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TOPIC PAPER

SIU–ICUD consultation on bladder cancer: treatment of muscle-invasive bladder cancer

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Abstract

Purpose To provide a comprehensive overview and update of the Joint Société Internationale d'Urologie–International Consultation on Urological Diseases (SIU–ICUD) Consultation on Bladder Cancer for muscle-invasive presumably node-negative bladder cancer (MIBC).

Methods Contemporary literature was analyzed for the latest evidence in treatment options, outcomes, including radical surgery, neoadjuvant and adjuvant treatment modalities, and bladder-sparing approaches. An international multi-disciplinary expert panel evaluated and graded the data according to guidelines from the Oxford Centre for Evidence-Based Medicine.

Results Radical cystectomy (RC) is the standard of care for MIBC patients considered to be surgical candidates. While associated with substantial morbidity and mortality, this has been mitigated with improved technique, minimally invasive technology, and better perioperative care pathways (e.g., enhanced recovery after surgery). Neoadjuvant (NA) cisplatin-based combination chemotherapy improves overall survival and should be offered to eligible ≥ cT2N0 patients. Adjuvant (Adj) cisplatin-based combination chemotherapy may be considered, particularly for pT3–4 and/or pN+ disease without prior NA chemotherapy. Trimodal bladder-preserving treatment via maximum transurethral resection of bladder tumor followed by concurrent chemoradiation is safe and, when combined with early salvage RC for recurrence, offers long-term survival rates in selected patients comparable to RC. Immunotherapy is still experimental and is given either alone or in combination with chemotherapy and/or radiation.

Conclusion A multi-disciplinary approach is paramount to achieving optimal outcomes for MIBC patients, irrespective of their age, performance and nutritional status, fitness/frailty, renal and other organ function, or disease severity.

Keywords Muscle-invasive bladder cancer · Urothelial carcinoma of bladder · Radical cystectomy · Transurethral resection of bladder tumor · Neoadjuvant chemotherapy · Adjuvant chemotherapy · Chemoradiation · Trimodal · Bladder-sparing · Variant histology · Enhanced recovery after surgery

Overview

This manuscript deals with patients with muscle-invasive, presumably node-negative bladder cancer (MIBC). It describes treatment options, including radical surgery, neoadjuvant/adjuvant treatment modalities, and bladder-sparing approaches, and outcomes after a clinical diagnosis of a circumscribed disease was made based on the guidelines in previous chapters of the Joint SIU–ICUD Consultation on Bladder Cancer.

Materials and methods

This is an update of the ICUD–EAU International Consultation on Bladder Cancer 2012 [1]. A detailed analysis of the literature was conducted reporting on treatment in localized MIBC. An international, multi-disciplinary expert

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committee evaluated and graded the published data according to the Oxford Centre for Evidence-Based Medicine [2]. This analysis focused on the following topics (keywords): indication and algorithm of treatment, radical cystectomy (RC), perioperative systemic therapy, bladder-sparing treatments, mixed histologic variants and follow-up after surgery. The results of this analysis were first presented during a joint international consultation of the ICUD and Société Internationale d'Urologie held in Lisbon, Portugal on October 2017, and its proceedings were later published in electronic book format, available via SIU Academy at https://www.siu-urology.org/society/siu-icud. For this updated publication, a systematic search was conducted in PubMed for recent relevant papers published between October 2017 and November 2018 using the afore-mentioned topics as keywords. Via this search, a total of 257 references were identified and 54 of them were finally eligible for analysis.

A summary of our recommendations is presented in the tables.

Algorithm of treatment

A potential treatment algorithm is shown in Fig. 1.

Surgery

Radical cystectomy is the standard treatment for MIBC in most countries worldwide [3]. In the pre-RC era, patients with muscle-invasive disease rarely exceed 5-year survival rates of more than 3% and performing radical surgery was associated with a considerably increased perioperative morbidity and mortality [4]. In the last decades, advances in the surgical technique as well as perioperative anaesthesiologic care have significantly decreased the complication rates associated with this procedure. Today, RC is considered the mainstay of treatment for MIBC patients considered to be surgical candidates.

In male patients, curative RC includes complete removal of the bladder with all macroscopically visible and resectable bladder tumor extensions, prostate, seminal vesicles, removal of the adjacent distal ureters, and the lymph nodes corresponding to the tumor-bearing bladder

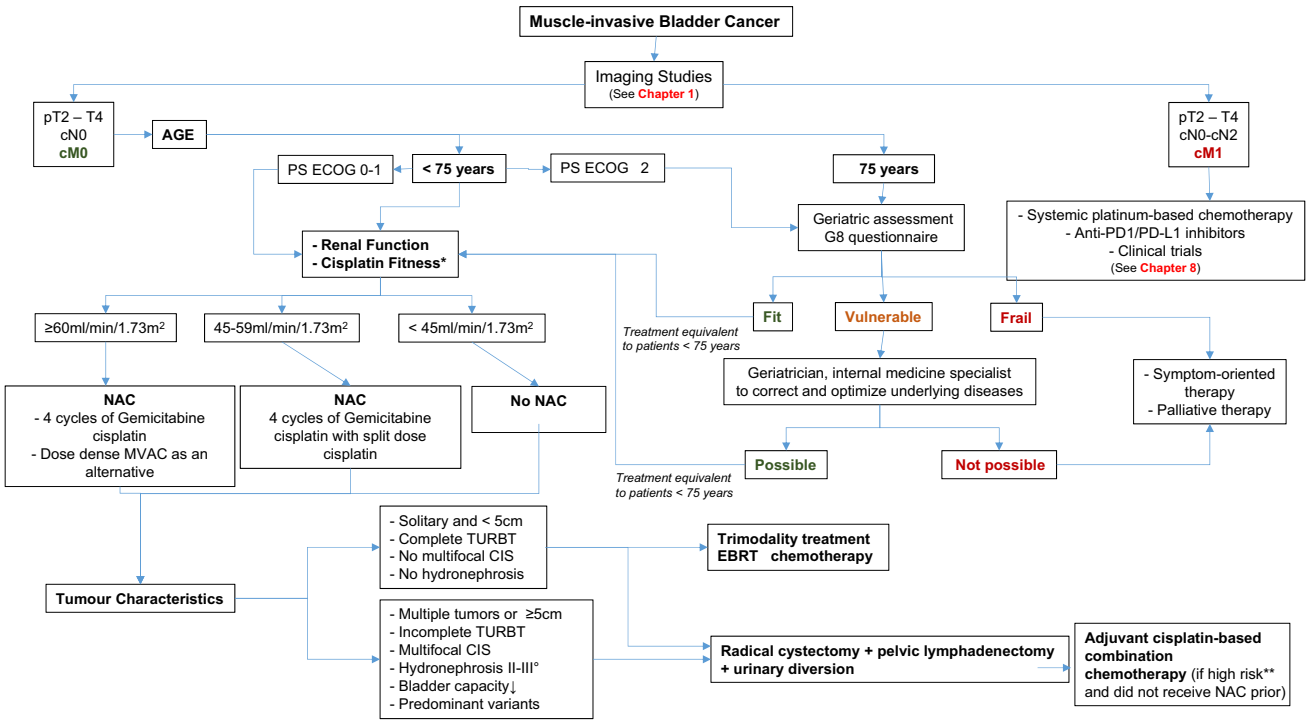

Fig. 1 Suggested management algorithm for muscle-invasive bladder cancer: recommendations from joint SIU–ICUD consultation on bladder cancer. *: cisplatin fitness based on a uniform definition of unfit proposed on the basis of the results of a survey of genitourinary medical oncologists (Ref. [91]; Galsky et al., J Clin Oncol 2011;29(17):2432–2438). **: high-risk disease defined as ≥ pT3–4 and/or pN+ disease. *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *NAC* neoadjuvant chemotherapy, *TURBT* transurethral resection of bladder tumor, *CIS* carcinoma in situ, *EBRT* external beam radiation therapy. Chapter 1 refers to SIU-ICUD Bladder Cancer Guideline 2017 "Committee 1: Epidemiology, Prevention, Screening, Diagnosis, and Evaluation, Section 1.7 - Imaging and Bladder Cancer". Chapter 8 refers to SIU-ICUD Bladder Cancer Guideline 2017 "Committee 8: Systemic Therapy for Metastatic Bladder Cancer"

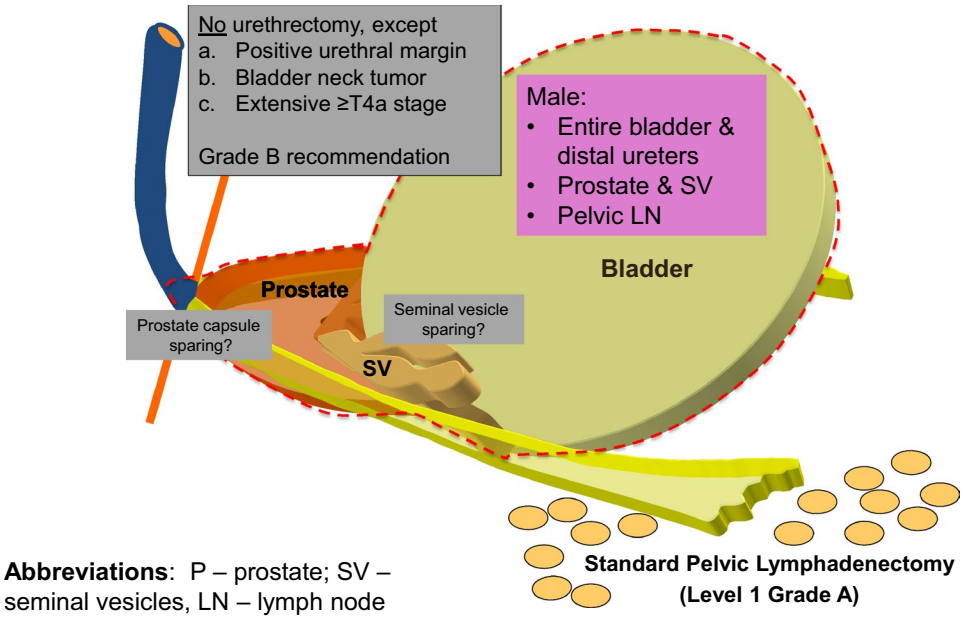

Fig. 2 Extent of radical cystectomy in males with muscle-invasive bladder cancer: recommendations from joint SIU–ICUD consultation on bladder cancer

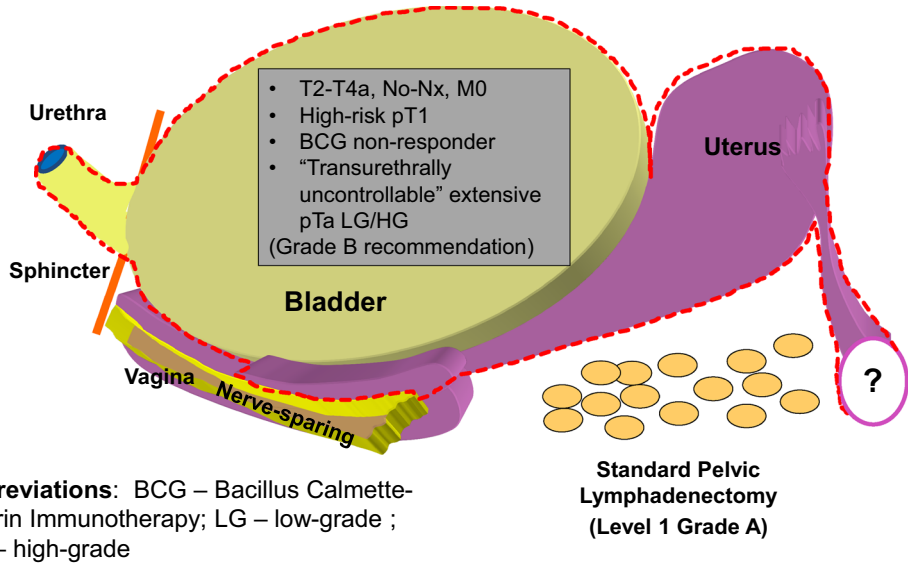

Fig. 3 Extent of radical cystectomy in female with muscle-invasive bladder cancer: recommendations from joint SIU–ICUD consultation on bladder cancer

(Fig. 2). In female patients standard anterior pelvic exenteration includes the proximal urethra, adjacent vagina, uterus, distal ureters and respective lymph nodes (Fig. 3) (LE: 3, GR: C). Unless the primary tumor is located at the bladder neck or in the urethra, a major part of the functioning female urethra and—provided a complete tumor resection is possible—its supplying autonomous nerves can be preserved in case of a planned orthotopic neobladder [5–9] (LE: 3, GR: C).

Pelvic lymphadenectomy provides staging information and may contribute to control locoregional disease and thus potentially improve cancer-specific survival. Disease-specific survival after RC is usually predicted by pathological tumor stage, status of surgical margins and involvement of lymph nodes [10]. In a prospective randomized phase III trial on the clinical efficacy of neoadjuvant chemotherapy plus RC [11], it was shown that surgical factors including the extent of lymph node dissection (LND) and the individual surgeon's experience have a major impact on the therapeutic outcome and overall survival [12] (LE: 1). This trial also indicated that chemotherapy was more likely to be beneficial if patients received a high-quality surgery by an experienced surgeon. It was concluded that it is extremely important to develop

universally accepted standards for radical cystectomy and pelvic LND in patients with invasive bladder cancer in order to improve outcome [13].

The anatomical extent of pelvic LND and the minimum number of lymph nodes to be retrieved for an accurate staging still have to be defined. The crossing of the ureters with the common iliac vessels may be regarded as the most cranial limit for a standard LND [14], whereas extended lymphadenectomy extends up to the aortic bifurcation. It is generally agreed that the more lymph nodes are removed the higher is the number of patients with positive lymph nodes [15–17] (LE 3). It has to be underlined that the number of retrieved lymph nodes can be influenced by many factors, such as the specifics of the surgeon [16], the extent of lymphadenectomy [14, 15, 18], presentation of the pathological specimen [19] and pathohistological work-up and techniques/methods of analysis [16]. The clinical reality seems to be different: an evaluation of the SEER database in 2003 demonstrated that the majority of patients in a population-based analysis had 4 or fewer nodes removed with RC [20, 21], but this may be changing more recently.

There are currently two phase III randomized trials evaluating the impact of different pelvic LND templates on survival. The recently published German trial (LEA AUO AB 25/02) randomized 401 patients with locally resectable T1G3 or T2–T4aM0 urothelial carcinoma of bladder patients to limited (obturator, internal and external iliac nodes) vs. extended LND (standard + deep obturator, common iliac, presacral, paracaval, interaortocaval and para-aortal nodes up to inferior mesenteric artery). Extended LND failed to show superiority over limited LND with regards to RFS (5-year RFS 65% vs 59%; hazard ratio [HR] = 0.84 [95% confidence interval 0.58–1.22]; $p = 0.36$), CSS (5-year CSS 76% vs. 65%; HR = 0.70; $p = 0.10$), and OS (5-year OS 59% vs. 50%; HR = 0.78; $p = 0.12$). Clavien grade ≥ 3 lymphoceles were more frequently reported in the extended LND group within 90 d after surgery (8.6% vs. 3.4%, $p = 0.04$) [22]. The other trial SWOG-1011 completed accrual, but results are pending (Clinicaltrials.gov Identifier: NCT01224665).

Table 1 summarizes our recommendations.

Minimally invasive approach: laparoscopic and robotic-assisted radical cystectomy (RARC)

Several meta-analyses have highlighted that minimally invasive techniques compared with open RC decrease blood loss and transfusion rates, have shorter time to resuming diet, and shorter length of stay [23–25]. A minimally invasive approach also reduces postoperative pain resulting in less opioid requirement and quicker return to normal day-to-day activities [26, 27]. Although the number of robotic-assisted radical cystectomy (RARC) performed in the United States is steadily increasing, < 20% of radical cystectomies are currently performed robotically [28]. Long-term oncological outcomes are currently limited to a few individual centers and cumulative series [29, 30].

Care should be taken in patient selection. Patients with decreased pulmonary compliance who cannot tolerate prolonged Trendelenburg positioning and those with a history of previous extensive abdominal surgery may be contraindicated for RARC. As agreed by the Pasadena Consensus Panel for RARC, challenging cases recommended for experienced RARC surgeons only include patients with high body mass index (BMI), clinical lymphadenopathy, clinically advanced disease (T4), large bulky tumor, multiple prior abdominal surgeries, prior pelvic radiation for pelvic malignancy, previous prostatectomy, abdomino-perineal resection, low anterior resection, or salvage RC cases [10]. Patients with clinical T3 and T4 disease should be carefully selected for such approach following consideration for neoadjuvant chemotherapy [26, 31].

Positive surgical margins (PSM) at RC are considered a measure of disease burden, predicting high local recurrence and resultant poor overall survival [12, 32]. Higher reported PSM rates in pT3/4 disease in a number of earlier multi-institutional RARC series suggest that caution should be taken in patient selection of higher stage early in the surgeon's learning curve [33]. However, series have shown no significant increase in the PSM rate despite an increasing proportion of patients with pT3/4 stage [34, 35]. Results from the latest multi-institutional phase III randomized trial (RAZOR) suggest that among the 302 patients randomized to either robot-assisted versus open RC, there were no significant differences in positive surgical, bladder or urethra margins [36].

In terms of LND a prospective, randomized, non-inferiority study by Nix et al. demonstrated a mean lymph node yield of 19 in the RARC group vs. 18 in the ORC group [37]. Second look (open) lymphadenectomy by a different experienced open surgeon showed minimal additional lymph node yield (range 0–8) to the previous median 43 lymph nodes removed by a robot-assisted approach [38]. Systematic reviews and meta-analyses have concluded that robot-assisted LND achieves similar lymph node yields to those of open LND [39–41]. There is also evidence that yield is related to expertise with high-volume surgeons more likely to perform extended LND, reflecting a correlation between their growing experience and increased comfort with advanced vascular dissection [41]. The number of lymph nodes retrieved depends on node viability, method of submission (en bloc or separately), and the processing technique.

A prospective randomized controlled trial (CORAL) comparing open (ORC) with robot and laparoscopic (LRC) RC reported that 30-day complication rates varied by type

Table 1 Summary of recommendations from the SIU–ICUD consultation on bladder cancer: treatment of muscle-invasive bladder cancer-surgery

(a) Removal of the tumor-bearing bladder and regional lymph nodes	Level of evidence	Grade of recommendation
Preservation of the anterior and membranous urethra including parts of the prostate and seminal vesicles for reasons of fertility, potency and continence are technical variations to the nerve-sparing approach which may improve patients' quality of life but must be attentively judged against possible oncological risks	3	C
In female patients standard anterior pelvic exenteration includes the entire urethra, adjacent vagina, uterus, distal ureters and respective lymph nodes	3	C
Part of the urethra and supplying autonomous nerves can be preserved in case of a planned orthotopic neobladder	3	C
Radical cystectomy in patients with muscle-invasive bladder cancer should be performed within 3 months after initial diagnosis of stage T2–T4 disease	3	B
The more lymph nodes are removed, the higher is the probability to detect at least one positive lymph node. However, there is no real threshold of the numbers of lymph nodes which need to be removed	2	B
Although there is some evidence from retrospective and prospective analysis that an extended pelvic lymphadenectomy might be associated with an improvement in 5-year progression-free survival, the most recent prospective randomized multicentre study (LEA AUO AB 25/02) did not show any recurrence-free or overall survival benefit, instead a significantly higher proportion of grade ≥ 3 lymphoceles	1	B
Standard lymph node dissection is recommended, and this should include removal of all lymphatic tissues up to the bifurcation of the common iliac artery, with the following boundaries: ureters (medial), genito-femoral nerve (lateral), pelvic floor below the obturator nerve (posterior) and the node of Cloquet (inferior). The following packets should be included: (a) external iliac, (b) internal iliac group and (c) obturator group bilaterally, since up to one-third of all positive nodes are located around the common iliac artery	1	A
1(b) Minimally invasive approach: laparoscopic and robotic-assisted radical cystectomy (RARC)	Level of evidence	Grade of recommendation
Robot-assisted radical cystectomy is a surgical option for locally advanced bladder cancer with oncological outcomes similar to open series	2	B
High-volume centers with dedicated minimally invasive surgical teams have shown better results than smaller centers	2	C
Difficult cases should be avoided early in the surgeon's learning curve	2	C
(c) Quality of life	Level of evidence	Grade of recommendation
There is evidence for improved HRQoL for orthotopic neobladder reconstruction compared to ileal conduit urinary diversion	2	B
Appropriate patient selection for urinary diversion type is critical to achieving improved HRQoL outcomes following radical cystectomy	3	C
More high-quality randomized controlled trials are needed to confirm current findings regarding HRQoL	3	C
1(d) Surgical outcome: morbidity and mortality	Level of evidence	Grade of recommendation
Surgical complications associated with radical cystectomy and urinary diversion should be reported in a uniform grading system. Currently, the best adapted graded system for cystectomy is the Clavien grading system	2	B
Surgical complications associated with radical cystectomy and urinary diversion should include the length of follow-up for the patient cohort, and a minimum of 30-day but preferable for 90-day reported outcome	3	C
ASA score, age, comorbidities, sarcopenic status, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volume of radical cystectomy, and type of urinary diversion influence surgical outcome	2	B
Reduction in blood loss and blood transfusion is afforded by meticulous technique, use of modern surgical devices, and improved understanding of pelvic anatomy	3	C
Reduction of urinary extravasation and leak can be achieved with careful closure of anastomosis or pouch, stenting of the uretero-enteric anastomosis, and maintenance of appropriate drainage	3	C
Reduction of symptomatic lymphocele formation can be achieved with appropriate identification of lymphatic channels, careful surgical technique, and an open peritoneal window. Initial treatment should begin with percutaneous drainage	3	C
Reduction of anastomotic strictures requires meticulous surgical technique, minimal ureteral dissection, well-perfused segment, generous spatulation, and careful apical suture placement	3	C

Table 1 (continued)

1(d) Surgical outcome: morbidity and mortality	Level of evidence	Grade of recommendation
Reduction of metabolic disorders after urinary diversion requires preservation of distal ileum, serial monitoring of electrolytes and vitamin B-12 levels, understanding of bowel segment physiology, and appropriate emptying of urinary diversion	3	C
Reduction of DVT and PE can be achieved with use of low molecular weight heparin, early ambulation, and sequential compression devices	2	B
There is increasing evidence that implemented of ERAS protocols can successfully reduce complication rates, length of stay in hospital and the time taken to get back to normal activities, following radical cystectomy	3	C
ERAS protocols should be standardized and outcomes audited following implementation	3	C
(e) Oncological outcome of radical surgery	Level of evidence	Grade of recommendation
The AJCC sub-stratifications in node-negative pT2 and pT3 bladder cancer are of prognostic value	2	B
According to the TNM staging system, organ-confined bladder cancer has to be defined as ≤ pT2bN0M0	2	B
Nomograms provide improved prognostic information for oncological outcomes before and after radical surgery as compared to predictions based on pathologic TNM staging. However, their general applicability has not yet been established sufficiently by external validation	3	C
In patients older than 80 years, radical cystectomy is associated with the highest risk reduction on cancer-related and non-cancer-related mortality	3	C
Based on the scarce data available, the routine use of molecular markers for risk assessment after radical cystectomy in invasive bladder cannot be recommended	3	D

of surgery and were significantly higher in the ORC arm than the LRC arm. There was no significant difference in 90-day Clavien-graded complication rates between the three arms [42].

Results from RAZOR trial showed that there were no significant differences in overall complications (Clavien I–V) or major complications (Clavien III–V), however, rates of intraoperative and postoperative blood transfusion were significantly lower for the RARC arm (13% and 25%) compared to the ORC arm (34% and 40%), respectively (both $p < 0.01$) [36]. Retrospective data have shown comparable postoperative complication rates among intracorporeal versus extracorporeal urinary diversion after RC [43]. Results from the British iROC trial, comparing mortality, morbidity, and functional outcomes of RARC with intracorporeal urinary diversion versus open RC, are eagerly anticipated [44].

Long-term oncological outcomes data failed to identify differences in oncological outcome between minimally invasive and open techniques [30]. The latest RAZOR trial provides the best evidence to support the fact that RARC was non-inferior to ORC for 2-year progression-free survival (71.6% vs. 72.3%, difference 0.7%; $p_{\text{non-inferiority}} = 0.001$) [36].

Impact of minimally invasive approach on HRQoL

A meta-analysis comparing complication rates and health-related quality of life (HRQoL) after RARC versus ORC which included four RCTs (239 patients overall) found that the quality of the evidence was of low to moderate and concluded that probably there was no significant difference regarding HRQoL [45].

Table 1 summarizes our recommendations.

Surgical outcome: morbidity and mortality

Despite major strides in improving perioperative care and an overall trend towards reduced mortality [46], RC continues to be one of the most morbid oncologic operations [23]. RC-related complications may arise due to pre-existing patient medical comorbidities, functional status, tobacco smoking, the surgical procedure itself, the bowel anastomosis, sarcopenia, or the urinary diversion. Factors, such as hospital volume, case mix, surgeon skill and experience can influence the rate, type, and severity of surgical complications. Other aspects, including the availability and breadth of consultative, diagnostic, and ancillary services can all influence the association between RC and surgical outcomes [47].

Perioperative complications

The most common intraoperative RC complications are acute blood loss requiring blood transfusion (up to 66%) [48] and injury to adjacent organs (up to 1.7%) [49]. Acute bleeding commonly occurs during ligation of the bladder pedicles or dorsal vein of the prostate (for men) and excision of anterior vagina (for women) [35, 50, 51].

Postoperative complications

Postoperative complications comprise a large proportion of the morbidity experienced by post-RC patients. These complications include thromboembolic (up to 5% [52]), cardiac events like heart failure, arrhythmia and myocardial infarction (up to 7% [53]), pulmonary events like respiratory distress, pneumonia or re-intubation (up to 7.8% [54]), infections like pyelonephritis, sepsis, wound infection or UTI (up to 13% [55]), and renal insufficiency requiring dialysis (up to 7%) [56]).

Surgical complications

Surgical complications may arise from the RC procedure, pelvic LND, bowel anastomosis, or urinary diversion. Paralytic ileus is quite common during the postoperative course, plaguing as many as 22.7% of patients [57]; fortunately, true small bowel obstructions or anastomotic leak are less common (up to 8.7% of patients) [56]. Despite an appropriate LND, the risk of symptomatic lymphocele is still up to 5% of patients [49]. Rates of wound infection, incisional hernia, pelvic hematoma, and fascial dehiscence are widely variable, and may occur in as many as 9% of patients [50].

Complications related to urinary diversion

A comprehensive overview and update on urinary diversion as part of the ICUD–SIU Consultation on Bladder Cancer has been published [58]. Early complications may manifest in the form of urine leak, pouch leak, excessive mucous, urethro-enteric and uretero-enteric stricture. Urine leak from either a pouch or uretero-enteric anastomosis is noted in as many as 7.7% of patients [59]. Ureteral stricture-related complications can occur early or late post-RC and have been reported in up to 14% of patients in some series [60]. The stricture may be benign or, of greater concern, a malignant recurrence. Treatment options include percutaneous nephrostomy with antegrade stenting, ureteroscopic balloon dilation, or open revision. The type of anastomosis (Bricker vs. Wallace) does not appear to affect uretero-enteric stricture incidence [61, 62].

Urinary diversions are accompanied by metabolic changes in up to 3% of patients. These metabolic alterations include Vitamin B-12 deficiency, metabolic acidosis, and electrolyte derangements. Metabolic changes may result in concomitant urinary stone disease. Furthermore, chronic bacterial colonization, mucous production, urinary retention, and enteric hyperoxaluria may exacerbate stone formation in patients with urinary diversions. Rates of stone formation may approach 30% in some cases [59].

Gastrointestinal (GI) complications

Gastrointestinal (GI) complications post-RC are common and occur in up to 25% of patients [63]. The most common GI complication reported after RC is postoperative ileus (POI) or partial bowel obstruction (PBO) [56, 64–68]. POI is generally defined as oral intake intolerance that persists beyond day 5 after surgery or by nausea and emesis accompanied by abdominal distention requiring GI rest (NPO, NGT or TPN) at any time post-operatively [56, 66]. Patients may experience persistent nausea, and require nasogastric tube (NGT) placement. Major complications can include complete bowel obstruction, GI bleeding, bowel leakage, and fistula involving the bowel [56, 65, 66, 69].

Postoperative mortality

30-day mortality from RC can be as high as 3.9% in larger series [70], with higher rates among patients with advanced age [71, 72]. Mortality is largely attributed to cardiovascular or septic complications. Careful patient selection and meticulous surgical technique may help decrease the incidence of perioperative mortality [73]. Multiple studies have found that hospital and surgeon volume have a significant impact on in-hospital mortality and LOS after RC. Patients undergoing RC procedures at higher volume centers experience overall better perioperative outcomes and lower mortality rates compared with their counterparts undergoing RC at lower volume institutions [74–78]. Factors such as age, comorbidity [79, 80], nutritional status [81, 82], sarcopenia [83, 84], and hospital volume [74–78] should be considered when stratifying perioperative risk for candidates for major extirpative surgical therapy for bladder cancer.

For recommendations please refer to Table 1.

Enhanced recovery after surgery (ERAS)

Commonly employed elements of an ERAS pathway included: avoidance of mechanical bowel preparation and carbohydrate loading preoperatively. Intra-operatively: epidural anesthesia, opioid-sparing analgesia, avoiding hypothermia and careful fluid management. Post-operatively:

avoidance or early removal of NG tube in recovery with early mobilization and early oral feeding.

Several components of ERAS are effective at accelerating GI recovery and decreasing LOS, including the use of alvimopan, a mu-opioid receptor antagonist that decreases the rate of POI and shortens length of stay, as demonstrated in multiple double-blind randomized studies [66, 68, 85, 86]. A recent meta-analysis of 13 distinct ERAS studies revealed a lower overall complication rate (especially minor Clavien grades) and faster return of bowel function in the ERAS group [87]. Ramirez and colleagues demonstrated that incidence of 30-day postoperative ileus (POI) were lower with enhanced recovery protocol than traditional pathways [66].

Recently the European Association of Urology (EAU) Robotic Urology Section (ERUS) published a consensus view on an ERAS pathway guiding standardized perioperative management of RARC patients [51].

Stage-specific oncologic outcomes

Patients with organ-confined, node-negative disease (≤pT2pN0; AJCC stages 0a–II) have an overall disease-specific survival rate of 60–85% over 5 and 10 years [76, 88]. In contrast, the 5-year disease-specific survival for patients with node-negative extravesical disease (pT3a–4a, pN0; AJCC stage III) is in the 50% range. Patients with node-positive disease who have undergone LND can expect up to a 30% chance of long-term recurrence-free survival [3] based on the number of positive nodes.

In a study by Soria and colleagues evaluating a cohort of 1652 patients with bladder cancer treated with RC, late recurrence (LR) was defined as occurring more than 5 years after RC, and 12.2% experienced LR, with a median time to recurrence of 86 months. LR was more likely to be located in the remnant urothelium. Older age, non-organ-confined disease at RC, and non-urothelial recurrence site were independently associated with post-recurrence OS. These findings reinforce the need for lifelong follow-up of bladder cancer patients after RC [89].

Williams and colleagues developed a validated nomogram assessing 3- and 5-year overall and cancer-specific survival following RC using Surveillance, Epidemiology, and End Results-Medicare data (available online as RC Survival Calculator https://www.utmb.edu/surgery/divisions-sections/urology/radical-cystectomy-survival-calculator) [90].

For recommendations, see Table 1.

Neoadjuvant chemotherapy

Medical suitability for neoadjuvant chemotherapy includes renal function and fitness for cisplatin-based chemotherapy, based on a uniform definition of "unfit" proposed on the basis of a survey of genitourinary medical oncologists [91].

Randomized trials evaluating role of neoadjuvant chemotherapy for bladder cancer

There are a total of 16 randomized phase 3 trials evaluating neoadjuvant chemotherapy compared to surgery or radiation alone, published from 1991 to 2014, with number of patients ranging from 60 to 976. Two trials stand out, namely the SWOG Intergroup trial published by Grossman et al. in *New England Journal of Medicine* [11], and MRC-EORTC/BA06 30894 trial by the International Collaboration of Trialists published in *Journal of Clinical Oncology* [92].

The SWOG Intergroup trial [11] randomized patients with T2–T4a urothelial bladder cancer to RC alone (154 patients) versus 3 cycles of MVAC followed by RC (153 patients) [11]. The use of neoadjuvant chemotherapy was associated with a higher rate of complete pathologic response (38% vs 15%, $p < 0.001$). At a median follow-up of 8.7 years, improvements in median overall survival (77 versus 46 months, $p = 0.06$) and 5-year survival (57% versus 43%, $p = 0.06$) favored the neoadjuvant MVAC arm [11]. There were no treatment-related deaths and neoadjuvant chemotherapy did not adversely impact the ability to proceed with RC or increase adverse events related to surgery.

In 2011, the International Collaboration of Trialists evaluated long-term oncological outcomes after neoadjuvant chemotherapy, updating their previously historical RCT [92]. With a median follow-up of 8 years, a significant OS benefit was demonstrated with 16% reduction in the risk of death from any cause (HR 0.84, 95% CI 0.72–0.99, $p = 0.037$), translating to a 6% improvement in 10-year OS (from 30 to 36%).

Meta-analysis of randomized trials for neoadjuvant chemotherapy

The first meta-analysis of neoadjuvant chemotherapy trials was performed by the Advanced Bladder Cancer group from the Cochrane collaboration [93]. Data from 2688 patients treated in ten randomized trials evaluating neoadjuvant chemotherapy for invasive UC was reviewed. Of note, this analysis did not include data from the SWOG Intergroup trial [11].

A subsequently reported meta-analysis including individual patient data from 3005 patients enrolled in 11

randomized trials (including the SWOG Intergroup trial) extrapolated from the published report [11], confirmed the overall survival benefit for neoadjuvant cisplatin-based compared to local therapy alone [93, 94] (HR = 0.86; 95% CI from 0.77 to 0.95; $p = 0.003$) with an absolute improvement of 5% in 5-year OS.

An updated meta-analysis of 15 randomized trials was published in 2016, showing persistent OS benefit with the use of neoadjuvant chemotherapy even after including all these negative trials (HR = 0.87; 95% CI from 0.79 to 0.96). This benefit was even greater when only considering patients who received cisplatin-based regimen (HR = 0.84; 95% CI from 0.76 to 0.93) [95].

Novel combinations as neoadjuvant therapy for bladder cancer

Only the conventional MVAC regimen has been extensively evaluated in the neoadjuvant setting for bladder cancer, with most trials using this regimen. On this basis, MVAC has the strongest evidence-based data for neoadjuvant use.

Novel combinations include dose-dense or accelerated MVAC, whose safety and efficacy has been described both retrospectively [96–98] and in prospective single-arm phase 2 trials [99, 100], with pathologic response rates (≤ pT1N0M0) up to 49%. No prospective evidence of superiority has been demonstrated versus the standard/conventional MVAC regimen in the neoadjuvant or adjuvant setting, but dose-dense MVAC is given in a shorter period of time. Dose-dense MVAC appeared superior in terms of response rate but not survival and less toxic in the advanced disease setting [101]. Several retrospective datasets have shown comparable pathologic response rates between gemcitabine/cisplatin (GC) and conventional MVAC with less toxicity noted with GC [102, 103]. Carboplatin should not be used instead of cisplatin in the neoadjuvant or adjuvant setting outside a clinical trial setting. Clinical trials overall are critical for the assessment of immunotherapy, novel single agents, combinations and putative biomarkers.

Selecting the best candidates for neoadjuvant chemotherapy

Molecular subtyping of MIBC using gene expression analysis has been performed on pre-chemotherapy transurethral resection specimens, and found that basal tumors derived the greatest overall survival benefit with neoadjuvant chemotherapy when compared with surgery alone [104]. This was consistent with another group's gene expression profiling efforts among patients enrolled in a phase 2 trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab, showing that the basal subtype had better survival [105]. Post-neoadjuvant chemotherapy RC specimens have also been examined and molecularly profiled to identify which subtypes do not respond well to cisplatin, paving the way toward personalized medicine [106].

Table 2 summarizes our recommendations.

Adjuvant chemotherapy

Adjuvant chemotherapy for bladder cancer is controversial. This controversy is fuelled by suboptimal outcomes for locally advanced patients treated with radical RC alone, a small potential benefit of chemotherapy and a sequence of trials that have been under-powered, some of them flawed and/or closed early due to poor accrual as well as the presence of more definitive evidence for neoadjuvant chemotherapy. Recently, this discussion was opened again due to the release of three randomized phase III trials and a meta-analysis that included two of these trials [107–110].

A historical account of each of the 10 clinical trials evaluating adjuvant chemotherapy for muscle-invasive bladder cancer is detailed in the complete Chapter 6 of the Joint SIU–ICUD Consultation on Bladder Cancer.

Of these 10 trials, 9 evaluated combination cisplatin-based chemotherapy regimens, which is the current standard practice, with the exception of Studer's initial single-agent cisplatin trial [111]. Of note, the latest published trial by Sternberg et al. (EORTC-30994) accrued patients with pT3–4 and/or lymph node-positive urothelial bladder cancer and with creatinine clearance > 60 ml/min to either four cycles of cisplatin-based combination chemotherapy of physician preference (GC, MVAC, or dose-dense MVAC [101]) or chemotherapy with the same regimen at relapse [110]. Median follow-up of the trial was 7 years, but trial was significantly under-accrued with less than half of intended patients and thus deemed under-powered. The primary endpoint of overall survival was not significantly improved in the immediate treatment compared to the deferred group despite a noted trend (HR 0.78, 95% CI 0.56–1.08, $p = 0.13$) with a median OS of 6.74 years (95% CI 3.85–not reached) and 4.60 years (2.15–6.25) which corresponds to a 5-year OS rate of 53.6% (immediate) and 47.7% (deferred). Progression-free survival was significantly prolonged in the immediate compared to the deferred treatment group (HR 0.54, 95% CI 0.4–0.73, $p < 0.0001$), with a 5-year PFS of 47.6% (95% CI 38.8–55.9) in the immediate treatment group and 31.8% (24.2–39.6) in the deferred treatment group [110].

Meta-analysis of existing trials for adjuvant chemotherapy

A meta-analysis by Leow et al. [108] included data from 945 patients from 9 randomized controlled trials, including three new trials and updated one compared to the 2006 Advanced

Table 2 Summary of recommendations from the SIU–ICUD consultation on bladder cancer: treatment of muscle-invasive bladder cancer—neoadjuvant and adjuvant chemotherapy

(a) Neoadjuvant chemotherapy	Level of evidence	Grade of recommendation
Cystectomy is considered the gold standard of treatment for localized muscle-invasive bladder cancer	2	B
A discrepancy between clinical/cystoscopic and pathologic staging can be anticipated after neoadjuvant chemotherapy and therefore cystectomy is not obviated by response	2	B
Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable. However, few data on quality of life are available	2	B
Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a modest but real benefit in favor of neoadjuvant chemotherapy	1	B
Cisplatin-based combination chemotherapy should be offered to all eligible patients with cT2–T4aN0M0 urothelial bladder cancer	1	A
We recommend using accelerated or dose-dense MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for appropriately selected cases as the neoadjuvant chemotherapy regimen	2	B
Although other regimens, such as gemcitabine plus cisplatin [GC], have comparable activity in patients with metastatic disease, there are no data from randomized trials in the neoadjuvant setting to support the use of regimens other than MVAC. Retrospective datasets in NAC setting show comparable pCR rates between GC and MVAC	2	B
Available data suggest that for "average-risk" cancer patients with cT2, the benefit of adding neoadjuvant chemotherapy to local therapy is at best modest, but still benefits outweigh the risks. Likewise, all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b/T4a cancers or those thought to have lymph node involvement	2	B
Carboplatin-based regimens should not be used in the neoadjuvant setting	2	B
No predictive biomarker has an established role to exclude patients from neoadjuvant cisplatin-based therapy	3	D
The quality of the surgery is a confounding factor in interpreting these studies	3	C
Presence of squamous or glandular differentiation in locally advanced UC of the bladder does not seem to confer resistance to MVAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy	3	C
(b) Adjuvant chemotherapy	Level of evidence	Grade of recommendation
Adjuvant cisplatin-based chemotherapy is supported by a recent large cohort analysis (LE: 2); several randomized clinical trials (LE: 1) and the results of two meta-analysis and composite analysis of randomized trials (LE: 1). However, the trials used in meta-analyses were flawed, mainly due to poor recruitment and early termination, so as to make definitive conclusions difficult. On that basis, the group provides a grade B recommendation for adjuvant cisplatin-based chemotherapy in the patient with pT3/4 and/or lymph node-positive cancer at cystectomy, who has not had neoadjuvant chemotherapy and is medically fit	2	B
Adjuvant regimens not containing cisplatin (including those containing carboplatin) should not be routinely used outside of clinical trials because of a lack of evidence for their benefit in that setting. Patients who cannot tolerate cisplatin-based combination therapy should be included in the clinical trials or observed	2	C
Until the current equipoise is resolved for adjuvant chemotherapy in this setting, clinical trial remains the best choice for patients with locally advanced bladder cancer	3	C
Adjuvant chemotherapy may be considered for patients who already had neoadjuvant chemotherapy, based on a hypothesis-generating well-conducted retrospective cohort study showing superior 5-year overall survival	3	C

Bladder Cancer Meta-analysis Collaboration [112]. Hazard ratio for overall survival in favor for adjuvant chemotherapy was reported to be 0.77 (95% CI 0.59–0.99; $p = 0.044$) and disease-free survival was improved by 34% (HR 0.66 (95% CI 0.48–0.92; $p = 0.014$). In the sensitivity analysis, this meta-analysis demonstrated heterogeneity in outcome due to different ratios of pN1+ vs. pN0 patients between the trials [108]. After stratification of studies by lymph node ratio, the observed heterogeneity was corrected. Interestingly, the HR for DFS was more favorable among studies consisting of > 50% of patients with pN+ disease (HR 0.39; 95% CI 0.28–0.54) compared to HR 0.89 (95% CI 0.69–1.15) for studies with less nodal involvement (< 50% pN+). This is in contrast to the results of the EORTC-30994 trial [110], in which patients with pN0 had the most prominent effect from immediate chemotherapy. Therefore, the risk group of patients who have the greatest benefit of adjuvant chemotherapy still remains to be defined.

The EORTC-30994 publication incorporated these results in a literature-based meta-analysis extending the results

of the meta-analysis by Leow et al. and noted a benefit of immediate treatment on overall survival (HR 0.77, 95% CI 0.65–0.91; $p=0.002$) [110].

Large cohort studies have also confirmed the utility and comparative effectiveness of adjuvant chemotherapy in real-world practice [113–115].

Role of adjuvant chemotherapy in patients who already had neoadjuvant chemotherapy

The role of adjuvant chemotherapy, after receipt of neoadjuvant chemotherapy followed by surgery, is under-investigated at this current juncture, with no randomized trials conducted.

The largest retrospective study to date came from Seisen et al. who used the National Cancer DataBase to further evaluate this on a larger scale, identifying 788 patients with pT3/4 and/or pN+ disease, all of whom received neoadjuvant chemotherapy followed by RC [116]. Of these, only 23% received adjuvant chemotherapy after RC. With a median follow-up of nearly 4 years, the authors found that those who also received adjuvant chemotherapy had improved 5-year overall survival rates (36.8%) compared to those who did not (24.7%), with a significant OS benefit shown on propensity-weighted Cox proportional hazards regression (HR 0.48, 95% CI 0.61–0.99, $p=0.046$). This may represent sufficient preliminary evidence to garner support for a randomized trial to determine if patients, particularly those with adverse pathological features, may benefit from further adjuvant chemotherapy after surgery.

Immunotherapy in localized muscle-invasive bladder cancer

Immune checkpoint inhibitors (ICI) demonstrated an overall survival advantage in salvage treatment of metastatic/unresectable urothelial bladder cancer [117] and are currently explored in the adjuvant setting in three large phase III trials with nivolumab vs. placebo (CheckMate 274, NCT02632409), atezolizumab vs. observation (IMvigor010, NCT02450331) and pembrolizumab vs observation (AMBASSADOR, NCT03244384).

Biomarkers and other indicators of potential neoadjuvant and adjuvant chemotherapy benefit

Current biomarker efforts led by the International Bladder Cancer Consortium have been directed at large-scale tissue microarray construction and analysis for putative biomarkers of chemotherapy response, such as ERCC1 [118–121], ERCC2 [122, 123], ATM, Rb1, FANCC [124] (platinum chemotherapy) ribonucleotide reductase (gemcitabine) [125, 126], topoisomerase II (doxorubicin, epirubicin) [127, 128] and beta-tubulin (taxanes) [126, 129, 130]. There are at least three neoadjuvant clinical trials evaluating the potential clinical utility of such molecular biomarkers, esp. in DNA repair genes. Data have also been published regarding gene expression profiling and protein biomarkers, however, validation is needed [104, 131]. Table 2 summarizes our recommendations.

Bladder-sparing treatments for localized disease

Transurethral resection of the bladder (TURBT) and partial cystectomy with or without multi-modal therapy

The 5-year survival rates for selected patients with cT2-3 tumors treated by TURBT alone ranged from 63 to 76.7% [132, 133]. An R0 TURBT is the essential first step of successful trimodal therapy (TMT). Performing a second TUR prior to initiating chemotherapy and radiation is also recommended since it is associated with better DSS (69% vs. 42% 5-year DSS, $p=0.046$) [134].

Partial cystectomy is not commonly performed. In the SEER and National Inpatient Sample databases from 1988 to 2000; partial cystectomy was performed in 13–17% of patients and more commonly in rural, non-teaching low-volume hospitals [135]. Investigators evaluating the US National Cancer Database from 2003 to 2007 found a lower utilization that decreased over time from 10 to 7% [136].

For recommendations, see Table 3.

Radiation-based trimodal therapy

Contemporary radiation-based bladder-sparing therapy algorithms consist of: (1) maximal transurethral resection of the tumor (TURBT); (2) induction external beam radiation therapy with concurrent chemotherapy; (3) cystoscopic assessment of treatment response with prompt RC for non-responders, and (4) active cystoscopic surveillance with RC at the first sign of invasive recurrence. These trimodal algorithms were developed as a result of the lack of adequate local control of MIBC treated by TURBT, by chemotherapy, or by radiotherapy when used without RC (Fig. 4). A recent meta-analysis and systematic review found no difference in disease-specific survival (at 5 or 10 years), progression-free survival (at 10 years), or overall survival (at 5 or 10 years) between RC versus trimodal therapy [137]. Additionally, a recent propensity score analysis that matched patients treated with RC and patients treated with trimodal therapy in a multi-disciplinary bladder cancer clinic found no significant difference in 5-year disease-specific survival rates (73.2% in the RC group versus 76.6% in the trimodal group [138]. The similarity in survival rates between

Table 3 Summary of recommendations from the SIU–ICUD consultation on bladder cancer: treatment of muscle invasive bladder cancer—bladder-sparing treatments

(a) Transurethral resection of the bladder and partial cystectomy with or without multi-modal therapy	Level of evidence	Grade of recommendation
TUR monotherapy is an alternative to radical cystectomy in appropriately selected (see 2. below) and counseled patients with T2–T3a N0Mx bladder cancer who are frail for standard approaches	3	C
Patients most appropriate for this approach have tumors that are: (a) Small (b) Completely resectable (c) Have negative tumor bed and periphery biopsies (d) Are not associated with upper tract compromise (i.e., hydronephrosis) (e) Are not associated with radiographic evidence of locoregional extension of disease (T3b, N+) at the time of first treatment	3	C
TUR monotherapy should be discussed as part of the informed consent process to patients contemplating management options for invasive bladder tumors (TNM stages T2–3a, N0Mx)	3	C
If technically feasible, an R0 resection should be attempted during TUR prior to multi-modal therapy since it is associated with higher CR, decreased need for salvage cystectomy, and more favorable survival	2	C
Highly selected patients with focal invasive cancers and cT0 or minimal residual disease after neoadjuvant chemotherapy may be candidates for bladder sparing with either TUR or partial cystectomy	3	C
(b) Radiation-based bladder-preserving strategies—trimodal therapy (TMT) for MIBC	**Level of evidence**	**Grade of recommendation**
Radiation therapy followed by salvage cystectomy for tumor recurrence has comparable survival to preoperative radiation therapy and cystectomy	1	A
Radiation therapy and chemotherapy result in a higher rate of locoregional disease-free survival than does radiation therapy alone	1	A
Radio-sensitizing drugs include: cisplatin, paclitaxel, 5-fluorouracil, mitomycin C, gemcitabine, and carbogen and nicotinamide	1	A
Combined radiation and chemotherapy allow good preservation of bladder function in the great majority of patients. Quality-of-life studies have demonstrated that the retained native bladder performs well and long-term toxicity to pelvic organs is low	2	B
There is no consistent clinical trial basis to indicate that neoadjuvant chemotherapy prior to (chemo)radiation therapy improves survival	1	A
Complete TURBT, when possible, is associated with higher rates of local tumor control and higher cure rates than does incomplete initial tumor resection for selected patients in trimodality radiation/chemotherapy trials	2	B
Data suggest that high expression of the molecular marker MRE 11 may be a putative predictor for cause-specific survival following radical (chemo)radiation therapy for MIBC	3	B
Trimodality therapy consisting of TURB plus concurrent radio-sensitizing chemotherapy and radiation is judged safely possible and, when combined with early salvage cystectomy for recurrence, this bladder-preserving treatment approach offers a chance for long-term cure and survival in selected patients comparable to radical cystectomy. Studies support the acceptance of modern bladder-sparing trimodality therapy for well selected patients* as a proven alternative to cystectomy	2	B
Combined radiation and chemotherapy affords a > 70% chance of preserving the native bladder	1	A
Following bladder preservation therapy, lifelong cystoscopic surveillance is recommended	2	C

*For discussion of appropriately selected patients, please see the discussion in the radiation-based trimodal therapy section of the text

RC and bladder-preserving trimodal therapy is likely in part to the prompt use of salvage RC when necessary for recurrence in the bladder-preservation series and also the appropriate selection of patients for trimodal therapy including, ideally, (1) tumors < 6 cm, (2) solitary tumors, (3) minimal to no hydronephrosis, (4) good bladder function, and (5) no multifocal or extensive carcinoma in situ [139]. Biomarkers may enable the identification of subgroups of patients who are more likely to benefit from one treatment over another, and guide the use of combination therapies that include other modalities, such as immunotherapy [140, 141].

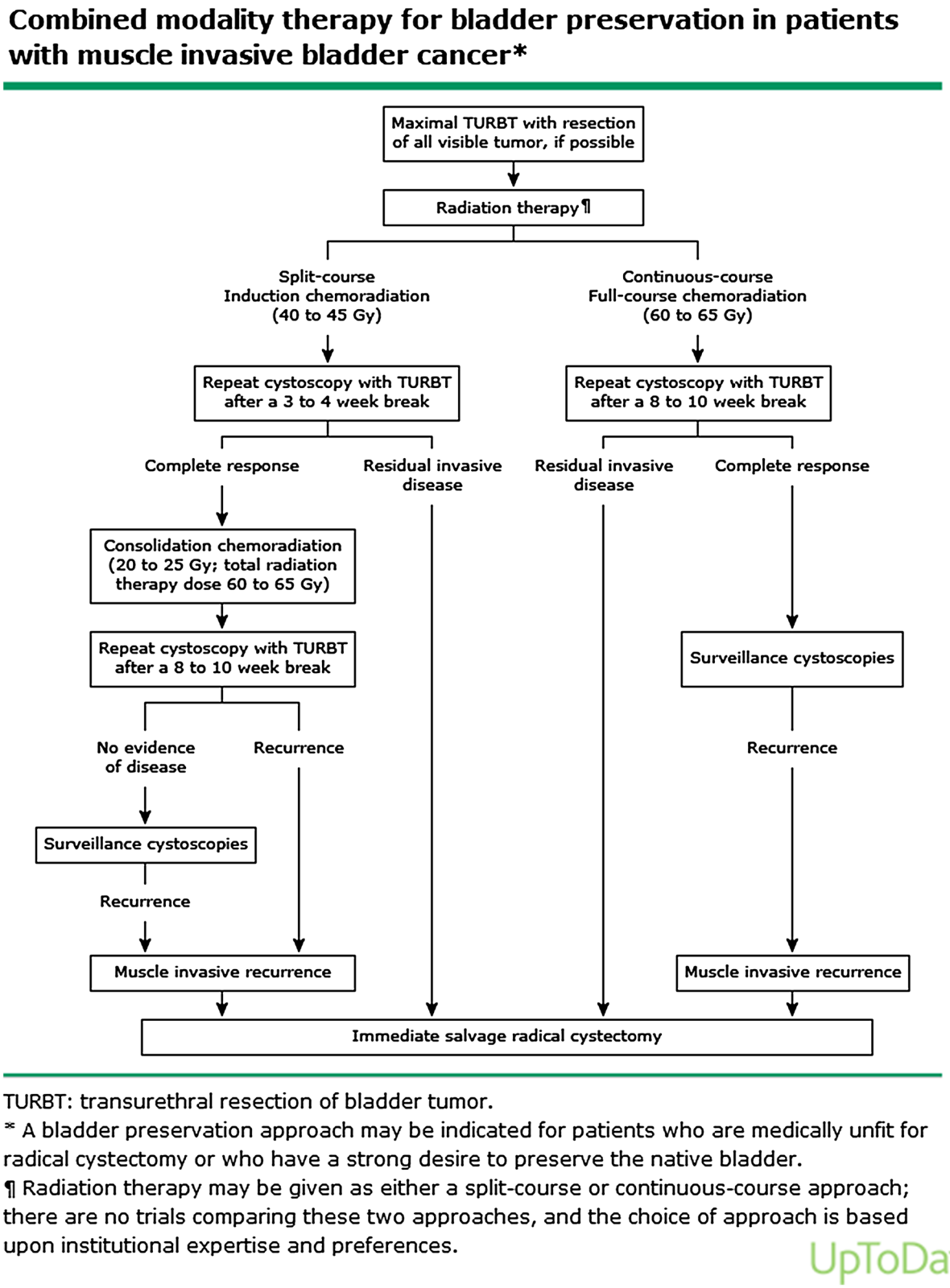

Fig. 4 Suggested trimodality algorithm for the management of muscle-invasive bladder cancer: recommendations from joint SIU–ICUD consultation on bladder cancer. Reproduced with permission from: Efstathiou JA, Saylor P, Wszolek M. Bladder preservation treatment options for muscle-invasive urothelial bladder cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (accessed on [1 Aug 2018]). Copyright© 2018 UpToDate, Inc. For more information visit https://www.uptodate.com

External beam radiation alone with salvage RC reserved for tumor recurrence

Radiation monotherapy has generally been reserved for patients judged too unfit for RC on the basis of co-morbid conditions and/or due to disease extent. These negative selection criteria may have contributed to the relatively poor results achieved with radiation therapy alone compared to RC.

Four randomized trials in the 1970s compared external beam radiation therapy alone (60 Gy) with RC reserved for local recurrence to the standard group receiving pre-operative radiation therapy (40–50 Gy) with immediate RC [142–144]. Three of these trials showed equivalent overall survival with either approach. These studies provided Level 1b evidence that a bladder-preserving approach with radiation therapy alone and salvage RC for local recurrence was not significantly different in overall survival in this "pre-neobladder" era; however, combined modality approaches are preferred as described in the following.

External beam radiation combined with concurrent radio-sensitizing chemotherapy

Updated results with long-term outcomes include pooled analyses of RTOG protocols 8802, 8903, 9506, 9706, 9906, 0524, 0712 and 0233 [139, 145, 146], with over 450 patients, median follow-ups of 4.3–7.2 years, and a 5-year and 10-year overall survival rates of 57% and 36–39%. There are also two randomized trials showing the benefit of concurrent chemoradiation over radiation alone, including the BC2001 trial [147] which showed significant increase in locoregional disease-free survival rate at 2 years (67% compared to 54% with radiation alone, $p = 0.02$) [148].

Quality of life after definitive radiation for MIBC

If the survival and cancer control outcomes appear similar (in the absence of level 1 evidence) between RC and trimodal therapy, then the different morbidity profiles and quality of life considerations of the treatment modalities become paramount. The instruments to assess quality of life have been well established for prostate cancers and gynecologic cancers, but not for bladder cancer. The instruments that are currently used for bladder cancer patients are adaptations and thus their validity is somewhat uncertain. These studies are also limited by incomplete sampling of all potential participants that leaves unclear whether or not the non-participants are those who have had worse or better outcome. [149].

Over 70% of patients undergoing trimodal therapy will retain their native bladder and minimal late pelvic toxicity is required to reap the potential reward of this bladder-sparing approach [139]. Long-term bowel and bladder toxicity after chemoradiotherapy was reported in patients enrolled in prospective sequential RTOG trials (8903, 9506, 9706 and 9906) and, in 157 patients who underwent combined modality therapy and survived at least 2 years with bladders intact. With a median follow-up of 5.4 years, 7% of patients experienced late Grade 3 or 4 pelvic toxicity (5.7% GU and 1.9% GI) [150]. Further, a separate series of 71 patients with a median follow-up of 6.3 years from trimodal therapy found that 75% of patients had normal functioning bladders on urodynamic study [151].

A more recent cross-sectional bi-institutional questionnaire study attempted to compare the quality of life of RC versus trimodal therapy in 226 patients treated over 20 years [152]. With a response rate of 77%, a median follow-up of over 5.5 years, using six different validated quality-of-life instruments and propensity score matching, multivariable analysis demonstrated better general quality of life in those who received trimodal therapy versus RC. Trimodal therapy was associated with superior physical, social, emotional, and cognitive functioning as well as bowel and sexual function. Urinary symptom scores were similar. Finally, a recent comparative effectiveness modeling study using the primary endpoint of quality-adjusted life years (QALY) showed a potential QALY gain with bladder-preserving tri-modality therapy relative to RC [153]. Results from these study designs remain hypothesis-generating and subsequent prospective investigations are warranted. Unfortunately, the randomized trial SPARE (selective bladder preservation against radical excision) closed early due to low accrual [154].

Recommendations for radiation-based bladder-preserving strategies for MIBC are summarized in Table 3.

Treatment of mixed-histology urothelial carcinoma with localized disease

The current WHO classification distinguishes different urothelial and non-urothelial variants of the bladder carcinoma and was updated recently in 2016 [155]. Six urothelial carcinoma variants, which all urologists and pathologists will see and need to be familiar with include: (a) nested variant urothelial cancer; (b) micropapillary urothelial cancer; (c) carcinosarcoma (sarcomatoid urothelial cancer), and urothelial cancer with (d) small cell, (e) squamous, and (f) glandular—components. We recommend treating the former three variants (a, b, c) with aggressive local extirpative surgery. Urothelial carcinoma with small cell component should be treated with neoadjuvant cisplatin (for fit patients) and etoposide prior to aggressive local extirpative surgery (or radiation), while those with squamous, and glandular components (not pure) are recommended to be treated as per standard practice-neoadjuvant multi-drug

Table 4 Summary of recommendations from the SIU–ICUD consultation on bladder cancer: treatment of muscle-invasive bladder cancer—mixed-histology urothelial carcinoma

Treatment of mixed-histology urothelial carcinoma	Level of evidence	Grade of recommendation
Nested variant and micropapillary urothelial cancers regardless of detection in non-muscle invading or muscle-invading stages should be treated with aggressive local extirpative therapy	3	B
Carcinosarcomas should be treated if possible with local extirpative surgery	3	B
Urothelial cancer with small cell components should be treated with neoadjuvant chemotherapy including cisplatin (for fit patients) and etoposide neoadjuvantly followed by aggressive local treatment	3	B
Muscle-invading urothelial cancers with squamous or glandular elements should be treated neoadjuvantly with multi-drug cisplatin-based urothelial cancer regimens before definitive surgery	3	C

cisplatin-based urothelial cancer regimens before definitive surgery (Table 4). Clinical trials are strongly recommended. Evidence underlying these recommendations may be found in the complete Chapter 6 of the Joint SIU–ICUD Consultation on Bladder Cancer. On the other hand, non-urothelial cancers of the urinary bladder are rare and their management is detailed in another chapter [156].

Follow-up after radical surgery

There is no one-size-fits-all follow-up protocol for patients with localized bladder cancer who had undergone radical surgery, due to the variability in early and late postoperative morbidity, incidence and location of recurrences, life expectancy, and uptake of various imaging modalities. The risk of disease recurrence post-RC can be predicted using a nomogram consisting of pT and pN stage, age, gender, tumor grade at RC, presence of lymphovascular invasion, presence of carcinoma in situ in the RC specimen, neoadjuvant chemotherapy, adjuvant chemotherapy and adjuvant radiotherapy [157]. This can help estimate an individual's risk of systemic relapse and develop a risk-adapted follow-up protocol.

To prevent local recurrence particularly in locally advanced (T3–4, N0–1, M0) bladder cancers, adjuvant chemotherapy should be considered to eradicate micrometastases, as discussed above. Adjuvant radiotherapy appears to decrease local recurrence rates and improve disease-free survival [158].

Should pelvic recurrence occur, median survival ranges from 4 to 8 months after diagnosis, even with treatment. Although definitive therapy (in the form of systemic chemotherapy, local surgery or radiotherapy) can prolong survival, it is mainly to palliate symptoms [159].

Conclusions

It is paramount to utilize a multi-disciplinary approach to achieve the best outcomes for MIBC patients, irrespective of their age, performance status, fitness, renal function, or disease severity. Neoadjuvant cisplatin-based combination chemotherapy (for fit patients) followed by RC, bilateral pelvic lymphadenectomy and urinary diversion is the standard treatment for MIBC. Adjuvant cisplatin-based chemotherapy (for fit patients) can be considered for high-risk disease if no prior neoadjuvant chemotherapy. Bladder-preserving trimodal treatment with maximum transurethral resection of bladder tumor followed by concurrent radio-sensitizing chemotherapy and radiation is safe and, when combined with early salvage RC for recurrence, can likely provide comparable oncologic outcomes in selected patients.

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Compliance with ethical standards

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