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TOPIC PAPER

# Salvage lymphadenectomy in recurrent prostate cancer: is there evidence of real benefit?

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## Abstract

**Purpose** Nodal recurrent prostate cancer (PCa) after primary radical treatment represents a heterogeneous entity with many treatment options. In some cases, surgical removal of metastatic nodes seems to improve cancer control and delay systemic treatments. The objectives of this study were to analyze the available literature on salvage lymphadenectomy for the treatment of nodal recurrent PCa and to elucidate the real oncological benefit deriving from this procedure.

**Methods** A PubMed search was performed using the following terms: prostate cancer, metastatic, oligometastatic, salvage lymphadenectomy, salvage lymph node dissection, salvage lymph node excision, and cytoreductive surgery. We included in the study all papers on salvage lymphadenectomy in nodal recurrent PCa, with no temporal limits. In addition, several papers addressing cytoreductive surgery and the biology of oligometastatic disease, published in different medical and basic research journals, were included.

**Results** Salvage lymphadenectomy is still characterized by a lack of standardization in patient selection and surgical template. Its primary objectives are to prolong progression-free survival and to delay the need for systemic therapy. The improvements in preoperative imaging techniques in conjunction with the wide use of minimally invasive surgery have generated growing interest in this procedure.

**Conclusion** Salvage lymphadenectomy is a promising treatment approach; however, its real oncological benefit is still far from proven. Prospective randomized trials need to be designed to improve understanding of this issue.


**Keywords** Prostate cancer · Biochemical recurrence · Salvage lymph node dissection · Positron emission tomography

## Introduction

The treatment of recurrent prostate cancer (PCa) after radical interventions continues to represent a challenge for the urological community. Regardless of the tumor volume, recurrent disease after radical prostatectomy has conventionally been treated with radiation therapy in cases of local recurrence or with androgen deprivation therapy (ADT) in cases of systemic relapse [1]. Targeted therapy for oligometastatic disease is a quite modern concept, its aim being to reduce the tumor burden. One of the obstacles to use of a highly selective treatment approach has been the difficulty in precisely locating metastases. The most recent technological improvements, however, allow better definition of sites of metastasis, making it feasible to use metastasis-directed treatment modalities [2]. Thanks to these new diagnostic tools it is now possible to identify a subgroup of patients with systemic disease "limited" to the regional and/or retroperitoneal lymphatic stations who have a more favorable prognosis compared to those with bone or visceral metastases [3]. Within this context, metastatic lymph node dissection (LND) in nodal recurrent PCa after radical treatments has become a feasible salvage approach, and salvage LND (sLND) has been proposed in patients with "node-only" biochemical recurrence (BCR) after definitive treatment of primary PCa.

In recent years a number of studies have reported the results of salvage surgery in patients with LN metastases in

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the small pelvis following previous local treatment. Unfortunately, all these emerging data derive from retrospective studies, and neither the template nor the real value of sLND has been clearly defined. Given this low level of evidence, EAU Guidelines recommend early or delayed hormonal therapy for nodal metastasis after radical prostatectomy, while sLND remains an experimental treatment to be used in study settings [4].

The aim of this review is to evaluate the role of sLND in the treatment of nodal recurrent PCa.

## Methods

This is a non-systematic review to perform an update on salvage lymphadenectomy in nodal recurrent PCa on the most recent and relevant articles. In addition, several papers addressing cytoreductive surgery and the biology of oligometastatic disease, published in different medical and basic research journals, were included.

An expert committee evaluated and graded the published data according to the Oxford System of Evidence-based Medicine [5]. For this updated publication, an exhaustive search was conducted in PubMed for recent relevant papers published with no temporal limits using the following topics: prostate cancer, metastatic, oligometastatic, salvage lymphadenectomy, salvage lymph node dissection, salvage lymph node excision and cytoreductive surgery. Only English publications were targeted. Relevant original articles addressing the role of sLND in PCa were selected.

## Results and discussion

### Definition and surgical limits of sLND

Oligometastatic PCa is defined by three or less to five metastatic lesions, absence of rapid spread to more sites, and feasibility of targeted treatment of all metastatic lesions with surgery or radiation therapy [6]. Even if ADT still represents the standard treatment, the possibility of postponing any kind of hormonal treatment and the associated adverse events is very attractive [7]. Promising results have recently been presented by Sivaraman et al. [8]: among 48 patients treated with sLND, 14.6% had undetectable PSA at 3 years of follow-up without any adjuvant treatment.

The appropriate extent of dissection during sLND remains an open issue since the patients who have undergone this type of surgery represent a heterogeneous group. According to the EAU guidelines, an initial LND is not recommended if the risk of nodal metastasis is < 5% (incidentally, 40% of patients undergoing surgery develop BCR with rising levels of prostate-specific antigen (PSA) [9]). As a consequence, some patients with nodal recurrence will have undergone an initial standard LND while others will not; moreover, in some cases the targeted nodal tissue will have been treated with radiation. All these aspects make it even more difficult to establish an LND template. Commonly, the area of sLND and its anatomical limits are guided by the results of preoperative staging imaging. Since no established criteria are available, the LND may be performed by dissection of suspicious nodes at imaging or using a predetermined template. In patients with clinically relapsing disease localized to the pelvic nodes, sLND should include obturator and internal and external iliac lymph nodes to the level of the aortic bifurcation. Similarly, such patients can benefit from the dissection of presacral nodes [10]. Even weaker evidence supports the performance of retroperitoneal LND, but this is warranted in cases of retroperitoneal LN involvement at preoperative imaging or positive common iliac nodes at frozen section. The superior limit of this procedure is represented by the level of the renal artery [11]. Here it is noteworthy that patients with suspected retroperitoneal metastatic disease are characterized by a worse prognosis, regardless of the extent of dissection (5-year clinical recurrence-free survival 11% vs 53%; $p < 0.001$) [12]. The fact that the extent of LND remains an eminence-based decision is all the more explicable if one bears in mind the low level of concordance between imaging findings and pathology reports in terms of both the number (58.3%) and the location (83%) of positive nodes [8].

Salvage LND seems to be characterized by a low morbidity. According to the literature, the overall complication rate ranges from 7.4 to 91.4%. The majority of complications do not require reintervention; paralytic ileus and deep venous thrombosis are the most frequent. The rate of Clavien–Dindo grade III complications ranges from 0 to 27% and no Clavien–Dindo V have been observed. Nevertheless, this statement is supported by a low level of evidence, since only a few authors have reported and classified intra- and postoperative complications [13]. Interestingly, no grade III postoperative complications were reported in a recent robotic series [14]. According to these authors, three of ten patients experienced Clavien–Dindo grade II complications that resolved spontaneously [14]. Similar results were presented by Monitors et al. who found that among a population of 16 patients who underwent robotic sLND, only four experienced intraoperative complications, none of whom required reintervention [15]. Globally, a minimally invasive approach yields better surgical results in terms of lower complication rates and shorter hospital stay.

### Use of imaging for patient selection

According to the EAU guidelines, choline positron emission tomography/computed tomography (PET/CT) is the preferred imaging technique for the detection of nodal metastases in patients with BCR [4]. Nevertheless, the sensitivity of choline PET is strictly dependent on PSA levels and kinetics. In the presence of PSA < 1 ng/ml, the detection rate of choline PET is quite unsatisfactory (5–24%), whereas it reaches 67–100% at PSA > 5 ng/ml [16]. Not only PSA but also hormonal and chemotherapy (CT) status may affect the diagnostic accuracy of choline PET, and the use of adjuvant treatments may increase the risk of false negatives, especially at PSA levels < 5 ng/ml [17].

Currently, most studies on sLND use preoperative choline PET to detect the site of nodal metastases. The data from these studies, based on histologic verification, confirm that $^{11}$C-choline PET/CT has a good sensitivity (64–95%) and specificity (40–93%) for the detection of nodal recurrence [18, 19]. Nonetheless, there are conflicting data on the accuracy of choline PET. In an interesting study published a few years ago [20], Passoni et al. analyzed 46 patients treated with sLND for a single suspected nodal metastasis after radical prostatectomy. The detection of nodal metastases was based on choline PET/CT, and median PSA before imaging was 0.5 ng/ml. Of the 46 patients, 38 (83%) had a positive pathology at sLND, but only 16 (35%) had a single metastasis limited to the nodes indicated by PET/CT. In view of this low accuracy, the authors concluded that even when a single positive site of metastasis is detected on choline PET/CT, an extensive LND is needed to improve the curative potential of the procedure. Better results have been presented recently by Oderda et al. In their retrospective study, 106 patients with BCR after primary treatment for PCa were evaluated with $^{11}$C-choline PET/CT prior to sLND. More than 80% of the patients had histologically confirmed nodal involvement, confirming that choline PET/CT offers good accuracy [21].

In recent years a novel radiotracer, Glu-NH-CO–NH-Lys-(Ahx)-[$^{68}$Ga(HBED-CC)], commonly known as $^{68}$Ga-PSMA, has shown promising results, with higher detection rates than choline PET even in the presence of low PSA levels. In particular, detection rates ranging from 25 to 73% have been reported at PSA levels of < 1 ng/ml [22]. The most relevant clinical implication is the possibility of earlier detection and treatment of nodal recurrence, even if there is still no evidence on the real benefit in terms of oncological outcomes. To date, few studies have assessed the role of PSMA PET in the detection of nodal metastases before surgery in patients with nodal recurrent PCa [23–28].

Siriwardana et al. have confirmed the diagnostic potential of PET [26]. Of 35 patients who underwent robot-assisted sLND after detection of nodal recurrent PCa on PSMA PET, 32 (91%) had pathologically confirmed nodal metastasis but only 31% achieved a complete response (6-week PSA < 0.05 ng/ml if primary treatment was radical prostatectomy). The BCR-free survival rate at 12 months of follow-up was 23% and the only significant predictor of treatment response was bilateral template dissection. The latest multicenter series on the use of PSMA PET for detection of nodal recurrent PCa analyzed its accuracy in a cohort of 23 patients who underwent PSMA PET before sLND. Overall, only 26.6% (29/109) of positive nodes at imaging harbored a histopathologically confirmed metastasis. In the field-based analysis, sensitivity and specificity were 75.9% and 87.5%, respectively [23]. Unfortunately, because this diagnostic tool was introduced only recently, data on long-term follow-up are unavailable and consequently it is impossible to define the real benefit deriving from earlier diagnosis of recurrence.

Few comparative studies have been conducted on the accuracy of choline PET and PSMA PET, but those that have been performed indicate that PSMA PET has a higher sensitivity, specificity, and positive and negative predictive values (86.9% vs 71.2%, $p < 0.001$; 3.1% vs 86.9%, $p < 0.001$; 75.7% vs 57.7%, $p < 0.001$; and 96.6% vs 88.8%, $p < 0.001$, respectively) [29].

## Oncological outcomes after sLND

Since the principal objective of sLND is not to cure patients but to delay systemic treatments, biochemical recurrence-free survival (BCRFS) represents the most interesting outcome. To make this scenario even more complex, there is a wide range of definitions of BCR and, moreover, no standardized treatment approaches for metastatic disease are available [30]. Due to these limitations, an accurate evaluation of oncological outcomes remains far from possible.

One of the first studies on this topic failed to find a significant improvement in oncological outcomes after sLND. Only 1 of the 15 patients had a PSA nadir < 0.1 ng/ml after sLND and, following a mean follow-up of 13.7 months, three patients had developed bone metastases [31]. Better outcomes were reported by Winter et al. in a small series of six patients who underwent sLND. Interestingly, all suspected metastases at presurgical imaging (PET/CT) were confirmed by the pathology report. During a median follow-up of 24 months, three patients presented a durable BCR with undetectable PSA. Despite the small number of patients, the authors concluded that sLND can significantly improve oncological outcomes in a well-selected population. An interesting series was published by Rigatti et al. in 2011 [12] and updated in 2015 by Suardi et al. [10]. In the first report, 41 patients (56.9%) achieved a complete BCR after surgery, of whom 13 (32%) were treated with ADT. During a mean follow-up of 3 years, further PSA progression was observed in 24 (85.7%) of the 28 patients with complete BCR who were not treated with ADT. According to the updated data published by Suardi et al. 35 of the 59 analyzed patients (59.3%) had a BCR after surgery and the 5- and 8-year BCR-free survival rates among these patients were 29.4% and 22.1%, respectively. The authors also identified

**Table 1** Main results of studies that have reported on sLND in patients with nodal recurrent PCa for which 5-year follow-up data are available

| Author | No. of patients | PSA at sLND (ng/ml) | No. of nodes removed | No. of positive nodes | BR (%) | 5-year BCRFS (%) | 5-year PFS (%) | 5-year CSS (%) |
|---|---|---|---|---|---|---|---|---|
| Rigatti et al. [12] | 72 | 1.2 (0.8–5.1) | 29 (16–40) | 2 (1–12) | 56.9 | 19 | 34 | 75 |
| Jilg et al. [27] | 52 | 52. (0.9–72) | 17 (1–57) | 4 (0–54) | 46 | 8.7 | 25.6 | 75.7 |
| Clayes et al. [33] | 13 | 2 (0.2–26) | 11 (1–219 | 1 (0–6) | 23 | NA | 38.4 | NA |
| Tilki et al. [34] | 58 | 9.8 | 18.6 | 6.3 | 22.4 | 0 | 35.9 | 71 |
| Karnes et al. [32] | 52 | 2.2 (1.4–3.7) | 21 (16–30) | 3 (1.2–6) | 73 | 45.5 | 47 | 92.5 |
| Suardi et al. [10] | 59 | 2 (0.8–5.3) | 26 (15–40) | 2 (1–11) | 59.3 | 29.4 | 52 | 89 |
| Zattoni et al. [35] | 117 | 2.3 (1.2–4.1) | 22 (15–30) | 3 (1–6) | 79.5 | 31 | 51 | 97 |
| Herlemann et al. [36] | 104 | 4.1 (2–7.4) | 13 (7–25) | 3 (1–7) | 29.8 | 6.2[a] | 26[a] | 82.8[a] |

Data are shown as median (IQR)

*PSA* prostate-specific antigen, *BCR* biochemical response, *BCRFS* biochemical recurrence-free survival, *PFS* progression-free survival, *CSS* cancer-specific survival

[a]Data refer to patients reporting BCR

a number of factors affecting the risk of BCR after sLND: PSA at surgery, time to BCR, and involvement of retroperitoneal nodes.

The best oncological results were achieved by Karnes et al. [32]. In their cohort of 52 patients, 73% presented a complete BCR and at 5-year follow-up the BCRFS, progression-free survival (PFS), and cancer-specific survival (CSS) were 45, 47, and 92%, respectively. In the largest published study, Zattoni et al. evaluated 117 men treated with sLND for nodal recurrent PCa. These authors defined BCR after surgery as a PSA > 0.2 ng/ml; recurrence was detected with choline PET/CT. According to final pathology, all patients had a confirmed nodal metastasis and 79.5% achieved BCR after sLND. At 5 years of follow-up, the BCR rate and CSS were 31% and 91%, respectively.

Table 1 reports the results of studies on sLND in patients with nodal recurrent PCa in which 5 years of follow-up data are available.

According to the literature, sLND appears a feasible procedure, and in this context it is to be borne in mind that most patients will experience a BCR after surgery. Even if some authors have reported a 5-year BCR rate of 45%, in most of the published studies the rate does not exceed 20%. Moreover, only 26–34% will not experience clinical recurrence. All these data suggest that sLND can prolong survival and delay the need for systemic therapy but is not really able to cure the disease [11]. Hence, patient selection for sLND plays a crucial role and should be undertaken carefully. Rigatti et al. [12] showed that patients with a presurgical PSA < 4 ng/ml and patients with no retroperitoneal involvement had a greater benefit from surgery, with a significant improvement in 5-year clinical recurrence-free survival (48% vs 13%; log-rank: $p = 0.004$). However, larger series and more homogenous cohorts are needed to develop a predictive nomogram able to improve the accuracy of patient selection.

## Conclusions

The aim of sLND is to reduce tumor burden and, consequently, to delay any systemic treatment. Even if a high percentage of patients will experience recurrence after surgery, this kind of treatment could prolong survival and should be considered as a treatment option in a well-selected group of patients. The role of sLND is supported by a growing evidence, but this procedure is still experimental and its use should be limited in the context of clinical studies. Larger and standardized trials are needed to improve the oncological outcomes and patient selection.

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## Compliance with ethical standards

**Conflict of interest** The author declares that they have no competing interest.

**Research involving human participants and/or animals** The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** For this type of study, informed consent is not required.

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