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Original research article

Target volume definition for post prostatectomy radiotherapy: Do the consensus guidelines correctly define the inferior border of the CTV?

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ABSTRACT

Aim: We compare urethrogram delineation of the caudal aspect of the anastomosis to the recommended guidelines of post prostatectomy radiotherapy.

Background: Level one evidence has established the indications for, and importance of, adjuvant radiotherapy following radical prostatectomy. Several guidelines have recently addressed delineation of the prostate bed target volume including identification of the vesico-urethral anastomosis, taken as the first CT slice caudal to visible urine in the bladder neck. The inferior border of clinical target volume is then variably defined 5–12 mm below this anastomosis or 15 mm cranial to the penile bulb.

Methods and materials: Thirty-three patients who received adjuvant radiotherapy following radical prostatectomy were reviewed. All underwent planning CT with urethrogram. The authors (MM, JC) independently identified the CT slice caudal to the last slice showing urine in the bladder neck (called the CT Reference Slice), and measured the distance between this and the tip of the urethrogram cone. Five patients also had a diagnostic MRI at the time of CT planning to better visualize the anatomy.

Results: Sixty-six readings were obtained. The mean distance between the Bladder CT Reference Slice and the most cranial urethrogram contrast slice was 16.1 mm (MM 16.4 mm, JC 15.8 mm), range: 6.8–34.2 mm. The mean distance between the urethrogram tip and the ischial tuberosities was 19.9 mm (range 12.5–29.8 mm). The mean distance between the CT Reference Slice and the ischial tuberosities was 36.9 mm (range 28.3–52.4 mm).

Conclusions: Guidelines for prostate bed radiation post prostatectomy have been developed after publication of the trials proving benefit of such treatment, and are thus untested. The anastomosis is a frequent site of local relapse but is variably defined by the existing guidelines, none of which take into account anatomic patient variation and all of which are at variance with urethrogram data. We recommend the use of planning urethrogram to better delineate the vesico-urethral junction and minimize the potential for geographic misses.

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1. Background

For maximum efficacy, post prostatectomy radiotherapy must accurately define the post-operative clinical target volume (CTV). Results from 3 mature randomized trials have demonstrated the benefits of adjuvant radiotherapy for men at high risk of recurrence, leading to a combined American Society of Therapeutic Radiation and Oncology (ASTRO) – American Urologic Association (AUA) guideline.[1] The guideline recommends that men with adverse pathologic findings, including extra capsular extension, seminal vesicle invasion or positive surgical margins, be informed of the potential benefits of post-operative radiotherapy to reduce biochemical recurrence, local recurrence and clinical progression. However, the trials indicating benefit in this clinical scenario accrued and treated patients 1–2 decades ago. Not surprisingly, target volumes were defined differently at that time. The Southwest Oncology Group study mandated that the inferior border of the field be at the ischial tuberosities and required retrograde urethrography for all patients to ensure that a particularly low anastomosis would not be missed.[2] The EORTC trial also required retrograde cystography, with the field covering from the seminal vesicles to the apex of the prostate with a safety margin.[3] ARO96 specified 3D treatment planning to cover the surgical bed from the seminal vesicles to the apex with a 1 cm margin.[4]

Several groups (Radiotherapy Oncology Group [RTOG], European Organization for the Research and Treatment of Cancer [EORTC], Genito-Urinary Radiation Oncologists of Canada [GUROC] and the Australian and New Zealand Faculty of the Radiation Oncology Genito-Urinary Group [FROGG]) have undertaken consensus guidelines for CTV delineation for post-prostatectomy radiotherapy; none requires a urethrogram as part of the simulation process.[5–8]

2. Aim

This paper reports the relationship of the former landmark for the vesico-urethral anastomosis (VUA), i.e. the tip of the urethrogram cone, and the current consensus guidelines.

3. Materials and methods

Thirty-three patients receiving post prostatectomy external beam radiotherapy (EBRT) had a urethrogram performed at the time of CT simulation (GE Light speed, 2.5 mm slices, no gap). Patients were positioned supine, with a leg rest, and were advised to have an empty rectum and a comfortably full bladder. Urethrograms were performed by retrograde injection of 5–10 cc of Hypaque sterile X-ray contrast and applying a Cunningham clamp to the penile shaft to retain the contrast during the subsequent scan.

Eight patients were treated in an adjuvant fashion for adverse pathologic features, while 25 were treated for biochemical recurrence or persistently elevated PSA. Median age was 63.5 years (range: 52–76). Pathologic stage at surgery was pT2c in 4 patients, pT2a in one and the remaining 28 were all stage pT3. The median PSA at time of treatment was 0.15 ng/ml (range 0.01–1.6; mean: 0.4 ng/ml). None had clinical evidence of local recurrence. The median interval from radical prostatectomy to radiation was 0.8 years (range 0.25–13.9; mean 1.77 years).

Treatment planning closely followed the RTOG guideline for post prostatectomy radiotherapy planning except in delineation of the inferior margin.[5] The CTV inferior border was taken 5 mm caudal to the tip of the urethrogram cone. The median radiation prescription dose was 6600 cGy in 33 fractions over 6.5 weeks with one patient prescribed 64 Gy in 32 fractions, one 65 Gy in 35 and 3 receiving 67 Gy/36 fractions. A 4-field conformal technique was most commonly used with only 2 patients treated using IMRT.

Retrospectively, images and contours were reviewed independently by 2 observers, MM and JC. In all cases, the Bladder CT Reference Slice was determined working from cranial to caudal on transverse slices, without prior knowledge of the urethrogram results. The distance from the tip of the urethrogram cone to the Bladder CT Reference Slice was then measured independently by the 2 observers as a horizontal

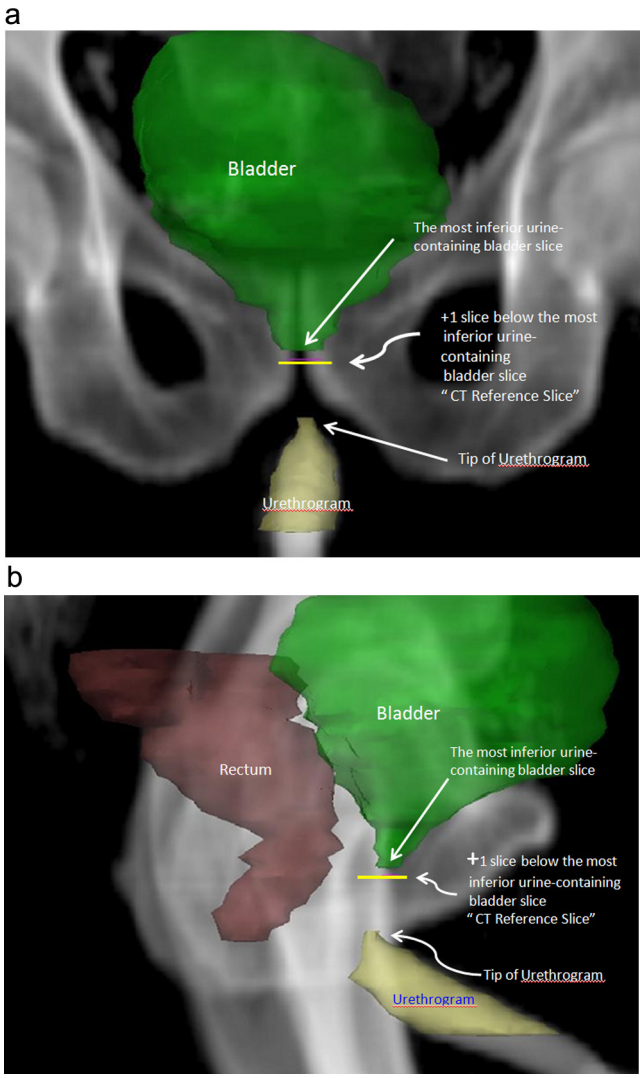

Fig. 1 – Comparison of Bladder CT Reference Slice to urethrogram. (a) Digitally reconstructed radiograph from CT simulation: anterior view; (b) lateral view.

distance (parallel to the table) (Fig. 1a and b). In addition, the distance from the CT Reference Slice to the middle of the line joining the caudal aspect of the 2 ischial tuberosities was measured.

Diagnostic MRI was performed at the time of CT planning in 5 recent patients to try to better delineate the post-surgical anatomy. The MR images were fused to the planning CT showing the urethrogram. The distance between the tip of the urethrogram cone and the clearly visible penile bulb on MRI was measured. Fusion was performed using bone alignment initially but adjusted so that the bladder neck was superimposed in the 2 sets of images.

4. Results

A total of sixty-six readings were obtained for the 33 patients. The mean distance between the tip of the urethrogram cone and the Bladder CT Reference Slice was 16.1 (MM 16.4 mm, JC 15.8 mm); range 6.8–34.2 mm. The correlation coefficient between the 2 independent sets of measurements was 0.96. The average shortest distance was 6.8 mm (MM 7.4 mm, JC 6.2 mm); the average longest distance was 34.2 mm (MM 35.7 mm, JC 32.6 mm); 79% (26/33) patients had a distance of more than 12 mm and 54% more than 15 mm between the tip of the urethrogram cone and the Bladder CT Reference Slice.

In addition, the mean distance between the tip of the urethrogram cone and the ischial tuberosities was 19.9 mm (range 12.5–29.5 mm). The mean distance between the Bladder CT Reference Slice and the ischial tuberosities was 36.7 mm (range 28.3–52.4 mm).

5. Discussion

External beam radiation therapy (EBRT) is often prescribed after surgery to improve outcome in high risk patients. Three phase 3 randomized trials of adjuvant EBRT versus observation have reported a reduction in biochemical failure, local recurrence and clinical progression.[4,9,10] Careful target

Table 1 – Shows measurements for all 33 patients in the study. Negative numbers indicate that the inferior limit of the CTV falls at or caudal to the tip of the cone. With the lower limit of the CTV defined 8 mm below the CT Reference Slice, only 1 patient (3%) has the CTV volume extend as far as the tip of the urethrogram cone. With the CTV inferior limit defined at 12 mm below the CT Reference Slice, this increases to 21% but even at 15 mm, fewer than half the patients have the CTV extend as far as the tip of the urethrogram cone. We recommend that the caudal limit of the CTV be 5 mm caudal to the tip of the urethrogram cone.

Patient #	CT Ref Slice to tip of urethrogram cone	CT Ref Slice +8 mm	CT Ref Slice +12 mm	CT Ref Slice +15 mm
1	9.6	1.55	−2.45	−5.45
2	19.7	11.65	7.65	4.65
3	16.5	8.45	4.45	1.45
4	19.8	11.8	7.8	4.8
5	9.8	1.75	−2.25	−5.25
6	19.8	11.8	7.8	4.8
7	13.8	5.75	1.75	−1.25
8	9.6	1.6	−2.4	−5.4
9	17.0	8.95	4.95	1.95
10	14.7	6.65	2.65	−0.35
11	12.9	4.9	0.9	−2.1
12	21.5	13.5	9.5	6.5
13	17.7	9.7	5.7	2.7
14	9.2	1.15	−2.85	−5.85
15	13.3	5.25	1.25	−1.75
16	12.5	4.45	0.45	−2.55
17	10.1	2.1	−1.9	−4.9
18	18.5	10.5	6.5	3.5
19	6.8	−1.2	−5.2	−8.2
20	17.9	9.85	5.85	2.85
21	25.0	16.95	12.95	9.95
22	34.2	26.15	22.15	19.15
23	15.8	7.75	3.75	0.75
24	12.6	4.55	0.55	−2.45
25	19.3	11.3	7.3	4.3
26	22.2	14.2	10.2	7.2
27	12.7	4.65	0.65	−2.35
28	20.3	12.3	8.3	5.3
29	12.8	4.75	0.75	−2.25
30	19.2	11.15	7.15	4.15
31	20.8	12.8	8.8	5.8
32	18.7	10.65	6.65	3.65
33	9.4	1.4	−2.6	−5.6

definition is critical for optimal therapy. Byar and Mostofi found that in 75% of 208 pathological radical prostatectomy specimens examined for localized prostate cancer, tumor was present in the two distal slices.[11] Stamey et al. found the apical surgical margin to be the most frequently pathologically involved margin in the patient undergoing radical prostatectomy.[12] The location of local relapse in the prostate bed after radical prostatectomy is frequently at the level of the anastomosis between the bladder neck and the urethra, establishing the importance of adequately treating the VUA.[13–16] Depending on the imaging modalities used to define the site of recurrence, transrectal ultrasound or magnetic resonance imaging (MRI), about two-thirds of positive biopsies are located in the vicinity of the anastomosis. Wang et al. reported that, in respect to MRI detected local recurrences after radical prostectomy, target volumes delineated using RTOG guidelines, showed that the coverage was marginal on recurrences occurring inferiorly at the posterior urogenital diaphragm.[21] Thus, for optimal post-operative radiation treatment, objective definition of the VUA is critical.

The RTOG, Canadian and Australian/New Zealand Groups have recently addressed the delineation of the prostate bed target volume including identification of the vesico-urethral anastomosis, taken as the first CT slice caudal to visible urine in the bladder neck (CT Reference Slice).[5,7,8] The RTOG recommends that the CTV limit be placed 8–12 mm caudal to it.[5] The Canadian GUROC recommend an 8 mm margin caudal to this level, although they also explored using a fiducial seed placed by a radiologist under trans-rectal ultrasound guidance. Since good agreement was found with placement of a fiducial seed, this was deemed unnecessarily invasive.[7] The Australian/New Zealand group recommend a 5 mm margin and the EORTC suggest placing the caudal limit of the CTV 15 mm cranial to the penile bulb.[8] Although the penile bulb as a landmark is clearly visible on MRI, we have found determination by CT to be subject to observer variation. As MRI simulation is not routinely performed for planning post-prostatectomy EBRT in our center, adequacy of this recommendation could not be confirmed.

It is important to note that all these guidelines for the delineation of prostate bed were developed after completion of the three randomized trials of adjuvant RT versus observation[4,9,10] and, thus, are untested regarding efficacy in the prevention of local recurrence. The RTOG Group established their consensus for the post-operative CTV from clinical investigators specializing in the treatment of prostate cancer. The Canadian guidelines were derived based on a review of published data, patterns of local failure, surgical practice and radiological anatomy and then reviewed by the members of GUROC. The EORTC used the patterns of failure to establish the appropriate CTV in the post-operative setting. All the consensus groups clearly recognize the importance of adequately covering the VUA, yet none incorporated a urethrogram in their planning or validated their recommendations by comparing the caudal limit of their recommended CTV to the standard by which the worth of treatment was established. The randomized trials established the caudal limit of the VUA using a urethrogram while the current guidelines establish the proximal limit without regard for variable length. The randomized trials will not be repeated, and it may be years before treatment is discredited because of a higher than expected local recurrence rate despite adjuvant radiotherapy.

Over three quarters of the patients in our report had a distance between the tip of the urethrogram cone and the recommended CT landmark for the VUA greater than 12 mm and over 50% of the patients had a distance greater than 15 mm (Table 1). The recommended caudal limit of the CTV is only 5–12 mm below the CT landmark. The current guidelines may result in geographic miss of a variable proportion of the VUA. These discrepant findings raise questions regarding the actual anatomic length of the anastomosis. Clearly, it is

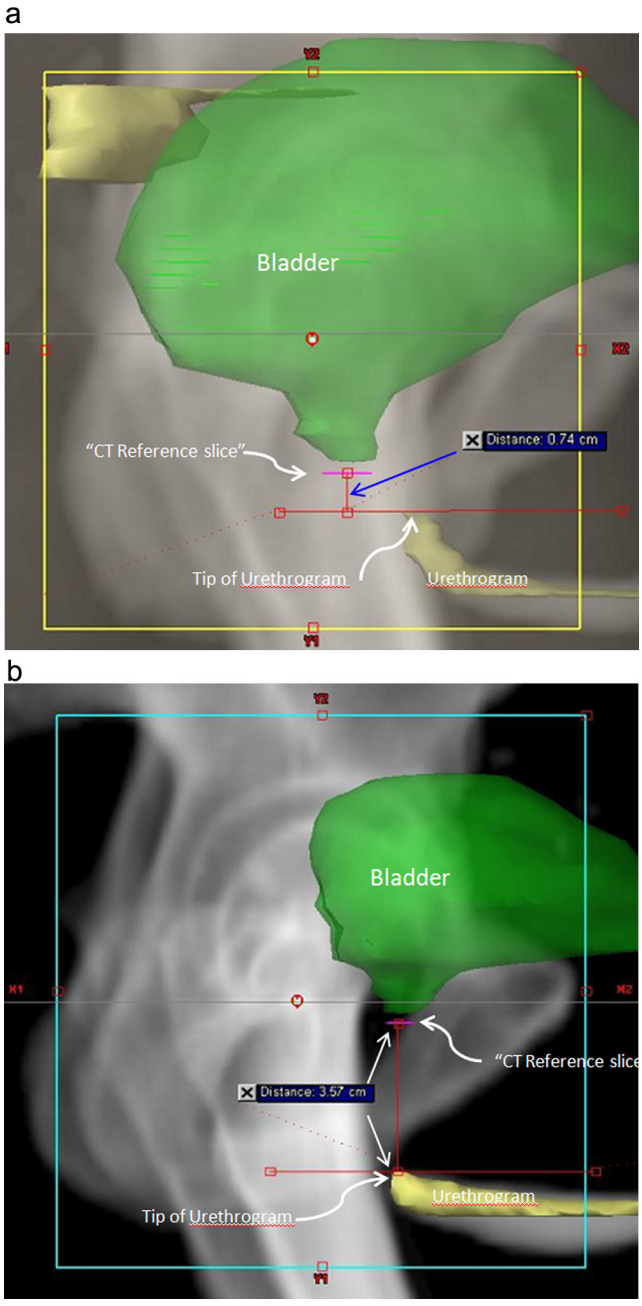

Fig. 2 – Examples of the range of anatomic variation in the distance between the tip of the urethrogram cone and the Bladder CT Reference Slice. (a) Short anastomosis 7.4 mm; (b) long anastomosis 35.7 mm.

not a clean junction a few mm thick. Bunching or retraction of mucosa and/or muscle and formation of post-surgical scar tissue implicate a much longer length of urethra. Whether it is critical to treat the entire length of the narrowed portion of the urethra that we call anastomosis is unknown. Based on the practice that fed the randomized clinical trials which proved the worth of post-operative radiotherapy for high risk patients and led to the current practice-changing ASTRO-AUA Guideline, it would be prudent to either individualize treatment by re-introducing urethrograms at the time of CT simulation for these patients, or extend the standard caudal limit of the CTV sufficiently to cover the VUA. Our results reveal considerable variation in the distance between the tip of the urethrogram cone and the recommended CT landmark (Fig. 2a and b). Without the benefit of a urethrogram, rather than adding 8–15 mm, a distance in our experience of 35 mm caudal to the Bladder CT Reference Slice would be required, in order to guarantee coverage, or 25 mm to cover 90% of cases (Figs. 3 and 4).

Similarly, our results also show variance with regard to the distance between the tip of the urethrogram cone and the ischial tuberosities and also the distance between the bladder reference slice and ischial tuberosities. The use of a fixed bony landmark is not recommended as it results in an excessive treatment volume in a substantial proportion of patients with a potential of additional toxicity.

One weakness of this study is that we do not have MR images for all these patients to look for an MR radiologic correlate of what we identify as the tip of the urethrogram cone. Certainly, nothing is visible in this regard on CT images. With this in mind, we obtained diagnostic MR scans on 5 patients at the time of radiation planning. Apart from clear visualization of the penile bulb, we did not find the scans helpful in localizing the anastomosis. Others have observed greater inter-observer variability when contouring on MRI than CT.[22] We did observe that the distance between the tip of the urethrogram cone and the penile bulb varied with a range of 0–8 mm in the 5 patients who had MR imaging. The correlation between urethrogram and MRI can be explored in the future as it would clearly be advantageous not to have to perform a urethrogram at simulation on all post-operative patients. Another potential issue is that the performance of a urethrogram can cause contraction of pelvic floor muscles and displace tissues cranially.[17] One would assume that the cranial and caudal limits of the anastomosis would move to the same degree with muscle contraction. If differential movement were possible, elevation of the pelvic floor should place the tip of the urethrogram cone closer to the bladder neck, thus decreasing the length of the measured gap. Use of fiducials in the prostate bed has shown greater stability of these tissues in the postoperative setting compared to de novo prostate radiotherapy.[18]

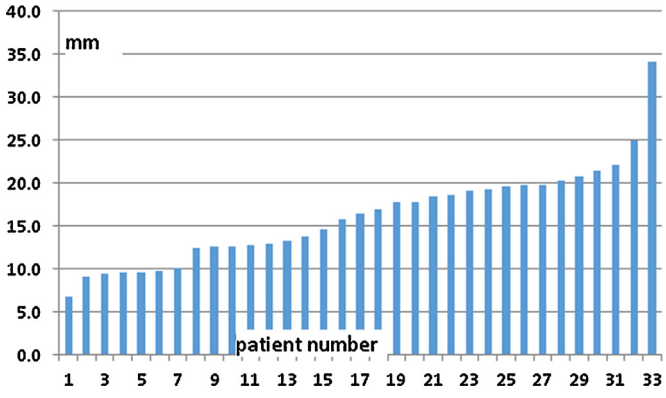

Fig. 3 – Waterfall plot showing distribution of the distance between the CT-bladder reference slice and the tip of the urethrogram cone.

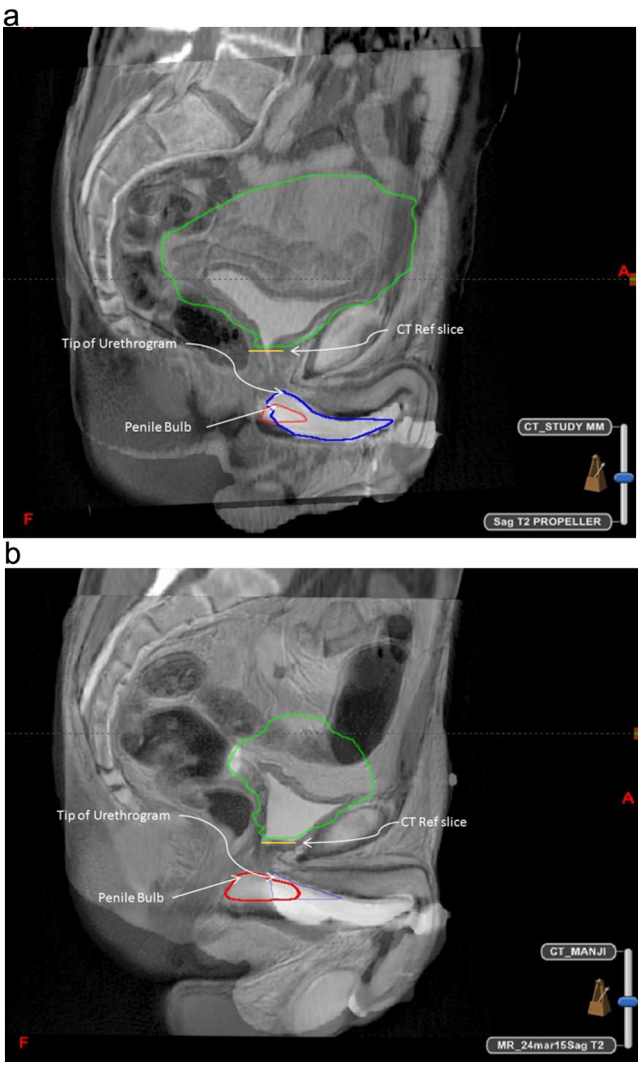

Fig. 4 – MR-CT fusion showing tip of urethrogram cone (identified on CT), penile bulb (identified on MRI), and CT Reference Slice (yellow line). The bladder is visible on MR and the bladder contour from the CT is superimposed. (a) Penile bulb is 8 mm caudal to tip of urethrogram cone, and 2.8 cm caudal to the Bladder CT Reference Slice. In this example, the caudal aspect of the EORTC CTV falls half way between the penile bulb and the Bladder CT Reference Slice. (b) Penile bulb is level with the tip of the urethrogram cone, and 1.6 cm from the Bladder CT Reference Slice. In this case, the caudal aspect of the EORTC CTV would be 1 mm caudal to the Bladder CT Reference Slice.

The EORTC is currently conducting a prospective randomized Phase 3 trial of dose escalation in the post operative setting, comparing 64–70 Gy. Sassowsky et al. have published a review of the international Guidelines and adherence to the EORTC recommendations in the Dummy Run for this trial.[19] The cranio-caudal extent of the prostate bed is defined as the VUA extending cranially to the bladder neck, and caudally including the apex. The CTV adds a 5 mm margin and the PTV a further 10 mm. Major deviations were found in the dummy runs of 70% of the centers, most frequently in the cranial and caudal extent of the definition of the prostate bed. As there is unacceptable inter-observer variation in definition of the site of the prostate apex and/or the penile bulb on CT, they recommend MR imaging for post prostatectomy radiotherapy planning, with appropriate modification of the EORTC guideline.[20]

6. Conclusions

A urethrogram delineates clearly and unambiguously the caudal aspect of the vesico-urethral anastomosis for definition of the inferior border of the CTV. We report considerable variation in the location and length of the anastomosis and recommend the use of urethrogram to delineate the caudal aspect of the vesico-urethral junction and thus the inferior limit of the CTV. Correlation of urethrogram with MRI findings would be useful in unambiguously establishing the target volume.

Summary

The three randomized trials demonstrating benefits of post prostatectomy radiotherapy for patients at higher risk of recurrence all identified the vesico-urethral anastomosis (VUA) by urethrogram. Data from 33 post prostatectomy patients comparing VUA identification by urethrogram to current guidelines which place the VUA one CT slice below visible urine in the bladder neck show that for 79% of patients, the tip of the urethrogram cone is >12 mm caudal to this CT slice.

Conflict of interest

None declared.

Financial disclosure

None declared.

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