Ann Surg Oncol (2019) 26:653–659
https://doi.org/10.1245/s10434-018-6805-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

The Value of ^{99m}Tc-PSMA SPECT/CT-Guided Surgery for Identifying and Locating Lymph Node Metastasis in Prostate Cancer Patients

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ABSTRACT

Background. This study evaluated the effect of technetium-99m (^{99m}Tc)-labeled prostate-specific membrane antigen (PSMA)-based image-guided surgery on the oncologic outcomes for patients with primary or recurrent prostate cancer (PCa).

Methods. This study retrospectively analyzed 54 consecutive patients with PCa who underwent ^{99m}Tc-labeled PSMA-based image-guided surgery between January 2016 and September 2017. These patients received a radical prostatectomy (RP) with pelvic lymph node dissection (PLND) or salvage lymph node dissection (sLND). The resected specimens were compared with findings of postoperative histologic analysis. The responses to the treatment were recorded during the follow-up period.

Results. In 31 patients, PSMA single-photon emission computerized tomography (SPECT) and computed tomography (CT) could find 52 suspicious lymph node metastases (LNMs). With the help of PSMA SPECT/CT, 12 patients with recurrence received sLND, 19 primary PCa patients received RP with extended PLND, and 23 primary PCa patients received RP with standard PLND. The findings showed that PSMA SPECT/CT could detect LNMs with high sensitivity and specificity. In six patients, PSMA SPECT/CT could find more LNMs that were not found by MRI and help to modify the extent of lymphadenectomy. At the latest follow-up evaluation, 39 patients showed a biochemical response (BR), 9 patients showed a biochemical recurrence (BCR) after BR, and 6 patients never exhibited BR. The patients who received RP with standard PLND or extended PLND had a better prostate-specific antigen (PSA) response than the patients who received sLND. The patients with pelvic LNMs also had a better PSA response than the patients with retroperitoneal LNMs.

Conclusions. This study showed that ^{99m}Tc-PSMA SPECT/CT-guided surgery can remove more LNMs than conventional imaging with high sensitivity and specificity and delay disease progression in PCa patients.

Heng-chuan Su, Yao Zhu, Si-long Hu and Chang Liu have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-6805-y) contains supplementary material, which is available to authorized users.

First Received: 14 February 2018;
Published Online: 15 October 2018

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Prostate cancer (PCa) is the second most common cause of death in developed countries and one of the most commonly diagnosed diseases in men.[1] Early detection and specific location of PCa is important for surgery planning because it is expected to improve the management of these patients.

Radiologic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy have retained a primary position in the initial diagnosis and staging of PCa. However, the use of MRI or CT alone has shown low sensitivity in the evaluation of

metastatic lesions, especially lymph node metastases (LNMs). Use of these methods, with threshold measurements of 10 mm for involved lymph nodes (LNs), has led to sensitivities of less than 40%.[2] A better diagnostic procedure is required to locate metastatic lesions in PCa patients.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein with a significantly increased expression in PCa cells.[3] The expression of PSMA increases progressively with higher-grade PCa, PCa metastasis, and castrate-resistant PCa.[4,5] As such, PSMA provides a promising target for PCa-specific imaging and therapy.

The use of ^{68}Ga-PSMA positron emission tomography (PET) imaging reportedly improves the detection of metastatic PCa and provides accurate staging of lymph node regions in PCa patients.[6,7] A prospective randomized multi-center study by Hofman et al.[8] is assessing whether PSMA PET/CT should replace conventional imaging in the primary staging of select high-risk localized PCa patients.

Apart from PSMA PET/CT, small-molecule inhibitors of PSMA labeled with technetium-99 m (^{99m}Tc) have been developed for imaging with single-photon emission computerized tomography (SPECT), a nuclear medicine (NM) imaging technique more widely available than PET.[9,10] In the previous study, we found that PSMA SPECT/CT could achieve a higher detection rate for PCa patients than conventional imaging methods.[11] In the current study, we used this imaging technique to guide the surgery and monitor both the prostate-specific antigen (PSA) level and the prognosis of these patients every month during the follow-up period.

MATERIALS AND METHODS

Patients

Between January 2016 and September 2017, 54 consecutive PCa patients, including 42 primary intermediate- and high-risk PCa patients and 12 recurrent PCa patients with biochemical recurrence (PSA $>$ 0.2 ng/mL), were referred for a ^{99m}Tc-PSMA SPECT/CT. The retrospective study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center, and written informed consent was obtained from all the patients for the purpose of anonymous evaluation and publication of their data.

The PSA levels of these patients were recorded during the follow-up period every month (range 3–18 months). Biochemical response (BR) was defined as a PSA lower than 0.2 ng/mL 40 days after the surgery, and biochemical recurrence (BCR) was defined as a PSA higher than 0.2 ng/mL with an increased trend after the surgery. Androgen deprivation therapy, radiation, or docetaxel or abiraterone were offered to patients if they showed no treatment response to the surgery.

For the primary PCa patients, if PSMA SPECT/CT showed LNMs in the pelvic regions, these patients received radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND) involving the right/left common iliac vessel, the iliac vessel (including the right/left internal iliac vessel, the right/left external iliac vessel, and the right/left obturator fossa) and presacral regions. If PSMA SPECT/CT showed no LNMs in the pelvic regions, the patients received a standard pelvic lymph node dissection (PLND) involving the right/left iliac vessel (including the right/left internal iliac vessel), the right/left external iliac vessel, and the right/left obturator fossa. The recurrent PCa patients received salvage lymph node dissection (sLND). If PSMA SPECT/CT showed LNMs in the pelvic regions, the patients received salvage ePLND, and if PSMA SPECT/CT showed LNMs in the retroperitoneal regions, the patients received salvage ePLND and retroperitoneal LND as previously reported.[12] All nodal specimens were prospectively mapped according to their anatomic locations and sent for pathologic assessment.[13]

^{99m}Tc-PSMA SPECT/CT

A new ^{99m}Tc-labeled PSMA inhibitor (^{99m}Tc-HYNIC-ALUG, ^{99m}Tc-PSMA) was synthesized as previously described.[14] Images were acquired about 120 min after intravenous injection. Discovery NM/CT 670 (General Electric Medical Systems, Waukesha, WI, USA), a rotating and large field-of-view gamma camera, was used. After the SPECT acquisition, low-dose CT was acquired, and image reconstruction was performed using filtered-back projection. The PSMA SPECT/CT images were visually analyzed by experienced NM physicians and radiologists. In the SPECT/CT images, any focal uptake higher than the surrounding background and not physiologic was considered suspicious.

The PSMA SPECT/CT findings were validated by histopathology performed by a uropathologist with more than 5 years of experience who was blinded to the PSMA SPECT/CT data. During lymphadenectomy, tissue from each resected lymph node (LN) field was sent separately for histologic evaluation, including the right/left common iliac vessel, the iliac vessel (including the right/left internal iliac vessel, the right/left external iliac vessel, and the right/left obturator fossa), and the presacral and paraaortic regions. The histopathologic results were compared with findings of PSMA SPECT/CT. Sensitivity and specificity for detection of histopathologically positive regions were calculated.

Statistical Analysis

The primary analysis used to estimate the ability of ^{99m}Tc-PSMA SPECT/CT to detect histologically confirmed PCa was based on the positive ^{99m}Tc-PSMA SPECT/CT scan of the whole body, using histopathologic results as the gold standard. For statistical analysis, dedicated statistical software was used (SPSS 15.0; SPSS Inc., Chicago, IL, USA). All results were expressed as the mean ± standard deviation, and *P* values lower than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

The study included 54 patients. Table 1 shows the clinical characteristics of all the patients. The mean age at the time of surgery was 65.69 ± 1.02 years (range 50–79 years). The time between imaging and surgery was within a 30-day period. The mean serum PSA level was 8.29 ± 1.79 ng/mL (range 0.1–62 ng/mL). The PSMA SPECT/CT could find 52 suspicious LNMs in 31 patients.

The regions of LNMs discovered by PSMA SPECT/CT are shown in Fig. 1. The average short-axis diameter of PSMA SPECT/CT-positive LNMs was 0.95 ± 0.1 cm. With the help of PSMA SPECT/CT, 12 recurrent patients received sLND, 19 primary patients received RP with ePLND, and 23 primary patients received RP with standard PLND. The detection rates of MRI and ^{99m}Tc-PSMA SPECT/CT for finding LNMs also were compared. Among the 54 patients, LNMs were found by PSMA SPECT/CT in 31 patients (57.4%) and by MRI in 25 patients (46.3%). The diagnostic efficiency in finding LNMs with PSMA SPECT/CT imaging was better than with MRI.

TABLE 1 Clinical characteristics of the patients in this study

Patient characteristics	
Pathologic Gleason score at RP	
6	6
7	12
8	12
9	12
10	8
Not available	4
Treatment before the surgery	
ADT	19
ADT + radiation	3
Multiple	8
None	24
Pathologic stage of the patients	
T2N0	18
T2N1	4
T3N0	8
T3N1	18
T4N1	4
Not available	2

RP radical prostatectomy, *ADT* androgen-deprivation therapy

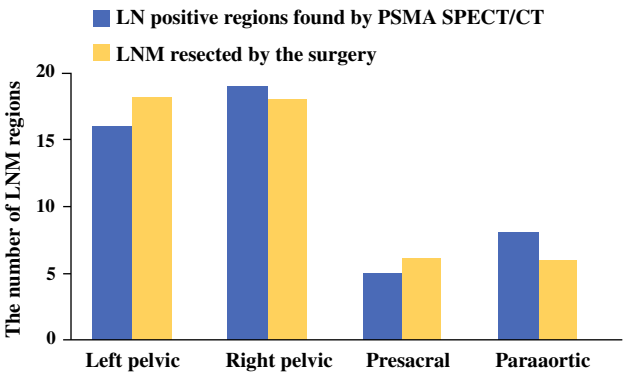

FIG. 1 High consistency could be found between positive lymph nodes (LN) discovered by PSMA SPECT/CT and lymph node metastases (LNMs) resected by surgery

Histopathologic Results of LNMs

Lymph node metastases were found in 30 patients after histopathologic workup, and 113 metastatic LNs were removed by surgery from the following regions: left common iliac vessel (*n* = 11), right common ilial vessel (*n* = 9), left iliac vessel (*n* = 24), right iliac vessel (*n* = 35), presacral region (*n* = 16), and paraaortic region (*n* = 18). The regions of LNMs verified by histopathology are shown in Fig. 1.

A total of 12 recurrent patients received sLND, and 47 nodes from six regions were histopathologically proven to be metastases. The LNMs were located in the following regions: left common iliac vessel (*n* = 8), left iliac vessel (*n* = 1), right common iliac vessel (*n* = 4), right iliac vessel (*n* = 2), presacral region (*n* = 14), and paraaortic region (*n* = 18).

Pelvic LNMs were found in 15 of 19 patients who received RP with ePLND, and 58 lymph nodes from five regions were histopathologically proven to be metastases. The LNMs were located in the following regions: left common iliac vessel (*n* = 3), left iliac vessel (*n* = 18), right common iliac vessel (*n* = 5), right iliac vessel (*n* = 30), and presacral regions (*n* = 2). Pelvic LNMs were found in 3 of 23 patients who received RP with standard PLND, and 8 LNMs were located in the following regions: left iliac vessel (*n* = 5) and right iliac vessel (*n* = 3).

Imaging Findings

In a field-based analysis, PSMA SPECT/CT could detect LNMs in 35 of 50 histopathologically proven metastatic LN fields. Of the 150 LN fields that proved to be negative by pathology, 142 also were proved to be negative by PSMA SPECT/CT. In a patient-based analysis, PSMA SPECT/CT could detect LNMs in 27 of 30 patients proved to be positive by pathology. Of the 24 patients proved to be negative by pathology, 20 also were proved to be negative by PSMA SPECT/CT. The performance of PSMA SPECT/CT for detection of diseased LN regions is given in Table 2.

Impact of PSMA SPECT/CT on the Management of PCa Patients

Of the 19 patients who received RP with ePLND, PSMA SPECT/CT could find more LNMs in three patients than were found by MRI. Of the 12 patients who received sLND, PSMA SPECT/CT could find more LNMs in 3 patients than were found by MRI. All these LNMs were confirmed by pathologic evaluation. Altogether, PSMA SPECT/CT could find more LNMs in six patients and could help to modify the extent of lymphadenectomy in these patients.

During the follow-up period, the PSA level declined in 52 patients immediately and continued to increase in 2 patients. The PSA response to the surgery are showed in Fig. 2a. The patients who received RP with standard pLND or ePLND had a better PSA response than the patients who received sLND. The patients with pelvic LNMs who received sLND also had a better PSA response than the patients with retroperitoneal LNMs. The BR ratio after the surgery was higher in the patients with pelvic LNMs (91%) than in the patients with retroperitoneal LNMs (50%) (Fig. 2b). Representative examples can be seen in Fig. 3 and Figs. S1 and S2. At the latest follow-up evaluation, 39 patients continued to have a BR, 9 patients had a BCR after BR, 6 patients never had a BR.

DISCUSSION

For PCa patients, the extent of PLND at the time of RP has been the object of a longstanding discussion in the urologic community. From a diagnostic standpoint, ePLND is the gold standard for nodal staging because it provides fresh tissue for pathologic analysis.[15,16] However, the rate of pathologic nodal involvement has dropped from 20% to 40% in the pre-PSA era to approximately 1% since the introduction of PSA screening, bringing the therapeutic use of ePLND into question.[17] As a result, how to evaluate which men could avoid an unnecessary ePLND and which men would benefit from an ePLND has attracted increasing attention. Currently, increasing research has found that PSMA PET (SPECT)/CT can exhibit a high detection rate for LNMs in PCa patients and may help to formulate PLND strategy.[18]

In this study, we used a new ^{99m}Tc-labeled PSMA inhibitor (^{99m}Tc-HYNIC-ALUG, ^{99m}Tc-PSMA) and found that ^{99m}Tc-PSMA SPECT/CT was an efficient tool for detecting LNMs with high sensitivity and specificity in PCa patients, consistent with the previous study.[19] With PSMA SPECT/CT, more LNMs than with MRI were found in six patients. These patients received PSMA SPECT/CT-guided surgery, and the LNMs were confirmed by pathologic evaluation. Thus, the results of PSMA SPECT/CT have helped surgeons to better target LNMs for lymphadenectomy and formulate postoperative treatment plans. In addition, PSMA SPECT/CT imaging was cheaper and more affordable than PSMA PET/CT and would have easier popularization and application in less-developed regions.

Systemic medical therapy currently is the standard for PCa patients with metastatic disease after local curative treatment. However, for patients with minimal or localized metastatic disease burden and good clinical status, salvage surgery as an individual treatment regimen might be a valid option favoring progression-free survival.[20,21] Rauscher et al. have reported that ^{111}In-PSMA-radioguided sLND could exactly resect small LNMs in recurrent PCa patients and that PSA declines of more than 50% could be observed

TABLE 2 Detection capability of PSMA SPECT/CT for LNMs in a field-based analysis and on a patient basis

	PSMA-positive	PSMA-negative	Detection capability
LN-positive regions	35	15	Sensitivity (70%)
LN-negative regions	8	142	Specificity (94.6%)
HP-positive patients	27	3	Sensitivity (90%)
HP-negative patients	4	20	Specificity (83.3%)

PSMA prostate-specific membrane antigen; *SPECT* single-photon emission computerized tomography, *CT* computed tomography, *LNMs* lymph node metastases, *LN* lymph node, *HP* histopathology

Sensitivity and specificity are given as percentages for detection of LNMs in prostate cancer (PCa) patients verified by HP

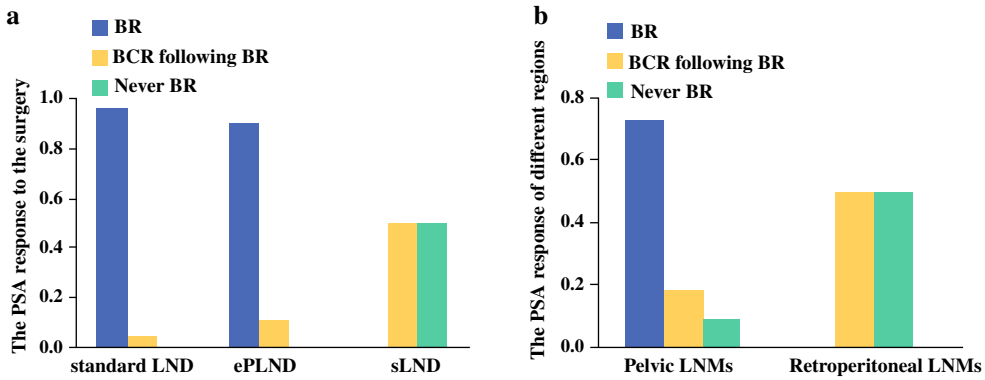

FIG. 2 Different prostate-specific antigen (PSA) responses to surgery depended on different patients. **a** The patients who received radical prostatectomy (RP) with standard pelvic lymph node dissection (PLND) or extended pelvic lymph node dissection (ePLND) had a better PSA response than the patients who received salvage lymph node dissection (sLND). **b** The ratio of patients with pelvic lymph node metastases (LNMs) who had a biochemical response (BR) was higher than that of the patients with retroperitoneal LNMs

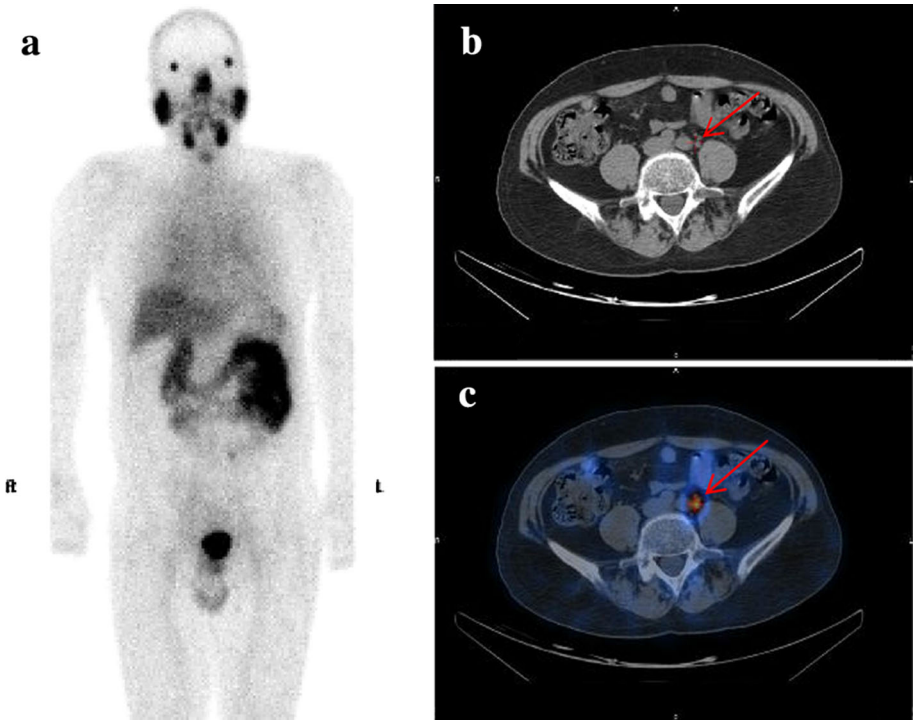

FIG. 3 Example of results for a patient who received salvage lymph node dissection (sLND). The patient was 66-year-old man with a biopsy-proven prostate cancer Gleason score of 10 and a prostate-specific antigen (PSA) level of 20 ng/mL. After radical prostatectomy (RP), this patient had a biochemical recurrence (BCR) following a biochemical response (BR) and received androgen deprivation therapy (ADT). A year later, his PSA had increased to 1 ng/mL. Bone scan and magnetic resonance imaging (MRI) showed no metastatic lesions in this patient. Use of PSMA SPECT/CT indicated that lymph node metastases were near the retroperitoneal regions, and this patient received sLND [(**a**) whole-body planar images, (**b**) CT plain scan, and (**c**) fused PSMA SPECT/CT images]. Histology proved that the PSMA-positive lesions near the retroperitoneal regions were prostate cancer. After surgery, the patient achieved BR initially but bounced back to BCR 8 months after the surgery. Arrows indicate metastatic lymph node lesions detected by PSMA SPECT/CT

in 23 of 30 patients during the follow-up period.[22] In our study, PSMA-guided sLND delayed disease progression in 10 of 12 patients, and these patients experienced a decline in PSA for about half a year, which indicated that PSMA SPECT/CT-guided sLND may delay cancer progression and represent a more suitable approach for patients with PCa recurrence.

In the previous study, Rigatti et al.[12] found that the 5-year clinical recurrence-free survival was lower for patients with positive retroperitoneal LNMs than for patients with pelvic LNMs (11% vs 53%; $P < 0.001$). In our study, we observed similar results. Of the 22 patients who presented with pelvic LNMs, 16 continued to have BR after the surgery, 4 had BCR after BR, and 2 never had BR, whereas of the 8 patients with retroperitoneal LNMs, 4 had BCR after BR, and 4 never had BR. The ratio of the patients with pelvic LNMs who had BR was higher than that of the patients with retroperitoneal LNMs. Despite the small retrospective study samples, the results have shown that patients with only pelvic LNMs may benefit more from the surgery than patients with retroperitoneal LNMs.

This retrospective analysis had certain limitations, such as its small patient population. Another limitation was that possible distant imaging-negative but histology-positive lesions could have been missed. It must be noted that PSMA-ligands could cause a reduced signal around the urinary bladder and the kidneys, potentially obscuring the visibility of tumor lesions, and a potential influence on the results of the presented study cannot be completely excluded. Nevertheless, it is known that despite the increased detection ability using PSMA SPECT/CT, microscopic lesions might still be missed.

CONCLUSIONS

This study indicated that PSMA SPECT/CT is a promising tool not only for detecting LNMs but also for guiding surgery. For patients with PCa recurrence, ^{99m}Tc-PSMA SPECT/CT-guided sLND may represent a more suitable approach. Patients with pelvic LNMs may benefit more from PSMA SPECT/CT-guided LND than patients with retroperitoneal LNMs.

ACKNOWLEDGMENT This work was supported by grants from the National Natural Science Foundation of China (No. 81602222), the Shanghai Rising Star Program (Grant No. 16QA1401100), and the Shanghai Young Doctor Training Programme. All these study sponsors had no roles in the study design, the collection, the analysis, or the interpretation of data.

CONFLICT OF INTEREST There are no conflicts of interest.

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