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Review Article

Salvage Lymphadenectomy as a Treatment of Prostate Cancer Recurrence

Donghua Xie^{1#}, Yanda Lu^{2#}, Di Gu¹, Ming Lei¹, Cong Cai¹, Wen Zhong¹, Defeng Qi¹, Wenqi Wu¹, Yongda Liu¹ and Guohua Zeng^{1*}

¹Department of Urology, Minimally Invasive Surgery Center, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Urology, Guangdong Key Laboratory of Urology, Guangzhou, Guangdong, China

²Department of Oncology, The First Affiliated Hospital of Hainan Medical University, Haikou, Hainan, China

[#]Contributed equally

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ABSTRACT

Biochemical recurrence (BCR) occurs up to 40% of men who had radical prostatectomy for localized prostate cancer. Regional nodes are usually involved in these cases. Salvage lymphadenectomy (sLND) has been advocated in patients with 'node-only' metastasis with biochemical recurrence, following a definitive treatment of primary prostate cancer. In general, limited case number was reported for each previous study. Four relatively larger reports so far with the highest case number of 189. One randomized controlled study has been completed so far at Phase II level. Salvage LND seems to be safe with relatively low incidence of complications without perioperative mortality. It may postpone adjuvant therapy in selected cases, avoiding systemic side effects and possibly reducing the cost. However, long-term outcome is not very encouraging.

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Introduction

Biochemical recurrence (BCR) occurs in up to 40% of men who had radical prostatectomy (RP) for localized prostate cancer (PCa) [1, 2]. Regional nodes are usually involved in these cases. Androgen deprivation therapy (ADT) as the standard of care (SOC) for many years. However, it is questionable to be able to provide overall survival benefit [2]. Multiple new systemic agents have been developed to treat metastatic PCa with benefit of decreasing disease progression. However, there was no cure. Surgical management is therefore gaining interest. However, metastasis-directed surgical intervention has not been often used [3]. Salvage lymphadenectomy (sLND) has been proposed in patients with 'node-only' metastasis with BCR, following a definitive treatment of primary PCa [4]. In general, limited case number was presented for each previous study. Three relatively larger reports include one study of 35 patients, the other study of 36 patients, and another study of 59 patients [5-7]. So far, only one prospective randomized study has

been reported with the majority of the case studies being case report or retrospective study without a control group [8].

Imaging Techniques

Positron emission tomography (PET) scanning is able to pick up even the smallest of recurrences [9]. 11 Choline PET/CT (Computed Tomography) has been reported useful for detecting metastatic sites for recurrent PCa for years, which utilizes 11C-choline or 18F-choline in order to generate 3D images produced from gamma ray emissions [10]. Currently, 11C-choline-PET is approved for use by the FDA for the detection of recurrent PCa [11, 12]. Recent years, 68Ga-PSMA (prostate-specific membrane antigen)-PET/CT has been reported with possible superiority over the Choline PET on accuracy and negative predictive value [6, 11, 13, 14]. The use of 68Ga has many potential advantages over other ligands; it is rapidly cleared from the blood stream and has a low background activity with high image quality achieved [11, 15]. Additionally, 68Ga demonstrates a high affinity to inhibitors of

*Correspondence to: Guohua Zeng, M.D., Ph.D., Department of Urology, Minimally Invasive Surgery Center, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Urology, Guangdong Key Laboratory of Urology, Guangzhou, Guangdong, 510230, China; E-mail: gzyzgh@vip.tom.com

PSMA and radiotracer can be exhibited even in small areas of metastasis [11, 16, 17].

The accuracy of both the PET/CT modalities in localizing metastatic lesions is related to prostate-specific antigen (PSA) level and PSA doubling time (PSAdt) [11, 18, 19]. The pooled detection rate (DR) of radiolabelled choline PET/CT in restaging PCa was 58%. Pooled DR increased to 65% when PSAdt was ≤ 6 months and to 71% and 77% when PSA level was >1 or >2 ng/mL per year, respectively. PSAdt ≤ 6 months and PSA level >1 or >2 ng/mL per year proved to be relevant factors in predicting the positive result of radiolabelled choline PET/CT [18]. In another pooled analysis including 1309 patients, the overall percentage of positive 68Ga-PSMA PET among patients was 40% for primary staging and 76% for BCR. Positive 68Ga-PSMA PET scans for BCR patients increased with pre-PET PSA. Shorter PSAdt increased 68Ga-PSMA PET positivity. On per-patient analysis, the summary sensitivity and specificity were both 86%. On per-lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively [19].

Surgical Approach

There are open, laparoscopic, and robot-assisted laparoscopic approaches [10, 20-28]. Extended field lymph node dissection usually includes at least the internal, external and common iliac arteries of both sides [10]. In the study with laparoscopic approach, 12 out of 13 patients who failed radiation therapy underwent successful laparoscopic pelvic lymph node dissection (PLND) while 1 sustained an enterotomy requiring conversion to open surgery. Laparoscopic PLND following full course pelvic irradiation seems to be technically feasible but more difficult than in nonirradiated patients, and appears to be an excellent minimally invasive technique for the clinical restaging of persistent PCa in patients being considered for salvage therapy [21].

In the other study with 11 cases, robot-assisted high-extended salvage retroperitoneal and pelvic lymphadenectomy (sRPLND+PLND) was performed for 'node-only' recurrent PCa identified by 11 C-acetate PET/CT imaging. Their anatomical template extends from bilateral renal artery/vein cranially up to Cloquet's node caudally, completely excising lymphatic-fatty tissue from aorto-caval and iliac vascular trees with RPLND preceding PLND. Meticulous node-mapping was performed for nodes at four prospectively assigned anatomical zones [22]. In a retrospective study with 16 patients, a PLND that included lymphatic stations overlying the external, internal, and common iliac vessels, the obturator fossa, and the presacral nodes was performed robotically. In 13 (81.3%) patients a RPLND that included all nodal tissue located between the aortic bifurcation and the renal vessels was performed [23]. However, a previous report has shown that patients with retroperitoneal involvement may not benefit from sLND as much as their counterparts with only pelvic involvement [7]. Also, using the new tracer method of the above-mentioned PSMA PET/CT with higher specificity for PCa may reduce the need for such extended templates, without compromising the oncological results [29]. In a study to analyse data of 189 patients with a unilateral positive PET scan of the pelvic lymph node areas, who were treated with bilateral pelvic sLND after RP at 11 high-volume centers. The primary endpoint was missed contralateral disease at final pathology, defined as lymph node positive for PCa in the side opposite to the positive spot(s) at the PET scan. Variability was found according

to the number of positive spots and PET tracer, with the lowest rate of missed PCa in men diagnosed with a single positive spot at a 68Ga prostate-specific membrane antigen PET scan (6%). If replicated, they thought these patients might be considered for unilateral extended pelvic sLND [30].

In a retrospective study, clinical data were collected from 60 patients undergoing open sLND and 30 patients undergoing robot-assisted sLND. They found that robot-assisted sLND is associated with significantly reduced peri-operative morbidity compared to open sLND. No difference in LN yield, BRFS (biochemical recurrence-free survival) and CRFS (clinical recurrence-free survival) was seen between both groups. They found that modern imaging techniques underestimate the tumor burden and therefore the surgical sLND template should not be limited to the positive spots on pre-operative imaging [31]. In another retrospective study with 31 patients to describe the technique, feasibility, and short-term outcomes of 99mTechnetium (99mTc)-based PSMA-radioguided surgery (99mTc-PSMA-RGS) for removal of recurrent PCa lesions, salvage surgery with intraoperative radioguidance using a gamma probe was performed after intravenous application of 99mTc-PSMA investigation and surgery (mean activity 571 MBq, mean time to surgery 19.7h). They were able to detect and remove these metastatic lesions during surgery. Following salvage surgery, 41.9% of patients remained BCR free (median follow-up of 13.8 month) and 64.5% continued to be treatment free (median follow-up of 12.2 month) [32].

Operative Data

The mean operative time is up to 4.8 hours; blood loss is up to 400mL; length of hospital stay ranges from 1-3.5 days [5, 6, 23]. Nodes resected range from 1 to 132 with positive nodes resected ranging from 0-109 [6, 20, 22]. In the study with 59 cases, on a per-site analysis, positive lymph nodes were found within the pelvis only in 22 patients, in the retroperitoneum only in 5 patients, and in the pelvis plus retroperitoneum in 20 patients [7].

Complications

Few expert surgeons reported sLND-related complications. However, sLND is a complex surgery and was found to be up to 13.8% of patients with Clavien–Dindo ≥ 3 complications in one pooled study. The most frequent complication after sLND was lymphorrhea, followed by fever and ileus [33]. In the study with 59 cases, for 30-day postoperative complications in patients receiving sLND, ileus and fever represented the most common postoperative complications, while complications of lymphorrhea at 20.3% and lymphocele requiring drainage at 11.2% [7]. In another study with 17 patients with PSA rise following local treatment for PCa with curative intent underwent open or minimally invasive salvage PLND for oligometastatic disease (<4 synchronous metastases) or as staging prior to salvage radiotherapy, Clavien–Dindo grade 1, 2, 3a, and 3b complications were seen in 6, 1, 1, and 2 patients, respectively. The postoperative complication rate seems higher than that for primary LND [32]. In the other study with 16 patients who underwent sLND, four (25.0%, one case of ureteral lesion and 3 cases of vascular injury) and five (31.2%) patients experienced intraoperative and postoperative complications, respectively. When considering nodal dissection-related complications, one patient experienced lymphedema and the other one

experienced lymphorrhea, which were managed conservatively. The other postoperative complications include fever, ileus, obturator nerve neuropraxia, hyponatremia, and hydronephrosis with one case each in this study [23].

Definition of BCR and Biochemical Response (BR)

Biochemical recurrence after complete biochemical response (cBR) was defined as 2 consecutive PSA increases >0.2 ng/mL; and after incomplete BR as 2 consecutive PSA rises [34]. There are different BR definitions in different studies [5, 7, 20, 23]. In one study, PSA treatment response to robot-assisted salvage node dissection (RASND) was defined as 6-week PSA <0.2 ng/mL (broad definition) or PSA <0.05 ng/mL (strict definition) in those who had undergone primary RP, and 6-week PSA level $<$ post-radiotherapy nadir in those who had undergone primary radiotherapy. Biochemical recurrence after RASND was defined as a PSA >0.2 ng/mL or PSA $>$ nadir, for those who had undergone primary RP and primary radiotherapy, respectively [5]. In the other study, BR was defined as a PSA level <0.2 ng/ml at 40 d after RASND [23]. Similarly, in another study, BR was defined as PSA <0.2 ng/ml at 40 d after surgery. Biochemical recurrence for those who achieved BR was defined as a PSA >0.2 ng/ml. Clinical recurrence (CR) was defined as a positive PET/CT scan after salvage LND in the presence of a rising PSA [7]. Yet in another study, cBR after sLND was defined as PSA <0.01 ng/ml [20].

Follow-Up Outcomes

Few long-term studies are available with most studies with a follow-up duration less than 2 years. There are only four studies so far with median follow-up duration more than 5 years [1, 7, 20, 35]. In the study with 11 patients who underwent robotic RPLND+PLND, 7 patients (70%) had positive nodes on final pathology. Node-positive rates per anatomical level I, II, III and IV were 28%, 32%, 33% and 33%, respectively. In patients with positive nodes, the median PSA level had decreased by 83% at the 2-month follow-up [22]. In the study with 16 patients, 5 (33.3%) patients experienced BR after surgery [23]. In a phase 2 randomized trial with 62 oligorecurrent PCa patients at a median follow-up time of 3 years, the median ADT-free survival was 13 months for the surveillance group and 21 months for the MDT (metastasis-directed therapy) group. Quality of life was similar between arms at baseline and remained comparable at 3-month and 1-year follow-up. Six patients developed grade 1 toxicity in the MDT arm without grade 2 to 5 toxicity observed [8]. In the aforementioned study with 17 patients, median follow-up time was 22 months. Among 13 patients treated for oligometastatic disease, 8 had a PSA decline with 3 patients showing cBR. Median PSA progression-free survival (PFS) was 4.1 months and median CP (clinical progression)-FS was 7 months. Three patients started ADT, resulting in a 2-year ADT-FS rate of 79.5%. Biochemical and clinical response duration seems to be limited, but as part of an oligometastatic PCa treatment regime it can postpone palliative ADT [34].

In the study with 36 patients, median postoperative PSA change was 57% in the PSMA-PET and 10% in the choline-PET group with statistical difference. 44% of patients in the PSMA group and 18% of patients in the choline-group experienced cBR. Median time from sLND

to the initiation of further therapy was 12 months in the PSMA-group and 4.7 months in the choline-group with significant difference [6]. For one of studies with the longer follow-up, at a median follow-up of 70 months, MDT was associated with an improved cancer-specific survival (CSS). The 5-yr CSS was 98.6% and 95.7% for MDT and SOC, respectively [1]. In the other study with a median follow-up of 72 months, 10 of 11 patients with histologically confirmed lymph node metastases showed a PSA response after sLND. Three of ten patients with single lymph node metastases had a cBR. In five cases with single lymph node metastasis PSA was decreased to <0.02 ng/ml. Thirteen of 16 metastasis suspicious lymph nodes were histologically confirmed. All of the additionally removed 30 lymph nodes were correctly negative [20]. In the other study with a median follow-up of 81.1 months after salvage LND, overall, 35 patients (59.3%) achieved BR. The 8-year BCR-free survival rate in patients with cBR was 23%. Overall, the 8-year CR- and cancer-specific mortality (CSM)-free survival rates were 38% and 81%, respectively. Analysis showed that PSA at salvage LND represented the only predictor of CR. BR and the presence of retroperitoneal lymph node metastases were significantly associated with the risk of CR. Approximately 40% of them experienced CR-free survival [7].

From the findings of a systematic review, half of patients post-sLND will have an immediate complete postoperative BR. One-third will be free of biochemical relapse for 5 years [8]. Overall, it was felt that patients with a PSA value <4 ng/ml, low-intermediate risk cancer and clinical small volume LN relapse limited to the pelvis may benefit the most [7, 33, 36]. Despite the encouraging results mentioned above, the other retrospective study with 43 hormone-naïve men who received transperitoneal sLND showed that transperitoneal sLND is neither an appropriate treatment to cure nor an option to delay the need for salvage hormone manipulation for most hormone-naïve men with a nodal recurrence of prostate cancer. 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. They also found that PSMA PET/CT scans in hormone-naïve patients are currently too imprecise to diagnose metastatic sites [37]. In another retrospective study with 54 patients, while they found that PSMA PET/CT scans are sensitive and specific, the PSA response in sLND group is still inferior to the group who received RP with standard PLND or extended PLND [38]. In the aforementioned study with 35 patients, although RASND appears safe and feasible, less than half of their cohort had a treatment response and less than a quarter experienced BCR-free survival at 12-month median follow-up. 68 Ga-PSMA imaging seems to underestimate micro-metastatic disease so RASND would rarely be curative [5].

In a most recent study to investigate long-term oncological outcomes after sLND in a large multi-institutional series including 189 patients who experienced PSA rise and nodal-only recurrence after radical prostatectomy and underwent sLND at 11 tertiary referral centers between 2002 and 2011. Lymph node recurrence was documented by PET/CT scan using either ^{11}C -choline or ^{68}Ga prostate-specific membrane antigen ligand. A third of men treated with sLND for PET-detected nodal recurrence of PCa died at long term, with PCa being the main cause of death. Salvage LND alone was associated with durable long-term outcomes in a minority of men who significantly benefited from additional treatments after surgery. Their data argued against the

use of metastasis-directed therapy alone for patients with node-only recurrent PCa. They thought these men should instead be considered at high risk of systemic dissemination already at the time of sLND [35].

Conclusion

In summary, recent studies support the role of image-guided metastasis-directed therapies in the oligo-recurrent setting. Salvage LND seems to be safe with relatively low incidence of complications without perioperative mortality. However, long-term outcome is not very encouraging. It may postpone adjuvant therapy in selected cases, avoiding systemic side effects and possibly reducing the cost. However, sLND remains a demanding procedure even in experienced hands. The extend of sLND has to be standardized and further and more randomized trials are needed to finally define the oncological effectiveness of this approach. Until a higher level of evidence is available, sLND should still be considered experimental.

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Author Contributions

Conception and design: all authors; data analysis and interpretation: all; manuscript writing: all authors; final approval of manuscript: all authors.

Conflicts of Interest

None.

Abbreviations

BCR: Biochemical Recurrence
RP: Radical Prostatectomy
PCa: Prostate Cancer
ADT: Androgen Deprivation Therapy
SOC: Standard of Care
PET: Positron Emission Tomography
CT: Computed Tomography
FDA: Food and Drug Administration
PMSA: Prostate-Specific Membrane Antigen
PSA: Prostate-Specific Antigen
PSAdt: PSA Doubling Time
DR: Detection Rate
sRPLND+PLND: Robot-Assisted High-Extended Salvage Retroperitoneal and Pelvic Lymphadenectomy
sLND: Salvage Lymphadenectomy
LND: Lymph Node Dissection
cBCR: complete Biochemical Response
RASND: Robot-Assisted Salvage Node Dissection
MDT: Metastasis-Directed Therapy
CR: Clinical Recurrence
FS: Free Survival
PFS: Progression-Free Survival
CP: Clinical Progression
CSS: Cancer-Specific Survival

CSM: Cancer-Specific Mortality

LN: Lymph Node

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