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ORIGINAL ARTICLE

Salvage radiotherapy for macroscopic local recurrences after radical prostatectomy

A national survey on patterns of practice

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Abstract

Introduction Although salvage radiotherapy (SRT) for PSA recurrence after radical prostatectomy provides better oncological outcomes when delivered early, in the absence of detectable disease many patients are treated for macroscopic locally recurrent tumors. Due to limited data from prospective studies, we hypothesized an important variability in the SRT management of these patients. Our aim was to investigate current practice patterns of SRT for local macroscopic recurrence after radical prostatectomy.

Material and methods A total of 14 Swiss radiation oncology centers were asked to complete a survey on treatment specifications for macroscopic locally recurrent disease including information on pretherapeutic diagnostic procedures, dose prescription, radiation delivery techniques and androgen deprivation therapy (ADT). Treatment recommendations on ADT were analyzed using the objective consensus methodology.

Results The majority of centers recommended pretreatment magnetic resonance imaging (MRI) of the pelvis and choline positron emission tomography (PET). The median prescribed dose to the prostate bed was 66 Gy (range 65–72 Gy) with a boost to the macroscopic lesion used by 79% of the centers with a median total dose of 72 Gy (range 70–80 Gy). Intensity-modulated rotational techniques were used by all centers and daily cone beam computed tomography (CT) was recommended by 43%. The use of concomitant ADT for any macroscopic recurrence was recommended by 43% of the centers while the remaining centers recommended it only for high-risk disease, which was not consistently defined.

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Conclusion We observed a high variability of treatment paradigms when SRT is indicated for macroscopic local recurrences after prostatectomy. These data reflect the need for more standardized approaches and ultimately further research in this field.

Keywords Postoperative radiotherapy · Salvage radiotherapy · Prostate cancer · Radiotherapy · Macroscopic recurrence

Salvage-Radiotherapie bei makroskopischen Lokalrezidiven nach radikaler Prostatektomie

Nationale Umfrage zu Behandlungsmustern

Zusammenfassung

Einleitung Obwohl die Evidenz für eine frühzeitige Salvage-Radiotherapie (SRT) bei einem PSA-Rezidiv nach radikaler Prostatektomie spricht, werden viele Patienten erst bei einem makroskopischen Lokalrezidiv behandelt. Hier scheint es jedoch aufgrund der fehlenden Daten aus prospektiven Studien eine Variabilität der Behandlungskonzepte zu geben. Das Ziel der Studie war es, die aktuelle Behandlungspraxis in der SRT des makroskopischen Rezidivs eines Prostatakarzinoms zu untersuchen.

Material und Methoden Insgesamt 14 Schweizer Strahlentherapiezentren wurden für eine Umfrage zu den Behandlungsparametern beim makroskopischen Lokalrezidiv eines Prostatakarzinoms kontaktiert und nach diagnostischen Maßnahmen, Dosisverschreibung, Strahlentherapietechniken und antihormoneller Therapie (ADT) befragt. Die variierenden Indikationen zur ADT wurden mittels der Objective-konsensus-Methodologie ausgewertet.

Ergebnisse Die Mehrheit der Zentren empfahl vor der Therapie eine Magnetresonanztomographie (MRT) des Beckens und eine Cholin-Positronenemissionstomographie (PET). Die mediane verschriebene Dosis für die Prostataloge war 66 Gy (65–72 Gy) mit einem Boost auf das makroskopische Lokalrezidiv in 79 % der Zentren bis zu einer medianen Dosis von 72 Gy (70–80 Gy). Alle Zentren verwendeten intensitätsmodulierte Rotationstechniken, ein tägliches Cone-beam-CT wurde in 43 % der Zentren empfohlen. Eine begleitende ADT wurde von 43 % für jedes makroskopische Lokalrezidiv empfohlen, während die übrigen Zentren dies nur bei Hochrisikogruppen (mit unterschiedlichen Definitionen) durchführten.

Schlussfolgerung Es wurde eine hohe Variabilität der Behandlungskonzepte für die SRT des makroskopischen Lokalrezidivs nach Prostatektomie beobachtet. Dies zeigt den Bedarf an standardisierten Behandlungskonzepten und weiteren Studien in diesem Bereich auf.

Schlüsselwörter Postoperative Strahlentherapie · Salvage-Radiotherapie · Prostatakarzinom · Strahlentherapie · Makroskopisches Rezidiv

Introduction

After radical prostatectomy up to 40% of prostate cancer (PCa) patients develop a biochemical relapse within 10 years [1] and the predominant site of relapse is local [2]. Salvage radiotherapy (SRT) is the only potentially curative therapy for these patients. Current best evidence shows better oncological outcomes when postoperative radiotherapy is delivered earlier in the course of the disease either as adjuvant treatment [3–5] or as early salvage [6] but the optimal timing is often debated [7]. In an attempt to avoid potential overtreatment, some physicians opt for a vigilant approach offering SRT solely at the first evidence of macroscopic relapse. Additionally, novel imaging modalities, such as multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography/computed tomography (PET/CT) have been increasingly used and may detect macroscopic recurrence at low prostate-specific antigen (PSA) levels [8]; therefore, the number of patients with detectable disease in the prostatic fossa is deemed relevant, and an increase is foreseen over the coming years due to better imaging tools.

Many strategies to optimize postoperative radiotherapy have been addressed in randomized trials, including dose escalation, elective treatment of pelvic nodes and use of androgen deprivation therapy (ADT) [9–12]; however, detectable disease in the prostate bed has not been markedly addressed in prospective studies. The aim of this study was to assess national patterns of practice in the radiotherapy management of patients with detected local recurrence in the prostate bed.

Methods

All Swiss university hospitals and radiation oncology centers that previously participated in the Swiss Group for Clinical Cancer Research (SAKK) prospective study (SAKK 09/10) to test dose-escalated salvage radiotherapy for biochemically recurrent disease [10] were contacted. They were asked to provide the following institutional treatment specifications for macroscopically recurrent disease: pretherapeutic diagnostic procedures, target volume definitions and planning target volume (PTV) margins, radiotherapy dose prescription, use of ADT, radiation delivery techniques and protocol as well as the recommendations and dose to the pelvic lymph nodes. Each institutional treatment recommendation was collected as free unrestricted

text until January 2017. Treatment recommendations regarding the use of ADT were additionally analyzed using the objective consensus methodology as previously described [13, 14]. Data were converted into center-specific decision trees and reviewed with the participants for an accuracy check. Individual treatment algorithms were compared semi-automatically and then analyzed for consensus and controversies. The level of consensus was determined by the number of participants recommending the most common treatment divided by the number of participants.

Results

A total of 14 Swiss radiation oncology centers were contacted. All participating centers returned the questionnaire by January 2017. The results are summarized in Tables 1–2 and Figs. 1, 2, 3.

Pretreatment diagnostics included PSA testing and MRI of the pelvis in all centers. Choline-PET was routinely utilized by 86% of the centers, and the median PSA threshold for the requisition of choline-PET was 1 ng/ml (range 0.5–2 ng/ml with 83% of the centers using a threshold ≥1 ng/ml). Additionally, three centers (21%) recommended choline-PET based on a PSA doubling-times lower than 6 months. Prostate-specific membrane antigen (PSMA) PET imaging was routinely used in only one department and occasionally used in three institutions (21%), with a PSA threshold ranging from 0.2 to 0.7 ng/ml. A biopsy of the radiologically detected recurrence(s) was considered in selected cases by 4 centers (29%), but no center performed routine biopsies. At the evidence of macroscopic disease in the prostate bed, a restaging bone scan was routinely recommended by 2 centers (14%) regardless of the PSA value.

The prostate bed target volume was contoured according to the Radiation Therapy Oncology Group (RTOG) guidelines [15] in 14% of the centers, according to the European Organisation for Research and Treatment of Cancer (EORTC) guidelines [16] in 43%, and adapted according to institutional guidelines in 43%. A median clinical target volume (CTV) to planning target volume (PTV) margin of 7 mm (range 3–15 mm) was recommended for the prostate bed. The median dose to the prostate bed was 66 Gy (range 65–72 Gy). Additionally, a boost to the macroscopic recurrence was performed by 79% of the centers with a median total dose of 72 Gy (range 70–80 Gy) (Fig. 1). Normal fractionation (2 Gy per fraction) was used by all centers.

The delineation of the macroscopic lesion on the planning CT scan was based on the available imaging modality, mostly pelvic MRI used for co-registration. Of the centers 45% that used a boost to the macroscopic lesion defined the gross target volume (GTV) based on MRI alone, 45% based on MRI and choline-PET and one center based on choline-PET alone. The majority of centers (82%) used sequential treatment plans and 18% used simultaneously integrated boost (SIB) with a daily dose to the macroscopic lesion ranging from 2 Gy to 2.12 Gy.

All departments used intensity-modulated rotational techniques (IMRT) while 3D-conformal radiotherapy (3DCR) was occasionally considered by one center. Daily image guidance using cone beam CT (CBCT) or mega-

Table 1 Summary of recommendations on pretreatment diagnostics and radiation treatment details for local macroscopic recurrence after radical prostatectomy

	Recommendations
Diagnostic method	100% serum PSA level
	86% choline PET (median PSA threshold 1 ng/ml, range 0.2–2 ng/ml)
	29% PSMA PET (median PSA threshold 0.2 ng/ml, range 0.2–0.7 ng/ml)
	14% bone scan
	29% biopsy in selected cases
Target volume definition	14% RTOG-based
	43% EORTC-based
	43% institutional adaptation
Dose to prostate bed	Median 66 Gy (range 64–72 Gy)
Dose to macroscopic tumor	Median 72 Gy (range 66–80 Gy)
Dose to pelvic lymph nodes	Median 50 Gy (range 45–50.4 Gy)
Indications for elective pelvic node irradiation (multiple answers allowed)	43% high-risk[a] pN0
	43% any pN1
	43% high risk[a] pN1
	7% no pelvic RT

[a] For the purpose of this study, high-risk for pelvic lymph node metastasis was defined according to the information provided by the centers, which includes D'Amico classification, MSKCC criteria, absence of extended pelvic lymph node dissection, PSA doubling time <6 months, Partin tables and Roach score.
PSA prostate-specific antigen, *PET* positron emission tomography, *MSKCC* Memorial Sloan-Kettering Cancer Center, *PSMA* Prostate-Specific Membrane Antigen, *RTOG* Radiation Therapy Oncology Group, *EORTC* European Organisation for Research and Treatment of Cancer, *RT* Radiotherapy

Table 2 Example for a controversial ADT recommendation in the following clinical situation: macroscopic recurrence of prostate cancer <1 cm in size, initial pT3b, Gleason score ≥ 9, PSA doubling time >6 months, recurrence >1 year from surgery

Number of centers	Recommendation
4	no ADT
4	6 months ADT
1	9 months ADT
2	12 months ADT
3	36 months ADT

ADT androgen deprivation therapy

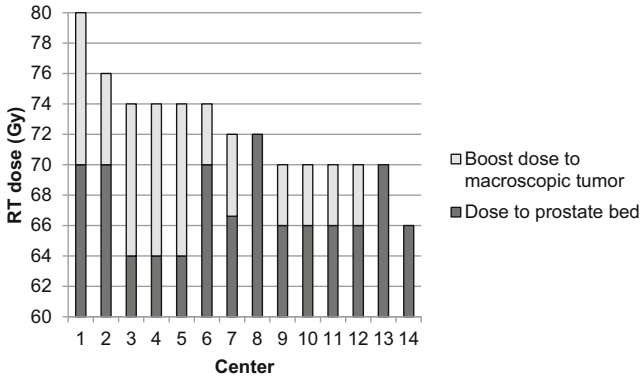

Fig. 1 Radiation dose prescription to the prostate bed (*black*) and additional boost dose to macroscopically recurrent disease (*light grey*). Each column represents a treating center ($n = 14$)

voltage (MV) CBCT for tomotherapy was performed by 43% of the centers for the whole treatment course, and by 1 center only for the boost volume. Of the centers 29% used CBCT 2–3 times weekly and 21% once weekly. No participating center reported a regular use of fiducial markers for tumor tracking. All centers utilized a bladder filling protocol, 86% used a specific rectal preparation protocol and 2 centers (14%) routinely used rectal balloons for simulation and treatment.

Regarding elective irradiation of the pelvic lymph nodes, 43% of the centers recommended it only in cases of positive node(s) on lymphadenectomy (pN1) irrespective of other risk factors, 43% recommended pelvic treatment in case of pN1 and presence of additional risk factors and another 43% in cases of node-negative disease after surgery (pN0) with risk factors, such as lack of extended lymph node dissection ($n = 2$), Gleason score ≥ 8 ($n = 1$), Gleason score 9–10 ($n = 1$), pT3b disease ($n = 1$), PSA doubling time <6 months ($n = 1$), initial high-risk disease according to the D'Amico classification [17] ($n = 2$) or the Memorial Sloan Kettering Cancer Center (MSKCC) score [18] ($n = 1$), Partin tables [19] ($n = 1$) or Roach score [20] ($n = 1$). One center did not perform pelvic lymph node irradiation independent of the extent of lymph node dissection or other risk factors. The median prescribed dose to the pelvic nodes was 50 Gy (range 45–50.4 Gy).

Of the centers 43% recommended ADT for any macroscopically recurrent disease for a duration of 6 months and 28% recommended a prolonged ADT duration of 9–36 months for high-risk disease. High-risk disease was defined inconsistently and included initial risk group (D'Amico classification) ($n = 2$), Gleason score ≥ 8 ($n = 4$), Gleason score ≥ 9 ($n = 4$), pT3b ($n = 3$), size of macroscopic recurrence >1 cm ($n = 1$) and PSA doubling time after surgery <6 months ($n = 2$). Recommendations for concomitant ADT were also analyzed using the objective consensus methodology as previously reported [13] and one center was excluded from this analysis as the referring urologists independently prescribed the ADT. A representative mode decision tree showing the most common recommendation for each defined clinical situation is depicted in Fig. 2. The most common recommendation among all combinations of parameters was the use of ADT for 6 months; however, a consensus of 75% for indications and duration could rarely be reached. An example for the spectrum of recommendations in a clinical situation without consensus is shown in Table 2. The individual institutional decision criteria for the indications and duration of ADT are shown in Fig. 3.

Discussion

This survey demonstrates significant variability in the radiotherapy management of PCa patients with macroscopic, locally recurrent tumors after radical prostatectomy. Among Swiss centers, there are different criteria for pretreatment diagnostics and imaging, radiation dose to prostate bed and macroscopic disease, indications and dose to the pelvic lymph nodes, and use of ADT.

Randomized clinical trials have shown the improvement in biochemical relapse-free survival for adjuvant radiotherapy after prostatectomy in patients with adverse pathological features [3–5, 21]. Despite an improvement in overall

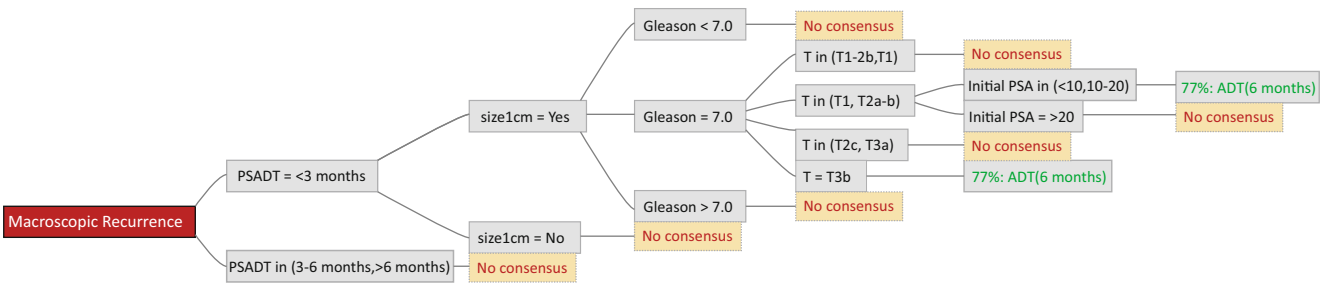

Fig. 2 The mode recommendation tree shows combinations of parameters that lead to a 75% consensus on the indications and duration of ADT. In all cases the recommendation (>75%) was 6 months of androgen deprivation therapy (*PSADT* PSA doubling time, *size1cm* size of lesion ≥1 cm, *Gleason* Gleason score, *T* T category, *initial PSA* preoperative prostate-specific antigen)

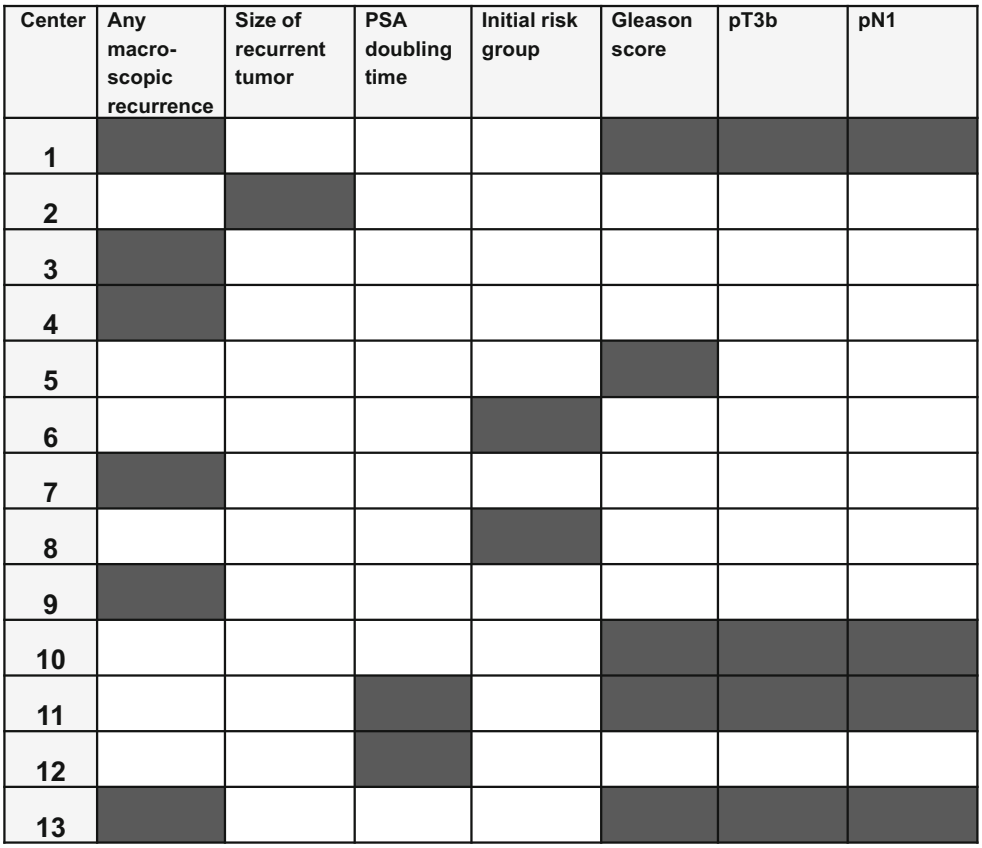

Fig. 3 Decision criteria for the use and duration of androgen deprivation therapy (ADT) with salvage radiotherapy for macroscopically recurrent prostate cancer. Institutional decision factors for the indication and duration of ADT for each center are highlighted in grey. One center was excluded from analysis as the decision criteria varied depending on the referring urologist

survival in the Southwest Oncology Group (SWOG) 8794 trial [4], the use of adjuvant radiotherapy is not universally implemented. Many clinicians offer SRT to patients with biochemical progression instead of adjuvant radiotherapy in order to avoid potential overtreatment, even in the presence of high-risk features [22]. The use of early SRT instead of adjuvant radiotherapy is being addressed in ongoing clinical trials (RADICALS, NCT00541047 and RAVES, NCT00860652).

The SRT constitutes the only established potentially curative therapy for patients with biochemical recurrence. It has been associated with improvement in distant metastasis-free survival, disease-specific survival and overall survival, and outcomes are better when SRT is delivered early and at low PSA levels [23]. In more contemporary series, an undetectable PSA using ultra-sensitive assays was associated with lower risk of relapse and consequently less possible benefit from adjuvant radiation. Conversely, SRT efficacy is indeed higher with an earlier detection of PSA relapse; therefore, early SRT is recommended in most international treatment guidelines [24, 25].

Choline PET and PSMA PET can often be used to identify early recurrences not revealed by traditional imaging modalities (e. g. bone scan, CT scan). Sobol et al. [26] used mpMRI and choline PET to map early patterns of relapse in 202 postsurgery patients not exposed to radiation or ADT. At a median PSA of 2.3 ng/ml (interquartile range IQR 1.4–5.5), 33% exhibited local only, 22% local plus metastatic and 45% metastatic only relapse. Pelvic node only relapse was observed in 19%. This shows that new imaging modalities could reveal an anatomically diverse pattern of recurrence and possibly guide treatment decisions more accurately, therefore challenging current treatment standards in the absence of visible disease on traditional imaging. Additionally, pre-PET PSA levels and PSA doubling time predict PSMA PET positivity [27]. This survey shows that the majority of centers perform metabolic imaging at the evidence of macroscopic recurrence in the prostate bed. Nevertheless, there is an important variation in the use and indication criteria for choline-PET and/or PSMA PET in Swiss centers. This is likely explained by the specific availability of each method (PSMA PET started to be regularly reimbursed in Switzerland after January 2017) as well as the evolving evidence on imaging in PCa management. Nevertheless, further validation of these novel imaging methods is essential to demonstrate the actual clinical benefits and cost-effectiveness of these approaches.

The elective treatment of pelvic nodes has been debated for a long time in PCa radiotherapy without a clear proof of benefits [28, 29]. In the salvage setting, the results of RTOG 0534 (NCT00567580) comparing SRT alone versus SRT plus short-term ADT versus SRT, short-term ADT

and pelvic lymph node radiotherapy are eagerly awaited. Our survey reflects the uncertainties in the use of elective radiation to the pelvic nodes [30]. Of the participating centers 43% responded that they treat the pelvis according to the presence of high-risk disease (a definition that was not uniform), the presence of pN1 or according to the extent of previous lymph node dissection. The latter is an interesting finding given the fact that lymphadenectomy has never been prospectively proven to add any clinical benefit [31]. Another important question in patients with macroscopic recurrence is the use of elective treatment to the whole prostate bed according to established contouring guidelines [15, 16]. To the best of our knowledge, adaptive SRT volumes solely to the site of macroscopic recurrence have never been prospectively addressed and could be an alternative to improve the therapeutic ratio.

The use of ADT combined with primary radiotherapy improves overall survival based on large prospective trials [32]. For patients with biochemical recurrence after surgery, the RTOG 9601 trial (NCT00002874) showed a 5% increase in 10-year overall survival (hazard ratio HR: 0.75; 95% confidence interval CI: 0.58–0.98) when patients were treated with SRT plus 2 years of bicalutamide [11]. Subgroup analyses showed the greatest benefits in patients with more aggressive disease and PSA higher than 1.5 ng/ml. Improved outcomes were also observed in the GETUG-16 trial (NCT00423475). Men with biochemical failure treated with SRT plus 6 months of luteinizing hormone-releasing hormone (LHRH) agonist had a 17.5% improvement in 5-year progression-free survival (HR: 0.50, 95% CI 0.38–0.66; $p < 0.0001$) [33]. Although the RADICALS study (NCT00541047) will hopefully shed further light on the role of ADT in the postoperative setting, in the context of macroscopic disease, we may extrapolate the results of previous trials, such as RTOG 9601 and GETUG 16; however, many questions still remain on the indication, timing and treatment duration.

In terms of radiation dose, retrospective studies suggest that there is a dose-response effect in the salvage setting, in the absence of macroscopic disease [34]. The SAKK 09/10 trial [10] in which patients were randomized to SRT with 64 Gy versus 70 Gy demonstrated low rates of acute toxicity and minor impact on the quality of life for dose escalation; however, oncological outcomes are still awaited. In the context of macroscopic recurrence our survey has shown an important variation in dose prescriptions. The median doses to the prostate bed and macroscopic recurrence were 66 Gy and 72 Gy, respectively, with one center reaching a final total dose of 80 Gy. Genitourinary toxicity may be further increased with dose escalation despite the use of IMRT. In a retrospective study where most patients were treated with doses ≥70 Gy, no differences in genitourinary toxicity were seen between IMRT versus 3DCRT [35]. An important retrospective study using IMRT and 76 Gy to the prostate bed showed a 5-year risk of grade 2–3 genitourinary toxicity of 22% and a 5-year risk of grade 2–3 gastrointestinal toxicity of 8% [36]. Other authors have shown that IMRT allows further dose escalation by reducing the dose to adjacent normal tissues with decrease morbidity [37]. Prospective randomized trials evaluating patient reported outcomes will allow us to derive definitive conclusions regarding the benefits and potential harms of dose escalated treatment.

Some of the participating centers used SIB, which corresponds to a moderately hypofractionated treatment of the macroscopic recurrence. Based on the estimated low α/β ratio of the prostate, this would provide a theoretical biological advantage over conventional fractionation [38]. The use of IMRT withg SIB could even provide a better coverage of the target volume and protect adjacent tissues with low toxicity rates compared with conformal sequential treatments or a combination of conformal treatment and IMRT [39]. It will be interesting to observe the results of the ongoing MAPS trial (NCT01411345) comparing SRT with 68 Gy in 34 fractions versus 68 Gy in 34 fractions plus boost to MRI-guided macroscopic disease to 76.5 Gy (2.25 Gy per fraction).

We believe our results represent a reliable snapshot of the practice patterns for macroscopic local recurrence among Swiss radiation oncology centers. Although the participating radiation oncologists are representatives of each institution, adherence to these policies cannot be assured.

On top of the previously mentioned uncertainties, evolving genomic data have opened up a new landscape in PCa management. New models such as the analysis of patient-specific molecular signatures could allow the individualization of radiotherapy dose according to tumor radiosensitivity [40]. In addition, a relationship between quantitative mpMRI and gene expression in MRI-guided prostate biopsies has been recently presented [41]. In the future, after adequate validation all these emerging advances could further improve risk stratification and advance precision radiation oncology.

Conclusion

Our results show that among Swiss radiotherapy centers, there are different patterns of treatment when salvage radiotherapy is indicated for macroscopic local recurrence after prostatectomy. These data reflect the need for more standardized approaches and ultimately further research in this field.

Acknowledgements ADP and CP contributed equally to the manuscript.

Compliance with ethical guidelines

Conflict of interest A. Dal Pra, C. Panje, T. Zilli, W. Arnold, K. Brouwer, H. Garcia, M. Glatzer, S. Gomez, F. Herrera, K. Kaouthar, A. Papachristofilou, G. Pesce, C. Reuter, H. Vees, D. Zwahlen, D. Engeler and P.M. Putora declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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