Recurrent Prostate Cancer after Radical Prostatectomy

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The main prostate cancer (PCa) treatments include surgery or radiotherapy (with or without ADT). None of the suggested treatments eliminates the risk of lymph node metastases. Conventional imaging methods, including MRI and CT scanning, are not sensitive enough for the diagnosis of lymph node metastases; the novel imaging method, PSMA PET/CT scanning, has provided valuable information about the pelvic LN involvement in patients with recurrent PCa (RPCa) after radical prostatectomy.

prostatic neoplasms recurrence lymph nodes PSMA PET/CT

1. Development of PSMA PET/CT Scan

The conventional imaging methods, such as magnetic resonance imaging (MRI) and computed tomography (CT) scanning, have limited diagnostic accuracy for lymph node (LN) involvement in patients with prostate cancer (PCa) since such methods are dependent on size and basic morphological criteria for the diagnosis of LN involvement [1]. Accordingly, pelvic lymph node dissection (LND) is considered the gold standard in LN staging. However, not all patients are candidates for or elect to undergo operative management. Moreover, surgery is also associated with a dramatic risk of complications, considering the relatively old age of the affected patients [2][3]; hence, an accurate noninvasive imaging technique is required to overcome these limitations.

Over the past few years, the development of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has transformed the diagnosis and management of PCa. This revolution goes back to 1996, when N-Acetylated alpha-linked acidic dipeptidase was introduced as a high-affinity agent that was primarily used for the treatment of neurologic disorders [4] and was further used for PET imaging of the brain to study glutamatergic transmission [5]. In the following years, carbon-11 (^{11}C)-choline, fluorine-18 (^{18}F)-fluoricholine, C-acetate, fluciclovine, gallium-68 (^{68}Ga), and F-radiolabeled chemicals were introduced as PET scan agents and gained popularity for a short period worldwide. This was because of their advantage in directly imaging cancer, rather than the surrounding bone, compared to bone-directed PET agents [6][7][8]. Although the diagnostic accuracy of these PET agents in the diagnosis of prostate cancer has been confirmed, variable sensitivity and specificity values have been reported regarding patient-related, cancer-related, and treatment-related factors [8]. In a comparison of the diagnostic accuracy of the two agents approved in the United States, C-choline and fluciclovine, the latter appeared to detect more local, nodal, and bony diseases with a higher sensitivity (37% vs. 32%) and specificity (67% vs. 40%) [9].

The first practical human PSMA PET agent, ^{18}F-DCFBC, was developed in 2008. This type II transmembrane protein, in human zinc-containing metalloenzyme with glutamate carboxypeptidase/folate hydrolase activity, is expressed in the apical side of the prostatic ducts and is upregulated by PCa cells. The binding of the PSMA ligand to its anchored cell membrane target mediates internalization through clathrin-dependent endocytosis, thereby enhancing the retention of conjugated radionuclides into the cells, even in small-volume sites [10][11]. The first radiometalated PSMA agent, technetium-99m, a labeled inhibitor of PSMA, was developed in 2008 [12], and later in 2010, the first ^{68}Ga-labeled PSMA inhibitor was synthesized as the first clinical agent for PSMA PET imaging, which gained popularity due to its high diagnostic accuracy. It can detect as many as 50% of patients with low serum levels of prostate-specific antigen (PSA < 0.5 ng/mL) and 60% of patients with moderate levels (0.5–1 ng/mL) [9]. Moreover, it can detect additional diseases that are not detected by choline imaging [13].

Researchers have developed several chelators for ^{68}Ga PSMA, including the HBED-CC chelators, known as PSMA-11 [14] and ^{18}F-DCFPyl [15], which have been widely used in recent years, especially in Europe and the USA [16]. The high levels of radiotracer excretion and urinary bladder activity result in uptake in other sites other than the prostate, including the salivary glands and lacrimal glands, kidneys and liver, spleen, small intestine, and urinary collecting system, which could mask small local recurrences in this vicinity or be misdiagnosed as metastasis [11]. The targeted radionuclide chelators PSMA-617 (^{177}Lu-labeled ligand) [17] and ^{18}F-PSMA-1007 were developed with less urinary excretion than ^{18}F-DCFPyl [18].

Following the rapid development of PSMA PET imaging (in no longer than a decade), hundreds of cohort and clinical trials with promising results have been published annually on its diagnostic accuracy in the diagnosis and staging of the disease and metastasis in patients with primary/recurrent PCa [19][20]. Further meta-analysis studies and prospective and randomized clinical trials also confirmed the high positive and negative predictive values (PPV and NPV) of PSMA PET for PCa [21][22][23][24].

2. Nodal Irradiation in PSMA-Positive Patients

Many studies have suggested a change in the therapeutic plan of a given patient, especially considering the treatment for LN involvement, according to PSMA PET/CT scan results [11][25][26]; however, most studies have reported the overall rates and have not reported the patient outcomes with PSMA-positive or -negative LNs. The treatment options for patients with localized or regional LN metastases of PCa include surgery (LND) or irradiation (LNRT, with or without androgen deprivation). There is controversy related to the preference for these methods in PSMA-positive LNs in patients with the recurrence of PCa after RP.

A systematic review of 27 studies (6 of which used PSMA) showed a mean complete biochemical response in 44.3% (13–79.5%) of cases after SLND with 2- and 5-year biochemical-recurrence-free survival rates (BCRFS) of 23–64% and 6–31%, respectively [27]. The inconsistencies in the reported patient outcomes could be caused by differences in the type of detection method used, the type of RT (LN-specific stereotactic body RT (SBRT) or whole-pelvis radiotherapy (WPRT)), and the variation in the RT regimens and doses [28]. In a recent study involving 100 patients with BCR (24%) or biochemical persistence (76%), the results showed that PSMA PET/CT could

detect 1, 2, 3, or more LN metastases in 35%, 23%, and 42% of the patients; the treatment of all LN cases with RT and ADT in 83% of patients showed improved BCR-free survival in these patients, thereby confirming the use of RT based on the results of a PET/CT scan [29]. Furthermore, another recent study showed that most patients with high PSA levels considered that a relapse of PCa could be successfully diagnosed as a recurrence by ^{68}Ga-PSMA (63%). This study also concluded that PSMA PET/CT scans have a high level of significance in predicting the outcomes of patients with PSA relapse [30].

The table below summarizes the results of studies evaluating the outcomes of patients with PSMA-positive LN, organized in chronological order (**Table 1**). Focuses on the PSMA PET/CT, those studies using a different diagnostic method (such as choline or FDG PET/CT, etc.) were not included. Researchers also evaluated the results of the studies addressing the patient outcomes after the diagnosis of LN by PSMA PET/CT and did not include studies reporting the results of radioguided treatment strategies using this imaging modality.

Table 1. The summary of studies reporting the treatment outcomes of PSMA-positive lymph nodes in patients with a recurrence of prostate cancer after primary treatment with radical prostatectomy.

Author, Year of Publication	Number of Patients	Imaging Method	Treatments Applied	Median Follow-Up (Months)	Conclusion	
					Recurrence or Response Rate	Survival
Porres et al. [31], 2017	87	^{18}FEC or ^{68}Ga-PSMA PET/CT	Salvage extended lymph node dissection	21	Complete biochemical response: 27.5%, Incomplete biochemical response: 40.6%	ADT-free: 62.2%, CSM: 3.7%, 3-year BCR-free: 69.3%, systemic-therapy-free survival: 77.0%, clinical-recurrence-free survival: 75%, for patients with complete biochemical response
Henkenberenz et al. [32], 2017	23	^{68}GA-PSMA PET/CT	Salvage LNRT	12.4	Recurrence outside the initial radiation field: 12.9%	BCR-free survival: 95.6%, systemic-therapy-free survival: 100%
Fossati et al. [33], 2019	654	^{11}C- or ^{68}Ga-PSMA PET/CT	Salvage LND	30	Early clinical recurrence: 25%	CSM: 20% in patients with and 1.4% in patients without early clinical recurrence
Schmidt-Hegemann et al. [34], 2020	100	^{68}GA-PSMA PET/CT	Salvage LNRT vs. LND	17 in SLND and 31 in salvage LNRT	LND had higher distant metastases (52% vs. 21%) and secondary	2-year BCR-free survival was 92% in salvage LNRT and 30% in SLND

Author, Year of Publication	Number of Patients	Imaging Method	Treatments Applied	Median Follow-Up (Months)	Conclusion	
					Recurrence or Response Rate	Survival
					treatments (39% vs. 15%).	
Kretschmer et al. [35], 2021	138	^{68}GA-PSMA PET/CT	Salvage LNRT vs. LND	47 in SLNRT and 31 in SLND	BCR: 40.3% for SLNRT and 86.4% for SLND, distant metastasis: 31.3% for SLNRT and 36.4% for SLND	Median metastasis-free survival: 70 months for all (57.6 months for SLNRT and 39.5 months for SLND; not different)
Rogowski et al. [29], 2021	100	^{18}FEC and ^{68}Ga-PSMA PET/CT	sENRT	37	Metastasis: 83% only pelvic, 2% only para-aortic, 15% pelvic and para-aortic LN metastases.	1, 2-, and 3-year BCR-free survival: 80.7%, 71.6%, and 65.8%, and 1, 2-, and 3-year distant-metastasis-free survival: 91.6%, 79.1%, and 66.4%, respectively

mortality; e antigen

positron emission tomography/computer tomography; LND, lymph node dissection; sLNRT, salvage elective nodal radiotherapy; PSA, prostate-specific antigen.

Porres et al. investigated the outcomes of radiation in patients with BCR and PET-positive LNs (^{18}FEC or ^{68}Ga-PSMA). In a seven-year study involving 87 patients, 87.4% of the cases had undergone RP, 57.9% of the patients had adjuvant/salvage RT (additionally), and 18.4% of the participants received ADT before sLND. The patients' favorable outcomes implied that extended salvage lymph node dissection is an appropriate and safe therapy in these patients, which allows for the postponement of systemic therapy [31]. A study involving 23 patients with PET-positive LNs also showed that RT significantly decreased PSA levels from the median of 2.75 to 1.37 ng/mL. The researchers concluded that RT is a promising therapy for the local treatment of patients with an isolated LN metastasis of PCa [32]. In an extensive multi-institutional analysis of patients with BCR and PET-positive LNs (^{11}C-choline or ^{68}Ga-PSMA), Fossati et al. showed that the patient outcomes after salvage LND depend on the clinical recurrence rate. According to their findings, they developed a model to predict the early clinical recurrence one year after salvage LND according to the Gleason score, the time from RP to PSA rising, hormonal therapy at PSA rise after RP, retroperitoneal or three or more spots on a PET/CT scan, and the PSA level at SLND. These researchers suggested the use of this tool for appropriate patient selection [33]. As shown above, the existing evidence indicates that PET-positive LNs are an appropriate diagnostic tool for the definite diagnosis of PCa recurrence. Other researchers have also confirmed ^{68}Ga-PSMA PET/CT for the diagnosis of positive pelvic LNs in patients with BCR or high-risk primary PCa (one false-negative LN and two false-positive LNs) [36] (this study was not included in the table since the table only addresses studies on RPCa).

Few studies have compared the patient outcomes for different treatment modalities. Schmidt-Hegemann et al. compared the results of 67 patients who underwent salvage LNRT with 33 patients who underwent salvage LND

and reported the priority of LNRT, considering the lower rates of distant metastasis (92% vs. 30%), the need for secondary treatments (5% vs. 39%), and prolonged BCRFS (HR = 4.204) [34]. In 2021, Kretschmer et al. compared the outcomes of 71 patients undergoing salvage LND with 67 patients undergoing salvage LNRT and reported similar MFS, general health-related quality of life, daily pad usage, and scores for the two modalities. However, the only significant difference was associated with a higher PSA-progression-free survival in the salvage LNRT group [35].

An important issue challenging the comparison of the rates of patient outcomes among studies is the presence of confounders, i.e., factors affecting the patient outcomes that are independent of the treatment plan or the diagnostic accuracy of the PSMA PET/CT scan. These factors include the number of positive LNs on the ^{68}Ga-PSMA PET/CT scan, the Gleason score, the duration of ADT before recurrence, and the duration from the initial diagnosis to relapse [30][37]. Fossati et al. have also developed a model to predict the outcome of salvage LND according to Gleason grade group 5, the time from RP to PSA rising, hormonal therapy at PSA rise after RP, retroperitoneal or three or more spots on a PET/CT scan, and the PSA level at SLND [33].

Interestingly, Farolfi et al. compared the results of ^{68}Ga-PSMA PET/CT before and after salvage LND in 16 patients with persistent BCR and determined the recurrence after LND in 25% of cases (n = 4) and repeated local therapy after salvage LND in 9 patients (7 with RT and 2 with surgery). They also reported that all regions detected by PET as positive were truly positive [38]. These findings suggest that the selected MDT was not a complete treatment. Considering the high mortality rate in patients with failed salvage therapy (above 60%) [39], it is important to select an appropriate treatment method to reduce the risk of failed treatment and recurrence after the treatment of LN metastasis [40]. De Bari et al. suggested that adopting larger target volumes treated at least 95% of lymph node regions with the risk of occult relapse [41]. It was also suggested to estimate the oncologic benefit of MDT and select the most appropriate treatment strategy regarding patients' conditions when this imaging tool was used for treatment decisions in LN-positive patients [33].

By the accumulation of the above data, in one of the most important ongoing trials the investigators are testing the benefit of treating PET- and/or MRI-defined involved nodes by IMRT or SBRT along with the elective treatment of the pelvic nodes and the prostatic bed in the salvage settings [42].

3. Nodal Irradiation in PSMA-Negative Patients

In the recently published SPPORT study, the elective treatment of the pelvic nodes in the pre-PSMA era has been associated with superior BCRFS compared to treatment of prostate bed alone in the salvage setting [43]. However, the treatment and/or outcome of patients diagnosed as LN-negative using a PSMA PET/CT scan has mainly been reported in the subgroup analyses of studies and scarcely as their main objective. Most studies have indicated that patients with PSMA-negative LNs had a lower PSA compared to those with PSMA-positive LNs [44], suggesting that they have a better prognosis (1- and 2-year BCRFS rates of 87% and 76%, respectively) [45]. Comparing the results of histological metastasis, as determined by LND, with the results of PSMA PET also showed that the consideration of a negative 68Ga-PSMA PET/CT as the basis of not performing pelvic LND can avoid unnecessary

LND treatments in 80% of patients [46]. However, the specificity of PSMA PET/CT in predicting pathologically confirmed positive nodes ranged from 87.5 to 97.3%, and only 24% of patients diagnosed as negative by PSMA were found to be positive histologically [27]. Comparing the histological reports with the PSMA PET results in patients before salvage LND showed specificity values of 74.1% in the side-based analysis and 87.5% in the LN field-based analysis and an NPV of 90.9% in the LN field-based analysis [47]. Nonetheless, the majority of studies have not reported the NPV of PSMA PET/CT in patients with RPCa [22][48], in which has been reported in patients with primary PCa [49][50].

As discussed earlier, small LNs cannot be captured by PET scans, and comparing the results of 68Ga-PSMA PET/CT or PET/MRI with histopathologic results showed a median diameter of 3.4 mm (IQR 2.1–5.4 mm) for metastatic LNs that were considered negative on a ^{68}Ga-PSMA PET/CT scan [51]. Furthermore, although the recurrence rate of PSMA-negative patients is lower than those with positive PSMA (16.7% vs. 50%, respectively) [52], some have reported similar BCRFS rates between PSMA-negative and -positive patients (82% vs. 74%, respectively) [53]. Accordingly, the BCR rate in PSMA-negative patients should be considered. A follow-up of 103 patients with BCR and negative PSMA LNs who were receiving no treatment detected clinical recurrence in the prostatic fossa (45.6%), nodes (38.6%), and bone (15.8%) at a median of 15.4 months, with overall clinical-recurrence-free survival rates of 61.4% after one year and 34.8% after two years, which was longer in patients with a lower ISUP grade group [54]. These findings support the necessity of active surveillance for these patients using on-time and appropriate therapeutic strategies. However, leaving these patients without treatment may be a great risk; some suggest salvage LNRT, even in the absence of PSMA-diagnosed LNs, considering the low sensitivity of PSMA PET/CT in diagnosing micrometastases [55][56]. The **Table 2** summarizes the results of studies reporting the outcomes of PSMA-negative LNs in patients suspected of BCR.

Table 2. The summary of studies reporting the treatment outcomes of patients with PSMA-negative results for prostate bed and lymph node metastasis in patients with the biochemical recurrence of prostate cancer (referred for treatment) after radical prostatectomy.

Author, Year of Publication	Ratio of Patients with Negative PSMA PET/CT to All Patients	Treatments Applied	Median Duration of Follow-up (Months)	Conclusion
Zschaek et al. [57], 2017	Not mentioned	Salvage LNRT	29	Median PSA response:9% decline for PSMA-negative patients and pathological N+ vs. 79% decline for PSMA negative and pathological N0
Emmett et al. [58], 2017	60/164	Salvage LNRT and prostate bed RT	10.5	In total, 85% with negative PSMA responded to treatment, and PSA increased in 65% of untreated patients.
Schmidt-Hegemann et	48/90	Salvage LNRT and/or ADT	23	Similar recurrence-free rates between positive and negative PSMA (74% vs. 82%)

Author, Year of Publication	Ratio of Patients with Negative PSMA PET/CT to All Patients	Treatments Applied	Median Duration of Follow-up (Months)	Conclusion
al. [53], 2019				
Emmett et al. [59], 2020	90/260	Salvage LNRT and prostate bed RT	68	Negative PSMA plus salvage LNRT was the best predictor of 3-year free-from-progression rate (82.5%), and 66% of untreated patients had a PSA increase.

e-specific

positron

emission tomography/computer tomography as the imaging method.

Emmet et al. focused on the predictive value of negative PSMA results for LN metastasis in patients with persistent PSA (with PSA readings between 0.05 and 1.0 ng/mL). In their first study (2017) among 60 patients with a negative PSMA result, 27 patients underwent SRT (45%), and the others did not; among those not receiving treatment, 65% had increased PSA levels. They also showed a high response to treatment in PSMA-negative patients, highlighting the value of treatment in these patients [58]. In 2021, they published the results of a three-year follow-up of 260 patients. In their study, 32% of PSMA-negative patients did not receive treatment, and 66% showed PSA progression (with a mean rise of 1.59 ng/mL over three years). They also reported the higher likelihood of salvage LNRT and ADT in PSMA-positive patients compared to PSMA-negative patients [59]. Zschaek et al. evaluated patients with extremely high risk PCa who underwent PSMA PET before salvage LNRT and showed that treatment with salvage LNRT significantly prevented PSA increase in patients with negative PSMA LNs [57]. Schmidt-Hegemann et al. evaluated 204 consecutive patients that were referred for salvage LNRT and underwent PSMA PET before treatment; about half of their study population had negative PET results, 81% of whom also had a low PSA level (≤0.5 ng/mL). None of the patients with a negative PET result underwent LNRT or other treatments (only one continued ADT). However, the results showed that the PSMA results (positive or negative) did not influence the outcome (BFRS), which was mainly due to the advantage of treatment intensification in patients with positive PSMA PET results [53]. A review of 27 studies (n = 2832 patients with a primary diagnosis of PCa) also confirmed that the patient risk score should be considered for the decision of pelvic LND, even in patients with negative PSMA PET/CT results [60]. Other studies have also concluded that a negative PSMA PET/CT result does not rule out LN metastasis [61][62]. Accordingly, it is speculated that a risk scoring system should be used for making decisions about the treatment of PSMA-negative patients in cases with BCR of PCa. However, such results have not been confirmed for these patients. Kiste et al. reported their results in their cohort based on PSMA-negative PET results and showed that the initial T status, the M status at recurrence, the PSA level at the time of salvage LNRT, additive ADR, and elective prostate bed RT could significantly predict the BCRFS during a median follow-up of 28 months [63]. Further studies are required to determine the most appropriate type of RT, the extent of irradiation in patients with BCR of PCa, and no evidence of LN metastasis on a PSMA PET/CT scan.

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