Radiotherapy and Oncology 126 (2018) 257–262

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Impact of dose intensified salvage radiation therapy on urinary continence recovery after radical prostatectomy: Results of the randomized trial SAKK 09/10

Pirus Ghadjar [a,n,*], Stefanie Hayoz [b], Jürg Bernhard [c,d], Daniel R. Zwahlen [e], Jürgen Stein [f], Tobias Hölscher [g], Philipp Gut [h,1], Bülent Polat [i], Guido Hildebrandt [j], Arndt-Christian Müller [k], Paul Martin Putora [l], Alexandros Papachristofilou [m], Corinne Schär [b], Alan Dal Pra [d], Christine Biaggi Rudolf [b], Peter Wust [n], Daniel M. Aebersold [d], George N. Thalmann [o], for theSwiss Group for Clinical Cancer Research (SAKK)

[a] Department of Radiation Oncology, Inselspital, Bern University Hospital, and University of Bern; [b] SAKK Coordinating Center, Bern; [c] IBCSG Coordinating Center, Bern; [d] Inselspital, Bern University Hospital; [e] Department of Radiation Oncology, Kantonsspital Graubünden, Chur, Switzerland; [f] Department of Urology, Bundeswehrkrankenhaus Berlin, Berlin; [g] Department of Radiation Oncology, University Hospital Dresden, Germany; [h] Kantonsspital Luzern, Switzerland; [i] University Hospital Würzburg; [j] University Hospital Rostock; [k] University Hospital Tübingen, Germany; [l] Kantonsspital St. Gallen; [m] University Hospital Basel, Switzerland; [n] Charité Universitätsmedizin Berlin, Germany; [o] Department of Urology, Inselspital, Bern University Hospital, Switzerland

ARTICLE INFO

Article history:
Received 18 July 2017
Received in revised form 15 October 2017
Accepted 15 October 2017
Available online 3 November 2017

Keywords:
Prostate cancer
Urinary continence
Salvage
Radiation therapy

ABSTRACT

Introduction: Adjuvant radiation therapy (aRT) after radical prostatectomy (RP) is associated with impaired urinary continence recovery as compared to surveillance. Less is known regarding the effect of salvage radiation therapy (sRT) dose intensification on continence outcomes.

Materials and methods: Urinary continence recovery was investigated within a multicentre randomized trial in biochemically recurrent prostate cancer patients who received either 64 Gy (32 fractions) or 70 Gy (35 fractions) sRT. Incontinence was assessed using Common Toxicity Criteria for Adverse Events v4.0 at baseline, at the end of sRT and 3 months afterward. Quality of life (QoL) was assessed with the EORTC QoL questionnaires C30 and PR25 at baseline and 3 months after completion of sRT. A total of 344 patients were evaluable.

Results: At baseline 233 (68%) of patients were fully continent and 14% in both arms became incontinent three months after treatment. Of the remaining 111 (32%) patients being incontinent at baseline, continence recovery was achieved 3 months after sRT by 44% vs. 41% with 64 vs. 70 Gy, respectively ($p = 0.8$). This analysis is limited by its short follow-up.

Conclusions: Dose intensification of sRT had no impact on early urinary continence recovery or prevalence of de novo incontinence.

Around 30% of contemporary patients treated with radical prostatectomy (RP) will present aggressive disease characteristics like extracapsular extension, seminal vesicle invasion, or lymph node invasion [1] and some of these patients may benefit from adjuvant radiation therapy (aRT) of the prostate bed in terms of freedom from biochemical progression [2]. However, another strategy in the post RP setting with undetectable prostate-specific antigen (PSA) values is observation with the conduction of early salvage radiation therapy (sRT) of the prostate bed in the presence of biochemical recurrence [2,3].

While sRT does not appear to compromise cure rates as indicated in retrospective comparisons [2,4] a negative effect on urinary continence recovery has been associated with aRT as compared to observation [5,6]. When compared aRT was associated with a higher rate of acute urogenital toxicities than sRT [7]. Additionally, sRT seemed to be associated with improved urinary continence recovery during longer term follow-up as compared to aRT [8]. While radiation dose intensification has been associated with improved biochemical outcomes [9,10] less is known on its impact on urinary continence recovery.

We have recently reported the acute genitourinary toxicity rates and early quality of life (QoL) of the randomized trial on dose intensified sRT (SAKK 09/10) [11]. In the present work, we specifically analyzed whether sRT dose has an impact on urinary continence recovery and de novo incontinence.

* Corresponding author now at: Charité Universitätsmedizin Berlin, Germany.
E-mail address: pirus.ghadjar@charite.de (P. Ghadjar).
[1] Present address: Hirslanden Hospital Group, Zürich, Switzerland.

https://doi.org/10.1016/j.radonc.2017.10.025
0167-8140/

Materials and methods

Trial design and conduct

We conducted an international randomized controlled phase III trial (SAKK 09/10) on dose-intensified vs. standard-dose sRT in biochemically relapsed prostate cancer patients without macroscopic disease in 28 hospitals in Switzerland, Germany and Belgium as previously described [11]. Patients were eligible if they had evidence of biochemical progression (two consecutive rises in PSA-level with the second rising PSA-level >0.1 ng/mL, or 3 consecutive rises) and a PSA-level at randomization of $\leq$2 ng/mL.

Randomization was centralized at the SAKK Coordinating Center. Patients were stratified according to Gleason score, tumor classification, lymphadenectomy, persistent PSA after surgery, PSA at randomization, center and SRT technique using the minimization method with 90% allocation probability. The trial was registered under ClinicalTrials.gov. Identifier: NCT01272050. The ethics committee at each center reviewed and approved the protocol.

Patients

Main inclusion and exclusion criteria have previously been described [11]. Briefly, patients with lymph node-negative adenocarcinoma of the prostate treated with RP at least 12 weeks before randomization with a tumor stage pT2a-3b, R0-1, pN0, or cN0 who experienced biochemical progression after RP was included.

Patients with a persistent PSA of >0.4 ng/mL (measured 4–20 weeks after RP), any form of ADT, macroscopic local recurrence or pelvic lymph node metastasis were excluded using magnetic resonance imaging (MRI) or multislice computed tomography (CT) of the abdomen and pelvis assessed within 16 weeks prior to randomization. The complete list of inclusion and exclusion criteria can be found on ClinicalTrials.gov. Identifier: NCT01272050.

Treatment and follow-up procedures

RP was performed at least 12 weeks before randomization and was not part of this trial. All RP techniques were permitted. SRT was administered in the standard arm to a total dose of 64 Gy in 32 fractions (2 Gy over 6.4 weeks) (arm A), and in the experimental arm to 70 Gy in 35 fractions (2 Gy over 7 weeks) (arm B). CT simulation for treatment planning was required. Patients were positioned in supine position and treated with comfortably full bladder and empty rectum. Prostate bed, clinical target volume (CTV), and planning target volume (PTV) were contoured according to the European Organisation for Research and Treatment of Cancer (EORTC) guidelines [12]. PTV was defined as CTV + 10 mm margins in all directions except for an 8–10 mm margin posteriorly. Margins were reduced for centers using image-guided SRT approved for the trial, but minimal margins around CTV were 5 mm. Dose prescription was done to the median dose $D_{50\%}$ of the PTV. Dose variation in the PTV was required to be within +7%/−5% of the prescribed dose, i.e. the 95%-isodose encompassed the PTV.

Organs at risk (OAR) included bladder, rectum, and femoral heads. The rectum was contoured from the anus to the rectosigmoid flexure or the caudal part of the sacroiliac joint. Besides whole organ delineation, bladder wall (BW) and rectal wall (RW) were contoured using a 5 mm internal margin. Constraints for OAR were: RW: V60Gy $\leq$ 50% and V70Gy $\leq$ 20%; BW: V65Gy $\leq$ 50%; Femoral heads: V50Gy $\leq$ 10%. Megavoltage equipment with nominal photon energies $\geq$6 MV was required. Three dimensional-conformal RT (3D-CRT), IMRT and rotational techniques including Tomotherapy® or volumetric modulated arc technique (VMAT) could be used. A three-step SRT QA program was carried out including a site and study-specific questionnaire completed by the local principle investigator, a mandatory dummy run, and central archiving of all treatment plans [13].

Endpoints and sample size

The primary endpoint was freedom from biochemical progression. The trial was designed as a two-arm phase III trial, assuming a median freedom from biochemical progression $\leq$3.8 years for the null hypothesis, and $\geq$5.8 years for the alternative hypothesis (hazard ratio = 0.65). Considering a one-sided type I error of 5% and 80% power, 350 patients were randomized with 139 events required for primary analysis.

Urinary incontinence was assessed according to NCI CTCAE v4.0. Baseline urinary incontinence was defined as grade $\geq$ 1 (occasional and pads not indicated or worse) at baseline. Incontinence change was assessed as change in grade from baseline to three months after completion of treatment and categorized into continence recovery (decreasing CTCAE grade), stable incontinence and worsening incontinence (increasing CTCAE grade) for patients who were incontinent at baseline and into stable continence and worsening incontinence (increasing CTCAE grade) for patients who were continent at baseline.

QoL was assessed using the EORTC QLQ-C30 (version 3) [14], the PC module QLQ-PR25 [15], and an adapted indicator for overall burden [16]. The urinary symptoms score (QLQ-PR25) was defined as the primary QoL endpoint. The early QoL period was defined as the first three months after completion of SRT.

Statistical analysis

Statistical analysis was based on the safety population, including all patients who completed at least one SRT session. Patients were analyzed according to the actual treatment they received.

Baseline urinary incontinence was compared between treatment arms using chi-squared tests. The influence of pre-selected covariates on baseline incontinence was assessed by multiple logistic regression with backward selection. The same methods were applied to assess the influence of pre-selected covariates on continence recovery for patients who were incontinent at baseline and on worsening incontinence for patients who were continent at baseline.

The symptom and function scales and single items of the QLQ-C30 and the QLQ-PR25 were scored and linearly transformed to 0–100 scales (EORTC manual). A higher score of a symptom scale or item indicates a worse condition, a higher score of a functional scale or global health status/QoL indicates a better condition. The indicator for overall burden was linearly transformed to a 0–100 scale, with higher scores indicating greater burden. Clinically meaningful changes were defined for the QLQ-C30 according to reference data ([17,18]; see Figs. 2 and 3), and for the QLQ-PR25 and overall burden according to a distribution-based measure ([19]; clinically meaningful change: $\geq$3.3 in either direction); we considered the cut-off for changes of QLQ-PR25 scales as defined in the trial protocol (i.e. 10 points) as too conservative [18]. Changes between baseline and month three were assessed by paired t-tests, and compared between continence recovery (Yes/No) for patients who were incontinent at baseline and on worsening incontinence (Yes/No) for patients who were continent at baseline by t-tests. The influence of pre-selected covariates on change in urinary symptoms and incontinence aid was assessed by multiple linear regression with backward selection separately for patients who were incontinent and continent at baseline.

Two-tailed tests with significance level 0.05 were used for all analyses. All analyses were post hoc and not pre-planned. As no adjustment for multiple testing for these analyses was made, they were exploratory and hypothesis generating. All analyses were

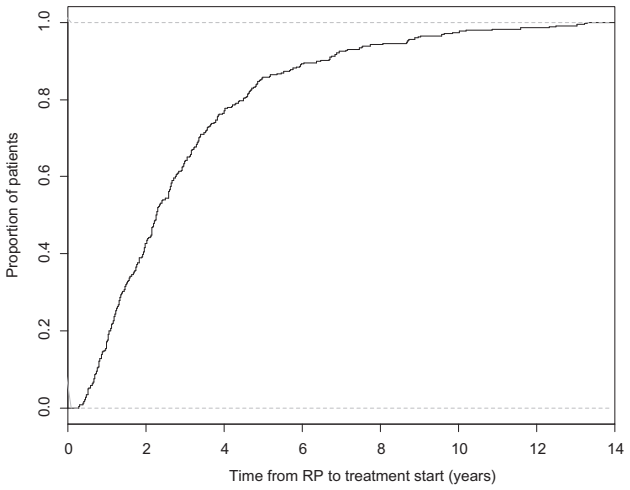

Fig. 1. Inverse Kaplan–Meier plot showing time from radical prostatectomy to treatment start.

performed using SAS 9.4 (SAS Institute) and R 3.2.4 (http://www.r-project.org).

Results

Patient characteristics

Between 02/2011 and 04/2014 350 patients were randomized (191 patients in Switzerland, 146 in Germany, and 13 in Belgium). Patient characteristics have been described in detail elsewhere [11].

Urinary continence at baseline

At baseline 233 (68%) of patients were fully continent (Table 1). Time from RP to randomization was depicted in Fig. 1. Only 61 patients received their sRT within 12 months after RP, of which 57% where fully continent at baseline. We observed that patients who had more time between RP and initiation of sRT had a better baseline urinary incontinence (30% for ≥1 year vs. 43% for <1 year, $p = 0.06$)

Patients with urinary incontinence at baseline had significantly worse QOL than those who were continent at baseline, with worse baseline scores for urinary symptoms ($p < 0.001$), use of incontinence aid ($p = 0.009$), overall burden ($p = 0.009$), physical functioning ($p = 0.002$) and role functioning ($p = 0.002$), but not for global health status/QoL ($p = 0.2$) (Fig. 2).

Urinary continence at 3 months

Of the 111 (32%) of patients scored as incontinent at baseline, continence recovery was achieved at 3 months after sRT in 44% vs. 41% in the 64 Gy and 70 Gy arms, respectively ($p = 0.8$) (Table 2). Neither time from RP to randomization nor grade of incontinence at baseline or dose to the bladder wall (V65Gy) was significantly associated with continence recovery after sRT. Patients who achieved urinary continence recovery had a significantly different change in physical functioning from baseline to 3 months compared to those who did not ($p = 0.005$), with a marginal improvement in patients with recovery (mean 1.6, sd 11.8), and a small but clinically relevant worsening in those without (mean −6.7, sd 15.9). A similar difference was observed in the change of role functioning from baseline to 3 months ($p = 0.049$) but not for the other QoL domains (Fig. 3).

Of the 233 patients fully continent at baseline, the proportion of patients who became incontinent was 14% in both arms (of these total 31 patients, only three patients experienced incontinence grade 2, the remaining patients experienced incontinence grade 1). Patients who experienced de novo incontinence at 3 months reported a significantly greater but clinically marginal worsening ($p = 0.04$) in physical functioning from baseline to 3 months (mean −4.1, sd 11.4) compared to those who did not (mean −0.7, sd 7.8). Change in role functioning was statistically significant in both

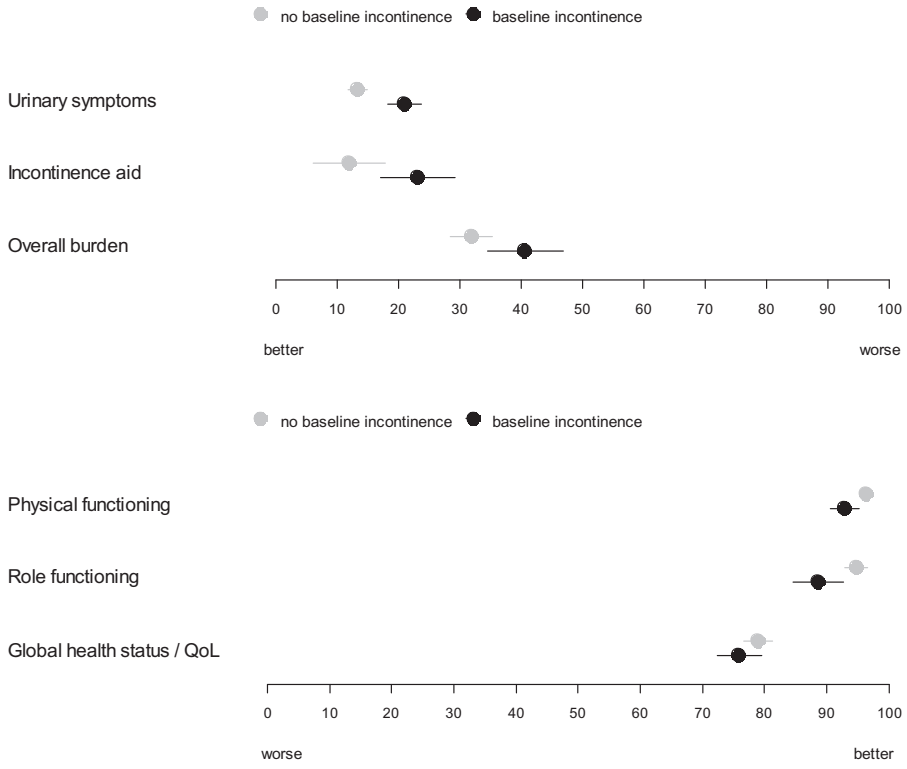

Fig. 2. Quality of life scores (scale ranges: 0–100; mean with 95% confidence intervals) at baseline by baseline incontinence.

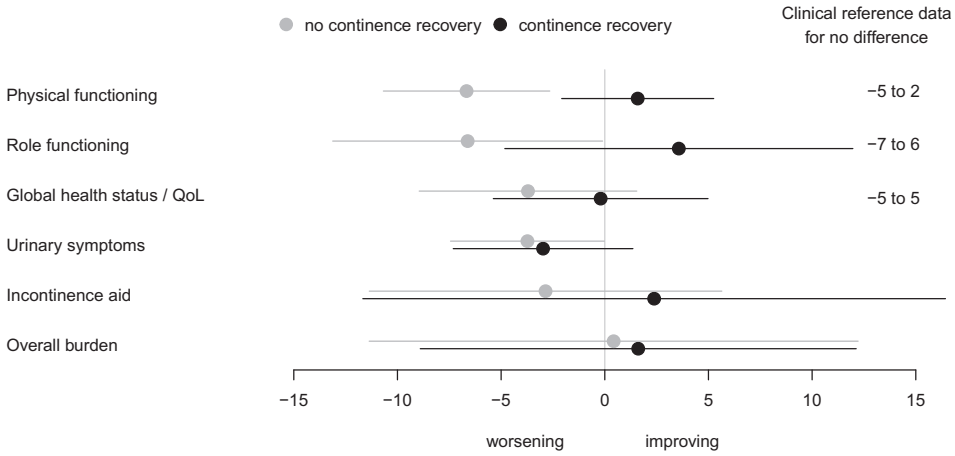

Fig. 3. Change in quality of life scores (mean with 95% confidence intervals) from baseline to 3 months postoperative by continence recovery.

Table 1
Baseline urinary continence and incontinence at 3 months.

Variable	Arm A (64 Gy) (N = 170) n (%)	Arm B (70 Gy) (N = 174) n (%)	Total (N = 344) n (%)
Baseline urinary incontinence (i.e. CTCAE grade ≥ 1)			
No	121 (71.2%)	112 (64.4%)	233 (67.7%)
Yes	49 (28.8%)	62 (35.6%)	111 (32.3%)
Baseline urinary incontinence (CTCAE grade)			
0	121 (71.2%)	112 (64.4%)	233 (67.7%)
1	36 (21.2%)	45 (25.9%)	81 (23.5%)
2	13 (7.6%)	15 (8.6%)	28 (8.1%)
3	0 (0.0%)	2 (1.1%)	2 (0.6%)
Urinary incontinence at 3 months			
No	118 (72.0%)	111 (66.9%)	229 (69.4%)
Yes	46 (28.0%)	55 (33.1%)	101 (30.6%)
Urinary incontinence at 3 months (CTCAE grade)			
0	118 (72.0%)	111 (66.9%)	229 (69.4%)
1	35 (21.3%)	38 (22.9%)	73 (22.1%)
2	1 (6.7%)	15 (9.0%)	26 (7.9%)
3	0 (0.0%)	2 (1.2%)	2 (0.6%)

Table 2
Continence results at 3 months of patients who were incontinent at baseline.

Variable	Arm A (64 Gy) (N = 48) n (%)	Arm B (70 Gy) (N = 61) n (%)	Total (N = 109) n (%)
Continence recovery			
No	27 (56.3%)	36 (59.0%)	63 (57.8%)
Yes	21 (43.8%)	25 (41.0%)	46 (42.2%)
Incontinence change from baseline to first FU			
Continence recovery	21 (43.8%)	25 (41.0%)	46 (42.2%)
Stable incontinence	24 (50.0%)	32 (52.5%)	56 (51.4%)
Worsening incontinence	3 (6.3%)	4 (6.6%)	7 (6.4%)

groups (Fig. 4). However, this change was clinically relevant only for patients who experienced de novo incontinence at 3 months (mean −8.1, sd 19.7) but not for those who did not (mean −2.6, sd 15.4). Neither de novo incontinence was significantly associated with time from RP to randomization nor grade of incontinence at baseline or dose to the bladder wall (V65Gy).

Discussion

Our results show that the use of dose intensified sRT was not associated with an impaired rate of urinary continence recovery nor a different rate in de novo incontinence three months after sRT. We were not able to detect an association between time of sRT and urinary continence after sRT. Patients with persistent incontinence after sRT reported a small but clinically relevant worsening in their personal and role functioning whereas those with a recovery indicated almost stable scores.

In a retrospective dataset of 431 patients it has been described, that aRT was associated with an increased rate of acute genitourinary toxicities as compared to sRT (Grade ≥ 2: 21% vs. 11%; p = 0.007) [7]. The acute grade ≥ 2 incontinence rate after sRT has been described as being 5% in another retrospective cohort of 135 men using a high-dose IMRT approach [20].

For sRT usually a higher dose is used (64 Gy – 70 Gy) as compared to aRT (60–64 Gy), toxicities of sRT, when documented prospectively, could potentially be increased. However, we have previously described low rates of acute genitourinary toxicity after both 64 and 70 Gy [11]. Detailed urinary incontinence outcome from this dose intensification trial has been requested by others [21] and our analysis revealed neither a difference in urinary continence recovery nor de novo incontinence for the two dose regimes.

In a trial by Thompson et al. which randomized 425 men with risk factors after RP to either aRT using 60–64 Gy vs. observation, after a median follow up of 10.6 years, total urinary incontinence was more common with aRT (6.5% of patients) than with observation (2.8%) (relative risk, 2.3; 95% CI, 0.9–5.9; p = 0.11) [5].

Similarly, a retrospective analysis of 361 patients with risk factors after RP who were or were not treated with aRT (mean dose 68.9 Gy) at a tertiary referral center reported the urinary continence recovery (no pads needed) after a median follow-up of 30 months [6]. The 1- and 3-year urinary continence recovery was 51% and 59% for patients submitted to aRT and 81% and 87% for patients not receiving aRT (p < 0.001). Besides conduction of aRT, younger age (p = 0.02), lower CAPRA score (p = 0.03), and nerve sparing surgery approach (p < 0.001) were all independent predictors of urinary continence recovery [6].

In a larger retrospective analysis of a tertiary referral center, 2190 patients underwent aRT, sRT or observation after RP [8]. After a median follow-up of 48 months the 3-year urinary continence recovery rates were 70.7%, 59.0% and 42.2% in patients who received observation, sRT and aRT, respectively (p < 0.001), and differed according to time to radiation therapy (RT) (43.5% vs. 62.7% for less than 1 year vs. 1 year or more, respectively, p < 0.001). No statistical difference was observed in patients who received no RT compared to those treated with RT after at least 12 months from surgery (p = 0.9) [8]. These data are in agreement with the findings of van Stam et al. who compared 241 patients treated with

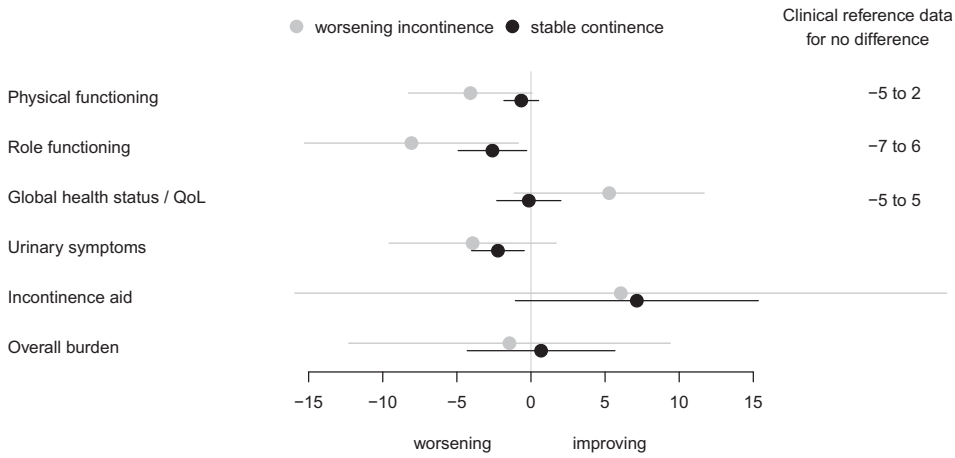

Fig. 4. Change in quality of life scores (mean with 95% confidence intervals) from baseline to 3 months postoperative by worsening or stable incontinence.

sRT to 1005 men followed by observation after RP, selected from prospective databases. They reported that delayed sRT (≥7 months after RP) was associated with better urinary function recovery [22]. Likewise, in our cohort we noted better baseline urinary continence in patients who had more time between RP and initiation of sRT.

In contrast to this, Hegarty et al. have reported an analysis based on the Surveillance, Epidemiology, and End Results (SEER)-Medicare database with a total of 6137 patients being eligible for aRT who were treated with RP followed by observation (n = 4509), or with RP followed by aRT (n = 894) or with RP followed by sRT (n = 734). Incontinence was assessed based on procedural codes available in the database. After a median follow up of 64 months, 62.9 months, and 84.2 months for the three groups, respectively, there was an increase in incontinence in patients who underwent postoperative RT but the time from RP to RT was not associated with incontinence [23]. However, this population-based analysis, in contrast to the aforementioned analyses from tertiary referral centers contains very heterogeneous patients in terms of quality of surgery and RT.

As the debate between aRT and early sRT is ongoing and the results of large ongoing randomized trials are pending (RADICALS: NCT00541047; GETUG-17: NCT00667069 and RAVES: NCT00860652), it appears that early sRT offers the same tumor control rates as compared to aRT [2] with potentially less side effects as mentioned above.

This analysis is not without limitations. The follow-up duration is rather short and it will be important to compare long-term urinary continence recovery between the two doses. Moreover, information on a direct comparison of continence rates between initially performed RP and sRT is lacking, however, baseline incontinence was recorded prior to sRT.

Despite these limitations we believe the current analysis is important given that dose intensified sRT is the preferred treatment strategy in many centers, and the present data are only derived from a randomized controlled study.

Conclusions

Dose intensification of sRT had no significant impact on early urinary continence recovery or prevalence of de novo incontinence after sRT.

Conflict of interest statement

There is no conflict of interest with regard to this manuscript.

Acknowledgments

The SAKK 09/10 trial is funded by grants provided by the Werner und Hedy Berger-Janser Foundation, Swiss Cancer Research foundation (KFS), Radio-Onkologie Berner Oberland AG Switzerland (ROBO AG) and Swiss State Secretariat for Education, Research and Innovation (SERI).

References

[1] Sineshaw HM, Gray PJ, Efstathiou JA, Jemal A. Declining use of radiotherapy for adverse features after radical prostatectomy: results from the national cancer data base. Eur Urol 2015;68:768–74.
[2] Gandaglia G, Briganti A, Clarke N, Karnes RJ, Graefen M, Ost P, et al. Adjuvant and salvage radiotherapy after radical prostatectomy in prostate cancer patients. Eur Urol 2017;72:689–709.
[3] Tendulkar RD, Agrawal S, Gao T, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 2016 [Epub ahead of print].
[4] Fossati N, Karnes RJ, Boorjian SA, et al. Long-term impact of adjuvant versus early salvage radiation therapy in pT3N0 prostate cancer patients treated with radical prostatectomy: results from a multi-institutional series. Eur Urol 2017;71:886–93.
[5] Thompson Jr IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006;296:2329.
[6] Suardi N, Gallina A, Lista G, et al. Impact of adjuvant radiation therapy on urinary continence recovery after radical prostatectomy. Eur Urol 2014;65:546–51.
[7] Jereczek-Fossa BA, Zerini D, Vavassori A, et al. Sooner or later? Outcome analysis of 431 prostate cancer patients treated with postoperative or salvage radiotherapy. Int J Radiat Oncol Biol Phys 2009;74:115–25.
[8] Zaffuto E, Gandaglia G, Fossati N, et al. Early postoperative radiotherapy is associated with worse functional outcomes in patients with prostate cancer. J Urol 2017;197:669–75.
[9] Briganti A, Karnes RJ, Joniau S, et al. Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. Eur Urol 2014;66:479–86.
[10] Ost P, Lumen N, Goessaert AS, et al. High-dose salvage intensity-modulated radiotherapy with or without androgen deprivation after radical prostatectomy for rising or persisting prostate-specific antigen: 5-year results. Eur Urol 2011;60:842–9.
[11] Ghadjar P, Hayoz S, Bernhard J, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: first results of the randomized trial SAKK 09/10. J Clin Oncol 2015;33:4158–66.
[12] Poortmans P, Bossi A, Vandeputte K, et al. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol 2007;84:121–7.
[13] Sassowsky M, Gut P, Hölscher T, et al. Use of EORTC target definition guidelines for dose intensified salvage radiation therapy for recurrent prostate cancer: results of the quality assurance program of the randomized trial SAKK 09/10. Int J Radiat Oncol Biol Phys 2013;87:534–41.
[14] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[15] van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008;44:2418–24.
[16] Bernhard J, Maibach R, Thürlimann B, et al. Patients' estimation of overall treatment burden: why not ask the obvious? J Clin Oncol 2002;20:65–72.
[17] http://groups.eortc.be/qol/manuals
[18] Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012;48:1713–21.
[19] Sloan JA, Dueck A. Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. J Biopharm Stat 2004;14:73–96.
[20] De Meerleer G, Fonteyne V, Meersschout S, et al. Salvage intensity-modulated radiotherapy for rising PSA after radical prostatectomy. Radiother Oncol 2008;89:205–13.
[21] Dell'Oglio P, Suardi N. Re: Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: first results of the randomized trial SAKK 09/10. Eur Urol 2016;69:966.
[22] van Stam MA, Aaronson NK, Pos FJ, et al. The effect of salvage radiotherapy and its timing on the health-related quality of life of prostate cancer patients. Eur Urol 2016;70:751–7.
[23] Hegarty SE, Hyslop T, Dicker AP, Showalter TN. Radiation therapy after radical prostatectomy for prostate cancer: evaluation of complications and influence of radiation timing on outcomes in a large, population-based cohort. PLoS One 2015;10:e0118430.