

18F-choline positron emission tomography/computed tomography guided laparoscopic salvage lymph node dissection in patients after radical prostatectomy

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Abstract

Introduction: Salvage lymph node dissection (sLND) using novel imaging methods is an interesting alternative to treat lymph node (LN) metastasis after radical prostatectomy (RP); however, recommendations for using sLND as such are still being developed.

Aim: To assess the clinical outcomes of prostate cancer (PCa) after fluorine-18-choline (18F-choline) positron emission tomography/computed tomography (PET/CT) guided sLND.

Material and methods: Ten patients who had undergone sLND under 18F-choline PET/CT guidance (positive nodes: median 1, range 1-3) and had biochemical recurrence or persistence of prostate-specific antigen (PSA: median PSA 2.05 ng/ml, range: 0.8–8.4) after RP were enrolled in this retrospective study. Complete biochemical response (cBCR) after salvage surgery was defined as PSA < 0.2 ng/ml.

Results: The median follow-up time after salvage surgery was 33 months. The median PSA level 6 weeks after sLND and at the end of follow-up was 0.93 and 2.95 ng/ml, respectively. At 6 weeks after targeted sLND only 1 patient had cBCR, whereas a PSA decrease was noted in 7 patients. No patient had cBCR at the end of follow-up.

Conclusions: Laparoscopic sLND in cases of LN metastatic PCa after RP is a feasible option with low morbidity. However, an initial cBCR occurs in a negligible proportion of patients, and a long-term response is unlikely to be achieved.

Key words: prostate cancer, radical prostatectomy, choline, salvage lymph node dissection, fluorine-18.

Introduction

Radical prostatectomy (RP) remains one of the most common treatment methods for prostate cancer (PCa) without metastasis [1–3]. As a result, within the last few years in Poland, the total number of procedures conducted and the number of the centres reporting the use of laparoscopic or robotic RPs have increased substantially [4]. This surgery is performed with curative intent, although between 27% and 53% of all patients develop biochemical recurrence (BCR) [5]. Subsequently, the most com-

mon choice of treatment is salvage radiotherapy (SRT), which is indicated when prostate-specific antigen (PSA) is below 0.5 ng/ml [6]. SRT is usually performed without additional imaging. However, novel imaging methods allow for the identification of tumour cell sites and further targeted management, such as salvage lymph node dissection (sLND) [7]. It is important to note that intra- and postoperative complications and the effectiveness of sLND are unknown, which limits the use of this approach [8]. Nevertheless, a reduction in operation time, which consequently leads to a decreased number of post-

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operative complications (such as lymphocele), may be achieved by performing targeted lymphadenectomy.

Aim

The aim of this study was to analyse the outcomes and evaluate the benefits of targeted sLND after RP.

Material and methods

Patients who underwent laparoscopic RP with pelvic lymph node (LN) dissection in the urology department between January 2016 and December 2017 were included in the study. Retrospective data analysis identified patients with PSA recurrence or persistence after surgery. Further, patients were selected according to the results of ^{18}F -choline positron emission tomography/computed tomography (PET/CT) scans. Patients had to have at least one PET-positive LN and no evidence of a local recurrence or bone metastases in conventional diagnostic imaging (ultrasound and/or computed tomography and/or magnetic resonance and/or bone scintigraphy) in order to be included. Finally, patients who underwent targeted sLND were identified, and those treated with other therapeutic options before sLND were not excluded. The final sample included 10 patients. Mean age was 66.8 years (standard deviation 5.25).

PSA level was tested before RP, the day of ^{18}F -choline PET/CT examination, 6 weeks after sLND and 3, 6, 9, and 12 months after sLND; and biannually thereafter. PET/CT scans were not routinely repeated after salvage surgery. The follow-up was ended when a second salvage therapy was initiated. Complete biochemical response (cBCR) after sLND was defined as PSA < 0.2 ng/ml. PSA decrease after surgery without reaching cBCR was defined as PSA-decrease–no response.

All salvage procedures were first theoretically planned in a consensus conference with at least 2 urological surgeons. Only PET/CT-positive and nearby LNs were resected. The nearby LNs were defined as LNs located in the same anatomical area as PET/CT-positive LN. For example, if the external iliac lymph node was positive on PET/CT, the residual LN overlapping the external iliac vessel was removed.

During surgery, the surgeons had access to the imaging material. Thus, if adjustments were needed, their approaches were based on the imaging infor-

mation. All salvage procedures were performed by a transperitoneal laparoscopic approach.

The resected LNs were labelled according to location, sectioned at 3-mm intervals, formalin fixed and submitted for paraffin embedding. Micro-slices were placed on glass slides and stained with haematoxylin and eosin. Immunohistochemistry was performed if needed.

All ^{18}F -choline PET/CT scans were performed at one external centre by experts using integrated PET/CT systems. Experienced radiologists and nuclear medicine specialists assessed the images and located the sites of pathological choline uptake. The diagnosis of tumour-positive LNs on PET/CT images was based on visual evidence of increased focal uptake on a choline PET scan, where the location corresponded to LNs on CT images.

Since only PET/CT-positive and adjacent LNs were removed and no extended lymphadenectomy was performed, it was not possible to calculate sensitivity (SN), specificity (SP) or negative predictive value (NPV). Positive predictive value (PPV) was calculated according to its definition (true-positive/(true-positive + false-positives)).

Results

Table I shows a summary of patient characteristics. The overall median (range) pre-sLND PSA value was 2.05 (0.8–8.4) ng/ml. Overall, 114 nodes in 10 patients were excised. The median number of positive nodes was 1 (range: 1–6). Before sLND, 4 patients received salvage radiotherapy (SRT). The PPV of ^{18}F -choline PET/CT in detecting LN metastases was 90%. Mean operation time and mean hospital stay were 97.5 min and 3 days, respectively. No patient had intra-operative complications, or required an open conversion or any blood transfusions. At follow-up, no lymphocele was reported.

Median (range) follow-up time after salvage surgery was 22 (10–33) months. The median PSA level 6 weeks after sLND and at the end of follow-up was 0.93 and 2.95 ng/ml, respectively. When assessing the dynamics of PSA level within 6 weeks after targeted sLND only 1 patient had cBCR (PSA level < 0.2 ng/ml), but PSA-decrease–no response was noted in 7 patients. The patient with cBCR developed local metastasis at follow-up and finally received chemotherapy with docetaxel. One patient with initial PSA-decrease–no response received androgen deprivation therapy (ADT) due to PSA rising at the

Table I. Baseline characteristics of patients

No.	Age [years]	PSA 1	TNM stage	Gleason score	PSA 2	Localization of positive uptake	Histology results	PSA 3	PSA 4
1	70	10.5	pT2b pNx cM0 R0	3 + 3	8.4	Left common iliac vessels	Positive	2.1	2.9
2	61	7.5	pT2c pN0 cM0 R1	4 + 4	2.1	Right external iliac vessels	Positive	0.9	1.6
3	76	3.7	pT2c pN0 cM0 R0	4 + 4	3.3	Left external iliac vessels	Positive	1.5	2.0
4	67	9.1	pT2c pN0 cM0 R1	4 + 3	7.54	Left common iliac vessels	Positive	0.3	11
5	62	7.8	pT2b pN0 cM0 R0	4 + 3	1.3	Right obturator fossa	Positive	0.8	2.0
6	72	3.4	pT3a pN1 cM0 R0	4 + 4	2.3	One paracaval lymph node	Positive	0.09	10.8
7	70	12.0	pT2c pN0 cM0 R0	4 + 3	1.3	Right obturator fossa and right parailiac lns	Negative	0.7	5.1
8	67	7.8	pT3a pN0 cM0 R0	3 + 4	2.0	Right common iliac vessels	Positive	1.4	1.9
9	63	17.0	pT3b pN0 cM0 R0	3 + 4	8.0	Right iliac external vessels	Positive	9.1	13.0
10	60	10	pT2c pN0 cM0 R1	3 + 3	0.8	Left iliac external and internal vessels	Positive	0.95	3.0

PSA 1 – PSA at diagnosis, PSA 2 – PSA at PET/CT, PSA 3 – PSA 6 weeks after sLND, PSA 4 – PSA at the end of follow-up.

follow-up. Remaining patients with PSA-decrease – no response were managed by close monitoring.

Increase in PSA level was noted in 2 patients at 6 weeks after sLND. One of them was treated with ADT.

Discussion

The role of different PET/CT tracers in detecting recurrence after radical therapy of PCa has been assessed in numerous studies. Prostate-specific membrane antigen (PSMA) PET/CT is considered to be better than conventional and PET imaging with other tracers, including choline PET/CT, especially in the context of BCR [8]. Hence, the European Association of Urology guidelines recommend PSMA PET/CT imaging in BCR when low PSA levels occur, particularly if the PSA level is 1 ng/ml or more after RP [5]. However, PSMA PET/CT imaging is not readily available in Poland. Therefore, choline PET/CT is commonly performed when BCR is detected. The pooled detection rate of choline PET/CT, SN and SP for BCR for all sites of recurrence is 62%, 89% and 89%, respectively [6]. In LN metastasis, a lesion-based analysis showed that ¹¹C-choline PET/CT SP, SP, PPV, NPV, and accuracy were 64%, 90%, 86%, 72%, and 77%, respectively [9]. The SN mainly depends on PSA level and may range between 38 and 98% [6]. The low NPV seems to depend on the restricted capability of ¹¹C-choline PET/CT to detect microscopic lesions. However, the high PPV, even with low PSA values, provides a basis for further treatment decisions [9].

The surgical management of LN metastases after RP has been the topic of several retrospective analyses. However, no consensus has been reached about the extent of LN dissection and the templates that need to be dissected during salvage procedures. Most studies reported results for an anatomically defined, extended sLND that included the obturator fossa; external, internal, and common iliac artery regions; and proximal removal of all lymph nodes along the common iliac vessels to the aortic bifurcation [10, 11]. In addition, in some studies the dissection was extended to the retroperitoneum in the case of positive spots above the aortic bifurcation [12–15]. Jilg *et al.* presented results of open extended sLND after radical radiotherapy or prostatectomy. PCa recurrence in LN was confirmed by ¹¹C/¹⁸F PET/CT [16]. During the histopathological evaluation of the removed LNs, PCa was verified in all patients. Jilg *et al.* emphasised the high diagnostic accuracy of choline PET/CT for pelvic and retroperitoneal LNs regions, and concluded that if there is one choline-positive LN in an iliac subregion, then all pelvic subregions on that side should be resected to sufficiently eradicate micro-metastatic lymphatic spread [16]. Deconinck *et al.* also assessed the diagnostic value of ¹¹C-choline PET/CT scan to detect LN metastases in patients with BCR after radically treated PCa [17]. Contrary to the findings of Jilg *et al.*, Deconinck *et al.* found that the overall detection using choline PET/CT rate was relatively low with a moderate PPV

for metastatic LNs in patients with BCR. Additionally, a high rate of false-positive nodes, which were mainly located in the external iliac regions, was observed. These findings seem to discourage the planning process of highly selective metastatic ablation, which focused only on positive spots of choline PET/CT scans [17].

Evidence for targeted sLNDs is limited. Winter *et al.* presented results of guided sLND in patients with PSA failure and single LN recurrence after RP [18]. Following the salvage surgery, 10 of 11 patients with histologically confirmed LN metastases showed a PSA response. In 5 patients, the PSA value decreased below 0.2 ng/ml. PSA was examined without ADT, and the median follow-up was 72 months. According to Winter *et al.*, this approach at least offers a therapeutic benefit in selected cases with minimal lymphatic dissemination [18]. In contrast to the Winter *et al.* study, the current study showed sLND with a less promising approach. Despite the fact that our study had a shorter median follow-up time (compared to Winter *et al.*), and 2 patients received ADT, no patient achieved long-lasting, complete PSA remission.

Siriwardana *et al.* compared different templates of LN resection [19]. After reviewing primary, adjuvant and salvage treatment history, preoperative PET/CT imaging, and intra-operative anatomical findings, patients were selected to undergo a targeted sLND limited to the PET/CT detected lesions and any surrounding lymph nodes and a unilateral or bilateral extended sLND. The Siriwardana *et al.* study revealed that the only significant predictor for treatment response was bilateral template dissection, with an odds ratio of 28.5 (95% CI: 4.17–584.92) for PSA level below 0.2 ng/ml [19].

Conflicting results for choline PET/CT based targeted sLND emphasise that this strategy remains controversial. Choline PET/CT cannot detect LNs smaller than 8 mm [20]. Of course, the positive predictive value is high. However, choline PET/CT can only identify patients with large nodes and advanced disease, whereas patients with smaller nodes are negative. In positive patients, when excising the large positive nodes only, a number of choline PET/CT negative metastatic nodes may remain. This explains our poor results. In contrast, patients with small metastatic nodes only and therefore more suited for sLND cannot be selected by means of choline PET/CT. Therefore, new PET/CT tracers were investigated in this issue. Recently, Maurer *et al.* assessed

the feasibility of 99m-technetium-based, PSMA-radioguided surgery in patients recurring after local treatment and selected by an initial ⁶⁸Ga-labelled PSMA (⁶⁸Ga-PSMA) ligand PET/CT. Oncological outcomes were overall at least as good as those previously reported in bilateral extended sLND series [10]. This may suggest that the improvements of preoperative imaging could outline more precise removal fields. Nonetheless, when ⁶⁸Ga-PSMA PET/CT was used, bilateral extended sLND was more likely to provide cBCR, suggesting that identification of small and/or atypically localised lesions during salvage surgery procedures is challenging [19]. Hence, the accuracy of PSMA-PET remains insufficient to justify resection of only PSMA-positive fields, but favours complete bilateral sLND.

Today, minimally invasive approaches are the most widely used for sLND. Kolontarev *et al.* presented results of 10 patients with only identified LN metastases of PCa. All patients underwent robotic extended sLND. Overall median PSA decreased by 31.4%, and no patient reached a PSA of zero postoperatively. One patient had Clavien-Dindo grade II complications. Kolontarev *et al.* concluded that a robotic approach is safe and allows for the majority of patients to postpone ADT, which theoretically decreases treatment costs [21]. A laparoscopic approach was assessed by Schilling *et al.*, and all 10 patients initially presented PSA regress after sLND. At follow-up, 2 patients were being closely monitored, 2 had received radiotherapy of the prostate fossa, and 2 had received chemotherapy with docetaxel. In addition, 4 patients were treated by ADT in the Schilling *et al.* study. No blood transfusions, conversion to open surgery, or perioperative complications were reported [22].

The current study provides valuable information about the clinical course after sLND in PCa patients. Nevertheless, this study had some limitations. First, there was insufficient information on PSA kinetics after RP available for the selected patients. PSA level, PSA doubling time and PSA velocity are correlated with PET/CT detection rates and should be taken into account when considering the use of choline PET/CT [23]. Also, additional ¹⁸F-choline PET/CT scans were not carried out as a standard procedure in all 10 patients after sLND. This means that some true-positive LNs might not have been removed, which can be a plausible explanation for failure of surgery in patient no. 7, who presented no histologically proven LN metastasis in the sLND specimen. Furthermore,

the study was limited by the small sample size and the non-homogeneous distribution of the study cohort. Some patients were previously treated by ADT or radiotherapy. Therefore, it is unclear if these results will be reproducible for a homogeneous population without previous therapy. Patients with previous hormonal therapy might have had suppressed PSA levels, which might not correlate with tumour size or metabolism [24].

Conclusions

Choline PET/CT sLND is associated with an initial cBCR in a negligible proportion of patients. Moreover, even if the initial response is achieved, a prolonged response without additional treatment is unlikely. This supports the hypothesis that targeted choline PET/CT sLND removes only the start of more micro-metastases that are likely to present at this stage. Therefore, based on the current study and conflicting results of previous studies, we cannot recommend this approach as proper treatment of LN metastasis. However, this study is not suited to draw conclusions on the effectiveness of salvage lymph node dissection with other new PET/CT tracers.

Conflict of interest

The authors declare no conflict of interest.

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