

Canadian Urological Association/Genitourinary Medical Oncologists of Canada consensus statement: Management of unresectable locally advanced and metastatic urothelial carcinoma



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All guidelines or consensus statements are current as of the date of writing and final editing but the field is constantly changing. As such, the current treatment landscape at time of publication may be different than what was in effect at the time a consensus statement was finalized.

Introduction

In Canada, bladder cancer ranks as the fifth most common cancer, with an estimated 8900 new cases and 2400 deaths in 2018.¹ Approximately 15% of patients have locally advanced or metastatic disease at presentation. A further 40–50% of those with muscle-invasive, early-stage disease will relapse after initial treatment. The majority of patients with advanced-stage disease will succumb to their disease. Cancers of the ureter, renal pelvis, and proximal urethra constitute approximately 5–10% of cases of urothelial carcinoma and are treated with similar systemic therapy as bladder cancer.

GUMOC (Genitourinary Medical Oncologists of Canada) is comprised of Canadian medical oncologists who specialize in the treatment of genitourinary cancers. With recent advances in systemic therapy, especially due to the emergence of immunotherapy as a therapeutic option, a consensus opinion has become necessary to guide the man-

agement of unresectable, locally advanced and metastatic urothelial carcinoma.

Methods

A literature review was undertaken evaluating studies of unresectable, locally advanced and metastatic urothelial carcinoma, with a greater emphasis on prospective randomized studies. A search of Medline, Embase, and PubMed, in addition to other published guidelines, was used to identify relevant studies. A summary of the evidence was created with draft recommendations pertaining to various aspects of the management of advanced urothelial carcinoma. This was distributed to members of GUMOC for review and discussion, through which a consensus opinion was established.

The following statements focus predominantly on systemic management, which falls in the realm of the medical oncology specialty. Additionally, the management of advanced, unresectable urothelial cancer is multidisciplinary in nature, as there are times when surgery and/or radiotherapy have a role to play, particularly in patients with oligometastatic disease and those with locally advanced disease. In this consensus statement, we define locally advanced disease as cT4b and/or cN1–3. Statements pertaining to these aspects of management are intended to provide guidance for treating clinicians as to when to consider referral for multidisciplinary discussion. They are not intended to mandate a particular management plan that arises from such a forum.

All recommended systemic treatment regimens are outlined in Table 1.

Systemic therapy for unresectable, locally advanced and metastatic urothelial carcinoma

Eligibility for cisplatin-based chemotherapy

- Routine eligibility for cisplatin chemotherapy includes all of: 1) creatinine clearance ≥ 60 ml/min; 2) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 ; 3) absence of hearing loss \geq Gr 2 (Common Terminology Criteria for Adverse Events [CTCAE]); 4) absence of neuropathy \geq Gr 2 (CTCAE); and 5) absence of New York Heart Association (NYHA) grade III/IV heart failure.
- In select cases, eligibility criteria may be extended to patients with glomerular filtration rate (GFR) of 45–60 mls/min and/or ECOG 2 performance status. Administering split-dose cisplatin is an option for these patients.

A consensus definition of eligibility for cisplatin chemotherapy was developed by members of a working party, who combined the results of a survey of 120 medical oncologists involved in research of urothelial carcinoma with an evaluation of the available literature on this topic. The purpose was to develop a consistent definition for clinical trial eligibility. The criteria generated were good performance status (ECOG 0–1); GFR > 60 mls/min, and absence of contra-indications to cisplatin, such as grade ≥ 2 neuropathy, grade ≥ 2 hearing loss,

and NYHA grade III/IV heart failure.² Several studies have used split-dose cisplatin to patients with a GFR as low as 35–40 mls/min and reported acceptable safety outcomes.^{3,4} In practice, cisplatin is rarely used in patients with a GFR < 45 mls/min.

First-line systemic therapy

Patient eligible for cisplatin-based chemotherapy

- In patients suitable for cisplatin-based chemotherapy, the preferred routine regimen is gemcitabine/cisplatin (GC).
- Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (DD-MVAC) with growth factor support may be considered in select cases where a more aggressive treatment approach is being considered.

GC was compared to the earlier standard of MVAC in a phase 3 randomized trial. GC demonstrated similar efficacy but with reduced toxicity. In an updated analysis with a minimum of five years of followup, median overall survival (OS) was 14 months in the GC arm, with a 13% five-year survival rate, which was not significantly different from the MVAC arm. The hazard ratio (HR) of GC compared to MVAC was 1.09 (95% confidence interval [CI] 0.88–1.34; $p=0.66$).⁵ Toxicity was increased in the MVAC arm with a higher rate of grade 3–4 neutropenic sepsis (12% vs. 1%), mucositis (22% vs. 1%), and toxic death (3% vs. 1%).⁶

The small proportion of long-term survivors is seen predominantly in patients with good performance status (ECOG 0–1, Karnofsky Performance Status [KFS] > 80) and in those patients without visceral metastases (bone, lung, liver).^{5,7} Further attempts have been made to improve on these results by intensifying doses and adding additional chemotherapy agents. One notable regimen is DD-MVAC, tested in the phase 3 EORTC 30924 study. This regimen consists of two weekly MVAC with growth factor support and was compared to standard MVAC. Seven-year followup demonstrated a statistically borderline improvement in OS, with a five-year OS of 21.8% in DD-MVAC-treated patients compared to 13.5% with standard MVAC. The HR of DD-MVAC compared to standard MVAC was 0.76 (95% CI 0.58–0.99; $p=0.042$). A complete response (CR) was seen in 21% of those receiving DD-MVAC compared with 9% of those receiving standard dose MVAC. The addition of growth factor support reduced neutropenic complications and mucositis in the DD-MVAC arm compared with the standard MVAC arm, however, there was still one death due to toxicity in each treatment arm.⁸

Evidence for other regimens is not sufficiently robust to endorse their inclusion as recommended treatments. Dose-dense GC (DD-GC) was compared to the DD-MVAC regimen in a phase 3 study performed by the Hellenic Oncology group. Although DD-GC demonstrated similar efficacy to DD-MVAC with reduced toxicity, the study was underpowered, with imbalances in the treatment arms.⁹ Concerns regarding vascular toxicity with this regimen were raised

Table 1. Recommended treatment schedules

Treatment regimen	Schedule
Gemcitabine, cisplatin (GC)	Cisplatin 70 mg/m ² day 1 (in split dose 35 mg/m ² day 1, 8) Gemcitabine 1200 mg/m ² day 1, 8, Cycle length 21 days
Dose dense-methotrexate, vinblastine, doxorubicin, cisplatin (DD-MVAC)	Methotrexate 30 mg/m ² day 1 Vinblastine 3 mg/m ² day 2 Doxorubicin 30 mg/m ² day 2 Cisplatin 70 mg/m ² day 2 G-CSF: day 3–7 Cycle length 14 days
Gemcitabine, Carboplatin (GCa)	Carboplatin AUC 5 day 1 Gemcitabine 1000 mg/m ² day 1, 8 Cycle length 21 days
Gemcitabine (G)	Gemcitabine 1200 mg/m ² day 1, 8, 15 Cycle length 28 days
Paclitaxel (P)	Paclitaxel 175 mg/m ² Cycle length 21 days
Docetaxel (D)	Docetaxel 75 mg/m ² Cycle length 21 days
Pembrolizumab	Pembrolizumab 200 mg IV Cycle length 21 days

as a result of a neoadjuvant study of DD-GC for muscle-invasive bladder cancer in which 23% of patients experienced grade 3–4 venous and arterial events.¹⁰ The addition of paclitaxel to GC (PGC) was tested in the phase 3 EORTC Intergrup 30987 study consisting of 626 patients. There was a non-significant 3.2-month median OS improvement favoring PGC in the intention-to-treat (ITT) patient population, which reached statistical significance when 47 patients not meeting the eligibility criteria were excluded. An unplanned subgroup analysis revealed benefit in the 81% of patients with bladder primary. Febrile neutropenia was increased in the PGC arm at 13.2% compared to 4.3%.¹¹

Currently, there are no completed clinical trials supporting the use of first-line immunotherapy in cisplatin-eligible patients. However, numerous trials are currently evaluating the role of first-line immunotherapy (Table 2).

Patient ineligible for cisplatin-based chemotherapy

- In patients ineligible for cisplatin-based chemotherapy, the preferred regimen is gemcitabine/carboplatin (GCa).
- In patients not suitable for combination chemotherapy, single-agent gemcitabine, paclitaxel, or docetaxel is recommended.
- Immunotherapy is not routinely recommended in the first-line setting for cisplatin-ineligible patients.

Chemotherapy in cisplatin-ineligible patients

Carboplatin-based regimens are inferior to cisplatin-based regimens, with lower response rates and trend towards inferior survival.¹² Nonetheless, carboplatin is active in urothelial carcinoma and is the cornerstone of preferred regimens in cisplatin-ineligible patients. GCa was compared to methotrexate, carboplatin, vinblastine (M-CAVI) in the phase 3 EORTC 30986 study. The population studied was ineligible for cisplatin on the basis of a GFR of 30–60 mls/min (55% of patients), World Health Organization Performance Status (WHO PS) of 2 (17.6%), or both (27.3%). Visceral metastases were present in 51% of patients. Efficacy was similar in both regimens, with

a median OS of 9.3 months for GCa and 8.1 months with M-CAVI. Only 8% of patients were still alive after a median followup of 4.5 years. Toxicity was reduced with GCa compared to M-CAVI, with 9% cases of severe acute toxicity (SAT) and two toxic deaths compared to 21% cases of SAT and four toxic deaths, respectively.¹³ GCa has thus become the preferred regimen in this generally less robust group of patients.

Several other carboplatin and non-carboplatin-based regimens have been evaluated in phase 2 studies. Although demonstrating encouraging results, none of these regimens has been further assessed in phase 3 studies and are not considered standard regimens.^{14–21} Paclitaxel and gemcitabine has demonstrated overall response rates of between 37–70%, however, pulmonary toxicity has been noted.¹⁹

In patients not suitable for combination therapy, single-agent gemcitabine, paclitaxel, or docetaxel has been studied in small, single-arm, phase 2 studies.^{22–25} Response rates have varied from 25–47%, but have generally been of short duration with median OS ranging from 8–12 months in these series.

Immunotherapy in cisplatin-ineligible patients

Checkpoint inhibitors active on the PD-1/PD-L1 interaction between tumor cells and cytotoxic T cells have demonstrated efficacy in a first-line setting in cisplatin-ineligible patients with advanced urothelial carcinoma. Pembrolizumab, a monoclonal antibody against the PD-1 receptor on T cells and other immune cells, was evaluated in 370 cisplatin-ineligible patients with advanced urothelial carcinoma in a single-arm, phase 2 study. An overall response rate (ORR) of 29% was in the range of that seen with chemotherapy, with a potential advantage over chemotherapy existing in both the durability of responses and overall tolerability of this regimen. Sixty-eight percent of responses were ongoing at 12 months and grade 3–4 toxicity mostly from immune-related adverse events (irAEs) was seen in 16% (Table 3). Median OS was 11.5 months. Responses were more likely in patients with PD-L1 posi-

Table 2. Current phase 3 studies of immunotherapy in locally advanced and metastatic urothelial carcinoma

Study	ClinicalTrials.gov identifier	Disease state	Treatment arms	Estimated completion date
Imvigor 130	NCT02807636	First-line	Atezolizumab vs. atezolizumab/platinum-based chemotherapy vs. platinum-based chemotherapy	November 2020
Keynote 361	NCT02853305	First-line	Pembrolizumab vs. pembrolizumab/platinum-based chemotherapy vs. platinum-based chemotherapy	May 2020
Danube	NCT02516241	First-line	Durvalumab + tremelimumab vs. durvalumab vs. standard chemotherapy	September 2019
Javelin Bladder 100	NCT02603432	Maintenance following first-line	Avelumab + BSC vs. BSC alone	July 2020
Checkmate 901	NCT03036098	First-line	Nivolumab/ipilimumab vs. platinum-based chemotherapy Nivolumab/cisplatin gemcitabine vs. cisplatin gemcitabine alone	December 2022

BSC: best supportive care.

Table 3. Summary of first-line immunotherapy studies in cisplatin-ineligible patients with advanced urothelial carcinoma

	Pembrolizumab: Keynote 052	Atezolizumab: Imvigor 210 cohort 1
Study type	Multicenter, single-arm, phase 2 cisplatin-ineligible, first-line	Multicenter, single-arm, phase 2 cisplatin-ineligible, first-line
Treatment regimen	Pembrolizumab 200 mg IV 3 weekly	Atezolizumab 1200 mg IV 3 weekly
Number of patients	370	119
Median followup (months)	11.5	17.2
ECOG 2%	42	27
Visceral metastases%	85	66
ORR%	29	23
CR%	8	9
Response duration	68% ongoing at 12 months	70% ongoing at time of assessment
Median OS (months)	11.5	15.9
Effect of PD-L1 positivity	CPS: >10%: ORR 47.3% 1–10%: ORR: 20% <1%: ORR 5%	IC 2/3: ORR 28% IC 1: ORR 21% IC 0: ORR 21%
Grade 3/4 toxicity	16%	16%
Reference	Balar 2017 ²⁶ Vuky ²⁷	Balar ²⁸

CPS: combined positive score; CR: complete response; ECOG: Eastern Cooperative Oncology Group; IC: immune cell PD-L1% (IC2/3 >5%, IC1=1–5%, IC0=0%); ORR: overall response rate; OS: overall survival.

tivity on immunohistochemistry (IHC), as measured by a combined positive score (CPS) $\geq 10\%$.^{26,27} Similar outcomes were obtained with atezolizumab, which is a monoclonal antibody against the PD-L1 receptor on tumor and immune cells. In a single-arm, phase 2 study in 119 patients, the ORR was 23%, with 70% of responses ongoing after a median followup of 17.2 months and a median OS of 15.9 months. Grade 3/4 toxicity was seen in 16% of patients. The differential effect of PD-L1 expression by IHC on ORR% was not as obvious (Table 3).²⁸ GUMOC currently does not endorse these agents for first-line therapy. This is discussed below in “Current approvals and status of the evidence of immunotherapy in advanced UC.”

Second-line systemic therapy

- In patients who have progressive disease during or after platinum-based chemotherapy, pembrolizumab is the preferred regimen (if available).
- Where pembrolizumab is unavailable or a patient is ineligible, single-agent paclitaxel or docetaxel is preferred for the majority of patients.

- Re-treatment with a platinum-based regimen is a reasonable option in a patient who has disease progression following a prolonged (>6–12-month) initial response to platinum-based chemotherapy.

Chemotherapy

Prior to the advent of checkpoint inhibitors in unresectable, locally advanced and metastatic urothelial carcinoma, there was no standout salvage chemotherapy regimen for patients progressing during or after platinum-based regimens. Re-treatment with a platinum regimen can be a successful strategy in patients with an initial response lasting greater than 6–12 months.^{29–31} Patients progressing within this timeframe are likely to be refractory to further platinum therapy. The only randomized phase 3 study in this group of patients compared vinflunine to best supportive care. Although OS was not improved in the ITT population, analysis of those patients fulfilling eligibility criteria revealed a median OS benefit of two months.³² Vinflunine is not available in North America. Although doublet chemotherapy regimens are associated with higher response rates, their greater toxicity combined with failure to impact meaningfully on OS has limited their use.³³ Despite low response rates of approximately 10%, paclitaxel and docetaxel are well-tolerated and have emerged as preferred regimens.^{34–36} Nab-paclitaxel has demonstrated efficacy in the second-line setting and is a reasonable alternative.³⁷

Immunotherapy: Checkpoint inhibitors

The evidence supporting the use of checkpoint inhibitors in the second-line setting is more robust than in the first-line setting. Five checkpoint inhibitors have been tested in this setting, including two in randomized phase 3 studies.

Pembrolizumab was compared to investigators' choice of single-agent paclitaxel, docetaxel, or vinflunine in 542 patients with progressive disease during or after platinum-based chemotherapy in the randomized phase 3 Keynote 045 study. ORR was 21% in the pembrolizumab-treated patients compared with 11% in chemotherapy-treated patients. Median progression-free survival (PFS) was only 2.1 months on pembrolizumab compared with 3.3 months on chemotherapy (HR 0.98; 95% CI 0.81–1.19; $p=0.42$) reflecting the small number of patients who responded to pembrolizumab. Nonetheless, responses were durable, with 68% ongoing at 12 months compared with only 35% of chemotherapy responses ongoing at 12 months. Median OS was 10.3 months with pembrolizumab compared to 7.4 months on chemotherapy (HR 0.73; 95% CI 0.59–0.91; $p=0.002$). Grade 3–5 toxicity was seen in 15% of patients on pembrolizumab compared to 49% on chemotherapy. Benefit was seen irrespective of the choice of chemotherapy given and irrespective of PD-L1 expression by CPS%.³⁸

Atezolizumab was compared with investigators' choice of paclitaxel, docetaxel, or vinflunine in the phase 3

IMvigor 211 study, sharing a similar overall design with the Keynote 045 study. One important study design difference was the use of a hierarchical fixed-sequence procedure for endpoint analysis, according to PD-L1 expression. The primary endpoint of OS was tested in successive subgroups defined by PD-L1 expression: IC2/3 ($\geq 5\%$ expression on tumor-infiltrating immune cells) followed by IC 1/2/3 ($\geq 1\%$ expression on tumor-infiltrating immune cells) followed by the overall ITT group. Demonstration of superior OS was required in each group before the next group could be tested. No OS benefit was seen for atezolizumab compared with chemotherapy in the first group of 234 patients with IC2/3 positive disease. In this population, median OS was 11.1 months vs. 10.6 months on chemotherapy (HR 0.87; $p=0.41$). A survival benefit favoring atezolizumab was seen in the exploratory analysis of the ITT population of 931 patients (HR 0.85; 95% CI 0.73–0.99). In this study, PD-L1 positivity seemed to predict benefit from chemotherapy, as well as immunotherapy. The theme of durable immunotherapy responses was seen in this study, with median duration of response of 21.7 months in the ITT population compared with 7.4 months for chemotherapy in the ITT population.³⁹

Several single-arm, phase 1 and 2 studies have evaluated outcomes of checkpoint inhibitors in the second-line setting (Table 4).^{40–47} Response rates have ranged from 15–31%, with complete responses ranging from 2–11%. Median PFS has ranged from 1.6–2.8 months, reflecting the relatively low proportion of patients who benefit. Nonetheless, those who do respond seem to obtain durable benefit. Grade 3–5 toxicity has been observed in 8–22% of patients.

The role of PD-L1 testing in selecting patients for immunotherapy

– In the second-line setting, PD-L1 testing by IHC should not be used to select patients for immunotherapy.

In the second-line setting, findings from both the Keynote 045 and IMvigor 211 randomized phase 3 studies suggest that benefit of checkpoint inhibitors is not limited to those with PD-L1-positive tumors by IHC. In Keynote 045, the ORR of pembrolizumab was similar in the CPS $\geq 10\%$ population (22%) compared to the overall population (21%). Superior OS of pembrolizumab compared with chemotherapy was demonstrated in both the CPS $\geq 10\%$ population and the overall population. In the IMvigor 211 trial, ORR was higher in the IC2/3 population (23%) compared to the ITT population (13%). Paradoxically, superior OS of atezolizumab compared with chemotherapy was seen in the exploratory analysis of the ITT population, but not in the primary analysis of the IC2/3 subgroup.

Di Nunno et al combined the results of both randomized control trials in a meta-analysis and found that immunotherapy improved OS in the ITT population but not in the high PD-L1 population. Heterogeneity between trials was greater in the PD-L1 high population compared with the ITT population, demonstrating the need to further elucidate the role of PD-L1 as a predictive biomarker.⁴⁸

As illustrated in Tables 3 and 4, numerous phase 1 and 2 studies of checkpoint inhibitors have evaluated ORR according to PD-L1 status in both first- and second-line settings. In some, but not all studies, PD-L1 positivity has been associated with a higher ORR. These findings are exploratory in nature. To date, no single biomarker has been able to predict response to immunotherapy in urothelial carcinoma.⁴⁹

In the first-line setting, the role of PD-L1 as a predictive biomarker will become clearer once results from ongoing

Table 4. Phase 1/2 studies of checkpoint inhibitors following platinum-based treatment

Checkpoint inhibitor	Nivolumab Checkmate 032	Nivolumab Checkmate 275	Durvalumab MEDI4736	Atezolizumab Imvigor 210 cohort II	Atezolizumab Solid Tumor	Avelumab Javelin Solid Tumor	Pembrolizumab Keynote 012
Study type	Phase 1/2	Phase 2	Phase 1/2	Phase 2	Phase 1	Phase 1	Phase 1b
Patients	86	270	191	315	95	161	33
ORR% (95% CI)	24 (15–35)	20 (15–24)	18 (13–24)	15 (11–19)	26 (18–36)	17 (11–24)	26 (11–46)
Cr%	6	2	4	5	9	6	11
Response duration	Median 9.4 months	77% ongoing at 6 months	50% ongoing at 6 months	84% ongoing at median followup 11.7 months	Median 22.1 months	Median NR	Median 10 months
mPFS months	2.8	2	1.4	2.1	2.7	1.6	2
mOS months	9.7	8.7	18	7.9	10.1	6.5	10
Grade 3–5 toxicity%	22	18	6.8	16	9%	8	15
Effect of PD-L1 on ORR%	$\geq 1\%$: 24% <1%: 26%	$\geq 1\%$: 24% <1%: 16%	$\geq 25\%$ IC/TC: 28% <25% IC/TC: 5%	IC2/3: 27% ITT: 15%	IC 2/3: 40% IC 0/1: 11%	$\geq 5\%$: 24% <5%: 14%	TC/IC $\geq 1\%$: 24% TC/IC <1%: 0%
Reference	Sharma 2016 ⁴⁰	Sharma 2017 ⁴¹	Massard 2016 ⁴² ; Powles 2018 ⁴³	Rosenberg 2016 ⁴⁴	Petrylak 2018 ⁴⁵	Patel 2016 ⁴⁶	Plimack 2017 ⁴⁷

CI: confidence interval; IC: immune cells; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TC: tumor cells.

randomized controlled trials become available. Recent safety reports have been issued from the Data Monitoring Committees of two current phase 3 trials comparing PD-1/PD-L1 inhibitors (pembrolizumab in Keynote – 361, and atezolizumab in IMvigor 130) to either cisplatin or carboplatin combined with gemcitabine in first-line urothelial carcinoma. Reduced efficacy of checkpoint blockade compared to chemotherapy was observed in patients with low PD-L1 expression.⁵⁰

Current approvals and the status of the evidence of immunotherapy in advanced urothelial carcinoma

In the first-line setting, neither pembrolizumab nor atezolizumab has been approved by Health Canada (Note: When this consensus statement was written, there was no Health Canada approval for pembrolizumab as first-line therapy for cisplatin-ineligible patients. Since this document was finalized, Health Canada has granted conditional approval [contingent on a positive phase 3 trial] for pembrolizumab as first-line therapy for cisplatin-ineligible patients.)⁵¹ Both agents received accelerated approval by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for cisplatin-ineligible patients,^{50,52} and are endorsed by the National Comprehensive Cancer Network (NCCN) in this population.⁵³ Recently, the indication has been narrowed to those patients whose tumors are PD-L1 positive, or who are not eligible for any platinum chemotherapy regardless of PD-L1 expression. An application for first-line pembrolizumab along similar lines to FDA and EMA approvals has been made to the Pan-Canadian Oncology Drug Review (pCODR).⁵⁴

In the second-line setting, pembrolizumab, atezolizumab, durvalumab, and avelumab have been approved by Health Canada for use in patients progressing during or following platinum-based chemotherapy or those who relapse within 12 months of receiving neoadjuvant or adjuvant platinum-based chemotherapy for earlier stage disease.⁵⁰ An expert review committee on behalf of pCODR recommended approval of pembrolizumab in this setting conditional upon “cost effectiveness being improved to an acceptable level.”⁵⁴ All five PD-1/PD-L1 inhibitors discussed have FDA approval in this setting and pembrolizumab, atezolizumab, and nivolumab have EMA approval.^{50,52}

There was robust debate about the level of evidence required to recommend these agents, particularly in first-line setting, for patients not suitable for platinum-based chemotherapy. Nonetheless, the majority of GUMOC members preferred to maintain the standard of endorsing new treatments on the basis of both statistically significant and clinically meaningful benefit demonstrated in randomized phase 3 trials. Currently, this level of evidence has not been achieved for pembrolizumab or atezolizumab in the first-line setting. By the same standard, pembrolizumab is the only checkpoint inhibitor to have demonstrated this level

of evidence in the second-line setting. GUMOC recognizes that the current consensus statements may need updating depending on the results of several ongoing phase 3 trials of checkpoint inhibitors (Table 5).

Management of cT4b and/or cN1-3 urothelial carcinoma of the bladder

- Patients with clinically staged T4b or N1-3 urothelial carcinoma of the bladder should be discussed in a multidisciplinary forum, including an experienced urologist/uro-oncologist, and radiation oncologist.
- Patients with cT4b and/or cN1-3 urothelial carcinoma of the bladder can be cured using multimodality treatment.
- In suitable patients, the preferred approach is to commence systemic chemotherapy with 4–6 cycles of platinum-based chemotherapy as per first-line systemic therapy.
- Depending on response to initial chemotherapy, consolidation with either radical cystectomy (RC) and pelvic lymph node dissection (PLND) or radical radiotherapy (± concurrent chemotherapy) can be administered.

In urothelial carcinoma of the bladder, clinical T4b disease is defined as a tumor that invades the pelvic wall, abdominal wall, or adjacent bowel/rectum and is unresectable unless significant down-staging can be achieved. Clinical N1–2 disease consists of lymph node involvement in the true pelvis, whereas N3 consists of common iliac lymph node involvement. Not all patients with regional node involvement will have distant metastases, particularly with cN1–2 stage disease. The definition of nodal metastases changed in 2010 with the seventh edition of the American Joint Committee on Cancer (AJCC).⁵⁵ In prior editions, common iliac lymph node involvement was considered to be metastatic and N1–3 defined nodes of varying number and size in the true pelvis.

Evidence defining the optimum treatment of cT4b and cN1–3 disease is limited to retrospective series. These patients have been routinely excluded from neoadjuvant chemotherapy trials and in the Advanced Bladder Cancer meta-analysis of neo-adjuvant chemotherapy, represented only 1% and 4% of cases, respectively.⁵⁶ Likewise, these patients have generally been excluded from chemo-radiotherapy studies.⁵⁷ Consequently, the optimum management of this subgroup of patients is not well-defined.

A commonly used treatment paradigm in published series has consisted of induction chemotherapy (IC) followed by RC or high-dose radiotherapy (HDRT) in select patients.⁵⁸⁻⁶⁷ Several studies using this approach are outlined in Table 2. Only the study by Nieuwenhuijzen required histological confirmation of involved lymph nodes.⁶⁰ RC/PLND was the most commonly used consolidation treatment, with HDRT only used in a subset of patients in two studies. The study by Urakami included 29 patients with upper tract urothe-

Table 5. Studies of cT4b and/or cN1-3 urothelial carcinoma treated with induction chemotherapy (IC) followed by consolidation with surgery or HDRT

	Clinical stage	Patients (n)	Induction chemotherapy	Consolidative treatment	Selection criteria for RC and/or HDRT	Survival
Zargar-Shostari ⁵⁸	T1-4a N1-3	304	GC 43% MVAC 42% Other 15%	RC/PLND	Not defined	Median OS 23m 50% died in followup
Herr ⁶⁵	T4bNx or T3-4N2-3	80 (selected from 207)	MVAC 75% Other 25%	RC ± PLND	Not defined	42% survived 9 months to 5 years MVAC treated pts: 32% OS at 5 years 5-year CSS: 23%
Nieuwenhuijzen ⁶⁰	Biopsy-proven N+ disease (40% FNA, 60% PLND)	40 (selected from 52)	MVAC/ DD-MVAC	RC/PLND	Response to induction chemotherapy	5-year CSS: 23%
Ho ⁶⁶	cN1-3: 53% cM1: retroperitoneal nodes 47%	55	Cisplatin- based 93%	RC, PLND ± RPLND	Not defined	5-year CSS: 40%
Black ⁶¹	Tb4	23	Preoperative chemotherapy in 83%	RC, PLND	Not defined, but generally major response to IC required	5-year OS: 60%
Als ⁶²	cTb4 or cN2-3	84 (25 observed after clinical CR, 7 RC 9 HDRT)	GC	CR: observation PR: RC/PLND or HDRT	Clinical CR: close observation Clinical PR: investigators choice of RC or RT	5-year OS: Overall 21% CR with observation 42% NED from surgery or XRT: 49%
Urakami ⁶³	cN1-3 and M1a lymph nodes only (30%)	51 (selected from 60: 29 upper tract, 31 bladder)	Platinum- based (GC based in 57%)	RC/PLND Resection of upper tract tumors/ extended LND	Stable disease or response	5-year OS (including non- operated candidates): 42%
Ghadjar ⁶⁴	T4, N1-3, M1 regional nodes	30	GC/GCa	RC/PLND	Not defined	5-year OS: 46%
Meijer ⁶⁷	cN1-3 M1a: retroperitoneal nodes	149 (118 RC/PLND 14 HDRT)	MVAC/ DD-MVAC 62% GC/CarbG 38%	RC/PLND	Not defined but did include pts with SD	Overall 5-year OS: 29%

CR: complete response; CSS: cancer-specific survival; DD-MVAC: dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; FNA: fine needle aspirate; GC: gemcitabine, cisplatin; GCa: gemcitabine/carboplatin; HDRT: high-dose radiotherapy; LND: lymph node dissection; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; NED: no evidence of disease; OS: overall survival; PLND: pelvic lymph node dissection; PR: partial response; RC: radical cystectomy; SD: stable disease; XRT: radiotherapy.

lial carcinoma out of 60 patients.⁶³ All other studies were restricted to urothelial carcinoma of the bladder. Most studies did not define specific selection criteria for RC or HDRT, however, the study by Nieuwenhuijzen required a response to induction chemotherapy in order to proceed to RC, and the study by Urakami selected patients with responsive or stable disease. The study by Als had a unique design whereby patients who obtained a CR based on both computed tomography imaging and cystoscopy and biopsy underwent close surveillance, whereas patients who had a partial response received either RC or HDRT.⁶² Although the study by Herr did not define criteria for RC, 80 patients out of an initial 207 receiving chemotherapy proceeded to RC, implying that patients were carefully selected for surgery.⁶⁵ The study by Black evaluated cT4b patients who had achieved sufficient down-staging from IC to become resectable.⁶¹ Most studies administered four cycles of chemotherapy.

Results from the above studies demonstrate the potential for cure, with reported five-year cancer-specific survival (CSS)/OS ranging from 23–60%. On this basis, GUMOC considered it reasonable to endorse the above treatment strategy for this group of patients. A further argument for a curative treatment approach is the potential for inaccurate clinical staging of lymph nodes. In studies of patients with cN1-3 who have proceeded directly to surgery, a proportion have had pN0 disease implying false-positive clinical staging.⁶⁸ A benefit of commencing treatment with IC is to spare patients who have significant disease progression the morbidity of surgery and/or HDRT.

Selection criteria that should be applied to the decision of consolidative treatment following IC are not clear from the above studies. In general, outcomes are better in patients with a response to IC; however, both Ho and Meijer report a 20% five-year OS in patients with stable disease on IC,^{66,67}

indicating these patients can still obtain benefit. In general, the choice of consolidative treatment is best made on an individual basis with multidisciplinary input. Nonetheless, there are two situations that would sway our decision towards HDRT as opposed to surgery. The first is a patient with persistent N3 disease after IC, where the risk of relapse is high and HDRT represents a less invasive treatment option. The second is for a patient with cT4b disease who fails to obtain down-staging with IC, where surgery is usually not feasible.

The role of aggressive surgical/radiotherapeutic management in oligometastatic disease

- Routine practice of metastasectomy/localized treatment to metastatic disease in patients with oligometastatic or limited metastatic disease is not recommended. However, such treatment may be appropriate in selected cases (see discussion).
- In metastatic urothelial carcinoma of the bladder, the routine practice of RC or HDRT (\pm chemotherapy) to the primary is not recommended. However, such treatment may be appropriate in selected cases (see discussion).
- The decision to treat oligometastatic disease with local therapies should be made in a multidisciplinary context with involvement of an experienced medical oncologist, uro-oncologist, and radiation oncologist where appropriate.

The targeting of oligometastatic disease with surgical resection and/or ablative radiotherapy has only been tested in small series of highly selected patients with no randomized studies to guide practice. While outcomes have been impressive, with reports of five-year OS of up to 65%,^{69,70} uncertainty exists as to whether favorable outcomes were the result of selection bias or from a therapeutic benefit of the localized therapy studied. Further compounding the problem of applying these studies to routine practice is the fact that the majority of studies were retrospective without clearly defined criteria for which patients should receive the localized treatment under consideration. The same limitation applies to the evidence for aggressive localized treatment of the pelvic primary with RC or HDRT (\pm concurrent chemotherapy) in a patient with metastatic disease. In short, the literature provides no level 1 evidence to be either prescriptive or proscriptive with regard to the above treatments. The existing literature is prone to methodological bias.⁷¹

Individualization of local treatment following systemic treatment is the most judicious approach. The aggressiveness of the local treatment will vary according to the initial local stage and the subsequent local and systemic response to the chemotherapy. In any given patient, trans-urethral resection of bladder tumor (TURBT), pelvic radiotherapy with or with-

out concurrent chemotherapy, metastasectomy, or ablative radiotherapy may be appropriate. Recognizing this dearth of compelling data emphasizes that individually tailored treatment by a multidisciplinary team will serve the patient best.

Patients for whom multidisciplinary input may be useful include those with oligometastatic disease, advanced pelvic disease (without hematogenous metastases) with a response to systemic therapy, and those with hematogenous metastases with a complete response at least pertaining to their metastatic disease.

Future directions

The management of locally advanced and metastatic urothelial carcinoma is a rapidly changing field. Ongoing randomized phase 3 studies of immunotherapy for advanced urothelial carcinoma are summarized in Table 2.⁷² Additionally, work is being done on identifying predictive biomarkers that will help in patient selection. Upper tract urothelial carcinoma is associated with microsatellite instability in 3–6% of cases and this may be a useful biomarker to evaluate with respect to the efficacy of immunotherapy.^{73,74} The association with Lynch syndrome should be noted and the role of universal screening vs. risk-adapted screening could be evaluated in subsequent updates.⁷² Immunotherapy studies are also taking place in the earlier stages of disease, which has the potential to alter the profile of the patient presenting with subsequent locally advanced or metastatic disease. Immunotherapy may also change the profile of patients being considered for aggressive local therapies in the context of metastatic disease. Due to the rapid evolution of therapy in this disease state, these consensus statements will need regular updating.

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