Management Options for Node-Positive Muscle-Invasive Bladder Cancer

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Abstract: Localized node-positive bladder cancer is characterized by a high degree of heterogeneity, leading to significant variability in overall survival outcomes among affected individuals. The absence of standardized treatment guidelines presents a critical challenge in managing these patients effectively. This comprehensive review article delves into the pathophysiology, clinical significance, and management of node-positive bladder cancer. It critically evaluates the current therapeutic landscape and explores emerging treatment strategies, including novel drugs currently undergoing clinical trials. By synthesizing the latest research findings, the review aims to provide valuable insights into the optimal management of node-positive urothelial cell carcinoma, ultimately contributing to improved patient outcomes and quality of life.

Introduction

Bladder cancer ranks as the sixth most prevalent cancer and the 10th leading cause of cancer-related deaths in the United States, posing a significant public health concern.[1] In 2024, 83,190 new cases and 16,840 deaths due to bladder cancer are anticipated. A comprehensive analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 2012 to 2018 shows that the 5-year survival rate is 70% for localized node-negative bladder cancer, 39% for node-positive disease, and 8% for metastatic disease.[2] It is well established through multiple studies that lymph node (LN) positivity is associated with a poor prognosis, significantly adversely influencing disease-specific survival.[3,4] However, it is important to note that in metastatic urothelial cancer, the presence of LN-only metastasis is considered a relatively good prognostic factor in comparison with metastasis in other sites, such as bone and liver. One retrospective study reported 5-year overall survival (OS) rates of 31% for patients who received neoadjuvant chemotherapy (NAC) and radical cystectomy (RC), 26% for those who received RC and adjuvant chemotherapy (AC), 19% for patients

who received RC alone, and 14% for those who received chemotherapy alone.[5]

Patients with localized LN (any T, N1-3, M0) involvement pose unique clinical challenges because they are at risk for distant metastases but still can possibly be cured with treatment. However, no consensus exists regarding the best treatment approach for patients with localized LN-positive (LN+) disease. This review aims to compile the available evidence to guide the management of localized LN+ bladder cancer, with a focus on regional or localized LN involvement (N1-3, stage III); it also touches briefly on key studies highlighting distant LN+ metastases (M1a, stage IV).

Pathophysiology of Nodal Metastases

The lymphatic drainage system of the bladder comprises a complex network of primary and secondary drainage sites. Understanding these drainage sites is crucial for understanding the pathophysiology of LN metastases. The primary lymphatic drainage sites include regional LNs within the true pelvis, such as the perivesical, obturator, internal iliac, external iliac, and sacral nodes. The secondary drainage site extends to the common iliac nodes. However, lymphatic drainage beyond these regions can lead to distant metastasis. Notably, a small proportion of cases demonstrate initial drainage beyond the true pelvis, with 15% of cases involving the common iliac nodes and 4% the para-aortic regions.[6]

Regional LN+ bladder cancer, a critical juncture in the clinical course of the disease, can be identified through various modalities. These include the identification of clinically node-positive disease through pretreatment imaging and the identification of pathologically node-positive disease through the examination of surgical specimens obtained during cystectomy. Notably, in patients with muscle-invasive bladder cancer (MIBC) who undergo RC with pelvic LN dissection, approximately 20% to 30% of cases are found to harbor regional LN metastases. In contrast, only 7% of patients initially present with clinically node-positive bladder cancer.[7]

Clinical Significance of Lymph Node Involvement in Bladder Cancer

LN involvement in bladder cancer is a critical turning point in disease progression, with profound prognostic and predictive implications. Patients with regional LN+ bladder cancer often face a challenging prognosis, as reflected by a 5-year OS rate of approximately 30%. Furthermore, regional LN+ bladder cancer is marked by significant heterogeneity, leading to notable variations in disease recurrence rates and cancer-specific mortality. The American Joint Committee on Cancer TNM (tumor, node, metastasis) classification system, which was revised in 2017, has a pivotal role in categorizing nodal disease in bladder cancer. This system takes into account both the number and location of affected LNs.

Key Prognostic Factors

The dominant pathologic predictors of disease recurrence and survival in bladder cancer are tumor stage and nodal status. Other significant prognostic factors also come into play, including gender, age, the presence of hydronephrosis and lymphovascular invasion, soft-tissue surgical margin status, molecular subtyping status, LN parameters (comprising the number of positive LNs, LN density, total number of LNs removed, and aggregate LN metastasis diameter), and the presence of extranodal extension. Specifically, a higher tumor grade, advanced T stage, younger age, and larger tumor size have all been correlated with an increased risk of nodal involvement.[8,9]

Treatment Strategies for Patients With Regional LN+ Bladder Cancer

The treatment of bladder cancer in patients with clinically or pathologically diagnosed node-positive disease remains an area with significant heterogeneity. Multimodality therapy is the cornerstone of treatment for patients with node-positive MIBC. The divergence in practice patterns by treating physicians is huge. Some multidisciplinary teams adopt a palliative approach in which they focus on systemic therapy, with local treatments aimed at symptom relief rather than a cure. Others pursue a more aggressive strategy with curative intent that involves RC, often combined with either NAC or AC. Another option is trimodal therapy, which aims to preserve the bladder by combining chemoradiotherapy with maximal transurethral resection of the bladder tumor (TURBT). Despite these options, no clear consensus exists on the best treatment for this intermediate-risk group. The following sections review the literature to explain the data and reasoning behind the various multimodality treatments used for node-positive bladder cancer.

Role of Perioperative Chemotherapy

Neoadjuvant Chemotherapy in Localized LN+ Bladder Cancer. The compelling benefits of NAC before RC in the treatment of MIBC have been substantiated through numerous high-quality clinical studies. Among the seminal works in this domain is a Southwest Oncology Group (SWOG) randomized trial involving 307 patients with a diagnosis of MIBC. This study demonstrated that an NAC regimen comprising methotrexate, vinblastine,

doxorubicin, and cisplatin (MVAC) followed by RC significantly improved median survival (77 vs 46 months) in comparison with RC alone and substantially increased the rate of achievement of no residual disease (38% vs 15%).[10]

Although an abundance of research advocates for NAC in MIBC, studies focused on patients who have clinically regional LN+ status are relatively sparse. Meijer and colleagues shed light on this overlooked patient cohort, reporting outcomes for 152 (115 LN+) patients with locally advanced MIBC and/or LN+ status.[11] This was a retrospective cohort of patients treated with induction chemotherapy followed by additional surgical interventions. The authors reported a median OS of 18 months and a pathologic complete response (pCR) in 26.3% of patients. Furthermore, the study estimated an encouraging 5-year OS rate of 54% (95% CI, 39%-74%). However, it is crucial to note that for those with persisting pathologic node-positive (pN+) disease after induction chemotherapy and surgery, OS was significantly diminished (P<.001).[11]

Complementing these findings, Ploussard and colleagues conducted an observational multicenter study involving 450 patients with a diagnosis of pN1-3 disease.[12] The study concluded that OS outcome was worse in patients who received NAC followed by RC than in those who received RC. The majority of patients in this cohort received AC, and patients who received AC had better OS than those who received NAC or no chemotherapy; therefore, the relevance of the results for NAC followed by RC was not clear. Patients who had residual MIBC disease after NAC had a significantly worse OS, with a hazard ratio (HR) of 2.40 (95% CI, 1.06-5.44).[12] Similarly, Ho and colleagues reported a stark difference between 5-year cancer-specific survival rates in the pN0 and pN+ categories in patients treated with NAC followed by RC (66% vs 12%; P<.001).[13] Moreover, radiologic CR to chemotherapy correlated with a significantly better 5-year cancer-specific survival rate (60% vs 33%; P=.038).[13] Corroborating these individual studies, a meta-analysis by Petrelli and colleagues that included 13 trials and 886 patients found a pCR rate of 28.6% when a combination of NAC and AC was used.[14] Importantly, achieving pCR in both the primary tumor and lymph nodes led to a relative risk for OS of 0.45 (95% CI, 0.36-0.56; P<.001). The number needed to treat to prevent 1 death was 3.7, with an absolute risk difference of –26%.[14]

The need for local treatment following NAC in the management of locally advanced LN+ bladder cancer is compelling. RC is often used in patients who have had a good response to NAC. This assertion is grounded in 2 key factors: the high incidence of disease relapse at sites initially responding to chemotherapy and the limitations of clinical methodologies in accurately assessing a CR to chemotherapy alone.[15] The argument for postchemotherapy surgery gains traction from observational data suggesting that surgical resection of the sites of locoregional disease, when chemotherapy was initially administered, can enhance relapse-free survival. Strikingly, 33.3% of patients who were believed to have achieved a clinical CR still had viable disease in their surgical specimens.[16] Additionally, 15.9% of patients deemed to have only a partial clinical response exhibited a pCR, which was surprising. This discrepancy underscores the unreliability of clinical assessments and fortifies the case for postchemotherapy surgery.

In a recent population-based analysis involving more than 3000 patients, RC with pelvic lymph node dissection and chemotherapy was associated with better 5-year OS when compared with radiation therapy (>50 Gy) along with chemotherapy and TURBT.[17] However, the retrospective nature of this study suggests potential bias, as patients with more comorbidities were more likely to be chosen for chemoradiation rather than surgery. It is also essential to recognize that not all patients are candidates for postchemotherapy surgery. Specifically, those who fail to achieve either a major complete or partial response to chemotherapy typically face a poor prognosis, and surgical intervention in such cases does not confer a survival advantage.[11,13]

Another dimension to consider is the eligibility criteria for NAC. Patients with hearing loss, neuropathy, poor performance status, or renal insufficiency may not be suitable candidates for cisplatin-based chemotherapy. It is worth noting that carboplatin, often considered an alternative, has failed to demonstrate a survival benefit and should not be employed as a substitute for cisplatin in the perioperative setting.[18] In summary, selected patients with LN+ MIBC do benefit from NAC followed by surgery.

Adjuvant Chemotherapy in Localized LN+ Bladder Cancer. The use of AC for LN+ bladder cancer has been a subject of investigation in various studies. These studies have shown that AC may delay recurrences and improve OS. However, it is important to note that the randomized trials exploring AC for bladder cancer have faced challenges such as being underpowered and terminated prematurely, leading to inconsistent results.

In a meta-analysis conducted by Leow and colleagues, which included data from 9 randomized controlled trials comprising 945 patients, the use of immediate postoperative cisplatin-based adjuvant chemotherapy was assessed.[19] Although many of these trials included patients with LN+ disease, their inclusion criteria were not specifically focused on nodal positivity. The pooled HR for OS was found to be 0.77, indicating a statistically

significant improvement in OS with the use of adjuvant cisplatin-based chemotherapy. Similarly, the pooled HR for disease-free survival (DFS) was 0.66 (95% CI, 0.45-0.91; *P*=.014). Notably, the benefit in DFS was more pronounced among patients with pN+ disease (*P*=.010). Specifically, the HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with a higher percentage of patients with nodal involvement (>50% with pN+ disease) was 0.39 (95% CI, 0.28-0.54), whereas the HR was 0.89 (95% CI, 0.69-1.15) in studies with fewer patients with nodal involvement (<50% with pN+ disease).

An updated meta-analysis of 10 randomized controlled trials involving 1183 participants, with 40% of them having LN+ disease, has affirmed that cisplatin-based AC provides a survival advantage, with an HR of 0.82. This translates to a 6% absolute improvement in survival at 5 years and a 9% absolute benefit after adjustment for age, sex, pathologic tumor (pT) stage, and pN category. Regarding the pN category, no clear evidence of interaction was found in comparison with the reference category of pN0.[20]

In a retrospective study conducted by Galsky and colleagues, which included 5653 patients with a diagnosis of pT3-4 or pN+ bladder cancer, the effectiveness of RC alone was compared with that of RC plus AC. Among these patients, 23% received AC, with 64% in the AC group having LN+ disease vs 32% in the observation group.[21] Their analysis demonstrated an improvement in OS in the AC group, with an HR of 0.70 (95% CI, 0.64-0.76). The 5-year OS rates were 37.0% (95% CI, 34.3%-39.7%) in the AC group and 29.1% (95% CI, 27.7%-30.5%) in the observation group (*P*<.001). Additionally, the benefit in OS was also evident in patients with nodal involvement (HR, 0.62; 95% CI, 0.56-0.69).[21]

Berg and colleagues identified 15,397 patients who received RC (without NAC) and had a diagnosis of T2 N+ or T3 N0/N+ disease or greater in the National Cancer Database. Among these, 6957 had pN+ disease, and 34% of them received AC after RC. An OS benefit was observed in the patients who had pure urothelial carcinoma (HR, 0.87; 95% CI, 0.82-0.91), whereas no significant differences were reported in the patients with other histologic variants.[22] Afferi and colleagues reported that only patients with a poor prognosis (pT any and pelvic lymph node count ≥3) benefited from cisplatin-based AC in terms of OS, with an HR of 0.51 (*P*<.001).[23]

In the VESPER phase 3 randomized controlled trial, which included 493 patients, a subgroup of 56 patients (37 of whom had nodal involvement) received either adjuvant dose-dense MVAC (dd-MVAC) or gemcitabine and cisplatin (GC); 437 patients received NAC. The 5-year OS rate was higher in the dd-MVAC arm than in the GC arm (64% vs 56%; HR, 0.77; 95% CI, 0.58-1.03; *P*=.078), as was the 5-year disease-specific survival (DSS) rate (72% vs 59%; HR, 0.63; 95% CI, 0.46-0.86; *P*=.004). In the NAC group, the 5-year OS rate was significantly higher in the dd-MVAC arm than in the GC arm (66% vs 57%; HR, 0.71; 95% CI, 0.52-0.97; *P*=.032), as was the 5-year DSS rate (75% vs 60%; HR, 0.56; 95% CI, 0.39-0.80; *P*=.001). However, the results were inconclusive in the AC group because of the limited sample size (n=56).[24]

It is worth noting that the data from randomized trials regarding the timing of AC after NAC and RC are limited. Kassouf and colleagues reported improved outcomes in a cohort of 37 patients with pN+ disease despite preoperative chemotherapy. Among them, 11 patients received AC; this was associated with improved recurrence-free survival (*P*=.02; HR, 0.29; 95% CI, 0.10-0.81), with a trend toward significance for prolonged OS (*P*=.08; HR, 0.44; 95% CI, 0.18-1.11) and DSS (*P*=.07; HR, 0.36, 95% CI, 0.12-1.07).[24] Median survival for those who received AC vs those who did not was 16 vs 12.6 months.[25]

In an observational study involving 788 patients with pT3/T4 and/or pN+ disease, Seisen and colleagues reported significantly longer median OS with NAC followed by RC followed by AC (29.9 months; interquartile range, 15.1-85.4) than with NAC and RC followed by observation (24.2 months; interquartile range, 12.9-58.9; *P*=.046; HR, 0.78; 95% CI, 0.61-0.99; *P*=.046).[25] The 5-year OS rates were 36.8% for NAC and RC followed by AC vs 24.7% for NAC and RC followed by observation. In this study, 23.4% of the patients received NAC and RC followed by AC, and 58.7% in the AC group had nodal involvement vs 41.7% in the observation group.[26]

The National Comprehensive Cancer Network guidelines support the administration of adjuvant therapy for certain patients at high risk of relapse.[27] However, they caution against substituting carboplatin for cisplatin because of a lack of demonstrated survival benefit in the perioperative setting. Tumors that are pT2 or less, without nodal involvement or lymphovascular invasion after cystectomy, are considered lower risk and may not benefit from adjuvant therapy.

Bladder Preservation Approach With a Multimodality Approach

Several studies have explored combining chemotherapy with radiotherapy after TURBT for MIBC. Unfortunately, most of these studies excluded patients with LN+ disease, leading to uncertainty about the best treatment for this group.

In 2002, an important study conducted by Rodel and colleagues investigated the outcomes of combined-mo-

dality treatment in patients with MIBC. Within this German registry, in which 28 of 415 patients presented with clinical LN+ disease, an overall CR rate of 72% was observed.[28] Furthermore, local control after CR without muscle-invasive relapse was sustained in 64% of patients over a 10-year period. Distant metastases were observed in 98 patients, with an actuarial rate of 35% at 10 years. The 10-year DSS rate stood at 42%, and the bladders of more than 80% of survivors could be preserved. An early tumor stage and a complete TURBT were identified as pivotal factors in predicting CR and OS.[28]

The Radiation Therapy Oncology Group (RTOG) undertook several trials to assess bladder preservation strategies of radiotherapy in combination with various chemotherapy regimens, confirming the efficacy and safety of this approach.[29-35] A combined analysis of survivors from 4 prospective RTOG trials, all excluding patients with LN+ disease and comprising 285 eligible patients with a median follow-up of 5.4 years, demonstrated that combined modality therapy resulted in low rates of late grade 3 toxicity (5.7% genitourinary and 1.9% gastrointestinal). Notably, no occurrences of late grade 4 toxicities or treatment-related deaths were documented.[36] On the basis of the compelling evidence derived from these trials, concurrent chemoradiotherapy for bladder preservation has attained category 1 recommendation status for the primary treatment of localized bladder cancer by the National Comprehensive Cancer Network. Using a comprehensive contemporary dataset, Haque and colleagues reported better median OS among patients who underwent chemoradiotherapy than in those who received chemotherapy alone for LN+ bladder cancer.[37] This improvement was observed despite the tendency for patients undergoing chemoradiotherapy to present with more advanced disease.

A phase 2 study conducted at a single center explored the feasibility of chemoradiotherapy in treating MIBC with confirmed or high-risk nodal involvement.[38] The study revealed a median OS of 1.9 years and a 5-year OS rate of 34%. Despite the modest sample size of 38 participants (60% with confirmed LN+ disease), the study demonstrated the ability to administer intensity-modulated radiation therapy (IMRT) with an 85% bladder preservation rate and a low incidence (5%) of late grade 3 gastrointestinal toxicity.[38]

A large real-world retrospective study conducted by Swinton and colleagues examined 287 patients with LN+ disease.[39] The study reported a median OS of 1.5 years. Radical treatment was notably associated with enhanced OS in comparison with palliative treatment, and survival outcomes were comparable between surgery and radical radiation therapy. Given the recognized challenges of RC in a group of patients with limited survival prospects, this study underscores that bladder-sparing trimodal therapy should be regarded as a viable treatment option for individuals with a diagnosis of LN+ bladder cancer.[39]

Collectively, these studies highlight the significance of concurrent chemoradiotherapy and its potential benefits in the treatment of invasive bladder cancer. However, they also emphasize the critical need for additional research, particularly concentrating on patients with node-positive disease and older populations.

Evolving Role of Immunotherapy in the Treatment of LN+ Bladder Cancer

The advent of immune checkpoint inhibitors (ICIs) was a watershed moment. The initial US Food and Drug Administration (FDA) approval of cisplatin for bladder cancer in 1978 and gemcitabine in 2008 was followed by a significant gap in therapeutic innovations. This changed dramatically between 2016 and 2017, when the FDA approved 5 different agents targeting the programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) pathways. The FDA initially granted accelerated approval for PD-1 inhibitors (pembrolizumab [Keytruda, Merck] and nivolumab [Opdivo, Bristol Myers Squibb) and PD-L1 inhibitors (atezolizumab [Tecentriq, Genentech], avelumab [Bavencio, EMD Serono/Pfizer], and durvalumab [Imfinzi, AstraZeneca]) as second-line treatment options for advanced bladder cancer in patients whose disease had progressed on platinum-based therapy and who had not previously received immunotherapy.[40-43] However, the sponsors of atezolizumab and durvalumab voluntarily withdrew their approvals after the confirmatory phase 3 trials failed to meet their primary endpoints.[44,45]

In recent years, the role of ICIs in the management of urothelial carcinoma has been widely studied. Numerous ongoing studies are evaluating the role of ICIs in combination with other agents as NAC or AC in the metastatic setting. In the following sections, we summarize key clinical trials that have provided significant evidence on the various uses of PD-1 and PD-L1 inhibitors in managing urothelial cancer, offering new options for patient care. Although several studies have shown promising efficacy of ICIs in MIBC in the NAC setting, we still await the results of some practice-changing studies.

It is worth noting that until 2017, patients with clinically node-positive disease were grouped with patients with metastatic disease, leading to their inclusion in trials of systemic therapy for metastatic bladder cancer. However, the specific outcomes of patients with localized LN+ disease within the ICI-based treatment trials have not typically been reported. Given the scarcity of studies with ICIs for disease that is LN+ only, in this section we

capture the role of ICIs as adjuvant therapy for MIBC and as maintenance therapy in the metastatic setting.

Role of Adjuvant Immune Checkpoint Inhibitors

One significant development in the field of adjuvant immunotherapy for the management of MIBC after surgery emerged from the CheckMate 274 trial.[46] This phase 3 study included patients with MIBC and upper tract urothelial carcinoma (capped at 20%) who had undergone RC; these patients were randomized to receive adjuvant nivolumab for 1 year or a placebo. Of the participants, 47% had LN+ disease and 43% had received NAC. The results demonstrated that nivolumab led to a median DFS of 20.8 months, a notable improvement in comparison with the 10.8 months observed in the placebo arm.[46] This benefit was particularly pronounced in patients with PD-L1 expression exceeding 1% and those with pN2 and pN3 disease. On August 19, 2021, the FDA approved nivolumab for the adjuvant treatment of bladder cancer in patients at high risk for recurrence after radical resection. Updated data presented at the 2024 Annual European Association of Urology Congress showed continued improvements in DFS, non-urothelial tract recurrence-free survival, and distant metastasis–free survival with adjuvant nivolumab vs placebo in both the intention-to-treat population and the population with PD-L1 of at least 1%. Additionally, a favorable trend toward OS was observed, although the data are still maturing.

Similarly, the phase 3 AMBASSADOR study enrolled patients with MIBC who underwent surgery, had residual disease (≥ypT2 and/or ypN+ following NAC or ≥pT3 and/or pN+ without NAC), and either were cisplatin-ineligible or declined adjuvant cisplatin-based therapy.[47] A total of 354 patients were randomized to receive pembrolizumab at 200 mg every 3 weeks for 1 year, and 348 patients were observed. Median DFS was 29 months vs 14 months, respectively, at a median follow-up of 22.3 months (HR, 0.69; 95% CI, 0.55-0.87; *P*=.0013). Further follow-up is ongoing for final DFS/OS, PD-L1 subgroups, and circulating tumor DNA (ctDNA) analyses.

In contrast, the IMvigor010 trial, a phase 3 study assessing the efficacy of 1 year of adjuvant atezolizumab in MIBC, did not reveal a significant advantage in DFS.[48] Of the participants, 52% had node-positive disease, and no difference in the effect of atezolizumab according to pathological nodal status could be discerned. However, patients with ctDNA benefited from atezolizumab.

Role of Immune Checkpoint Inhibitors in the First-Line Setting for LN+ Disease

Traditionally, cisplatin-based chemotherapy has been used to treat locally advanced or metastatic bladder cancer, with a median OS ranging from 13 to 15 months.[49] An alternative approach for patients who are ineligible for cisplatin is carboplatin-based chemotherapy. However, this regimen is limited in efficacy and often poorly tolerated, resulting in a median OS of merely 9 months.[50] The FDA has approved maintenance avelumab on the basis of the phase 3 JAVELIN Bladder 100 trial, which involved 700 patients with locally advanced or metastatic bladder cancer who achieved a CR, partial response, or stable disease after 4 to 6 cycles of cisplatin- or carboplatin-based chemotherapy.[51] Maintenance avelumab significantly improved OS (21.4 vs 14.3 months; HR, 0.69; 95% CI, 0.56-0.86; *P*=.001),[51] and the benefit was sustained during a median follow-up of more than 2 years (23.8 vs 15 months; HR, 0.76; 95% CI, 0.63-0.91; *P*=.0036).[52] In this study, 45.4% of patients had nonvisceral disease.

A noteworthy phase 2 trial, led by Galsky and colleagues, used pembrolizumab in a switch maintenance therapy approach and demonstrated a progression-free survival (PFS) benefit (5.4 months in the pembrolizumab arm vs 3 months in the placebo arm; HR, 0.65; *P*=.04).[53] The objective response rate (ORR) was 23% with pembrolizumab and 10% with placebo. The median OS results were comparable in the 2 arms as a result of crossover, at 22 months with pembrolizumab and 18.7 months with placebo. Interestingly, no significant difference in the PFS and OS effects of pembrolizumab on the basis of a PD-L1 combined positive score of at least 10 was noted. Collectively, these findings have solidified the role of maintenance immunotherapy in the population of patients with locally advanced unresectable/metastatic disease, and one can assume that these therapies might show a similar benefit in patients with LN+ disease, although it is hard to tease out the difference between regional and nonregional LN+ disease.

In the context of cisplatin-ineligible patients with locally advanced or metastatic bladder cancer, robust evidence supporting pembrolizumab as a first-line therapy has been derived from the KEYNOTE-052 study,[54] which demonstrated an ORR of 28.9% with a median OS of 11.3 months for the entire patient cohort and particular benefit in patients with high PD-L1 expression. The KEYNOTE-361 trial, which involved 1010 patients, showed no significant benefit from adding pembrolizumab to chemotherapy.[55] The DANUBE trial also did not show benefit from adding durvalumab plus tremelimumab (Imjudo, AstraZeneca) to chemotherapy.[46] The IMvigor130 trial highlighted a significant improvement in median PFS with atezolizumab combined with platinum-based chemotherapy vs chemotherapy alone.[56] The same trial showed no significant difference between the median OS of the atezolizumab-alone arm and that of the chemotherapy-alone arm.

The groundbreaking EV-302/KEYNOTE-A39 trial marks a significant advancement in the field of urothelial cancer (UC) treatment.[57] This phase 3 clinical trial enrolled 886 patients with previously untreated locally advanced or metastatic bladder cancer. The patients were randomized to receive either enfortumab vedotin (EV; Padcev, Astellas) in combination with pembrolizumab or platinum-based chemotherapy. The EV-302 trial achieved remarkable success, meeting its dual primary endpoints of OS and PFS. Patients treated with the combination of EV and pembrolizumab exhibited a median OS of 31.5 months (95% CI, 25.4 to not reached), a substantial improvement in comparison with the 16.1 months (95% CI, 13.9-18.3; HR, 0.47; 95% CI, 0.38-0.58; *P*<.001) observed in the chemotherapy arm.[57] Additionally, the median PFS for patients in the combination therapy group was 12.5 months (95% CI, 10.4-16.6), in contrast to the 6.3 months (95% CI, 6.2-6.5; HR, 0.45; 95% CI, 0.38-0.54; *P*<.001) observed in the chemotherapy arm. Remarkably, these favorable OS outcomes were consistent across various predefined subgroups, including those based on cisplatin eligibility and PD-L1 expression levels. Of the 444 patients in the chemotherapy group, 260 (58.6%) received PD-1 inhibitor– or PD-L1 inhibitor–containing therapy as their first subsequent systemic treatment, including maintenance therapy with avelumab in 135 patients (30.4%). Patients with LN+ disease made up 23% of the study population, so one can assume that EV/pembrolizumab is an effective treatment for LN+ bladder cancer. However, the assumption is that these were probably cases of nonregional LN+ disease.

Another recent trial is CheckMate 901, a multinational, open-label, phase 3 study that focused on previously untreated unresectable or metastatic UC.[58] In this trial, patients were randomly assigned to receive nivolumab in combination with GC every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy every 4 weeks for a maximum of 2 years, or GC alone every 3 weeks for up to 6 cycles. The results from CheckMate 901 demonstrated a noteworthy improvement in OS in a comparison of nivolumab/GC therapy with GC alone. The median survival was 21.7 months in the combination therapy group vs 18.9 months in the GC arm (HR, 0.78; 95% CI, 0.63-0.96; *P*=.02). PFS was also prolonged with nivolumab/GC therapy (HR, 0.72; 95% CI, 0.59 to 0.88; *P*=.001). Notably, the 12-month PFS rate favored nivolumab/GC therapy vs GC alone, with rates of 34.2% and 21.8%, respectively. The trial further revealed a significant difference in the ORRs: 57.6% (CR, 21.7%) in the nivolumab/GC group and 43.1% (CR, 11.8%) in the GC-alone group. The median duration of CR was substantially longer with nivolumab/GC therapy, at 37.1 months, than with GC alone, at 13.2 months. Analyses of the LN+ UC subgroup (patients with nonregional LN+ disease were included) included 54 treated patients in the nivolumab/GC arm and 56 in the GC-alone arm.[59] The ORR and CR rates were impressive in this subgroup, indicating that patients with nonregional LN+ disease perhaps have a better outcome than patients with metastatic UC and greatly advanced disease (ORR and CR rate were 81.5% and 63% for the nivolumab/GC arm vs 64.3% and 33.9% for the GC-alone arm, respectively). The trial also showed that among patients who achieved a CR (102/608, or 16.8%), 34 (51.5%) in the nivolumab/GC arm and 19 (52.8%) in the GC-alone arm had LN+ only metastatic UC.[59] Of the 304 patients in the chemotherapy group, 216 (41.5%) received PD-1 inhibitor– or PD-L1 inhibitor–containing therapy as their first subsequent systemic treatment.

The data from these phase 3 studies highlight the importance of using ICI treatment in patients with LN+ bladder cancer but does not clarify the role of this regimen in regional or localized LN+ disease. Given the scarcity of data, patients—especially those with N2-3 disease—should be treated similarly to those with advanced bladder cancer, with a role for consolidation therapy. However, patients with distant LN+ bladder cancer should be treated similarly to those with metastatic or advanced bladder cancer.

Immune Checkpoint Inhibitors in Combination With Radiation in Localized LN+ Bladder Cancer

Studies are being conducted to evaluate the role of combining ICI treatment with radiotherapy (RT) in localized bladder cancer. DUART is a phase 2 study that evaluated the efficacy of combining ICI treatment with RT in patients with localized bladder cancer.[60] The enrolled patients had T2-4, N0-2, M0 bladder cancer with unresectable tumors, were unfit for surgery, or were cisplatin-ineligible. Patients with T2-3, N0 bladder cancer had to be ineligible for cisplatin. Despite the small sample size (26 participants), 31% had confirmed LN+ disease. Patients received durvalumab concurrently with RT for 7 weeks, followed by adjuvant durvalumab for 1 year. The ORR was 15 of 22 patients (68.2%) at the time adjuvant treatment was discontinued. After adjuvant durvalumab, the disease control rate was 72.7%, with a CR of 54.5%. The PFS probability at 1 year was 71.5%, with a median PFS of 21.8 months. The OS probability at 1 year was 83.8%, with a median OS of 30.8 months. Patients with LN+ disease had a similar median PFS and OS. Durvalumab/RT was well tolerated in the study.

The EA8185 study was the first prospective study designed to determine the role of concurrent and adjuvant durvalumab in patients with LN+ bladder cancer when treated with induction chemotherapy followed by

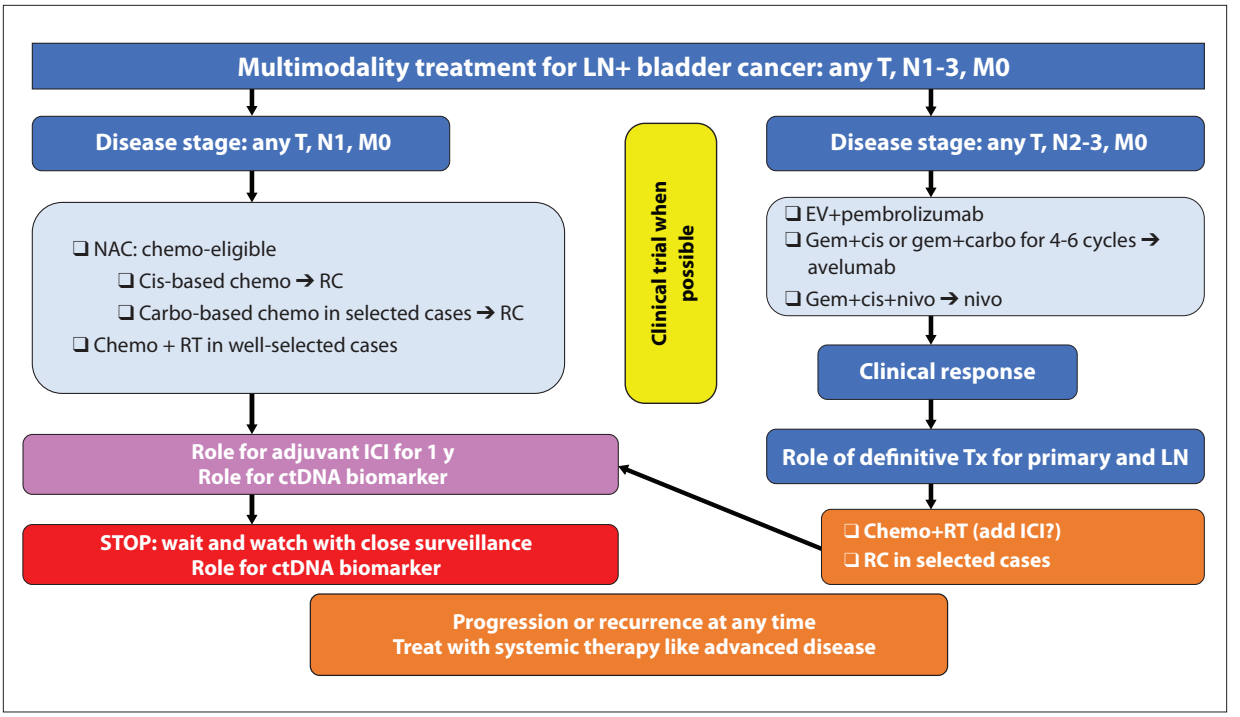

Figure. Proposed treatment algorithm for localized LN+ bladder cancer. →, followed by; carbo, carboplatin; chemo, chemotherapy; cis, cisplatin; clinical response, radiology/cystoscopy-based complete response, partial response, or stable disease; ctDNA, circulating tumor DNA; EV, enfortumab vedotin; gem, gemcitabine; ICI, immune checkpoint inhibitor; LN+, lymph node–positive; NAC, neoadjuvant chemotherapy; nivo, nivolumab; RC, radical cystectomy; RT, radiation therapy; Tx, treatment; y, year.

concurrent chemotherapy/RT.[61] Unfortunately, the study was terminated early because of slow accrual. This study could have paved the way for a new treatment paradigm for patients with LN+ bladder cancer. ANZUP 1502 showed the feasibility of combining ICI treatment with chemoradiation in MIBC (T2-4, N0, M0), with manageable toxicity and a promising CR rate of 88%. However, this study did not include any patients with node-positive disease.[62] Similarly, phase 3 studies are evaluating the role of ICI treatment in combination with chemoradiation in patients with non–node-negative MIBC (MK-3475-992/KEYNOTE 992 study, SWOG S1806 study). The results of these studies may guide the design of future studies in regional LN+ disease as well.[63]

Biomarkers

In the continually evolving landscape of cancer diagnostics and therapeutics, the identification of reliable biomarkers remains a cornerstone for patient stratification and treatment optimization. Unlike in lung cancer, PD-L1 has not been a consistent predictive biomarker in bladder cancer. Tumor characteristics such as ERBB2 positivity, *FGFR* mutation, tumor mutation burden, and microsatellite instability have appeared to be of prognostic value in advanced bladder cancer. The predictive and prognostic biomarker ctDNA is emerging as a revolutionary biomarker that promises to redefine our approach to the management of bladder cancer.

Derived from a minimally invasive blood draw, ctDNA serves as a surrogate marker for tumor burden. It provides invaluable insights into the detection of disease recurrence, prediction of treatment response, and monitoring of ongoing response. Christensen and colleagues conducted a pivotal study involving 68 patients with localized advanced bladder cancer and highlighted the utility of ctDNA for early risk stratification, therapy monitoring, and early relapse detection.[64]

Further cementing the relevance of ctDNA was the IMvigor010 trial, a randomized phase 3 study comparing adjuvant atezolizumab vs placebo in operable urothelial cancer.[65] Although the trial did not meet its primary endpoints, its exploratory analysis revealed a critical finding: patients who were ctDNA-positive had a significantly poor prognosis. Markedly improved DFS and OS were observed among patients treated with atezolizumab vs placebo (for DFS: HR, 0.58; 95% CI, 0.43-0.79; for OS: HR, 0.59; 95% CI, 0.41-0.86).[64] Intriguingly, no such survival advantage was observed in patients who were ctDNA-negative. At a median follow-up of 36 months,

ctDNA clearance or reduction occurred at higher rates with atezolizumab vs observation. The implications of these findings are profound. The IMvigor010 trial unequivocally demonstrated that ctDNA has the potential to serve not only as a prognostic biomarker but also as a predictive tool for treatment response in UC. We need to await the results of ctDNA-based treatment from the key ongoing studies of IMvigor011, Alliance A032103 (MODERN), and TOMBOLA (NCT04138628). In addition to paving the way for tailoring treatment, the ctDNA biomarker could be used in monitoring patients with LN+ bladder cancer.

Conclusion

Localized or regional node-positive bladder cancer (any T, N1-3, M0) presents a unique clinical challenge, requiring a comprehensive and multifaceted treatment approach that currently lacks standardized guidelines. This heterogeneity in treatment strategies can be attributed to the limited availability of prospective data and the adaptation of treatment paradigms from MIBC and metastatic bladder cancer. It is crucial to note that patients with localized N1-3, and especially N2-3, LN+ bladder cancer are underrepresented in clinical trials. Our proposed algorithm summarizes the possible treatment for localized LN+ bladder cancer (Figure). Currently endorsed treatments for localized LN+ bladder cancer span a broad spectrum of options. However, the backbone of treatment includes systemic therapy. RC in combination with NAC, either with or without AC, and trimodal therapy that aims for bladder preservation could be reasonable treatment options in selected patients. When postsurgical pathology indicates T3-4 or pN+ disease, AC should be considered. Unfortunately, studies focusing solely on RC have yielded less favorable outcomes in this patient group. In cases in which cystectomy or definitive chemoradiotherapy is not feasible, RT alone may be considered as a last-resort option to mitigate locoregional recurrence and preserve bladder function. ICIs combined with RT need further evaluation in larger studies for patients with localized LN+ disease. Results from the MK-3475-992/KEYNOTE 992 study and the SWOG S1806 study could guide future trial designs. Importantly, the available evidence highlights that although local therapies like RC and RT are not sufficient as standalone treatments for localized LN+ bladder cancer, they can significantly improve outcomes when integrated into a multimodal approach involving systemic chemotherapy. Additionally, with emerging biomarkers such as ctDNA, it is possible that systemic therapy alone could result in durable responses and improved survival in patients with localized LN+ bladder cancer. The data for the use of fibroblast growth factor receptor–directed therapies in localized LN+ MIBC are insufficient, but ongoing studies may pave the way for incorporating these in this unique cohort of patients. The complexity and diversity of treatment options emphasize the need for a multidisciplinary team approach to optimize patient outcomes. Current clinical practices offer valuable insights, and ongoing clinical trials are expected to reveal the best treatment sequences and potentially curative strategies for this complex and rare condition. The field looks forward to new insights that could improve the management of node-positive bladder cancer.

Disclosures

Drs Polimera, Bhatia, Wheelden, Perimbeti, and Warrick have no conflicts of interest. Dr Joshi has served on the advisory boards of Seagen and Gilead; has received research funds to her institution from AstraZeneca and Bristol Meyers Squibb; has received travel and accommodation from Dava Oncology and Caris Life Sciences; and has presented an educational talk on bladder cancer to Curio Science. She has no conflicts of interest for this manuscript.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. *Med Sci (Basel)*. 2020;8(1):15.
3. Bruins HM, Dorin RP, Rubino B, et al. Critical evaluation of the American Joint Committee on Cancer TNM nodal staging system in patients with lymph node-positive disease after radical cystectomy. *Eur Urol*. 2012;62(4):671-676.
4. Reitblat C, Bellmunt J, Gershman B. Management of clinically regional node-positive urothelial carcinoma of the bladder. *Curr Oncol Rep*. 2021;23(2):24.
5. Galsky MD, Stensland K, Sfakianos JP, et al. Comparative effectiveness of treatment strategies for bladder cancer with clinical evidence of regional lymph node involvement. *J Clin Oncol*. 2016;34(22):2627-2635.
6. Shankar PR, Barkmeier D, Hadjiiski L, Cohan RH. A pictorial review of bladder cancer nodal metastases. *Transl Androl Urol*. 2018;7(5):804-813.
7. Venkatesulu B, Liauw SL, Joshi M, et al. Multidisciplinary management and radiotherapy recommendations for clinically and pathologically node-positive bladder cancer. *Semin Radiat Oncol*. 2023;33(1):35-50.
8. Fajkovic H, Cha EK, Jeldres C, et al. Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis. *Eur Urol*. 2013;64(5):837-845.
9. Holzbeierlein J, Bixler BR, Buckley DI, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/SUO guideline (2017; Amended 2020, 2024). *J Urol*. 2024;212(1):3-10.
10. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349(9):859-866.
11. Meijer RP, Nieuwenhuijzen JA, Meinhardt W, et al. Response to induction chemotherapy and surgery in non-organ confined bladder cancer: a single institution experience. *Eur J Surg Oncol*. 2013;39(4):365-371.
12. Ploussard G, Pradere B, Beauval JB, et al. Survival outcomes of patients with pathologically proven positive lymph nodes at time of radical cystectomy with or without neoadjuvant chemotherapy. *J Clin Med*. 2020;9(6):1962.
13. Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: the M.D. Anderson Cancer Center Experience. *Urol Oncol*. 2016;34(2):59.e1-8.
14. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol*. 2014;65(2):350-

357. doi:10.1016/j.eururo.2013.06.049
15. Dimopoulos MA, Finn L, Logothetis CJ. Pattern of failure and survival of patients with metastatic urothelial tumors relapsing after cis-platinum-based chemotherapy. *J Urol*. 1994;151(3):598-600; discussion 600-1.
16. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol*. 2001;165(3):811-814. doi:10.1016/S0022-5347(05)66533-0
17. Sood A, Keeley J, Palma-Zamora I, et al. High-intensity local treatment of clinical node-positive urothelial carcinoma of the bladder alongside systemic chemotherapy improves overall survival. *Urol Oncol*. 2022;40(2):62.e1-e11.
18. Bellmunt J, Ribas A, Eres N, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer*. 1997;80(10):1966-1972.
19. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol*. 2014;66(1):42-54.
20. Advanced Bladder Cancer (ABC) Meta-analysis Collaborators Group. Adjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and meta-analysis of individual participant data from randomised controlled trials. *Eur Urol*. 2022;81(1):50-61.
21. Galsky MD, Stensland KD, Moshier E, et al. Effectiveness of adjuvant chemotherapy for locally advanced bladder cancer. *J Clin Oncol*. 2016;34(8):825-832.
22. Berg S, D'Andrea D, Vetterlein MW, et al. Impact of adjuvant chemotherapy in patients with adverse features and variant histology at radical cystectomy for muscle-invasive carcinoma of the bladder: does histologic subtype matter? *Cancer*. 2019;125(9):1449-1458.
23. Afferi L, Lonati C, Montorsi F, et al; European Association of Urology Young Academic Urologists Urothelial Carcinoma Working Group. Selecting the best candidates for cisplatin-based adjuvant chemotherapy after radical cystectomy among patients with pN+ bladder cancer. *Eur Urol Oncol*. 2022;5(6):722-725.
24. Pfister C, Gravis G, Fléchon A, et al; VESPER Trial Investigators. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: results of the GETUG-AFU V05 VESPER Trial. *J Clin Oncol*. 2022;40(18):2013-2022.
25. Kassouf W, Agarwal PK, Grossman HB, et al. Outcome of patients with bladder cancer with pN+ disease after preoperative chemotherapy and radical cystectomy. *Urology*. 2009;73(1):147-152.
26. Seisen T, Jamzadeh A, Leow JJ, et al. Adjuvant chemotherapy vs observation for patients with adverse pathologic features at radical cystectomy previously treated with neoadjuvant chemotherapy. *JAMA Oncol*. 2018;4(2):225-229.
27. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Bladder cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Updated May 9, 2024.
28. Rödel C, Grabenbauer GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol*. 2002;20(14):3061-3071.
29. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*. 1998;16(11):3576-3583.
30. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist*. 2000;5(6):471-476.
31. Hagan MP, Winter KA, Kaufman DS, et al. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. *Int J Radiat Oncol Biol Phys*. 2003;57(3):665-672.
32. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. 2009;73(4):833-837.
33. Mitin T, Hunt D, Shipley WU, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. *Lancet Oncol*. 2013;14(9):863-872.
34. Coen JJ, Zhang P, Saylor PJ, et al. Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712-a randomized phase II Trial. *J Clin Oncol*. 2019;37(1):44-51.
35. James ND, Hussain SA, Hall E, et al; BC2001 Investigators. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012;366(16):1477-1488.
36. Efstathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol*. 2009;27(25):4055-4061.
37. Haque W, Verma V, Butler EB, Teh BS. Chemotherapy versus chemoradiation for node-positive bladder cancer: practice patterns and outcomes from the National Cancer Data Base. *Bladder Cancer*. 2017;3(4):283-291.
38. Tan MP, Harris V, Warren-Oseni K, et al. The Intensity-Modulated Pelvic Node and Bladder Radiotherapy (IMPART) trial: a phase II single-centre prospective study. *Clin Oncol (R Coll Radiol)*. 2020;32(2):93-100.
39. Swinton M, Mariam NBG, Tan JL, et al. Bladder-sparing treatment with radical dose radiotherapy is an effective alternative to radical cystectomy in patients with clinically node-positive nonmetastatic bladder cancer. *J Clin Oncol*. 2023;41(27):4406-4415.
40. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med*. 2021;384(22):2102-2114.
41. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(3):312-322.
42. Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
43. Apolo AB, Ellerton JA, Infante JR, et al. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN solid tumor study: 2-year updated efficacy and safety analysis. *J Immunother Cancer*. 2020;8(2):e001246.
44. Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389(10064):67-76.
45. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2018;391(10122):748-757.
46. Powles T, van der Heijden MS, Castellano D, et al; DANUBE study investigators. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2020;21(12):1574-1588.
47. Apolo AB, Ballman KV, Sonpavde GP, et al. AMBASSADOR Alliance A031501: phase III randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma (MIUC) vs observation [ASCO GU abstract LBA531]. *J Clin Oncol*. 2024;42(4)(suppl).
48. Bellmunt J, Hussain M, Gschwend JE, et al; IMvigor010 Study Group. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(4):525-537.
49. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2000;18(17):3068-3077.
50. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012;30(2):191-199.
51. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383(13):1218-1230.
52. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 trial after ≥2 years of follow-up. *J Clin Oncol*. 2023;41(19):3486-3492.
53. Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38(16):1797-1806.

54. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(11):1483-1492.
55. Powles T, Csőszi T, Özgüroğlu M, et al; KEYNOTE-361 Investigators. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(7):931-945.
56. Galsky MD, Arija JAA, Bamias A, et al; IMvigor130 Study Group. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395(10236):1547-1557.
57. Powles T, Valderrama BP, Gupta S, et al; EV-302 Trial Investigators. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390(10):875-888.
58. van der Heijden MS, Sonpavde G, Powles T, et al; CheckMate 901 Trial Investigators. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med*. 2023;389(19):1778-1789.
59. Galsky MD, Sonpavde GP, Powles T, et al. Characterization of complete responders to nivolumab + gemcitabine-cisplatin vs gemcitabine-cisplatin alone and patients with lymph node–only metastatic urothelial carcinoma from the CheckMate 901 trial [ASCO abstract 4509]. *J Clin Oncol*. 2024;42(16)(suppl).
60. Joshi M, Tuanquin L, Zhu J, et al. Concurrent durvalumab and radiation therapy (DUART) followed by adjuvant durvalumab in patients with localized urothelial cancer of bladder: results from phase II study, BTCRC-GU15-023. *J Immunother Cancer*. 2023;11(2):e006551.
61. Joshi M, Kim SE, Solanki AA, et al. EA8185: phase II study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node-positive urothelial carcinoma (INSPIRE), ECOG-ACRIN/nrg collaboration [ASCO GU abstract TPS500]. *J Clin Oncol*. 2021;39(6)(suppl).
62. Weickhardt A, Foroudi F, Lawrentschuk N, et al. Pembrolizumab with chemoradiation as treatment for muscle-invasive bladder cancer: analysis of safety and efficacy of the PCR-MIB phase 2 clinical trial (ANZUP 1502). *Eur Urol Oncol*. 2024;7(3):469-477.
63. Tissot G, Xylinas E. Efficacy and safety of pembrolizumab (MK-3475) in combination with chemoradiotherapy versus chemoradiotherapy alone in muscle-invasive bladder cancer: the MK-3475-992/KEYNOTE-992 trial. *Eur Urol Focus*. 2023;9(2):227-228.
64. Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol*. 2019;37(18):1547-1557.
65. Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature*. 2021;595(7867):432-437.