CONTROVERSIES AND PERSPECTIVES IN THE USE OF POSTOPERATIVE RADIOTHERAPY FOR PROSTATE CANCER

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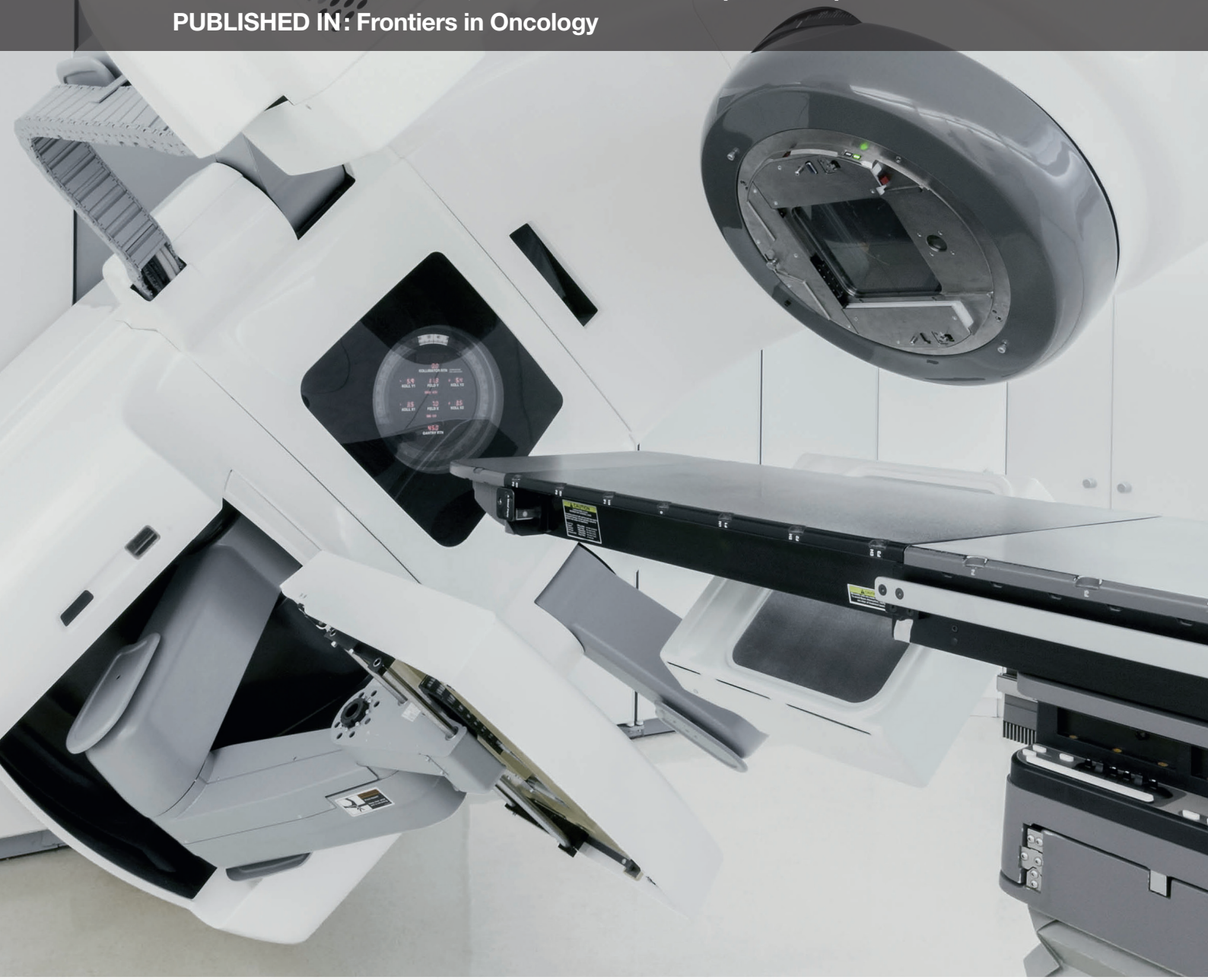

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CONTROVERSIES AND PERSPECTIVES IN THE USE OF POSTOPERATIVE RADIOTHERAPY FOR PROSTATE CANCER

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The use of radical prostatectomy in patients with high risk of recurrence has significantly increased during the past 10 years. Thus, adjuvant radiation as a part of multimodality treatment or salvage radiation at the evidence of prostate-specific antigen (PSA) progression represents mainstay curative-intent options for a great number of prostate cancer patients. Although, few randomized trials and many retrospective studies have been published, many uncertainties still mold the discussions on the best treatment management for men after prostatectomy. This research topic (https://www.frontiersin.org/research-topics/3739/controversies-and-perspectives-in-the-use-of-postoperative-radiotherapy-for-prostate-cancer) successfully intended to foster discussions on current controversies in the use of postoperative radiotherapy and to present novel perspectives for treatment optimization.

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EDITORIAL
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Editorial: Controversies and Perspectives in the Use of Postoperative Radiotherapy for Prostate Cancer

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Editorial on the Research Topic

Controversies and Perspectives in the Use of Postoperative Radiotherapy for Prostate Cancer

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The use of radical prostatectomy in patients with high risk of recurrence has significantly increased during the past 10 years (1). Thus, adjuvant radiation as a part of multimodality treatment or salvage radiation at the evidence of prostate-specific antigen (PSA) progression represents mainstay curative-intent options for a great number of prostate cancer patients. Although, few randomized trials and many retrospective studies have been published, many uncertainties still mold the discussions on the best treatment management for men after prostatectomy. This research topic (https://www.frontiersin.org/research-topics/3739/controversies-and-perspectives-in-the-use-of-postoperative-radiotherapy-for-prostate-cancer) successfully intended to foster discussions on current controversies in the use of postoperative radiotherapy and to present novel perspectives for treatment optimization.

Several randomized trials have shown that dose intensification in the primary treatment of prostate cancer improves local control. However, the data are scarcer in the postoperative setting. Beck et al. review the literature and present the only randomized phase III trial addressing dose-intensified salvage radiotherapy (64 vs. 70 Gy), SAKK (Swiss Group for Clinical Cancer Research) 09/10 (2). Recent publication showed that acute toxicity (gastrointestinal and urinary) and early quality of life data were not significantly different between the two treatment arms; however, a significant worsening of urinary quality of life was noted in the 70-Gy arm. The primary endpoint analysis (biochemical relapse free survival) and long-term endpoints are eagerly awaited.

Potential overtreatment and/or radiation-related toxicity with subsequent impact on patient's quality of life are common arguments for withdrawing or deferring postoperative radiotherapy by urologists. By revealing gaps between evidence and clinical practice, Raziee et al. (Raziee and Berlin) claim that concerns with toxicities and/or quality of life should not preclude the utilization of curative-intent postoperative radiotherapy. Also, Herrera and Berthold review level I evidence on adjuvant radiotherapy that demonstrates improvements in biochemical progression-free survival, clinical progression-free survival, and overall survival in patients with high-risk pathological features (Herrera and Berthold). However, they point out that offering immediate adjuvant radiotherapy to all men with high-risk features would overtreat around 50% of men who would anyway be cancer-free, exposing them to unnecessary toxicity and adding important costs to the health-care system.

The assessment of adjuvant versus early salvage radiation is being addressed in important randomized trials to be published in the forthcoming years (Radiotherapy and Androgen Deprivation in Combination After Local Surgery, Radiotherapy–Adjuvant versus Early Salvage, and Groupe d' Étude des Tumeurs Uro-Génitales) [Raziee and Berlin; Herrera and Berthold].

The role of ADT in combination with primary radiotherapy for intermediate- and high-risk prostate cancer is well established. Recently, two prospective phase III trials (RTOG 9601 and GETUG-16) have shown improvements in disease outcomes when ADT is combined with salvage radiotherapy (3, 4). However, in the setting of early salvage, the role of ADT remains debatable. In patients with pre-SRT PSA <0.7 ng/ml, which comprised >50% of the RTOG 9601 study population, the addition of ADT provided no improvement in overall survival or metastasis-free survival. ADT is not devoid of important side effects, and many questions are still open on which patients benefit the most, ADT type, and treatment duration.

In parallel, the impact of the increasing aging population on the worldwide burden of cancer is well known, and the management of prostate cancer in the elderly is a topic of utmost importance. Goineau et al. specifically shed light on the care of elderly patients with prostate cancer after prostatectomy. The authors propose a decision tree based on the International Society of Geriatric Oncology recommendations.

Novel imaging modalities are reshaping the use of postoperative radiotherapy in prostate cancer patients. Molecular imaging has provided increasing accuracy in the localization of recurrence, and it has progressively changed clinical practice. Novel imaging tools can define the site of the recurrence and the extent of disease and thus individualize salvage treatments. In this research topic, Amzalag et al. comprehensively review most important novel targeted tracers for the evaluation of recurrent disease.

Analyses of large multi-institutional retrospective series along with predictive nomograms have importantly helped clinicians to estimate individual patient's risks and tailor treatment decisions (5, 6). More lately, genomic classifiers have been added to the armamentarium of clinicopathological parameters and novel imaging modalities, representing an emerging tool able to provide exciting prognostic information for patients with recurrent disease (7–10). A better identification of patients with indolent and more aggressive tumors will help to select which patients may derive the greatest benefits from treatment intensification or deintensification and thus reducing therapy-associated costs and unnecessary adverse effects.

In terms of radiotherapy technique, important variability in the delineation of the prostate bed is observed. At least four international contouring consensus guidelines are available, but present discrepancies in target definition. This is a relevant topic when comparing outcome data from different retrospective and prospective cohorts. Latorzeff et al. from the GETUG group highlight some controversies to help clinicians create an appropriate volume delineation of the prostate bed in the setting of adjuvant and salvage radiotherapy (Latorzeff et al.). Also addressing variability in contour delineation, Delpon et al. critically report on automated atlas-based segmentation algorithms (Delpon et al.). The authors compare different commercially available options that could assist radiation oncologists in potentially improving contour delineation. Not to mention on the unclear benefits of elective treatment of the pelvic nodes which is currently addressed in the ongoing RTOG 0534 trial.

Image-guided radiotherapy is a key advancement in modern radiotherapy to decrease normal tissue toxicity. Vilotte et al. reviewed the literature on image guidance techniques in the postoperative setting (Vilotte et al.). The authors highlight key points on different techniques applicable to the prostatic bed and discuss potential reductions in planning target volume margins to reduce treatment complications.

By using an innovative approach for locally advanced tumors with high risk of local recurrence, Buge et al. present a preclinical evaluation of intraoperative low-energy photon radiotherapy using spherical applicators. With cadaveric models assessed by MRI, the authors show that intraoperative radiotherapy of the prostate bed is feasible, with good coverage of targeted tissues, and is potentially able to replace external beam radiotherapy in the future. Clinical studies are warranted to validate this exciting approach that could further decrease normal tissue toxicity.

Finally, in view of current and evolving data, the use of postoperative radiotherapy should be made in the context of a multidisciplinary discussion on treatment benefits and potential risk of side effects. Patients should take a proactive role in the decision-making process with unbiased, transparent, and evidence-based information. New imaging modalities and commercially available biomarkers have been increasingly utilized in the clinic, but unfortunately have not been timely incorporated into prospective studies. This dissonance between novel tools and lack of robust validation is a destiny not only in Radiation Oncology but also in other disciplines with rapidly evolving technologies. Hopefully, all this progress will ultimately lead to improvements in outcomes that matter most to our patients.

AUTHOR CONTRIBUTIONS

All the authors contributed either for initial writing and/or review of this editorial.

REFERENCES

1. Mahmood U, Levy LB, Nguyen PL, Lee AK, Kuban DA, Hoffman KE. Current clinical presentation and treatment of localized prostate cancer in the United States. *J Urol* (2014) 192:1650–6. doi:10.1016/j.juro.2014.06.017
2. Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Holscher T, Gut P, 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. doi:10.1200/JCO.2015.63.3529
3. Carrie C, Hasbini A, de Laroche G, Richaud P, Guerif S, Latorzeff I, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* (2016) 17:747–56. doi:10.1016/S1470-2045(16)00111-X

4. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med* (2017) 376:417–28. doi:10.1056/NEJMoa1607529
5. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) 25:2035–41. doi:10.1200/JCO.2006.08.9607
6. Tendulkar RD, Agrawal S, Gao T, Efstathiou JA, Pisansky TM, Michalski JM, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. *J Clin Oncol* (2016) 34:3648–54. doi:10.1200/JCO.2016.67.9647
7. Den RB, Yousefi K, Trabulsi EJ, Abdollah F, Choeurng V, Feng FY, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J Clin Oncol* (2015) 33:944–51. doi:10.1200/JCO.2014.59.0026
8. Freedland SJ, Choeurng V, Howard L, De Hoedt A, du Plessis M, Yousefi K, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. *Eur Urol* (2016) 70:588–96. doi:10.1016/j.eururo.2016.01.008
9. Dalela D, Santiago-Jimenez M, Yousefi K, Karnes RJ, Ross AE, Den RB, et al. Genomic classifier augments the role of pathological features in identifying optimal candidates for adjuvant radiation therapy in patients with prostate cancer: development and internal validation of a multivariable prognostic model. *J Clin Oncol* (2017) 35:1982–90. doi:10.1200/JCO.2016.69.9918
10. Zhao SG, Chang SL, Spratt DE, Erho N, Yu M, Ashab HA, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. *Lancet Oncol* (2016) 17(11):1612–20. doi:10.1016/S1470-2045(16)30491-0

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ORIGINAL RESEARCH
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Comparison of Automated Atlas-Based Segmentation Software for Postoperative Prostate Cancer Radiotherapy

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Automated atlas-based segmentation (ABS) algorithms present the potential to reduce the variability in volume delineation. Several vendors offer software that are mainly used for cranial, head and neck, and prostate cases. The present study will compare the contours produced by a radiation oncologist to the contours computed by different automated ABS algorithms for prostate bed cases, including femoral heads, bladder, and rectum. Contour comparison was evaluated by different metrics such as volume ratio, Dice coefficient, and Hausdorff distance. Results depended on the volume of interest showed some discrepancies between the different software. Automatic contours could be a good starting point for the delineation of organs since efficient editing tools are provided by different vendors. It should become an important help in the next few years for organ at risk delineation.

Keywords: postoperative radiotherapy, prostate bed, atlas, automatic segmentation, contour comparison

INTRODUCTION

Prostate bed radiotherapy after radical prostatectomy may present some clinical benefits in term of clinical outcome (1, 2). Although intraoperative irradiation is a possible treatment modality (3), irradiation is mainly delivered by external beam radiotherapy. Advances in radiation oncology led to intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). Those advances allow to either increase dose to target tissues or spare surrounding healthy structures. The development of state-of-the-art technologies including imaging modalities, treatment planning systems, and linacs have enabled radiotherapy treatments to be highly specific (4). In this context, the delineation of target and normal organs is the prerequisite inputs to the planning process. Consequently, the implementation of modern radiotherapy treatment plans focuses on the need of contouring guidelines (5). A recent development in radiotherapy is the use of automated atlas-based auto-segmentation algorithms to aid in organ delineation (6). The aim of the study was to compare the different atlas-based auto-segmentation software available when used for prostate bed and organs at risk. The study was limited to a single radiation oncologist to avoid inter-rater variations.

Indeed, significant levels of interobserver variability in target volume delineation have been demonstrated in prostate cancer radiotherapy (7–10). This variability is the most important source of uncertainties in radiotherapy (11, 12). However, this variability is out of the scope of our study as at least four consensuses originating from four scientific groups were validated (13). Therefore, no ground truth can be considered. The aim of our study was to assess how segmentation software are able to learn from the single radiation oncologist habits in order to reproduce these habits to novel patients.

MATERIALS AND METHODS

Population and Treatment

Twenty consecutive patients, treated in a clinical center, were included in this study from January to September 2015 for a pT3aR0-R1N0M0 prostate cancer after surgery. They were treated by postoperative salvage IMRT. Treatment aimed at delivering 66 Gy to the prostatic bed as clinical target volume (CTV) (1). Computed Tomography scans (CT) were contoured by only one physician according to the Radiation Therapy Oncology Group (RTOG) guidelines for target volumes (5). The following organs at risk were also delineated: bladder, rectum, and femoral heads (14).

Ethics

As French laws (data, data-collection, and freedom law, January, 6, 1978) agreed for single-center retrospective study, no specific written informed consent is needed. All patients have been orally informed about potential use of already recorded data for potential study.

Atlas-Based Auto-Segmentation Software

Five software were compared. WorkFlow Box (Mirada Medical) (WFB), MIM Maestro (MIM Software), SPICE (Philips), ABAS (Elekta), and the atlas-based segmentation module included in RayStation (RaySearch Laboratories). WFB is a black-box server that performs atlas-based contouring automatically. WFB fits seamlessly in to your current process *via* standard DICOM protocols. WFB uses deformable registration algorithm to automatically apply contours to planning CTs based on multiple expert atlases.

Alternatively, clinicians can define their own atlases. In the current study, atlases were based on patient contours delineated by the expert physician. Auto-contouring is a feature of MIM Maestro software. Automatic contours may be based on either user-defined atlas libraries or automatic atlas subject selection. This software includes features to sort atlases depending on TNM status, lesion laterality, or physician. If several atlases are chosen to start the auto-segmentation, a structure set was generated per atlas, and data were gathered to create the simultaneous truth and performance level estimation (STAPLE) contours for each organ. STAPLE is an expected maximization algorithm that computes a probabilistic estimate of the true segmentation by weighting each segmentation on its estimated performance level (15). In addition, it provides tools to correct auto-contours and a scripting platform. ABAS (Elekta) approximates the anatomy contours by scanning a library of reference images, applying elements of those forms to a new patient image, and creating a structure set to fit the patient's anatomy. The user may either choose an atlas among the library or use the STAPLE algorithm. In this study, the STAPLE algorithm was used. The operator cannot see or edit the contours within ABAS, but contours may be imported in any contouring solution, such as Focal or Monaco considering Elekta software. SPICE (Philips) that stands for Smart Probabilistic Image Contouring Engine, is an option of Pinnacle, a treatment planning system. This system computes contours from a probabilistic segmentation based on its own expert atlases, and the user cannot import his datasets to create another expert library. Consequently, only a limited number of treatment sites and organs is available. The transformation is based on a dense deformable registration method (Enhanced Demons), which further initializes organ-specific deformable models. The method is based on adaptation and probabilistic refinement (16). In addition to plan design and optimization features, RayStation Treatment Planning System (RS) provides an auto-segmentation solution based on ANAtomically CONstrained Deformation Algorithm (ANACONDA). ANACONDA combines image information (i.e., intensities) with anatomical information as provided by contoured image sets (17). It is a hybrid algorithm due to the combination of using image similarity and anatomical information. Model-based segmentation (MBS) and atlas-based segmentation (ABS) are available. MBS includes models with adjustable shape, size, and property parameters provided by RayStation for the different organs at risk, including femoral heads and bladder. ABS requires user-defined atlases with image sets and contours. In this study, only ABS was used, even for femoral heads and bladder.

Atlas and Evaluation Databases

The first 10 patients were selected to build the atlas database except for SPICE that is working differently and used its own atlas database. The 10 following patients constituted the evaluation database. The aim of the study was to compare the contours produced by the different automatic tools against the physician contours. For each patient of the evaluation database, atlas-based auto-segmentation software produced a DICOM Structure Set using the provided atlas database. Automatic contours without any modification were then exported in DICOM format for the comparison.

Contour Comparison

CTV, bladder, rectum, and femoral heads delineated by the physician and computed by the automatic tools were imported in DICOM format in the Slicer open source freeware (http://www.slicer.org). Automatic and expert contours defined on the different CT slices constituted volumes. The additional module DICOM RT was used to compare those volumes. Physician contours were used as reference contours. Different metrics were calculated to quantify the similarity between the automatic and the expert volumes.

The simple ratio R of the automatic volume (in cubic centimeter) divided by the expert volume (in cubic centimeter) was calculated.

TABLE 1 | Results obtained for the evaluation dataset with the five commercial solutions [WFB (Mirada Medical), MIM (MIM Software), SPICE (Philips), ABAS (Elekta), and RS (RayStation)] compared to expert delineation for both femoral heads.

		WFB	MIM	ABAS	SPICE	RS
Left femoral head	*R*	0.93 ± 0.06	0.96 ± 0.13	0.96 ± 0.06	0.59 ± 0.06	0.98 ± 0.09
	DSC mean	0.89 ± 0.05	0.89 ± 0.08	0.91 ± 0.04	0.70 ± 0.05	0.91 ± 0.03
	DSC median	0.91	0.91	0.92	0.72	0.92
	$H_{95\%}$ (mm)	9.2 ± 6.4	9.9 ± 7.9	8.6 ± 6.9	29.7 ± 9.0	8.8 ± 7.2
Right femoral head	*R*	0.93 ± 0.05	0.97 + 0.07	0.95 ± 0.05	0.60 ± 0.04	1.01 ± 0.07
	DSC mean	0.91 ± 0.03	0.92 ± 0.02	0.92 ± 0.02	0.72 ± 0.03	0.92 ± 0.02
	DSC median	0.92	0.93	0.92	0.72	0.92
	$H_{95\%}$ (mm)	8.1 ± 5.6	8.2 ± 5.3	8.5 ± 6.1	30.0 ± 6.5	6.4 ± 5.0

R is the volume ration, DSC is the Dice Similarity Coefficient, and $H_{95\%}$ is the Hausdorff distance.

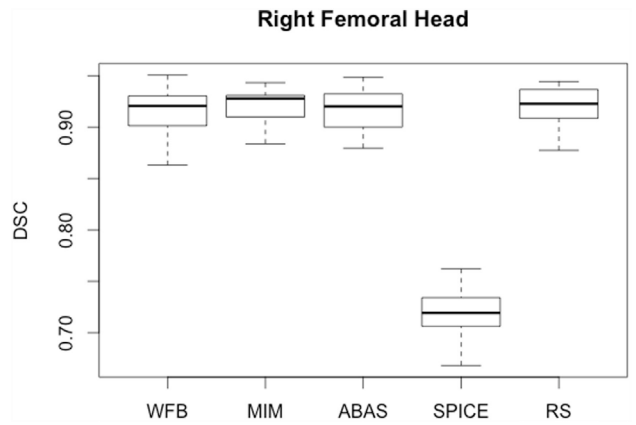

FIGURE 1 | Boxplots obtained for the dice similarity coefficient analysis of the right femoral head between the reference contours defined by the physician and the automatic contours computed by the different softwares.

The Dice Similarity Coefficient (DSC) was used to quantify the overlap between the expert and the automatic contours (18). DSC corresponds to the ratio of two times the intersection of two volumes divided by the sum of the two volumes (Eq 1).

$$\mathrm{DSC} = \frac{2 \times |A \cap B|}{|A| + |B|} \quad (1)$$

where, *A* and *B* are the two volumes to be compared.

The Hausdorff distance (95% confidence interval) was used to quantify the magnitude of gross deviations between contour surfaces (19). The Hausdorff distance computation utilizes a maximum–minimum function as defined by Eq 2:

$$h(a,b) = \max_{a \in A} \left\{ \min_{b \in B} \{ d(a,b) \} \right\} \quad (2)$$

where *a* and *b* are points of contour sets *A* and *B*, and $d(a,b)$ is the Euclidian distance between *a* and *b*. The Hausdorff distance (95% confidence interval) is calculated from the set H, which is composed of calculated Hausdorff distance $h(a,b)$ values for all contour vertices of a contour set A. The value recorded $H_{95\%}$ is the largest distance that falls within the 95% confidence interval for the set of distances in *H*. The use of $H_{95\%}$ value minimizes the impact of large outliers in the Hausdorff distance calculation on the overall data (19).

RESULTS

For the 10 patients included in the evaluation dataset, the results are presented volume of interest by volume of interest.

For femoral heads, results were obviously similar for the left and the right sides (**Table 1**). *R* values were higher than 0.93, except for SPICE. But for this latter, the problem was that femoral heads were automatically delineated on too many slices. The lowest slice on which a SPICE contour was defined differed from the expert. Those results were confirmed by the DSC analysis. Results were really consistent from one patient to another (**Figure 1**). Except for SPICE, DSC and $H_{95\%}$ were, respectively, about 0.90 and less than 10 mm for both femoral heads with small discrepancies whatever the patient. Femoral heads contours were acceptable, and only slight corrections would have been necessary to validate the automatic segmentation.

Bladder *R* values were larger than those obtained for femoral heads, and differences were observed between patients and software (**Table 2**). SD was very large whatever the automatic solution. However, lower values were obtained with WFB and SPICE. Probably results would have been improved if CT scans had been injected with some contrast product. But DSC were satisfactory for most algorithms, with an average value higher than 0.75. For most algorithms, results were degraded by one or two cases. For example, SPICE median DSC was higher than 0.90, but average value was only 0.76 due to a very bad contour for Patient 10 (**Figure 2**). Similarly, ABAS and MIM failed for Patients 2 and 3. $H_{95\%}$ was about 15 mm, except for RS. RaySearch results were disappointing, but the MBS option was not used for this study. Automatic contours were globally satisfactory for most algorithms. However, results really depended on the patient case. Verification and corrections were required.

Rectum *R* values were lower than those obtained for bladder, but SDs were still high, about 30% (**Table 3**). Rectum automatic contours were larger than expert contours, except for WFB (**Figure 3**). Despite the lower *R* values, DSC mean values were slightly lower than for bladder. However, less discrepancies were observed between patients, average, and median DSC were approximately equal. Globally, DSC results were similar for the

TABLE 2 | Results obtained for the evaluation dataset with the five commercial solutions [WFB (Mirada Medical), MIM (MIM Software), SPICE (Philips), ABAS (Elekta), and RS (RayStation)] compared to expert delineation for the bladder.

	WFB	MIM	ABAS	SPICE	RS
R	1.01 ± 0.42	1.49 ± 0.77	1.31 ± 0.48	0.89 ± 0.31	1.62 ± 0.69
DSC mean	0.76 ± 0.12	0.80 ± 0.14	0.81 ± 0.13	0.76 ± 0.26	0.59 ± 0.15
DSC median	0.77	0.84	0.85	0.91	0.58
$H_{95\%}$ (mm)	15.0 ± 9.0	14.0 ± 6.3	13.6 ± 7.9	9.2 ± 11.7	28.5 ± 13.1

R is the volume ration, DSC is the Dice Similarity Coefficient, and $H_{95\%}$ is the Hausdorff distance.

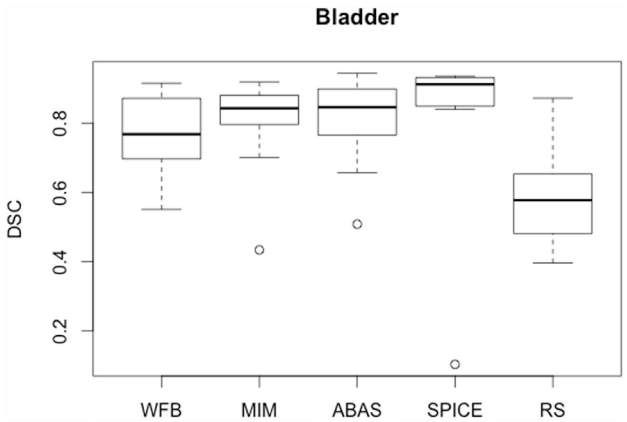

FIGURE 2 | Boxplots obtained for the DSC analysis of the bladder between the reference contours defined by the physician and the automatic contours computed by the different sotwares.

TABLE 3 | Results obtained for the evaluation dataset with the five commercial solutions [WFB (Mirada Medical), MIM (MIM Software), SPICE (Philips), ABAS (Elekta), and RS (RayStation)] compared to expert delineation for the rectum.

	WFB	MIM	ABAS	SPICE	RS
R	0.87 ± 0.19	1.27 ± 0.28	1.27 ± 0.38	1.30 ± 0.34	1.08 ± 0.28
DSC mean	0.73 ± 0.07	0.75 ± 0.07	0.75 ± 0.09	0.68 ± 0.12	0.49 ± 0.12
DSC median	0.76	0.77	0.75	0.73	0.51
$H_{95\%}$ (mm)	10.0 ± 3.0	9.9 ± 3.4	9.9 ± 4.4	13.0 ± 4.9	16.5 ± 3.7

R is the volume ration, DSC is the dice similarity coefficient, and $H_{95\%}$ is the Hausdorff distance.

different algorithms, except RS (**Figure 4**). $H_{95\%}$ was in the same order of magnitude, less than 15 mm, except for RS. Atlas-based contours presented discrepancies with the expert, and manual corrections were necessary.

Automatic prostate bed contours were less satisfactory with large volume variations (**Table 4**). *R* values varied from 0.49 for SPICE to 1.37 for MIM. DSC was lower than 0.70 for all solutions, demonstrating that prostate bed cannot be automatically defined (**Figure 5**). Many corrections would be required to adapt

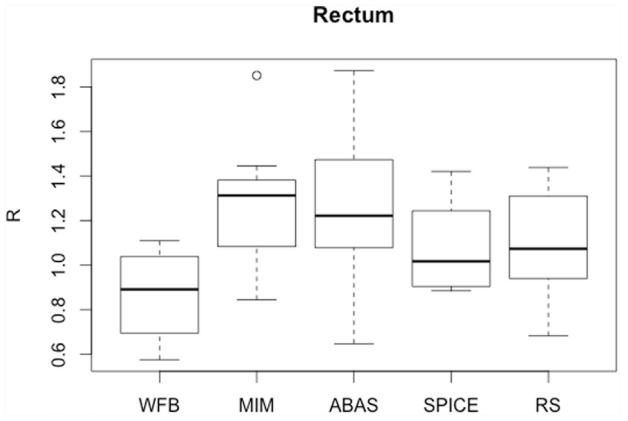

FIGURE 3 | Boxplots obtained for the *R* analysis of the rectum between the reference volumes defined by the physician and the automatic volumes computed by the different sotwares.

TABLE 4 | Results obtained for the evaluation dataset with the five commercial solutions [WFB (Mirada Medical), MIM (MIM Software), SPICE (Philips), ABAS (Elekta), and RS (RayStation)] compared to expert delineation for the prostate bed CTV.

	WFB	MIM	ABAS	SPICE	RS
R	0.53 ± 0.11	1.37 ± 0.35	1.04 ± 0.13	0.49 ± 0.15	0.82 ± 0.12
DSC mean	0.56 ± 0.10	0.61 ± 0.09	0.67 ± 0.13	0.37 ± 0.09	0.51 ± 0.17
DSC median	0.56	0.61	0.70	0.35	0.52
$H_{95\%}$ (mm)	11.9 ± 3.5	11.4 ± 4.0	8.4 ± 3.0	15.3 ± 2.6	12.4 ± 3.4

R is the volume ration, DSC is the dice similarity coefficient, and $H_{95\%}$ is the Hausdorff distance.

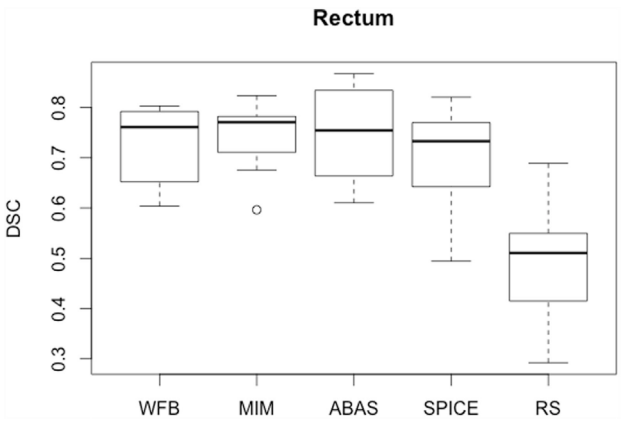

FIGURE 4 | Boxplots obtained for the DSC analysis of the rectum between the reference contours defined by the physician and the automatic contours computed by the different sotwares.

automatic contours. However, ABAS had the best average DSC (**Figure 5**). Automatic prostate bed contours were insufficient. Manual segmentation should be preferred for this target volume whatever the algorithm.

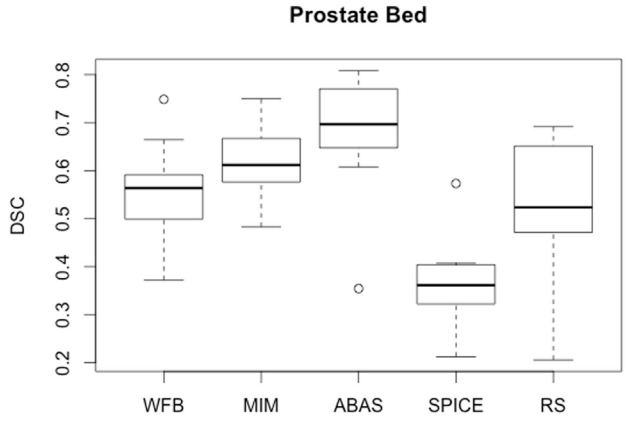

FIGURE 5 | Boxplots obtained for the DSC analysis of the prostate bed between the reference contours defined by the physician and the automatic contours computed by the different softwares.

CONCLUSION

To the best of our knowledge, no other study compared automatic delineation software for prostate cancer in the postoperative setting. The comparison of five different automatic-based segmentation software used for prostate bed and nearby organs showed these algorithms were very efficient for high contrast organs such as femoral heads. For other organs at risk, results were nuanced. Automatic contours were quite close to the expert contours, but corrections were required and for some cases, depending on the algorithm, computed contours were bad. Prostate bed contours were insufficient, but automatic segmentation aims essentially to delineate organs at risk. Postoperative CTV can be considered as a virtual volume without difference in terms of contrast or gray level over a large part of its volume. This difference compared to automatic prostate delineation may explain the bad outcomes in postoperative situation. A study shortcoming was the limited number of patients used to create the reference database. But the objective was mainly to compare the different software with the same settings, except for SPICE that considered its own reference datasets. In this context, a single physician defined the reference contours, and an arbitrary choice of 10 patients was done. For each automatic delineation software, an optimization study may lead to a different number of patients to build the reference database. Such studies may improve the coherence between automatic and physician contours (20). For example, RayStation recommends the use of up to 20 cases for atlas creation. However, results were consistent with the study published by Hwee et al. (6) that focused on MIM solution. Although proposed contours differed from one algorithm to another, the present study cannot establish a ranking of the software. Indeed, only 10 cases delineated by a single physician were selected to create the expert database, and 10 other cases were used for evaluation. In addition, this study did not consider the extra features proposed by some tools to modify the computed segmentation. Nevertheless, it allowed to state that atlas-based automatic segmentation has reached an interesting level of accuracy, especially for high contrast organs. Automatic contours could be a good starting point for the delineation of organs since efficient editing tools are provided by different vendors. It should become an important help in the next few years for organ at risk delineation.

AUTHOR CONTRIBUTIONS

AE, SS, and DP selected the patients and delineated the volumes of interest. GD, TR, JD, and TL generated the automatic contours. GD, JF, and CN analyzed the data. All authors contributed to the redaction of the manuscript.

REFERENCES

1. Bolla M, Collette L. pT3N0M0 prostate cancer: a plea for adjuvant radiation. *Nat Rev Urol* (2009) 6(8):410–2. doi:10.1038/nrurol.2009.103
2. Thoms J, Goda JS, Zlotta AR, Fleshner NE, van der Kwast TH, Supiot S, et al. Neoadjuvant radiotherapy for locally advanced and high-risk prostate cancer. *Nat Rev Clin Oncol* (2010) 8(2):107–13. doi:10.1038/nrclinonc.2010.207
3. Buge F, Chiavassa S, Hervé C, Rigaud J, Delpon G, Supiot S. Preclinical evaluation of intraoperative low-energy photon radiotherapy using spherical applicators in locally advanced prostate cancer. *Front Oncol* (2015) 5:204. doi:10.3389/fonc.2015.00204
4. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol* (2012) 9(12):688–99. doi:10.1038/nrclinonc.2012.194
5. Michalski JM, Lawton CA, El-Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) 76(2):361–8. doi:10.1016/j.ijrobp.2009.02.006
6. Hwee J, Louie AV, Gaede S, Bauman G, D'Souza D, Sexton T, et al. Technology assessment of automated atlas based segmentation in prostate bed contouring. *Radiat Oncol* (2011) 6:110. doi:10.1186/1748-717X-6-110
7. Lawton CA, Michalski JM, El-Naqa I, Kuban D, Lee WR, Rosenthal SA, et al. Variation in the definition of clinical target volumes for pelvic nodal conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2009) 74(2):377–82. doi:10.1016/j.ijrobp.2008.08.003
8. Lawton CA, Michalski JM, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* (2009) 74(2):383–7. doi:10.1016/j.ijrobp.2008.08.002
9. Livsey JE, Wylie JP, Swindell R, Khoo VS, Cowan RA, Logue JP. Do differences in target volume definition in prostate cancer lead to clinically relevant differences in normal tissue toxicity? *Int J Radiat Oncol Biol Phys* (2004) 60(4):1076–81. doi:10.1016/j.ijrobp.2004.05.005
10. Mitchell DM, Perry L, Smith S, Elliott T, Wylie JP, Cowan RA, et al. Assessing the effect of a contouring protocol on postprostatectomy radiotherapy clinical target volumes and interphysician variation. *Int J Radiat Oncol Biol Phys* (2009) 75(4):990–3. doi:10.1016/j.ijrobp.2008.12.042
11. Jameson MG, Holloway LC, Vial PJ, Vinod SK, Metcalfe PE. A review of methods of analysis in contouring studies for radiation oncology. *J Med Imaging Radiat Oncol* (2010) 54(5):401–10. doi:10.1111/j.1754-9485.2010.02192.x
12. Ost P, De Meerleer G, Vercauteren T, De Gersem W, Veldeman L, Vandecasteele K, et al. Delineation of the postprostatectomy prostate bed using computed tomography: interobserver variability following the EORTC delineation guidelines. *Int J Radiat Oncol Biol Phys* (2011) 81(3):e143–9. doi:10.1016/j.ijrobp.2010.12.057
13. Malone S, Croke J, Roustan-Delatour N, Belanger E, Avruch L, Malone C, et al. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy

IMRT. *Int J Radiat Oncol Biol Phys* (2012) 84(3):725–32. doi:10.1016/j.ijrobp.2011.12.081
14. Beckendorf V, Bachaud J-M, Bey P, Bourdin S, Carrie C, Chapet O, et al. Target-volume and critical-organ delineation for conformal radiotherapy of prostate cancer: experience of French dose-escalation trials. *Cancer Radiother* (2002) 6(Suppl 1):78s–92s. doi:10.1016/S1278-3218(02)00217-2
15. Warfield SK, Zou KH, Wells WM. Simultaneous truth and performance level estimation (STAPLE): an algorithm for the validation of image segmentation. *IEEE Trans Med Imaging* (2004) 23(7):903–21. doi:10.1109/TMI.2004.828354
16. Pekar V, McNutt TR, Kaus MR. Automated model-based organ delineation for radiotherapy planning in prostatic region. *Int J Radiat Oncol Biol Phys* (2004) 60:973–80. doi:10.1016/S0360-3016(04)00964-2
17. Weistrand O, Svensson S. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* (2015) 42(1):40–53. doi:10.1118/1.4894702
18. Dice LR. Measures of the amount of ecologic association between species. *Ecology* (1945) 26:297–302. doi:10.2307/1932409
19. Gardner SJ, Wen N, Kim J, Liu C, Pradhan D, Aref I, et al. Contouring variability of human- and deformable-generated contours in radiotherapy for prostate cancer. *Phys Med Biol* (2015) 60(11):4429–47. doi:10.1088/0031-9155/60/11/4429
20. Larrue A, Gujral D, Nutting C, Gooding M. The impact of the number of atlases on the performance of automatic multi-atlas contouring. *Phys Med* (2015) 31(Suppl 2):e30. doi:10.1016/j.ejmp.2015.10.020

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Delineation of the Prostate Bed: The "Invisible Target" Is Still an Issue?

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For pathological high-risk prostate cancer, adjuvant irradiation has shown a survival benefit. Phase III studies have highlighted that half men would face biochemical relapse and would be candidate for radiotherapy at adjuvant or salvage times. Despite at least four published international contouring guidelines from different collaborative groups, discrepancies remain for volumes, delineation, and margins to be considered in order to optimize radiotherapy planning. This article from "Groupe d'Etude des Tumeurs UroGénitales (GETUG)" members will focus on controversies to help clinicians to create best volume delineation for adjuvant or salvage post prostatectomy radiotherapy.

Keywords: prostate cancer, postoperative, radiotherapy, volume delineation, clinical target volume

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INTRODUCTION

Radiotherapy (RT) after radical prostatectomy (RP) is indicated in the adjuvant setting for patients with high-risk pathological features (1) in the salvage setting at prostate-specific antigen (PSA) relapse or when the PSA remains elevated after RP (2). With long-term follow-up, it has been demonstrated that in 40% of patients treated with adjuvant RT who develop a recurrence, the predominant site remains local (3). The potential reasons for local failure include an inadequate radiation dose and inadequate definition of the clinical target volume (CTV). Successful RT in the era of three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) requires physicians to accurately delineate treatment targets while simultaneously avoiding normal tissue to limit organ at risk (OAR) toxicity. Four consensus guidelines have been published for CTV delineation in postoperative RT. Significant differences exist between these guidelines with respect to CTV delineation. In the postoperative setting where the macroscopic target volume has been removed completely both the delineation of the CTV and the precision of dose delivery become crucial especially when attempting increasing dose, as IMRT allows it. The use of image-guided radiotherapy (IGRT), to optimize patient positioning for postoperative RT, is increasing and is directly derived from accurate target volume definition and appropriate margins (4). This article will focus on CTV delineation discrepancies with modern 3D conformational radiotherapy based on computed tomography (CT) scan or magnetic resonance imaging (MRI) used for planning.

DEFINITION OF CTV FOR PROSTATE BED

For postoperative RT, gross tumor volume (GTV) does not exist clearly in adjuvant setting and it can be hardly estimated, clinically or radiologically, for salvage purpose in condition of a rising PSA

because it remains microscopic most of the time. CTV definition is based from pathological study of the prostate: size of the gland, seminal vesicle (SV) invasion, and location of positive margins (5). This volume corresponds to the prostate bed, and we are going to highlight how challenging is the definition of CTV for the prostate fossa.

CTV Delineation following Locations of Recurrence after RP

Following RP, the rate of biochemical failure is relatively high, >50%, within the first 5 years among patients with pathological high-risk features (positive surgical margins, extracapsular extension, and SV involvement) (6). To determine the optimal CTV for planning, it is necessary to appreciate the most common sites of local relapse after surgery. In few cases, a local relapse can be confirmed by physical examination, TRUS-guided biopsy, MRI, and sometimes choline positron emission tomography (PET). Some studies describe the site of a biopsy proven relapse in the prostatic bed after prostatectomy. For Silverman and Krebs, all the 31 local clinically detected relapses were located at the vesicourethral anastomosis (VUA) (7) and that was the case for 2/3 of the patients in Connolly study (location anterior, posterior or both) (8). Leventis et al. reported 17/31 positive biopsies at the VUA in a TRUS series of 41 biochemically relapsing patients after RP. Other sites of interest were bladder neck and retrovesical space and residual SV (9). Contrast-enhanced, endorectal coil MRI has a high sensitivity and specificity for detecting local recurrence after RP (10, 11). In a study on 48 patients, Sella et al. showed that local recurrences were perianastomotic in 29% of patients, retrovesical in 40%, in residual SV in 22%, and at surgical margins (anterior or lateral) in 9% (10). In a series by Miralbell et al., MRI was capable of documenting a recurrent or residual disease in the setting of PSA levels ranging from 0.05 to 13.3 ng/mL (median: 0.87), typically in the inferior and posterior region of the vesicourethral anastomosis (11). These results from an MRI series of 60 men are consistent with another MRI study showing recurrences largely around the VUA (12). At last, ^{18}F-fluorodeoxyglucose or ^{11}C-acetate PET were tested in 20 consecutive patients with suspected residual or recurrent prostate cancer after RP and with PSA levels of <1 ng/mL with PET/CT co-registration, and 5 and 6 local recurrences were identified, respectively, following techniques used (13). On 33 patients with biological and histopathological evidence of recurrence, focally increased [(11)C]choline uptake in the prostatic bed reliably predicted local low volume occult relapsing prostate adenocarcinoma after RP and identified 71% of patients with a favorable biochemical response to local radiotherapy in a study by Reske et al. (14). These results emphasized similarity, whatever diagnosis methods used, in recurrence location that helps to create a CTV on a planning CT scan, even if correlation between anatomically described location and radiographic positioning remain difficult in a postoperative setting. As described in a comparison between pre- and postsurgery planning CT scan by Sanguinetti et al., the positions of bladder and rectum are shifted in the prostate fossa and the volume of CTV is reduced by 30% after surgery following variations of these anatomical strictures (15). To help clinicians to detect regions of interest (ROI), clips placement by the surgeon during prostatectomy could locate anastomosis between bladder neck and urethra and could be used as fiducial markers for IGRT (4, 16). On the other hand, sometimes the risk of compromising ROI delineation could exist with the great numbers of hemostatic surgical clips placed in the prostate fossa as they can also hinder this identification due to the image artifacts that they can cause. Hence, due to the complexity of CTV definition after surgery (due to changes in anatomy caused by the surgery itself and the limited information on the preoperative location of the prostate), consensus and guidelines for prostate bed delineation became crucial.

Guidelines to Delineate the Prostate Bed

Nowadays, in the literature exists at least four consensus guidelines for postoperative external beam radiotherapy for prostate cancer focusing on CTV consensus guidelines using CT, in the era of 3D-CRT: the European Organization for Research and Treatment of Cancer (EORTC) (17), the Australian and New Zealand Radiation Oncology Genito-Urinary Group [the Faculty of Radiation Oncology Genito-Urinary Group (FROGG-RANZCR)] (18), the Princess Margaret Hospital (PMH) (19), and the Radiation Therapy Oncology Group (RTOG) (20). The CTV definitions based on each consensus are listed and summarized in **Table 1**. Most of them explore two patients' cases scenarios (pT2R1 or pT3a as case 1 and pT3b as case 2) to describe best guidelines recommendations. Of note, each working group developed its CTV definition following a limited number of experts gathered in a delineating task group panels. The FROGG consensus was refined during a consensus conference in June 2006 attended by 63 specialists (radiation oncologists, urologists, diagnosis imaging experts) and issues were developed subsequently in working groups to generate the published guidelines (18). For PMH consensus, 3 experienced urologists then 2 radiation oncologists delineated first boundaries contours for CTV (on CT or MRI), and this result was revised and approved during a GU tumor board meeting gathering 15 medical experts, and second, this proposal was validated by 2 radiation oncologists (19). The EORTC panelist board conducted a review of the likelihood of cancer recurrence from literature to publish its final consensus revised by EORTC members (17). Finally, during an RTOG-sponsored meeting, 11 radiation oncologists delineated prostate fossa CTV (pfCTV) on 2 cases (pT2c R1 with rising PSA and pT3bR0 with undetectable PSA) and their results were matched and statistically compared to finally accept a general agreement concordance (20). It is accepted that CTV should encompass the prostate and the SV surgical bed at risk of harboring microscopic disease or involved following pathological features. The planning process should include then preoperative imaging (CT and/or MRI), intraoperative reports and histopathological findings. The CTV delineation was reported on non-contrast CT (except for FROGG guideline) or CT/MRI images for simulation. The four consensus groups also agree that the vesicourethral anastomosis and periurethral tissue should be treated but they highlight discrepancies in including differently surrounding tissues like bladder or SV bed resulting in a great difference of CTV volume as shown in **Table 1**. The CTV volume from EORTC consensus has been showed to be significantly smaller than the others (21).

TABLE 1 | Description of consensus guidelines.

Protocols/ boundaries	Princess Margaret Hospital	European Organization for Research and Treatment of Cancer (EORTC)	Faculty of Radiation Oncology Genito-Urinary Group (FROGG)-ANZR	Radiation Therapy Oncology Group
Superior	Superior surgical clips if present, or 5 mm above the inferior border of the vas deferens. Retained seminal vesicle (SV) included when pathologically involved	Bladder neck +5 mm in all directions Original site of the base of SV should be included. If SV involved, include original position ± the remnants	Encompass all of the SV bed as defined by non-vascular clips and should include distal portion of the vas deferens. If SV pathologically involved, include any residual SV	Level of cut end of vas deferens or 3–4 cm above top of symphysis. Include SV remnants if pathologically involved
Inferior	8 mm below the vesicourethral anastomosis (VUA) or the top of the PB, whichever is most superior	Apex −15 mm cranially from the PB +5 mm in all directions	5–6 mm below the VUA, but should include all surgical clips inferiorly. If VUA not clearly defined, then slice above the PB	8–12 mm, below VUA, may include more if concern for apical margin. Can extend to slice above PB if VUA not well visualized
Lateral	Caudal: medial border of the levator ani and obturator internus. Cranial: sacrorectogenitopubic fascia	Up to the neurovascular bundles (if removed up to the ilio-obturatic muscles) + 5 mm in all directions	Medial border of the levator ani muscle or obturator internus muscle	Below superior edge of symphysis pubis: levator ani muscles, obturator internus Above superior edge of symphysis pubis:sacrorectogenitopubic fascia
Anterior	Caudal: posterior edge of the symphysis pubis up to the top of the symphysis pubis. Cranial: posterior 1.5 cm of the bladder wall	Anastomosis and urethral axis +5 mm in all directions	Lower border of clinical target volume (CTV) to 3 cm superior, posterior aspect of the symphysis pubis. More superiorly: posterior 1.5 cm of the bladder	Below superior edge of symphysis pubis: posterior edge of pubic bone. Above superior edge of symphysis pubis: posterior 1–2 cm of bladder wall
Posterior	Caudal: anterior border of the rectal wall and levator ani. Cranial: mesorectal fascia	Up to but not including the outer rectal wall, cranially including the most posterior part of the bladder neck +5 mm in all directions	Levator ani and anterior rectal wall. More superiorly, anterior mesorectal fascia	Below superior edge of symphysis pubis: anterior rectal wall Above superior edge of symphysis pubis: mesorectal fascia
CTV (cm^3)	104 ± 25	60 ± 17	88 ± 16	102 ± 24

The caudal border is defined in the EORTC guidelines as 15 mm above the penile bulb or at the apex of the prostate whereas FROGG and PMH guidelines suggest that it should be 5–6 and 8–12 mm below the VUA, respectively. For RTOG group, the inferior treatment volume should end immediately superior to the penile bulb and it employs sagittal reconstruction to identify the most inferior urine in the bladder. At mid plan, all four consensus advocate the region extending anteriorly to posteriorly from the pubic symphysis to the rectum should be included. The superior border is also controversial following these guidelines: FROGG guidelines suggest the volume encompassing the entire SV bed and distal portion of the vas deferens; the bladder neck for EORTC guideline; the superior surgical clip or 5 mm above the vas deferens for PMH guideline; and the level of the cut end of vas deferens or 3–4 mm above the top of the symphysis in the RTOG guideline. The EORTC does not include the bladder in its CTV definition while the RTOG, FROGG, and PHM groups include 1.5 cm of posterior bladder and bladder wall. A special focus seems interesting with the recommendations to include or not the SV bed following VS invasion or not (pT2–pT3a/pT3b): for RTOG guideline, the VS bed should be delineated based on surgical clip visualization or VS remnants partially in case of pT2 or pT3a at apex and pT3a at the base or involvement of VS required inclusion of the SV remnants totally; for PHM guideline in case of pT2–pT3a, the superior boundary is the superior surgical clip or 5 mm above the inferior border of the vas deferens and retained VS are included in case of pT3b but with 1 cm extension beyond the gross recurrent disease; for FROGG guideline, pT2–pT3a case should include VS bed and any residual VS should be included in CTV delineation in case of pT3b; and for EORTC guideline, the site of the base of VS should be included in any case with a 5 mm in all directions to account for microscopic extension, with the original location of VS in case of pT3b.

CTV Delineation Using Multiparametric MRI

The previous four consensus guidelines were published considering CT as reference imaging system except for PHM guideline that used postoperative MRI to contribute in CTV delineation if local recurrence was detected. Multiparametric MRI scans (T2-weighted and dynamic contrast-enhanced images) have been shown to be an effective tool for evaluation of the prostatic fossa and to detect local recurrence (11, 22). As published guidelines propose to include the cut end of the vas deferens (RTOG, PHM) as a distinct postoperative feature, this organ is visible on MRI (22). Furthermore, postoperative findings of the SV are highly variable, and it has been showed by Sella et al. that in a postoperative MRI study, 20% of the patients had SV remnants, with similar location of the preoperative SV position, with an additional 38% with fibrotic SV tips (10). In most European countries, a preoperative MRI is not still routinely carried out as part of the workup before RP. Croke et al. looked on 20 patient candidates for postoperative RT

whose preoperative staging MRIs were fused with postoperative planning CT scans on whom the 4 CTV delineation guidelines had been applied previously. In all the 20 cases, the CTVs from guidelines did not cover the MRI-defined prostate generating an average prostate volume geographic miss of 35% (23). A second study on 30 patients analyzed CTVs contoured from RTOG Consensus guidelines (CTV RTOG) to CTV based on preoperative MRI (CTV MRI). CTV MRI was a mean of 18.6% larger than CTV RTOG with a mean volume of 138 cc versus 116.3 cc, respectively (24). On 10 patients MRI-detected biopsy proven local tumor recurrence with postprostatectomy prostate cancer, Wang et al. showed that in the superoinferior direction, recurrences ranged from the superior retrovesical region, to the inferior retrovesical region, to the posterior anastomosis, and as inferiorly as the posterior urogenital diaphragm. They reported that RTOG CTV contours did not appear adequate posterolaterally near the rectum/mesorectal fascia and at the posterior urogenital diaphragm inferiorly (25).

Potential benefit of postoperative MRI is to enable a clinician to better delineate areas of identified local recurrence. Based on a study of 113 patients diagnosed with prostate cancer recurrence by MRI scan, Park et al. showed that almost 95% lesions were located within 10 mm of the midline. With the use of the inferior border of the pubic symphysis as a reference point they showed that 87.3% lesions were located within 30 mm in the cranial direction from the reference point (12). For pT2–pT3a patients, VUA site and bladder neck represented most recurrence locations whereas for pT3b patients VUA site and retrovesical area were predominant. Hence, the authors recommended optimal CTV guidelines based on the pattern of local recurrence detected with an MRI acquired before salvage RT (SRT) and they displayed a CTV suggestion encompassing 97% of suspected tumor recurrences (representing a mean CTV volume of 15 ± 5 cm^3). A similar study was conducted by Miralbell et al., and they suggested a 4×3 cm sized, cylindrically shaped CTV, centered 5 mm posteriorly and 3 mm inferior to the VUA site (11).

ONGOING TRIALS FOR POSTOPERATIVE PROSTATE CANCER RADIOTHERAPY

Radiotherapy might have a meaningful benefit after RP, but there are no good data on the optimum timing of RT (26). A policy of adjuvant RT would result in significant overtreatment, while an early SRT policy might be equally effective. Likewise the optimum duration of HT combined with RT after RP is an important issue. Hence, different collaborative groups worldwide have started randomized controlled trials (RCT) to assess the benefit of RT ± HT and its best timing between adjuvant or salvage settings (see **Table 2**). These prospective studies are currently using a delineation policy following one of the already published guidelines.

In France, GETUG members set up a meeting with 12 radiation oncologists held on 5 March 2008 for contouring session in postoperative prostate cancer. These results were published in French for CTV delineation (27) and atlas (28) and a report of the GETUG guidelines are listed in **Table 2**. This workshop helped to create CTV planning for the already published GETUG-AFU 16 study (29) and for the ongoing GETUG-AFU studies: GETUG-AFU 22 (questioning RT vs RT + HT for early SRT, NCT01994239) in a phase II study and GETUG-AFU 17 (adjuvant versus salvage treatment with a combination of RT and HT, NCT00667069) in a phase III study.

Interestingly, the important number of RCT could validate guidelines used as reference for contouring in a prospective setting and might help clinicians to choose among these protocols the best to cope with postoperative RT.

DISCUSSION

The debate to promote adjuvant or SRT is still an important issue and prostate bed target delineation remains in this context difficult as location and size of recurrences can be different (i.e., being macroscopically detectable by MRI) with time from PR. Considering the four published guidelines, anyone should be aware that despite different methods used some aspects remained similar and others showed discrepancies especially in volume delimitations, including also GETUG guidelines (17–20). Moreover, definition of recurrences to limit target contouring from these guidelines comes from macroscopic imaging description, generally assessed lately in the history of postoperative RT indication (30). These discrepancies explain why there are so different CTV volumes among these four guidelines and a comparison of theses four consensus has been carried out in a Canadian study (16). For each patient of the 20 treated in this study, a CTV delineation following these four guidelines was performed and analyzed. Results showed that EORTC-CTV covered a larger volume of normal tissue posteriorly (more rectal volume) than the other guidelines. A greater coverage of the bladder was noticed for RTOG/PMH-CTV compared to EORTC-CTV (21). The inherent difficulty in defining the "virtual" prostate bed target is reflected in the presence of interobserver variability in the delineation of the prostate bed that appears to persist even despite the use of rigorous contouring protocols and guideline (31, 32). Ost et al. assessed interobserver agreement (six observers participated in this study) of prostate bed delineation using CT alone as proposed by EORTC guidelines and found a moderate agreement with an overall standard deviation of the outer margins ranged from 4.6 to 7 mm (31). For Symon et al., 38 pfCTV were delineated on postradical prostatectomy CT scans of 8 patients by 5 observers. Interphysician variability was considerable with a mean pfCTV of 39.09 cm (range, 11.8–72.5 cm). pfCTV delineation was subject to considerable interobserver variability associated with a significant risk of inadequate targeting of the anastomosis/bladder neck region and the retrovesical space (32).

The validation of existing consensus through ongoing clinical trials arose the need for high quality assurance (QA) program. The practice of dummy run (DR) in RCT has already be shown as an efficient tool for QA optimization (33). In order to assess the compliance to the 3D-CRT protocol guidelines, 30 participating centers were requested to participate in a DR procedure for the EORTC trial 22991 and patients files harbored no major protocol

TABLE 2 | Overview of ongoing phase III studies on postoperative RT.

Protocols	Randomization/RT dose	Guidelines used in trials				
RAVES (NCT00860652)	ART commenced at ≤4 months of RP or early SRT triggered by a PSA level of >0.20 ng/mL RT dose 64 Gy	FROGG guidelines				
Radiation Therapy Oncology Group (RTOG) 0534 (NCT00567580)	SRT with or without HT 6 months or pelvic fields RT dose 64.8–70.2 Gy prostate bed and 45 Gy pelvic lymph node	RTOG guidelines				
GETUG-AFU 17 (NCT00667069)	ART vs SRT with 6 months HT RT dose 66 Gy/33 Fract	GETUG guidelines				
		Superior	Inferior	Lateral	Anterior	Posterior
		Include VUA, bladder neck and prostate fins laterally. 4.5–5 cm above penile bulb, fatty space between bladder and rectum is delineated. In case of SV invasion or pT3a at prostate base, SV bed should be included on 1,5–2 cm high with rectum wall to be spared	5–10 mm above the penile bulb	Medial border of the levator ani muscle	To posterior part of cavernous corpus to 1/3 superior zone of pubic symphysis and bladder neck	From anal canal to anterior rectal wall and mesorectal fascia with a posterior limit following prostate fins
RADICALS (NCT00541047)	First randomization: ART or SRT Second randomization: RT only/RT + HT 6 months/RT + HT 24 months RT dose 66 Gy/33 Fract or 55 Gy/20 Fract	RADICALS guidelines modified from Wiltshire and colleagues				
EORTC 22043 (NCT00949962)	ART or SRT with or without HT 6 months	EORTC guidelines				
SAKK 09/10 (NCT01272050)	SRT with RT dose 64 or 70 Gy	EORTC guidelines				
MAPS (NCT01411345)	SRT with or without boost RT dose 68 Gy or 74.8 Gy/34 Fract	–				

ART, adjuvant RT; SRT, salvage RT; RP, radical prostatectomy; PSA, prostate-specific antigen; HT, hormonal treatment; VUA, vesicourethral anastomosis; SV, seminal vesicle; Fract, fractions; GETUG, Groupe d'Etude des Tumeurs UroGénitales; RT, radiotherapy.

deviation (34). The SAKK 09/10 study including a site-specific and study-specific questionnaire and a DR, following EORTC contouring guidelines. In the first submitted version of the DR, major deviations were noted for 70% of the centers. These results were improved after DR completion for 83% of the centers in this study. A moderate interobserver agreement was noticed in prostate bed delineation initially, and DR protocol achieved to improve the acquaintance of the participating centers with the trial protocol (35).

Education can be useful to correct for existing discrepancies and to drive professionals toward a harmonization of practice. Mitchell et al. had showed that interclinicians variability in target volume outlining existed but adherence to evidence-based protocol (RADICALS protocol) can achieve reduction in this variability (36). Pasquier et al. conducted in 11 RT centers a prospective work to improve homogeneity of delineation of volume of interest on 3 clinical cases of which a case for a postoperative prostate cancer (37). After collecting each initial delineated volume and comparing these volumes with validated indexes [volume ratio (VR), volume overlap, and Dice similarity coefficient (DSC)], a second delineation was secondly performed after discussion of the slice results. For the selected case, VR and AV were significantly improved and DSC remained high, so the authors showed that a collaborative discussion about clinical case and the choice of shared guidelines (RTOG in this article) could improve the homogeneity of CTV delineation (37). Another study from the same team analyzed automated atlas-based segmentation supplied by software vendors compared to radiation oncologist contours for prostate bed cases. They showed that these algorithms for segmentation were essentially aimed to delineate OAR (high-contrast organs) and were insufficient for prostate bed contours (38).

CONCLUSION

Adjuvant or SRT in the era of 3D-CRT or IMRT are based on optimal contouring methods to avoid geographic miss in an invisible target. Delineating the prostate bed remains an issue as current CTV consensus definitions do not adequately cover the prostate bed and/or GTV based on preoperative imaging. These published guidelines based on postoperative CT ± MRI imaging, even if discrepancies between them exist, have played an important role for professional support. Adopting one of them as a standard of care in its own practice provide better delineation homogeneity

and best covering of the entire surgical bed in postoperative radiotherapy. This statement might be relevant as long as ongoing clinical trials carry new standard of care and might emphasize which guideline offer the most appropriate long-term local control following postoperative prostate cancer radiotherapy with an acceptable toxicity profile.

AUTHOR CONTRIBUTIONS

IL wrote the manuscript, reviewed it, and sent it to the correspondent author; responsible for charts. PS reviewed the manuscript and made corrections. GL, SS, SG, and CC reviewed the final manuscript. SS is in charge for topic selection.

REFERENCES

1. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) 181:956–62. doi:10.1016/j.juro.2008.11.032
2. Valicenti RK, Thompson I Jr, Albertsen P, Davis BJ, Goldenberg SL, Wolf JS, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. American Society for Radiation Oncology/American Urological Association. *Int J Radiat Oncol Biol Phys* (2013) 86(5):822–8. doi:10.1016/j.ijrobp.2013.05.029
3. Swanson GP, Riggs M, Hermans M. Pathologic findings at radical prostatectomy: risk factors for failure and death. *Urol Oncol* (2007) 5:110–44. doi:10.1016/j.urolonc.2006.06.003
4. Vilotte F, Antoine M, Bobin M, Latorzeff I, Supiot S, Richaud P, et al. Post-prostatectomy image-guided radiotherapy: the invisible target concept. *Front Oncol* (2017) 7:34. doi:10.3389/fonc.2017.00034
5. Cox J, Gallagher M, Hammond E, Kaplan RS, Schellhammer PF. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology Oncology Consensus Panel. *J Clin Oncol* (1999) 17:1155.
6. Zietman AL, Coen JJ, Shipley WU, Willett CG, Efird JT. Radical radiation therapy in the management of prostatic adenocarcinoma: the initial prostate specific antigen value as a predictor of treatment outcome. *J Urol* (1994) 151:640–5.
7. Silverman JM, Krebs TL. MR imaging evaluation with a transrectal surface coil of local recurrence of prostatic cancer in men who have undergone radical prostatectomy. *AJR Am J Roentgenol* (1997) 168(2):379–85. doi:10.2214/ajr.168.2.9016212
8. Connolly JA, Shinohara K, Presti JC Jr, Carroll PR. Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. *Urology* (1996) 47:225–31. doi:10.1016/S0090-4295(99)80421-X
9. Leventis AK, Shariat SF, Slawin KM. Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. *Radiology* (2001) 219:432–9. doi:10.1148/radiology.219.2.r01ma20432
10. Sella T, Schwartz LH, Swindle PW, Onyebuchi CN, Scardino PT, Scher HI, et al. Suspected local recurrence after radical prostatectomy: endorectal coil MR imaging. *Radiology* (2004) 231(2):379–85. doi:10.1148/radiol.2312030011
11. Miralbell R, Vees H, Lozano J, Khan H, Mollà M, Hidalgo A, et al. Endorectal MRI assessment of local relapse after surgery for prostate cancer: a model to define treatment field guidelines for adjuvant radiotherapy in patients at high risk for local failure. *Int J Radiat Oncol Biol Phys* (2007) 67:356–61. doi:10.1016/j.ijrobp.2006.08.079
12. Park JS, Park W, Pyo HR, Park BK, Park SY, Choi HY, et al. Suggestion for the prostatic fossa clinical target volume in adjuvant or salvage radiotherapy after a radical prostatectomy. *Radiother Oncol* (2014) 110(2):240–4. doi:10.1016/j.radonc.2014.01.001
13. Vees H, Buchegger F, Albrecht S, Khan H, Husarik D, Zaidi H, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. *BJU Int* (2007) 99(6):1415–20. doi:10.1111/j.1464-410X.2007.06772.x
14. Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging* (2008) 35(1):9–17. doi:10.1007/s00259-008-0839-5
15. Sanguineti G, Castellone P, Foppiano F, Franzone P, Marcenaro M, Tognoni P, et al. Anatomic variations due to radical prostatectomy. Impact on target volume definition and dose-volume parameters of rectum and bladder. *Strahlenther Onkol* (2004) 180(9):563–72. doi:10.1007/s00066-004-1245-y
16. Song S, Yenice KM, Kopec M, Liauw SL. Image-guided radiotherapy using surgical clips as fiducial markers after prostatectomy: a report of total setup error, required PTV expansion, and dosimetric implications. *Radiother Oncol* (2012) 103(2):270–4. doi:10.1016/j.radonc.2011.07.024
17. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, 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(2):121–7. doi:10.1016/j.radonc.2007.07.017
18. Sidhom MA, Kneebone AB, Lehman M, Wiltshire KL, Millar JL, Mukherjee RK, et al. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol* (2008) 88(1):10–9. doi:10.1016/j.radonc.2008.05.006
19. Wiltshire KL, Brock KK, Haider MA, Zwahlen D, Kong V, Chan E, et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. *Int J Radiat Oncol Biol Phys* (2007) 69(4):1090–9. doi:10.1016/j.ijrobp.2007.04.068
20. Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) 76(2):361–8. doi:10.1016/j.ijrobp.2009.02.006
21. Malone S, Croke J, Roustan-Delatour N, Belanger E, Avruch L, Malone C, et al. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. *Int J Radiat Oncol Biol Phys* (2012) 84(3):725–32. doi:10.1016/j.ijrobp.2011.12.081
22. Allen SD, Thompson A, Sohaib SA. The normal post-surgical anatomy of the male pelvis following radical prostatectomy as assessed by magnetic resonance imaging. *Eur Radiol* (2008) 18:1281–91. doi:10.1007/s00330-008-0867-3
23. Croke J, Malone S, Roustan Delatour N, Belanger E, Avruch L, Morash C, et al. Postoperative radiotherapy in prostate cancer: the case of the missing target. *Int J Radiat Oncol Biol Phys* (2012) 83(4):1160–8. doi:10.1016/j.ijrobp.2011.09.039
24. Croke J, Maclean J, Nyiri B, Li Y, Malone K, Avruch L, et al. Proposal of a post-prostatectomy clinical target volume based on pre-operative MRI: volumetric and dosimetric comparison to the RTOG guidelines. *Radiat Oncol* (2014) 9:303. doi:10.1186/s13014-014-0303-6
25. Wang J, Kudchadker R, Choi S, Pettaway CA, Choi H, Hobbs BD, et al. Local recurrence map to guide target volume delineation after radical prostatectomy. *Pract Radiat Oncol* (2014) 4(6):e239–46. doi:10.1016/j.prro.2014.02.007
26. Guérif S, Latorzeff I, Lagrange JL, Hennequin C, Supiot S, Garcia A, et al. [Postoperative radiotherapy of prostate cancer]. *Cancer Radiother* (2014) 18(5–6):517–23. doi:10.1016/j.canrad.2014.07.149
27. Richaud P, Sargos P, Henriques de Figueiredo B, Latorzeff I, Mongiat-Artus P, Houédé N, et al. [Postoperative radiotherapy of prostate cancer]. *Cancer Radiother* (2010) 14(6–7):500–3. doi:10.1016/j.canrad.2010.07.224
28. Vieillot S, Fenoglietto P, Ailleres N, Hay MH, Dubois JB, Azria D. Postoperative radiotherapy for prostate cancer. *Cancer Radiother* (2010) 14(Suppl 1):S174–81. doi:10.1016/S1278-3218(10)70021-4
29. Carrie C, Hasbini A, de Laroche G, Richaud P, Guerif S, Latorzeff I, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* (2016) 17(6):747–56. doi:10.1016/S1470-2045(16)00111-X

30. Hernandez D, Salas D, Giménez D, Buitrago P, Esquena S, Palou J, et al. Pelvic MRI findings in relapsed prostate cancer after radical prostatectomy. *Radiat Oncol* (2015) 10:262. doi:10.1186/s13014-015-0574-6
31. Ost P, De Meerleer G, Vercauteren T, De Gersem W, Veldeman L, Vandecasteele K, et al. Delineation of the postprostatectomy prostate bed using computed tomography: interobserver variability following the EORTC delineation guidelines. *Int J Radiat Oncol Biol Phys* (2011) 81(3):e143–9. doi:10.1016/j.ijrobp.2010.12.057
32. Symon Z, Tsvang L, Wygoda M, Ben-Yoseph R, Corn BW, Poortmans P, et al. An interobserver study of prostatic fossa clinical target volume delineation in clinical practice: are regions of recurrence adequately targeted? *Am J Clin Oncol* (2011) 34(2):145–9. doi:10.1097/COC.0b013e3181d2edc3
33. Fairchild A, Collette L, Hurkmans CW, Baumert B, Weber DC, Gulyban A, et al. Do results of the EORTC dummy run predict quality of radiotherapy delivered within multicentre clinical trials? *Eur J Cancer* (2012) 48(17):3232–9. doi:10.1016/j.ejca.2012.06.002
34. Matzinger O, Poortmans P, Giraud JY, Maingon P, Budiharto T, van den Bergh AC, et al. EORTC Radiation Oncology Group. Quality assurance in the 22991 EORTC ROG trial in localized prostate cancer: dummy run and individual case review. *Radiother Oncol* (2009) 90(3):285–90. doi:10.1016/j.radonc.2008.10.022
35. Sassowsky M, Gut P, Hölscher T, Hildebrandt G, Müller AC, Najafi Y, 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(3):534–41. doi:10.1016/j.ijrobp.2013.06.2053
36. Mitchell DM, Perry L, Smith S, Elliott T, Wylie JP, Cowan RA, et al. Assessing the effect of a contouring protocol on postprostatectomy radiotherapy clinical target volumes and interphysician variation. *Int J Radiat Oncol Biol Phys* (2009) 75(4):990–3. doi:10.1016/j.ijrobp.2008.12.042
37. Pasquier D, Boutaud de la Combe-Chossiere L, Carlier D, Darloy F, Degrendel-Courtecuisse AC, Dufour C, et al. Harmonization of the volume of interest delineation among all eleven radiotherapy centers in the North of France. *PLoS One* (2016) 11(3):e0150917. doi:10.1371/journal.pone.0150917
38. Delpon G, Escande A, Ruef T, Darréon J, Fontaine J, Noblet C, et al. Comparison of automated atlas-based segmentation software for postoperative prostate cancer radiotherapy. *Front Oncol* (2016) 6:178. doi:10.3389/fonc.2016.00178

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MINI REVIEW
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Gaps between Evidence and Practice in Postoperative Radiotherapy for Prostate Cancer: Focus on Toxicities and the Effects on Health-Related Quality of Life

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Adjuvant radiotherapy (ART) after prostatectomy for patients with high-risk features [extracapsular extension (ECE), seminal vesicle invasion (SVI), and positive margin] has been shown to be associated with improved biochemical disease-free survival in three large randomized trials and with improved overall survival in one. Similarly, salvage radiotherapy (SRT) can effectively achieve biochemical control in a significant proportion of patients with a rising PSA after surgery. Nonetheless, both approaches of postoperative RT remain highly underutilized. This might be partly due to concerns with overtreatment inherent to adjuvant approaches, and/or hesitance about causing radiation toxicities and their subsequent effects on the patient's quality of life. Herein, we review the literature lending evidence to these arguments. We show recent series of ART/SRT and their low rates of acute and long-term toxicities, translating only in transient decline in quality-of-life (QoL) outcomes. We conclude that concerns with side effects should not preclude the recommendation of an effective and curative-intent therapy for men with prostate cancer initially treated with radical surgery.

Keywords: prostate cancer, adjuvant, salvage, radiotherapy, quality of life, toxicities

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INTRODUCTION: ROLE OF ADJUVANT AND SALVAGE RADIOTHERAPY AFTER PROSTATECTOMY AND THE UNDERUTILIZATION PROBLEM

There were approximately 220,800 new cases of prostate cancer (PCa) diagnosed only in the US in 2015, with 27,540 patients dying from the disease (1). According to a recent analysis based on SEER data, 90% of prostate cancer cases in the US are diagnosed in localized stages, and 40% of these are treated with radical prostatectomy (2). After surgery alone, 30–40% of patients will experience biochemical failure (3–5), and one-third of recurrent cases will be subsequently diagnosed with metastatic disease (6). Nonetheless, death from prostate cancer remains infrequent, and cancer-specific survival rates are above 90% after 15 years of surgery alone (5).

In order to decrease the risk of biochemical failure, particularly in patients with high-risk features (including positive surgical margins, high grade disease, and/or pT3-stage) (7), postoperative

radiotherapy has been studied and shown efficacious. Three randomized trials from cooperative groups (SWOG-8794, EORTC 22911, and ARO 96-02) have demonstrated significant biochemical disease-free survival improvement with adjuvant radiotherapy for patients with high-risk features (8–11). Moreover, one of these trials showed superior overall survival in the radiation arm (11). Given these benefits, adjuvant radiotherapy in high-risk patients has been endorsed and recommended by practice guidelines from leading European and North American societies (12–14).

In patients presenting with biochemical recurrence (rising PSA) after prostatectomy, salvage radiation has been reported to achieve an overall biochemical response rate of 50%, translating into a threefold increase in prostate cancer specific survival (15). However, long-term disease control rates are highly variable, ranging from 10 to 40%, mostly due to the intrinsic patients' heterogeneity in this high-risk population. To date, there is lack of robust predictive markers to identify those with PSA increase due to local recurrence (who are likely to benefit from salvage radiation) from those with already microscopic distant spread (in whom further local therapies is likely futile) (16, 17). At present, no prospective study has directly compared ART vs. SRT approaches. Although such efforts are currently underway, the optimal postoperative RT timing conundrum remains a topic of controversy (18).

Despite the demonstrated benefits of both adjuvant and salvage radiotherapy, these treatments remain strikingly underutilized, with <15% of eligible patients with high-risk features receiving radiotherapy across different jurisdictions (19–25). Moreover, during the last decade, the absolute utilization rates have not significantly changed despite the publication of the three large ART randomized trials (21, 24, 26), notwithstanding the fact that recommendation for the use of adjuvant radiation has increased (25). This discrepancy between evidence and practice is more pronounced in older patients, plausibly due to the uncertainty about treatment benefits in the context of a shorter life span and/or higher comorbidities (21).

To explain this underutilization, some plausible reasons have been suggested in relation to the pivotal trials' design and outcomes. Related to design, the comparison of ART with observation instead of early SRT (19), not ascertaining the use or timing of SRT in the observation arm, and the inclusion of patients with detectable PSA pre-ART (27) have been mainly discussed. Regarding outcomes, particularly the absence of survival benefit in two of the trials has been highlighted, with improvements shown only in SWOG study, which could have been confounded by comorbidities in the control group (28). Additionally, physician's specialty appears also to influence ART/SRT use, as demonstrated by urologists being less likely to recommend it compared to radiation oncologists (29, 30). Patient factors, such as age, comorbidities, and life expectancy estimates, have also been suggested to influence endorsement of post-prostatectomy radiation (21).

However, current literature has mostly focused on two major reasons for withholding or deferring the use of postoperative radiotherapy, namely, concerns with overtreatment and radiation toxicities with their subsequent impact on patient's quality of life. To better understand the delay in practice change, herein, we summarize the literature focusing on these two potential factors. The evidence presented here could also serve to guide treatment individualization and shared decision-making between physicians and patients regarding curative-intent adjuvant and salvage radiotherapy after radical prostatectomy.

Avoiding Overtreatment or Favoring Undertreatment? Nuances until Superiority (or Non-Inferiority) of SRT Is Proven

Although the bulk of evidence supports the use of immediate postoperative radiation, its proper timing is a matter of debate (28) mainly due to the concerns related to the possibility of overtreatment with early adjuvant radiation. A considerable proportion of high-risk patients achieve good disease control with surgery alone, with slightly over half of them remaining free from biochemical failure at 5 years (10, 31). In patients with adverse pathological features, such as ECE, positive margins, and SVI, the 10-year progression-free probability can be as high as 71, 44, and 37%, respectively (32, 33). Therefore, the alternative concept of delaying radiotherapy to the time of recurrence (i.e., rising PSA) has been proposed by some as an effective method to provide the same results while avoiding the intrinsic overtreatment risk of adjuvant approaches (16).

This treatment strategy, at present time, is supported by retrospective evidence (34), and as the core, assumes that SRT or delayed ART could be as effective as immediate ART (26). Indeed, a pooled analysis of 10 SRT studies has yielded bRFR rates similar to historic reports of adjuvant radiation (71 vs. 67–74%, respectively) (34). However, this indirect comparison in the absence of randomized prospective data cannot safely answer whether early salvage is really equivalent to adjuvant radiation. In fact, matched group analyses have shown superiority of adjuvant over salvage radiotherapy with regards to freedom from biochemical failure (35–37). Solving this clinical conundrum is the objective of ongoing phase III trials, including RADICALS (34), RAVES (35), and GETUG-17 (http://ClinicalTrials.gov identifier NCT00667069), from which informative results will likely be available in the upcoming decade.

Although SRT approaches might be inferior to ART in general, within the former, earlier rather than delayed salvage has shown superior outcomes. The aforementioned pooled analysis on retrospective studies demonstrates improved 5-year biochemical relapse-free survival with early salvage compared to delayed salvage radiation, with improved outcomes in those patients with a PSA level of <0.5 ng/ml. Other studies have suggested different threshold values (34, 38, 39). Acknowledging that within SRT approach, earlier salvage renders more favorable results, the comparison with adjuvant radiation remains unclear given the lack of prospective studies. In addition, clinically applicable and validated PSA thresholds have been hard to determine. The available cutoff points below which SRT is assumed to be equal to ART mostly represent study-specific statistical considerations and might not be used to guide clinical practice until properly validated in a prospective fashion.

Intention to avoid potential overtreatment inherent to adjuvant approaches is a longing that is not exclusive to prostate cancer (40), and one of the principles of personalized cancer treatments is to tailor management to each patient's disease and individual unique characteristics. When robust and consistent evidence supports the use of adjuvant treatment, the goal for avoiding overtreatment should be to precisely identify those patients in whom the treatment is futile, without precluding *a priori* a significant proportion of patients to derive benefit from such therapy. This requires prospective studies with sufficient follow-up (41), which at present are lacking in postoperative prostate cancer setting. A similar scenario was experienced in determining the role of axillary node dissection in breast cancer patients with positive sentinel node biopsy. Almost 7000 patients were randomized in three separate trials [IBCSG 23-01 (42), AOCSOG Z0011 (43), and EORTC 10981-22023-AMAROS (44)] before a conclusion could be reached regarding the subset of patients where elimination of axillary dissection is safely warranted.

Even if justified, favoring delayed over adjuvant radiotherapy does not seem sufficient to explain the overall low utilization of radiotherapy in post-prostatectomy setting. In a recent US nation-wide practice analysis, the use of immediate (ART) and delayed (SRT) was relatively stable over time, with only a slight increase in delayed RT between 2007 and 2009 (24). Contrary to this, another study has reported a minimal shift toward earlier radiation after the publication of the ART randomized studies (23). These findings together challenge the assertion that the underutilization of ART is due to increased use of SRT, and it seems safe to state that neither immediate nor delayed radiation has been increasingly used despite large trials demonstrating benefits. In current practice, some patients are being precluded of a potentially curable treatment for PCa after initial radical prostatectomy.

Concerns with Radiation Toxicities: How Much More Evidence Is Needed?

Radiation toxicities and their impact on the quality of life (20, 45) might be another deterrent for the use of ART/SRT. This, in part, can be explained by EORTC and SWOG trials' reports of increased incidence of late toxicities in the adjuvant RT arm (8, 9). In EORTC trial, grade 2 or higher late GU toxicity was significantly higher in radiation arm (21.3 vs. 13.5%), but late grade 2 GI toxicity rates were similar. Nonetheless, more clinically relevant grade 3 side effects were not significantly different between the two arms (2.5–5%), and no grade 4 events were reported (8). Although the SWOG trial did not report graded toxicity, complications were generally more frequent in the radiation arm (23.8 vs. 11.9%), mainly due to rectal complications (3.3 vs. 0%) and urethral strictures (17.8 vs. 9.5%) (9). Although ART seems to double the relative risk of complications as compared to observation, the absolute rates of long-term toxicities remain low, particularly for high grade side effects. From a benefit/risk analysis based on these early studies, the NNT for improving biochemical relapse rates (1.6 at 10 years) remains significantly better than the NNH (5 for grade 2 or higher and 20 for grade 3 or higher) to present any toxicity during 10-year follow-up.

Both EORTC and SWOG trials used conventional two-dimensional radiotherapy planning (e.g., four-field box), which does not represent state-of-the-art radiation oncology practice. Over the last decade, various and significant technological innovations have been realized in radiation planning and delivery (46). The advent of high-precision radiotherapy has positively impacted the delivery of lower doses to surrounding normal tissues and the subsequent risk of toxicities. With intensity-modulated radiotherapy (IMRT), even more conformal planning is feasible compared to three-dimensional radiotherapy (3DCRT), translating in improved early GI/GU (47) and late GI toxicity profiles (48). Moreover, daily image guidance added to IMRT planning for accurate delivery allows prioritizing rectal dose constraints over target volume coverage. When tested in a recent phase II trial, this technique translated in excellent biochemical control without grade 3–4 acute or late toxicities (45). Although longer follow-up is warranted, the implementation of modern radiotherapy techniques in the post-prostatectomy setting will likely reflect in declining rates of long-term toxicities and subsequent QoL impact, as have indeed been observed in other PCa radiotherapy scenarios (49). Whereas no randomized study has directly compared the toxicities of conventional vs. high-precision planning (and it is unlikely to be conducted), **Table 1** summarizes and contrasts the results of benchmark randomized trials and contemporary studies employing state-of-the-art radiotherapy techniques, reporting the toxicity profile of postoperative radiotherapy. Despite variations among groups in the definition of target volumes, doses, and radiation techniques, a very low rate of high grade acute or chronic toxicities is consistent across studies. The majority of adverse events are grade 2, and none of the available reports have described grade 4 toxicities.

There is very limited literature on the quality of life (QoL) and/or patient-reported outcomes after postoperative radiotherapy (**Table 2**). Moreover, the methodology for measuring and reporting QoL is not uniform, which further limits drawing definite conclusions. After radiation, the available longitudinal data show a transient decline in GI and GU QoL indicators, particularly during the first months. With longer follow-up (e.g., 3–12 months after ART/SRT), QoL metrics return to patient's pre-radiation baseline or become comparable to reference values in GI, GU, and sexual domains. However, among the studies quantifying long-term symptoms and their impact on QoL, the results are not fully consistent. In the study by Moinpour et al. (50) reporting QoL of SWOG trial's participants, bowel tenderness and urgency were significantly higher in radiation arm (47 vs. 5% at 6 weeks); however, this negative impact of ART was transient, and no difference between treatment arms was present after 2 years. Pinkawa et al. also report higher rates of bowel bother at a follow-up longer than 12 months, although the mean decrease in score is 4 points compared to baseline (90 vs. 94) (67). This long-term detrimental impact in GI-related QoL has not been observed in other studies. The SWOG quality-of-life analysis also reported long-term impact on urinary frequency subscale (50), where patients reported 15% more frequent urination over the follow-up duration (5 years). Again, this effect trend has not been observed in other reports. Overall differences between these two earlier and the most recent studies could in part be explained by

TABLE 1 | Summary of post-prostatectomy radiotherapy studies, outcomes, and toxicities.

Study	Prospective	Number of patients, median follow-up	Technique, total dose	bRFR	Acute G ≥ 2 toxicity (%)		Acute G3–4 toxicity (%)		Late G ≥ 2 toxicity (%)		Late G3–4 toxicity (%)		Change in ED (%)
					GU	GI	GU	GI	GU	GI	GU	GI	
Thompson et al. (9)/ Moinpour et al. (50)	Yes (RCT)	425, 10.6 years	Conventional, 60–64 Gy	65.1% (ART) vs. 36% (Obs) (10 years)	NR	NR	NR	NR	24.3[a]	3.3[a]	NR	NR	NR
Bolla et al. (8)	Yes (RCT)	1005, 10.6 years	Conventional, 60 Gy	60.6% (ART) vs. 41.1%(Obs) (10 years)	NR	NR	NR	NR	21.3	2.5	5.3		NR
Wiegel et al. (10)	Yes (RCT)	385, 53.7 months	Conventional, 60 Gy	72% (ART) vs. 54% (Obs) (5 years)	NR	NR	NR	NR	2	1.4	0.5	0	NR
Choo/Pearse et al. (51, 52)	Yes	75, 45.1 months	3DCRT, 66 Gy	78.6% (7 years)	12	18	3	3	22.6	8.7	2.8	1.6	NR
Eldredge et al. (53)	No	68, 15 months	IG-3DCRT, 68.4 Gy	93% (3 years)	15	13	2	0	13.6	5.4	0	3	NR
De Meerleer et al. (54)	No	135, 9 months	IMRT, 74 Gy	67% (3 years)	28	15	3	0	33.8	16	3	3	NR
Ost et al. (55)	No	104, 36 months	IMRT, 74 Gy	93% (3 years)	34.6	22	8	0	26	7	4	0	NR
Goenka et al. (48)	No	176, 53 months	3DCRT, IMRT, ≥70 Gy	39.9% (5 years)	16.3	9.8	NR	0	17	5.2	6	1.4	27
Shelan et al. (56)	No	76, 52 months	IMRT, 70 Gy	62.5% (4 years)	NR	NR	NR	NR	NR	NR	4	0	NR
Wong et al. (57)	No	50, 18.9 months	IG-IMRT, 65 Gy	72.9% (2 years)	8	2	0	0	4	4	0	0	NR
Sandhu et al. (58)	Yes	26, NR	IG-IMRT, 68 Gy	NR	12	4	0	0	NR	NR	NR	NR	NR
Cheng et al. (59)	No	70, 10.6 months	IG-IMRT, 68.8 Gy	NR	36	41	0	0	NR	NR	NR	NR	NR
Nath et al. (47)	No	50, 24 months	IG-IMRT, 68 Gy	NR	14	8	0	0	16	2	2	0	NR
Deville et al. (60)	No	67, 25.5 months	IG-IMRT, 70.2 Gy	NR	16	46	3	0	24	1.5	9	0	NR
Hunter et al. (61)	No	104, 33 months	IG-IMRT, 70 Gy	NR	NR	NR	NR	NR	11.6	0	5.4	0	NR
Chua et al. (62)	Yes	75, NR	IG-IMRT, 66 Gy	NR	30.6	22.6	4	1	NR	NR	NR	NR	NR
Cremers et al. (63)	No	197, 40 months	3DCRT, 63 and 58.5 Gy (2.25 Gy/fr)	59% (5 years)	NR	NR	NR	NR	29.4	1.5	6	0.6	NR
Cortes-Gonzalez et al. (64)	No	184, 48 months	3DCRT, 70 Gy	63% (4 years)	NR	NR	3	0	NR	NR	9	5	NR
Corbin et al. (65)	Yes	78, 24 months	IMRT, 66.6 Gy	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS
van Gysen et al. (66)	Yes	64, 24 months	IMRT, 66 Gy	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS
Berlin et al. (45)	Yes	68, 71.2 months	IG-IMRT, 66 Gy	72.7% (5 years)	38.2	22	0	0	10.6	12.3	0	0	NS

bRFR, biochemical relapse-free rate; G, grade; G3–4, grade 3–4; GU, genitourinary; GI, gastrointestinal; ED, erectile dysfunction; RCT, randomized controlled trial; 3DCRT, three-dimensional conformal radiation therapy; IG-3DCRT, image-guided three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; ART, adjuvant radiotherapy; Obs, observation arm; NR, not reported; NS, non-significant.

[a]*Toxicity grade not reported.*

TABLE 2 | Summary of studies on patient-reported QoL indicators.

Study	Setting	Technique	QoL tool	Urinary domain, mean	Bowel domain, mean	Sexual domain, mean	Global health domain, mean	Comparator [a]	Difference from comparator	Last reported measurement (months)
Moinpour et al. (50)	ART vs. RP only	3DCRT	SWOG QoL Questionnaire	NA	NA	NA	NA	Baseline	SS in favor of control arm: urinary frequency at 60 months, bowel function until 24 months, global QoL at 6 weeks SS in favor of radiation arm: global QoL at 60 months NS at other time points	60
Pinkawa et al. (67)	SRT/ART	4F Box	EPIC	Function, 84 Incontinence, 74	Function, 91 Bother, 90	Function, 11	NR	Baseline	SS in favor of control arm: urinary function at 6 weeks, bowel function at 2 months, bowel bother at >1 year NS at other time points	>12
Cremers et al. (63)	SRT	3DCRT	EPIC	Function, 80	Function, 93	Function, 23	NR	Reference	NS	NA
Cortes-Gonzalez et al. (64)	SRT + NHT	3DCRT	QLQ-C30, PR-25	Symptoms, 24.7[b]	Symptoms, 9.4[b]	Symptoms, 50.4[b]	Function, 77.9[b]	Reference	NS	NA
Corbin et al. (65)	SRT/ART	IMRT	EPIC 26, IPSS	Irritations, 86 Incontinence, 78	Function, 89	Function, 36	NR	Baseline	NS	24
van Gysen et al. (66)	SRT/ART	IMRT	EPIC	Function, 82 Incontinence, 74	Function, 94	Function, 14	Physical component, 48	Baseline	NS	15
Berlin et al. (45)	SRT/ART	IG-IMRT	EPIC	Function, 85 Incontinence, 76	Function, 94 Bother, 90	Function, 25 Bother, 58	NR	Baseline	SS in favor of control arm: urinary irritation at 5 weeks, bowel function at 3 months, sexual function at 3 months NS at other time points	60

QoL, quality of life; ART, adjuvant radiation therapy; RP, radical prostatectomy; SRT, salvage radiation therapy; NHT, neoadjuvant hormone therapy; 3DCRT, three-dimensional conformal radiation therapy; 4F, four field; IMRT, intensity-modulated radiation therapy; NA, not applicable; NR, not reported; NS, not significant; SS, statistically significant.

[a]*Reference: reference values in age-matched healthy population. Baseline: patient's pre-RT baseline.*

[b]*According to QLQ-C30 PR-25, higher mean for functional and general health domains shows higher functioning and lower mean for symptoms demonstrates less symptom burden.*

the fact that the former correspond to the pre-IMRT and image-guidance era.

The impact of ART/SRT on sexual function represents a particular concern influenced by the low residual function post-prostatectomy. The latter also translates into challenges in evaluating the potential superimposed impact of ART/SRT on this QoL domain. Nonetheless, most of the studies that have evaluated this area have shown absence of ART/SRT impact on residual erectile function (see **Table 2**). This indeed contrasts with evidence of RT as primary treatment for localized disease, where a negative long-term impact has been reported (68). However, a possible explanation for this difference could be the prescribed doses between the two settings. Interestingly, an improvement trend of "sexual bother" subscale with time has been shown despite stability of sexual function scores, in keeping with patients getting used to a steady level of sexual functioning (45).

As an interesting corollary of these findings, the global quality of life was only transiently lower at 6 weeks in the SWOL QoL study, despite radiation toxicities and subsequent negative impact on GI- and GU-related QoL domains. In fact, it remained higher at 5 years for patients receiving ART as compared to control group (50). This in part could be explained by the effect of improved disease control on overall QoL in the RT arm. These latter observations serve to reinforce the complexity of QoL-related outcomes and studies. At any rate, considering the well-known mismatch in perception of QoL outcomes between physicians and patients (69), additional effort should be made by practitioners to convey unbiased information, which is more consistent with current evidence showing absence of detrimental effect (or even overall improvement) on QoL domains with the use of modern state-of-the-art post-prostatectomy RT.

CONCLUSION AND FUTURE STEPS

Postoperative adjuvant and salvage radiotherapy are effective and safe treatments in patients with high-risk factors or rising PSA after prostatectomy, respectively. Their underutilization might have several reasons, including concerns with overtreatment and radiation-related side effects. The current available data on toxicity demonstrate increased incidence of acute and long-term grade 2 events, but no significant increase of grade 3–4 long-term side effects with the use of ART/SRT. Although patients' quality of life is affected transiently, it returns to pre-radiotherapy baseline during the first year after therapy. Despite the lack of randomized data comparing conventional with modern radiation techniques and lack of long-term follow-up of the latter, studies are consistent in suggesting an improved therapeutic index with the use of image-guided high-precision radiation, mainly due to better sparing of organs-at-risk translating into decreased toxicity rates. With the use of adjuvant radiation, a proportion of patients will be overtreated; however, present evidence does not seem robust enough to support similar effectiveness between delayed and adjuvant radiotherapy, and the latter should continue to represent the standard of care approach.

The literature on QoL and patient-reported outcomes after post-prostatectomy RT remains scarce, and continuous efforts in gathering prospective QoL data using validated tools seems necessary. Integration of QoL outcomes into both decision-making process and evaluation of treatments' impact on survival outcomes remains an unmet challenge (70).

In conclusion, concerns with toxicities and/or impact in QoL outcomes should not preclude patients from gaining the proven benefits of either ART or SRT. Pending the results of prospective studies comparing adjuvant vs. early salvage radiotherapy, the former should represent the standard approach during shared decision-making process between physicians and patients for treatment individualization in men with localized prostate cancer after radical prostatectomy.

AUTHOR CONTRIBUTIONS

HR contributed in the literature search, analysis, and manuscript preparation. AB contributed in the literature search, analysis, and manuscript design and preparation.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* (2015) **65**(1):5–29. doi:10.3322/caac.21254
2. Mahmood U, Levy LB, Nguyen PL, Lee AK, Kuban DA, Hoffman KE. Current clinical presentation and treatment of localized prostate cancer in the United States. *J Urol* (2014) **192**(6):1650–6. doi:10.1016/j.juro.2014.06.017
3. Ward JF, Blute ML, Slezak J, Bergstralh EJ, Zincke H. The long-term clinical impact of biochemical recurrence of prostate cancer 5 or more years after radical prostatectomy. *J Urol* (2003) **170**(5):1872–6. doi:10.1097/01.ju.0000091876.13656.2e
4. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* (2005) **66**(5 Suppl):83–94. doi:10.1016/j.urology.2005.06.116
5. Boorjian SA, Eastham JA, Graefen M, Guillonneau B, Karnes RJ, Moul JW, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. *Eur Urol* (2012) **61**(4):664–75. doi:10.1016/j.eururo.2011.11.053
6. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* (1999) **281**(17):1591–7. doi:10.1001/jama.281.17.1591
7. Khan MA, Partin AW, Mangold LA, Epstein JI, Walsh PC. Probability of biochemical recurrence by analysis of pathologic stage, Gleason score, and margin status for localized prostate cancer. *Urology* (2003) **62**(5):866–71. doi:10.1016/S0090-4295(03)00674-5
8. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) **380**(9858):2018–27. doi:10.1016/S0140-6736(12)61253-7
9. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* (2006) **296**(19):2329–35. doi:10.1001/jama.296.19.2329
10. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Storkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* (2009) **27**(18):2924–30. doi:10.1200/JCO.2008.18.9563
11. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) **181**(3):956–62. doi:10.1016/j.juro.2008.11.032

12. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* (2013) **190**(2):441–9. doi:10.1016/j.juro.2013.05.032
13. Pickles T, Morgan S, Morton G, Souhami L, Warde P, Lukka H. Adjuvant radiotherapy following radical prostatectomy: genito-urinary radiation oncologists of Canada consensus statement. *Can Urol Assoc J* (2008) **2**(2):95–9.
14. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Van Der Kwast T, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent – update 2013. *Eur Urol* (2014) **65**(1):124–37. doi:10.1016/j.eururo.2013.09.046
15. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* (2008) **299**(23):2760–9. doi:10.1001/jama.299.23.2760
16. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) **25**(15):2035–41. doi:10.1200/JCO.2006.08.9607
17. Bristow RG, Berlin A, Dal Pra A. An arranged marriage for precision medicine: hypoxia and genomic assays in localized prostate cancer radiotherapy. *Br J Radiol* (1035) **2014**:87.
18. King CR. Adjuvant versus salvage radiotherapy for high-risk prostate cancer patients. *Semin Radiat Oncol* (2013) **23**(3):215–21. doi:10.1016/j.semradonc.2013.01.009
19. Daniels CP, Millar JL, Spelman T, Sengupta S, Evans SM. Predictors and rate of adjuvant radiation therapy following radical prostatectomy: a report from the Prostate Cancer Registry. *J Med Imaging Radiat Oncol* (2015). doi:10.1111/1754-9485.12407
20. Hoffman KE, Nguyen PL, Chen MH, Chen RC, Choueiri TK, Hu JC, et al. Recommendations for post-prostatectomy radiation therapy in the United States before and after the presentation of randomized trials. *J Urol* (2011) **185**(1):116–20. doi:10.1016/j.juro.2010.08.086
21. Kalbasi A, Swisher-McClure S, Mitra N, Sunderland R, Smaldone MC, Uzzo RG, et al. Low rates of adjuvant radiation in patients with nonmetastatic prostate cancer with high-risk pathologic features. *Cancer* (2014) **120**(19):3089–96. doi:10.1002/cncr.28856
22. Schreiber D, Rineer J, Yu JB, Olsheski M, Nwokedi E, Schwartz D, et al. Analysis of pathologic extent of disease for clinically localized prostate cancer after radical prostatectomy and subsequent use of adjuvant radiation in a national cohort. *Cancer* (2010) **116**(24):5757–66. doi:10.1002/cncr.25561
23. Sheets NC, Hendrix LH, Allen IM, Chen RC. Trends in the use of postprostatectomy therapies for patients with prostate cancer: a surveillance, epidemiology, and end results Medicare analysis. *Cancer* (2013) **119**(18):3295–301. doi:10.1002/cncr.28222
24. Maurice MJ, Zhu H, Abouassaly R. Low use of immediate and delayed postoperative radiation for prostate cancer with adverse pathological features. *J Urol* (2015) **194**(4):972–6. doi:10.1016/j.juro.2015.03.122
25. Mahal BA, Hoffman KE, Efstathiou JA, Nguyen PL. National trends in the recommendation of radiotherapy after prostatectomy for prostate cancer before and after the reporting of a survival benefit in March 2009. *Clin Genitourin Cancer* (2015) **13**(3):e167–72. doi:10.1016/j.clgc.2014.12.005
26. Thompson IM, Tangen CM, Klein EA. Is there a standard of care for pathologic stage T3 prostate cancer? *J Clin Oncol* (2009) **27**(18):2898–9. doi:10.1200/JCO.2008.20.9460
27. Morgan SC, Waldron TS, Eapen L, Mayhew LA, Winquist E, Lukka H. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: a systematic review and meta-analysis. *Radiother Oncol* (2008) **88**(1):1–9. doi:10.1016/j.radonc.2008.04.013
28. Cheng T, Heng DY, Stewart D. Re: adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) **181**:956–62. J Urol 2009; 182(5):2531–2; discussion 2–4. doi:10.1016/j.juro.2009.07.053
29. Showalter TN, Ohri N, Teti KG, Foley KA, Keith SW, Trabulsi EJ, et al. Physician beliefs and practices for adjuvant and salvage radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2012) **82**(2):e233–8. doi:10.1016/j.ijrobp.2011.04.003
30. Kim SP, Tilburt JC, Karnes RJ, Ziegenfuss JY, Han LC, Shah ND, et al. Variation in treatment recommendations of adjuvant radiation therapy for high-risk prostate cancer by physician specialty. *Urology* (2013) **82**(4):807–12. doi:10.1016/j.urology.2013.04.060
31. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* (2005) **366**(9485):572–8. doi:10.1016/S0140-6736(05)67101-2
32. Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol* (2002) **167**(2 Pt 1):528–34. doi:10.1097/00005392-200202000-00018
33. Boorjian SA, Karnes RJ, Crispen PL, Carlson RE, Rangel LJ, Bergstralh EJ, et al. The impact of positive surgical margins on mortality following radical prostatectomy during the prostate specific antigen era. *J Urol* (2010) **183**(3):1003–9. doi:10.1016/j.juro.2009.11.039
34. Pfister D, Bolla M, Briganti A, Carroll P, Cozzarini C, Joniau S, et al. Early salvage radiotherapy following radical prostatectomy. *Eur Urol* (2014) **65**(6):1034–43. doi:10.1016/j.eururo.2013.08.013
35. Trabulsi EJ, Valicenti RK, Hanlon AL, Pisansky TM, Sandler HM, Kuban DA, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. *Urology* (2008) **72**(6):1298–302; discussion 302–4. doi:10.1016/j.urology.2008.05.057
36. Ost P, De Troyer B, Fonteyne V, Oosterlinck W, De Meerleer G. A matched control analysis of adjuvant and salvage high-dose postoperative intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2011) **80**(5):1316–22. doi:10.1016/j.ijrobp.2010.04.039
37. Kowalczyk KJ, Gu X, Nguyen PL, Lipsitz SR, Trinh QD, Lynch JH, et al. Optimal timing of early versus delayed adjuvant radiotherapy following radical prostatectomy for locally advanced prostate cancer. *Urol Oncol* (2014) **32**(3):303–8. doi:10.1016/j.urolonc.2013.09.004
38. Hagan M, Zlotecki R, Medina C, Tercilla O, Rivera I, Wajsman Z. Comparison of adjuvant versus salvage radiotherapy policies for postprostatectomy radiotherapy. *Int J Radiat Oncol Biol Phys* (2004) **59**(2):329–40. doi:10.1016/j.ijrobp.2003.11.038
39. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* (2004) **291**(11):1325–32. doi:10.1001/jama.291.11.1325
40. Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, et al. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. *Lancet Oncol* (2014) **15**(6):e234–42. doi:10.1016/S1470-2045(13)70598-9
41. Katz SJ, Morrow M. Addressing overtreatment in breast cancer: the doctors' dilemma. *Cancer* (2013) **119**(20):3584–8. doi:10.1002/cncr.28260
42. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* (2013) **14**(4):297–305. doi:10.1016/S1470-2045(13)70035-4
43. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* (2011) **305**(6):569–75. doi:10.1001/jama.2011.90
44. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* (2014) **15**(12):1303–10. doi:10.1016/S1470-2045(14)70460-7
45. Berlin A, Cho E, Kong V, Howell KJ, Lao B, Craig T, et al. Phase 2 trial of guideline-based postoperative image guided intensity modulated radiation therapy for prostate cancer: toxicity, biochemical, and patient-reported health-related quality-of-life outcomes. *Pract Radiat Oncol* (2015) **5**(5):e473–82. doi:10.1016/j.prro.2015.02.015
46. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol* (2012) **9**(12):688–99. doi:10.1038/nrclinonc.2012.194
47. Nath SK, Sandhu AP, Rose BS, Simpson DR, Nobiensky PD, Wang JZ, et al. Toxicity analysis of postoperative image-guided intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) **78**(2):435–41. doi:10.1016/j.ijrobp.2009.08.023

48. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol* (2011) **60**(6):1142–8. doi:10.1016/j.eururo.2011.08.006
49. Michalski JM, Yan Y, Watkins-Bruner D, Bosch WR, Winter K, Galvin JM, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys* (2013) **87**(5):932–8. doi:10.1016/j.ijrobp.2013.07.041
50. Moinpour CM, Hayden KA, Unger JM, Thompson IM Jr, Redman MW, Canby-Hagino ED, et al. Health-related quality of life results in pathologic stage C prostate cancer from a Southwest Oncology Group trial comparing radical prostatectomy alone with radical prostatectomy plus radiation therapy. *J Clin Oncol* (2008) **26**(1):112–20. doi:10.1200/JCO.2006.10.4505
51. Choo R, Danjoux C, Gardner S, Morton G, Szumacher E, Loblaw DA, et al. Efficacy of salvage radiotherapy plus 2-year androgen suppression for postradical prostatectomy patients with PSA relapse. *Int J Radiat Oncol Biol Phys* (2009) **75**(4):983–9. doi:10.1016/j.ijrobp.2008.12.049
52. Pearse M, Choo R, Danjoux C, Gardner S, Morton G, Szumacher E, et al. Prospective assessment of gastrointestinal and genitourinary toxicity of salvage radiotherapy for patients with prostate-specific antigen relapse or local recurrence after radical prostatectomy. *Int J Radiat Oncol Biol Phys* (2008) **72**(3):792–8. doi:10.1016/j.ijrobp.2008.05.063
53. Eldredge HB, Studenski M, Keith SW, Trabulsi E, Lallas CD, Gomella LG, et al. Post-prostatectomy image-guided radiation therapy: evaluation of toxicity and inter-fraction variation using online cone-beam CT. *J Med Imaging Radiat Oncol* (2011) **55**(5):507–15. doi:10.1111/j.1754-9485.2011.02305.x
54. De Meerleer G, Fonteyne V, Meersschout S, Van den Broecke C, Villeirs G, Lumen N, et al. Salvage intensity-modulated radiotherapy for rising PSA after radical prostatectomy. *Radiother Oncol* (2008) **89**(2):205–13. doi:10.1016/j.radonc.2008.07.027
55. Ost P, Fonteyne V, Villeirs G, Lumen N, Oosterlinck W, De Meerleer G. Adjuvant high-dose intensity-modulated radiotherapy after radical prostatectomy for prostate cancer: clinical results in 104 patients. *Eur Urol* (2009) **56**(4):669–75. doi:10.1016/j.eururo.2009.05.041
56. Shelan M, Abo-Madyan Y, Welzel G, Bolenz C, Kosakowski J, Behnam N, et al. Dose-escalated salvage radiotherapy after radical prostatectomy in high risk prostate cancer patients without hormone therapy: outcome, prognostic factors and late toxicity. *Radiat Oncol* (2013) **8**:276. doi:10.1186/1748-717X-8-276
57. Wong GW, Palazzi-Churas KL, Jarrard DF, Paolone DR, Graf AK, Hedican SP, et al. Salvage hypofractionated radiotherapy for biochemically recurrent prostate cancer after radical prostatectomy. *Int J Radiat Oncol Biol Phys* (2008) **70**(2):449–55. doi:10.1016/j.ijrobp.2007.06.042
58. Sandhu A, Sethi R, Rice R, Wang JZ, Marcus L, Salem C, et al. Prostate bed localization with image-guided approach using on-board imaging: reporting acute toxicity and implications for radiation therapy planning following prostatectomy. *Radiother Oncol* (2008) **88**(1):20–5. doi:10.1016/j.radonc.2008.05.009
59. Cheng JC, Schultheiss TE, Nguyen KH, Wong JY. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2008) **71**(2):351–7. doi:10.1016/j.ijrobp.2007.09.043
60. Deville C, Vapiwala N, Hwang WT, Lin H, Ad VB, Tochner Z, et al. Comparative toxicity and dosimetric profile of whole-pelvis versus prostate bed-only intensity-modulated radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2012) **82**(4):1389–96. doi:10.1016/j.ijrobp.2011.04.041
61. Hunter GK, Brockway K, Reddy CA, Rehman S, Sheplan LJ, Stephans KL, et al. Late toxicity after intensity modulated and image guided radiation therapy for localized prostate cancer and post-prostatectomy patients. *Pract Radiat Oncol* (2013) **3**(4):323–8. doi:10.1016/j.prro.2012.08.004
62. Chua B, Min M, Wood M, Edwards S, Hoffmann M, Greenham S, et al. Implementation of an image guided intensity-modulated protocol for post-prostatectomy radiotherapy: planning data and acute toxicity outcomes. *J Med Imaging Radiat Oncol* (2013) **57**(4):482–9. doi:10.1111/1754-9485.12043
63. Cremers RG, van Lin EN, Gerrits WL, van Tol-Geerdink JJ, Kiemeney LA, Vergunst H, et al. Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high-risk patients suited for adjuvant radiotherapy. *Radiother Oncol* (2010) **97**(3):467–73. doi:10.1016/j.radonc.2010.05.023
64. Cortes-Gonzalez JR, Castellanos E, Sandberg K, Eriksson MH, Wiklund P, Carlsson S, et al. Early salvage radiation therapy combined with short-term hormonal therapy in recurrent prostate cancer after radical prostatectomy: single-institution 4-year data on outcome, toxicity, health-related quality of life and co-morbidities from 184 consecutive patients treated with 70 Gy. *Int J Oncol* (2013) **42**(1):109–17. doi:10.3892/ijo.2012.1694
65. Corbin KS, Kunnavakkam R, Eggener SE, Liauw SL. Intensity modulated radiation therapy after radical prostatectomy: early results show no decline in urinary continence, gastrointestinal, or sexual quality of life. *Pract Radiat Oncol* (2013) **3**(2):138–44. doi:10.1016/j.prro.2012.05.005
66. van Gysen KL, Kneebone AB, Guo L, Vaux KJ, Lazzaro EM, Eade TN. Health-related quality of life using intensity-modulated radiation therapy for post-prostatectomy radiotherapy. *J Med Imaging Radiat Oncol* (2013) **57**(1):89–96. doi:10.1111/j.1754-9485.2012.02464.x
67. Pinkawa M, Fischedick K, Asadpour B, Gagel B, Piroth MD, Holy R, et al. Health-related quality of life after adjuvant and salvage postoperative radiotherapy for prostate cancer – a prospective analysis. *Radiother Oncol* (2008) **88**(1):135–9. doi:10.1016/j.radonc.2007.10.022
68. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* (2008) **358**(12):1250–61. doi:10.1056/NEJMoa074311
69. Wilson KA, Dowling AJ, Abdolell M, Tannock IF. Perception of quality of life by patients, partners and treating physicians. *Qual Life Res* (2000) **9**(9):1041–52. doi:10.1023/A:1016647407161
70. Valicenti RK, Thompson I Jr, Albertsen P, Davis BJ, Goldenberg SL, Wolf JS, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. *Int J Radiat Oncol Biol Phys* (2013) **86**(5):822–8. doi:10.1016/j.ijrobp.2013.05.029

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Integrating geriatric assessment into decision-making after prostatectomy: adjuvant radiotherapy, salvage radiotherapy, or none?

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Despite current advancements in the field, management of older prostate cancer patients still remains a big challenge for Geriatric Oncology. The International Society of Geriatric Oncology (ISGO) has recently updated its recommendations in this area, and these have been widely adopted, notably by the European Association of Urology. This article outlines the principles that should be observed in the management of elderly patients who have recently undergone prostatectomy for malignancy or with a biochemical relapse following prostatectomy. Further therapeutic intervention should not be considered in those patients who are classified as frail in the geriatric assessment. In patients presenting better health conditions, salvage radiotherapy is to be preferred to adjuvant radiotherapy, which is only indicated in certain exceptional cases. Radiotherapy of the operative bed presents a higher risk to the elderly. Additionally, hormone therapy clearly shows higher side effects in older patients and therefore it should not be administered to asymptomatic patients. We propose a decision tree based on the ISGO recommendations, with specific modifications for patients in biochemical relapse.

Keywords: post-operative radiotherapy, prostate cancer, elderly patients, geriatric assessment, adjuvant radiotherapy, salvage radiotherapy

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INTRODUCTION

Prostate cancer is the most common form of cancer in European and American men, particularly afflicting older patients by missing the target of an effective therapy quite often toward under-treatment (1–5). However, two large studies of non-curative approaches to prostate cancer have demonstrated, independently of age, that patients at low and intermediate risk have a lower specific mortality when compared to high-risk patients (64%) (6, 7) and therefore professional bodies are not following these directories (8, 9). Indeed, the importance of patient's age is going to be considered, as reported by the recent recommendations of the European Association of Urology (EAU) (10). In the meantime, the International Society of Geriatric Oncology (ISGO) piloted a multi-disciplinary working group (of urologists, radiotherapists, medical oncologists, and geriatricians), delivering a set of guidelines for

the treatment of prostate cancer-affected elderly patients (based on the available literature), which were updated in 2013 (11, 12).

However, while this guidance addresses both localized prostate cancers and metastatic disease, the question of post-operative radiotherapy was not addressed, nor the problem of biochemical relapse, though these are frequent scenarios in elderly patients. We propose here a revision of the model that addresses this particular situation.

WAIT AND SEE POLICY AND BEST SUPPORTIVE CARE

The first question in a clinician's mind when confronted with a patient presenting with high-risk pT3 prostate cancer with positive margins, detectable post-operative PSA levels, or a biochemical relapse, is the importance and relevance of all treatments, whatever they might be. The life expectancy of a patient at the time of biochemical relapse can be considerable (13). PSA doubling time and the initial Gleason score are the variables that are currently considered the best predictors of prostate cancer-specific mortality (14–16). In an illustrative study, Antonarakis followed a series of 450 patients in biochemical relapse, observing a metastasis-free survival rate (MFS) at 10 years of 94% (Gleason score 4–6) and 19% (Gleason score 8–10). In those cases where the PSA doubling time (PSA DT) was more than 15 months, the MFS rate reached the 72%, in contrast to those where the PSA DT was less than 9 months (7% only) (17). Indeed, tumor aggressiveness and specific mortality risks should be discussed between urologists and radiation oncologists and integrated with a general onco-geriatric opinion regarding patient's conditions or any existing co-morbidity (as specifically recommended by the new paragraph in the EAU guidance). Therefore, further therapeutic interventions should be considered only in patients presenting an aggressive prostate cancer (Gleason score $\geq$8 and/or short PSA DT), in accordance with a geriatric opinion. If any decision will be taken at this regard, the choice of therapy and its timing is the next consideration.

ADJUVANT OR EARLY SALVAGE RADIOTHERAPY FOR OLDER PATIENTS

The rationale for post-operative irradiation is addressed to eradicating any microscopic residual of tumor after prostatectomy. In case of a detectable disease (a treatable PSA level), such therapy is termed "salvage radiotherapy (SRT)," while in cases where there are concerns about the completeness of the surgical resection, either positive excision margins or capsular rupture, though with sub-treatable PSA levels, the therapy would be termed "adjuvant radiotherapy" (ART).

For high-risk prostate cancers (pT3, R1), three large trials have validated the use of ART with respect to follow-up in terms of survival with no biochemical relapse: EORTC 22911, ARO 9602, and SWOG 8794 [reviewed in Thoms et al. (18–21)]. In the EORTC trial, 5-year survival without biochemical relapse was 77% in the ART arm against 55% in controls (which included patients who had late SRT). However, the survival data from these trials in patients with distant metastases are inconsistent. Of the three trials, only the EORTC trial specifically analyzed the data with respect to age, though patients older than 75 years were excluded from the trial. Patients over 70 years nevertheless represented 20% of all patients recruited (196/1,105 of whom 94 patients were in the radiotherapy arm and 102 in the control arm), against the 47% who were under 65 years old. It is important to note that it was only in this over-70 patient group that survival without biochemical relapse was not improved by adjuvant treatment compared with watchful waiting. This study also showed that ART clearly led to worse outcomes for the over-70 group in terms of survival free from clinical relapse [HR = 1.78 (1.14–2.78), $p = 0.0003$] and overall survival [HR = 2.94 (1.75–4.93), $p = 0.0008$]. The criterion of age was the only significant predictor among the many survival variables studied, which included PSA level, resection margins, extra-capsular invasion, invasion into the seminal vesicles, and pT staging.

Three multi-center randomized controlled trials are currently underway (GETUG 17, RAVES, and RADICALS), comparing immediate ART with radiotherapy according to biochemical parameters, with no upper age limit for study inclusion. Until these trials report (which will not be for several further years), the current recommendation for elderly patients is to refrain from ART, but to consider SRT early, should the PSA rise above 0.2 ng/ml, whereas younger patients may benefit more from ART (20, 22).

SALVAGE RADIOTHERAPY: EFFECTIVENESS AND ADVERSE EFFECTS

Salvage radiotherapy is the only potentially curative treatment available in biochemical relapse. Early SRT is thought to prevent tumor progression in around half of patients (23). In the study by Stephenson, 501 patients (between 40 and 79 years at the time of their prostatectomy procedure) were given SRT, and 50% were relapse-free at 4 years. For patients with progressive disease, the median time to progression (TTP) was 12.5 months. It should be noted that this analysis does not take account of the age of the patients. This author has also developed a predictive model of relapse-free survival (biochemical or clinical) within 6 years of SRT (15). The model was developed using a retrospective series of 1,540 patients between 58 and 67 years at the time of prostatectomy (though with no age data at the time of irradiation). The relevant variables in this nomogram are: PSA level before SRT, Gleason score, PSA DT, surgical margins, lymph node status, and the administration of hormonal treatment before or after SRT. This nomogram, which is suitable for patients of all ages, may assist decision-making when the PSA level is rising.

Radiotherapy to the prostatic bed can have long-term adverse effects. In the EORTC study, late grade 3 complications (from all sources) occurred in 5.3% of cases (compared with 2.5% in the observation arm, $p = 0.052$) with all genitourinary toxicity of grade $\geq$2 at 21% (compared with 13% in the observation arm, $p = 0.003$), though no significant difference in gastro-intestinal toxicity of grade $\geq$2 were observed (2.5 versus 1.9%, $p = 0.47$) (18). These potential late complications are mainly urethral stenosis, urinary incontinence, and rectal bleeding. They were not specifically analyzed with respect to patient age. However, there are reasons to believe that SRT leads to fewer late side effects than ART. In a

large multi-center retrospective study of 959 patients treated with radiotherapy to the prostatic bed, ART independently predicted late urinary toxicity of grade 2 or greater compared with SRT (24). This study reminds us of the importance of a delay between prostatectomy and irradiation to maximize sphincter recovery, recommending an interval of at least 2 years in order to minimize the risk of late complications. It seems that post-operative radiotherapy leads to a greater number of adverse effects in elderly patients compared with their younger counterparts (25–27) (see **Table 1**). In another retrospective study of 742 patients, the age and the dose of radiation were the most relevant parameters for predicting grade 3 urinary toxicity in the long term (8 years) (25). The mean age at the time of radiotherapy was 65 years, with 117 patients less than 72 years and 69 patients aged over 71 years. Grade 3 urinary toxicity occurred in 16% of patients aged over 71 years, in comparison with 6% aged less than 72 years ($p = 0.006$). In a multivariate analysis, age was in independent prognostic predictor of long-term grade 3 urinary toxicity, with an HR of 4.26 (1.45–12.47), $p = 0.004$.

We have not yet raised the question of hypofractionated treatment. In prostate cancer, and particularly in the elderly patient, increasing the dose of radiation in each fraction, whilst reducing the number of sessions, is an attractive concept. Retrospective studies have evaluated the potential risks of increased toxicity associated with hypofractionation and studies are under way to evaluate its effectiveness and the potential risks of increased toxicity associated with hypofractionation (28, 29).

ANDROGEN-DEPRIVATION THERAPY

Patients presenting a localized prostate cancer who are currently considered ineligible for a curative local therapy (though most often the radiotherapist or urologist uses "intuitive criteria" to make this decision) are often offered androgen-deprivation therapy (ADT) instead. Scientifically, there is no evidence of benefit in survival to giving early treatment (30, 31). It is therefore currently advised to treat these patients only if they become symptomatic, except for patients who present with rapidly progressive disease (PSA DT <12 months). However, this evidence is balanced in practice by the concerns of patients, who, knowing that their PSA is climbing, are often very demanding that some treatment have to be instituted. It is important to note that very few patients are then referred for an onco-geriatric assessment, and that local treatment is judged more hazardous than hormone therapy. However, the long-term adverse effects of hormone therapy are now well-recognized and of particular concern in the elderly (32). Such adverse effects include bone demineralization (33), increased fracture risk (34, 35), and increased cardio-vascular risk (36, 37). Several studies have found that patients rapidly decline physically, with marked effect on the quality of life, when treated with hormone therapy (38). Numerous physical activity programs have been devised to limit this, with very encouraging results (39–41). The other option to improve tolerability is to give intermittent hormone therapy rather than continuous treatment (42). This therapeutic strategy has been found to be equivalently effective, and is associated with a reduction in the unwanted effects of hormone therapy in several trials, notably in one of the largest trial, that of Calais da Silva, which recruited more than 900 patients and was also confirmed in a meta-analysis published by Shaw (43, 44).

It is also important to underline that, in practice, brief hormone therapy can be used alongside SRT. In high-risk localized cancers, a combination of radiotherapy and hormone therapy has generally been found to be more effective in comparison with radiotherapy alone (45). Among these trials, it should be noted that the 85.31 trial organized by the RTOG, included patients whose pT3a or b stage disease had been operated on, representing around 15% of the total number of 977 patients recruited to the study (46). The authors of this trial also concluded that combined radiotherapy and hormone therapy was superior, both in terms of overall survival (39 versus 49%, $p = 0.002$) and disease-specific mortality (16 versus 22%, $p = 0.005$). Similarly, post-operative radiotherapy combined with ADT may represent the new standard in the near future, based on the results of different clinical trials such as RTOG 9601, RTOG 0534, GETUG 16, and GETUG 22 trials (47). However, the risk of cumulative toxicity following the two treatments has to be considered. Mature results of these different trials are needed prior to concluding that all biochemically relapsing prostate cancer patients need to be treated with prostate bed radiotherapy and 6-month ADT.

TABLE 1 | Post operative radiotherapy adverse events according to age.

Reference	N	Adverse event studied	cut off (years)	Hazard ratio/ odds ratio
Cozzarini et al. (2012) (25)	742	G3 long-term GU complications	71	HR = 4.26 (1.45–12.47), $p = 0.004$
Longobardi et al. (2011) (26) 2011	178	≥G2 acute bowel complications	66	OR = 4 (0.9–18.6), $p = 0.08$*
Perna et al. (2010) (27)	96	≥G2 acute bowel complications	Continuous	OR = 1.13 (1.02–1.25), $p = 0.021$

*This study designated $p < 0.1$ as significant.
GU: Genito-urinary

GERIATRIC ASSESSMENT AND ISGO GUIDELINES

It is currently considered that a patient will benefit from local treatment for his prostate disease if his life expectancy exceeds 10 years. But life expectancy is not only determined by age. This is why it is fundamentally necessary to conduct an evaluation that takes into consideration co-morbidities, independent living, nutritional status, cognitive function, and other important predictors of death not linked to the cancer of the elderly patient in localized prostate cancer, before making treatment decisions. Among the multi-dimensional geriatric evaluations used in onco-geriatrics, several tools and scoring systems have been developed. The burden of co-morbidities can be assessed using the Charlson score, or preferably, the Cumulative Illness Score Rating-Geriatrics (CIRS-G) (48). In that study of 2,273 patients whose prostate cancer was treated with the objective of cure, a CIRS-G score of 1 translated into a relative risk of death within 10 years from another cause than prostate cancer of 1.64 (1.52–1.76), when compared with a CIRS-G score of 0. The

relative risk rose by 1.18 (1.15–1.21) with each additional point gained using the scoring system. Independent living is assessed using the activities of daily living (ADL) and instrumental activities of daily living (IADL) scores (49, 50). In a study of 9,467 men and women over 70 years old, the survival rate at 10 years was 54.2% in ADL score 0 patients (fully independent), versus 31.3, 22.5, 16.7, and 4.2%, respectively, for ADL score groups 1–4 (reflecting increasing dependence), differences which were all statistically significant (50). Nutritional status may be evaluated by using body weight, the rate of loss of body mass, and the Mini Nutritional Assessment (MNA) (51). For a MNA <17, the risk of death within a year is 50%, while that of patients with an MNA score between 17 and 23.5 is halved, at 25%. It is also important to evaluate cognitive functions and patients behavior systematically.

The onco-geriatric assessment enables the development of an accurate picture, which represents the patient's overall condition, enabling appropriate interventions to be instituted where possible, such as the provision of help at home, the introduction of an anti-depressant, dietetic advice, and modification of the home environment. The outcome of this assessment is to place patients in one of three groups: fit, vulnerable (with potentially ameliorable conditions), and frail (whose condition is irreversible) (52). Such thorough assessment is extremely time-consuming, and may not be possible in routine practice for every elderly patient who presents with prostate cancer. The G8, a geriatric rating instrument with only eight questions yielding up to 17 points, has been developed for screening in this situation (**Table 2**). Patients who score 14 or more are fit, and should be treated similarly to younger patients. Patients scoring ≤14 should ideally be referred for complete onco-geriatric assessment (53, 54). The usefulness of systematic onco-geriatric assessment has largely been demonstrated, by improving the patient's overall condition, or by informing therapeutic decision-making (55–57). The International Society of Geriatric Oncology (SIOG) convened a multi-disciplinary working group of urologists, radiotherapists, medical oncologists, and geriatricians charged with reviewing the literature and produced a set of guidelines on the treatment of prostate cancer in elderly patients (11, 12). These guidelines were then adopted by the EAU in its specific section on the elderly patient. However, prostate cancers are dealt with in two categories depending on whether the disease presents with localized or metastatic disease. The guidelines do not specifically consider the problem of biochemical relapse, though it is a frequently encountered situation in routine clinical practice.

In the case of biochemical relapse following prostatectomy in patients over 70 years of age, we propose that the G8 screening questionnaire should be administered by the urologist, radiotherapist, or medical oncologist (**Figure 1**). If the G8 score is >14, the patient is considered fit and will be preferentially offered SRT if his PSA >0.2 ng/ml. (ART may be considered on a case by case basis in particularly aggressive disease). If the G8 score ≤14, the patient will be referred to the onco-geriatric

TABLE 2 | ONCODAGE scoring chart for establishing G8 score.

Has the patient lost his appetite? Has he eaten less in the last 3 months because of poor appetite, gastro-intestinal symptoms, dysphagia, or problems with mastication?
0: Severe anorexia
1: Moderate anorexia
2: No anorexia
Recent weight loss (in the last 3 months)
0: Weight loss >3 kg
1: Not known
2: Weight loss >1 kg and <3 kg
3: No weight loss
Mobility
0: Bed-bound or wheelchair-bound
1: Mobile within the home
2: Independently mobile
Neuropsychological problems
0: Severe dementia or depression
1: Moderate dementia or depression
2: No psychological problem
Body mass index (BMI)
0: BMI < 18.5
1: 18.5 ≤ BMI < 21
2: 21 ≤ BMI < 23
3: BMI ≥ 23
Taking more than three drugs
0: Yes
1: No
Does the patient consider his own health too be better or worse than others of his own age?
0: Less good
0.5: Don't know
1: As good as others
2: Better than others
Age (years)
0: >85
1: 80–85
2: <80
Total 0–17

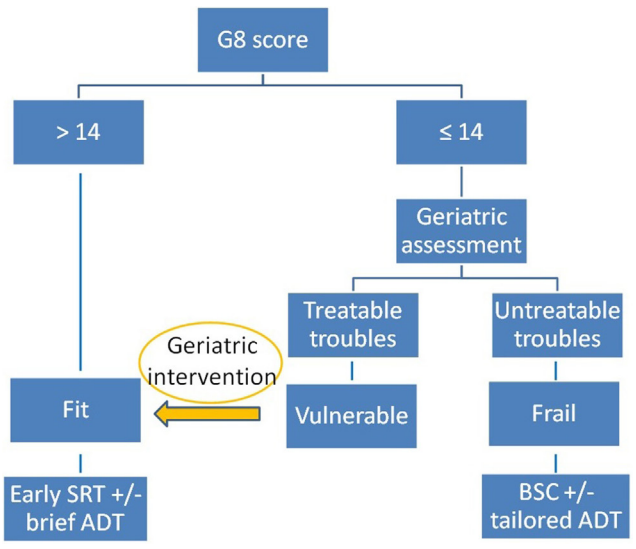

FIGURE 1 | SRT: Salvage radiotherapy; ADT: androgen deprivation therapy; BSC: best supportive care.

service for complete assessment. If this finds the patient to be vulnerable or frail, any treatable conditions should be addressed in order that the patient may benefit from SRT. If the patient is considered to be frail or unfit, with irreversible decline, supportive care should be offered, and hormone therapy delayed as long as possible, to be used only in the advent of bony or urinary symptomatology.

CONCLUSION

Appropriate assessment and management of elderly patients with prostate cancer is a key issue. The appropriate balance between the risk of under-treatment (on the grounds of age alone), and the risk of adverse effects that may excessively compromise the patient's general status and independence, must be determined for each patient. In practice, in the post-operative situation in the elderly patient, the following principles may be adopted:

- No ART except in exceptional cases, while favoring SRT.
- Radiotherapy of the prostate bed presents higher risk in the elderly patient compared with his younger counterpart.
- Hormone therapy as a monotherapy is clearly toxic to elderly patients, and should not be given in the absence of symptoms.
- Short-term Hormone therapy combined with salvage prostate bed radiotherapy may represent a new standard treatment in the near future, but more mature data from clinical trials are needed.

Onco-geriatrics has been a growth specialty for several years now, and professional bodies increasingly provide guidance specific to the needs of older patients. Nevertheless further onco-geriatric trials remain necessary with the aim of establishing the place of more aggressive treatments such as SRT or hormone therapy in the treatment of elderly patients, compared with watchful waiting.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* (2013) **63**:11–30. doi:10.3322/caac.21166
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* (2013) **49**:1374–403. doi:10.1016/j.ejca.2012.12.027
3. Chen RC, Carpenter WR, Hendrix LH, Bainbridge J, Wang AZ, Nielsen ME, et al. Receipt of guideline-concordant treatment in elderly prostate cancer patients. *Int J Radiat Oncol Biol Phys* (2014) **88**:332–8. doi:10.1016/j.ijrobp.2013.11.004
4. Hamilton AS, Fleming ST, Wang D, Goodman M, Wu X-C, Owen JB, et al. Clinical and demographic factors associated with receipt of non guideline-concordant initial therapy for nonmetastatic prostate cancer. *Am J Clin Oncol* (2014). doi:10.1097/COC.0000000000000017
5. Shumway DA, Hamstra DA. Ageism in the undertreatment of high-risk prostate cancer: how long will clinical practice patterns resist the weight of evidence? *J Clin Oncol* (2015) **33**:676–8. doi:10.1200/JCO.2014.59.4093
6. Rider JR, Sandin F, Andrén O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol* (2013) **63**:88–96. doi:10.1016/j.eururo.2012.08.001
7. Akre O, Garmo H, Adolfsson J, Lambe M, Bratt O, Stattin P. Mortality among men with locally advanced prostate cancer managed with noncurative intent: a nationwide study in PCBaSe Sweden. *Eur Urol* (2011) **60**:554–63. doi:10.1016/j.eururo.2011.05.047
8. Freedland SJ, Rumble RB, Finelli A, Chen RC, Slovin S, Stein MN, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* (2014) **32**:3892–8. doi:10.1200/JCO.2014.58.8525
9. Horwich A, Parker C, de Reijke T, Kataja V, ESMO Guidelines Working Group. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2013) **24**(Suppl 6):vi106–14. doi:10.1093/annonc/mdt208
10. Guidelines. *Uroweb*. (2015). Available from: http://uroweb.org/guidelines
11. Droz J-P, Balducci L, Bolla M, Emberton M, Fitzpatrick JM, Joniau S, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. *BJU Int* (2010) **106**:462–9. doi:10.1111/j.1464-410X.2010.09334.x
12. Droz J-P, Aapro M, Balducci L, Boyle H, Van den Broeck T, Cathcart P, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. *Lancet Oncol* (2014) **15**:e404–14. doi:10.1016/S1470-2045(14)70018-X
13. Hamstra DA, Bae K, Pilepich MV, Hanks GE, Grignon DJ, McGowan DG, et al. Older age predicts decreased metastasis and prostate cancer-specific death for men treated with radiation therapy: meta-analysis of radiation therapy oncology group trials. *Int J Radiat Oncol Biol Phys* (2011) **81**:1293–301. doi:10.1016/j.ijrobp.2010.07.2004
14. Zhou P, Chen M-H, McLeod D, Carroll PR, Moul JW, D'Amico AV. Predictors of prostate cancer–specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol* (2005) **23**:6992–8. doi:10.1200/JCO.2005.01.2906
15. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) **25**:2035–41. doi:10.1200/JCO.2006.08.9607
16. Paller CJ, Antonarakis ES, Eisenberger MA, Carducci MA. Management of patients with biochemical recurrence after local therapy for prostate cancer. *Hematol Oncol Clin North Am* (2013) **27**:1205–19. doi:10.1016/j.hoc.2013.08.005
17. Antonarakis ES, Feng Z, Trock BJ, Humphreys EB, Carducci MA, Partin AW, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* (2012) **109**:32–9. doi:10.1111/j.1464-410X.2011.10422.x
18. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) **380**:2018–27. doi:10.1016/S0140-6736(12)61253-7
19. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* (2009) **27**:2924–30. doi:10.1200/JCO.2008.18.9563
20. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* (2006) **296**:2329–35. doi:10.1001/jama.296.19.2329
21. Thoms J, Goda JS, Zlotta AR, Fleshner NE, van der Kwast TH, Supiot S, et al. Neoadjuvant radiotherapy for locally advanced and high-risk prostate cancer. *Nat Rev Clin Oncol* (2011) **8**:107–13. doi:10.1038/nrclinonc.2010.207
22. King CR. Adjuvant versus salvage radiotherapy for high-risk prostate cancer patients. *Semin Radiat Oncol* (2013) **23**:215–21. doi:10.1016/j.semradonc.2013.01.009
23. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* (2004) **291**:1325–32. doi:10.1001/jama.291.11.1325
24. Feng M, Hanlon AL, Pisansky TM, Kuban D, Catton CN, Michalski JM, et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. *Int J Radiat Oncol Biol Phys* (2007) **68**:1417–23. doi:10.1016/j.ijrobp.2007.01.049
25. Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, et al. Clinical factors predicting late severe urinary toxicity after postoperative

radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. *Int J Radiat Oncol Biol Phys* (2012) **82**:191–9. doi:10.1016/j.ijrobp.2010.09.027
26. Longobardi B, Berardi G, Fiorino C, Alongi F, Cozzarini C, Deli A, et al. Anatomical and clinical predictors of acute bowel toxicity in whole pelvis irradiation for prostate cancer with tomotherapy. *Radiother Oncol* (2011) **101**:460–4. doi:10.1016/j.radonc.2011.07.014
27. Perna L, Alongi F, Fiorino C, Broggi S, Cattaneo Giovanni M, Cozzarini C, et al. Predictors of acute bowel toxicity in patients treated with IMRT whole pelvis irradiation after prostatectomy. *Radiother Oncol* (2010) **97**:71–5. doi:10.1016/j.radonc.2010.02.025
28. Cozzarini C, Fiorino C, Deantoni C, Briganti A, Fodor A, La Macchia M, et al. Higher-than-expected severe (Grade 3-4) late urinary toxicity after postprostatectomy hypofractionated radiotherapy: a single-institution analysis of 1176 patients. *Eur Urol* (2014) **66**:1024–30. doi:10.1016/j.eururo.2014.06.012
29. Katayama S, Striecker T, Kessel K, Sterzing F, Habl G, Edler L, et al. Hypofractionated IMRT of the prostate bed after radical prostatectomy: acute toxicity in the PRIAMOS-1 trial. *Int J Radiat Oncol Biol Phys* (2014) **90**:926–33. doi:10.1016/j.ijrobp.2014.07.015
30. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) trial 30891. *J Clin Oncol* (2006) **24**:1868–76. doi:10.1200/JCO.2005.04.7423
31. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knönagel H, et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. *Eur Urol* (2014) **66**:829–38. doi:10.1016/j.eururo.2013.07.024
32. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. *BJU Int* (2013) **111**:543–8. doi:10.1111/j.1464-410X.2012.11774.x
33. Butoescu V, Tombal B. Practical guide to bone health in the spectrum of advanced prostate cancer. *Can J Urol* (2014) **21**:84–92.
34. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* (2005) **352**:154–64. doi:10.1056/NEJMoa041943
35. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* (2005) **23**:2918–25. doi:10.1200/JCO.2005.01.529
36. Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* (2008) **93**:2042–9. doi:10.1210/jc.2007-2595
37. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol* (2013) **189**:S34–42. doi:10.1016/j.juro.2012.11.017
38. Alibhai SMH, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, et al. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. *J Clin Oncol* (2010) **28**:5038–45. doi:10.1200/JCO.2010.29.8091
39. Chambers SK, Newton RU, Girgis A, Nielsen L, Lepore S, Mihalopoulos C, et al. Living with prostate cancer: randomised controlled trial of a multimodal supportive care intervention for men with prostate cancer. *BMC Cancer* (2011) **11**:317. doi:10.1186/1471-2407-11-317
40. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol* (2011) **29**:726–32. doi:10.1200/JCO.2010.31.5226
41. Truong PT, Gaul CA, McDonald RE, Petersen RB, Jones SO, Alexander AS, et al. Prospective evaluation of a 12-week walking exercise program and its effect on fatigue in prostate cancer patients undergoing radical external beam radiotherapy. *Am J Clin Oncol* (2011) **34**:350–5. doi:10.1097/COC.0b013e3181e841ec
42. Martin JM, Supiot S, Berthold DR. Pharmacotherapeutic management of locally advanced prostate cancer: current status. *Drugs* (2011) **71**:1019–41. doi:10.2165/11591500-000000000-00000
43. Calais da Silva F, Calais da Silva FM, Gonçalves F, Santos A, Kliment J, Whelan P, et al. Locally advanced and metastatic prostate cancer treated with intermittent androgen monotherapy or maximal androgen blockade: results from a randomised phase 3 study by the South European Uroncological Group. *Eur Urol* (2014) **66**:232–9. doi:10.1016/j.eururo.2013.03.055
44. Shaw GL, Wilson P, Cuzick J, Prowse DM, Goldenberg SL, Spry NA, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. *BJU Int* (2007) **99**:1056–65. doi:10.1111/j.1464-410X.2007.06770.x
45. Locke JA, Dal Pra A, Supiot S, Warde P, Bristow RG. Synergistic action of image-guided radiotherapy and androgen deprivation therapy. *Nat Rev Urol* (2015) **12**:193–204. doi:10.1038/nrurol.2015.50
46. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* (2005) **61**:1285–90. doi:10.1016/j.ijrobp.2004.08.047
47. Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): Results of the GETUG-AFU 16 phase III randomized trial – NCT00423475. *J Clin Oncol* (2015). Available from: http://meetinglibrary.asco.org/content/147682-156
48. Groome PA, Rohland SL, Siemens DR, Brundage MD, Heaton J, Mackillop WJ. Assessing the impact of comorbid illnesses on death within 10 years in prostate cancer treatment candidates. *Cancer* (2011) **117**:3943–52. doi:10.1002/cncr.25984
49. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. the index of adl: a standardized measure of biological and psychosocial function. *JAMA* (1963) **185**:914–9. doi:10.1001/jama.1963.03060120024016
50. Stineman MG, Xie D, Pan Q, Kurichi JE, Zhang Z, Saliba D, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. *J Am Geriatr Soc* (2012) **60**:485–92. doi:10.1111/j.1532-5415.2011.03867.x
51. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc J-F, Ceccaldi J, Mertens C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* (2012) **30**:1829–34. doi:10.1200/JCO.2011.35.7442
52. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* (2000) **5**:224–37. doi:10.1634/theoncologist.5-3-224
53. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* (2012) **23**:2166–72. doi:10.1093/annonc/mdr587
54. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ONCODAGE prospective multicenter cohort study. *PLoS One* (2014) **9**:e115060. doi:10.1371/journal.pone.0115060
55. Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol* (2013) **24**:1306–12. doi:10.1093/annonc/mds619
56. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* (1993) **342**:1032–6. doi:10.1016/0140-6736(93)92884-V
57. Chaïbi P, Magné N, Breton S, Chebib A, Watson S, Duron J-J, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. *Crit Rev Oncol Hematol* (2011) **79**:302–7. doi:10.1016/j.critrevonc.2010.08.004

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REVIEW
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Post-Prostatectomy Image-Guided Radiotherapy: The Invisible Target Concept

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In the era of intensity-modulated radiation therapy, image-guided radiotherapy (IGRT) appears crucial to control dose delivery and to promote dose escalation while allowing healthy tissue sparing. The place of IGRT following radical prostatectomy is poorly described in the literature. This review aims to highlight some key points on the different IGRT techniques applicable to prostatic bed radiotherapy. Furthermore, methods used to evaluate target motion and to reduce planning target volume margins will also be explored.

Keywords: post-prostatectomy, prostate neoplasm, radiotherapy, image-guided radiotherapy, spacers, endorectal balloons, diet protocol

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INTRODUCTION

Intrapelvic anatomical variations occurring between radiotherapy fractions (inter-fractions) or during the fraction (intra-fraction), corresponding to movement and/or deformation of target volumes and/or adjacent organs at risk (OAR), can result in differences between the distribution of the pretreatment-delivered dose and the initially planned distribution. If not corrected, these variations can particularly cause severe overdose to healthy tissues and underdose to target tumor, leading to an increased risk both of toxicity and of local recurrence (1). In this context, radiotherapy following radical prostatectomy represents a challenge for the radiation oncologist. The absence of a visible target within a complex pelvic anatomical region requires, firstly, accurate target volume delineation and, secondly, a qualitative approach to ensure radiation delivery.

Regarding the first condition, to date, only four articles have published consensus guidelines to delineate the clinical target volume (CTV) corresponding to the prostatectomy bed. According to the Radiation Therapy Oncology Group (RTOG) Consensus Guidelines, CTV can be defined as "the tissue volume at risk of subclinical microscopic and macroscopic tumor growth for the prostate fossa following radical prostatectomy" (2–5). Even if such definition results in lower interobserver variability in the CTV delineation (6), the characterization of the volume of interest still differs from one article to another. This uncertainty arises from both the anatomical modifications after surgery and the difficulty in using the data on preoperative target volume localization. In turn, with the development of intensity-modulated radiation therapy (IMRT), the possibility of increasing the dose to the target while sparing the surrounding OARs has led to significantly improving the biochemical

control for localized prostate cancers (7–9). In the postsurgery setting, the prescribed dose has been shown to be correlated to a biochemical control with both adjuvant radiotherapy and salvage radiation therapy (10–13). The use of IMRT for the irradiation of the prostatectomy bed has also allowed reducing significantly late grade ≥2 gastrointestinal toxicity compared to 3D conformal radiation therapy (14, 15). Nevertheless, with the increase of elderly patients, the choice of treatment must be discussed, and the toxicity threshold re-defined (16). If clinical benefits appear to be obvious with IMRT, the goal of image-guided radiation therapy (IGRT) is to ensure an effective treatment delivery by precisely targeting the radiation to the tumor. The use of planning target volume (PTV), which takes into consideration the uncertainties linked to patient positioning and target volume movements and deformation during treatment, becomes a determining element to guarantee the quality of radiation therapy in the postsurgery setting (17). Dosimetry inaccuracies resulting from positioning errors may decrease biochemical control (18) and increase toxicity if the OARs are not spared (19–21). Prostatectomy bed movements and/or deformations are mainly dictated by changes in the volume and shape of rectum and bladder (18, 22). The aim of this review is to provide an overview of prostatectomy bed motion (PBM) and/or deformation in post-prostatectomy radiotherapy. Repositioning imaging techniques used in IGRT and potential corrective, preventive, and stabilizing measures will also be explored.

CONCEPTS AND STRATEGY FOR IGRT OF THE PROSTATECTOMY BED

What Errors Must Be Taken into Account?

Image guidance is defined as a 3D adjustment of the target position such that the treatment target and the planned target positions correspond. IGRT allows tracking the position of the patient and the target isocenter, of the PTV and of adjacent OARs, as well as analyzing possible deformations for those volumes during the radiotherapy schedule. Minimizing these repositioning errors could lead to reduced PTV margins, which facilitates OAR sparing. Positioning errors can be divided into three main categories:

- Setup errors (SUEs) correspond to the necessary displacements to align bony anatomy on the electronic portal image and the digitally reconstructed radiograph, after patient positioning using skin landmarks.
- PBM corresponds to target volume movement relative to bony anatomy.
- Total positioning error (TPE) is the sum of the two previous errors.

Both systematic (mean value of the displacement) and random (SD of the displacement) errors can be calculated, the systematic error impacting strongly in dose variations (17). In addition to displacement uncertainties, the prostatectomy bed may present large deformations, which are less observed with the intact prostate. Such anatomical variations are much more complex to quantify and to take into account than displacements, unless using elastic registration methods.

How to Evaluate and Reduce These Errors?

The different IGRT techniques allow viewing the tumor either directly through 2D or 3D images, or indirectly using markers or bony structures closely related to the tumor and/or OAR motion. **Table 1** presents potential advantages and limitations of prostatectomy bed IGRT techniques. **Table 2** synthetizes the results of main IGRT studies evaluating PBM.

IMAGE-BASED POSITIONING TECHNIQUES IN POST-PROSTATECTOMY IGRT: WHAT RESULTS WITH WHICH TECHNIQUE?

Bony Anatomy Alignment Captured by 2D Imaging

Klayton et al. studied PBM using electromagnetic transponders in order to evaluate the quality of bony anatomy as a localization method using 2D imaging. After patient positioning based on laser and skin landmarks, the evaluation of target volume isocenter position was carried out with electromagnetic transponders. Deviation of the isocenter position in this case corresponded to TPE. Once the first alignment completed, 2D kv–kv imaging was performed. PBM was estimated by measuring the 3D shifts needed to align bony anatomy. For 9% of fractions, anterior–posterior (AP) direction PBM exceeded 5 mm. In 21% of fractions, a repositioning in the superior–inferior (SI) direction was necessary. Finally, 70% of patients were repositioned at least once during treatment. According to the authors, patient setup margins were 5 mm in left–right (LR), 13 mm in SI, and 9 mm in AP based on 2D kv–kv image guidance. The results of this study are summarized in **Table 2**. 2D imaging on its own only takes into consideration SUEs, omitting the contribution of the PBM component and of volume variations. As a result, it is not adapted to estimate prostatectomy bed movements (23).

Soft Tissue Anatomy Alignment Evaluated by 3D Imaging

Ost et al. analyzed a series of 547 cone beam computed tomography (CBCT) daily images from 15 patients successively treated by post-prostatectomy radiotherapy. PBM was determined considering the motion of the anterior rectal wall. Systematic inter-fraction movements in the LR, SI, and AP were 0.44, 0.92, and 2.50 mm, respectively. Similarly, random deviations of 0.99 mm in LR, 1.38 mm in SI, and 2.32 mm in AP axes were observed. These results, based on imaging modalities that take into account PBM, emphasize the prevalence of AP shifts of the prostatectomy bed, as reported for prostate, and highlight that an approach relying only on bony anatomy appears insufficient (24). Despite the larger TPE described with 2D kv–kv imaging compared to CBCT, no correlation was found between TPE and acute toxicity (25). Using computed tomography (CT)-on-rails

TABLE 1 | Description of post-prostatectomy image-guided radiotherapy (IGRT) techniques.

IGRT technique	Concept	Advantages	Limitations
2D imaging	Displacement determined by bonny anatomy or fiducial marker misalignment between the image acquired by the treatment device compared to DRR	– Quick – Low dose	– No visualization of soft tissues
3D imaging	Image reconstructed by rotation around the patient through several 2D projections	– Alignment using skin landmarks possible – Visualization of target volume and OAR allowing to take into consideration variations due to rectal and bladder filling – Low energy (on board imaging or X-ray volume imaging)	– Artefacts related to materials with high electronic density – High energy (high-energy scan of tomotherapy devices) – Image quality
Transabdominal or transperineal ultrasound	Follow-up of target volume positioning during treatment sessions	Non-ionizing	Inter-operator variability
MRI	Treatment devices coupled to an MRI system	– Non-ionizing – Follow-up of motions during sessions – Mage quality	– Image distortion – Calculation of dose distribution
Fiducial markers	Implanted in the target volume, and theoretically follow target motion	– Account of prostatectomy bed motion contribution in case of bidimensional imaging modalities – Potential improvement in the precision of alignment using 3D imaging	Invasive procedure
Electromagnetic transponders	A real-time follow-up of transponder displacements, implanted in the target volume, allows studying intra-fraction motion	Intra-fraction and inter-fraction evaluation	Invasive procedure

DRR, digitally reconstructed radiograph; MRI, magnetic resonance imaging; OAR, organs at risk.

IGRT on 10 patients, Liu et al. analyzed volume variations and deformations of CTV, rectum, and bladder. They showed daily volume variations of 75–116% for CTV, 50–270% for rectum, and 30–180% for bladder compared to planning CT (26).

Soft Tissue Anatomy Alignment Evaluated by Ultrasonography (US)

Studies on the use of US for post-prostatectomy IGRT are scarce. Chinnaiyan et al. analyzed PBM in six consecutive patients by comparing transabdominal US (taking the bladder neck as reference for post-prostatectomy fossa localization) with 2D imaging. Regarding repositioning accuracy, there was a difference of 5 ± 3 mm between the two techniques in favor of US imaging. This result supports the use of the US-IGRT for daily pretreatment patient repositioning as stated by the authors (27).

A comparison of transabdominal US and CBCT imaging was carried out by Fargier-Voiron et al. in 11 post-prostatectomy patients. The differences between US and CBCT shifts were -0.7 ± 4.3, 1 ± 4.6, and 0.2 ± 2.7 mm in AP, SI, and LR axes, respectively. For these three directions, the shift agreements (percentage of sessions for which the shift difference between the two modalities is below or equal to 5 mm) between US and CBCT were 80.2, 86.8, and 96.2%, respectively. During radiotherapy schedule, 20% of the US images were excluded due to poor quality, the authors concluding that transabdominal US imaging alone should not be used as IGRT modality (28). The same group evaluated a novel method of transperineal US imaging (Clarity, Elekta®) that offers a better image quality (100 vs 80% exploitable), a reduction of inter-operator variability, and a consistent probe pressure during examination. Shift agreements at ±5 mm improved to 90.3, 85, and 97.6% in AP, SI, and LR directions, respectively, leading the authors to propose this method as a non-ionizing alternative to CBCT (29).

What PTV Margins Are Used with Which IGRT Technique?

It appears essential to adapt PTV margins to the IGRT techniques used by the physician. According to the literature, these margins range from 3 to 10 mm (30). For example, in cases of bony anatomy alignment, PTV margins vary from 5 to 15 mm. Indeed, recommendations for target volume definitions differ substantially: at least 5 mm according to the European Organization For Research and Treatment of Cancer, 10 mm according to the Australian and New Zealand Radiation Oncology Genito-Urinary Group (in case of rectal dose–volume histogram limitations, a reduction of the posterior PTV margin expansion to 5 mm is possible), from 6 to 15 mm according to the RTOG study 0534, and from 5 to 15 mm according to the recommendations from the Groupe d'Etude des Tumeurs Uro-Génitales (2–5).

CAN IGRT BE IMPROVED USING PROSTATECTOMY BED REPOSITIONING MARKERS?

Surgical Clips As Markers

Similar to prostate radiotherapy, several studies have analyzed the use of surgical clips during post-prostatectomy irradiation

TABLE 2 | Results of IGRT main studies evaluating prostatectomy bed movements.

Reference	IGRT technique	Patient/images	Positioning error (mean or average)	AP mm (SD)	SI mm (SD)	LR mm (SD)	Proposed PTV margins (mm)
Ost et al. (24)	CBCT	15/547	PBM mean PBM average TPE mean SUE mean	2.7 (3) 2.2 3.1 (2.3) 1.9 (1.8)	0.9 (1.4) 0.6 1.9 (1.6) 1.9 (1.5)	0.6 (0.9) 0 2.9 (2.2) 2.9 (2.2)	AP 8[c] SI 6[c] LR 8[c]
Song et al. (32)	Surgical clips kv	17/364	TPE Absolute shifts	–2.1 3.1 (2.3)	0.6 2.5 (1.4)	–0.1 2.3 (0.7)	AP 8[c] SI 9[c] LR 6[c]
Sandhu et al. (31)	Surgical clips kv	26/692	PBM TPE SUE	2.7 (2.1) 3.8 (5.5) 5.2 (7.1)	2.4 (2.1) 5.3 (8.1) 4.9 (7.5)	1 (1.7) 3.9 (5.9) 3.6 (5.6)	
Bell et al. (34)	Surgical clips CBCT	40/377	PBM upper PBM lower	0.5 (0.5) 0.18 (0.16)	0.28 (0.26) 0.18 (0.17)	0.10 (0.12) 0.08 (0.1)	
Huang et al. (33)	Surgical clips CBCT	14/420	PBM inter-fraction PBM intra-fraction	1.9 0.2	–0.9 –0.4	0 0.1	AP 4.8[a]/6.3[c] SI 4.6[a]/6.1[c] LR 3.1[a]/3.9[c]
Kupelian et al. (35)	Surgical clips MVCT	4/140	PBM	0.39 (1.27)	0.1 (0.86)	0.06 (0.37)	
Ålander et al. (39)	Gold seeds CBCT	13/466	PBM TPE SUE	0.8 (1.6) 0.4 (2.7) –0.2 (2.2)	0.7 (2.1) 0.3 (2.9) –0.5 (2)	0 (0.5) 1.2 (1.8) 1.2 (1.8)	AP 6.6[b] SI 6.5[b] LR 2.4[b]
Schiffner et al. (40)	Gold seeds kv (EPID)	10/163	PBM TPE SUE	–1.1 (2.1) –0.3 (4.5) –0.2 (5.1)	0.4 (2.4) 1.2 (5.1) 1.1 (3.9)	0.3 (0.9) 0.2 (4.5) 0.1 (4.5)	
Klayton et al. (23)	Calypso kv	20/87	PBM mean TPE mean SUE mean PTV-CTVm1	2.5 (3.2) 4 (4.9) 4.1 (4.7) 9	3.6 (4.2) 3.8 (5.2) 4.1 (5.2) 13	1.3 (1.8) 3 (4.1) 3.9 (5.2) 5	AP 5[a]/9[b]/15[c] SI 5[a]/13[b]/13[c] LR 5[a]/5[b]/9[c]
Cavalieri et al. (36)	CT on rail	17/661	TPE mean TPE average	4.7 (3.3) –2.2 (5.3)	3.8 (3.0) –1.1 (4.7)	2.9 (2.5) –0.6 (3.8)	
Simpson et al. (25)	CBCT kv	23/585	PBM (CBCT)	0.9 (1.6)	0.5 (1.5)	0.4 (0.9)	

Margin recipe used: 2.5Σ + 0.7σ and 1.96Σ + 0.7σ.

[a]PTV-CTV margins calculated with respect to PBM (using IGRT technique analyzed in the study).

[b]PTV-CTV margins calculated with respect to TPE (verification of bony anatomy alignment).

[c]PTV-CTV margins calculated in case of absence of IGRT.

PBM, prostatectomy bed motion; SUE, setup error; TPE, total positioning error; AP, anteroposterior; SI, superoinferior; LR, left–right; CTV, clinical target volume; PTV, planning target volume; IGRT, image-guided radiotherapy; Surg. Clips, surgical clips; CBCT, cone beam computed tomography; MVCT, megavoltage computed tomography; kv, kilovoltage; EPID, electronic portal imaging device; CT, computed tomography.

(31–35). Sandhu et al. studied two orthogonal kv images to localize the prostatectomy bed in 26 patients using surgical clips as target volume landmarks. In total, 692 images were analyzed. Target volume displacements were mainly related to SUE. PBM was most prominent in the AP axis, with an average magnitude of 2.7 ± 2.1 mm. PBM in the SI and LR directions was 2.4 ± 2.1 and 1 ± 1.7 mm, respectively (31). Series using 3D imaging with the same approach have also reported the prominence of the displacements in the AP direction (2–5 mm) compared to those in the SI (0.5–2.5 mm) and lateral (less than 1 mm) directions (33, 35). Cavalieri et al. used surgical clips as markers to analyze the repositioning of 17 consecutive patients using CT-on-rail IGRT. Systematic errors led to displacements ranging from 6 to 10 mm, mainly in the AP dimension (5.5%) (36). Hence, the use of surgical clips as markers to guide radiotherapy could reduce the impact of PBM. **Figure 1** presents an example of CBCT for post-prostatectomy radiotherapy.

Gold Fiducial As Markers

Historically used for prostate radiotherapy, fiducial markers facilitate the detection of the CTV. Additionally, their radiopacity allows using low ionizing imaging modalities. Even though the transrectal implantation of gold fiducial markers under US guidance is an invasive technique, very few complications have been described. Langenhuijsen et al. implanted three gold markers (two at the dorsal bladder base and one next to the anastomosis) in 77 consecutive post-prostatectomy patients and showed the feasibility of the procedure (37). Fortin et al. reported a reduction

FIGURE 1 | **Example of post-prostatectomy image-guided radiotherapy**. Initial computed tomography (CT) scan and cone beam computed tomography (CBCT) used for analysis of repositioning show a good correlation for rectum, bladder, and clinical target volume.

of inter-operator variability during online and offline localization compared to surgical clips. Furthermore, fiducial markers resulted in a repositioning quality greater than that of surgical clips, often out of the prostatectomy bed and closely clustered, limiting daily SUE and errors related to PBM (38). After implanting gold fiducial markers into the prostate bed, daily CBCT of 13 patients was analyzed by Ålander et al. They reported displacements (mean ± SD) of 0.0 ± 0.5 mm in the LR, 0.7 ± 2.1 mm in the SI, and 0.8 ± 1.6 mm in the AP directions, which were deemed non-significant by the authors (39). In a similar manner, Schiffner et al. used 2D imaging for 10 patients. Positioning errors of more than 5 mm in the LR, SI, and AP axes were observed in 14.1, 38.7, and 28.2% of the cases, respectively, mainly related to SUE, while PBM remained modest. Over the total duration of treatment, gold seed fiducial migration was small (0.4 mm on average) (40). Confirming the difficulties in matching predominant in the AP direction, also reported with the use of surgical clips, gold fiducial markers with CBCT or kv–kv imaging appear to be more robust despite their invasive nature.

IS THERE A NEED FOR GLOBAL POSITIONING SYSTEM FOR PROSTATE BED RADIOTHERAPY?

The Calypso® 4D Localization System commercialized by Varian enables real-time intra-fraction localization and tracking with three electromagnetic transponders (41). Already studied in the prostate irradiation setting (42), intra-fraction motion was analyzed in 20 patients undergoing post-prostatectomy radiotherapy. A displacement of more than 5 mm during 30 s was reported for at least 11% of delivered fractions. For 16 (80%) patients, PBM was observed in the SI and AP axes, and the 5-mm threshold margin was exceeded in a third of cases. Interruptions for repositioning were reported in 15% of the delivered fractions. Over the treatment course, only 25% of the patients were repositioned more than five times, and 30% of the patients did not need any repositioning. Further studies are needed in order to select patients that can benefit most from this approach (23).

PREVENTIVE, CORRECTIVE, AND STABILIZING APPROACHES TO LIMIT PBM DUE TO RECTAL AND BLADDER MOVEMENTS

Prostatectomy bed motion is essentially correlated with adjacent OAR displacements or volume variations. Disregarding rectal distension could result in an increase of up to 18 or 24 mm of posterior margins and, consequently, in dosimetry inaccuracies (43, 44). **Figure 2** illustrates a case of inadequate rectal filling during treatment. Concerning bladder volume variations during treatment, Fiorino et al. detected a ratio between the largest and smallest volume of 3.8 (range 1.9–8.3), which had an impact on PTV (18). Preventive, corrective, and stabilizing approaches to limit PBM due to rectal and bladder movements are presented below.

Bladder Filling

Variations in bladder volume are frequent in both post-prostatectomy and non-operated patients, with a trend in decreasing volume during treatment (18, 45). These bladder volume variations could impact on PTV coverage (22). Bell et al. showed that bladder filling variations of >2, ±1, or <2 cm happened in 3.4–56.2% of cases, with most size changes occurring in the AP direction. These variations resulted in potential geographic misses (movement of surgical clips greater than 0.5 cm posteriorly, 1 cm in other directions). Further, if the bladder or rectum remained

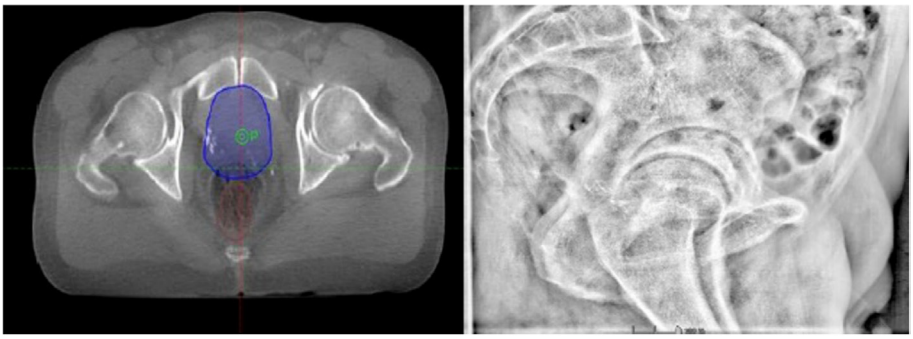

FIGURE 2 | Example of a patient treated by prostate-bed radiotherapy with inadequate rectal filling during image-guided radiotherapy (3D image-based positioning).

within 1 cm of the planned size, less than 10% of the images revealed a geographic miss (46). These results demonstrate the importance of a consistent and stable bladder and rectal volume during treatment. Patients at risk of variations should be detected early in order to offer them the most secure treatment.

Diet Recommendations

Studies on diet changes, in order to prevent the production of gas, primarily in cases of prostate irradiation, have led to conflicting results. Smitsmans et al. compared the CBCT of 26 patients irradiated following a diet poor in fibers and 23 patients following no diet. Diet was beneficial, preventing the presence of stool, gas pockets, and moving gas pockets during radiotherapy, and resulted in a reduction of inter-fraction and intra-fraction motion (47). On the contrary, Lips et al. evaluated the same type of diet in 105 patients and observed an increase in inter-fraction prostate motion for patients following the dietary protocol. The median of the average inter-fraction motion ranged from 2.53 mm in the non-diet group to 3 mm in the diet group (48). Using magnetic resonance imaging (MRI) as IGRT technique, Nichol et al. evaluated an antiflatulent diet and a milk of magnesia-based laxative in 42 patients and did not observe a reduction in inter-fraction prostate motion. This study demonstrated that moving gas only (56%) and moving gas and stool (18%) accounted for 74% of inter-fraction movements (49). Concerning inter-fraction motion, Oates et al. could not demonstrate any significant difference in favor of a diet associated to psyllium but observed a trend toward rectal volume reduction (50). A randomized trial including 40 patients studied the use of probiotics, such as *Lactobacillus acidophilus*, and reported a significant reduction in rectal volume variations over the treatment course (51). Evaluations on other molecules preventing the production of intestinal gas, such as the alpha-galactosidase, are ongoing (52). Although encouraging, these results need to be further validated.

Strategies for Rectal Emptying

Several studies have analyzed the efficacy of different strategies to empty rectal gases in order to minimize prostate motion. Yahya et al. compared three strategies to reduce rectal distension: (i) the use of microenema before each treatment; (ii) a recommended dietary protocol; and (iii) no bowel preparation or dietary advice. After the analyses of the CBCT scans of these three groups, a reduction of almost half of scans showing geometric miss (shifts $\geq$5 mm) was observed in the microenema group compared to the other two (53). Ogino et al. analyzed the impact of rectal gas self-evacuation using the index finger on the average prostate and seminal vesicle motion in 76 patients. A significant reduction (0.3–4.4 mm) of the prostate and the seminal vesicle displacement was observed (54). Diot et al. analyzed in a series of 17 post-prostatectomy patients an intervention involving the use of a rectal catheter to deflate the rectum, evacuation of stools, and adjustment of bladder filling. These corrective measures were applied in cases of rectal or bladder wall displacements larger than 5 mm. The median number of interventions per patient was 5. The procedure led to a reduction in the motion of the target volume during radiotherapy schedule, which dropped from 45 to 21% in the AP, from 7 to 4% in the SI, and from 7 to 8% in the LR direction. These measures, more effective for AP displacements, decreased the PTV margin by 3.3 mm (55). Nevertheless, no benefit in terms of dosimetry was observed with conventional fractionation both for PTV coverage or OAR sparing. These results suggest that daily CBCT localization alone could be enough to take into consideration the motion of the target volume. For hypofractionated treatments, however, the rectal emptying interventions could have a greater impact in terms of dosimetry (56).

Endorectal Balloons (ERBs)

Rectal filling has been identified as predictive of prostate motion by cine-MRI studies assessing intra-fraction movements (57, 58). The introduction of an ERB could optimize the rectal volume and conformation, minimizing at the same time target volume positioning errors.

In a comparative study on 14 post-prostatectomy patients, 7 of which were treated with ERB, shift agreement of CTV and rectal volumes with planning CT were improved by 4 and 21%, respectively. This stability is also reflected in a reduction of median motion, particularly the AP margin of the lower part of the CTV motion of 0.43 $\pm$ 0.45 cm without ERB to 0.37 $\pm$ 0.27 cm with ERB. The lower part of CTV moves dropped

from 0.16 ± 0.17 to 0.11 ± 0.11 cm. ERB also reduced the impact of vesicle filling on shift agreement (59). Jameson et al. analyzed the use of ERB on post-prostatectomy patients and observed no significant dosimetry improvements in terms of PTV coverage or OAR sparing with the use of ERB (60). On the other hand, some dosimetry studies have demonstrated an improvement in rectum and anal canal sparing, mainly for intermediate and high doses, with the use of ERB. Smeenk et al. compared the dosimetry in 20 patients that had undergone surgery, with or without ERB, for a prescription dose of 70 Gy. Regarding rectal dose–volume histogram, rectal V30 and V40 dropped by 8 and 5%, respectively. CTV volume was considerably reduced in the presence of ERB (117 ± 27 vs 110 ± 20 cc), but no correlation could be found between this volume and rectal sparing (61, 62).

Concerning the clinical impact, Ishiyama et al. carried out a retrospective study on 107 patients treated by salvage radiotherapy with ERB at a dose of 70 Gy in 32 fractions. Late gastrointestinal and genitourinary toxicities of grade 2 were reported in 6 and 13% of patients, respectively, and grade 3 in 3 and 6% of patients, respectively (63).

The development of new stabilizers, such as the ProSpare of the Institute of Cancer Research in London, opens up a new study field in this domain. ProSpare proposes to add radio-opaque markers that allow a better identification of the anterior rectal wall, as well as ventilation holes for the evacuation of rectal gases (64, 65). A phase II study is currently ongoing (postoperative ProSpare).

Spacers

The injection or implantation of a biodegradable substance in the anterior perirectal fatty space was studied for patients receiving prostate radiotherapy (66). This approach allows displacing the prostate away from the rectal wall reducing the rectal volume exposed to high level doses (67). Pinkawa et al. found a significant reduction of systematic posterior displacements superior to 6.5 mm (dropping from 27 to 0%) (68–71). For prostate radiotherapy, a wide range of spacers have been studied, and the prostate-rectum separation varied from 7 to 20 mm depending on the technique used, reducing the rectal V70 by about 43–84% (66, 72, 73). Spacer utilization has been less explored in the postoperative radiotherapy setting. Pinkawa et al. published a case report on a patient presenting a macroscopic recurrence at the uretho-vesical anastomosis. Polyethylene glycol spacer injection allowed them to create a space of more than 1 cm between the recurrence site and the rectal wall. This led to significantly reducing the rectal V70, V60, and V50 compared to treatment planning based on computer tomography. PTV dose prescription was 76 Gy, and a good global tolerance led the authors to propose this approach for specifically selected patients (74).

CONCLUSION

Radiotherapy of the prostatectomy bed in an adjuvant or salvage setting, mostly under IMRT and IGRT conditions, constitutes a routine situation for the clinician. 2D imaging modalities are in themselves insufficient to evaluate target volume displacement and deformation, and the soft tissue anatomy alignment using a 3D approach appears crucial. The utility of fiducial markers or surgical clips, as well as preventive, corrective, or stabilizing measures, has been shown to limit these displacements. At present, due to lack of substantial literature, reducing the margin that constitutes the PTV to less than 5 mm (independent of the IGRT technique used) is not recommended; however, an anisotropic approach can be justified in view of the predominant displacements in the AP dimension on the prostatectomy bed. The development of MRI and of tracking strategies could therefore improve imaging quality and, as a result, increase the precision of soft tissue anatomy alignment. The trend toward dose augmentation and hypofractionation requires not only precise target localization to ensure dose distribution but also tolerance and efficacy. Confirming the impact of IGRT by means of larger studies seems necessary with, notably, an evaluation of patient-reported outcomes.

AUTHOR CONTRIBUTIONS

Drafting the article: FV and PS. Critical revision of the article; final approval of the version to be published: FV, MA, MB, IL, SS, PR, LT, NL, SG, JI-A, RC, and PS.

REFERENCES

1. Gill S, Isiah R, Adams R, Dang K, Siva S, Tai KH, et al. Conventional margins not sufficient for post-prostatectomy prostate bed coverage: an analysis of 477 cone-beam computed tomography scans. *Radiother Oncol* (2014) 110(2):235–9. doi:10.1016/j.radonc.2013.12.004
2. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, 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(2):121–7. doi:10.1016/j.radonc.2007.07.017
3. Wiltshire KL, Brock KK, Haider MA, Zwahlen D, Kong V, Chan E, et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. *Int J Radiat Oncol Biol Phys* (2007) 69(4):1090–9. doi:10.1016/j.ijrobp.2007.04.068
4. Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) 76(2):361–8. doi:10.1016/j.ijrobp.2009.02.006
5. Sidhom MA, Kneebone AB, Lehman M, Wiltshire KL, Millar JL, Mukherjee RK, et al. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol* (2008) 88(1):10–9. doi:10.1016/j.radonc.2008.05.006
6. Mitchell DM, Perry L, Smith S, Elliott T, Wylie JP, Cowan RA, et al. Assessing the effect of a contouring protocol on postprostatectomy radiotherapy clinical target volumes and interphysician variation. *Int J Radiat Oncol Biol Phys* (2009) 75(4):990–3. doi:10.1016/j.ijrobp.2008.12.042
7. Kupelian PA, Ciezki J, Reddy CA, Klein EA, Mahadevan A. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* (2008) 71(1):16–22. doi:10.1016/j.ijrobp.2007.09.020
8. Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess* (2010) 14(47):1–108, iii–iv. doi:10.3310/hta14470
9. Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* (2011) 117(7):1429–37. doi:10.1002/cncr.25467

10. Bernard JR, Buskirk SJ, Heckman MG, Diehl NN, Ko SJ, Macdonald OK, et al. Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. *Int J Radiat Oncol Biol Phys* (2010) 76(3):735–40. doi:10.1016/j.ijrobp.2009.02.049
11. King CR. The dose-response of salvage radiotherapy following radical prostatectomy: a systematic review and meta-analysis. *Radiother Oncol* (2016) 121(2):199–203. doi:10.1016/j.radonc.2016.10.026
12. Herrera FG, Berthold DR. Radiation therapy after radical prostatectomy: implications for clinicians. *Front Oncol* (2016) 6:117. doi:10.3389/fonc.2016.00117
13. Beck M, Barelkowski T, Kaul D, Wecker S, Thieme AH, Zwahlen DR, et al. Role of dose intensification for salvage radiation therapy after radical prostatectomy. *Front Oncol* (2016) 6:48. doi:10.3389/fonc.2016.00048
14. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol* (2011) 60(6):1142–8. doi:10.1016/j.eururo.2011.08.006
15. Raziee H, Berlin A. Gaps between evidence and practice in postoperative radiotherapy for prostate cancer: focus on toxicities and the effects on health-related quality of life. *Front Oncol* (2016) 6:70. doi:10.3389/fonc.2016.00070
16. Goineau A, d'Aillières B, de Decker L, Supiot S. Integrating geriatric assessment into decision-making after prostatectomy: adjuvant radiotherapy, salvage radiotherapy, or none? *Front Oncol* (2015) 5:227. doi:10.3389/fonc.2015.00227
17. van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. *Int J Radiat Oncol* (2002) 52(5):1407–22. doi:10.1016/S0360-3016(01)02805-X
18. Fiorino C, Foppiano F, Franzone P, Broggi S, Castellone P, Marcenaro M, et al. Rectal and bladder motion during conformal radiotherapy after radical prostatectomy. *Radiother Oncol* (2005) 74(2):187–95. doi:10.1016/j.radonc.2004.10.002
19. de Crevoisier R, Tucker SL, Dong L, Mohan R, Cheung R, Cox JD, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* (2005) 62(4):965–73. doi:10.1016/j.ijrobp.2004.11.032
20. Potters L, Gaspar LE, Kavanagh B, Galvin JM, Hartford AC, Hevezi JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT). *Int J Radiat Oncol Biol Phys* (2010) 76(2):319–25. doi:10.1016/j.ijrobp.2009.09.042
21. Korreman S, Rasch C, McNair H, Verellen D, Oelfke U, Maingon P, et al. The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide. *Radiother Oncol* (2010) 94(2):129–44. doi:10.1016/j.radonc.2010.01.004
22. Haworth A, Paneghel A, Herschtal A, Duchesne G, Williams S, Tai KH, et al. Verification of target position in the post-prostatectomy cancer patient using cone beam CT. *J Med Imaging Radiat Oncol* (2009) 53(2):212–20. doi:10.1111/j.1754-9485.2009.02057.x
23. Klayton T, Price R, Buyyounouski MK, Sobczak M, Greenberg R, Li J, et al. Prostate bed motion during intensity-modulated radiotherapy treatment. *Int J Radiat Oncol Biol Phys* (2012) 84(1):130–6. doi:10.1016/j.ijrobp.2011.11.041
24. Ost P, De Meerleer G, De Gersem W, Impens A, De Neve W. Analysis of prostate bed motion using daily cone-beam computed tomography during postprostatectomy radiotherapy. *Int J Radiat Oncol Biol Phys* (2011) 79(1):188–94. doi:10.1016/j.ijrobp.2009.10.029
25. Simpson DR, Einck JP, Nath SK, Sethi RA, Wang JZ, Mundt AJ, et al. Comparison of daily cone-beam computed tomography and kilovoltage planar imaging for target localization in prostate cancer patients following radical prostatectomy. *Pract Radiat Oncol* (2011) 1(3):156–62. doi:10.1016/j.prro.2010.12.002
26. Liu F, Ahunbay E, Lawton C, Li XA. Assessment and management of interfractional variations in daily diagnostic-quality-CT guided prostate-bed irradiation after prostatectomy. *Med Phys* (2014) 41(3):031710. doi:10.1118/1.4866222
27. Chinnaiyan P, Tomée W, Patel R, Chappell R, Ritter M. 3D-ultrasound guided radiation therapy in the post-prostatectomy setting. *Technol Cancer Res Treat* (2003) 2(5):455–8. doi:10.1177/153303460300200511
28. Fargier-Voiron M, Presles B, Pommier P, Munoz A, Rit S, Sarrut D, et al. Ultrasound versus Cone-beam CT image-guided radiotherapy for prostate and post-prostatectomy pretreatment localization. *Phys Med* (2015) 31(8):997–1004. doi:10.1016/j.ejmp.2015.07.147
29. Fargier-Voiron M, Presles B, Pommier P, Munoz A, Rit S, Sarrut D, et al. Evaluation of a new transperineal ultrasound probe for inter-fraction image-guidance for definitive and post-operative prostate cancer radiotherapy. *Phys Med* (2016) 32(3):499–505. doi:10.1016/j.ejmp.2016.01.481
30. Ramiandrisoa F, Duvergé L, Castelli J, Nguyen TD, Servagi-Vernat S, de Crevoisier R. [Clinical to planning target volume margins in prostate cancer radiotherapy]. *Cancer Radiother* (2016) 20(6–7):629–39. doi:10.1016/j.canrad.2016.07.095
31. Sandhu A, Sethi R, Rice R, Wang J-Z, Marcus L, Salem C, et al. Prostate bed localization with image-guided approach using on-board imaging: reporting acute toxicity and implications for radiation therapy planning following prostatectomy. *Radiother Oncol* (2008) 88(1):20–5. doi:10.1016/j.radonc.2008.05.009
32. Song S, Yenice KM, Kopec M, Liauw SL. Image-guided radiotherapy using surgical clips as fiducial markers after prostatectomy: a report of total setup error, required PTV expansion, and dosimetric implications. *Radiother Oncol* (2012) 103(2):270–4. doi:10.1016/j.radonc.2011.07.024
33. Huang K, Palma DA, Scott D, McGregor D, Gaede S, Yartsev S, et al. Inter- and intrafraction uncertainty in prostate bed image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* (2012) 84(2):402–7. doi:10.1016/j.ijrobp.2011.12.035
34. Bell LJ, Cox J, Eade T, Rinks M, Kneebone A. Prostate bed motion may cause geographic miss in post-prostatectomy image-guided intensity-modulated radiotherapy. *J Med Imaging Radiat Oncol* (2013) 57(6):725–32. doi:10.1111/1754-9485.12089
35. Kupelian PA, Langen KM, Willoughby TR, Wagner TH, Zeidan OA, Meeks SL. Daily variations in the position of the prostate bed in patients with prostate cancer receiving postoperative external beam radiation therapy. *Int J Radiat Oncol Biol Phys* (2006) 66(2):593–6. doi:10.1016/j.ijrobp.2006.05.071
36. Cavalieri R, Gay HA, Liu J, Ferreira MC, Mota HC, Sibata CH, et al. Total error shift patterns for daily CT on rails image-guided radiotherapy to the prostate bed. *Radiat Oncol* (2011) 6:142. doi:10.1186/1748-717X-6-142
37. Langenhuijsen JF, Donker R, McColl GM, Kiemeney LA, Witjes JA, van Lin EN. Postprostatectomy ultrasound-guided transrectal implantation of gold markers for external beam radiotherapy. Technique and complications rate. *Strahlenther Onkol* (2013) 189(6):476–81. doi:10.1007/s00066-013-0323-4
38. Fortin I, Carrier J-F, Beauchemin M-C, Béliveau-Nadeau D, Delouya G, Taussky D. Using fiducial markers in the prostate bed in postprostatectomy external beam radiation therapy improves accuracy over surgical clips. *Strahlenther Onkol* (2014) 190(5):46771. doi:10.1007/s00066-014-0631-3
39. Ålander E, Visapää H, Kouri M, Keyriläinen J, Saarilahti K, Tenhunen M. Gold seed fiducials in analysis of linear and rotational displacement of the prostate bed. *Radiother Oncol* (2014) 110(2):256–60. doi:10.1016/j.radonc.2013.10.037
40. Schiffner DC, Gottschalk AR, Lometti M, Aubin M, Pouliot J, Speight J, et al. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. *Int J Radiat Oncol Biol Phys* (2007) 67(2):610–9. doi:10.1016/j.ijrobp.2006.09.042
41. Balter JM, Wright JN, Newell LJ, Friemel B, Dimmer S, Cheng Y, et al. Accuracy of a wireless localization system for radiotherapy. *Int J Radiat Oncol Biol Phys* (2005) 61(3):933–7. doi:10.1016/j.ijrobp.2004.11.009
42. Willoughby TR, Kupelian PA, Pouliot J, Shinohara K, Aubin M, Roach M, et al. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* (2006) 65(2):528–34. doi:10.1016/j.ijrobp.2006.01.050
43. Li XA, Yu C, Holmes T. A systematic evaluation of air cavity dose perturbation in megavoltage x-ray beams. *Med Phys* (2000) 27(5):1011–7. doi:10.1118/1.598966
44. Pinkawa M, Siluschek J, Gagel B, Demirel C, Asadpour B, Holy R, et al. Influence of the initial rectal distension on posterior margins in primary and postoperative radiotherapy for prostate cancer. *Radiother Oncol* (2006) 81(3):284–90. doi:10.1016/j.radonc.2006.10.028
45. O'Doherty UM, McNair HA, Norman AR, Miles E, Hooper S, Davies M, et al. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. *Radiother Oncol* (2006) 79(3):335–40. doi:10.1016/j.radonc.2006.05.007
46. Bell LJ, Cox J, Eade T, Rinks M, Kneebone A. The impact of rectal and bladder variability on target coverage during post-prostatectomy intensity

modulated radiotherapy. *Radiother Oncol* (2014) 110(2):245–50. doi:10.1016/j.radonc.2013.10.042
47. Smitsmans MHP, Pos FJ, de Bois J, Heemsbergen WD, Sonke J-J, Lebesque JV, et al. The influence of a dietary protocol on cone beam CT-guided radiotherapy for prostate cancer patients. *Int J Radiat Oncol Biol Phys* (2008) 71(4):1279–86. doi:10.1016/j.ijrobp.2008.03.036
48. Lips IM, Kotte ANTJ, van Gils CH, van Leerdam ME, van der Heide UA, van Vulpen M. Influence of antiflatulent dietary advice on intrafraction motion for prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* (2011) 81(4):e401–6. doi:10.1016/j.ijrobp.2011.04.062
49. Nichol AM, Warde PR, Lockwood GA, Kirilova AK, Bayley A, Bristow R, et al. A cinematic magnetic resonance imaging study of milk of magnesia laxative and an antiflatulent diet to reduce intrafraction prostate motion. *Int J Radiat Oncol Biol Phys* (2010) 77(4):1072–8. doi:10.1016/j.ijrobp.2009.06.005
50. Oates RW, Schneider ME, Lim Joon M, McPhee NJ, Jones DK, Foroudi F, et al. A randomised study of a diet intervention to maintain consistent rectal volume for patients receiving radical radiotherapy to the prostate. *Acta Oncol* (2014) 53(4):569–71. doi:10.3109/0284186X.2013.854927
51. Ki Y, Kim W, Nam J, Kim D, Lee J, Park D, et al. Probiotics for rectal volume variation during radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2013) 87(4):646–50. doi:10.1016/j.ijrobp.2013.07.038
52. Di Stefano M, Miceli E, Gotti S, Missanelli A, Mazzocchi S, Corazza GR. The effect of oral alpha-galactosidase on intestinal gas production and gas-related symptoms. *Dig Dis Sci* (2007) 52(1):78–83. doi:10.1007/s10620-006-9296-9
53. Yahya S, Zarkar A, Southgate E, Nightingale P, Webster G. Which bowel preparation is best? Comparison of a high-fibre diet leaflet, daily microenema and no preparation in prostate cancer patients treated with radical radiotherapy to assess the effect on planned target volume shifts due to rectal distension. *Br J Radiol* (2013) 86(1031):20130457. doi:10.1259/bjr.20130457
54. Ogino I, Uemura H, Inoue T, Kubota Y, Nomura K, Okamoto N. Reduction of prostate motion by removal of gas in rectum during radiotherapy. *Int J Radiat Oncol Biol Phys* (2008) 72(2):456–66. doi:10.1016/j.ijrobp.2008.01.004
55. Diot Q, Olsen C, Kavanagh B, Raben D, Miften M. Impact of anatomical interventions on the localization of post-prostatectomy cancer patients. *Med Phys* (2010) 37(2):629–37. doi:10.1118/1.3284249
56. Diot Q, Olsen C, Kavanagh B, Raben D, Miften M. Dosimetric effect of online image-guided anatomical interventions for postprostatectomy cancer patients. *Int J Radiat Oncol Biol Phys* (2011) 79(2):623–32. doi:10.1016/j.ijrobp.2010.04.020
57. Ghilezan MJ, Jaffray DA, Siewerdsen JH, Van Herk M, Shetty A, Sharpe MB, et al. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). *Int J Radiat Oncol Biol Phys* (2005) 62(2):406–17. doi:10.1016/j.ijrobp.2003.10.017
58. Padhani AR, Khoo VS, Suckling J, Husband JE, Leach MO, Dearnaley DP. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *Int J Radiat Oncol Biol Phys* (1999) 44(3):525–33. doi:10.1016/S0360-3016(99)00040-1
59. de Leon JF, Jameson MG, Windsor A, Cloak K, Keats S, Vial P, et al. Superior target volume and organ stability with the use of endorectal balloons in post-prostatectomy radiotherapy. *J Med Imaging Radiat Oncol* (2015) 59(4):507–13. doi:10.1111/1754-9485.12300
60. Jameson MG, De Leon J, Windsor AA, Cloak K, Keats S, Dowling JA, et al. Endorectal balloons in the post prostatectomy setting: do gains in stability lead to more predictable dosimetry? *Radiother Oncol* (2013) 109(3):493–7. doi:10.1016/j.radonc.2013.08.024
61. Smeenk RJ, van Lin EN, van Kollenburg P, McColl GM, Kunze-Busch M, Kaanders JH. Endorectal balloon reduces anorectal doses in post-prostatectomy intensity-modulated radiotherapy. *Radiother Oncol* (2011) 101(3):465–70. doi:10.1016/j.radonc.2011.07.019
62. Smeenk RJ, Teh BS, Butler EB, van Lin EN, Kaanders JH. Is there a role for endorectal balloons in prostate radiotherapy? A systematic review. *Radiother Oncol* (2010) 95(3):277–82. doi:10.1016/j.radonc.2010.04.016
63. Ishiyama H, Teh BS, Blanco AI, Paulino AC, Mai W-Y, Caillouet J, et al. Salvage intensity modulated radiotherapy using endorectal balloon after radical prostatectomy: clinical outcomes. *Int J Urol* (2013) 20(12):1178–83. doi:10.1111/iju.12145
64. Effect of ProSpare (PS), a rectal obturator, on inter- and intrafraction prostate motion and anorectal doses in prostate radiotherapy (RT). *J Clin Oncol* (2016). Available from: http://meetinglibrary.asco.org/content/158265-172
65. Murray JR, McNair HA, Dearnaley DP. Rationale and development of image-guided intensity-modulated radiotherapy post-prostatectomy: the present standard of care? *Cancer Manag Res* (2015) 7:331–44. doi:10.2147/CMAR.S51955
66. Zilli T, Benz E, Miralbell R. [Prostate-rectum spacers: optimization of prostate cancer irradiation]. *Cancer Radiothér* (2014) 18(3):215–21; quiz 243–4, 247. doi:10.1016/j.canrad.2014.03.001
67. Susil RC, McNutt TR, DeWeese TL, Song D. Effects of prostate-rectum separation on rectal dose from external beam radiotherapy. *Int J Radiat Oncol Biol Phys* (2010) 76(4):1251–8. doi:10.1016/j.ijrobp.2009.07.1679
68. Rouzaud M, Zilli T, Vallée JP, Weber DC, Miralbell R. EP-1261: impact of polyethylen glycol spacer injections on interfraction prostate motion in patients undergoing IGRT. *Radiother Oncol* (2013) 106:S476–7. doi:10.1016/S0167-8140(15)33567-2
69. Picardi C, Rouzaud M, Kountouri M, Lestrade L, Vallée JP, Caparrotti F, et al. Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. *Acta Oncol* (2016) 55(7):834–8. doi:10.3109/0284186X.2015.1128118
70. Juneja P, Kneebone A, Booth JT, Thwaites DI, Kaur R, Colvill E, et al. Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: a comparative study. *Radiat Oncol* (2015) 10:215. doi:10.1186/s13014-015-0526-1
71. Pinkawa M, Piroth MD, Holy R, Escobar-Corral N, Caffaro M, Djukic V, et al. Spacer stability and prostate position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall. *Radiother Oncol* (2013) 106(2):220–4. doi:10.1016/j.radonc.2012.11.010
72. Pinkawa M. Current role of spacers for prostate cancer radiotherapy. *World J Clin Oncol* (2015) 6(6):189–93. doi:10.5306/wjco.v6.i6.189
73. Mok G, Benz E, Vallee J-P, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. *Int J Radiat Oncol Biol Phys* (2014) 90(2):278–88. doi:10.1016/j.ijrobp.2014.06.044
74. Pinkawa M, Schubert C, Escobar-Corral N, Holy R, Eble MJ. Application of a hydrogel spacer for postoperative salvage radiotherapy of prostate cancer. *Strahlenther Onkol* (2015) 191(4):375–9. doi:10.1007/s00066-014-0769-z

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Preclinical evaluation of intraoperative low-energy photon radiotherapy using spherical applicators in locally advanced prostate cancer

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Background: Surgery plus adjuvant radiotherapy is standard care for locally advanced prostate cancer (stage pT3R1). Intraoperative low-energy photon radiotherapy offers several advantages over external beam radiotherapy, and several systems are now available for its delivery, using spherical applicators, which require only limited shielding. The aim of this study was to evaluate the feasibility of this technique for the prostate bed.

Materials and methods: Applicators were assessed using MRI image data and cadaveric dissection. In cadavers, targeted tissues, defined as a urethral section, both neurovascular bundle sections, the bladder neck and the beds of the seminal vesicles, were marked with metallic surgical clips. Distances between clips and applicator were measured using CT. A dosimetric study of the application of 12 Gy at 5 mm depth was performed using CT images of prostatectomized cadavers.

Results: Using MRI images from 34 prostate cancer patients, we showed that the ideal applicator diameter ranges from 45 to 70 mm. Using applicators of different sizes to encompass the prostate bed in nine cadavers, we showed that the distance between target tissues and applicator was <2 mm for all target tissues except the upper extremity of the seminal vesicles (19 mm). Dosimetric study showed a good dose distribution in all target tissues in contact with the applicator, with a low probability of rectum and bladder complication.

Conclusion: Intraoperative radiotherapy of the prostate bed is feasible, with good coverage of targeted tissues. Clinical study of safety and efficacy is now required.

Keywords: prostate cancer, prostatectomy, radiotherapy, intraoperative radiotherapy, combined modality therapy

Abbreviations: CT, computed tomography; EBRT, external beam radiotherapy; IORT, intraoperative radiation therapy; NTCP, normal tissue complication probabilities.

Introduction

Increasing numbers of patients are undergoing surgery for high-risk prostate cancer (1). Despite adequate surgery, half of all patients with locally advanced prostate adenocarcinoma (stage pT3) will present in biochemical relapse in the fifth year after operation, suggesting that many patients may not be curable by surgery alone. Three studies have been evaluated the role of a multi-modal approach that combines surgery with adjuvant irradiation in the prevention of relapse after prostatectomy (2–4). All three studies showed reduction in the rate of biochemical relapse, and one showed better metastasis-free survival and overall survival among patients who had received adjuvant irradiation (2). These studies emphasized that the main mode of relapse in prostate cancer is local and that intensifying local treatment reduces the risk of tumor recurrence (5). The relapse site is primarily anastomotic in more than two-thirds of cases, but may also occur at the level of the bladder neck, and occasionally retrovesically (6). This means that the prostate bed boundaries should be defined anteriorly by the posterior wall of the pubic bone, posteriorly by the anterior wall of the rectum, laterally by the levator ani muscles, caudally by the pelvic floor, and cranially by the level of section of the *vas deferens* (7).

Post-operative irradiation is usually carried out between 3 and 6 months after surgery in order to allow a better sphincter recovery. However, this long-time period exposes the patients to the risk of residual tumor growth and metastatic spread, especially for poorly differentiated tumors. To avoid delayed post-operative radiotherapy, perioperative radiotherapy strategies have been developed. Four studies have shown that it is possible to combine prostatectomy with preoperative radiotherapy at the same doses as those used for rectal cancers, without any increase in perioperative toxicity (8). The complication rate appears comparable to that observed among patients irradiated within 6 months of prostatectomy after long-term follow-up (9). Moreover, three studies have demonstrated the feasibility of intraoperative radiation therapy (IORT) using 7–12 MeV electrons during radical prostatectomy (10–12). Single fraction doses ranging from 10 to 22 Gy were administered immediately before or after prostatectomy. pT3 patients also received an additional dose of 45 Gy to the pelvis after surgery. No increase in long-term complications was observed. The rectum was assessed intraoperatively to have received a dose of 3.9 Gy, well below its maximum tolerated dose, which permitted additional external beam radiotherapy (EBRT) if needed (10). However, the use of electrons implies that surgery must be performed in a dedicated shielded operating room or that the patient be moved to a bunker for the treatment delivery.

More recently, the use of low-energy photon IORT has been developed for other cancer types, notably breast cancer (Intrabeam™, Carl Zeiss Meditec, Iena, Germany and Axxent eBx™ System, Xoft, San Jose, CA, USA) (13, 14). Isotropic x-ray irradiation is delivered rapidly to the tissues surrounding the tumor area during surgery. Compared with high-energy photon EBRT, the rapid absorption of low-energy photons limits the dose spread to surrounding tissues, with <35% of the dose delivered to the surface of the applicator at a distance of 10 mm. In contrast to the extensive shielding required for electron therapy, IORT using low-energy photons requires only limited shielding similar to that required for diagnostic x-rays. Moreover, low-energy photons are biologically more destructive than either high-energy photons or electrons, since the relative biological efficacy (RBE) of low-energy photons is estimated between 1.2 and 1.5, whereas the RBE is 1 for high-energy photons or electrons (15). Treatment lasts about 30–50 min, depending on the size of the applicator and the prescribed dose. Intraoperative irradiation is now routinely used in breast cancer patients, with very good clinical short- and long-term efficacy and tolerance (16). This irradiation reduces the delay between surgery and radiotherapy and reduces the travel burden induced by the repeated visits necessary for EBRT.

We performed a preclinical study using both the Intrabeam™ and the Axxent™ systems in prostate cancer patients and in prostatectomized corpses to evaluate the feasibility of intraoperative radiotherapy in prostate cancer.

Patients and Methods

This study was carried out in accordance with the recommendations of local ethics committee with written informed consent from all subjects.

Low-Energy Photon IORT Systems

Two systems are commercially available for low-energy photon IORT. Both systems deliver a 50-kV beam.

Intrabeam™(Zeiss, Germany) uses a miniaturized accelerator introduced in rigid or inflatable spherical applicators, which range from 10 to 50 mm in diameter. The prescribed dose is delivered around the applicator with an isotropic distribution. Axxent™(Xoft, CA, USA) uses a 2.25-mm diameter X-ray source placed in an inflatable spherical or ovoid applicator whose diameter varies from 30 to 70 mm. The source can be moved into the applicator to modulate the dose distribution. This new technology is called "electronic brachytherapy" (eBx). **Table 1** and **Figure 1** summarize these characteristics.

Evaluation of the Sphericity and Dimensions of the Prostate Bed in Prostatectomized Cadavers

Radical prostatectomy without conservation of the neurovascular bundles was performed in nine cadavers in the anatomy laboratory of the University of Nantes. Radio-opaque clips were placed at potential recurrence sites, which were defined as the urethral section, bladder neck, neurovascular bundles, anterior wall of the

TABLE 1 | Characteristics of Zeiss Intrabeam™ or Xoft Axxent eBx™ low-energy photon intraoperative radiotherapy (IORT).

	Intrabeam™	Axxent eBx™
Photon max energy	50 keV	50 keV
Applicators	Rigid or inflatable: 10–50 mm	Inflatable: 30–70 mm
Stalk length	Rigid: 135 mm Inflatable: 65 mm	250 mm
Dose rate (Gy/min)	0.15	0.6
Delivery time (12 Gy, 5 mm depth, 50 mm applicator) (min)	52.8	21

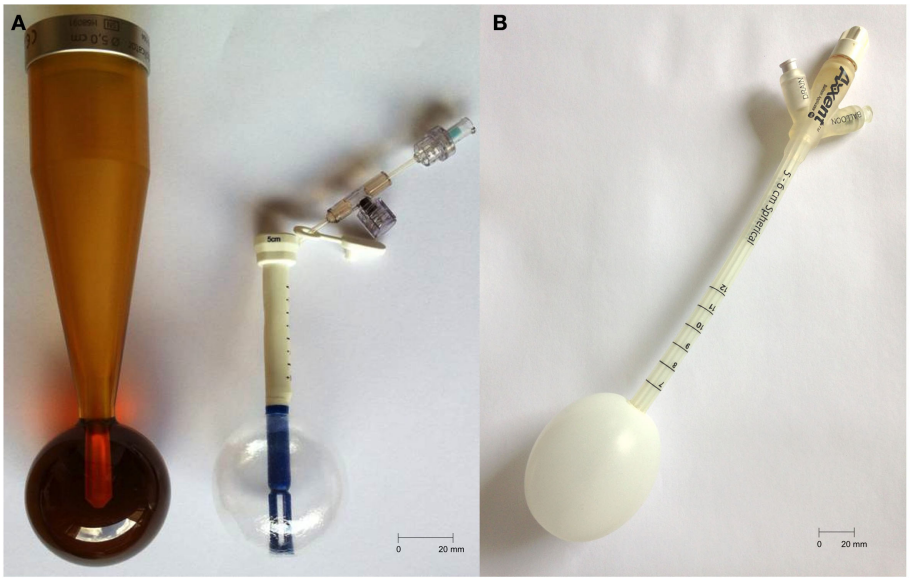

FIGURE 1 | (A) Intrabeam: 50 mm rigid (left) and balloon (right) applicators, stalk length = 135 and 65 mm, respectively; **(B)** Xoft: 50–60 mm applicator, stalk length = 250 mm.

rectum, and the beds of the seminal vesicles. After prostatectomy and identification of target tissues, applicators (Intrabeam™ or Axxent™ applicators) were inserted in the prostate bed until they were in contact with the urethral section of the pelvic floor. The applicator was then applied to the anterior rectal wall, as closely as possible to the clips marking the neurovascular bundles. The most suitable size was selected visually. Finally, the bladder was lowered to apply the bladder neck against the applicator, and sutured to the pubic symphysis on both sides of the applicator. A CT scan was later performed to measure the distance between the clips and the spherical applicator (**Figure 2**).

MRI Evaluation of the Dimensions of the Prostate Bed Prior to Surgery

To determine the size of the prostate bed prior to surgery in prostate cancer patients, spheres of increasing diameter (45–70 mm) were generated on 3D-reconstructed T2-weighted sequences (4 mm thick) prostate MRI images using Iplan® (BrainLab, Germany). The pelvic organs – prostate, rectum, seminal vesicles, and the pubic symphysis – were contoured. The smallest sphere to completely encompass the prostate volume was considered the most suitable (**Figure 3**).

Dose Distribution and Estimation of the Probability of Normal Tissue Complications

A 50-mm applicator (Intrabeam™ system) and a 50-to 60-mm applicator (Axxent™ system) were inserted in the prostate bed of two cadavers. CT images were then acquired. Pelvic organs at risk (bladder and rectum) were delineated on the images. Dose distribution was calculated using a Monte Carlo simulation for the Intrabeam™ system (17) or using Brachyvision software (Varian medical systems, San Jose, CA, USA) for the Axxent™ system. Dose–volume histograms were computed. A dose of 12 Gy at 5 mm depth, corresponding to 20 Gy at the surface of the applicator, was prescribed, similar to that used for breast cancer IORT (16) and prostate bed IORT using electrons (10, 11). The dose distribution was computed to calculate normal tissue complication probabilities (NTCP) for rectum and bladder using relevant radiobiological parameters (alpha/beta for rectum and bladder 5.4 and 7.5 Gy, respectively) using EBRT and HDR models similar to those outlined by Takam et al. (18).

Results

Evaluation of the Shape and Dimensions of the Prostate Bed in Cadavers

Nine cadavers without prostate cancer (mean age 83, range 78–92) were dissected and prostatectomy without neurovascular preservation performed. Applicators or plastic spheres were then inserted in the prostate bed. Congruence with the anatomical boundaries was evaluated visually when the sphere came into contact with all target tissues. The best-adapted sphere measured 50 mm in four cases, 60 mm in four cases, and 50–60 mm (ovoid applicator) in one case.

Once the positioning had been optimized visually, CT scans were performed to evaluate the congruence of the applicator to the prostate bed and distances between the applicator and radiopaque clips were measured. In all cases, the congruence of the applicator to the prostate bed was not affected by the shape of the applicator, whether spherical (Intrabeam™) or slightly ovoid (Axxent™) (**Table 2**).

The Axxent™ applicator can easily be inserted in a laparoscopic trocar before placement, allowing it to be used whatever the surgical approach chosen (open or laparoscopic, with or without robotic assistance).

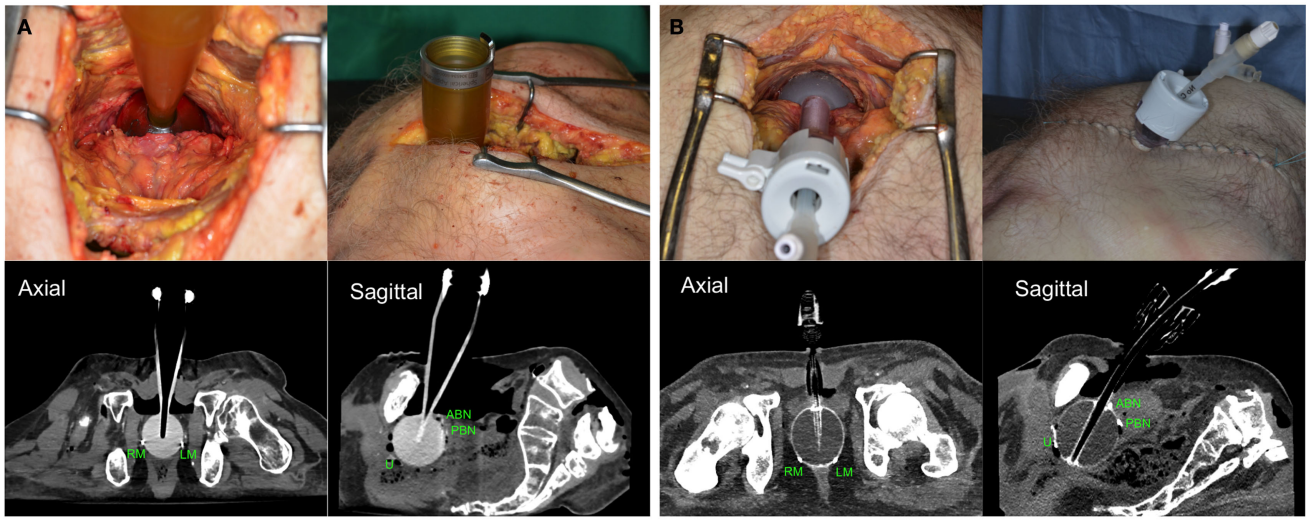

FIGURE 2 | Positioning of Zeiss Intrabeam™(A) or Xoft Axxent eBx™[(B) through laparoscopic trocar] applicators and CT scans of prostatectomized corpses with radiopaque clips located at different target tissues. U, urethra; ABN, anterior bladder neck; PBN, posterior bladder neck; LA, left apex; RA, right apex.

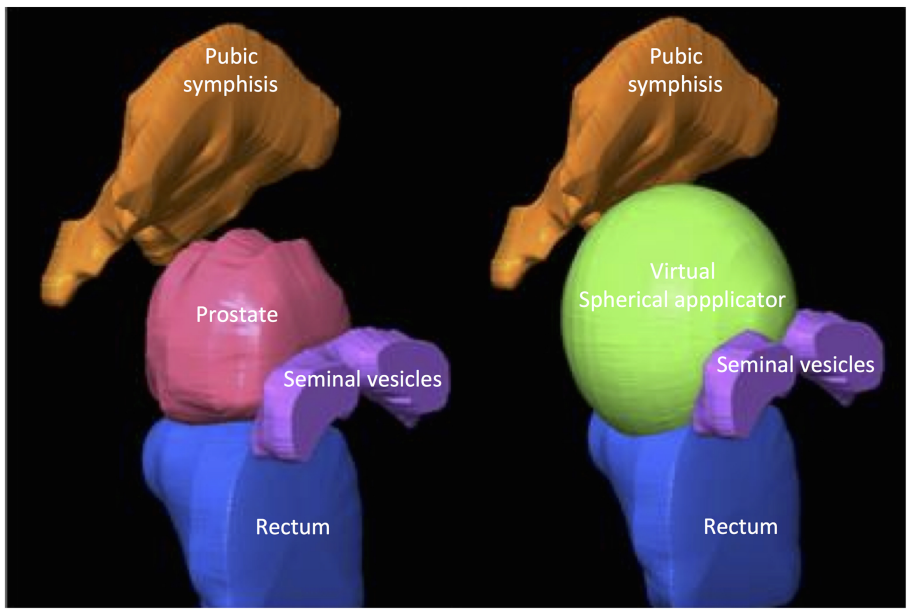

FIGURE 3 | Graphical representation of the determination of applicator size on MRI images.

Rectal filling increased the distance between the applicator's surface and the urethral or neurovascular bundle clips by up to 15 mm (cadavers 2 and 6). After removing rectal stool, this distance reduced to <2 mm (cadaver 6). Clips at the distal extremity of the seminal vesicles were always located more than 2 mm from the applicator's surface in the first two cadavers, so the marking of this target site was abandoned in the next six cadavers studied. In the other cases, the CT scan measured distance between the applicator's surface and clips ranged between 0 and 6 mm. The size of the applicator did not influence the distance between the clips and applicator's surface.

MRI Evaluation of the Dimensions of the Prostate Bed Prior to Surgery

To determine the dimensions of the prostate bed in a larger cohort of patients, we simulated the positioning of applicators of different sizes in 34 prostate cancer patients using MRI (**Figure 3**). Prostate volume ranged from 25 to 106 ml (median = 39.7 ml).

TABLE 2 | Distance (millimeter) between radio-opaque clips and applicator surface on CT scan in nine prostatectomized cadavers.

	#1	#2	#3	#4	#5	#6	#6[a]	#7	#8	#9
Age	82	79	92	90	84	80	80	80	78	83
Applicator size (mm)	60	60	60	60	50	50	50	50	50	50–60
Applicator type	rig. S	rig. S	rig. S	rig. S	rig. IB	rig. IB	rig.IB	rig. IB	inf. IB	inf. Ax
Urethra	–	14	–	–	–	6	–	–	–	–
Ant BN	–	–	–	–	–	–	–	–	–	–
Post BN	–	–	–	–	–	–	–	–	–	–
Retrovesical	–	–	–	–	1.3	–	–	–	nd	1.1
Left apex	1.5	15	–	–	–	3	–	–	–	–
Right apex	–	9	–	–	–	1.5	–	–	4	–
Left NVB	–	10	–	–	nd	–	–	–	nd	–
Right NVB	–	–	–	–	–	–	–	–	nd	–
Left base	–	–	–	–	–	–	–	–	–	–
Right base	–	–	–	–	–	–	–	–	–	–
Left distal SV	19	10	nd	nd	nd	nd	nd	nd	nd	nd
Right distal SV	5	2.5	nd	nd	nd	nd	nd	nd	nd	nd
Rectum	Empty	Full	Empty	Empty	Empty	Full	Empty	Empty	Empty	Empty

[a]*Same cadaver after rectal emptying.*

rig. S, rigid plastic sphere; rig. IB, rigid intrabeam applicator; inf. IB, inflatable intrabeam applicator; inf. Ax, inflatable Axxent applicator; –, 0 mm; BN, bladder neck; NVB, neurovascular bundles; SV, seminal vesicles; nd, not determined.

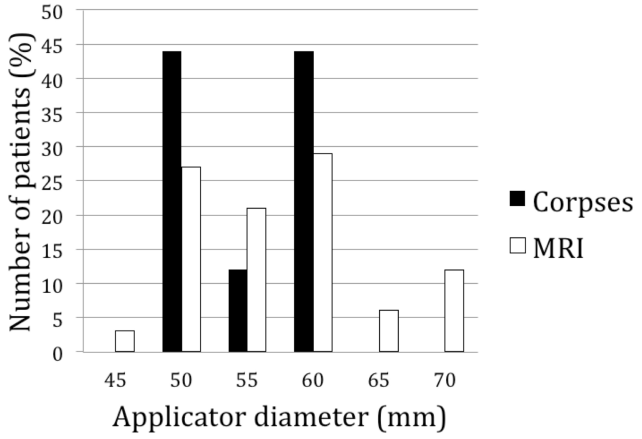

FIGURE 4 | Distribution of the diameter of the applicator among 9 prostatectomized cadavers (plain bars), and in MRI images from 34 prostate cancer patients (empty bars).

After 3D reconstruction and virtual applicator testing, the size ranged between 50 and 70 mm. In 78% of patients, the applicator's diameter ranged between 50 and 60 mm, confirming the cadaveric measurements (**Figure 4**). Neither prostatic volumes nor prostate dimensions were predictive of the ideal applicator diameter (data not shown).

Dose Distribution and Estimation of the Probability of Normal Tissue Complications

Dose distribution was calculated in two cadavers in which a 50-mm applicator (Intrabeam™ or Axxent™) had been inserted. A similar dose distribution to target tissues in contact or in the close vicinity of the applicator was obtained (**Figure 5**). In the cadaver with rectal distension (cadaver 6), the dose to the urethra was decreased by 28% (full rectum: 8.6 Gy; empty rectum: 12 Gy). Using either the EBRT (e) or HDR (h) model, the NTCP for the rectum was 2.3% (e) and 1.0% (h) for the Intrabeam™ irradiation and <1% (e) and (h) for the Axxent™ irradiation. The NTCP for the bladder was 2.8% (e) and 2.0% (h) for the Intrabeam™ irradiation and <1% (e) and (h) for the Axxent™ irradiation. NCTP were lower with (h) because the distances from the applicator to the bladder and the rectum were larger for those cases.

Discussion

We have shown that low-energy photon IORT using spherical applicators can be adapted for treatment of the prostate bed with the exception of the upper extremity of the seminal vesicles, and that the radiation dose received by the pelvic organs at risk is consistent with a low probability of acute and late toxicity.

The spherical shape of the applicators was suitable for the anatomical configuration of the prostate bed. The applicator shape could be fully spherical (Intrabeam™) or ovoid (Axxent™) without incongruence of the applicator to the prostate bed. However, it is important to empty the rectum since the distance between the applicator's surface and the urethral section was increased in the cadaver with a full rectum, which significantly reduced the dose to this target tissue.

The applicator positioning was standardized. It was impacted in the rectum in order to be in contact with the neurovascular bundle section. Then, it was applied close to the urethral section. Finally, bladder neck was lowered into contact with the applicator. The choice of the size was visual, testing different applicators. Using this approach (standardized positioning verified visually), CT scan confirmed adequate positioning of the applicator and good dosimetric coverage in all cadavers, with the exception of the one whose rectum was initially full.

Applicators could be rigid (Intrabeam only) or inflatable (Intrabeam and Axxent). This property had no effect neither on positioning in cadaver nor on CT scan image quality. However, inflatable applicators could easily be inserted in a laparoscopic trocar before placement, allowing them to be used whatever the surgical approach chosen (open or laparoscopic, with or without robotic assistance). Among inflatable applicators, we found that

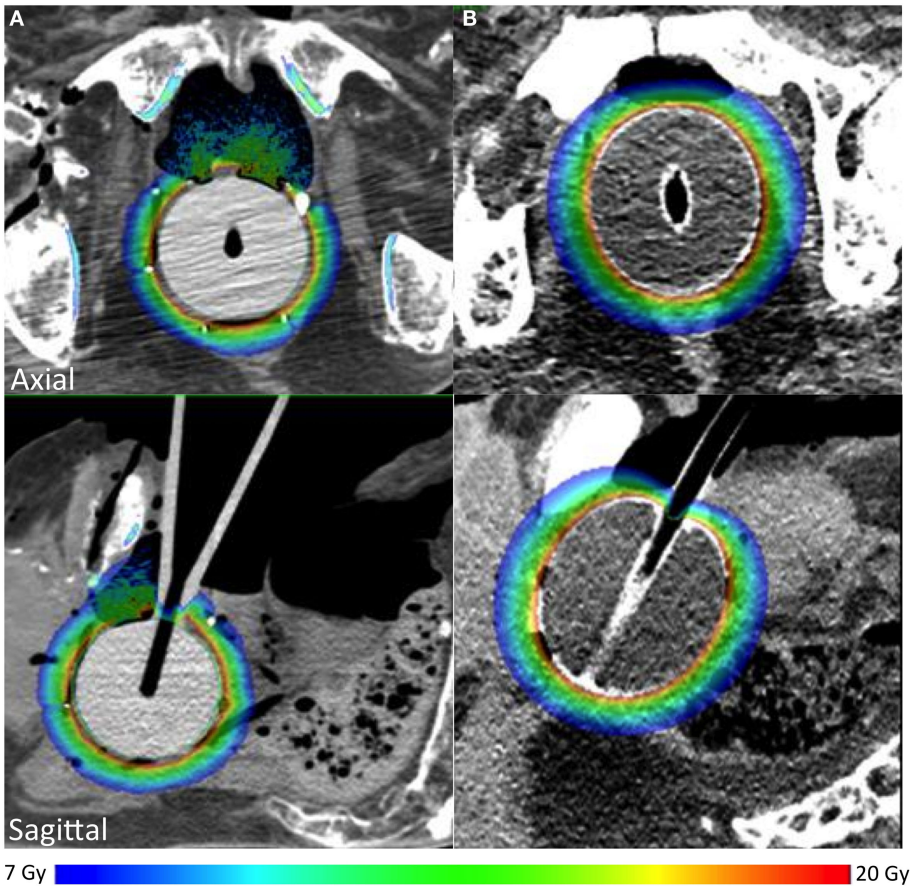

FIGURE 5 | Dose distribution in targeted tissues using Zeiss Intrabeam™(A) or Xoft Axxent™(B).

the Axxent one seemed more convenient because (1) the longer stalk allows a better adaptation to the anatomy of patients and (2) the four times higher dose rate should reduce operating time.

We selected areas at risk – positive margins and/or areas frequently involved in local recurrences (19) – as target tissues, and determined whether all target tissues would receive the prescribed dose. Our results showed that all target tissues would be irradiated at the same dose, including the proximal, but not the distal, part of the seminal vesicles. Invasion into the seminal vesicles is usually limited to the proximal part; the distal part is invaded only in 20% of pT3b cases (20), so IORT would only miss a very limited number of remaining tumor cells. Moreover, pT3b patients are at high risk of metastatic disease (21), which implies that systemic therapies would be probably more important than increased local treatment in this clinical situation.

We simulated a dose of 12 Gy at a 5-mm depth, 20 Gy at the surface of the applicator. The 5-mm depth encompassed all radio-opaque clips, which suggests that all target tissues would receive a dose ranging between 12 and 20 Gy, which is equivalent to 36–92 and 46–123 Gy in 2 Gy fractions for alpha/beta equal, respectively, to 3 and 1.5 Gy (22). We selected a dose of 12 Gy at a 5-mm depth since (1) this dose is routinely used for breast IORT (16), (2) no increased acute and late toxicity was seen in clinical series following a 12 Gy irradiation using IORT with electrons, and (3) it may be combined with post-operative irradiation without increasing acute and late toxicity (10–12). Higher single-dose treatment seems to be well tolerated, since 22 Gy in one single fraction of IORT using electrons did not increase perioperative or late toxicity (12).

Both Intrabeam and Axxent systems deliver low-energy photons (50 keV) limiting shielding measures necessary to avoid medical staff exposure. In our institution, we performed measures with Intrabeam system (40 mm applicator, 50 kV, 40 µA) before beginning IORT for breast cancer. We found a dose rate of 1700 µSv/h at 1 m from the source and 1.6 µSv/h behind a movable lead shield at 3 m from the source. As dose rate decreases when applicator diameter increases, the exposure should be lower with a 50-mm applicator. Slightly similar dose rates are observed with Axxent system with a dose rate of 2000 µSv/h at 30 cm from the treated area that decreases more than 95% behind a movable lead shield (23).

The main limitation of our study is the determination of the NTCP. NTCP models are based on fractionated irradiation. To determine the complication probabilities of low-energy photon IORT, we assumed that this model could be applied to high single-dose irradiation, which is not definitively proven (24). This model has been developed for high-energy photons; models for low-energy photons are lacking. We could not specifically determine

the probability of urethral stenosis using this NTCP model. One adjuvant radiotherapy study showed an increased frequency of urethral stenosis (2), whereas two other studies did not show any differences between adjuvant irradiation and observation (3, 4). A clinical phase I study will be required to carefully evaluate the perioperative toxicity of low-energy photon IORT.

Conclusion

Our study suggests that low-energy photon IORT, using spherical applicators, is feasible during radical surgery for localized prostate cancer. Selection of the precise applicator and low-energy photon IORT machine will depend on patient characteristics (prostate volume, prostate depth). The current indication for adjuvant radiotherapy is pT3 disease based on the post-operative pathological examination (25). It would be reasonable to select patients who might benefit from low-energy photon IORT prior to surgery based on the probability of pT3 stage disease: according to PSA level, Gleason score >7, or cT3a disease with resectable disease or extra-capsular extension on MRI, though patients with T3b disease should be excluded (26).

Author Contributions

All the authors equally contributed to the preparation of this manuscript.

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References

1. Budäus L, Spethmann J, Isbarn H, Schmitges J, Beesch L, Haese A, et al. Inverse stage migration in patients undergoing radical prostatectomy: results of 8916 European patients treated within the last decade. *BJU Int* (2011) **108**:1256. doi:10.1111/j.1464-410X.2010.09982.x
2. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) **181**:956. doi:10.1016/j.juro.2008.11.032
3. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) **380**:2018. doi:10.1016/S0140-6736(12)61253-7
4. Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol* (2014) **66**:243. doi:10.1016/j.eururo.2014.03.011
5. Swanson GP, Hussey MA, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* (2007) **25**:2225. doi:10.1200/JCO.2006.09.6495
6. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, 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. doi:10.1016/j.radonc.2007.07.017
7. Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2010) **76**:361. doi:10.1016/j.ijrobp.2009.02.006
8. Thoms J, Goda JS, Zlotta AR, Fleshner NE, van der Kwast TH, Supiot S, et al. Neoadjuvant radiotherapy for locally advanced and high-risk prostate cancer. *Nat Rev Clin Oncol* (2011) **8**:107. doi:10.1038/nrclinonc.2010.207
9. Supiot S, Shubbar S, Fleshner N, Warde P, Hersey K, Wallace K, et al. A phase I trial of pre-operative radiotherapy for prostate cancer: clinical and translational studies. *Radiother Oncol* (2008) **88**:53. doi:10.1016/j.radonc.2008.03.019
10. Krengli M, Terrone C, Ballarè A, Loi G, Tarabuzzi R, Marchioro G, et al. Intraoperative radiotherapy during radical prostatectomy for locally advanced prostate cancer: technical and dosimetric aspects. *Int J Radiat Oncol Biol Phys* (2010) **76**:1073. doi:10.1016/j.ijrobp.2009.03.037
11. Rocco B, Jereczek-Fossa BA, Matei DV, Verweij F, Santoro L, Vavassori A, et al. Intraoperative radiotherapy during radical prostatectomy for intermediate-risk to locally advanced prostate cancer: treatment technique and evaluation of perioperative and functional outcome vs standard radical prostatectomy, in a matched-pair analysis. *BJU Int* (2009) **104**:1624. doi:10.1111/j.1464-410X.2009.08668.x
12. Saracino B, Gallucci M, De Carli P, Soriani A, Papalia R, Marzi S, et al. Phase I-II study of intraoperative radiation therapy (IORT) after radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2008) **71**:1049. doi:10.1016/j.ijrobp.2007.11.076
13. Park CC, Yom SS, Podgorsak MB, Harris E, Price RA Jr, Bevan A, et al. American society for therapeutic radiology and oncology (ASTRO) emerging technology committee report on electronic brachytherapy. *Int J Radiat Oncol Biol Phys* (2010) **76**:963. doi:10.1016/j.ijrobp.2009.10.068
14. Dickler A, Dowlatshahi K. Xoft Axxent electronic brachytherapy. *Expert Rev Med Devices* (2009) **6**:27. doi:10.1586/17434440.6.1.27
15. Liu Q, Schneider F, Ma L, Wenz F, Herskind C. Relative biologic effectiveness (RBE) of 50 kV X-rays measured in a phantom for intraoperative tumor-bed irradiation. *Int J Radiat Oncol Biol Phys* (2013) **85**:1127. doi:10.1016/j.ijrobp.2012.08.005
16. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* (2014) **383**:603. doi:10.1016/S0140-6736(13)61950-9
17. Chiavassa S, Buge F, Hervé C, Delpon G, Rigaud J, Lisbona A, et al. Monte Carlo evaluation of the effect of inhomogeneities on dose calculation for low energy photons intra-operative radiation therapy in pelvic area. *Physica Medica* (In press)
18. Takam R, Bezak E, Yeoh EE, Marcu L. Assessment of normal tissue complications following prostate cancer irradiation: comparison of radiation treatment modalities using NTCP models. *Med Phys* (2010) **37**:5126. doi:10.1118/1.3481514
19. Liauw SL, Pitroda SP, Eggener SE, Stadler WM, Pelizzari CA, Vannier MW, et al. Evaluation of the prostate bed for local recurrence after radical prostatectomy using endorectal magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* (2013) **85**:378. doi:10.1016/j.ijrobp.2012.05.015
20. Samaratunga H, Samaratunga D, Perry-Keene J, Adamson M, Yaxley J, Delahunt B. Distal seminal vesicle invasion by prostate adenocarcinoma does not occur in isolation of proximal seminal vesicle invasion or lymphovascular infiltration. *Pathology* (2010) **42**:330. doi:10.3109/00313021003767330
21. Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* (2003) **21**:483. doi:10.1200/JCO.2003.12.043
22. Oliveira SM, Teixeira NJ, Fernandes L. What do we know about the alpha/beta for prostate cancer? *Med Phys* (2012) **39**:3189. doi:10.1118/1.4712224
23. Mobit PN, Rajaguru P, Brewer M, Baird M, Packianathan S, Yang CC. Radiation safety consideration during intraoperative radiation therapy. *Radiat Prot Dosimetry* (2015) **164**:376. doi:10.1093/rpd/ncu292

24. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* (2010) **76**:S123. doi:10.1016/j.ijrobp.2009.03.078
25. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. *J Urol* (2013) **190**:441. doi:10.1016/j.juro.2013.05.032
26. Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int* (2013) **111**:22. doi:10.1111/j.1464-410X.2012.11324.x

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REVIEW
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Radiation Therapy after Radical Prostatectomy: Implications for Clinicians

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Depending on the pathological findings, up to 60% of prostate cancer patients who undergo radical prostatectomy (RP) will develop biochemical relapse and require further local treatment. Radiotherapy (RT) immediately after RP may potentially eradicate any residual localized microscopic disease in the prostate bed, and it is associated with improved biochemical, clinical progression-free survival, and overall survival in patients with high-risk pathological features according to published randomized trials. Offering immediate adjuvant RT to all men with high-risk pathological factors we are over-treating around 50% of patients who would anyway be cancer-free, exposing them to unnecessary toxicity and adding costs to the health-care system. The current dilemma is, thus, whether to deliver adjuvant immediate RT solely on the basis of high-risk pathology, but in the absence of measurable prostate-specific antigen, or whether early salvage radiotherapy would yield equivalent outcomes. Randomized trials are ongoing to definitely answer this question. Retrospective analyses suggest that there is a dose–response favoring doses >70 Gy to the prostate bed. The evidence regarding the role of androgen deprivation therapy is emerging, and ongoing randomized trials are underway.

Keywords: adjuvant radiotherapy, prostate cancer, androgen deprivation

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INTRODUCTION

Prostate cancer is the most frequently diagnosed non-skin cancer in the western of world (1).

For such a frequent cancer, surprisingly, little certainties exist around its management.

After radical prostatectomy (RP), patients with high-risk pathological features, such as extracapsular prostatic extension (ECE), positive margins, seminal vesicle involvement (SVI), high Gleason score, and prostate-specific antigen (PSA) have a 40–70% risk of developing biochemical failure at some point in the future (2). Approximately, two-thirds of men with biochemical relapse will develop metastatic disease if left untreated (3).

Radiotherapy to the prostate loge has been used in both the adjuvant (ART) and the salvage (SRT) setting. Which of the two strategies is better remains an area of controversy despite the fact that there are three phase III randomized controlled trials that showed an improvement in biochemical progression-free survival (BPFS) when ART is administered as compared with RP alone (4–6). At the present time, there are no published randomized trials, and we dispose only of retrospective data for the use of SRT, making a direct comparison between ART and SRT flawed. While several trials comparing ART vs. SRT are on going, in this article, we summarize the available evidence on ART vs. SRT.

ADJUVANT RADIATION THERAPY TRIALS

Three randomized controlled trials are summarized in **Table 1** showing the benefit of ART over RP alone. In these trials, ART was usually administered to the prostate loge within 4 months after RP (4–6). Two of the three randomized trials included patients with detectable PSA and therefore some patients actually received SRT, indirectly supporting its benefits over watchful waiting (4–6). With the introduction of ultrasensitive PSA, a new tool to detect low-volume disease became available, and therefore nowadays the term "adjuvant therapy" is used when the PSA is very low or undetectable (≤0.1 ng/ml) immediately or within 4 months of RP. This highlights the temporal variation in practice patterns and limits the generalizability of the results of the randomized trials to the contemporary population of prostate cancer patients. Nevertheless, these important studies provided evidence to support the use of postoperative RT in men with adverse pathologic features (ECE, SVI, or positive surgical margins). The question of whether all patients with the aforementioned adverse features should undergo immediate ART vs. initial observation with more selective – but early – SRT in the event of biochemical failure (using pre-defined PSA thresholds) remains a subject of controversy.

Certainly, men with prostate cancer will not necessarily die from the disease and even those who experience a biochemical failure will not necessarily become symptomatic from the disease (7).

Thus, the argument for postoperative radiotherapy (RT) is predicated on the assumption that some patients may have residual local disease of a potentially lethal phenotype after surgery and that the delivery of secondary local therapy may interrupt the natural history of disease and prevent progression to systemic disease. A basic question in this context is the extent to which this sequence of events – vs. the presence of occult metastases at surgery or the presence of a tumor that will never become symptomatic – characterizes the natural history of the disease.

EORTC 22911

The European Organization for Research and Treatment of Cancer (EORTC) recruited 1005 patients between 1992 and 2001 to a randomized controlled trial (8). Patients with stage pT2–3, N0, M0 prostate cancer, and undetectable PSA defined as ≤0.4 ng/ml with at least one adverse prognostic factor: positive surgical margins, ECE and/or SVI were randomized to receive ART with 60 Gy in 6 weeks to the prostate bed or observation. After a median follow-up of 10.6 years, the intervention arm was significantly superior based on BPFS (74 vs. 53%; HR 0.49, 95% CI 0.41 to 0.59, $p < 0.0001$). The cumulative rate of loco-regional and any clinical failure was lower in the irradiated group (15 vs. 5%, $p < 0.0001$ and 19 vs. 9%, $p < 0.0001$, respectively). However, no significant benefit was observed in distant failures. Importantly, from the 265 patients in the observation arm who had biochemical progression 84% underwent an active treatment after progression (54.4% received pelvic radiotherapy, and 22.2% received androgen deprivation therapy-ADT). Salvage radiotherapy was administered to 23% of patients in the observation group. There was also a significant increase in late side effects of any type and any grade in the RT arm [10-year cumulative incidence 70.8% (66.6–75.0) vs. 59·7% (55.3–64.1); $p = 0.001$]. After 10 years of follow-up, improvements in clinical progression-free survival vanished, and overall survival (OS) was not improved (4).

SWOG 8794

From 1988 to 1997, the South West Oncology Study Group (SWOG) 8794 trial randomized 430 men with pT3, pN0, M0, ECE, positive margins, and/or SVI prostate cancer to ART (60–64 Gy) or observation (5, 9). There was no restriction on PSA level at enrollment. The primary endpoint was metastasis-free survival. Secondary endpoints were PSA relapse, recurrence-free survival, OS, and postoperative complications. With a median follow-up of 12.7 years, the study was positive for metastases-free survival favoring the RT arm (43 vs. 54%, HR 0.71, 95% CI 0.54–0.94; $p = 0.016$). Also the OS was improved significantly with ART (41 vs. 52%, HR 0.72, 95% CI 0.55–0.96; $p = 0.023$).

Swanson et al. reported that the pattern of failure was local with 22% of patients having a clinical local failure in the observation arm compared to 8% in the ART arm. An additional 11 patients in the observation arm had local and distant failures compared to 1 patient in the treated arm (10). The time to initiation of hormonal therapy differed in both groups with 21% of patients in the observation group having received ADT within 5 years post biochemical relapse vs. 10% of patients in the ART group (HR 0.45; 95% CI 0.29–0.68, $p < 0.001$) (9).

TABLE 1 | Randomized controlled trials comparing adjuvant postoperative radiotherapy vs. observation.

Reference	*N*	Inclusion criteria	Dose (Gy)	Follow-up median (years)	10-year BPFS ART vs. NFT	10-year OS ART vs. NFT	10-year toxicity rate (%) ART vs. NFT
Thompson et al. (5)	425	pT3 cN0/pN0 R0/R1	60–64	12.7	52 vs. 26% $p < 0.001$	74 vs. 66% $p = 0.023$	GI, G3 = 3.3 vs. 0 GU, G3 17.8 vs. 9.5
Bolla et al. (4)	1005	pT2–3 pN0 R0/R1	60	10.6	60 vs. 41% $p < 0.0001$	77 vs. 81% $p = 0.2$	GU > G2 = 21.3 vs. 13.5 ($p = 0.003$) GI > G2 = 2.5 vs. 1.9 ($p = 0.47$)
Wiegel et al. (6)	388 (307)	pT3 pN0 R0/R1 PSA 0	60	9.3	56 vs. 35% $p < 0.0001$	84 vs. 86% $p = 0.59$	ART: GU, G3 = 1 patient, G2 = 2 patients, GI, G2 = 2 patients

BPFS, Biochemical progression-free survival; OS, overall survival; ART, adjuvant radiation therapy; NFT, no further therapy; GU, genitourinary; GI, gastro-intestinal; G, grade.

It has, however, been argued that the survival benefit may be due to hazard considering that the trial was not powered to detect an OS advantage as well as the fact that such clinical benefit was not found in the European Study (11). The most significant problem with the SWOG 8794 trial was the lack of disclosure of cause of death. There were 110 men (52%) who died in the observational group vs. 88 (41%) in the radiation group, but because of the long follow-up period it was not possible for the authors to ascertain if these patients died from metastatic prostate cancer or from competing hazards, which jeopardizes the impact of ART on OS.

Another observation from this trial is that the pre-radiation PSA level immediately after RP was predictive of subsequent outcome. For instance, for patients with an undetectable PSA (≤0.2 ng/ml), the 5-year PSA failure rate was 77% (very similar to the EORTC 22911 trial, 74%). However, patients with a post-prostatectomy PSA between 0.2 and ≤1 ng/ml had a PSA failure rate of 34% at 5 years: this last group had an 8% increase in the risk of metastases indicating thus that RT with these PSA values is less efficient in eradicating larger tumor deposits (10). On the contrary, patients in the observation arm had a significant delay in initiating SRT. The median PSA at which patients were referred for salvage radiation was 1–1.5 ng/ml. A better comparison would have been made if patients in the observation arm had been offered RT at the first PSA failure.

ARO 96/02

The German study was the only real adjuvant study as the inclusion criteria permitted only patients with undetectable PSA. Those with persistently detectable PSA after surgery were declared as having progressive disease. The study recruited 307 patients from 1997 to 2004. Eligible patients had pT3 pN0 tumors with positive or negative margins. PSA failure was defined as two consecutive rises above undetectable. BPFS after 5 years was significantly improved with ART (72%, 95% CI 65–81%, vs. 54%, 95% CI 45–63%, HR = 0.53, 95% CI 0.37–0.79, $p = 0.0015$). Despite a 10-year follow-up period, the study did not show any clinical benefit.

Grade 2 genitourinary and gastrointestinal toxicity in the RT arm were 2 and 1.4%, respectively (6).

WHO MIGHT BENEFIT FROM IMMEDIATE POSTOPERATIVE RADIOTHERAPY?

In summary, the 3 studies included together over 1100 patients and had a substantial follow-up assessment that permits some conclusions: ART compared with watch and see strategy reduced by about 20% the risk of PSA relapse.

Van der Kwast et al. reviewed about 50% of the pathology specimens in the EORTC 22911 trial, in particular with regard to positive surgical margins (12). After 5 years, immediate postoperative radiation was shown to prevent 191 events in 1000 patients with positive margins vs. 88 events in 1000 patients with negative margins. The hazard ratio for immediate radiation was 0.38 (95% CI 0.26–0.54) and 0.88 (95% CI 0.3–1.46) in the group with positive and negative margins, respectively. The finding of a significant association between margin status and adjuvant RT benefit was also reported in the subgroup analyses of ARO 96-02 (6). The data indicate that patients with a pT3 tumor but negative margins may potentially benefit less or not at all from immediate ART. Exploratory analyses suggested that postoperative irradiation might improve clinical progression-free survival in patients younger than 70 years old. Radiotherapy could have a detrimental effect in patients aged 70 years or older (13).

An important point to consider in the equation balance between ART and observation is that one-third of the patients in the wait and see arm of the randomized trials have received ADT within the first 5 years after biochemical progression. Therefore, the use of ART would lead to a diminished use of ADT. However, early initiation of ADT has not shown convincing benefit on OS (14, 15).

It is also important to note that the standard routine clinical practice has evolved since the publication of the three aforementioned randomized trials, and contemporary patients have access to ultra-sensitive PSA assays, consequently in modern clinical practice patients with an undetectable postoperative PSA level have a lower risk of relapse than those patients in the past and so less potential benefit from adjuvant immediate radiation. Ultra-sensitive PSA assays also lead to an earlier detection of biochemical relapse than clinical relapse, and this early detection may lead to an improvement in the efficacy of SRT as a therapeutic option. There is at the moment no consensus among clinicians on whether to use adjuvant or salvage radiotherapy, highlighting the need for offering these patients a randomized trial (16).

The potential for toxicity needs to be considered when counseling patients for postprostatectomy RT, and this information provides support for more selective use.

SALVAGE RADIATION THERAPY

Salvage radiation therapy is supported by some clinicians based on the rationale that an elevated PSA in the postoperative setting or a delayed PSA rise is caused, at least in some patients, by the persistence of local disease. However, while the disease is localized to the surgical bed and curable with SRT, the presence of occult metastatic disease cannot be excluded. Certainly, adverse prognostic factors in the pathology specimen such as ECE, positive margins, and SVI, support the concept of a local residual tumor and thus the use of salvage treatment (17). The lower the PSA at the time of salvage therapy, the better the outcome. Investigators have tried to use PSA cut-off points ranging from ≥0.1 to 10 ng/ml (18–23). However, it should be noted that the relationship between pre-radiotherapy PSA and radiotherapy outcome is a continuum. In general, PSA recurrence rates have been reported to be higher when the PSA is ≥0.2 ng/ml (20, 21, 24). Other factors should also be considered such as the PSA doubling time as well as time to biochemical failure (25).

There have been multiple retrospective studies, which have looked at the clinical question of how adjuvant or salvage radiation affects local control, BPFS, and OS. Significant improvements in local control and BPFS have been observed in patients treated in the adjuvant or early adjuvant setting compared to those treated with late salvage therapy. The inherent caveat when comparing

ARC vs. SRT in retrospective studies is that the patient receiving salvage treatments have in most of the cases confirmed recurrent disease, consequently the outcome of salvage radiation will always seem worse than ART (11). The 5-year BPFS rates were approximately 59–80% after ART (19–21) and 26–66% after salvage radiotherapy (22, 26). In some series, patients who had an undetectable PSA after SRT had a 75% chance to have an undetectable PSA at 3.5 years (6).

Table 2 summarizes the retrospective studies on SRT. It is clear from these retrospective studies that oncological outcomes are better when SRT is initiated at the lowest PSA values. Several studies showed that the biochemical relapse free survival can be >75% with pre-radiotherapy PSA of <0.5 ng/ml (24, 27).

A recent report by Pfister et al. analyzed 10 retrospective reports on patients with early salvage radiotherapy (ESRT) (27). The term ESRT refers to patients with undetectable PSA after prostatectomy who have subsequent PSA rise ≤0.5 ng/ml. Significantly, increased cancer control rates have been reported with ESRT compared to late SRT. The mean 5-year biochemical relapse-free survival was 71% in a polled analysis of 886 patients treated with ESRT. However, no data on clinically outcomes such as metastasis-free survival or OS were available. Siegmann et al. (28) reported a BPFS of 83% at 2 years for patients with PSA ≤0.2 ng/ml at the time of SRT compared to 61% for those with a PSA of ≥0.28 to ≤1 ng/ml, pointing out that further reducing the PSA cut-off point may increase biochemical outcomes.

The nomograms introduced by Stephenson et al. may help in the decision-making process (2). This nomogram was created from a pooled database of 1818 patients with a median follow-up of 53 months after RT. Pre-surgical prognostic factors such as PSA, Gleason score, SVI, ECE, surgical margins, lymph node status, PSA at SRT, PSA doubling-time, time-to-recurrence, time from recurrence to radiation, radiation dose, and the use of ADT are considered to allow individualized risk stratification. Briganti et al. (24) restricted the nomogram to patients with PSA <0.5 ng/ml and validated it with 200 bootstrap resamples demonstrating a good discrimination in outcome with a *c*-index of 0.74. By incorporating genomic tests into nomogram models, Den et al. (29) analyzed 188 patients with pT3 or positive margin prostate cancer looking at 22 pre-specified gene-signatures and reported an improvement in the Stephenson nomogram from a *c*-index of 0.70–0.80 for BPFS as well as distant metastases. Novel gene signatures describing the biology of prostate cancer progression have recently being summarized in a comprehensive

TABLE 2 | Selected series of salvage radiotherapy for PSA relapse after radical prostatectomy.

Reference	*N*	Comparison	PSA pre-RT (ng/ml)	ADT (%)	Median follow-up (months)	BPFS (%)	Important prognositc factors	RT technique/ dose (Gy)	Grade 3 toxicity (%)
Pfister (27)	737	Early salvage	<0.5	6.7	51	71	PSA pre RT <0.2	2D/3D/IMRT	0.6–1.3
Trock (23)	160	SRT with PSA >0.2–22	Median 0.7	12	72	89		2D/3D/66.5	
Swanson (26)	92	ART (*n* = 36) with postoperative PSA <0.4 vs. SRT (*n* = 56)	Median 1.5	0	146.4	35 vs. 25	GS >8 PSA >0.5	2D/3D/60–70	NR
Trabulsi (22)	449	ART <12 months from surgery (*n* = 211) SRT >12 months from surgery (*n* = 238)	<2	0	94	75 vs. 66	GS >8 Use of SRT	2D/3D/64	NR
Fossati (20)	955	Early salvage	<0.5	0	57	82	PSA >0.2, >pT3, GS >7	2D/3D/66.6	NR
Cremers (19)	197	SRT (>6 months after RP)	45.7% with PSA <10 and 53.8% with PSA > 10	0	40	59	GS >7, ECE, PSA >1ng/ml	3D/66	GU = 6 GI = 0.6
Jereczek-Fossa (21)	431	ART <6 months after RP (*n* = 258) SRT >6 months after RT (*n* = 173)	ART 0–4 SRT 0.1–13.7	100	32	81 vs. 60.5	PSA >0.2 GS >6 Age <65	70	GI = 0.7 GU = 1.9
Briganti (24)	390	PSA <0.3 vs. PSA >0.3 to <0.5	58	0	40.6	81.8	stage, GS, and positive SM	3D/66.2	NR
Siegmann (28)	301	SRT (median time to RT 23 months) In 151 patients, SRT commenced at PSA ≤0.28 ng/ml, in 150 at >0.28	0.28	0	30	78 vs. 61% for a PSA ≤ or >0.28 ng/ml	pT3b, positive SM, pre-SRT PSA, PSA doubling time	3D/68.4	GU = 1.3
Stephenson (2)	1540	Nomogram for disease progression after SRT	<0.5 to ≥0.5	0	53	PSA <0.5 = 48, PSA >0.51–1.00 = 40, PSA 1.01–1.50 = 28, PSA >1.50 = 18	GS, PSA doubling time, SM, ADT	64.8	NR

GS, Gleason score; PSA, prostate-specific antigen; RT, radiotherapy; ADT, androgen deprivation therapy; BPFS, biochemical progression-free survival; ART, adjuvant radiation therapy; SRT, salvage radiation therapy; RP, radical prostatectomy; SM, surgical margins; GU, genitourinary; GI, gastro-intestinal; NR, not-reported; 2D, two dimensional radiotherapy; 3D, three-dimensional conformal radiotherapy.

review (30). **Table 3** describes biomarker studies in the postoperative setting (31–34).

Certainly, when analyzing this data, one must consider that not all the patients treated with a PSA under 0.2 ng/ml will benefit clinically from SRT. The natural history of men with PSA relapses after RP is long: in the series described by Freedland et al., the median survival has not been reached after 16 years of follow-up. Patients at risk of prostate cancer death had shorter time to relapse, shorter PSA doubling times, and higher Gleason scores (7).

So far, only a few retrospective analyses have data on clinical significant endpoints. In the analysis by Boorjian et al., ART and SRT were independent predictors for biochemical and local control. In addition, SRT decreased the rate of systemic failures (35). Jereczek-Fossa et al. reported on 431 patients treated between 1996 and 2006: 258 men received immediate RT for a rising PSA between 0.1 and 4 ng/ml vs. 173 men who received SRT >6 months after surgery for a rising PSA that was between 0.1 and 13.7 ng/ml. Interestingly, in this study >78% of patients had biopsy-confirmed prostate relapse at the time of SRT, and 10 patients had palpable disease in the prostate bed. After a median follow-up time of 48 months, failure-free survival including BPFS and clinical failure was significantly longer in the immediate RT group (79.8 vs. 60.5%, $p < 0.0001$). In multivariate analysis, pre-radiotherapy PSA ≥0.2 ng/ml ($p < 0.001$) correlated with worst clinical outcome highlighting the more advanced tumors included in the SRT group (21). Swanson et al. reported a series of 92 patients referred to SRT for a rising PSA level at the time of referral from 0.1 to 30.5 ng/ml (median 1.5 ng/ml). The median time from surgery to radiation was 2.1 years (range 0.3–7.4 years). After a median follow-up time of 12.2 years, the 5- and 10-year BPFS was 35 and 26%, respectively, and OS was 86 and 67%, respectively. The median biochemical-free survival after SRT was 2.3 years (26).

The benefits of SRT should always be balanced against the morbidity of the therapy. Many large retrospective series assessing oncological outcomes after SRT did not include long-term toxicity data. In a retrospective series of 742 patients who underwent ART or SRT, the incidence of acute toxicity grade 2 or more was 19% after ART and 17% after SRT. The incidence of grade 3 toxicity was 8 and 6%, respectively. No differences in grade 2 or more late toxicity were observed. However, there were slightly more grade 3 late toxicity events in the ART group (12.2 vs. 10%) (36).

SALVAGE RADIOTHERAPY AND ANDROGEN DEPRIVATION THERAPY

GETUG-AFU 16 was the first randomized trial comparing SRT vs. SRT and short ADT as salvage treatment for biochemical recurrent prostate cancer after radical prostatectomy and was presented in abstract form at the American Association of Clinical Oncology (ASCO) 2015 Annual Meeting. The trial randomized 743 patients most of them having high intermediate risk features (pT2ac: 54%, pT3ac: 46%, gleason >6: 76%, positive margins: 51%, seminal vesicles' involvement 13%, and PSA doubling time at relapse was >6 months in 74%). The 5-year PFS was 62.1% (CI 95%: 57–67) vs. 79.6% (CI 95%: 75–84) for SRT and SRT + ADT, respectively ($p < 0.0001$). The 5-year OS was 94.8% for RT vs. 96.2% for SRT + ADT ($p = 0.18$). Cause of death was progressive disease in 2.1% of the patients on SRT arm vs. 0.8% in the SRT + ADT arm. Acute toxicities occurred more frequently in SRT + ADT arm (89 vs. 79%). This trial will require longer follow-up to see if the benefits observed in progression-free survival translate into the same OS benefit (37).

A recent phase I/II study evaluated 75 patients with PSA relapse after RP who were treated with SRT followed by 2-year ADT. Androgen ablation therapy started within 1 month after the completion of SRT. The study used a PSA rise above 0.2 ng/ml with two consecutive increases over a minimum of 3 months as the definition of PSA relapse post-therapy. All achieved initially complete PSA response (<0.2 ng/ml) with the protocol treatment. With the median follow-up of 6.4 years (range: 2–9.8) from SRT, the study reported that a relapse-free rate including the freedom from PSA relapse was 91.5% at 5 years and 78.6% at 7 years, and OS rate was 93.2% at both 5 and 7 years (17). Some retrospective data suggest that adding ADT to SRT increases patient's BPFS outcome. Tiguert et al. published a 5-year BPFS rate of 50% for 81 patients treated with 3 months of neoadjuvant ADT followed by SRT (38). In another series of 115 patients, 45 patients received 3 months of ADT followed by SRT and 70 patients were treated with SRT alone. The 4-year BPFS was better for patients treated with neoadjuvant ADT (59 vs. 39%) (39). King compared treatment outcomes between SRT plus 4-month ADT (2-months before and 2-months during RT) and SRT alone in a retrospective study of 122 patients (40). A 5-year BPFS rate was better for those treated with SRT plus 4-month ADT than for those receiving SRT alone (57 vs. 31%). Taylor et al. (41) reported on 35 out of 71 patients treated with adjuvant ADT for a median duration of 24 months. After a

TABLE 3 | Selected biomarkers tested in the postoperative setting.

Reference	*N*	Biomarker	Assay	Adverse prognostic factor for:
Den et al. (29)	188 (T3, margins positive)	22 genes	Tumor-derived RNA	Score ≥0.4, 6 vs. 23% probability of metastases for adjuvant vs. salvage RT
Parker et al. (33)	147	Ki-67	IHC	BR after SRT
Cuzick et al. (31)	366	31 cell cycle progression genes	Tumor-derived RNA	BR after radical prostatectomy defined as PSA >0.3
Wu et al. (34)	270	32 genes	Tumor derived real-time PCR	BR after RP >20% risk if index score >3
Erho et al. (32)	546	22 genes of cell proliferation and mobility	Tumor-derived RNA	BR after RP and metastatic progression

BR, Biochemical relapse; SRT, salvage radiation therapy; RP, radical prostatectomy; IHC, immunohistochemistry; RNA, ribonucleic acid; PCR, polymerase chain reaction.

median follow-up of 39 months, the 5-year BPFS rate was 81% for patients receiving adjuvant ADT, compared with 54% for those treated with SRT alone.

On the other hand, Trock et al. published a retrospective analysis of 635 men treated from 1982 to 2004 who received no SRT ($n = 397$) with a median PSA level of 9.6 ng/ml, SRT ($n = 160$) with a median PSA level of 8.3 ng/ml, and SRT combined with ADT ($n = 78$) who had a median PSA level of 7.7 ng/ml (23). The groups were otherwise not well balanced regarding pathological and clinical factors and patients who had SRT combined with ADT had a shorter time to recurrence, shorter PSA doubling time, and a higher PSA level at the time RT was initiated. The primary outcome was prostate cancer-specific survival defined from time to recurrence to death. SRT alone was associated with a significant threefold increase in prostate cancer-specific survival relative to those who received no further treatment (HR 0.34, 95% CI 0.17–0.69, $p = 0.003$). In this study, the addition of ADT was not associated with any additional increase in prostate cancer-specific survival. Notably, patients in the no-SRT group had a much higher prevalence of positive pelvic lymph nodes at recurrence.

RADIOLOGICAL ASSESSMENT

It should also be noted that patients undergoing SRT should be correctly staged. However, conventional imaging investigations such as bone scan and computed tomography of the chest, abdomen, and pelvis have been very insensitive for patients with biochemical-relapsed prostate cancer after RP. Nevertheless, we perform these tests in our routine clinical practice because the detection of any distant metastasis obviates the need for local salvage treatment. Cher et al. reported in a series of 93 patients with PSA relapse that the probability of a positive bone scan was <5%, unless a PSA level was above 40 ng/ml (42).

Similarly, the sensitivity of abdominopelvic CT scans is limited when PSA levels are low. Okotie reported that when the PSA was <10 ng/ml, the probability of a positive CT scan was non-existent (43). However, the use of MRI has enabled clinicians to assess the prostate bed more accurately. Miralbell et al. showed that MRI was capable of documenting a recurrent or residual disease in the setting of PSA levels ranging from 0.05 to 13.3 ng/ml (median: 0.87), typically in the inferior and posterior region of the vesicourethral anastomosis (44).

The use of conventional positron emission tomography (PET) tracers such as ^{18}F-fluorodeoxyglucose (FDG) is of no help in prostate cancer due to a low glycolysis rate and the renal excretion of the isotope into the bladder, enabling any local uptake.

In this context, recent studies showed that for patients with biochemical recurrence choline PET/CT may visualize the site of recurrence earlier and with higher accuracy than conventional imaging modalities. Rinnab et al. reported that ^{11}C-choline PET/CT had a sensitivity of 89% and a specificity of 40% for patients with post-RP PSA levels <2.5 ng/ml (45). A higher PSA level, PSA velocity, and PSA doubling time are predictive factors for having a positive ^{11}C-choline PET/CT (46). In a series of 21 patients with post-RP PSA relapse (median PSA: 1.98 ng/ml), ^{11}C-choline PET/CT improved the detection of lymph node metastases that were subsequently confirmed by histological assessment in 19 of the 21 patients (90%) (47). On a nodal site-based analysis, it was estimated that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{11}C-choline PET/CT was 64, 90, 86, 72, and 77%, respectively (48).

The information gained with PET/CT in this clinical setting has the potential to change disease management. In a recent clinical series reported by Alongi et al., 15 patients with biochemical recurrence after HIFU therapy and a median pre-RT PSA of 5.2 ng/ml (range: 2–64.2) underwent 11 C-choline PET/CTs, documenting intra-prostatic-only failure and allowing a better tailored salvaged treatment using volumetric modulated arc therapy (VMAT) (49).

Conversely, a recent study raised some doubt over the sensitivity of PET/CT in the clinical setting of low PSA levels. Vees et al. reported, in a series of 20 patients with post-RP PSA levels ≤1 ng/ml, that only 11 were found to have a positive PET/CT using either ^{18}F-choline or ^{11}C-acetate (50).

This highlights the fact that PET/CT often remains negative in early relapse situations when PSA levels are still very low (<1 ng/ml). Unfortunately, these levels are the "window" where ESRT will be most effective. Other tracers such as Ga-68-Prostate Specific Membrane Antigen (PSMA) are emerging in recent literature with preliminary promising results (51, 52).

RADIATION DOSE, TECHNIQUE, AND THE EFFECT OF DOSE ESCALATION

Traditionally, the three randomized trials for ART used 60–65 Gy typically with 3D simulation (4–6). In some cases, the treatment volumes were typically very generous being described as approximately 10 cm × 10 cm in the anterior–posterior fields with the inferior border at the ischial tuberosities. The lateral fields extended from the anterior aspect of the pubic symphysis and split the rectum posteriorly (8). In 3-Dimensional Conformal Radiation Therapy (3D-CRT), the target volume should include the bladder neck (pulled into the prostate bed), periprostatic tissues/clips, and the seminal vesicle bed (including any seminal vesicle remnants if present). Inferiorly, the vesicourethral anastomosis should be included. The anastomosis is the most frequent area of positive prostate biopsies (53, 54). By placing the inferior field edge at the top of the bulb of the penis and adding a margin for uncertainties, there should be adequate coverage. Laterally, the field should extend to about the medial aspect of each obturator internus muscle. Although the rectum is a landmark posteriorly, and its movement has been a matter of possible target missing, for this reason, a generous margin posteriorly is recommended in international guidelines (55). The superior margin is more subjective and should be guided by the extent of disease at the prostate base and whether the seminal vesicles are involved (56).

In accordance with the well-described dose-escalation trials for primary RT of localized prostate cancer, it has recently been proposed that dose intensification either for SRT or ART would be more effective in terms of cancer control (57).

Also, it has been suggested that each Gy increase in total dose may improve the BPFS by more than 3% (58). Therefore,

a total dose toward 70 Gy might be considered in the salvage situation, when the risk of severe toxicity can be minimized by using modern radiation techniques. In the absence of results from randomized trials, the potentially improved local tumor control by a higher RT dose should be carefully weighted up against possibly increased toxicity.

An increase in the RT dose will certainly increase grade 3 or more late toxicity. In a retrospective study where 70 Gy were administered using intensity-modulated radiation therapy (IMRT) to the prostate bed, urinary incontinence reached 13% and erectile dysfunction 26% (59). With higher doses of IMRT 76 Gy, the genitourinary and intestinal toxicity increased to 22 and 8% of the patients, respectively (60).

Although theoretical assumptions might claim a benefit in escalating the RT dose, a randomized trial is needed to definitely answer this question. The Swiss Group for Clinical Cancer Research (SAKK) conducted a randomized controlled international trial comparing SRT with 64 vs. 70 Gy without ADT in patients with prostate cancer and biochemical relapse after RP (SAKK 09/10, NCT01272050). The trial included men ≤75 years with pT2–3 N0 R0-1, with a PSA of at least ≥0.1 ng/ml and above but not higher than 2 ng/ml. Patients with evidence of macroscopic recurrence or metastatic disease were excluded. The primary endpoint was freedom from biochemical progression including a PSA of ≥0.4 ng/ml and above and/or clinical failure. The trial included quality of life analysis, quality assurance of RT, and a central pathology review. Three-dimensional conformal or IMRT were allowed per protocol. Three hundred and forty-four patients were randomized. The 13% grade 2 acute genitourinary toxicity and 0.6% grade 3 acute intestinal toxicity with 64 Gy were reported in comparison to 16.6% grade 2 and 1.7% grade 3 genitourinary toxicity with 70 Gy ($p = 0.2$). The 16% grade 2 acute intestinal toxicity and 0.6% grade 3 acute intestinal toxicity with 64 Gy were reported in comparison to 15.4% grade 2 and 2.3% grade 3 with 70 Gy ($p = 0.8$). Patients who received 70 Gy reported a more pronounced and clinically relevant genitourinary toxicity (mean difference in change score between arms, 3.6; $p = 0.02$) (61). Considering that this is an early report on toxicity, long-term toxicity as well as efficacy analysis is still pending.

CURRENT PHASE III STUDIES FOR PSA RELAPSE

The Radiation Therapy Oncology Group completed a phase III clinical trial (RTOG 9601) comparing ART with SRT (64.6 Gy in 36 fractions) plus 2 years of a high dose bicalutamide (150 mg per day) for patients with post-RP PSA relapse. The study group included patients with PSA levels from 0.2 to 4.0 ng/ml with prostate tumors classified as either pT2pN0 and a positive surgical margin or pT3pN0. The study closed in 2003 after accruing a total of 840 patients. Its final publication is pending at present. A recent presentation at the American Society for Radiation Oncology (ASTRO) reported that at a median follow-up of 12.6 years, there was an improvement in OS of 82% for the RT plus ADT vs. 78% for the RT plus placebo patients; with a hazard ratio of 0.75 (95 percent CI: 0.58–0.98) with a two-sided p-value = 0.036. Data indicated that the addition of ADT decreased the rate of death by prostate cancer and decreased the risk of the cancer metastasizing. The 12-year incidence of prostate cancer centrally-reviewed deaths was 2.3% for the RT plus ADT group, compared to 7.5% for the radiation plus placebo group ($p < 0.001$). At 12 years, the cancer had metastasized in 51 patients (14%) in the RT plus ADT group, compared to 83 patients (23%) in the radiation plus placebo group ($p < 0.001$). Additionally, late grade 3 and grade 4 bladder and bowel side effects were similar in both groups, whereas 70% of men in the RT plus ADT reported swelling of the breasts, compared to 11% from the radiation plus placebo group (62).

Currently, the RTOG is conducting another phase III, three-arm, study (RTOG 0534) to examine the potential benefit of adding 4–6 months of ADT to SRT and to address a potential role of treating pelvic lymph nodes. The United Kingdom is conducting a phase III study called RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery), and part of this study is to assess the benefit of adding 6-months or 24-months of ADT to SRT. A French group is conducting a phase III study comparing SRT with SRT plus 6-months of ADT (Clinical Trials Gov. Identifier: NCT00423475). Unfortunately, the EORTC 22043, a two-arm phase III trial, which compared 6 months of ADT concomitant to ART, closed in 2014 due to lack of patient accrual.

CONCLUSION

Radiotherapy represents a curative approach to treat prostate cancer in patients with postoperative detectable PSA. However, its efficacy is affected by the presence of adverse clinical/pathological prognostic factors. In this context, a patient with PSA relapse after RP represents a clinical dilemma. Treatment decisions have been jeopardized by a variety of retrospective trials that have used different postoperative PSA cut-off points and the lack of clear evidence demonstrating which therapeutic attitude is best, particularly in prolonging the patient's life without significant side effects. The use of ART over observation has been proven to prolong BPFS in phase III randomized trials, but its benefit in prolonging OS has also been questioned. The challenge of managing these patients in current clinical practice will be solved in the near future when the results of different on-going randomized trials become available.

AUTHOR CONTRIBUTIONS

FH and DB both collected the data and drafted the manuscript. DB approved the submitted version of the manuscript.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* (2015) **136**(5):E359–86. doi:10.1002/ijc.29210
2. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) **25**(15):2035–41. doi:10.1200/JCO.2006.08.9607
3. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* (1999) **281**(17):1591–7. doi:10.1001/jama.281.17.1591
4. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) **380**(9858):2018–27. doi:10.1016/S0140-6736(12)61253-7
5. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) **181**(3):956–62. doi:10.1016/j.juro.2008.11.032
6. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Storkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* (2009) **27**(18):2924–30. doi:10.1200/JCO.2008.18.9563
7. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* (2005) **294**(4):433–9. doi:10.1001/jama.294.4.433
8. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* (2005) **366**(9485):572–8. doi:10.1016/S0140-6736(05)67101-2
9. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* (2006) **296**(19):2329–35. doi:10.1001/jama.296.19.2329
10. Swanson GP, Hussey MA, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* (2007) **25**(16):2225–9. doi:10.1200/JCO.2006.09.6495
11. Parker CC, Sydes MR. Postoperative radiotherapy after radical prostatectomy: let's work together to tackle the known unknowns. *Eur Urol* (2014) **65**(6):1044–5. doi:10.1016/j.eururo.2013.09.035
12. Van der Kwast TH, Bolla M, Van Poppel H, Van Cangh P, Vekemans K, Da Pozzo L, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. *J Clin Oncol* (2007) **25**(27):4178–86. doi:10.1200/JCO.2006.10.4067
13. Collette L, van Poppel H, Bolla M, van Cangh P, Vekemans K, Da Pozzo L, et al. Patients at high risk of progression after radical prostatectomy: do they all benefit from immediate post-operative irradiation? (EORTC trial 22911). *Eur J Cancer* (2005) **41**(17):2662–72. doi:10.1016/j.ejca.2005.06.024
14. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol* (2006) **24**(12):1868–76. doi:10.1200/JCO.2005.04.7423
15. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knonagel H, et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. *Eur Urol* (2014) **66**(5):829–38. doi:10.1016/j.eururo.2013.07.024
16. Daly T, Hickey BE, Lehman M, Francis DP, See AM. Adjuvant radiotherapy following radical prostatectomy for prostate cancer. *Cochrane Database Syst Rev* (2011) **12**:CD007234. doi:10.1002/14651858.CD007234.pub2
17. Choo R, Danjoux C, Gardner S, Morton G, Szumacher E, Loblaw DA, et al. Prospective study evaluating postoperative radiotherapy plus 2-year androgen suppression for post-radical prostatectomy patients with pathologic T3 disease and/or positive surgical margins. *Int J Radiat Oncol Biol Phys* (2009) **75**(2):407–12. doi:10.1016/j.ijrobp.2008.12.049
18. Budiharto T, Perneel C, Haustermans K, Junius S, Tombal B, Scalliet P, et al. A multi-institutional analysis comparing adjuvant and salvage radiation therapy for high-risk prostate cancer patients with undetectable PSA after prostatectomy. *Radiother Oncol* (2010) **97**(3):474–9. doi:10.1016/j.radonc.2010.07.008
19. Cremers RG, van Lin EN, Gerrits WL, van Tol-Geerdink JJ, Kiemeney LA, Vergunst H, et al. Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high-risk patients suited for adjuvant radiotherapy. *Radiother Oncol* (2010) **97**(3):467–73. doi:10.1016/j.radonc.2010.05.023
20. Fossati N, Karnes RJ, Cozzarini C, Fiorino C, Gandaglia G, Joniau S, et al. Assessing the optimal timing for early salvage radiation therapy in patients with prostate-specific antigen rise after radical prostatectomy. *Eur Urol* (2015) **4**:728–33. doi:10.1016/j.eururo.2015.10.009
21. Jereczek-Fossa BA, Zerini D, Vavassori A, Fodor C, Santoro L, Minissale 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**(1):115–25. doi:10.1016/j.ijrobp.2008.07.057
22. Trabulsi EJ, Valicenti RK, Hanlon AL, Pisansky TM, Sandler HM, Kuban DA, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. *Urology* (2008) **72**(6):1298–302. doi:10.1016/j.urology.2008.05.057 discussion 302–4
23. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* (2008) **299**(23):2760–9. doi:10.1001/jama.299.23.2760
24. Briganti A, Karnes RJ, Joniau S, Boorjian SA, Cozzarini C, Gandaglia G, et al. Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol* (2014) **66**(3):479–86. doi:10.1016/j.eururo.2013.11.045
25. D'Amico AV, Chen MH, Sun L, Lee WR, Mouraviev V, Robertson CN, et al. Adjuvant versus salvage radiation therapy for prostate cancer and the risk of death. *BJU Int* (2010) **106**(11):1618–22. doi:10.1111/j.1464-410X.2010.09447.x
26. Swanson GP, Du F, Michalek JE, Hermans M. Long-term follow-up and risk of cancer death after radiation for post-prostatectomy rising prostate-specific antigen. *Int J Radiat Oncol Biol Phys* (2011) **80**(1):62–8. doi:10.1016/j.ijrobp.2010.01.043
27. Pfister D, Bolla M, Briganti A, Carroll P, Cozzarini C, Joniau S, et al. Early salvage radiotherapy following radical prostatectomy. *Eur Urol* (2014) **65**(6):1034–43. doi:10.1016/j.eururo.2013.08.013
28. Siegmann A, Bottke D, Faehndrich J, Brachert M, Lohm G, Miller K, et al. Salvage radiotherapy after prostatectomy – what is the best time to treat? *Radiother Oncol* (2012) **103**(2):239–43. doi:10.1016/j.radonc.2011.10.024
29. Den RB, Yousefi K, Trabulsi EJ, Abdollah F, Choeurng V, Feng FY, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J Clin Oncol* (2015) **33**(8):944–51. doi:10.1200/JCO.2014.59.0026
30. Dal Pra A, Locke JA, Borst G, Supiot S, Bristow RG. Mechanistic Insights into Molecular Targeting and Combined Modality Therapy for Aggressive, Localized Prostate Cancer. *Front Oncol* (2016) **6**:24. doi:10.3389/fonc.2016.00024
31. Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol* (2011) **12**(3):245–55. doi:10.1016/S1470-2045(10)70295-3
32. Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One* (2013) **8**(6):e66855. doi:10.1371/journal.pone.0066855
33. Parker AS, Heckman MG, Wu KJ, Crook JE, Hilton TW, Pisansky TM, et al. Evaluation of ki-67 staining levels as an independent biomarker of biochemical recurrence after salvage radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2009) **75**(5):1364–70. doi:10.1016/j.ijrobp.2008.12.061

34. Wu CL, Schroeder BE, Ma XJ, Cutie CJ, Wu S, Salunga R, et al. Development and validation of a 32-gene prognostic index for prostate cancer progression. *Proc Natl Acad Sci U S A* (2013) **110**(15):6121–6. doi:10.1073/pnas.1215870110
35. Boorjian SA, Thompson RH, Tollefson MK, Rangel LJ, Bergstralh EJ, Blute ML, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. *Eur Urol* (2011) **59**(6):893–9. doi:10.1016/j.eururo.2011.02.026
36. Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, et al. Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. *Int J Radiat Oncol Biol Phys* (2012) **82**(1):191–9. doi:10.1016/j.ijrobp.2010.09.027
37. Carrie C, Hasbini A, De Laroche G, Habibian M, Richaud P, Guérif S, et al. Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): results of the GETUG-AFU 16 phase III randomized trial – NCT00423475. *J Clin Oncol* (2015) **33**(15–Suppl):5006.
38. Tiguert R, Rigaud J, Lacombe L, Laverdiere J, Fradet Y. Neoadjuvant hormone therapy before salvage radiotherapy for an increasing post-radical prostatectomy serum prostate specific antigen level. *J Urol* (2003) **170**(2 Pt 1):447–50. doi:10.1097/01.ju.0000075351.51838.b3
39. Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* (2003) **21**(3):483–9. doi:10.1200/JCO.2003.12.043
40. King CR, Presti JC Jr, Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *Int J Radiat Oncol Biol Phys* (2004) **59**(2):341–7. doi:10.1016/j.ijrobp.2003.10.015
41. Taylor N, Kelly JF, Kuban DA, Babaian RJ, Pisters LL, Pollack A. Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* (2003) **56**(3):755–63. doi:10.1016/S0360-3016(03)00069-5
42. Cher ML, Bianco FJ Jr, Lam JS, Davis LP, Grignon DJ, Sakr WA, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol* (1998) **160**(4):1387–91. doi:10.1016/S0022-5347(01)62545-X
43. Okotie OT, Aronson WJ, Wieder JA, Liao Y, Dorey F, De KJ, et al. Predictors of metastatic disease in men with biochemical failure following radical prostatectomy. *J Urol* (2004) **171**(6 Pt 1):2260–4. doi:10.1097/01.ju.0000127734.01845.99
44. Miralbell R, Vees H, Lozano J, Khan H, Molla M, Hidalgo A, et al. Endorectal MRI assessment of local relapse after surgery for prostate cancer: a model to define treatment field guidelines for adjuvant radiotherapy in patients at high risk for local failure. *Int J Radiat Oncol Biol Phys* (2007) **67**(2):356–61. doi:10.1016/j.ijrobp.2006.08.079
45. Rinnab L, Simon J, Hautmann RE, Cronauer MV, Hohl K, Buck AK, et al. [(11) C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. *World J Urol* (2009) **27**(5):619–25. doi:10.1007/s00345-009-0371-7
46. Castellucci P, Fuccio C, Nanni C, Santi I, Rizzello A, Lodi F, et al. Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med* (2009) **50**(9):1394–400. doi:10.2967/jnumed.108.061507
47. Scattoni V, Picchio M, Suardi N, Messa C, Freschi M, Roscigno M, et al. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. *Eur Urol* (2007) **52**(2):423–9. doi:10.1016/j.eururo.2007.03.032
48. Schilling D, Schlemmer HP, Wagner PH, Bottcher P, Merseburger AS, Aschoff P, et al. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. *BJU Int* (2008) **102**(4):446–51. doi:10.1111/j.1464-410X.2008.07592.x
49. Alongi F, Liardo RL, Iftode C, Lopci E, Villa E, Comito T, et al. 11C choline PET guided salvage radiotherapy with volumetric modulation arc therapy and hypofractionation for recurrent prostate cancer after HIFU failure: preliminary results of tolerability and acute toxicity. *Technol Cancer Res Treat* (2014) **13**(5):395–401. doi:10.7785/tcrtexpress.2013.600268
50. Vees H, Buchegger F, Albrecht S, Khan H, Husarik D, Zaidi H, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. *BJU Int* (2007) **99**(6):1415–20. doi:10.1111/j.1464-410X.2007.06772.x
51. Demirkol MO, Acar O, Ucar B, Ramazanoglu SR, Saglican Y, Esen T. Prostate-specific membrane antigen-based imaging in prostate cancer: impact on clinical decision making process. *Prostate* (2015) **75**(7):748–57. doi:10.1002/pros.22956
52. Sah BR, Burger IA, Schibli R, Friebe M, Dinkelborg L, Graham K, et al. Dosimetry and first clinical evaluation of the new 18F-radiolabeled bombesin analogue BAY 864367 in patients with prostate cancer. *J Nucl Med* (2015) **56**(3):372–8. doi:10.2967/jnumed.114.147116
53. Foster LS, Jajodia P, Fournier G Jr, Shinohara K, Carroll P, Narayan P. The value of prostate specific antigen and transrectal ultrasound guided biopsy in detecting prostatic fossa recurrences following radical prostatectomy. *J Urol* (1993) **149**(5):1024–8.
54. Naya Y, Okihara K, Evans RB, Babaian RJ. Efficacy of prostatic fossa biopsy in detecting local recurrence after radical prostatectomy. *Urology* (2005) **66**(2):350–5. doi:10.1016/j.urology.2005.03.014
55. Fiorino C, Foppiano F, Franzone P, Broggi S, Castellone P, Marcenaro M, et al. Rectal and bladder motion during conformal radiotherapy after radical prostatectomy. *Radiother Oncol* (2005) **74**(2):187–95. doi:10.1016/j.radonc.2004.10.002
56. Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, 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**(2):121–7. doi:10.1016/j.radonc.2007.07.017
57. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* (2009) **74**(5):1405–18. doi:10.1016/j.ijrobp.2008.10.091
58. King CR, Spiotto MT. Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2008) **71**(1):23–7. doi:10.1016/j.ijrobp.2007.09.047
59. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol* (2011) **60**(6):1142–8. doi:10.1016/j.eururo.2011.08.006
60. Ost P, Lumen N, Goessaert AS, Fonteyne V, De Troyer B, Jacobs F, 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**(4):842–9. doi:10.1016/j.eururo.2011.04.021
61. Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Holscher T, Gut P, 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**(35):4158–66. doi:10.1200/JCO.2015.63.3529
62. Shipley WU, Seiferheld W, Lukka H, et al. Report of NRG Oncology/RTOG 9601, a phase III trial in prostate cancer: anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) in patients following radical prostatectomy (RP) with pT2-3pN0 disease and an elevated PSA. *Presented at the American Society of Radiation Oncology (ASTRO) 57th Annual Meeting, LBA 5*. (2015).

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REVIEW
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Role of Dose Intensification for Salvage Radiation Therapy after Radical Prostatectomy

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For primary radiation therapy (RT) of prostate cancer, dose intensification is established as standard of care. Less is known on the role of dose intensification in the postprostatectomy setting for salvage RT. Thus, we aimed to identify and summarize the existing literature. In retrospective analyses, dose-intensified salvage RT showed a superior biochemical control compared to standard dose salvage radiation with favorable acute and late gastrointestinal and genitourinary toxicity rates, especially when modern radiation techniques such as intensity modulated RT were applied. We identified one randomized phase III trial addressing the potential benefits of dose-intensified salvage RT (SAKK 09/10). Recently, acute gastrointestinal and genitourinary toxicities and early quality of life data of this trial were reported, and no significant difference in acute toxicities between both treatment arms were found; however, a significant worsening of genitourinary quality of life was noted in the dose-intensified treatment arm. Whereas dose-intensified salvage RT appears to be feasible and well tolerated, the improved biochemical control rates using dose intensified RT as suggested by retrospective analyses have yet to be validated by prospective trials.

Keywords: prostate cancer, salvage, radiation therapy, prostatectomy, dose

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INTRODUCTION

Around 30,000 men will experience recurrence of prostate cancer after radical prostatectomy annually in the United States (1). For the majority of these patients, the only evidence of recurrent disease is an increasing serum PSA level without evidence of macroscopic recurrence. After radical prostatectomy approximately 15–40% of men develop a biochemical relapse within 5 years (2, 3). It has been described that the site of relapse in prostate cancer patients after prostatectomy is predominantly local, with a relatively low incidence of distant failures (4). Patients with biochemical relapse develop bone metastasis with a rate of 37 and 65% at 5 and 10 years, respectively. A median time of 8 years until development of bone metastasis was reported and the observed median time between the development of bone metastasis and death was 5 years (5).

Generally, two main strategies are being used to increase long-term tumor control after prostatectomy: either adjuvant radiation therapy (RT) in the presence of positive surgical margins, extracapsular extension or seminal vesicle invasion, or salvage RT at biochemical relapse. The advantages of dose intensification in primary prostate cancer were already shown in several randomized controlled

trials. The meta-analysis by Viani et al. reported a reduction of biochemical relapse rates after dose intensified RT vs. conventional dose RT. However, the dose intensification was associated with increasing rates of grade 2 or higher gastrointestinal toxicity (6).

For the postprostatectomy setting, retrospective analyses have demonstrated the effectiveness of salvage RT in terms of biochemical relapse-free survival and cancer-specific survival (7, 8), and thus salvage RT is considered the only potentially curative treatment at the earliest sign of biochemical failure. Further analyses showed that dose-intensified salvage RT achieved superior biochemical relapse-free survival compared to standard doses (9–11).

As standard for salvage RT, a dose of 64–66 Gy is recommended in the guidelines of the European Association of Urology (EAU) at PSA serum levels of ≤0.5 ng/ml (12). The American Society of Radiation Oncology (ASTRO) guidelines recommend using the highest RT dose deliverable with acceptable toxicity rates and suggest a minimum dose of 64–65 Gy with conventional dose fractionation (13).

Less is known regarding dose intensification in the salvage RT setting. We have thus reviewed and summarized the literature for dose-intensified salvage RT.

MATERIALS AND METHODS

Data for this Review were identified by non-systematic searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using medical subject headings including "prostate cancer," "postoperative," "radiotherapy," "radiation," "adjuvant," "salvage, dose," "escalation," "escalated," "intensified," and "intensification."

RESULTS

Retrospective Data

King et al. described improved biochemical relapse-free survival rates for dose-intensified salvage RT (70 Gy) compared to doses of 60 Gy. One hundred twenty-two patients were treated either with a dose of 60 Gy ($n = 38$) or 70 Gy ($n = 84$) using two-dimensional (2D) conformal, three-dimensional (3D) conformal, or intensity modulated RT (IMRT) between 1984 and 2004. Sixty-eight patients received additional androgen deprivation therapy (ADT). The median follow up was >5 years, and patients with 70 Gy treatment had a biochemical relapse-free survival of 58 vs. 25% when treated with 60 Gy. In a multivariate analysis, higher dose was an independent factor for superior biochemical relapse-free survival (9).

Likewise, Ost et al. evaluated 136 patients who received a salvage IMRT with a median dose of 76 Gy alone ($n = 39$) or combined with ADT ($n = 97$) between 1999 and 2008. After a median follow up of 5 years, a biochemical relapse-free survival of 56% and a clinical relapse-free survival of 86% were observed (14). Moreover, Goenka et al. published a retrospective study analyzing 285 salvage RT patients, 72% were treated with a RT dose ≥70 Gy using either 3D or IMRT techniques. Thirty-one percent received additional ADT. The median follow up was 60 months. After 7 years, biochemical relapse-free survival was 37% and distant metastases-free survival was 77% (15). Moreover, a systematic review with regression meta-analysis and radiobiological modeling performed by Ohri et al. analyzed 25 studies with 3,828 patients with a median follow up of 50 month. The RT dose ranged from 60 to 72 Gy (median dose: 65 Gy) and 2D, 3D, or IMRT techniques were applied. The authors observed a median 5-year biochemical relapse-free survival of 47% and detected a dose-related increase of 5-year biochemical relapse-free survival. Each increase of 1 Gy led to an increase of 2.5% of 5-year biochemical relapse-free survival rates (10). Another systematic review published by King analyzed 41 studies with 5,597 patients. The median follow up was 47 ± 22 months, and the applied median dose was 64.6 ± 3.1 Gy. King reported a median relapse-free survival of 34% when RT dose was 60 Gy and 54% with an applied dose of 70 Gy. For each additional 1 Gy, a 2% improvement of relapse-free survival was estimated (16).

The systematic review by Ohri et al. also analyzed the dose-dependent toxicity of 3,828 salvage RT patients treated with 2D/3D or IMRT techniques with a median dose of 65 Gy. A toxicity model was generated and showed increasing dose-dependent rates of ≥grade 3 genitourinary and gastrointestinal toxicity. The authors estimated that with each dose increase of 1 Gy, the rate of ≥grade 3 gastrointestinal late toxicity would increase about 1.2% and grade 3 genitourinary late toxicity rates would increase 0.8%. Furthermore, it was assumed that a rate of >10% late grade 3 gastrointestinal and genitourinary side effects would occur when RT dose exceeds 72 Gy (10). One important limitation of this toxicity model was, however, its dependency on series with 2D/3D treatment techniques. Moreover, the applied doses in the analyzed series were ≤70 Gy. So this model may not be valid to estimate toxicity rates for more modern RT approaches and application of doses >70 Gy (17).

Cozzarini et al. described the long-term toxicity rates of 742 patients treated between 1993 and 2005 with adjuvant RT or salvage RT using 2D and 3D conformal techniques (median follow up 8 years). The salvage RT ($n = 186$) with a median dose of 72 Gy resulted in ≥grade 2 late genitourinary toxicity in 23.7% of the patients. Grade 3 late genitourinary toxicity occurred in 10% of the patients. Grade 2 or higher acute toxicity and a dose of >72 Gy were identified as independent prognostic factors for late grade 3 genitourinary toxicity (18).

Goenka et al. evaluated toxicity rates of 285 patients treated between 1988 and 2007 with salvage RT (median follow up 60 months). One hundred nine patients who received 3D conformal RT ($n = 12$: <66 Gy; $n = 57$: 66 to <70 Gy; $n = 40$: ≥70 Gy) were compared to 176 patients who underwent IMRT ($n = 3$: <66 Gy; $n = 8$: 66 to <70 Gy; $n = 165$: ≥70 Gy). A 8.3% reduction of late ≥grade 2 gastrointestinal toxicity was reported using IMRT (toxicity rate: 1.9%) compared to 3D conformal RT (toxicity rate: 10.2%). In this series, no acute grade 3 gastrointestinal toxicity and only 1.4% late grade 3 gastrointestinal toxicity were observed. The overall ≥grade 2 late genitourinary toxicity rate was 16.3% with no significant difference between the different RT techniques (15, 19). Similar low grade 3 late gastrointestinal toxicity rates were reported by Ost et al. (grade 3 gastrointestinal

toxicity <1%) using IMRT (mean dose: 76 Gy) for salvage RT of 136 patients. Late genitourinary ≥grade 2 toxicity rates were 22%, and the grade 3 late genitourinary toxicity rate was 3% (14).

Prospective Randomized Data

Only one randomized prospective phase III trial testing dose-intensified salvage RT was identified (conducted by the Swiss Group for Clinical Cancer Research, SAKK). The SAKK 09/10 trial was closed for accrual after it met its accrual goal of 350 patients (2011–2014). In this trial, salvage RT with 70 Gy was compared to a dose of 64 Gy. A recent analysis of this trial reported acute toxicity rates and early quality of life in 344 patients being eligible in the safety population (20). European Organization for Research and Treatment of Cancer (EORTC) delineation guidelines were used (21), and toxicity was scored according to National Cancer Institute Common Terminology Criteria for Adverse events (CTC AE, version 4.0). Quality of life was analyzed with the EORTC Quality of Life Questionnaires C30 and PR25. Acute grade 2 genitourinary toxicity occurred in 13%, grade 3 genitourinary toxicity in 0.6% treated with 64 Gy compared to 16.6 and 1.7% grade 2 and 3 genitourinary toxicity after 70 Gy, respectively. Acute grade 2 gastrointestinal toxicity occurred in 16%, grade 3 gastrointestinal toxicity in 0.6% treated with 64 Gy compared to 15.4 and 2.3% acute grade 2 and 3 gastrointestinal toxicity after 70 Gy, respectively. There was no significant difference in acute toxicity rates (CTC AE based) between both arms. Generally, changes in health related quality of life were minor; however, there was a more pronounced and clinically relevant worsening of genitourinary symptoms in the 70 Gy arm. Thus, the initial results of SAKK 09/10 trial confirmed low acute toxicity rates even after dose intensified RT of up to 70 Gy, whereas only slight but significant increase in patient reported early urinary symptoms was shown. In 44% of the patients, the RT was applied using a 3D-conformal approach and in 56% of the patients using an IMRT/rotational RT approach (RT technique was a stratification factor). There was no significant difference in acute gastrointestinal or genitourinary toxicity associated with RT technique (20). The first randomized prospective data regarding freedom from biochemical recurrence (primary trial endpoint) and late toxicity after dose-intensified salvage RT are awaited in 2017.

DISCUSSION

Retrospective analyses showed improved biochemical control rates after dose-intensified salvage RT with a dose-dependent increase of biochemical relapse-free survival (9–11). The available data suggested slightly increased toxicity rates for dose-intensified salvage RT, when compared to standard dose salvage RT, but both gastrointestinal and genitourinary toxicity rates are generally favorably, even after dose-intensified salvage RT (14, 15, 18, 19).

These findings are confirmed by recent published data from the randomized SAKK 09/10 prospective trial, where low rates of grade 2 and 3 gastrointestinal and genitourinary acute toxicity were described without a significant difference between the two trial arms (total dose 64 vs. 70 Gy). However, there was a significant worsening of genitourinary early quality of life after treatment with 70 Gy. Therefore, some caution might be directed toward impairment of genitourinary early quality of life, which has to be weighed up against potential improvements in biochemical control (20). It was assumed that the necessity to include the bladder neck and the vesico-urethral anastomosis in the high dose salvage RT volume would result in similar genitourinary toxicity regardless of RT technique (17). A worsening of urinary symptoms after high dose RT to urethra, bladder neck, and bladder trigonum was also described in the primary prostate cancer RT (22). This might be the reason for the observed significant worsening of patient who reported urinary symptom burden in the quality of life analysis of SAKK 09/10 (20). It has been well described that patient-reported toxicity scoring systems are more reliable and more sensitive as compared to physician-reported toxicity scoring systems (23), which might be the reason that there was no significant difference in the acute CTC AE-based toxicity scores between the two trial arms.

Interestingly, the SAKK 09/10 trial did stratify for RT technique (3D-conformal RT vs. IMRT/rotational techniques). However, no association was found between RT technique and acute toxicity or early quality of life. This is in contrast to several retrospective analyses that reported that IMRT was associated with a reduced rate of gastrointestinal toxicity as compared to 3D conformal RT in the setting of dose-intensified salvage RT (without a significant difference in genitourinary toxicity) (14, 15, 19). Interestingly, despite being based on retrospective data only, a survey asking physicians in the United States for implemented techniques showed that a majority used IMRT for the salvage RT setting (24). However, in the primary RT setting of prostate cancer (using a higher total dose), preliminary results of the prospective randomized RTOG 0126 trial showed significantly reduced gastrointestinal and genitourinary acute toxicity rates using IMRT compared to 3D conformal RT (25).

In this context, it is important to consider different delineation guidelines with obviously different target volume sizes and its implication for clinical practice. For example, the SAKK 09/10 trial used the EORTC delineation guidelines for clinical (CTV) and planning (PTV) target volumes (20, 21) that were described to be significantly smaller compared to other recommendations such as the Faculty of Radiation Oncology Genito-Urinary Group (FROGG), the Princess Margaret Hospital (PMH), and the RTOG guidelines (26). Hence, the toxicity rates observed in SAKK 09/10 trial and maybe also the differences between the two dose levels in terms of toxicity results could potentially be higher if other delineation guidelines were used.

Otherwise, recently published data confirm that there are other promising treatment options to improve the efficacy of salvage RT. The use of ADT as an additional treatment in the salvage setting was analyzed by two randomized phase III studies. The GETUG-AFU 16 trial compared standard dose salvage RT (66 Gy) alone vs. salvage RT combined with short-term ADT (66 Gy plus 6-month goserelin) and detected a significant improvement in 5-year progression-free survival for the combined treatment. More acute toxicities (<grade 3) were observed after combined treatment but acute grade 3 or late toxicity was not significantly

different between the trial arms (27). Moreover, the long-term results of RTOG 9601, a trial that compared standard dose salvage RT (64.8 Gy) vs. salvage RT with long-term ADT (64.8 Gy plus 24-month bicalutamide), showed a significant overall survival benefit after 10 years with 78% for RT alone vs. 82% for the combined treatment (hazard ratio 0.75, 95% CI: 0.58–0.98). No significant difference in grade 3 or 4 late toxicity was described, whereas significantly more gynecomastia was observed in the bicalutamide group (70%) vs. RT (11%) (28). However, both studies applied a standard dose RT, and thus no firm conclusions about combination of ADT with dose-intensified salvage RT can be made and whether this would lead to a similar or better outcome or to unacceptable toxicity. Thus, it has to be considered that ADT is associated with multiple short and long-term side effects like bone loss, sexual dysfunction, hot flashes, metabolic changes, fatigue, gynecomastia among others (29). It might be that dose-intensified salvage RT alone achieves similar results without ADT-associated side effects or at least might be capable to significantly delay the use of ADT. Another potential option to achieve improved outcome in the salvage RT is regional hyperthermia, which will be investigated in a novel phase II trial (30).

Finally, until biochemical relapse-free survival and late toxicity rates from the SAKK 09/10 trial become available, the described worsening of genitourinary quality of life after 70 Gy must be weighted up against benefits in cancer control, potentially being obtained by dose intensification. For patients without macroscopic recurrence, one practical solution could be to deliver dose-intensified salvage RT up to 70–72 Gy in the absence of acute genitourinary toxicity but to stop the salvage RT after 66 Gy in the presence of significant acute toxicity. Alternatively, a simultaneous integrated boost technique (SIB) might be applied to selectively apply a higher dose to the high-risk quadrant of the prostatic bed (e.g., pT3, R1) while sparing the vesico-urethral anastomosis/urethra if possible. Patients with macroscopic recurrences will probably benefit from higher doses (toward 76 Gy) and the addition of ADT.

CONCLUSION

According to retrospective data, dose-intensified salvage RT appears to be well tolerated and effective. However, a slight increase in acute and late toxicities using dose-intensified salvage radiation treatment could be detected. A prospective trial reported favorable acute toxicity rates after dose-intensified salvage RT, but biochemical control rates and late toxicity data of this trial are still pending. As long as these prospective data are not available, the potential benefits in biochemical control and the mild increase of toxicities in dose-intensified salvage RT (both reported in retrospective studies) have to be weighed up.

AUTHOR CONTRIBUTIONS

MB and PG participated in drafting and revising the manuscript; TB, DK, SW, AT, DZ, PW, DA, and VB participated in revising the manuscript.

REFERENCES

1. Moul JW. Prostate specific antigen only progression of prostate cancer. *J Urol* (2000) **163**(6):1632–42. doi:10.1016/S0022-5347(05)67511-8
2. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol* (2003) **169**(2):517–23. doi:10.1016/S0022-5347(05)63946-8
3. Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. *Nat Clin Pract Urol* (2005) **2**(4):174–82. doi:10.1038/ncpuro0145
4. Swanson GP, Hussey MA, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* (2007) **25**(16):2225–9. doi:10.1200/JCO.2006.09.6495
5. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* (1999) **281**(17):1591–7. doi:10.1001/jama.281.17.1591
6. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* (2009) **74**(5):1405–18. doi:10.1016/j.ijrobp.2008.10.091
7. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) **25**(15):2035–41. doi:10.1200/JCO.2006.08.9607
8. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs. observation in men with biochemical recurrence after radical prostatectomy. *JAMA* (2008) **299**(23):2760–9. doi:10.1001/jama.299.23.2760
9. King CR, Spiotto MT. Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2008) **71**(1):23–7. doi:10.1016/j.ijrobp.2007.09.047
10. Ohri N, Dicker AP, Trabulsi EJ, Showalter TN. Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. *Eur J Cancer* (2012) **48**(6):837–44. doi:10.1016/j.ejca.2011.08.013
11. King CR, Kapp DS. Radiotherapy after prostatectomy: is the evidence for dose escalation out there? *Int J Radiat Oncol Biol Phys* (2008) **71**(2):346–50. doi:10.1016/j.ijrobp.2007.10.008
12. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* (2014) **65**(2):467–79. doi:10.1016/j.eururo.2013.11.002
13. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* (2013) **190**(2):441–9. doi:10.1016/j.juro.2013.05.032
14. Ost P, Lumen N, Goessaert AS, Fonteyne V, De Troyer B, Jacobs F, 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**(4):842–9. doi:10.1016/j.eururo.2011.04.021
15. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. *Int J Radiat Oncol Biol Phys* (2012) **84**(1):112–8. doi:10.1016/j.ijrobp.2011.10.077
16. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. *Int J Radiat Oncol Biol Phys* (2012) **84**(1):104–11. doi:10.1016/j.ijrobp.2011.10.069
17. Ost P, Cozzarini C, Bossi A, De Meerleer G. Salvage radiotherapy: a plea for dose-escalation with intensity-modulated radiotherapy. *Eur J Cancer* (2012) **48**(9):1415–6. doi:10.1016/j.ejca.2012.01.024
18. Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, et al. Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. *Int J Radiat Oncol Biol Phys* (2012) **82**(1):191–9. doi:10.1016/j.ijrobp.2010.09.027

19. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol* (2011) **60**(6):1142–8. doi:10.1016/j.eururo.2011.08.006
20. Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Holscher T, Gut P, 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**(35):4158–66. doi:10.1200/JCO.2015.63.3529
21. Sassowsky M, Gut P, Holscher T, Hildebrandt G, Muller AC, Najafi Y, 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**(3):534–41. doi:10.1016/j.ijrobp.2013.06.2053
22. Ghadjar P, Zelefsky MJ, Spratt DE, Munck af Rosenschold P, Oh JH, Hunt M, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* (2014) **88**(2):339–44. doi:10.1016/j.ijrobp.2013.10.042
23. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys* (2010) **76**:S116–22. doi:10.1016/j.ijrobp.2009.02.090
24. Showalter TN, Ohri N, Teti KG, Foley KA, Keith SW, Trabulsi EJ, et al. Physician beliefs and practices for adjuvant and salvage radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2012) **82**(2):e233–8. doi:10.1016/j.ijrobp.2011.04.003
25. Michalski JM, Yan Y, Watkins-Bruner D, Bosch WR, Winter K, Galvin JM, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys* (2013) **87**(5):932–8. doi:10.1016/j.ijrobp.2013.07.041
26. Malone S, Croke J, Roustan-Delatour N, Belanger E, Avruch L, Malone C, et al. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. *Int J Radiat Oncol Biol Phys* (2012) **84**(3):725–32. doi:10.1016/j.ijrobp.2011.12.081
27. Carrie C. Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): results of the GETUG-AFU 16 phase III randomized trial–NCT00423475. *J Clin Oncol* (2015) **33**(suppl):abstr5006.
28. Shipley WU, Seiferheld W, Lukka H, Major P, Heney NM, Grignon D, et al. Report of NRG oncology/RTOG 9601, a phase 3 trial in prostate cancer: anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) in patients following radical prostatectomy (RP) with pT2-3pN0 disease and an elevated PSA. *Int J Radiat Oncol Biol Phys* (2016) **94**(1):3. doi:10.1016/j.ijrobp.2015.10.048
29. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* (2015) **67**(5):825–36. doi:10.1016/j.eururo.2014.07.010
30. Muller AC, Zips D, Heinrich V, Lamprecht U, Voigt O, Burock S, et al. Regional hyperthermia and moderately dose-escalated salvage radiotherapy for recurrent prostate cancer. Protocol of a phase II trial. *Radiat Oncol* (2015) **10**:138. doi:10.1186/s13014-015-0442-4

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MINI REVIEW
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Target Definition in Salvage Radiotherapy for Recurrent Prostate Cancer: The Role of Advanced Molecular Imaging

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Salvage radiotherapy (SRT) represents the main treatment option for relapsing prostate cancer in patients after radical prostatectomy. Several open questions remain unanswered in terms of target volumes definition and delivered doses for SRT: the effective dose necessary to achieve biochemical control in the SRT setting may be different if the tumor recurrence is micro- or macroscopic. At the same time, irradiation of only the prostatic bed or of the whole pelvis will depend on the localization of the recurrence, local or locoregional. In the "theragnostic imaging" era, molecular imaging using positron emission tomography (PET) constitutes a useful tool for clinicians to define the site of the recurrence, the extent of disease, and individualize salvage treatments. The best option currently available in clinical routine is the combination of radiolabeled choline PET imaging and multiparametric magnetic resonance imaging (MRI), associating the nodal and distant metastases identification based on PET with the local assessment by MRI. A new generation of targeted tracers, namely, prostate-specific membrane antigen, show promising results, with a contrast superior to choline imaging and a higher detection rate even for low prostate-specific antigen levels; validation studies are ongoing. Finally, imaging targeting bone remodeling, using whole-body SPECT–CT, is a relevant complement to molecular/metabolic PET imaging when bone involvement is suspected.

Keywords: prostate cancer, PET, MRI, salvage radiotherapy, choline, PSMA

INTRODUCTION

Although radical prostatectomy (RP) with or without lymphadenectomy remains one of the main curative options for prostate cancer (PCa), more than 30% of the patients will relapse during follow-up (1). Salvage radiotherapy (SRT) represents the main treatment option for relapsing patients after RP, and durable biochemical response rates have been reported (2). Despite gains in understanding how to select patients for salvage treatment, the variable clinical course of these patients still leaves uncertainties about how and when to appropriately manage these patients.

Early identification of relapsing disease by modern imaging techniques has been demonstrated to significantly influence final treatment decisions and drive SRT in locally or locoregionally relapsing patients in terms of target volume definition as well as planned doses. Indeed, the effective dose necessary to achieve biochemical control in the SRT setting may be different if the tumor recurrence is micro- or macroscopic (3). At the same time, irradiation of only the prostatic bed or of the whole pelvis will depend on the precise location of the recurrence, local or loco-regional.

In the "theragnostic imaging" era, molecular imaging using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) constitutes a useful tool for clinicians to define the site of the recurrence, the extent of disease, and allows, therefore, for individualizing salvage treatments. In the following review, we report on the evidence concerning the use of molecular imaging in the SRT setting in patients presenting with biochemical relapse after RP, with a special focus on new PCa-specific PET tracers. **Table 1** provides a summary of the most relevant tracers available in the setting of post-prostatectomy relapsing PCa.

EVALUATION OF LOCAL AND LYMPH NODE INVOLVEMENT RECURRENCE BY CHOLINE PET TRACERS

^{18}F-fluorodeoxyglucose (FDG) PET imaging is a well-established tool in radiation therapy planning, extensively used in many tumor types. The lack of FDG avidity in most PCa has motivated the search for alternative metabolic tracers, and among them, the most commonly used are choline tracers. Three main choline-based PET tracers exist, namely, ^{11}C-choline, ^{18}F-methylcholine, and ^{18}F-ethylcholine: regardless of the slight chemical differences impacting overall distribution and the lack of formal comparative studies, available data suggest that their diagnostic performance is overall similar (4). ^{11}C-acetate is another tracer, less commonly used in PCa, sharing with choline tracers a similar distribution, and being transformed to phosphatidylcholine after uptake (5). Studies have shown that performance is similar to ^{18}F-choline (6).

The literature on the use of choline PET in recurrent PCa is vast but inhomogeneous, and for this reason, its use in recent guidelines is suggested but not established, yet. Two recent meta-analyses have tried to overcome this limitation, with encouraging and converging results when selecting studies with common inclusion criteria, protocols, and standard of reference (7, 8). Both analyses obtained pooled sensitivities and specificities above 85% in patients with biochemical recurrence. For local recurrence, in particular, the sensitivity was 61% and the specificity 97% (8).

Indeed, when assessing a biochemical recurrence of PCa after RP, it should be taken in account that the detection rates vary with prostate-specific antigen (PSA) levels when using choline-labeled tracers (9–11). Choline PET–CT has shown interesting results when assessing lymph node recurrences with PSA >1 ng/mL, with sensitivity of 90% and specificity of 100% in a per-patient analysis, and 67 and 96% in a per-region analysis, respectively (12). Below this level of PSA, the recurrence detection rate with choline-labeled tracers decreases, essentially because of the lack of ability for PET to detect small lesions (of a few millimeters), presenting with low metabolism due to the spatial resolution limit of the technique (9, 10, 13, 14). Nevertheless, the sensitivity of choline PET is still above 50% in patients with PSA <1 ng/mL when PSA doubling time is <6 months or PSA velocity is >1 ng/mL/year (10, 15, 16). When the 1 ng/mL threshold is not reached and other criteria, such as PSA doubling time and velocity, are not met, prostate-targeted magnetic resonance imaging (MRI) is considered the best choice to detect local recurrences. Conventional imaging, including CT and standard MRI, is, however, of limited value to identify metastatic lymph nodes since up to 80% of involved lymph nodes are smaller than 1 cm (17–19), and the evaluation of nodal involvement in prostate MRI studies is limited to the pelvic field of view. Integrated whole-body choline PET/MRI might thus be the modality of choice to overcome these limitations.

Choline PET–CT has been used to guide SRT planning, as recently reviewed (20). Despite the lack of large multicenter validation studies, single-center experiences consistently show that nodal and oligometastatic disease can be efficiently targeted (21–24). The limited spatial resolution remains the main obstacle for accurate targeting of the local relapse. Finally,

TABLE 1 | Summary of the most relevant tracers available for the evaluation of recurrent PCa.

Tracer	Target	Technique	Use	Site of PCa recurrence	Main advantage	Main limitation
^{18}F/^{11}C-choline	Cell membrane synthesis and phospholipid metabolism	PET/CT PET/MR	Established	Any	Sensitivity	Lack of specificity for PCa
^{18}F-NaF	Bone remodeling	PET/CT PET/MR	Established	Bone metastases	Sensitivity	Lack of specificity for PCa
^{99m}Tc-diphosphonates	Bone remodeling	SPECT/CT	Established	Bone metastases	Sensitivity	Lack of specificity for PCa
^{68}Ga-HBED-CC	PSMA	PET/CT PET/MR	Under evaluation	Any	Preliminary data showing higher sensitivity than choline-based tracers	To be assessed
^{111}In–^{111}In Capromab Pendetide (ProstaScint®)	PSMA	SPECT/CT	Established	Any	Specificity	Spatial resolution

PCa, prostate cancer; PSMA, prostate-specific membrane antigen.

more recent evidence has shown that choline PET also has a prognostic value among the candidates for curative radiation treatment (24, 25).

The Added Value of Combined PET–MRI

Magnetic resonance imaging is the most frequently used imaging modality to evaluate local PCa recurrence. T2-weighted imaging depicts recurrence with wide ranges of sensitivity and specificity with values of 48–100 and 50–100%, respectively, after RP and of 25–86 and 64–100%, respectively, after radiation therapy (26). Multiparametric imaging, such as spectroscopy, diffusion-weighted imaging, and dynamic contrast-enhanced MRI, have gained acceptance to complement T2-weighted MRI for primary and recurrent PCa detection (27–29). However, there is still an important need to further improve the accuracy of PCa imaging. The question arises whether associating metabolic PET data with MRI might potentially enhance PCa imaging. Preliminary reports using both modalities have provided contradictory results that could be explained in part by the difficulty to perform an accurate coregistration of the PET and MR images (30, 31). To solve this issue, hybrid PET–MRI systems have been designed to allow serial or simultaneous PET and MRI acquisitions during a single examination, with a common referential of the patient's position. Acquiring fluorocholine PET and MRI in one single examination session showed a relevant improvement of the accuracy of PCa lesions' detection (32–34) (**Figure 1**).

The adjunction of the PET acquisition leads to an important gain of the specificity of cancer detection when compared to MRI alone, without significant reduction of sensitivity for primary PCa staging. The sensitivity and specificity for the multiparametric MRI alone were 84.4 and 68.6%, respectively, and 81.2 and 87.1%, respectively, for the use of integrated PET–MRI (33). Another study showed that PCa was correctly detected in 80% of patients using ^{18}F-choline PET alone, in 83.3% of patients using multiparametric MRI, and in 93.3% using integrated PET–MRI (34). These data show the ability of the PET–MRI scanner to perform MRI examinations of high diagnostic quality without artifacts related to the presence of the PET gantry and demonstrate that the information obtained from MRI (T2 anatomical sequences, diffusion, and perfusion) and PET (SUVmax) are complementary. Hitherto, no study has been published concerning the specific use of hybrid PET–MRI systems for recurrence detection or radiation therapy planning. However, there are ongoing studies scoping the development of dedicated positioning devices and dosimetric approaches (35, 36).

BONE METASTASES ASSESSMENT

Current guidelines recommend bone imaging only in selected high-risk cases. However, this definition is not homogenous in the literature (37, 38). In clinical practice, bone imaging is frequently performed in patients presenting with biochemical recurrence. Several choices exist, including bone scintigraphy, ^{18}F-NaF PET–CT, or choline-labeled (^{18}F or ^{11}C) PET–CT (39).

Bone scintigraphy remains a widely used imaging modality in the metastatic workup of PCa patients. It allows for whole-body screening and is highly sensitive in the detection of metastases, but its specificity is limited due to benign conditions presenting also with altered tracer uptake (e.g., degenerative joint diseases, fractures, infections, or benign bone tumors) (40, 41). During the last decade, SPECT–CT has gained a wide acceptance for bone scanning. Many studies have shown that SPECT–CT reduces the rate of equivocal lesions compared to planar bone scan due to better anatomic localization of lesions and higher lesion-to-background contrast. By consequence, it increases diagnostic accuracy over SPECT alone or planar scintigraphy alone (42–46). Some authors use SPECT–CT only to clarify the origin of equivocal lesions based on planar scintigraphy, whereas others recommend to systematically acquire whole-body SPECT–CT from the cervical spine to the proximal femurs (43, 47). The proportion of indeterminate bone lesions can be reduced from a rate between 48 and 72% with planar whole-body scintigraphy and/or SPECT without CT, to a rate between 0 and 15% when adding SPECT with CT. Furthermore, SPECT–CT has been able to correctly convert a metastatic status into a non-metastatic status (downstaging) in 29.5% of the patients, with a sensitivity and specificity of 96.4 and 94.2%, respectively, on a per-patient analysis (47).

^{18}F-NaF PET–CT is considered to have superior pharmacokinetic characteristics, such as high bone affinity, rapid clearance, and low protein binding, compared to ^{99m}Tc-diphosphonates. Its impact in PCa management has been recently evaluated by the National Oncologic PET Registry (NOPR) in the US, showing a 44% rate of change in management in recurrent PCa (48). The patient-based analysis showed that sensitivity and specificity of ^{18}F-fluoride PET–CT and bone scan were 96 versus 88% and 91 versus 80%, respectively (49). Although ^{18}F-NaF PET–CT has been reported to be more sensitive for detection of metastases than planar bone scan, the question arose to know whether ^{18}F-NaF PET–CT outperforms whole-body SPECT–CT. Indeed, the comparative studies available hitherto only compare ^{18}F-NaF PET–CT to standalone SPECT acquisitions, which are intrinsically limited by the lack of anatomical correlation (50).

Radiolabeled choline PET–CT is used in the assessment of PCa recurrence in the prostate bed or in lymph nodes but can also highlight bone metastases (9, 14, 51). It has been reported that ^{18}F-choline PET–CT was more specific than ^{18}F-NaF PET–CT (99 versus 93%) but that ^{18}F-choline PET–CT suffered from slightly lower sensitivity (74 versus 81%) (49, 52). There is still an uncertainty whether these choline-negative lesions could be a result of androgen-deprivation therapy, since many patients enrolled in trials are under androgen deprivation. Based on this finding, it is recommended to systematically carry out imaging reflecting bone remodeling (^{18}F-NaF PET–CT or whole-body SPECT–CT) in addition to choline PET imaging for bone assessment, both for diagnostic and for treatment planning purposes, whenever bone involvement is suspected clinically.

FUTURE TRACERS

While PET imaging currently validated for clinical practice is based on relatively unspecific tracers, such as FDG and choline,

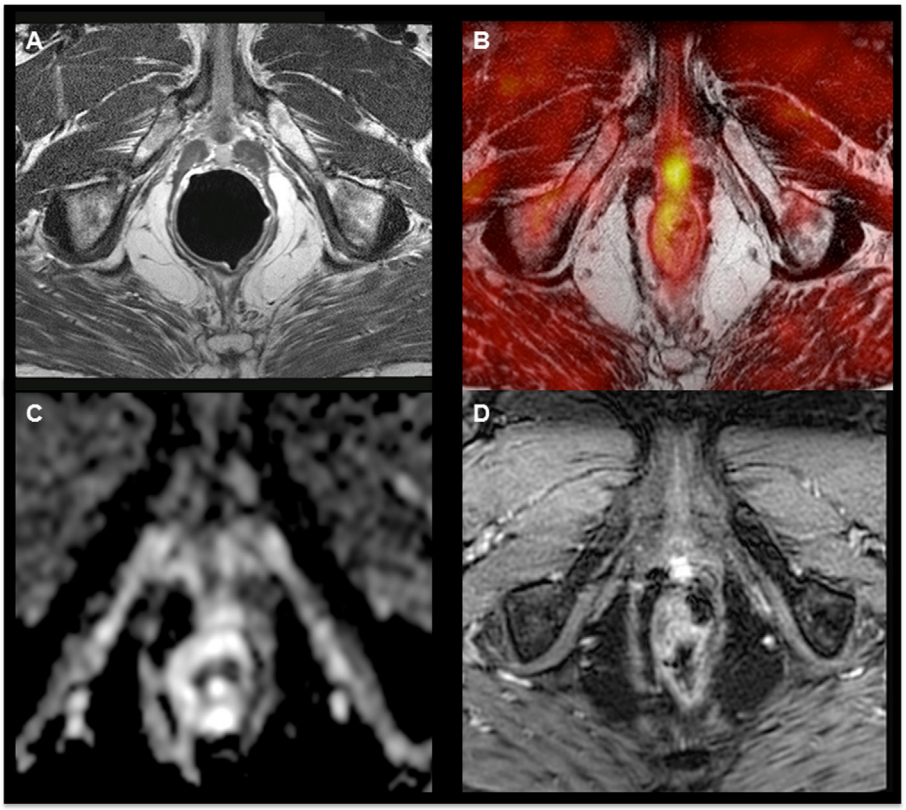

FIGURE 1 | **^{18}F-Fluorocholine hybrid PET–MRI images showing hyperintensity on the T2-weighted sequence (A) and focal hypermetabolism (B) in a nodule with limited diffusion restriction on ADC map (C) and hyperperfusion (D) in a patient with a biochemical relapse (PSA = 1.75 ng/mL, doubling time = 11 months) 9 years after radical prostatectomy**.

ongoing research focuses on the development of new tracers targeting tumor-specific antigens. The most promising tracers for prostate imaging are summarized below. No validation about their use in SRT is yet available, even if this has been tested for prostate-specific membrane antigen (PSMA) and anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC) tracers (53, 54).

Prostate-Specific Membrane Antigen Tracers

Prostate-specific membrane antigen is a transmembrane protein overexpressed in PCa and highly expressed in androgen-independent disease (55). Preclinical and *in vitro* studies suggest a good specificity of this target when compared to normal prostatic tissue or post-radiation therapy fibrotic changes (56). The high specificity of this target has also motivated the development of therapeutic or combined diagnostic/therapeutic (or "theragnostic") agents, radiolabeled with ^{111}In or ^{177}Lu (57, 58). PSMA imaging is performed using ^{111}In Capromab Pendetide (ProstaScint®), a monoclonal murine antibody. This tracer is FDA approved for staging high-risk PCa and for recurrent PCa post-prostatectomy. Prostascint imaging has, however, some disadvantages: a complex biodistribution, requiring imaging up to 6 days after administration, an intracellular epitope, not accessible in living cells, non-specific signal in the presence of inflammation, and the intrinsic lower resolution of SPECT imaging as compared with PET (59).

A comprehensive description of all tracers developed in preclinical studies for this target goes beyond the scope of this paper. Therefore, we will only briefly summarize the results of the clinical studies performed so far in recurrent PCa. Four tracers have been used in human studies, three of them using ^{18}F as radioisotope and one using ^{68}Ga.

^{18}F-DCFBC

A dosimetry study in five metastatic patients showed the ability of the tracer to detect probable metastatic lesions in lymph nodes and the skeleton (60). The tracer has also been evaluated in primary PCa cancer characterization in 13 patients, showing a high specificity for tumor lesions over benign hypertrophy, even higher than MRI (61).

^{18}F-BAY1075553

Only a single phase I study has been published, including 12 patients (9 at staging and 3 with recurrent PCa), and comparing the diagnostic performance of this tracer to ^{18}F-choline, showing a similar performance of the two tracers for the characterization of prostatic lesions. However, ^{18}F-choline has

been shown to be superior for nodal and bone marrow lesions' detection (62).

^{18}F-DCFPyL

Only two studies used this tracer in patients, one of them performing whole-body dosimetry and the other providing a preliminary comparison with ^{68}Ga-HBED-CC in 14 patients with recurrent PCa (63, 64).

^{68}Ga-HBED-CC

This is the most extensively evaluated PSMA tracer so far, with already over 20 published studies. All of them showed high proportions of positive findings in recurrent disease, with detections rates ranging from 82.8 to 89.5%, in the two largest studies (65, 66). In patients with PSA values between 0.2 and 0.5 ng/mL, the detection rate was 57.9% (66). One study suggests superiority in comparison with ^{18}F-choline, with higher contrast and more lesions identified by the PSMA marker (67). Discordant results were found with respect to the impact of PSA doubling time on PET positivity (66, 68). Only one recent study has evaluated the impact of this tracer on radiation therapy planning, showing a change in strategy in about 50% of the cases, which is in line with the range of the management changes rate reported for choline (54, 69, 70).

Amino Acids

Amino acid demand and transport are increased in malignant prostatic cells, reflecting protein synthesis. Some radiolabeled amino acids have been developed in order to explore this metabolic pathway. Anti-(^{18}F)-FACBC (anti-1-amino-3-^{18}F-FACBC or fluciclovine) appears to be a promising PET amino-acid radiotracer: it is a synthetic L-leucine analog, leucine being an essential nutrient for protein synthesis and cell growth, with high uptake in the majority of PCa lesions and metastasis. In a recent meta-analysis of six studies concerning the performances of ^{18}F-FACBC PET–CT in patients with a suspicion of PCa recurrence, the pooled sensitivity and specificity for this radiotracer were 87 and 66%, respectively (71). Comparative studies with choline tracers showed a higher sensitivity and specificity, with an approximately 20% higher detection rate when using ^{18}F-FACBC (72–75).

Gastrin-Releasing Peptide Receptors

Gastrin-releasing peptide receptors (GRPR) are overexpressed in a majority of PCa cells. Therefore, they represent a potential target for diagnostic imaging procedures. Bombesin, which can be labeled with positron-emitting radionuclides, is one of those tracers. Different radiolabeled bombesin analogs have been tested in primary and metastatic PCa (76, 77) as well as in cases of biological recurrence after surgery or hormonal therapy (76). Kähkönen et al., using ^{68}Ga-labeledDOTA-4-amino-1-carboxymethyl-piperidine-D-Phe–Gln–Trp–Ala–Val–Gly–His–Sta–Leu-NH2 peptide (BAY 86-7548), found satisfying results in detection of recurrence in prostatic bed and nodal relapse but poor ability to detect bone metastases (76). Sah et al. published a first-in-man study concerning BAY 864367, a slightly different ^{18}F-labeled bombesin tracer (78). They found that the tracer uptake was higher in primary PCa than in recurrent lesions. Mitsakis et al. compared ^{68}Ga-NODAGA-MJ9 (MJ9) PET–CT with ^{18}F-flurocholine in 33 patients with recurrent PCa and concluded that MJ9 missed 75% of the 24 bone lesions identified on ^{18}F-choline PET. However, 18% of metastatic lymph nodes that were positive on 18-flurocholine were negative on MJ9, and inversely, 13% of lesions in lymph nodes were positive on MJ9 but negative on ^{18}F-flurocholine PET/CT, with a greater signal-to-background ratio on MJ9 images (79).

Fluoro-5-Dihydrotestosterone

16β-(^{18}F)-fluoro-5-dihydrotestosterone (FDHT) is a fluorinated testosterone analog that can detect the overexpression of androgen receptors in PCa lesions. The first study concerning the use of FDHT in patients with progressive metastatic PCa showed a high tumor-to-background ratio and a detection rate of 78% of the 59 lesions identified on conventional imaging methods in a group of seven patients (80). Tumor uptake of FDHT is receptor mediated (81), and thus, the results of the FDHT–PET may be able to predict which lesions will show a good response to androgen deprivation therapy and which ones will not, therefore, needing another type of treatment (82). Moreover, the intensity of FDHT uptake in bone metastases of castration-resistant PCa patients was a negative prognostic factor in terms of patient survival (83). No studies on the use of FDHT in recurrent PCa after RP have been published, yet.

CONCLUSION

The combination of radiolabeled-choline PET and MRI appears to be the modality of choice in clinical routine for the assessment of recurrence of PCa, associating the identification of nodal and distant disease based on PET and the local assessment by multiparametric MRI. While the availability of integrated PET–MRI systems will presumably remain confined to academic centers, at least in the near future, the use of software allowing automated fusion of PET and MRI sequences acquired at different times is already widely used in SRT planning. A new generation of targeted tracers, such as PSMA and FACBC, has shown promising results, with a lesion-to-background contrast superior to choline imaging and a higher detection rate of lesions even for very low PSA levels. Results of ongoing validation studies are warranted. Bone remodeling tracers, including standard bone scans with SPECT–CT, remain of great interest in assessment of bone extension and should be systematically associated with metabolic imaging.

AUTHOR CONTRIBUTIONS

TZ, VG, ORager, and GA are responsible for the study design and contributed equally to the manuscript. TZ, VG, ORager, GA, and CT-V drafted the manuscript. RM, GG, ORatib, TP, and ES revised the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* (2005) **66**:83–94. doi:10.1016/j.urology.2005.06.116
2. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* (2007) **25**:2035–41. doi:10.1200/JCO.2006.08.9607
3. Zilli T, Jorcano S, Peguret N, Caparrotti F, Hidalgo A, Khan HG, et al. Results of dose-adapted salvage radiotherapy after radical prostatectomy based on an endorectal MRI target definition model. *Am J Clin Oncol* (2014). doi:10.1097/COC.0000000000000130
4. Calabria F, Gallo G, Schillaci O, Cascini GL. Bio-distribution, imaging protocols and diagnostic accuracy of PET with tracers of lipogenesis in imaging prostate cancer: a comparison between 11C-choline, 18Ffluoroethylcholine and 18F-methylcholine. *Curr Pharm Des* (2015) **21**:4738–47. doi:10.2174/1381612821666150818110422
5. Yoshimoto M, Waki A, Yonekura Y, Sadato N, Murata T, Omata N, et al. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. *Nucl Med Biol* (2001) **28**:117–22. doi:10.1016/S0969-8051(00)00195-5
6. Buchegger F, Garibotto V, Zilli T, Allainmat L, Jorcano S, Vees H, et al. First imaging results of an intraindividual comparison of (11)C-acetate and (18) F-fluorocholine PET/CT in patients with prostate cancer at early biochemical first or second relapse after prostatectomy or radiotherapy. *Eur J Nucl Med Mol Imaging* (2014) **41**:68–78. doi:10.1007/s00259-013-2540-6
7. Umbehr MH, Muntener M, Hany T, Sulser T, Bachmann LM. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: a systematic review and meta-analysis. *Eur Urol* (2013) **64**:106–17. doi:10.1016/j.eururo.2013.04.019
8. Fanti S, Minozzi S, Castellucci P, Balduzzi S, Herrmann K, Krause BJ, et al. PET/CT with C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. *Eur J Nucl Med Mol Imaging* (2016) **43**(1):55–69. doi:10.1007/s00259-015-3202-7
9. Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C, et al. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. *Eur Urol* (2011) **59**:51–60. doi:10.1016/j.eururo.2010.09.004
10. Giovacchini G, Picchio M, Garcia-Parra R, Mapelli P, Briganti A, Montorsi F, et al. [11C]choline positron emission tomography/computerized tomography for early detection of prostate cancer recurrence in patients with low increasing prostate specific antigen. *J Urol* (2013) **189**:105–10. doi:10.1016/j.juro.2012.09.001
11. Mapelli P, Panebianco V, Picchio M. Prostate cancer recurrence: can PSA guide imaging? *Eur J Nucl Med Mol Imaging* (2015) **42**:1781–3. doi:10.1007/s00259-015-3091-9
12. Kitajima K, Murphy RC, Nathan MA, Froemming AT, Hagen CE, Takahashi N, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. *J Nucl Med* (2014) **55**:223–32. doi:10.2967/jnumed.113.123018
13. Castellucci P, Fuccio C, Rubello D, Schiavina R, Santi I, Nanni C, et al. Is there a role for (1)(1)C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? *Eur J Nucl Med Mol Imaging* (2011) **38**:55–63. doi:10.1007/s00259-010-1604-0
14. Mamede M, Ceci F, Castellucci P, Schiavina R, Fuccio C, Nanni C, et al. The role of 11C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level <0.5 ng/mL. *Clin Nucl Med* (2013) **38**:e342–5. doi:10.1097/RLU.0b013e31829af913
15. Schillaci O, Calabria F, Tavolozza M, Caracciolo CR, Finazzi Agro E, Miano R, et al. Influence of PSA, PSA velocity and PSA doubling time on contrast-enhanced 18F-choline PET/CT detection rate in patients with rising PSA after radical prostatectomy. *Eur J Nucl Med Mol Imaging* (2012) **39**:589–96. doi:10.1007/s00259-011-2030-7
16. Castellucci P, Ceci F, Graziani T, Schiavina R, Brunocilla E, Mazzarotto R, et al. Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-choline PET/CT scan before salvage radiation therapy? *J Nucl Med* (2014) **55**:1424–9. doi:10.2967/jnumed.114.138313
17. Heesakkers RA, Hovels AM, Jager GJ, van den Bosch HC, Witjes JA, Raat HP, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. *Lancet Oncol* (2008) **9**:850–6. doi:10.1016/S1470-2045(08)70203-1
18. Hovels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* (2008) **63**:387–95. doi:10.1016/j.crad.2007.05.022
19. Mapelli P, Picchio M. Initial prostate cancer diagnosis and disease staging-the role of choline-PET-CT. *Nat Rev Urol* (2015) **12**:510–8. doi:10.1038/nrurol.2015.191
20. De Bari B, Alongi F, Lestrade L, Giammarile F. Choline-PET in prostate cancer management: the point of view of the radiation oncologist. *Crit Rev Oncol Hematol* (2014) **91**:234–47. doi:10.1016/j.critrevonc.2014.04.002
21. Vees H, Steiner C, Dipasquale G, Chouiter A, Zilli T, Velazquez M, et al. Target volume definition in high-risk prostate cancer patients using sentinel node SPECT/CT and 18 F-choline PET/CT. *Radiat Oncol* (2012) **7**:134. doi:10.1186/1748-717X-7-134
22. Schick U, Jorcano S, Nouet P, Rouzaud M, Vees H, Zilli T, et al. Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. *Acta Oncol* (2013) **52**:1622–8. doi:10.3109/0284186X.2013.764010
23. Miralbell R, Buchegger F. PET/CT imaging and the oligometastatic prostate cancer patient: an opportunity for a curative approach with high-dose radiotherapy? *Eur J Nucl Med Mol Imaging* (2014) **41**:1267–9. doi:10.1007/s00259-014-2793-8
24. Picchio M, Berardi G, Fodor A, Busnardo E, Crivellaro C, Giovacchini G, et al. (11)C-Choline PET/CT as a guide to radiation treatment planning of lymph-node relapses in prostate cancer patients. *Eur J Nucl Med Mol Imaging* (2014) **41**:1270–9. doi:10.1007/s00259-014-2734-6
25. Incerti E, Fodor A, Mapelli P, Fiorino C, Alongi P, Kirienko M, et al. Radiation treatment of lymph node recurrence from prostate cancer: is 11C-choline PET/CT predictive of survival outcomes? *J Nucl Med* (2015) **56**(12):1836–42. doi:10.2967/jnumed.115.163741
26. Barchetti F, Panebianco V. Multiparametric MRI for recurrent prostate cancer post radical prostatectomy and postradiation therapy. *Biomed Res Int* (2014) **2014**:316272. doi:10.1155/2014/316272
27. Kitajima K, Kaji Y, Fukabori Y, Yoshida K, Suganuma N, Sugimura K. Prostate cancer detection with 3 T MRI: comparison of diffusion-weighted imaging and dynamic contrast-enhanced MRI in combination with T2-weighted imaging. *J Magn Reson Imaging* (2010) **31**:625–31. doi:10.1002/jmri.22075
28. Padhani AR. Integrating multiparametric prostate MRI into clinical practice. *Cancer Imaging* (2011) **11**(Spec No A):S27–37. doi:10.1102/1470-7330.2011.9007
29. Schlemmer HP. Prostate cancer: localizing the cancer in patients with persistent negative biopsies. *Cancer Imaging* (2011) **11**(Spec No A):S1. doi:10.1102/1470-7330.2011.9001
30. Jambor I, Borra R, Kemppainen J, Lepomaki V, Parkkola R, Dean K, et al. Improved detection of localized prostate cancer using co-registered MRI and (11)C-acetate PET/CT. *Eur J Radiol* (2012) **81**(11):2966–72. doi:10.1016/j.ejrad.2011.12.043
31. Van den Bergh L, Koole M, Isebaert S, Joniau S, Deroose CM, Oyen R, et al. Is there an additional value of (11)C-Choline PET-CT to T2-weighted MRI images in the localization of intraprostatic tumor nodules? *Int J Radiat Oncol Biol Phys* (2012) **83**(5):1486–92. doi:10.1016/j.ijrobp.2011.10.046
32. Souvatzoglou M, Eiber M, Takei T, Furst S, Maurer T, Gaertner F, et al. Comparison of integrated whole-body [11C]choline PET/MR with PET/CT in patients with prostate cancer. *Eur J Nucl Med Mol Imaging* (2013) **40**:1486–99. doi:10.1007/s00259-013-2467-y

33. de Perrot T, Rager O, Scheffler M, Lord M, Pusztaszeri M, Iselin C, et al. Potential of hybrid (1)(8)F-fluorocholine PET/MRI for prostate cancer imaging. *Eur J Nucl Med Mol Imaging* (2014) **41**:1744–55. doi:10.1007/s00259-014-2786-7
34. Kim YI, Cheon GJ, Paeng JC, Cho JY, Kwak C, Kang KW, et al. Usefulness of MRI-assisted metabolic volumetric parameters provided by simultaneous (18) F-fluorocholine PET/MRI for primary prostate cancer characterization. *Eur J Nucl Med Mol Imaging* (2015) **42**:1247–56. doi:10.1007/s00259-015-3026-5
35. Paulus DH, Thorwath D, Schmidt H, Quick HH. Towards integration of PET/MR hybrid imaging into radiation therapy treatment planning. *Med Phys* (2014) **41**:072505. doi:10.1118/1.4881317
36. Kim J, Garbarino K, Schultz L, Levin K, Movsas B, Siddiqui MS, et al. Dosimetric evaluation of synthetic CT relative to bulk density assignment-based magnetic resonance-only approaches for prostate radiotherapy. *Radiat Oncol* (2015) **10**:239. doi:10.1186/s13014-015-0549-7
37. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* (2014) **65**:467–79. doi:10.1016/j.eururo.2013.11.002
38. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer* (2016). Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
39. Picchio M, Mapelli P, Panebianco V, Castellucci P, Incerti E, Briganti A, et al. Imaging biomarkers in prostate cancer: role of PET/CT and MRI. *Eur J Nucl Med Mol Imaging* (2015) **42**:644–55. doi:10.1007/s00259-014-2982-5
40. Love C, Din AS, Tomas MB, Kalapparambath TP, Palestro CJ. Radionuclide bone imaging: an illustrative review. *Radiographics* (2003) **23**:341–58. doi:10.1148/rg.232025103
41. Damle NA, Bal C, Bandopadhyaya GP, Kumar L, Kumar P, Malhotra A, et al. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. *Jpn J Radiol* (2013) **31**:262–9. doi:10.1007/s11604-013-0179-7
42. Schillaci O, Danieli R, Manni C, Simonetti G. Is SPECT/CT with a hybrid camera useful to improve scintigraphic imaging interpretation? *Nucl Med Commun* (2004) **25**:705–10. doi:10.1097/01.mnm.0000130240.83949.54
43. Romer W, Nomayr A, Uder M, Bautz W, Kuwert T. SPECT-guided CT for evaluating foci of increased bone metabolism classified as indeterminate on SPECT in cancer patients. *J Nucl Med* (2006) **47**:1102–6.
44. Utsunomiya D, Shiraishi S, Imuta M, Tomiguchi S, Kawanaka K, Morishita S, et al. Added value of SPECT/CT fusion in assessing suspected bone metastasis: comparison with scintigraphy alone and nonfused scintigraphy and CT. *Radiology* (2006) **238**:264–71. doi:10.1148/radiol.2373041358
45. Helyar V, Mohan HK, Barwick T, Livieratos L, Gnanasegaran G, Clarke SE, et al. The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate. *Eur J Nucl Med Mol Imaging* (2010) **37**:706–13. doi:10.1007/s00259-009-1334-3
46. Zhang Y, Shi H, Gu Y, Xiu Y, Li B, Zhu W, et al. Differential diagnostic value of single-photon emission computed tomography/spiral computed tomography with Tc-99m-methylene diphosphonate in patients with spinal lesions. *Nucl Med Commun* (2011) **32**:1194–200. doi:10.1097/MNM.0b013e32834bd82e
47. Palmedo H, Marx C, Ebert A, Kreft B, Ko Y, Turler A, et al. Whole-body SPECT/CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients. *Eur J Nucl Med Mol Imaging* (2014) **41**:59–67. doi:10.1007/s00259-013-2532-6
48. Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF, Coleman RE. Impact of 18F-fluoride PET in patients with known prostate cancer: initial results from the National Oncologic PET Registry. *J Nucl Med* (2014) **55**:574–81. doi:10.2967/jnumed.113.130005
49. Shen CT, Qiu ZL, Han TT, Luo QY. Performance of 18F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. *Clin Nucl Med* (2015) **40**:103–10. doi:10.1097/RLU.0000000000000592
50. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single – and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J Nucl Med* (2006) **47**:287–97.
51. Chondrogiannis S, Marzola MC, Ferretti A, Maffione AM, Rampin L, Grassetto G, et al. Role of (1)(8)F-choline PET/CT in suspicion of relapse following definitive radiotherapy for prostate cancer. *Eur J Nucl Med Mol Imaging* (2013) **40**:1356–64. doi:10.1007/s00259-013-2433-8
52. Beheshti M, Vali R, Waldenberger P, Fitz F, Nader M, Loidl W, et al. Detection of bone metastases in patients with prostate cancer by 18F fluorocholine and 18F fluoride PET-CT: a comparative study. *Eur J Nucl Med Mol Imaging* (2008) **35**:1766–74. doi:10.1007/s00259-008-0788-z
53. Brunocilla E, Schiavina R, Nanni C, Borghesi M, Cevenini M, Molinaroli E, et al. First case of 18F-FACBC PET/CT-guided salvage radiotherapy for local relapse after radical prostatectomy with negative 11C-Choline PET/CT and multiparametric MRI: new imaging techniques may improve patient selection. *Arch Ital Urol Androl* (2014) **86**:239–40. doi:10.4081/aiua.2014.3.239
54. Sterzing F, Kratochwil C, Fiedler H, Katayama S, Habl G, Kopka K, et al. Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. *Eur J Nucl Med Mol Imaging* (2016) **43**:34–41. doi:10.1007/s00259-015-3188-1
55. Mease RC, Foss CA, Pomper MG. PET imaging in prostate cancer: focus on prostate-specific membrane antigen. *Curr Top Med Chem* (2013) **13**:951–62. doi:10.2174/1568026611313080008
56. Rybalov M, Ananias HJ, Hoving HD, van der Poel HG, Rosati S, de Jong IJ. PSMA, EpCAM, VEGF and GRPR as imaging targets in locally recurrent prostate cancer after radiotherapy. *Int J Mol Sci* (2014) **15**:6046–61. doi:10.3390/ijms15046046
57. Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with (177) Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res* (2015) **5**:114. doi:10.1186/s13550-015-0114-2
58. Maurer T, Weirich G, Schottelius M, Weineisen M, Frisch B, Okur A, et al. Prostate-specific membrane antigen-radioguided surgery for metastatic lymph nodes in prostate cancer. *Eur Urol* (2015) **68**:530–4. doi:10.1016/j.eururo.2015.04.034
59. Feneley MR, Jan H, Granowska M, Mather SJ, Ellison D, Glass J, et al. Imaging with prostate-specific membrane antigen (PSMA) in prostate cancer. *Prostate Cancer Prostatic Dis* (2000) **3**:47–52. doi:10.1038/sj.pcan.4500390
60. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. *J Nucl Med* (2012) **53**:1883–91. doi:10.2967/jnumed.112.104661
61. Rowe SP, Gage KL, Faraj SF, Macura KJ, Cornish TC, Gonzalez-Roibon N, et al. (1)(8)F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. *J Nucl Med* (2015) **56**:1003–10. doi:10.2967/jnumed.115.154336
62. Beheshti M, Kunit T, Haim S, Zakavi R, Schiller C, Stephens A, et al. BAY 1075553 PET-CT for staging and restaging prostate cancer patients: comparison with [18F] Fluorocholine PET-CT (Phase I Study). *Mol Imaging Biol* (2015) **17**:424–33. doi:10.1007/s11307-014-0800-x
63. Dietlein M, Kobe C, Kuhnert G, Stockter S, Fischer T, Schomacker K, et al. Comparison of [F]DCFPyL and [Ga]Ga-PSMA-HBED-CC for PSMA-PET imaging in patients with relapsed prostate cancer. *Mol Imaging Biol* (2015) **17**:575–84. doi:10.1007/s11307-015-0866-0
64. Szabo Z, Mena E, Rowe SP, Plyku D, Nidal R, Eisenberger MA, et al. Initial evaluation of [F]DCFPyL for prostate-specific membrane antigen (PSMA)-targeted PET imaging of prostate cancer. *Mol Imaging Biol* (2015) **17**:565–74. doi:10.1007/s11307-015-0850-8
65. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* (2015) **42**:197–209. doi:10.1007/s00259-014-2949-6
66. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of hybrid (6)(8)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med* (2015) **56**:668–74. doi:10.2967/jnumed.115.154153
67. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* (2014) **41**:11–20. doi:10.1007/s00259-013-2525-5

68. Ceci F, Uprimny C, Nilica B, Geraldo L, Kendler D, Kroiss A, et al. (68) Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging* (2015) **42**:1284–94. doi:10.1007/s00259-015-3078-6
69. Ceci F, Herrmann K, Castellucci P, Graziani T, Bluemel C, Schiavina R, et al. Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. *Eur J Nucl Med Mol Imaging* (2014) **41**:2222–31. doi:10.1007/s00259-014-2872-x
70. Goldstein J, Even-Sapir E, Ben-Haim S, Saad A, Spieler B, Davidson T, et al. Does choline PET/CT change the management of prostate cancer patients with biochemical failure? *Am J Clin Oncol* (2014). doi:10.1097/COC.0000000000000139
71. Ren J, Yuan L, Wen G, Yang J. The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: a meta-analysis. *Acta Radiol* (2016) **57**:487–93. doi:10.1177/0284185115581541
72. Schuster DM, Savir-Baruch B, Nieh PT, Master VA, Halkar RK, Rossi PJ, et al. Detection of recurrent prostate carcinoma with anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT and 111In-capromab pendetide SPECT/CT. *Radiology* (2011) **259**:852–61. doi:10.1148/radiol.11102023
73. Nanni C, Schiavina R, Boschi S, Ambrosini V, Pettinato C, Brunocilla E, et al. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. *Eur J Nucl Med Mol Imaging* (2013) **40**(Suppl 1):S11–7. doi:10.1007/s00259-013-2373-3
74. Nanni C, Schiavina R, Brunocilla E, Borghesi M, Ambrosini V, Zanoni L, et al. 18F-FACBC compared with 11C-choline PET/CT in patients with biochemical relapse after radical prostatectomy: a prospective study in 28 patients. *Clin Genitourin Cancer* (2014) **12**:106–10. doi:10.1016/j.clgc.2013.08.002
75. Nanni C, Schiavina R, Brunocilla E, Boschi S, Borghesi M, Zanoni L, et al. 18F-fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-choline PET/CT. *Clin Nucl Med* (2015) **40**:e386–91. doi:10.1097/RLU.0000000000000849
76. Kähkönen E, Jambor I, Kemppainen J, Lehtio K, Gronroos TJ, Kuisma A, et al. In vivo imaging of prostate cancer using [68Ga]-labeled bombesin analog BAY86-7548. *Clin Cancer Res* (2013) **19**:5434–43. doi:10.1158/1078-0432.CCR-12-3490
77. Wieser G, Mansi R, Grosu AL, Schultze-Seemann W, Dumont-Walter RA, Meyer PT, et al. Positron emission tomography (PET) imaging of prostate cancer with a gastrin releasing peptide receptor antagonist – from mice to men. *Theranostics* (2014) **4**:412–9. doi:10.7150/thno.7324
78. Sah BR, Burger IA, Schibli R, Friebe M, Dinkelborg L, Graham K, et al. Dosimetry and first clinical evaluation of the new 18F-radiolabeled bombesin analogue BAY 864367 in patients with prostate cancer. *J Nucl Med* (2015) **56**:372–8. doi:10.2967/jnumed.114.147116
79. Mitsakis P, Zilli T, Kosinski M, Delage J, Maecke H, Mansi R, et al. A direct comparison study of Ga-68-NODAGA-MJ9 (MJ9 bombesin) to F-18-FCH in recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* (2015) **42**(Suppl 1):S124–5. doi:10.1007/s00259-015-3198-z
80. Larson SM, Morris M, Gunther I, Beattie B, Humm JL, Akhurst TA, et al. Tumor localization of 16beta-18F-fluoro-5alpha-dihydrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. *J Nucl Med* (2004) **45**:366–73.
81. Dehdashti F, Picus J, Michalski JM, Dence CS, Siegel BA, Katzenellenbogen JA, et al. Positron tomographic assessment of androgen receptors in prostatic carcinoma. *Eur J Nucl Med Mol Imaging* (2005) **32**:344–50. doi:10.1007/s00259-005-1764-5
82. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* (2010) **375**:1437–46. doi:10.1016/S0140-6736(10)60172-9
83. Vargas HA, Wassberg C, Fox JJ, Wibmer A, Goldman DA, Kuk D, et al. Bone metastases in castration-resistant prostate cancer: associations between morphologic CT patterns, glycolytic activity, and androgen receptor expression on PET and overall survival. *Radiology* (2014) **271**:220–9. doi:10.1148/radiol.13130625

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