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Review

Postmastectomy radiotherapy in T1-2 patients with one to three positive lymph nodes – Past, present and future

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ABSTRACT

Past: The role of post-mastectomy radiotherapy (PMRT) in patients with tumor <5 cm and one to three positive lymph nodes after axillary dissection (ALND) is vigorously debated. Initial doubts over the efficacy and safety of PMRT in these patients were partially overcome by improvement in technology and systemic treatments. Several randomized controlled clinical trials confirmed benefit of PMRT in N1 patients, which were meta-analyzed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). This meta-analysis provides the sole high-level evidence to guide clinical decision-making.
Present: Nevertheless, concerns have been evoked around these results, most notably concerning the patient selection bias and the era in which the patients were treated. More recent studies, albeit retrospective, are in contrast with this level I evidence, unequivocally reporting inferior recurrence rates in control arms than those of the EBCTCG meta-analysis. Taken together, these results suggest that one solution would not fit all N1 patients and that patient selection for PMRT shall be stratified upon risks factors. Most prominent of such factors identified are: patient age; number and ratio of positive lymph nodes; histological features such as lymphovascular invasion; and hormone receptor expression.
Future: A prospective randomized controlled trial SUPREMO will release its final results in 2023 and shed light onto the subject. Genomic tumor cell profiling will likely provide further guidelines in terms of risk stratification. SUPREMO translational sub-study will also offer material for genomic analyses. A cross-field tendency to forgo nodal dissection in favor of sentinel lymph node biopsy followed by nodal irradiation might eventually render the question of PMRT indication after ALND irrelevant.

Contents

1. Introduction 74
2. Past doubts and present evidence 74
3. Current uncertainties 74
4. PMRT-induced toxicities 75
5. Risk factors to guide indication 75
   5.1. Age 75
   5.2. Number of dissected axillary lymph nodes and positive-to-dissected ratio 76
   5.3. Absolute number of positive lymph nodes and size of nodal metastases 76
   5.4. Primary tumor size and stage 77
   5.5. Histological grade, lymphovascular invasion and receptor expression status 77
   5.6. Other factors associated with worse prognosis 77
   5.7. Nuclear and molecular medicine 77
6. Clinically N1 patients and neoadjuvant chemotherapy 78
7. Determination of radiation target volumes 78
8. Discussion 78

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9. Conclusions 79
10. Methods of literature research 79
Acknowledgement 79
References 79

1. Introduction

In the era of ever-more-preferred breast conserving surgery (BCS), the role of adjuvant radiation therapy is well established and allows selected patient to forgo mastectomy [1]. However, some patients still need, or opt for, a more radical surgery, i.e. mastectomy. In this case, evidence-based international guidelines recommend post-mastectomy radiation therapy (PMRT) for patients with advanced stage-tumor, those with positive or close surgical margins and those with four or more axillary lymph node metastases documented by axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) [2–4].

Nevertheless, the indication of a PMRT and its extent to the chest wall and/or the derivative lymph nodes in patients with one to three axillary lymph node metastases (N1 patients) with axillary staging performed by ALND has been a recurrent subject of debate for the past twenty years.

2. Past doubts and present evidence

Historically, the added value of PMRT has been disputed even in higher risk patients, such as those with four or more positive lymph nodes. While a clear reduction in loco-regional recurrence rates (LRR) was mostly present, equal or even worse overall survival (OS) was being observed in patients treated with PMRT. This was mainly due to less effective systemic treatment not preventing distant recurrences and radiotherapy-induced cardiovascular morbidity [5,6]. A gradual transformation of discourse succeeded with completion of more recent trials showing PMRT benefit also in the terms of OS. Among these were most notably the Danish Breast Cancer Cooperative Group trials DBCG 82b [7] and c [8] and the British Columbia trial [9].

This trend culminated with the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis published in 2014. This work serves to this day as a cornerstone proof of importance of PMRT in breast cancer patients by showing its added value not only in pooled node-positive patients, but also in N1-patient subgroup [10]. The meta-analysis including 1314 pN1 patients after ALND substantiated a significant reduction in 10-year LRR from 20.3% to 3.8%, 10-year overall recurrence rate (OR) from 45.7% to 34.2% and 20-year breast cancer-specific mortality (BCM) from 50.2% to 42.3% in patients receiving PMRT to the chest wall and regional lymph nodes as compared to no PMRT. Furthermore, this positive effect of PMRT was even present in a subgroup analysis of patients with a single axillary lymph node metastasis. This work has led to an almost unequivocal adoption of PMRT recommendation in T1-2N1 patients by international guidelines [2–4] and the clinical practice [11,12].

3. Current uncertainties

However, serious concerns have been evoked surrounding this meta-analysis [13]. Firstly, while this analysis meticulously describes the PMRT-dependent improvement in different nodal subgroups, it does not take into the account the primary tumor stage. In the era of BCS preferred over mastectomy in patients with early breast cancer, it can be suspected that patients undergoing radical surgery might have had more advanced tumors *i.e.* higher risk of recurrence, constituting a selection bias.

Additional meta-analyses have addressed this issue, but included retrospective studies. A 2013 work by Li et al. analyzing pooled prospective and retrospective studies, yielded a relative risk ratio (RR) of LRRs in T1-2N1 patients receiving or not PMRT of 0.348 [95% confidence intervals (CI) = 0.254 to 0.477] in favor of PMRT. Yet, no significant effect on OS was observed [14]. Another meta-analysis of retrospective studies in T1-2N1 patients was published in 2016 by Headon et al. and reproduced similar results, with a LRR RR of 0.3 [95% CI = 0.23 to 0.38] and a very modest increase in OS [RR = 1.03, 95% CI = 1.00–1.07] [6].

Second, the EBCTCG analysis dealt with a significant number of patients treated more than 50 years ago, at a time when systemic treatment of breast cancer was far from optimal. A retrospective analysis of patients treated at the MD Anderson Cancer Center has shown a clear decrease in 5-year LRR rates from 9.5% to 2.8% in non-irradiated patients depending on if they were treated before or after the year 2000 [15]. Also, only the former cohort of patients benefited from PMRT in terms of LRR [15]. Similar dependence on era of treatment was observed by a Japanese group as reported by Miyashita et al. [16] and by a Korean group, reported by Chang et al. [17]. Moreover, recent trials comparing different contemporary systemic treatment protocols were analyzed to assess PMRT efficacy and shown again no benefit in T1-2N1 patients in terms of OS [18,19]. On the other hand, such results were contested on the basis of selection bias in analysis not randomized for PMRT and insufficient propensity score matching [20].

In consideration of these depicted drawbacks, it is often argued that the LRR observed in the control arm of the EBCTCG meta-analysis (20.3% at 10 years) is an obsolete estimate. In well-defined populations of T1-2N1 patients treated by mastectomy without PMRT after the year 2000, the usual LRR varied from less than five to about 10% [5,15,16,18,19,21–34]. These were, however, assessed often at five or 8 years and less frequently at 10 years, as in the EBCTCG meta-analysis (Table 1).

Furthermore, a number of these recent works compared the prognoses of patients undergoing or not PMRT [15,16,18,19,21,26,27,30,33]. While some of these studies were able to demonstrate a decreased LRR rate [18,21,26,30], none of the above-mentioned studies could show a benefit of PMRT in terms of OS. Also, all these studies were retrospective and as such, the highest evidence level in favor of omitting PMRT in all T1-2N1 patients could be IV, whereas the most recent level I evidence provided by EBCTCG speaks in favor of PMRT. Therefore, the aforementioned results do invoke caution and the need for further randomized trials. More recent studies don't yield sufficient evidence level and/or are not primarily designed to address this specific issue.

One notable exception is the ongoing trial SUPREMO [35,36]. This large international randomized controlled trial enrolled 1688 women with intermediate risk cancer defined as T1-2N1, T3N0 or T2N0 with other unfavorable characteristics, who underwent mastectomy between 2006 and 2013 and were randomized to receive or not PMRT. Results are awaited by the end of 2023.Of note,

Table 1
Locoregional recurrence rates at various time points in non-irradiated cohorts of patients after mastectomy. Systematic review of studies including T1-2N1 patients published in the second decade of twentieth century with clearly-stated available LRR rates. Values mentioned refer to the relevant cohorts of T1-2N1 patients treated by mastectomy without PMRT in the most recent era (even in cases where studies include other patient cohorts not fulfilling these criteria). LRR – loco-regional recurrence rate. [A]These two studies follow the same cohort.

Study reference	Year	Patient number (N) – no PMRT cohort	5y LRR	8y LRR	10y LRR
EBCTCG [10]	2014	682 (Mast + AD + sys) +594 (Mast + AD)	–	–	20.3%
Huang et al. [30]	2012	155	–	11%*	–
Tendulkar et al. [31]	2012	271	8.9%	–	–
Lu et al. [32]	2013	368	7.2%	10.7%	–
Moo et al. [33][A]	2013	924	4.3%	–	–
Hamamoto et al. [34]	2014	248	–	5%	–
McBride et al. [15]	2014	385 (modern era)	2.8%	–	–
Jwa et al. [5]	2015	83	3%	–	–
Lai et al. [22]	2016	293	–	–	10%
Shen et al. [21]	2016	1030	17.6%	–	–
Miyashita et al. [16]	2017	558 (modern era)	–	4.7%	–
Park et al. [23]	2017	1382	6.1%	–	–
Tam et al. [18]	2017	317	–	–	9%
Wadasadawala et al. [24]	2017	242	6.6%	–	–
Abdel-Rahman [19]	2018	485	6%	–	7%
Bazan et al. [25]	2018	468	4.1%**	–	–
Luo et al. [26]	2018	623	6%	–	–
Wu et al. (reported by Ohri and Haffty [27])[A]	2018	924	–	–	7%
Asaga et al. [28]	2019	428	–	–	4.7%

the sample size of SUPREMO is actually comparable with the size of N1-cohort of the entire EBCTCG's 2014 meta-analysis.

The 2016 American Society of Clinical Oncology, American Society for Radiation Oncology and Society of Surgical Oncology's guidelines underlined the fact that while PMRT was shown to be effective in risk reduction in all node-positive patients, in some low-risk T1-2N1 cases, the low LRR rates may not justify the radiation-induced toxicities [37]. The St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017 has also proposed consideration of PMRT omission in cases of T1-2 tumors with one to three positive lymph nodes and favorable biological and histological characteristics [3]. In contrast, the British National Institute for Health and Care Excellence (NICE) breast cancer management guidance suggests PMRT for all N+ patients [38].

4. PMRT-induced toxicities

In the discussion regarding the radiotherapy indication, treatment efficacy in terms of LRR and BCM risk reduction is vigorously debated, but the treatment-induced toxicities and their evolution in time is often somewhat underestimated. In fact, late toxicities are of the utmost importance for breast cancer patients' quality of life and non-oncological morbidity and mortality. These late side-effects vary from mostly aesthetical problems of subcutaneous fibrosis to severe heart dysfunctions.

Late cardiac toxicity includes radiation-induced valvular disease, conduction disorders, cardiac muscle damage and fibrosis, coronary artery damage with accelerated atherosclerosis and pericarditis with the dominant manifestation of congestive heart failure [39,40]. These cardiac toxicities were frequent and pronounced in mid-twentieth century and were at least partially responsible for the discrepancy between the positive effect of PMRT on LRR and no or even negative effect on OS [41,42]. However, since then, much progress has been made in heart protection during chest-wall and draining lymph node-irradiation by introducing more sophisticated radiation dose-delivery techniques and maneuvers, such as breath-hold techniques [43]. Some progress was already achieved by the time the EBCTG meta-analysis trials were conducted, partially explaining the shift in OS benefit. However, most of these novel techniques are more recent and are likely to improve cost-benefit ratio of PMRT further.

On the other hand, although arm edema is a described side-effect of axillary, infra- and supra-clavicular radiotherapy, the recent AMAROS trial as well as smaller national studies yielded similar levels of efficacy between axillary radiotherapy and surgical axillary dissection, while operated patients experienced significantly more severe arm and shoulder symptoms, especially arm edema [44,45]. A report on the 2-year follow-up results of the SUPREMO trial showed a higher risk of chest wall symptoms in the study arm receiving PMRT, but all other symptoms, self-reported cosmesis, as well as overall quality of life were similar in both groups [36].

5. Risk factors to guide indication

To optimize guidelines for PMRT in N1 patients, a more specific risk stratification appears to be essential. Many retrospective studies have identified different factors associated with increased LRR, OR and BCM risks and worked out nomograms to calculate the differential risk. We performed a systematic review of literature, identifying poor prognostic factors to include into clinical decision-making processes (Table 2).

5.1. Age

The most important patient-inherent characteristic that determinates the LRR risk and breast cancer-related mortality seems to be patient's age at the time of diagnosis. Young age is generally considered a risk factor for breast cancer aggressiveness. Moreover, with current high cure rates, old patients often decease from other ailments and an ultimate late recurrence thus does not affect their survival as markedly as in younger patients.

This concept was also substantiated in patients with T1-2N1 breast cancer, suggesting that young age is associated with significantly higher recurrence rates and worse survival. Often, age of <40y [7,19,21,22,32,46,47] or even <35y [23,48,49] at the time of diagnosis was associated with worse LRR and OS, but the efficacy of PMRT defined as a percent decrease in LRR or BCM was not higher in younger patients, *i.e.* younger patients do not benefit from PMRT

Table 2
Conventional risk factors associated with worse prognosis. Systematic review of studies including T1-2N1 patients treated by mastectomy with or without PMRT since 1995 with individual risk factors associated with worse prognosis in a multivariate analysis. Where association was positive, threshold value is included. If not stated otherwise, n (patient sample size) refers to T1-2N1 patients unless otherwise indicated. LN number – number of positive axillary lymph nodes. LNR – lymph node ratio. LVI – lymphovascular invasion. HR – hormone receptors. ER – estrogen receptor. PR – progesterone receptor. ECE – extracapsular extension in lymph nodes. EIC – extensive intraductal component. [A]Involved all T1-3N1 patients. [B]Involved all T1-4N0-2 patients. [C]Involved all T1-4N1-2 patients. [D]Involved all T1-3N + patients, hereby presented is a subanalysis of T1-3N1 patients.

Reference	*N*	Age	LNR	LN number	LVI	Tumor size	Grade	HR	HER2	Margins	ECE/EIC
Abdel-Rahman [19]	1053	40y	–	–	–	2 cm	–	ER/PR	–	–	–
Asaga et al. [28]	428	–	–	1 vs. 2-3	–	2 cm	–	ER/PR	–	–	–
Bazan et al. [25]	468	–	–	1 vs. 2-3	–	–	–	–	–	–	ECE
Chen et al. [60]	8049[A]	–	–	–	–	5 cm	I-II vs. III	PR	–	–	–
Cosar et al. [61]	90	–	–	–	+	–	–	–	–	–	–
Geng et al. [67]	12203[B]	–	–	–	–	–	–	–	–	–	ECE
Harris et al. [56]	250[A]	–	–	–	–	2 cm	–	–	–	–	–
Huang et al. [30]	318	–	25%	–	+	–	–	–	–	–	–
Huo et al. [54]	93,793 (NCDB) + 36,299 (SEER)	–	–	1 vs. 2 vs. 3	–	2 cm	–	–	–	–	–
Jwa et al. [5]	390	–	–	–	–	–	–	ER/PR	–	–	–
Kim et al. [48]	3477	35y	18%	–	–	2 cm	I vs. II-III	ER/PR	–	–	–
Lai et al. [22]	293	40y	–	–	–	3 cm	–	–	–	–	EIC
Lale Atahan et al. [47]	939[C]	40y	25%–50%	–	+	2 cm–5cm	–	–	–	–	ECE
Lu et al. [32]	368	40y	–	–	+	3 cm		ER	–	–	–
Luo et al. [26]	1141	–	–	1-2 vs. 3	+	2 cm	I-II vs. III	ER	–	–	–
Matsunuma et al. [55]	1994[D]	50y	–	1-2 vs. 3	+	5 cm	–	–	–	–	–
Park et al. [23]	1382	35y	–	–	–	2 cm	I-II vs. III	ER/PR	+	2 mm	–
Shen et al. [21]	1369	40y	25%	–	+	3 cm	–	–	–	–	–
Truong, Berthel et al. [51]	542	–	20%	–	–	–	I-II vs. III		–	–	–
Truong, Lee et al. [50]	2362[B]	>70y	–	–	+	2 cm–5cm	I-II vs. III	ER	–	0 mm	–
Truong, Woodward et al. [52]	82 (BC) + 462 (MDACC)[A]	–	20%	–	–	–	–	–	–	–	–
Wadasadawala et al. [24]	242	–	15%	–	–	Cont.	–	ER/PR	+	3 mm	–
Wu et al. [49]	488	35y	–	1 vs. 2-3	–	2 cm	–	ER/PR	–	–	–
Yang et al. [59]	544	40y	–	–	+	2 cm	I-II vs. III	ER	–	–	–
Yin et al. [46]	1674	40y	20%	–	–	–	–	–	+	–	–

more than older ones.

Nonetheless, most of these studies are retrospective and none of them is directly assessing young age as a risk factor with or without the administration of the PMRT. Furthermore, many other reports found no impact of age on LRR or survival and some studies suggest that older populations are again at higher risk of LRR [7,50]. At the present state of knowledge, advanced age should not be held as a surrogate for PMRT omission.

5.2. Number of dissected axillary lymph nodes and positive-to-dissected ratio

Historically, the treatment-dependent risk factor most frequently associated with worse outcome was the ratio of positive to the total of dissected axillary lymph nodes. This factor is specific to N1 patients, where it is a result not only of the disease spread stage, but also the extent of the axillary surgery performed.

Cited studies determine cut-off values between low- and high-risk disease almost unequivocally at around 20% of positive-to-dissected lymph nodes [21,24,30,46–48,51,52]. In the well-defined population of patients with one to three positive lymph nodes, this translates into the total number of five to 15 dissected nodes. Such extent of ALND can be judged suboptimal by today's standards. This issue is partially addressed by a recent shift in ALND extent towards a more complete dissection [27], from less than 10 ALN dissected originally [10] to more than 15 (with exceptions of up to 60) being today's standard [23,28].

5.3. Absolute number of positive lymph nodes and size of nodal metastases

The current American Joint Committee on Cancer (AJCC) category of nodal involvement N1 *sensu lato* comprises, except from the hereby-discussed pN1a disease (one to three positive lymph nodes), also pN1b-c disease with the involvement of ipsilateral mammary chain nodes (not discussed here) and pN1mi with a single lymph node metastasis of less than 2 mm [53]. Even the pN1a disease *sensu stricto* is a heterogeneous nosological unit, likely divisible in various prognostic subgroups.

Many of the analyzed studies show better prognosis either in the terms of LRR or OS for patients with a single ALN metastasis as opposed to two or three positive nodes [25,28,49,54]. More rarely, patients with three nodal metastases as opposed to one or two had worse outcomes [26,54,55]. Besides, the above-discussed ratio of positive-to-dissected ALN also takes into account the absolute number of positive nodes, but seeing as it is also influenced by the ALND extent, this ratio seems to be a more sensitive risk factor [21,24,30,46–48,51,52].

However, as portrayed in Table 2, many other works found no dependence of LRR on the number of positive ALN as long as it is in between one and three. Moreover, the highest currently available level of evidence provided by the EBCTCG meta-analysis has also shown improved LRR rate and OS in patients with a single nodal metastasis, despite its above-discussed limitations [10]. The LRR and BCM risks are likely to be a function of the number of positive nodes, the mathematical form of which we do not presently grasp and our stratification with the limit of three positive nodes is likely only arbitrary. Without other evidence-based threshold in international staging, all patients with one to three positive ALN are currently included into the same prognostic group N1, but clearer sub-stratification may orientate patient management in future.

The size of nodal metastases might also play a role in the eventual recurrence risk, but evidence is generally insufficient or inconclusive [56]. On the other hand, patients with nodal micrometastases smaller than 2 mm classified as pN1mi have LRR rates very close to zero [25,57,58]. A large retrospective study with a meticulous analysis of 14,019 pN1mi patients found no impact of PMRT on OS and even in patients only undergoing SLNB, the LRR

difference was only borderline significant ($p = 0.053$) [57]. Therefore, in regard to the absence of such patients in the EBCTCG meta-analysis, it is suggested that with the reserve of the lack of prospective trials, pT1-2 pN1mi patients can be spared PMRT if no other risk factor is present [58].

5.4. Primary tumor size and stage

As discussed below, most recurrences happen in the chest wall. Therefore, the original tumor size, defined as its volume, greatest dimension or AJCC pT stage, might play at least an equally important role in the LRR risk determination as the number (relative or absolute) of affected ALNs.

The importance of tumor size in N1 patient population has been documented by most of the cited studies, typically sorting patients into risk groups by pT stage, i.e. limit of 2 cm in the greatest dimension [19,23,26,28,47–50,54,56,59]. Authors analyzing also T3 and bigger tumors have found a similar correlation at the cut-off of 5 cm between T2 and T3 [47,55,60]. Other works determined a threshold size of 3 cm [21,22,32] or proposed a continuous nomogram determining the risk as a semi-linear function of tumor size [24].

Nevertheless, it might not be incorrect to group T1 and T2 patients together, seeing as other works show no dependence of LRR risk and BCM on size in this category (Table 1) and as often, biological and pathological determinants have closer association with patient prognosis [5,30,61].

5.5. Histological grade, lymphovascular invasion and receptor expression status

Among historically but also contemporarily most important pathological parameters associated with worse prognosis, lymphovascular invasion (LVI) has been consistently identified. Seeing as tumor cells require invasion to lymph vessels to form lymph node metastases, the lack of apparent LVI in N+ patients might be disputably viewed as a failure to detect minor LVI rather than its true absence and the added prognostic value of LVI in N+ patients could be disputed [62,63]. Nonetheless, empirical evidence ascertains its role in prognosis determination [64,65]. Accordingly, LVI has been continuously identified as an independent risk factor for LRR and/or BCM by multivariate analyses in many studies of N1 patients after mastectomy [21,26,30,32,47,50,55,59,61] and its importance might even surpass that of the category-defining T2/T3 and N1/2 stage thresholds [55].

An essential pathological prognostic determinant is the apparent microscopic pathological behavior of tumor cells, as defined by the encompassing characteristic of histopathological grade. In N1 patients undergoing mastectomy, higher grade tumors had more LRR and worse OS than lower grade tumors, independently of other risk factors [25,26,28,49,54,55].

In the past decades, the analysis of tumor cell expression of hormone receptors (HR), i.e. the estrogen receptor (ER), the progesterone receptor (PR) and more recently the human epidermal growth factor receptor 2 (HER2/neu) has transformed the breast cancer management practice. On one hand, the expression profile of these proteins stratifies patients into at least four prognostic groups as defined by ESMO [2] and NCCN [4]. On the other hand, the presence of the differential expression of individual HRs allows for a better adaptation of administered systemic treatment.

While presently no formal consideration is paid to receptor expression status in guiding indication to radiotherapy, it may help in clinical decision-making in borderline, grey zone cases, as is PMRT in T1-2N1 patients. In this clinical setting, ER expression [26,32,50,59], PR expression [60], ER and PR expression [5,19,23,24,28,48,49] and HER2 expression [23,24,66] have all been shown to be important risk factors in various studies. In addition, at the 2017 St. Gallen Conference, an expert consensus accepted PMRT omission in selected T1-2N1 patients with favorable biological profile [3]. For higher-level evidence that would allow for a universal guideline adoption of this principle, prospective trials are needed.

5.6. Other factors associated with worse prognosis

Considerably less frequently, positive [50] or close [23,24] surgical margins after mastectomy were associated with increased LRR rate, albeit this factor was not often analyzed, as study inclusion criteria often required negative margins or no margin information was available. Furthermore, the current general trend shift to accept closer resection margins after BCS followed by whole breast irradiation without compromising the cure rates, while no such trend is observed in usually non-irradiated patients undergoing mastectomy, suggests that radiation therapy might be effective in decreasing the probability of local tumor regrowth after R1 or close margin operation.

Also rather uncommonly, presence of tumoral extra-capsular extension (ECE) in positive lymph nodes and infiltration of perinodal tissues were, too associated with worse prognosis [25,47,67]. One work associated presence of extensive intraductal component with higher LRR rate, which might seem somewhat antithetical seeing as mastectomy might be a better surgery for such patients due to the frequent subclinical spread inside the residual mammary gland after BCS [22].

5.8. Nuclear and molecular medicine

With the increasing availability and thus employment of nuclear imaging methods in breast cancer management, especially in disease extension evaluation, the question of its utility in borderline indication decisions can be evoked. Nuclear imaging, notedly ^{18}Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) provides functional metabolic information alongside with their topographical localization and as such could rapidly and non-invasively estimate tumor biological behavior and thus treatment failure risk. An early retrospective study on 109 T1-2N1 patients by Cheng et al. was able to observe association of high metabolic intensity capture on ^{18}F-FDG PET with increased LRR risk [68]. Maximum standardized uptake value (SUV_{max}) was most closely associated with disease-free survival and the association was continuous. A Contal and O'Quigley regression was used to determine a cut-off value of whole-body tumor SUV_{max} of 5.36, discerning low-risk population with 100% LRR-free survival and high-risk population with 92.9% LRR-free survival. Prognosis was much worse if the SUV_{max} localized to nodal disease.

The last revolution in diagnostic senology was brought about by progressive identification of 'high risk' genomic signatures of tumors. Commercially available multi-gene assays have been gradually adopted to guide indication to systemic treatment by providing estimated (particularly distant) recurrence risks and benefit that can be drawn from chemotherapy. Of these, copious and high-level evidence is available for the 21-gene expression assay (Oncotype Dx™) [69–73] and the 70-gene expression assay (MammaPrint™) [74].

Slower progress has been made in molecular radiobiology [75]. This field encountered difficult beginnings with negative studies [76], works discovering genomic signatures too complex for routine use [77], or ones only significant in subgroup analyses [78]. It was not until 2015, five years after clinical validation of Oncotype Dx™ in systemic treatment guidance [70,71], that first convincing

translational study presented by Speers et al. identified a 51-gene genomic radiosensitivity signature (RSS) successfully associated with radiation sensitivity and 10-year LRR risk [79]. Another enticing work by Scott et al. characterized tumor radiation sensitivity by enriching the conventional α/β coefficient by a radiosensitivity index obtained from differential expression of 10 genes previously associated with radiation response [80]. A genomic-adjusted radiation dose (GARD) thus obtained was able to predict 5y distant metastasis-free survival in one studied cohort of 263 breast cancer patients (RR 2.11, 95% CI [1.13–3.94], $p = 0.018$). Another possible way of improving prognosis in an individual patient-specific manner would be to increase the radiation dose without causing worse toxicity in patients with higher normal tissue tolerance based on germinal genomic polymorphisms, such as was found in the case of DNA-repair- and cell cycle-associated genes TP53 and P21 [81].

In our specific clinical scenario of T1-2N1 patients after mastectomy where the indication to PMRT can be contested, such a prognostic test would be of the utmost relevance. By a microarray analysis of tissue specimens from the original DBCG82b and c trials, Tramm, Mohammed et al. discovered a seven gene prognostic pattern that was able to classify the patients with almost a 25-year follow-up into low-risk and high-risk groups [66]. Among 94 non-irradiated patients of the 146-patient 'training group', low-risk patients experienced an astounding 8-fold lower 20-year LRR rate than the high-risk group (57% vs. 8%, RR 0.09, 95%CI 0.02–0.36, $p < 0.0001$). The most striking, however, was the utility of this assay to predict PMRT response. The low-risk patients drew no significant benefit from PMRT, whereas in high-risk patients, PMRT was capable of decreasing the 20-year LRR rate about four-fold and obtaining thus the same values as in the low-risk group. This stratification function was successfully confirmed by its application in an independent 112-patient validation set, albeit with a different four-gene profile. The only contributive risk factor to this genomic classifier was the HER2-receptor expression status.

More recently, Keene et al. performed a next-generation whole-exome and whole-transcriptome sequencing of 110 HER2-negative patient samples of which 32 presented LRRs, 34 DMs and 49 were controls without recurrence [82]. While no difference in RNA sequencing was observed, exome sequencing associated (mostly) deleterious mutations in mitogen activated protein kinase (MAPK) pathway and especially in neurofibromin 1 (NF1) gene with recurrence risk ($p = 0.007$).

6. Clinically N1 patients and neoadjuvant chemotherapy

While current treatment guidelines invoke neoadjuvant chemotherapy (NAC) in many patients with breast cancer with confirmed upfront nodal metastases [2,4], the role of PMRT in cN1 patients is still debated. One retrospective analysis of 10,283 patients of the National Cancer Database questioned on the utility of radiation therapy in upfront cN1 patients treated with NAC and surgery. PMRT to the chest wall resulted in OS benefit throughout the analyzed cohorts [83]. Therefore, this level IV evidence suggests that all clinically N+ patients should be treated by RT, no matter the ypN stage.

7. Determination of radiation target volumes

Most of the recurrences do not actually occur in the axilla - irradiated or not - but rather close to the site of the primary tumor in the chest wall. The presence of nodal metastases is often a mere risk factor of this recurrence [84–86]. N+ patients undergo extensive surgical axillary dissection and in patients with no sign of extracapsular spread, axillary recurrence is somewhat less probable than chest-wall recurrence where the tumor mass has no natural boundaries of spread. This is supported by evidence from EBCTCG meta-analysis [10] that has shown that irradiating axillary LNs only in N+ patients has no impact on LRR rate.

A European Organisation for Research and Treatment of Cancer (EORTC) phase 3 trail analyzed the effects of different extents of irradiation and included 955 patients undergoing mastectomy. Patients receiving elective adjuvant irradiation to the breast/chest wall plus supraclavicular and internal mammary lymph nodes were compared with ones receiving breast/chest-wall radiotherapy only. Extended field cohort had LRR, BCM and borderline OS benefit (OS RR 0.87; 95% CI 0.76–1.00; $p = 0.06$). However, in the mastectomy subgroup, the benefit of extending the radiation field was not evident (OS RR 0.91; 95% CI 0.72–1.15). Moreover, N2-3 patients did not draw more benefit from this extensive irradiation than N1 patients [87]. Similar results with no OS benefit were reproduced in 1832 women after BCS [88].

Equally importantly, in upfront cN1 patients, including the axilla in PMRT after ALND did not convey any survival benefit [83]. Hence, while prophylactic radiotherapy to the nodal area conveys little or no benefit, PMRT to chest wall only might have similar efficiency to extensive field irradiation, if sufficient ALND is performed.

At any rate, SNLB is replacing ALND in ever-increasing number of patients. If SLNB grants any N+ stage and no further axillary surgery is performed, patients are at a high risk of LRR [89] and an extended field PMRT (chest wall and axillary with or without supraclavicular and internal mammary LNs) should be discussed [44]. There is emerging evidence that RT can replace complete axillary surgery with less toxicity [44,45]. Hence, SLNB followed by nodal field irradiation will likely gradually replace ALND in all mastectomized N+ patients as it is the case already after BCS with positive SLNB. It is intriguing to postulate that the question of 'PMRT versus no PMRT' may evolve to 'PMRT to chest wall and axillary LNs versus PMRT to axillary LNs only'. While after ALND, irradiating only axillary LNs brings no benefit [10], after a positive SLNB, it likely will. Also, the exact extent of axillary PMRT after positive SLNB remains a somewhat open question. Therefore, trials investigating the optimal extent of loco-regional PMRT after positive SLNB will be of crucial importance.

8. Discussion

A considerable change in the attitude towards indication of PMRT in patients with breast tumors smaller than 5 cm with one to three axillary lymph node metastases is likely imminent. With gradually increasing amount of evidence at our disposition, we have been experiencing substantial shifts in professional public's view on this topic. Initial skepticism was first replaced by a wave of evidence-supported enthusiasm, only to be once more contested by somewhat substantiated disbelief, accompanied by present confusion guided more by consensuses than by hard evidence. It becomes clear that a unified solution to fit all patients in such a heterogenous arbitrarily defined group shall not be possible. Hence, further substratification of T1-2N1 patients is perceived by many as a priority in the PMRT field.

The accelerated evolution in risk stratification in breast cancer field, powered mostly by efforts to personalize systemic treatment algorithms, has honed our diagnostic capabilities to a point where these can well be exploited by radiation biology and oncology. In an effort to address the question of PMRT in intermediate-risk patients, dozens of retrospective works have provided only partially concerting findings. The most significant factors capable of prognostic prediction were: patient age at diagnosis, number of positive ALNs and axillary surgery extent, presence or absence of lympho-vascular invasion, primary tumor size, hormone receptor and HER2

expression.

These factors have been integrated by some authors based on their statistical power into nomograms useful for LRR and OS prediction [21,24,26]. Nevertheless, only very sporadically were these studies capable of proving differential response to irradiation and in general no risk factor was able to give grounds for a specific PMRT necessity and utility [59]. This means that while we might be able to identify patients at higher risk of LRR or BCM, by forgoing PMRT we would be simply satisfying ourselves with slightly worse absolute recurrence risks in cases where this risk is already low, knowing that PMRT would further decrease this risk. This can be acceptable once the toxicity risk outweighs the treatment benefit, but we have not been able to distinguish reliably those patients in which PMRT has no effect at all and would rather be omitted.

Where conventional tumor determinants have come out shorthanded, new genomic classification methods seem to bring about a hope on a horizon. First results of molecular profiling-based stratification appear indeed promising and able to cross the asymptote of differential PMRT efficacy determination discussed above. As claimed by Tramm et al., tumor cell analysis has the potential to replace most of other clinical and pathological determinants [66]. Seeing as tumor behavior is a function of it gene expression, NGS could become the sole modality required for clinical patient management apart from surgical determinants such as resection margins.

With the increasing accessibility and decreasing costs of genome-based methods, most notably whole-genome sequencing and RNA sequencing, we are gaining access to the entirety of functional pathophysiological information in myriads of patients investigated in most varied trials. Future studies will probably succeed in identifying complex genomic signatures connected to varied tumor responses simply by analyzing extensive datasets of available cancer genome libraries such as the Cancer Genome Atlas project [90]. Thus, also the radiobiological research shall partially move from benchside and bedside to *in silico*.

Among such efforts is a translational sub-study of the SUPREMO trial termed TRANS-SUPREMO. Genomic, transcriptomic and/or proteomic characteristics of tumor- and patient-derived conserved samples may help identify molecular signatures that are associated with recurrence risks, mortality and most importantly differential radiation utility [35]. This is unique because patients are randomized for PMRT and no selection bias is induced, as is the case when re-purposing translational sub-studies of systemic treatment trials.

9. Conclusions

There is presently a considerable degree of confusion in the subject of PMRT indication in intermediate-risk breast cancer patients undergoing mastectomy with many conflicting studies and little high-level evidence. Various retrospective studies have associated various biological and pathological determinants with worse prognosis suggesting that these high-risk patients should be directed towards PMRT, but there is much discord in presented data and little evidence confirms higher proportional efficacy of PMRT in high-risk patients. Prospective randomized trials will likely shed more light on the topic but might not solve the issue altogether. More specific stratification is needed and some state-of-the-art diagnostic methods such as genome-based classifiers provide hope for an ultimate solution. In the meantime, the increasing practice of SLNB might change considerably the discourse, seeing as all pN+ (sn) patients will likely be directed towards PMRT, while the extension of radiation target volumes remains to be determined.

10. Methods of literature research

Data used in this review were identified on February 20, 2019 by a systematic Medline search of English-language articles for which a full text was available online. A command defined as follows was entered: "(post-mastectomy OR postmastectomy) AND radiotherapy AND (N1 OR ((one AND three) OR 1–3) AND nodes))". This search granted 155 results, of which 55 were included in bibliography based on relevancy to the topic upon preliminary manual abstract analysis. Remaining 35 references were either added by cross-reference within initially included articles; or by additional searches in case of off-theme references. Only systematically mined articles were included in tables.

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