Brief Correspondence

Oncologic Outcomes of Template Versus Radioguided Salvage Lymph Node Dissection for Node-only Recurrent Prostate Cancer on Prostate-specific Membrane Antigen Positron Emission Tomography Scan: Results from a Multi-institutional Collaboration

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Abstract

In patients treated with salvage lymph node dissection (sLND) for nodal recurrence of prostate cancer, whether radioguided surgery (RGS) might improve oncologic outcomes as compared with template sLND remains unknown. This study included 259 patients who experienced a prostate specific antigen (PSA) rise and nodal only recurrence after radical prostatectomy and underwent pelvic sLND at 11 tertiary referral centers between 2012 and 2022. Lymph node recurrence was documented by prostate specific mem brane antigen positron emission tomography scans. The outcomes included biochemical

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Prostate-specific membrane antigen positron emission tomography

recurrence (BCR) and clinical recurrence (CR) after sLND. The probability of freedom from each outcome was calculated using Kaplan Meier analyses. A Cox regression anal ysis was used to test the hypothesis that surgical technique for sLND (template vs RGS) might be associated with oncologic outcomes. Overall, 80 (31%) and 179 (69%) patients received template and radioguided sLND, respectively. PSA level at sLND was higher in the template than in the radioguided group (median: 1.3 vs 0.6 ng/ml; $p < 0.0001$), whereas the number of positive nodes on final pathology did not differ between the groups ($p = 0.13$). The first postoperative PSA level was higher in the template than in the radioguided group (median: 0.5 vs 0.1 ng/ml; $p < 0.0001$). Overall, there were 181 cases of BCR and 76 cases of CR after sLND. The median follow up for survivors was 21 mo (interquartile range: 7, 36). The 2 yr BCR free survival rate for patients in the template versus RGS sLND group was 18% (95% confidence interval [CI]: 9%, 29%) versus 30% (95% CI: 22%, 37%). The 2 yr CR free survival rate for the template versus RGS sLND group was 51% (95% CI: 35%, 65%) versus 73% (95% CI: 65%, 80%). On multivariable anal yses, we did not find evidence of a statistically significant difference between the groups with respect to BCR after sLND ($p = 0.7$), whereas men treated with RGS had a lower risk of CR after sLND than those receiving template sLND (hazard ratio: 0.51; 95% CI: 0.29, 0.92; $p < 0.026$). Results of the sensitivity analyses were generally consistent with our main findings. Our data suggest that, in men with node recurrent prostate cancer treated with sLND, RGS may offer important surgical guidance for surgeons, and this may even tually translate into improved oncologic outcomes. Awaiting further evidence on long term outcomes of RGS, our study represents the most solid comparative data on different techniques for sLND and provides relevant data for counseling patients with node only recurrent prostate cancer.

ADVANCING PRACTICE

What does this study add?

In patients treated with salvage lymph node dissection (sLND) for nodal recurrence of prostate cancer, surgical guidance through dedicated probes, that is, radioguided surgery, has shown great potential in assisting surgeons to precisely identify and dissect the targeted area, but whether this implementation might translate into better oncologic outcomes remains controversial. First of its kind, our study compared oncologic outcomes in patients with node-recurrent prostate cancer who underwent sLND using either a template-based approach or radioguided surgery. We found that, as compared with traditional template dissection, patients treated with radioguided surgery had better short-term oncologic outcomes, especially with respect to clinical recurrence–free survival after sLND. Awaiting studies with longer follow-up, our study represents the most solid comparative data on different techniques for sLND and provides relevant data for counseling patients with node-only recurrent prostate cancer.

Patient Summary

We compared oncologic outcomes of patients treated with template versus radioguided surgery (RGS) salvage lymph node dissection (sLND) for node-recurrent prostate cancer. Awaiting data on long-term follow-up, our results suggest that oncologic outcomes after sLND might be improved by RGS as compared with template sLND.

In men with node-only recurrent prostate cancer after primary treatment, salvage lymph node dissection (sLND) is among potential treatment options [1,2]. After the initial enthusiasm surrounding this treatment modality, concerns have risen after long-term data showed suboptimal cancer control [3]. Among possible explanations, sLND has historically been performed as a template dissection procedure when restaging scans detect recurrence restricted to the lymph nodes. However, given the limitations of restaging imaging, sLND remained limited by a non-negligible rate of negative findings on final pathology [4]. With the growing utilization of more accurate restaging modalities such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans [5], it has been proposed that this may also improve the accuracy of sLND by guiding surgeons in the dissection of truly positive nodes. The outcomes might even be further enhanced with intraoperative PSMA-sensitive probes, that is, radioguided surgery (RGS). This implementation showed promising results [6,7], but whether it might improve oncologic outcomes of sLND as compared with template sLND remains unknown. For this reason, we tested the hypothesis that the surgical technique utilized for sLND (template vs RGS) might be associated with oncologic outcomes after sLND.

We retrospectively analyzed the data of 339 patients with two or fewer pelvic lymph-node recurrence(s) of prostate cancer after radical prostatectomy, documented on a PSMA PET scan, and treated with pelvic sLND at 11 institutions between 2012 and 2022. No retroperitoneal lymph node dissections were included. Similarly, no patient with evidence of bone metastases was included. We excluded patients with prostate-specific antigen (PSA) at sLND of >4 ng/ml (n = 35), who were on androgen deprivation therapy at the time of the PET scan (n = 2) or who had missing covariates (n = 43), resulting in 259 patients eligible for the analyses (Supplementary Fig. 1).

Patients were stratified in two groups according to the surgical strategy utilized for sLND, either template sLND or sLND using RGS. Template sLND included bilateral excision of the external iliac, obturator, internal iliac, common iliac, and presacral nodes [3,8,9]. With respect to RGS, a gamma probe for open (Crystal Probe CXS-SG603; Crystal Photonics, Berlin, Germany) or robotic surgery (Drop-in probe CXS-OP-DP by Crystal Photonics, or SENSEI probe by Lightpoint, a Telix Pharmaceuticals Company, London, UK) was used. For radiolabeling, ^{111}In-PSMA-I&T, ^{99m}Tc-PSMA-I&S, or ^{99m}Tc-MIP-1404 was used; there was no fluorescence labeling. In case of recurrent tumor within the extended pelvic lymph node dissection template, RGS was performed for the entire extended template of the affected side, and in some cases, also for the contralateral extended template if deemed necessary according to the surgeon's discretion [6,7]. In vivo and ex vivo measurements were performed with a gamma probe; if no elevated radioactivity was obtained on ex vivo measurements (at least twice the background), further resection and in vivo measurements within the extended template were triggered. For suspicious lesions located elsewhere (eg, pararectal), resection of the corresponding region with surrounding tissue was performed. Additional therapies after sLND included radiation and androgen deprivation therapy. Biochemical recurrence (BCR) was defined as a PSA level of $\geq$0.2 ng/ml and rising. Clinical recurrence (CR) was defined as positive imaging in the presence of a rising PSA level in two consecutive measurements.

Kaplan-Meier curves assessed BCR- and CR-free survival rates, stratified by the surgical technique. Multivariable Cox regression models assessed whether the surgical technique was associated with BCR and CR after sLND. The adjustment for case-mix included the following variables that were selected a priori: International Society of Urological Pathology grade at radical prostatectomy, PSA level at sLND, age at sLND, number of nodes removed at sLND, number of positive nodes at sLND (0 vs 1–2 vs 3+), PSA response after sLND (continuous), and administration of additional therapies within 6 mo after sLND (no vs yes). This temporal window

Table 1 Baseline characteristics of 259 patients with node-only recurrent prostate cancer on PSMA PET treated with radioguided versus template salvage lymph node dissection

	Template sLND (*N* 80; 31%)	Radioguided surgery (*N* 179; 69%)	*p* value
ISUP group at RP, *n* (%)			
1	9 (11)	11 (6.1)	0.3
2	19 (24)	51 (28)	
3	28 (35)	76 (42)	
4	11 (14)	14 (7.8)	
5	13 (16)	27 (15)	
pT stage at RP, *n* (%)			
pT2	35 (44)	74 (41)	0.14
pT3a	30 (38)	55 (31)	
pT3b	13 (16)	50 (28)	
Unknown	2 (2)	–	
pN stage at RP, *n* (%)			
pN0	53 (66)	143 (80)	0.022
pN1	8 (10)	27 (15)	
pNx	11 (14)	9 (5)	
Unknown	8 (10)	–	
Radiotherapy after RP, *n* (%)	45 (56)	101 (56)	0.10
Unknown	14 (18)	–	
Age at sLND (yr)	68 (62, 71)	66 (60, 70)	0.15
PSA at sLND (ng/ml)	1.3 (0.7, 2.3)	0.6 (0.3, 1.2)	<0.0001
Number of positive PET spots, *n* (%)			
1	62 (78)	136 (76)	0.8
2	18 (22)	43 (24)	
Number of nodes removed at sLND	10 (5, 22)	13 (8, 19)	0.2
Number of positive nodes at sLND, *n* (%)			
0	23 (29)	46 (26)	0.3
1–2	43 (54)	86 (48)	
3+	14 (18)	47 (26)	
First PSA after sLND	0.5 (0.1, 1.4)	0.1 (0.0, 0.3)	<0.0001
First PSA <0.1 ng/ml after sLND, *n* (%)	17 (21)	96 (54)	<0.0001
Additional therapies after sLND, *n* (%)	12 (15)	8 (4)	0.003

ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; sLND = salvage lymph node dissection.
All numbers are frequencies (proportions) and medians (interquartile range).

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was chosen to reproduce a multimodal treatment strategy delivered right after surgery, according to a previously defined cutoff [10]. Since data from different institutions are correlated, we incorporated institution clustering in our analysis using the *cluster* option in Stata statistical software. Finally, we performed sensitivity analyses to assess the robustness of our findings.

Overall, 80 (31%) and 179 (69%) patients in our cohort received template and radioguided sLND, respectively (Table 1). While disease characteristics at radical prostatectomy did not differ between the groups, PSA level at sLND was higher in the template than in the radioguided group (median: 1.3 vs 0.6 ng/ml; $p < 0.0001$). The distribution of positive spots on the PSMA PET scan, total number of nodes removed, and positive nodes on sLND pathology did not differ between the groups (all $p \geq 0.13$). As compared with the patients treated with template sLND, the first PSA level after sLND was lower for those in the RGS group (median 0.1 vs 0.5 ng/ml; $p < 0.0001$). The rate of additional therapies after sLND was significantly higher in the template than in the RGS group (15% vs 4%; $p = 0.003$).

Overall, there were 181 cases of BCR and 76 cases of CR after sLND. The median follow-up for survivors in the template versus RGS group was 7 (interquartile range [IQR]: 2, 17) mo versus 24 (IQR: 12, 41) mo. The 2-yr BCR-free survival rate for patients in the template versus RGS sLND group was 18% (95% confidence interval [CI]: 9%, 29%) versus 30% (95% CI: 22%, 37%; Supplementary Fig. 2). The 2-yr CR-free survival rate for the template versus RGS sLND group was 51% (95% CI: 35%, 65%) versus 73% (95% CI: 65%, 80%; Fig. 1).

On multivariable analyses, we did not find evidence of a statistically significant difference for BCR after sLND between patients treated with template and RGS sLND (hazard ratio [HR]: 1.15; 95% CI: 0.57, 2.33; $p = 0.7$; Supplementary Table 1). As compared with men who received template sLND, those treated with RGS had a lower risk of CR (HR: 0.51; 95% CI: 0.29, 0.92; $p = 0.026$; Supplementary Table 1). Results of the sensitivity analyses were generally consistent with our main findings (Supplementary Table 2).

Our study suggests that men receiving sLND with RGS might have better oncologic outcomes than those undergoing traditional template sLND. These findings may have several explanations.

Although surgical innovations are often appealing, what has the potential to establish a new standard of care is ultimately determined by improvement of outcomes. While many implementations in the field of urologic surgery showed promising results, their widespread adoption was often limited by the lack of relevant changes in outcomes. RGS for node-recurrent prostate cancer could probably be perceived as one of these. Now, our data suggest that RGS might not only represent an innovative solution for surgeons, but also improve outcomes of patients treated with sLND. This might be a consequence of the advantages offered to the operating surgeon, such as the possibility to modify surgical template in case of additional positive findings in adjacent tissue—especially during immediate ex vivo

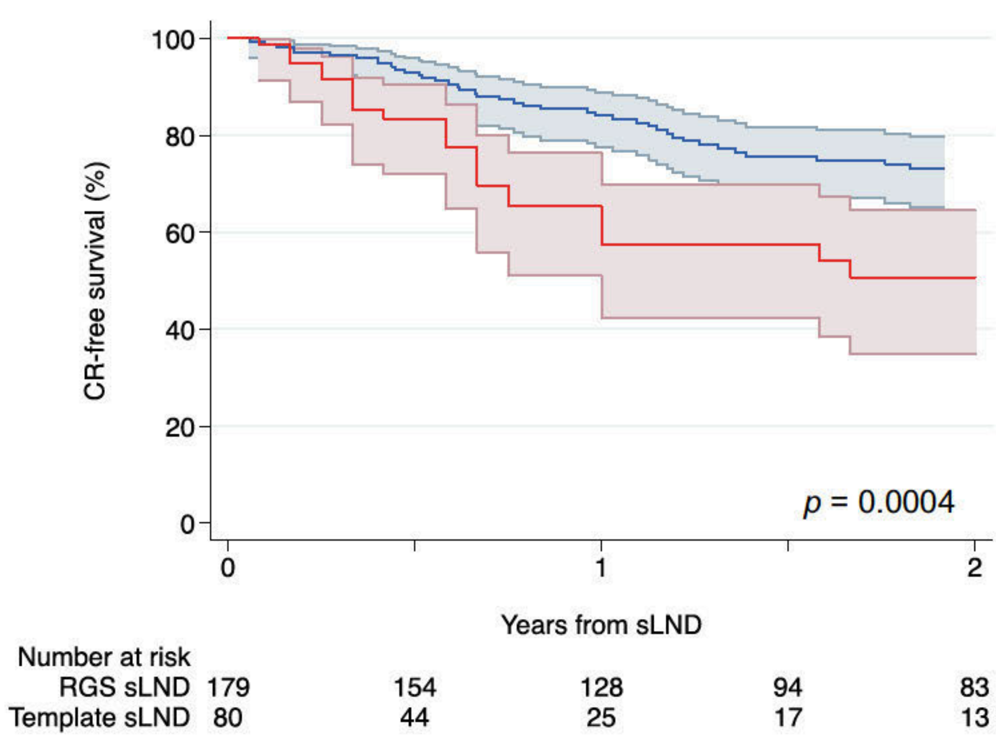

Fig. 1 – Kaplan-Meier curve assessing clinical recurrence–free survival (and 95% confidence interval) between template and radioguided sLND for 259 patients with node-only recurrent prostate cancer documented on a PSMA PET scan. Blue color represents radioguided sLND and red template sLND. The *p* value from log-rank test is 0.0004. CR = clinical recurrence; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery; sLND = salvage lymph node dissection.

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measurements—or to continue surgical dissection in case of a negative signal by gamma probe measurements. That said, these results should also be commensurate with the short follow-up of our study as we previously found that long-term outcomes of sLND might be suboptimal [3]. Another possible limitation pertains to the administration of adjuvant treatment that, given the multi-institutional nature of our study, might have differed between centers. However, this parameter was included in our multivariable adjustment, and results of sensitivity analyses after the exclusion of patients who received additional treatments after sLND were consistent with our main findings. The retrospective nature of our study represents another limitation, resulting in possible unmeasured confounding. For instance, the fact that template sLND was performed at different centers might have translated into different lymph node yields on final pathology. To address this issue, we have run sensitivity analyses including the number of lymph nodes removed on sLND, with no difference with our main results. We have also investigated whether baseline characteristics were different between men with available and missing covariates, with no significant discrepancy (Supplementary Table 3). Finally, we have to acknowledge that, for some men in the RGS group, resection was extended to nonregional lymph nodes (eg, pararectal), raising concerns about a selection bias. Yet, our data suggested better CR-free survival for patients in the RGS group than in the template sLND group. As for prior papers [10], any selection bias in the study would operate in the opposite direction to our findings, and as such, we are positive that this factor did not affect our findings significantly.

In conclusion, our data suggest that, in candidates for sLND for node-only recurrent prostate cancer, RGS might offer important surgical guidance for surgeons, and this may eventually translate into improved oncologic outcomes. Awaiting further evidence on long-term outcomes of RGS, our findings represent the first multicentric comparative evidence on different techniques for sLND and provide relevant data for counseling patients with node-only recurrent prostate cancer.

Author contributions: Carlo Andrea Bravi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bravi, Knipper, Maurer.
Acquisition of data: Bravi, Knipper, Fossati, Gandaglia, Dell'Oglio, Suardi, Osmonov, Juenemann, Kretschmer, Budäus, Falkenbach, Buchner, Stief, Hiester, Devos.
Analysis and interpretation of data: Bravi, Knipper, Maurer.
Drafting of the manuscript: Bravi, Knipper, Maurer.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2025.05.019.

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