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ORIGINAL ARTICLE

Oncological outcome of patients treated with spot-specific salvage lymphnode dissection (sLND) for positron-emission tomography (PET)-positive prostate cancer (PCa) relapse

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Abstract

Objectives To report pre-, postoperative and oncological outcomes in patients treated with spot-specific sLND for patients with exclusive nodal recurrence after PCa primary treatment.

Materials and methods With regard to salvage treatment failure (sTF), 46 consecutive patients, undergoing 52 sLND for nodal recurrence detected by PET/CT scan were stratified in 3 groups (group A: post-sLND PSA nadir < 0.01 ng/ml and in follow-up reaching a value > 0.2 ng/ml, group B: post-sLND PSA nadir > 0.01 ng/ml and in follow-up reaching a value equal to pre-sLND PSA; group C: additional salvage treatment administration). Surgical outcome of patients was analyzed by descriptive statistics (Student's *t* test for continuous variables, Chi-square and Fisher's test for categorial ones). Time to sTF of each group was analyzed and compared by Kaplan–Meier method and correlations regarding sTF and pre-sLND PSA, time from PCa primary treatment to PET/CT scan, time from PCa primary treatment to sLND and number of positive PET/CT scan spots were assessed.

Results Median PSA at PET/CT scan was 2.9 ng/ml (IQR 1.2–6.1). Open and laparoscopic sLND were performed in 40/52 (77%) and 12/52 (23%), respectively. Median number of removed lymph nodes was 6 (IQR 4–13). Histological report was positive for PCa in 39/52 sLND (75%). Median blood loss was 50 ml (IQR 0–50, range 0–600). Median length of hospital stay was 5 days (IQR 4–6). 4 and 7 patients had low-grade (I/II) and high-grade (≥ III) Clavien–Dindo complications, respectively. Readmission rates at 30 and 90 days were 5/52 (9.6%) and 1/52 (2%), respectively. sTF was observed in 2/7 (group A), 12/12 (group B) and 22/22 patients (group C). Median time to sTF in group B and C was 3.5 (IQR 1.7–13.2) and 4 months (IQR 2.0–10), respectively.

Conclusion Even spot-specific PET/CT sLND harbors a measurable (CD > III) morbidity in 1 out of 7 patients. Only patients with positive histological report and a PSA nadir < 0.01 ng/ml after sLND seem to experience a long-term benefit. Patients with a PSA nadir > 0.01 ng/ml have a delay of systemic treatment of up to 4 months. sLND remains an experimental approach and long-term oncological benefit needs an improved selection of patients.

Keywords Prostate cancer · Nodal recurrence · Salvage surgery · PET/CT scan

Introduction

Among men treated with radical prostatectomy (RP), up to 50% have been reported to develop biochemical recurrence (BCR) [1], although, clinical recurrence occurs only in 14% of them at a 25-year follow-up [2]. The recent introduction of radiotracer imaging techniques has allowed to increase accuracy of recurrence identification, even at low PSA values [3, 4]. This is of utmost importance, since published clinical series have shown that in selected patients, salvage lymph node dissection (sLND) could lead to an

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improvement of oncologic outcomes and quality of life by delaying the time to ADT administration, with an acceptable safety profile [5–7]. The potential therapeutic role of sLND has also been recently acknowledged by European Association of Urology Guidelines on Prostate Cancer [8]. However, due to several factors, including inconsistent use of multimodal therapies, the absence of standardization regarding endpoint definitions and sLND templates, discrepancies in patient characteristics and treatment regimens among published studies, it is difficult to prove the efficacy of sLND on oncological outcomes and its impact on survival. Therefore, the aim of the present study was to describe perioperative and oncological outcomes of patients treated with spot-specific sLND for exclusive nodal relapse at PET/CT scan after PCa primary treatment.

Materials and methods

Study population

After institutional review board approval, we prospectively identified 46 consecutive patients with BCR (defined as two consecutive total PSA values > 0.2 ng/ml, in the same laboratory) after curative primary PCa treatment and nodal uptake at PET/CT scan, treated with sLND at a single tertiary referral center. After primary treatment, total PSA was systematically monitored every 3 months. Patients underwent PET/CT scan (11C-choline; Ga68-PSMA 11C-acetate; 18F-FDG; Ga68-Bombesin), once BCR was assessed. All patients presented at least one nodal single uptake. After sLND, PSA values were measured systemically every 3 months (Fig. 1).

Surgical technique

After identification of the PET/CT-positive area, a "spot-specific" approach was performed. "Spot-specific" was defined as an anatomical template nodal dissection of the nodal stations corresponding to the anatomical area, where the PET/CT signal was identified, only. Anatomical templates were described as common iliac region, external iliac region, internal iliac region, obturator region, presacral region and retroperitoneal region.

Covariates and outcomes

Complete preoperative and pathologic data, namely data on pathologic disease characteristics at primary treatment, age at sLND, PSA at sLND, time to BCR after primary treatment, use of adjuvant and/or salvage therapies after RP, and site and number of the positive PET/CT scan spots were documented for each patient. Perioperative outcomes were defined as operative time, blood loss, intraoperative complications, length of hospital stay (LoS) and postoperative complications (categorized according to the Clavien–Dindo classification [9]). Readmission and mortality rates at 30 and 90 days after sLND were recorded, as well as follow-up after sLND (PSA values, imaging, death).

Salvage treatment failure (sTF) represented the oncologic outcome after surgery and was defined differently according to post-operative total PSA-nadir value. Group A consisted of those patients whose PSA nadir after sLND was < 0.01 ng/ml and sTF was defined by a PSA value > 0.2 ng/ml. When post-sLND PSA nadir was > 0.01 ng/ml, sTF was defined as a post-operative PSA value equal to the preoperative PSA value (Group B) or, any additional salvage PCa therapy was administered (Group C).

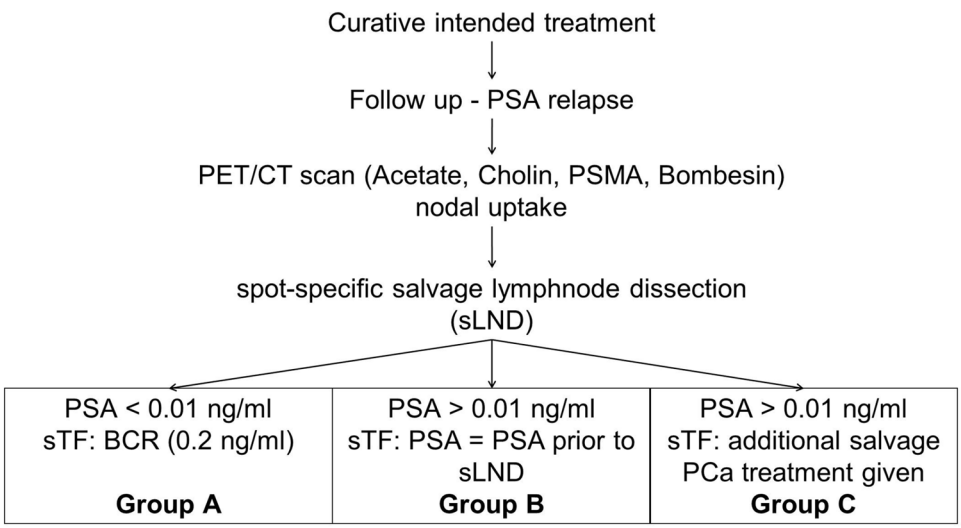

Fig. 1 Study workflow

Statistical analyses

Statistical analyses, as well as reporting and interpretation of the results consisted of three steps: first descriptive analyses were used to assess features of each group (A, B, C). Frequencies and proportions were reported for categorical variables. Means, medians and interquartile ranges (IQR) were reported for continuously coded variables. Second, Kaplan–Meier method was used to assess features of each group (A, B, C). Third, Student's *t* test was used to compare means. Fourth, linear correlations between sTF and pre-sLND PSA values, time from PCa primary treatment and PET/CT scan, time from primary treatment and sLND and number of PET/CT scan spots were tested. All statistical tests were performed using the SPSS software (Version 22.0. Armonk, NY: IBM Corp.). Statistical significance was set at $p < 0.05$.

Results

Patients' characteristics

Table 1 shows the baseline characteristics of the study population. Between 2009 and 2017, 52 sLNDs were performed in 46 patients. The median age at diagnosis was 66 years. The median PSA value at the time of primary PCa treatment was 18.3 ng/ml. Forty-five patients were treated with radical prostatectomy (RP); one patient underwent brachytherapy. 59% of the patients had extracapsular disease (≥ pT3a), 92% of the patients underwent LND during initial surgery including bilateral external and internal iliac template as well as obturator template, but only 9% had lymph node metastasis. The surgical margins were negative in 68% of the patients undergoing RP. Half of the patients received adjuvant radiotherapy, 26% of patients received ADT for more than 12 months after RP. After initial treatment, PSA values were measured systemically. In case of a BCR, PET/CT scan was performed. Due to implementation in imaging, PET/CT scans were undertaken with 11C-acetate in 22 cases, with 68 Ga-PSMA in 18 cases, with 11-C-choline in 9 cases, with 18F-FDG twice and with Ga68-Bombesin in one patient. All patients had at least one single nodal uptake. The median number of spots on PET/CT scan was 1 (mean 1.3; IQR 1–6). Spot-specific sLND was performed laparoscopically in 23% (12/52) and open in 77% (40/52).

Table 1 Descriptive statistics of baseline characteristics in the overall population

Patients	*N* = 46
sLND	*N* = 52
Age (years)	66 (47–83)
Total PSA at diagnosis (ng/ml)	18.3 (4.5–100)
Gleason score	
6	4 (8%)
7a	14 (30%)
7b	10 (23%)
8	11 (24%)
9	5 (11%)
n/a	2 (4%)
Initial treatment	
Radical prostatectomy (RP)	45 (98%)
Brachytherapy (BT)	1 (2%)
Tumor stage (pT) at primary treatment	
pT1c	1 (2%)
pT2a	3 (6%)
pT2b	2 (4%)
pT2c	13 (28%)
pT3a	10 (22%)
pT3b	17 (37%)
Nodal status at primary treatment (*N*)	
pN0	39 (85%)
pN +	4 (9%)
pNx	3 (6%)
Surgical margins at primary treatment (*R*)	
R0	31 (68%)
R1	12 (26%)
Rx	3 (6%)
Adjuvant radiotherapy	
Yes	23 (50%)
No	23 (50%)
Adjuvant ADT	
Yes	17 (26%)
No	30 (72%)

Surgical outcomes

Median time from primary PCa treatment to sLND was 50 months (IQR 21–102). Median PSA value at sLND was 2.9 ng/ml (IQR 1.2–6.1). Histological report was positive in 39/52 (75%) patients. Median blood loss was 50 ml (IQR 0–50 ml; range 0–600 ml). Median time of hospital stay was 5 days (IQR 4–6).

The median number of lymph nodes removed was 6 (IQR 4–13). The median number of positive lymph nodes removed was 1 (IQR 0–2.7). Considering all 52 PET/CT scans, there were 66 spots being suspicious for nodal recurrence. Overall, 514 lymph nodes were removed and 133 were histologically positive for PCa. The ratio of spots on PET/CT scan to number of positive lymph nodes was 1:2. To evaluate the accuracy of PET/CT scan in detecting each single involved lymph node, a subtraction of the number of histologically positive lymph nodes to the number highlighted positive spots on PET/CT scan was performed and mean was − 1.1, median 0 (IQR − 1; 0). After stratification for the type of

radiotracer, mean missed nodal metastases was − 0.5, − 1.1 and − 1.8 for PSMA, Cholin and other radiotracer, respectively (all p values > 0.2).

The distribution on PET/CT-positive regions and positive histology report in the corresponding region is shown in Fig. 2.

Perioperative outcomes

In 11/52 (21%) sLND, patients experienced complications of any level. Grades I–II Clavien–Dindo were recorded in four cases and grade III or higher Clavien–Dindo in 7 patients (1 in laparoscopic group, Table 2). 30- and 90-day readmission rates were 5/52 (10%) and 1/52 (2%), respectively.

Oncological outcomes

Group A consisted of seven cases. The median PSA value before sLND in Group A was 1.2 ng/ml (IQR 0.3–2.6), two of them had sTF after 8 and 10 months. The median follow-up after sLND was 18 months (IQR 8–55 months). Mean time to sTF in Group A was significantly superior to mean time in Groups B and C together ($p = 0.01$; Fig. 3). Group B consisted of 12 cases. The median PSA value before sLND in Group B was 3.4 ng/ml (IQR 1–18). The median PSA nadir after sLND was 1.4 ng/ml (IQR 0.3–2.6). At a median follow-up of 4 months (IQR 1.7–13.2), all patients had sTF (Fig. 4). Group C consisted of 22 cases. The median PSA value before sLND in Group C was 3.7 ng/ml (IQR 2.4–6.2). Median PSA nadir after sLND was 2.6 ng/ml (IQR 0.9–4.4). At a median follow-up of 4 months (IQR 2.0–10), all patients had sTF (Fig. 5).

21/22 Patients in Group C started an antiandrogen therapy after a median follow-up of 4 months. 10 patients received salvage radiotherapy, 3 patients were treated with chemotherapy and 4 patients underwent additional surgery. Five patients were lost to follow-up.

Correlations between sTF and pre-sLND PSA value, time from primary treatment to PET/CT scan, time from primary treatment to sLND and number of positive nodal PET/CT scan spots are shown in Table 3. In the overall population, no correlation was identified. When considering only Group A, pre-sLND PSA value was significantly correlated with sTF (coefficient = 1; $p < 0.001$).

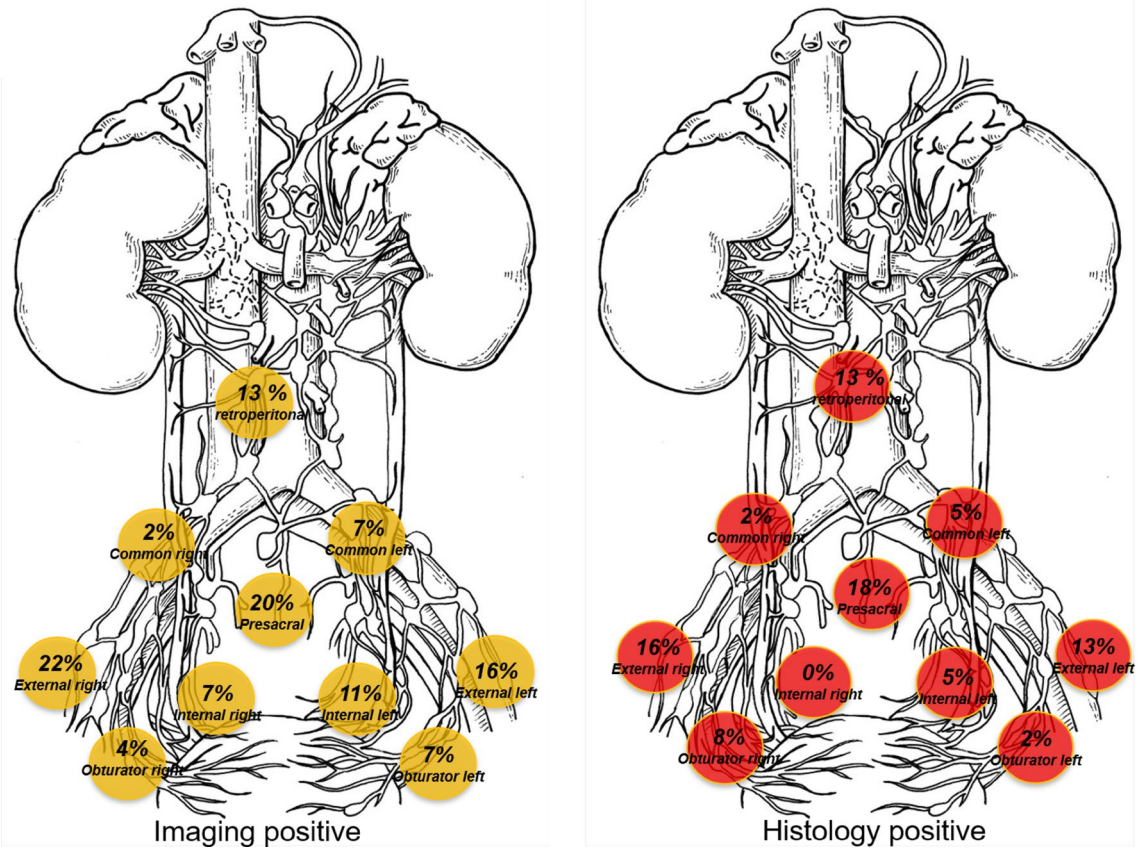

Fig. 2 Distribution of PET/CT-positive spots and positive histology report after sLND; yellow: percentage of patients with PET/CT-positive spots in the respective region; red: percentage of patients with a positive histology report in the PET/CT-positive corresponding region

Table 2 Descriptive statistics of type and rates of complication after classification according to Clavien–Dindo, readmission and mortality rates

Complications	Patients $n = 11$	
Clavien–Dindo		
0	0	–
I	3	Wound infection; lymphocele; subileus
II	1	Blood transfusion
IIIa	3	3 × lymphocele with the need of radiological drainage
IIIb	3	Haematoma with the need of surgical intervention
		Lymphocele with the need of laparoscopic drainage
		Injury of the ureter with ureter re-implantation
IV	1	Cardio pulmonary reanimation (CPR) because of subarachnoidal bleeding
Readmission rate		
30 days	5/52 (10%)	–
90 days	1/52 (2%)	–
MortaliTy	0/52	–

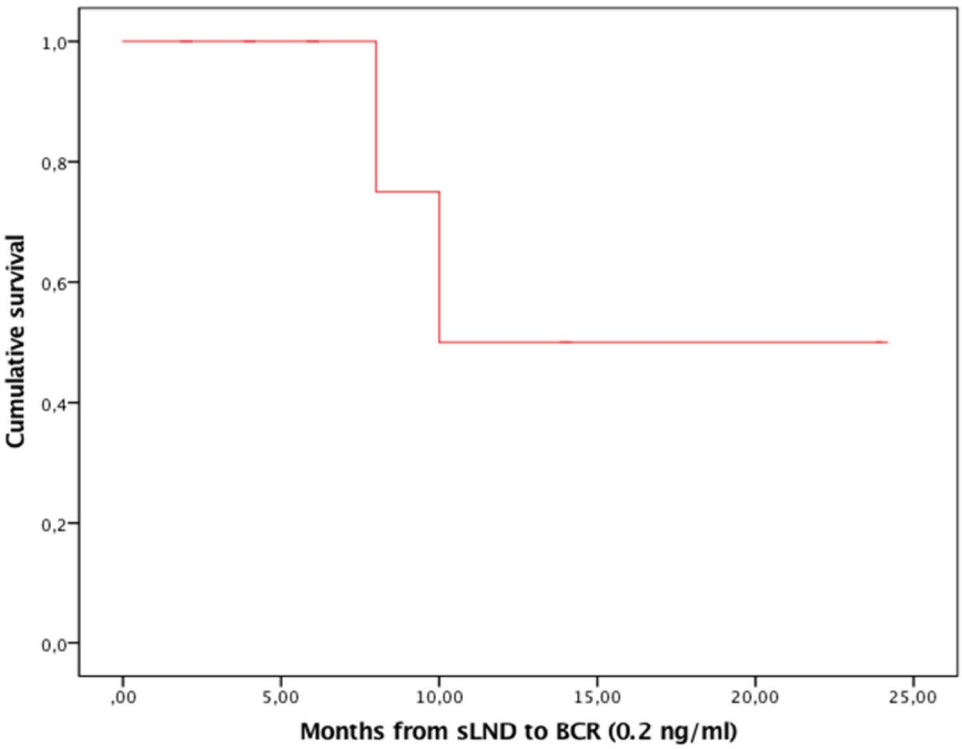

Fig. 3 Kaplan–Meier depicting time to sTF (defined as PSA > 0.2 ng/ml after PSA nadir < 0.01 ng/ml) in Group A

Discussion

sLND has been given the dignity of treatment by EAU guidelines for node-only recurrent PCa patients after primary treatment [8]. Although it can be performed either with open technique [10] or with minimally invasive technique [11], neither the extent of the dissection nor the real oncologic efficacy and its impact on survival have been addressed [8]. This is mainly due to the fact that a clear consensus is lacking on the extent of nodal template at surgery (limited vs. extended [5, 6, 12]), on the oncologic outcome to be awaited (delay in salvage treatment administration vs. complete remission from PCa), and to the fact that the majority of studies are submitting patients to an extent sLND. Moreover, the implementation of new radiotracers through time in the clinical practice and the limited incidence of node-only recurrence after primary treatment have made scientific/clinical evaluation of sLND outcomes more complex. Therefore, we aimed at reporting for the first time an original series of patients with node-only recurrence after primary treatment for PCa treated

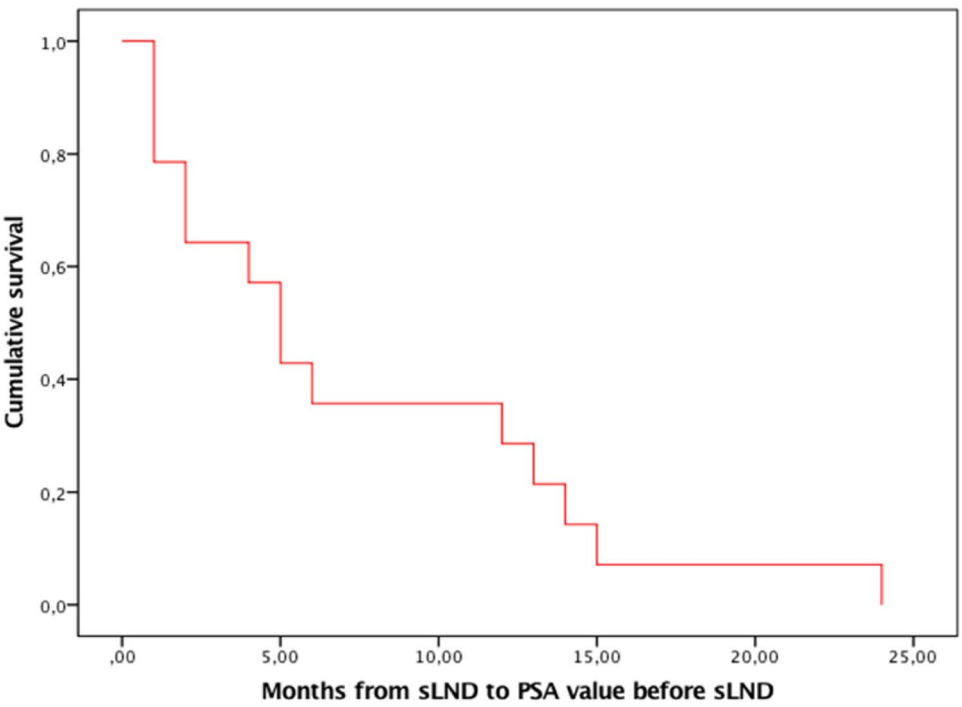

Fig. 4 Kaplan–Maier depicting time to sTF (defined as PSA value after sLND reaching PSA value before sLND) in Group B

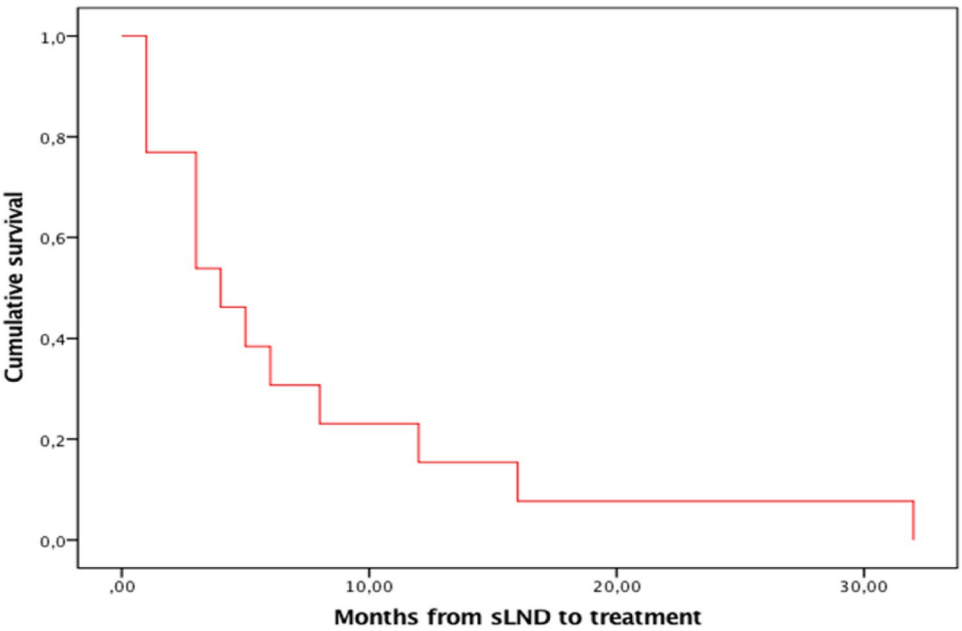

Fig. 5 Kaplan–Maier depicting time to sTF (defined as additional treatment given before PSA value after sLND reached PSA value before sLND) in Group C

Table 3 Correlation of sTF with preoperative PSA values, time from primary PCa treatment to PET/CT scan and time from primary PCa treatment between sLND

	Overall		Group A	
	Pearson's correlation coefficient	*p* value	Pearson's correlation coefficient	*p* value
Pre-sLND PSA	0.28	0.19	1	< 0.001
Time from primary PCa treatment to PET/CT scan	− 0.05	0.8	− 0.18	0.69
Time from PCa primary treatment to sLND	− 0.04	0.8	− 0.16	0.71
Number of PET/CT scan spots	− 0.01	0.9	0.09	0.8

with PET/CT scan spot-specific sLND, to understand if a spot-specific sLND would have the same outcome as an extended sLND.

Several results of our study are noteworthy. First, we reported a high-grade Clavien–Dindo (grade III or higher) perioperative morbidity of 13.5%. A recent paper by Mandel et al. [13], studying salvage RP, found that 12.7% patients are facing Clavien–Dindo grade III or higher complication. When considering studies on open extended sLND, the rate of higher-grade Clavien–Dindo complications was 22% [10], on minimally invasive approach complication rate dropped to 0% [11]. In the subpopulation undergoing laparoscopic limited sLND in the present study, a Clavien–Dindo complication grade III or higher was recorded for 1 patient (IIIb, lymphocele laparoscopic unroofing). Explanation for the outperformance of minimally invasive sLND may be explained by a more careful surgical dissection, better visualization of the operative field and a more accurate selection of the candidates. Taken these figures together, it can be stated that spot-specific sLND yielded a reduced risk of major complication when compared to extended open sLND. Moreover, the rate of postoperative lymphoceles in the present series was seen in 8% of cases which is comparable to reported series of pelvic LND at the time of RP [14–18], inferior to open extended sLND series (35%, lymphorrea and lymphoceles) [10] and similar to minimally invasive approach (12.6%, lymphedema and lymphorrhea) [11]. Taking into account that 94% of the patients underwent LND during initial treatment and 50% of the patients received adjuvant radiotherapy, lymphocele rate in the present series was not unexpectedly high.

Ureteral injuries during pelvic surgery are quite rare [16, 17, 19, 20] with a rate going from 0.5 to 1.5%, as this was the case for our study population (Table 2). Rigatti's [10] and Montorsi's series [11] are both reporting ureter injury in one patient, as in the present series. No specification on vascular lesions was found in open extended sLND [10], while it was reported for 3 patients in minimally invasive series [5]. To sum up, limited sLND harbors a measurable morbidity in 1 out of 7 patients regarding high-grade complications (Clavien–Dindo ≥ III); while the rates of higher-grade complications and intraoperative injuries are different from open and minimally invasive extended sLND, type of complication is comparable.

Secondly, only 5/7 patients with positive histology report and a post-operative PSA nadir of < 0.01 ng/ml were BCR free at a median follow-up of 18 months. Patients with a PSA nadir > 0.01 ng/ml had a delay of systemic treatment of up to 4 months; patients without PSA response did not benefit from sLND. In the current literature, BCR-free survival after extended sLND is reported to range from 19 to 70% at 5-year follow-up [6, 7, 10, 11, 21, 22]. It is difficult to make any comparison due to difference of sLND extent. However, we could evaluate that 1 out of 10 patients who could be candidate for sLND would profit from a limited/spot-specific sLND approach.

Thirdly, nodal uptake at PET/CT scan is underestimating the number of positive lymph nodes also in case of limited sLND. Fossati et al. [23] recently reported the higher the number of spots on preoperative imaging, the higher the number of the positive nodes that are missed by operative imaging and the effect is greater with 11C-Cholin in comparison to 68 Ga-PSMA. This result was used to justify an extended sLND approach. In the present series, PSMA was performing better than Cholin and other radiotracers, although this was not statistically significant. Taking in consideration that 1/10 patients would, however, profit from a limited sLND, we can speculate that instead of suggesting an extended sLND for any patient, PET/CT scan accuracy should be improved. In order to improve the intraoperative detection of positive lymph nodes, a gamma probe for radioguided surgery using Tc-99 m-labeled PSMA was implemented at our institution. This is especially important if PET/CT signals are found outside of the anatomical lymph node regions like in the mesentery of the rectum (Figs. 6, 7).

Despite several strengths, our analyses are not devoid of limitations. First, our report is intrinsically limited by its retrospective and noncomparative nature. Secondly, we could

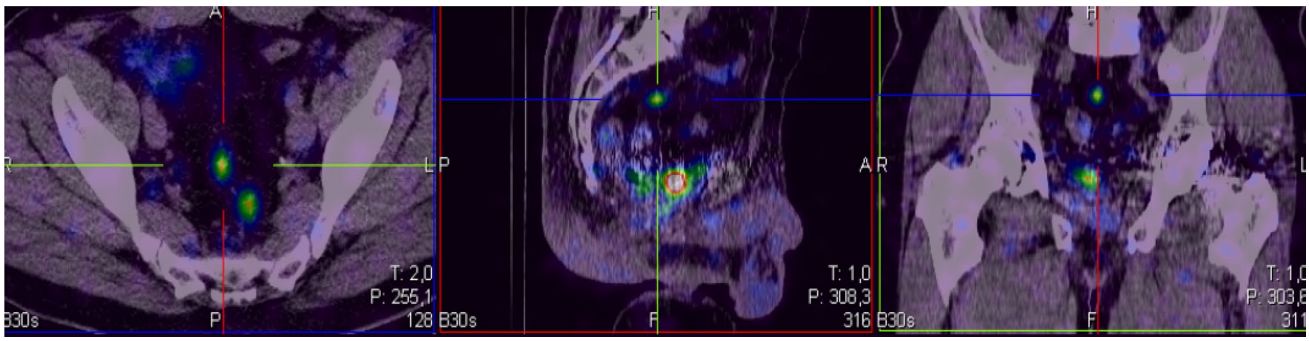

Fig. 6 Pre-operative SPECT/CT with PSMA-Tc99m Pertechnetate from a patient with nodal recurrence of PCa

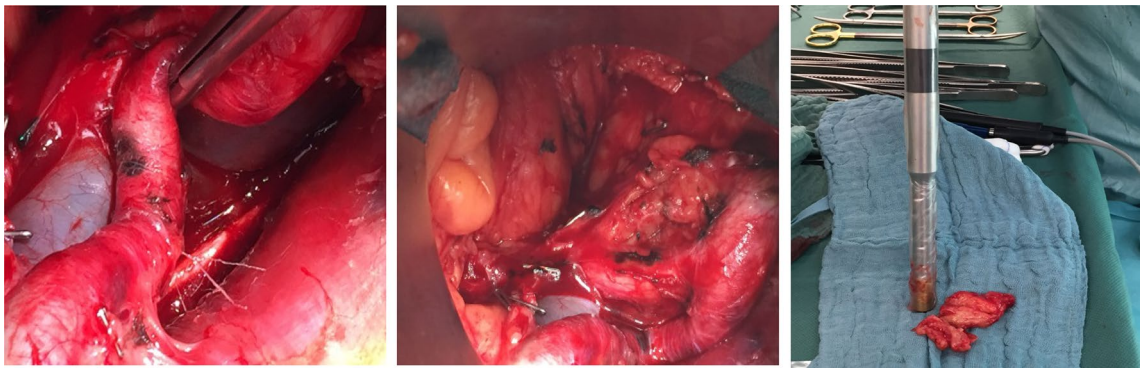

Fig. 7 Intraoperative gamma probe-guided identification of a nodal SPECT/CT positive spot in common iliac nodal station (anatomical references: common iliac vein and artery)

not compare data to a control group of patients treated with extended sLND for node-only recurrence PCa after primary treatment. Moreover, postoperative PET/CT scans in patients with negative histology after sLND and/or persisting PSA were not uniformly performed. So, it cannot be excluded that tumor-positive and PET/CT-negative lymph nodes or PET/CT-positive lymph nodes were not resected within the limited field. Radioguided surgery with PSMA-Technetium labeling may improve this in the future [24]. Nevertheless, our study relied on the largest cohort of PET/CT scan spot-specific sLNDs at a single tertiary care referral center. Moreover, we demonstrated that 10% of patients would benefit from a limited sLND (in terms of PSA response) and by that, they would not have to undergo overtreatment by an extended sLND approach with all the implications of the case. Further multiinstitutional scientific initiatives are needed to validate therapeutic efficacy of sLND and to better select patients for this still experimental surgical approach.

Conclusions

Even spot-specific sLND in PCa patients has a high-grade morbidity in 1/7 patients (Clavien–Dindo ≥ III), at a median follow-up of 18 months, 11% were BCR free and this correlates with low PSA value before surgery. Any tracer used is underestimating the real nodal tumor burden. Multiinstitutional studies are needed to evaluate the optimal extent of sLND template and to improve on the selection of patients. Until then, this approach remains experimental.

Author's contributions AH: project development, data collection/management/analysis, manuscript writing. AN: project development, data collection/management/analysis, manuscript writing. GN: manuscript editing, data analysis. CA: manuscript editing, data analysis. HH: data management PET/CT, manuscript editing. CA: data management PET/CT. LS: data management CT; manuscript editing, data collection. PA: manuscript editing, data collection. RR: manuscript editing, data collection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The current study has been approved by the institutional ethics review board (No. 2014082777).

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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