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Review

Patients with positive lymph nodes after radical prostatectomy and pelvic lymphadenectomy – do we know the proper way of management?

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Simple Summary: Prostate cancer (PCa) is the second most frequent malignancy in male population worldwide. Men with nodal invasion established after radical prostatectomy with lymph node dissection are heterogeneous group of patients, requiring more thorough stratification and therapy individualization, which remains uncovered by current guidelines. Considering a multitude of prognostic factors and novel diagnostic techniques, classifying patients into narrower and more specified risk groups should be a vital part of lymph node positive PCa management in the future.

Abstract: Lymph node invasion in prostate cancer is a significant prognostic factor indicating worse prognosis. While it affects significantly both survival rates and recurrence, proper management remains a heated issue. Thorough evaluation of risk factors associated with nodal involvement, such as lymph node density or extracapsular extension, is crucial to establish potential expansion of the disease and to substratify patients clinically. There are multiple strategies that may be taken into consideration for patients with positive lymph nodes. Nowadays therapeutic methods are generally based on observation, radiotherapy, and androgen deprivation therapy. However current guidelines are incoherent in terms of indication of the most effective management approach. Future management strategies will be expected to reach for novel diagnostic tools and therapies, such as photodynamic therapy or diagnostic imaging with prostate specific membrane antigen. Nevertheless, this heterogeneous group of men remains a vast therapeutic concern, and both clarification of the guidelines and optimal substratification of patients is required.

Keywords: prostate cancer; lymph node invasion; radical prostatectomy

1. Introduction

Prostate cancer (PCa) is the second most common cancer in male population worldwide, with an estimated 1.4 mln new cases annually. It is the fifth leading cause of cancer-related death among men with a total of over 375.000 deaths each year [1].

The prognosis among PCa patients varies and depends on many individual disease characteristics. Accurate staging is necessary for appropriate risk assessment and choosing further therapeutic measures. Multiple staging procedures including digital rectal examination (DRE), prostate specific antigens (PSA) serum levels, transrectal ultrasonography (TRUS), but also positron emission tomography–computed tomography

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(PET/CT) and multi-parametric magnetic resonance imaging (mpMRI) are aimed at evaluating PCa expanse preoperatively. Nevertheless, pelvic lymph node dissection (PLND) and postoperative evaluation by a pathologist is still the most sensitive procedure for detecting lymph node invasion (LNI) and as such remains the gold standard in PCa staging. Lymph node metastases (LNM) are present among 3–80% PCa patients after radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND) [2].

The occurrence of LNM is a relevant prognostic factor, as it affects cancer-specific survival (CSS), as well as recurrence, thus its proper detection and assessment is crucial in post-prostatectomy choice of therapeutic pathway [3]. Most of therapeutic strategies are essentially based on observation with or without salvage therapy, external beam radiation therapy and/or androgen deprivation therapy (ADT). However, both American and European guidelines concerning management of patients with nodal invasion after RP with ePLND provide no clear path of disease's further diagnostic and therapeutic process.

The purpose of this narrative review was to sum up the available data on prognostic factors and treatment options in patients with pathological LNM detected after RP (pN+), confront them with therapeutic strategies proposed in available guidelines, and search for optimal clinical solutions.

2. Risk or Prognostic factors

There are many known risk factors associated with presence of lymph node metastses and worse prognosis in PCa patients. Those include classic factors as well as pathological features of the excised tissues and novel biomarkers (Fig. 1).

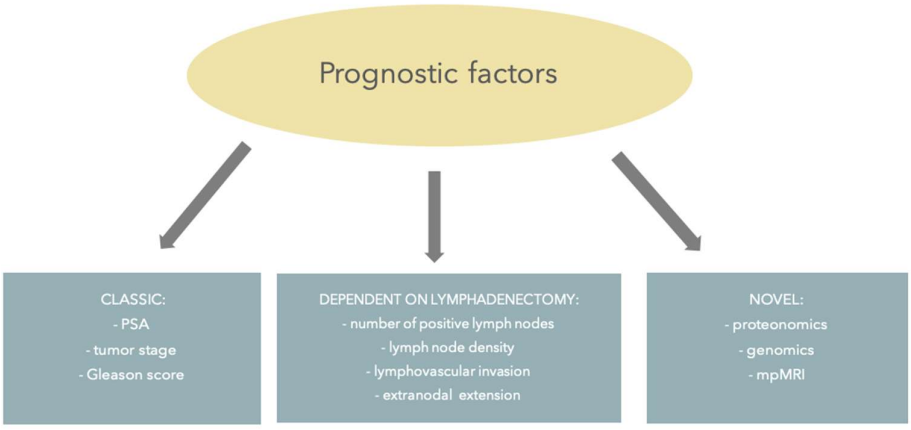

Figure 1. Prognostic factors influencing outcomes in PCa patients after RP.

2.1. PSA

The predictive role of PSA in pN + patients is of particular importance as it has been commonly used in clinical practice. Postoperative PSA takes part in the therapeutic procedure, more precisely it serves as an indicator of the effectiveness of RP and of biochemical recurrence. It is a feature which allows monitoring of possible progression of the disease after prostatectomy. During the observation of pN+ patients, as soon as PSA increases, more aggressive management should be introduced. Depending on the clinical center, the PSA level which indicates the threshold for biochemical recurrence varies between 0,1-0,4 ng/ml [4]. Preoperative PSA is an important value as it is a known prognostic factor for pN+ patients. Swanson et al. noted that among the patients with PSA below 10, 25% of them had biochemical failure in comparison with 57% with PSA equal

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or higher than 10 (p<0,0001). Importantly, this correlation was observed regardless of other disease characteristics [5]. However, preoperative PSA has not always been recognized as an independent predictor. In a study that demonstrated an association between preoperative PSA and advent of biochemical progression the median time to BCR for patients with a PSA level greater than 20 ng/mL was significantly shorter (16 months) than for those with a PSA level of 10.1 to 20 ng/mL (27 months) or others with lower PSA levels (P = 0.0005). Only the difference in the results among the groups of patients with low PSA (2.6 to 4 ng/mL versus < 2.6 ng/mL) was not statistically significant (p=0,4). The preoperative PSA correlated with the interval to biochemical cancer progression. However, a multivariate analysis, which included other characteristics such as Gleason score or tumor stage, revealed that PSA should not be considered as a significant independent prognostic factor [6].

2.2. pT – pathological tumor stage

One of the most impactful factors is the extent of the primary tumor, included in the TNM staging classification described in pathological reports. Generally, a lower T value is associated with improved oncological results. In a study focusing on pT2-staged PCa patients only 241(2,5%) out of 9,631 have had positive lymph nodes on pathological examination [7]. This result indicates pT2 to be a very beneficial stage in terms of potential LNI and further oncological outcomes. Less favorable results are documented in groups with a higher T-stage, where patients have a higher risk of LNI. One study discovered pT3b (HR: 1.9; 95% CI, 1.1–3.3) and pT4 (HR: 3.4; 95% CI, 1.7–7.3) to be independent predictors of cancer specific mortality [8].

2.3. ECE – extracapsular extension

The presence of extracapsular extension (ECE) corresponds to pT3a stage and is associated with worse prognosis in patients after radical prostatectomy. Hubanks in his study on 1,132 pT3bN0 patients with seminal vesicle invasion noted that men with concurrent pathologic ECE had significantly worse disease progression parameters such as 15-year BCR-free survival (29% vs. 39%; P o 0.001), overall survival (50% vs. 63%; P o 0.001) and systemic progression-free survival (71% vs. 81%; P o 0.001) in comparison with those without ECE. The presence of ECE correlated with increased risks of systemic progression also after adjusting data for other clinicopathological features and use of additional therapies [9]. Similar conclusions were presented in a study where the multivariate analysis showed that the level of capsular invasion was an independent prognostic factor (p<0,001). The focal and extensive ECE were associated with an increased risk of seminal vesicles invasion, positive lymph nodes and lower progression-free probability (73% and 42%, respectively) [10]. Evaluation of extracapsular extension and seminal vesicles invasion is important in planning the treatment of patients undergoing RP. Currently, preoperative imaging diagnostics such as multiparametric magnetic resonance are used for this purpose, which helps to predict the risk of ECE before the surgery.

2.4. GS - Gleason Score

The degree of histological differentiation constitutes one of the most important prognostic factor. A higher Gleason score correlates with worse clinical results in PCa patients. As shown by results obtained by Moschini et al., pathological Gleason score 7 vs 6 (HR 1.74, p=0.04) and 8-10 vs 6 (HR 2.63, p=0.001) was associated with increased cancer specific mortality [11]. Another study proved a twofold risk of experiencing unfavorable oncological outcomes in patients with pathological Gleason score ≥8 as compared to patients with Gleason score ≤7 [12]. Abdollah et al. found pathologic Gleason score ≥8 (HR: 3.8; 95% CI, 1.9–7.6) to be an independent predictor of CSM [8].

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2.5. GGG - Gleason Grade Group

Apart from the value of Gleason score itself, an important prognostic aspect is the affiliation with the relevant Gleason Grade Group. The fact of a differentiated oncologic outcome between Gleason score 7 patients was highlighted by the International Society of Urological Pathology in 2014 with the introduction of a Grade Group 2 for GS 3 + 4 and a Grade Group 3 for GS 4 + 3. Previously, the heterogeneity of Gleason score 7 patients has been confirmed by various studies, documenting threefold increased risk of distant metastasis for patients with GS 4+3 disease compared to those with GS 3+4 ($P < 0.005$), as well as an increased risk of biochemical progression after radical prostatectomy for patients with Gleason score 4 + 3 on biopsy ($p = 0.0001$) [13,14].

2.6. Cribriform Architecture

An additional independent factor in predicting patient outcomes is the type of architectural pattern within Gleason Grade 4. ISUP introduced four such types in 2014, including ill-formed, fused, glomeruloid and cribriform. Studies have proven cribriform pattern to be an adverse independent predictor for distant metastasis-free survival (HR 8.0, 95% CI 3.0-21; P<0.001) and disease-specific survival (HR 5.4, 95% CI 2.0-15, P=0.001) [15]. It is also associated with more frequent occurrence of BCR after RP [16–18].

2.7. IDC – Intraductal Carcinoma

Another histopathological characteristic influencing prognosis is the presence of intraductal carcinoma (IDC). It is believed that atypical cancer cells may spread via existing acini and ducts. This ductal spread leads to formation of a type of architecture morphologically similarly to cribriform pattern, but in case of IDC the preservation of basal cells is maintained. The presence of IDC is proven to be an independent prognostic factor related to early BCR. In a series of 246 PCa patients Trudel et al. presented that even a small component of IDC in a prostate cancer specimen at pathological examination is associated with worse prognosis and earlier biochemical failure as compared to patients without IDC (HR=4.45, 95% CI: 2.64–7.49, p−value=1.1e−09). The authors of this study furthermore suggest that the presence of any amount of IDC should be considered an unfavorable prognostic feature, even in low risk Gleason score 6(3+3) patients [19].

2.8. pN – pathological node stage

Various studies have established that a major risk factor associated with increased death from PCa is constituted by the number of lymph nodes containing micrometastases. Up to this moment, there is no widely accepted consensus on the exact number of positive nodes unambiguously translating into higher cancer-specific-mortality. Touijer et al. found the presence of three or more positive nodes to be associated with a higher risk of cancer-specific death [4]. Boorjian et al., on the other hand, assessed the number of 2 or more positive modes as an independent predictor of mortality [20]. A cut-off value for cancer specific survival of more than 2 positive lymph nodes was established by Briganti et al., indicating a worse CSS in those patients compared to men with up to 2 positive nodes [21]. Qin et al. conducted a cohort study on a Chinese population, also concluding that an increased risk of biochemical recurrence from prostate cancer after RP occurs in patients with 2 or more positive nodes [22]. Similarly, Stolzenbach et al. established 3 or more positive lymph nodes to be an independent risk factor of BCR [7].

2.9. LND - Lymph node density

Lymph node density is the ratio of the number of positive lymph nodes removed to the overall number of lymph nodes removed. This variable is closely related to a well-established prognostic factor - number of pN+. Froehner et al. in his study on the prognostic factors of pN+ patients distinguished low lymph node density as an independent predictor of a good prognosis. Patients with above or equal to the median of 11.1% lymph

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node density were associated with a higher prostate cancer mortality (hazard ratio [HR] 1.66, 95% CI 1.04–2.64, p = 0.0340). On the contrary, a higher total number of removed lymph nodes did not correlate with a better survival [23]. An approach to evaluate oncological outcome depending on positive lymph node density was also made by Daneshmand et al., showing increased risk for clinical recurrence in individuals with a >20% ratio of positive nodes to the complete number of nodes removed during surgery [24]. Likewise, a study on pN+ patients' prognosis also confirms the independent prognostic role of lymph node density. Lower lymph node density was associated with a better CSS (an average density 11.1%). In addition, a 30% cut-off was presented as a key value. Exceeding this threshold might be a suggestion for the introduction of adjuvant systemic therapy as it significantly aggravates the patients' prognosis [25].

2.10. LVI - Lymphovascular invasion

LVI is defined as the unequivocal presence of tumor cells within an endothelium-lined space. The presence of LVI is associated with a worse BCR-free survival, but studies are inconclusive whether it should be treated as an independent risk factor. In 2006, Loeb described greater biochemical progression in patients with LVI (34% compared with 10% without LVI, p <0.0001). However, LVI was associated with other pathologic tumor features such as high histopathological degree and was not an independent risk factor in the multivariate model [26]. In the recent studies, the role of LVI as an independent risk factor becomes more relevant. Hong noted a significant correlation between the presence of the LVI and the BCR in multivariate analysis (HR: 2.167; 95% CI: 1.099-4.273; P = 0.026) [27]. Similarly, in meta-analysis on 25 570 patients, positive LVI status was associated with a higher risk of BCR (univariate analysis HR=1.50, 95% CI: 1.34-1.68, P <.001, multivariate analysis HR=1.25, 95% CI: 1.17-1.34, P <.001) [28]. In addition, positive LVI status correlated with advanced clinicopathological characteristics (e.g. extracapsular extension, seminal vesicle involvement) and may be considered as an unfavorable prognostic factor in patients after RP [29].

2.11. ENE - Extranodal extension

Extranodal extension (ENE) is defined as the presence of cancer cells outside the LN capsule infiltrating into peri-nodal tissue. The role of ENE as a predictor of oncological outcome in prostate cancer remains controversial. An early study by Griebling et al. on patients with mostly advanced PCa showed ENE to be a strong predictor of survival [30]. This finding was not proven by further series. As shown by results obtained in a study conducted by Passoni et al., patients without ENE experienced better BCR-free survival at 12 months than their counterparts with ENE (65% vs 53%; P < 0.01). However, in a multivariable Cox regression analysis predicting BCR the presence of ENE did not reach statistical significance as an independent predictor. Similar conclusions were drawn by Fleischmann et al., who failed to report an association between ENE as an independent predictor and BCR-free, overall or disease-specific survival [31]. Another study by Carlsson et al. also found no statistically significant predictive value for ECE [32]. Nevertheless, a conclusion in regard to clinical characteristics of PCa patients can be made based on the above studies, namely that the presence of ENE was connected to more aggressive disease characteristics such as higher cancer stage, grade and higher number of positive lymph nodes.

2.12. mpMRI

At present, imaging diagnostics are not particularly applied in risk stratification of prostate cancer patients after radical prostatectomy. The current guidelines focus mainly on the clinical staging parameters. However, novel radiological features also proved to matter. The multiparametric magnetic resonance imaging (mpMRI) has gained in importance some time ago as it has become an essential part of the diagnostic procedure of

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PCa. Despite the large use in diagnostics, it was only recently noticed that some features can also be used as predictive tools in determining the risk groups for biochemical recurrence after RP. In a large study on 2565 patients with particular reference to the use of mpMRI, 4 variables were identified as independent risk factors of BCR: high PSA level, large diameter of index lesion at mpMRI, MRI-based imaging stage - presence of extracapsular extension (ECE) or seminal vesicle invasion (SVI) and grade group >2 at biopsy. On this basis, novel nomograms predicting BCR were proposed to stratify patients into risk groups. Introduction of mpMRI improved accuracy of preoperative risk stratification when compared with available tools. At external validation, the novel risk stratification resulted in higher discrimination (c-index 70%) in comparison with EAU risk groups. The diameter of the index lesion and the extent of the disease at mpMRI included in the novel stratification system were associated with a significant risk of extraprostatic extension and lymph node invasion. Contrary to current risk group systems a significant difference of 9% in BCR-free survival (95% vs 86%, $p < 0.001$) concerned low and intermediate risk groups. Better identification of low-risk patients might be applied in a clinical practice to a more accurate selection of active surveillance candidates. Novel risk groups developed on the basis of a combination of clinical and radiological parameters may allow for a more precise risk stratification of patients who are candidate to radical prostatectomy and the associated pN+ risk, which will enable planning proper management before surgery. The introduced classification is promising but requires external validation [33].

2.13. Genomic and proteomic methods

Taking into consideration the fact that PCa is a heterogeneous disease, the genomic methods are promising in the stratification of patients with pN1 PCa after RP. Until now there are three (Decipher, Oncotype DX, and Prolaris) broadly discussed assays in management decision making among post-prostatectomy patients [34]. The Oncotype DX assay is a molecular test evaluating 17 genes and is expressed by Genomic Prostate Score (GPS) (scale from 0 to 100) and provide prognostic results about clinicopathological features of PCa (higher score indicate more aggressive disease) Moschovas and co-workers demonstrate on the group of 749 patients that Oncotype DX assay score correlate with PCa pathology after RP and was an independent predictor of extraprostatic extension (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.4-2.3) and seminal vesicle invasion (OR 2.1, 95% CI 1.3-3.4) [35]. It is also shown that GPS positively correlates with PCa metastasis, PCa-specific death and biochemical recurrence [36]. The systematic review of Jairath reveals that based on 22 gens Dephicer test is an independent prognostic factor and influences long-term therapy results [37]. In the prospective analysis of 121 patients Dephicer shows as a favorable predictor of biochemical recurrence and metastasis of intermediate-risk PCa and potentially indicate as a tool allowing to avoid unnecessary adjuvant therapy – ADT [38]. Moreover, Prolaris is test approved by Federal Drug Agency, analyzes the largest number of genes from the above-mentioned tests (46 genes). The function is similar, allow to assess the postprostatectomy aggressiveness and risk of PCa [39]. Until now a wide array of proteins predisposing to be candidates for biomarkers of PCa aggressiveness. In the article of Signore and co-workers evaluating the effectiveness of 12 proteins from 160 described in literature, they emphasize the need for further investigation of protein biomarkers [40].

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3. pN+ management options

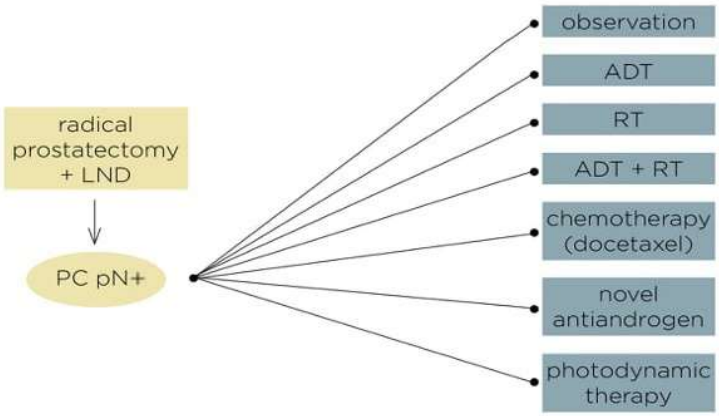

Figure 2. Therapeutic strategies in the management of patients with prostate cancer and lymph node metastases after radical prostatectomy (pN+).

3.1. Observation

Pathologically node-positive patients after radical prostatectomy represent a heterogeneous population. Depending on the disease characteristics, an appropriate method of further treatment can be chosen (Fig. 2). Therefore, observation as a postoperative management strategy has its beneficial oncological outcomes only in a selected group of men. The term observation is defined as refraining from treatment until BCR occurs and then salvage therapies are introduced.

Not all node-positive patients will be affected by a systemic disease. Touijer et al reported that almost one third of patients with LNI (28%) were free of BCR 10 years after RP and PLND alone. The estimated 5- and 10-year overall survival was 91% (95% confidence interval [CI], 86–94) and 60% (95% CI, 49–69), respectively. The estimated 5 and 10-year cancer specific survival was also favorable (94 and 72%). The study recommends a risk-stratified approach. Factors such as increased Gleason score (>7), increased PSA, and high nodal metastatic burden (three or more positive nodes removed) correlated with an increased risk of BCR after RP. The metastasis in seminal vesicle and higher Gleason score (>7) were associated with increased risk of death after RP [4]. Similarly, Gupta distinguished adverse pathological features such as: ≥pT3b stage of PCa, Gleason score ≥9, at least 3 pathologically positive nodes and positive surgical margins. Men who lacked any of these characteristics did not benefit from any adjuvant therapy. In these patients initial observation may be a better management strategy to avoid complications caused by non-essential treatment [41].

In comparative studies observation generally is associated with less favorable outcomes than adjuvant therapies. Tilki et al in a study of 773 patients found aRT to be more beneficial for pN+ patients than no treatment or salvage radiation therapy (sRT) at the time of BCR. The 4-year metastasis-free survival (MFS) was 91.8% vs 82.5% for aRT and observation, respectively [42]. Another study, which analyzed different treatment strategies after RP, showed that observation led to worse survival outcomes than adjuvant therapies, but with one exception. Even though ADT had preferable CSS in comparison with observation (HR: 0.64, 95% CI: 0.43–0.95), it was also linked to an increased risk of other-cause mortality (HR: 3.05, 95% CI: 1.45–6.40), which resulted in similar overall survival (OS) for ADT and observation (HR: 0.90, 95% CI: 0.65–1.25, p = 0.5) [43]. Also, Gupta in his analysis claimed that there was no difference in OS between ADT and observation (HR

1.01, 95%CI 0.87–1.18, p=0.88). Conversely, trial by the Eastern Cooperative Oncology Group (ECOG) found that early ADT compared with deferred treatment was associated with better overall survival (HR: 1.84, 95% CI 1.01–3.35, p=0.04) [44]. However, the study was repeatedly criticized due to the lack with PSA level controls and withholding therapy until osseous metastasis developed.

The EAU guidelines recommend considering expectant management in pN+ patients after PLND when ≤ 2 nodes and PSA level < 0,1 ng/mL. Marra et al compared many studies and observed the presence of prognostic factors such as undetectable postoperative PSA, maximum 2 positive nodes, negative surgical margins, and low pathological stage where observation can be considered [45]. In cases of patients with less advanced features, observation until developing BCR may be a good alternative to avoid unnecessary exposure to treatment complications. This risk-stratified approach should guarantee both oncological safety and quality of life.

3.2. ADT

The use of pharmacological methods to reduce androgen levels to a castration-level was of key importance in the treatment of patients with hormone-dependent prostate cancer (PCa). In the past, the dominant view was that the presence of nodal metastases denoted a disseminated disease requiring systemic treatment. This paradigm changed, as subsequent studies revealed excellent oncological outcomes in patients with nodal metastases, in whom ADT was not administered. A study by Touijer et al. compared patient outcomes between different postoperative management strategies. The analysis showed, that there was no significant difference in OS between patients treated with ADT and observation, although a lower rate of CSM has been observed for the ADT group [43].

The only prospective randomized phase III clinical trial evaluating the impact of immediate vs deferred ADT after RP on oncological results was conducted by Messing et. al in 1999, as part of the Eastern Cooperative Oncology Group (ECOG), on a cohort of 98 patients [46]. The results of this study indicated a beneficial impact on OS and CSS in patients, in whom early postoperative ADT was initiated. Observation or deferred application of ADT was associated with a 3-fold higher risk of death compared to the immediate ADT group. However, the results obtained by Messing et al. are of limited application in the contemporary treatment of PCa pN+ patients. The group of patients studied in this trial consisted of men with a high-volume nodal burden, high percentage of positive surgical margins, as well as other oncological characteristics indicating advanced disease, and therefore of patients clearly benefiting from androgen deprivation. Since the clinical introduction of common PSA screening, the likelihood of developing multiple nodal metastases decreased, hence the modern PCa patient is unlikely to benefit to the same extent as the patients in the ECOG trial have.

Apart from those findings it should also be taken into consideration, that there are multiple adverse effects associated with ADT [47–50]. This raises the question in whom to appropriately start ADT treatment. Studies show that usually patients with aggressive disease characteristics are the ones, in whom this kind of treatment is introduced most frequently. A systematic review on pN+ PCa patients after RP with PLND by Marra et al. mentions 6 retrospective studies including 1319 men treated with aADT. In 39% of the cases the patients had three or more positive nodes [45]. Another attempt to answer that question was made by Touijer et al. in creating a point system based on tumor characteristics, that quantifies the survival benefit of adjuvant ADT + EBRT compared to no adjuvant treatment. In accordance to this, a clinical decision on whether to start ADT could be based upon that model [43].

The last decade resulted in the emergence of second generation NSAA's, including enzalutamide and apalutamide, introduced in 2012 and 2018, respectively, which are showing greater AR-blocking and decreased side effects in comparison to first-generation drugs [51,52]. New NSAA's are still under development, but there are already promising

results in treatment of patients with PCa, as shown by the trials involving use of apalutamide or enzalutamide [53,54]. In 2019 the results of a randomized trial involving another NSAA – darolutamide – were published [55]. Fizazi et al. reported a prolonged metastasis-free survival of 40.4 months after administration of darolutamide vs. 18.4 months in the placebo group (HR 0.41, 95%CI 0.34 - 0.50, P<0.001), with a comparable adverse effect incidence-rate in both groups.

In conclusion to that data, as pointed out earlier, patients with beneficial oncologic status, e.g. low-volume nodal burden, no distant metastases, can profit from a watchful waiting strategy. However, in case of patients with a higher nodal burden, as well as other more aggressive oncological characteristics, the application of ADT seems to be justified, despite its potential side effects. Therefore, a precise selection of patients potentially benefiting from ADT in accordance to their clinical condition and pathological nodal status is of key importance.

3.3. RT and ADT

Adjuvant RT combined with ADT is another treatment strategy that should be taken into consideration in patients with node positive PCa without distant metastasis. Current guidelines recommend multiple strategies among which is the combination of RT and ADT or ADT alone [56–59]. RT commonly consists of radiation to the prostatic fossa, pelvic lymph nodes or whole pelvis. RT alone is not recommended and is rarely performed in patients of these characteristics, although improvement of OS in high-risk and locally advanced PCa associated with this technique is clear [60].

There is strong evidence though that the addition of adjuvant RT to ADT is both statistically and clinically significant when compared to ADT alone in pN1 patients, while it remains unclear patients of which characteristics will benefit the most [61].

Firstly, it is crucial to mention that most of the collected data is based on retrospective studies. Guo et al. analyzed five studies for their meta-analysis and concluded that the addition of RT to ADT was associated with statistically significant benefit of both OS (HR: 0.74) and CSS (HR: 0.40) in comparison with ADT alone [62]. The authors of the study described the results as a dramatic improvement, although pointed out the need for the cautious selection of patients. Touijer et al. observed that patients benefiting the most from the combined therapy are those with higher-risk disease [43]. Abdollah et al. on the other hand reported that aRT with ADT improved CSS and OS only in intermediate or high-risk patients [63]. Gupta et al. indicated in their cohort study certain pathologic features, which enabled identification of the population that benefited from aRT+ADT: ≥pT3b pathologic stage, Gleason score ≥9, ≥3 positive nodes involved, or positive surgical margin status. Men with one or more adverse features gained survival benefit from the described strategy, while up to 30% of patients without these hallmarks did not confer increase in OS [41]. In the recently published systematic review of Marra et. al. investigating 26 studies (23 retrospective and 3 randomized clinical trials) again suggests the choice of therapeutic strategy based on the clinical and histopathological aspects e.g. Gleason score, quantity of positive nodes, burden of surgical margin or pathological stage and aggressiveness. Hence, observation strategy could be used in patients of lower-risk features: undetectable postoperative PSA, <3 positive nodes, negative margins and nonaggressive histology, while in patients with higher-risk histopathological characteristics RT and/or ADT should be taken into consideration [45]. Last but not least, one of recent studies from Bravi et al. showed not so promising results; no significant improvement of OS or CSS was found when comparing ADT alone with the combined therapy [64].

It is also worth noting that some data suggests aRT with ADT in comparison with ADT alone is associated with improved OS in patients with nodal metastasis identified using staging tools different from histopathological discovery after RP (modern imaging techniques, cN1 patients) [65].

Concluding, one of future goals would be to specifically identify patients which will benefit the most from the combined RT+ADT procedure. Certain histopathologic features

should be precisely indicated, and the definition of the most profiting patient ought to be established. This will hopefully reduce morbidity and complications associated with over-treating patients with the combined therapy. Further studies are required since most of the data is based on retrospective studies.

3.4. Docetaxel and new antiandrogens (abiraterone acetate, enzalutamide, apalutamide)

However, not mentioned in official guidelines several interventional studies, indirectly looking for new multimodal therapeutic options among patients with pathologically confirmed LMN after RP (pN1), were conducted. Taken into consideration are chemotherapeutics (mainly docetaxel), new antiandrogens and others, potentially photodynamic therapy. Docetaxel which is a semi-synthetic derivative of paclitaxel and belongs to the chemotherapeutic group of taxane. Mechanism of action is caused by its binding to beta tubulin (stabilising microtubules) and consequently lead to apoptosis and cell cycle arrest [66]. Docetaxel until now remains the first line therapy in metastatic, resistant to castration PCa [67]. The toxicity of chemohormonal toxicity seems to be tolerable. On the population of 42 patients and median follow-up 3,4 years the outcomes of adjuvant high-dose intensity-modulated RT with docetaxel and long-term ADT brought favorable effects of toxicity and clinical results and authors suggest this multimodal treatment for patients with LNM after RP. The trial included 16 (38.1%) patients with LNM, but the results of this subpopulation were not provided [68].

Any study designed strictly to assess the effect of chemotherapy among patients with LNM after RP was conducted so far. In STAMPEDE trial the subset of patients with PCa and LNM (cN1 without previous local treatment or RT) the subgroup treated with standard of care and docetaxel (n=298) had favorable survival effect in comparison to patients with LNM treated only with standard of care (n=296) (Hazard Ratio HR : 0,85; 95% CI 0,68–1,07) [69].

GETUG-12 is a randomised phase III clinical trial (NCT00055731) examining the role of first-line chemotherapy: docetaxel and estramustine with ADT in treatment of patients with high-risk localised PCa. In group of patients with LNM management with ADT plus docetaxel and estramustine (n=59) had beneficial impact on relapse-free survival at 8 years in comparison to group treated with ADT only (n=60) (HR 0,66, 95% CI 0·43–1,01; p=0·017) [70].

On the other hand, the recent results from randomised multinational III phase clinical trial of Scandinavian Prostate Group 12 investigate the possible role of docetaxel in treatment of patients with high-risk PCa (pT2 margin positive or pT3a Gleason score ≥4+3, pT3b, or lymph node positive disease Gleason score ≥3+4) after RP. In total 459 patients were enrolled to study and assigned into two groups: first treated only with docetaxel (n=230, 219 (95%) received at least one dose of docetaxel, 182 (79%) received all 6 cycles per protocol.) and second observation (n=229). The statistical analysis do not reveal a favourable effect of use of docetaxel after RP. Moreover the same observation was in a subgroup of patients with LNM (pN1) [71]. Up to now there is one interventional, randomized phase II/III trial with open enrollment examining the impact of ADT and EBRT compared with or without docetaxel among patients after RP. The estimated primary outcomes will be revealed in 2026 [72]. The II phase clinical trial investigating efficacy and safety of enzelatumid and standard care (ADT and RT) included 8 patients with LNM after RP (eligible if fewer than 3 positive lymph nodes were dissected during RP and no lymph nodes >2 cm were shown on screening imaging). Patients with LNM in comparison had poorer outcomes, with a 2-year progression-free survival rate of 25% (95% CI: 3.7, 55.8) with the historical control rate of 51% (95% CI: 33, 67) in a similar population of men with high-risk biochemically recurrent PC [73]. One arm of the mentioned before STAMPEDE randomized controlled trial investigated addition of abiraterone acetate and prednisolone to standard management (ADT and RT - depending on cofactors) into treatment

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of non-metastatic PCa. In population with local LNM the use abiraterone acetate, prednisolone and ADT enhance failure-free HR 0.26, 95% CI 0.17-0.40 and metastasis-free survival HR 0.47 95%CI 0.29-0.78 [74].

3.5. Novel therapies

Photodynamic therapy is a method that use photosensitizing chemical agents conjugated with molecular oxygen which accumulate in tumor cells. Stimulation of photosensitizers by light leads to formation of reactive oxygen species and by apoptosis or necrosis to death of cancer cells [75]. There are several photosensitizing substances that could be potentially use in treatment of PCa like: porfimer sodium (Photofrin), 5- aminolevulinic acid (5-ALA), mesotetra (hydroxyphenyl) chlorin (Foscan), motexafin lutetium (MLu) or padeliporfin di-potassium with the brand name TOOKAD. The listed substances differs in activation wavelength, way of administration or mechanism of action [76]. The safety, tolerance and effectiveness of mentioned TOOKAD was proved in randomized, III-phase clinical trial investigating male population with low-risk, localized PCa (Gleason 3) without previous oncological treatment [77]. Moreover European Medicine Agency approved in 2017 TOOKAD to management of localized PCa [77]. Extremely promising is the concept of using prostate specific membrane antigen (PSMA). Such created molecules could not only be used as a photosensitizing agent in photodynamic therapy of PSMA-positive PCa, but also for intraoperative detection of PCa surgical margins [78].

The application of drugs already known in management of metabolic disorders like metformin or statins are broadly discussed and investigated as a potential additive agents to standard management of PCa [79,80].

4. Current guidelines

Current guidelines differ from one another significantly and they recommend a variety of management options for pN+ patients. The EAU identifies three major treatment possibilities, and these are observation, early adjuvant HT and ART with ADT. Observation is the strategy recommended as an optimal for patients with 1-2 positive lymph nodes. Two remaining therapies are beneficial but require certain conditions to be fulfilled to use as a most advantageous treatment option. Early adjuvant HT significantly improves both CSS and OS, although available data on this subject includes mostly patients with high-volume nodal burden and multiple adverse tumor characteristics. Adjuvant RT with ADT on the other hand is beneficial mostly for patients with PCa features such as <3 LNs, ISUP grade 2-5, pT3-4 or R1, or 3-4 positive nodes [56,57].

The NCCN indicates two groups of patients associated with LNM. The first one includes patients with high or very high-risk PCa with nodal metastasis discovered after RP. A patient with a high-risk disease is defined as having one of the following: T3a or GG 4-5 or PSA>20 ng/mL; on the other hand very high-risk group is described with characteristics of: T3b-T4 or primary Gleason pattern 5 or >4 biopsy cores with GG 4-5. For these patients the NCCN recommends only three options: ADT with or without ERBT or observation if postoperative PSA is undetectable. The second group includes patients with regional cancer which is described as N+ PCa of any size (any T); the nodal metastasis can be found during RP, PLND or during other tests. In these patients several strategies are proposed based on life expectancy. If life expectancy is 5 years or less and a patient has no symptoms, the guidelines suggest taking observation or ADT into consideration. Observation may be followed by palliative ADT if the symptoms start to occur. However, if life expectancy is more than 5 years or a patient has symptoms, then five different strategies are mentioned: ERBT + ADT, ERBT + ADT + abiraterone, ERBT + ADT + fine-particle abiraterone, ADT + abiraterone, and ADT + fine-particle abiraterone. ERBT + ADT is considered to be a preferred solution [59].

The ESMO guidelines point out ART with ADT have good results for men with 2 positive lymph nodes associated with pT3b or pT4 and/or positive surgical margins when compared to RT alone [58].

NICE's guidelines consider PCa with LNI as locally advanced PCa and suggest considering pelvic radiotherapy, but this guidance applies to patients before RP. Immediate post-operative radiotherapy, adjuvant hormonal therapy and high-intensity focused ultrasound and cryotherapy are not recommended, so the most efficient management remains unclear [81].

In summary, unification of guidelines approach to management of pN+ patients with PCa is strongly anticipated. Unclear indications for this group of patients is the reason we did not describe the role of Canadian or American guidelines, which do not differentiate LN-positive patients as a separate group [82,83]. However, the guidelines described above fail to provide urologists with the most optimal management solutions as well. Future guidelines should thoroughly describe the management options, while considering the heterogeneity of pN+ patients.

5. Conclusions

The optimal management of patients with lymph node metastases after RP is still unclear. These patients constitute a heterogeneous group and need substratification to choose the best therapeutic method, which will allow for the optimization of treatment results. The quality of current evidence is low and most of the available studies are retrospective. However, new, ongoing clinical trials with existing and new therapeutic approaches are promising and the results may help to systematize the guidelines.

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