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Salvage lymph node dissection in hormone-naïve men: How effective is surgery?

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Abstract

Objective: Salvage lymph node dissection (SLND) is still a questionable treatment approach for patients with nodal recurrence of prostate cancer after radical prostatectomy. We assessed the oncological benefit after SLND in hormone-naïve patients as well as the diagnostic accuracy of preoperative prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET/CT) scanning.

Material and methods: The study relied on retrospective collected data of 43 hormone-naïve men who received transperitoneal SLND between February 2011 and March 2017 at our institution. The oncological outcome for each patient was observed by serum prostate-specific antigen testing. Postoperative complications within 30 and 90 days were assessed according to the Clavien-Dindo classification. The accuracy of PSMA PET/CT was characterized by calculated sensitivity, specificity, positive, and negative predictive values.

Results: Overall 8 patients (18.6%) had a complete biochemical response 40 days after SLND. The median time from SLND to biochemical recurrence was 2 months. Adjuvant treatment encompassing radiotherapy, androgen deprivation therapy, or a combination of both, was administrated in 62.8%. According to the Clavien-Dindo classification, no high-grade complications were observed. Sensitivity and specificity for PSMA PET/CT were respectively 32% (95% confidence interval [CI]: 17.21–51.59) and 91.74% (95% CI: 85.45–95.45). Calculated positive predictive values (PPV) and negative predictive values (NPV) of PSMA PET/CT were 44.44% (95% CI: 25.98–64.58) and 86.72% (95% CI: 83.23–89.57).

Conclusions: For most hormone-naïve men with a nodal recurrence of prostate cancer transperitoneal SLND is neither an appropriate treatment to cure nor an option to delay the need for salvage hormone manipulation. PSMA PET/CT scans in hormone-naïve patients are currently too imprecise to diagnose metastatic sites.

Keywords: Prostate cancer; Staging; Hormone-naïve; Salvage lymph node dissection; Salvage therapy

1. Introduction

The treatment of nodal metastatic prostate cancer (CaP) is still challenging. Studies indicate that up to 35% of men undergoing radical prostatectomy (RP) with curative intent will experience biochemical recurrence (BCR) [1]. More importantly, the rate of nodal recurrence is calculated up to 20% in high-risk tumors 10 years after RP, and lymph node (LN) positivity is a surrogate marker for a systematic disease [2,3].

For these patients the administration of androgen deprivation therapy (ADT) was the only guideline-concordant first-line salvage treatment option for years [4]. Its association with significant adverse events (e.g., cardiovascular morbidity and mortality, diabetes, acute kidney injury, fractures, and venous thromboembolism), and its increased risk

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of developing castration-resistant CaP, requires alternative diagnostic and therapeutic pathways [4,5].

Several published studies described salvage LN dissection (SLND) as a potential treatment option that delays the need for salvage ADT. In these retrospective studies, the 5-year BCR-free survival rate and 5-year cancer-specific survival rate range respectively from 6.2% to 29.4%, and from 75% to 89.1% after SLND [6–9]. Adjuvant ADT before SLND was administered in up to 78.7%, which manipulates postoperative oncological outcomes, even when ADT withdrawal was conducted ≥6 months before surgical salvage treatment [7,10].

Established imaging techniques, such as the bone scan and abdominopelvic CT scan showed low diagnostic values in asymptomatic patients with a PSA relapse after RP in terms of differentiation between systematic micrometastasis, local, or nodal CaP recurrence. A Positron Emission Tomography-Computed Tomography (PET/CT) is recommended for these patients. Depending on PSA level and kinetics, a choline PET/CT or a prostate-specific membrane antigen (PSMA) PET/CT should be performed [4]. For the choline PET/CT reported detection rates of LN metastases vary from 65% to 77% in case PSA doubling time was <6 months and PSA velocity was >2 ng/ml/y [11]. For PSA levels from 0.2 to 0.5 ng/ml and from 1.0 to 2.0 ng/ml, PSMA PET/CT scanning showed respectively detection rates up to 58%, and from 69% to 100% [12,13]. This data suggests that the PSMA PET/CT is more sensitive than the choline PET/CT especially for lower PSA relapse levels. Therefore, we only focused in this study on the diagnostic accuracy of PSMA PET/CT scans. Nonetheless, basic research indicated that an increased PSMA expression might influence those false positive findings in PSMA PET/CT scans as a response to administered ADT [14].

We considered that recently published studies overestimated the oncological benefit of SLND. Furthermore, we assumed that these studies evaluated a multimodal treatment concept based on salvage ADT and salvage SLND after RP. To our knowledge, there is no published data on oncological outcomes after salvage SLND in hormone-naïve men.

The purpose of this study was to evaluate the oncological outcome after transperitoneal salvage SLND in hormone-naïve patients as well as the diagnostic accuracy of staging PSMA PET/CT scans.

2. Methods

2.1. Data source and study population

The current study relied on institutionally collected data from medical records between February 2011 and March 2017 from our institution. After receiving ethical study approval by an institutional research committee, (research authorization number 5039-14 and 5575-15) 43 hormone-naïve men with PSA relapse after RP and suspected nodal CaP recurrence were enrolled. An experienced board-certified specialist in nuclear medicine analyzed the PET/CT images. Patients presenting with bone or visceral metastases or local CaP recurrence detected by preoperative guideline-concordant imaging techniques were not eligible. Patients treated with ADT or chemotherapy following RP, and those with suspicious LNs outside the target field of SLND were excluded.

BCR was defined as PSA levels >0.2 ng/ml on 2 consecutive measurements. After SLND, a complete biochemical response (BR) was identified as a serum PSA level <0.2 ng/ml whereas a partial BR was determined by PSA levels less than the initial individual PSA value before SLND.

2.2. Surgical procedure and pathological processing

The extraperitoneal pelvic LN dissection for RP included the removal of LNs and fatty tissue, using an established standardized template limited distal by the femoral canal, lateral by the border of the pelvic sidewall, medial by the perivesical fat, and cranial by the ureter crossing over the iliac vessels (Fig. 1).

The transperitoneal SLND additionally encompassed, the presacral and common iliac artery (left/right) LN region limited cranial by the aortic bifurcation (Fig. 1) [15].

All surgical specimens were sent to the same pathological institute and histopathological processing relied on standard protocols that included stepwise LN analysis in 200 μm slices. Specimen slices were stained with hematoxylin and eosin. In the presence of equivocal findings, slices were additionally immunohistochemically stained with pan-cytokeratin.

2.3. Outcome measures

For this study, we investigated the oncological benefit of a hormone-naïve patient cohort that underwent salvage SLND to treat the nodal recurrence of CaP after RP. We hypothesized that the intrinsic surgical value of SLND in hormone-naïve men would differ from those who underwent salvage ADT administration. For study purposes, PSA levels were monitored and time to PSA progression after SLND without the application of adjuvant therapies was defined as the oncological outcome. Furthermore, postoperative complications within 30 and 90 days were assessed according to the Clavien-Dindo classification [16].

To evaluate if PSMA PET/CT scanning was affected by salvage ADT before SLND, we analyzed sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of our cohort and compared these findings to the broadest published ADT-contaminated cohorts [7–9].

2.4. Variables

Baseline characteristics for all patients encompassed histopathological data, surgical approach, use of salvage

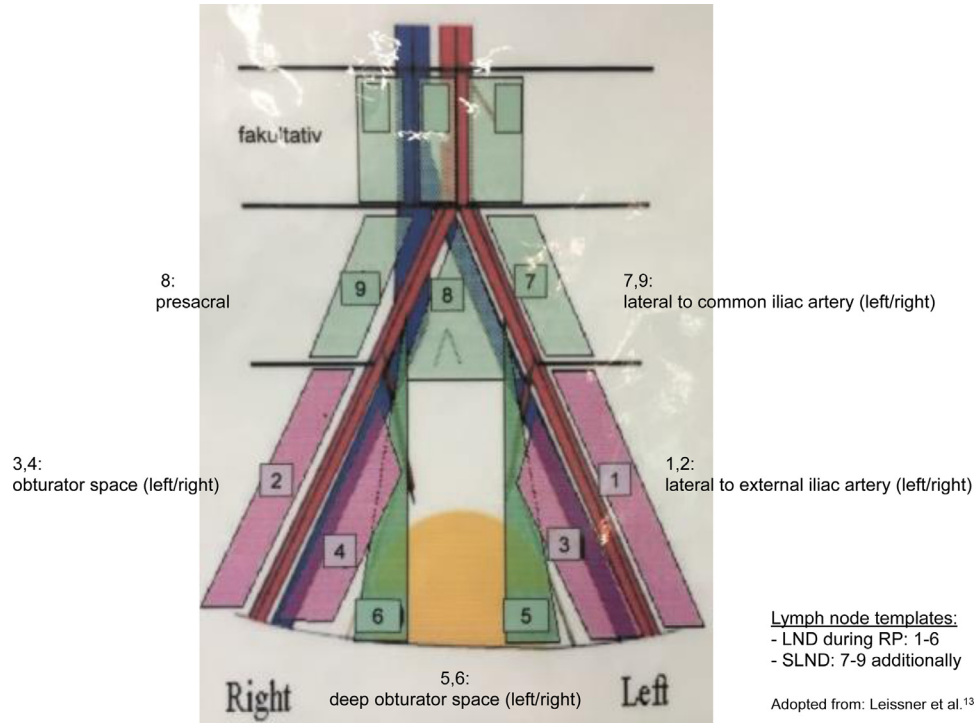


Fig. 1. Lymph node template for LND/SLND.

radiotherapy (RT) after RP, age at SLND, serum PSA levels at SLND, and time to SLND after RP. Perioperative outcomes covered operative time, blood loss, and surgery-related complications. Apart from the complete histopathological data and adjuvant therapies after SLND, PSA levels for each patient were monitored as mentioned above.

2.5. Statistical analyses

Summary statistics were constructed using frequencies and proportions of categorical variables, as well as medians and interquartile ranges for continuous variables. A Kaplan-Meier was created to display the proportion of patients with complete or partial BR compared to their PSA values after SLND. Sensitivity, specificity, PPV and NPV were separately calculated for each LN region (Fig. 1) based on suspicious PSMA PET/CT findings. Analyses were performed using SPSS, version 22 (IBM, Chicago, IL).

3. Results

3.1. Baseline characteristics

Overall, 43 hormone-naïve men were eligible for our study. Clinical characteristics are displayed in Table 1. Data taken from the previous RP showed a proportion of 18 patients (41.86%) with a pT3b tumor, 33 patients (76.74%) underwent a pelvic LN dissection, and 19 patients (44.18%) had a Gleason score 8–9. The median number of removed LNs during RP was 12. Out of this cohort, 18 patients (41.86%) received salvage RT after RP.

The median age at SLND was 62 years. The median time from RP to salvage treatment was 24 months with a median PSA at SLND of 0.8 ng/ml. In total, 22 patients (51.16%) had a preoperative ^{68}Ga-PSMA PET/CT scanning.

3.2. Perioperative outcomes

Perioperative variables captured operative time, and blood loss with a median of 155 minutes and a median of 0 ml, respectively. None of these patients received a postoperative blood transfusion (Table 2). Data on postoperative complications within 30 and 90 days are summarized in Table 3. According to the Clavien-Dindo classification, no serve complications (Grade IIIb or higher) were observed. Moreover, RT-naïve patients experienced more complications within 30 days after surgery as their counterparts who underwent adjuvant RT post-RP (Supplementary Table 1).

3.3. Histopathological results and oncological outcomes

Table 2 reports the histopathological results and follow-up data of the study cohort. The median number of removed LNs according to the LN template was respectively 21, and 1 for positive LNs. Overall 30 patients (69.77%) had at least 1 positive LN at SLND.

Overall 8 patients (18.6%) had a complete and 26 patients (60.47%) had a partial BR 40 days after surgery (Table 2). Focusing on subgroup analysis (No RT vs.

Table 1
Baseline characteristics of 43 patients with diagnosed localized prostate cancer, who underwent radical prostatectomy as primary treatment (01/2002–07/2016).

Variable	Value
Patients, *n* (%)	43 (100)
Age at RP (yr)	
Median (IQR)	57 (54–62)
PSA at RP (ng/ml)	
Median IQR)	9.3 (5.8–16.4)
Pathological *T*-stage, *n* (%)	
pT2c	13 (30.23)
pT3a	12 (27.91)
pT3b	18 (41.86)
Positive surgical margins at RP, *n* (%)	5 (11.63)
Number of removed LN at RP	
Median (IQR)	12 (6–20)
Pathological *N*-stage, *n* (%)	
pN0	33 (76.74)
pN1	1 (2.33)
pNx	9 (20.93)
Pathologic Gleason score, *n* (%)	
≤6	3 (6.98)
2 + 3	1 (2.33)
3 + 3	2 (4.65)
7	21 (48.84)
3 + 4	10 (23.26)
4 + 3	11 (25.58)
≥8	19 (44.18)
4 + 4	8 (18.6)
4 + 5	9 (20.93)
5 + 4	2 (4.65)
Adjuvant RT post-RP, *n* (%)	18 (41.86)

Abbreviations: IQR = interquartile range; LN = lymph nodes; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy.

Table 2
Peri-/postoperative characteristics of 43 patients with biochemical recurrence after radical prostatectomy, who underwent transperitoneal salvage lymph node dissection (02/2011–03/2017).

Variable	Value
Patients, *n* (%)	43 (100)
Age at SLND (y)	
Median (IQR)	62 (55–66)
PSA at SLND (ng/ml)	
Median (IQR)	0.8 (0.44–1.73)
Surgery time (min)	
Median (IQR)	155 (140–180)
Blood loss (ml)	
Median (IQR)	0 (0–100)
Blood transfusion rate	0
Number of removed LN at SLND	
Median (IQR)	21 (11–31)
Number of positive LN at SLND	
Median (IQR)	1 (0–2)
Time to SLND after RP (mo)	
Median (IQR)	24 (10–42)
Biochemical response at 40 days after SLND, *n* (%)	
Complete (PSA < 0.2 ng/ml)	8 (18.6)
Partial (postoperative PSA < preoperative PSA)	26 (60.47)
Follow up after SLND (mo)	
Median (IQR)	22 (9–39)
Time to BCR after SLND (mo)	
Median (IQR)	2 (1–3)
Time to salvage treatment after SLND (mo)	
Median (IQR)	3 (1–5)
Secondary treatment after SLND, *n* (%)	27 (62.79)
RT	9 (20.93)
ADT	12 (27.91)
Combined RT and ADT	6 (13.95)

Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence; IQR = interquartile range; LN = lymph node; PET/CT = positron emission tomography/computed tomography; PSA = prostate specific antigen; PSMA = prostate specific membrane antigen; RP = radical prostatectomy; RT = radiotherapy; SLND = salvage lymph node dissection.

adjuvant RT post-RP) a slightly higher proportion of 5 (20%) vs. 3 (16.67%) patients reached a complete BR (Supplementary Table 2).

At study closure, 3 patients (6.98%) still had a complete BR with a postoperative follow-up of respectively 14, 55, and 64 months. The median follow-up after SLND was 22 months, with a median time range from SLND to BCR of 2 months. After 6 months, 34 patients (79.07%) had a PSA progression displayed in the Kaplan-Meier curve (Fig. 2). In total, 27 patients (62.79%) underwent adjuvant treatment after SLND. Subgroups revealed a proportion of 9 (20.93%), 12 (27.91%), and 6 (13.95%) men receiving RT, ADT, or a combination of both (Table 2).

3.4. Diagnostic accuracy of PSMA PET/CT

The diagnostic accuracy of ^{68}Ga-PSMA PET/CT scans based on the final pathologic reports is summarized in Table 4. According to the template, the LN regions are numbered from 1 to 9 (superficial LN regions labeled with 1, 2, 7, and 9; deep LN regions labeled with 3, 4, 5, 6, and 8; Fig. 1). Overall sensitivity and specificity rates were respectively 32% (95% confidence interval [CI]: 17.21–51.59) and 91.74% (95% CI: 85.45–95.45). Calculated PPV and NPV of PSMA PET/CT were 44.44% (95% CI: 25.98–64.58) and 86.72% (95% CI: 83.23–89.57).

4. Discussion

The value of SLND has been intensively debated in the past. Several published studies discussed SLND as a potential treatment option for nodal recurrence of CaP after RP to avoid, or at least delay the need for hormonal manipulation [6–9]. However, actual guidelines still postulate SLND as an experimental approach with an unproven efficacy regarding cancer-specific or overall survival and an insurmountable cleavage to distinguish between nodal or systematic CaP recurrence [4].

To our knowledge, this is the first and most extensive series of hormone-naïve patients that underwent SLND for

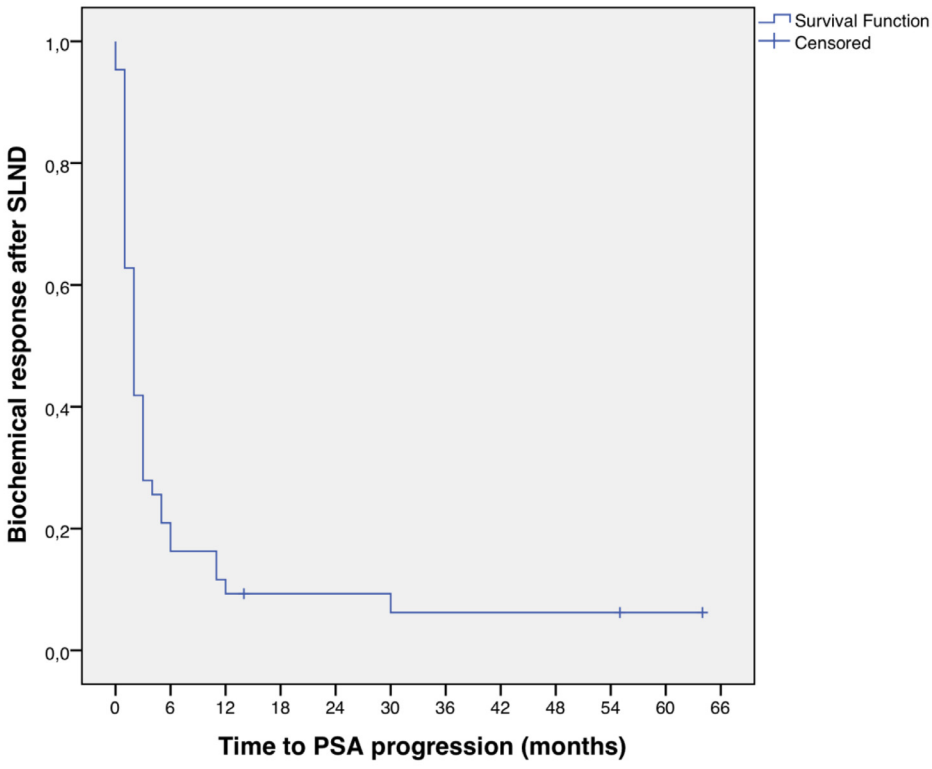
Table 3
Postoperative complications according to the Clavien-Dindo Classification within 30 and 90 days after SLND, respectively.

Variable	30 d after surgery		90 d after surgery	
Patients, *n* (%)	43 (100)		43 (100)	
Overall complications, *n* (%)	10 (23.26)		2 (4.65)	
Grade I	7 (16.28)		1 (2.33)	
Grade II	1 (2.33)		1 (2.33)	
Grade IIIa	2 (4.65)		0 (-)	
Grade IIIb	0 (-)		0 (-)	
Grade IV	0 (-)		0 (-)	
Type of complication	*n*	Grade	*n*	Grade
Lymphorrhoea	2	I	-	-
Lymphocele	4	I, IIIa	1	II
Fever	2	I	-	-
Pneumonia	1	II	-	-
Infected wound	1	I	-	-
Incisional hernia	-	-	1	I

Abbreviations: SLND = salvage lymph node dissection.

nodal recurrence of CaP after RP. Several of our findings are noteworthy.

Several studies described salvage SLND as a potential treatment with low morbidity rates, which delays the need for salvage ADT [7–9]. The percentage of patients with a complete BR (40 days after SLND) in our cohort was 18.6%. Compared to other studies with rates ranging from 29.8% to 59.3%, our oncological outcome seemed unsatisfactory [6–9]. However, these studies were contaminated by salvage hormone manipulation after RP in up to 78.7% of included participants, and the oncological benefit of the SLND was consistently overestimated [7]. In other words, these studies evaluated a multimodal treatment concept for CaP patients with nodal recurrence of CaP and not the sole oncological impact of SLND. Moreover, no information was given if or when ADT withdrawal was conducted [6–9]. A recently published study from Nam et al. investigated the testosterone recovery after ADT withdrawal in 221 CaP patients. Their data showed that after 6 months only 25 and <10% recovered out of hypogonadism (serum testosterone level > 300 ng/dL) when ADT was respectively administered for ≤18 and >18 months [10]. Based on these findings, conclusions from all lager published cohorts assessing the impact on SLND for nodal recurrence of CaP were insignificant because presurgery ADT administration might significantly affect the oncological outcome. In contrast to ADT-contaminated cohorts, our data of hormone-naïve patients were more granular and detected the sole impact of transperitoneal SLND with further disappointing results. Focusing on the 1-year BCR free survival rate after surgical treatment, our proportion of 6.98% deviated remarkably from published



Months	0	6	12	18	30	66
N.R.	41	9	4	3	2	0
C.E.	2	34	39	39	40	40

Fig. 2. Kaplan-Meier curve is illustrating the proportion of patients with biochemical response across time to PSA progression. Abbreviations: C.E. = cumulative events; N.R. = number at risk. Censored: *n* = 3, at follow-up of 14, 55, and 64 months PSA < 0.03 ng/ml.

Table 4
Predictive values of 22 PSMA PET/CT based on the predefined lymph node template.

LN-station	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	0	100	0	88.89
2	0	93.75	0	93.75
3	75	92.86	75	92.86
4	40	91.67	66.67	78.57
5	0	50	0	80
6	50	80	33.33	88.89
7	0	92.86	0	81.25
8	50	100	100	94.44
9	20	100	100	77.78
Total	32 (17.21–51.59)	91.74 (85.45–95.45)	44.44 (25.98–64.58)	86.72 (83.23–89.57)
Superficial (1,2, 7, 9)	9.09 (1.62–37.74)	96.67 (88.64–99.08)	33.33 (4.72–83.48)	85.29 (82.71–87.55)
Deep (3, 4, 5, 6, 8)	50 (26.8–73.2)	86.89 (76.2–93.2)	46.67 (27.58–66.78)	88.33 (81.63–88.35)

Abbreviations: NPV = negative predictive value; PET/CT = positron emission tomography/computed tomography; PPV = positive predictive value; PSMA = prostate specific membrane antigen.

survival rates up to 79% [9]. This massive difference was very likely to be caused by preoperative ADT administration and the overlapping effect of SLND and ADT. The single surgical effect of SLND was overestimated and entailed worse oncological results. Three months after surgical intervention, more than 60% of all hormone-naïve men required salvage therapies.

Secondly, according to the Clavien-Dindo classification, transperitoneal SLND seemed to be a safe procedure associated with low complication rates [16]. The proportion of high-grade complications (Clavien-Dindo Grade IIIa) within 30 days after surgery in our cohort was 4.65%. In detail, 2 patients experienced symptomatic lymphoceles requiring drainage. Considering established complication assessments, our results aligned with previously published studies reporting high-grade complication rates (≥Clavien-Dindo Grade IIIa) of 3.9% to 13.8% after SLND [6,7,9,17]. In our cohort, salvage RT post-RP did not lead to a higher complication rate after SLND as it might be expected because of the risk of fibrosis and wound healing issues.

Apart from the ordinary standard questionnaires or examinations for complication assessments, recently published findings from a subgroup of our cohort revealed a proportion of up to 78.5 % with de novo neurogenic bladder dysfunctions after SLND diagnosed by pre- and postoperative urodynamics [18]. These severe, so far unreported postoperative complications were most likely to be caused by iatrogenic damage of pelvic neuronal structures, in particular the inferior hypogastric plexus. Therefore, the extension of the LN template up to the inferior mesenteric artery and consecutive radical LN removal for a better oncological outcome should be discussed carefully. In a recently published systematic literature review from Ploussard et al., SLND above the aortic bifurcation seemed only beneficial when it was guided by PET/CT scan with positive spots [19]. Based on these findings, a radioguided approach appeared to be the most balanced approach.

Finally, the diagnostic accuracy of the ^{68}Ga-PSMA PET/CT in our hormone-naïve cohort based on the lesion-histology comparison differed from previous reports. Pfister et al. investigated the diagnostic accuracy of the PSMA PET/CT in 28 patients who underwent SLND [20]. Controversially to our data, they reported higher values for sensitivity (89.9% vs. 32%), and PPV (75.7% vs. 44.4%). This discrepancy could be a result of salvage hormone manipulation after RP before SLND in at least 57% of the included patients. Another study evaluated the value of ^{68}Ga-PSMA PET/CT in treatment-naïve patients with CaP [21]. Subgroup analysis of 28 patients that underwent RP and LND revealed a notable lower sensitivity of 46.2% for PSMA PET/CT imaging. These findings underline the assumption that adjuvant ADT administration could affect PSMA PET/CT findings. Similarly, basic research reported an increased PSMA uptake (1.5- to 2.0-fold higher) after short-term ADT application in xenograft mouse models [14,22]. In contrast to this, recently published clinical data showed a correlation between PSMA PET/CT lesion visibility before and during long-term ADT administration (duration median: 230 days) [23]. After rescanning, only 14 out of initially 31 CaP lesions were still visible.

Several studies have provided data on the impact of ADT administration and the consecutive accuracy of PSMA PET/CT scans. At this point, it is still debatable who is right or who is wrong. Nonetheless, all these studies have 1 central message in common: Refer hormone-naïve patients to PSMA PET/CT before planning further therapy steps.

Despite its strengths, our study is not devoid of limitations. First, this study relied on retrospective collected data from 1 high volume center. Prospective randomized multicenter trials are necessary to substantiate our findings in larger cohorts. These studies should declare when ADT withdrawal was conducted and differentiate those individuals from hormone-naïve men. This approach is elementary to characterize the individual effect of SLND and to take these findings into account during patient counseling. Secondly, all

our patients underwent open transperitoneal SLND. It is debatable if an alternative operation technique, such as the recently reported robot-assisted SLND could affect the oncological outcome [24]. Prospective randomized multicenter trials should discuss the value of this approach. Finally, not all patients underwent preoperative imaging at our institution. During the time of this study, no standard protocol for performing, interpretation, and reporting of PSMA PET/CT scans were available. Due to these circumstances, the accuracy and precision of the executed PSMA PET/CT might be influenced by different study protocols, even though all scans were analyzed by an experienced board-certified specialist in nuclear medicine. New studies should be carried out following the recently released guidelines from the European Association of Nuclear Medicine to prevent false results [25].

5. Conclusions

Focusing on the 3 major aspects of our study, we eliminated every scientific argument to justify the presence of elective SLNDs. The individual impact of SLND in hormone-naïve men entails worse oncological outcomes, more severe complications as generally reported, and potentially higher rates of false positive PSMA PET/CT scans in ADT-contaminated patient cohorts. Taken all together, SLND is still a debatable treatment strategy for nodal recurrence of CaP. Treating physicians should accept the challenge of improving diagnostic and therapeutic pathways, although basic and clinical research present controversial findings to expected objectives.

Conflict of interest

All authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.023.

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