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ORIGINAL ARTICLE

Consensus and differences in primary radiotherapy for localized and locally advanced prostate cancer in Switzerland

A survey on patterns of practice

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Abstract
Introduction External beam radiotherapy (EBRT), with or without androgen deprivation therapy (ADT), is an established treatment option for nonmetastatic prostate cancer. Despite high-level evidence from several randomized trials, risk group stratification and treatment recommendations vary due to contradictory or inconclusive data, particularly with regard to EBRT dose prescription and ADT duration. Our aim was to investigate current patterns of practice in primary EBRT for prostate cancer in Switzerland.
Materials and methods Treatment recommendations on EBRT and ADT for localized and locally advanced prostate cancer were collected from 23 Swiss radiation oncology centers. Written recommendations were converted into center-specific decision trees, and analyzed for consensus and differences using a dedicated software tool. Additionally, specific radiotherapy planning and delivery techniques from the participating centers were assessed.
Results The most commonly prescribed radiation dose was 78 Gy (range 70–80 Gy) across all risk groups. ADT was recommended for intermediate-risk patients for 6 months in over 80 % of the centers, and for high-risk patients for 2 or 3 years in over 90 % of centers. For recommendations on combined EBRT and ADT treatment, consensus levels did not exceed 39 % in any clinical scenario. Arc-based intensity-modulated radiotherapy (IMRT) is implemented for routine prostate cancer radiotherapy by 96 % of the centers.
Conclusion Among Swiss radiation oncology centers, considerable ranges of radiotherapy dose and ADT duration are routinely offered for localized and locally advanced prostate cancer. In the vast majority of cases, doses and durations are within the range of those described in current evidence-based guidelines.

Keywords Radiotherapy, intensity-modulated · Radiation oncology · Guidelines · Decision trees · Risk

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Gemeinsamkeiten und Unterschiede der primären Radiotherapie beim lokalisierten und lokal fortgeschrittenen Prostatakarzinom in der Schweiz

Eine Analyse der der Behandlungskonzepte

Zusammenfassung

Einleitung Die Radiotherapie (RT) ist als Monotherapie oder in Kombination mit einer Androgendeprivationstherapie (ADT) eine etablierte Behandlungsoption für das lokalisierte und lokal fortgeschrittene Prostatakarzinom. Trotz der guten Evidenzlage durch zahlreiche randomisierte Studien bestehen weiterhin unterschiedliche Behandlungskonzepte, die besonders hinsichtlich der Gesamtdosis der RT sowie der Dauer der ADT variieren. Das Ziel der vorliegenden Studie ist eine Analyse der Behandlungskonzepte für die kurative RT des Prostatakarzinoms in der Schweiz.

Material und Methoden Die Behandlungsempfehlungen für das lokalisierte und lokal fortgeschrittene Prostatakarzinom bezüglich Bestrahlungsdosis und ADT-Dauer wurden von 23 Schweizer Zentren für Strahlentherapie eingeholt. Die einzelnen Empfehlungen wurden mittels einer speziellen Software in zentrumsspezifische Therapiealgorithmen umgewandelt und automatisch auf Konsens und Differenzen mit den übrigen Zentren verglichen. Zusätzlich erfolgte eine Umfrage über den Einsatz besonderer Behandlungstechniken.

Ergebnisse Die am häufigsten verschriebene Gesamtdosis war 78 Gy für alle Risikogruppen (Spanne 70–80 Gy). Eine ADT wurde für Patienten der mittleren Risikogruppe für 6 Monate von über 80 % der Zentren und für Hochrisiko-Patienten für 2–3 Jahre von über 90 % der Zentren empfohlen. Für die kombinierten Therapieempfehlungen bezüglich RT-Gesamtdosis und ADT-Dauer ergab sich in keinem klinischen Szenario ein Konsens von mehr als 39 %. Intensitätsmodulierte Rotationstechniken werden in 96 % der Zentren als Standard für die RT des Prostatakarzinoms verwendet.

Schlussfolgerung In der Therapie des lokalisierten und lokal fortgeschrittenen Prostatakarzinoms werden in der Schweiz verschiedene Therapiekonzepte bezüglich RT-Gesamtdosis und ADT-Dauer angeboten, die in der überwiegenden Mehrheit innerhalb der von evidenzbasierten Leitlinien empfohlenen Spanne liegen.

Schlüsselwörter Intensitätsmodulierte Strahlentherapie · Radioonkologie · Leitlinien · Entscheidungsbäume · Risiko

Prostate cancer is the most common noncutaneous tumor diagnosed in men [1]. External beam radiotherapy (EBRT) is an established treatment option for localized prostate cancer. EBRT has been recommended in several guidelines as an optimal primary treatment, in addition to surgery and -for specific subgroups -brachytherapy, watchful waiting, or active surveillance [2–4]. Depending on risk classification, androgen deprivation therapy (ADT) may be added to radiotherapy in order to increase recurrence-free and overall survival rates [5–7]. In prostate cancer, dose escalation using 3D-conformal radiotherapy, and more recently intensity-modulated radiotherapy (IMRT) and intensity-modulated arc therapy (IMAT), has proven its benefits in randomized phase III trials, with better biochemical control of disease [8–10]. Novel techniques such as image-guided radiotherapy (IGRT), as well as IMRT and IMAT, have demonstrated potential for performing dose escalation without increasing toxicity [11].

Recent evidence from randomized trials and technological advances in prostate cancer radiotherapy have resulted in significant changes in treatment delivery [12–14]. Patterns of care studies on primary EBRT for prostate cancer have been performed in several countries using population-based or survey-based analyses [15–18].

The aim of our study was to assess current patterns of practice in risk group-adapted primary EBRT and ADT for nonmetastatic prostate cancer in Switzerland. Using the objective consensus methodology [19], treatment recommendations from all participating parties were transformed into center-specific algorithms and further analyzed.

Additionally, treatment specifications in radiation oncology are often dependent on other parameters—such as the technology implemented in clinical routine. For this reason, this analysis was accompanied by a survey covering multiple technical aspects of radiotherapy planning and delivery for prostate cancer.

Materials and methods

All independent Swiss radiation oncology centers offering photon-based prostate cancer radiotherapy were identified using the registry of the Scientific Association of Swiss Radiation Oncology (SASRO) and contacted separately. Treatment recommendations regarding EBRT dose and ADT duration depending on prognostic factors, such as prostate-specific antigen (PSA) value, Gleason score, and T category, were collected as free unrestricted text from the participating Swiss radiation oncology centers up until November 2014. The centers were asked to provide exact information on their risk group definitions (e.g., according to National Comprehensive Cancer Network, NCCN, guidelines [3]; D'Amico [20]; or center-specific definitions). These recommendations were then converted into center-specific treatment algorithms in the form of decision trees [21] by two of the investigators (PMP and CP) and then discussed with the participants. A sample decision tree is shown in Fig. 1.

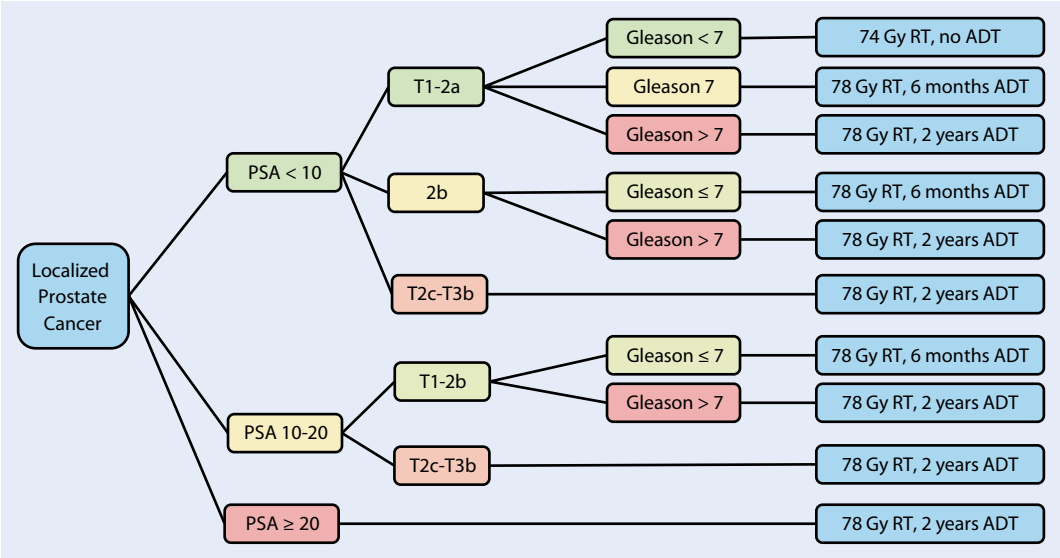

Fig. 1 A sample decision tree from a participating center showing radiotherapy (*RT*) dose and the duration of androgen deprivation therapy (*ADT*) depending on prostate-specific antigen (*PSA*) value, T category, and Gleason score. National Comprehensive Cancer Network (NCCN) risk groups are color coded: low risk (*green*), intermediate risk (*yellow*), and high risk (*red*); color gradients represent two groups

After obtaining a full set of decision trees, treatment recommendations for every possible combination of prognostic factors were evaluated, based on the previously published objective consensus methodology. The objective consensus method analyzes every input with equal weight and can determine the most common recommendation for every possible combination of parameters. The level of consensus is determined by the number of participants recommending the most common treatment, divided by the number of participants. Where a single recommendation was dominant for any specific combination of parameters, this was identified and termed the mode recommendation (the most common recommendation). The lack of a mode recommendation in any specific situation was defined as no consensus. The analysis was performed semiautomatically by a software tool developed in Java programming language using a BigTable database and run on the Google Cloud Platform AppEngine [19].

In addition to the analysis of recommendations for radiation dose and ADT duration, a survey on techniques used for treatment planning and radiation delivery was distributed to the participants, and the input was subjected to descriptive statistics. The following aspects were included regarding treatment planning: pretreatment diagnostic magnetic resonance imaging (MRI), MRI-based target volume delineation, penile bulb dose constraints, clinical target volume (CTV) definition, planning target volume (PTV) margins, and whole pelvic lymph node irradiation. Concerning radiation delivery, the following items were addressed: use of IMRT or arc-based techniques, image guidance, use of fiducial markers, prostate–rectum spacers, rectal balloon, bladder filling protocol, and rectal filling protocol.

Tab. 1 List of recommendations for two specific scenarios demonstrating a considerable variability of recommendations

Representative recommendations provided for two specific scenarios			
PSA < 10 ng/ml, T1-2a, Gleason score < 7		PSA 10–20 ng/ml, T2c, Gleason score 7	
Number of centers	Recommendation	Number of centers	Recommendation
1	70 Gy, no ADT	2	74 Gy, 6 months ADT
2	72 Gy, no ADT	1	74 Gy, 2 years ADT
6	74 Gy, no ADT	1	75.6 Gy, 1 year ADT
1	75.6 Gy, no ADT	1	76 Gy, 6 months ADT
4	76 Gy, no ADT	2	76 Gy, 2 years ADT
7	78 Gy, no ADT	1	76 Gy, 3 years ADT
1	80 Gy, no ADT	6	78 Gy, 6 months ADT
1	56 Gy hypofractionated, no ADT	2	78 Gy, 2 years ADT
		5	78 Gy, 3 years ADT
		1	80 Gy, 6 months ADT
		1	56 Gy hypofractionated, 6 months ADT

ADT androgen deprivation therapy.

Results

Of the centers contacted, 23 out of 24 (96 %) participated and were represented by department heads or senior physicians responsible for prostate cancer therapy. Among all centers, 22 % ($n=5$) were university hospitals, 43 % ($n=10$) public centers, and 35 % ($n=8$) private practices.

In all scenarios of nonmetastatic prostate cancer with specific combinations of prognostic factors, multiple treatment recommendations were found. Table 1 shows the results for two specific sample scenarios, where 8 and 11 different

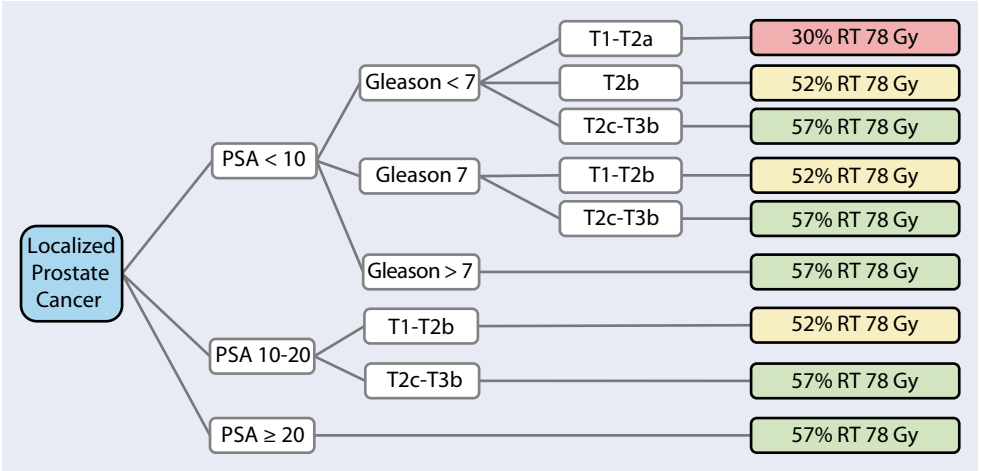

Fig. 2 Consensus on radiotherapy (*RT*) dose recommendations for prostate cancer depending on the prognostic factors prostate-specific antigen (*PSA*), T category, and Gleason score. For all prognostic factor combinations, a dose of 78 Gy was that most commonly recommended, with the highest consensus level for high-risk disease. The level of consensus is represented by a *red–green* gradient (*green* representing higher consensus)

treatment recommendations were returned by 23 participating centers.

Risk group definition was based in 57% ($n=13$) on NCCN guidelines [3], in 30% ($n=7$) on D'Amico [20], and in 13% ($n=3$) on individual adaptations of both stratifications. The median radiotherapy dose for standard fractionation (1.8–2 Gy/fraction) for low-risk disease was 76 Gy (range 70–80 Gy), and for intermediate- and high-risk disease, 78 Gy (range 74–80 Gy). The most common dose recommendation was 78 Gy for all risk groups, with consensus levels of 30, 52 and 57% for low-, intermediate-, and high-risk disease, respectively (Fig. 2). One center used hypofractionated radiotherapy to 56 Gy (4 Gy per fraction, three times a week), with whole pelvic radiotherapy in standard fractionation in the case of high-risk disease.

ADT was recommended for intermediate-risk disease for a median duration of 6 months, with an 83% consensus level and a range from no ADT to 36 months of ADT. For high risk-disease, ADT duration was recommended for a median duration of 36 months (52% consensus level) with a range of 6–36 months. No center recommended ADT use for low-risk disease (Fig. 3).

Additionally, the combined treatment recommendations for ADT and radiotherapy dose were analyzed for every specific combination of prognostic factors separately, using the objective consensus methodology (Fig. 4). Overall, a consensus level above 50% could not be found for any prognostic factor combination. The highest consensus level achieved in our study was 39% for specific prognostic factor combinations generally classified as intermediate-risk disease, with recommendations for a radiotherapy dose of 78 Gy and 6-months ADT duration. For low-risk prostate cancer, the most common recommendation was 78 Gy without ADT, with a consensus level of 30%. For high-risk prostate cancer, consensus levels ranged from 26 to 35%, depending on the specific prognostic factor combination.

Treatment planning and radiation delivery techniques

The survey on technical specifications for prostate radiotherapy was returned by 88% of all contacted institutions ($n=21$). The results are summarized in Figs. 5 and 6. Before treatment planning, a diagnostic MRI of the prostate before radiotherapy was performed for tumor staging by 76% routinely and by another 19% occasionally. MRI/computed tomography (CT) fusion was used for target volume delineation in 62% regularly and in 29% occasionally. CTV definition was based on the risk group in 68%, Partin tables in 5%, the radiological tumor stage in 16%, and unchanged for all patients in 11%. Median PTV margins were 5 mm posteriorly (range 3–10 mm) and 6 mm (range 5–15 mm) in all other directions. Fiducial markers were used by 43% routinely. In centers without use of fiducial markers as standard, IGRT was adapted by daily cone beam CT (CBCT) in 42% and in the remaining 58% at least once weekly, but not daily. Depending on the IGRT protocol, median PTV extensions were 5 mm (range 5–10 mm) with fiducial markers, 6 mm (range 5–10 mm) for daily CBCT, and 7 mm (range 5–15 mm) for the remaining centers. Median dorsal PTVs were with fiducial markers 4 mm (range 0–6 mm), with daily CBCT 5 mm (range 3–7 mm), and for the remaining centers 5 mm (range 4–10 mm). Penile bulb dose constraints were considered by 52% routinely and by 14% occasionally. One center also performed planning CTs in prone position using a belly board. Additional whole pelvic lymph node irradiation was performed by 62% based on risk scores such as the Roach [22] or MSKCC score [23], by 5% only in individual cases, by 9% only in node-positive prostate cancer, and not at all by 24%.

Preferred techniques for radiotherapy delivery were arc-based techniques in 85%, including one center using helical tomotherapy as their standard modality. IMRT was used as standard procedure in 10% and 3D-conformal radiotherapy

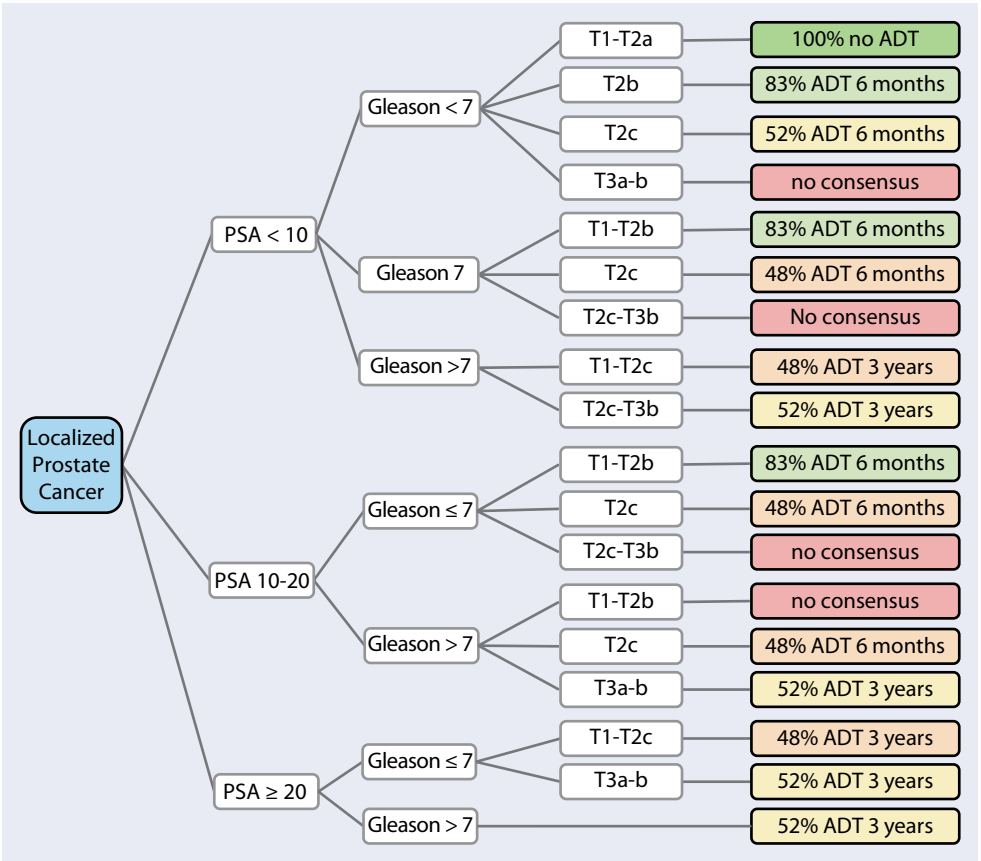

Fig. 3 Consensus on recommendations for androgen deprivation therapy (*ADT*) duration based on prostate-specific antigen (*PSA*), T category, and Gleason score. No consensus was achieved for T3a-b disease when combined with PSA 10–20 and/or Gleason 7 or lower. In contrast, all centers agreed to omit ADT for low-risk prostate cancer. The level of consensus is represented by a *red–green* gradient (*green* representing higher consensus)

in 5%. No center implemented a brachytherapy boost as part of their prostate cancer radiotherapy strategy.

A rectal balloon was used routinely by 19%, a bladder filling protocol by 90%, and a rectal filling protocol in 81%. Rectoprostatic pacer gel was used by 19% occasionally.

Discussion

Several patterns of practice studies on prostate cancer radiotherapy have been performed in different countries, either by population-based analyses [18, 24, 25] or as multicenter surveys [15, 17, 26, 27], in order to assess adherence to national guidelines or to provide an additional source of standards of care and therapeutic recommendations [28]. Our study provides a comprehensive overview of current patterns of practice for risk group-adapted primary radiotherapy and ADT for prostate cancer in Switzerland. Besides a survey, we implemented an algorithm-based approach. We could demonstrate a wide range of treatment variations offered, with a total radiotherapy dose ranging from 70 to 80 Gy in standard fractionation and ADT duration of up to 3 years.

The median recommendation for radiotherapy dose prescription was 76 Gy for low-risk disease, and 78 Gy for intermediate- and high-risk prostate cancer. The dose recommendations were in congruence with current international guidelines [3, 4] and similar to IMRT dose recommendations from other recent national surveys [17, 26]; however, they were clearly higher when compared to patterns of care studies from previous years [18, 24, 29]. Most interestingly, one center has adopted a hypofractionated radiotherapy schedule as standard treatment for all risk groups, which has also been recognized as a valid treatment option in the most recent NCCN guidelines [3]. Our data demonstrate that the majority of Swiss cancer centers currently prescribe radiation doses above 74 Gy, which have shown improved biochemical failure-free rates in recent phase III trials [8, 10], as well as, in some publications, improved local control [30, 31] and metastasis-free survival [9, 31]. However, these benefits of dose escalation have to be balanced against the uncertain impact on cancer-specific and overall survival, and potentially increased toxicity [8, 9]. High-dose radiotherapy of the prostate with reduced acute and late toxicity appears only feasible with the use of more conformal techniques [11, 32]. In fact, 96% of Swiss centers already use IMRT, IMAT, or tomotherapy as standard techniques. Other technical aspects aimed at reducing toxicity that are adopted into clinical routine by most of the Swiss centers are adaptation of the treatment volume by MRI-based treatment planning [33] and IGRT, resulting in reduced PTV margins—particularly when fiducial markers or daily CBCT are used [34–36].

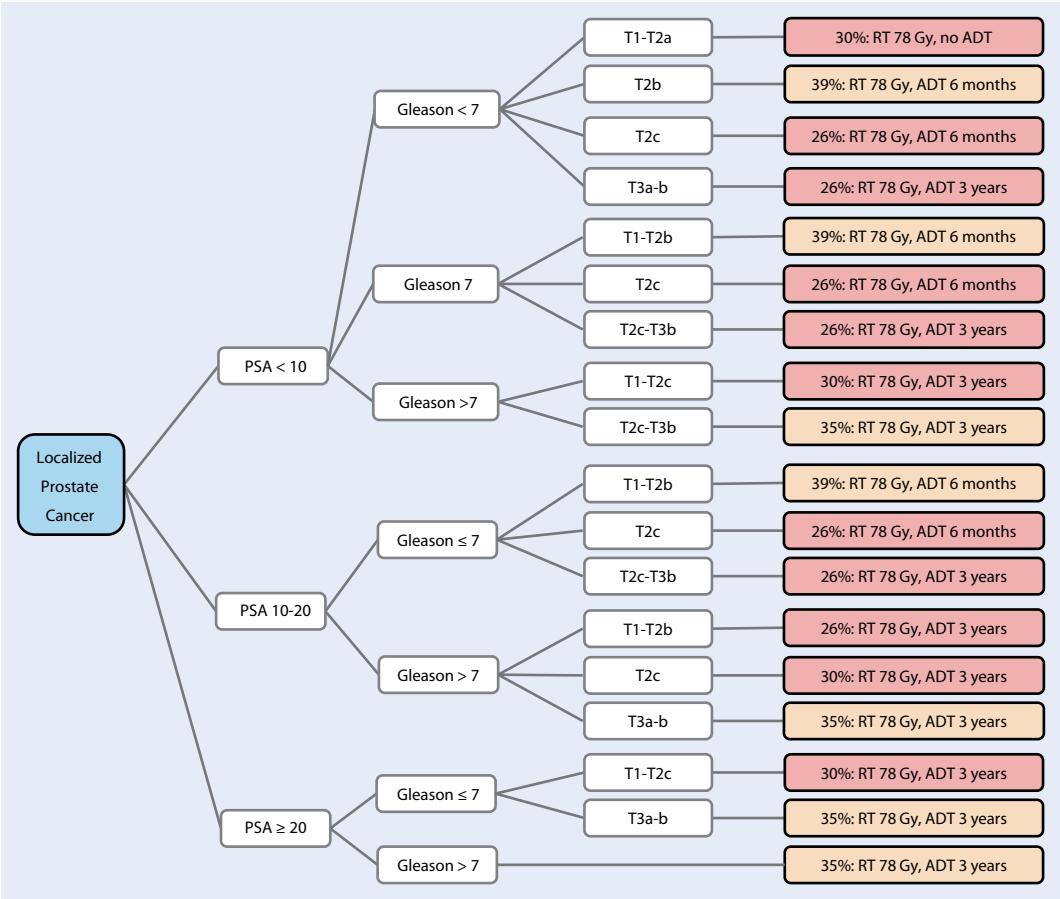

Fig. 4 Consensus levels for combined radiotherapy (*RT*) and androgen deprivation therapy (*ADT*) depending on prostate-specific antigen (*PSA*), T stage and Gleason score. No single recommendation was agreed upon by more than 39% of centers. The level of consensus is represented by a *red–green* gradient (*green* representing higher consensus)

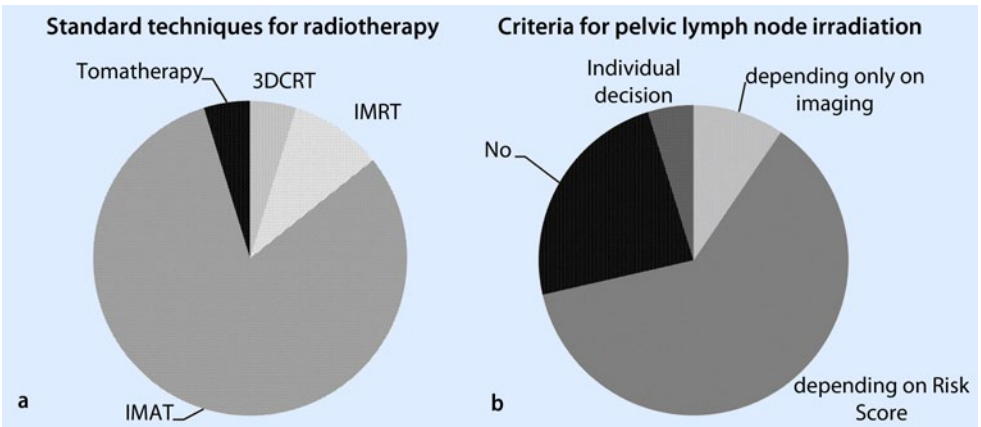

Fig. 5 Radiotherapy delivery techniques as implemented by the participating centers. **a** Standard techniques for radiotherapy. **b** Criteria for whole pelvic lymph node irradiation. *3DCRT* 3D-conformal radiotherapy, *IMRT* intensity-modulated radiotherapy, *IMAT* intensity-modulated arc therapy

In contrast to dose escalation, there is clear evidence for improved overall survival using ADT in varying durations in combination with EBRT for prostate cancer [37]. For high-risk patients, a prolonged ADT duration of 2–3 years seems to be superior to short-term ADT of 4–6 months [5, 6]. This has been confirmed in the high-dose radiotherapy era by the preliminary results of the DART 01/05 trial [38]; although recent data suggest that a reduction to 18 months might be safe [39]. In our survey, the vast majority of Swiss centers recommended—in accordance with evidence-based guidelines—ADT for intermediate risk disease, with a clear consensus of 83% for 6 months as standard. In high-risk disease, ADT was recommended for a duration of 2–3 years in over 90% of centers.

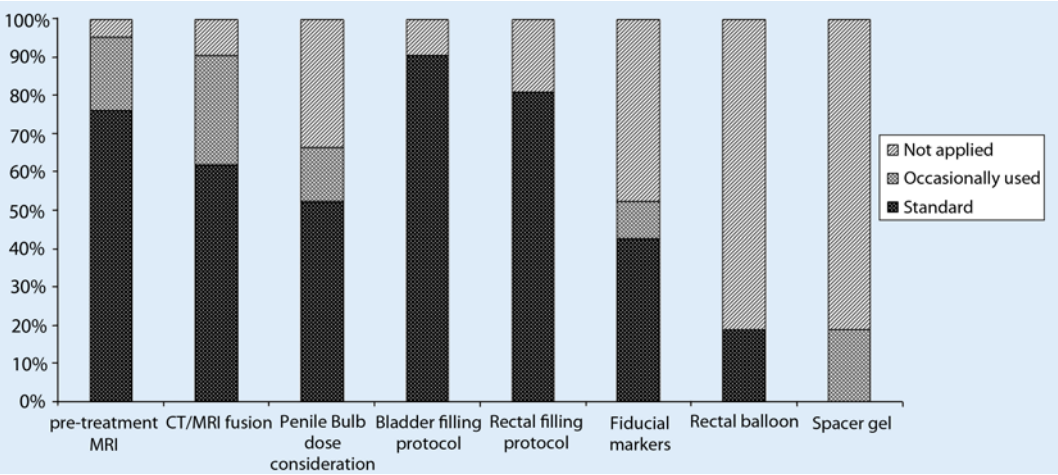

Fig. 6 Utilization of additional protocols and techniques for treatment planning and daily treatment by the participating centers. *MRI* magnetic resonance imaging, *CT* computed tomography

This study was intended as a survey on primary EBRT for nonmetastatic prostate cancer, without evaluation of alternative strategies such as surgery, brachytherapy, active surveillance, or watchful waiting. The recommendations analyzed here represent recommendations for an otherwise average prostate cancer patient. We have not considered further characteristics such as age, comorbidities, or patient preferences, which may influence the final decision. Of note, prostate cancers demonstrate heterogeneous clinical behavior, even within the established risk groups; thus novel risk stratifications have recently been proposed [40]. The recommendations provided by the participants did not take into account other clinicopathological prognostic factors, such as the percentage of positive biopsy cores or differences in Gleason scores of 7 (4+3 versus 3+4). Additionally, we cannot be certain that all physicians within a center would provide the same recommendations, particularly with regard to ADT, which is often prescribed by the referring urologist in Switzerland.

In contrast to previous survey studies, the objective consensus methodology in our analysis allowed for a detailed comparison of treatment recommendations for any specific combination of prognostic factors, such as PSA, Gleason score, and T stage. This facilitates a more accurate comparison of treatment recommendations in the case of varying risk group definitions according to D'Amico [20] or NCCN [3] among the participating centers, which mainly differ by classifying T2c tumors as intermediate- or high-risk, respectively. Additionally, our methodology could take into account the circumstance that some centers based the ADT duration primarily on Gleason score and PSA, rather than on tumor stage, although all three parameters contribute equally to the established risk group stratifications.

The analysis of treatment recommendations demonstrates varying interpretations of the available data on radiotherapy and ADT for prostate cancer. However, in the vast majority of clinical scenarios, these varying interpretations are within the range recommended in current evidence-based guidelines [2–4].

One of the strengths of our study was that the participants were able to provide their decision trees anonymously (only known to the coordinating center) and could receive feedback and benchmarking compared to all other centers via the presentation of the analysis. The presented data may potentially serve as a basis for Swiss-wide consensus guidelines.

Conclusion

Our study demonstrates considerable variability among treatment recommendations for primary radiotherapy of prostate cancer in Swiss radiation oncology centers, but with a high congruence with current evidence-based guidelines. Consensus levels for combined EBRT and ADT never extended beyond 39%, mainly due to a wide range of radiotherapy dose prescriptions. The majority of centers utilize arc-based IMRT routinely. These findings may serve as a means to further unify Swiss treatment recommendations or serve as a basis for future trials where discrepancies remain.

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Compliance with ethical guidelines

Conflict of interest C. Panje, A. Dal Pra, T. Zilli, D. Zwahlen, A. Papachristofilou, F.G. Herrera, O. Matzinger, L. Plasswilm, and P.M. Putora state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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