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Sentinel lymph node imaging guided IMRT for prostate cancer: Individualized pelvic radiation therapy versus RTOG guidelines

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Abstract

Purpose/Objectives: Current Radiation Therapy Oncology Group (RTOG) guidelines for pelvic radiation therapy are based on general anatomic boundaries. Sentinel lymph node (SLN) imaging can identify potential sites of lymph node involvement. We sought to determine how tailored radiation therapy fields for prostate cancer would compare to standard RTOG-based fields. Such individualized radiation therapy could prioritize the most important areas to irradiate while potentially avoiding coverage in areas where critical structures would be overdosed. Individualized radiation therapy could therefore increase the therapeutic index of pelvic radiation therapy.

Methods and materials: Ten intermediate or high-risk prostate cancer patients received androgen deprivation therapy with definitive radiation therapy, including an SLN imaging–tailored elective nodal volume (ENV). For dosimetric analyses, the ENV was recontoured using RTOG guidelines (RTOG_ENV) and on SLNs alone (SLN_ENV). Separate intensity modulated radiation therapy (IMRT) plans were optimized using RTOG_ENV and SLN_ENV for each patient. Dosimetric comparisons for these IMRT plans were performed for each patient. Dose differences to targets and critical structures among the different IMRT plans were calculated. Distributions of dose parameters were analyzed using non-parametric methods.

Results: Sixty percent of patients had SLNs outside of the RTOG_ENV. The larger volume IMRT plans covering SLN imaging–tailored elective nodal volume exhibited no significant dose differences versus plans covering RTOG_ENV. IMRT plans covering only the SLNs had significantly lower doses to bowel and femoral heads.

Conflicts of interest: None.

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Conclusions: SLN-guided pelvic radiation therapy can be used to either treat the most critical nodes only or as an addition to RTOG guided pelvic radiation therapy to ensure that the most important nodes are included.

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Introduction

High- and intermediate-risk prostate cancer (PCa) patients have increased risk of lymph node involvement (LNI). Recent studies suggest that the incidence of LNI is underestimated.¹ One recent study of high-risk PCa treated with radical prostatectomy and extended pelvic lymph node and retroperitoneal lymph node dissection showed that 78% of patients had both common and para-aortic involvement.² Pathological evaluation of surgical specimens may also underestimate LNI as reverse transcriptase-polymerase chain reaction detects lymph node micrometastases in ~30% of cases.³ In addition, conventional noninvasive imaging with computed tomography (CT) and magnetic resonance imaging has low sensitivity.^{4,5} Therefore, although accurate identification of LNI in PCa is critical, there is currently no sensitive and accurate means to determine nodal status in patients undergoing radiation therapy (RT).

Sentinel lymph node (SLN) imaging has been successfully applied to evaluate LNI in other cancers, such as breast cancer.⁶ Although SLN imaging is not a key component of treatment in PCa, several studies have used SLN imaging to guide more accurate nodal dissections.^{7,8} Of note, SLNs are found to reside outside of normally dissected areas in 30% to 40% of cases.⁸ Therefore, SLN imaging offers an attractive modality to accurately identify potential sites of LNI in PCa before definitive treatment.

One treatment strategy for select intermediate- and high-risk PCa patients is definitive RT, including whole-pelvis RT (WPRT) with androgen deprivation.⁹ The role of WPRT is controversial, but the goal is to sterilize microscopic disease in patients with pelvic LNI. The Radiation Therapy Oncology Group (RTOG) 9413 trial initially demonstrated an advantage for neoadjuvant hormone therapy and WPRT.⁹ The progression-free survival benefit seen in RTOG 9413 remains controversial.¹ The recent French Genitourinary Tumor Group Trial-01 found no survival benefit for WPRT,¹⁰ but the study may have been too small ($n = 444$); only 45% of the patients had a risk of nodal involvement greater than 15%, and the fields would have been described as “mini-pelvis” rather than whole pelvis according to the RTOG 9413 protocol.¹ There is evidence supporting WPRT for high-risk PCa,¹ and several ongoing trials seek to further define the role of WPRT, including RTOG 0924 and Prostate and Pelvis

Versus Prostate Alone Treatment for Locally Advanced Prostate Cancer (PIVOTAL) phase 2 trial.

With accurate identification of potential lymph node metastases, elective WPRT in PCa may be better planned and delivered. However, dosimetric and toxicity information on SLN-guided image guided RT (IMRT) for PCa patients is limited. We thus present a study incorporating SLN imaging guided IMRT for PCa patients to compare its dosimetric characteristics with RTOG-based IMRT plans.

Methods and Materials

Patients

Ten patients at our institution were serially accrued. Eligibility criteria include pathologically confirmed cN0 cM0 PCa with Gleason score ≥ 7 and LNI risk $\geq 15\%$ based on the Roach formula. Patients who had prior prostatectomy or pelvic RT were excluded. Patient and tumor characteristics are summarized in Table 1. Clinical stages of patients were as follows: 2 T1c, 4 T2a/b, and 4 T3a. Six patients had Gleason score of 3+4, 3 Gleason 4+3, and 1 Gleason 4+5.

SLN mapping and treatment

Before RT, all patients had gold marker fiducials placed into the prostate. During fiducial placement, lymphatic drainage mapping was performed as described previously. Briefly, filtered Tc-sulfur nanocolloid was divided equally into 6 fractions and administered evenly into three locations (apex, mid-gland, and base) for each lobe. After 1.5 to 3 hours of tracer administration, a combined single-photon emission computed tomography (SPECT)/CT was performed.¹¹ Reportable adverse events were communicated 1

Table 1 Summary of patient demographics

	Median	Range
Age of diagnosis, y	74	(56-81)
Clinical stage		(T1c-T3a)
Gleason score	7	(7-9)
Pretreatment prostate-specific antigen, ng/mL	14.7	(4.8-70)
Body mass index	29.9	(24.6-41.9)

week after radiotracer administration. Toxicity and morbidity of SLN imaging were tabulated.

Patients received at least 4 months of androgen deprivation and were treated with definitive RT, including elective nodal irradiation. For RT, patients received a planning CT after undergoing SLN mapping. Planning CT image sets were registered to the SPECT/CT image sets using rigid registration with MIMVista (version 4.1.2, Cleveland, OH). Afterwards, manual segmentation of SLNs was performed. SLNs were contoured on the planning CT only when there was a CT correlate. In addition, the nodal regions that included the SLNs were contoured in a similar fashion as suggested by RTOG, whereby a 7-mm radial margin was used. All patients had 3 sets of nodal volumes generated. First, the RTOG-based guidelines were used to create RTOG_ENV.¹² Next, SLN-only plans were generated using the sentinel nodes and a 7-mm radial margin around the sentinel nodes (SLN_ENV). The final and largest nodal volume generated is the Tx_ENV, which is a nodal volume generated using RTOG guidelines plus the SLN and a 7-mm margin. Therefore, Tx_ENV is the summation of RTOG_ENV and SLN_ENV. All nodal volumes were modified by excluding bowel and bone. Organs at risk (OARs) were contoured similar to RTOG guidelines. The bowel was the entire abdominal cavity with the exclusion of muscle, bone, and blood vessels. The superior border of the bowel contour was 1.5 cm above the planning target volume. The rectum was contoured from the anus to the rectosigmoid flexure. The femur was contoured for the ischial tuberosity to the top of the ball of the femur. The bladder was contoured in its entirety. Segmentation of target and OAR structures was performed and reviewed by the treating physician.

All patients were planned and treated in the supine position. An optimized IMRT plan was created for each patient using ADAC Pinnacle (Version 8.0d, Philips, Madison, WI). Patients received either (1) 78 Gy at 2 Gy per fraction to the prostate and 45 Gy at 1.8 Gy per fraction to Tx_ENV or (2) 45 Gy at 1.8 Gy per fraction to the prostate and Tx_ENV followed by a HDR brachytherapy prostate boost of 19 Gy in 2 fractions or 15 Gy in 1 fraction. This report only considers the dosimetry during the initial pelvic nodal treatment, so the dosimetry resulting from boost treatment is not reported.

Dosimetric analysis

To compare the dosimetric characteristics of SLN imaging guided pelvic IMRT to standard RTOG-based IMRT plans, three optimized IMRT plans were created, one using Tx_ENV (the largest volume), a second using RTOG_ENV, and a third using SLN_ENV (the smallest volume).

Dosimetric analyses were performed comparing dosimetric values and relevant dose-volume histogram parameters

among the three IMRT plans. Mean, maximum, and minimum dose to targets and OARs were recorded. OARs were also assessed by the relative percent volumes receiving 50 Gy, 45 Gy, 40 Gy, and 20 Gy (rV50, rV45, rV40, and rV20, respectively) and absolute volume receiving 45 Gy, 40 Gy, and 20 Gy (aV45, aV40, and aV20).

Statistics

Descriptive statistics were calculated for doses to target volumes and OARs. Because of the sample size, the distributions of dosing parameters were analyzed using nonparametric methods for dependent measures. The Friedman test was used to compare the distributions of the mean, maximum, and minimum doses for targets and OARs for the three treatment plans.¹³ If overall statistical significance was determined, then pairwise comparisons were tested. This was carried out based upon the Friedman test using the sum of the ranks for each group to identify which plans differed. Significance was defined as a probability value less than .05 and no adjustments were made for multiple testing.

Results

SLN mapping and elective nodal volumes

All patients had at least one SLN identified. SLNs were identified in the internal/external iliac nodal basins in all cases, common iliacs in 50%, and para-aortics in 50%. Thirty percent of patients had both common iliac and para-aortic SLNs. In regard to SLN coverage, standard RTOG nodal volumes encompassed all identified SLNs in only 30% of cases. SLN imaging information altered the Tx_ENV in 60% of cases. In one case, the physician did not increase the volume as suggested by SLN imaging because of concern of potential acute morbidity. The median percent increase with respect to the standard RTOG ENV was 97.9% (range, 40.2%-152.4%). [Figure 1](#) provides an illustrative case. When SLNs were located outside of standard RTOG nodal volumes, the median distance from the SLNs to the RTOG nodal volumes was 6.2 cm (range, 0.5-11.2 cm).

Dosimetric analyses

[Figure 2](#) presents illustrative IMRT plans covering Tx_ENV, RTOG_ENV, and SLN_ENV. Significant differences among the distributions of the mean, maximum, and minimum dose were observed. [Table 2](#) summarizes the significant comparisons.

Overall, there is no evidence found suggesting a difference for mean dose between plans with Tx_ENV and RTOG_ENV. However, the mean doses for OARs were

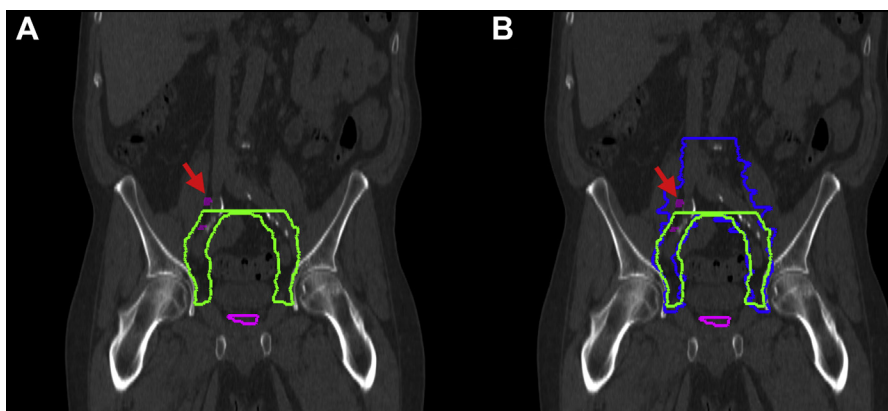


Figure 1 Illustrative case in which standard pelvic nodal volumes fail to include identified sentinel lymph nodes (SLNs). (A) Radiation Therapy Oncology Group elective nodal volume (ENV) (green) fails to cover right proximal common iliac SLN (red arrow). (B) Treated ENV (blue) covers all identified SLNs.

lower in the plans with SLN_ENV than with either Tx_ENV or RTOG. The median difference in mean dose for targets was often less than 1 Gy (Table 3). Small differences of <2 Gy were seen for most OARs, including bladder and rectum. However, increased mean dose to the bowel and femoral heads (FHs) occurred in plans with Tx_ENV and RTOG_ENV as compared with plans with the smaller SLN_ENV. The mean dose to bowel was higher for 8 of 10 patients with Tx_ENV plan versus either of the other two plans and significantly higher compared with plans using SLN_ENV. The median difference in mean dose to either the right or left FH was >3 Gy when using plans with Tx_ENV or RTOG_ENV versus with SLN_ENV. Although there were increased bowel and FH doses, the total dose to these structures were still within our institution's dose constraints.

A similar pattern was observed for differences between plans in maximum dose and minimum dose. Higher maximum and minimum doses are delivered to the bowel and FH when using Tx_ENV compared with SLN_ENV. As for other OARs, although statistically significant, differences were small and usually <2 Gy. Overall, the

maximum and minimum doses to OARs were lower with plans with SLN_ENV, but no significant differences in maximum or minimum dose were observed between plans with Tx_ENV and RTOG_ENV (see Table 4). Analysis of dose-volume histogram parameters again does not suggest any differences between plans with Tx_ENV versus those with RTOG_ENV, whereas consistent dose differences are observed for bowel and FH (Table 5).

In regard to target structures, although statistically significant differences in mean, maximum, and minimum dose occurred for the seminal vesicles, prostate, and ENV, the dose differences were often small (<1 Gy). Overall, target structures had few dose differences. Again, no significant dose differences in target structures occurred between Tx_ENV and RTOG_ENV.

Toxicity

SLN imaging morbidity was minimal with only 2 patients noting prostate pain during or 1 week after the procedure. However, the patients also had gold marker seed placement at the time of the colloid injection, so the

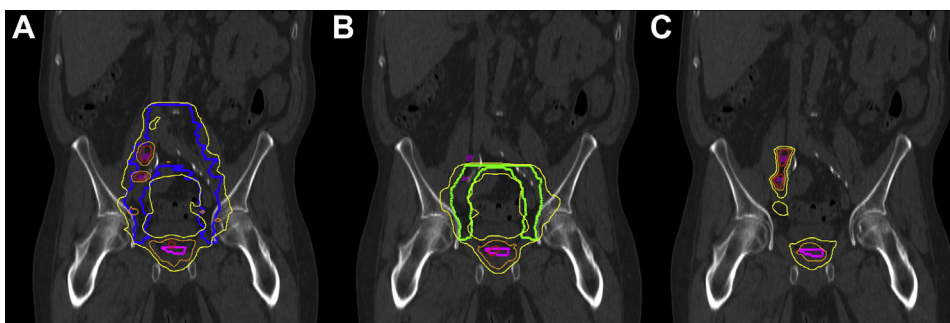


Figure 2 Illustrative case comparing image guided radiation therapy plan with treated elective nodal volume (Tx_ENV), Radiation Therapy Oncology Group (RTOG)_ENV, or sentinel lymph node (SLN)_ENV. (A) Tx_ENV includes nodal regions where SLNs were identified. (B) RTOG_ENV is based on consensus RTOG guidelines and, in this case, fails to cover a proximal right SLN, which is underdosed. (C) SLN_ENV only includes SLNs without the nearby nodal region, which allows for good coverage of all targets while minimizing dose to OARs. The yellow isodose line represents 45 Gy; the orange isodose line represents 54 Gy.

Table 2 Median differences in mean doses for target and critical structures

Target/OAR	Tx_ENV (range in Gy)	RTOG_ENV (range in Gy)	SLN_ENV (range in Gy)
Prostate	48.47 (46.87-58.63)	49.36 (46.88-59.25)	48.9 (46.8-59.29)
Seminal vesicle	48.26 (46.59-57.62)	49.21 (46.70-57.91)	49.05 (46.87-58.07)
Elective nodal volume	48.23 (46.87-52.03)	48.42 (46.98-51.54)	47.61 (46.54-52.58)
Bladder	29.68 (26.55-35.92)	30.5 (25.71-34.58)	28.52 (19.40-33.80)
Rectum	25.74 (20.72-28.99)	26.24 (20.89-30.63)	24.36 (20.42-29.24)
Right femoral head	27.33 (20.27-34.50)	22.86 (17.60-29.21)	20.75 (12.88-34.25)
Left femoral head	27.41 (21.97-33.54)	25.08 (18.79-33.75)	17.30 (11.64-30.53)
Bowel	12.78 (5.01-22.39)	7.39 (4.17-12.58)	4.98 (0.48-13.47)

OAR, organs at risk; RTOG_ENV, Radiation Therapy Oncology Group guidelines–based elective nodal volume; SLN_ENV, sentinel lymph node elective nodal volume; TX_ENV, elective nodal volume generated using RTOG guidelines plus the SLN and a 7-mm margin.

pain may have been due to the fiducial placement. No episodes of fever, hematuria, hematospermia, and rectal bleeding were reported. In regard to RT, no grade 3 or higher acute gastrointestinal or genitourinary toxicity were noted.

Discussion

In our study, we determined the feasibility and dosimetric consequences of incorporating SLN imaging information into IMRT plans for PCa. SLN imaging has low morbidity and resulted in modification of ENV in a significant proportion of cases. Our analyses did not suggest any differences between IMRT plans with Tx_ENV versus those with RTOG_ENV. However, plans using SLN_ENV exhibited lower bowel and femoral head doses. Overall, SLN guided IMRT is feasible with minimal dosimetric impact except to bowel and femoral heads. The clinical significance of dose differences to these structures remains to be clarified with further follow-up.

This study importantly demonstrates that SLN guided IMRT should likely have toxicity profiles similar to that

seen in prior studies using WPRT and a four-field RT technique. From RTOG 9413, only an increased rate of late gastrointestinal toxicity ≥ 3 was seen with WPRT + neoadjuvant hormone therapy.¹⁴ In RTOG 9413, the ENV included the standard consensus RTOG nodal regions, but SLN guided IMRT would incorporate Tx_ENV that could be larger than RTOG-based ENV. This could result in larger bowel aV45. However, IMRT can provide superior dose sparing to OARs and thus potentially decrease toxicities.^{15,16} On the other hand, if only SLNs are irradiated, then lower bowel doses would be expected. Therefore, application of SLN imaging guided IMRT would likely result in a comparable if not lower toxicity profile than that seen in RTOG 9413.

Additionally, some argue that current patients may have lower LNI than historical cohorts.¹⁷ Hence, elective pelvic RT to large ENV may not be needed. In our study, IMRT plans covering SLN_ENV address the likely areas of LNI while reducing bowel and femoral head doses. Nonetheless, such an approach may not be ideal because there is an increased chance of involved non-SLNs in the same drainage region when positive SLNs were detected in surgical series.¹⁸

Table 3 Median difference in mean dose between plans for target or OAR

Target/OAR	Tx vs RTOG	Tx vs SLN	RTOG vs SLN
Prostate	0.05 (–1.94 to 0.80)	–0.08 (–1.51 to 0.50)	0.04 (–1.24 to 0.84)
Seminal vesicle	–0.23 (–1.35 to 0.72) <i>P</i> > .05	–0.40 (–1.15 to 0.52) <i>P</i> = .019	–0.05 (–0.96 to 0.53) <i>P</i> > .05
Elective nodal volume	0.12 (–1.09 to 0.94)	0.39 (–0.70 to 3.81)	0.52 (–1.04 to 3.87)
Bladder	–0.53 (–1.10 to 1.32) <i>P</i> > .05	1.49 (0.36-7.15) <i>P</i> < .01	1.82 (0.57-6.31) <i>P</i> < .01
Rectum	–0.85 (–2.41 to 1.01) <i>P</i> > .05	0.51 (–1.02 to 2.86) <i>P</i> > .05	1.62 (–0.25 to 3.66) <i>P</i> < .01
Right femoral head	3.72 (2.33-11.64) <i>P</i> > .05	7.98 (–2.39 to 11.17) <i>P</i> < .013	3.05 (–5.04 to 7.62) <i>P</i> > .05
Left femoral head	3.31 (–2.12 to 5.41) <i>P</i> > .05	7.53 (1.10-12.42) <i>P</i> < .013	5.00 (2.83-7.90) <i>P</i> = .026
Bowel	4.80 (–0.22 to 12.80) <i>P</i> > .05	8.89 (–2.79 to 14.61) <i>P</i> < .01	2.15 (–2.56 to 6.71) <i>P</i> > .05

OAR, organs at risk. *P* values reflect differences between the largest nodal volume generated (Tx) vs the Radiation Therapy Oncology Group recommended (RTOG); Tx vs sentinel lymph node only volume (SLN); and RTOG vs SLN, respectively.

Table 4 Pairwise dose differences among plans^a

Target/OAR	Mean dose			Maximum dose			Minimum dose		
	Tx vs RTOG	TX vs SLN	RTOG vs SLN	Tx vs RTOG	TX vs SLN	RTOG vs SLN	Tx vs RTOG	TX vs SLN	RTOG vs SLN
Prostate						X			
SV		X							
LN					X	X		X	X
Bladder		X	X					X	X
Rectum			X			X		X	
Right Femoral Head		X			X			X	
Left Femoral Head		X	X		X	X		X	
Bowel		X			X	X		X	

LN, lymph node; RTOG, Radiation Therapy Oncology Group; RTOG_ENV, RTOG-based elective nodal volume; RTOG vs SLN, dose from plan with RTOG_ENV minus dose from plan with SLN_ENV; SLN_ENV, sentinel lymph node only volume; SV, seminal vesicles; Tx_ENV, treated elective nodal volume; Tx vs RTOG, dose from plan with Tx_ENV minus dose from plan with RTOG_ENV; Tx vs SLN, dose from plan with Tx_ENV minus dose from plan with SLN_ENV.

^a Statistically significant comparisons are marked with X. $P < .05$.

Our rates of SLN involvement are somewhat different in comparison to prior studies.^{8,15,19} Ganswindt and co-workers found common iliac and para-aortic SLNs in about

48% and 23% to 25% of patients, respectively.¹⁹ However, we observed a higher proportion of SLNs in the common iliacs (50%) and para-aortics (50%). Factors that may have

Table 5 Dose-volume histogram parameter comparison for critical structures

	Tx vs RTOG	Tx vs SLN	RTOG vs SLN
Bladder			
rV50 (%)	NS	NS	NS
rV45 (%)	NS	NS	NS
rV40 (%)	NS	NS	NS
aV40 (mL)	NS	NS	NS
Rectum			
rV50 (%)	NS	NS	NS
rV45 (%)	NS	NS	NS
rV20 (%)	NS	NS	NS
aV20 (mL)	NS	NS	NS
Right femoral head			
rV50 (%)	NS	NS	NS
aV50 (mL)	NS	NS	NS
rV20 (%)	NS	29.57 (−0.60 to 86.93%) $P < .01$	NS
aV20 (mL)	NS	25.20 (−0.45 to 74.78) $P < .01$	NS
Left femoral head			
rV50 (%)	NS	NS	NS
aV50 (mL)	NS	NS	NS
rV20 (%)	NS	40.70 (11.06-85.90%) $P < .01$	26.76 (0.28-85.96%) $P = .019$
aV20 (mL)	NS	33.89 (−0.08 to 64.30) $P < .01$	NS
Bowel			
aV50 (mL)	NS	0.95 (0-28.14) $P = .037$	0.67 (0-20.39) $P = .037$
aV45 (mL)	NS	59.15 (8.15-117.26) $P < .01$	43.99 (2.88-104.27) $P = .019$

Median difference and range shown for each dosimetric parameter. Values are only shown for those with statistically significant differences.

NS, not significant; RTOG, Radiation Therapy Oncology Group; RTOG_ENV, RTOG-based elective nodal volume; SLN_ENV, sentinel lymph node only volume; Tx_ENV, treated elective nodal volume; Tx vs RTOG, dose from plan with Tx_ENV minus dose from plan with RTOG_ENV; Tx vs SLN, dose from plan with Tx_ENV minus dose from plan with SLN_ENV.

contributed to this difference include our smaller sample size of 10 versus their 61 patients and their inclusion of 10% patients having Gleason score of 6 or less. Also, our alternative technique using ^{99m}Tc -sulfur nanocolloid for prostate lymphoscintigraphy rather than the ^{99m}Tc -Nanocoll may have resulted in a different tracer distribution. Nonetheless, our ultimate conclusions were similar. In our study, 70% of patients would have inadequate coverage of all identified SLNs, which is comparable to a prior study.¹⁵

Few studies incorporate SLN imaging into RT planning. One approach involves a SPECT-derived atlas for SLNs.¹⁹ This atlas can be used to modify or enhance RTOG-based consensus nodal volumes. Alternatively, an IMRT approach treating patients in the prone position and using a clinical target volume that receives 50 Gy that was expanded to include identified SLNs was proposed. Seven SLNs were not included to avoid an “unacceptable” increase in treatment volume.¹⁵ Although our technique differed in patient positioning, our treatment inclusion of SLNs and findings are similar. Nonetheless, both our study and prior studies have been small in regard to patient number and will need further validation.

Another limitation is that SLN imaging cannot confirm pathological LNI. Preoperative SLN imaging has found false-positive nodal staging.²⁰ In a more recent report, preoperative SLN imaging led to a false-negative rate of 10%.²¹ Nonetheless, in a larger study of high-risk PCa patients, SLN imaging had a positive predictive value of 72.3% and a negative predictive value of 98.5%.¹⁸ Therefore, SLN imaging has potential to detect LNI, but given the variability of published results, another diagnostic modality may be needed to help confirm the presence of LNI.

Conclusions

Several contouring guidelines have been suggested, most recently by the Royal Marsden Hospital,²² but no existing guideline incorporates patient-specific nodal drainage pathways. The RTOG-based guidelines result in nodal volumes that may omit critical drainage pathways in some patients. Despite enlarging the elective pelvic nodal region in a significant proportion of cases, SLN-guided RT (Tx_ENV) is feasible with no significant difference in doses to OARs. Toxicity from SLN guided IMRT should be comparable to current standard RTOG-based IMRT plans. In fact, in select cases with bowel comorbidities, SLN-only RT may offer lower bowel doses. The results warrant further follow-up and future consideration for clinical trials to compare the long-term efficacy of SLN-guided RT with standard treatment fields.

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