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Narrative review

Utility of Lymphadenectomy in Prostate Cancer: Where do We Stand?

Bartosz Małkiewicz [1,*], Paweł Kiełb [1], Jakub Karwacki [1], Róża Czerwińska [1], Paulina Długosz [1], Artur Lemiński[2] Łukasz Nowak[1], Wojciech Krajewski[1] and Tomasz Szydełko [1]

1. University Center of Excellence in Urology, Department of Minimally Invasive and Robotic Urology, Wroclaw Medical University, 50-556 Wroclaw, Poland; bartosz.malkiewicz@umw.edu.pl (B.M.); pawel.kielb@student.umw.edu.pl (P.K.); jakub.karwacki@student.umw.edu.pl (J.K.); roza.czerwinska@student.umw.edu.pl (R.C.); paulina.dlugosz@student.umw.edu.pl (P.D.); lukasz.nowak@student.umw.edu.pl (Ł.N.); wojciech.krajewski@umw.edu.pl (W.K.); tomasz.szydelko@umw.edu.pl (T.S.)
2. Department of Urology and Urological Oncology, Pomeranian Medical University, Powstańców Wielkopolskich 72, 70-111 Szczecin, Poland; artur.leminski@pum.edu.pl (A.L.)
* Correspondence: bartosz.malkiewicz@umw.edu.pl ; Tel.: +48 506-158-136

Abstract: The purpose of this review is to summarize current knowledge on lymph node dissection (LND) in prostate cancer (PCa) patients undergoing radical prostatectomy (RP). Despite a growing body of evidence, utility, therapeutic and prognostic value of such approach as well as optimal extent of LND, remain unsolved issues. Although LND is the most accurate staging procedure, the direct therapeutic effect is still not evident from the current literature which limits the possibility of establishing clear recommendations. This indicates the need for further robust and adequately designed high quality clinical trials.

Keywords: prostate cancer; lymph node dissection; lymphadenectomy; radical prostatectomy

1. Introduction

Prostate cancer is the second most common cancer in men (after lung cancer) and the fifth leading cause of death worldwide [1]. One man in eight is going to be diagnosed with PCa. Lymph node metastases constitute a poor prognostic factor for patients with PCa, both in terms of biochemical recurrence (BCR) and survival [2]. Although nowadays LND can be avoided more frequently by using various nomograms assessing probability of lymph nodes invasion (LNI), lymphadenectomy performed during prostatectomy remains the first choice procedure for evaluating metastasis presence [3]. Despite LND is an excellent staging tool and some studies have indicated its positive effect on BCR-free survival, the overall therapeutic benefit of LND is questioned and unclear [4]. Moreover, this surgical approach entails an increased risk of peri- and postoperative complications, longer operative time, and increased morbidity. According to current guidelines PLND (pelvic LND) should be performed especially among patients with high-risk and intermediate-risk PCa when the probability of LNI exceeds 5% [5]. In this review we aim to establish the benefits and harms of present-day approach, describe the role of PLND in management of PCa and seek for future possibilities.

2. Diagnosis and prediction

The stage of the cancer is described by the TNM classification, where T stands for the progression of the disease within the prostate gland, N - lymph nodes metastases and M - distant metastases. TNM-confirmed extent of PCa is crucial for planning treatment strategy.

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There are several diagnostic methods used to determine whether LNI or distant organ metastases occur. The imaging procedures play an important complementary role in primary detection, staging, posttreatment assessment and recurrence of prostate cancer.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the conventional imaging techniques confirmatory of the shape and size of the nodes. Although they might be helpful in detecting the metastases, their efficiency is low and may misdirect the patient's therapy [6], [7]. One of the meta-analyses show not statistically significant, but comparable poor performance of those two methods. Pooled sensitivity for CT was 0,42 and for MRI 0,39. In the case of pooled specificity the result was 0,82 for both diagnostic methods [6].

Currently, the MRI imaging offers more advanced procedures. One of them is diffusion-weighted imaging (DWI). DWI sequences show the Brownian movements of water's molecule. MRI DWI LN staging has low sensitivity but high specificity and performs better than standard MRI imaging [8], [9]. One study reports a sensitivity of DWI-MRI in detection of lymph node invasion at the level of 41% and specificity at the level of 94% [7].

PET imaging in LNI found a few different radiotracers which can be used in the field of PCa. The most thoroughly tested substances are radiolabeled glucose, choline, fluciclovine, acetate or NaF [10].

The scope of application of 18F-Fluorodeoxyglucose (18F-FDG) is very limited, yet can be used to detect LNI in some cases [7], [11]–[13]. For example, Jadvar (2016) points out that FDG can only be useful in detecting and staging of high-grade tumors (Gleason score >7). What is more, FDG PET-CT detected metastatic disease in LN and/or bone only in six of the nine (67%) patients [12].

Globally, two choline derivatives are used - radiolabeled with Carbone-11 (11C) or Fluor-18 (18F). The strength of this method lies in the possibility of detecting LNI, bones and distant organs metastases, however the detection rate is low. Fraum et al. (2018) point out that 11C choline has sensitivities for nodal metastatic disease of 60% in case of a per-patient basis and 41% per-node basis respectively [11]. This method gains on diagnostic accuracy when PSA serum level is high enough. Therefore, according to the EAU, it is recommended to use choline-based PET imaging in BCR patients after RP if their PSA serum level is ≥1 ng/ml [7], [11], [14], [15].

Another radiotracer used in PET Imaging is acetate, which seems to be better than choline at detecting the local recurrences and LN metastases [10]. Some researchers point out that its sensitivity is rather unsatisfactory and the methods using this substance as a tracer have several limitations, for example the minimum detectable tumor size of 5 mm, what is an important constraint [16].

The imaging methods are in constant improvement and new substances tested. Another interesting PET/CT method is using a protein called PSMA - prostate-specific membrane antigen. PSMA is physiologically expressed by prostate cells and overexpressed in PCa cells as well as some other malignant tissues and it is presumed to be a valuable metastases marker [11], [17]. Derivative radiolabeled tumor targeting molecules were created - 68Ga-PSMA and 18F-DCFPyL. They are not FDA-approved yet but show promising clinical potential. They seem to be helpful in initial staging as well as suspecting recurrences or even treatment assessment [11], [18]–[20]. One meta-analysis indicates that in retrospective studies, the method using 68Ga achieved widely varying sensitivity and specificity (33.3% to 100%). The detection rate of 68-Ga-PSMA PET in patients with BCR after RP in the PSA subgroups <0,2 ng/mL, 0,2-0,49 ng/mL and 0,5 to <1,0 ng/mL ranged from 11,3% to 50%, 20% to 72,7% and 25% to 87,5%, respectively [18].

Another discovery related to PSMA pertains to its similarity to the N-acetylaspartylglutamate peptidase (NAAALDASE). Metastasis detection is possible using inhibitors targeting the expressed PSMA, an example is a small molecule inhibitor 99mTc-labelled - MIP-1404. Research indicates its potential for finding LNI and soft tissue or bone metastases [17], [19], [21]. However, there are significant limitations for the use of this method. Primarily researchers point out that PSMA uptake is not specific for PCa but also

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characterizes many benign tissues. Moreover, inhibition of PSMA expression is common in advanced stages of the disease and up to 10% of PCa cases do not overexpress this protein. The same meta-analyses reported high specificity at the level of 95% but a poor sensitivity at the level of 49% in primary nodal staging [20].

In conclusion, none of the imaging methods are efficient enough to be considered a gold standard. All of them have some strengths and weaknesses, although the simultaneous use of several methods may be useful in improving the accuracy of detection. They might be helpful when it comes to optimizing the treatment and localizing recurrences. Currently, even highly developed, imaging techniques are not sufficient enough to fully replace PLND, therefore more studies are required [6], [7], [9], [10].

Due to the fact that lymphadenectomy is an invasive staging procedure, and markers of PCa metastases are difficult to be interpreted as single parameters, several nomograms were created to enhance decision-making and establish estimated probability of LNI and more (e.g. positive margins or extracapsular extension) [22]. Most of the PCa-related nomograms can be divided into diagnostic, post-diagnostic and before or after-treatment tools. The nomograms predicting LNI are before-treatment assessment tools and are widely used to facilitate decision-making whether to apply PLND during RP or not [23].

Briganti nomogram, one of the most widely used nomograms predicting LNI in PCa, is based on serum PSA levels, clinical T-stage, primary and secondary Gleason grades and percentage of positive cores [24]. It suggests performing PLND if calculated risk is higher or equal to 5%. Its internal validation evaluated the accuracy of prediction at the level of 87,6%; LNI would be missed in 1,5%. The 2018 Briganti nomogram (also known as Gandaglia nomogram) is a model that predicts LNI in patients diagnosed with MRI-targeted and systematic biopsies. It considers PSA levels, clinical stage at multiparametric-MRI, maximum lesion diameter and biopsy results; suggested cutoff is 7% [25]. Other nomograms used in anticipating LNI are the Partin tables and Memorial Sloan Kettering Cancer Center (MSKCC) nomogram. They are based on TNM, preoperative PSA level and biopsy Gleason score [26]–[28].

There are more tools such as Godoy nomogram, Roach formula or CAPRA score being used, though many of those lack external validations. Briganti, Partin and MSKCC nomograms have similar prediction accuracy and (along with Roach formula) are recommended by the EAU as a preoperative LNI prediction tool [29], [30].

3. Anatomical extent of PLND

Prostate cancer disseminates through venous routes, perineural spaces and lymphatic network. Main causes of lymphadenopathy in prostate cancer are: metastases, hyperplastic and regressive alterations [31].

The goal of PLND is to remove lymph nodes and lymphatic vessels/trunks from the landing zones for metastases. Prostate cancer originally distributes to regional LN [32]. The first site to which lymph flow carries cancer cells is known as a sentinel node. According to this theory, presence of metastasis in sentinel nodes can suggest them being present in other LN, similarly, lack thereof suggests other LN being cancer-free, too. It reflects disease progression in some cancers well, despite its role in deeply located cancers (such as prostate cancer) requires further investigation, with lack of concrete data [33]. Sentinel node navigation surgery (SNNS) is employed to find out if there is a need for a radical surgery and determine its extent to perform the least invasive procedure possible. In PCa it's not a standard clinical procedure, mostly performed in clinical trials. A promising technique seems to be the radioisotope guided laparoscopic and robotic sentinel lymph node dissection [34], [35], [36].

SN concept holds poor value for regional metastases in prostate cancer, as recent findings imply the existence of a multitude of primary landing sites, putting into question whether isotope-based imagining accurately represents nodal status of the entire pelvic basin and thus explaining the high false-negative rate of this procedure [32], [37], [38]. In high-risk PCa patients, Weckermann et al., presented that in a group of 228 men, had there

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only SN been removed, then ~ ⅓ of nodal metastases would have remained [39]. These drawbacks and high false-negative rate for the detection of metastatic nodes are the major reasons why the sentinel node technique has not gained wide acceptance. However, according to Wawroschek et al., and Egawa et al., a patient is more likely LN-negative if he is SN metastasis-free [33], [38].

Earlier it was believed that the primary landing site consists of obturator, internal and external iliac LN [40]. Researchers concluded that patterns of dissemination and drainage for prostatic gland are not identical, but data is too little [41]. As proven by isotope-based studies, metastatic cells do not sequentially spread, but rather can be detected all the way to the inferior mesenteric artery area. A multimodal mapping study held by Mattei et al. discredits this theory - in 34 patients who underwent RP for biopsy-confirmed cN0cM0 prostate cancer, preoperative SPECT/CT plus intraoperative gamma probe was used after injection of technetium-99m into the prostate gland. Positive nodes were detected along the external iliac vessels and obturator fossa (38%), internal iliac vessels (25%), common iliac vessels (16%), perirectal and presacral area (8%) and the paraaortic/paracaval (12%) and inguinal regions (1%) [32]. Another research, a SPECT-based virtual 3D atlas of the landing sites demonstrated sentinel nodes present in 61 high-risk patients, who underwent PLND and RP [37]. Furthermore, some studies suggest that a larger positive lymph node can interfere with lymphatic flow [39], [42].

In recent years, attention was paid to anatomical region called Marcille's fossa (limited by the ala of the sacrum, the medial border of the psoas muscle and the anterolateral side of the fifth lumbar vertebra/promontory, covered by the iliac vessels). It was proven to be connected with the prostatic lymphatic system and linked with high metastatic load involvement - positive Marcille's nodes are correlated with metastases in other locations in high-risk prostate cancer patients [43]. Marcille's triangle can only be accessed by full exposure, medial retraction and mobilization of the external iliac vessels along with the ureter [43]. At the moment, Marcille's lymphadenectomy, also known as "marcillectomy" is not recommended as a standard procedure, as there are no prediction factors available yet.

The main objective of PLND is to find out the locoregional extent of cancer, the risk of progression or recurrence and to determine if a therapy is needed. Secondly, it can be a form of treatment for patients who already underwent chemotherapy, to rid of leftover tumor. Therefore, it is necessary to study the overall lymphatic drainage pattern for the prostate.

The prostatic lymphatic drainage mostly occurs in cephalad direction, following the blood supply route of the organ. It incorporates the external and internal iliac arteries area and the obturator fossa. According to anatomic studies held, there are: ascending flow (which drains the cranial prostate into external iliac LN), lateral flow (draining into the hypogastric node chain) and posterior flow (draining lymph from the caudal prostate into the subaortic LN of the sacral promontory) ducts groups [44], [45]. Surgical studies showed limited usefulness, as they can only evaluate exposed and removed LN - in areas spared in lymphadenectomy it is impossible to know if there are positive nodes [46]. Bayer et al. conducted an embryological study arguing that the knowledge of the ontogenesis of the contents of pelvis compartments is crucial for the ability to propose suitable and optimal PLND templates [47].

The template for LND is defined by the localization of metastases and the lymphatic drainage pattern of a particular cancer as well as the state of the primary lesion. Regarding the theoretical anatomical extent of the procedure, we can divide it into following types: limited, standard, extended and super-extended (Fig 1). As of today, there is no standardization proposed. There seems to be no consensus neither to what is the optimal extent for each type of procedure nor to what terminology should be used. It doesn't help that in some research papers a unique take is employed, or even, sometimes the extent is not specified at all. Creating a standardized nomenclature is desired as it would allow for better regularity in practice between institutions and would make it easier to accurately

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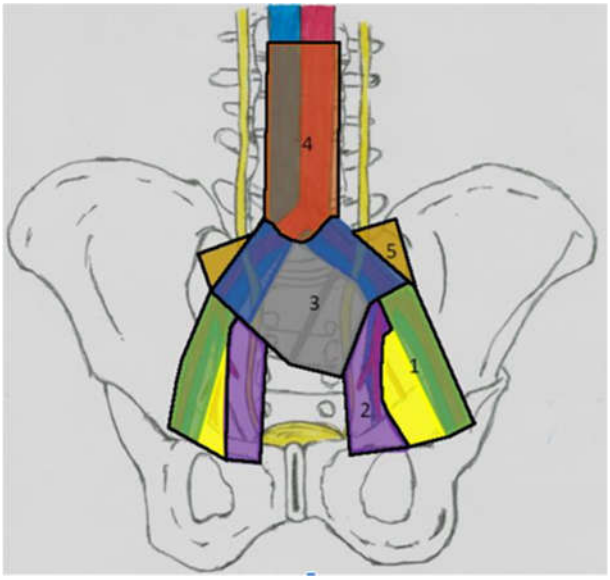
compare results for future studies on the subject. The Committee on Classification of Regional Lymph Nodes of the Japan Society of Clinical Oncology created guidelines aiming to help with overcoming these drawbacks and should be used in future research [47], [48].



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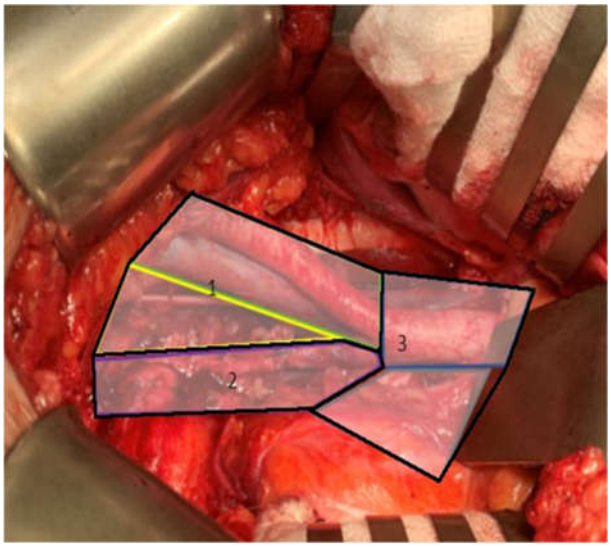

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Figure 1. Anatomical extent of lymphadenectomy: 1 - limited; 2 - standard; 3 - extended; 4 - super-extended; 5 - Marcille's Fossa.; A – topography B – anatomical superimposing.

The limited PLND (lPLND) engages obturator fossa area LN only (located mediocaudally to the external iliac vein, atop the tendinous arch of the levator ani muscle and internal obturator muscle), while the standard PLND covers obturator and external iliac nodes (proximally located along or between external iliac vessels, distally next to deep inguinal ring, crossed by the deep circumflex iliac vessels) [49], [50].

The extended PLND (ePLND) consists of lymph nodes groups covered by the standard procedure as well as additional ones, such as hypogastric, presacral (along the sacral concavity), internal, common iliac nodes (stretching on the common iliac vessels before the aortic bifurcation) [50], [51]. Salvage extended PLND is recommended in recurrent prostate cancer, with the additional removal interiliac and paraaortic LN [47], [52]. Total number of nodes removed is crucial to maintain the accuracy of the staging procedure.

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The higher the number, the greater the chances of detecting a node-positive case [53]. Based on research led by Weingärtner et al., a mean LN yield of 20 was suggested to be a sufficient PLND guideline [31]. It is recommended by the EAU and NCCN to adapt PLND usage with the help of nomograms and other risk stratification tools in order to predict lymph nodes metastases preoperatively [54]. It allows for disqualification of low risk PCa patients, in whom the probability of being node-positive is <3% [40], [55]. It is worth noting that these tools might require a revisit by cause of them being developed predominantly on data collected from lPLND performed in older patient series [51].

Substantial debate takes place to what the proper boundaries of PLND ought to be. In clinical practice, it is usually enough to dissect the obturator LN only due to reportedly relatively low total of node-positive cases (<8%), with only 25% of total positive nodes found surrounding the internal iliac artery [30], [49], [51], [56], [57]. Presacral and common iliac LN metastases are uncommon [40]. High diagnostic staging accuracy was presented for standard PLND [30], [58]. On the contrary, addition of more nodal areas improve survival in pN0 in patients, effectually by the elimination of micrometastases [43].

An attempt was made to determine patterns of prostate dissemination regarding dominant tumor mass location. It was discovered in various studies, that 10-46% positive LN were located contralaterally, with only 10-17% rate of contralateral only cases, with false predictive rates of 14-29% [59]. Based on those results some authors suggest that the only reliable lymph node staging method is complete bilateral lymphadenectomy [60], [61].

4. Oncological outcomes

There are several approaches to treating patients with localized PCa. According to researchers, the efficacy of radical prostatectomy with ePLND is more beneficial than just radiotherapy itself [62]. The ePLND is not only a reliable tumor staging tool but may also have the potential therapeutic effect, however, it is not explicit [5], [63], [64].

Clinical recurrence can be evaluated by examining the presence of distant metastasis. Some researches show that the patients who underwent PLND present higher risk of recurrence. However, in low-risk PCa patients no recurrences have been observed [5]. None available studies provided with any relevant survival rate (both cancer-specific and overall mortality) difference between the PLND and no PLND treatment [5]. Additional parameter taken into consideration is increase in PSA level, which can indicate the BCR [65].

Taking into consideration the clinical recurrences, there were no studies which reported on the difference in distant metastasis between sPLND and ePLND procedure [5], [63]. There are trials that seek to determine whether lPLND or ePLND for PCa have better oncological outcome.

Lestingi et al. investigate a prospective randomized phase 3 trial in total of 300 patients with intermediate- or high-risk clinically localized PCa [63]. The group was split in two halves, one having ePLND and one having lPLND carried out. They found that extended removal of LN did not reduce BCR of PCa in the expected range. The median biochemical relapse-free survival (BRFS) was 61.4 mo in the lPLND group and not reached in the ePLND group (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.63–1.32; p = 0.6). Median metastasis-free survival (MFS) was not reached in either group (HR 0.57, 95% CI 0.17–1.8; p = 0.3). In summary, the differences in early oncological outcomes were not demonstrated [63].

The second trial provided by Touijer et al. is a single-center randomized trial in total 1440 of patients assigned to limited or extended PLND [66]. 700 were randomized to lPLND and 740 to ePLND. In this clinical trial they did not find a difference in the rate of biochemical recurrence of prostate cancer between the two procedures. The median number of nodes retrieved was 12 (interquartile range [IQR] 8–17) for lPLND and 14 (IQR 10–20) ePLND; the corresponding rate of positive nodes was 12% and 14% (difference 1.9%, 95% confidence interval [CI] 5.4% to 1.5%; p = 0.3). With median follow-up of 3.1 yr, there was no significant difference in the rate of biochemical recurrence between the groups

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(hazard ratio 1.04, 95% CI 0.93–1.15; p = 0.5) [66]. Extended PLND did not improve chances of BCR-free outcome for men with clinically localized PCa over lPLND. Moreover, the observed difference both in nodal count and the rate of positive nodes between the two templates was lesser than expected [66]. Subsequent trials comparing those methods are still recommended.

Despite the drawbacks, performing the ePLND still appears to be warranted. It allows assessment of the cancer spread including micrometastases not detectable by imaging techniques [67]. As a cancer staging tool, ePLND helps in a non-direct manner to enhance the oncological outcome [5]. This argument would need to be examined in subsequent research.

Considering available data, the therapeutic role and oncologic efficacy prospects of PLND remain unclear. There is no evidence to back up the claim that PLND improves oncological outcomes over no PLND performed. Only some particular subgroups of the patients might benefit from the procedure. In addition, weighing non-oncological outcomes, performing PLND was associated with a higher risk of intraoperative and perioperative complications however there was no evidence seeing the difference in functional outcomes such as erectile function and urinary continence.

Since there still are controversies associated with this procedure, further clinical trials are required [5], [63], [64]. The shortage of solid evidence should lead to individual patient eligibility for surgery or disqualification. The personal risk ought to be taken into consideration and the patients therefore judiciously selected. As long as we do not have certain trial results, the clinicians ought to follow the recommendations of the EAU guideline and perform ePLND for PCa patients who present more than 5% risk of LNI [14].

5. Complications of PLND

PLND is a procedure bearing a relatively low both short- and long-term complications and mortality rates, resting at 20-35% overall complication rate and mortality of under 1%. None of the available studies showed any relevant survival rate difference (both cancer-specific and overall mortality) between the PLND and no PLND treatment [50].

Postoperative complications stay in relation to dissection template extent - more invasive procedure leads to increased postoperative organ impairment [33], [68]. Among the most common minor complaints we can name: wound infection (< 5% of patients), atelectasis, small bowel obstruction (<2% of patients), ureteral and vascular injuries (<1%, usually recognized and fixed at the time of the original operation) [69]. Lymphoceles are positively linked with a greater dissection template. During surgical lymphadenectomy, both afferent and efferent lymphatic vessels are susceptible to thermal or mechanical injury, more likely to occur by blunt dissection or gross plucking (in contrary, en block harvesting reduces probability of these complications) [47]. They are extremely common, yet unlikely to be symptomatic or cause morbidity. Patients with lymphocele presented higher rates of deep venous thrombosis and pulmonary embolism [68], [70]. When it comes to severe complications the most serious ones are pulmonary insufficiency, chylous ascites (lymphatic leak) and lymphatic cysts, lymphatic fistula or chylopelvic fistula [47], [71], [72]. Thromboembolic complications are rare enough and in the majority of cases (over 99%) do not require treatment [70]. Routine pharmacological prophylaxis is currently recommended to be considered for intermediate and high thromboembolic risk indicated for ePLND. Mechanical prophylaxis however is recommended for all PLND patients [70]. Patients with deep venous thrombosis presented increased pulmonary embolism risk and were more likely to be reoperated [68].

Intraoperatively, a bleeding may occur, especially from damaged aorta, vena cava or iliac blood vessels. Serious bleeding may require blood transfer. This adverse effect frequency is related to the operating time and surgeon's experience [68]. Another complication may arise if retroperitoneal lymph nodes are very close or adherent to a blood vessel, sometimes forcing a removal of a part of the vessel. While the obturator vessels may be dissected, the obturator nerve must be spared [47].

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PLND related morbidity incorporates damage to sympathetic nerves, which can result in infertility. Damage to the obturator nerve may occur if it is clipped or otherwise injured, causing motor (adduction) and sensory impairments (in medial thigh). Dealing with this consequence requires intensive physiotherapy, vitamin B6 and pain relievers administration [70]. Respecting the parietal pelvic fascia provides best results in the preservation of the autonomic pelvic nerves, since they are vital for the maintenance of the urogenital and anorectal functions [47]. Incidences of anatomic structures pre-operatively present have strong correlation with postoperative urine retention [68].

Attempts were made on comparing risk of complications between different PLND extends. Several studies were held, producing conflicting results. Schwerfeld-Bohr et al. observed that lymphocele developed more frequently in patients who underwent ePLND (17%) in comparison to lPLND (8%) [73]. These findings are supported by another RCT, where ePLND and lPLND were performed at the same time, on the right and left hemipelvis, respectively. Lymphocele and lower extremity oedema were reported more often on the ePLND-performed side [74]. Fossati et al. analyzed data from 15 retrospective studies discovering that some of them showed significant spike in intra- and postoperative complications for ePLND, while others claim the difference to not bear statistically significant. The same conclusion was reached on the matter of lymphocele presence [5]. One study showed that differences in urinary continence and erectile function recovery to be insignificant [74]. Due to wilder usage of modified templates (first introduced by P. C. Walsh) over 90% of patients have potency-preserving and nerve-sparing results [44], [75]. Similarly, larger surgical template paired with worse preoperative state may explain higher risk of complications in patients who underwent ePLND [33], [76], [77].

6. New perspectives for PLND

The most promising innovation, though still being tested and considered as an experimental therapy, is sentinel lymph node dissection (SLND). At present PLND performed during prostatectomy remains the gold standard for nodal staging in prostate cancer, despite the fact that the rate of post-LND complications, as well as morbidity, rises as the number of dissected LN grows [69], [78]. Therefore SLND, already being a first choice procedure in melanoma, breast and penile cancers, is taken into consideration as an alternative [79]. According to the concept of metastatic spread of the tumor along the lymph drainage pathways, an assumption can be made that the absence of cancer invasion in the sentinel nodes is coequal with the lack of the metastasis in other LN [80]. Implementation of SLND would ideally prevent patients with PCa from overtreating them with ePLND [81].

The concept of SLND may carry many advantages including a more tailored and balanced approach. Moreover, techniques used to detect SLN revealed lymph drainage pathways that weren't investigated before [69]. According to collected data some of the LN on SLND may be observed outside of ePLND template and a few of these nodes may occur positive [69], [82]. Some studies show that SLND and ePLND has equal predictive value in the identification of metastatic lymph nodes. Adding SLND to ePLND improves BCR-free outcome compared with ePLND only [79].

SLND concept is unfortunately limited by current technical determinants, which produce the inability to properly detect all metastatic lymph nodes and the duress to only use intraoperative, rather than preoperative, methods of imaging SLN. Furthermore, the technique is bounded by experimental protocols and lack of standardized procedure guidelines.

Currently most frequently used methods of imaging SLN are radio-isotope injection of Technetium-99m and indocyanine green (ICG) technique. Radioisotope SLN technique employs transrectal injection of ^{99m}Tc bound to a pharmaceutical in a prostate. Then preoperative lymphoscintigraphy and SPECT-CT are being performed which is a valuable advantage for the creation of the surgical plan. Additional intraoperative usage of gamma-ray detection probes or gamma cameras enable detection of sentinel lymph nodes and can

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provide the urologist with the precise location while performing lymphadenectomy [83]. Meta-analyses evaluating detection of LN metastases suggested sensitivity of approximately 95% [7]. Another study, the first sentinel nomogram, shows a high degree of accuracy at the level of 82% and may be the first to aid clinicians in making a decision whether to implement SLND or go for the conservative solutions [84]. Fluorescence imaging technique using ICG is based on the intraoperative detection of SLN with polarized light. Several studies have been reported and the median intraoperative SLN detection rates extended between 76 and 97% [7]. Despite these promising results ICG is still an unreliable SLN imaging method due to its poor diagnostic accuracy among patients with intermediate and high risk PCa. It is worth considering the usage of hybrid technique engaging both fluorescence and radioisotope method, combination of which improves the detection rate.

Most recent diagnostic methods used in PCa concentrate on detecting metastatic and sentinel LN with higher predictive value and sensitivity. Doughton et al. investigated the first-in-human usage of ^{68}Ga-Nanocolloid as the radiotracer for PET/CT lymphoscintigraphy and its results were promising though this technique of SLN imaging requires further research. What's interesting is discovering unexpected lymph drainage patterns including pathways leading to perivesicular, mesorectal, inguinal and Virchow nodes [85]. Another innovative technique engages prostate specific membrane antigen - PSMA-labeled radiotracer (111In-PSMA-I&T). Maurer et al. were able to detect metastasis in LNs unrevealed by ^{68}Ga-PSMA PET method. One of the most promising techniques seems to be the usage of supermagnetic iron oxide (SPIO) nanoparticles as magnetic tracer for MRI procedure proposed by Winter et al. [7].

7. Current guidelines

Despite the growing body of evidence supporting the use of PLND during radical prostatectomy (RP), consensus regarding optimal management is distinctly absent. Guidelines for PLND in prostatectomy provided by the European Association of Urology (the EAU) indicate lymphadenectomy as the only available procedure for nodal staging, though failing to improve oncological outcomes. The EAU suggests engaging pre-operative tools predicting LNI in individual cases to avoid overtreating patients of low risk of nodal metastasis with PLND. A probability of LNI should be evaluated using either Briganti nomogram or Roach formula as well as Partin and MSKCC nomograms; in case of both of the tools a risk of nodal invasion exceeding 5% should be considered a cut-off point above which ePLND is advisable to be performed [14].

American Urological Association (AUA) suggests considering PLND for any localized PCa of intermediate-risk or high risk. Patients should always be informed about the benefits of the procedure as well as the possible common complications such as lymphocele. The guidelines also explain that evidence is lacking as to whether the removal of LN containing metastatic prostate cancer has therapeutic benefits [86].

National Institute for Health and Care Excellence (NICE) proposes RP as one of treatment options to people with low, intermediate and high risk localized PCa, and in said guidelines procedures of PR and PLND are unseparated, which indicates that the lymphadenectomy of some extension should always be performed during PR. High risk localized PCa is defined by PSA level (over 20 ng/ml), or Gleason score (8 to 10), or clinical stage (T2c or more) and in this case RP should be taken into consideration when it is likely that the patient's outcome can be controlled in the long term [87].

8. Conclusions

Prostate cancer is among the top three most common cancers affecting men worldwide. It goes without saying that it needs ever more investigation and care put into developing improved methods and strategies of handling this huge issue. There is a lot of potential in newer diagnostic methods, for instance SPIO and PSMA. Despite ongoing efforts, more trials are required.

Although PLND is a coming-of-age procedure, it has presented itself as a gold standard for determining tumor staging, also leaving room for plasticity of appliance and personalization. Still, it does come with many drawbacks and confusion regarding both technical and outcome aspects. It is also not a flawless diagnostic tool, either. Our research concluded that the need for guidelines unification is tremendous.

Data received from ongoing trials will hopefully define the role of lymphadenectomy more clearly in patients undergoing surgery for prostate cancer. With all this in mind, we remain rather optimistic for the future of PLND in modern medicine.

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