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Review – Prostate Cancer

Salvage Lymph Node Dissection for Nodal Recurrent Prostate Cancer: A Systematic Review

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Abstract

Context: Identification of early nodal recurrence after primary prostate cancer (PCa) treatment by functional imaging may guide metastasis-directed therapy such as salvage lymph node dissection (SLND).
Objective: The aim of this systematic review was to assess the oncological role and the safety of SLND in the era of modern imaging in case of exclusive nodal recurrence after primary PCa treatment with curative intent.
Evidence acquisition: A systematic literature search in the PubMed and Cochrane databases was performed up to August 2018 according to Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Overall, 27 SLND series have been selected for synthesis.
Evidence synthesis: Prostate-specific membrane antigen or choline positron emission tomography/computed tomography was the reference detection technique. SLND was performed by open or laparoscopic approach with <10% of grade 3 or more complication rate. Mean follow-up was 29.4 mo. Complete biochemical response after SLND was achieved in 13–79.5%of cases (mean 44.3%). The 2- and 5-yr biochemical progression-free survival rates ranged from 23% to 64% and from 6% to 31%, respectively. Fiver-year overall survival was approximately 84%. Main drawbacks limiting the interpretation of the effectiveness of SLND were the retrospective design of single-center series, heterogeneity between series in terms of adjuvant treatment, endpoints, definitions of progression and study population, as well as the absence of long-term follow-up.

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Conclusions: A growing body of accumulated data suggests that SLND is a safe metastasis-directed therapy option in nodal recurrence after primary treatment. However, to date, high level of evidence is still missing to draw any clinically meaningful conclusion about the oncological impact of SLND on long-term endpoints.
Patient summary: When imaging identifies exclusive nodal recurrent prostate cancer, surgery directed to the positive lesions is safe and can offer at least a temporary biochemical response. The oncological role assessed by strong clinical endpoints remains uncertain.

1. Introduction

Clinical extra-prostatic recurrence after primary treatment is mainly treated by immediate or delayed androgen deprivation therapy (ADT) in clinical practice [1]. Nevertheless, only patients affected by nodal metastases showed better prognosis compared with their counterparts with skeletal or visceral metastases [2,3]. Current guidelines do not differentiate between location and number of metastases for guiding salvage therapy, whereas recent advances in functional imaging provide ever earlier detection of clinical recurrence. The aims of metastasis-directed therapy in patients with node-only recurrence would be to optimize locoregional control, limit the risk of distant progression, avoid immediate ADT, and potentially improve cancer-specific survival. Thus, positive node-directed therapy of oligometastatic recurrence is a novel approach in prostate cancer (PCa) management with fast evolving literature [4]. Recent published literature of metastasis-directed treatment by surgery or stereotactic body radiotherapy (RT) has suggested that this strategy could improve outcomes in terms of delayed systemic treatment with acceptable toxicity [4–6]. Several studies of salvage lymph node dissection (SLND) have been published during the last years, including the evaluation of the robotic approach.

The aim of this article was to analyze all available studies assessing the oncological role and safety of SLND in patients with nodal recurrence on functional imaging after primary PCa treatment with curative intent through a systematic review process.

2. Evidence acquisition

We performed a systematic review of the literature up to August 2018, starting from January 2000, using the PubMed, Web of Sciences, and Embase databases according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (registration number CRD42018109079). Inclusion criteria were patients with nodal recurrence on functional imaging by positron emission tomography/computed tomography (PET/CT) or PET/magnetic resonance imaging (PET/MRI) after primary PCa treatment with curative intent, undergoing pelvic (with or without retroperitoneal) SLND. Patients with surgically resectable N1 up to retroperitoneal M1a disease were included. Exclusion criteria were patients with synchronous bone or visceral disease (M1b or M1c disease) at the time of SLND on conventional or functional imaging. Search results were restricted to English language. Keywords arranged in variable combinations included “salvage,” “lymph node dissection,” “prostate cancer,” “biochemical recurrence,” “clinical recurrence,” “choline,” “prostate-specific membrane antigen (PSMA),” and “PET/CT.” Additional references were identified from the reference list of each article. In the light of the expected low level of evidence across studies, no exclusion criteria according to study design were applied, except for a sample size of over 10 cases within the case series. Two authors independently selected studies. Discrepancies between the two authors were resolved via consensus. The primary endpoints were the oncological outcomes after SLND assessed by the biochemical response rate after SLND (prostate-specific antigen [PSA] $<$0.2 ng/ml 1 mo after SLND before any further treatment), biochemical disease-free survival, and cancer-specific survival. The secondary endpoints included the complication rate after surgery evaluated by the modified Dindo-Clavien classification. The study selection process is shown in the PRISMA diagram (Fig. 1). All articles except one were single-arm series [5].

3. Evidence synthesis

3.1. Study selection and quality assessment

Overall, 27 studies assessing SLND in 1370 patients were included in the evidence synthesis. All articles are listed in Table 1 [5,7–32]. Identified articles were reviewed using the Quality Appraisal tool for case series using a Modified Delphi technique [33]. Quality assessment is detailed in Table 2.

3.2. Preoperative imaging and diagnosis of node-only recurrence

In 15/27studies, nodal recurrences were diagnosed with choline as a tracer. A PSMA-labeled radionuclide was used in six of 27 studies, and both tracers were included in five of 27studies. Radionuclide was not mentioned in one series [27]. For a minority of patients, recurrent PCa was confirmed before salvage treatment by node biopsy. PET/MRI was also used in two studies [29,32].

The rate of associated or isolated extrapelvic node disease on preoperative imaging ranged from 6.9% to 81.3%. One robotic series included only 10 patients undergoing retroperitoneal SLND (100% of extrapelvic disease) [28].

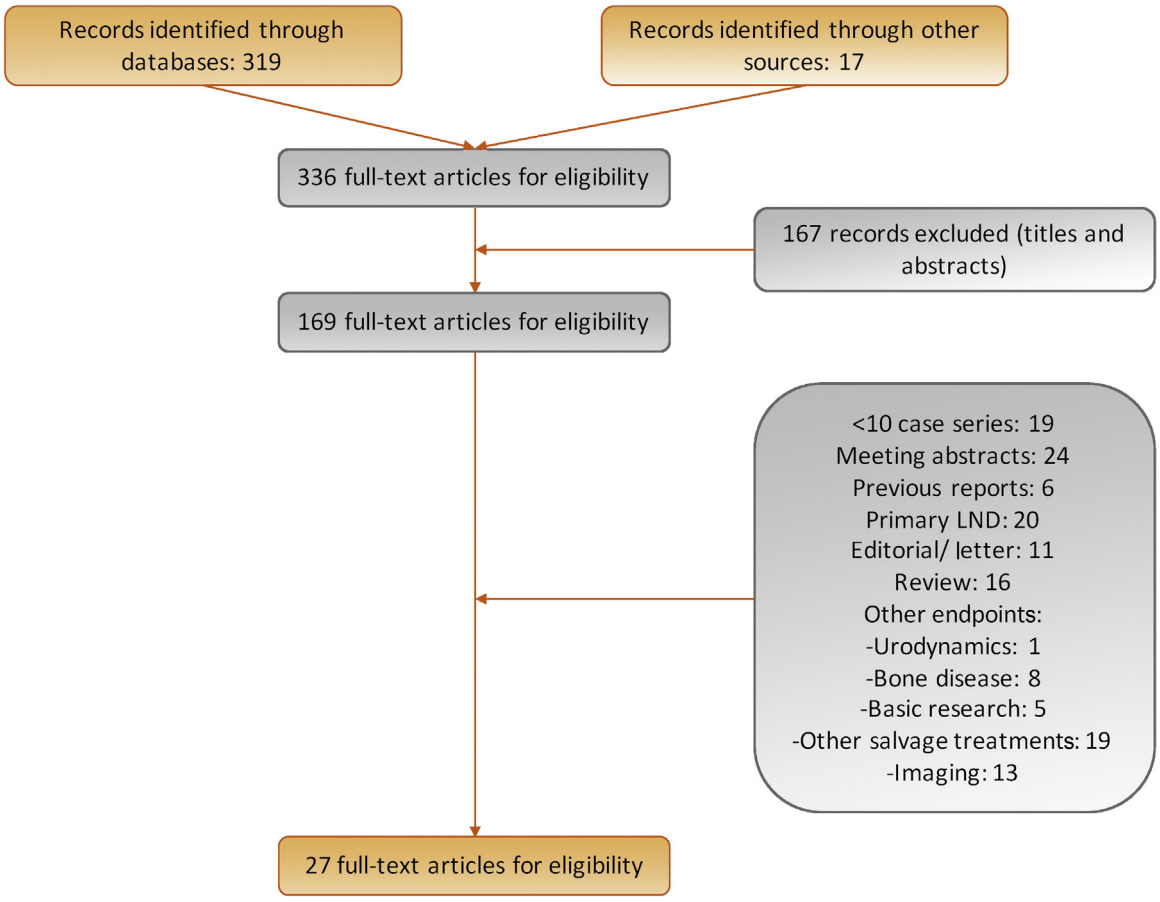

Fig. 1 – Flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) showing the searches resulting in the full studies included in the review. LND = lymph node dissection.

3.3. *Patient characteristics before SLND*

Most of the series including the largest ones included only patients who had undergone radical prostatectomy as primary treatment [5,9,10,12,14,17–19,21,24,25). In studies also including other modalities, the proportion of patients receiving RT, brachytherapy, or high-intensity focused ultrasound (HIFU) as primary treatment was <15% [8,22–24,27,28,30). Only Osmonov et al. [27] reported RT as primary treatment in 28.6% of cases. Pfister et al. [30] reported 85% of patients previously treated by radical prostatectomy, 12% with RT, and 3% with HIFU. Interestingly, when surgery was performed as initial treatment at diagnosis, pelvic lymph node dissection (LND) was performed at the time of radical prostatectomy in most patients. The median number of lymph nodes removed at the time of RP ranged from 6 to 15 [10,11,14,17,18,20,21,28,32]. In the series of Zattoni et al. [21] (n = 117), only 23% of patients did not undergo pelvic LND at the time of radical prostatectomy. The percentage of patients without LND at the time of radical prostatectomy ranged from 10.2% to 23.0% (mean 14.7%). Lymph node–positive disease at the time of radical prostatectomy (pN1 disease) was detected in only 11.1% of cases. Local salvage treatment by RT had often been performed at first PSA failure after radical prostatectomy. In the long-term study by Suardi et al. [14], at least 58% of patients were treated by adjuvant or salvage RT in line with other studies [21]. Some studies included patients previously treated by ADT for PSA recurrence, before SLND. Suardi et al. [14] reported a previous treatment line by ADT in 62.7% of patients. In the study by Osmonov et al. [27], 80% of patients had castration-resistant disease at the time of SLND, and approximately 73% of patients had received ADT before SLND. In the series by Zattoni et al. [21], 18.8% of patients received long-term ADT prior to nodal recurrence diagnosis and had a castration-resistant disease at the time of SLND.

Median patient age before SLND was <70 yr in all series (mean age 65 yr). The median pre-SLND PSA value ranged from 0.5 to 11.1 ng/ml (mean 3.2 ng/ml).

3.4. *Lymph node yield and anatomical extent of SLND*

The main results are listed in Table 1 [5,7–32]. The mean number of nodes removed was 19.8 (range: 3.8–83). The mean number of positive lymph nodes was 4.7, ranging from 1 to 23 nodes. When retroperitoneal dissection was performed, positive lymph nodes were located in the retroperitoneum in 23–54% of the cases. In the 19 surgical series associating pelvic and retroperitoneal SLND in case of

Table 1 – Salvage lymph node dissection studies ($n = 27$): patient and cancer characteristics, pre-SLND imaging, surgical template, oncological outcomes, and follow-up

Study	Patient number	Extrapelvic LN	PSA level	Imaging method/mean number of positive spots	Surgical template	Adjuvant treatment	Complete PSA response	Follow-up (mo)	PFS	OS/CSS	Predictive factors	LN+/total LN (mean)
Rinnab et al (2008) [7]	15	NR	1.9	Choline PET/CT (1.4)	SLND (pelvic + RP)	ADT (73%) RT (7%)	13%	13.7	NR	NR	NR	NR/13.9
Schilling et al (2008) [8]	10	NR	8.8	Choline PET/CT (2.2)	SLND (pelvic ± RP according to PET/CT)	ADT (60%)	NR	11	NR	1 yr: 90%	NR	2.8/7.1
Winter et al (2010) [9]	13	NR	2.7	Choline PET/CT (1.2)	SLND (pelvic ± RP according to PET/CT)	No	38.5%	30.9	NR	NR	NR	1.0/NR
Rigatti et al (2011) [10]	72	25 (34.7%)	1.5	Choline PET/CT (1.7)	SLND (pelvic ± RP according to PET/CT)	ADT (65.3%)	57%	39.8	5 yr: 19%	5 yr: 75%	PSA >4 Time to recurrence No CR RP LNM No. of LNM	9.1/30.6
Jilg et al (2012) [14]	47	18 (34.6%)	11.1	Choline PET/CT	SLND (pelvic ± RP according to PET/CT)	ADT (65%) RT (52%)	46%	35.5	5 yr: 9%	5 yr: 77.7%	No CR RP LNM No. of LNM	9.7/23.3
Karnes et al (2015) [12]	52	4 (7.7%)	2.2	Choline PET/CT (1.25)	SLND (pelvic ± RP according to PET/CT)	ADT (83%)	73%	20	3 yr: 45.5%	3 yr: 92.5%	None	5.3/23.8
Jilg et al (2014) [14]	43	13 (28.3%)	3.2	Choline PET/CT	SLND (pelvic ± RP according to PET/CT)	RT (100%)	NR	32	NR	NR	NR	7.9/29.3
Suardi et al (2015) [14]	59	23 (38.9%)	2.0	Choline PET/CT (1.3)	SLND (pelvic ± RP according to PET/CT)	ADT (66%)	59%	76.6	NR 8 yr: 22.1% if CR	8 yr: 80.6%	No CR RP LNM	8.9/29.5
Claeys et al (2015) [15]	17	4 (23.5%)	2.0	Choline or FDG PET/CT	Bilateral SLND: $n = 13$ (+RP: $n = 4$) Unilateral: 1 Limited: 3	RT (24%)	23%	22	2 yr: 79.5% [a]	NR	NR	1/11
Rischke et al. (2015) [16]	93	NR	3.5	Choline PET/CT	SLND (pelvic ± RP according to PET/CT)	RT (51%)	NR	38	3 yr: 38.4% [b]	5 yr: 79%	No RT No, of LNM RP LNM	8.9/30.8
Tilki et al (2015) [17]	58	34 (60.4%)	9.8	Choline PET/CT	SLND (pelvic ± according to PET/CT)	ADT (67%)	22%	39	5 yr: 22.4%	5 yr: 71%	PSA >4 Extranodal uptake	6.3/18.6
Linxweiler et al (2018) [18]	36	3 (8%)	1.98	Choline ($n = 11$) PSMA ($n = 25$) PET/CT (1.6)	Robotic SLND: Targeted ($n = 7$) Unilateral ($n = 11$) Bilateral	No	36% (44% if PSMA, 18% if choline)	14 (PSMA) 48 (choline)	Median 12 mo if PSMA 4.7 mo if choline	NR	PSMA PET/CT	1/6.5
Maurer et al (2018) [19]	31	45%	1.13	99Tc-PSMA PET/CT (1.2)	Radioguided SLND	No	64.5%	12.2	1 yr: 43%	NR	NR	1.5/4.3

Table 1 (*Continued*)

Study	Patient number	Extrapelvic LN	PSA level	Imaging method/mean number of positive spots	Surgical template	Adjuvant treatment	Complete PSA response	Follow-up (mo)	PFS	OS/CSS	Predictive factors	LN+/total LN (mean)
Steuber et al (2018) [5]	166	NR	NR	Choline PET/CT	SLND (pelvic ± according to PET/CT)	NR	NR	70.0	NR	5 yr: 99.1%	NR	NR
Herlemann et al (2017) [20]	104	51.9%	4.1	Choline or PSMA PET/CT	SLND (pelvic ± according to PET/CT)	NR	29.8%	39.5	5 yr: 6.2%	5 yr: 83%	PSA >4 PSMA PET/CT	3/13
Zattoni et al (2016) [21]	117	13.7%	2.3	Choline PET/CT (1.2)	SLND (pelvic ± according to PET/CT)	Multiple 25.7% ADT 36.8%	79.5%	20.2	5 yr: 31%	5 yr: 97%	pT stage CRPC disease	3/22
Siriwardana et al (2017) [22]	35	4 (6.9%)	2.2	PSMA PET/CT (1.5)	Robotic SLND	ADT (n = 12) Chemo (n = 2) RT (n = 2)	43%	12.0	1 yr: 23%	NR	Bilateral SLND	2/9
Jilg et al (2017) [23]	30	14 (46%)	1.7	PSMA PET/CT	SLND (pelvic ± according to PET/CT)	NR	NR	NR	NR	NR	NR	1/33
Porres et al (2017) [24]	87	3.5%	2.63	Choline or PSMA PET/CT	n = 70, SLND (pelvic ± according to PET/CT) n = 17, Unilateral SLND	ADT 37.8%	27.5%	21.0	3 yr: 69.3%	92.7%	No CR >2 positive LNs Gleason 8–10	2.2/12.5
Montorsi et al (2017) [25]	16	13 (81.3%)	1.0	Choline (n = 3) or PSMA (n = 13) PET/CT	Robotic SLND (pelvic ± according to PET/CT)	ADT 50%	33%	1.3	NR	NR	NR	4.0/16.5
Passoni et al (2014) [26]	46	36.9%	0.5	Choline PET/CT (1)	SLND (pelvic ± according to PET/CT)	NR	NR	NR	NR	NR	NR	2/21
Osmonov et al(2016) [27]	45 [c]	NR	6.7	PET/CT	SLND (pelvic + presacral + para-aortic)	ADT % NR (at least n = 16)	48.9%	42.7	2 yr: 50% 5 yr: 30%	5 yr: 80.6%	Bone metastasis pT stage No CR	4.1/21.6
Abreu et al (2017) [28]	10	100%	2.78	Choline PET/CT	Robotic SLND pelvic + retroperitoneal	NR	Mean decrease–83% Mean PSA post-SLND 0.8	NR	NR	NR	NR	23/83
Rauscher et al (2016) [29]	48	NR	1.31	PSMA PET/CT or PET/MRI	SLND depended on patient/surgeon	NR	NR	NR	NR	NR	NR	1.4/3.8
Pfister et al (2016) [30]	66	NR	2.5	Choline (n = 38) or PSMA (n = 28) PET/CT	SLND (pelvic ± according to PET/CT)	NR	NR	NR	NR	NR	NR	2.5/7.9

Table 1 (*Continued*)

Study	Patient number	Extrapelvic LN	PSA level	Imaging method/mean number of positive spots	Surgical template	Adjuvant treatment	Complete PSA response	Follow-up (mo)	PFS	OS/CSS	Predictive factors	LN+/total LN (mean)
Rauscher et al (2017) [31]	31	9.7%	13	111-In PSMA PET/CT	Radioguided SLND	33% ADT (n = 1) RT (n = 3) RT + ADT (n = 6)	60%	11.2	1 yr [d]: 64%	NR	NR	1.5/4.7
Mandel et al (2018) [32]	23		3.9	PSMA PET/CT (n = 17) or PET/MRI (n = 6) (2)	SLND (pelvic)	NR	NR	NR	NR	NR	NR	3 [e]/15

ADT = androgen deprivation therapy; CR = complete biochemical response; CRPC = castration-resistant prostate cancer; CSS = cancer-specific survival; LN = lymph node; LNM = lymph node metastases; MRI = magnetic resonance imaging; NR = not reported; OS = overall survival; PET/CT = positron emission tomography/computed tomography; PFS = progression-free survival; PSA = prostate-specific membrane antigen; RP = retroperitoneal; RT = radiotherapy; SLND = salvage lymph node dissection.

[a] ADT-free survival: SLND, ADT.

[b] Radiological criteria: CR, RP.

[c] 80% of patients with CRPC before SLND.

[d] Treatment-free survival.

[e] In pN1 cases.

extrapelvic positive spots on imaging, the rate of extrapelvic positive lymph nodes on imaging ranged from 7% to 60.4%.

In the majority of studies, SLND consisted of an anatomically defined extended nodal dissection that included the obturator fossa; external, internal, and common iliac artery regions; and proximally the removal of all lymph nodes along common iliac vessels up to the aortic bifurcation. Presacral dissection depended on the center [26]. In addition, SLND was also guided by choline or PSMA PET/CT scans, and thus, the dissection might be not limited to pelvic region and might be extended to the retroperitoneum in case of positive spots above the aortic bifurcation. Few series have limited SLND to the positive spots on functional imaging using PSMA as a radionuclide [19].

Initial series involving choline PET/CT seemed to discourage the planning process of highly selective metastatic ablation focused on only positive spots [26]. Nevertheless, recent developments in imaging have suggested that SLND might be guided completely by PSMA imaging. Recently, Maurer et al. [19] demonstrated the feasibility of 99mTc-PSMA–based radioguided surgery in patients recurring after local treatment and selected by an initial ^{68}Ga-labeled PSMA ligand PET/CT. Short-term oncological outcomes were at least as good as those previously reported in bilateral extended SLND series, suggesting that the improvements of preoperative imaging could delineate more precise removal fields. Nevertheless, even when ^{68}Ga-labeled PSMA ligand PET/CT was used, bilateral extended SLND was more likely to provide complete biochemical response. In the series by Siriwardana et al. [22], 90% of patients achieved a complete response after bilateral template dissection compared with 33.3% and 21.4% in those undergoing unilateral and targeted node dissection, respectively. Radioguided surgery was also assessed using the 111-In PSMA-labeled PET/CT showing a high value for intraoperative detection of even small metastatic lesions [31]. In that series including 31 patients, 111-In PSMA PET/CT was able to detect five additional suspicious specimens in 10% of patients. Despite better results compared with choline PET scans, the accuracy of PSMA-PET still seems insufficient to justify resection of only PSMA-positive fields, but favors complete bilateral SLND [32]. To date, no comparative study assessing the optimal extent of SLND (targeted, unilateral, and bilateral) has been published.

3.5. *Complications and surgical approach*

Mean duration of SLND ranged from 90 to 288 min and median blood loss was <250 ml in all series (Table 3). Hospital stay ranged from 1 to 5 d. Complications were mostly reported according to the Dindo-Clavien classification [7–10,12,14,15,18–25,27–29]. Overall, lymphorrhea and symptomatic lymphoceles requiring drainage were the most frequent complications in addition to fever and wound management. Most complications were of low grade. The rate of grade I complications ranged from 0% to 62.5% with a mean of 21%. The rate grade 2 complications ranged from 0% to 37.5% (mean 11%). Grade 3 complications were reported in <10% of cases [22]. The rate of grade IIIa and IIIb

Table 2 – Quality assessment of included studies using the Quality Appraisal tool for case series using a modified Delphi technique [33]

Study objective	Number of included studies fulfilling the criteria
1. Is the hypothesis/aim/objective of the study stated clearly in the Abstract, Introduction, or Methods section?	23/27
Study population	
2. Are the characteristics of the participants included in the study described?	25/27
3. Were the cases collected in more than one center?	4/27
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	22/27
5. Were the participants recruited consecutively?	13/27
6. Did participants enter the study at a similar point in the disease?	22/27
Intervention and cointervention	
7. Was the intervention clearly described in the study?	26/27
8. Were additional interventions (cointerventions) clearly reported in the study?	19/27
Outcome measure	
9. Are the outcome measures clearly defined in the Introduction or Methods section?	19/27
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	19/27
11. Were outcomes measured before and after intervention?	20/27
Statistical analysis	
12. Were the statistical tests used to assess the relevant outcomes appropriate?	19/27
Results and conclusions	
13. Was the length of follow-up reported?	21/27
14. Was the loss to follow-up reported?	4/27
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	13/27
16. Are adverse events reported?	20/27
17. Are the conclusions of the study supported by results?	22/27
Competing interests and sources of support	
18. Are both competing interests and sources of support for the study reported?	27/27

complications varied among studies from 0% to 20% and from 0% to 15.6%, respectively (mean 4.9% and 4.5%, respectively). Rauscher et al. [29] reported a 12.9% rate of grade 3b complications requiring reinterventions (pararectal abscess, ureteral stenting, and ureter injury requiring psoas hitch reconstruction). The most frequent high-grade complications were lymphocele drainage, ureteral stenting due to stricture or sepsis, and pulmonary embolism. One grade IVa complication (bilateral pulmonary embolism) has been reported. Only one potentially surgery-related death was reported in all series due to pulmonary embolism, which occurred 2 mo after the surgery [29].

Minimally invasive surgery using robot-assisted laparoscopy has been suggested to offer potential advantages in terms of reduced surgical trauma, reduced bleeding, and better control of lymphatic vessels. Four dedicated series of robot-assisted SLND have been published to date [18,22,25,28]. In a series of 36 patients, Linxweiler et al. [18] did not report major high-grade complications after robotic surgery (mean blood loss 50 cc). In a multicenter series of 16 patients, Montorsi et al. [25] found a 25% complication rate represented by ureteral and vascular injuries in one (6.3%) and three (18.7%) cases, respectively. No major grade III/IV complications occurred after robot-assisted SLND. To date, the lack of high-level-evidence studies did not allow any relevant comparison between open and minimally invasive SLND in terms of both safety and oncological outcomes.

3.6. *Oncological outcomes*

Outcomes are reported in Table 1 [5,7–32]. Patients included in at least 13 studies received adjuvant ADT after SLND in a varying proportion (from 34% to 83%) of patients. Adjuvant RT was given in eight series to the prostatic fossa and to the pelvic region. In the study by Jilg et al. [13], all patients received adjuvant RT. The two largest studies reporting outcomes of adjuvant RT after SLND have included 43 and 47 patients [13,16]. Rischke et al. [16] compared oncological outcomes between 46 patients treated by SLND only and 47 patients receiving additional RT after SLND. Patients undergoing adjuvant RT after SLND were more likely to have clinical relapse in the treated field (5-yr relapse-free rate 71%) compared with those undergoing SLND (5-yr relapse-free rate 26%). The absence of adjuvant treatment after SLND was clearly noted in only three studies: those by Winter et al. [9], Linxweiler et al. [18], and Maurer et al. [19]. In the latter series, the 1-yr progression-free survival rate was 43%, without any adjuvant treatment.

Mean follow-up after SLND widely varied among studies from 1.3 to 76.6 mo. Overall, mean follow-up was 29.4 mo. Only 41% of studies reported post-SLND follow-up of >2 yr. In the majority of studies, a post-SLND complete response was defined by postoperative PSA of at least <0.2 ng/ml within 2 mo after surgery. Complete biochemical response rates ranged from 13.0% to 79.5% among the series (mean 44%). The 2- and 5-yr biochemical progression-free survival rates ranged from 23% to 64% and from 6% to 31%, respectively. The 5-yr overall survival rate was approximately 84%. Suardi et al. [14] published 8-yr clinical recurrence-free and cancer-specific survival rates of 38% and 81%, respectively. Clinical recurrence was often located in nodes without conclusive data regarding the location of recurrence compared with the SLND template. Rischke et al. [16] highlighted that recurrences after SLND were located in 40% of cases in the pelvic region, in 18% in both pelvic and retroperitoneal nodes, 9% in bones, and in 30% in combined

Table 3 – Intra- and postoperative parameters and reported complications after salvage lymph node dissection

Study	Patient number	Age	SLND duration (min)	Blood loss (ml)	Grade I/II	Grade III	Robot-assisted SLND	Template SLND	Hospital stay (d)
Rinnab et al	15	62	NR	NR	Grade II: Ileus 6.7%	Grade IIIa: 6.7% Drainage lymphocele Grade IIIb: 6.7% Ureteral stenting	No	Pelvic ± RP	NR
Schilling et al	10	NR	90	NR	Grade I/II: 0	Grade III/IV: 0	No	Pelvic	5.3
Winter et al	13	61	NR	NR	Grade I/II: 0	Grade IIIb: 7.7% Ureteral stenting	No	Pelvic ± RP	NR
Rigatti et al	72	67	NR	NR	Grade I: Lymphorrhea 20.8% Fever 25% Grade II: DVT/PE 4.1% Ileus 19.4%	Grade IIIa: Drainage lymphocele 13.8% Wound dehiscence 4.1% Grade IIIb: Ureteral injury 1.4% Surgical reinterventions 2.7%	No	Pelvic ± RP	NR
Karnes et al	52	60	NR	NR	Grade I: 0 Grade II: DVT/PE 1.9%	Grade IIIa: 1.9% Wound management Grade IIIb: 3.8% Ureteral stenting (1) Exploratory laparotomy (1)	No	Pelvic ± RP	NR
Suardi et al	59	66	NR	NR	Grade I: Lymphorrhea 20.3% Fever 30.5%% Grade II: DVT/PE 1.7% Ileus 20.3%	Grade IIIa: Drainage lymphocele 11.2% Wound infection 5.1% Grade IIIb: Surgical reinterventions 1.7%	No	Pelvic ± RP	NR
Claeys et al	17	65	NR	NR	Grade I: 35% Scrotal lymphedema Sensitivity loss Ileus Grade II: 6% Pneumonia	Grade IIIa: 6% DVT + lymphocele Grade IIIb: 12% Partial bladder necrosis Abcedated lymphocele	Yes 35.2%	Pelvic ± RP	NR
Linxweiler et al	36	66	129	50	Grade I: 2.8% Grade II: 0	Grade IIIa: 5.6% DVT Grade IIIb: 8.3% Dehiscence (1) Vascular injury (2)	Yes	Pelvic ± RP	4
Maurer et al	31	67	116	150	Grade I: 38.7% Lymphedema 22.6% Paresthesia 9.7% Wound healing disorder 3% Bladder leakage 3%	Grade IIIb: 3.2% Ureteral stenting	No	Radioguided SLND	NR
Herlemann et al	104	64	120	200	Grade I: Lymphorrhea 7.7% Hematoma 1.9% Grade II: Ileus 4.8% Blood transfusion 1% DVT/PE 3.8%	Grade IIIa: Drainage lymphocele 1.9% Grade IIIb: 3% Dehiscence Bladder injury Fenestration lymphocele	No	Pelvic ± RP	NR
Zattoni et al	117	65	NR	NR	Grade I: 5.1% Grade II: 8.5% Anemia Fever Wound infection Delirium Scrotal edema Ileus	Grade IIIa: 3.4% Lymphocele Would infection Acute renal failure Grade IIIb: 1.7% Ileus Grade IVa: 0.9% Bilateral PE/DVT	Yes 40.1%	Pelvic ± RP	NR

Table 3 (*Continued*)

Study	Patient number	Age	SLND duration (min)	Blood loss (ml)	Grade I/II	Grade III	Robot-assisted SLND	Template SLND	Hospital stay (d)
Siriwardana et al	35	67	NR	NR	Grade I: 62.5% Grade II: 37.5% Lymphedema (2) Neuropraxia (2) Cardiac arrhythmia (1) PE (1)	Grade III: 0	Yes	Pelvic	NR
Jilg et al	30	NR	NR	NR	Grade I: 62% Grade II: 0	Grade IIIa: Drainage lymphocele 13.3% Ureteral stent 6.7%	No	Pelvic ± RP	NR
Porres et al	87	67	124	NR	Grade I: 6.9% Grade II: 6.9% Lymphocele Nerve lesion	Grade III: 9.2% Ileus Lymphocele	No	Pelvic ± RP	NR
Montorsi et al	16	66	210	250	Grade I: 6.3% Grade II: 25% Ureteral and vascular injury	Grade III: 0	Yes	Pelvic ± RP	3.5
Osmonov et al	45	NR	NR	NR	Grade I/II: 0	Grade IIb: 15.6% Bleeding (2) Ureteral stricture (2) Rectovesical fistula (1) Lymphocele (2)	No	Pelvic ± RP	NR
Abreu et al	10	65	288	100	Grade II: 30% Flank ecchymosis Chylous ascites Neuropraxia/ foot drop	Grade III/IV: 0	Yes	RP	1
Rauscher et al	31	68	123	NR	Grade I: 19.3% Incisional hernia Paralytic bladder Incontinence Lymphedema Digestive pain Grade II: 0	Grade IIIb: 12.9% Pararectal abscess Ureter injury Septic hydronephrosis -One death by PE 2 mo after surgery	No	Pelvic ± RP	NR

DVT/PE = deep vein thrombosis/pulmonary embolism; NR = not reported; RP = retroperitoneal; SLND = salvage lymph node dissection.

locations. In the series by Zattoni et al. [21], radiological sites of recurrence after SLND were in the pelvic region in most of the cases (45.7%), retroperitoneum in 20%, both locations in 5.7%, and bone in 28.5%. Distant metastasis rates (bone 20%, visceral 6.7%) have been noted in comparable percentages in other series [22]. Median time from SLND to PSA failure was <12 mo in the majority of cases, followed rapidly by radiological progression. Most series reported the mean time to clinical progression after SLND approaching 1 yr.

Some studies have assessed the predictive value of preoperative and post-SLND factors on the risk of biochemical and clinical recurrence after SLND (Table 1). The main preoperative predictive factors of biochemical complete PSA response after SLND were the absence of positive extrapelvic lymph nodes on PET/CT and a preoperative PSA level of <4 ng/ml. Regarding the PSA value, a cutoff of 4 ng/ml has been correlated significantly with poorer outcomes after SLND in univariable analyses by Rigatti et al. [10], Suardi et al. [14], Tilki et al. [17], and Herlemann et al. [20]. Pathological staging at the time of radical prostatectomy was also correlated with SLND outcomes in some series: number of lymph node metastases, pT stage, and Gleason score [10,13,14,16,21,24,27]. The absence of LND at the time of radical prostatectomy has not been evaluated separately as a predictive factor. Nevertheless, the number of positive lymph nodes at the time of primary surgery was correlated to poorer outcomes [10,11,14,16]. The postoperative predictive factors significantly associated with favorable outcomes after SLND were a small number of positive lymph nodes at SLND, a complete biochemical response after SLND (PSA <0.2 ng/ml), and the absence of extrapelvic lymph nodes in the final pathology. The impact of the number of positive lymph nodes was mainly assessed as a quantitative variable [11,16,21]. Suardi et al. [14] and Porres et al. [24] identified a cutoff of one to two versus two or more positive lymph nodes as significant for predicting clinical recurrence-free survival (8-yr rate 62% vs 28%, in the

study by Suardi et al). The presence of pathologically confirmed retroperitoneal positive lymph nodes has been correlated negatively with outcomes in the study by Suardi et al. [14] (hazard ratio [HR] 2.48), suggesting different profiles between nodal recurrence with or without retroperitoneal positive nodes. However, other studies did not find any significant correlations [10,21]. The impact of primary treatment (surgery vs RT or HIFU) has not been assessed as a predictive factor of response to SLND. The castration-resistant disease stage at the time of SLND has been correlated independently with shorter biochemical and clinical recurrence-free survival by Zattoni et al. [21] (HR 2.56) and Rigatti et al. [10] (HR 2.92), respectively.

3.7. *Limitations and perspectives*

Traditionally, lymph node involvement is treated only by ADT, which is considered the optimal treatment option in this setting [1]. Nevertheless, patients affected by nodal metastases showed only better prognosis compared with their counterparts with skeletal or visceral metastases [2,3]. In addition, recent developments in PCa recurrence PET/CT imaging have improved the detection of clinical recurrence even at a low PSA level and could guide node-directed salvage therapy at an early stage of biochemical recurrence.

Detection performance of choline and PSMA PET/CT has previously been confirmed in large series, and depends on the PSA cutoff and PSA kinetics at the time of imaging [5]. The surgical series included in this review corroborated these findings. Performance calculation depended on the lesion of analysis: patient-, side-, region-, subregion-, and node-based analysis. In a systematic review including 750 patients undergoing PET/CT before SLND, pooled sensitivities of choline PET/CT were 85.3%, 56.2%, 75.3%, and 63.7%, respectively, for patient-, lesion-, pelvic site–, and retroperitoneal site–based analysis [34]. The specificity of PSMA PET/CT for predicting pathologically confirmed positive nodes ranged from 87.5% to 97.3% in a field-based analysis among series [29,32]. It is worthy to note that the rate of patients without any positive lymph nodes at final pathology after SLND ranged from 20% to 35% among series (mean 28%) [10,14,17,24,32].

As compared with choline PET/CT, ^{68}Gall-labeled PSMA ligand has been suggested to improve early nodal or local recurrence detection, and thereby, salvage treatment management. Maurer et al. [19] recently demonstrated that on a specimen basis, PSMA radioactive rating yielded a sensitivity of 83.6%, a specificity of 100%, and an accuracy of 93.0%, after a confirmatory series of radioguided surgery. Jilg et al. [23] have evaluated the sensitivity and specificity of PSMA PET/CT at 93.2% and 100%, respectively, in a main region-based analysis. PSMA could outperform choline as a tracer for identifying small nodal lesions. In that article, the authors suggested that the estimated longitudinal diameters of tumor deposits in node metastases to reach detection rates of 50% and 90% are 3.7 and 6.0 mm, respectively, whereas identification of small lesions of $<$5 mm with choline PET/CT is not well studied [23]. SLND directed by ^{68}Ga-labeled PSMA ligand PET/CT demonstrated a better biochemical complete response rate (44% vs 18%), a greater PSA decrease (mean–57% vs +10%, $p = 0.015$), and a longer ADT-free period (4.7 vs 12 mo, $p = 0.001$) compared with SLND performed after choline PET/CT [18]. Maurer et al. [19] reported a 64.5% complete response rate after PSMA radioguided SLND. In a comparative but retrospective study, Pfister et al. [30] suggested that Ga-PSMA PET/CT had better performance than choline PET/CT, with a significantly higher negative predictive value and accuracy for the detection of locoregional recurrence. Individual comparison between both modalities was not done.

Improvements in functional imaging are still awaited. To date, PET imaging appears to be the best method to identify suitable candidates for SLND. However, performance of functional imaging still depends on various factors (PSA level and kinetics, hormonal status) and fails in precisely locating the extent of nodal disease, despite the development of new radiotracers. Pathological data from SLND studies suggested that only a small proportion of patients have lymph node metastases limited to the positive spots and, therefore, any nodal salvage treatment should not be directed only to the suspicious lymph nodes at imaging but also to contiguous nodal areas [26]. In a recent study by Mandel et al. [32], PSMA PET/CT was negative in 10.5% histologically positive sides and in 24.1% histologically positive lymph node fields. Conversely, up to 30% of false positive cases with choline PET/CT (pN0 at SLND) have been reported, leading to potential overuse of SLND [10,14].

Oncological outcomes were interesting. Globally, 50% of patients remained disease free after a short-term follow-up. Some limitations have to be highlighted. First, the definition of biochemical recurrence after SLND remains empirical without consensus. A clear threshold for defining biochemical response after SLND is undefined. Moreover, the type of primary treatment (RT or surgery) may have an impact on this endpoint; the PSA $>$0.2 ng/ml threshold could be inadequate in case of RT as primary treatment. Second, approximately one-third of patients received adjuvant treatment after SLND, by ADT or RT, leading to an overestimation of PSA-free survival rates that could be obtained after SLND alone. Thus, the interpretation of the oncological role of SLND should be done with caution. A non-negligible proportion of clinical recurrences after SLND were located in the operated pelvic region. This could be explained by the location of new involved nodes outside the surgical template, in the perivesical and perirectal fat. An insufficient extended template due to false negative cases on imaging or the presence of micrometastases involving the perinodal tissue is more unlikely. These findings led some teams to add systematic pelvic RT after SLND [13,16]. However, given the retrospective natures of these studies, it is not possible to assess the real benefit of additional adjuvant therapies after SLND. No control group of patients receiving only ADT was reported in the majority of studies. In the study by Steuber et al. [5], node-directed treatment (by SLND or RT) was compared with the standard of care in a large multi-institutional case-control series. The standard of care cohort included 1816 patients receiving immediate or delayed ADT, and their cancer-specific

survival rate was compared with that of 263 patients treated by SLND and 97 patients receiving stereotactic body RT. After a median follow-up of 70 mo, cancer-specific survival was improved in the intervention arm in both univariable and multivariable analysis. In the metastatic oligorecurrent cancer setting, Ost et al. [4] recently demonstrated in a phase II trial that metastasis-directed therapy (surgery or stereotactic body RT) significantly improved the ADT-free survival compared with surveillance alone. This trial also included patients suffering from bone oligometastatic disease. Thus, all these comparative data suggested the potential biochemical impact of metastasis-directed therapy in the oligorecurrence setting. The oncological role of such approaches assessed by clinically meaningful endpoints remains unproven. To date, no head-to-head comparison between SLND and RT as metastasis-directed therapy in the node-only recurrence setting could favor one technique over another.

The optimal selection of candidates for SLND remains elusive. This literature review adds some data regarding predictive factors that could help clinicians in decision making, as favorable oncological outcomes have been reported mainly in patients having only positive nodes in the pelvic region in PET/CT and with a PSA level of <4 ng/ml. Good disease-free survival could also be anticipated by taking into account the number of positive nodes during SLND, PSA decrease after surgery, and absence of confirmed extrapelvic positive nodes at the final pathology. Thus, patients with pure pelvic involvement and favorable pathology features may be the ideal candidates for node-directed salvage strategies, without systematic adjuvant strategy.

Long-term oncological, functional, and quality-of-life outcomes are not available. The impact of SLND on bladder function should also be assessed more thoroughly. In a recent series of urodynamic measurements after transperitoneal SLND, the authors suggested a potential impact of SLND on postoperative functional bladder dysfunctions despite a good safety profile of surgery according to the Dindo-Clavien classification [35].

Studies with longer follow-up and comparisons of SLND with the current standard of care and other interventional strategies (stereotactic body RT) are critically needed to provide high-level evidence [36]. Ongoing clinical trials are awaited. The NCT02974075 has currently recruited 70 patients in a phase I/II prospective trial assessing the role of SLND. No comparative arm has been designed. The PEACE V trial (STORM) has just started to enroll patients with nodal recurrence and planned to include 178 patients. This phase II trial will randomize patients between metastasis-directed therapy (SLND or RT) alone and combined with long-term ADT, and assess metastasis-free survival as the primary endpoint.

Almost all single-center studies are case series from tertiary centers of highly selected patients with significant heterogeneity. The selection bias is of major concern in this setting, especially since a control group (standard of care) is lacking in all except one series. Moreover, the majority of patients have been operated in high-volume referral centers, leading to potential nonreproducibility of postoperative outcomes, including the low complication profile. Last, a pathological analysis of lymph nodes may be variable among studies, due to different surgical templates and macroscopic examination. This highlights the need for a centralized review of SLND pieces as part of dedicated clinical trials.

4. Conclusions

SLND in the setting of node-only recurrence after primary treatment is associated with an early biochemical response in a non-negligible proportion of patients. Its safety profile is acceptable. Long-term prospective studies and randomized trials comparing this interventional approach with ADT alone and with other interventional strategies (RT) are awaited to better assess the oncological role of SLND in clinically meaningful endpoints and its impact on patients' quality of life. Well-designed clinical trials assessing this question are critically needed.

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Study concept and design: Ploussard.
Acquisition of data: Ploussard.
Analysis and interpretation of data: Ploussard, Gandaglia, Heidegger, Tilki, Tsaur, Valerio, van den Bergh, Ost.
Drafting of the manuscript: Ploussard.
Critical revision of the manuscript for important intellectual content: Ploussard, Gandaglia, Borgmann, de Visschere, Heidegger, Kretschmer, Mathieu, Surcel, Tilki, Tsaur, Valerio, van den Bergh, Ost, Briganti.
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References

[1] Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017;71:630–42.
[2] Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 2016;34:1652–9.
[3] Ost P, Decaestecker K, Lambert B, et al. Prognostic factors influencing prostate cancer-specific survival in non-castrate patients with metastatic prostate cancer. Prostate 2014;74:297–305.
[4] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.

[5] Steuber T, Jilg C, Tennstedt P, et al. Standard of care versus metastases-directed therapy for PET-detected nodal oligorecurrent prostate cancer following multimodality treatment: a multi-institutional case-control study. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2018.02.015.
[6] Ploussard G, Almeras C, Briganti A, et al. Management of node only recurrence after primary local treatment for prostate cancer: a systematic review of the literature. J Urol 2015;194:983–8.
[7] Rinnab L, Mottaghy FM, Simon J, et al. [11 C]Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Preliminary results of a prospective study. Urol Int 2008;81:191–7.
[8] Schilling D, Schlemmer HP, Wagner PH, et al. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. BJU Int 2008;102:446–51.
[9] Winter A, Uphoff J, Henke RP, Wawroschek F. First results of [11 C] choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy. Urol Int 2010;84:418–23.
[10] Rigatti P, Suardi N, Briganti A, et al. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11 C]choline positron emission tomography/computed tomography. Eur Urol 2011;60:935–43.
[11] Jilg CA, Rischke HC, Reske SN, et al. Salvage lymph node dissection with adjuvant radiotherapy for nodal recurrence of prostate cancer. J Urol 2012;188:2190–7.
[12] Karnes RJ, Murphy CR, Bergstralh EJ, et al. Salvage lymph node dissection for prostate cancer nodal recurrence detected by (11)c-choline positron emission tomography/computerized tomography. J Urol 2015;193:111–6.
[13] Jilg CA, Leifert A, Schnell D, et al. Toxicity and quality of life after choline-PET/CT directed salvage lymph node dissection and adjuvant radiotherapy in nodal recurrent prostate cancer. Radiat Oncol 2014;9:178.
[14] Suardi N, Gandaglia G, Gallina A, et al. Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. Eur Urol 2015;67:299–309.
[15] Claeys T, Van Praet C, Lumen N, et al. Salvage pelvic lymph node dissection in recurrent prostate cancer: surgical and early oncological outcome. Biomed Res Int 2015;2015:198543.
[16] Rischke HC, Schultze-Seemann W, Wieser G, et al. Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. Strahlenther Onkol 2015;191:310–20.
[17] Tilki D, Mandel P, Seeliger F, et al. Salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy. J Urol 2015;193:484–90.
[18] Linxweiler J, Saar M, Al-Kailani Z, et al. Robotic salvage lymph node dissection for nodal-only recurrences after radical prostatectomy: perioperative and early oncological outcomes. Surg Oncol 2018;27:138–45.
[19] Maurer T, Robu S, Schottelius M, et al. (99m)Technetium-based prostate-specific membrane antigen-radioguided surgery in recurrent prostate cancer. Eur Urol 2019;75:659–66.
[20] Herlemann A, Kretschmer A, Buchner A, et al. Salvage lymph node dissection after (68)Ga-PSMA or (18)F-FEC PET/CT for nodal recurrence in prostate cancer patients. Oncotarget 2017;8:84180–92.
[21] Zattoni F, Nehra A, Murphy CR, et al. Mid-term outcomes following salvage lymph node dissection for prostate cancer nodal recurrence status post-radical prostatectomy. Eur Urol Focus 2016;2:522–31.
[22] Siriwardana A, Thompson J, van Leeuwen PJ, et al. Initial multicentre experience of (68) gallium-PSMA PET/CT guided robot-assisted salvage lymphadenectomy: acceptable safety profile but oncological benefit appears limited. BJU Int 2017;120:673–81.
[23] Jilg CA, Drendel V, Rischke HC, et al. Diagnostic accuracy of Ga-68-HBED-CC-PSMA-ligand-PET/CT before salvage lymph node dissection for recurrent prostate cancer. Theranostics 2017;7:1770–80.
[24] Porres D, Pfister D, Thissen A, et al. The role of salvage extended lymph node dissection in patients with rising PSA and PET/CT scan detected nodal recurrence of prostate cancer. Prostate Cancer Prostatic Dis 2017;20:85–92.
[25] Montorsi F, Gandaglia G, Fossati N, et al. Robot-assisted salvage lymph node dissection for clinically recurrent prostate cancer. Eur Urol 2017;72:432–8.
[26] Passoni NM, Suardi N, Abdollah F, et al. Utility of [11C]choline PET/CT in guiding lesion-targeted salvage therapies in patients with prostate cancer recurrence localized to a single lymph node at imaging: results from a pathologically validated series. Urol Oncol 2014;32, 38.e9–16.
[27] Osmonov DK, Aksenov AV, Trick D, et al. Cancer-specific and overall survival in patients with recurrent prostate cancer who underwent salvage extended pelvic lymph node dissection. BMC Urol 2016;16:56.
[28] Abreu A, Fay C, Park D, et al. Robotic salvage retroperitoneal and pelvic lymph node dissection for 'node-only' recurrent prostate cancer: technique and initial series. BJU Int 2017;120:401–8.
[29] Rauscher I, Maurer T, Beer AJ, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med 2016;57:1713–9.
[30] Pfister D, Porres D, Heidenreich A, et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with(18)F-fluoroethylcholine PET/CT. Eur J Nucl Med Mol Imaging 2016;43:1410–7.
[31] Rauscher I, Düwel C, Wirtz M, et al. Value of (111)In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. BJU Int 2017;120:40–7.
[32] Mandel P, Tilki D, Chun FK, et al. Accuracy of (68)Ga-prostate-specific membrane antigen positron emission tomography for the detection of lymph node metastases before salvage lymphadenectomy. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2018.07.025.
[33] Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. 2012. http://www.ihe.ca/documents/Case%20series%20studies%20using%20a%20modified%20Delphi%20technique.pdf.
[34] Evangelista L, Zattoni F, Karnes RJ, Novara G, Lowe V. Radiolabeled choline PET/CT before salvage lymphadenectomy dissection: a systematic review and meta-analysis. Nucl Med Commun 2016;37:1223–31.
[35] Hanske J, Müller G, van Ophoven A, et al. De novo neurogenic bladder dysfunction after salvage lymph node dissection in patients with nodal recurrence of prostate cancer. Neurourol Urodyn. In press. https://doi.org/10.1002/nau.23545.
[36] Ost P, Jereczek-Fossa BA, As NV, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69:9–12.