.1093/jnci/djt001

3. Ahmad SS, Duke S, Jena R, Williams MV, Burnet NG. Advances in radiotherapy. *BMJ* (2012) 345:e7765. doi:10.1136/bmj.e7765

4. Hellebust TP, Tanderup K, Lervåg C, Fidarova E, Berger D, Malinen E, et al. Dosimetric impact of interobserver variability in MRI-based delineation for cervical cancer brachytherapy. *Radiother Oncol* (2013) 107:13–9. doi:10.1016/j.radonc.2012.12.017

5. Loo SW, Martin WMC, Smith P, Cherian S, Roques T. Interobserver variation in parotid gland delineation: a study of its impact on intensity-modulated radiotherapy solutions with a systematic review of the literature. *Br J Radiol* (2012) 85:1070–7. doi:10.1259/bjr/32038456

6. Eminowicz G, Rompokos V, Stacey C, McCormack M. The dosimetric impact of target volume delineation variation for cervical cancer radiotherapy. *Radiother Oncol* (2016) 120:493–9. doi:10.1016/j.radonc.2016.04.028

7. Jameson MG, Kumar S, Vinod SK, Metcalfe PE, Holloway LC. Correlation of contouring variation with modeled outcome for conformal non-small cell lung cancer radiotherapy. *Radiother Oncol* (2014) 112:332–6. doi:10.1016/j.radonc.2014.03.019

8. Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol* (2010) 28(18):2996–3001. doi:10.1200/JCO.2009.27.4498

9. Vinod SK, Jameson MG, Min M, Holloway LC. Uncertainties in volume delineation in radiation oncology: a systematic review and recommendations for future studies. *Radiother Oncol* (2016) 121:169–79. doi:10.1016/j.radonc.2016.09.009

10. International Commission on Radiation Units and Measurements. *ICRU Report No. 50. Prescribing, Recording and Reporting Photon Beam Therapy*. Washington, DC: International Commission on Radiation Units and Measurements (1993).

11. Van de Steene J, Linthout N, de Mey J, Vinh-Hung V, Claassens C, Noppen M, et al. Definition of gross tumor volume in lung cancer: interobserver variability. *Radiother Oncol* (2002) 62:37–9. doi:10.1016/S0167-8140(01)00453-4

12. Caldwell CB, Mah K, Ung YC, Danjoux CE, Balogh JM, Ganguli SN, et al. Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: the impact of 18FDG-hybrid PET fusion. *Int J Radiat Oncol Biol Phys* (2001) 51:923–31. doi:10.1016/S0360-3016(01)01722-9

13. Morarji K, Fowler A, Vinod SK, Shon IH, Laurence JM. Impact of FDG-PET on lung cancer delineation for radiotherapy. *J Med Imaging Radiat Oncol* (2012) 56:195–203. doi:10.1111/j.1754-9485.2012.02356.x

14. Hanna GG, McAleese J, Carson KJ, Stewart DP, Cosgrove VP, Eakin RL, et al. 18F-FDG PET-CT simulation for non-small-cell lung cancer: effect in patients already staged by PET-CT. *Radiat Oncol Biol* (2010) 77:24–30. doi:10.1016/j.ijrobp.2009.04.045

15. Cattaneo GM, Reni M, Rizzo G, Castellone P, Ceresoli GL, Cozzarini C, et al. Target delineation in post-operative radiotherapy of brain gliomas: interobserver variability and impact of image registration of MR(pre-operative) images on treatment planning CT scans. *Radiother Oncol* (2005) 75:217–23. doi:10.1016/j.radonc.2005.03.012

16. Viswanathan AN, Erickson B, Gaffney DK, Beriwal S, Bhatia SK, Lee Burnett O III, et al. Comparison and consensus guidelines for delineation of clinical target volume for CT- and MR-based brachytherapy in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* (2014) 90:320–8. doi:10.1016/j.ijrobp.2014.06.005

17. Riegel AC, Berson AM, Destian S, Ng T, Tena LB, Mitnick RJ, et al. Variability of gross tumor volume delineation in head-and-neck cancer using CT and PET/CT fusion. *Int J Radiat Oncol Biol Phys* (2006) 65(3):726–32. doi:10.1016/j.ijrobp.2006.01.014

18. Weiss E, Richter S, Krauss T, Metzelthin SI, Hille A, Pradier O, et al. Conformal radiotherapy planning of cervix carcinoma: differences in the delineation of the clinical target volume. A comparison between gynaecologic and radiation oncologists. *Radiother Oncol* (2003) 67:87–95. doi:10.1016/S0167-8140(02)00373-0

19. ICRU. Prescribing, recording, and reporting photon beam therapy (report 62). ICRU Report. *Br J Radiol* (1999) 74:294. doi:10.1259/bjr.74.879.740294

20. Warfield SK, Zou KH, Wells WM. Simultaneous truth and performance level estimation (STAPLE): an algorithm for the validation of image segmentation. *IEEE Trans Med Imaging* (2004) 23(7):903–21. doi:10.1109/TMI.2004.828354

21. Vinod SK, Min M, Jameson MG, Holloway LC. A review of interventions to reduce inter-observer variability in volume delineation in radiation oncology. *J Med Imaging Radiat Oncol* (2016) 60(3):393–406. doi:10.1111/1754-9485.12462

22. Eminowicz G, Hall-Craggs MA, Diez P, McCormack M. Improving target volume delineation in intact cervical carcinoma: literature review and step-by-step pictorial atlas to aid contouring. *Prac Radiat Oncol* (2016) 6(5):e203–13. doi:10.1016/j.prro.2016.01.006

23. Small W Jr, Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* (2008) 71:428–34. doi:10.1016/j.ijrobp.2007.09.042

24. Lobefalo F, Bignardi M, Reggiori G, Tozzi A, Tomatis S, Alongi F, et al. Dosimetric impact of inter-observer variability for 3D conformal radiotherapy and volumetric modulated arc therapy: the rectal tumor target definition case. *Radiat Oncol* (2013) 8(176):1–10. doi:10.1186/1748-717X-8-176

25. EMBRACE. *EMBRACE II Study Protocol* (2017). Available from: https://www.embracestudy.dk

26. Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* (2009) 74(2):383–7. doi:10.1016/j.ijrobp.2008.08.002

27. Harris VA, Staffurth J, Naismith O, Esmail A, Gulliford S, Khoo V, et al. Consensus guidelines and contouring atlas for pelvic node delineation in prostate and pelvic node intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* (2015) 92(4):874–83. doi:10.1016/j.ijrobp.2015.03.021

28. Ng M, Leong T, Chander S, Chu J, Kneebone A, Carroll S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. *Int J Radiat Oncol Biol Phys* (2012) 83(5):1455–62. doi:10.1016/j.ijrobp.2011.12.058

29. Muirhead R, Adams RA, Gilbert DC, Glynne-Jones R, Harrison M, Sebag-Montefiore D, et al. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol (R Coll Radiol)* (2014) 26(11):720–1. doi:10.1016/j.clon.2014.08.001

30. Sharp G, Fritscher KD, Pekar V, Peroni M, Shusharina N, Veeraraghavan H, et al. Vision 20/20: perspectives on automated image segmentation for radiotherapy. *Med Phys* (2014) 41(5):1–13. doi:10.1118/1.4871620

31. Konert T, Vogel WV, Everitt S, MacManus MP, Thorwarth D, Fidarova E, et al. Multiple training interventions significantly improve reproducibility of PET-CT-based lung cancer radiotherapy target volume delineation using an IAEA study protocol. *Radiother Oncol* (2016) 121(1):39–45. doi:10.1016/j.radonc.2016.09.002

32. Eriksen JG, Salembier C, De Bari B, Berger D, Mantello G, Müller AC, et al. Four years with FALCON – an ESTRO educational project: achievements and perspectives. *Radiother Oncol* (2014) 112(1):145–9. doi:10.1016/j.radonc.2014.06.017

33. Marks LB, Adams RD, Pawlicki T, Blumberg AL, Hoopes D, Brundage MD, et al. Enhancing the role of case-oriented peer review to improve quality and safety in radiation oncology: executive summary. *Pract Radiat Oncol* (2013) 3(3):149e156. doi:10.1016/j.prro.2012.11.010

34. Brundage MD, Dixon PF, Mackillop WJ, Shelley WE, Hayter CR, Paszat LF, et al. A real-time audit of radiation therapy in a regional cancer center. *Int J Radiat Oncol Biol Phys* (1999) 43:115–24. doi:10.1016/S0360-3016(98)00368-X

35. Mackenzie J, Graham G, Olivotto IA. Peer review of radiotherapy planning: quantifying outcomes and a proposal for prospective data collection. *Clin Oncol (R Coll Radiol)* (2016) 28(12):e192–8. doi:10.1016/j.clon.2016.08.012

36. Dimigen M, Vinod SK, Lim K. Incorporating a radiologist in a radiation oncology department: a new model of care? *Clin Oncol (R Coll Radiol)* (2014) 26(10):630–5. doi:10.1016/j.clon.2014.04.030

37. Gwynne S, Spezi E, Sebag-Montefiore D, Mukherjee S, Miles E, Conibear J, et al. Improving radiotherapy quality assurance in clinical trials: assessment of target volume delineation of the pre-accrual benchmark case. *Br J Radiol* (2013) 86:1–11. doi:10.1259/bjr.20120398

38. Kirisits C, Federico M, Nkiwane K, Fidarova E, Jürgenliemk-Schulz I, de Leeuw A, et al. Quality assurance in MR image guided adaptive

brachytherapy for cervical cancer: final results of the EMBRACE study dummy run. *Radiother Oncol* (2015) 117(3):548–54. doi:10.1016/j.radonc.2015.08.001

39. Fokas E, Spezi E, Patel N, Hurt C, Nixon L, Chu KY, et al. Comparison of investigator-delineated gross tumour volumes and quality assurance in pancreatic cancer: analysis of the on-trial cases for the SCALOP trial. *Radiother Oncol* (2016) 120(2):212–6. doi:10.1016/j.radonc.2016.07.002

40. Medilis C, Bosch WR, Izewska J, Fidarova E, Zubizarreta E, Ishikura S, et al. Radiation therapy quality assurance in clinical trials – Global Harmonisation Group. *Radiother Oncol* (2014) 111(3):327–9. doi:10.1016/j.radonc.2014.03.023

Electronic Support for Retrospective Analysis in the Field of Radiation Oncology: Proof of Principle Using an Example of Fractionated Stereotactic Radiotherapy of 251 Meningioma Patients

Sandra Rutzner[1†‡], Rainer Fietkau[1], Thomas Ganslandt[2], Hans-Ulrich Prokosch[2] and Dorota Lubgan[1†]*

[1] *Department of Radiation Oncology, Erlangen University Hospital, Erlangen, Germany,* [2] *Chair of Medical Informatics, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany*

Introduction: The purpose of this study is to verify the possible benefit of a clinical data warehouse (DWH) for retrospective analysis in the field of radiation oncology.

Material and methods: We manually and electronically (using DWH) evaluated demographic, radiotherapy, and outcome data from 251 meningioma patients, who were irradiated from January 2002 to January 2015 at the Department of Radiation Oncology of the Erlangen University Hospital. Furthermore, we linked the Oncology Information System (OIS) MOSAIQ® to the DWH in order to gain access to irradiation data. We compared the manual and electronic data retrieval method in terms of congruence of data, corresponding time, and personal requirements (physician, physicist, scientific associate).

Results: The electronically supported data retrieval (DWH) showed an average of 93.9% correct data and significantly ($p = 0.009$) better result compared to manual data retrieval (91.2%). Utilizing a DWH enables the user to replace large amounts of manual activities (668 h), offers the ability to significantly reduce data collection time and labor demand (35 h), while simultaneously improving data quality. In our case, work time for manually data retrieval was 637 h for the scientific assistant, 26 h for the medical physicist, and 5 h for the physician (total 668 h).

Conclusion: Our study shows that a DWH is particularly useful for retrospective analysis in the radiation oncology field. Routine clinical data for a large patient group can be provided ready for analysis to the scientist and data collection time can be significantly reduced. Furthermore, linking multiple data sources in a DWH offers the ability to improve data quality for retrospective analysis, and future research can be simplified.

Keywords: clinical data warehouse, MOSAIQ®, routine clinical data, secondary use of data, data retrieval, stereotactic radiotherapy, meningioma

INTRODUCTION

Routinely documented clinical data are of great importance for patient care as well as for research purposes (1, 2).

So far, the retrospective analyses in medical research have been predominantly performed manually, meaning that clinical data are often transferred by hand from routine clinical reports into a separate research database (3) and stored in standard office tools (e.g., Microsoft Excel spreadsheets), which are not validated for clinical research. The continuously increasing expansion of electronic documentation in the clinical treatment process creates a large amount of various databases (4); thus, manual retrospective analysis is currently quite ambitious and time consuming.

In the field of radiation oncology, data sets are large and heterogeneous (5). Electronic information systems contain patients' data for imaging in the Radiology Information System and Picture Archiving and Communication System, for irradiation in the Clinical Information System (CIS), e.g., Oncology Information System (OIS, MOSAIQ®) and data of the current course of the patients' disease in the electronic health record (EHR, e.g., Soarian® Clinicals).

With the increasing amount of patient information captured in EHRs and CISs, more opportunities should be established to facilitate clinical research by obtaining routine clinical data from distributed databases for secondary use, though providing access to routine clinical data for secondary use is challenging in practice (6). One of the greatest challenges in clinical research is to define and implement health data standards for integration between routinely used subsystems (7, 8). Medical data are frequently distributed across multiple electronic information systems of several departments in different forms of documentation styles (9). Although most university hospitals already implemented commercial hospital information systems and started to develop comprehensive EHRs, there is still a gap between clinical care and using this data for medical research that needs to be filled (10, 11). Recent studies have focused on providing routine clinical data for research purposes, e.g., by using a single-source tumor documentation or supporting systems for patient recruitment into clinical trials in the field of radiation oncology (12) and intensive care (13).

Data warehouses (DWHs) are central repositories of integrated data from one or more disparate sources. They store current and historical data and are used for creating analytical reports for knowledge workers throughout the enterprise (14). The purpose of this study is to verify the possible benefit of a DWH for retrospective analysis and reflect differences in manual and automated data retrieval.

Using meningioma patients as an example, we performed a therapy evaluation by utilizing an integrated electronic research database system DWH (clinical DWH) of the Erlangen University Hospital (UKER) to make routine radiotherapy data available from various operational subsystems. This is one of the largest populations of meningioma patients treated with stereotactic radiotherapy (SRT) in a single institution with a comprehensive database due to a high overall survival rate and a long observation period of meningioma patients after SRT.[1]

We manually and electronically collected basic information (patient characteristics), radiotherapy, and outcome data of 251 meningioma patients, who were irradiated from January 2002 to January 2015 at the Department of Radiation Oncology of the UKER (see text footnote 1). Currently, manual data collection represents the "gold standard." In our study, we compared the results of both the electronic and manual data retrieval process and determined the congruence of data. Moreover, we measured the corresponding time requirements for both retrieval methods and the involvement of personnel (physician, physicist, scientific associate).

MATERIALS AND METHODS

Environment

Erlangen University Hospital (UKER) is a tertiary care hospital that has 1.368 beds and combines 24 departments, 18 independent divisions, 7 institutes, and 25 interdisciplinary centers. In 2015, over 60,000 inpatient and nearly 475,000 outpatient cases were treated (15). At the Department of Radiation Oncology, 130–150 patients with many different tumor entities are irradiated daily. Approximately, 32 patients with meningioma are irradiated annually.

For our study, an agreement for the usage of routine clinical data was signed by those departments of the UKER that were involved in the patients' treatment (Neurosurgery, Neurology, Neuropathology, and Radiology). These regulatory requirements and institutional policies need to be reconciled to use clinical routine data for clinical research activities.

Principles of Radiotherapy of Intracranial Meningioma

During the past two decades, SRT has become increasingly well known as a treatment option for meningiomas (16, 17). Adjuvant SRT is offered to all grades II and III meningioma patients, whereas symptomatic grade I meningioma patients only received SRT after incomplete resection. Inoperable grade I (symptomatic only), grades II and III meningioma are treated with primary SRT. SRT was performed using the stereotactic radiosurgery system Novalis™ (BrainLAB, Feldkirchen, Germany). Patients were treated on consecutive workdays, with one fraction per day (see text footnote 1). SRT was mostly given in 28, 30, or 25 fractions to a median reference dose of 54.0 Gy.

Scientific Objective of the Retrospective Analysis

Based on the example of 251 patients with 275 intracranial meningiomas treated between January 2002 and January 2015

---

[1]Lubgan D, Rutzner S, Semrau S, Lambrecht U, Roessler K, Buchfelder M, et al. Effective long-term local results and prognostic factors after fractionated stereotactic radiotherapy of 257 intracranial meningeoma. *J Neuro Oncol* (submitted for publication).

with SRT at the department of Radiation Oncology of the UKER, we have illustrated the workflow of manual and electronical supported data retrieval for this analysis. For determination of efficacy of SRT on long-term outcome (e.g., overall survival, local control), the relevant parameters (age, gender, tumor localization, WHO grading, and current disorders after radiotherapy), data of the computed tomography (CT) or magnetic resonance (MR) imaging (to determine the tumor status after therapy), and temporal dose distribution [fractionation, target volume (PTV), dose distribution of risk organs] were evaluated.

Workflow of Manual and Electronical Supported Data Collection for Retrospective Analysis

Manual Data Retrieval

For the purpose of retrospective analysis, the Department of Radiation Oncology begins with specifying the research question and defining the patient collective. Here, the patient collective was identified by multiple reference sources (e.g., outdated medical records and databases, institutional statistics) and manually summarized in a separate chart (Microsoft Excel 2010). All medical data in the routine CISs and necessary data elements for each patient were manually and separately noted in an electronic document using Microsoft Excel 2010. The systems used for manual analysis are listed in **Table 1**.

To evaluate the time required for manual data retrieval, we documented the time needed to collect all necessary data elements from clinical source systems and manually transcribed them into an Excel spreadsheet.

Electronically Supported Data Retrieval

In order to simplify retrospective analysis, we decided to use a tool that obtains routine clinical data from multiple CISs for secondary use. Since 2003, the UKER provides the clinical DWH research platform to scientists for numerous analyses. It has the ability to combine data from multiple clinical source systems and to provide it to the hospital users. The DWH stores

clinical and administrative data from 22 different data sources (e.g. Accounting, Pharmacy, Surgery, Anesthesia, Pathology, and Radiology). For transformation of routine clinical data, it utilizes the open enterprise-class platform Cognos Data Manager. The database language Structured Query Language (SQL) is used for defining data structures, editing, and querying the databases.

We used the DWH for defining a patient collective and obtaining routine clinical data from multiple CISs. The workflow of manual and electronical supported data retrieval for retrospective analysis is illustrated in **Figure 1**.

A database query based on routine clinical data from patient care was initiated to design a core data set for retrospective analysis (date of the last contact, date of the last imaging, life-status, beginning and end of the radiotherapy, fractionation, and dose). Selected data elements and the related data source system are shown in **Table 2**.

The official system which was used for coding of the diagnosis is the 10th Revision of German Modification of the International Statistical Classification of Diseases (ICD-10) and for procedures the German "Operationen- und Prozedurenschlüssel Version 2015."

Currently, not all listed data elements or source systems are accessible for the DWH (e.g., tumor as cause of death in the GDTS, the minimum or maximum dose, PTV-volume, coverage PTV, dose distribution on risk organs documented in the treatment planning software) or there were no suitable methods available for the extraction of the data elements (e.g., tumor localization, WHO grading, or several radiotherapy documented in Soarian® Clinicals) at the time of analysis (**Table 2**). Therefore, they are not included in the electronical analysis.

Integrating OIS MOSAIQ® into the Clinical DWH of the UKER: Reusing Data from the OIS MOSAIQ® for Retrospective Analysis

Since 2012, the Department of Radiation Oncology uses the OIS MOSAIQ® developed by Elekta (Hamburg, Deutschland). It provides medical oncology data (e.g., demographic data,

TABLE 1 | Summary of clinical information systems (CISs) for manual data retrieval to evaluate routine medical data for retrospective analysis of patients with meningioma treated with stereotactic radiotherapy.

Clinical application	Data source	Description
SAP IS-H®	Patient administration	SAP®-based CIS for patient administration and documentation of diagnosis and procedure during the clinical treatment process
Soarian Clinicals®	Electronic health record	Web-based clinical workstation that offers health information in a digital form
Web-RIS®	Imaging	Web-based CIS that offers medical, administrative, and imaging data in the field of radiology
GTDS®	Medical record for tumor documentation	Supports clinical cancer registry and provides information about medical treatment and follow-up
MOSAIQ®	Radiation Oncology	Oncology information system for radiation treatment and the control of the respective linear accelerator. It is integrated with imaging, planning, and therapy systems and contains the planned and actual dispense treatment parameters
Pinnacle³®	Radiation Oncology	Treatment planning software for localization of tumor volumes and verification of the individual radiation treatment plan
I-Plan RT®	Radiation Oncology	Treatment planning software for localization of tumor volumes and verification of the individual radiation treatment plan
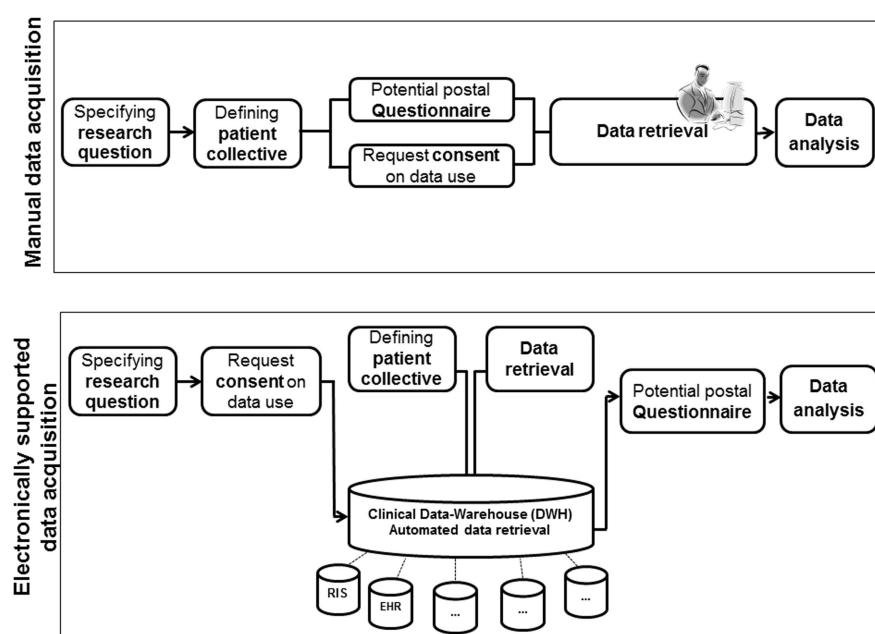
FIGURE 1 | Workflow of manually and electronically [data warehouse (DWH)] supported data retrieval for retrospective analysis.

diagnoses, beginning and end of the radiotherapy, planned and administered fractionation and doses), regulates the respective linear accelerator, and is linked to imaging, planning, and therapy systems.

In order to make irradiation data available for retrospective analysis, we analyzed the table structure from the clinical system and transferred a copy of relevant data tables as read-only user during the non-productive clinical stage of radiotherapy (after 5 p.m.) into the staging area of the DWH. This process is called "*extraction*." As a next step, we queried the DWH to select patients with a diagnosis of meningioma (ICD10-GM code D32.0, D32.9, C70.0, C70.9) and to identify the data elements *beginning and end of the radiotherapy*, *planned and administered fractionation and dose distribution*. Subsequently, we compared the results of the data base query and the manual data retrieval.

In addition, unnecessary or inconsistent data can be corrected or extinguished at the staging area. This process is called "*transformation*." The entire process is called *ETL* (*extraction, transformation, loading*) (18). The structure of the DWH and technical implementation of the clinical source system MOSAIQ® is illustrated in **Figure 2**.

Statistical Analysis and Ethics Committee Vote

Standard summary statistics and two-tailed 95% confidence intervals were calculated as appropriate. All statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (IBM Corp., Armonk, NY, USA). The level of significance for all analyses was set at $\alpha = 0.05$ (two-tailed).

Our institution obtained a positive ethics committee vote from the ethical review board for our research

(reference number 347_16 Bc). All data used for the retrospective analysis was in anonymized form.

RESULTS

Effectiveness of Patient Data Collection—DWH

A total amount of 275 data sets (case ID) from 251 (patients ID) patients were manually collected and stored in a Microsoft Excel spreadsheet. We counted 275 data sets (case ID) due to the fact that some patients had more than one lesion and thus were irradiated at multiple times.

Two hundred seventy-four electronic data sets (100%) from 250 patients were electronically collected because one patients' data were not available for data protection reasons. The data congruence of the data elements "*beginning and end of the radiotherapy*, *date of the last contact*, *date of the last imaging and life-status (alive, dead)*," were evaluated on the basis of manual data retrieval compared with the results of the DWH report.

Manual Data Retrieval Compared with the Results of the DWH Report

The summary of selected data elements determined by manual and electronical supported data retrieval is shown in **Table 3**.

Data Element "Beginning of the Radiotherapy" and "End of Radiotherapy"

Two hundred fifty-two (92.0%) for manual and 257 (93.8%) for the electronical method out of 274 (100%) data elements "beginning of the radiotherapy" and "end of the radiotherapy" were

TABLE 2 | Overview of selected data elements and the related data source system for retrospective analysis.

Data element	Description	Data type	Data source
Beginning of radiotherapy	First day of radiotherapy	Date [TT.MM.JJJJ]	SAP IS-H®
End of radiotherapy	Last day of radiotherapy	Date [TT.MM.JJJJ]	SAP IS-H®
Beginning of radiotherapy	First day of radiotherapy	Date [TT.MM.JJJJ]	MOSAIQ®
End of radiotherapy	Last day of radiotherapy	Date [TT.MM.JJJJ]	MOSAIQ®
Fractionation	Distribution of the total dose in separate doses	Numeric	MOSAIQ®
Dose	Dose value in Gy	Numeric [Gy]	MOSAIQ®
Date of last contact	Date of last contact/treatment at the Erlangen University Hospital (UKER)	Date [TT.MM.JJJJ]	SAP IS-H®
Date of the last imaging	Date of the last computed or magnetic resonance tomography of the brain	Date [TT.MM.JJJJ]	SAP IS-H®
Life-status	Date of death	Date [TT.MM.JJJJ]	Soarian Clinicals®
Actual patient contact details[a]	Master data of a patient (street, house number, postcode, and place of residence)	Free text	SAP IS-H®
Death due to tumor[a]	Death caused by tumor	Coded 1 = yes 2 = no 999 = cannot be determined	GTDS®
Tumor localization[a]	Localization of the tumor in the brain	Coded 1 = skull base 2 = falx 3 = convexity 4 = meningeomatosis	Soarian Clinicals® Web-RIS®
Histology/pathology[a]	Resection of the tumor enables the classification of the WHO-Grade (I,II,III)	Coded 1 = WHO I 2 = WHO II 3 = WHO III 999 = cannot be determined	Soarian Clinicals®
Previous radiotherapy[a]	Preceding radiation on the tumor area	Coded 1 = yes 2 = no	Soarian Clinicals® SAP IS-H®
Minimum/maximum dose[a]	Lowermost or paramount dose at radiation volume	Numeric [Gy]	i-Plan RT®, Pinnacle3®
PTV – volume[a]	Size of the planning target volume in cm^3	Numeric [Gy]	i-Plan RT®, Pinnacle3®
Coverage PTV[a]	Proportion of the target volume within the reference isodose	Numeric [Gy]	i-Plan RT®, Pinnacle3®
Dose distribution on risk organs[a]	Tolerance dose on the critical organs (opticus right/left, chiasm, hippocampus)	Numeric [Gy]	i-Plan RT®, Pinnacle3®

[a]Not included in the electronical [data warehouse (DWH)] analysis (currently not all listed data elements are accessible for the DWH or there were no suitable methods available for the extraction of the data elements).

identical. Thirty-nine (22 manual, 17 electronical) data elements were not identical.

Deviating results are more often generated by the manual than the electronical data retrieval method. Manual data retrieval produced 22/274 (8%) deviating results: this difference was caused by the fact that in 22 cases the treatment date of radiation was incorrectly documented in the discharge letter and the incorrect dates were transferred into the Microsoft Excel spreadsheet.

The DWH determined the correct treatment date for these 22 patients. However, the DWH query produced 17/274 (6.2%) deviating results due to an error in the data base query. The query was carried out patient-based (patients ID) instead of case-based (case ID). If a patient (patients ID) was treated multiple times over several years (case ID) only the latest "date of beginning and the end" was identified. For a flawless determination of the treatment (case ID), date the SQL statement of the data base query has to be adjusted for future data exports.

Data Element "Date of the Last Imaging"

Of the 274, 248 (90.5%) by manual and 236 (86.1%) by electronical retrieval data elements were identical.

Differing results are more often generated by the electronical (38/274) than the manual (26/274) data retrieval method. Manual data retrieval produced 9.5% of inconsistent data: this difference
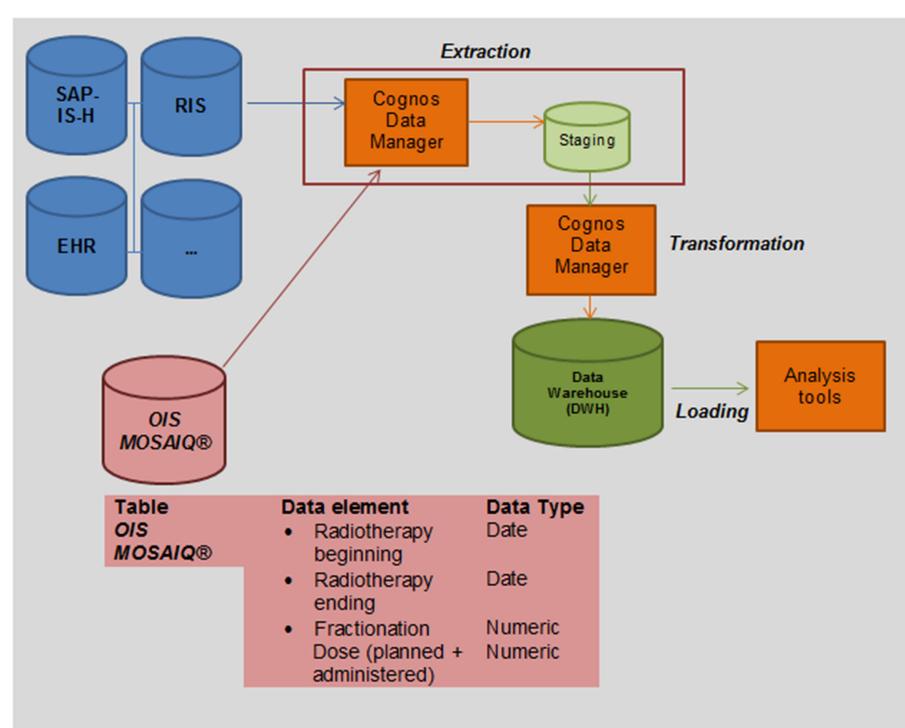
FIGURE 2 | Integrating Oncology Information System (OIS) MOSAIQ® into the clinical data warehouse (DWH) of the UKER for secondary use: we transferred a copy of relevant data tables as read-only user during the non-productive clinical stage of radiotherapy (after 5 p.m.) into the staging area of the DWH (extraction). As a next step, we queried the DWH to identify relevant data elements (beginning and end of the radiotherapy, fractionation and dose).

TABLE 3 | The comparison of manual data retrieval and the result of the data warehouse report.

Data element	Data type	Data source *manual* correctness of the data (%)	Data source *electronical* correctness of the data (%)	Data source *MOSAIQ®* correctness of the data (%)
Beginning of radiotherapy = first day of radiotherapy	Date [TT.MM.JJJJ]	252/274 (92.0)	257/274 (93.8)	
End of radiotherapy = last day of radiotherapy	Date [TT.MM.JJJJ]	252/274 (92.0)	257/274 (93.8)	
Beginning of radiotherapy = first day of radiotherapy	Date [TT.MM.JJJJ]	88/110 (80.0)		110/110 (100)
End of radiotherapy = last day of radiotherapy	Date [TT.MM.JJJJ]	88/110 (80.0)		110/110 (100)
Fractionation = distribution of the total dose in separate doses	Numeric	70/74 (94.6)		74/74 (100)
Dose = dispense dose value in Gy	Numeric [Gy]	70/74 (94.6)		74/74 (100)
Date of the last imaging = date of the last magnetic resonance or computed tomography imaging	Date [TT.MM.JJJJ]	248/274 (90.5)	236/274 (86.1)	
Date of last contact = date of the last contact/treatment at the UKER	Date [TT.MM.JJJJ]	232/274 (84.7)	274/274 (100)	
Life-status = date of death	Date [TT.MM.JJJJ] manual coded 0 = dead 1 = alive	14/14 (100)	7/14 (50.0)	

χ^2 test data source manual compared to data source electronical (MOSAIQ® included) $p = 0.009$.
Data are number of data elements (%) unless otherwise stated. p-value: analysis of covariance, χ^2 test in case of categorical data.

was caused by the fact that over the course of time of manual data retrieval, an additional imaging was performed for 26 patients; thus, manually collected data were already outdated.

The DWH report determined 38 cases (13.9%) of diverging data: for 38 patients an imaging was performed at an external hospital. The information about external imaging is not

accessible by a database query as it is based on the documented procedure code in the source system of the UKER.

Data Element "Date of the Last Contact"

All data elements collected electronical were identical. Deviating results are only caused by the manual (42/274, 15.3%) data retrieval method. There were two reasons for this: first, for 18 patients the date of the last contact was incorrectly transferred from the source system into the Excel spreadsheet. Second, during the time of analysis, 24 patients were being treated again in another department at the UKER, and subsequently, manually collected data were already outdated.

Data Element "Life-Status"

Overall 14 (5.6%) of 251 evaluated patients died. For all 14 patients, the day of death was manually collected. Seven (50.0% of all deceased) patients were overlooked by the DWH report because no information about their death was documented in the EHR (Soarian® Clinicals) as the date of death is only documented for patients who died at the UKER.

Effectiveness of Patient Data Collection—OIS

Fractionated SRT is documented in the OIS MOSAIQ® since June 2012. We identified 110 suitable values for 74 patients (74 stereotactic irradiation + 36 data values for boost irradiation) since the system went into operation at the department of Radiation Oncology and transferred them into the DWH. We collected the data elements "beginning and end of radiotherapy, distributed dose and fractionation" by querying the DWH and compared the results with the manual data retrieval.

Manual Data Retrieval Compared with the Results of the Mosaiq® Report

Data Element "Beginning of the Radiotherapy" and "End of Radiotherapy"

Differing results were only caused by the manual data collection method (22/110): due to an incorrect date in the medical discharge letter manually retrieved data produced the deviating data for the beginning of radiotherapy and for the end of radiotherapy.

There were no deviating results by querying the source system MOSAIQ® (DWH report) because the linear accelerator is regulated by the OIS that uses validation rules for data entry for every single fractionation in the primary source system.

Data Element "Administered Dose and Fractionation"

In all, 94.6% (70/74) data elements were identical. The manual data retrieval methods lead to 4 (5.4%) deviating results because a medical physicist determined 4 false data elements of administered dose and fractionation on the basis of the paper-based health record, OIS MOSAIQ® and the treatment planning systems I-plan RT® or Pinnacle³®. There were no deviating results by querying the source system MOSAIQ® (DWH report).

Time Invested in Manual Data Retrieval
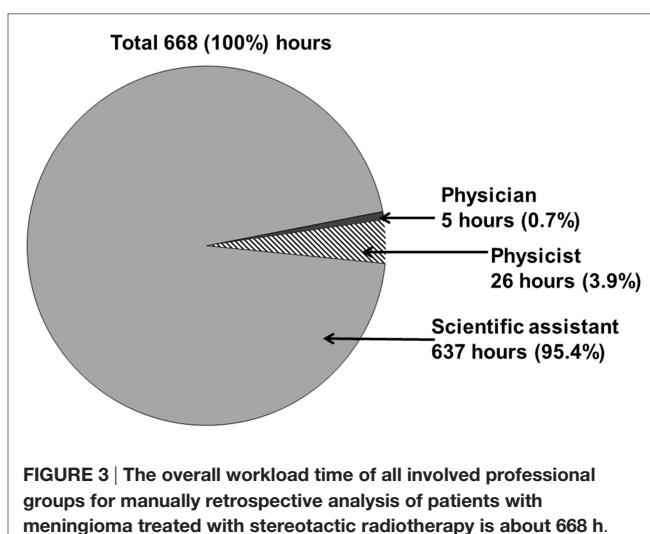
To evaluate the time required for manual data retrieval, we documented the time needed to collect all necessary data elements from clinical source systems and manually transmit them into a Microsoft Excel spreadsheet. The manual data retrieval required 668 h (**Figure 3**). The collection of all data elements took place over an extended period of time of about 24 weeks.

The scientific assistant required the largest amount of time while manually collecting routine clinical data in 637 h (95.4%) The support of a physician (5 h, 0.7%) and a medical physicist (26 h, 3.9%) was required (**Figure 3**). The physician analyzed actual MR or CT imaging (to determine localization, relapse, and progression of the tumor) and the medical physicist evaluated necessary data elements (PTV volume, fractionation, doses, minimum/maximum dose, coverage PTV, dose distribution of risk organs) on the basis of the paper-based health record and the treatment planning systems I-plan RT® or Pinnacle³®.

Time Consumption for Electronical Data Retrieval

In collaboration with a computer scientist of the Department of Medical Informatics and two scientific assistants of the Department of Radiation Oncology of the UKER, the DWH report was developed. Implementing the DWH query took 30 h that are composed of the definition, adjustment, and execution of the database query. For administrative activities (e.g., obtaining permission for data access by those departments of the UKER, which were involved in the patients' treatment), we need additional 5 h.

The support of a medical physicist was not required to evaluate data elements (beginning and end of radiotherapy, administered fractionation, and dose) on the basis of the paper-based health record and the treatment planning systems I-plan RT® or Pinnacle³®. For evaluating the data elements (PTV volume, minimum/maximum dose, coverage PTV, dose distribution of

FIGURE 3 | The overall workload time of all involved professional groups for manually retrospective analysis of patients with meningioma treated with stereotactic radiotherapy is about 668 h.

risk organs), the support of the medical physicist (approximately 20 h) and a physician (5 h) to analyze actual MR or CT imaging is still required.

DISCUSSION

The purpose of this study is to verify possible benefits of a clinical DWH for retrospective analysis in the field of radiation oncology.

We compared two different methods of collecting routine clinical data: manually and electronically using DHW for secondary use of the scientific retrospective analysis.

In summary, our results indicated that the electronically supported data retrieval (DWH) showed an average of 93.9% correct data and a significantly better ($p = 0.009$) result compared to manual data retrieval (91.2%). Using a research, database (DWH) replaces manual activities and offers the ability to significantly reduce data collection time and labor while improving data quality. However, data integrity depends on the quality of a structured routine clinical documentation as well as the system requirements to get access to medical data in the clinical source systems. Furthermore, expert knowledge for the transformation of routine clinical data is necessary in practice.

In our study, manual data retrieval needed significantly more overall workload time (668 h) of all involved professional groups compared to implementing the DWH query (30 h). We needed the support of a physician (5 h) to manually analyze CT or MR imaging and a medical physicist (26 h) for evaluating necessary irradiation data elements (fractionation, dose distribution, coverage/PTV volume, minimum/maximum dose, dose distribution at risk organs). Up to now, the support of a physician (5 h) to analyze actual MR or CT imaging is still required. In order to completely automate the assignment of the medical physicist for retrospective analysis (evaluating the data elements coverage/PTV-volume, minimum/maximum dose, dose distribution at risk organs), the departmental planning-systems I-plan® RT and Pinnacle3® need to be made accessible for the DWH.

In addition, the long period of time necessary for retrieving data manually produced outdated databases and caused errors when transmitting data into an electronic format such as Microsoft Excel, which became evident in some cases of our study. Furthermore, data retrieval errors can easily be introduced because medical record data are not guaranteed to be accurate (e.g., incorrectly documented treatment date of radiation in the discharge letter of radiotherapy) and depend on the care and knowledge level of the scientific assistant. A related study by Roelofs et al. [19] that examined the benefit of a clinical DWH combined with tools for extraction of relevant parameters data for a radiotherapy trial supports this point of view. A DWH is beneficial for data collection time in addition to offering the ability to improve data quality.

Besides of benefits of data collection times and improving data quality, the strength of a DWH its ability to combine data from multiple clinical source systems and make it easily accessible for researchers. Though, before using routine data for research purposes, it is important to carefully verify this data and determine data integrity. In this context, Galster [20] has reviewed existing barriers for reusing routine data, he came to the conclusion that clinical data are not available when or where it is needed, even though data is present, the usage of the existing source is prohibited or cannot be routinely used in its available form. In our study, there are regulatory requirements and institutional agreements that need to be reconciled from the departments of the UKER that are involved in the patients' treatment in order to use clinical routine data for clinical research activities.

Next to the challenges of gaining access to multiple data sources, another major barrier for data reuse is the fact that routine data cannot be used in its available form. Usually, clinical data are distributed across several tables in a generic form with coded values [21]. In our analysis, some data (e.g., tumor localization, histology/pathology) are semi-structured values (mostly free-text format) and therefore can't be used for automatically analysis. The data recorded in structured fields are more readily to be extracted from an EHR than data that was recorded in free text notes. Therefore, expert knowledge for the transformation of this data is necessary, and the accuracy of database queries mainly depends on a specific SQL statement. In addition, EHR data are frequently recorded inconsistently in a variety of formats that are complex, inaccurate, and often incomplete [22]. For our study, it is a necessary condition that medical data are recorded completely in a specific data schema in order to automatically capture as much information as possible for retrospective analysis.

Furthermore, EHRs often do not tell a complete patient story, whether it may be those of a single institution or those aggregated across institutions [23]. An example for this problem in our study is the date of death that is only documented in the clinical source system (EHR) for patients who died at the UKER. Moreover, the information about an external imaging is not routinely documented in a coded form in the EHR and is therefore not accessible for database queries. Consequently, medical details from external sources (e.g., life status in the GTDS®, imaging at an external hospital) must be requested or made available for automated data abstraction. This would be worthwhile in order to determine a patients' life status as an electronical life-status comparison with the residents' registration offices is prohibited due to privacy policy since 2008 and an amendment to the Bavarian Cancer Registry is made for provision in 2016 [24]. To keep the medical routine data up to date, we send a specially designed questionnaire to the patients in order to assess the health-related outcome that are completed by patients themselves.

Additionally, routine clinical documentation in the primary source systems affects the research outcome: data quality for retrospective analysis is only as good as the routine clinical documentation in the primary source systems e.g., EHR. Therefore, Kessel et al. [5] have developed a professional data-based documentation system for analysis purposes where information about radiation therapy, diagnostic images, and dose distributions has been imported into a web-based system. They showed that the central storage of data outside of EHR leads to benefits of digital management, data analysis, and reusability of the results. In this context, Kirrmann et al. [9]

TABLE 4 | Limitations for using a data warehouse (DWH) for retrospective analysis in the radiation oncology field.

Limitations	Example in our study	Potential solution	Benefit
Restricted data access	• Regulatory requirements and institutional agreements need to be reconciled from those departments, which were involved in the patients' treatment	• Amendment of agreement between the departments of UKER about using clinical routine data for clinical research activities	• Data integrity
Variety of data formats	• Data cannot be routinely used in its available form: expert knowledge for the transformation of this data is necessary	• Implementing data standards for the secondary use of health data to support clinical research	• Availability of all data elements for retrospective analysis
Data quality of routine clinical documentation	• Medical data generated in the clinical treatment process are not guaranteed to be accurate • Electronic health records often do not tell a complete patient story: e.g., life-status (GTDS®), imaging (e.g., computed tomography/MRT) at an external hospital	• Using original and unprepared data from primary source systems • Making external source systems (e.g., GTDS®) accessible for the DWH • Request external sources	• Higher data quality • Data integrity

developed and described a flexible browser based reporting and visualization system for clinical and scientific use by linking web-services/MOSAIQ®, the physician letter system MEDATEC, and central server MiraPlus (laboratory, pathology and radiology). They reported that all relevant data were available at all times in a simple manner, which improved their effectiveness resulting in a considerable amount of time saving.

In this context, one benefit of our retrospective analysis was that the gain of access to radiotherapy data from the clinical source system MOSAIQ®. Besides the data sets "beginning and the end of radiotherapy" for evaluating treatment outcomes of patients with meningioma, we also extracted irradiation parameters "planned and effectively implemented fractionation and dosage distribution" from the existing primary source (OIS). Due to the fact that the linear accelerator and the OIS both use validation rules for data entry in the primary source system, original routine data are not subsequently changed. As we have shown in our analysis, using original and unprepared data leads to a higher percentage of accurate data.

A summary of described limitations and potential solutions using a DWH are shown in **Table 4**.

Although only a selected data set of the evaluation of patients with meningioma was examined and not all data were directly available in a DWH, our present study highlights the benefit of electronical supported data retrieval for secondary use. Thus, our goal is to adapt our approach to other types of tumors in radiation oncology and extract more parameters from the existing routine care documentation systems.

CONCLUSION

Our present study shows that a DWH is particularly beneficial for retrospective analysis in the field of radiation oncology. Routine clinical data for a large patient group can be provided

ready for analysis to the scientific operator, and data collection time can be reduced significantly. Furthermore, using a DWH provides the ability to improve data quality for retrospective analysis; thus, future research can be simplified. However, expert knowledge for the transformation of routine clinical data is still necessary and the quality of a structured routine clinical documentation in the CISs as well as the system requirements allowing access to medical data also affect the outcome.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethical review board of the Friedrich-Alexander-University of Erlangen-Nuremberg (FAU) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethical review board of the Friedrich-Alexander-University of Erlangen-Nuremberg (FAU) (reference number 347_16 Bc).

AUTHOR CONTRIBUTIONS

SR: conducted data analysis, described throughout the manuscript, and major contributor to the writing of the manuscript and literature search. RF: clinical oncologist and principal of the research organization, involved in the design of the study, and reviewed the manuscript. TG: made substantial contributions to the acquisition of data, developed the data warehouse report, and reviewed the manuscript. H-UP: was involved in the design of the study and reviewed the manuscript. DL: major contributor to the writing of the manuscript, supervised the study, and major contributor to organization of the data analysis and manuscript. All authors read and approved the manuscript.

REFERENCES

1. Dentler K, ten Teije A, de Keizer N, Cornet R. Barriers to the reuse of routinely recorded clinical data: a field report. *Stud Health Technol Inform* (2013) 192:313–7. doi:10.3233/978-1-61499-289-9-313

2. Hailemichael MA, Marco-Ruiz L, Bellika JG. Privacy-preserving statistical query and processing on distributed OpenEHR data. *Stud Health Technol Inform* (2015) 210:766–70. doi:10.3233/978-1-61499-512-8-766

3. Rosolski T, Hergert M, Mauermann K, Blomel D. Präklinisches management von TIA/Insult/Blutung: Eine retrospektive Analyse von drei

aufeinanderfolgenden Jahren. *Der Notarzt* (2003) 19(03):114–9. doi:10.1055/s-2003-39534

4. Miriovsky BJ, Shulman LN, Abernethy AP. Importance of health information technology, electronic health records, and continuously aggregating data to comparative effectiveness research and learning health care. *J Clin Oncol* (2012) 30(34):4243–8. doi:10.1200/JCO.2012.42.8011

5. Kessel K, Habermehl D, Bohn C, Jäger A, Floca R, Zhang L, et al. Datenbankbasierte digitale retrospektive Auswertung von Patientenkollektiven in der Radioonkologie. *Strahlentherapie und Onkologie* (2012) 188(12):1119–24. doi:10.1007/s00066-012-0214-0

6. Davies JM, Gao W, Sleeman KE, Lindsey K, Murtagh FE, Teno JM, et al. Using routine data to improve palliative and end of life care. *BMJ Support Palliat Care* (2016) 6:257–62. doi:10.1136/bmjspcare-2015-000994

7. Hackl WO, Ammenwerth E. SPIRIT: systematic planning of intelligent reuse of integrated clinical routine data. A conceptual best-practice framework and procedure model. *Methods Inf Med* (2016) 55(2):114–24. doi:10.3414/ME15-01-0045

8. Richesson RL, Andrews JE, Krischer JP. Use of SNOMED CT to represent clinical research data: a semantic characterization of data items on case report forms in vasculitis research. *J Am Med Inform Assoc* (2006) 13(5):536–46. doi:10.1197/jamia.M2093

9. Kirrmann S, Gainey M, Röhner F, Hall M, Bruggmoser G, Schmucker M, et al. Visualization of data in radiotherapy using web services for optimization of workflow. *Radiat Oncol* (2015) 10(1):1. doi:10.1186/s13014-014-0322-3

10. Prokosch H-U, Ganslandt T. Perspectives for medical informatics – reusing the electronic medical record for clinical research. *Methods Inf Med* (2009) 48(1):38–44. doi:10.3414/ME9132

11. Wagner S, Beckmann MW, Wullich B, Seggewies C, Ries M, Burkle T, et al. Analysis and classification of oncology activities on the way to workflow based single source documentation in clinical information systems. *BMC Med Inform Decis Mak* (2015) 15:107. doi:10.1186/s12911-015-0231-x

12. Ries M, Prokosch H-U, Beckmann MW, Bürkle T. Single-source tumor documentation-reusing oncology data for different purposes. *Oncol Res Treatment* (2013) 36(3):136–41. doi:10.1159/000348528

13. Köpcke F, Kraus S, Scholler A, Nau C, Schüttler J, Prokosch H-U, et al. Secondary use of routinely collected patient data in a clinical trial: an evaluation of the effects on patient recruitment and data acquisition. *Int J Med Inform* (2013) 82(3):185–92. doi:10.1016/j.ijmedinf.2012.11.008

14. Jyoti B, Munjal R, Upasna S. Investigation into data warehouse to meet the growing demand of information analysis. *Int J Adv Res Comp Sci Manag Stud* (2015) 3(8):45–8.

15. Universitätsklinikum Erlangen (UKER). *Universitätsklinikum Erlangen, Zahlen und Fakten.* (2016). Available from: http://www.uk-erlangen.de/presse-und-oeffentlichkeit/zahlen-und-fakten/

16. El-Khatib M, El Majdoub F, Hunsche S, Hoevels M, Kocher M, Sturm V, et al. Stereotactic LINAC radiosurgery for the treatment of typical intracranial meningiomas. Efficacy and safety after a follow-up of over 12 years. *Strahlenther Onkol* (2015) 191(12):921–7. doi:10.1007/s00066-015-0880-9

17. Maranzano E, Draghini L, Casale M, Arcidiacono F, Anselmo P, Trippa F, et al. Long-term outcome of moderate hypofractionated stereotactic radiotherapy for meningiomas. *Strahlenther Onkol* (2015) 191(12):953–60. doi:10.1007/s00066-015-0915-2

18. Mate S, Kopcke F, Toddenroth D, Martin M, Prokosch HU, Burkle T, et al. Ontology-based data integration between clinical and research systems. *PLoS One* (2015) 10:e0116656. doi:10.1371/journal.pone.0122172

19. Roelofs E, Persoon L, Nijsten S, Wiessler W, Dekker A, Lambin P. Benefits of a clinical data warehouse with data mining tools to collect data for a radiotherapy trial. *Radiother Oncol* (2013) 108(1):174–9. doi:10.1016/j.radonc.2012.09.019

20. Galster G. Why is clinical information not reused. *Stud Health Technol Inform* (2012) 180:624–8. doi:10.3233/978-1-61499-101-4-624

21. Johnson SB, Chatziantoniou D. Extended SQL for manipulating clinical warehouse data. *Proc AMIA Symp* (1999):819–23.

22. Hripcsak G, Albers DJ. Next-generation phenotyping of electronic health records. *J Am Med Inform Assoc* (2013) 20(1):117–21. doi:10.1136/amiajnl-2012-001145

23. Hersh WR, Weiner MG, Embi PJ, Logan JR, Payne PR, Bernstam EV, et al. Caveats for the use of operational electronic health record data in comparative effectiveness research. *Med Care* (2013) 51(8):S30–7. doi:10.1097/MLR.0b013e31829b1dbd

24. Bayerischer Rechts- und Verwaltungsreport (BayRVR). *Staatskanzlei: Kabinett beschließt Bayerisches Krebsregistergesetz.* (2016). Available from: http://bayrvr.de/2016/05/10/staatskanzlei-kabinett-beschliesst-bayerisches-krebsregistergesetz/

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Integrating Hyperthermia into Modern Radiation Oncology: What Evidence Is Necessary?

Jan C. Peeken[1], Peter Vaupel[1] and Stephanie E. Combs[1,2]*

[1] Department of Radiation Oncology, Klinikum rechts der Isar, Technische Universität München, München, Germany,
[2] Department of Radiation Sciences (DRS), Institute of Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Neuherberg, Germany

Hyperthermia (HT) is one of the hot topics that have been discussed over decades. However, it never made its way into primetime. The basic biological rationale of heat to enhance the effect of radiation, chemotherapeutic agents, and immunotherapy is evident. Preclinical work has confirmed this effect. HT may trigger changes in perfusion and oxygenation as well as inhibition of DNA repair mechanisms. Moreover, there is evidence for immune stimulation and the induction of systemic immune responses. Despite the increasing number of solid clinical studies, only few centers have included this adjuvant treatment into their repertoire. Over the years, abundant prospective and randomized clinical data have emerged demonstrating a clear benefit of combined HT and radiotherapy for multiple entities such as superficial breast cancer recurrences, cervix carcinoma, or cancers of the head and neck. Regarding less investigated indications, the existing data are promising and more clinical trials are currently recruiting patients. How do we proceed from here? Preclinical evidence is present. Multiple indications benefit from additional HT in the clinical setting. This article summarizes the present evidence and develops ideas for future research.

Keywords: hyperthermia, radiation oncology, reirradiation, infrared-A, thermoradiotherapy

INTRODUCTION

Hyperthermia (HT) is defined as an exogenous, supraphysiological elevation of tissue/body temperature. The beginning of modern HT dates back to the 1700s when remissions of malignant tumors were repeatedly associated with concomitant bacterial infections. This effect was first systematically investigated at the break of the 19th century by Coley (1). Patients with unresectable sarcomas received injections of bacterial vaccines for fever induction. In total, a cure rate of 20% was achieved (2). It took several decades of technological developments for local/locoregional heat application until HT alone became available for clinical application.

Abbreviations: BT, brachytherapy; CT, chemotherapy; DFS, disease-free survival; EBRT, external beam radiotherapy; HPV, human papilloma virus; HR, hazard ratio; HSP, heat shock protein; HT, hyperthermia; HTP, hyperthermia treatment planning; LC, local control; NK, natural killer; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OR, odds ratio; pCR, pathologic complete response; PFS, progression-free survival; RR, risk ratio; RT, radiation therapy; RTHT, thermoradiotherapy; RTCT, chemoradiotherapy; RTHTCT, thermochemoradiotherapy; SAR, specific absorption rate; TER, thermal enhancement ratio; TRTP, thermoradiotherapy planning; TTP, time to progression; WBHT, whole-body hyperthermia; wIRA, water-filtered infrared-A; y, year.

Nowadays, HT is either administered independently or, more often, in combination with radiotherapy (RT) or chemotherapy (CT). HT alone is being used for direct ablation of single tumor lesions with temperatures exceeding 50°C. Multiple techniques are being used to obtain necessary temperature coverage such as high-intensity focused ultrasound and radiofrequency-, microwave-, or infrared laser-based heating *via* ablation catheters directly inserted into the tumor (3).

In bimodal treatment schemes such as thermoradiotherapy (RTHT) and chemoradiotherapy (RTCT) as well as in trimodal thermochemoradiotherapy (RTHTCT), HT is utilized for augmentation of treatment effects of the concomitant oncological therapy. Necessary tissue temperatures are significantly lower ranging from 39 to 43°C (4, 5).

In this literature-based review, a brief introduction to HT physiology, cell biology, and immune response is given to examine the underlying modes of action of HT. Currently used HT techniques for heat delivery and temperature control are described. The clinical evidence of combining RT with HT is summarized and sorted per tumor entity. To this end, a PubMed search was conducted searching for the term "hyperthermia" in combination with tumor entities treatable by RT, and terms describing technical aspects such as "biology," "physiology," "chemotherapy," and "radiation therapy." Special emphasis is given to recent meta-analyses and published prospective trials.

PRECLINICAL EVIDENCE

Changes in Perfusion and Oxygenation

Data and the respective interpretation of HT-induced changes in perfusion and oxygenation remain controversial and are briefly described in the following. A comprehensive review of this topic has been published by Vaupel and Kelleher (6). There is evidence that mild HT can increase blood perfusion of the heated tissue, preferentially at the beginning of tumor heating (7, 8). It has been reported that this can lead to increased oxygen delivery *via* an improvement of microcirculation (9). This is especially true in cases when the oxygen demand of the tissue is reduced. It has been proposed that direct heat-dependent cell killing and loss of mitochondrial membrane potential contribute to this phenomenon (10, 11). On the contrary, other studies showed increased oxygen consumption at elevated tissue temperature (van't Hoff's law!) counteracting the oxygenating effect of increased perfusion (12). An increase in oxygen availability may favor oxygenation of hypoxic cells (7). The effect appears to be preferentially in diffusion-limited, chronic hypoxia (13, 14). Whether the radiosensitizing effect outlasts the time frame of increased perfusion remains so far unclear. Some studies have reported increased perfusion extending over 24 h after HT, which would benefit following RT/CT sessions (15, 16). Other studies could not reproduce this result (17). As hypoxia is a central causative factor for radioresistance, a decrease in hypoxia by HT may be responsible for the observed radiosensitization.

Induction of Cell Death

Hyperthermia has been shown to confer cell death by apoptosis or mitotic catastrophe (18, 19). It has been reported that HT triggers unfolding of especially heat-labile non-histone nuclear proteins leading to aggregation, due to exposition of hydrophobic groups, with surrounding proteins and subsequent association with the nuclear matrix. As consequence, basic nuclear matrix-dependent functions such as transcription, replication, or DNA repair are impaired (20, 21). Malfunction of DNA replication finally causes chromosome aberrations, genome instability, and cell death by mitotic catastrophe (22). Apoptosis may be mediated by cell death membrane receptor activation and subsequent caspase 3 activation (23). The extent of apoptosis appears to differ among different tumor types (24). In addition, the permeability of the cellular and mitochondrial membranes is altered leading to cellular Ca^{2+}-spikes as well as mitochondrial depolarization with resulting bursts of reactive oxygen species. Both mechanisms may further enhance protein instability and apoptosis (25–27).

Inhibition of DNA Repair Mechanisms

As mentioned above, there is sufficient evidence showing inhibition of DNA repair mechanisms upon HT. Krawczyk et al. have demonstrated inhibition of homologous recombination at clinically achievable mild HT temperatures (41–42.5°C) associated with BRCA2 degradation and its reduced accumulation at double-strand break sites (28). Further on, HT impairs the function of the Ku heterodimer by reducing its DNA-binding capacity and preventing the initiation of non-homologous end joining at DNA double-strand breaks sites (29). In addition, base excision after cell radiation has been shown to be reduced upon heat administration (30). In summary, HT acts on multiple levels including excision repair, non-homologous end joining, and homologous recombination influencing the repair of DNA lesions as well as single-strand and double-strand breaks (29–31). As a consequence, the effects of DNA damaging treatments such as CT or RT are enhanced. A more detailed review was recently published discussing existing evidence (32).

Immune Stimulation

Besides direct effects on cell metabolism, HT appears to trigger multiple immune responses on local and systemic levels. Toraya-Brown and Fiering published a thorough review covering this aspect (33). In summary, HT increases expression of immunogenic surface receptors such as MICA and MHC-I enhancing effectiveness and function of natural killer (NK) cells and of CD8+ cells, respectively (34, 35). The expression of heat shock proteins (HSPs) such as HSP70 is increased. After binding intracellular proteins, HSPs get secreted stimulating the activity of NK cell- and antigen-presenting dendritic cells (36, 37). Presentation of these tumor antigens can cause specific antitumor immune responses effected by CD8+ cells (38). Tumor antigens are also provided by increased release of exosomes (39). Direct enhancement of immunogenic activity of leukocytes is mediated by increased lysis acitivy of NK cells, activation of macrophages, maturation of dendritic cells, and increased IFNy production as well as cytotoxicity of CD8+ cells (34, 40–42). In addition, immune cell trafficking is enhanced by increased perfusion and permeability (43). Following elevated intratumoral IL-6 signaling, it may further be facilitated by increased cell adhesion molecule expression such as ICAM-I (44).

HEAT DELIVERY AND TEMPERATURE CONTROL

Heating Techniques

Heating techniques can be divided by the size, penetration depth, and region of energy deposition. Local or regional HT is mostly used to enhance local therapy such as RT or CT. Alternatively, hyperthermic isolated limb perfusion to administer CT agents is performed. Whole-body hyperthermia (WBHT) has been applied either alone or in combination with CT for the treatment of metastatic disease. Different approaches including capacitive, radiative, infrared-A, or ultrasound have been used for clinical HT treatments (45). The clinically most relevant methods are described in the following.

Capacitive Heating Systems

Capacitive heating systems work with two electrodes positioned on both sites of the body with direct body contact using a water bolus. Heat is induced by the resulting currents and is directed toward the smallest electrode (46). Capacitive heating tends to create high power densities around the bolus' edges but good heat coverage of targets inside of the fat layer (47). On the contrary, in obese patients, therapy-limiting local hot spots can occur causing painful subcutaneous burns (48).

Radiative Heating Systems

Radiative heating systems work with frequencies ranging from 75 to 915 MHz (spectrum of radiowaves and microwaves) and use a water bolus for electromagnetic coupling. Compared to capacitive heating, radiative systems appear to yield better power disposition and temperature distribution leading to better target coverage (47). The applicable temperature is sometimes limited due to local temperature hot spots. The accuracy of such systems depends on construction details such as the number, positioning and design of antennas or properties of the water bolus (49). In recent years, increasingly complex systems have been introduced comprising multiple antennas such as the commercially available Sigma applicators, build in a circular arrangement, or the AMC-8 phased array HT system (50, 51). Site-specific systems such as the HYPERcollar3D system, which was developed for the treatment of carcinomas of the head and neck, take into account local characteristics of target areas to optimize temperature coverage (52). Alternatively, antennas can be interstitially implanted or used for endocavitary HT in direct approximation to tumors (45). In order to perform superficial or interstitial HT, heating systems are used applying higher frequencies such as 915 MHz (53).

Walter-Filtered Infrared-A (wIRA)-Based Systems

Walter-filtered infrared-A-based systems have successfully been used for the treatment of superficial tumors (54, 55). Infrared-A radiation is generated by a halogen lamp, passing through a water filter. The range of therapeutically relevant temperatures is limited to a depth of 15–20 mm [with good therapeutic temperature coverage (56)]. Due to the technical setup a very short interval between HT and RT combined with heat isolation procedures enables quasi-simultaneous RTHT, optimizing the synergistic effect (see below).

Pretherapeutic hyperthermia treatment planning can be used to optimize tumor temperatures. It uses dielectric models created on the basis of segmented CT or MRI data assigning literature-based dielectric properties to distinct tissue types. So, the specific absorption rate (SAR) of the respective tissue can be calculated and used for a finite element-based prediction of temperature distributions. In clinical studies, calculated SAR values correlated well with measured SAR values, relative temperature increase and clinical data regarding hot spots in patients with pelvic tumors (57–59).

Treatment Temperatures

Preclinical experiments were initially performed with relatively high temperatures ranging from 43 to 45°C focusing on direct cytotoxic effects. However, in the clinical setting, temperatures above 42.5°C were only achieved in small tumor subvolumes. While trying to reach targeted temperatures, therapy-limiting hotspots occurred causing substantial side effects. In these cases, this led to a reduction of target temperatures or early termination of HT (60, 61). This was regarded as failure of delivering adequate thermal doses, which lead to a rapid decline in HT-usage in the mid-to-late 1990s. It took several more years until the beneficial effects of mild HT (39.5–43°C), as described above, became known. Nowadays, mild HT has become the standard in modern clinical trials and daily clinical usage (5). Modern HT technology has been developed and optimized for minimal hot spot occurrence as a main focus (51, 52). As a consequence, therapy-limitation due to focal hot spots has not been an issue in many recent HT trials (62–64).

Temperature Control

As important as heat generation, measurement of the actual tissue temperature distribution is crucial for effective heating of tumors. A homogenous temperature distribution is necessary for optimal treatment effects. Local dose-limiting hotspots have to be avoided. Originally, temperature assessment was restricted to single-point measurements. It can be performed either invasively by insertion of intratumoral catheters or, as applicable in tumors with close proximity to natural cavities such as rectal, cervical, vaginal, urethral or vesical tumors, equally efficient by endoluminal catheters. Insertion of catheters inherits the risk of complications such as pain, inflammation, or abscess formation (65). Thus, the latter option should be used if possible. In superficial tumors, surface skin measurements by contact electrodes constitute a further alternative. In addition, by using infrared thermography cameras, two-dimensional data can be obtained for superficial tumors even though calibration with contact electrodes is necessary for absolute temperature assessment (56). A promising method for deep temperature monitoring is MRI-guided thermometry capable of measuring three-dimensional temperature distributions non-invasively. Temperature can be measured by exploiting either T1w-imaging, diffusion weighted imaging or proton resonance frequency shift-imaging (66). Proton resonance frequency shift-imaging appears to be the most accurate method in the clinical setting. By combining HT with online MRI thermometry, direct changes of temperature delivery can be performed to optimize temperature distribution and suppress hot spots (67). To this end,

an adaptive iterative algorithm has been developed (68). First studies have confirmed its applicability in the clinical setting (69).

Interval of Administration

In general, a dose–effect relationship of HT has been shown (70). The interval of administration of HT relative to RT has great influence on its effectiveness. The actual effect is quantified with the thermal enhancement ratio (TER) defined as the ratio of the respective radiation doses of RT alone divided by the RT + HT dose necessary to receive equal survival curves (4). However, biological aspects of HT react differently to the extent of heating sequence of HT. In the clinical setting, the maximal achievable TER should be combined with the most limited TER for healthy tissue to retain a tumor-specific effect reducing toxicity.

The inhibition of DNA repair has its highest effect when HT is given simultaneously to RT. The effect declines with the end of DNA repair mechanisms approximately 4 h after RT. However, inhibition of DNA repair mechanisms is not tumor specific since it is also present in normal tissues (71, 72). In contrast, direct cell killing is specific to malignant tissue at target temperatures. The respective TER is estimated at 1.5 deriving most likely from direct radiation-independent cell damage to radioresistant hypoxic cells (73). To summarize, optimal effects can be achieved by simultaneous RTHT treatment with no tumor-directed specificity. Treatment selectiveness would completely depend on accuracy of radiation delivery. In the time frame of 1–4 h before or after radiation, a maximal selective TER can be achieved by adding up DNA repair inhibition and direct cell damage. For optimization of the oxygenation-effect, RT should be applied shortly after HT (72). So far, the shortest interval between HT and RT has been described for wIRA followed by RT (56).

When considering time schedules and fractionation schemes, one should also take into account two phenomena termed cellular and vascular thermotolerance. The underlying mechanisms remain incompletely understood (74–77). For this reason, detailed description of these phenomena is not performed in the context of this review. Most probably, thermotolerance in currently used clinical HT schedules (i.e., once or twice/week) seems to play no limiting role.

CLINICAL EVIDENCE OF COMBINED THERMORADIOTHERAPY

In the following, key studies providing evidence for a clinical benefit of a combined treatment with HT and RT is presented, sorted by tumor entity and the extent of existing evidence (see **Tables 1**–**3** for a detailed overview). In the following paragraph, existing clinical evidence of combined HT with CT is summarized (see **Table 4**).

Breast Cancer

Breast cancer constitutes the most widely investigated malignant entity. Vernon et al. published the results of five randomized trials conducted between 1981 and 1991 that were combined due to insufficient patient accrual. The pooled analysis of 306 patients with inoperable primary or recurrent disease yielded a significantly better complete response (CR) (RTHT: 59%, RT alone: 41%, odds ratio (OR): 2.3, $p < 0.001$) but no survival benefit. However, 50% of patients had metastases at the time of randomization. The effect was most prominent in preirradiated recurrent lesions. Skin toxicities such as blisters, ulceration, and necrosis were higher in the HT group, however with low impact on the patients well-being and generally treatable with conservative measures (60).

In cases of locoregional recurrence, breast surgery is recommended if possible. However, radical resection only appears to be feasible in 65% of patients and may cause significant treatment-related morbidity (78). Thus, RT constitutes a significant alternative, and depending on the time interval between first and second RT and other pretreatment characteristics offers substantial clinical benefit. Since nowadays most patients receive RT in the primary situation, HT may help to enhance the effects of reirradiation in the recurrence scenario, especially since in some clinical situations only reduced radiation doses may be prescribed. A recent meta-analysis by Datta et al. included 8 two-arm studies and 24 single-arm studies involving 2,110 patients with locoregional recurrent disease (79). CR was similar between one-arm studies (CR: 63.4%) and two-arm studies as well as significantly higher compared to RT alone (RTHT: 60.2%, RT: 38.1%, OR 2.6, $p < 0.001$). In preirradiated patients (779 patients), a CR of 66.4% was achieved (mean re-RT dose: 36.7 Gy). Treatment-related toxicity was overall not increased with mean acute grade 3/4 toxicities of 14.4%. Among the analyzed studies, there was great heterogeneity in RT dose, HT fraction schedules, total number of HT fractions, HT duration, or average achieved temperatures. However, no prognostic treatment variables could be identified in a subgroup analysis and meta-regression. Similar results were recently published by Linthorst et al. In a retrospective study encompassing 248 patients with unresectable recurrences, reirradiation + HT yielded a CR of 70% (80). In resectable cases, a regimen including surgery, RT, HT, and partly CT or hormone therapy, a local control (LC) rate of 78% after 5 years was achieved (81). Notter et al. have treated patients with locally recurrent breast cancer with RTHT using a hypofractionation scheme of 5 × 4 Gy with one fraction per week. A wIRA system was used for superficial HT. A CR rate of 61% was achieved without any treatment-related toxicities (56). In summary, there is sustained evidence demonstrating a value of adjunct HT in locoregional, recurrent breast cancer as definitive or adjuvant treatment.

Cervical Cancer

Several randomized trials have been conducted to test HT in combination with RT. A Cochrane database meta-analysis was performed analyzing six trials involving a total of 487 patients (82). The studies included mostly patients with locally advanced disease (74% FIGO stage IIIB). Except in one study, RT was delivered as a combination of external beam therapy (EBRT) and brachytherapy (BT). The pooled data analysis showed a significantly higher CR [CR relative risk (RR): 0.56, $p < 0.001$] and OS [hazard ratio (HR): 0.67, $p = 0.05$] in favor of RTHT as well as a reduced local recurrence rate (HR: 0.48, $p < 0.001$). No difference was found regarding acute and late toxicity rates. The

TABLE 1 | Summary of cited meta-analyses and randomized trials for breast cancer and cervical cancer.

Reference	Year	Entity	Study type	Treatment arms	RT/CT schedule	P #	HT frequency	Outcome
Breast cancer								
Vernon et al. (60)	1995	Inoperable primary/ recurrent breast cancer	MA (5 r trials)	RTHT	Various: effective RT dose 39.8–60 Gy	171	mostly 1x/w	CR 59%,
				RT		135	–	41%, OR 2.3, p < 0,001
Datta et al. (79)[a]	2016	Locoregional recurrence	MA (24 1a.s.) 8 (5 r 2a.s.)	RTHT	Various: 24–60 à 1.8–4 Gy	1,483	1–5x/w	Single arm: CR 63.4%
					m: 38.2	309	(m: 2)	Two arm: CR 60.2%
				RT		318	–	CR: 38.1%, OR 2.6, p < 0.001
				reRTHT[b]	m: 36.7 à m: 2.7 Gy[b]	779[b]	1–5x/w[b]	CR 66.4%[b]
Cervical cancer								
Lutgens et al. (82)	2010	Locally advanced cervix carcinoma	Cochrane MA: 6 r 2a.s.	RTHT	Various concepts: EBRT (40–70 Gy) ±BT (16–50 Gy)	135	1–3x/w	CR HR 0.56, p < 0.001
								LR HR 0.48, p < 0.001
								OS HR 0.67, p < 0.05
				RT		132	–	
Datta et al. (84)	2016	Locally advanced cervix carcinoma	Network MA: 6 r 2a.s.	RTHT	Various concepts: EBRT (40–70 Gy) ±BT (16–60 Gy)	170	1–3x/w	CR: vs. HT: OR 2.85, s
				RTCT	+Cisplatin	281	–	
				RTHTCT	+Cisplatin	231	2x/w	CR: vs. HT: OR 4.52, s vs. HTCT: OR 2.91, s
								PA: vs. RT: OR 5.57, s vs. CTRT: OR 2.65, s
				RT		125	–	
Lutgens et al. (86)	2016	Locally advanced cervix carcinoma	r pIII	RTCT	EBRT 50 Gy + BT 21/29 Gy +Cisplatin	43	–	EFS: HR 1.15, ns
								OS: HR 1.04, ns
								PRFS: HR 0.94, ns
				RTHT		44	1x/w	

RT, CT, and HT schemes, p-value or significance status (s/ns) are described as mentioned in the original publications.
a.s., arm study; BT, brachytherapy; CT, chemotherapy; CR, complete response; EFS, event-free survival; HR, hazard ratio; HT, hyperthermia; m, mean; ns, not significant; LR, local recurrence; MA, meta-analysis; OS, overall survival; OR, odds ratio; PRFS, pelvic recurrent-free survival; P #, patient number; p, phase; PA, patients alive; w, week; r, randomized; RT, radiotherapy; s, significant; RTHT, thermoradiotherapy; RTCT, chemoradiotherapy; EBRT, external beam therapy; à, with a single dose of; x/w, times per week.
[a]Including 4 two-arm studies reported in the study by Vernon et al.
[b]Subgroup analysis.

authors criticized a lack of uniformity among the trials concerning HT delivery, HT schedules, as well as RT treatment protocols, RT dose, and RT techniques. Therefore, the authors conclude that the results do not suffice for a definitive recommendation to apply HT along standard treatment regimen. The included Dutch deep HT trial was updated for long-term results after 12 years of follow-up showing sustained improved LC (RT: 37%, RTHT: 57%, p = 0.01) and survival (RT: 20%, RTHT: 37%, p = 0.03) (83). All studies have in common that concurrent CT was not included in the treatment regimen.

In recent years, many trials have discussed the value of the combined treatment regimes such as RTHT, RTCT, or trimodal RTHTCT. A recently published meta-analysis has revised all relevant publications including 23 articles with a total patient number of 1,160 (84). In a network meta-analysis (NMA), all four possible treatment modalities (RT, RTHT, RTCT, RTHTCT) were compared. All studies, but one, included patients with locally advanced disease. RT always comprised EBRT + BT. The

comparison of RTHT and RT yielded similar results as the previously described Cochrane analysis. The same six trials with minor updates were included. For the direct comparison of RTHTCT and RTCT, only one study including 68 patients was available (85). It showed a significant better CR for the trimodal treatment arm (RTCT: 46.7%, RTHTCT: 83.3%, risk difference 36.7%, p = 0.0001). No significantly increased grade 3/4 toxicities were found. The NMA showed a significant advantage of RTHTCT over all other treatment combinations in direct and indirect comparisons as well as in the SUCRA value-based ranking for CR and patients alive. RTCT and RTHT had similar performance even though RTHT had a small advantage over RTCT regarding CR. In coherence, a recent randomized phase III trial, which was closed early due to poor accrual with only 87 of 376 planned patients, did not show any significant difference in event-free survival and pelvic recurrence-free survival between RTHT and RTCT (86). In summary, by adding radiosensitizing treatments such as CT or HT to RT, better treatment outcomes are achievable. In locally

TABLE 2 | Summary of cited meta-analyses and randomized trials for head and neck cancer and rectal cancer.

Reference	Year	Entity	Study type	Treatment arms	RT/CT schedule	P #	HT frequency	Outcome
Head and neck cancers								
Datta et al. (87)	2015	Head and neck cancers	MA (5 r 2a.s., 1 nr 2a.s.)	RT	32–80 à 1.8–2 Gy	232	–	CR: 39.6%
				RTHT		219	1–2x/w	CR: 62.5%, OR 2.92, $p = 0.001$, RR 1.61, $p < 0.001$
Kang et al. (88)	2013	Nasopharyngeal cancer (N2/3)	r pIII	RTCT	50/78 à 2 Gy +cisplatin	78	–	CR: 62.8%
								5y-DFS: 20.5%
								5y-OS: 50%
				RTCTHT	+cisplatin	76	3 groups: 0.5–2x/w	CT: 81.6%, $p < 0.05$
								5y-DFS: 51.3%, $p < 0.05$
								5y-OS:68.4%, $p < 0.05$
Hua et al. (89)	2011	Nasopharyngeal cancer	r pIII	RT(CT)	50/60/70 Gy ± BT: (15–20 Gy) ±(T3/4) cisplatin/5FU	90	–	CR: 81.1%
								5y-DFS: 63.1%
								5y-OS: 70.3%
				RT(CT)HT	+(T3/4) cisplatin/5FU	90	2x/w	CR: 95.6%, $p = 0.003$
								5y-DFS: 72.7%, $p = 0.039$
								5y-OS: 78.2%, $p = 0.14$
Zhao et al. (90)	2014	Nasopharyngeal cancer	r pIII	RTCT	50/70–74 Gy +cisplatin/paclitaxel	40	–	3y-OS: 53.5%
								mPFS: 37.5
				RTCTHT	+cisplatin/paclitaxel	43	3x/w	Better quality of life
								3y-OS: 73%, $p = 0.041$
								mPFS: 48 mo, $p = 0.05$
Rectal cancer								
De Haas-Kock et al. (93)	2009	Locally advanced rectal cancer	MA (6 r 2a.s.)	RT	40–50 Gy	258	–	
				RTHT		262	1–5x/w	2y-OS: HR 2.06, $p = 0.001$
								CR: RR 2.81, $p = 0.01$

RT, CT, and HT schemes, p-value are described as mentioned in the original publications.
a.s., arm study; BT, brachytherapy; CT, chemotherapy; CR, complete response; DFS, disease-free survival; HR, hazard ratio; HT, hyperthermia; m, mean; mo, months; nr, non-randomized; MA, meta–analysis; OS, overall survival; OR, odds ratio; P #, patient number; p, phase; w, week; PFS, progression-free survival; r, randomized; RR, relative risk; RT, radiotherapy; y, years; RTHT, thermoradiotherapy; RTCT, chemoradiotherapy; à, with a single dose of; x/w, times per week.

advanced cervical cancers, RTHT appears to be a valuable substitute for RTCT if CT is not applicable. By combining all three modalities, the best treatment effect may be possible. Additional phase III trials are necessary directly comparing RTHT, RTCT, and RTHTCT for optimal treatment stratification.

Head and Neck Cancers

To evaluate the effect of HT in head and neck carcinomas, a meta-analysis was recently performed including six 2-armed studies encompassing 451 patients. Five of the six studies were randomized trials. The CR rate appeared to be significantly better in patients treated with combined RTHT compared to RT alone (RT alone: 39.6%, RTHT: 62.5%, OR 2.92, $p < 0.0001$). Acute and late grade 3/4 toxicities were not significantly different (87). One study included exclusively nasopharyngeal carcinomas, whereas all other studies considered all cancer sites of the head and neck. However, all studies involving surgery or concurrent CT were excluded.

Three other randomized trials with a total of 417 patients recently analyzed the effects of trimodal treatment combing RT,

CT, and HT in patients with nasopharyngeal carcinomas (88–90). Two studies reporting CR showed a significant advantgae for RTHTCT treatment. The same patients had an increased OS in two of the studies. Progression-free survival (PFS) or disease-free survival (DFS) was significantly better in the RTHTCT group in all three studies. Patients with higher tumor temperatures and higher HT fraction numbers showed a better outcome (88). In all three studies, no difference in treatment-related toxicity has been described. Patients receiving HT showed even better quality of life scores after completion of therapy (90). These studies demonstrate that trimodal therapy including RT, CT with different agents, and HT constitute an effective and safe treatment alternative. To our knowledge, no other randomized studies have been published in other head and neck sites investigating trimodal therapy. As shown in other malignancies, re-treatment may constitute a further clinical situation in which HT may be a valuable treatment option. In a small cohort receiving reirradiations combined with HT, a CR of 46% was achieved showing feasibility of such an approach (91). To conclude, HT constitutes a valuable treatment option in cancers of the head and neck.

TABLE 3 | Summary of cited randomized trials for bladder cancer, melanoma, NSCLC, glioblastoma, and sarcoma.

Reference	Year	Entity	Study type	Treatment arms	RT/CT schedule	P #	HT frequency	Outcome
Bladder cancer								
Matsui et al. (99)	1991	Bladder cancer	r pII	RT	50–70 à 2 Gy	16	–	Response: 56%
				RTHT	40 à 2 Gy	38	2x/w	Response: 84%, $p < 0.001$
van der Zee et al. (61)[a]	2000	Bladder cancer	r pIII	RT	40/66–70 à 2 Gy	38	–	CR: 51%
								3y-OS: 22%
								3y-LC: 33%
				RTHT		52	1x/w	CR: 73%, $p = 0.01$
								3y-OS: 28%, ns
								3y-LC: 42%, ns
Melanoma								
Overgaard et al. (101)	1995	recurrent or metastatic malignant melanoma	r pIII	RT	24–27 à 8–9 Gy - 4-day interval	34	–	CR: 35%
								2y-LC: 28%
				RTHT		34	After each RT	CR: 62%, $p < 0.05$
								2y-LC: 46%, $p = 0.008$
NSCLC								
Mitsumori et al. (102)	2007	NSCLC (St. II–III)	r pIII	RT	40/66–70 à 2 Gy	40	–	1y-PFS: 29%
								OS: 38.1%
				RTHT	20.0–76.0 Gy	40	1x/w	1y-PFS: 69%, $p < 0.036$
								OS: 43%, $p = 0.868$
Glioblastoma								
Sneed et al. (112)	1998	Glioblastoma	r pII/III	RTHT	59,4 à 1,8 Gy + BT 60 Gy (0.4–0.6 Gy/h)	40	1x before + after BT	2y survival: 31%
								TTP: 49 mo
Sarcoma								
Leopold et al. (116)	1989	STS	r pII	RTHT	50/50,4 à 2/1,8 Gy	8	1x/w	Severe histopathologic changes 9/9
				RTHT		9	2x/w	Severe histopathologic changes 3/8

RT, CT, and HT schemes, p-value or significance status (s/ns) are described as mentioned in the original publications.
a.s., arm study; BT, brachytherapy; CT, chemotherapy; CR, complete response; HT, hyperthermia; LC, local control; m, mean; mo, months; ns, not significant; OS, overall survival; P #, patient number; p, phase; w, week; PFS, progression-free survival; r, randomized; RT, radiotherapy; RTHT, thermoradiotherapy; NSCLC, non-small cell lung cancer; TTP, time to progression; STS, soft tissue sarcomas; à, with a single dose of; x/w, times per week.
[a]As part of the Dutch hyperthermia trial.

However, due to relatively high perfusion rates and fast adaptation to local temperature changes, HT delivery appears to be especially challenging. By using a site-tailored radiative heating device, treatment outcomes may be better in the future (92). HT could be used in multimodal treatment schemes further improving treatment outcome. Alternatively, it may constitute a toxicity-sparing alternative for concurrent CT in elderly or multimorbid patients. Further clinical studies are necessary to evaluate the true clinical value.

Rectal Cancer

In 2009, a Cochrane analysis of six phase II and III randomized-controlled trials including 520 patients with locally advanced rectal carcinomas was performed. Patients received neoadjuvant RT with or without HT. Increased CR (RR 2.81, $p = 0.01$) as well as increased OS at 2y follow-up (HR 2.06, $p = 0.001$) could be observed. The survival benefit, however, could not be measured for any later time point. No difference in acute toxicity was found in the two studies reporting on this side effect (93). A positive

impact on pathologic complete response (pCR) could as well be shown in a retrospective study of 106 patients. Sphincter-sparing surgery was higher for tumors in close proximity to the anal verge (94). In a further retrospective study encompassing 235 patients, HT appeared to confer better downstaging of the primary tumor and involved lymph nodes (95). Two small studies evaluated hypofractionated RTHTCT schemes showing principal efficacy and safety (96, 97). Additional HT appears to be well tolerated without increased impairment of quality of life (98). To conclude, the Cochrane analysis demonstrated a fundamental possibility of increased response by applying adjunct HT. However, further randomized prospective trials are necessary to evaluate the true value of neoadjuvant RTHTCT as well as of treatment of recurrent disease.

Bladder Cancer

For the treatment of bladder carcinomas, HT has been predominantly applied in combination with intravesical CT. However, a few trials have evaluated RTHT. In an early study, 56 patients

TABLE 4 | Cited studies for RTHT indications with limited data.

Reference	Year	Entity	Study type	P #	RT/CT schedule	Treatment arms	HT frequency	Outcome
Indications with limited data								
Milani et al. (125)	2008	Preirradiated painful recurrent rectal cancer	nr pII	24	30.0–45.0 à 1,8 Gy + 5FU	RTHTCT	2x/w	Pain relief: 70%
								Local PFS: 15 mo
Kalapurakal et al. (127)	2003	Locally advanced or recurrent prostate cancer	nr pI/II	13	m: 39.6 Gy for ReRT	ReRTHT	2x/w	25% grade IV toxicities
					m: 66.6 Gy for RT	RTHT		Symptom relief: 100%
								OR 46%, RR 54%
Maluta et al. (128)	2011	Primary or recurrent locally advanced pancreatic cancer	nr pII	40	30–66 Gy	RTHTCT	2x/w	OS: 15 mo
					gemcitabine ± oxalilatin, cisplatin, 5FU			
				28		RTCT	2x/w	OS: 11 mo, p = 0.025
Dong and Wu (129)	2016	Hepatocellular carcinoma	r pII	40	Not specified	RTHT	2x/w	1y-recurrence: 10%
								1y-mortality: 12.5%
				40		RT	2x/w	1y-recurrence: 15%, p < 0.001
								1y-mortality: 20%, p < 0.001
Yu et al. (130)	2016	Chemorefractory liver metastasis of colorectal cancer	nr pII	10	whole liver RT: 21 à 3 Gy	RTHT	2x/w	Pain relief 30%
								PR 30%, stable disease 50%
Aktas et al. (131)	2007	Primary vaginal cancer	nr pII	7	48 à 2 Gy + BT (17 à 8,5 Gy)	RTHT	Not specified	Tumor size > 4 cm
								5y-OS: 68%
				32		RT(CT)	–	Tumor size < 4cm
								5y-OS: 57%, ns
Jones et al. (64)	2005	Superficial tumors: breast cancer, head and neck, melanoma	r pIII	56	m: 50 Gy	RTHT		CR: 66.1%
				52	m: 55 Gy	RT	–	CR: 42.3%, OR 2.7, p = 0.02

RT, CT, and HT schemes, p-value or significance status (s/ns) are described as mentioned in the original publications.

CR, complete response; PR, partial response; BT, brachytherapy; CT, chemotherapy; HT, hyperthermia; m, mean; mo, months; nr, non-randomized; ns, not significant; OS, overall survival; OR, odds ratio; P #, patient number; p, phase; w, week; PR, partial response; PFS, progression-free survival; r, randomized; RT, radiotherapy; s, significant; RTHT, thermoradiotherapy; RTCT, chemoradiotherapy; à, with a single dose of; x/w, times per week.

with bladder carcinomas were treated with intravesical CT (bleomycin) simultaneously to RTHT with reduced total dose (40 Gy) or RT alone with higher dose prescription (50–70 Gy). HT was delivered by intravesical infusion of warmed saline solution containing bleomycin. The RTHT group had a higher response rates (RTHT: 84%, RT: 56%, p < 0.001) with decreased toxicity rates (less bladder capacity reduction) (99). In a different approach, 49 patients with nodal-negative disease of all T stages were treated with a hypofractionated RT scheme (24 Gy, 4 Gy/fraction) with or without HT. The HT group was split into a high (Tmean > 41.5°C) and a low temperature cohort (Tmean < 41.5°C). The high temperature cohort showed significantly better downstaging compared to both other groups indicating the importance of adequate temperature delivery (100). In a more recent German trial, high-risk T1 and T2 cancers were treated with transurethral resection followed by RTHTCT (50.4 Gy + 5.4–9 Gy; cisplatin and 5FU). At six weeks follow-up, a pCR of 96% was achieved. After a median follow-up of 34 months, OS was 89% with 80% of the patients being satisfied with their bladder function (63). The Dutch deep HT trial also included bladder carcinomas besides cervical and rectal carcinomas. In a randomized protocol, 101 patients with T2–T4 N0 M0 bladder carcinoma were treated with either RT or RTHT.

RTHT yielded a significantly better CR (RTHT: 73%, RT: 51%, p = 0.01). However at 3y, LC and OS were not significantly different. There was no difference in toxicity (61). Taken together, some studies exist demonstrating a clinical benefit for adjunct HT with no additional toxicity. However, the patient cohorts in the different studies appeared to be quite heterogeneous by mixing locally restricted and advanced tumors. The treatment regimens used differed among studies impairing adequate comparisons. Randomized studies are necessary with clearly defined risk profiles and adequate direct comparisons with guideline-based treatment regiments.

Melanoma

One multicentric randomized trial analyzed the benefit of adjunct HT in melanomas treated with RT. Patients either received RT (24 Gy or 27 Gy in three fractions) alone or with HT (43°C for 60 min). There was no significant difference in toxicity. CR (RT alone: 35%, RTHT: 62%, p < 0.05) and LC after 2y were significantly increased (RT alone: 28%, RTHT: 46%, p = 0.008) (101). As these results are very promising, more randomized trials would help to establish a distinct role for RTHT in the treatment of melanomas, for example in combination with less hypofractionated treatment schemes.

Non-Small Cell Lung Cancer (NSCLC)

Only few studies have investigated the role of HT for the treatment of NSCLC. A multi-institutional prospective randomized trial investigated the role of HT in addition to primary RT for locally advanced NSCLCs. No significant difference of OS, local response, or treatment-related toxicity could be observed. However, with a significantly higher 1y-PFS, a certain benefit was apparent (67.5%, 29%, $p = 0.036$) (102). In a small case–control study encompassing 13 patients with direct bone invasion treated with RTHT (60–70 Gy) showed a possibly high efficacy in LC and survival under this unfavorable condition (103). The benefit of HT in addition to reirradiation for recurrent NSCLC after primary RT was investigated in a small retrospective study involving 33 patients. Median doses used initially and for reirradiation were 70 and 50 Gy, respectively. Toxicity was moderate and limited to a maximum toxicity of grade 3 in 9% of patients. In patients with smaller tumors (<4 cm) and no distant metastases, long time survival was partly achieved (104). All three studies employed radiofrequency capacitive heating systems. So far, only limited evidence exists showing a true benefit of HT in NSCLC treatment. More studies are necessary to explore potential areas of application.

Prostate Cancer

Feasibility of adjuvant HT treatment for prostate carcinomas has first been shown in two phase I/II studies involving locally advanced disease or recurrences after radical prostatectomy. Toxicity was limited to grades 2 and 3, respectively. Quality of life was not significantly changed by addition of HT to RT treatment (105). A HT-dependent burn occurred in one patient indicating critical temperature delivery (106, 107). Similar results were obtained in a larger phase II study involving 144 patients with high-risk disease (T2 + serum-PSA > 10 ng/ml or Gleason score $\geq$ 7) or locally advanced disease (T3/4) treated with RTHT and antihormonal therapy (108). A 5y-OS of 87% and 5y-biochemical PFS of 49% was observed with limited toxicity (maximum grade 2). Hurwitz et al. combined radiation with or without hormone deprivation therapy and transrectal ultrasound HT in locally advanced disease showing promising results with a 2y-DFS of 84% compared to historical 2y-DFS of 64% observed in patients in the 4-month androgen suppression cohort of the RTOG 92-02 trial (62). Currently, a phase II study examines the safety of combining HT and dose-escalated external salvage RT for recurrent prostate cancer (109). Another study is examining salvage BT combined with interstitial HT (110). In a retrospective analysis of 146 patients, no significant difference was found between patients receiving HT or not. The authors discussed that this might be due to insufficient heat delivery, since a significant difference was apparent for patients receiving a high thermal dose (111). To summarize, a set of phase II studies show promising results. However, randomized phase III trials are necessary to evaluate the actual value of adjuvant HT in the treatment of prostate carcinomas.

Glioblastoma Multiforme (GBM)

In 1998, Sneed et al. investigated the impact of adjuvant interstitial HT after a BT boost for patients with newly diagnosed, supratentorial GBM smaller than 5 cm treated with postoperative RT and concomitant hydroxyurea. After patient exclusions, 68 patients were randomized to BT with or without HT (112). HT was administered 30 min before and after a BT boost *via* placement of helical-coil microwave antennas. The HT group showed significantly increased survival (2y-survival 31% vs. 15%, $p = 0.02$) and time to progression (TTP) (median TTP 49 vs. 33 months, $p = 0.045$); however, this treatment was accompanied by increased grade 3 toxicity rates. In recent years, efforts were made to optimize HT delivery by improving interstitial catheters or applying focused ultrasound (113, 114). No data exist so far validating these new techniques or the combination with temozolomide.

Sarcomas

Randomized trials have shown a significant benefit of HT in addition to CT (115). However, evidence of combined RTHT in sarcoma treatment remains scarce. An early phase II study involving 17 soft tissue sarcomas (STS) patients neoadjuvant RTHT with twice weekly HT showed significantly more extensive changes in histopathological examinations than the once weekly HT group (116). In another study, 16 patients received irradiation with concurrent HT for the treatment of radiation-associated sarcomas (predominantly angiosarcoma) showing a total response rate of 75%. Toxicity was mild except one grade 4 adverse event (117). First clinical results show general feasibility of applying RTHT to sarcoma treatment. However, randomized trials are necessary to assess whether a similar benefit exists as it has been shown for neoadjuvant HTCT.

Esophageal Cancer

Several phase II studies have investigated the feasibility of trimodal neoadjuvant RTHTCT treatment. Nakajima et al. treated 24 patients with neoadjuvant RTHTCT using docetaxel. A general response rate of 41.7% with a pCR rate of 17.6% was observed (118). Described toxicities were limited to grade 2 and grade 3. In a further study, 28 patients received RTHTCT with carboplatin and paclitaxel. R0 resection was possible in all patients with mild toxicity. Pathologic evaluation yielded a pCR rate of 19%. Treatment was tolerated well with mild toxicity rates (maximum grade 2) (119). A third study treated 35 patients with advanced disease with RTHTCT (bleomycin/cisplatin and 5FU) yielding a good CR rate of 33.3% (120). In addition, multiple retrospective analyses have shown a significantly increased survival benefit in favor of RTHTCT over RTCT (121–123). In summary, there is existing evidence promising a substantial clinical value of RTHTCT. However, randomized trials are necessary directly comparing RTHTCT to standardized treatment protocols involving RTCT.

RTHT in Indications with Limited Data

Apart from the described entities, in multiple trials, RTHT has been applied to rather rare RT indications with only low levels of evidence (see **Table 4** for a detailed summary of the cited trials).

A Dutch retrospective trial analyzed the efficacy of hypofractionated (28/32 Gy with a single dose of 4 Gy) reirradiation with

concurrent HT for the palliation of painful unresectable recurrent rectal cancer with good to complete response in 72% of 47 patients (124). Similar results (70% pain relief) were reproduced in a prospective phase II trial by Milani et al. with normofractionated RTCTHT (125). Klaver et al. proposed a novel treatment strategy in a case series for locally advanced rectal cancer with concurrent peritoneal carcinomatosis by combing hyperthermic intraperitoneal chemotherapy with intraoperative RT showing general feasibility (126).

Thermoradiotherapy was evaluated for the palliation of symptomatic locally advanced or recurrent hormone-refractory prostate cancer in a small phase I/II study. All patients demonstrated partial response or complete response as well as complete symptom relief (127). However, two of eight preirradiated patients developed grade IV toxicities.

Primary or recurrent locally advanced pancreatic cancer was subject to an open-label study comparing RTCT with RTHTCT (gemcitabine ± 5FU/cisplatin/oxaliplatin) showing a significantly increased survival benefit without increased toxicity (mean OS: RTHTCT: 15 months, RTCT: 11 months, $p = 0.025$) (128). Moreover, the influence of adjunct HT for the treatment of liver lesions has been assessed. In a randomized Chinese trial of hepatocellular carcinoma patients, 1y-recurrence (RTHT: 10%, RT: 15%, $p < 0.001$) and mortality rates (RTHT: 12.5, RT: 20%, $p < 0.001$) were significantly lower for combined RTHT compared to RT alone (129). Chemorefractory colorectal cancer metastases were treated with whole-liver RT and concimittant HT showing partial response and pain relief in 30% of treated patients, respectively (130). Vaginal cancers have been chosen as target for HT in small prospective Dutch trial. Patients with vaginal carcinomas with a tumor size larger than 4 cm were treated with RTHT, whereas smaller tumors were primarily treated with RT showing no significant difference in 5y-survival (131).

In a more general approach, Jones et al. performed a randomized prospective trial pooling superficial tumors of various entities (breast carcinoma, melanoma, head and neck cancer, and others). Only tumors that appeared to be heatable on a pretest were randomized. Addition of HT to RT lead to significantly increased CR (RTHT: 66.1%, RT 42.3%, OR 1.7, $p = 0.02$). In coherence with many other studies, the highest difference was achieved in preirradiated patients (CR: RTHT: 68.2%, CR 23.5%) (64).

Despite the limited amount of evidence, substantial benefits of RTHT, especially for preirradiated, locally advanced and recurrent tumors, became apparent. Since there is a lack of randomized trials, definite recommendations for treatment cannot be made. In situations of recurrent or metastatic disease, RTHT may be justifiable as "individual treatment approach" on the basis of the existing evidence. In order to reach necessary patient number in potential future randomized trials, multiple entities with a similar condition (such as "recurrent," "preirradiated," or "locally advanced") could be combined, following the approach of Jones et al. (64). In addition, HT centers should work more closely together for the establishment of multicenter trials capable of gathering critical patient numbers.

Combined Thermochemotherapy (CTHT)

Thermochemotherapy has been evaluated in multiple clinical trials. In contrast to RTHT, CTHT is also being combined with WBHT. A limited number of phase II studies have shown feasibility of applying WBHT to CTHT treatment of various entities such as recurrent ovarian cancer, malignant pleural mesothelioma, metastatic STS, melanoma, and pretreated metastatic colorectal cancer (132–136). Up to date, no phase III trials exist. In contrast, regional HT has been evaluated in a large phase III trial (341 patients) of STS performed as joint effort by the European Organization for the Research and Treatment of Cancer and European Society for Hyperthermic Oncology. It showed a substantially and significantly improved local PFS, DFS, and OS after adding HT to EIA (etoposide, ifosfamide, doxorubicin) CT (HR for local progression/death: 0.58, $p = 0.003$, local 2y-PFS: HTCT: 76%, CT: 61%; 2y-DFS: CTHT: 58%, CT: 44%, $p = 0.011$; per-protocol OS: HR 0.66, $p = 0.038$) changing daily clinical practice in HT treatment centers (115). Further randomized trials have evaluated neoadjuvant CTHT in esophageal carcinoma (40 patients; histologic effectiveness: CTHT 58.3, CT: 14.3, $p < 0.05$) and adjuvant CTHT after transurethral resection of bladder carcinomas (83 patients; 10y-DFS: CTHT: 53%, CT: 15%, $p < 0.001$) demonstrating increased treatment efficacy (137, 138). A randomized trial with NSCLC showed a small benefit regarding "clinical benefit response" (80 patients, CTHT: 82.5%, CT: 47.5%, $p < 0.05$) (139). General feasibility of local CTHT has also been shown in other entities such as refractory or recurrent non-testicular germ cell carcinomas, recurrent or persistent ovarian cancer, breast carcinoma, or peritoneal carcinomatosis in several phase II studies (140–143). As alternative to regional HT, hyperthermic isolated limb perfusion has been established for the treatment of STS and unresectable melanomas showing favorable results (144, 145). In summary, the few existing randomized trials suggest substantial benefit by adding HT to CT. More randomized trials are necessary to broaden the spectrum of CTHT.

OUTLOOK

Review of the current literature has shown various retrospective and prospective trials exploring the value of adding HT to RT or RTCT regiments in multiple tumor entities. As in some entities, the real benefit of HT remains elusive, in other malignancies sustained evidence has been acquired. When considering the currently existing studies, a substantial part of evidence was gathered between the 1980s and early 2000s. Apart from technical aspects of HT, RT techniques have dramatically evolved since then. Nowadays, even better results in regard to treatment outcome as well as toxicity could be expected. Still, no widespread use of HT has been established in the last decades. Several reasons, such as reimbursement issues in certain countries, technical complexities, and challenges of homogenous heating and temperature monitoring, may have contributed to this fact. As more and more clinical trials are being published, the willingness/memorandum to make the effort of establishing HT in a rising number of institutions has increased.

The development of novel techniques with more exact heat delivery and temperature monitoring capacities may help to gain higher acceptance among physicians. HT may as well be further improved by better planning techniques. Mathematical modeling of the earlier mentioned HT effects on cell biology has paved the way to actual thermoradiotherapy planning (4). By integrating the biological HT effect into the LQ-model, a more exact RTHT treatment planning becomes possible. By adding online temperature control, as it can be achieved by MRI thermometry, temperature distribution could be optimized even further by real-time adjustments.

In the trials performed so far, HT delivery specifications were highly heterogeneous. HT frequency varied between once weekly to daily applications. Mean achieved temperature profiles differed vastly between 39 and 43°C. In trials using multiple HT specification, higher temperatures or HT frequencies were associated with better outcome (88, 100, 116). This underlines the necessity of optimizing HT schedules to optimize the treatment effect. To this end, larger randomized studies are necessary directly comparing distinct HT specifications.

Even though there are still a lot of open questions, basic research has revealed many ways of action of HT. Regarding the biological mechanisms of HT, combining HT with drugs exploiting underlying mechanisms may further increase radiosensitization. As an example, HT has been combined with antiangiogenesis agents. HT itself appears to directly impair angiogenesis at least in part by plasminogen activator inhibitor 1 induction (146). By combining HT with VEGFR2-inhibitor treatment, a synergistic antiangiogenesis effect *in vivo* has been shown to inhibit tumor growth (147). Regarding the immunogenic effects of HT, adjunct immunotherapy, such as checkpoint inhibition, constitutes a further interesting field of research. Before clinical trials can be designed, more basic research is necessary to evaluate the effects of thermo-immunotherapy in preclinical models.

All studies mentioned above have used HT in combination with photon-based irradiation. However, all over the world, an increasing number of particle beam facilities are being installed. Due to technical improvements, smaller and low-cost proton facilities may become available in the future possibly enabling a further widespread use. In contrast, facilities capable of delivering heavy ion-based irradiation with ^{12}C remain scarce. In a brief summary, proton and ^{12}C-ions share similar favorable dose distributions with low entry dose, a high dose in the "Bragg peak" followed by a more or less steep dose decline (148). In contrast to protons, ^{12}C-ions inherit a significantly higher linear energy transfer and relative biological effectiveness (149). Several biological factors have been identified such as a low oxygen enhancement ratio (OER), less cell-cycle-dependent cell killing, inhibition of non-homologous DNA repair, cluster damages to the DNA, and more efficient cell killing of tumor stem cells (150). HT triggers killing of hypoxic, acidic as well as energy-deprived tumor cells, decreases OER, and confers direct killing of S-phased cells. Therefore, it has been proposed that combined therapy of proton irradiation with HT may have similar effectiveness as ^{12}C beam therapy

alone (151, 152). To the best of our knowledge, no data of the clinical use of simultaneous thermo-particle therapy has been published. The HYPROSAR phase I/II study is currently recruiting patients with unresectable STS at the Paul Scherrer Institut in Switzerland. Weekly HT is combined with proton beam therapy to achieve tumor downstaging with subsequent resection. There has only been one randomized trial treating 151 patients with uveal melanoma with or without adjuvant transpupillary thermotherapy months after the end of proton irradiation (153). Indeed, the rate of secondary enucleation was significant lower. Since the therapy was not conducted in direct temporal proximity, the abovementioned factors would not have taken effect. Hence, clinical trials are necessary to explore the benefit of combinational therapy. Direct comparison of thermo-particle therapy with ^{12}C beam therapy should be performed in randomized trials.

Different technical solutions of external HT delivery have been discussed. Advances in the field of nanomedicine have introduced a novel approach for targeted HT by development of magnetic or superparamagnetic nanoparticles as recently reviewd by Datta et al. (154). Particles with cores of iron oxide or gold shells have already made their way into clinical phase I trials. Bergs et al. recently reviewed the existing particle constructs (155). Tumor-specific targeting might be achieved by passive accumulation in the tumor due to the aberrant vasculature with increased leakage and simultaneous impairment of lymphatic drainage (156). Alternatively, active targeting could be achieved by coating with tumor-specific antibodies or ligands (157). Heat can then be generated by applying external magnetic fields with rapid field alternations (158). In clinical phase I trials, dispersed nanoparticles were directly deposited at the tumor side either by percutaneous injection or intraoperatively. Only mild toxicities and quality of life impairments were observed. A maximum temperature of up to 55°C was achieved but target coverage remained insufficient (159–161). The advantage of nanoparticle-based HT may lead to a more selective heat delivery to the tumor with possibly higher temperatures and lower toxicity to adjacent normal tissues. By carrying chemotherapeutic agents, antibodies, or gene silencing RNA residues, nanoparticles may open completely new therapeutic opportunities (154). On the other side, tumor volume coverage is still far from optimal. Poorly perfused regions of tumors, in which HT has its greatest potential for radiosensitization, tend to "collect" lower particle numbers. Accumulation of particles in non-malignant tissues such as the reticuloendothelial system or by the glomerular filter of the kidney carries the risk of side effects (162). Microscopic disease, e.g., in lymphatic tissue may not be reached by sufficient high temperatures. Until safe appliance in the clinic becomes possible, more research is necessary to assess the biological risks and to optimize particle distribution and targeting. If these problems can be addressed, nanoparticles may be a valuable alternative to external HT.

Besides enhancement of RT effects, HT may also be used for radiation dose reduction. As described above, Notter et al. used a hypofractionation treatment scheme (5 × 4 Gy, one fraction per week) to treat patients with locally recurrent breast cancer.

A similar CR rate of 61% was achieved compared to other studies using mean doses of 38.2 Gy (79). The relatively low dose enabled the authors to perform re-reirradiations. 17 patients with re-recurrences of lymphangiosis carcinomatosa received re-reirradiation following the same therapy scheme. A CR rate of 31% could be achieved (56).

Infections with human papilloma virus (HPV) are commonly found in carcinomas of the head and neck or cervix. HPV-positive tumors appear to be more radiosensitive than HPV-negative tumors. HT has been shown to trigger the degradation of the oncogenic HPV-derived E6 protein. As functional E6 binds and inactivates p53, HT may indirectly renew p53 activity favoring p53-dependent apoptosis. Thus, a combination of RT and HT may be particularly effective. To evaluate this effect, future trials should include HPV status for risk stratification (87). As a next step, clinical trials should test further RT dose de-escalation with concurrent HT in HPV-positive patients as it is already performed for RT alone (163, 164).

CONCLUSION

There is abundant evidence demonstrating that HT constitutes a valuable supplement to currently performed RT or RTCT schemes improving tumor response in tumor entities such as head and neck or cervix. It also inherits great potential to enhance RT-based therapy of recurrent disease as it has been shown for breast cancer. Through continuous improvement of HT delivery, planning, and monitoring techniques, treatment effects may further improve. Novel combinations with targeted therapy agents, immunotherapy, nanomedicine, or particle therapy constitute promising fields of further research and interesting areas for future clinical application.

AUTHOR CONTRIBUTIONS

JP: reviewed literature and wrote the manuscript. PV: reviewed literature and wrote the manuscript. SC: reviewed literature and wrote the manuscript.

REFERENCES

1. Coley W. The therapeutic value of the mixed toxins of the *Streptococcus* of erysipelas and *Bacillus prodigiosus* in the treatment of inoperable malignant tumors, with a report of one hundred and sixty cases. *Am J Med Sci* (1896) 112:251–81. doi:10.1097/00000441-189609000-00001

2. Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. *Pharmacol Ther* (1994) 64(3):529–64. doi:10.1016/0163-7258(94)90023-X

3. Quinn SD, Gedroyc WM. Thermal ablative treatment of uterine fibroids. *Int J Hyperthermia* (2015) 31(3):272–9. doi:10.3109/02656736.2015.1010608

4. Crezee H, van Leeuwen CM, Oei AL, Stalpers LJ, Bel A, Franken NA, et al. Thermoradiotherapy planning: integration in routine clinical practice. *Int J Hyperthermia* (2016) 32(1):41–9. doi:10.3109/02656736.2015.1110757

5. Dewhirst MW, Vujaskovic Z, Jones E, Thrall D. Re-setting the biologic rationale for thermal therapy. *Int J Hyperthermia* (2005) 21(8):779–90. doi:10.1080/02656730500271668

6. Vaupel PW, Kelleher DK. Pathophysiological and vascular characteristics of tumours and their importance for hyperthermia: heterogeneity is the key issue. *Int J Hyperthermia* (2010) 26(3):211–23. doi:10.3109/02656731003596259

7. Vujaskovic Z, Poulson JM, Gaskin AA, Thrall DE, Page RL, Charles HC, et al. Temperature-dependent changes in physiologic parameters of spontaneous canine soft tissue sarcomas after combined radiotherapy and hyperthermia treatment. *Int J Radiat Oncol Biol Phys* (2000) 46(1):179–85. doi:10.1016/S0360-3016(99)00362-4

8. Song CW, Rhee JG, Haumschild DJ. Continuous and non-invasive quantification of heat-induced changes in blood flow in the skin and RIF-1 tumour of mice by laser Doppler flowmetry. *Int J Hyperthermia* (1987) 3(1):71–7. doi:10.3109/02656738709140374

9. Vaupel PW, Otte J, Manz R. Oxygenation of malignant tumors after localized microwave hyperthermia. *Radiat Environ Biophys* (1982) 20(4):289–300. doi:10.1007/BF01323754

10. Song CW, Shakil A, Griffin RJ, Okajima K. Improvement of tumor oxygenation status by mild temperature hyperthermia alone or in combination with carbogen. *Semin Oncol* (1997) 24(6):626–32.

11. Moon EJ, Sonveaux P, Porporato PE, Danhier P, Gallez B, Batinic-Haberle I, et al. NADPH oxidase-mediated reactive oxygen species production activates hypoxia-inducible factor-1 (HIF-1) via the ERK pathway after hyperthermia treatment. *Proc Natl Acad Sci U S A* (2010) 107(47):20477–82. doi:10.1073/pnas.1006646107

12. Thews O, Li YP, Kelleher DK, Chance B, Vaupel P. Microcirculatory function, tissue oxygenation, microregional redox status and ATP distribution in tumors upon localized infrared-A-hyperthermia at 42°C. *Adv Exp Med Biol* (2003) 530:237–47. doi:10.1007/978-1-4615-0075-9_23

13. Dewey WC, Thrall DE, Gillette EL. Hyperthermia and radiation – a selective thermal effect on chronically hypoxic tumor cells in vivo. *Int J Radiat Oncol Biol Phys* (1977) 2(1–2):99–103. doi:10.1016/0360-3016(77)90013-X

14. Overgaard J, Grau C, Lindegaard JC, Horsman MR. The potential of using hyperthermia to eliminate radioresistant hypoxic cells. *Radiother Oncol* (1991) 20(Suppl 1):113–6. doi:10.1016/0167-8140(91)90197-O

15. Song CW, Park H, Griffin RJ. Improvement of tumor oxygenation by mild hyperthermia. *Radiat Res* (2001) 155(4):515–28. doi:10.1667/0033-7587(2001)155[0515:IOTOBM]2.0.CO;2

16. Thrall DE, Larue SM, Pruitt AF, Case B, Dewhirst MW. Changes in tumour oxygenation during fractionated hyperthermia and radiation therapy in spontaneous canine sarcomas. *Int J Hyperthermia* (2006) 22(5):365–73. doi:10.1080/02656730600836386

17. Kelleher DK, Vaupel P. No sustained improvement in tumor oxygenation after localized mild hyperthermia. *Adv Exp Med Biol* (2010) 662:393–8. doi:10.1007/978-1-4419-1241-1_57

18. Mackey MA, Ianzini F. Enhancement of radiation-induced mitotic catastrophe by moderate hyperthermia. *Int J Radiat Biol* (2000) 76(2):273–80. doi:10.1080/095530000138925

19. Harmon BV, Corder AM, Collins RJ, Gobé GC, Allen J, Allan DJ, et al. Cell death induced in a murine mastocytoma by 42-47°C heating in vitro: evidence that the form of death changes from apoptosis to necrosis above a critical heat load. *Int J Radiat Biol* (1990) 58(5):845–58. doi:10.1080/09553009014552221

20. Roti Roti JL, Kampinga HH, Malyapa RS, Wright WD, vander Waal RP, Xu M. Nuclear matrix as a target for hyperthermic killing of cancer cells. *Cell Stress Chaperones* (1998) 3(4):245–55. doi:10.1379/1466-1268(1998)003<0245:NMAATF>2.3.CO;2

21. Lepock JR. Role of nuclear protein denaturation and aggregation in thermal radiosensitization. *Int J Hyperthermia* (2004) 20(2):115–30. doi:10.1080/02656730310001637334

22. Wong RS, Kapp LN, Dewey WC. DNA fork displacement rate measurements in heated Chinese hamster ovary cells. *Biochim Biophys Acta* (1989) 1007(2):224–7. doi:10.1016/0167-4781(89)90043-2

23. Vertrees RA, Das GC, Coscio AM, Xie J, Zwischenberger JB, Boor PJ. A mechanism of hyperthermia-induced apoptosis in ras-transformed lung cells. *Mol Carcinog* (2005) 44(2):111–21. doi:10.1002/mc.20124

24. Sakaguchi Y, Stephens LC, Makino M, Kaneko T, Strebel FR, Danhauser LL, et al. Apoptosis in tumors and normal tissues induced by whole body hyperthermia in rats. *Cancer Res* (1995) 55(22):5459–64.

25. Calderwood SK, Stevenson MA, Hahn GM. Effects of heat on cell calcium and inositol lipid metabolism. *Radiat Res* (1988) 113(3):414–25. doi:10.2307/3577239

26. Dressler C, Beuthan J, Mueller G, Zabarylo U, Minet O. Fluorescence imaging of heat-stress induced mitochondrial long-term depolarization in breast cancer cells. *J Fluoresc* (2006) 16(5):689–95. doi:10.1007/s10895-006-0110-z

27. Yu D-Y, Matsuya Y, Zhao Q-L, Ahmed K, Wei Z-L, Nemoto H, et al. Enhancement of hyperthermia-induced apoptosis by a new synthesized class of furan-fused tetracyclic compounds. *Apoptosis* (2007) 12(8):1523–32. doi:10.1007/s10495-007-0080-x

28. Krawczyk PM, Eppink B, Essers J, Stap J, Rodermond H, Odijk H, et al. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. *Proc Natl Acad Sci U S A* (2011) 108(24):9851–6. doi:10.1073/pnas.1101053108

29. Burgman P, Ouyang H, Peterson S, Chen DJ, Li GC. Heat inactivation of Ku autoantigen: possible role in hyperthermic radiosensitization. *Cancer Res* (1997) 57(14):2847–50.

30. Warters RL, Roti Roti JL. Excision of X-ray-induced thymine damage in chromatin from heated cells. *Radiat Res* (1979) 79(1):113–21. doi:10.2307/3575026

31. Ihara M, Suwa A, Komatsu K, Shimasaki T, Okaichi K, Hendrickson EA, et al. Heat sensitivity of double-stranded DNA-dependent protein kinase (DNA-PK) activity. *Int J Radiat Biol* (1999) 75(2):253–8. doi:10.1080/095530099140717

32. Oei AL, Vriend LEM, Crezee J, Franken NAP, Krawczyk PM. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. *Radiat Oncol* (2015) 10:165. doi:10.1186/s13014-015-0462-0

33. Toraya-Brown S, Fiering S. Local tumour hyperthermia as immunotherapy for metastatic cancer. *Int J Hyperthermia* (2014) 30(8):531–9. doi:10.3109/02656736.2014.968640

34. Ostberg JR, Dayanc BE, Yuan M, Oflazoglu E, Repasky EA. Enhancement of natural killer (NK) cell cytotoxicity by fever-range thermal stress is dependent on NKG2D function and is associated with plasma membrane NKG2D clustering and increased expression of MICA on target cells. *J Leukoc Biol* (2007) 82(5):1322–31. doi:10.1189/jlb.1106699

35. Ito A, Tanaka K, Kondo K, Shinkai M, Honda H, Matsumoto K, et al. Tumor regression by combined immunotherapy and hyperthermia using magnetic nanoparticles in an experimental subcutaneous murine melanoma. *Cancer Sci* (2003) 94(3):308–13. doi:10.1111/j.1349-7006.2003.tb01438.x

36. Multhoff G, Mizzen L, Winchester CC, Milner CM, Wenk S, Eissner G, et al. Heat shock protein 70 (Hsp70) stimulates proliferation and cytolytic activity of natural killer cells. *Exp Hematol* (1999) 27(11):1627–36. doi:10.1016/S0301-472X(99)00104-6

37. Noessner E, Gastpar R, Milani V, Brandl A, Hutzler PJS, Kuppner MC, et al. Tumor-derived heat shock protein 70 peptide complexes are cross-presented by human dendritic cells. *J Immunol* (2002) 169(10):5424–32. doi:10.4049/jimmunol.169.10.5424

38. Suto R, Srivastava PK. A mechanism for the specific immunogenicity of heat-shock protein-chaperoned peptides. *Science* (1995) 269(5230):1585–8. doi:10.1126/science.7545313

39. Dai S, Wan T, Wang B, Zhou X, Xiu F, Chen T, et al. More efficient induction of HLA-A*0201-restricted and carcinoembryonic antigen (CEA)-specific CTL response by immunization with exosomes prepared from heat-stressed CEA-positive tumor cells. *Clin Cancer Res* (2005) 11(20):7554–63. doi:10.1158/1078-0432.CCR-05-0810

40. Mace TA, Zhong L, Kokolus KM, Repasky EA. Effector CD8+ T cell IFN-γ production and cytotoxicity are enhanced by mild hyperthermia. *Int J Hyperthermia* (2012) 28(1):9–18. doi:10.3109/02656736.2011.616182

41. Yoshioka H, Koga S, Maeta M, Shimizu N, Hamazoe R, Murakami A. The influence of hyperthermia in vitro on the functions of peritoneal macrophages in mice. *Jpn J Surg* (1990) 20(1):119–22. doi:10.1007/BF02470725

42. Basu S, Srivastava PK. Fever-like temperature induces maturation of dendritic cells through induction of hsp90. *Int Immunol* (2003) 15(9):1053–61. doi:10.1093/intimm/dxg104

43. Kong G, Braun RD, Dewhirst MW. Characterization of the effect of hyperthermia on nanoparticle extravasation from tumor vasculature. *Cancer Res* (2001) 61(7):3027–32.

44. Fisher DT, Chen Q, Skitzki JJ, Muhitch JB, Zhou L, Appenheimer MM, et al. IL-6 trans-signaling licenses mouse and human tumor microvascular gateways for trafficking of cytotoxic T cells. *J Clin Invest* (2011) 121(10):3846–59. doi:10.1172/JCI44952

45. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, et al. Hyperthermia in combined treatment of cancer. *Lancet Oncol* (2002) 3(8):487–97. doi:10.1016/S1470-2045(02)00818-5

46. Abe M, Hiraoka M, Takahashi M, Egawa S, Matsuda C, Onoyama Y, et al. Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (Thermotron RF-8) in combination with radiation for cancer therapy. *Cancer* (1986) 58(8):1589–95. doi:10.1002/1097-0142(19861015)58:8<1589::AID-CNCR2820580802>3.0.CO;2-B

47. Kok HP, Crezee J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. *Int J Hyperthermia* (2017) 33(4):378–86. doi:10.1080/02656736.2016.1268726

48. Rhee JG, Lee CK, Osborn J, Levitt SH, Song CW. Precooling prevents overheating of subcutaneous fat in the use of RF capacitive heating. *Int J Radiat Oncol Biol Phys* (1991) 20(5):1009–15. doi:10.1016/0360-3016(91)90198-D

49. Seebass M, Beck R, Gellermann J, Nadobny J, Wust P. Electromagnetic phased arrays for regional hyperthermia: optimal frequency and antenna arrangement. *Int J Hyperthermia* (2001) 17(4):321–36. doi:10.1080/02656730110049529

50. Wust P, Fähling H, Wlodarczyk W, Seebass M, Gellermann J, Deuflhard P, et al. Antenna arrays in the SIGMA-eye applicator: interactions and transforming networks. *Med Phys* (2001) 28(8):1793–805. doi:10.1118/1.1388220

51. Crezee J, Van Haaren PMA, Westendorp H, De Greef M, Kok HP, Wiersma J, et al. Improving locoregional hyperthermia delivery using the 3-D controlled AMC-8 phased array hyperthermia system: a preclinical study. *Int J Hyperthermia* (2009) 25(7):581–92. doi:10.3109/02656730903213374

52. Togni P, Rijnen Z, Numan WCM, Verhaart RF, Bakker JF, van Rhoon GC, et al. Electromagnetic redesign of the HYPERcollar applicator: toward improved deep local head-and-neck hyperthermia. *Phys Med Biol* (2013) 58(17):5997–6009. doi:10.1088/0031-9155/58/17/5997

53. Mittal BB, Sathiaseelan V, Kies MS. Simultaneous localized 915 MHz external and interstitial microwave hyperthermia to heat tumors greater than 3 cm in depth. *Int J Radiat Oncol Biol Phys* (1990) 19(3):669–75. doi:10.1016/0360-3016(90)90495-6

54. Seegenschmiedt MH, Klautke G, Walther E, Feldmann HJ, Katalinic A, Stuschke M, et al. Water-filtered infrared-A-hyperthermia combined with radiotherapy in advanced and recurrent tumors. Initial results of a multicenter phase I-II study. *Strahlenther Onkol* (1996) 172(9):475–84.

55. Vaupel P, Kelleher DK, Krüger W. Water-filtered infrared-A radiation: a novel technique to heat superficial tumors. *Strahlenther Onkol* (1992) 168(11):633–9.

56. Notter M, Piazena H, Vaupel P. Hypofractionated re-irradiation of large-sized recurrent breast cancer with thermography-controlled, contact-free water-filtered infra-red-A hyperthermia: a retrospective study of 73 patients. *Int J Hyperthermia* (2017) 33(2):227–36. doi:10.1080/02656736.2016.1235731

57. Gellermann J, Wust P, Stalling D, Seebass M, Nadobny J, Beck R, et al. Clinical evaluation and verification of the hyperthermia treatment planning system hyperplan. *Int J Radiat Oncol Biol Phys* (2000) 47(4):1145–56. doi:10.1016/S0360-3016(00)00425-9

58. Sreenivasa G, Gellermann J, Rau B, Nadobny J, Schlag P, Deuflhard P, et al. Clinical use of the hyperthermia treatment planning system HyperPlan to predict effectiveness and toxicity. *Int J Radiat Oncol Biol Phys* (2003) 55(2):407–19. doi:10.1016/S0360-3016(02)04144-5

59. van Haaren PMA, Kok HP, van den Berg CAT, Zum Vörde Sive Vörding PJ, Oldenborg S, Stalpers LJA, et al. On verification of hyperthermia treatment planning for cervical carcinoma patients. *Int J Hyperthermia* (2007) 23(3):303–14. doi:10.1080/02656730701297538

60. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* (1996) 35(4):731–44. doi:10.1016/0360-3016(96)00154-X

61. van der Zee J, González González D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective,

randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet* (2000) 355(9210):1119–25. doi:10.1016/S0140-6736(00)02059-6

62. Hurwitz MD, Hansen JL, Prokopios-Davos S, Manola J, Wang Q, Bornstein BA, et al. Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer. *Cancer* (2011) 117(3):510–6. doi:10.1002/cncr.25619

63. Wittlinger M, Rödel CM, Weiss C, Krause SF, Kühn R, Fietkau R, et al. Quadrimodal treatment of high-risk T1 and T2 bladder cancer: transurethral tumor resection followed by concurrent radiochemotherapy and regional deep hyperthermia. *Radiother Oncol* (2009) 93(2):358–63. doi:10.1016/j.radonc.2009.09.018

64. Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vujaskovic Z, Yu D, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* (2005) 23(13):3079–85. doi:10.1200/JCO.2005.05.520

65. Wust P, Gellermann J, Harder C, Tilly W, Rau B, Dinges S, et al. Rationale for using invasive thermometry for regional hyperthermia of pelvic tumors. *Int J Radiat Oncol Biol Phys* (1998) 41(5):1129–37. doi:10.1016/S0360-3016(98)00165-5

66. Gellermann J, Wlodarczyk W, Feussner A, Fähling H, Nadobny J, Hildebrandt B, et al. Methods and potentials of magnetic resonance imaging for monitoring radiofrequency hyperthermia in a hybrid system. *Int J Hyperthermia* (2005) 21(6):497–513. doi:10.1080/02656730500070102

67. Weihrauch M, Wust P, Weiser M, Nadobny J, Eisenhardt S, Budach V, et al. Adaptation of antenna profiles for control of MR guided hyperthermia (HT) in a hybrid MR-HT system. *Med Phys* (2007) 34(12):4717–25. doi:10.1118/1.2804617

68. Stakhursky VL, Arabe O, Cheng K-S, Macfall J, Maccarini P, Craciunescu O, et al. Real-time MRI-guided hyperthermia treatment using a fast adaptive algorithm. *Phys Med Biol* (2009) 54(7):2131–45. doi:10.1088/0031-9155/54/7/019

69. Kok HP, Ciampa S, de Kroon-Oldenhof R, Steggerda-Carvalho EJ, van Stam G, Zum Vörde Sive Vörding PJ, et al. Toward online adaptive hyperthermia treatment planning: correlation between measured and simulated specific absorption rate changes caused by phase steering in patients. *Int J Radiat Oncol Biol Phys* (2014) 90(2):438–45. doi:10.1016/j.ijrobp.2014.05.1307

70. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys* (1984) 10(6):787–800. doi:10.1016/0360-3016(84)90379-1

71. Sapareto SA, Hopwood LE, Dewey WC. Combined effects of X irradiation and hyperthermia on CHO cells for various temperatures and orders of application. *Radiat Res* (1978) 73(2):221–33. doi:10.2307/3574816

72. Overgaard J. Simultaneous and sequential hyperthermia and radiation treatment of an experimental tumor and its surrounding normal tissue in vivo. *Int J Radiat Oncol Biol Phys* (1980) 6:1507–17. doi:10.1016/0360-3016(80)90008-5

73. Marino C, Cividalli A. Combined radiation and hyperthermia: effects of the number of heat fractions and their interval on normal and tumour tissues. *Int J Hyperthermia* (1992) 8(6):771–81. doi:10.3109/02656739209005025

74. Rhee JG, Schuman VL, Song CW, Levitt SH. Difference in the thermotolerance of mouse mammary carcinoma cells in vivo and in vitro. *Cancer Res* (1987) 47(10):2571–5.

75. Overgaard J, Nielsen OS. The importance of thermotolerance for the clinical treatment with hyperthermia. *Radiother Oncol* (1983) 1(2):167–78. doi:10.1016/S0167-8140(83)80019-X

76. Nah BS, Choi IB, Oh WY, Osborn JL, Song CW. Vascular thermal adaptation in tumors and normal tissue in rats. *Int J Radiat Oncol Biol Phys* (1996) 35(1):95–101. doi:10.1016/S0360-3016(96)85016-4

77. Griffin RJ, Dings RPM, Jamshidi-Parsian A, Song CW. Mild temperature hyperthermia and radiation therapy: role of tumour vascular thermotolerance and relevant physiological factors. *Int J Hyperthermia* (2010) 26(3):256–63. doi:10.3109/02656730903453546

78. Petrella F, Radice D, Borri A, Galetta D, Gasparri R, Casiraghi M, et al. Chest wall resection and reconstruction for locally recurrent breast cancer: from technical aspects to biological assessment. *Surgeon* (2016) 14(1):26–32. doi:10.1016/j.surge.2014.03.001

79. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys* (2016) 94(5):1073–87. doi:10.1016/j.ijrobp.2015.12.361

80. Linthorst M, Baaijens M, Wiggenraad R, Creutzberg C, Ghidey W, van Rhoon GC, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: results in 248 patients. *Radiother Oncol* (2015) 117(2):217–22. doi:10.1016/j.radonc.2015.04.019

81. Linthorst M, van Geel AN, Baaijens M, Ameziane A, Ghidey W, van Rhoon GC, et al. Re-irradiation and hyperthermia after surgery for recurrent breast cancer. *Radiother Oncol* (2013) 109(2):188–93. doi:10.1016/j.radonc.2013.05.010

82. Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DFM, Buijsen J, Mastrigt GAV, et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* (2010) 3:CD006377. doi:10.1002/14651858.CD006377

83. Franckena M, Stalpers LJA, Koper PCM, Wiggenraad RGJ, Hoogenraad WJ, van Dijk JDP, et al. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch Deep Hyperthermia Trial. *Int J Radiat Oncol Biol Phys* (2008) 70(4):1176–82. doi:10.1016/j.ijrobp.2007.07.2348

84. Datta NR, Rogers S, Klingbiel D, Gomez S, Puric E, Bodis S. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. *Int J Hyperthermia* (2016) 6736:1–34. doi:10.1080/02656736.2016.1195924

85. Chen HW, Jei JWL. A randomized trial of hyperthermoradiochemotherapy for uterine cervix. *Chin J Oncol* (1997) 24(249):51.

86. Lutgens LCHW, Koper PCM, Jobsen JJ, van der Steen-Banasik EM, Creutzberg CL, van den Berg HA, et al. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: results of the randomized RADCHOC trial. *Radiother Oncol* (2016) 120(3):378–82. doi:10.1016/j.radonc.2016.02.010

87. Datta NR, Rogers S, Ordonez SG, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: a systematic review and meta-analysis. *Int J Hyperthermia* (2016) 32(1):31–40. doi:10.3109/02656736.2015.1099746

88. Kang M, Liu WQ, Qin YT, Wei ZX, Wang RS. Long-term efficacy of microwave hyperthermia combined with chemoradiotherapy in treatment of nasopharyngeal carcinoma with cervical lymph node metastases. *Asian Pac J Cancer Prev* (2013) 14(12):7395–400. doi:10.7314/APJCP.2013.14.12.7395

89. Hua Y, Ma S, Fu Z, Hu Q, Wang L, Piao Y. Intracavity hyperthermia in nasopharyngeal cancer: a phase III clinical study. *Int J Hyperthermia* (2011) 27(2):180–6. doi:10.3109/02656736.2010.503982

90. Zhao C, Chen J, Yu B, Chen X. Improvement in quality of life in patients with nasopharyngeal carcinoma treated with non-invasive extracorporeal radiofrequency in combination with chemoradiotherapy. *Int J Radiat Biol* (2014) 90(10):853–8. doi:10.3109/09553002.2014.916579

91. De Wee E, Verduijn GM, Rijnen Z, Togni P, Hardillo JAU, Ten Hove I, et al. OC-0335: feasibility of deep head and neck hyperthermia. *Radiother Oncol* (2015) 115:S165–6. doi:10.1016/S0167-8140(15)40333-0

92. Paulides MM, Verduijn GM, van Holthe N. Status quo and directions in deep head and neck hyperthermia. *Radiat Oncol* (2016) 11:21. doi:10.1186/s13014-016-0588-8

93. De Haas-Kock DFM, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, Mastrigt GAV, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. *Cochrane Database Syst Rev* (2009) 3:CD006269. doi:10.1002/14651858.CD006269.pub2

94. Schroeder C, Gani C, Lamprecht U, von Weyhern CH, Weinmann M, Bamberg M, et al. Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone. *Int J Hyperthermia* (2012) 28(8):707–14. doi:10.3109/02656736.2012.722263

95. Kang MK, Kim MS, Kim JH. Clinical outcomes of mild hyperthermia for locally advanced rectal cancer treated with preoperative radiochemotherapy. *Int J Hyperthermia* (2011) 27(5):482–90. doi:10.3109/02656736.2011.563769

96. Barsukov YA, Gordeyev SS, Tkachev SI, Fedyanin MY, Perevoshikov AG. Phase II study of concomitant chemoradiotherapy with local hyperthermia and metronidazole for locally advanced fixed rectal cancer. *Colorectal Dis* (2013) 15(9):1107–14. doi:10.1111/codi.12281

97. Rasulov AO, Gordeyev SS, Barsukov YA, Tkachev SI, Malikhov AG, Balyasnikova SS, et al. Short-course preoperative radiotherapy combined with chemotherapy, delayed surgery and local hyperthermia for rectal cancer: a phase II study. *Int J Hyperthermia* (2016) 33:1–9.

98. Schulze T, Wust P, Gellermann J, Hildebrandt B, Riess H, Felix R, et al. Influence of neoadjuvant radiochemotherapy combined with hyperthermia on the quality of life in rectum cancer patients. *Int J Hyperthermia* (2006) 22(4):301–18. doi:10.1080/02656730600665504

99. Matsui K, Takebayashi S, Watai K, Kakehi M, Kubota Y, Yao M, et al. Combination radiotherapy of urinary bladder carcinoma with chemohyperthermia. *Int J Hyperthermia* (1991) 7(1):19–26. doi:10.3109/02656739109004973

100. Masunaga SI, Hiraoka M, Akuta K, Nishimura Y, Nagata Y, Jo S, et al. Phase I/II trial of preoperative thermoradiotherapy in the treatment of urinary bladder cancer. *Int J Hyperthermia* (1993) 10(1):31–40. doi:10.3109/02656739409009329

101. Overgaard J, Bentzen SM, Overgaard J, Gonzalez DG, Hulshof MC, Arcangeli G, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. *Lancet* (1995) 345(8949):540–3. doi:10.1016/S0140-6736(95)90463-8

102. Mitsumori M, Zhi-Fan Z, Oliynychenko P, Park JH, Choi IB, Tatsuzaki H, et al. Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency. *Int J Clin Oncol* (2007) 12(3):192–8. doi:10.1007/s10147-006-0647-5

103. Sakurai H, Hayakawa K, Mitsuhashi N, Tamaki Y, Nakayama Y, Kurosaki H, et al. Effect of hyperthermia combined with external radiation therapy in primary non-small cell lung cancer with direct bony invasion. *Int J Hyperthermia* (2002) 18(5):472–83. doi:10.1080/02656730210146917

104. Ohguri T, Imada H, Yahara K, Moon SD, Yamaguchi S, Yatera K, et al. Re-irradiation plus regional hyperthermia for recurrent non-small cell lung cancer: a potential modality for inducing long-term survival in selected patients. *Lung Cancer* (2012) 77(1):140–5. doi:10.1016/j.lungcan.2012.02.018

105. Van Vulpen M, de Leeuw JRJ, van Gellekom MPR, van der Hoeven J, de Graeff A, van Moorselaar RJA, et al. A prospective quality of life study in patients with locally advanced prostate cancer, treated with radiotherapy with or without regional or interstitial hyperthermia. *Int J Hyperthermia* (2003) 19(4):402–13. doi:10.1080/0265673031000063855

106. Tilly W, Gellermann J, Graf R, Hildebrandt B, Weißbach L, Budach V, et al. Regional hyperthermia in conjunction with definitive radiotherapy against recurrent or locally advanced prostate cancer T3 pN0 M0. *Strahlenther Onkol* (2005) 181(1):35–41. doi:10.1007/s00066-005-1296-8

107. Van Vulpen M, de Leeuw AAC, Raaymakers BW, van Moorselaar RJA, Hofman P, Lagendijk JJW, et al. Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: preliminary results. *BJU Int* (2004) 93(1):36–41. doi:10.1111/j.1464-410X.2004.04551.x

108. Maluta S, Dall'Oglio S, Romano M, Marciai N, Pioli F, Giri MG, et al. Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: preliminary results of a prospective phase II study. *Int J Hyperthermia* (2007) 23(5):451–6. doi:10.1080/02656730701553260

109. Müller A-C, Zips D, Heinrich V, Lamprecht U, Voigt O, Burock S, et al. Regional hyperthermia and moderately dose-escalated salvage radiotherapy for recurrent prostate cancer. Protocol of a phase II trial. *Radiat Oncol* (2015) 10:138. doi:10.1186/s13014-015-0442-4

110. Kukiełka AM, Strnad V, Stauffer P, Dabrowski T, Hetnał M, Nahajowski D, et al. Salvage brachytherapy in combination with interstitial hyperthermia for locally recurrent prostate carcinoma following external beam radiation therapy: a prospective phase II study. *J Contemp Brachytherapy* (2015) 7(3):254–8. doi:10.5114/jcb.2015.51871

111. Yahara K, Ohguri T, Yamaguchi S, Imada H, Narisada H, Ota S, et al. Definitive radiotherapy plus regional hyperthermia for high-risk and very high-risk prostate carcinoma: thermal parameters correlated with biochemical relapse-free survival. *Int J Hyperthermia* (2015) 31(6):600–8. doi:10.3109/02656736.2015.1062214

112. Sneed PK, Stauffer PR, McDermott MW, Diederich CJ, Lamborn KR, Prados MD, et al. Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost ± hyperthermia for glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* (1998) 40(2):287–95. doi:10.1016/S0360-3016(97)00731-1

113. Hulshof MC, Raaymakers BW, Lagendijk JJW, Koot RW, Crezee H, Stalpers LJA, et al. A feasibility study of interstitial hyperthermia plus external beam radiotherapy in glioblastoma multiforme using the multi electrode current source (MECS) system. *Int J Hyperthermia* (2004) 20(5):451–63. doi:10.1080/02656730410001668357

114. Borasi G, Nahum A, Paulides MM, Powathil G, Russo G, Fariselli L, et al. Fast and high temperature hyperthermia coupled with radiotherapy as a possible new treatment for glioblastoma. *J Ther Ultrasound* (2016) 4(1):32. doi:10.1186/s40349-016-0078-3

115. Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem B-C, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* (2010) 11(6):561–70. doi:10.1016/S1470-2045(10)70071-1

116. Leopold KA, Harrelson J, Prosnitz L, Samulski TV, Dewhirst MW, Oleson JR, et al. Preoperative hyperthermia and radiation for soft tissue sarcomas: advantage of two vs one hyperthermia treatments per week. *Int J Radiat Oncol Biol Phys* (1989) 16(1):107–15. doi:10.1016/0360-3016(89)90017-5

117. de Jong MAA, Oldenborg S, Bing Oei S, Griesdoorn V, Kolff MW, Koning CCE, et al. Reirradiation and hyperthermia for radiation-associated sarcoma. *Cancer* (2012) 118(1):180–7. doi:10.1002/cncr.26252

118. Nakajima M, Kato H, Sakai M, Sano A, Miyazaki T, Sohda M, et al. Planned esophagectomy after neoadjuvant hyperthermo-chemoradiotherapy using weekly low-dose docetaxel and hyperthermia for advanced esophageal carcinomas. *Hepatogastroenterology* (2015) 62(140):887–91.

119. Hulshof MC, van Haaren PMA, van Lanschot JJB, Richel DJ, Fockens P, Oldenborg S, et al. Preoperative chemoradiation combined with regional hyperthermia for patients with resectable esophageal cancer. *Int J Hyperthermia* (2009) 25(1):79–85. doi:10.1080/02656730802464078

120. Sakamoto T, Katoh H, Shimizu T, Yamashita I, Takemori S, Tazawa K, et al. Clinical results of treatment of advanced esophageal carcinoma with hyperthermia in combination with chemoradiotherapy. *Chest* (1997) 112(6):1487–93. doi:10.1378/chest.112.6.1487

121. Kuwano H, Sumiyoshi K, Watanabe M, Sadanaga N, Nozoe T, Yasuda M, et al. Preoperative hyperthermia combined with chemotherapy and irradiation for the treatment of patients with esophageal carcinoma. *Tumori* (1995) 81(1):18–22.

122. Liming S, Yongling J, Qiner W, Xianghui D. Regional hyperthermia combined with radiotherapy for esophageal squamous cell carcinoma with supraclavicular lymph node metastasis. *Oncotarget* (2016) 8(3):5339–48. doi: 10.18632/oncotarget.14148

123. Nozoe T, Kuwano H, Sadanaga N, Watanabe M, Yasuda M, Sugimachi K. Hyperthermia combined with chemotherapy and irradiation for the prolongation of the postoperative prognosis in the patients with esophageal carcinoma invading neighbouring structures. *Int Surg* (1996) 81(1):21–6.

124. Juffermans JHM, Hanssens PEJ, van Putten WLJ, van Rhoon GC, van der Zee J. Reirradiation and hyperthermia in rectal carcinoma: a retrospective study on palliative effect. *Cancer* (2003) 98(8):1759–66. doi:10.1002/cncr.11719

125. Milani V, Pazos M, Issels RD, Buecklein V, Rahman S, Tschoep K, et al. Radiochemotherapy in combination with regional hyperthermia in pre-irradiated patients with recurrent rectal cancer. *Strahlenther Onkol* (2008) 184(3):163–8. doi:10.1007/s00066-008-1731-8

126. Klaver YLB, Lemmens VEPP, Nienhuijs SW, Nieuwenhuijzen GAP, Rutten HJT, de Hingh IHJT. Intraoperative radiotherapy and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Strahlenther Onkol* (2013) 189(3):256–60. doi:10.1007/s00066-012-0282-1

127. Kalapurakal JA, Pierce M, Chen A, Sathiaseelan V. Efficacy of irradiation and external hyperthermia in locally advanced, hormone-refractory or radiation recurrent prostate cancer: a preliminary report. *Int J Radiat Oncol Biol Phys* (2003) 57(3):654–64. doi:10.1016/S0360-3016(03)00625-4

128. Maluta S, Schaffer M, Pioli F, Dall'Oglio S, Pasetto S, Schaffer PM, et al. Regional hyperthermia combined with chemoradiotherapy in primary or recurrent locally advanced pancreatic cancer. *Strahlenther Onkol* (2011) 187(10):619–25. doi:10.1007/s00066-011-2226-6

129. Dong Y, Wu G. Analysis of short and long term therapeutic effects of radiofrequency hyperthermia combined with conformal radiotherapy in hepatocellular carcinoma. *J BUON* (2016) 21(2):407–11.

130. Yu JI, Park HC, Choi DH, Noh JM, Oh D, Park JS, et al. Prospective phase II trial of regional hyperthermia and whole liver irradiation for numerous

chemorefractory liver metastases from colorectal cancer. *Radiat Oncol J* (2016) 34(1):34–44. doi:10.3857/roj.2016.34.1.34

131. Aktas M, de Jong D, Nuyttens JJ, van der Zee J, Wielheesen DHM, Batman E, et al. Concomitant radiotherapy and hyperthermia for primary carcinoma of the vagina: a cohort study. *Eur J Obstet Gynecol Reprod Biol* (2007) 133(1):100–4. doi:10.1016/j.ejogrb.2006.05.005

132. Atmaca A, Al-Batran S-E, Neumann A, Kolassa Y, Jäger D, Knuth A, et al. Whole-body hyperthermia (WBH) in combination with carboplatin in patients with recurrent ovarian cancer – a phase II study. *Gynecol Oncol* (2009) 112(2):384–8. doi:10.1016/j.ygyno.2008.11.001

133. Bruns I, Kohlmann T, Wiedemann GJ, Bakhshandeh A. Bewertung des therapeutischen Gewinns von Patienten mit Pleuramesotheliom unter Therapie mit 41,8°C Ganzkörperhyperthermie plus Ifosfamid, Carboplatin und Etoposid (ICE) anhand des Modifizierten Brunner-Score (MBS). *Pneumologie* (2004) 58(4):210–6. doi:10.1055/s-2003-812525

134. Richel O, zum Vörde Sive Vörding PJ, Rietbroek R, vander Velden J, van Dijk JDP, Schilthuis MS, et al. Phase II study of carboplatin and whole body hyperthermia (WBH) in recurrent and metastatic cervical cancer. *Gynecol Oncol* (2004) 95(3):680–5. doi:10.1016/j.ygyno.2004.08.023

135. Hegewisch-Becker S, Gruber Y, Corovic A, Pichlmeier U, Atanackovic D, Nierhaus A, et al. Whole-body hyperthermia (41.8°C) combined with bimonthly oxaliplatin, high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer: a phase II study. *Ann Oncol* (2002) 13(8):1197–204. doi:10.1093/annonc/mdf216

136. Engelhardt R, Müller U, Weth-Simon R, Neumann HA, Löhr GW. Treatment of disseminated malignant melanoma with cisplatin in combination with whole-body hyperthermia and doxorubicin. *Int J Hyperthermia* (1980) 6(3):511–5. doi:10.3109/02656739009140947

137. Colombo R, Salonia A, Leib Z, Pavone-Macaluso M, Engelstein D. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int* (2011) 107(6):912–8. doi:10.1111/j.1464-410X.2010.09654.x

138. Sugimach K, Kuwano H, Ide H, Toge T, Saku M, Oshiumi Y. Chemotherapy combined with or without hyperthermia for patients with oesophageal carcinoma: a prospective randomized trial. *Int J Hyperthermia* (1994) 10(4):485–93. doi:10.3109/02656739409009352

139. Shen H, Li X-D, Wu C-P, Yin Y-M, Wang R, Shu Y-Q. The regimen of gemcitabine and cisplatin combined with radio frequency hyperthermia for advanced non-small cell lung cancer: a phase II study. *Int J Hyperthermia* (2011) 27(1):27–32. doi:10.3109/02656736.2010.500645

140. Wessalowski R, Schneider DT, Mils O, Friemann V, Kyrillopoulou O, Schaper J, et al. Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: an open-label, non-randomised, single-institution, phase 2 study. *Lancet Oncol* (2013) 14(9):843–52. doi:10.1016/S1470-2045(13)70271-7

141. Cho CH, Wust P, Hildebrandt B, Issels RD, Sehouli J, Kerner T, et al. Regional hyperthermia of the abdomen in conjunction with chemotherapy for peritoneal carcinomatosis: evaluation of two annular-phased-array applicators. *Int J Hyperthermia* (2008) 24(5):399–408. doi:10.1080/02656730801929915

142. Fotopoulou C, Cho C-H, Kraetschell R, Gellermann J, Wust P, Lichtenegger W, et al. Regional abdominal hyperthermia combined with systemic chemotherapy for the treatment of patients with ovarian cancer relapse: results of a pilot study. *Int J Hyperthermia* (2010) 26(2):118–26. doi:10.3109/02656730903369200

143. Vujaskovic Z, Kim DW, Jones E, Lan L, Mccall L, Dewhirst MW, et al. A phase I/II study of neoadjuvant liposomal doxorubicin, paclitaxel, and hyperthermia in locally advanced breast cancer. *Int J Hyperthermia* (2010) 26(5):514–21. doi:10.3109/02656731003639364

144. Trabulsi NH, Patakfalvi L, Nassif MO, Turcotte RE, Nichols A, Meguerditchian AN. Hyperthermic isolated limb perfusion for extremity soft tissue sarcomas: systematic review of clinical efficacy and quality

assessment of reported trials. *J Surg Oncol* (2012) 106(8):921–8. doi:10.1002/jso.23200

145. Koops HS, Vaglini M, Suciu S, Kroon BB, Thompson JF, Göhl J, et al. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. *J Clin Oncol* (1998) 16(9):2906–12.

146. Roca C, Primo L, Valdembri D, Cividalli A, Declerck P, Carmeliet P, et al. Hyperthermia inhibits angiogenesis by plasminogen activator inhibitor. *Cancer Res* (2003) 63(7):1500–7.

147. Nie W, Ma XL, Sang YX, Li YL, Gao X, Xu GC, et al. Synergic antitumor effect of SKLB1002 and local hyperthermia in 4T1 and CT26. *Clin Exp Med* (2014) 14(2):203–13. doi:10.1007/s10238-012-0225-2

148. Wilkens J, Elfke U. Direct comparison of biologically optimized spread-out Bragg peaks for protons and carbon ions. *Int J Radiat Oncol Biol Phys* (2008) 70(1):262–6. doi:10.1016/j.ijrobp.2007.08.029

149. Dokic I, Mairani A, Niklas M, Zimmermann F, Jäkel O, Debus J, et al. Next generation multi-scale biophysical characterization of high precision cancer particle radiotherapy using clinical proton, helium-, carbon- and oxygen ion beams. *Oncotarget* (2016) 7(35):56676–89. doi:10.18632/oncotarget.10996

150. Schlaff CD, Krauze A, Belard A, Connell JJO, Camphausen KA. Bringing the heavy: carbon ion therapy in the radiobiological and clinical context. *Radiat Oncol* (2014) 9(1):1–19. doi:10.1186/1748-717X-9-88

151. Datta NR, Puric E, Schneider R, Weber DC, Rogers S, Bodis S. Could hyperthermia with proton therapy mimic carbon ion therapy? Exploring a thermo-radiobiological rationale. *Int J Hyperthermia* (2014) 30(7):524–30. doi:10.3109/02656736.2014.963703

152. Robinson JE, Wizenberg MJ, McCready WA. Combined hyperthermia and radiation suggest and alternative to heavy particle therapy for reduced oxygen enhancement ratios. *Nature* (1974) 251(5475):521–2. doi:10.1038/251521a0

153. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, Dendale R, Delacroix S, Nauraye C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res* (2006) 38(5):255–60. doi:10.1159/000094834

154. Datta NR, Krishnan S, Speiser DE, Neufeld E, Kuster N, Bodis S, et al. Magnetic nanoparticle-induced hyperthermia with appropriate payloads: Paul Ehrlich's "magic (nano)bullet" for cancer theranostics? *Cancer Treat Rev* (2016) 50:217–27. doi:10.1016/j.ctrv.2016.09.016

155. Bergs JWJ, Wacker MG, Hehlgans S, Piiper A, Multhoff G, Rödel C, et al. The role of recent nanotechnology in enhancing the efficacy of radiation therapy. *Biochim Biophys Acta* (2015) 1856(1):130–43. doi:10.1016/j.bbcan.2015.06.008

156. Huynh E, Zheng G. Cancer nanomedicine: addressing the dark side of the enhanced permeability and retention effect. *Nanomedicine* (2015) 10:15–7. doi:10.2217/nnm.15.86

157. Zhang J, Dewilde AH, Chinn P, Foreman A, Barry S, Kanne D, et al. Herceptin-directed nanoparticles activated by an alternating magnetic field selectively kill HER-2 positive human breast cells *in vitro* via hyperthermia. *Int J Hyperthermia* (2011) 27(7):682–97. doi:10.3109/02656736.2011.609863

158. Carrey J, Mehdaoui B, Respaud M. Simple models for dynamic hysteresis loop calculations of magnetic single-domain nanoparticles: application to magnetic hyperthermia optimization. *J Appl Phys* (2011) 109(8):83921. doi:10.1063/1.3551582

159. Maier-Hauff K, Ulrich F, Nestler D, Niehoff H, Wust P, Thiesen B, et al. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *J Neurooncol* (2011) 103(2):317–24. doi:10.1007/s11060-010-0389-0

160. Stern JM, Kibanov Solomonov VV, Sazykina E, Schwartz JA, Gad SC, Goodrich GP. Initial evaluation of the safety of nanoshell-directed

photothermal therapy in the treatment of prostate disease. *Int J Toxicol* (2016) 35(1):38–46. doi:10.1177/1091581815600170

161. Wust P, Gneveckow U, Johannsen M, Böhmer D, Henkel T, Kahmann F, et al. Magnetic nanoparticles for interstitial thermotherapy – feasibility, tolerance and achieved temperatures. *Int J Hyperthermia* (2006) 22(8):673–85. doi:10.1080/02656730601106037

162. Durymanov MO, Rosenkranz AA, Sobolev AS. Current approaches for improving intratumoral accumulation and distribution of nanomedicines. *Theranostics* (2015) 5(9):1007–20. doi:10.7150/thno.11742

163. Owadally W, Hurt C, Timmins H, Parsons E, Townsend S, Patterson J, et al. PATHOS: a phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human papillomavirus (HPV) positive oropharyngeal cancer. *BMC Cancer* (2015) 15(1):602. doi:10.1186/s12885-015-1598-x

164. Marur S, Li S, Cmelak AJ, Gillison ML, Zhao WJ, Ferris RL, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx-ECOG-ACRIN Cancer Research Group. *J Clin Oncol* (2017) 35(5):490–7. doi:10.1200/JCO.2016.68.3300

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Parenchymal and Functional Lung Changes after Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer— Experiences from a Single Institution

Juliane Hörner-Rieber[1,2], Julian Dern[1,2], Denise Bernhardt[1,2], Laila König[1,2], Sebastian Adeberg[1,2], Vivek Verma[3], Angela Paul[1,2], Jutta Kappes[4], Hans Hoffmann[5,6], Juergen Debus[1,2], Claus P. Heussel[5,7,8] and Stefan Rieken[1,2]*

[1] Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany, [2] Heidelberg Institute of Radiation Oncology, Heidelberg, Germany, [3] University of Nebraska Medical Center, Department of Radiation Oncology, Nebraska Medical Center, Omaha, NE, United States, [4] Department of Pneumology, Thoraxklinik, Heidelberg University, Heidelberg, Germany, [5] Translational Research Unit, Thoraxklinik, Heidelberg University, Germany Translational Lung Research Centre Heidelberg (TLRC-H), German Centre for Lung Research (DZL), Heidelberg, Germany, [6] Department of Thoracic Surgery, Thoraxklinik, Heidelberg University, Heidelberg, Germany, [7] Department of Diagnostic and Interventional Radiology, University-Hospital, Heidelberg, Germany, [8] Department of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik at University-Hospital, Heidelberg, Germany

Introduction: This study aimed to evaluate parenchymal and functional lung changes following stereotactic body radiotherapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) patients and to correlate radiological and functional findings with patient and treatment characteristics as well as survival.

Materials and methods: Seventy patients with early-stage NSCLC treated with SBRT from 2004 to 2015 with more than 1 year of CT follow-up scans were analyzed. Incidence, morphology, severity of acute and late lung abnormalities as well as pulmonary function changes were evaluated and correlated with outcome.

Results: Median follow-up time was 32.2 months with 2-year overall survival (OS) of 83% and local progression-free survival of 88%, respectively. Regarding parenchymal changes, most patients only developed mild to moderate CT abnormalities. Mean ipsilateral lung dose (MLD) in biological effective dose and planning target volume size were significantly associated with maximum severity score of parenchymal changes ($p = 0.014$, $p < 0.001$). Furthermore, both maximum severity score and MLD were significantly connected with OS in univariate analysis ($p = 0.043$, $p = 0.025$). For functional lung changes, we detected significantly reduced total lung capacity, forced expiratory volume in 1 s, and forced vital capacity (FVC) parameters after SBRT ($p \leq 0.001$). Multivariate analyses revealed SBRT with an MLD ≥ 9.72 Gy and FVC reduction ≥ 0.54 L as independent prognostic factors for inferior OS ($p = 0.029$, $p = 0.004$).

Conclusion: SBRT was generally tolerated well with only mild toxicity. For evaluating the possible prognostic impact of MLD and FVC reduction on survival detected in this analysis, larger prospective studies are truly needed.

Keywords: non-small cell lung cancer, stereotactic body radiotherapy, radiation pneumonitis, radiation fibrosis, pulmonary function, lung injury

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is the standard of care for medically inoperable, early-stage non-small cell lung cancer (NSCLC) patients (1–3). After the introduction of SBRT, substantially higher overall survival (OS) rates were reported for this patient group by three large population-based analyses from the Netherlands and the US (4–6). Several prospective studies then demonstrated excellent 3-year local control around 90%, and survival rates of more than 50% in a highly comorbid population (7–9). SBRT has hence become the most optimal treatment option for patients with highly reduced pulmonary function [forced expiratory volume in 1 s (FEV$_1$) < 30%] suffering from severe chronic obstructive pulmonary disease (COPD) (GOLD III–IV) (10, 11).

However, despite the high conformality of SBRT, toxicities are a non-trivial result of SBRT, especially in a population with poor pulmonary function. Depending on the study, symptomatic radiation pneumonitis occurs in about 10–30% of patients, which can impair patient quality of life (12–15). Fatal (grade 5) radiation pneumonitis following SBRT is only reported in very rare cases (15–17). An understudied aspect of adverse effects is the association with parenchymal remodeling following SBRT, which is detected to some degree in nearly all patients (18). Fibrosis in the high-dose regions is found in about 80% of patients and can make for a challenging differentiation between benign radiologic changes and local recurrence (18, 19).

Whether post-SBRT lung scarring correlates with significant clinical changes in pulmonary function is controversial (20, 21). Stone et al. recently showed significant impairment in pulmonary function after SBRT in a prospective trial, but though this was not associated with worse OS (22). On the basis of these results, we conducted a toxicity analysis examining post-SBRT parenchymal and functional changes, and the influence on outcome in patients who are deemed inoperable due to medical comorbidities.

MATERIALS AND METHODS

Patient Population

Seventy consecutive patients treated between February 2004 and May 2015 were chosen for this analysis. Inclusion criteria were as follows: (1) receipt of SBRT for medically inoperable early-stage NSCLC (cT1-3cN0cM0) and (2) regular follow-up CT scans for at least 1 year at the Department of Radiation Oncology at the University Hospital Heidelberg, the Thoraxklinik Heidelberg, or at the German Cancer Research Center. The study and the study protocol were reviewed and approved by the Ethics committee of the University Hospital Heidelberg (S-140/2016). According to the decision of the Ethics committee, obtaining of written informed consent was not necessary due to the retrospective character of the study. Patients included in the analysis were identified from our cancer database. Anonymized patient data were used for analysis.

Treatment Characteristics

Patient selection, imaging protocols, and detailed treatment techniques have been reported previously (23–25).

Risk-adapted fractionation schemes were used, meaning that dose and fractionation schemes were adjusted based on tumor size and location (peripheral vs. central). Until 2011, patients were generally treated with a single fraction of 20–24 Gy prescribed to the 80% isodose line, depending on proximity to critical structures ($n = 32$). Thereafter, peripheral lesions were irradiated with three fractions of 15–18 Gy, prescribed to the conformally enclosing 65% isodose line, while central lesions received eight fractions of 7.5 Gy prescribed to the 80% isodose line ($n = 38$). Delivery techniques were 3-D ($n = 49$), helical TomoTherapy® ($n = 11$), and volumetric-modulated arc therapy ($n = 10$).

Outcome Evaluation

Routine follow-up visits involved a contrast-enhanced CT scan of the thorax around the 3-, 6-, and 12-month intervals following SBRT. If no tumor recurrence was detected in the CT scan after 12 months, CTs and X-rays were done alternately every 6–12 months thereafter. Patients with reduced performance scores often only received X-rays after 12 months. Local progression referred to progression of the tumor within the high-dose volume. Differentiation between local progression and benign fibrosis in the high-dose volume is known to be challenging. Positron emission tomography (PET)-CT scans or biopsy was used to distinguish between benign lesions and tumor recurrence.
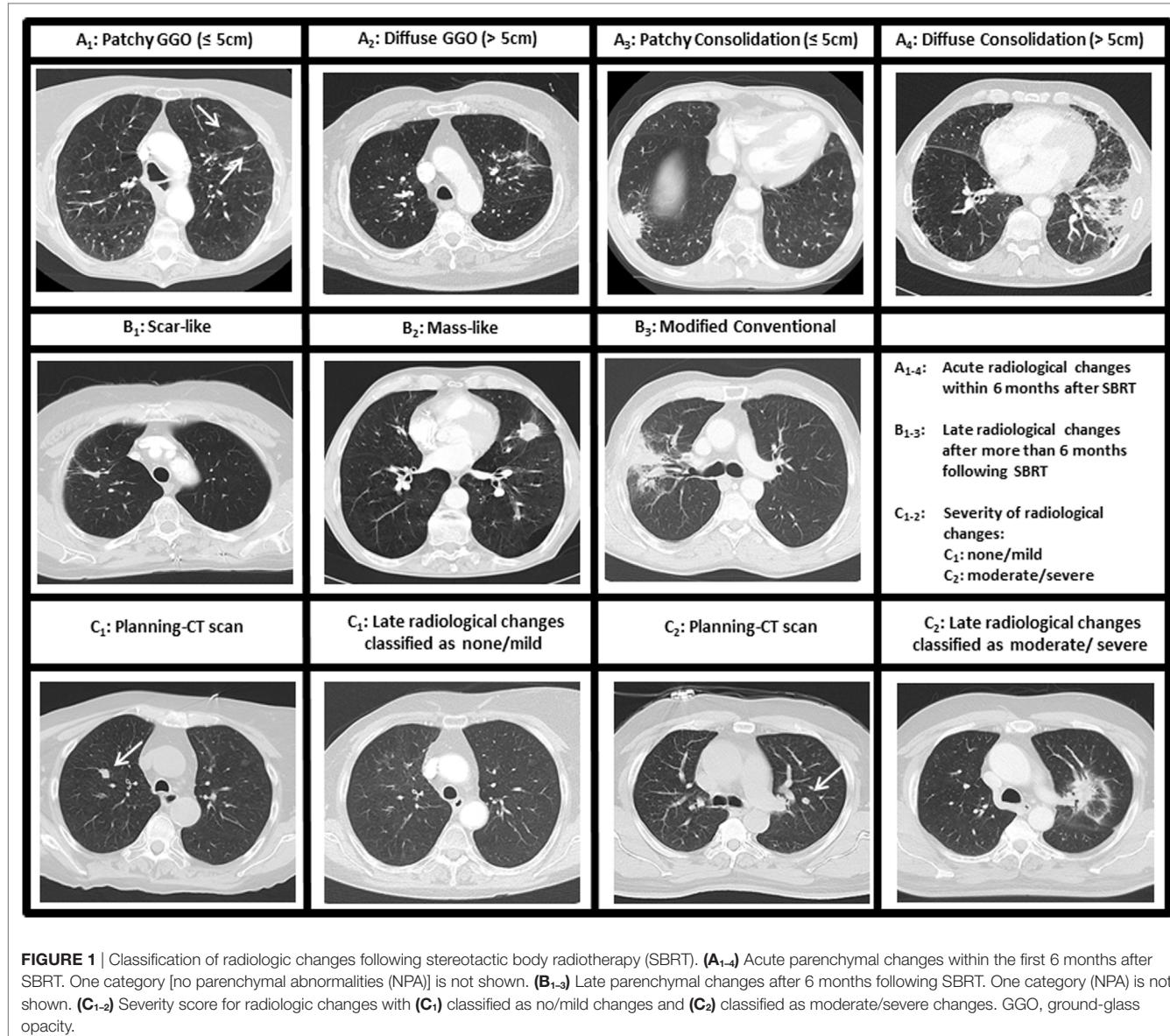
To correlate irradiated doses with clinical results, biological effective doses (BEDs) were calculated: an α/β ratio of 10 and 3 Gy was assumed for the tumor and lung tissue, respectively. BED was calculated using the linear-quadratic model:

$$\text{BED}(\text{Gy}) = \text{fractional dose}$$
$$\times \text{ number of fractions}\left(1 + \frac{\text{fractional dose}}{\alpha/\beta}\right).$$

Pulmonary function tests (PFTs) of all patients as performed 1–0 month before SBRT and in median 9.3 months after SBRT (5.8–18.1 months) were analyzed. These included the following: FEV$_1$, forced vital capacity (FVC), total lung capacity (TLC), residual volume, and airway resistance (R).

Radiologic changes were defined as acute changes when they were registered within the first 6 months following SBRT, and late changes when they occurred at or after 6 months. The applied classification system was initially described by Trovo et al. and later specified by Dahele et al. (18, 26). Herein, acute findings were grouped into five categories: no parenchymal abnormalities (NPA), patchy ground-glass opacity (PGGO), diffuse GGO (DGGO), patchy consolidation (PCO), and diffuse consolidation (DCO) (**Figure 1A**). Late CT changes were classified into four different categories: NPA, scar-like fibrosis (SLF), mass-like fibrosis (MLF), and modified conventional pattern of fibrosis (MCPF) (**Figure 1B**) (18, 26). Radiologic changes were categorized by two experienced radiation oncologists with the support of an experienced pulmonary radiologist.

For general scoring, the severity score that was introduced by Dahele et al. was applied. Radiographic changes were classified as "severe" (massive changes), "moderate" (extensive, but commonly

FIGURE 1 | Classification of radiologic changes following stereotactic body radiotherapy (SBRT). **(A₁₋₄)** Acute parenchymal changes within the first 6 months after SBRT. One category [no parenchymal abnormalities (NPA)] is not shown. **(B₁₋₃)** Late parenchymal changes after 6 months following SBRT. One category (NPA) is not shown. **(C₁₋₂)** Severity score for radiologic changes with **(C₁)** classified as no/mild changes and **(C₂)** classified as moderate/severe changes. GGO, ground-glass opacity.

expected changes), "mild/minor" (rare changes only), or "none" (**Figure 1C**).

Statistical Analysis

Overall survival, local progression-free survival (LPFS), and distant progression-free survival (DPFS) were calculated using the Kaplan–Meier method. Survival curves were compared between groups in a univariate analysis applying the log-rank test or Cox regression analysis. Multivariable Cox models were performed including all variables with $p \leq 0.05$ in univariate analysis. Correlations between baseline factors as well as irradiation doses and severity of CT changes were assessed using Spearman's or Pearson's correlation coefficients. McNemar's test was applied to calculate the association between early and late severity scores. Descriptive statistics were performed by using Mann–Whitney U tests or χ^2 tests for continuous or categorical data, respectively.

The non-parametric Wilcoxon signed-rank test was applied for assessing pulmonary function changes. Receiver operating characteristics (ROC) curves and the Youden's index were performed to determine the optimal cutoff for FVC reduction or mean ipsilateral lung dose in BED (MLD) in predicting OS after 2 years. A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0).

RESULTS

Survival and Local Control

Patient and treatment characteristics are displayed in **Table 1**. With a median follow-up time of 32.2 months (range 14.6–104.3 months), 2- and 3-year OS was 83% and 60%, respectively (**Figure 2A**). Two- and three-year LPFS was 88% and 80%

TABLE 1 | Patient and treatment characteristics.

Patients	
Sex	
Male	50 (71.4%)
Female	20 (28.6%)
Median age (range)	70.8 years (56.5–90.4)
≥70 years	43 (61.4%)
<70 years	27 (38.6%)
Median Karnofsky performance score (range)	65% (40–80)
Staging FDG-PET	
Yes	47 (67.1%)
No	23 (32.9%)
Histology	
Adenocarcinoma	29 (41.4%)
Squamous cell carcinoma	17 (24.3%)
Others	17 (24.3%)
No histological confirmation	7 (10.0%)
TNM stage	
Stage Ia	42 (60.0%)
Stage Ib	26 (37.1%)
Stage IIa	0 (0%)
Stage IIb	2 (2.9%)
Tumor location	
Peripheral	58 (82.9%)
Central	12 (17.1%)
Smoking status	
Active smokers	22 (31.4%)
Former smokers	42 (60.0%)
Never smokers	1 (1.4%)
Smoking status not known	5 (7.2%)
Median packyears	40 pys (5–120)
Median total dose in BED (PTV encompassing)	105.0 Gy (60–151.2)
Median PTV-encompassing single dose	18.0 Gy (7.5–24.0)
Median number of fractions	3 (1–8)
Median PTV size (range)	52.0 ml (5.9–169.1)
Median ipsilateral lung dose in BED	8.31 Gy (0.62–32.5)

SBRT, stereotactic body radiotherapy; FDG-PET, fluoro-deoxy-glucose positron emission tomography; BED, biological effective dose; PTV, planning target volume.

(**Figure 2B**), while 2- and 3-year DPFS was, respectively, 84% and 74%. OS, LPFS, and DPFS were not significantly affected by any potential risk factor investigated (**Table 2**).

Parenchymal Lung Changes after SBRT

In total, 463 CT scans of 70 patients were reviewed for parenchymal lung changes. A median of five CT scans (range 3–17) could be evaluated per patient covering a time frame of in median 20.0 months after SBRT (range 12.2–78.8 months). The median time to onset of CT changes was 2.5 months (range 1.6–8.8 months).

Acute radiologic changes within the first 6 months (113 CT scans available) following SBRT were assessed for each patient: NPA were detected in 10% of the cases, while 63 patients (90%) displayed acute parenchymal changes. From this cohort, 11% PGGO, 25% DGGO, 25% PCO, and 29% DCO (**Figure 1A**).

Late parenchymal changes were detected to some degree in all CT scans available (**Figure 1B**). After 6 months following SBRT (60 patients with CT scans available), 10% of the cases showed SLF, 7% MLF, and in 83% of the patients MCPF was detected. Parenchymal changes slightly decreased 12 months post-SBRT with 14% SLF, 9% MLF, and 77% MCPF (64 patients with CT scans available). After 18 months, a further reduction in parenchymal changes was registered (156 CT scans in 41 patients): 20% SLF, 9% MLF, and 71% MCPF.

Most of the tumors had an acute severity score of 0 (none, $n = 10$, 14%), 1 (mild, $n = 43$, 62%), or 2 (moderate, $n = 16$, 23%). Only one patient each suffered from acute severe changes (score = 3) after SBRT. The pattern for chronic severity score was as follows: mild (score 1): 66%, moderate (score 2): 33%, and severe (score 1): 1%. The two patients with severe radiologic changes developed radiation pneumonitis CTCAE grade III requiring corticosteroids and oxygen support until resolution of symptoms. Two additional patients developed CTCAE grade
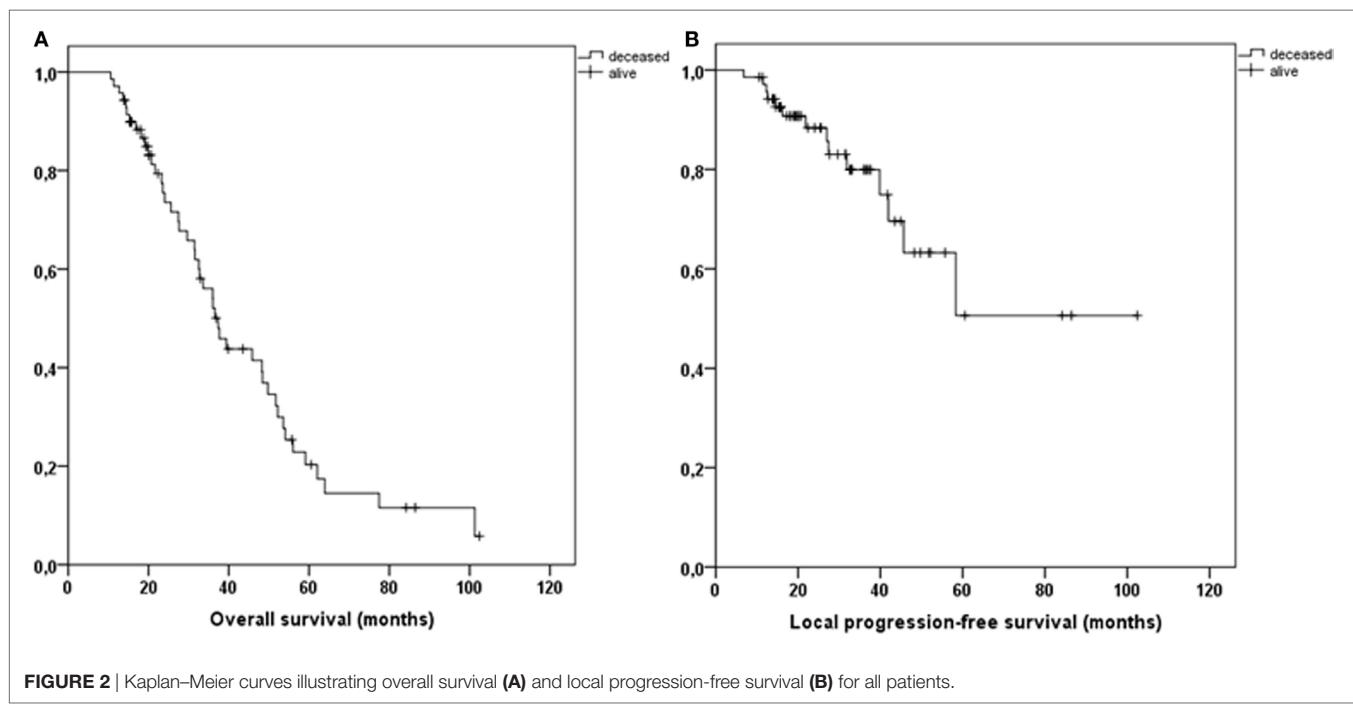

FIGURE 2 | Kaplan–Meier curves illustrating overall survival **(A)** and local progression-free survival **(B)** for all patients.

TABLE 2 | Univariate analysis of overall survival (OS), local progression-free survival (LPFS), and distant progression-free survival (DPFS).

Factor	*p*-Value		
	OS	LPFS	DPFS
Sex	0.837	0.701	0.716
Male			
Female			
Age	0.382	0.930	0.276
Karnofsky performance score	0.600	0.318	0.674
Staging FDG-PET	0.494	0.085	0.824
Yes			
No			
Histology	0.950	0.339	0.245
Adenocarcinoma			
Squamous cell carcinoma			
Others			
No histological confirmation			
TNM stage	0.608	0.671	0.656
Stage Ia			
Stage Ib			
Stage IIa			
Stage IIb			
Tumor location	0.369	0.196	0.115
Peripheral			
Central			
Smoking status	0.491	0.512	0.674
Active smokers			
Former smokers			
Never smokers			
Smoking status not known			
Median packyears	0.734	0.764	0.222
Total dose in BED (PTV encompassing)	0.854	0.395	0.522
BED ≥ 100 Gy			
BED < 100 Gy			
PTV-encompassing single dose	0.696	0.380	0.781
Number of fractions	0.407	0.419	0.823
PTV size	0.408	0.675	0.324

FDG-PET, fluoro-deoxy-glucose positron emission tomography; BED, biological effective dose; PTV, planning target volume.
The variables sex, staging FDG-PET, histology, TNM stage, tumor location, smoking status, and PTV-encompassing biological effective total dose were analyzed as categorical variables, while the other variables were taken as continuous variables for analysis.

II radiation pneumonitis. In total, 5.7% of the patients suffered from grade ≥II radiation pneumonitis.

The severity of acute CT changes predicted for those of late changes ($p = 0.027$). We did not detect any significant correlations between maximum severity score for each tumor and gender ($p = 0.085$), patient age ($p = 0.366$), Karnofsky performance score ($p = 0.426$), tumor histology ($p = 0.333$), TNM stage ($p = 0.190$), tumor location ($p = 0.329$), smoking status ($p = 0.502$), smoking history in number of packyears ($p = 0.473$), total dose in BED ($p = 0.705$), single dose ($p = 0.643$), and number of fractions ($p = 0.625$). However, both planning target volume (PTV) size and MLD in BED were predictive for parenchymal lung changes measured as the maximum severity score (respectively, $p < 0.001$ and $p = 0.014$).

Furthermore, OS was significantly reduced if scans showed moderate or severe parenchymal lung changes ($p = 0.043$, HR 1.928 [CI 1.020–3.644]) (**Figure 3A**). Specifically, patients with

a maximum severity score of 0–1 (none/mild) showed 2- and 3-year OS of 83 and 65%, while patients with a maximum severity score of 2–3 (moderate/severe) experienced 2- and 3-year OS of 78 and 51%, respectively ($p = 0.043$, HR 1.928 [CI 1.020–3.644]). In addition, OS was significantly influenced by MLD but not by PTV size ($p = 0.025$, HR 1.046 [CI 1.002–1.092]; $p = 0.408$, HR 1.004 [CI 0.995–1.013]) (**Figure 3B**). A cutoff MLD of 9.72 Gy was calculated in ROC analysis. Hence, patients treated with an MLD < 9.72 Gy showed 2- and 3-year OS of 89.2% and 67.7%, while patients with an MLD ≥ 9.72 Gy only had 2- and 3-year OS rates of 73.6% and 48.6%, respectively ($p = 0.042$; 1.904 [CI 1.017–3.563]). Both LPFS and DPFS were not significantly affected by maximum severity score, MLD, or PTV size ($p ≥ 0.05$).

Functional Lung Changes after SBRT

In total, paired PFTs were available for 57 of the analyzed 70 patients before and after SBRT. PFTs were obtained at a median of 44 days before SBRT (range 3–70 days) and 9.3 months (range 5.8–18.1 months) after SBRT. Detailed PFT data are illustrated in **Table 3**.

All analyzed baseline pre- and posttreatment PFT parameters did not significantly affect OS, LPFS, and DPFS ($p > 0.05$). However, SBRT treatment significantly reduced post-SBRT lung function: TLC (-0.52 L; $p = 0.001$), FVC (-0.45 L, $p < 0.001$), FEV_1 (-0.17 L, $p < 0.001$), $FEV_{1\%}$ (-5.2%, $p < 0.001$), and airway resistance ($+0.09$ kPa s/L, $p = 0.003$) (**Table 3**).

As a next step, we evaluated whether absolute differences between pre- and post-interventional PFT parameters could predict outcome. While we did not detect a significant effect of TLC, FEV_1, $FEV_{1\%}$, and resistance, treatment-related reduction in FVC significantly affected survival ($p = 0.007$, 3.910 [CI 1.445–10.575]). A cutoff FVC reduction of 0.54 L was calculated in ROC analysis. Patients with a reduction in FVC ≥ 0.54 L showed significantly worse 2- and 3-year OS of 71% and 35%, while patients with an FVC reduction <0.54 L had 2- and 3-year OS rates of 93% and 73%, respectively ($p = 0.011$, 2.439 [CI 1.227–4.849]) (**Figure 3C**). Absolute reductions in FVC did not significantly correlate with MLD ($p = 0.913$), PTV size ($p = 0.334$), and maximum severity score of parenchymal changes ($p = 0.546$).

Finally, we performed multivariate analysis revealing MLD ≥ 9.72 Gy and FVC reduction ≥0.54 L to be statistically significant independent prognostic factors for OS ($p = 0.029$, 1.037 [CI 1.011–1.089]; $p = 0.004$, 2.347 [CI 1.167–4.723]). Maximum severity score of parenchymal changes was not identified as an independent prognostic factor for OS ($p = 0.140$, 1.289 [CI 0.601–2.766]).

DISCUSSION

Pulmonary SBRT is believed to be a milder way of treatment with less side effects compared to surgery involving lobectomy and systematic lymphadenectomy as it is primarily offered to patients with reduced performance score who are classified medically inoperable (2, 11, 27). In this study, we investigated early and late radiographic lung injury as well as pulmonary function changes following SBRT. In general, most patients only showed mild to
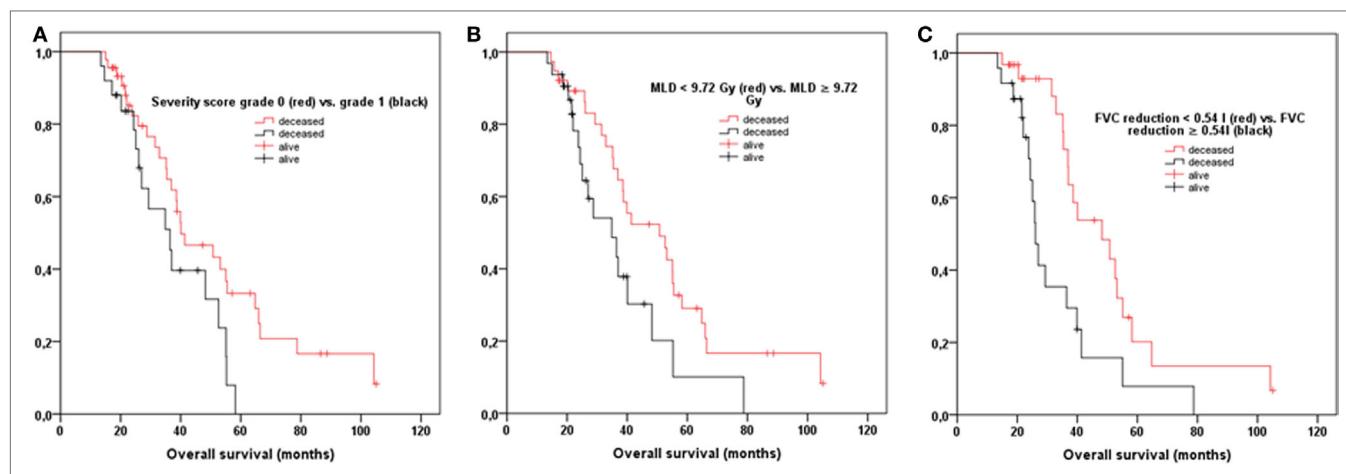
FIGURE 3 | **(A)** Overall survival (OS) was significantly reduced if patients showed moderate/severe radiologic changes following stereotactic body radiotherapy (SBRT) compared to patients with only none/mild parenchymal changes (p = 0.043). **(B)** Patients with treated with an MLD ≥ 9.72 Gy suffered from worse OS (p = 0.042). **(C)** OS was significantly impaired if patients had an absolute reduction in FVC ≥ 0.54 L following SBRT (p = 0.007). FVC, forced vital capacity; MLD, mean ipsilateral lung dose in biological effective dose.

TABLE 3 | Mean pulmonary function tests (PFTs) for 58 patients before and after SBRT.

PFT parameter (range)	Before SBRT	After SBRT	Absolute difference	Relative difference (%)	p-Value
TLC	6.96 l (3.77–11.34)	6.44 l (3.10–12.51)	−0.52 l (−3.10 to +2.20)	−7.50 (−28.5 to +12.8)	0.001*
FVC	2.81 (1.19–4.30)	2.36 (1.09–3.85)	−0.45 l (−1.36 to +1.10)	−16.0 (−34.1 to +5.4)	<0.001*
FEV$_1$	1.51 l (0.50–2.93)	1.36 l (0.50–2.84)	−0.17 l (−0.79 to +0.52)	−9.8 (−33.9 to +33.3)	<0.001*
FEV$_{1\%}$ predicted	57.5% (25.3–89.9)	52.29% (−24.2 to 90.3)	−5.18% (−28.2 to +4.8)		<0.001*
FEV$_1$/FVC	52.1% (21.4–81.5)	41.8% (22.2–89.1)	−10.3% (−21.6 to +23.1)		0.103
Air way resistance	0.49 kPa s/l (0.09–1.80)	0.58 kPa s/l (0.13–1.49)	+0.09 kPa s/l (−0.81 to +0.87)	+18.4 (+90.0 to −30.6)	0.003*

SBRT, stereotactic body radiotherapy; TLC, total lung capacity; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; FEV$_1$/FVC, forced expiratory volume in 1 s divided by forced vital capacity.

$*p \leq 0.05$

moderate parenchymal and functional lung alterations that did not translate into reduced clinical performance in the majority of cases.

Regarding parenchymal lung changes in follow-up imaging studies, nearly all patients only developed minor changes, while severe changes were only noticed in two patients (2.9%) and were transient. All patients were diagnosed with radiological changes following SBRT at some time of follow-up, which is known to impair diagnosis of local recurrence (19, 28). Similar acute and chronic patterns of CT changes were reported by Trovo et al. and Dahele et al. (18, 26).

However, to the best of our knowledge, this is the first investigation describing a significant association between MLD and survival following SBRT (**Figures 3A,B**).

Several groups have shown a dose–response relationship for radiation-induced pneumonitis following SBRT (29, 30). Furthermore, a recent pooled analysis of 88 studies investigating lung toxicity after SBRT reported MLD as well as large tumor size to be significant adverse risk factors for pneumonitis and lung fibrosis (15). Indeed, we also detected a significant correlation between both MLD as well as PTV size and maximum severity score of radiological CT changes. In comparison, when regarding radiotherapy for locally advanced NSCLC patients,

an association between radiation exposure to normal lung and severe pneumonitis is also well known (31). Furthermore, development of radiation pneumonitis and generalized radiological changes after radiotherapy in locally advanced NSCLC patients were shown to be independent negative prognostic factors for survival (32). A recent study even underlined the predictive impact of lung dose and especially MLD on survival analyzing prognostic factors in 468 patients with stage IIIA–IIIB NSCLC (33). Our study now shows that SBRT with an MLD ≥ 9.72 Gy was associated with significantly worse survival. However, due to the low number of patients and the limited number of events recorded in this analysis, this finding has to be interpreted with caution. All patients included in this study were classified medically inoperable and suffered from severe pulmonary comorbidities, which probably highly impaired survival. Nevertheless, a recent study showed that dose to heart substructures was associated with non-cancer death after SBRT in stage I–II NSCLC patients (34). Hence, dose spillage to the heart and healthy lung tissue should be kept as low as reasonably possible when performing SBRT.

In a second step, we analyzed functional lung changes and detected a significant decline following SBRT for TLC, FVC, FEV$_1$, and FEV$_{1\%}$ ($p \leq 0.001$). In contrast to our results, Stanic

et al. and Stephans et al. did not show any significant change in pulmonary function examining lung function in 55 and 92 patients after SBRT (21, 35). However, a recent study by Stone et al. also reported a significant decline for FEV_1, diffusion capacity, FVC, and TLC following SBRT (22). Nevertheless, most studies did not show any association of lower baseline or post-SBRT pulmonary function with worse survival (21, 22, 36, 37). Guckenberger et al. only described a significant impact of pretreatment, and not posttreatment, diffusion capacity of carbon monoxide on survival (thus not treatment-related) (10). Notably, absolute reduction in FVC was shown to be an independent prognostic factor for OS in this analysis (**Figure 3C**), indicating a possible influence of radiation-induced restrictive lung disease upon survival. This might be due to the fact that this analysis is the only study investigating the prognostic impact of absolute loss in PFTs and not only pre- and posttreatment pulmonary function parameters.

Similar to other studies reduction in FVC did not significantly correlate with prognostic factors for lung toxicity such as MLD, and PTV size in this analysis (20, 21). There was no significant correlation between absolute reduction in FVC and maximum severity score of parenchymal changes. This finding is supported by reports about conventionally fractionated radiotherapy in which a dose–effect relationship for posttreatment PFT changes is also missing (38). This might be explained by the fact that irradiation of lung tumors may even improve PFT by tumor shrinkage or reopening of atelectasis (39). Furthermore, the vast majority of these patients had severe COPD with decline in pulmonary function on the basis of natural disease progression (40, 41). Hence, the detected loss in pulmonary function has to be interpreted with caution and might also be caused by the natural progression of preexisting COPD (40, 41). Larger, multicenter studies are truly needed to evaluate the possible prognostic impact of MLD and lung function changes following SBRT on survival. In this study, we did not detect distinct factors for surely predicting possible lung toxicity following SBRT. Nevertheless, other factors such as pretreatment immune status are reported to predict for toxicity after SBRT (42).

Despite the reported parenchymal and functional lung changes, survival and local control rates detected in this analysis were comparable to other studies and still much higher in comparison to conventionally fractionated radiotherapy (7–9, 16, 43). In detail, 3-year OS, progression-free survival (PFS), LPFS, and DPFS rates were 60, 65, 80, and 74%, respectively. Regarding current guidelines, a benchmark is the 3-year local rate following SBRT which is supposed to be 90% and higher when a BED > 100 Gy is applied (2). As this study included data from 2004 to 2015, several patients were treated with lower doses which might have led to the slightly reduced local control rates in this analysis.

The higher PFS compared to the detected OS in this analysis might raise the question whether some patients were overtreated, although other studies reported similar results (42, 44). Furthermore, not all patients received histopathological confirmation of disease due to reduced performance score but had fluoro-deoxy-glucose positron emission tomography positive tumors. The severity of pulmonary comorbidities is known to be an important predictor for survival for lung cancer patients—not only after SBRT (45, 46). However, two recent reports stated that withholding SBRT in patients with severe COPD is not justified (47, 48). Hence, in some patients SBRT might transfer the cause of death from tumor disease to pulmonary comorbidities.

As pulmonary SBRT for early-stage NSCLC was analyzed between 2004 and 2015 in this study, patients were mainly treated with less advanced radiation techniques while survival data were available therefore as a tradeoff. For example, regular performance of 4-D-CT scans to account for tumor motion started in 2009 in our department. Hence, larger safety margins leading to larger PTV sizes and higher MLD were needed. Today, advances in radiation planning and delivery techniques such as intensity-modulated radiotherapy (IMRT) and elaborate image guidance including gating and tracking help to further minimize the dose to normal tissue and therefore reduce side-effects. Some limitations of this study deserve mention. Aside from the smaller sample size and retrospective nature, paired PFTs were not available for all patients. Second, further lung dose parameters as V_{5Gy} and V_{20Gy} were not accessible. Third, a larger cutoff interval for follow-up CT scans of more than one year was not possible, as several patients only received X-ray scans for follow-up imaging after 1 year due to their poor performance status. Fourth, due to the retrospective character of this study, detailed analysis of cardiopulmonary comorbidities and their potential impact on survival in this study was not possible.

Analyzing parenchymal and functional lung injury following SBRT, we detected only mild radiological changes and tolerable reduction in pulmonary function for most patients. However, this study showed a significant association between SBRT with a higher MLD and inferior survival. Furthermore, higher absolute reduction in FVC significantly impaired survival in this analysis. Nevertheless, these results have to be interpreted with caution due to the limited number of patients and the retrospective character of this study. Natural progression of pulmonary comorbidities including COPD surely also led to reduced survival in this patient group. If toxicity of SBRT had an impact on survival in this study, this was potentially caused by the interaction with preexisting pulmonary comorbidities.

Based on this study, modern radiotherapy methods including delivery techniques such as IMRT and daily image guidance should be applied for minimizing PTV sizes and keeping MLD as low as reasonable possible. Furthermore, larger prospective and multicenter studies are highly needed for evaluating the potential prognostic impact of parenchymal and functional lung changes on survival.

ETHICS STATEMENT

This retrospective study was carried out in accordance with the recommendations of the Ethics committee of the University Hospital Heidelberg. According to the committee's decision based on the retrospective character of this analysis, no additional written informed consent of all patients was needed.

AUTHOR CONTRIBUTIONS

FUNDING

REFERENCES

1. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. Non-small cell lung cancer, version 1.2015. *J Natl Compr Canc Netw* (2014) 12:1738–61. doi:10.6004/jnccn.2014.0176
2. Guckenberger M, Andratschke N, Alheit H, Holy R, Moustakis C, Nestle U, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. *Strahlenther Onkol* (2014) 190:26–33. doi:10.1007/s00066-013-0450-y
3. Verma V. Stereotactic radiotherapy versus surgery for early-stage operable lung cancer: more questions than answers. *J Natl Compr Canc Netw* (2015) 13:1293–5. doi:10.6004/jnccn.2015.0155
4. Haasbeek CJ, Palma D, Visser O, Lagerwaard FJ, Slotman B, Senan S. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. *Ann Oncol* (2012) 23:2743–7. doi:10.1093/annonc/mds081
5. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* (2010) 28:5153–9. doi:10.1200/JCO.2010.30.0731
6. Shirvani SM, Jiang J, Chang JY, Welsh JW, Gomez DR, Swisher S, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* (2012) 84:1060–70. doi:10.1016/j.ijrobp.2012.07.2354
7. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* (2009) 27:3290–6. doi:10.1200/JCO.2008.21.5681
8. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a phase II trial. *Int J Radiat Oncol Biol Phys* (2011) 80:1343–9. doi:10.1016/j.ijrobp.2010.04.056
9. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* (2009) 75:677–82. doi:10.1016/j.ijrobp.2008.11.042
10. Guckenberger M, Kestin LL, Hope AJ, Belderbos J, Werner-Wasik M, Yan T, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? *J Thorac Oncol* (2012) 7:542–51. doi:10.1097/JTO.0b013e31824165d7
11. Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. *Int J Radiat Oncol Biol Phys* (2012) 82:1149–56. doi:10.1016/j.ijrobp.2011.03.005
12. Ricardi U, Filippi AR, Guarneri A, Giglioli FR, Mantovani C, Fiandra C, et al. Dosimetric predictors of radiation-induced lung injury in stereotactic body radiation therapy. *Acta Oncol* (2009) 48:571–7. doi:10.1080/02841860802520821
13. Ueki N, Matsuo Y, Togashi Y, Kubo T, Shibuya K, Iizuka Y, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. *J Thorac Oncol* (2015) 10:116–25. doi:10.1097/JTO.0000000000000359
14. Yamashita H, Nakagawa K, Nakamura N, Koyanagi H, Tago M, Igaki H, et al. Exceptionally high incidence of symptomatic grade 2-5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. *Radiat Oncol* (2007) 2:21. doi:10.1186/1748-717X-2-21
15. Zhao J, Yorke ED, Li L, Kavanagh BD, Li XA, Das S, et al. Simple factors associated with radiation-induced lung toxicity after stereotactic body radiation therapy of the thorax: a pooled analysis of 88 studies. *Int J Radiat Oncol Biol Phys* (2016) 95:1357–66. doi:10.1016/j.ijrobp.2016.03.024
16. Guckenberger M, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, et al. Safety and efficacy of stereotactic body radiotherapy for stage 1 non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. *J Thorac Oncol* (2013) 8:1050–8. doi:10.1097/JTO.0b013e318293dc45
17. Rieber J, Streblow J, Uhlmann L, Flentje M, Duma M, Ernst I, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases—a pooled analysis of the German working group "stereotactic radiotherapy". *Lung Cancer* (2016) 97:51–8. doi:10.1016/j.lungcan.2016.04.012
18. Dahele M, Palma D, Lagerwaard F, Slotman B, Senan S. Radiological changes after stereotactic radiotherapy for stage I lung cancer. *J Thorac Oncol* (2011) 6:1221–8. doi:10.1097/JTO.0b013e318219aac5
19. Huang K, Dahele M, Senan S, Guckenburger M, Rodrigues G, Ward A, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR) – can we distinguish fibrosis from recurrence? A systematic review of the literature. *Pract Radiat Oncol* (2013) 3:S11–2. doi:10.1016/j.prro.2013.01.039
20. Guckenberger M, Klement RJ, Kestin LL, Hope AJ, Belderbos J, Werner-Wasik M, et al. Lack of a dose-effect relationship for pulmonary function changes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* (2013) 85:1074–81. doi:10.1016/j.ijrobp.2012.09.016
21. Stanic S, Paulus R, Timmerman RD, Michalski JM, Barriger RB, Bezjak A, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early-stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *Int J Radiat Oncol Biol Phys* (2014) 88:1092–9. doi:10.1016/j.ijrobp.2013.12.050
22. Stone B, Mangona VS, Johnson MD, Ye H, Grills IS. Changes in pulmonary function following image-guided stereotactic lung radiotherapy: neither lower baseline nor post-SBRT pulmonary function are associated with worse overall survival. *J Thorac Oncol* (2015) 10:1762–9. doi:10.1097/JTO.0000000000000670
23. Rudofsky L, Aynsley E, Beck S, Schubert K, Habl G, Krause S, et al. Lung and liver SBRT using helical tomotherapy – a dosimetric comparison of fixed jaw and dynamic jaw delivery. *J Appl Clin Med Phys* (2014) 15:4664. doi:10.1120/jacmp.v15i3.4664
24. Hof H, Muenter M, Oetzel D, Hoess A, Debus J, Herfarth K. Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer (NSCLC). *Cancer* (2007) 110:148–55. doi:10.1002/cncr.22763
25. Rieber J, Tonndorf-Martini E, Schramm O, Rhein B, König L, Adeberg S, et al. Establishing stereotactic body radiotherapy with flattening filter free techniques in the treatment of pulmonary lesions – initial experiences from a single institution. *Radiat Oncol* (2016) 11:80. doi:10.1186/s13014-016-0648-0
26. Trovo M, Linda A, El Naqa I, Javidan-Nejad C, Bradley J. Early and late lung radiographic injury following stereotactic body radiation therapy (SBRT). *Lung Cancer* (2010) 69:77–85. doi:10.1016/j.lungcan.2009.09.006
27. Ettinger DS, Akerley W, Borghaei H, Chang AC, Cheney RT, Chirieac LR, et al. Non-small cell lung cancer. *J Natl Compr Canc Netw* (2012) 10:1236–71. doi:10.6004/jnccn.2012.0130

28. Huang K, Senthi S, Palma DA, Spoelstra FO, Warner A, Slotman BJ, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* (2013) 109:51–7. doi:10.1016/j.radonc.2013.06.047

29. Guckenberger M, Baier K, Polat B, Richter A, Krieger T, Wilbert J, et al. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol* (2010) 97:65–70. doi:10.1016/j.radonc.2010.04.027

30. Hof H, Zgoda J, Nill S, Hoess A, Kopp-Schneider A, Herfarth K, et al. Time- and dose-dependency of radiographic normal tissue changes of the lung after stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* (2010) 77:1369–74. doi:10.1016/j.ijrobp.2009.06.082

31. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* (2010) 76:S70–6. doi:10.1016/j.ijrobp.2009.06.091

32. Farr KP, Khalil AA, Knap MM, Moller DS, Grau C. Development of radiation pneumopathy and generalised radiological changes after radiotherapy are independent negative prognostic factors for survival in non-small cell lung cancer patients. *Radiother Oncol* (2013) 107:382–8. doi:10.1016/j.radonc.2013.04.024

33. Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. *Radiother Oncol* (2016) 119:495–500. doi:10.1016/j.radonc.2016.04.025

34. Stam B, Peulen H, Guckenberger M, Mantel F, Hope A, Werner-Wasik M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I–II NSCLC patients. *Radiother Oncol* (2017) 123:370–5. doi:10.1016/j.radonc.2017.04.017

35. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol* (2009) 4:838–44. doi:10.1097/JTO.0b013e3181a99ff6

36. Henderson M, McGarry R, Yiannoutsos C, Fakiris A, Hoopes D, Williams M, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2008) 72:404–9. doi:10.1016/j.ijrobp.2007.12.051

37. Navarro-Martin A, Aso S, Cacicedo J, Arnaiz M, Navarro V, Rosales S, et al. Phase II trial of SBRT for stage I NSCLC: survival, local control, and lung function at 36 months. *J Thorac Oncol* (2016) 11:1101–11. doi:10.1016/j.jtho.2016.03.021

38. De Jaeger K, Seppenwoolde Y, Boersma LJ, Muller SH, Baas P, Belderbos JS, et al. Pulmonary function following high-dose radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* (2003) 55:1331–40. doi:10.1016/S0360-3016(02)04389-4

39. Fan M, Marks LB, Hollis D, Bentel GG, Anscher MS, Sibley G, et al. Can we predict radiation-induced changes in pulmonary function based on the sum of predicted regional dysfunction? *J Clin Oncol* (2001) 19:543–50. doi:10.1200/JCO.2001.19.2.543

40. Boutou AK, Shrikrishna D, Tanner RJ, Smith C, Kelly JL, Ward SP, et al. Lung function indices for predicting mortality in COPD. *Eur Respir J* (2013) 42:616–25. doi:10.1183/09031936.00146012

41. Leivseth L, Brumpton BM, Nilsen TI, Mai XM Johnsen R Langhammer A et al. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway. *Thorax* (2013) 68:914–21. doi:10.1136/thoraxjnl-2013-203270

42. Shaverdian N, Veruttipong D, Wang J, Kupelian P, Steinberg M, Lee P, et al. Pretreatment anemia portends poor survival and nonlocal disease progression in patients with stage I non-small cell lung cancer treated with stereotactic body radiation therapy. *J Thorac Oncol* (2016) 11:1319–25. doi:10.1016/j.jtho.2016.04.030

43. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). *Cochrane Database Syst Rev* (2001) 2001:CD002935. doi:10.1002/14651858.CD002935

44. Verma V, Shostrom VK, Kumar SS, Zhen W, Hallemeier CL, Braunstein SE, et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors. *Cancer* (2016). doi:10.1002/cncr.30375

45. Iachina M, Jakobsen E, Møller H, Lüchtenborg M, Mellemgaard A, Krasnik M, et al. The effect of different comorbidities on survival of non-small cells lung cancer patients. *Lung* (2015) 193:291–7. doi:10.1007/s00408-014-9675-5

46. Kopek N, Paludan M, Petersen J, Hansen AT, Grau C, Høyer M. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. *Radiother Oncol* (2009) 93:402–7. doi:10.1016/j.radonc.2009.06.002

47. Jeppesen SS, Hansen N-CG, Schytte T, Nielsen M, Hansen O. Comparison of survival of chronic obstructive pulmonary disease patients with or without a localized non-small cell lung cancer. *Lung Cancer* (2016) 100:90–5. doi:10.1016/j.lungcan.2016.08.006

48. Louie AV, Rodrigues G, Hannouf M, Lagerwaard F, Palma D, Zaric GS, et al. Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: outcomes of a Markov model analysis. *Radiother Oncol* (2011) 99:161–5. doi:10.1016/j.radonc.2011.04.005

Relationships between Regional Radiation Doses and Cognitive Decline in Children Treated with Cranio-Spinal Irradiation for Posterior Fossa Tumors

Elodie Doger de Speville[1,2,3], Charlotte Robert[4,5,6,7], Martin Perez-Guevara[8], Antoine Grigis[9], Stephanie Bolle[4], Clemence Pinaud[1,2], Christelle Dufour[3], Anne Beaudré[4,7], Virginie Kieffer[3,10], Audrey Longaud[3,11], Jacques Grill[3,11], Dominique Valteau-Couanet[3,11], Eric Deutsch[4,5,6,7], Dimitri Lefkopoulos[4,7], Catherine Chiron[1,2], Lucie Hertz-Pannier[1,2] and Marion Noulhiane[1,2]*

[1] INSERM U1129, CEA, Paris Descartes University, Paris, France, [2] UNIACT, Institut Joliot, DRF, Neurospin, CEA, Paris Saclay University, Gif-sur-Yvette, France, [3] Department of Pediatric and Adolescent Oncology, Gustave Roussy, Villejuif, France, [4] Radiation Oncology Department, Gustave Roussy Cancer Campus, Villejuif, France, [5] INSERM, U1030, Villejuif, France, [6] Paris Sud University, Paris-Saclay University, Villejuif, France, [7] Gustave Roussy, Paris-Saclay University, Department of Medical Physics, Villejuif, France, [8] INSERM U992 Unicog CEA, Neurospin, Paris Descartes University, Paris, France, [9] Institut Joliot, Neurospin, CEA, Paris-Saclay University, Gif-sur-Yvette, France, [10] CSI Department for Children with Acquired Brain Injury, Hopitaux de Saint Maurice, Saint-Maurice, France, [11] Paris Sud University, Orsay, France

Pediatric posterior fossa tumor (PFT) survivors who have been treated with cranial radiation therapy often suffer from cognitive impairments that might relate to IQ decline. Radiotherapy (RT) distinctly affects brain regions involved in different cognitive functions. However, the relative contribution of regional irradiation to the different cognitive impairments still remains unclear. We investigated the relationships between the changes in different cognitive scores and radiation dose distribution in 30 children treated for a PFT. Our exploratory analysis was based on a principal component analysis (PCA) and an ordinary least square regression approach. The use of a PCA was an innovative way to cluster correlated irradiated regions due to similar radiation therapy protocols across patients. Our results suggest an association between working memory decline and a high dose (equivalent uniform dose, EUD) delivered to the orbitofrontal regions, whereas the decline of processing speed seemed more related to EUD in the temporal lobes and posterior fossa. To identify regional effects of RT on cognitive functions may help to propose a rehabilitation program adapted to the risk of cognitive impairment.

Keywords: pediatric, posterior fossa, radiotherapy, cognitive impairments, radiation effects

INTRODUCTION

Posterior fossa tumors (PFTs) account for two-thirds of all pediatric brain tumors (1). The most common malignant PFT is medulloblastoma (40%), followed by ependymoma (10%) (2). As a result of improved treatment, event-free survival has significantly increased (3). However, these children suffer from varied cognitive impairments, the most frequently described being decreased sustained attention, working memory, and information processing speed (4). This latter impairment

seems to appear first in PFT patients treated with cranio-spinal irradiation (CSI) (4). These cognitive impairments might relate to the decline of global intellectual functioning (full scale IQ, FSIQ) reported to be between two and four points per year (5–9). Several factors have been shown to predict cognitive impairments in PFT patients. Radiotherapy (RT) has been considered to be the major one, especially in young children (6, 8). Three RT-associated risk factors have been highlighted as predictors of cognitive impairments: (i) CSI (6, 7, 10), (ii) the volume receiving the boost [i.e., to the posterior fossa (PF)] (11), and (iii) the dose per fraction (12, 13). Grill et al. (10) observed that PFT survivors with low CSI (25 Gy) showed better cognitive outcomes than those receiving high CSI (36 Gy). Nonetheless, the reduction of CSI dose (14) did not prevent IQ decline (9). An alternative way to decrease cognitive impairments has been to reduce the volume of the PF irradiated, in addition to the reduced CSI. While the PF received the highest dose, the boost dose also contributed to higher doses in other regions such as the temporal lobes, the brainstem, and the hypothalamus (11). Moxon-Emre et al. (15) showed that medulloblastoma survivors for whom the CSI was reduced, and the boost volume was reduced from the entire PF to the tumor bed, had preserved IQ over time. Nonetheless, medulloblastoma survivors treated *via* either a CSI dose reduction or a diminution of PF volume irradiated (tumor bed boost) still experienced a decline of IQ.

Recent studies reported a higher contribution of specific brain regions to the development of RT-induced cognitive decline. Jalali et al. (16) observed that more than 43.2 Gy to >13% of the left temporal lobe was predicting IQ decline in patient treated for a benign tumor with stereotactic conformal RT. Merchant et al. (6) assessed the impact on IQ change of different mean dose values in distinct regions (whole brain, temporal lobe, hippocampus, infratentorial, and supratentorial spaces) in patients treated for a medulloblastoma, and suggested that supratentorial space was the most sensitive across the brain. Using a neurocognitive questionnaire, Armstrong et al. (17) pointed out a strong association between maximum radiation dose to the temporal lobe and poor performance in *Task efficiency* (i.e., attention and processing speed) and *Organization*. These subscores were measured as given by the Childhood Cancer Survivor Study Neurocognitive Questionnaire. While these studies did not identify a relationship between radiation dose of PF and changes in cognitive scores, such associations have been reported in children with ependymoma (18).

Despite marked progress, the regional effect of RT on cognitive impairment still remains unclear. So far, research on this question has been mainly carried out on either single (19) or large (6) brain regions, limiting the analysis to specific anatomical structures. In this study, we implemented a whole brain analysis; to investigate the relation between regional biological dose and changes over time of different cognitive scores (IQ, processing speed, and working memory) in 30 patients treated for a PFT. The use of a principal component analysis (PCA) was an innovative way to cluster correlated irradiated regions due to similar radiation therapy protocols across patients. We aimed to describe the relationships between regional radiation dose and declines in specific cognitive functions.

PATIENTS AND METHODS

Patient's Characteristics

Inclusion criteria were (1) PFT patients treated at Gustave Roussy Cancer Campus between 2000 and 2014; (2) 17 years of age or under at diagnosis (3) multiple (>2) IQ assessments after treatment onset (4); for the PFT patients treated with radiation therapy, the computed tomography (CT) scan, T1-weighted MRI, and dosimetric maps had to be available. Thirty patients (14 males and 16 females) matched these criteria. Information was gathered from medical files about the history of the illness (i.e., age at diagnosis) and the type of treatment (i.e., surgery, chemotherapy, and radiation therapy protocol). The underlying malignancy of the 30 patients studied was medulloblastoma, ependymoma, astrocytoma, and embryonal tumor in 25, 3, 1, and 1 patients, respectively. Twenty patients had a localized disease and 10 had a metastatic disease. Complete tumor resection was achieved in 20 PFT. Post-operative complications occurred in 10 patients. No patient relapsed between the two evaluations, but the patient with an astrocytoma whose relapse before the first evaluation, was treated with chemotherapy alone. The mean age at diagnosis was 4.62 years (SD = 3.05; [0.49; 12.24]). The mean delay between treatment and the last assessment was 4.60 years (SD = 4.60; [1.28; 14.24]). Pre-operative hydrocephalus was present in 19 patients (63%). Seventeen patients were treated with RT alone (N = 7) or RT and chemotherapy (N = 10). The remaining patients were treated with chemotherapy alone and were used as controls. All patients with RT received a CSI and a boost in the PF and were treated with three-dimensional conformal radiation therapy (**Table 1**). This study was approved by an ethical committee (CPP no. 14973, Gustave Roussy, Villejuif, France).

TABLE 1 | Absorbed dose and type of fractionation [conformational fractionation (CF) vs. hyperfractionated radiotherapy (HFRT)] prescribed to the cranio-spinal irradiation (CSI) and posterior fossa (PF) for the 17 patients.

Patients	CSI (Gy)	PF (Gy)	Fractionation
Patient 1	18	54	CF
Patient 2	18	54	CF
Patient 3	25.2	50.4	CF
Patient 4	18	36	CF
Patient 5	18	55.4	CF
Patient 6	18	50.4	CF
Patient 7	36	54	CF
Patient 8	25.2	54	CF
Patient 9	36	68	HFRT
Patient 10	36	68	HFRT
Patient 11	18	45	CF
Patient 12	36	54	CF
Patient 13	36	68	HFRT
Patient 14	36	68	HFRT
Patient 15	36	68	HFRT
Patient 16	36	68	HFRT
Patient 17	36	68	HFRT

The number of fractions per day and the dose per fraction varied from one patient to another. Some patients received two fractions of 1 Gy per day with an inter fraction of 8 h with HFRT, whereas other patients were treated by CF, i.e., one fraction of 1.82 Gy per day.

Neuropsychological Assessments

Three cognitive indices were estimated from age appropriate Wechsler Intelligence Scale (20, 21): FSIQ in all patients and the processing speed index (PSI) and working memory index (WMI) when available. Neuropsychological assessments were done by formally trained neuropsychologists from the pediatric department. Because of age or time constraints, not all participants were administered all the tests. Thus, the numbers of patients assessed varied across cognitive scores [N (ΔFSIQ) = 30, N (ΔPSI) = 23, N (ΔWMI) = 14]. Patients were evaluated at variable time points after treatment onset. Thus, the delay (T) between two neuropsychological assessments varied from one patient to the other (**Table 2**). The change in cognitive scores (ΔFSIQ, ΔPSI, and ΔWMI) of each patient was calculated from the difference between the first and last scores (ΔT). We did not consider intermediate scores. Changes in cognitive scores (ΔFSIQ, ΔWMI, and ΔPSI) were compared using two-tailed Student's *t*-tests.

NEUROIMAGING DATA

To study regional dose effects on changes in cognitive scores, 3D-T1 MRI, CT scan, and absorbed dose maps of patients treated with RT (*n* = 17) were collected and processed to create individual dose distribution maps into selected brain regions of interest (ROI) covering the whole brain.

Image Collection

3D T1-MR images were acquired on a 3-T scanner using a 32-channel head coil (General Electric, Milwankee, MN, USA). In this clinical retrospective study, two types of T1-weighted images were collected: 3D T1-weighted sagittal slices (matrices: 256 mm × 256 mm, pixel size: 0.5 mm, slice thickness: 1 mm, FOV: 240 mm) and 3D-T1 weighted axial slices (matrices: 224 × 288, pixel size: 0.5 mm, slice thickness: 1 mm).

Computed tomography scans were acquired on a SIEMENS Sensation Open scanner located in Gustave Roussy RT department (matrices: 512 mm × 512 mm, pixel size: 0.8 mm, slice thickness: 3 mm). Radiation dose maps (RD maps) were computed with the ISOgray™ Treatment Planning System (DOSIsoft, version 4.1, Cachan, France). The Clarkson–Cunningham model was used for dose calculation. Dose maps resolution was 3 mm × 3 mm × 1 mm.

Image Analysis
Image Preprocessing
We designed a five-step preprocessing pipeline to identify anatomical ROI on dose maps (**Figure 1**).

Step 1: We chose three MRI templates specific to ages 0–2, 2–5, and 5–9 years (151 × 192 × 152 voxels, 1 mm × 1 mm × 1 mm voxel size) and three corresponding anatomical atlases (151 × 192 × 152 voxels, 1 mm × 1 mm × 1 mm) from the Neurodevelopmental MRI DataBase (22). The atlases contained 56 ROIs extracted from the LPBA40 atlas (23) that were adapted to selected ages thanks to label propagation and decision fusion methods (24). For each child, we selected both the atlas and associated template according to the age at which the child received radiation therapy, to be as close as possible to the individual anatomy, which varies significantly during development (22, 25). Since the atlases did not included some particular regions (i.e., corpus callosum, a part of internal capsule, and ventricles), we created a supplementary label that encompassed these regions, resulting in 57 ROIs.

Step 2: The selected template was warped to individual patient 3DT1 image using a non-linear registration tool [Advanced Normalization Tools, SyN (26), and ANTS (27)].

Step 3: Individual MR images were also registered to the corresponding individual CT scan by applying a linear transformation with FSL [FLIRT (28)].

Step 4: Each CT scan was then down sampled to match the corresponding RD map voxel sampling.

Step 5: Finally, we combined the computed transformations into a single concatenated transformation from the template space to the individual dose map coordinate system. This enabled us to perform statistical radiation dose analyses over the group in each ROI extracted from the template.

Individual registrations have been assessed qualitatively by two experimenters independently and by consensus. From this check, four subjects were excluded from the study. In the majority of cases, registrations have been adjusted manually to optimize intersubject comparisons.

Data Analysis
We designed a four-step analysis pipeline to determine the associations between both clinical variables and ROI dose distribution with changes in cognitive scores (**Figure 2**).

Equating Dose Maps across Patients: EQD₂ Computation
Step 1: Given the differences in fractionation parameters (dose per fraction and number of fractions per day varied from one patient to another), even at equal total doses, the biological effectiveness of these two types of irradiation will be different (**Figure 2**, step 1). However, using the linear quadratic model (29), it is possible to calculate the total dose equivalent in terms of biological effects for two different fractionations (dose per fraction, time interval between two fractions) and a given tissue (EDQ2). Using this equation, all treatments are thus reduced to biological dose equivalent to treatments performed with fractions of 2 Gy, which is the standard fractionation scheme. Therefore, we corrected the dose of all fractionation types in a uniform way by calculating in each voxel the equivalent dose with the EQD_2 formula (30) (Eq. 1; **Figure 2**, step 1). The EQD_2 was calculated taking into account a function (H_m) depending on the number of equally spaced fractions per day; the dose per fraction (*d*) and the sensitivity of the tissue (α/β). *D* (the total delivered dose in Gy) and *d* varied across

TABLE 2 | Changes in the three measured cognitive scores [Delta (Δ)] with the corresponding number of evaluated patients: mean score change (±SD, range) and mean test interval ΔT (±SD, range).

Δ scores	N	Mean (±SD)	Range	Mean [ΔT in years (±SD)]	Range
ΔFIQ	30	−2.03 (11.70)	[−29; 28]	3.97 (±2.74)	[1.00; 12.29]
ΔPSI	23	−0.6 (14.44)	[−28; 41]	3.74 (±2.30)	[0.89; 9.93]
ΔWMI	14	−3.66 (9.15)	[−24; 6]	2.81 (±1.85)	[1.00; 8.14]
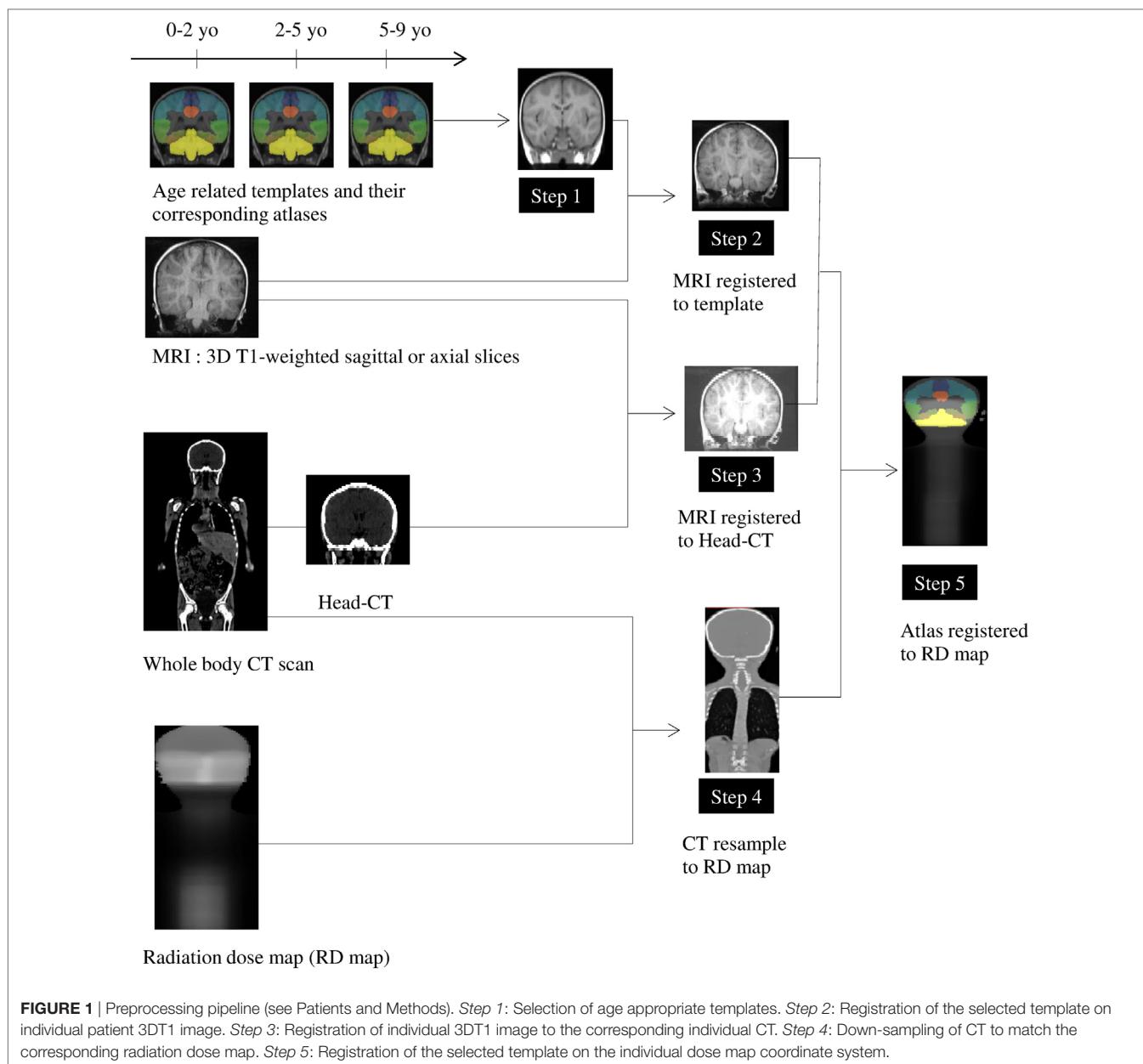
FIGURE 1 | Preprocessing pipeline (see Patients and Methods). *Step 1*: Selection of age appropriate templates. *Step 2*: Registration of the selected template on individual patient 3DT1 image. *Step 3*: Registration of individual 3DT1 image to the corresponding individual CT. *Step 4*: Down-sampling of CT to match the corresponding radiation dose map. *Step 5*: Registration of the selected template on the individual dose map coordinate system.

patients. Based on the current literature, α/β was fixed to 2 and T1/2 to 3 h (31):

$$EQD2 = D.\frac{d(1 + H_m) + \alpha/\beta}{2 + \alpha/\beta} \quad (1)$$

Calculation of Dose Index: Equivalent Uniform Dose (EUD) Computation

Step 2: After calculating the biological dose map of each patient, for all subjects and ROIs we computed the EUD that accounts for heterogeneity of dose distribution, as follows (Eq. 2) (**Figure 2**, step 2):

$$EUD = \left(\sum_j v_j D_j^k\right)^{\frac{1}{k}}. \quad (2)$$

Equivalent uniform dose corresponds to the value of a homogeneous dose that would cause the same clinical effect than the corresponding heterogeneous dose distribution (30). *k* was fixed at 5 according to the work of Emami et al. (32). We standardized EUD across the 17 subjects for each of the 57 ROIs.

Taking into Account the Spatial Correlation of Radiation Doses across ROIs: PCA Approach

Step 3: Because of the radiation therapy protocol (i.e., CSI and boost in the PF with three-dimensional conformal radiation therapy), EUD was highly correlated across brain regions (**Figure 2**, step 3). Therefore, it was not possible to assess the effect of irradiation on cognitive scores in each region with an ordinary least square regression, as regression weights would be highly unstable. Thus, we ran a PCA, a data-driven method
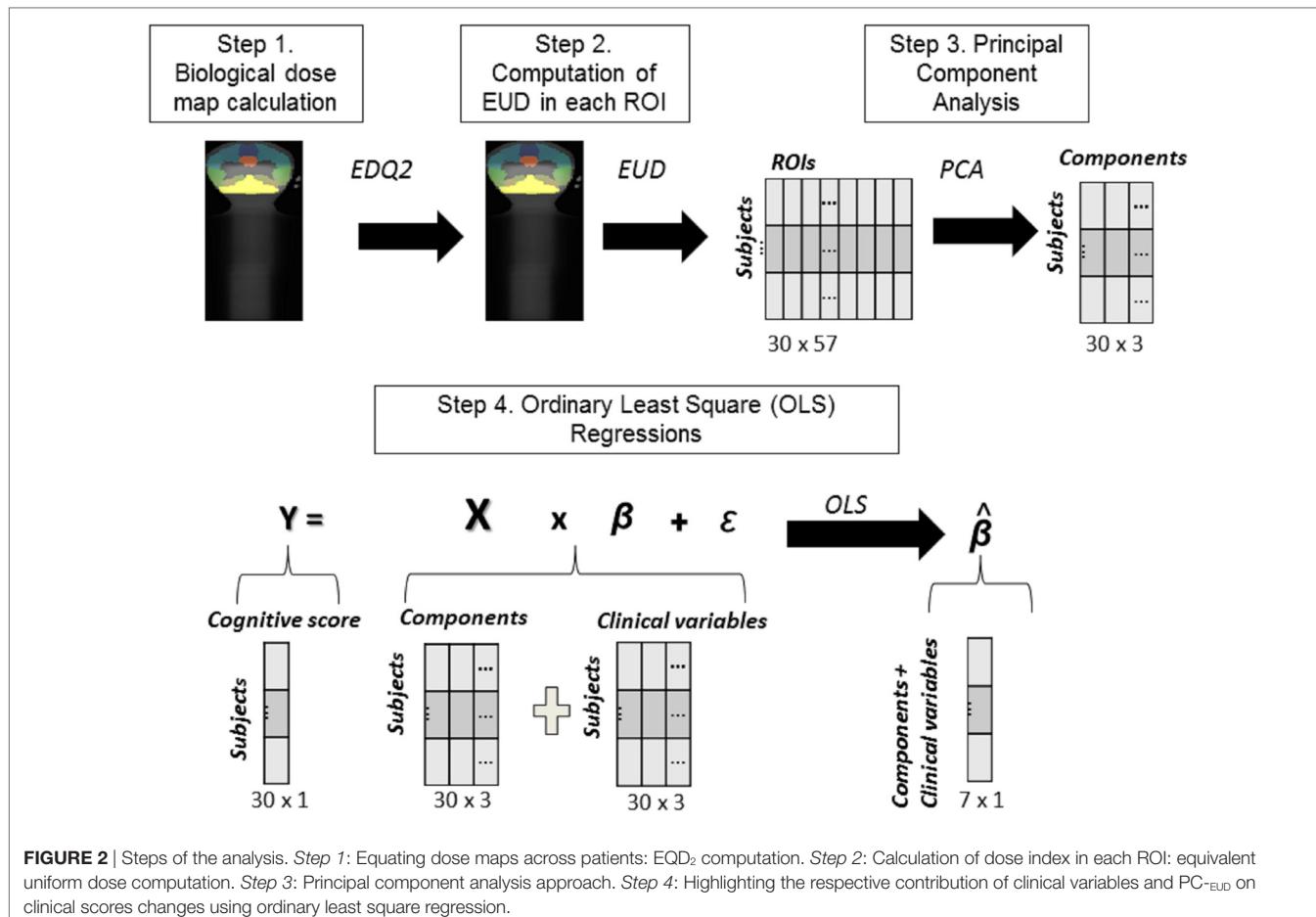
FIGURE 2 | Steps of the analysis. *Step 1*: Equating dose maps across patients: EQD$_2$ computation. *Step 2*: Calculation of dose index in each ROI: equivalent uniform dose computation. *Step 3*: Principal component analysis approach. *Step 4*: Highlighting the respective contribution of clinical variables and PC-$_{EUD}$ on clinical scores changes using ordinary least square regression.

that clusters correlated variables into common factors named principal components (PCs). In this approach, highly correlated variables share higher weights within each factor/component, but components are uncorrelated. The PCA enabled us (1) to obtain uncorrelated components representative of the radiation dose distribution variability across subjects, each component revealing a brain network with a particular radiation pattern and (2) to reduce the number of variables in our model, as sample size was limited. We performed a PCA taking the ROIs normalized EUD as variables (**Figure 2**, step 3). Then, we selected the $n < 57$ PCs accounting for 90% of the variance (33). Due to the high correlation between regions, we recovered only three components (PCs). To figure out the spatial contribution of the ROIs on each PC-$_{EUD}$, we computed the correlations between EUD in each ROI and each PC-$_{EUD}$, and projected the correlation coefficients onto a glass brain.

Highlighting the Respective Contribution of Clinical Variables and EUD-PCs on Clinical Score Changes

Step 4: We then considered the computed PCs-$_{EUD}$ and the clinical variables (chemotherapy, time since diagnosis, age at diagnosis, and ΔT) in a least square regression (**Figure 2**, step 4). We first checked for multicollinearity that could induce a biased estimation and a loss of power (34), using the variance inflation factor, which summarizes how an independent variable is explained by

other variables. We removed regressors with a variance inflation factor >10 (35). In each regression, we examined *t*-scores to determine which variable had the most important effect on the cognitive scores of these 30 patients.

All analyses and plots were computed using the *Python libraries*, *Nilearn*, *Scikit Learn*, and *Statsmodels* (36, 37).

RESULTS

Neuropsychological Performance

At time of first neuropsychological assessment, the mean estimated IQ over the whole population was 87.5 (SD = 18.4; [45–130]). A declining performance over time was observed in 67, 64, and 48% of the patients for ΔFSIQ, ΔWMI, and ΔPSI, respectively. The remaining patients showed either preserved or better performance over time. However, there were no statistically significant differences between cognitive scores [ΔFSIQ vs. ΔWMI: $t(32) = -0.64$, $p = 0.52$; ΔPSI vs. ΔWMI: $t(35) = -0.81$, $p = 0.42$; ΔFSIQ vs. ΔPSI: $t(51) = -0.37$, $p = 0.70$] (**Table 2**). Moreover, ANOVAs were conducted to compare the three treatment groups (chemotherapy alone vs. RT and chemotherapy vs. RT alone) on their cognitive scores (ΔFSIQ, ΔWMI, and ΔPSI). There was no statistically significant difference between treatment groups in ΔFSIQ [$F(2,30) = 2.36$; $p = 0.11$; RT alone: M = -10.5 (± 9.11), chemotherapy alone: M = 1.57

(± 11.28), RT and chemotherapy: M = -2.0 (± 11.03)]; and ΔWMI [$F_{(2,14)}$ = 1.17; p = 0.34; RT alone: M = -10 (± 9.90), chemotherapy alone: M = -0.29 (± 5.90), RT and chemotherapy: M = -4.60 (± 10.15)], and ΔPSI [$F_{(2,24)}$ = 2.28; p = 0.12; RT alone: M = -10 (± 9.90), chemotherapy alone: M = -0.29 (± 5.90), RT and chemotherapy: M = -4.60 (± 10.15)].

PCs Extracted from EUD of Anatomical ROIs

$PC1$-$_{EUD}$, which explained 67% of the variance of original data, was strongly correlated (>0.50) with the dose (EUD) in all regions, especially in the supratentorial space. $PC2$-$_{EUD}$ explained 19% of the variance and was positively correlated with 16 regions in the PF, inferior occipital and temporal regions (see Table S1 in Supplementary Material). Meanwhile, three regions in the left superior occipital and parietal regions correlated negatively and moderately (>0.40) with $PC2$-$_{EUD}$ (see Table S1 in Supplementary Material). $PC3$-$_{EUD}$ explained 5% of the variance and had a moderate positive correlation (>0.40) with the EUD in the left orbitofrontal area. By contrast, the precuneus and the right cuneus negatively correlated with $PC3$-$_{EUD}$. Values of all correlation coefficients are shown in Table S2 in Supplementary Material.

Effects of Clinical Variables and EUD Components on Cognitive Score Changes

Our final regression models included the three PCs-$_{EUD}$, chemotherapy, age at diagnosis, and delay between assessments (ΔT). Indeed, in all models, time since diagnosis (variance inflation factor >10) was highly correlated with ΔT (variance inflation factor >10), while it was not the case between PCs (variance inflation factor <10), chemotherapy (variance inflation factor <10), and age at diagnosis (variance inflation factor <10). We thus removed time since diagnosis from the analysis and checked that all remaining variance inflation factor indices were below 10.

Clinical Variables and Cognitive Score Changes

ΔFSIQ was significantly negatively affected by age at diagnosis and interval between assessments (ΔT), and positively influenced by chemotherapy. These variables had no significant effect on the other scores (**Table 3**).

EUD Components and Cognitive Score Changes

ΔWMI was clearly negatively associated with both $PC1$-$_{EUD}$ and $PC3$-$_{EUD}$ and marginally by $PC2$-$_{EUD}$ (**Table 3**) $PC3$-$_{EUD}$ had the highest effect on ΔWMI, followed by $PC1$-$_{EUD}$ and

$PC2$-$_{EUD}$ (**Figure 3**). The decline of WMI was first associated with an increase of EUD in left orbitofrontal area ($PC3$-$_{EUD}$) and then with an increase of EUD in all regions, especially in the supratentorial space ($PC1$-$_{EUD}$). By contrast, an EUD increase in the precuneus and right cuneus was positively associated with ΔWMI (**Figure 3**).

Only $PC2$-$_{EUD}$ and $PC3$-$_{EUD}$ were found to have a negative and significant effect on ΔPSI, with a seemingly higher effect of $PC2$-$_{EUD}$ than of $PC3$-$_{EUD}$, contrarily to ΔWMI (**Table 3**). The decline of PSI was first associated with an EUD increase in the PF, inferior occipital and temporal regions ($PC2$-$_{EUD}$) followed by an increase in the left orbitofrontal area ($PC3$-$_{EUD}$). By contrast, $PC2$-$_{EUD}$ and $PC3$-$_{EUD}$ were positively associated with ΔPSI in superior occipital and parietal regions (**Figure 3**).

Finally, $PC2$-$_{EUD}$ and $PC3$-$_{EUD}$ had similar and nearly significant negative effects on ΔFSIQ (**Table 3**) The decline of FSIQ was similarly associated with the increase of EUD in the PF, inferior occipital, temporal regions, and left orbitofrontal areas ($PC3$-$_{EUD}$ and $PC2$-$_{EUD}$). By contrast, EUD in superior occipital and parietal regions was positively associated with ΔFSIQ ($PC2$-$_{EUD}$ and $PC3$-$_{EUD}$) (**Figure 3**).

DISCUSSION

Our main results suggest different regional associations between radiation dose (EUD) and changes in cognitive scores in patients treated for PFTs. In particular, we highlighted a link between working memory decline and radiation dose in the orbitofrontal region, whereas the decline in processing speed seemed more related to irradiation of the temporal lobes and the PF.

Effect of Clinical Variables on Cognitive Score Changes

Consistently with previous studies (5, 6), the FSIQ decline depended on the delay between the two IQ tests. As shown in previous studies (5, 38), chemotherapy does not seem to have a significant negative impact on PSI and WMI functioning. The surprising positive effect of chemotherapy on FSIQ change might be linked to the positive impact of repeated measurements, also known as the carry over effect (or IQ test–retest) (39). Children acquired expertise concerning neuropsychological task along many neuropsychological tests, improving their performances. Therefore, the change in cognitive scores of each patient calculated from the difference between the first and last scores was positive. A large portion of children with chemotherapy alone showed an IQ improvement which confirms the absence of cognitive effect of chemotherapy (5, 38).

TABLE 3 | Effects on changes of cognitive scores (ΔFSIQ, ΔPSI, and ΔWMI) of the clinical variables and the components of the principal component analysis, according to our models (see Patients and Methods).

Δ score	N	Age at diagnosis	ΔT	Chemotherapy	EUD_{PC1}	EUD_{PC2}	EUD_{PC3}	R^2
ΔFSIQ	30	-2.14 (0.04)	-2.26 (0.04)	3.08 (0.01)	-0.35 (0.73)	-1.98 (0.06)	-1.98 (0.06)	0.43
ΔPSI	23	-1.38 (0.18)	-0.31 (0.76)	1.49 (0.15)	-1.15 (0.27)	-2.31 (0.03)	-2.05 (0.05)	0.43
ΔWMI	14	0.44 (0.67)	-1.32 (0.22)	0.44 (0.67)	-3.13 (0.01)	-2.12 (0.06)	-4.09 (0.0001)	0.80

For each variable, t score and p value (under parenthesis) are given, and for each model, the adjusted R^2 indicates the total proportion of the scores variance that was predicted from the variables.
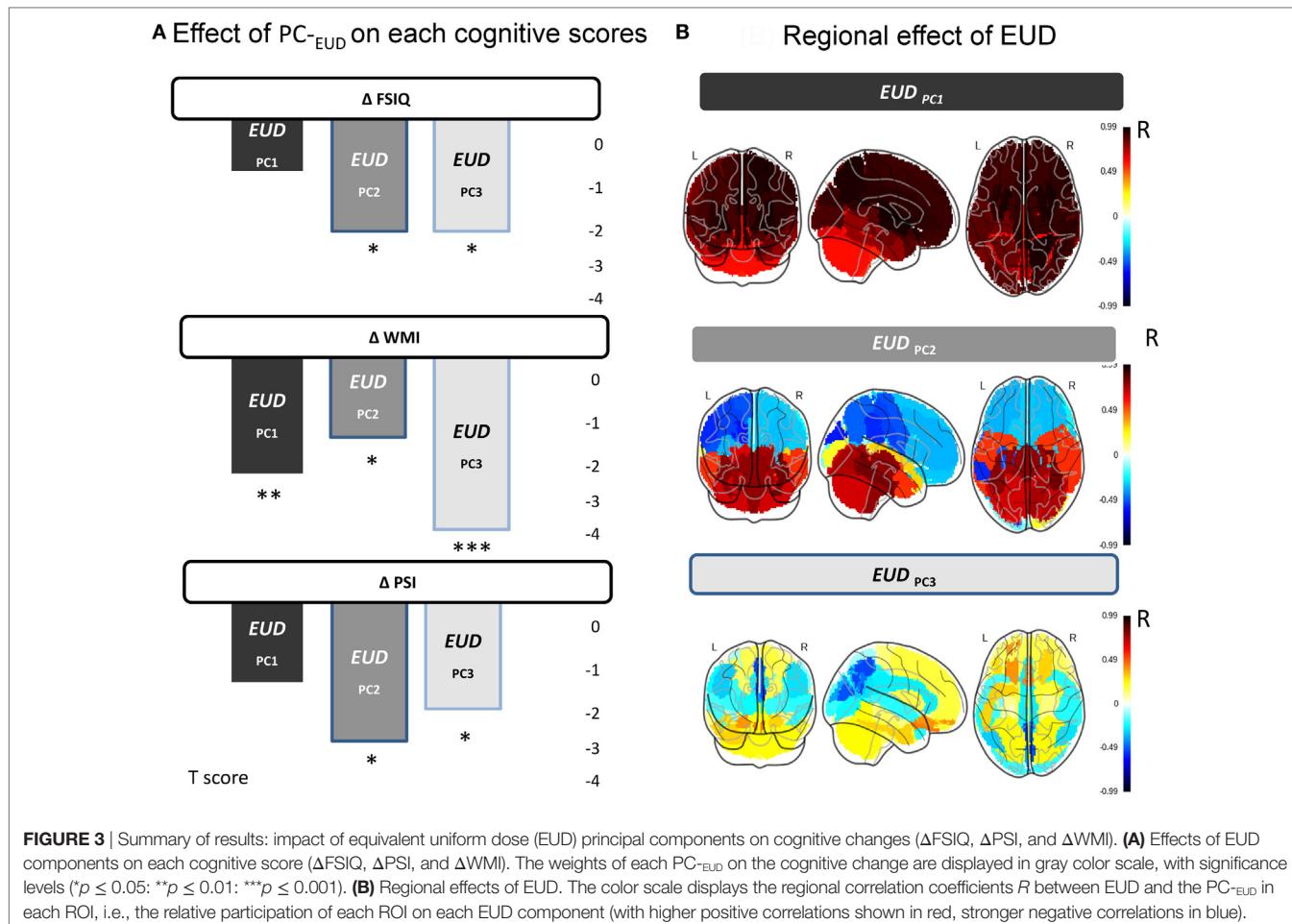
FIGURE 3 | Summary of results: impact of equivalent uniform dose (EUD) principal components on cognitive changes (ΔFSIQ, ΔPSI, and ΔWMI). **(A)** Effects of EUD components on each cognitive score (ΔFSIQ, ΔPSI, and ΔWMI). The weights of each PC-$_{EUD}$ on the cognitive change are displayed in gray color scale, with significance levels (*$p \leq 0.05$: **$p \leq 0.01$: ***$p \leq 0.001$). **(B)** Regional effects of EUD. The color scale displays the regional correlation coefficients R between EUD and the PC-$_{EUD}$ in each ROI, i.e., the relative participation of each ROI on each EUD component (with higher positive correlations shown in red, stronger negative correlations in blue).

This also explains the unexpected negative effect of age at diagnosis on FSIQ change, as children treated with chemotherapy alone are usually young (below 5 years) at diagnosis.

ROIs EUD and Cognitive Score Changes

All components seem to have specific impacts on changes of the working memory score (WMI). The radiation distribution pattern involving the left orbitofrontal regions (*PC3-$_{EUD}$*) had the most negative impact on working memory. Interestingly, this result could be in line with Mabbott et al.'s findings (40). They observed that working memory performance over time was different according to the tumor location in children treated for a central nervous system germ cell tumor. Patients with pineal tumors showed early, but stable, working memory deficit, whereas patients with suprasellar tumors experienced a significant working memory decline over time. Mabbott et al. suggested the observed decline was related to the radiation field rather than to the tumor location (40). In addition, this observation fits well with the compelling neuroimaging evidence of orbitofrontal implication in tasks relying on working memory [for meta-analysis, see Ref. (41, 42)]. *PC1-$_{EUD}$*, however, corresponds to a distributed radiation pattern across the whole brain, suggesting that a global increase of radiation dose (EUD) impacts working memory negatively. From its patterns of spatial radiation distribution, this

last component could be interpreted as CSI dose variability across subjects. However, such an overall radiation effect does not allow us to distinguish specifically irradiated brain networks that could be particularly involved in working memory impairment.

More specific brain network radiation patterns are found to influence processing speed. The large impact of *PC3-$_{EUD}$* is strongly related to radiation to the temporal lobes and the PF. Previous studies have shown significant associations between radiation dose to the temporal lobe and processing speed impairments (16, 17, 43). The cerebellum has also been shown to play a role in processing speed capabilities (44). Importantly, temporal lobe regions are close to the PF upon which the dose was escalated. Thus, *PC3-$_{EUD}$* impact could also reflect the radiation field boost trajectory to the PF across subjects. This would support the hypothesis that the volume receiving the highest dose has the greatest impact on cognitive functions. Accordingly, these findings would support current volume–reduction efforts.

Finally, *PC2-$_{EUD}$* and *PC3-$_{EUD}$* carry the exact same negative effect on IQ change. As reported earlier, *PC2-$_{EUD}$* that includes the temporal lobes and the PF showed the most significant impact on processing speed changes. As for processing speed, previous studies have found associations between radiation dose to the temporal lobe and PF and IQ impairments (16, 18). In the same way, the role on IQ impairment of *PC3-$_{EUD}$*, which strongly involves

the left orbitofrontal cortex, is somehow expected, as many VBM studies in adults and adolescents have shown a link between IQ and gray matter density in this region (45–47). Alternatively, the equal contribution of these two components on ΔFSIQ might be the expression of an averaging effect as FSIQ is a composite index encompassing both working memory and processing speed.

Higher EUD in the superior occipital and parietal regions did not seem to be associated with lower cognitive scores. We may note that Armstrong et al. (17) did not find any significant association between occipito-parietal radiation dose and cognitive or social problems either. In addition, with the same amount of radiation dose, the parietal lobe white matter was shown to be less affected compared to frontal lobe in medulloblastoma (48, 49). Thus, it would be interesting to test whether the parietal lobe is less susceptible to radiation than other regions.

There are limitations in this study, and results should be interpreted with caution. First, the small size and heterogeneity of the patient population make it difficult to control for other variables that could affect the scores (i.e., hydrocephalus shunt, education, rehabilitation, surgical approach, molecular group, etc.). Moreover, considering only PFT patients prevented us from taking into account several potentially confounding variables such as type and localization of the tumor. However, this was a disadvantage regarding the large spatial correlations between close irradiated regions induced by similar radiation protocol. We could not access separately specific regions that are known to play an important role in working memory [e.g., dorsolateral area (50)] or processing speed [e.g., left middle frontal gyrus (51)]. Second, noise could be induced by intersubject variability of the brain morphology, even if we minimized possible segmentation errors by using atlases specific to age groups. Finally, we have to acknowledge that seven patients (that received hyperfractionated radiotherapy, HFRT) had the same total dose and could be considered as a subgroup that could influence the results (see Figure S1 in Supplementary Material). We recognize the possibility that the HFRT subgroup smaller variance might influence the result in other less crucial ways (see Figure S2 in Supplementary Material).

CONCLUSION

This study confirms two cases for which there is a relationship between the radiation dose in particular brain areas and specific cognitive decline. The first case shows a correlation between orbitofrontal radiation and working memory decline, whereas the second case portrays a correlation between temporal lobe and PF radiation and slower processing speed. As this study is exploratory, it does aim to provide information regarding brain regions to avoid, but to describe relationships between radiation and cognitive function. The relationship between the cognitive profiles and the irradiation of these regions should be further confirmed in a prospective randomized with both, a bigger cohort and different radiation protocols.

ETHICS STATEMENT

This retrospective study was approved by the Comite de Protection des Personnes CPP no. 14973 (Ile de France, France). All patient's parents gave a written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

All authors carried a substantial contribution to the article and approved the final version of the manuscript. None of them has any conflict of interest. Guarantor of integrity of entire study: EDS, MN, and LH-P. Study concepts and design or data collection or data analysis and interpretation: all authors. Data preprocessing: EDS, CR, AG, and CP. Statistical analysis: EDS and MP-G. Drafting the work or revising it critically for important intellectual content: all authors.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fonc.2017.00166/full#supplementary-material.

REFERENCES

1. Danjoux CE, Jenkin RD, McLaughlin J, Grimard L, Gaspar LE, Dar AR, et al. Childhood medulloblastoma in Ontario, 1977–1987: population-based results. *Med Pediatr Oncol* (1996) 26(1):1–9. doi:10.1002/(SICI)1096-911X(199601)26:1<1::AID-MPO1>3.0.CO;2-Q

2. Hanzlik E, Woodrome SE, Abdel-Baki M, Geller TJ, Elbabaa SK. A systematic review of neuropsychological outcomes following posterior fossa tumor surgery in children. *Childs Nerv Syst* (2015) 31(10):1869–75. doi:10.1007/s00381-015-2867-3

3. Pollack IF, Jakacki RI. Childhood brain tumors: epidemiology, current management and future directions. *Nat Rev Neurol* (2011) 7(9):495–506. doi:10.1038/nrneurol.2011.110

4. Mabbott DJ, Penkman L, Witol A, Strother D, Bouffet E. Core neurocognitive functions in children treated for posterior fossa tumors. *Neuropsychology* (2008) 22(2):159–68. doi:10.1037/0894-4105.22.2.159

5. Palmer SL, Gajjar A, Reddick WE, Glass JO, Kun LE, Wu S, et al. Predicting intellectual outcome among children treated with 35–40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology* (2003) 17(4):548–55. doi:10.1037/0894-4105.17.4.548

6. Merchant TE, Schreiber JE, Wu S, Lukose R, Xiong X, Gajjar A. Critical combinations of radiation dose and volume predict intelligence quotient and academic achievement scores after craniospinal irradiation in children with medulloblastoma. *Int J Radiat Oncol Biol Phys* (2014) 90(3):554–61. doi:10.1016/j.ijrobp.2014.06.058

7. Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol* (2004) 22(4):706–13. doi:10.1200/JCO.2004.05.186

8. Mulhern RK, Palmer SL, Merchant TE, Wallace D, Kocak M, Brouwers P, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *J Clin Oncol* (2005) 23(24):5511–9. doi:10.1200/JCO.2005.00.703

9. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *J Clin Oncol* (2001) 19(15):3470–6. doi:10.1200/JCO.2001.19.15.3470

10. Grill J, Renaux VK, Bulteau C, Viguier D, Levy-Piebois C, Sainte-Rose C, et al. Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. *Int J Radiat Oncol Biol Phys* (1999) 45(1):137–45. doi:10.1016/S0360-3016(99)00177-7

11. Merchant TE, Kiehna EN, Li C, Shukla H, Sengupta S, Xiong X, et al. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. *Int J Radiat Oncol Biol Phys* (2006) 65(1):210–21. doi:10.1016/j.ijrobp.2005.10.038

12. Carrie C, Muracciole X, Gomez F, Habrand JL, Benhassel M, Mege M, et al. Conformal radiotherapy, reduced boost volume, hyperfractionnated radiotherapy and on-line quality control in standard risk medulloblastoma without chemotherapy, results of the French M-SFOP 98 protocol. *Int J Radiat Oncol Biol Phys* (2003) 57(2):S195. doi:10.1016/S0360-3016(03)00995-7

13. Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* (2010) 76(3):S20–7. doi:10.1016/j.ijrobp.2009.02.091

14. Packer RJ, Cogen P, Vezina G, Rorke LB. Medulloblastoma: clinical and biologic aspects. *Neuro Oncol* (1999) 1(3):232–50. doi:10.1215/15228517-1-3-232

15. Moxon-Emre I, Bouffet E, Taylor MD, Laperriere N, Scantlebury N, Law N, et al. Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. *J Clin Oncol* (2014) 32(17):1760–8. doi:10.1200/JCO.2013.52.3290

16. Jalali R, Mallick I, Dutta D, Goswami S, Gupta T, Munshi A, et al. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. *Int J Radiat Oncol Biol Phys* (2010) 77(4):974–9. doi:10.1016/j.ijrobp.2009.06.025

17. Armstrong GT, Jain N, Liu W, Merchant TE, Stovall M, Srivastava DK, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. *Neuro Oncol* (2010) 12(11):1173–86. doi:10.1093/neuonc/noq104

18. Merchant TE, Sharma S, Xiong X, Wu S, Conklin H. Effect of cerebellum radiation dosimetry on cognitive outcomes in children with infratentorial ependymoma. *Int J Radiat Oncol Biol Phys* (2014) 90(3):547–53. doi:10.1016/j.ijrobp.2014.06.043

19. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* (2014) 32(34):3810–6. doi:10.1200/JCO.2014.57.2909

20. Wechsler D. *The Wechsler Intelligence Scale for Children*. 3rd ed. San Antonio, TX: The Psychological Corp (1991).

21. Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd ed. San Antonio, TX: The Psychological Corp (1997).

22. Richards JE, Sanchez C, Phillips-Meek M, Xie W. A database of age-appropriate average MRI templates. *Neuroimage* (2016) 124:1254–9. doi:10.1016/j.neuroimage.2015.04.055

23. Shattuck DW, Mirza M, Adisetiyo V, Hojatkashani C, Salamon G, Narr KL, et al. Construction of a 3D probabilistic atlas of human cortical structures. *Neuroimage* (2008) 39(3):1064–80. doi:10.1016/j.neuroimage.2007.09.031

24. Gousias IS, Rueckert D, Heckemann RA, Dyet LE, Boardman JP, Edwards AD, et al. Automatic segmentation of brain MRIs of 2-year-olds into 83 regions of interest. *Neuroimage* (2008) 40(2):672–84. doi:10.1016/j.neuroimage.2007.11.034

25. Sanchez CE, Richards JE, Almli CR. Neurodevelopmental MRI brain templates for children from 2 weeks to 4 years of age. *Dev Psychobiol* (2012) 54(1):77–91. doi:10.1002/dev.20579

26. Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, et al. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage* (2009) 46(3):786–802. doi:10.1016/j.neuroimage.2008.12.037

27. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* (2008) 12(1):26–41. doi:10.1016/j.media.2007.06.004

28. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* (2001) 5(2):143–56. doi:10.1016/S1361-8415(01)00036-6

29. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* (1989) 62(740):679–94. doi:10.1259/0007-1285-62-740-679

30. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys* (1997) 24(1):103. doi:10.1118/1.598063

31. Thames HD. An "incomplete-repair" model for survival after fractionated and continuous irradiations. *Int J Radiat Biol Relat Stud Phys Chem Med* (1985) 47(3):319–39. doi:10.1080/09553008514550461

32. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* (1991) 21(1):109–22. doi:10.1016/0360-3016(91)90171-Y

33. Jolliffe I. Principal component analysis. *Wiley StatsRef: Statistics Reference Online*. John Wiley & Sons, Ltd (2014). doi:10.1002/9781118445112.stat06472

34. Yoo W, Mayberry R, Bae S, Singh K, He QP, Lillard JW Jr. A study of effects of multicollinearity in the multivariable analysis. *Int J Appl Sci Technol* (2014) 4(5):9.

35. Kennedy P. *A Guide to Econometrics*. 6th ed. Malden, MA: Wiley-Blackwell (2008).

36. Seabold S, Perktold J. Statsmodels: econometric and statistical modeling with python. *Proceedings of the 9th Python in Science Conference*. (Vol. 57) (2010). 61 p. Available from: https://conference.scipy.org/proceedings/scipy2010/pdfs/seabold.pdf

37. Abraham A, Pedregosa F, Eickenberg M, Gervais P, Mueller A, Kossaifi J, et al. Machine learning for neuroimaging with scikit-learn. *Front Neuroinformatics* (2014) 8:14. doi:10.3389/fninf.2014.00014

38. von der Weid N, Mosimann I, Hirt A, Wacker P, Nenadov Beck M, Imbach P, et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. *Eur J Cancer* (2003) 39(3):359–65. doi:10.1016/S0959-8049(02)00260-5

39. Kempf-Leonard K, editor. *Encyclopedia of Social Measurement*. 1st ed. Amsterdam: Elsevier (2004).

40. Mabbott DJ, Monsalves E, Spiegler BJ, Bartels U, Janzen L, Guger S, et al. Longitudinal evaluation of neurocognitive function after treatment for central nervous system germ cell tumors in childhood. *Cancer* (2011) 117(23):5402–11. doi:10.1002/cncr.26127

41. Wager TD, Smith EE. Neuroimaging studies of working memory. *Cogn Affect Behav Neurosci* (2003) 3:255–74. doi:10.3758/CABN.3.4.255

42. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* (2005) 25:46–59. doi:10.1002/hbm.20131

43. Redmond KJ, Mahone EM, Terezakis S, Ishaq O, Ford E, McNutt T, et al. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. *Neuro Oncol* (2013) 15(3):360–9. doi:10.1093/neuonc/nos303

44. Eckert MA. Slowing down: age-related neurobiological predictors of processing speed. *Front Neurosci* (2011) 5:25. doi:10.3389/fnins.2011.00025

45. Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, et al. Intellectual ability and cortical development in children and adolescents. *Nature* (2006) 440(7084):676–9. doi:10.1038/nature04513

46. Jung RE, Haier RJ. The parieto-frontal integration theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behav Brain Sci* (2007) 30(02):135. doi:10.1017/S0140525X07001185

47. Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, et al. Relationships between IQ and regional cortical gray matter thickness in healthy adults. *Cereb Cortex* (2007) 17(9):2163–71. doi:10.1093/cercor/bhl125

48. Qiu D, Kwong DL, Chan GC, Leung LH, Khong PL. Diffusion tensor magnetic resonance imaging finding of discrepant fractional anisotropy between the frontal and parietal lobes after whole-brain irradiation in childhood medulloblastoma survivors: reflection of regional white matter radiosensitivity? *Int J Radiat Oncol Biol Phys* (2007) 69(3):846–51. doi:10.1016/j.ijrobp.2007.04.041

49. Qiu D, Leung LHT, Kwong DLW, Chan GCF, Khong P-L. Mapping radiation dose distribution on the fractional anisotropy map: applications in the

assessment of treatment-induced white matter injury. *Neuroimage* (2006) 31(1):109–15. doi:10.1016/j.neuroimage.2005.12.007

50. Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res* (2000) 133(1):23–32. doi:10.1007/s002210000397

51. Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JDE. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *Neuroimage* (2008) 42(2):1032–44. doi:10.1016/j.neuroimage.2008.03.057

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, JB, and the handling editor declared their shared affiliation, and the handling editor states that the process nevertheless met the standards of a fair and objective review.

Tangential Field Radiotherapy for Breast Cancer—The Dose to the Heart and Heart Subvolumes: What Structures Must Be Contoured in Future Clinical Trials?

Marciana Nona Duma[1,2,3]*, Anne-Claire Herr[1,4], Kai Joachim Borm[1], Klaus Rüdiger Trott[1,5], Michael Molls[1,6], Markus Oechsner[1,2] and Stephanie Elisabeth Combs[1,2,3]

[1] Department of Radiation Oncology, Technical University of Munich (TUM), Munich, Germany, [2] Center for Stereotactic and Highprecision Radiation Therapy (StereotakTUM), Technische Universität München (TUM), Munich, Germany, [3] Department of Radiation Sciences (DRS), Institute of Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Munich, Germany, [4] Medical School, Technische Universität München, Munich, Germany, [5] Cancer Institute, University College of London, London, United Kingdom, [6] Technische Universität München, Munich, Germany

Background and purpose: The aim of the present study was to evaluate if it is feasible for experienced radiation oncologists to visually sort out patients with a large dose to the heart. This would facilitate large retrospective data evaluations. And in case of an insufficient visual assessment, to define which structures should be contoured and which structures can be skipped as their dose can be derived from other easily contoured structures for future clinical trials.

Material and methods: Planning CTs of left-sided breast cancer patients treated with 3D-conformal radiotherapy by tangential fields were visually divided into two groups: with an estimated high dose (HiD) and with an estimated low dose (LoD) to the heart. For 46 patients (22 HiD and 24 LoD), the heart, the left ventricle, the left anterior descending artery (LAD), the right coronary artery, and the ramus circumflexus were contoured. A helper structure (HS) around the LAD was generated in order to consider if contouring uncertainties of the LAD could be acceptable. We analyzed the mean dose (Dmean), the maximum dose, the V10, V20, V30, V40, and the length of the LAD that received 20 and 40 Gy.

Results: The two groups had a significant different Dmean of the heart ($p < 0.001$). The average Dmean to the heart was 4.0 ± 1.3 Gy (HiD) and 2.3 ± 0.8 Gy (LoD). The average Dmean to the LAD was 26.2 ± 7.4 Gy (HiD) and 13.0 ± 7.5Gy (LoD) with a very strong positive correlation between Dmean LAD and Dmean HS in both groups. The Dmean heart is not a good surrogate parameter for the dose to the LAD since it might underestimate clinically significant doses in 1/3 of the patients in LoD group.

Conclusion: A visual assessment of the dose to the heart could be reliable if performed by experienced radiation oncologists. However, the Dmean heart is not always a good surrogate parameter for the dose to the LAD or for the Dmean to the left ventricle. Thus, if specific late toxicities are evaluated, we strongly recommend contouring of the specific heart substructures as a heart Dmean is not highly specific.

Keywords: breast cancer, heart, tangential field, left anterior descending artery, radiotherapy

INTRODUCTION

The heart is probably the most radiosensitive organ in the human body. Long-term follow-up of the Japanese A-bomb survivors demonstrated that a mean body dose (and thus mean heart dose) of 1 Gy increased the mortality from heart diseases by 14% (1). Follow-up studies in patients treated for various malignant and non-malignant diseases yielded similar risk values (2). Careful analysis of the pathologies of radiation-induced heart diseases after mantle field radiotherapy of patients for Hodgkin's disease (thus receiving a near-homogeneous dose to their hearts) demonstrated that five different radiation-induced heart diseases were diagnosed, namely, pericarditis, myocardial fibrosis, coronary atherosclerosis leading to myocardial infarction, conduction defects such as bundle branch blocks and valvular insufficiency. Each of these manifestations of cardiac radiation injury occurs in different substructures of the heart, follows different pathogenic pathways, and may have different dose dependence. This means, however, that different manifestations of cardiac radiation damage would be expected to occur after different anatomical dose distributions, such as from adjuvant radiotherapy of breast cancer patients and that mean heart doses may not be a relevant dose criterion for estimating cardiac complications from particular treatment plans.

Notwithstanding this argument, large retrospective data have demonstrated a relationship between the delivered heart dose and major coronary events. A recent study by Darby et al. (3) analyzed the risk of ischemic heart disease in women after radiotherapy for breast cancer. They have found that the average mean dose (Dmean) to the heart of patients treated between 1958 and 2001 was 4.9 Gy with a significant correlation between the mean heart dose and major coronary events. However, no individual dosimetric data were available for this retrospective study. In order to assess the mean heart doses and the Dmean to the anterior descending coronary artery, the 2D-plans were recalculated on a "typical" patient in the Darby et al. study. Studies have also shown a direct link between radiation dose in the coronary arteries and the location of coronary stenosis (4).

Although heart dose from breast cancer radiotherapy has been significantly reduced over the past decades, parts of the heart may still be located in the radiation field in modern 3D-conformal radiotherapy (3D-CRT) (5–7). Hence, it is essential to select all patients, which, with conventional techniques, could receive a significant dose to critical structures of the heart and offer them a cardiac sparing radiotherapy.

However, contouring of all the heart subvolumes is time consuming. Moreover, it has to be considered that there may be clinically and dosimetrically significant interobserver variations in heart and heart subvolume delineations (8). Lorenzen et al. found substantial interobserver variation in the estimated dose of the left anterior descending artery (LAD), which even guidelines could not reduce. The coefficients of variation in the estimated doses to the LADCA were for Dmean 27% without and 29% with guidelines. For the heart, variation was little, especially when guidelines were used (9). Thus, it is essential to understand the dosimetric impact of contouring uncertainties in the LAD.

The aim of the present study was to evaluate if it is feasible for experienced radiation oncologists to visually sort out patients with a large dose to the heart. This would facilitate large retrospective data evaluations. And in case of an insufficient visual assessment, to define which structures should be contoured and which structures can be skipped as their dose can be derived from other easily contoured structures. More specifically, two questions were addressed: (1) is the visual evaluation a reliable indicator of mean heart dose and (2) is the mean heart dose a reliable indicator of the radiation exposure of the left anterior descending coronary artery/left ventricle?

MATERIALS AND METHODS

201 consecutive patients with left-sided breast cancer treated in our institution between March 2009 and November 2010 were identified.

These patients were all treated with 3D-CRT by tangential fields, half beam technique. Patients were placed on a breast board with the left arm above the head. The treatment planning was performed with the Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA, USA). All patients underwent a planning kVCT scan (Siemens Inc., Erlangen, Germany) with an axial slice thickness of 5 mm before treatment. The CT scans were not contrast enhanced. The treatment plans consisted of two opposing tangential wedged beams. Additional segments (1–2) were used to improve target dose homogeneity, if necessary. Both medial and lateral beams were wedged. The PTV prescribed dose was 50 Gy for the whole breast (ICRU reference point), followed by an electron boost of 10–16 Gy. All treatments were performed with daily single doses of 2 Gy.

The planning CTs of the 201 patients were visually reviewed. The CTs with the calculated dose distributions for the whole breast radiotherapy (50 Gy) were presented to a radiation oncologist who was asked to assess whether the heart Dmean would be high or low. **Figure 1** exemplarily depicts two CTs with the isodoses (10–105%) used in this study. No structures were superimposed on the CT scan. Assessment was performed visually. Taking for example the patient in **Figure 1A**, as a large part of the heart is within the 10% isodose, the patient was estimated by the radiation oncologist to have a high dose (HiD) to the heart. Thus, two groups were generated: one with a visually estimated HiD to the heart (86 patients) and the other one with an estimated low dose (LoD) to the heart (115 patients).

The treatment records of the 201 patients were reviewed and we excluded from this analysis: patients who underwent systemic therapy beforehand, patients who were treated for breast cancer relapse, patients who received irradiation to the locoregional lymph nodes, patients with mastectomy, and patients with concomitant bilateral breast cancer radiotherapy. This was done because in an ongoing study, we perform functional imaging to assess correlations between heart toxicities and dose distributions. From the remaining patients, the first 46 consecutive patients were chosen (24 from the LoD group and 22 patients from the HiD group) for this dosimetric study. The left ventricle, the LAD (LAD), the ramus circumflexus (RCX), and the right coronary artery (RCA) were retrospectively contoured according to the
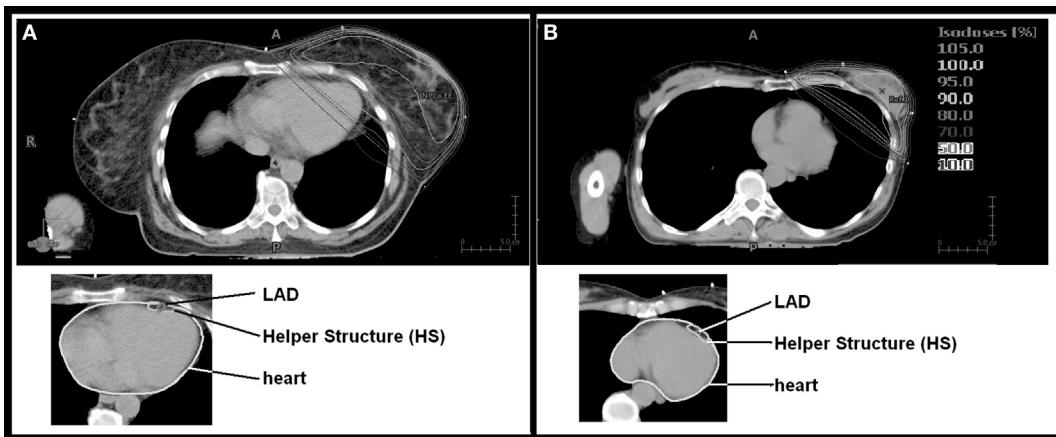
FIGURE 1 | Isodose distribution and contouring of organs at risk. Depicted are the two patients with the largest [**(A)** mean dose (Dmean) 8.9 Gy] and the lowest [**(B)** Dmean 0.8 Gy] Dmean heart doses.

Feng et al. heart atlas (10). In order to test whether contouring uncertainties could be acceptable for the LAD, a helper structure (HS) with a width of 0.5 cm anterior–posterior and 1 cm left right around the LAD was generated (**Figure 1**). This was performed in order to test whether a significantly larger contouring of a very small region of interest can be safely performed.

For all contoured structures, dose volume histograms were analyzed. We assessed the minimum dose, maximum dose (Dmax), Dmean, absolute volume in cubic centimeters, V10 (the relative volume that receives 10 Gy or more), V20, V30, and V40. Additionally, the absolute volume V10, V20, V30, and V40 of the heart in cubic centimeters was assessed.

Since neither clinical nor radiobiological data provide a reliable data on the dose/volume dependence of radiation-induced atherosclerosis, different criteria of dose specification in the LAD were determined which would, in a second step, permit the determination of the anatomical relationship between local dose and local tissue injury. Therefore, in addition to V10 etc., also the absolute LAD length and the length of the LAD that lies within the 20 Gy isodose and within the 40 Gy isodose were evaluated. The statistical analyses were performed using SPSS Software for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were performed two-sided and a p-value <0.05 was considered to indicate statistical significance. Mean values are reported with SD, median values with range. Pearson correlations are presented.

RESULTS

In the 46 patients, the volume of the heart ranged between 471 and 1,013 cm^3, the volume of the left ventricle between 141.2 and 275.3 cm^3, the volume of the LAD between 1.1 and 2.6 cm^3, the HS volume between 11.2 and 20.8 cm^3, the RCX volume between 0.3 and 1.0 cm^3, and the RCA volume between 0.7 and 1.8 cm^3.

The median (range) Dmean/Dmax to the whole heart was 3.6 Gy (2.6–8.9 Gy)/49.3 Gy (47.7–51.6 Gy) for the HiD group

and 2.6 Gy (0.8–3.5 Gy)/44.6 Gy (6.1–57.3 Gy) for the LoD group, respectively. The median (range) Dmean/Dmax to the left ventricle was 6.3 Gy (3.8–15.5 Gy)/49.2 Gy (46.1–51.4 Gy) for the HiD group and 4.0 Gy (1.0–6.0 Gy)/48.1 Gy (4.8–57.2 Gy) for the LoD group, respectively. Doses for the RCA or RCX were <1.0 Gy.

The two groups had a significant different Dmean of the heart ($p < 0.001$). Thus overall, the clinical assessment whether the heart will receive a HiD or LoD was good (**Figure 1**), yet, there was considerable overlap considering individual patients. In the HiD group 3 patients out 22 were wrongly estimated—Dmean within 0.5 Gy of the average Dmean heart of the LoD group. In the LoD group, 3 out of 24 patients were within 0.5 Gy of the average Dmean heart of the HiD group.

The overall average length of the LAD was 8.4 ± 0.8 cm (Mean ± SD). The length of the LAD that received 20 Gy/40 Gy was 4.5 ± 1.8 cm/2.9 ± 2.3 cm for the HiD group and 1.9 ± 1.7 cm/0.7 ± 1.1 cm for the LoD group, respectively.

The average Dmean to the LAD/HS was 26.2 ± 7.4 Gy/23.3 ± 6.9 Gy for the HiD group and 13.0 ± 7.5 Gy/13.0 ± 7.2 Gy for the LoD group. In both groups, there were very strong positive correlations between the Dmean LAD and the Dmean HS ($r \geq 0.964$; $p < 0.001$) (**Figure 2**).

For both groups, there was a very strong positive correlation between the Dmean ventricle and the Dmean heart ($r \geq 0.902$; $p < 0.001$) and a strong and very strong positive correlation between the Dmean heart and Dmean LAD/HS, respectively (HiD: $r = 0.731/r = 0.724$, $p < 0.001$; LoD: $r = 0.834/r = 0.849$, $p < 0.001$) (**Figure 3**). The correlation between Dmean ventricle and Dmean LAD was strong but not as strong as the one between Dmean heart and Dmean LAD (HiD: $r = 0.642$; LoD: $r = 0.605$; $p \leq 0.001$). We found strong and very strong positive correlations between heart (relative volume) V10, V20, V30, and V40 and LAD V10, V20, V30, and V40 in the high as well as in the LoD group. **Table 1** presents the absolute and relative V10, V20, V30, and V40 of the heart (**Table 1**). **Figure 4** depicts exemplary scatterplots of the V30 of the LAD and the Dmean heart, which highlights the clinical problem. Despite significant correlation,
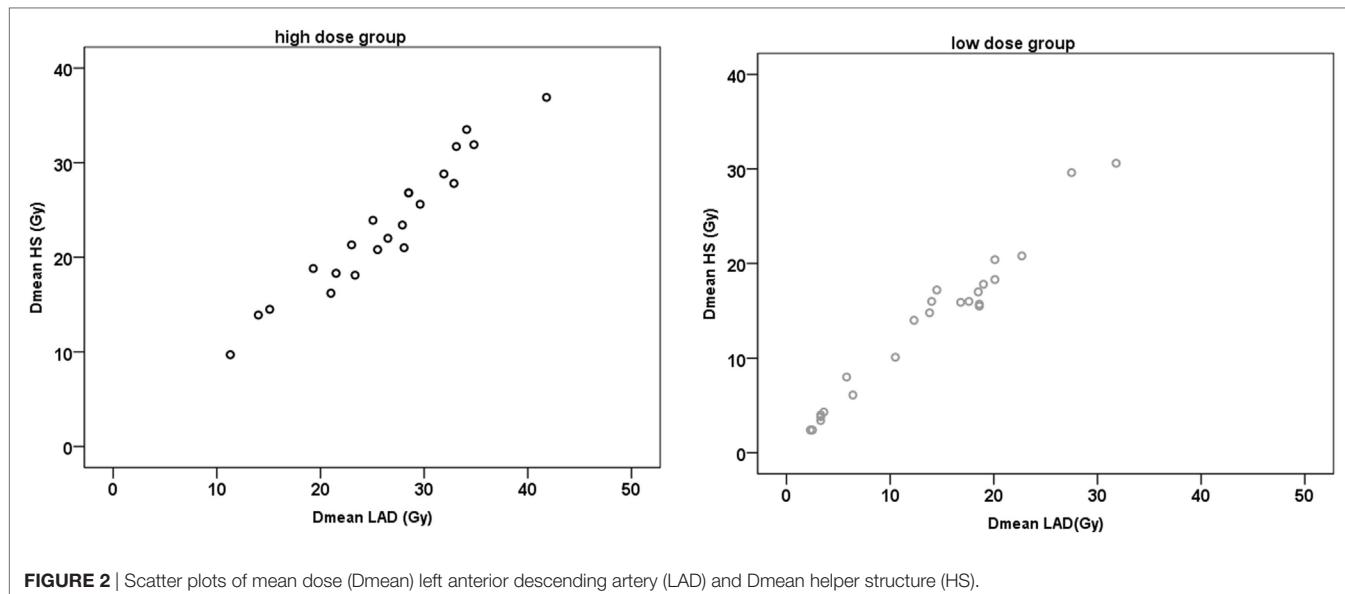
FIGURE 2 | Scatter plots of mean dose (Dmean) left anterior descending artery (LAD) and Dmean helper structure (HS).
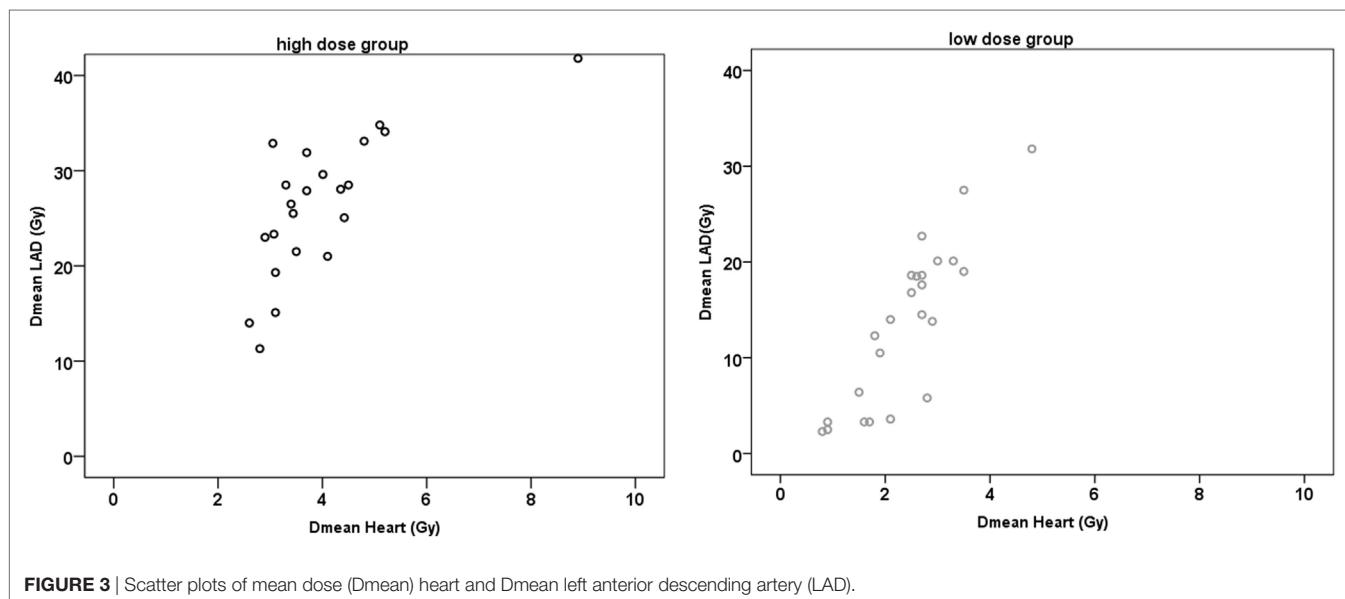
FIGURE 3 | Scatter plots of mean dose (Dmean) heart and Dmean left anterior descending artery (LAD).

the predictive value of the mean heart dose and high doses to critical volumes of the LAD may not be good enough.

DISCUSSION

As breast cancer is the most common cancer in women and long-term survivorship is nowadays the rule, morbidity and mortality from radiation-induced heart disease has become a major concern in treatment planning. There is evidence that the risk of different potential late cardiac radiation injury depends on local radiation dose, which opens the possibility to reduce the risk by optimizing the dose distribution in the heart of the individual patient. This does, however, require detailed cardiac dosimetry for the individual patient as a basis
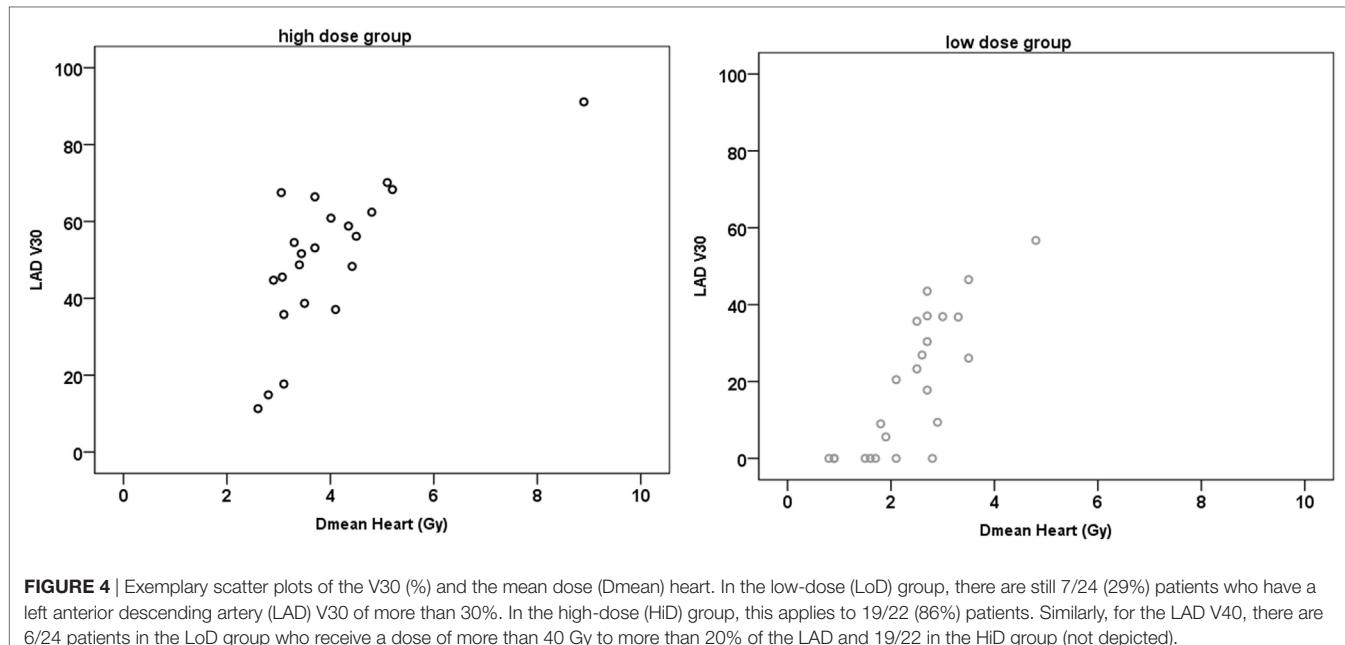
for treatment plan optimization. Studies are available on modern heart dosimetry in breast cancer patients, revealing that even with contemporary treatment and planning techniques, some patients still receive important doses to the heart or to its substructures such as the LAD.

The aim of this study was to assess which structures should be contoured and which structures could be skipped as the dose could be derived from correlations with other structures.

The result of our study is that a visual assessment by experienced radiation oncologists often gives a reliable estimate of Dmean doses to the heart. There is a significant ($p < 0.001$) statistical difference in the Dmean to the heart between the two chosen groups. If the heart is not contoured due to workload,

TABLE 1 | The V10, V20, V30, and V40 of the heart.

	Heart V10 (%)	Heart V10 (cm³)	Heart V20 (%)	Heart V20 (cm³)	Heart V30 (%)	Heart V30 (cm³)	Heart V40 (%)	Heart V40 (cm³)
High-dose group								
Median	6.1	46.3	4.9	36.7	4.1	30.1	3.0	22.8
Minimum	3.2	19.2	2.2	13.3	1.7	10.1	1.2	7.3
Maximum	19.0	129.6	16.8	114.5	15.0	102.7	11.9	81.1
Low-dose group								
Median	3.4	22.8	2.5	16.2	1.9	11.7	1.2	7.9
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	5.4	40.3	4.1	30.3	3.2	23.6	2.3	14.8

FIGURE 4 | Exemplary scatter plots of the V30 (%) and the mean dose (Dmean) heart. In the low-dose (LoD) group, there are still 7/24 (29%) patients who have a left anterior descending artery (LAD) V30 of more than 30%. In the high-dose (HiD) group, this applies to 19/22 (86%) patients. Similarly, for the LAD V40, there are 6/24 patients in the LoD group who receive a dose of more than 40 Gy to more than 20% of the LAD and 19/22 in the HiD group (not depicted).

a retrospective visual examination of planning CTs from the department database with predefined range of isodoses (e.g., 10–105% isodose) would be very informative and the Dmean to the heart could be estimated for future patients.

However, some patients in our study were not perfectly matched to their group. We reviewed each patient's CTs individually and found two main confounding factors.

First, our contouring—according to the Feng et al. (10) atlas—included the pericardium. Our group of patients, however, had some variations of the amount of epicardial fatty tissue. A simple scrolling through CT slices without definition of heart boundaries might visually group patients with larger epicardial fatty tissue into the LoD group as the pericardium is not always easily seen on every single CT slice. A large epicardial fatty tissue translates into a higher Dmean (since structures of the heart that were not visually considered, would now lie within the HiD region). These patients do not receive a large dose to the myocardium (left ventricle), but a significant dose to the LAD. Thus, either contouring of the heart including pericardium or contouring of all heart structures is necessary in these patients in order to estimate specific late toxicities.

Second, patients with a large dose to the heart on a few CT slices were wrongly categorized into to the HiD group. The HiD levels (40–50 Gy isodoses) extended into the heart on only very few CT slices (2–3 slices). Visually this can be misleading.

Focusing on mean heart dose solely, our findings suggest that visual grouping into the low heart dose category might be an acceptable way to eliminate detailed contouring in about half the patients with an error margin of 10%. In the other half of patients, detailed contouring should be recommended.

Yet, which structures should be contoured? Lorenzen et al. (9) found substantial interobserver variation in the estimated dose of the LAD, which even guidelines could not reduce. The spatial distance variation between the delineations was up to 7–8 mm. Thus, a structure like a HS might depict the whole uncertainties region. Overall, in our study, we found a very strong positive correlation between Dmean LAD and the Dmean HS ($r \geq 0.964$; $p < 0.001$). As the HS represents the relative region in which we can assume that the LAD lays, we can conclude that contouring uncertainties might be acceptable. Even a rough contouring will be helpful for the clinician in order to assess the magnitude of dose to the LAD (i.e., 13 vs. 23 Gy Dmean in the two groups, respectively).

However, even significant correlations between values of dose specification are of limited use in the practice of treatment planning for the individual patient. Although the dose to the LAD correlates very strongly with the dose to the heart, even in the LoD group there are still patients who will receive a significant dose to the LAD (>30 Gy). To stress this point, in **Figure 4,** patients with the same Dmean heart (e.g., ≈2.7 Gy) had a LAD V30 value that ranged between 0% and approx. 50% in the LoD group and in the HiD group the LAD V30 even ranged from 10 to 70%. Thus, despite the strong positive correlation of the Dmean of the heart to the Dmean to the LAD, even in the LoD group, one-third of the patients will receive over 30 Gy to one-third of their LAD. In order not to skip any patients with a HiD to the LAD. we therefore recommend a contouring of the LAD/HS in all patients with left-sided breast cancer, independent of the estimated or calculated mean heart dose.

CONCLUSION

A visual assessment could be reliable if experienced radiation oncologists have to assess whether a patient receives a higher or a lower Dmean to the heart. Even a rough contouring of the region LAD (i.e., the HS) provides clinically valuable information on the magnitude of the LAD dose. The Dmean heart is not always a good surrogate parameter for the dose to the LAD as it might underestimate clinically significant doses in one-third of the patients with a LoD. The Dmean heart is a good surrogate for the Dmean to the left ventricle, except for patients with a large epicardial fatty tissue. Thus, if specific late toxicities are evaluated, we strongly recommend contouring of the specific heart substructures as a heart Dmean is not highly specific.

CONSENT PROCEDURES

All patients gave their informed consent both informed and written before starting the radiotherapy that they will undergo CT radiotherapy treatment planning. Data from the CT radiotherapy treatment planning were retrospectively analyzed.

ETHICS STATEMENT

This study was approved by the ethics committee of Klinikum rechts der Isar, Technical University Munich.

AUTHOR CONTRIBUTIONS

MD, A-CH, KB, KT, MM, and MO participated in the study design, contributed to the data collection, and drafted the manuscript. SC made important contributions in revising the content. All authors read and approved the final manuscript.

REFERENCES

1. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res* (2003) 160:381–407. doi:10.1667/RR3049

2. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* (2007) 67:10–8. doi:10.1016/j.ijrobp.2006.08.071

3. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* (2013) 368:987–98. doi:10.1056/NEJMoa1209825

4. Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjogren I, Lagerqvist B, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* (2012) 30:380–6. doi:10.1200/JCO.2011.34.5900

5. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* (2008) 72:501–7. doi:10.1016/j.ijrobp.2007.12.058

6. Johansen S, Tjessem KH, Fossa K, Bosse G, Danielsen T, Malinen E, et al. Dose distribution in the heart and cardiac chambers following 4-field radiation therapy of breast cancer: a retrospective study. *Breast Cancer* (2013) 7:41–9.

7. Chung E, Corbett JR, Moran JM, Griffith KA, Marsh RB, Feng M, et al. Is there a dose-response relationship for heart disease with low-dose radiation therapy? *Int J Radiat Oncol Biol Phys* (2013) 85:959–64. doi:10.1016/j.ijrobp.2012.08.002

8. Li XA, Tai A, Arthur DW, Buchholz TA, Macdonald S, Marks LB, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG multi-institutional and multiobserver study. *Int J Radiat Oncol Biol Phys* (2009) 73:944–51. doi:10.1016/j.ijrobp.2008.10.034

9. Lorenzen EL, Taylor CW, Maraldo M, Nielsen MH, Offersen BV, Andersen MR, et al. Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: a multi-centre study from Denmark and the UK. *Radiother Oncol* (2013) 108:254–8. doi:10.1016/j.radonc.2013.06.025

10. Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys* (2011) 79:10–8. doi:10.1016/j.ijrobp.2009.10.058

Advantages of publishing in Frontiers

OPEN ACCESS

Articles are free to read, for greatest visibility

COLLABORATIVE PEER-REVIEW

Designed to be rigorous – yet also collaborative, fair and constructive

FAST PUBLICATION

Average 85 days from submission to publication (across all journals)

COPYRIGHT TO AUTHORS

No limit to article distribution and re-use

TRANSPARENT

Editors and reviewers acknowledged by name on published articles

SUPPORT

By our Swiss-based editorial team

IMPACT METRICS

Advanced metrics track your article's impact

GLOBAL SPREAD

5'100'000+ monthly article views and downloads

LOOP RESEARCH NETWORK

Our network increases readership for your article

Find us on