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Professional paper

THE ROLE OF LYMPHADENECTOMY IN PROSTATE CANCER PATIENTS

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SUMMARY – Prostate cancer is one of the most important men's health issues in developed countries. For patients with prostate cancer a preoperative staging of the disease must be made. Involvement of lymph nodes could be assessed using imaging methods (CT or/and MRI), however, newer methods also exist (PET/CT, PSMA PET/CT). For some patients during radical prostatectomy a pelvic lymphadenectomy is recommended. Pelvic lymphadenectomy is indicated in intermediate- and high-risk group patients and with increased probability of lymph node invasion. The most used prediction tools for preoperative assessment of lymph nodes are Briganti and MSKCC nomograms and Partin tables. Pelvic lymphadenectomy can include different lymph nodes group, but extended lymphadenectomy is the recommended procedure. In 1-20% of patients, the lymph node invasion is present. Pelvic lymphadenectomy is primarily a diagnostic and staging method, and in minority of patients with positive lymph nodes it can be a curative method, too. In other patients with positive lymph nodes adjuvant therapy (radiotherapy and androgen deprivation therapy) can be beneficial.

Key words: *Prostate cancer; Radical prostatectomy; Pelvic lymph node dissection; Radiotherapy*

Introduction

Prostate cancer (PCa) is one of the men's leading health issues, especially in the more developed countries. These is a consequence of its high incidence, different types of therapy which are usually prolonged over time with regularly check-up and substantial mortality. PCa is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed[1]. It is also the fifth cause of cancer death. The frequency of autopsy-detected PCa is roughly the same worldwide and increases from 5% in men below 30 years to 59% with age >79 years[2,3]. The incidence of PCa varies widely between different geographical areas. The highest incidence was noticed in Norway (129.7/100.000) and Sweden, compared to lowest rates in Bangladesh, Nepal and Bhutan[1]. Compared to other European countries, Croatia has an intermediate incidence rate of 64.8/100.000 in the 2014 with the cumulative incidence rate (0-74 years) of 5%[4]. As the incidence, mortality from PCa is also different between regions. The age-standardized mortality rate for Croatia in 2014 was 54.9/100.000 and assigned our country among top ten EU countries in prostate cancer mortality[4].

Incidence of PCa is mainly dependent on age. Family history and racial/ethnic background are associated with an increased PCa incidence which suggests genetic predisposition[5,6]. A variety of exogenous/envi-

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ronmental factors (metabolic syndrome, diabetes, cholesterol, obesity, dietary factors, hormonally active medications as 5-alpha-reductase inhibitors and testosterone) may have impact on PCa incidence and the risk of progression[7-15].

Staging of prostate cancer

After the establishing diagnosis of PCa a proper clinical staging of the disease must be made. This staging includes tumor relationship with prostate and surrounded organs (T stage), status of lymph nodes (N stage) and presence of distant metastases (M stage).

T staging historically included transrectal ultrasound (TRUS). TRUS and derived techniques (3D-TRUS, colour Doppler) cannot differentiate between T2 and T3 tumors with adequate accuracy and cannot be recommended for the staging[15-18]. Modern imaging techniques as computed tomography (CT) and magnetic resonance imaging (MRI) are currently preferred diagnostic methods. Multiparametric magnetic resonance imaging (mp-MRI) with 1.5 Tesla or 3 Tesla is currently the best modality for local staging of the disease[15,19-21]. But because of its low sensitivity for focal (microscopic) extraprostatic extension, mp-MRI is still not recommended for local staging in low-risk patients[15,20,22,23].

N staging in PCa patients was evaluated using CT, MRI, choline PET/CT and prostate specific membrane antigen-based PET/CT[15].

M staging is determined using bone scan, fluoride PET/CT, choline PET/CT, MRI and prostate-specific membrane antigen-based PET/CT[15].

Preoperative assessment of the lymph nodes

Different diagnostic modalities are included to establish preoperative status of lymph nodes. Preoperative assessment of lymph nodes standardly includes abdominopelvic CT scan or T1-T2-weighted MRI (Fig. 1). These methods indirectly assess nodal invasion using lymph nodes diameter and morphology. Generally, the pelvic lymph nodes with a short axis > 8 mm and >10 mm outside pelvis are considered positive, e.g. malignant[15]. Meta-analysis of diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in PCa patients which included 24 studies showed sensitivity of 42% and specificity of 82% for

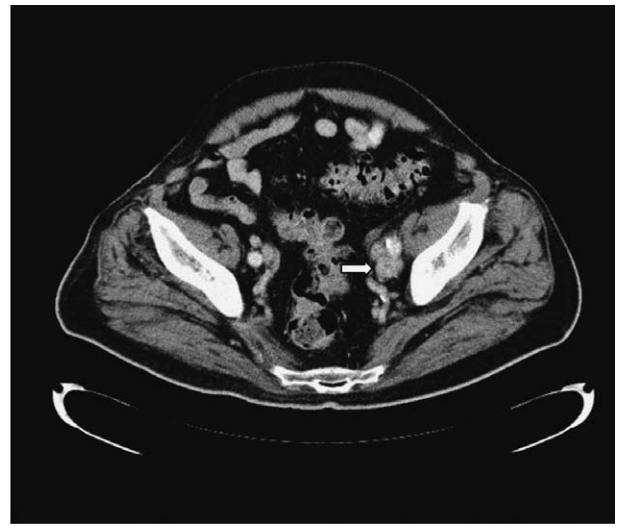

Fig. 1. Selected image from contrast enhanced computed tomography imaging in 70-year old male patient with biopsy proven prostate cancer demonstrated an enlarged left external iliac lymph node (white arrow). The size and irregular margins of the node are highly suspicious for a lymph node metastasis

CT and 39% sensitivity and 82% specificity for MRI[24]. Analysis of EUREKA database showed that CT has a sensitivity of 8.8% and specificity of 98% in predicting lymph nodes involvement with significant association only with high-risk subgroup with a sensitivity of 11.8% and positive predictive value of 44.4%[25]. According to previous data the role of CT and conventional MRI in prediction of lymph node involvement is still limited and must be combined with clinical predictive nomograms.

Detection of microscopic lymph node involvement using CT is < 1% in patients with ISUP < 4 cancer, PSA<20 ng/ml or localized disease[15]. Diffusion-weighted MRI has a potential to improve preoperative detection of positive lymph nodes. This modality enables detection of metastases in normal-sized lymph nodes in 64-79% of patients with prostate or bladder cancer (21 and 26 of 33 patients with positive lymph nodes); these positive lymph nodes would be missed with conventional MRI or CT[26].

The meta-analysis of 609 patients showed that choline PET/CT has a sensitivity of 62% and specificity of 92% for detection of lymph node involvement[27]. Other studies showed that the sensitivity of choline PET/CT increased from 8.2% in intermediate risk to

Table 1. European Association of Urology risk groups for biochemical recurrence of localized and locally advanced prostate cancer

Definition			
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/mL and GS<7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP) cT3-4 or cN+
Localized			Locally advanced

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen

50% (high risk) and 71% (very high risk)[27-29]. Due to its relatively low sensitivity choline PET/CT is not included in routinely assessment of lymph node involvement[15].

Prostate-specific membrane antigen-based PET/CT (PSMA PET/CT) is a promising technique for detection of lymph node involvement[15]. PSMA is usually labelled with ^{68}Ga or ^{18}F as a tracer. This technique has a sensitivity and specificity of 80%[30].

Prostate cancer – the risk groups

The preoperative different diagnostic modalities must be used according to different risk group affiliation of the patient. The most frequently used are EAU risk group classification (essentially based on D'Amico classification system for PCa) and International Society of Urological Pathology 2014 grades (Table 1 and 2)[15]. EAU guidelines for prostate cancer recommended that in the patients with low-risk localized disease additional imaging modalities are not needed. Patients with intermediate-risk and ISUP grade > 3 and with high-risk localized disease/locally advanced disease should perform cross-sectional abdominopelvic imaging and bone scan for metastatic screening[15].

Radical prostatectomy and pelvic lymphadenectomy

Radical prostatectomy (RP) is one of the therapy options for patients with PCa with the main goal of cancer removal. In some patients the pelvic lymph node dissection (PLND) is also needed. The EUA guidelines about prostate cancer recommended performing extended PLND in intermediate- and high-risk group patients when the estimated risk for positive lymph nodes exceeds 5%[15]. PLND is indicated only in selected patients with a higher risk for lymph node invasion (LNI) because this procedure is associated with prolonged operative time and increased risk of complications[15,31].

Table 2. International Society of Urological Pathology (ISUP) 2014 grades

Gleason score	ISUP grade
2-6	1
7(3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Prediction of lymph node invasion among patients undergoing radical prostatectomy

One of the very important issues of PCa patients is preoperative prediction of lymph node invasion (LNI). Depending on this prediction the need for pelvic lymphadenectomy is determined. The three most used nomograms for predicting positive lymph nodes in PCa patients are Briganti, Partin and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms[15].

Initially, Briganti nomogram is based on routinely available clinical variable (clinical stage, PSA and biopsy Gleason sum) (Fig. 2)[32]. Later the nomogram is strengthened by the inclusion of percentage of positive cores as a covariate (Fig. 3)[33]. Using the nomogram cut-off of 5% the sensitivity was 87.8%, specificity 70.3% and negative predictive value 98.4%[32]. Using this updated nomogram with cut-off of 5%, 385 of 588 patients (65.5%) would be spared from ePLND, and LNI would be missed in only 6 patients (1.5%). All these six patients had two or fewer positive lymph nodes[33].

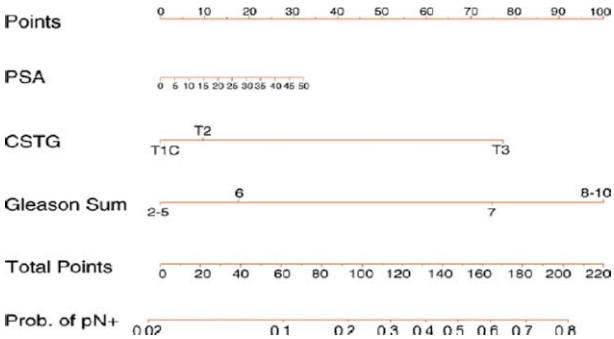

Fig. 2. Briganti nomogram (2006) predicts the probability of lymph node invasion based on pre-treatment PSA, clinical stage and biopsy Gleason sum; adapted from (32)

Recently, the new Briganti nomogram (2017) included more prostate biopsy details including biopsy Gleason grade group, percentage of cores with highest-grade PCa, and percentage of cores with lower-grade disease is developed[34]. Using a cut-off of 7% this nomogram can help to significantly reduce the number of unnecessary PLND with a risk of missing only 1.5% of patients with LNI[34]. Since the number of inclusion data needed for using this nomogram has increased, its clinical value as a routine tool is doubtful.

Also, a novel model for LNI risk assessment is developed for men diagnosed with PCa via MRI-targeted biopsies. This model includes PSA, clinical stage and maximum diameter of the index lesion on mp-MRI, grade group on targeted biopsy, and the presence of clinically significant PCa on concomitant systematic biopsy[35].

Memorial Sloan Kettering Cancer Center (MSKCC) nomogram includes analysis of patients age, PSA, primary and secondary Gleason number, clinical tumor stage, number of positive biopsy cores and calculated probability of lymph node involvement[36].

Partin tables make prediction of pathological stage based on clinical stage, serum prostate-specific antigen and biopsy Gleason score[37].

The comparison between these three nomograms showed that their accuracy is similar without significant advantages of each one[38]. But, in Europe and Croatia the most frequently used nomogram is still Briganti from 2012. All these nomograms can be found on the Internet or downloaded as mobile phone applications, what facilitates their use in everyday practice.

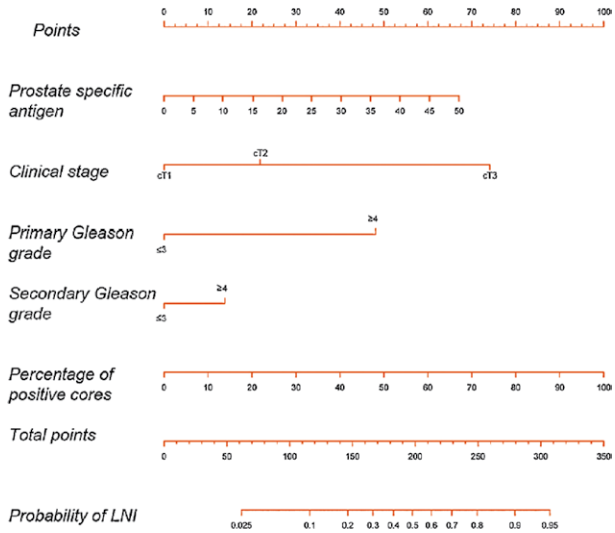

Fig. 3. Updated Briganti nomogram (2012) with the inclusion of percentage of positive cores as a covariate; adapted from (33)

Extent of pelvic lymph node dissection

PLND is primarily a staging procedure for detection of nodal metastases in PCa patients and in some patients potentially could be a curative procedure[15]. The presence of lymph node metastases is one of the strongest prognostic factors of poor oncologic outcome[15,39]. Anatomic definitions of PLND distinguish limited, standard, extended and super-extended PLND (Fig. 4)[40]. Limited PLND includes removal of lymph nodes in obturator fossa and standard PLND includes lymph nodes around external iliac vessels and in obturator fossa. Extended PLND (ePLND) includes bilateral dissection of the right and left common iliac vessels (up to the ureteral crossing), internal iliac vessels, external iliac vessels and obturator fossa. Super-extended include all nodes as extended plus all common iliac, presacral nodes and even some authors include cranially positioned lymph nodes (paraaortic and paracaval)[40-42].

Incidence of positive lymph nodes at radical prostatectomy

The incidence of positive lymph nodes (Fig. 5) at radical prostatectomy varies as an operative technique and the extent of lymph node dissection changes during time. In the beginning, when the lymphadenecto-

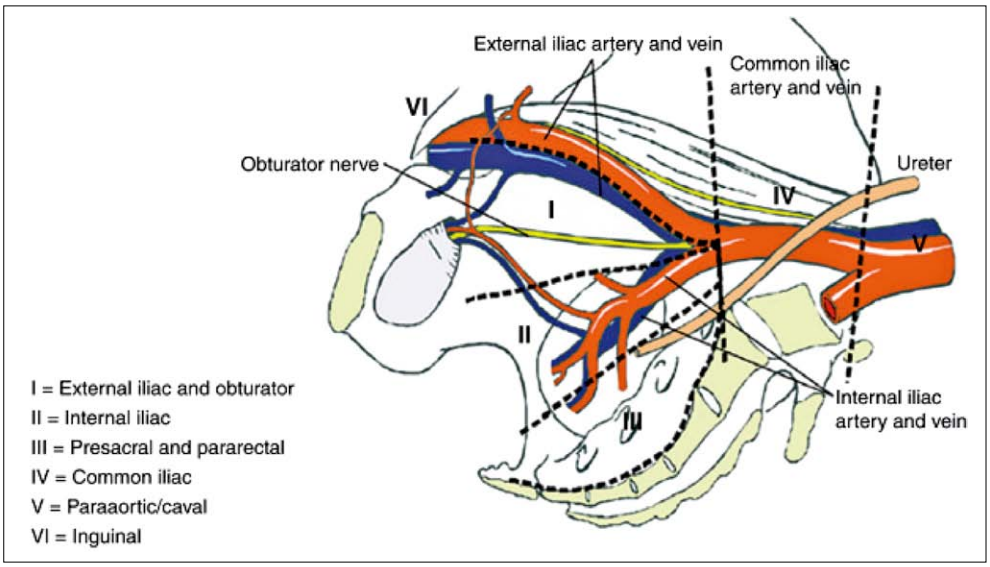

Fig. 4. Anatomical classification of pelvic lymph nodes

my included only obturator lymph nodes the incidence of positive lymph nodes was around 1-3%[43]. Recently, the extended lymphadenectomy has become a standard procedure and incidence of positive lymph nodes increased up to 10%[33,44]. Probably the largest single institution study from Mayo Clinic included 19 946 men treated with RP and 1011 (5.1%) of them had positive lymph nodes[45]. Men with positive lymph nodes had a higher PSA, higher clinical T stage, higher pathological T stage, higher Gleason score and higher rate of positive margin compared to lymph node negative patients[45].

Overall, LNI can be found in 1.1-26% of patients undergoing PLND[32,46-48]. Such variability of the positive lymph nodes relates to clinical characteristics of PCa at diagnosis as well as to extent of PLND. Few authors proved that extended PLND (ePLND) is associated with the higher lymph node detection rate compared to limited PLND, regardless of PCa agressiveness[32,49-52]. For this reason, whenever PLND is indicated it must be performed as ePLND[15,53]. Standard or limited PLND must be omitted due to high rates of false-negative findings[15].

In patients undergoing ePLND, LNI is detected in 5-6%, 20-25% and 30-40% related to low-, intermediate-, and high-risk PCa[52]. Consequently, EAU guidelines recommended ePLND for lymph node staging during RP in patients with intermediate- and high-risk PCa, and this can be abandoned in low-risk PCa patients[15].

The influence of PLND on biochemical and clinical recurrence, cancer-specific and overall mortality

Most studies which compared biochemical and clinical recurrence, cancer-specific and overall mortality after PLND or noPLND did not find any difference between these two groups[40]. Also, comparison between different type of PLND did not show any difference in the abovementioned variables[31,40,54,55-67]. These studies strongly support that PLND is primarily staging procedure.

The influence of PLND on surgical complications and functional outcomes

Extended PLND is associated with increased operative time, intraoperative complications, bleeding and hospital stay[40,68]. Also, extended PLND prolonged operative time for about 30 minutes compared to limited PLND and increased development of lymphocele[40,69]. Other studies did not find any difference in complications rate between different lymphadenectomy approach[40,70,71].

Functional outcomes after radical prostatectomy included assessment of urinary continence and erectile function. In a study of almost 1000 patients neither limited nor extended PLND did not have additional negative impact regarding urinary continence and

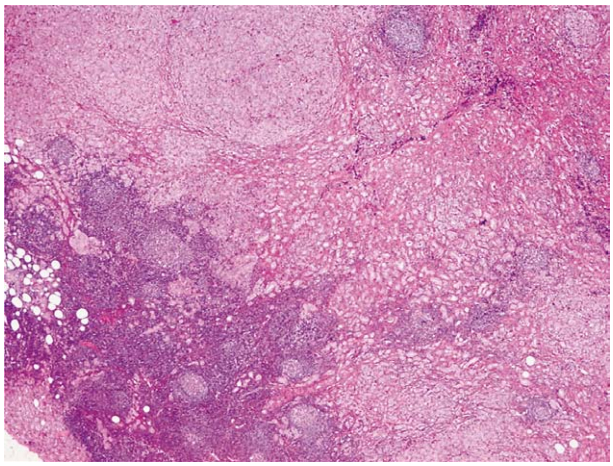

Fig. 5. Microscopic photography of pelvic lymph node metastasis. The lymph node is infiltrated with prostate adenocarcinoma, HE 40x (from archives of the Department of Pathology, University Hospital Rijeka).

erectile function recovery[72]. Only patient age at surgery, preoperative erectile function and pathological tumor stage represent predictors of erectile function recovery[72].

Sentinel lymph node biopsy analysis

Sentinel lymph node is the first one in which tumor cells from primary tumor migrate. If this node is without malignant cells, the lymphadenectomy can be avoided. This concept is well established in some tumors, such as breast and penile cancer. Different tracers are used for marking the sentinel lymph node including indocyanine green, 99mTc-NC and SPION (superparamagnetic iron oxide nanoparticles)[73]. A systematic review of 19 studies about diagnostic accuracy of sentinel lymph node biopsy (SNB) in PCa showed median sensitivity of 95.2%, specificity of 100%, positive predictive value of 100%, negative predictive value of 98% and false negative rate of 4.8%[73]. This is almost comparable with ePLND and some authors recommended removal of only sentinel lymph nodes in low- and intermediate-risk groups because this(ese) node(s) are often the only tumor-bearing nodes[74,75]. With this procedure the staging accuracy is maintained without possible surgical complications of ePLND. Comparison of ePLND and SNB showed that one in 20 patients who underwent ePLND has positive lymph nodes outside extended lymphadenectomy border because the lymphatic drainage for the prostate gland is very variable and complex[73]. Combined ePLND with SNB provided better nodal staging for about 5%. The possible oncological outcome of this finding is still unknown. Some authors advocate performing combined ePLND with SNB in high-risk group patients[73]. SNB is a promising technique, but due to heterogeneity of different techniques it is still considered experimental in EAU guidelines[15].

Management of prostate cancer patients with positive lymph nodes

Generally, the presence of malignant cells in lymph nodes after radical prostatectomy has a poor prognostic sign. Positive lymph nodes are connected with an increased long-term risk of death (20-42%)[76,77]. Currently, the modality and starting of therapy are different between institutions but therapeutic strategy includes observation until biochemical recurrence, adjuvant (mostly lifelong) androgen deprivation therapy (ADT) and combination of ADT and external beam radiotherapy (EBRT)[78-82].

The outcome of 369 men with lymph node-positive PCa after radical prostatectomy followed only by observation showed that 5- and 10-years overall survival was 91% and 60%. The predicted 5- and 10-year cancer-specific survival was 94% and 72%. 28% of patients remain free of biochemical recurrence and 65% of them remain free of distant metastasis up to 10 years of follow-up. Most recurrences occurred within the first five years. If the patients were recurrence free after first five years, the probability of remaining free from recurrence after 10 years is 81%. Based on this observation, lymphadenectomy could be potentially curative in some patients, but 2/3 will need further therapy and in one third of patients prostate cancer leads to death[79]. This suggest that patients with positive lymph nodes are a heterogenous group with different outcomes, which mainly depends on Gleason score (7 or more), the number of lymph nodes involved (3 or more), adjuvant radiotherapy and positive surgical margins[45,79]. According to the previously mentioned variables, patients with LNI can be stratified in low-, intermediate- and high-risk group with 20-year cancer specific mortality rates of 19.1% vs 34% vs 46% (Table 3)[45]. For PCa patients with LNI as a whole, the 20-year rate of biochemical recurrence, metastasis,

cancer-specific mortality and overall mortality were 69%, 36%, 31% and 70%[45].

The Eastern Cooperative Oncology Group randomized clinical trial (ECOG 3886) compared immediate hormonal therapy and observation in 98 PCa patients with positive lymph nodes after radical prostatectomy[78]. After the median follow-up of 7 years survival was significantly higher in the men who received ADT. The overall survival at 7 years was 85.1 % (ADT group) and 64.7% (observation group). Prostate cancer specific survival was 93.6% (ADT group) and 68% (observation group). At the last follow-up only 16% of patients in observation group were without recurrence (defined as detection of local or disseminated disease) compared to 43% in ADT group. Authors concluded that immediate ADT improves survival and reduces the risk of recurrence in PCa patients with LNI[78].

Da Pozzo et al. compared using of ADT versus ADT+EBRT and showed a beneficial impact on survival in combination group, especially in men with no more than two positive nodes, non-organ-confined and intermediate- to high-grade disease[81].

A retrospective study of 577 patients from Surveillance, Epidemiology and End Results (SEER)-Medicare data showed no significant difference between patients with LNM treated with adjuvant ADT+EBRT and adjuvant ADT alone[83].

The most recent study retrospectively analyzed data of 1388 patients with LNI after radical prostatectomy in three tertiary oncological centers[82]. 28% of patients were observed, 49% received lifelong adjuvant ADT and 23% received adjuvant EBRT and ADT. Observation consisted of no treatment until biochemical recurrence (defined as two consecutive PSA≥ 0.1-0,4 ng/ml depending of institution) at which point patients started with therapy. Adjuvant radiotherapy included local radiation of prostate and seminal vesicle bed and pelvic lymph node areas with a median dose of 68 Gy. Adjuvant ADT included surgical or chemical castration. These types of therapy were usually lifelong. Most of the patients had pT3b stage, Gleason 7 and more and most of them had one or two positive lymph nodes. When combined with EBRT, the median duration of ADT was 5.9 years. Combination therapy was associated with better overall and cancer-specific survival compared to other methods. Ten-year mortality risk was different between ADT+EBRT, ADT alone and observation group and range from 5% in low-risk patients to 40% in high-risk patients. In concordance with these studies, EAU guidelines recommended combined adjuvant ADT and EBRT in lymph node-positive PCa patients after radical prostatectomy[15].

Table 3. Stratification of prostate cancer patients with positive lymph nodes into different risk groups of cancer specific mortality

Parameters and risk score for different risk groups of cancer specific mortality			
Parameters	Points	Risk group	Point Range
Gleason 7 Gleason 8-10 3 or more + lymph nodes Positive margin No adjuvant radiotherapy	5 8 5 6 6	Low Intermediate High	<14 14≤ x < 19 ≥19

Modern studies showed that patients with LNI after radical prostatectomy could benefit from a multimodal approach using maximal local eradication of the disease (radical prostatectomy + extended pelvic lymphadenectomy + adjuvant radiotherapy)[15,79,82]. Previously, patients with LNI were considered as patients with systematic disease and were not considered for further curative treatment.

The optimal timing of adjuvant EBRT and adjuvant ADT it still a matter of debate. Messing showed that immediate treatment (ADT) after radical prostatectomy improves survival of patients with positive lymph nodes[78]. Because of a long natural history of prostate cancer, the influence of adjuvant therapy on the quality of life of these patients must be considered. It is well known that long-term ADT is connected with increased cardiovascular and metabolic effects which increase morbidity and mortality of these patients[84]. Also, EBRT has possible negative impact on voiding, bowel function and erectile function[85]. To prevent these negative effects some authors suggested starting the therapy after biochemical recurrence (early salvage radiation therapy) but this concept must be tested by using randomized trials[86].

Other prognostic factors

LNI is not the only prognostic factor in patients undergoing radical prostatectomy. Other prognostic

variables include seminal vesicle invasion, extracapsular extension and positive surgical margins and all are associated with a poor prognosis[15]. The incidence of these factors in patients treated with RP is more frequent than LNI. Also, patients with LNI are more likely to have simultaneously seminal vesicle invasion (up to 67,3%), extracapsular extension (up to 97%) and positive surgical margin (up to 64.3%)[87]. So, even when all positive lymph nodes were removed during ePLND it was unlikely that all cancer sites are removed in patients with positive surgical margins, for example.

Conclusion

Pelvic lymphadenectomy (PLND) represents an essential staging procedure for patients undergoing radical prostatectomy and it is performed in selected patients. A very important role of ePLN is that defining lymph nodes as positive or negative can determine the risk of progression. In subset of patients ePLND can also be the curative procedure with removal of all involved lymph nodes. In other patients, especially in the intermediate and high-risk group, multimodal approach using adjuvant radiotherapy and hormonal therapy has a potentially positive effect on their overall and cancer-specific survival.

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Sažetak

ULOGA LIMFADENEKTOMIJE U BOLESNIKA S KARCINOMOM PROSTATE

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Karcinom prostate je jedan od značajnijih zdravstvenih problema muškaraca u razvijenom dijelu svijeta. U bolesnika s dijagnosticiranim karcinomom prostate neophodno je učiniti prijeoperacijsko stupnjevanje bolesti. Zahvaćenost limfnih čvorova se standardno određuje uz pomoć slikovnih metoda (CT i/ili/ MR) iako postoje i novije metode (PET/CT, PSMA PET/CT). U određenog broja bolesnika prilikom radikalne prostatektomije treba učiniti i zdjeličnu limfadenektomiju. Odluka o potrebi za zdjeličnom limfadenektomijom se donosi na osnovu svrstavanja bolesnika u umjerenu odnosno grupu visokoga rizika i ako je vjerojatnost za zahvaćenost limfnih čvorova povećana. Najčešće danas korišteni nomogrami za prijeoperacijsku procjenu zahvaćenosti limfnih čvorova su Briganti i MSKCC nomogram te Partin-ove tablice. Zdjelična limfadenektomija može obuhvaćati različite skupine limfnih čvorova ali se preporuča učiniti proširenu zdjeličnu limfadenektomiju. U 1-20% bolesnika nalaze se pozitivni limfni čvorovi. Iako zdjelična limfadenektomija ima prvenstveno dijagnostički i prognostički značaj, u manjeg broja bolesnika s pozitivnim limfnim čvorovima može biti i definitivna terapijska metoda. U ostalih bolesnika s pozitivnim limfnim čvorovima adjuvantna terapija (radioterapija i androgen deprivacijska terapija) može biti od terapijskog značaja.

Ključne riječi: *Karcinom prostate; Radikalna prostatektomija; Zdjelična limfadenektomija; Radioterapija*