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Current controversies on the role of lymphadenectomy for prostate cancer

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Abstract

Lymph node dissection is part of the standard treatment protocol for various cancers, but its role in prostate cancer has been debatable for some time. Pelvic lymphadenectomy has been shown to better help stage prostate cancer patients, but has yet to be definitively proven to be of any benefit for survival. Various templates for lymph node dissections exist, and though some national guidelines have endorsed an extended pelvic node dissection, the choice of template is still controversial. Pelvic lymphadenectomy may lead to a slightly higher rate complications and operative time, and their use must be judiciously applied to patients with a high enough risk of lymph node involvement. We present a comprehensive review of the literature regarding the benefits and harms of lymph node dissection in prostate cancer.

Keywords: Prostate cancer; Lymph node; Lymphadenectomy

Abbreviations: NCCN, National Comprehensive Cancer Network; ePLND, extended pelvic node dissection; lPLND, limited pelvic node dissection; PLND, pelvic lymphadenectomy; VTE, venous thromboembolism; PSA, prostate-specific antigen; LNI, lymph node invasion; AUC, area under the curve; BCR, biochemical recurrence; ADT, androgen deprivation therapy; HR, hazard ratio; ^{68}Ga-PSMA=, Gallium-68-prostate-specific membrane antigen

1. Introduction

Pelvic lymphadenectomy (PLND) at the time of radical prostatectomy (RP) still stands as the most accurate method for definitive diagnosis of lymph node metastasis despite the advent of sophisticated imaging. Surprisingly, even when a lymph node dissection is indicated following guidelines (e.g., National Comprehensive Cancer Network [NCCN] guidelines), a large series in 2010 showed that a surgeon's adherence rate to these recommendations was reported to be 65 to 70% [1].

As delays in correct staging could sometimes impact outcomes and cancer-free survival, urologists are challenged to perform or omit lymph node dissections at time of surgery to spare patients potential morbidity such as lymphoceles, which are reported to be as high as 10% in some series [2,3]. The aim of this review is to offer a guide to surgeons in patient-tailored decision making in an era where recent literature on numerous nomograms and novel imaging techniques have been produced.

2. Historical and anatomical considerations of lymph node dissection

The template for lymph node dissection during a RP was subject to multiple modifications paralleling the technical innovations of this procedure from open to laparoscopic and then to robotic approaches. Quite early in the robotic experience, this topic was reviewed in a 2009 study by Polcari et al. who found that lymph node yield obtained using similar templates during robot-assisted pelvic lymphadenectomy for prostate cancer is comparable to an open approach (7.2 vs. 8.6 nodes) [4]. Unfortunately, a limitation to this study was the lack of a robotic group with an extended lymphadenectomy template. Later it was suggested that the number of lymph nodes removed would

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dictate the rate of nodal positivity [5]. Therefore, it was recommended that at least 10 lymph nodes should be removed in order to reliably detect lymph node invasion (LNI), though this number has been debated on given the results of different studies. From an anatomic perspective, there is enough data to demonstrate that the lymphatic spread follows an ascending pathway from the pelvis to the retroperitoneum, in which the internal and common iliac nodes represent critical landmarks.

During surgery, extended pelvic node dissection (ePLND) consists of removal of the obturator, external iliac, and hypogastric nodes, with or without including the presacral and common iliac nodes. The ePLND significantly improves the detection of lymph node metastases when compared to more limited templates. The limited pelvic node dissection (lPLND), defined as removal of the obturator nodes with or without the external iliac nodes, was found to be associated with poor staging accuracy [3]. The converse of the lPLND is the super ePLND and it is in clinical use currently. For example, in a mapping study of pelvic lymph nodes by Joniau et al., it was estimated that 21% of sentinel nodes could be found in the presacral and perirectal regions, and concluded that 8% of lymph node positive patients would have been missed if a standard ePLND had been performed [6]. Inguinal lymph nodes were also considered as landing sites for prostatic lymphatic drainage by some investigators and therefore a template encompassing the area covered by ePLND plus the nodes along the common iliac arteries up to where the ureter crosses, would remove 75% of all lymph nodes [7]. Maderthaner et al. illustrated this by assessing 451 patients and examining the locations and number of nodal metastasis. They concluded that a more extended template detects LNI in the common iliac region and the Triangle of Marcille with no increased complication rates [8].

Nodal metastases can be as high as 6% of low-risk, 25% of intermediate-risk, and 40% of high-risk prostate cancer patients in some series. The internal iliac nodes comprise of 25% of all positive nodes [9]. For all these reasons and prior cumulative data collected over the years, whenever a PLND is indicated in prostate cancer, most guidelines have suggested it should be performed in an extended fashion [10].

3. Complications of PLND

The morbidity of pelvic lymph node dissection should always be considered, especially when it is anticipated to add little clinical information. Due to the variability in prostatic lymphatic drainage, a substantial number of lymphadenectomies will have to be performed in order to slightly improve oncologic outcomes. A highly structured study by Klein et al. attempted to determine the number needed to treat to potentially cure 1 patient. In fact, when the preoperative probability of lymph node involvement is near 10%, number needed to treat was 67, whereas it increases to more than 660 in low-risk disease or patients with <1% risk of positive lymph nodes. This shines the light on the potential morbidity of a possibly "unnecessary" lymphadenectomy [11].

3.1. Lymphoceles

Of all complications, the most common remains lymphoceles caused by disruption of lymphatic drainage during pelvic lymphadenectomy. Although lymphoceles were described almost 40 years ago in urological surgery, it remains unclear whether robotic or minimally invasive techniques are associated with an increased incidence due to suboptimal lymphostasis. A recent prospective randomized trial compared the incidence of lymphoceles during robotic prostatectomy using bipolar coagulation vs. titanium clips applied on the femoral lymphatic canal. Though the study showed no difference in the appearance of lymphoceles, others have thought that this may be due to the location of where clips were applied and that the results may actually support the use of clips [12]. Some series report overall rates of lymphoceles as high as 54% when postoperative imaging modalities are used, but the majority of these are less than <5 cm and remain subclinical. Briganti et al. report a 10.3% rate of lymphocele in extended lymphadenectomies vs. 4.6% for lPLND [13]. These numbers vary considerably among series, and the most feared complication is mainly superinfection of these collections. The differential diagnosis should always include a urine leak in the setting of infection. Otherwise, the treatment options for symptomatic lymphoceles include percutaneous drainage, sclerotherapy, and laparoscopic marsupialization when other options fail. For subclinical collections, conservative management is preferable whenever possible. Lebeis et al. described a surgical technique to prevent lymphocele formation by interposing and fixating the ipsilateral peritoneal flap on the bladder itself. Such techniques, however, need randomized large scale studies for ultimate practice recommendations [14].

3.2. Injury to adjacent structures

Injuries to the major vessels demarcating lymphadenectomy templates are dreaded perioperative events. Most venous injuries can be repaired robotically with nonabsorbable fine sutures. Robotic vascular clamps can always be applied to control bleeding and aid in repair of the external or internal iliac veins. Major arterial injuries, however, may require open conversion and a vascular surgical consult. The obturator or circumflex vessels travel along and across the obturator nerve, respectively, and can be safely ligated in case of injury.

The obturator nerve provides important sensory function to the inner thigh and motor function to the adductor muscles. Clips placed over the nerve will have to be removed and a transected nerve will need repair by approximating both ends with 7-0 nonabsorbable sutures along with

intensive early postoperative physical therapy. Recent data suggest significantly lower rates of nerve injury compared to the early experience of minimally invasive surgery: 0.1% risk of obturator nerve injury vs. 5.1% in some early series with the proximal part being at the highest risk representing 77.8% of reported injuries [15,16].

Ureteral injury although uncommon is also described. These are infrequent and ureteral reimplantation is the preferred method for successful repair if technically feasible.

3.3. Deep venous thrombosis and pulmonary embolism

In a recent population based observational study on over 90,000 men undergoing RP, venous thromboembolism (VTE) events were identified in 0.25% of all procedures (open and robotic). Men who had robotic surgery or received antithrombotic prophylaxis were less likely to have VTE; the latter reducing the risk by 40%. Interestingly, heparin prophylaxis was still not used in almost a third of the patients nationwide [17]. The risk of VTE after lymphadenectomy seems to increase considerably with a hazard ratio of 6 compared to 1.7 when a PLND was omitted. The risk for VTE was also noted to be most prominent during the second half of the first postoperative month [18].

Lymphoceles also increase the risk of thromboembolic events, with reported rates as high as 8.2% [19]. Some have suggested that use of prophylactic heparin has been associated with an increased risk of lymphoceles and may be secondary to inhibition of lymphovascular sealing. Use of heparin prophylaxis along with sequential compression devices is currently an acceptable practice for deep pelvic operations for malignancy. The patient's personal risk factors for VTE have to always be taken into account when considering VTE prophylaxis.

4. Emergence and re-emergence of predictive nomograms for LNI in prostate cancer patients

In the absence of definite preoperative imaging techniques to predict LNI with certainty, adjunctive measures such as nomograms and predictive tables still play a role in clinical decision making. Most practitioners use available preoperative variables such as prostate-specific antigen (PSA), clinical stage, and Gleason score. Various comparisons have been made between available nomograms with overlapping and misleading statements and results. For example, in a systematic review, the accuracy of the Briganti, Partin, and Memorial Sloan Kettering Cancer Center (MSKCC) models were similar in predicting the presence of LNI. The head to head comparison of each of these nomograms against each other utilizing the area under the curve models revealed no statistical difference in each scenario [20]. Multiple analysis looking at different patient populations show that the various nomograms are accurate in prediction of LNI though they can fall short in predicting seminal vesicle invasion in different populations [21]. A recent study assessed some of the nomograms for prediction of LNI and showed a statistically similar and strong receiver operating characteristic curve of 0.88 for Briganti, 0.83 for Cagiannos, and 0.84 for the Partin/Makarov 2007 tables suggesting that they are quite accurate [22].

The Partin tables were later evaluated in different patient populations including a population-based cohort and in European patients. In these settings, the nomogram had a decreased predictive value in identifying LNI with accuracy rates of 76% [23]. However, while all these studies relied on series undergoing lPLND, Briganti attempted to overcome this limitation by analyzing patients who underwent ePLND. A recent validation comparison of 4 main preoperative nomograms (Briganti, Godoy, MSKCC, and Cagiannos) showed that the ability to avoid unnecessary lymph node dissections was very similar among all [24].

The decision for performing pelvic lymph node dissection should be directed by established nomograms. One example is the MSKCC nomogram that relies on preoperative PSA, Gleason score and clinical stage and has the best predictive power pertaining to the risk of nodal involvement. When this risk is less than 2%, PLND can be avoided. The NCCN guidelines panel set up this threshold in order to avoid up to 47.7% of PLNDs at the cost of missing 12.1% of positive lymph nodes. With this 2% cutoff and based on recent studies from the SEER database, it was shown that only 3% of metastatic nodes would be missed while avoiding 22.3% of unnecessary lymphadenectomies.

According to NCCN guidelines, in the low-risk group with Gleason < 6, PSA <10 and fewer than 3 positive cores with <50% cancer, PLND is only indicated when expected patient survival is more than 20 years and when risk of nodal involvement is more than 2% as calculated by validated nomograms. The same applies for all cT2 lesions, Gleason 7 or PSA between 10 and 20 with an anticipated survival of more than 10 years. In the high-risk group including Gleason 8-10, cT3 stages or when the PSA is over 20, PLND is indicated at time of RP. Adjuvant therapies are indicated depending on nodal involvement on pathology and other disease features. Select patients with very high-risk disease (i.e., T3b, T4, or primary Gleason 5 lesions) should undergo RP with ePLND.

The adherence to NCCN guidelines for RP is another aspect that was analyzed by many some centers. Adherence was in part dependent on the size of institution where surgery was performed and depended on the surgical approach itself. For example, in one study by Schiffman et al., the robotic approach was associated with lower adherence rates to lymphadenectomy recommendations compared to the open approach [25,26]. On the other hand, more nodes were removed during surgery in tertiary centers or high volume centers. These disparities among others, highlight the suboptimal adherence to guidelines of lymph node dissection (LND) at time of RP.

5. Low-risk prostate cancer

Since the early 2000s, authors have suggested omission of PLND in patients with favorable tumor characteristics i.e., PSA < 10 ng/ml, biopsy Gleason score <7, and clinical Stage T1 or T2 [27].

A systematic review by Peneau et al. in 2004, differentiated the indication for PLND during RP depending on the approach in this patient category. When the RP is done open, exploration of the lymph nodes by palpation at the beginning of the operation is recommended. If exploration shows induration or a mass deforming the shape of the lymph nodes, lymphadenectomy is recommended otherwise it remains optional (without frozen section). While macroscopic assessment of LNI is less accurate via laparoscopy, lymphadenectomy without frozen section examination is considered optional in the case of laparoscopic total prostatectomy [28].

Although it is established that lymph node dissection in low-risk prostate cancer is of little benefit, an interesting review of 50,000 patients with low-risk prostate cancer from the national cancer database between 2010 and 2013 showed that in 36% of patients undergoing RP, a PLND was performed. The predictors for PLND were high volume facility, academic center, and rural residence. The mean number of harvested lymph nodes was lower and nodal positivity was similar to the incidence predicted by the D'Amico risk classification or the updated Partin nomograms [29]. One of the reasons that could explain that is the risk of upstaging and/or upgrading reported in many studies. The LAPRO prospective cohort evaluated 4000 men and reported an adverse pathology (higher grade or pathology) rate as high as 35%, giving more motives for PLND in this category of patients [30]. This was also assessed by another study by Weckermann D et al. who found a risk of upstaging and upgrading between 46% and 80% [31]. Given the significant rate of upstaging, there is more motivation for surgeons to perform PLND in low-risk patients and consideration for even very low-risk patients.

On the other hand, the volume of nodal metastases is another important factor to consider; if low, this was not seen to negatively impact survival and prostate cancer progression rates regardless of adjuvant therapies. Another question that is raised is whether an ePLND could be potentially curative in this setting especially that biochemical recurrence rates (BCRs) are known to be lower even with positive nodes in this group? Prospective case control studies are still mandatory to assess these questions.

6. Intermediate-risk prostate cancer

Intermediate-risk disease is characterized by PSA between 10 and 20 ng/ml, Gleason 7 disease, or a prostate cancer clinical stage T2b. The risk of having positive lymph nodes in intermediate-risk prostate cancer is between 3.7% and 20.1%.

The European Association of Urology guidelines recommend an ePLND approach when the estimated risk of positive lymph nodes exceeds 5% risk of LNI calculated by ePLND-based nomograms [32]. An ePLND should be performed in this group otherwise the lymph node dissection is not necessary assuming a low risk of node positive disease [33].

In this patient category, even slight morbidity contests the utility of ePLND. Therefore a multiple strategies-based series form MD Anderson compared ePLND to standard PLND and yielded a higher node positivity and had the highest impact on the percentage of positive nodes for high-risk disease (32.8 vs. 9.3%, $P = 0.002$), modest impact for intermediate risk (10.9% vs. 4.2%, $P = 0.003$), and minimal impact on low risk (0% vs. 4.1%, $P = 0.401$) [34]. On the other hand, nomograms or risk categories that predict the probability of LNI found that lPLND underestimate the actual risk of LNI, and ePLND-based prediction tools are preferable to avoid the risk of understaging prostate cancer, especially in patients with intermediate risk disease. In fact, surgeons are aware that a subset of patients within this category are at risk for upstaging and could carry aggressive disease unrecognized preoperatively. Another study gleaned from the national cancer database assessed 10,000 men with Gleason 3 + 4 prostate cancer, showed that 1 in 3 patients approximately harbored a higher grade/stage disease [35]. These findings were confirmed again by a retrospective analysis from Harvard stating that 25.5% patients with PSA of 10 to 20 ng/ml and 12.4% with cT2b to T2c disease were upgraded or upstaged [36]. This rate was higher than 30% when considering patients with PSA between 15 to 20 ng/ml. In reality, intermediate-risk patients are a very heterogeneous group and more work is being done to further characterize patients within this group and identify the minority of patients with a more favorable prognosis for which conservative approaches would be acceptable. One recent study in 2017 that tended more toward a less aggressive, less extended Lymph node dissection (LND) found no statistical link between biochemical free relapse and lymph node yield among 667 patients with intermediate-risk disease managed with RP and PLND. While the weakness of this study was a relatively short median follow-up interval of 21 months, these results still align with another single-institution investigation at Columbia University [37,38]. However, this is very conflicting with other reports which correlate higher lymph node yield in association with biochemical free recurrence survival mainly due to identification of an increased number of positive lymph nodes [39]. It becomes evident that the discrepancy in recommendations within this patient category would put the urologist at the center of decision making rather than following clear cut guidelines.

7. High-risk prostate cancer

This category includes any patient with a PSA >20, Gleason score 8 or higher, or a locally advanced cancer

(i.e., ≥T3 prostate cancer). All of those are associated with worse outcomes and concerns about progression and death from prostate cancer make RP, whenever indicated, a crucial moment in the management of the disease. When surgery is planned, ePLND should be performed in all cases of high-risk prostate cancer, as the estimated risk of positive lymph nodes can be as high as 15% to 40% in some series [33]. lPLND should no longer be performed in this patient category. Mapping studies of lymph nodes metastasis showed that limited template lymph node dissections would miss more than half of involved lymph nodes.

In locally advanced cases, surgical treatment has been historically discouraged. Increasing recent evidence in literature push urologists to opt for RP in T3 Prostate cancer patients assuming no lymph node involvement is shown. There is no existing robust data to support RP in patients with positive nodes; for this reason, individual based management in these specific cases have to be discussed with the patient and tailored as part of a multimodal approach [40].

8. Sentinel lymph nodes in prostate cancer

In the last decade, sentinel lymph node guided lymphadenectomy has gained popularity to prevent morbidity associated with a potentially avoidable ePLND. Many techniques are described in the literature using different radiotracers. A 2017 sentinel node panel meeting agreed on the use of indocyanine Green tracers and technetium-nanocolloid, hybrid (99mTc/indocyanine Green) tracer. The administration route is transrectal, and the time interval is dependent on the tracer being used, though it usually ranges between 8 hours and 30 minutes preoperatively [41]. In a systematic review of 21 studies evaluating 2,509 patients, sentinel node biopsy seemed to have diagnostic accuracy comparable to ePLND with high sensitivity and specificity. In the same analysis, sentinel node biopsy did not have any diagnostic value over ePLND, although combining both in high-risk disease seemed appropriate since it yielded more affected nodes [42].

Following that, the updated Winter nomogram emerged as a predictor of lymph node positivity based on sentinel node dissections. In a comparison of area under the curves with other tools like Briganti and MSKCC, it showed better accuracy in the low/intermediate risk patients undergoing sentinel node, while in the high-risk population, an overestimation of the risk for LNI was observed [43].

9. Patients with lymph node positive disease

A certain paradigm shift in treatment modalities of patients with prostate cancer and positive lymph nodes can be noticed recently, although this is not based on any treatment guidelines or high level of evidence. In fact, radical prostatectomies with extended lymph node dissections coupled with adjuvant therapy or radiation as part of a multidisciplinary management was shown to offer superior clinical free progression and cancer-specific survival rates when compared to controls in which surgery was not completed [44]. This is particularly noticeable for younger, high-risk patients less than 60 years old in whom cancer-specific mortality exceeds mortality from other causes. In the past years, The 2014 NCCN guidelines support only radiation plus androgen deprivation therapy (ADT) or ADT alone as the 2 recommended treatment options for node positive
disease. Beyond these treatment modalities, attempts of maximizing local control of the primary, by adding prostatectomy and extended pelvic lymph node dissection were still considered highly unlikely to translate into any survival benefit [45].

Currently, a proposed model to treat those patients could involve a RP and an ePLND to as much as an extent as possible. This would be followed by a multimodal adjuvant approach, changing the management of these patients from a palliative concept to a multistage treatment plan that would result in a significant improvement in survival and possible cure. The perfect scheme needs considerably more elucidation as individual components such as the role and parameters of adjuvant radiotherapy have to be analyzed in prospective studies [46].

10. Postoperative impact and survival of lymph node positive patients

Lymph node positivity is rarely diagnosed at time of surgery, especially when the number of involved nodes is limited. Currently, most patients are first diagnosed with node positive disease pathologically when assessing the final specimen postoperatively. While counseling patients on such results can be challenging, many studies have evaluated cancer-specific mortality and can be a remarkable aid for the urologist. A recent study examined 30,000 patients who underwent RP, of which 6.2% (1,869 patients) exhibited positive nodes and were originally classified as D'Amico intermediate or high-risk disease. At 60 months after RP, cancer-specific mortality rates were 6.0% vs. 0.8% for patients with and without LNI respectively (hazard ratio (HR) 4.4, $P < 0.001$). Cancer-specific mortality rates were, respectively, 0.8% for 0 positive nodes, 2.4% for 1 or 2 positive nodes (HR: 3.5, $P < 0.001$), and a sharply increased 7.2% for ≥3 nodes (HR: 10.3, $P < 0.001$). It was concluded that the number of positive nodes is an independent predictor of higher cancer-specific mortality rate [47]. The impact of lymph node dissection and positivity is even more pronounced in locally advanced disease and when secondary treatments are considered. In a recent study by Zareba et al. looking on approximately 8,000 patients with positive lymph nodes at time of prostatectomy, it was shown that initial management with only observation was adopted in 63% of patients [48]. Secondary treatments were employed in the remainder with 20% of patients getting ADT only, 5%

radiation only and 12% getting a combination of both. Younger age, higher surgical grade or stage, and positive surgical margins were all determining factors for combined secondary treatments. In fact, in this latter subgroup better overall survival was achieved when combined androgen deprivation and radiation were achieved when compared to observation (HR:0.69, $P = 0.01$)[48]. Fossati et al. evaluated the beneficial effects of the extent of lymph node dissection and numbers of nodes resected on BCR and clinical recurrence in patients receiving salvage radiotherapy after prostatectomy [49]. The rate of BCR after salvage radiation therapy was inversely associated with the number of nodes resected. The increased extent of dissection also proved similar results with decreased risk of clinical recurrence (HR:0.97, $P = 0.042$). Although it is known to be associated with an increase in prostate cancer mortality, the optimal management of patients with positive lymph node is not clearly established. In a comparative analysis by Touijer et al., it was shown that given the heterogeneity of the group of patients with positive lymph nodes, those with the more adverse pathological features benefit the most from adjuvant therapies in the form of androgen deprivation or radiation to achieve better local control; another important f actor affecting cancer-specific survival [50]. A risk adjusted tool based on patient characteristics and disease features becomes crucial in directing management strategies following the diagnosis of lymph node metastases.

11. Other benefits of lymph node dissections

Lymph node dissection benefits are not restrained to patients with positive node diseases. In fact, in a series by Chenam et al. extended lymph node dissection even when negative was shown to confer a higher biochemical recurrence free survival in intermediate-risk prostate cancer patients in comparison to patients who did not undergo a lymphadenectomy at time of surgery (93% vs. 80%) [51]. Similar findings are reported by Preisser et al. who state that the number of removed nodes had a greater impact on cancer-specific mortality reducing it by 4.5% for each additional node removed (HR: 0.955, $P = 0.01$) [52]. it was then concluded that ePLND provided better staging and improved cancer-specific mortality in D'Amico high-risk and intermediate-risk prostate cancer patients without any evidence of lymph node metastasis. Touijer et al. evaluated also the outcomes of LND and RP alone without antiandrogen therapy for treating patients with lymph node metastasis [53]. They concluded that a considerable subset of men with Gleason score <8 and low burden of nodal metastasis (less than <3 positive nodes) remained free of disease and distant metastases at 10 year (65% with confidence interval CI [56–73]). Many of these studies present limitations and are retrospective in nature but they can serve as a cornerstone for better knowledge of the clinical impact and benefits of lymph node dissection in different scenarios.

12. New perspectives with PSMA and theranostics

Gallium-68-prostate specific membrane antigen (^{68}Ga-PSMA) positron emission tomography (PET)/computed tomography imaging has been a strong exploration into the new frontier of prostate imaging and therapy since its introduction in 2013. PSMA is a 750-amino acid transmembrane protein. In benign prostatic tissue, it is found within the apical epithelium of secretory ducts. While the physiologic role of PSMA in the prostate remains unclear, in malignant transformation PSMA is translocated and overexpressed to the luminal surface of the ducts.

Despite its presence in other tissues (lacrimal, salivary, kidneys etc.), PSMA is a very appealing agent for targeted imaging using nanoparticles with small specific ligands such as the most widely used ^{68}Ga-PSMA-11 [54]. In a recent systematic review in European Urology, the overall percentage of positive ^{68}Ga-PSMA PET scans among patients was 40% (95% CI 19%–64%) for primary staging and 76% (95% CI 66%–85%) for BCR. Positive ^{68}Ga-PSMA PET scans for BCR patients increased with PSA level categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml and the following rates of positive scans 42%, 58%, 76%, and 95%, respectively. This resulted in both a sensitivity and specificity of 86% when assessing it on a per patient basis but when examined on a per lesion basis, the values were 80% and 97% respectively [55]. Based on these striking numbers, new clinical applications for ^{68}Ga-PSMA PET scans continue to emerge such as ^{68}Ga-PSMA guided biopsies, directed surgery, targeted radiotherapy, and monitoring response of treatment. The experience of ^{68}Ga-PSMA PET/computed tomography have opened the way similarly to somatostatin receptors targeted PET to radiotracers that can help triage patients and initiate theranostic endoradiotherapy; the combined diagnostic and therapeutic potential of single agents and particles in order to offer a specific cancer/disease treatment, in this case prostate cancer radiation [56].

13. Conclusion

In the relentless search for the robust tool to predict preoperative lymph node positivity, surgical lymph node dissection remains the gold standard for accurate staging of patients undergoing RP. The indications for that tend to be conservative in low-risk disease while more imperative in patients with aggressive disease or high tumor volume burden. In between these 2 starkly contrasting scenarios, a gray zone exists where there is a role for novel investigative techniques such as new imaging techniques or sentinel lymph node investigation. It is the role of the urologist to analyze this information and make a case-based decision by balancing the benefits of lymphadenectomy with its risks.

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