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ESTRO ACROP consensus recommendation on the target volume definition for radiation therapy of macroscopic prostate cancer recurrences after radical prostatectomy

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ABSTRACT

Background: The European Society for Radiotherapy & Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (ACROP) panel on prostate bed delineation reflected on macroscopic local recurrences in patients referred for postoperative radiotherapy (PORT), a challenging situation without standardized approach, and decided to propose a consensus recommendation on target volume selection and definition.
Methods: An ESTRO ACROP contouring consensus panel consisting of 12 radiation oncologists and one radiologist, all with subspecialty expertise in prostate cancer, was established. Participants were asked to delineate the prostate bed clinical target volumes (CTVs) in two separate clinically relevant scenarios: a local recurrence at the seminal vesicle bed and one apically at the level of the anastomosis. Both recurrences were prostate-specific membrane antigen (PSMA)-avid and had an anatomical correlate on magnetic resonance imaging (MRI). Participants also answered case-specific questionnaires addressing detailed recommendations on target delineation. Discussions via electronic mails and videoconferences for final editing and consensus were performed.
Results: Contouring of the two cases confirmed considerable variation among the panelists. Finally, however, a consensus recommendation could be agreed upon. Firstly, it was proposed to always delineate the entire prostate bed as clinical target volume and not the local recurrence alone. The panel judged the risk of further microscopic disease outside of the visible recurrence too high to safely exclude the rest of the prostate bed from the CTV. A focused, "stereotactic" approach should be reserved for re-irradiation after previous PORT. Secondly, the option of a focal boost on the recurrence was discussed.
Conclusion: Radiation oncologists are increasingly confronted with macroscopic local recurrences visible on imaging in patients referred for postoperative radiotherapy. It was recommended to always delineate and irradiate the entire prostate bed, and not the local recurrence alone, whatever the exact location of that recurrence. Secondly, specific dose-escalation on the macroscopic recurrence should only be considered if an anatomic correlate is visible. Such a focal boost is probably feasible, provided that OAR constraints are prioritized. Possible

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dose is also dependent on the location of the recurrence. Its potential benefit should urgently be investigated in prospective clinical trials.

Introduction

A European Society for Radiotherapy & Oncology (ESTRO) panel recently proposed an Advisory Committee for Radiation Oncology Practice (ACROP) guideline regarding prostate bed delineation for postoperative radiotherapy (PORT) in prostate cancer [1]. This guideline was based on three common scenarios (adjuvant PORT, salvage PORT because of persistent prostate-specific antigen (PSA), and salvage PORT because of initially undetectable but rising PSA), with various clinical risk factors for local recurrence but without evidence of macroscopic disease. Simultaneously, the panel envisioned another scenario that is becoming more frequent, i.e., a macroscopic local recurrence identified on imaging.

Multi-parametric magnetic resonance imaging (mpMRI), typically with diffusion-weighted (DW) and/or diffusion contrast-enhanced (DCE) sequences, is the gold standard for local re-staging after radical prostatectomy, with a sensitivity and specificity above 90% [2]. Indeed, the Prostate Imaging for Recurrence Reporting (PI-RR) assessment system has been recently proposed to standardize the acquisition, interpretation, and reporting of mpMRI for prostate cancer recurrence detection, both after radical prostatectomy and radiation therapy [3]. This system demonstrated a promising diagnostic accuracy for the diagnosis of local tumor recurrence, with high inter-reader agreement [4]. The opportunity to undertake a MRI in the treatment position would enable accurate identification of recurrent lesions and aid treatment planning by avoiding a geographical miss and/or permitting a treatment boost [5,6].

Additionally, position emission tomography (PET) is emerging as an innovative imaging modality in the restaging of prostate cancer. In the postoperative setting, choline-PET is inferior to mpMRI regarding specificity and especially sensitivity for the detection of local recurrences [7]. Prostate-specific membrane antigen (PSMA)-PET/computed tomography (CT) has a higher detection rate than choline-PET, especially at lower PSA levels, but still misses about half of local lesions identified on mpMRI performed in the setting of PORT [8–10]. Nonetheless, PSMA-PET/CT is being increasingly used in the case of biochemical recurrence after radical prostatectomy, especially to exclude lymph node or distant metastases, where its detection rate is much higher [11].

Furthermore, radical prostatectomy is being used more frequently for high risk or locally advanced stages, resulting in an accompanying increase in PORT [12–15]. This might arguably also contribute to the contemporary occurrences of biochemical progression with macroscopic disease found in the prostatectomy bed, with earlier identification using improved imaging methods outlined above. Because such recurrences are a fairly recent phenomenon, there is insufficient data to define an evidence-based approach [16]. In view of a lack of agreement regarding radiation treatment in this situation, the panel decided to propose a consensus recommendation on target volume selection and definition.

Methods

The ACROP committee, in close interaction with the ESTRO clinical committee, selected twelve European radiation oncologists (PD, AD, VK, CC, CC, VF, PG, AGI, NSH, AZ, AB, TW) and one radiologist (VP) to develop a consensus recommendation. The consensus generating process was previously described in detail and consisted of:

1. Contouring exercises via the FALCON (Fellowship in Anatomic deLineation and CONtouring) platform from ESTRO and the software EduCase^{TM} (EduCase - Home) from RadOnc eLearning Center, Inc. Fremont, CA, USA [17]. This is a web-based contouring and analysis tool that has a graphical user interface for the management, storage and publishing of contouring of clinical cases. The software allows image fusion of the simulation CT scan with PET and/or MRI, as well as an integrated analysis on contouring proficiency. Delineations were analyzed qualitatively using heatmaps which provided a visual assessment of controversial regions and quantitatively analyzed using Sorensen-Dice (SD) similarity coefficients.

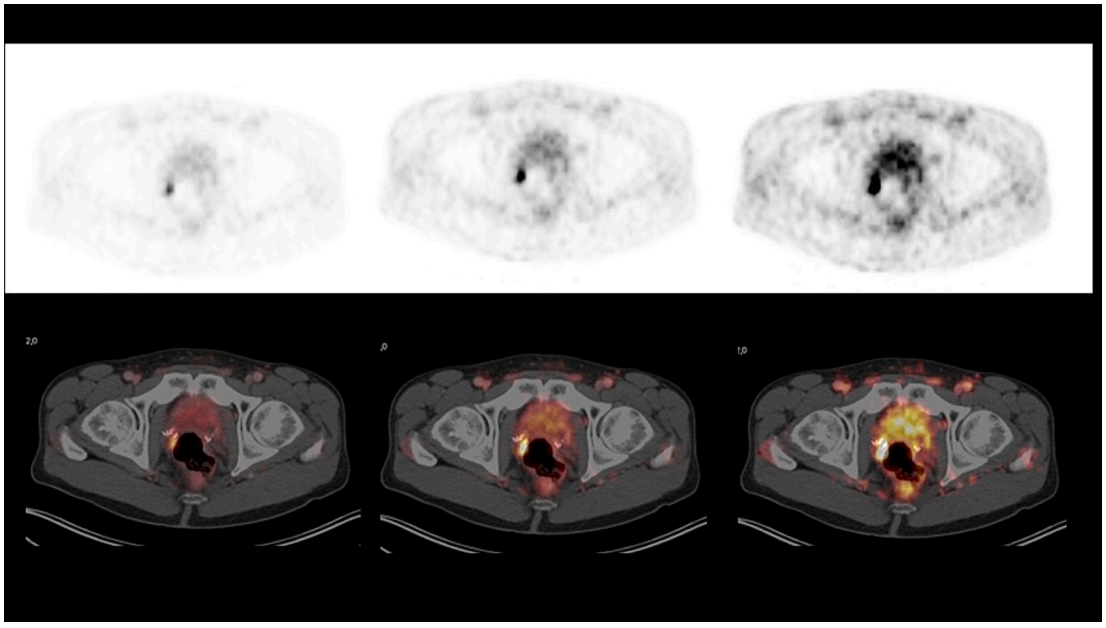

Fig. 1. ^{68}Ga- PSMA & CT images of a suspect lesion at the right seminal vesicle bed (case 1). First row with Standardized Uptake Value (SUV) 0–10; second row with SUV 0–5 (standard), and third row with SUV 0–2,5. Images provided by Ulm University, Department of Nuclear Medicine.

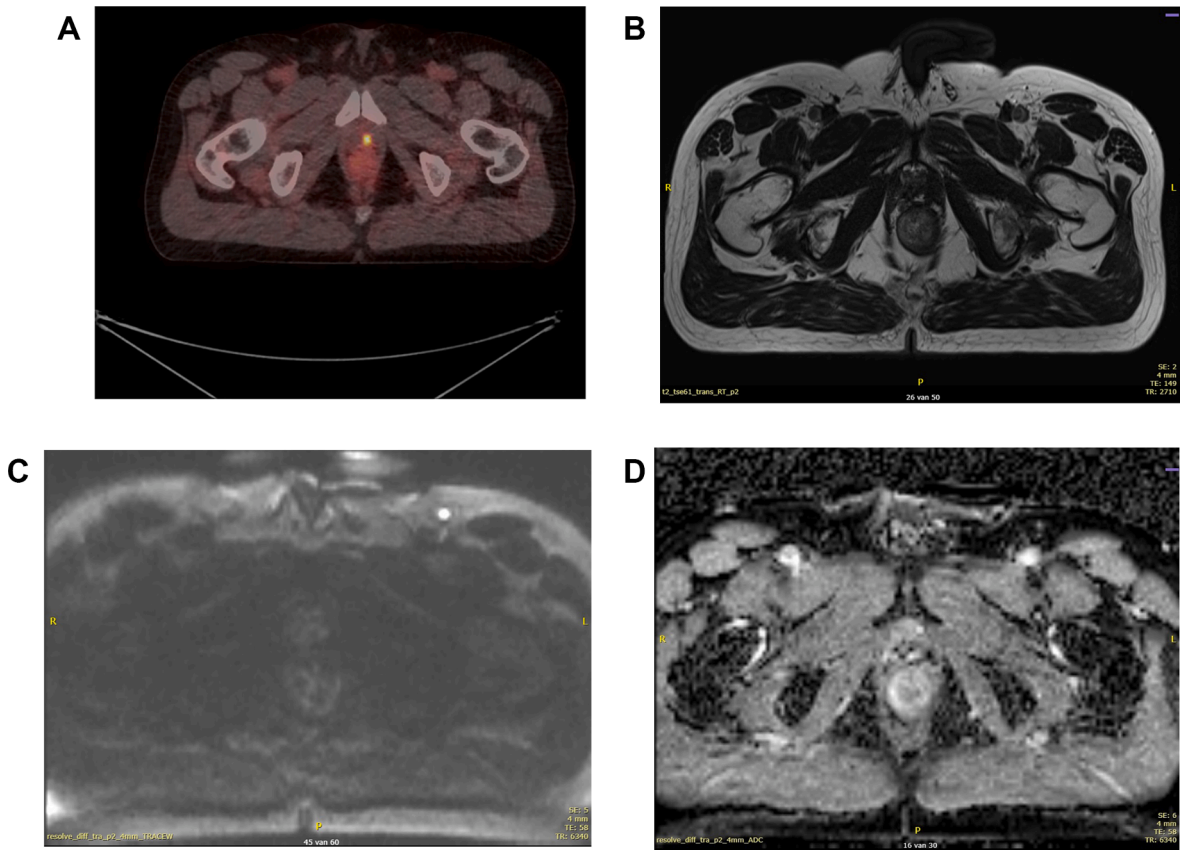

Fig. 2. Suspect lesion to the left of the anastomosis (case 2). Images provided by GZA Hospitals, Department of Radiation Oncology. 2A. ^{68}PSMA-PET image. 2B. MRI T2-weighted image. 2C. MRI diffusion-weighted (DW) image. 2D. MRI apparent diffusion coefficient (ADC) map.

2. Case-specific questions addressing detailed recommendations on target volume delineation (Supplementary Table). For each question, the quality of consensus in terms of percentage of agreement was measured and documented. Consensus was defined when 75% or more agreement were achieved for each recommendation as per the German S3 guidelines [18].
3. Multiple discussions by electronic mail and videoconferences, from June 2018 to March 2021, with minutes sent out and approved after each meeting.

All discussions, questionnaires and meetings were based on two representative clinical cases focusing on prostate cancer patients with biochemical recurrence and/or persistence after radical prostatectomy referred for postoperative radiotherapy after re-staging with PSMA-PET/CT showed a local recurrence (confirmed on MRI) without any other (nodal or metastatic) evidence of disease.

1. Case 1: patient underwent a robotic-assisted laparoscopic radical prostatectomy (RALP) with extensive lymph node dissection (eLND,

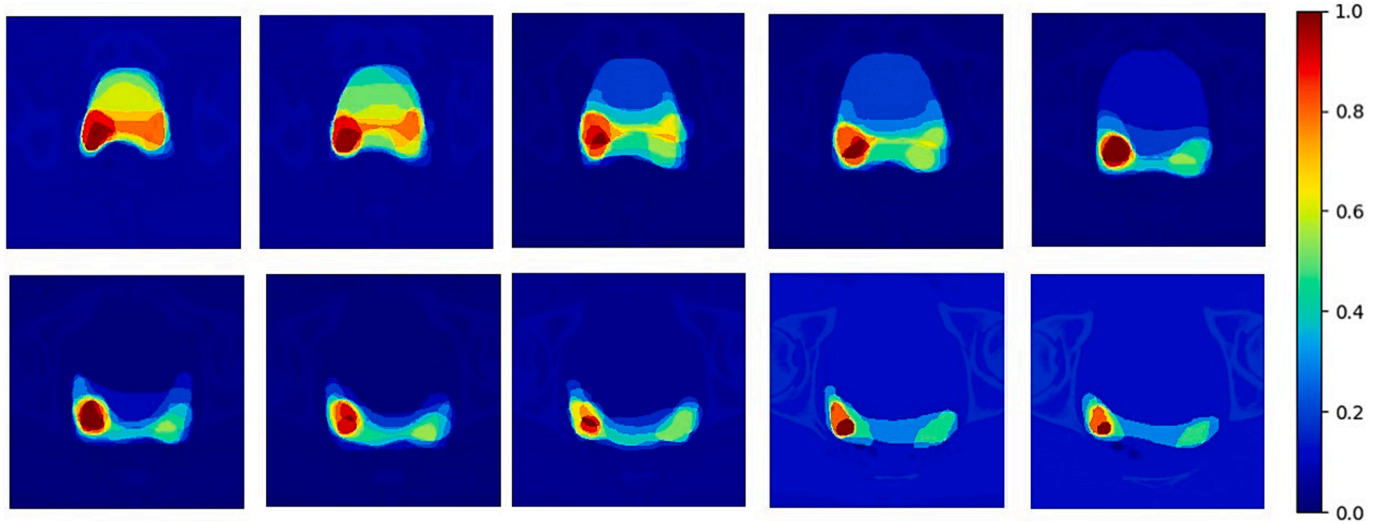

Fig. 3. Heatmaps showing the initial contouring of case 1 by the consensus panel. The mean volume was 57.64 cc with 40.26 cc standard deviation and coefficient of variability of 0.70.

15 lymph nodes removed) for pathologic pT2 pN0 R0, Gleason score 5 + 4 = 9 prostate cancer. A biochemical recurrence (PSA of 0.058 μg/L) was observed at approximately 1 year after surgery and rose to 0.34 μg/L after another 6 years. A ^{68}Ga-PSMA-PET/CT was performed and showed a suspect lesion at the right seminal vesicle (bed), confirmed on mpMRI (see Fig. 1).
2. Case 2: patient underwent a RALP with eLND (22 lymph nodes removed) for a pathologic pT3a pN0, Gleason score 5 + 4 = 9 prostate cancer. Pathology revealed extracapsular extension at the left apex with 5 mm positive focal surgical margin at this level (R1). His PSA was undetectable (<0.01 μg/L) at 6 months after surgery but rose to 0.2 μg/L at 12 months after surgery. A PSMA-PET/CT was performed and showed a suspect lesion to the left of the anastomosis, confirmed on mpMRI (see Fig. 2).

In both cases, the gross tumor volume (GTV), i.e., the macroscopic local recurrence itself, was already provided and participants were asked to only contour the clinical target volume (CTV). Also, the organs at risk (OAR) were already provided, as they fell outside the scope of the current paper [1]. Similarly, the indication and delineation of elective pelvic nodes fell outside the scope of this exercise [1].

Results

All but one panelist delineated the entire prostate bed as CTV in both cases. One panelist delineated only a small expansion around the GTV as CTV. This was consistent with the results of the questionnaires: all but one panelist answered "yes" to the first question ("Do you contour the entire prostate bed in the setting of a macroscopic recurrence?"). Moreover, the prostate bed delineations differed considerably between panelists (see for instance Fig. 3). However, it should be noted that these initial delineations were made before the consensus on prostate bed delineation for postoperative radiotherapy in prostate cancer were agreed between the panel [1]. Consequently, further deliberations were initiated, and a consensus gradually emerged.

First of all, an unanimous agreement developed among the panel that the entire prostate bed should be delineated as CTV in both cases. Limiting the radiation therapy to the GTV (with or without a certain (an) isotropic margin) was unequivocally discouraged. The experts judged the risk of further microscopic disease outside of the visible recurrence too high to safely exclude the rest of the prostate bed from the CTV.

It was moreover suggested to consistently delineate the prostate bed according to the recent ESTRO ACROP guideline [1]. The only distinction between the delineation of both cases was regarding the superior margin. For the first case (right seminal vesicle (bed) recurrence), it was encouraged to include the entire seminal vesicles (bed) and include all cranial surgical clips (if present). For the second case (apical recurrence), the CTV can be limited to the region of the seminal vesicles base (lower third), i.e., up to the level of cut end of vas deferens, as there was no initial seminal vesicle invasion.

Secondly, it was discussed to boost the GTV with a supplementary dose. There was a unanimous agreement that this should only be contemplated if a clear correlate was visible on anatomical imaging. A suspect lesion on PSMA-PET/CT alone was regarded as insufficient for targeted dose-escalation. If a convincing anatomical correlate was visible on MRI or diagnostic CT, a focal boost on the GTV could be considered, preferably in the context of a clinical trial. Delineation of the GTV should be based on the anatomical imaging, and not on the PSMA-avid region as there are currently no validated gradient- or threshold-based segmentation methods [19]. This poses a risk of underestimating or overestimating the size of the tumor, with consequent dosing errors and a potential impact on tumor control as well as toxicity. A majority would use an isotropic 3–5 mm margin around the GTV towards a "boost" CTV. However, a substantial minority would boost the GTV directly so no clear consensus was achieved on this issue.

Outside a clinical trial, a majority of the panel would boost the macroscopic recurrence to a higher dose. Regarding suggested total dose, a large variation existed, with a median suggested dose of 74.0 Gy (range, 70.0 Gy–76.0 Gy) in conventional (i.e. 1.8 to 2.0 Gy per fraction) fractionation. However, the proposed dose was dependent on localization, with a higher dose suggested for case 1 (seminal vesicle bed) than for case 2 (near the anastomosis). Whatever the prescribed dose, OAR constraints should always be prioritized over the focal boost.

The role of androgen-deprivation therapy (ADT) was not explicitly addressed for both cases, but the panel would recommend discussing the use of ADT with the patients [20–22]. The ESTRO ACROP recommendations for evidence-based use of ADT in combination with external-beam radiotherapy in prostate cancer have been recently published [23].

Discussion

While the intent of postoperative radiotherapy for prostate cancer is to encompass supposed microscopic disease, recent implementation of innovative imaging as well as broader use of radical prostatectomy for high-risk or even locally advanced prostate cancer is increasingly confronting radiation oncologists with the presence of a suspected macroscopic local recurrence. Salvage PORT is most effective when initiated early, preferably before PSA reaches 0.2 μg/L [11]. Even if conventional imaging is currently recommended to detect local recurrence, it still has inherent diagnostic limitations at such low PSA levels [3,4]. However, PSMA-PET can already detect disease recurrence in approximately one third of such patients and MRI and the used PI-RR score equally showed a strong accuracy in detecting local recurrence [3,4,9,24]. When patients are referred at higher PSA levels, the detection rate of PSMA-PET/CT increases significantly [25].

Although a macroscopic local recurrence is the exact situation that postoperative radiotherapy is intended to avoid, it is nonetheless a clinical reality that radiation oncologists sometimes are required to address. As often in such developing indications, the scientific evidence lags behind the clinical incidence [16]. While there is no standardized approach, consensus recommendations can be useful in guiding treatment and the design of trials [26]. Therefore, the ESTRO ACROP panel on prostate bed delineation for postoperative radiotherapy decided to also address this particular situation.

The findings of the initial contouring exercises on both clinical cases confirmed a wide variation among the panel. This further emphasized the urgent need to define a consensus for this situation [16,26]. Therefore, additional deliberations were initiated through questionnaires and video conferencing and a proposal was agreed upon.

First of all, the major recommendation of the panel was to always delineate and irradiate the entire prostate bed, whatever the exact location of the local recurrence. While specificity is typically acceptable for both PSMA-PET/CT and mpMRI, their sensitivity is lower [7–10]. In other words, the possibility of microscopic disease outside the area of suspected macroscopic disease is too high to allow focal irradiation of the GTV. This is consistent with a retrospective analysis by Francolini and colleagues from 3 Italian institutes which showed only 43% complete biochemical response (PSA nadir < 0.2 μg/L) rate in 90 patients treated with stereotactic salvage radiotherapy on a macroscopic prostate bed recurrence only [27]. However, it should be noted that patients had adverse features, foremost a pre-radiotherapy PSA of 2.3 μg/L, as is to be expected [27]. Another Italian prospective multicenter study (STARR, NCT05455736) recently reported preliminary results (up to 3 months after treatment) in the first 19 patients treated with stereotactic radiotherapy alone (so no ADT was allowed) to a Choline- or PSMA-PET/CT detected local recurrence only [28]. Again, a complete biochemical response was only observed in a minority (26.3% on this case) of patients. However, overall biochemical response was 58% and no significant (Grade 3 or higher) toxicity was observed in the short follow-up [28]. Clearly, more mature results of this interesting prospective trial will have to be awaited before any definitive conclusions can be made.

But it is notable that in a recent systematic review such a focused, "stereotactic" approach was typically reserved for re-irradiation after previous PORT [29].

In consensus, it was recommended to continue delineating the entire postoperative CTV as outlined in the recent ESTRO ACROP guideline by the same authors [1]. Only the superior border should be adapted to the location of the suspected local recurrence: if located at the seminal vesicles (bed), it was suggested to include the entire region independent of initial seminal vesicle invasion. Otherwise, it is sufficient to include only the base of the seminal vesicles (i.e. up to the level of cut end of vas deferens), unless of course there was initial seminal vesicle invasion [1]. This approach is similar to the recent multicentric, prospective, observational POPART trial, testing extreme hypofractionation in patients with biochemical and/or clinical relapse [30]. Even when a local relapse was visible on PSMA PET/CT or mpMRI (in 26% of patients), the entire prostate bed was (albeit stereotactically) irradiated.

Secondly, the feasibility and desirability of dose-escalation on the macroscopic lesion was discussed. The FLAME trial indicated a biochemical disease-free survival, local control and distant metastasis-free survival benefit with mpMRI-guided, *iso*-effective dose-escalation on the GTV in the primary setting [31,32]. It can therefore be hypothetically assumed that macroscopic prostate cancer needs higher doses than microscopic disease, although evidence in the postoperative setting is currently lacking [33,34]. However, much depends on the certainty that the suspected recurrence indeed harbors macroscopic disease. In that regard, the positive predictive value of PET with any tracer remains inferior to mpMRI [7–10]. Therefore, the panel strictly advised to only consider dose-escalation or focal boosting if an anatomical correlate was visible. Obviously, pathology validation would be best, but the suspect areas are typically very small and the biopsy yield is consequently very low [2].

The presence of an anatomical correlate does obviously not automatically substantiate the need for dose-escalation [35]. Therefore, it was suggested to evaluate this option in prospective clinical trials. However, few of such trials are currently running. In fact, a recent search on https://www.clinicatrials.gov only identified NCT05328505 and NCT01411345. At the moment, the clinical experience is also limited and mostly retrospective [36–44]. A similar approach was used in the recent phase 2, dual-center, open-label, single-arm SCIMITAR trial, testing extreme hypofractionation in patients with biochemical and/or clinical relapse [45]. When a local relapse was visible on preradiation imaging (in 27% of patients), it was contoured as gross tumor volume (GTVboost) and irradiated to 40 Gy in 5 fractions. A current multicentre retrospective study across 16 European centres of 363 patients with a macroscopic recurrence identified on functional imaging showed that when the prescribed dose on the lesion was $\geq$ 72 Gy, an improvement in 5-year progression-free survival could be observed (72.8% (95 %CI 64.6–79.4) versus 60.3% (95 %CI 48.4; 70.3; P = 0.03), with an acceptable toxicity profile [46]. Ultimately, most of the panel would consider a moderate dose-escalation on the GTV, irrespective of the fractionation regimen for standard to hypofractionation, provided that OAR constraints were prioritized over the focal boost. Ideally this should be best undertaken within a clinical trial.

Conclusion

Radiation oncologists are increasingly confronted with macroscopic local recurrences visible on imaging in patients referred for postoperative radiotherapy, a challenging situation with no standardized approach. An ESTRO ACROP consensus panel on prostate bed delineation therefore addressed this clinical reality. Initial contouring of two clinical cases showed important variation between delineations, significantly higher than was observed in the postoperative cases without evidence of disease. This further emphasized the urgent need to define a recommendation on this situation. Through additional deliberations, a consensus was agreed upon. First of all, it was recommended to always delineate and irradiate the entire prostate bed, and not the local recurrence alone, whatever the exact location of that recurrence. Secondly, specific dose-escalation on the macroscopic recurrence should only be considered if an anatomic correlate is visible. Such a focal boost is probably feasible, provided that OAR constraints are prioritized. Possible dose is probably also dependent on the location of the recurrence. Its potential benefit should urgently be investigated in prospective clinical trials.

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CRediT authorship contribution statement

Piet Dirix: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Visualization, Project administration. **Alan Dal Pra:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Vincent Khoo:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Christian Carrie:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Cesare Cozzarini:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Valérie Fonteyne:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Pirus Ghadjar:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Alfonso Gomez-Iturriaga:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Nina-Sophie Schmidt-Hegemann:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Valeria Panebianco:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Almudena Zapatero:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Alberto Bossi:** Validation, Investigation, Resources, Writing – review & editing, Supervision. **Thomas Wiegel:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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