

Prostate radiotherapy - EORTC

Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group

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Abstract

The appropriate application of 3-D conformal radiotherapy, intensity modulated radiotherapy or image guided radiotherapy for patients undergoing post-operative radiotherapy for prostate cancer requires a standardisation of the target volume definition and delineation as well as standardisation of the clinical quality assurance procedures. Recommendations for this are presented on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Radiation Oncology Group and in addition to the already published guidelines for radiotherapy as the primary treatment.

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Although radical prostatectomy is an effective treatment for many patients with clinically localised prostate cancer, treatment may fail in up to 20–40% of the cases, depending on prognostic factors and patient selection. The possible patterns of post-prostatectomy relapse can be a true local recurrence in the prostatic bed, regional recurrence in the lymph nodes, metastatic disease or a combination of these. Often, the first sign will be only biochemical progression [3,16,31,32]. Detectable PSA levels after surgery may be due to residual disease, suggested by positive surgical margins reported in the pathological report. However, low and constant PSA levels may occur because of a microscopic amount of secreting benign prostate tubules left behind during the radical prostatectomy, either at the level of the bladder neck (in bladder neck sparing radical prostatectomy) or at the level of the urethral sphincter. Indeed there is no prostate capsule at the level of the bladder neck or at the level of the apex. Moreover, some prostate tubules often continue within the urethral sphincter that extends into the prostate. In

this case therefore, delaying radiotherapy until confirmed PSA rising could be considered.

In a randomised controlled trial comparing radical prostatectomy followed by immediate conventional external irradiation to a dose of 60 Gy in 30 fractions with prostatectomy alone, the EORTC has demonstrated that patients at high risk for local recurrence based on pathological features have a significantly reduced risk of progression after immediate post-operative radiotherapy. At a median follow-up of 5 years, biochemical progression-free survival was significantly improved in the irradiated group (74.0% vs 52.6%; $p < 0.0001$). Clinical progression-free survival and the cumulative rate of locoregional failure were also significantly improved in the irradiated group ($p = 0.0009$ and $p < 0.0001$, respectively). Grade 2 or 3 RTOG/EORTC late effects were more frequent in the postoperative irradiation group ($p = 0.0005$), but severe toxicity (grade 3 or higher) occurred rarely, with a 5-year rate of 2.6% in the wait-and-see group and 4.2% in the postoperative irradiation group ($p = 0.0726$) [2,9]. The Southwest Oncology Group (SWOG)

recently published the results of a similar randomised trial confirming that immediate post-operative irradiation improved biochemical free-survival at 5 and 10 years follow-up when compared to observation alone [42]. In the German prospective randomised trial, that randomised patients with pT3 prostate cancer before achieving an undetectable PSA, adjuvant RT significantly reduced the risk of biochemical progression from 40% to 19% at 4 years after radical prostatectomy. The rate of late grade II side effects for the rectum was 3% [44]. It has been hypothesized that similar results may be obtained with initial observation followed by timely salvage radiotherapy on evidence of biochemical progression, however this approach remains speculative [5,8,19].

The International Commission of Radiation Units and Measurements has introduced standard definitions for volumes of targets and organs at risk in patients undergoing external beam radiotherapy [20,21]. Although these definitions have been thoroughly introduced and are used by most radiation oncologists since their publication, there exists still a huge variation in the volume delineation within the radiotherapy community. It appears that the interpretation of the unequivocal target volume definitions differs substantially from one radiotherapy department to another and for many disease sites even between the different radiation oncologists in one department. This is especially true for definitions in prostate cancer radiotherapy [12]. The various imaging modalities for treatment planning as well as different patient positioning- and verification procedures further increase this diversity. A special case is the post-operative setting where the macroscopic target volume has been removed completely. Symon et al. studied the inter-observer variability of target volume delineation in postoperative radiotherapy for prostate cancer performed by 5 radiation oncologists for 8 patients. The CTV varied between the physicians from 39 to 53 cm³ for the patient with the smallest and from 16 to 69 cm³ for the patient with the largest variation. The missed high-risk

volume ranged from 2 to 79%. These results confirm the urgent need for guidelines for target volume delineation [39].

The Genitourinary working party of the Radiation Oncology Group of the European Organisation for Research and Treatment of Cancer (EORTC) has committed itself to promote an initiative on the definition of volumes in prostate cancer radiotherapy. This manuscript focuses on the case of radiotherapy planned immediately after surgical removal of the prostate and should be regarded as an extension of the published EORTC guidelines for radiotherapy with an intact prostate [1]. For more general items of radiotherapy in prostate cancer, we refer to this paper.

Location of local recurrence after radical prostatectomy

In order to define the appropriate target volumes for prostate cancer patients after prostatectomy, we first address the item of the *location* of local recurrences after surgery. In a number of cases, a local relapse can be confirmed by physical examination, TRUS guided biopsy, endorectal coil MRI [25,36] or PET [26,28,35].

A number of studies describe the site of a biopsy proven relapse in the prostatic bed after prostatectomy (Table 1). Silverman found in his series that all 31 local relapses were located at the anastomosis while Connolly identified also 10 out of 61 relapses at the level of the bladder neck and 8/61 in the retrovesical space [10,38]. Seventeen of the 31 positive biopsies in 41 biochemically relapsing patients after radical prostatectomy reported by Leventis were located at the anastomosis [24]. Sella evaluated the accuracy of endorectal coil MRI to assess the exact location of a local relapse. Local recurrences were perianastomotic in 12 (29%) patients and retrovesical in 17 (40%), within retained seminal vesicles in nine (22%), and at anterior or lateral surgical

Table 1
Location of the local relapses in the prostatic bed after radical prostatectomy

	Patients	Diagnosis	Anastomosis	Other sites
Silverman [38]	31	Clinically detected or PSA rising, biopsy confirmed	31	Posterior: 16 Anterior: 9 Combination: 6
Connolly [10]	61	PSA rising biopsy confirmed	42	Posterior: 26 Anterior: 5 Lateral: 11
Leventis [24]	31	Clinically detected or PSA rising, biopsy confirmed	17	Retrovesical: 2 Bladder neck: 7 Combination: 5
Sella [36]	39	MRI detected (15/39 biopsy confirmed)	12	Retrovesical: 17 Residual SV: 9 Combination: 1
Total	162		102 (63%)	Retrovesical: 27 (17%) Bladder neck: 17 (10%) Other: 16 (10%)

margins in four (9%) [36]. Overall, in spite of the different diagnostic methods employed (transrectal ultrasound and/or MRI with endorectal coil) the results are remarkably similar: about two-thirds of the positive biopsies are located exclusively in the vicinity of the anastomosis (of which 60% posteriorly, 20% anteriorly, and 15% laterally), 17% are situated in the retrovesical space and 10% each at the bladder neck and elsewhere (Fig. 1). This implies that a particular emphasis should be placed in defining these structures as accurately as possible while delineating the clinical target volume (CTV) on the planning CT scan.

The identification of the anatomical structures around the prostate bed on a planning CT-scan is a difficult task. Therefore, a number of possible aids are suggested, including the placement of clips by the surgeon during the prostatectomy at predefined sites in order to unambiguously locate the anastomosis, the retrovesical space and the bladder neck. As most recurrences occur at the level of the anastomosis between the bladder neck and the urethra, the surgeon can place a distinctive metal marker at the anterior part of the anastomosis just before suturing. In order to distinguish between the multiple surgical haemostatic clips and the marker, a piece of an orthopaedic wire (such as the one used for fixating fractured patella or sternum) may be used. A supplementary advantage is that this marker can be seen on portal imaging.

Target volume definition

In the postoperative setting, no GTV is present. In order to define appropriate clinical and planning target volumes, knowledge of the biology of tumour spread beyond the anatomical borders of the prostate, and thereby the surgical resection margins, is of utmost importance, as is the knowledge about the site of recurrent disease. As most patients will have had a radical prostatectomy together with resection of the seminal vesicles and the internal iliac lymph nodes, a comprehensive and careful look at the pathological specimen has to be done to evaluate seminal vesicle invasion, extracapsular extension with or without invasion of the surgical margin and lymph node metastases.

The extent of extracapsular tumour extension (ECE) is an important issue for postoperative prostate cancer target

definition in radiotherapy, and may depend on the quality assurance of the pathological examination. The largest study evaluating the radial distance of ECE was performed on 712 prostatectomy patients by Teh et al. They found a focal ECE, ECE <2 mm, ECE 2–5 mm and ECE >5 mm in 38.1%, 19.1%, 36.1% and 6.7% of the prostatectomy specimens, respectively (evaluated according to Wheeler et al.) [40,41]. These results imply that a margin of 5 mm of periprostatic tissue should encompass the clinical target volume. Chao et al. also noticed that almost all identifiable ECE occurred in the posterolateral region of the prostate, with all significant ECE (≥ 2 mm) in that region. Therefore, we could conclude that the supplementary margin of 5 mm to account for ECE could be limited to the posterolateral region [6]. Further results are needed before individualising the CTV margin for the extent of ECE rather than adopting a uniform margin.

Miralbell et al. used an endorectal coil MRI in 60 patients with a local relapse after radical prostatectomy for prostate cancer to define its location. Based on this, they proposed a CTV for postoperative radiotherapy with an approximately cylindrical shape ($\approx 4 \times 3$ cm) centred 5 mm posterior and 3 mm inferior to the urethro-vesical anastomosis. The use of this CTV might reduce the irradiation of neighbouring normal tissue in the pelvis and thereby potentially improve treatment tolerance [25]. Due to the present inability to visualize microscopic disease, the suggestion that the volume may be reduced remains still hypothesis generating and might not only reduce toxicity but also compromise disease control.

The role of MRI and PET imaging in the case of immediate postoperative radiotherapy still has to be defined. On the contrary, in patients with a detectable PSA level, an endorectal coil MRI can help in detecting macroscopical residual disease. If this is the case, this should be defined as GTV and treated to a higher dose.

Recommendations for CTV definition

The following areas are at the greatest risk for relapse after prostatectomy and should therefore be included (= prostate bed):

- Centrally: the urethra-vesical anastomosis;
- Cranially: the bladder neck;

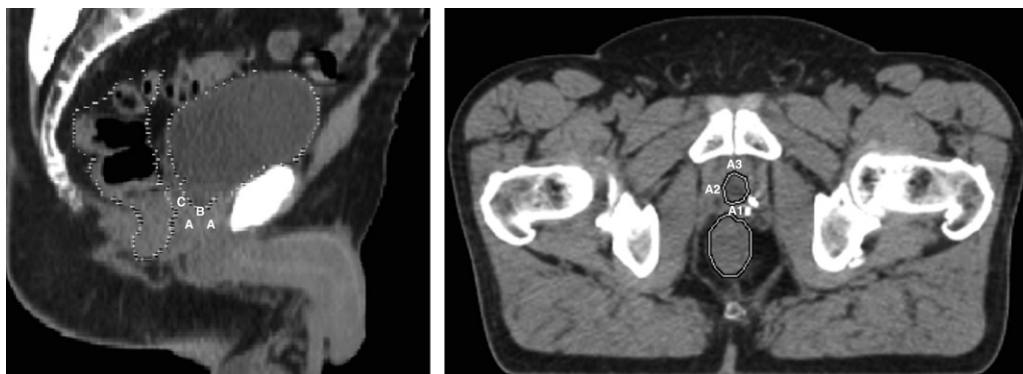


Fig. 1. Sites of local recurrence of prostate cancer displayed on a longitudinal and a transverse view, adapted from Connolly et al. [10]. A = perianastomotic (A1 = posterior, A2 = lateral, A3 = anterior); B = bladder neck; C = retrovesical.

- Posteriorly: up to but not including the outer rectal wall, cranially including the most posterior part of the bladder neck;
- Caudally: including the apex (15 mm cranially from the penile bulb) [30];
- Laterally: up to the neurovascular bundles (if removed up to the ilio-obturatoric muscles);
- Anteriorly: including the anastomosis and the urethral axis.

The CTV will include the above-mentioned high risk areas with the following proposed margins:

- 5 mm in all directions (except the rectal wall) to account for microscopical extension;
- Supplementary 5 mm in the posterior and lateral directions in the presence of incompletely resected ECE, but excluding the rectal wall;
- Supplementary 5 mm in the direction of microscopically involved tumour margins as reported by the pathologist (except the rectal wall).

In all cases, the original site of the base of the seminal vesicles should be included. In the case of involvement of the seminal vesicles, we propose to include their original position and/or the remnants (present in 20% of the cases), without a further margin and treated to a lower dose (unless the rare case of involved margins at that level).

- In Fig. 2, a contouring example for patients scheduled for postoperative radiotherapy based on ECE is shown. Only the prostate bed, including the apex and the base of the seminal vesicles, is included and displayed.
- For patients with invasion of the seminal vesicles, Fig. 3 shows the inclusion of the prostate bed including the apex and the original location of the seminal vesicles.

Post-operative pelvic lymph nodes irradiation?

Most patients referred for postoperative radiotherapy will have undergone a staging lymphadenectomy confirming tumour-free lymph nodes. No strict rules are specified in the TNM classification concerning the minimum number of lymph nodes required to adequately stage a patient as pN0, but the TNM supplement reports that at least 8 lymph nodes are usually examined to classify pN0 [43]. In the case of a pN0 patient, the inclusion of regional lymph nodes has no rationale. In view of the anticipated higher complication rate due to increased treatment volumes, and the lack of any study that properly addressed this issue, we suggest that the regional nodes should not be irradiated electively for cN0/pNx patients [13].

Though lymph node invasion is considered by many as a systemic disease, some patients may be cured by surgery whenever nodes are minimally invaded [4,18]. Whereas the role of adjuvant nodal radiotherapy in this situation is subject of debate, some support can be given to irradiation of the internal iliac lymph nodes to an elective dose when they are invaded by tumour [11,23]. The decision must balance the anticipated advantages and the possible additional toxicity of a larger irradiated volume.

Recommendations for PTV definition

Fiorino performed weekly CT-scans in 9 patients treated with 3D-CRT after radical prostatectomy. A trend of reduced bladder filling over time was found, leading to a worsening up to 20% of the bladder dose in 6/9 patients. The rectal wall motion seemed to be higher than in patients treated with radiotherapy exclusively, with a gradual anterior shift of especially the upper part of the rectum, influencing the CTV. These movements can be explained by post-surgery settlement effects of the upper part of the irradiated volume as well as by modification of the rectal mobility due to radiotherapy [14,29]. The overall impact

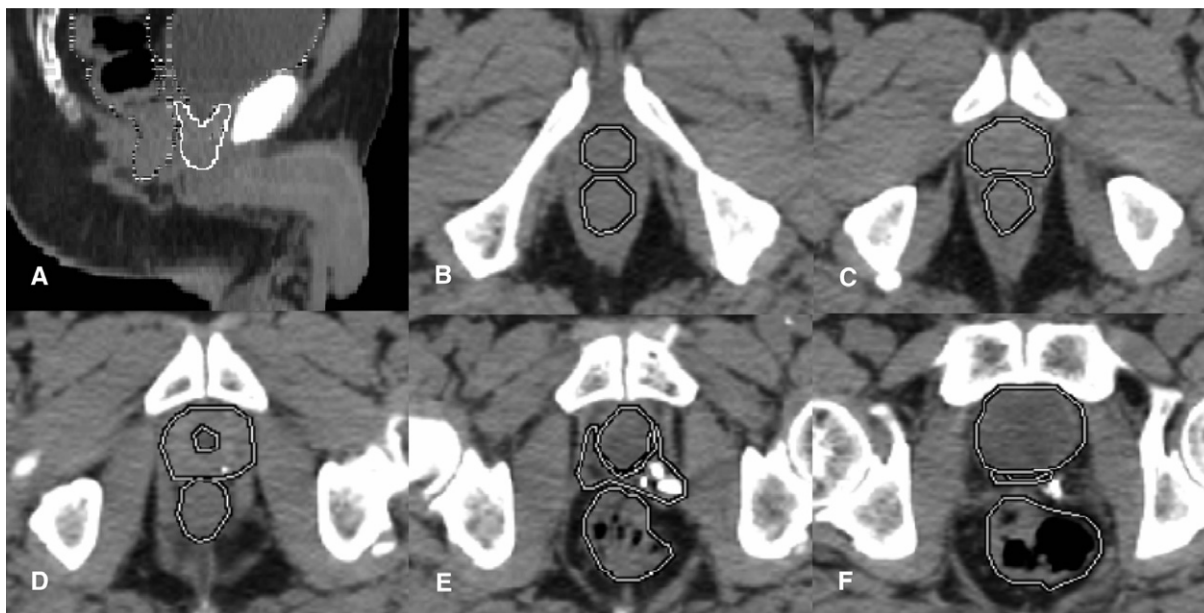


Fig. 2. Contouring example for a patient scheduled for postoperative radiotherapy on the base of extracapsular extension. A = longitudinal view; B–F = transverse slices in caudo-cranial direction. Margins to CTV and PTV have to be added as described in the text.

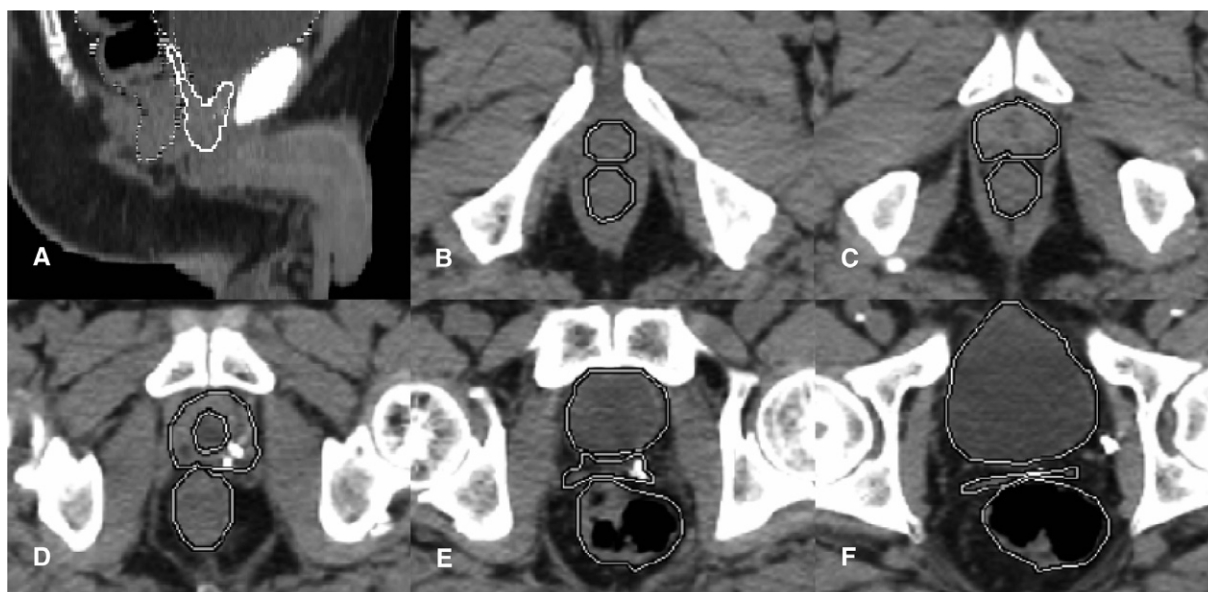


Fig. 3. Contouring example for a patient scheduled for postoperative radiotherapy on the base of invasion of the seminal vesicles. A = longitudinal view; B–F = transverse slices in caudo-cranial direction. Margins to CTV and PTV have to be added as described in the text.

of all these aspects is difficult to assess. Schiffner examined 10 patients who were treated with postoperative or salvage radiotherapy with radio-opaque markers implanted transrectally into the prostate bed using ultrasound. Although the motion of the prostate bed seemed to be less than that of the intact prostate, positioning errors exceeded 5 mm in many treatment fractions. Therefore, they recommend using daily image-guided verification using fiducial markers to improve the precision of postoperative radiotherapy [34]. In a study by Kupelian et al, the extent of variation in the position of the prostate bed with respect to the bony anatomy was evaluated by performing a megavoltage CT before each treatment fraction [22]. They concluded that significant motion (≥ 3 mm) of the prostate bed with respect to the bony anatomy was infrequent. Still, the small differences might have implications on treatment margins. The authors also pointed out the importance of the definition of what should be considered as the prostate bed in estimating the movement of the target volume.

In general, the margin from CTV to PTV depends on the experience and procedures of each individual centre. This can be reduced by daily on line image guided treatment execution but even then a minimum of 5 mm seems to be appropriate to account for organ motion.

Organ at risk volume definition

For recommendations on the filling of the bladder and the rectum as well as for delineation of these volumes, we refer to our earlier paper [1]. A peculiar situation is the filling of the bladder because patients after prostatectomy often experience problems in maintaining consistent bladder filling, especially early after surgery but also during radiotherapy [14]. Depending on the degree of continence, the instruction to every individual patient should remain to

maintain a stable bladder volume throughout treatment either by ensuring its emptying before each fraction of radiotherapy or by the intake of a repeatable quantity of fluid prior to each treatment. The penile bulb could be outlined separately to limit the dose to this structure, which may translate into a reduced effect on potency. However, in practice this may be difficult in view of the proximity of the high risk area and the resulting CTV since Miralbell et al. have shown that relapses occur not infrequently low at the urethra-vesical anastomosis and close to - if not clearly infiltrating - the penile bulb [25]. Moreover, most patients that are referred for postoperative radiotherapy already experience irreversible sexual problems. With the extension of the inferior limit of the CTV, the anal canal and lower rectal tract may be exposed to high doses leading to not only acute toxicity but also to late anal dysfunction and should therefore be taken into account as well.

Apart from these aspects, patients who have undergone a prostatectomy are at a higher risk for late urinary complications, especially when radiotherapy is started at a short interval after surgery [1,37]. It is recommended therefore to initiate radiotherapy only 3 months, with a maximum of 4 months, after surgery and after recovery from reversible postoperative urinary symptoms. Apart from the possible increased risk of side effects due to the combined toxicity with surgery, the risk for complications might, on the other hand, be reduced in comparison to exclusive radiotherapy because of the smaller target volumes and lower radiation doses. This was suggested by Sanguineti who compared a planning CT-scan performed shortly before and after a radical prostatectomy in six patients. All relevant volumes, including the bladder, rectum and CTV, were delineated and the corresponding PTV was generated. The CTV was reduced after surgery with a mean of 30 cm³ (range 0–60 cm³), mainly due to a lowering of the cranial edge (average 1.5 cm, range 0–2.5 cm). A systematic posterior shift of the bladder base with an average of 1.5 cm resulted in a

significant reduction of the V95 for the bladder with an average of 10 cm³. The average reduction of the V95 for the rectum was 2.5 cm³ [33].

Treatment planning imaging

The inter-observer variability concerning target volume definition, which is already marked in patients with an intact prostate, is even more marked for patients after prostatectomy [15,39]. To better define this, a preoperative CT-scan might be useful according to some [17]. On the other hand, the postoperative target volume hardly concurs with the original prostate. Whereas an endorectal coil and contrast enhanced MRI might be the most appropriate and therefore preferred tool, if available, for patients with a local relapse and for delineation of the penile bulb [25], we suggest to perform delineation on a planning CT scan only in the postoperative setting.

Treatment verification

Chinnaiyan et al. reported on the use of a daily transabdominal ultrasound for targeting the prostate bed [7]. They found important ultrasound-based shifts in all dimensions, justifying the implementation of daily targeting during conformal RT to the prostate bed. However, the accuracy of such ultrasound-based alignment is questioned for the entire prostate, and the same inaccuracies can lead to a misalignment of the prostate bed too. A study reported by Paskalev et al., evaluating the accuracy of ultrasound localisation in the postoperative setting with serial CT-scans, demonstrated the uncertainty of this technique [27]. As mentioned earlier, implanting the radio-opaque markers during surgery might be an attractive option, which needs however still to be investigated properly. Indeed, up to now, it has not been demonstrated that these markers can be used as reliable surrogates for the location of the CTV. Therefore, position verification based on this should routinely be coupled to other types of position verification. Currently, image guided radiotherapy using cone beam CT-scans is being introduced in the clinic. This might also be very interesting for radiotherapy verification in patients after prostatectomy.

In summary, there exists at this date no definite system or procedure that can be regarded as standard for treatment verification in this particular situation. We recommend that, as a strict minimum, at least weekly portal imaging, based on bony landmarks, with correction protocols should be used.

Summary

There are sufficient data available on which the definition of the clinical and planning target volumes in the postoperative setting can be based. Pathology data on the presence of extraprostatic tumour extension and of seminal vesicle involvement should be used. An optimal cooperation

with the surgeon and the pathologist within the frame of a multidisciplinary approach is of obvious importance in this combined modality setting. The possibility to agree on the placement of radio-opaque markers, preferably of a type that can be used as well for target volume delineation as for treatment verification, into the prostate bed at fixed anatomical sites during surgery should be discussed with the referring urologists.

General standardisation on target volume delineation, as described in this paper, is highly warranted to limit the inter-observer variability and to improve consistency of treatment in the framework of ongoing and future clinical trials.

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