Review Article

Perioperative therapy in muscle invasive bladder cancer

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ABSTRACT

Radical cystectomy with bilateral pelvic lymph node dissection is the standard of care for muscle invasive bladder cancer (MIBC). The role of neoadjuvant and adjuvant therapy has evolved over the last 3–4 decades, and neoadjuvant chemotherapy (NACT) has now become the standard recommended treatment. However, there are many nuances to this and the utilization of chemotherapy has not been universal. The optimum chemotherapy regimen is still debated. Adjuvant radiation has a role in high-risk patients although not established and immunotherapy has shown promising results. We reviewed the evidence on NACT and adjuvant chemotherapy (ACT) regimens, NACT versus ACT, and the role of adjuvant radiotherapy and immunotherapy in MIBC.

INTRODUCTION

Cancers of urothelial lining can arise anywhere from renal pelvicalyceal system to proximal urethra. Nearly all cases of urothelial carcinoma (UC) are urinary bladder cancers (BCs), whereas upper tract urothelial cancer accounts for 5%–10% of all urothelial malignancies. Worldwide, BC is the 10th most-common cancer, sixth most-common cancer in men, and ninth most-common cause of cancer-related deaths.[1] Radical cystectomy (RC) and bilateral pelvic lymph node dissection are the standard of care for muscle invasive BC (MIBC). While the surgical management of this cancer has remained the same for the last 3–4 decades, evidence exploring the role of perioperative therapy has been evolving. This article compiles the established and evolving evidence favoring neoadjuvant and adjuvant systemic (chemo and immuno) therapy, trends and hurdles in its utilization, and rationale and ongoing research exploring the role of adjuvant radiotherapy (RT) in urothelial cancer.

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METHODOLOGY

The literature search was performed for a narrative review. The electronic search included a PubMed database using MeSH terms: "bladder cancer," "urothelial cancer," "neoadjuvant chemotherapy," "adjuvant chemotherapy," "immunotherapy," and "radiotherapy." The inclusion criteria were randomized controlled trials, ongoing trials, systematic reviews and meta-analyses, and selected retrospective analyses related to the above terms. The exclusion criteria were articles that were not in English. From the articles retrieved in the first round of search, additional references were identified by a manual search among the cited references. Each article was critically evaluated for key results, limitations, quality of the results, interpretation of the results, and impact of the conclusions in the field.

DRUG REGIMENS FOR NEOADJUVANT CHEMOTHERAPY

The choice of regimen differs across institutions and depends primarily on the patients' performance status and glomerular

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filtration rate (GFR) [Table 1]. For cisplatin-ineligible candidates, there are no data to support a recommendation for perioperative chemotherapy. Carboplatin should not be substituted for cisplatin in the perioperative setting.[2] Neoadjuvant chemotherapy (NACT) is preferred over adjuvant chemotherapy (ACT) with a higher level of evidence. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) regimen is preferred over classic MVAC based on evidence from metastatic or advanced disease where it was better tolerated and more effective than classic MVAC.[3,4] Gemcitabine-Cisplatin (GC) regimen is an alternative to dd-MVAC based on evidence from metastatic or locally advanced disease which showed equivalence to classic MVAC.[5,6] The preliminary results of a recently conducted phase III trial (GETUG/AFU V05 VESPER trial) were presented in ASCO GU 2020.[7] The trial compared four cycles of GC with six cycles of dd-MVAC as perioperative chemotherapy for MIBC patients. The trial showed that pathological complete responses (pCRs) and organ-confined diseases were more frequently observed in the dd-MVAC arm (42% vs. 36% [$P = 0.02$]). However, it should be noted that the primary end point of this study is 3-year progression-free survival (PFS), which has not been reported yet. The toxicities were manageable in both the groups with more severe asthenia and gastrointestinal side effects in the dd-MVAC arm. The results are intriguing, but we need to wait for the final results before changing our practice.

NEOADJUVANT CHEMOTHERAPY IN MUSCLE INVASIVE BLADDER CANCER

The risk of local recurrence and distant failures in BC is dependent on the grade and stage of the tumor. In case of MIBC, the predominant cause of distant failures is occult micrometastatic disease. NACT has advantages through treatment of occult micrometastatic disease, downstaging and making local therapy more effective, increase in pT0 rates which translates into survival benefit, assessing disease biology and response to chemotherapy, and assessing patient's tolerance to chemotherapy.

Table 1: Chemotherapy regimens

Agents	Schedule
Classic MVAC	Methotrexate (30 mg/m^2 on D1, D15, and D22) Vinblastine (3 mg/m^2 on D2, D15, and D22) Doxorubicin (30 mg/m^2 on D2) Cisplatin (70 mg/m^2 on day D2) Repeated every 28 days for three cycles
DD-MVAC	Methotrexate (30 mg/m^2 on D1) Vinblastine (3 mg/m^2 on D2) Doxorubicin (30 mg/m^2 on D2) Cisplatin (70 mg/m^2 on D2) Filgrastim (240 mcg/m^2 subcutaneously on D4-D10) Repeated every 14 days, if toxicity permits, for 3-4 cycles
GC	Gemcitabine (1000 mg/m^2 on D1, D8, D15) Cisplatin (70 mg/m^2 on D2) Given every 28 days for a maximum of six cycles
CMV	Methotrexate (30 mg/m^2) Vinblastine (4 mg/m^2) on D1 and D8 Cisplatin (100 mg/m^2 on D2) Leucovorin (15 mg every 6 h for four doses) on D2 and D9 Repeated every 28 days for three cycles

MVAC=Methotrexate, vinblastine, doxorubicin, and cisplatin, DD-MVAC=Dose-dense MVAC, GC=Gemcitabine and cisplatin, CMV=Cisplatin-methotrexate and vinblastine

Randomized control trials

SWOG-8710 Study, JCOG-0209 Study, and International Collaboration of Trialists Study[8-10] were three multicenter phase III randomized control trials (RCTs) [Supplementary Table 1] that evaluated the role of NACT in MIBC. The SWOG-8710 Study showed that NACT was associated with overall survival (OS) and Disease-Specific Survival (DSS) benefit, and it reduced the risk of death by 33%. The JCOG-0209 Study[9] concluded that NACT is associated with OS and PFS benefit, significant pCR rates, and less lymphatic leaks and acceptable toxicity. However, the trial was terminated early due to slow accrual. The International Collaboration of Trialists Study[10] showed that NACT was associated with statistically nonsignificant improvement in 3-year OS. Patients with NACT had 15% and 13% decrease in risk of death and locoregional disease, respectively. There was statistical significant improvement in 3-year metastasis-free survival (21% decrease in risk of metastases). NACT arm had higher pCR rates with no increase postoperative complications.

Griffiths *et al.* published the long-term results of International Collaboration of Trialists Study[11] in 2011. The data had matured with a median follow-up of 8 years. The authors concluded that NACT was associated with 3-year and 10-year OS benefit (50% vs. 56% and 30% vs. 36%, respectively), with 16% reduction in risk of death (hazard ratio: 0.84; 95% confidence interval: 0.72–0.99; $P = 0.037$), 18% reduction in risk of disease ($P = 0.008$), 23% reduction in risk of metastases ($P = 0.001$), 13% reduction in local disease ($P = 0.067$) and 4% reduction in risk of locoregional relapse ($P = 0.632$), and median survival improvement of 7 months (37–44 months).

Meta-analysis

Advanced Bladder Cancer (ABC) meta-analysis collaboration group[12] analyzed 3005 individual patients' data (IPD) from 11 RCTs that compared NACT and local treatment versus local treatment alone. They found a statistically significant 5-year OS and DFS benefit with platinum-based combination NACT; 5% and 9% absolute improvement in OS (from 45% to 50%) and DFS, and 14% reduction in the risk of death with NACT. There was a statistically significant difference in the effect of chemotherapy between groups of single-agent (SA) and platinum-based combination NACT regimen favoring combination NACT ($P = 0.024$). The evidence was not sufficiently reliable to determine the effect of SA cisplatin on survival.

Winquist *et al*.[13] identified 3315 patients from 16 RCTs, and four review articles (which included three meta-analyses) on NACT for locally advanced BC. The stage of the disease varied from T1G3 to T4b (majority had T2–T4a), Nx to N2. The NACT regimens used were SA cisplatin, cisplatin-methotrexate (CM), cisplatin-doxorubicin, CMV, or MVAC, and the number of planned cycles ranged from 2 to 4. The local therapy included cystectomy, definitive RT, RT + cystectomy, or chemoradiation (CTRT). The largest among the 16 RCTs was the one published by the International Collaboration of Trialists.[10] The authors concluded that NACT was associated with statistical significant improvement in OS (P = 0.02) and PFS with 5% absolute improvement in OS (50%–55%) and 10% decrease in risk of death. Combination NACT had significant OS benefit (P = 0.006) with 13% decrease in the risk of death and 6.5% absolute improvement in OS (50%–56.5%). SA chemotherapy did not show significant survival benefit (P = 0.41). The pCR rates with combination NACT was 14%–38% while pathological "major response" (pT0, pTis, pTa/pT1) was seen in 33.9% (SA chemo) to 43.1% (MVAC) patients.

ADJUVANT CHEMOTHERAPY

The data on ACT are less robust; trials have been either inadequately powered, closed prematurely due to slow accrual or remained unpublished. The theoretical advantages of ACT over NACT include early definitive treatment, availability of accurate pathological staging and prognostic factors, and avoiding overtreatment to clinically over-staged patients.

Disadvantage of adjuvant chemotherapy

Only 50% of patients who are proposed to receive ACT actually receive it due to low GFR, older age, poor ECOG status, comorbidities, and refusals.

Randomized controlled trials

EORTC-30994 Intergroup Trial, Italian Trial, and Spanish (SOGUG-99/01) Trial[14-16] were three phase III RCTs evaluating the role of cisplatin-based combination chemotherapy (CCC) ACT [Supplementary Table 2]. The EORTC-30994 trial showed that ACT benefits patients who have not received NACT with nonsignificant improvement in OS and significant improvement in PFS. Combining the analysis of this trial with two other trials (Italian[15] and Spanish[16] Cooperative Groups) and with the updated results of Leow *et al*.,[17] there was an overall benefit with ACT (P = 0.002).

Meta-analysis

Advanced BC meta-analysis[18] analyzed IPD from six trials (491 patients) which represented 90% of all patients randomized in CCC trials. All the patients were administered CCC and the choice of local treatment was cystectomy. The meta-analysis concluded that ACT was associated with 25% decrease in the risk of death (29% for CCC) (P = 0.019), 9% absolute improvement in 3-year OS (11% for CCC), 32% decrease in risk of recurrence (38% for CCC) (P = 0.004), and 12% absolute improvement in 3-year DFS. This meta-analysis had analyzed IPD and was hence able to answer some criticism of the individual trials, as all the individual trials were underpowered with major criticism against their design, analysis, and reporting.

Ruggeri *et al*.[19] analyzed five phase III RCTs and extracted data to analyze OS (350 patients) and DFS (273 patients). The authors found a significant OS and DFS benefit with ACT. The absolute benefit in 5-year OS and DFS was 11% and 16%, respectively. For OS and DFS benefit of one patient, the number needed to treat (NNT) was nine and six, respectively. The limitations of this meta-analysis were that trials analyzed were old, with problems in their design, accrual, and when analyzed individually, all trials had questionable conclusions. The numbers were too small to sustain ACT as a standard practice (required data of >1000 patients to be reliable). Chemotherapy given in few trials was not standard and was inferior in terms of response rates and survival. There was clinical heterogeneity among trials with respect to surgical technique, chemotherapy regimen, and patient selection (i.e., lymph node status).

The 2013 Updated Systemic Review and Meta-analysis of Randomized Trials[17] was built on the 2005 Cochrane meta-analysis,[20] which previous published as ABC meta-analysis[18] and incorporated additional RCTs published after 2005 (ACT arm: 475 patients, control arm: 470 patients). The inclusion criteria were ≥pT2, N0/N+ M0, except the RCT by Stadler *et al*.[21] and Studer *et al*.[22] which included pT1 patients also. The primary and secondary outcomes were OS and DFS, respectively. The meta-analysis concluded that ACT was associated with 23% decrease in risk of death (P = 0.049), 34% decrease in risk of recurrence (P = 0.014), and greater absolute DFS benefit in pN+ (hazard ratio HR =0.39). This updated meta-analysis had greater statistical power due to inclusion of additional trials and improved statistical methods. The flaws of this meta-analysis were small sample size across nine trials with heterogeneity among them (n = 945), methodological flaws in their trials, difference in chemotherapy regimens, eligibility criteria, DFS definitions and time to randomization across trials, and lack of information on the T stage across trials.[21,22]

The 2017 Systematic Review and Network Meta-analysis of Randomized Clinical Trials[23] assessed the optimal ACT regimen for improving survival outcomes with data obtained from 1546 patients from 11 RCTs (1995–2015). The primary and secondary end points were PFS and OS, respectively. The authors found that ACT improved PFS and OS by 36% and 21%, respectively. Among ACT regimens, CMV and Paclitaxel-Gemcitabine-Cisplatin (PGC) had significant PFS benefit and PGC had significant better

OS as compared to controls. The positive aspects of these trials were that it included only prospectively designed RCTs with consistent number and dose-specific regimens. However, it was limited by enrolling studies across several decades (1990s–2010s), resulting in different ACT regimens, different baseline characteristics (pT1-pT2/N0 to pT3-pT4/N+), and hence different survival outcomes. Some trials were underpowered (small sample size, difficult patient accrual, early termination, and statistical flaws).

The 2019 Systematic Review and Meta-Analysis of Randomized Trials[24] evaluated the role of ACT in locally advanced MIBC (pT3/pT4 and/or pN+) from four RCTs.[14,25-27] The meta-analysis concluded that ACT was associated with significant PFS and OS benefit.There was 17% and 10% absolute increase in PFS (NNT = 5.9; $P < 0.00001$) and OS (NNT = 10; $P = 0.0009$), respectively, and 52% and 48% relative risk reduction in progression and death, respectively. However, when pT2 was included, ACT had marginal OS benefit (4% increase; NNT = 25). The strength of this meta-analysis was that it focused only on locally advanced disease, whereas it was limited by flaws in methodology and design of the trials (definitions of PFS and OS, early termination).

TRENDS IN UTILIZATION OF PERIOPERATIVE CHEMOTHERAPY

Despite statistical significant survival benefit, the utilization of perioperative chemotherapy has historically been poor due to the following commonly cited reasons:[28-30]

i. Lack of knowledge and motivation physicians and surgeons
ii. Treatment in low-volume centers and nonacademic facilities
iii. Lack of multidisciplinary tumor (MDT) clinics
iv. Patients' ineligibility for cisplatin, poor performance status (PS), advanced age.
v. Patients declining chemotherapy
vi. Geographical location, accessibility, and socioeconomic status.

Booth *et al.*[28] studied the uptake of perioperative chemotherapy (NACT and ACT) and medical oncology (MO) referral patterns among 5582 MIBC patients who had undergone cystectomy. The use of NACT increased significantly from 4% (1994–2008) to 27% (2013). The use of ACT has remained constant between 19% (1994–2008) and 20% (2009–2013). There was increase in referral rates to MO during 2009–2013 as compared to 1994–2008 (32% vs. 11%) and continued to increase in recent years (44% in 2013). The proportion of referred patients treated with NACT increased significantly, from 32% (1994–1998) to 54% (2009–2013) ($P < 0.001$).

Duplisea *et al.*[29] examined the trends of utilization of NACT among 18,188 patients who underwent cystectomy from the National Cancer Database from 2006 to 14. 21.7% of patients received NACT and its use increased from 9.7% (2006) to 32.2% (2014). Reardon *et al.*[30] studied the temporal changes in utilization of perioperative chemotherapy from 5692 MIBC patients' data who underwent RC for ≥ cT2N0M0 between 2006 and 2010. The use of perioperative chemotherapy increased from 29.5% (2006) to 39.8% (2010) and the use of NACT significantly increased from 10.1% (2006) to 20.8% (2010). The use of ACT remained stable between 18.1% and 21.3% ($P = 0.68$).

Martini *et al.*[31] prospectively analyzed 235 patients' data from the PROMETRICS 2011 database.Only 2.2% of patients received NACT; in 69% of cases the decision was made by individual clinicians, and only 29% of cases were discussed in MDT. Sixty-nine percent of urologists declared that tumor stage cT3-T4/N1M0 was the best indication for NACT.

Data from Tata Memorial Hospital[32] showed that the utilization of NACT has increased from 27.7% (2014) to 60% (2019) ($P < 0.01$). These figures show that the utilization of NACT has increased than that in Western literature.

NEOADJUVANT CHEMOTHERAPY VERSUS ADJUVANT CHEMOTHERAPY

Retrospective data comparing the outcomes of NACT and ACT[33] of 687 patients from single institution (1988–2009) showed that the utilization of perioperative chemotherapy was 21%. Out of 146 patients who received chemotherapy (50% NACT/ACT each) for locally advanced MIBC, CCC was given to 83.6% of patients, while remaining received carboplatin-based chemotherapy. Majority of patients on CCC received MVAC (64.8%), while remaining received GC (35.2%). The median follow-up was 12.8 months for NACT and 14 months for ACT. The primary end points analyzed were DSS and OS. The study concluded that there was no significant difference in DSS ($P = 0.46$) and OS ($P = 0.76$). In CCC group, there were no significant differences in DSS and OS. There was no significant difference in DSS ($P = 0.555$) and OS ($P = 0.573$) between NACT-MVAC and ACT-MVAC (median survival: 16 months vs. 22 months). There was significant difference in DSS between NACT-GC and ACT-GC ($P = 0.049$), with no significant difference in OS (median survival 11 months vs. 16 months) ($P = 0.607$). In carboplatin-based group, there was no significant difference between NACT and ACT with respect to DSS and OS and CCC was a significant predictor of improved OS and DSS ($P \leq 0.001$). The drawbacks of this study were retrospective nature, single-center data, heterogeneous population, different chemotherapy regimen, no record of comorbidity, performance status, complication rates, recurrence, and the follow-up period being short. There are some data to suggest that ACT post-NACT and RC might lead to OS benefit in patients with pT3/T4 and/or pN+.[34] However, such strategy is not suggested to be a

routine clinical practice as there are no randomized data to support the same.

RADIOTHERAPY

The 5-year survival rates post-RC + PLND for pT2 and pT3 diseases are 60% and 10%–50%, respectively.[35] Pelvic recurrences in locally advanced MIBC range from 32% to 58%.[8,11] Locoregional recurrence (LRR) is associated with metastasis and locoregional control improves oncologic end points.[36,37] Salvage treatment is rarely successful with a median survival of only 9 months.[36,38] Perioperative chemotherapy does not reduce LRR.[39] Factors affecting LRR are pT3, N+, PLND, number of nodes dissected, positive surgical margin, hospital volume, and risk groups.[39,40] The University of Pennsylvania developed a risk stratification model to predict LRR[39] and subsequently has been validated in several studies.[41-44] These facts suggest a potential role of adjuvant RT in high-risk MIBC patients. The data on adjuvant RT are not yet robust and await the results from ongoing trials (NRG, GETUG-AFU, Tata Memorial Hospital, NCRI, University of Ghent, and NCI Cairo). At present, the NCCN guidelines recommends adjuvant RT for ≥pT3 and N+ disease.[2]

Number of RCTs conducted by Zaghloul *et al.*[45-49] has evaluated the role of postoperative RT (PORT) for MIBC or locally advanced disease [Supplementary Table 3]. Studies have concluded that in high-risk patients, PORT or adjuvant CTRT reduces LR and DFS without significant improvement in OS. However, these studies included majority of squamous carcinoma patients and their applicability to UC (the most common type worldwide) needs further study. A retrospective multicenter study for adjuvant RT in MIBC was conducted by Orré *et al.*[50] [Supplementary Table 3F]. The study concluded that PORT is feasible in high-risk MIBC with oncological benefits and acceptable toxicities, and neobladders can tolerate moderate doses of RT without significant morbidity.

In a systematic review and meta-analysis on RT with RC, McAlpine *et al.*[51] evaluated the efficacy and safety of RT as neoadjuvant and adjuvant modality in MIBC patients undergoing RC. The study concluded that there was statistically nonsignificant improvement in OS with NART and there was improved OS with PORT in locally-advanced disease. This article had numerous limitations at individual study level and review level which is beyond the scope of our discussion.

Adjuvant RT to bladder bed and nodal basins renders the bowel at risk of radiation-induced injury, a condition called pelvic radiation disease (PRD) which encompasses radiation enteritis and radiation proctitis. PRD can present in three clinical phases: acute, chronic, and delayed (latent). PRD increases the risk of bowel wall strictures, adhesions, fissures, bleeding, and perforation. PRD may also cause acute or subacute small bowel obstruction. Concurrent chemotherapy can delay the reparative process, thus aggravating the condition.[52]

Table 2: ABACUS and PURE-01 studies

Salient Features	ABACUS study[59]	PURE-01 study[58]
Study design	Single-arm Phase II RCT to establish efficacy, safety and biomarker signals	Single-arm Phase II
Method	2 cycles atezolizumab (1200 mg) ×3 weekly followed by RC	3 cycles pembrolizumab (200 mg) every 3 weeks followed by RC
Sample size	95	50
Eligibility criteria	cT2-T4aN0M0 ECOG 0-1 Adequate hematologic and end-organ function Ineligible or refusal of cisplatin-based NACT	cT2-T3bN0M0 ECOG 0-2 GFR≥20 ml/min Regardless of their cisplatin eligibility
Duration	May 2016-June 2018	February 2017-March 2018
Median follow-up (months)	13.1	6.2
Primary endpoint	pCR	pCR
Secondary endpoint	Safety, RFS and biomarker analysis	Down-staging to<pT2
Median time to surgery	5.6 weeks	22 days
Overall pCR rate	27/88 (31%)	21/50 (42%) Down-staging to<pT2: 27/50 (54%)
1 year RFS	79%	-
Grade 3/4 surgical complications	15/87 (17%)	15/50 (30%)
Grade 3/4 AEs	10/95 (11%)	3/50 (6%)
PD-L1-positive patients	35/88 (40%) No significant correlation between PD-L1 expression and outcome, on either immune cells or tumor cells (P>0.05)	35/50 (70%) 54.3% patients with PD-L1 CPS≥10% had pT0 compared to 13.3% patients with CPS<10% (P=0.001)
TMB	The pCR rate was not increased in TMB-high (≥10 mutations/Mb; 31%) tumors	TMB score≥15 mutations/Mb in pretreatment tumors predicted high pCR rate

RFS=Relapse-free survival, CPS=Combined positive score, TMB=Tumor mutational burden, RCT=Randomized control trials, RC=Radical cystectomy, NACT=Neoadjuvant chemotherapy, GFR=Glomerular filtration rate, pCR=Pathological complete responses, AE=Adverse events, PD-L1=Programmed cell death-1 protein ligand, ECOG=Eastern Cooperative Oncology Group

Table 3: International Guideline Recommendations

Guidelines	Recommendations
NACT	
EAU 2019 guidelines[61]	Offer NACT for T2-T4a, cN0M0 disease. Always use cisplatin-based combination therapy (strong) Do not offer NACT to patients who are ineligible for cisplatin-based combination chemotherapy (strong) Only offer neoadjuvant immunotherapy to patients within a clinical trial setting (strong)
NCCN guidelines Version 5.2020[2]	Neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (Category 1) OR Radical cystectomy alone for those not eligible to receive cisplatin-based chemotherapy OR Concurrent chemoradiatherapy (Category 1)
AUA guidelines 2017[62]	Offer cisplatin-based NACT to eligible radical cystectomy patients prior to cystectomy (strong recommendation; evidence level: Grade B) Clinicians should not prescribe carboplatin-based NACT for clinically resectable stage cT2-T4aN0 BC. Patients ineligible for cisplatin-based NACT should proceed to definitive locoregional therapy (expert opinion)
ACT	
EAU 2019 guidelines[61]	Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/T4 and/or pN+disease if no NACT has been given (strong) Offer immunotherapy with a checkpoint inhibitor only in a clinical trial setting (strong)
NCCN guidelines Version 3.2020[2]	Based on pathologic risk (pT3-4, or positive nodes or positive margins), consider adjuvant cisplatin-based chemotherapy or consider adjuvant RT (Category 2B) if no neoadjuvant treatment given
AUA guidelines 2017[62]	Eligible patients who have not received cisplatin-based NACT and have nonorgan confined (pT3/T4and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. (moderate recommendation; evidence level: Grade C)

NACT=Neoadjuvant chemotherapy, RT=Radiotherapy, BC=Bladder cancer, ACT=Adjuvant chemotherapy, EAU=European Association of Urology, NCCN=National Comprehensive Cancer Network, AUA=American Urological Association

IMMUNOTHERAPY IN BLADDER CANCER

Programmed cell death-1 protein (PD-1)/PD-1 ligand checkpoint inhibitors have promising role in treating locally advanced and metastatic UC as the first-line therapy and also have potential in for neoadjuvant setting.[53-56] Further clinical trials with longer follow-up are required to define their role as first-line therapy in cisplatin-eligible patients. Based on level 1 evidence, atezolizumab and pembrolizumab have been approved by the US Food and Drug Administration for locally advanced and metastatic UC patients who are cisplatin ineligible.[57]

Neoadjuvant immunotherapy

Two phase II studies, PURE-01[58] and ABACUS,[59] [Table 2] evaluated the role immunotherapy in neoadjuvant setting. ABACUS study[59] is yet to complete with final results; however, the clinical efficacy and biomarker analysis have been published.[60]

Adjuvant immunotherapy

Adjuvant immunotherapy is experimental and is not indicated outside of a clinical trial setting. Based on the results in patients with advanced disease, three phase III trials are in progress; Atezolizumab versus observation (NCT02450331), Nivolumab versus placebo (NCT02632409), and Pembrolizumab versus observation (NCT03244384).

The current international guidelines recommendations are summarized in Table 3.

CONCLUSIONS

NACT is strongly recommended for cT2-T4aN0M0 disease with cisplatin-based combination chemotherapy regimens. ACT is advisable to pT3/T4 and/or pN+ disease if NACT has not been given. Adjuvant RT can be considered in pT3/T4 and/or pN+ and/or positive margin patients. Immunotherapy should only be used under trial setting and awaits further results.

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Supplementary Table 1: Neoadjuvant chemotherapy trials

Supplementary Table 1 (A): SWOG-8710 Study

Multicenter Phase III RCT (1987-1998) across 126 institutions
T2-T4aN0M0 - AJCC 4th edition
Upfront RC+BPLND versus 3 cycles of NACT (MVAC) followed by RC+BPLND
Primary end-point: OS
Secondary end-point: Tumor down-staging

Salient Features	RC-arm	NACT-arm	*P*
Sample size (*n*=307)	154	153	
Median follow-up (years)	8.4	8.7	
5-year OS (%)	43	57	0.06
Median OS (months)	46	77	
DSS	77 deaths	54 deaths	0.002 (HR: 1.66; 95% CI: 1.22-2.45)
pCR (%)	15	38	<0.001
Postoperative complications		No statistical significant difference	

NACT was a/w OS and DSS benefit and reduced risk of death by 33% (HR: 1.33; 95% CI 1.00-1.76)
Increased pCR rates translated into survival benefit (85% pT0 patients were alive at 5-year)
MVAC did not adversely affect chance to undergo RC and did not increase risk of death or complications
33% Grade 4 granulocytopenia with MVAC
Limitations
- No ACT in RC-arm
- Uniform central pathologic review
- 18% and 19% patients in NACT- and RC-arm did not undergo RC respectively

Supplementary Table 1 (B): JCOG-0209 Study

Multicenter Phase III RCT (2003-2009) across 28 Japanese institutions
T2-T4aN0M0
Upfront RC versus 2 cycles of NACT (MVAC) followed by RC
Primary end-point: OS
Secondary end-point: PFS, surgery-related complications, AEs during chemotherapy, pCR and QOL

Salient Features	RC-arm	NACT-arm	*P*
Sample size (*n*=130)	66	64	
Median follow-up	55 months		
5-year OS (%)	62.4	72.3	0.07 (HR: 0.65; multiplicity adjusted 99.99% CI: 0.19-2.18)
Median OS (months)	82	102	
5-year PFS (%)	56.4	67.9	0.054 (HR: 0.64; 95% CI: 0.37-1.11)
Median PFS (months)	78	99	
pCR (pT0) (%)	9.4	34.4	0.0011
pN0 (%)	65.6	79.7	0.11
Anastomotic leaks (%)	1.5	12.1	0.026
Lymph leak (%)	12.3	1.7	0.035

Limitations
- Small numbers resulting in low power to show benefit
- Better OS in both arms attributed to more T2 cases
- Lack of GC regimen

Supplementary Table 1 (C): International Collaboration of Trialists Study

Multicenter RCT (1989-1995) across 106 institutions in 20 countries
T2G3, T3, T4aN0/NxM0
Upfront definitive treatment versus 3 cycles of NACT (CMV) followed by definitive treatment
Choice of definitive treatment (surgery, RT, or NART and cystectomy) according to patient or physician

Salient Features	No NACT-arm	NACT-arm	*P*
Sample size (*n*=976)	485	491	
Median follow-up	4 years		
3-year OS (%)	50	55.5	0.075 (HR: 0.85; 95% CI: 0.71-1.02)
Median OS (months)	37.5	44	
3-year DFS (%)	39	46	0.019 (HR: 0.82; 95% CI: 0.70-0.97)
Median DFS (months)	16.5	20	
3-year LR-DFS (%)	42	47	0.087 (HR: 0.87; 95% CI: 0.73-1.02)
Median LR-DFS (months)	20	23.5	
3-year MFS (%)	45	53	0.007 (HR: 0.79; 95% CI: 0.66-0.93)
Median MFS (months)	25	32	
pCR (%)	12	32.5	

Contd...

Supplementary Table 1: Contd...

Supplementary Table 1 (C): International Collaboration of Trialists Study

Limitations
Tumors >7 cm were ineligible
20% in NACT-arm did not receive chemotherapy and 20% received <3 intended cycles
All patients did not undergo RC (60 underwent total cystectomy) and two underwent partial cystectomy
23% patient did not receive the full dose RT as planned

RT=Radiotherapy, MVAC=Methotrexate, vinblastine, doxorubicin, and cisplatin, OS=Overall survival, DSS=Disease-specific survival, pCR=Pathological complete response, ACT=Adjuvant chemotherapy, CMV=Cisplatin, methotrexate, and vinblastine, NART=Neoadjuvant RT, PFS=Progression-free survival, AE=Adverse events, QOL=Quality of life, RCT=Randomized control trials, BPLND=Bilateral pelvic lymph node dissection, RC=Radical cystectomy, NACT=Neoadjuvant chemotherapy, HR=Hazard ratio, GC=Gemcitabine and cisplatin, DFS=Disease-free survival, LR-DFS=Local recurrence-DFS, MFS=Metastasis-free survival, CI=Confidence interval

Supplementary Table 2: Adjuvant chemotherapy trials

Supplementary Table 2 (A): EORTC 30994 trial

Open-label, multicenter, Phase III RCT conducted between 2002 and 2008
pT3-T4/pN+M0 (AJCC 5th ed..ition)
R0 resection and≥15 LNs dissected
Four cycles ACT (within 90 days) versus 6 cycles deferred-chemotherapy i.e., no treatment until relapse
Regimens: MVAC, high-dose MVAC or GC
Primary end point: OS
Secondary end points: PFS

Salient Features	ACT-arm	Deferred-chemo-arm	*P*
Sample size (*n*=284)	141	143	
Median follow-up		7 years	
5-year OS (%)	53.6	47.7	0.13 (HR: 0.78; 95% CI: 0.56-1.08)
Median OS (years)	6.74	4.60	
5-year PFS (%)	47.6	31.8	<0.0001 (HR: 0.54; 95% CI: 0.40-0.73)
Median PFS (years)	3.11	0.99	
5-year BC mortality (%)	38.6	43.5	0.22
Percent progressed (%)	45	62	

Limitations
- Underpowered to detect OS and DFS benefit with slow accrual and premature termination
- pT2 patients were not enrolled
- No central pathology review
- Patient reported outcomes were not recorded

Supplementary Table 2 (B): Italian Multicenter Trial

Phase III trial across 45 Italian centers between 2001 and 2007≥75 years, ECOG 0-2, pT2G3-T4N0-N2/pN+R0 resection and≥10 LNs dissected
Observation (treatment on relapse - Arm A), or ACT (Arm B)
Arm B further randomized to two different schedules (B2, B15) total 4 cycles every 28 days

Salient Features	Arm-A	Arm-B		*P*
Sample size (*n*=194)	92	102		
Median follow-up		35 months		
5-year OS of the entire study		48.5%		
5-year OS (%)	53.7	43.4		0.24 (HR: 1.29; 95% CI: 0.84-1.99)
		B2: 46.6	B15: 39.9	0.88
5-year DFS of the entire study (%)		39.5		
5-year DFS (%)	42.3	37.2		0.70 (HR: 1.08, 95% CI: 0.73-1.59)
Grade 3/4 thrombocytopenia (%)		B2: 25.6	B15: 4.3	0.006
Grade 3/4 leukopenia (%)		B2: 9.3	B15: 15.2	
Grade 3/4 neutropenia (%)		B2: 21	B15: 34.8	

Arm B2: Gemcitabine 1000 mg/m2 i.v. on D1, D8 and D5 and cisplatin 70 mg/m2 i.v. on D2
Arm B15: Same gemcitabine schedule as in arm B2, with same dose cisplatin on D15
Limitations
- Underpowered to detect OS benefit due to low accrual rate
- Small sample size and premature termination
- Poor compliance to ACT
- No central pathologic review

Supplementary Table 2 (C): SOGUG-99/01 Trial

Published as abstract only
pT3-4/pN+, ECOG≥1, CrCl>50 ml/min, ≥8 weeks postcystectomy, no relevant co-morbidities
4 cycles of ACT PGC versus observation

Salient Features	ACT-arm	Observation-arm	*P*
Sample size (*n*=142)	68	74	
Median follow-up		30 months	
5-year OS (%)	60	31	<0.0009
5-year DFS	NA	NA	<0.0001
TTP	NA	NA	<0.0001
DSS	NA	NA	<0.0002

Limitations
- Small sample size
- Premature closure due to poor accrual
- Firm conclusions cannot be drawn

PGC=Paclitaxel+gemcitabine+cisplatin, TTP=Time to tumor progression, LNs=Lymph nodes, ACT=Adjuvant chemotherapy, MVAC=Methotrexate, vinblastine, doxorubicin and cisplatin, GC=Gemcitabine and cisplatin, OS=Overall survival, CI=Confidence interval, HR=Hazard ratio, PFS=Progression-free survival, BC=Bladder cancer, DFS=Disease-free survival, ECOG=Eastern Cooperative Oncology Group, i.v.=Intravenous, NA=Not available

Supplementary Table 3: Adjuvant radiotherapy in muscle invasive bladder cancer

Supplementary Table 3 (A): Postoperative RT for carcinoma in bilharzial bladder[45]

Randomized 236 patients in two phases (first phase: 1981-1984, second phase: 1984-1988) into three arms
Post-RC pT3a-pT4a disease (TNM 3rd edition)
MDF: Three fractions daily of 1.25 Gy each, total dose 37.5 Gy in 12 days
CF: Total dose 50 Gy/5 weeks

Salient Features	RC-alone	RC+PORT (MDF)	RC+PORT (CF)	*P*
Sample size (*n*=236)	83	75	78	
5-year DFS (%)	25	49	44	<0.0001
5-year LRC (%)	50	87	93	<0.0001

Conclusions
- No difference in the two PORT arms
- Therapeutic benefit of PORT was preserved across different grades and stage
- Nodal involvement did not show DFS benefit with PORT
- PORT led to higher local control in all histologic types, grades, stages, irrespective of LN involvement
- Factors affecting DFS: PORT, LN status, stage, and grade

Limitations
- Conducted in 1980s and the RT techniques cannot be extrapolated in present time
- 80% had SCC which is common in middle east, only 20% patients had UC
- Small sample size in each arm

Supplementary Table 3 (B): Adjuvant CTRT after RC+PLND[46]

Prospective randomized trial at NCI, Cairo, Egypt
Post-RC+PLND, advanced high risk patients (pT3b-pT4a, G3/N+)
Arm I: PORT 45 Gy/30 fractions/3 weeks
Arm II: 2 GC+RT+2 GC

Salient Features	Arm I	Arm II	*P*
Sample size (*n*=142)	71	71	
2-year DFS (%)	61.5±7.4	70.9±6.1	0.2
2-year DFS (%)		67.6±5.9	

Conclusions
- Factors affecting DFS: PS, stage, tumor type, nodal involvement, number of risk factors
- Patients with one risk factor, low pathological stage, or no nodal involvement in Arm II had better DFS than in Arm I (*P*=0.07, *P*=0.08, and *P*=0.09, respectively)

Limitations
- Small sample size
- Proportion of SCC/UC not mentioned
- Published as abstract only in ASCO 2006

GC: Gemcitabine 1 g/m^2 i.v. D1 and D8 and cisplatin 70 mg/m^2 i.v.

Supplementary Table 3 (C): Adjuvant sandwich CTRT versus ACT alone[47]

Phase II study at NCI, Cairo, from 2002 to 2008
Inclusion criteria: Age≥70 years, ECOG 0-2, post-RC+PLND with R0 resection, locally advanced disease (≥pT3bG3/N+AJCC 4th Edition)
Third arm opened later and hence randomization weighted toward ACT-alone arm (1:1:4)
Only patients in the CTRT and ACT-alone arm were included in this analysis (*n*=120)
PORT: 45 Gy/twice daily/3 weeks at cystectomy bed+bilateral pelvic nodes
Chemotherapy regimen: GC
Primary end point: LRFS
Secondary end points: DFS, DMFS, OS, and adverse effects

Salient Features	PORT-alone	Sandwich CTRT	ACT-alone	*P*
Sample size (*n*=198)	78	75	45	
Median follow-up		24-27 months		
2-year LRFS (%)	-	96	69	<0.001
2-year DFS (%)	-	68	56	0.07
2-year OS (%)	-	71	60	0.11

Conclusions
- First prospective study to compare CTRT with ACT alone in locally advanced disease
- Statistical significant improvement in 2-year LRFS with RT
- Chemotherapy and RT act synergistically to reduce local and distant recurrence
- Study used 3D conformal RT techniques

Limitations
- Imbalances between CTRT and ACT-alone arms
- Small sample size
- Sizable patients with non-UC histology (46.7%)
- PLND included up to but not common iliac nodes (recurrences cephalad to iliac bifurcation or in inguinal nodes were labeled as distant metastases)
- <10 LNs dissection in many patients - raising the possibility that PORT compensated for less extensive surgery
- Patient being treated in different time-lines

GC: Gemcitabine 1 g/m^2 i.v. D1, D8, and D15 and cisplatin 70 mg/m^2 i.v. on D2

Contd...

Supplementary Table 3: Contd...

Supplementary Table 3 (D): PORT-alone versus ACT-alone of the above study[47] presented in ASCO 2019[48]

Aim: Whether PORT is noninferior to ACT for DFS with a noninferiority margin of 10% at 2 years
Results
- Non-significant improvement in 2-year DFS favoring PORT by 7% (54% vs. 47%)
- No significant difference in DMFS, and OS
- Significant improvement in LRFS with PORT
- For LRFS: PORT, age, and number of LNs removed had a statistically significant association

Conclusion
- For patients who cannot tolerate ACT, PORT with different contraindications may be a good option to reduce recurrence

Limitations
- Study was not designed as a non-inferiority trial
- Imbalances between the arms
- Heterogeneity of histology (UC: 51%, SCC: 49%)

Supplementary Table 3 (E): Adjuvant sequential chemotherapy plus radiotherapy versus adjuvant radiotherapy alone[49]

Phase III RCT at NCI, Cairo from 2002 to 2008
Post-hoc subgroup analysis of patients with urothelial histology only
Inclusion criteria: Age≥70 years, post-RC+PLND R0 resection, locally advanced disease (≥pT3bG3/N+)
PORT: 45 Gy/1.5 Gy BD
Chemotherapy: GC
Primary end point: DFS
Secondary end point: OS, late GI toxicity

Salient Features	PORT	Sequential chemo+PORT	*P*
Sample size (*n*=81)	40	41	
Median follow-up (months)	15	21	
2-year DFS (%)	48	62	0.031
2-year OS (%)	51	71	0.048
Late Grade-3 GI toxicity (%)	8	7	

Conclusions
- Chemo+PORT was significant predictor of improved DFS (P=0.016) and OS (P=0.039)
- 20% absolute benefit in 2-year OS

Supplementary Table 3 (F): Retrospective study: Adjuvant radiotherapy after radical cystectomy[50]

Retrospective study on 57 patients across three institutions from 2000 to 2013
Majority patients were pT3 (43.9%), N+ (68.4%), R0 resection (73.3%), and received perioperative chemotherapy (84.2%)
Patients classified into: low-risk, intermediate-risk, and high-risk
The most common site of LRR was pelvic nodes

Salient Features	Low-risk	Intermediate-risk	High-risk
	≥pT2	≥pT3 Extended LND i.e., ≥10 LNs dissected R0 resection	≥pT3 Limited LND i.e., <10 LNs dissected R1 resection
Percentage of patients (%)	19	26	53
Median follow-up (months)		40.4	
3-year LRR-free survival (%)		45	
MFS (%)		37	
OS (%)		49	
LRR (%)	9	27	7
Expected LRR (%)(35)	8	22	50

Limitations
- Retrospective design, small sample size, lack of events, heterogeneous study population, and mixed histology
- Most patients did not receive NACT
- Heterogeneous RT technique
- Lack of consensus in indications of concurrent CTRT

RT=Radiotherapy, LND=Lymphnode dissection, TNM=Tumor, node, metastasis, MDF=Multiple daily fractions, CF=Conventional fraction, RC=Radical cystectomy, PORT: Postoperative RT, DFS: Disease-free survival, LRC=Locoregional control, LN=Lymph node, SCC=Squamous cell carcinomas, UC=Urothelial cancer, GC=Gemcitabine and cisplatin, PS=Performance status, CTRT=RT+cystectomy, or chemoradiation, PLND=Pelvic LND, ACT=Adjuvant chemotherapy, DMFS=Distant metastasis-free survival, LRFS: Local recurrence free survival, OS=Overall survival, GI=Gastrointestinal, LRR=Locoregional recurrence, NACT=Neoadjuvant chemotherapy