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Review

Management of Bladder Cancer Patients with Clinical Evidence of Lymph Node Invasion (cN+)

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Abstract: The purpose of this review is to present the current knowledge about the diagnostic and treatment options in bladder cancer (BCa) patients with clinically positive lymph nodes (cN+). In this review compaction of CT and MRI performance in preoperative prediction of lymph node invasion (LNI) in BCa patients was presented, along with other diagnostic methods. Most scientific societies do not distinguish cN+ patients in their guidelines, recommendations concern muscle-invasive bladder cancer (MIBC) and differ between associations. Currently, the standard treatment of patients with MIBC is radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND). The template of PLND and its therapeutic value remain debatable. Moreover, most guidelines recommend neoadjuvant chemotherapy (NAC). However, there is still lack of definitive evidence of the superiority of neoadjuvant chemotherapy over adjuvant chemotherapy. Nevertheless, the curative treatment that provides the best long-term survival in cN+ patients is a multimodal approach with a combination of chemotherapy and RC. Recent studies demonstrate the growing importance of immunotherapy. Special attention should be paid to cN+ BCa patients as the oncological outcomes are significantly worse for this group.

Keywords: bladder cancer; clinically positive lymph nodes; diagnosis; treatment; lymphadenectomy

1. Introduction

Bladder cancer (BCa) is considered the most common malignancy of the urinary tract. The incidence is greater in men than in women and the highest rate is observed in Europe, reaching in Spain 36.7 per 100 000. The highest mortality rate reaches in Eastern Europe 8.4 per 100 000 [1,2]. The management of the lymph nodes (LNs) requires insightful reflection, as, apart from the local stage, nodal metastases are the most significant prognostic factor in BCa patients, and the current guidelines regarding clinically-positive lymph nodes (cN+) patients are imprecise, differing in recommendations. The presence of LN metastasis in patients with muscle invasive bladder cancer (MIBC) is associated with a worse prognosis and each additional positive LN in the range of 1 to 4-6 is associated with lower survival rates [3–5]. 5-year overall survival in node positive bladder cancer (N+ BCa) was established at 30%-32% in patients receiving treatment while in patients without lymphatic spread it reached 39%-56%. N+ BCa persists conceivably curable prior

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to systemic metastasis [5–8]. The standard of treatment in MIBC involves radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND). Moreover, in eligible patients neoadjuvant chemotherapy (NAC) is advisable [9]. Due to occult metastasis, relapses after surgery are observed [10]. Considering the survival rates and the number of relapses after surgery, additional or novel treatment options are needed. The debate is still ongoing as to whether chemotherapy and radiation therapy can improve survival [11–13]. Diagnosis of N+ patients might be challenging as in around 25% of patients lymph node involvement may not be noticeable at the time of imaging [14]. As patients with N+ status have been linked with worse oncological outcomes, in this review we summarize current knowledge about diagnostic and treatment options in cN+ BCa.

2. Diagnosis of Lymph Node Invasion (LNI)

The staging of lymph node metastases is one of the three elements of the TNM classification system. While transurethral resection (TURB) is usually used to confirm the diagnosis of a suspected bladder tumor, additional imaging is required for staging, including the detection of LN metastases [15]. The most popular techniques are CT and MRI, with 18F-FDG PET being increasingly utilized in clinical practice, albeit still not considered as a standard. As discussed below, most guidelines do not indicate which technique is better for detecting LN metastases. Nevertheless, contrast-enhanced CT remains, both in theory and in practice, the mainstay of imaging used for BCa staging, being recommended as first-line imaging in nearly all guidelines of major urological and oncological societies [16].

According to the European Association of Urology (EAU) guidelines, both MRI and CT demonstrate similar, relatively low sensitivity and specificity in detection of LN metastases, emphasizing that the possibility of the assessment based solely on their performance is limited. In both of these imaging techniques, enlarged nodes should be considered pathological if the maximum short-axis diameter exceeds 8 mm for pelvic nodes and 10 mm for abdominal nodes. Overall, CT of the chest, abdomen, and pelvis including some form of CT urography is recommended as first line imaging for staging [17,18]. The American Society of Clinical Oncology (ASCO) has not issued its own BCa guidelines and instead has announced its endorsement of the guidelines from EAU [19]. The advices from the European Society for Medical Oncology (ESMO) are very similar to those of the EAU, postulating similar results of CT and MRI in detection of LN metastases. The dimensions of the LN requiring attention are also the same. No clear recommendation is given with regard to what CT or MRI should be utilized as first line imaging in staging. However, it is recommended to choose MRI when accurate determining of depth of invasion is needed due to its higher accuracy [20]. The guidelines issued jointly by the American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO) do not discuss the diagnosis of LNI in BCa. A CT scan with contrast of the pelvis and abdomen and a X-ray/CT of the chest are recommended for staging. MRI should be counseled if CT cannot be performed [21]. The joint Société Internationale d'Urologie (SIU) and the International Consultation on Urological Diseases (ICUD) guidelines state that CT and MRI are equivalent in detection of the metastatic LNs. They point out the lack of well-established criteria to distinguish between malignant and benign LNs being a significant limit in the successful detection of metastases in normal-sized nodes. They also mention the promising results of lymphotropic nanoparticle–enhanced MRI in the detection of micrometastases in normal-sized lymph nodes (with a sensitivity of up to 96%), listing the small amount of research and lack of studies on its impact on patient management as the major obstacles of wider usage. Overall, a CT scan with contrast of the abdomen and pelvis, which includes an excretory phase study, is recommended for the investigation of nodal and distant metastases in patients with BCa. MRI is advised only if CT contrast is not tolerated [22]. According to the National Comprehensive Cancer Network (NCCN) guidelines CT or MR urography, a renal ultrasound

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or CT without contrast with retrograde ureteropyelography, a ureteroscopy or a combination of these are recommended. The issue of the superiority of CT or MRI as well as diagnostics of metastatic LN is not discussed [23]. The National Institute for Health and Care Excellence (NICE) guidelines recommend CT or MRI, without specifying which is better for staging in BCa. Additional CT urography and CT of the thorax (carried out with other planned CT imaging if possible) should be considered if the risk of metastasis is high. If the findings in MRI or CT are indeterminate and if the risk of metastatic disease is high, it is also recommended to consider 18F-FDG PET before the radical treatment [24].

The number of studies directly comparing CT to MRI in nodal staging of BCa is limited. The high heterogeneity of the patient population and the large variety of techniques used (contrast materials, protocols) make it difficult to compare the results of studies involving only one type of imaging. Despite significant advances in imaging technology, multiple reviews on this topic confirmed comparable, relatively low accuracy of staging in both modalities [25–28]. Evidence of the superiority of either technique remains ambiguous – where for instance McKibben et al. indicate clear predominance of MRI (with accuracy of 54–97% and 73–98% for CT and MRI respectively), while Bostrom *et al.* describes virtually identical results of both modalities (with accuracy of 70–97% and 73–98% for CT and MRI respectively) [29,30]. The results of selected studies are presented in Table 1.A recent meta-analysis by Woo *et al.* published in 2018 pooled 2928 patients from 23 studies, showing a combined sensitivity of MRI in detection of metastatic LN to be 56%, with a specificity of 94% [31]. Taking into consideration the similar results of both techniques with some studies indicating the superiority of MRI, no need for use of ionizing contrasts agents and no radiation exposure, the use of MRI is encouraging [32,33]. Further research, particularly a RCT directly comparing the two techniques, would be very valuable in providing definitive evidence.

Table 1. The comparison of CT and MRI performance in preoperative prediction of LNI in BCa patients.

Study Authors	Year	n	Sensitivity (%)	Specificity (%)	Accuracy (%)
Computer Tomography (CT)					
Vock et al. [34]	1982	77	-	-	89
Buszello et al. [35]	1994	50	33	100	-
Paik et al. [36]	2000	82	19.1	96.7	-
Ficarra et al. [37]	2005	156	42.2	100	76.9
Baltaci et al. [38]	2008	100	30.7	94.3	86
Tritschler et al. [39]	2012	219	30.4	90	71.2
Magnetic resonance imaging (MRI)					
Buy et al. [40]	1988	40	83.3	100	-
Tavares et al. [41]	1990	29	50	100	82
Deserno et al. [42]	2004	58	96	95	95
Daneshmand et al. [33]	2012	122	40.7	91.5	80.3
Thoeny et al. [43]	2014	120	63-78	79-85	75-83
Wu et al. [44]	2018	103	44.8	93.2	79.6

In most guidelines as well as in clinical practice, the size of the LN is the main criterion to distinguish between normal and suspicious LN [45]. However, normal

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sized nodes can be malignant, and conversely, reactively enlarged ones may reveal no cancer deposits [46]. This is probably one of the primal causes of low accuracy in detection of LNI, mainly due to the relative common presence of metastases in normal sized LNs [16]. As a solution, different additional criteria, such as LN shape, internal architecture, number of loco-regional LNs and utilization of new contrast agents were proposed [42,47]. However, they have not gained widespread use so far.

The utilization of 18F-FDG PET/CT in staging of BCa has been under consideration for many years [48–50]. Combining the anatomical information from CT with glucose metabolism (which has been shown to be increased in metastatic LNs) is a widely accepted method in oncology [46]. However, as of today no major guideline recommends its routine use. While some studies investigating the accuracy of 18F-FDG PET demonstrated promising results, other ones show no significant improvement of diagnostic efficacy compared with conventional techniques [48,51–58]. To improve specificity and accuracy of 18F-FDG PET potential alternative radiotracers, such as C11-Choline and C11-methionine were proposed. A meta-analysis performed by Kim *et al.* pooled 282 patients from 10 studies which used C11-Choline and demonstrated sensitivity of 66% (with a specificity of 89%) [59]. The data on C11-Choline is limited but demonstrates results comparable to conventional imaging techniques [60]. Overall, more research is needed to make a firm recommendation for routine use of 18F-FDG PET.

Ultra–small-particle superparamagnetic iron oxide (USPIO) has been suggested as a possible alternative technique for the detection of BCa LN metastases [61,62]. This method is based on the intravenous administration of iron oxide nanoparticles which are then phagocyted by macrophages and taken up to LNs where they remain for a few days. This uptake is reduced in malignant LNs, where healthy tissue is replaced with malignant cells. The superparamagnetic iron oxide can then be detected by T2 MRI. Due to the higher density of macrophages, benign LNs have higher signal intensity compared to the malignant ones [29]. Several studies have reported encouraging results with excellent accuracy in detection of metastatic LNs [63]. However, due to the complex, time consuming, expensive, and requiring expertise for interpretation procedure USIPO will be utilized in clinical trials and selected cases, but it's usage is unlikely to become standard practice [30,64].

Due to the low accuracy of traditional methods in staging of BCa, various risk-stratification models and nomograms were designed to improve it. The first nomogram to predict LNI in the patients treated with RC and ePLND developed by Moschini *et al.* based only on routinely available parameters has a prediction accuracy of 73% which could lead to avoidance of up to 12% lymphadenectomies at the cost of missing only 3% cN+ patients [65]. A similar nomogram designed and tested on a much larger group of patients (10653) demonstrated comparable accuracy and high reliability in predicting LNI [66]. As these tools are already available and proven effective, their wider adoption in combination with other prognostic factors and imaging could lead to better detection rates, and consequently to better treatment outcomes. Further research into clinical application and the impact on patient management is required.

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3. Extent of Lymphadenectomy

Radical cystectomy (RC) with lymphadenectomy remains the primary treatment strategy in patients with muscle-invasive bladder cancer (MIBC). As already stated, nodal involvement is one of the most important prognostic factors, next to the local advancement, in bladder cancer (BCa) patients [67,68]. Lymph node dissection (LND) is inextricably linked with surgical treatment because its diagnostic role is crucial and therapeutic effect remains debatable. Unfortunately its uncertain which lymphadenectomy template should be choosen. In a systematic review, Bruins et al. analyzed data from twenty-three studies, and pointed the advantage of LND over no LND in terms of oncological outcomes [69].

Lymphadenectomy templates are inconsistent in nomenclature and may differ depending on the center and clinicians' practice. Definitions of certain templates are evolving with time and the optimal extent remains unestablished [70]. Nevertheless, there are four major LND templates: limited, standard, extended, and superextended (Figure 1). The limited template commonly covers the obturator fossa bilaterally, although variations occur frequently, such as comprising the obturator fossa and external iliac lymph nodes (LN) [71–75]. The standard template provides dissection of the obturator fossa, as well as external and internal iliac LNs, and presacral LNs, although the LND pattern may also be described with certain boundaries: division of the common iliac artery being the proximal border, inguinal ligament being the distal border, the genitofemoral nerve being the lateral border, and bladder wall being the medial border [73,76,77]. The extended template covers aforementioned LNs groups and additionally lymphatic tissue in the area between the aortic bifurcation and the common iliac vessels (proximal border), the circumflex iliac vein, the lacunar ligament, and the LN of Cloquet (distal), the genitofemoral nerve (lateral), and the bladder wall (medial) [77–79]. The superextended template contains all mentioned areas, but it extends to the inferior mesenteric artery as a proximal border, thereby additionally comprising paraaortic LN [80,81]. Figure 2 illustrates anatomical compartments of LND performed during RC.

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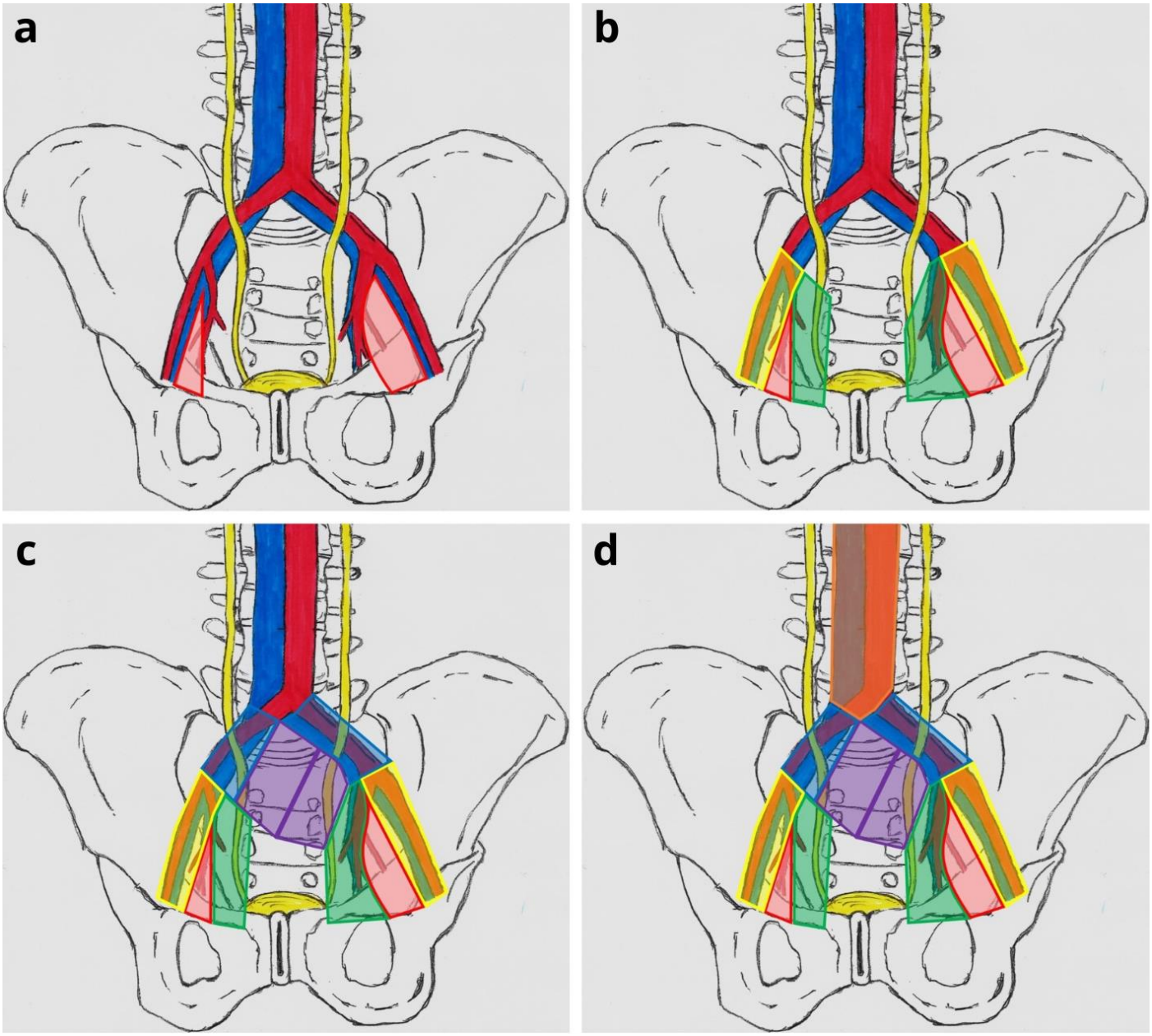

Figure 1. Anatomical diagram of LND divided into templates: a - limited, b - standard, c - extended, and d - superextended; the obturator fossa (red), external iliac vessels (yellow), internal iliac vessels (green), common iliac vessels (blue), the presacral area (purple), and the paraaortic area (orange).

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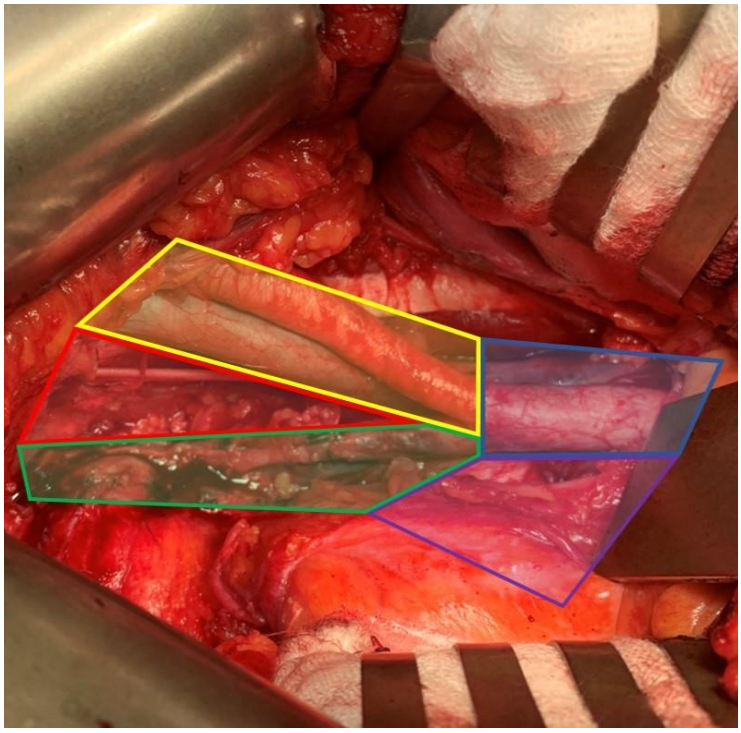

Figure 2. Superimposing of the anatomical areas of LND during radical cystectomy; the obturator fossa (red), external iliac vessels (yellow), internal iliac vessels (green), common iliac vessels (blue), and the presacral area (purple).

Different templates present heterogeneous oncological outcomes. Though the choice of the LND pattern remains an unsolved issue, somewhat of a consensus has been established. Limited LND is associated with lower progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS), as well as an inadequately small number of staged LN, in comparison with standard or extended LND [72,82–85]. Wang et al. in a meta-analysis of 10 studies investigated data from 3,979 patients who underwent extended LND or non-extended LND. Extended lymphadenectomy was associated with better recurrence free survival (RFS) (HR: 0.74, 95% CI: 0.62-0.90, p = 0,002) and DSS (HR: 0.66, 95% CI: 0.55-1.58, p < 0.001). Nevertheless, extended LND and better OS were not correlated [86]. Furthermore, the randomized clinical trial (RCT) conducted by Gschwend et al. revealed no significant advantage of extended LND over limited LND in RFS, CSS, and OS [87,88]. However, as of now, the extended LND remains the gold standard template. Several studies have been conducted on the oncological outcomes of the superextended template, though none of them showed benefits in RFS, DSS, or OS [89–91].

Although RC is a major surgical procedure with a burden of possible complications on its own, LND seems not to affect overall surgical morbidity [92]. Moreover, extended LND, as well as the increase in the amount of LN, is not associated with more perioperative complications than non-extended LND [86,93–95]. Further global prevalence of minimally invasive robot-assisted surgery may decrease the frequency of complications and morbidity rates to even greater extent in the future [96–98].

4. Treatment of cN+ Patients

Currently, the standard treatment of patients with muscle-invasive bladder cancer is radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) [99]. The available publications emphasize the oncological benefits of lymph node (LN) resection during cystectomy in comparison with its absence [77,79,100–102]. During observation, a 5-year survival rate without all caused mortality (ACM) was 36% (RC alone) vs. 45% (RC

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with PLND) and a 5-year survival rate without cancer specific mortality (CSM) was 54% (RC alone) vs. 65% (RC with PLND). These differences were observed in the group of younger patients (age ≤75 years) with a limited number of comorbidities. [103]

Lymph node metastases are detected in 16.7-29.3% of patients treated with PLND and this is associated with worse long-term oncological results [75,79,100,104,105]. Depending on the exclusion criteria, number of patients in the study, stage of the tumor, method of diagnosis, and the chosen treatment method, lymph node metastases (pN+) were observed in 12.6% to 79.6% of patients with cN+, and even up to 91% when focused on a specific group of patients [65,99,106–108]. An overview of the results is demonstrated in Table 2. This disproportion may be due to the use of NAC or AC. Based on a study of 3241 cN+ patients, Darwish et al. observed that treatment with NAC was associated with significantly higher rate of downstaging to pN0 in comparison to surgical treatment alone (40.0% vs. 8.8%, OR = 6.88, $p < 0.0001$) [99]. The authors revealed that up to 91% of patients treated with RC without chemotherapy (ChT) were pN+. Contrary, in that cohort patients who received neoadjuvant chemotherapy (NAC) were pN+ in 60% of the cases. It was demonstrated that correct response to NAC and downstaging from cN1 to pN0 is associated with overall improved survival outcomes up to 44% [109]. Moreover, PLND allows for the removal of LNs with micrometastases present, brings oncological benefits, and allows patients to be reassigned after surgery [110]. A patient who would be classified as N0 after cystectomy, is more likely to obtain pN+ status after PLND. This means that the improvement in prognosis may be due to the Will Rogers phenomenon, which is the result of more accurate identification. Patients classified at a lower stage are reclassified to a higher stage after surgery. This shift also affects the survival outcomes, as pN0 patients do not have nodal metastases and some pN+ patients have micrometastases examined only on histopathological assessments. The Will Rogers phenomenon may also explain the correlation between the number of LNs removed during RC and survival. For this reason, this phenomenon should be considered when comparing new research results with historical ones. [111–113].

Table 2. The comparison of studies presenting percentage of pN+ in cN+ patients.

Study Authors	Year	cN+	pN+	pN0	% of pN+
Moschini M et al. [65]	2020	221	28	193	12.7%
Herr H et al. [108]	2004	1091	216	875	19.8%
Zargar-Shoshtari et al. [106]	2015	cN1 = 133	59	74	44.4%
		cN2 = 134	68	66	50.7%
		cN3 = 15	8	7	53.3%
		cN+ = 282	135	147	47.8%
Ho et al. [107]	2016	55	25	30	45.5%
Darwish et al. [99]	2020	3241	1286*	330*	79.6%
* Missing data of pN+ in 1625 patients					

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cN+ - clinically positive lymph nodes; cN1 – clinically metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral) ; cN2 - clinically metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral); cN3 – clinically metastasis in a common iliac lymph node(s); pN+ - pathologically positive lymph nodes pN0 – no nodal metastases

4.1 Guidelines

Current guidelines remain inconsistent in establishing proper management strategies for N+ patients, both for cN+ and pN+ subgroups. Table 3 presents summary of the most pivotal recommendations from popular guidelines.

Table 3. Overview of cN+ patients management strategies according to guidelines provided by the EAU, the AUA, the ESMO, the NCCN, and the NICE.

Guidelines	Management Strategies
EAU	- RC + AC - Radical ChRT
AUA	- RC + cisplatin-based NAC - RC + cisplatin-based AC (for patients who have not received NAC)
ESMO	- RC ± NAC
NCCN	For N1 patients: - RC + cisplatin-based NAC (especially for cN1 patients) - RC (for ChT-disqualified patients) - Bladder preservation + ChRT - ChRT - RT For N2-3 patients: - Downstaging ChT

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	- ChRT
NICE	- RC + NAC - RC + AC

EAU: The European Association of Urology; AUA: The American Urological Association; ESMO: The European Society for Medical Oncology; NCCN: The National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; RC: radical cystectomy; ChT: chemotherapy; ChRT: chemoradiotherapy; NAC: neoadjuvant chemotherapy; RT: radiotherapy

The European Association of Urology (EAU) guidelines point out low sensitivity and specificity of computer tomography (CT) and magnetic resonance imaging (MRI) in terms of nodal staging. This may be the reason why the guidelines do not provide information on cN+ management. Nevertheless, the EAU proposes three major management options for N+ patients, and these are radical cystectomy (RC) with adjuvant chemotherapy (AC), radical chemoradiotherapy (ChRT), and immunotherapy with nivolumab. The guidelines further emphasize that benefits of adjuvant ChT are still under debate. Immunotherapeutic approach with nivolumab is advised only for selected pT3/4 and/or pN+ patients. cN+ patients are not included in this recommendation [18].

The American Urological Association (AUA) guidelines do not distinguish between dofferent approaches for cN1 and pN1 groups. However, they recommend that N1 patients should receive RC with cisplatin-based neoadjuvant chemotherapy (NAC). The patients who have not received cisplatin-based NAC and have non-organ confined disease (pT3/4 and/or N1) should be offered adjuvant cisplatin-based ChT [21].

The European Society for Medical Oncology (ESMO) guidelines indicate that cN1 patients should receive surgical treatment, but it should be considered whether to institute neoadjuvant platinum-based ChT or not [20].

The National Comprehensive Cancer Network (NCCN) guidelines advise five primary therapeutic pathways for N1 patients. These include neoadjuvant cisplatin-based combination ChT followed by RC or RC alone for ChT-disqualified patients, bladder preservation with concurrent ChRT, ChRT alone, and radiotherapy (RT). The guidelines point out that cN1 patients have better outcomes when RC is proceeded by cisplatin-based ChT. For cN2-3 patients, which belong to stage IIIB disease, the guidelines advise either downstaging systemic therapy or concurrent ChRT [114].

The National Institute for Health and Care Excellence (NICE) guidelines do not differentiate cN+ and pN+ patients as well. They propose two therapeutic options: RC with NAC, and RC with adjuvant ChT. The latter should be a primary therapeutic option for patients for whom NAC was not suitable [24].

4.2 Clinical Evidence, Surgery

As no conclusive evidence regarding cN+ management exists in the guidelines, it is mandatory to discuss this common clinical situation. Since cN+ bladder cancer is generally considered in the same context as metastatic disease (despite the local stage), multiple studies have investigated the outcomes of different treatment of those patients [106,115–118]. Patients with cN+ are generally considered for systemic induction chemotherapy (IC) [119]. The researchers found NAC followed by RC as the curative treatment with the best long-term survival, particularly in patients with a good response to NAC. Several researchers reported encouraging outcomes in extending the treatment to multimodal therapy, demonstrating survival improvement, and even a long-term survival in patients

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with initially unresectable BCa who underwent IC with subsequent RC after good response to ChT [117,120]. Including radiotherapy in the treatment did not improve the survival of cN+ patients [121]. Whenever possible, patients should be eligible for curative treatment, as palliative treatment is associated with overall significantly worse survival rate [122]. However, due to impaired renal function ChT might be difficult to perform in the elderly, which is one of the major limitations of this treatment. In fact, the proportion of curative and palliative treatment decreases with age to less than 10% in octogenarians, which is an important issue considering the fact that the average age of BCa diagnosis is 73 years [123,124]. As the value of ChT in the therapeutic pathway of the cN+ patients is crucial, we specifed this aspect further in the article, and discussed below the details of the surgery. There are many reasons which may be utilized for the rationale behind post-ChT RC. Firstly, despite the fact BCa is chemosensitive, IC is rarely curative [125]. Secondly, RC is the best possible method for the assessment of patients' response to IC because radiological techniques are not always satisfactory [107,116]. Thirdly, RC enables eradication of residual disease and achieve a complete response in patients with partial remissions, and in patients with an erroneous finding of complete response [107,126,127]. Finally, approximately three out of four patients who initially responded well to IC will experience a relapse at the site of the response [128].

Taking into consideration cN+ patients, the utility of lymphadenectomy remains a controversial topic. As discussed, the gold standard template during RC for now is ePLND. However, it is important to remember that some researchers demonstrated only 12.6% of cN+ patients to be truly N+ in post-PLND histopathological examination (pN+). Therefore, the therapeutic value of PLND remains subject of debate. In a multicenter, retrospective study by Necchi et al. authors analyzed the outcomes of post-IC RC with LND (n = 242) versus observation after IC (n = 280) in 522 cN+ patients, either with positive pelvic or retroperitoneal LN [129]. It resulted in non-statistically significant improvement in OS for post-IC surgery group (HR: 0.86, 95% CI: 0.56-1.31, p = 0,479). In another study, Al-Alao et al. revealed a poor OS, with 5-year OS of 34%, in cN+ patients treated with IC and RC [130]. Additionally, the authors observed heterogeneity in survival, ranging from 10% to 59% within 5 years, and proposed a risk-stratification tool. The study by Pak et al. showed incoherent results in different cN+ groups [131]. In the IC (followed by RC) group, the 5-year CSS of cN1-2 patients was improved in comparison to the RC group (68.1% vs. 52.9%; p = 0.035). Nevertheless, the 5-year CSS rate of cN3 patients was lower in the IC group than the RC group (19.2% vs. 44.5%; p = 0.015). This study once again points the importance of proper patient selection. Furthermore, multitude of studies revealed improved oncological outcomes of PLND, although most of them pointed considerably higher efficacy of chemotherapy-surgery combination [121,132–135]. Moreover, several researchers demonstrated optimistic results of PLND in cN+ patients, especially when put into a proper clinical context. For example, it has been proved that removing more nodes can improve survival [67,136–139]. The researchers agreed that survival improvement positively correlates with the number of removed LNs, and this trend was independent of patients' nodal status. Zargar-Shoshtari et al. indicated better OS, if PLND excised 15 or more LNs, while Capitanio et al. and Shariat et al., based on two multicenter studies, suggested removing a minimum of 25 LNs to ensure the absence of lymphatic metastases [106,140,141]. Konety et al. observed lower death risk when at least 10-14 LNs were resected [142]. However, a consensus about the threshold number of removed LNs during PLND has not been reached. Not only is the number of LNs affected by the surgeon's skill and template of PLND, but also by pathological handling, submission method and inter-individual differences [143,144]. For example, it was reported that the same four surgeons utilizing the same PLND template yielded a statistically significant difference in LN numbers performing the surgeries in two different hospitals with two different pathological departments (16 vs. 28, p <0.001) [145]. Nonetheless, several studies demonstrated better OS and a lower local recurrence in patients with more LNs resected, regardless of whether the patients were pN+ or pN0 [137,138,146–149]. The first reason behind this observation

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is that the number of LNs resected may reflect the quality of the surgery. The second possible reason is that LNs with micrometastases, undetected in classic histological examination, might be eradicated with PLND [150]. Yet, it was reported that to achieve optimal oncological outcomes a proper template of PLND is more important than focusing only on the total LN count [76].

Although the therapeutic value of PLND might not be conclusive, the diagnostic and prognostic values are clear. Histological evaluation of the PLND specimen provides crucial information for further management. The number of LNs with metastases is an excellent indicator of the extent of disease. Various factors have been reported as prognostic factors of BCa. Nevertheless, the pN status, next to pT stage, is paramount. The increasing number of positive nodes is reflected in the worse patients' prognosis. It was demonstrated that the median 3-year survival in patients with pN+ was 58.6%, 31.8%, and 6.8%, respectively for one, two, and to five and more positive LNs [151]. Other researchers obtained similar correlation utilizing cutoff values of four, five, and six positive LNs [93,136,152]. Bruins et al. in an analysis of 369 pN+ patients demonstrated better results in patients with maximum two positive LNs, achieving a 5-year relapse-free survival of 44% vs. 24% in the group with more than two positive LNs [87]. It seems that if the number of positive LNs is within range of 1 to 4, the OS worsens with each additional metastatic LN. On the other hand, any positive LN after five does not alter the clinical outcome because the mass of metastases is so significant. With such an unfavorable outcome of pN+ disease, it is recommended to treat every pN+ patients who did not undergo NAC with AC [17,21]. Therefore, information obtained performing PLND can be not only utilized for prognosis and recurrence risk stratification, but also indicate the need for subsequent treatment. Another prognostic factor obtained from PLND is extranodal invasion – a microscopic perforations of LN capsules by neoplastic cells, which indicates higher aggressiveness of the cancer and poorer survival outcomes [152,153]. The diagnostic information obtained from resected LNs is essential and for now cannot be replaced by any other method.

4.3 Neoadjuvant Chemotherapy (NAC)

ChT given before RC, as part of a multimodal approach, is currently recommended by most guidelines for all eligible MIBC patients, as well as in selected patients with moderate or high risk NMIBC [18,20,154]. While the optimal specific regimen has not yet been established, the utilization of cisplatin based NAC is now considered as the gold standard, which is based on multiple studies confirming its major impact on OS in patients with Bca [155]. In 2016 Yin et al. performed a systematic review and meta-analysis which pooled 3285 patients from 15 randomized clinical trials and 13 retrospective studies, demonstrating a significant OS benefit (HR 0.87, 95% CI: 0.79-0.96) [156]. A more recent study by Hermans *et al*. examined a larger group of patients (5517) and showed even greater benefit of NAC in BCa patients, particularly in cT3-4a group (HR 0.67, 95% CI: 0.51-0.89). In cT2 group the OS improvement was not that significant (HR 0.91, 95% CI: 0.72-1.15) [157]. Furthermore, this improvement was achieved without noticeably affecting surgical morbidity [158]. However, the ChT effectiveness is not as clear as it might seem and there are large discrepancies in the results. In another recent meta-analysis Li *et al.* demonstrated similar OS in patients treated with NAC + RC versus RC alone (HR 0.92, 95% CI: 0.84 - 1.00, p=0.056) [159]. On the other hand, in 2020 Hamid et al. in a meta-analysis of 13391 patients addressed the former results and demonstrated an unequivocally positive effect of NAC on OS (HR 0.82, 0.71-0.95: p = 0.009) [160].

The side effects of cisplatin, including nephrotoxicity, neurotoxicity, and decreased heart function, preclude 30-50% of BCa patients from the safe cisplatin-based treatment [161]. The ineligibility criteria are summarized in Table 4. Various non-cisplatin-based alternatives, such as gemcitabine/carboplatin, pembrolizumab and atezolizumab have

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shown promising results, but there is insufficient high-level evidence to support their recommendation [162,163]. According to the EAU guidelines, NAC is recommended only for patients eligible for cisplatin-based ChT [18]. For ineligible patients, it is reasonable to consider a referral to a clinical trial [154].

Table. 4 BCa patients ineligible for cisplatin-based ChT [161]

• WHO or ECOG performance status of 2, or Karnofsky performance status of 60–70%
• Creatinine clearance (calculated or measured) less than 1 mL/s
• CTCAE version 4, grade 2 or above audiometric hearing loss
• CTCAE version 4, grade 2 or above peripheral neuropathy
• NYHA class III heart failure

Miscellaneous combinations of cisplatin-based regimens exist, methotrexate / vinblastine / doxorubicin / cisplatin (MVAC) and cisplatin / carboplatin (GC) being the most widely used for young and old patients (due to its less toxic profile), respectively. Alternatives include dose dense MVAC (DDMVC), cisplatin / methotrexate (CM), cisplatin / 5-fluorouracil (5-FU) and cisplatin / methotrexate / vinblastine (CMV) [156]. Numerous studies have been conducted comparing the effectiveness of different regimens, however the results are inconsistent, so further research is needed to definitively determine the best option [164–167]. The previously cited meta-analysis by Yin *et al.* also examined this problem and compared the most popular regimens, showing similar pathological complete response (pCR) of GC and MVAC, but a significantly reduced OS of GC (HR 1.26, 95% CI: 1.01–1.57), which was probably influenced by the older age of GC patients [156]. An additional issue is the lack of consensus as to the number of cycles to be administered, with most regimens recommending four cycles, but other options mentioned as well, which further hinders the comparison of the results [168].

The pCR to NAC appears to be one of the key parts in predicting survival in MIBC patients. In a meta-analysis which pooled 886 patients from 13 trials Petrelli *et al.* reported that patients who achieved pCR presented a relative risk for OS of 0.45 (95% CI: 0.36-0.56, $p < 0.0001$) [169]. This factor seems to be even more important in patients with N+ BCa – the decision to continue further (including surgical) treatment depends on the response to ChT [107]. The reason is the very poor prognosis of patients with residual pathologic nodal disease after ChT, contrasting with the relatively good outcomes of patients who achieved pCR [132,170]. This approach is called induction chemotherapy (IC). Different studies have reported its significant benefit for N+ patients, especially those achieving pN0 category followed by consolidative surgery while initially presenting with node-positive disease, with one study reporting a 66% cancer-specific survival rate [107,116,171,172]. Patients with complete response after ChT who did not undergo consolidative surgery are at a high risk of relapse, therefore the surgery should not be spared [117,173]. On the other hand, most patients with weak or without response to IC will not benefit from consolidative surgery, with very poor prognosis regardless of the undertaken treatment [107,116]. A study by Ploussard *et al.* compared OS outcomes in 450 N+ BCa patients at the time of RC according to ChT response. The authors revealed a significant association of the persistence of bladder invasion in RC specimens and OS, with an enormous HR of 2.40 (95% CI: 1.06 – 5.44) for those patients [174]. This demonstrates that the post-IC nodal status is very important, as it allows for an appropriate selection of patients for surgery.

4.4 Adjuvant Chemotherapy (AC)

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The role of adjuvant chemotherapy (AC) with RC in the treatment of cN+ BCa has not been fully established. Indicated benefits of this approach are that it allows immediate surgical treatment and enables proper pathological staging. There is still lack of evidence from well-designed randomized phase III trials. With regard to cN+ BCa, another difficulty is that in many trials inclusion criteria are not focused on cN+ but involve pT3/4 tumor stage and/or pN+ status. Based on a meta-analysis of nine randomized control trials the utilization of immediate postoperative cisplatin-based AC resulted in an improvement of the OS. Nonetheless, statistical significance level of this observation was borderline (p = 0.049) [175] In available trials authors used following AC regimens: monotherapy with cisplatin, gemcitabine/cisplatin plus paclitaxel/gemcitabine/cisplatin, cisplatin, methotrexate, and vinblastine (CMV), cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin/epirubicin, and cisplatin (MVA(E)C), and cisplatin plus methotrexate (CM) [176–181].

Sternberg et al. in the randomized clinical trial evaluated immediate versus deferred ChT after RC in 284 pT3/pT4 or N+ patients [182]. In their study ChT regimen of four cycles of gemcitabine plus cisplatin, high-dose methotrexate, vinblastine, doxorubicin, cisplatin (high-dose MVAC), or MVAC was used. The improvement in OS in patients with immediate ChT was not significant, but the authors emphasized that their study is limited in power. Therefore, it is believed that particular groups of patients might still benefit from immediate ChT, and for this purpose a large meta-analysis with updated individual patient data is required. In another randomized clinical trial of 194 patients Cognetti et al. evaluated the benefit of gemcitabine/cisplatin AC after RC versus RC alone [183]. Focusing on N+ patients, there was no differences between mentioned groups in 5-year DFS. This parameter in AC patients reached 18.9% compared to 19.4% in RC group (p = 0.80). It should be noted that performed clinical trials had some methodological flaws and that is why all results should be carefully analyzed. With the low statistical significance of the prospective trials, it is mandatory to discuss the outcomes of retrospective ones. In the multicenter study Svatek et al. identified 3,947 patients with BCa treated with RC without NAC, of whom 932 (23.6%) received AC [184]. The treatment with AC was independently associated with OS benefit (HR: 0.83; 95% CI: 0.72 – 0.97, p = 0.017). In this analysis OS improvement was demonstrated especially in N+ and advanced pathologic stage patients. Furthermore, Galsky et al. in another retrospective study of 5,653 patients diagnosed with pT3-4 and/or pN+ BC compared the effectiveness of RC with RC plus AC. Their analysis showed improvement of OS in the group receiving AC (HR: 0.70; 95% CI: 0.64 - 0.76) [185]. Finally, Berg et al. retrospectively enrolled15,397 patients who underwent RC (without NAC) and were diagnosed with T2N+ or ≥T3N0/N+ [186]. The patients were identified in the National Cancer Database. The authors analyzed the impact of AC on OS in regard to patients variant histology. In N+ patients OS benefit was observed in pure urothelial carcinoma (HR: 0.87; 95% CI: 0.82 – 0.91), while no differences were reported in patients with other histological variants. In the urothelial carcinoma group median OS was 17.49 (95% CI: 16.79 – 18.07) and 26.78 (95% CI: 25.34 – 28.17), respectively for all patients treated with RC and those with an addition of AC. Moreover, several studies reported that AC administration was associated with survival benefit in a group of N+ patients [187–192]. A recent report by Afferi et al. indicated that patients with more than 3 metastatic nodes are the group that will benefit from cisplatin-based AC after RC [193].

Another question consider AC after NAC. There is limited data on this topic and only retrospective data is available. Recurrence-free and disease-specific survival was reported after such management [194]. There are reports indicating that in N+ and/or pT3/T4 previously treated with NAC, AC might be associated with better OS [195].

4.5 Immunotherapy

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NAC is now standard in the treatment of eligible patients with muscle-invasive urothelial carcinoma. The utilization of NAC increased from 9.7% in 2006 to 32.2% in 2014. However, there are patients ineligible for the classical chemotherapy [196]. Factors influencing the use of NAC are: higher comorbidity score, older age, disease-related impairment of renal function, poor performance status, presence of comorbidities that may be exacerbated by treatment-related toxicity, lower cT stage, patient poverty and undergone partial cystectomy [196–198]. These patients may benefit from the new neoadjuvant and adjuvant treatment modalities.

One of the new lines of therapy for patients is the treatment with pembrolizumab. Pembrolizumab is a potent monoclonal antibody of humanized immunoglobulin G4. It binds to PD-1 and inhibits the interaction with PD-L1 and PD-L2 ligands on tumor cells, thus blocking the PD-1/PD-L1 pathway prevents T-cell inactivation [199]. Phase III KEYNOTE-045 results demonstrated OS benefit of pembrolizumab in all subgroups as second-line therapy in patients with locally advanced and unresectable or metastatic bladder cancer including liver metastases and visceral metastasis that has progressed after platinum-based ChT. The median OS was 10.1 months (95% CI: 8.0-12.3) for pembrolizumab and 7.3 months (95% CI: 6.1-8.1) for chemotherapy. Additionally, median progression-free survival was 2.1 months (95% CI: 2.0-2.2) for pembrolizumab and 3.3 months (95% CI: 2.4-3.6) for chemotherapy. Median 1- and 2-year OS rates were higher with pembrolizumab than chemotherapy (1-year OS: 44.2% vs. 29.8% and 2-year OS: 26.9% vs. 14.3%, respectively) [200,201]. The KEYNOTE-052 study demonstrated efficacy and safety of first-line pembrolizumab therapy in cisplatin-ineligible patients with locally advanced and unresectable or metastatic bladder cancer [202–204]. Prolonged OS was observed, with objective response rate (ORR) of 28.6% (95% CI: 24.1–33.5) [202]. The improvement in OS was reported especially in patients with PD-L1 expression and lymph node-only disease. Pembrolizumab is currently approved in locally advanced or metastatic BCa patients who do not qualify for a cisplatin treatment. Additionally, it can be utilized in patients with advanced or metastatic BCa who are progressing during or after platinum-containing chemotherapy or within 12 months of platinum-based NAC or AC. Treatment is also approved in the patients with: bacillus Calmette-Guerin (BCG)-unresponsive BCa, high-risk BCa, NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for RC or have not settled on undergo surgery [18,199,205].

Atezolizumab is another PD-1/PD-L1 immune checkpoint inhibitor that has been approved by the FDA for the treatment of patients with metastatic or locally advanced urothelial carcinoma whose disease progressed during or following platinum-containing ChT or within 12 months of NAC or AC platinum-containing treatment [206–209]. Results from the Phase 3 IMvigor211: 24-month OS rate was 23% with atezolizumab vs. 13% with chemotherapy. Patients treated with chemotherapy had more 3/4 grade TRAE than patients treated with atezolizumab: 43% vs 22% [210]. The SAUL study allowed for the assessment of the effectiveness of the treatment in patients not eligible for the IMvigor211 phase 3 trial. In this study, median OS was 8.7month (CI: 7.8-9.9), the 6-month OS was 60% (95% CI: 57-63%), median progression-free survival (PFS): 2.2 months (95% CI: 2.1-2.4), and the ORR was 13% (95% CI: 11-16%) [211]. Additionally, in a phase II trial ABACUS, atezolizumab administered preoperatively demonstrated clinical activity in patients with MIBC ineligible for cisplatin. The pathologic complete response (pCR) rate was 31% (95% CI: 21-41%) [212].

Results from JAVELIN Bladder 100 proved that maintenance treatment with avelumab (anti–PD-L1 antibody) significantly improves overall survival: 21.4 months (from the start of immunoglobulin administration) in patients with advanced or metastatic urothelial carcinoma that has not progressed on 1L platinum-containing chemotherapy. Avelumab 1L maintenance is approved as a level 1 evidence treatment in the particular group of patients [213,214].

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Erdafitinib has been approved by the FDA for the treatment of locally advanced or metastatic bladder cancer which progressing on platinum-based chemotherapy and has FGFR3 or FGFR2 alterations. It is a tyrosine kinase inhibitor of FGFR1-4 that binds to receptors and blocks the activity of FGF and leads to cell death [20,215–217]. FGFR changes are present in 15-20% of metastatic BCa patients. Previous studies have shown an ORR of 40% (95% CI: 31-50% including 3% complete response). However, erdafitinib exhibits ocular toxicity that calls for special attention [218–220]. The long-term follow-up of phase II study showed a similar safety profile to the first analysis. Grade 3-4 TRAE occurred in 72/101 enrolled patients but there were no treatment-related deaths in follow-up analysis [221].

New research is emerging to develop drugs that can be combined with PD-1/PD-L1 inhibitors or administered interchangeably. Enfortumab vedotin was created by combining an antibody and a drug. The antibody is directed against nectin-4, the drug leads to disruption of the microtubules. This causes a cell cycle arrest in nectin-4 expressing cells [222,223]. Enfortumab vedotin in the first phase study (EV-101 NCT02091999) demonstrated safety, tolerability, and antitumor activity in patients with Nectin-4-positive solid tumors who progressed on ≥ 1 prior chemotherapy regimen and/or anti-PD-1/L1 [224–226]. Phase II study results show that the drug is effective: overall response rate (ORR): up to 52%, duration of response (DOR): 7.6 months (95% CI: 4.93–7.46), OS: 11.7 months (95% CI: 9.1 - not reached) and the drug was safe. The most common treatment-related adverse events (TRAEs) were peripheral neuropathy, rash, decreased appetite, fatigue, dysgeusia and alopecia [222,226]. Enfortumab vedotin is utilized in the treatment of patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing NAC or AC [223].

In 2021 FDA has issued expedited approval for the utilization of Sacituzumab govitecan in metastatic BCa or locally advanced patients who have previously received platinum-based ChT and a PD-1/PD-L1 inhibitor. Sacituzumab govitecan is an antibody-drug conjugate, consisting of an active metabolite of irinotecan and Trop-2 directed anti-Trop-2 immunoglobulins. A phase II study (TROPHY-U-01) has shown the benefits of this drug. ORR was 27.4% (95% CI: 19.6-36.9), median DOR was 7.2 months (95% CI: 4.7-8.6), median PFS was 5.4 months (95% CI: 3.5-7.2) and OS was 10.9 months (95% CI: 9.0-13.8) [227–229].

4.6 Future Perspectives

Research is currently being carried out on new molecules and a new application of the current drugs. Phase III trials are currently underway with perioperative pembrolizumab monotherapy or combined with enfortumab vedotin and RC plus PLND versus RC plus PLND alone in cisplatin-ineligible patients with MIBC (KEYNOTE-905/EV-303). Additionally, in the phase III trial KEYNOTE-866, researchers will check the effectiveness of neoadjuvant chemotherapy with either perioperative pembrolizumab or placebo in previously untreated cisplatin-eligible patients with MIBC [199]. In the Phase II study PURE-01 (NCT02736266), pembrolizumab monotherapy demonstrated promising pathologic complete responses (pCR). pCR was 38.5% (95% CI, 30.5–46.5), 12-month Event-free survival (EFS) was 84.5% (95% CI: 78.5–90.9) and 24-month EFS was 71.7% (95% CI: 62.7–82.0) [230,231]. Furthermore, pembrolizumab as a neoadjuvant treatment has proved to be effective in combination with gemcitabine and cisplatin. Pathologic nonmuscle invasive rate (PaIR i.e., ≤pT1N0) was 61.1% (95% CI: 0.45–0.75), 36- month RFS and OS was 63% and 82% [232]. Additionally, in patients not eligible for cisplatin treatment, pembrolizumab has proved to be effective in combination with gemcitabine. The 12-month RFS and OS was 74.9% and 93.8% [233].

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There are also clinical trials on the combination of pembrolizumab with enfortumab vedotin in the treatment of patients with cisplatin ineligible locally advanced or metastatic BCa. The results of the conducted studies confirm the safety of the treatment. In addition, the ORR was 73.3% (95% CI: 58.1–85.4), 12-month DOR was 53.7% (95% CI: 27.4–74.1), 12-month OS was 81.6% (95% CI: 62.0–91.8) [234,235]. Currently, phase II trials are underway using Durvalumab (PD-L1 inhibitor) and Tremelimumab (CTLA-4 inhibitor) as a neoadjuvant treatment in patients with MIBC. It was found to be safe and active in patients with MIBC regardless of tumor immune score [236]. Phase 2 trials also confirm the antitumor effect of Camrelizumab (PD-1 inhibitor) with famitinib in patients with advanced or metastatic BCa who had progressed after platinum-based ChT. The subgroup of BCa patients achieved a median PFS of 8.3 months (95% CI: 4.1 - not reached) and ORR of 38.9% (95% CI: 17.3-64.3%) [237]. Famitinib malate is a tyrosine kinase inhibitor (TKI) against VEGFR-2, PDGFR, c-kit, and FGFR [238]. The phase I NABUCCO study showed the effectiveness of neoadjuvant therapy with ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor). In patients with stage III BCa treated with this combination, resection was possible within 12 weeks of starting therapy in 23 patients (96%) [239]. CheckMate 275 has been certified with durable antitumor activity of nivolumab [240]. An overview of currently conducted clinical trials is demonstrated in Table 5.

Table 5. Currently ongoing clinical trials on immunotherapy in BCa.

Name of clinical trial	Phase	Drug	Recruitment status on 07/22/2022	Number of Participants	Participants with:
MK-3475-045/KEYNOTE-045 (NCT02256436) [200,241]	III	Pembrolizumab	Completed	542	metastatic or locally advanced / unresectable BCa with recurrence or progression after platinum-based ChT.
KEYNOTE-052 (NCT02335424) [242]	II	Pembrolizumab	Completed	374	metastatic or locally advanced / unresectable BCa ineligible for cisplatin-based ChT.
EV-101 (NCT02091999) [243]	I	Enfortumab vedotin	Active, not recruiting	155 (BCa)	nectin-4-positive BCa / other solid tumors, with progression or ineligible for platinum-based ChT and/or anti-PD-1 / L1 therapy.
EV-201 (NCT03219333) [244]	II	Enfortumab vedotin	Active, not recruiting	125	cisplatin ineligible metastatic or locally advanced BCa who progress on / after PD-1 / L1 inhibitors.
EV-301 (NCT03474107) [245]	III	Enfortumab vedotin	Active, not recruiting	608	metastatic or locally advanced BCa with recurrence or progression after PD-1/PD-L1 inhibitors.
IMvigor211 (NCT02302807) [246]	III	Atezolizumab	Completed	931	metastatic or locally advanced BCa with progression during / after platinum-based ChT.

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SAUL (NCT02928406) [211,247]	III	Atezolizumab	Active, not recruiting	1004	metastatic or locally advanced / unresectable BCa with progression during / after one to three prior therapies.
ABACUS (NCT02662309) [212,248]	II	Atezolizumab	Unknown	95	histologically confirmed (T2-T4a) transitional cell BCa.
JNJ-42756493 (NCT02365597) [219,249]	II	Erdafitinib	Recruiting	236	metastatic or unresectable BCa that harbor specific FGFR genomic alterations.
JAVELIN Bladder 100 (NCT02603432) [250]	III	Avelumab	Active, not recruiting	700	metastatic or locally advanced / unresectable BCa without progression after first-line ChT.
TROPHY-U-01 (NCT03547973) [251]	II	Sacituzumab govitecan	Recruiting	321	metastatic BCa unresponsive to platinum-based ChT or PD-1 / PD-L1 inhibitors.
KEYNOTE-905/EV-303 (NCT03924895) [252]	III	Pembrolizumab + Enfortumab vedotin + RC + PLND	Recruiting	857	MIBC who are cisplatin-ineligible or decline ChT.
KEYNOTE-866 (NCT03924856) [253]	III	Pembrolizumab	Recruiting	870	MIBC who are cisplatin-eligible.
PURE-01 (NCT02736266) [254]	II	Pembrolizumab	Recruiting	90	T2-T4aN0 BCa with residual disease after TURB.
GU14-188 (NCT02365766) [255]	II	neoadjuvant Pembrolizumab	Active, not recruiting	83	T2-4aN0 BCa who are cisplatin-eligible / ineligible.
EV-103/KEYNOTE-869 (NCT03288545) [256]	I / II	Enfortumab vedotin + Pembrolizumab	Recruiting	457	metastatic or locally advanced BCa who are cisplatin-ineligible.
DUTRENEO (NCT03472274) [257]	II	Durvalumab + Tremelimumab	Active, not recruiting	99	cT2-T4N0-1M0 BCa who are Cisplatin-eligible, candidates to RC.
SHR-1210 (NCT03827837) [258]	II	Camrelizumab + Famitinib	Recruiting	265	unresectable BCa after failure of ≤2 platinum-based ChT.
CheckMate 275 (NCT02387996) [259]	II	Nivolumab	Completed	270	metastatic or locally advanced/unresectable BCa with recurrence or progression after platinum-based ChT.

The results of these studies will introduce new guidelines for the treatment of advanced, metastatic or ChT-ineligible patients with BCa.

5. Conclusion

The management of patients with the cN+ bladder cancer remains imprecise in many aspects. From diagnostics to surgical treatment and ending with systemic treatment, high-value clinical research is lacking. However, the available data allow for some important statements. Multimodal treatment with ChT and RC achieves the best prognosis for patients with cN+ BCa, however there is still lack of definitive evidence whether to perform NAC or AC. Nevertheless, the response to ChT is crucial as a prognostic factor for these patients. Due to the high percentage of ChT-ineligible BCa patients, immunotherapy is gaining more and more importance in the clinical practice. The results of many currently carried out clinical trials regarding immunotherapy may implement changes to the guidelines in the near future. In cN+ patients if RC is performed, the LND should not be omitted and the extended template should be utilized to provide necessary diagnostic data. Moreover, the total resected node count is less important than the range of LND.

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