Review Article

Quality indicators for the management of muscle-invasive bladder cancer in the perioperative setting of radical cystectomy: a narrative review

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Background and Objective: Identifying evidence-based and measurable quality-of-care indicators is crucial for optimal management of patients requiring radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC). RC with urinary diversion and lymphadenectomy is the standard treatment for patients with MIBC. Preoperatively, neoadjuvant chemotherapy (NAC) with cisplatin-based combinations improves survival outcomes and is the recommended standard of care for eligible patients. Intraoperatively, lymph node dissection (LND) by, at least, following a standard pelvic lymph node template improves overall- and recurrence-free survival and allows for accurate tumour staging. Avoiding positive soft tissue surgical margins (STSM) should be a main target intraoperatively since they are almost universally associated with mortality. Implementing enhanced recovery after surgery (ERAS) programs can reduce lengths of hospital stay (LOS) and postoperative complication rates without increasing readmission rates after RC. Moreover, several studies have shown that smoking negatively affects local and systemic treatment outcomes in bladder cancer (BC) patients. Therefore, smoking cessation counselling for smokers should be an essential part of bladder cancer management regardless of the disease state.

Methods: We performed a comprehensive, non-systematic review of the latest literature to define indicators representing the best evidence available for optimal care of MIBC patients treated with RC.

Key Content and Findings: In this review, we propose five major quality indicators that are easily implementable for optimized management of MIBC patients treated with RC, including: usage of cisplatin-based NAC in eligible patients, ensurance of negative STSM, performance of (at least) a standard pelvic template LND, implementation of ERAS strategies, and professional smoking cessation counselling.

Conclusions: Optimal management of MIBC needs to be framed by evidence-based, reproducible, and

measurable quality indicators that will allow for guidance and comparative effectiveness assessment of clinical practices; adherence to them is likely to improve patients' prognoses by a tensible margin. For the treatment of MIBC patients with RC, we identified five essential quality indicators.

Keywords: Assessment; bladder cancer (BC); muscle-invasive bladder cancer (MIBC); cystectomy; radical cystectomy (RC); quality

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Introduction

Urothelial carcinoma of the bladder is a common malignancy. It ranks fourth most frequent of solid cancers in men and tenth most frequent in women, with approximately 83,000 new cases annually in the US (1,2). Around 21% of bladder cancer (BC) cases are muscle-invasive at diagnosis, and a significant proportion of high-risk non-muscle invasive bladder cancer progresses eventually to muscle-invasive bladder cancer (MIBC) (3-6).

The standard of care for localized MIBC is the administration of neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (RC) with lymph node dissection (LND) and urinary diversion (7,8). Depending on perioperative findings, adjuvant cisplatin-based combination chemotherapy might be an option in patients at high risk of relapse if no neoadjuvant chemotherapy (NAC) was given before surgery (7).

There are several guidelines created by the relevant national and international institutions that provide surveillance and treatment recommendations in order to improve care for BC patients (7-13).

However, adherence to these recommendations is inconsistent and suboptimal, with substantial variability in clinical practices and differences in practice patterns, costs, and outcomes (14-19).

To optimize compliance and patient-centred care, the usage of implementation science was proposed as a systematic process to better align practice patterns with risk-adapted, individual treatment recommendations (20).

However, to reach reproducible and comparable quality metrics in clinical practices and ensure outcomes at the highest possible level, consensus on evidence-based quality indicators and their constant adherence and measurement remain an unmet need. To address this need, we propose five key factors as essential quality indicators for the optimal management of MIBC and suggest their systematical assessment for every patient and reporting. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1116/rc).

Methods

We performed a comprehensive, non-systematic review of the latest literature to define indicators that represent the best evidence available for optimal care of MIBC patients undergoing RC. We included relevant articles in English available in the MEDLINE/PubMed database up to 31 December 2021. Search terms included "radical cystectomy", "muscle-invasive bladder cancer", "outcome", "management", "quality", and associated terms. Additionally, guidelines of the relevant urological societies and references of the selected articles were reviewed. In this article, we propose the selected indicators that may guide uro-oncologic physicians in their daily practice and as key reporting measures for future study designs (*Table 1*).

Main body

NAC

Despite radical removal of the urinary bladder with curative intent, patients with MIBC are at high risk for disease recurrence and progression. Indeed, RC alone with lymphadenectomy provides 5-year relapse-free survival (RFS) and -overall survival (OS) estimates of only about 69% and 50% in the patients with muscle-invasive disease, respectively (21-26).

General advantages for chemotherapy in the neoadjuvant setting include better chemo-tolerability, early treatment of micrometastases, and an *in vivo* assessment of the response/

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	31 May 2021
Databases and other sources searched	MEDLINE/PubMed, guidelines of relevant urological societies
Search terms used (including MeSH and free text search terms and filters)	Radical cystectomy, muscle-invasive bladder cancer outcome, management, quality, and asscociated terms
Timeframe	Up to 31 December 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	All study types and reviews, written in English language
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Consensus between co-authors

sensitivity to chemotherapy.

Despite Cisplatin-based neoadjuvant combination chemotherapy being a standard that should be recommended and offered to all eligible patients with MIBC, it remains underused, with only around 19% of eligible patients receiving it (7,8,27).

In 2003, the Southwest Oncology Group (SWOG) reported in a well-designed randomized controlled trial (RCT) comprising clinically MIBC patients, a median survival benefit of 31 months with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen prior to RC compared to local treatment alone (28). Moreover, there was a higher rate of pathologic complete response (pCR) (pT0) on the final specimen (38% *vs.* 15%) (28).

The most recent meta-analysis on NAC prior to RC in MIBC patients, which included 15 RCTs with 3,285 patients, showed a significant OS benefit for patients receiving cisplatin-based NAC before surgery compared to RC alone (HR =0.87; 95% CI: 0.79–0.96; P=0.004) (29). The best regimen to use, however, remains debated. Therefore, the authors performed another meta-analysis of 12 retrospective studies comparing MVAC with gemcitabine plus cisplatin/carboplatin (GC) without finding statistically significant differences with regard to pCR (GC *vs.* MVAC: OR =1.17; 95% CI: 0.92–1.50; P=0.37) and pathological downstaging (pDS) to non-muscle invasive disease (OR =1.07; 95% CI: 0.85–1.34; P=0.19). However, regarding OS, GC seemed inferior to MVAC (HR =1.26; 95% CI: 1.01–1.57) (29). Additionally, the first results of the phase-III-GETUG/AFU V05 VESPER Trial showed a higher local control rate (pCR and pDS) for dose-dense MVAC compared to GC, while an association with survival still has to be confirmed (30). However, since a relevant proportion of MIBC patients may not be eligible for cisplatin-based therapies, further investigations for the role of alternate regimens in the neoadjuvant setting are needed.

For example, promising data from the prospective phase-II PURE-01 study have been published with a pCR rate of 42% and pDS of 54% for the neoadjuvant use of pembrolizumab (31). Larger, well-controlled trials with long-term survival data are awaited to confirm these preliminary results and possibly add a new option to our neoadjuvant systemic therapy armamentarium.

In conclusion, based on solid, reliable, and sufficient evidence, cisplatin-based combination NAC should be used in every clinically eligible MIBC patient and is therefore proposed as a quality indicator in the preoperative setting prior to RC. Discussions regarding postoperative chemotherapy/immunotherapy may also become increasingly important in the coming years (32-34).

Surgical margin status

Positive soft tissue surgical margin status in patients undergoing RC is a strong predictor for a poor survival outcome and is almost invariably associated with disease-specific death (35-38). The incidence of positive soft tissue margins in RC specimens is reported in 4.2% to 13% in retrospective studies (36-41). Surgical experience is quintessential for optimal results, as studies from high case-load centres report lower positive rates (42). For example, the Memorial Sloan-Kettering Cancer Center (MSKCC) reported in a single-centre series (n=1,589) a rate of 4.2% positive soft tissue surgical margins (STSM) compared to an average rate of 11.3% in a large meta-analysis across 36 studies (35,39). The authors from the MSKCC study showed that the five-year disease-specific survival (DSS) was significantly lower in the positive STSM group

compared to the negative STMS group (32% *vs.* 72%) after RC (39). In addition, a systematic review by Hong *et al.* including 38,384 BC patients who underwent RC, found a significant association between positive STSM status and poor outcomes of OS, CSS, and RFS [summary relative risk estimates (SRRE) 1.68, 95% CI: 1.58–1.80; 1.82, 95% CI: 1.63–2.04; 1.63, 95% CI: 1.46–1.83; respectively], when compared to negative STSM status (35). Regarding these data, avoiding positive STSM status should be a primary target intraoperatively for every surgeon performing RC. Especially in centres with less experience and lower case-loads, surgeons should be alert during the dissection and use frozen section evaluation in case of any doubt (43).

Since positive STSM constitute a relevant factor that impacts survival, bladder dissection should be performed with caution, especially in the case of a large tumour. In case of any doubt, intraoperative frozen sections should be completed, especially urethral and ureteral sections. Ensuring negative STSM is therefore proposed as an essential quality indicator intraoperatively.

LND

To achieve the best possible eradication of local and regional cancer cells during surgery, radical cystectomy must be completed by a pelvic lymphadenectomy (7). Indeed, lymph node status was shown as a strong surrogate for predicting OS and RFS subsequent to RC (44). Since preoperative clinical staging or actual biomarkers are not accurate for detecting positive lymph nodes and CT scan sensitivity reaches only 53% (45), concomitant LND offers the most reliable pathological staging and helps identify high-risk patients who may benefit from further treatment (7). International and national guidelines recommend at least the dissection of a standard pelvic template, comprising lymphatic tissue around the common, internal and external iliac vessels as well as the obturator regions on both sides (7,12). Nevertheless, it was shown that a higher number of removed lymph nodes are associated with better survival without increasing complications (46,47). A recent RCT (LEA AUO AB 25/02 Trial), including 401 patients with T1G3 or T2-T4aM0 tumours, compared survival outcomes of limited (internal and external iliac plus bilateral obturator nodes) versus extended LND (additionally common iliac, bilateral deep obturator fossa, presacral, para- and interaorto-caval plus paraaortic lymph nodes up to the inferior mesenteric artery) (48). At 5 years, there was no significant difference between extended LND and limited LND regarding OS (5-year OS 59% *vs.* 50%; HR =0.78; P=0.12), CSS (5-year CSS 76% *vs.* 65%; HR =0.70; P=0.10) and RFS (5-year RFS 65% *vs.* 59%; HR =0.84; P=0.36) (48). Among the potential confounders, the inclusion of T1G3 patients (14%) might have biased the results. Shortly, results from the ongoing prospective phase-III-trial SWOG-1011 (NCT01224665) investigating standard/limited *vs.* extended LND only in MIBC patients are eagerly awaited. It remains true that a significant number of patients still do not receive any or a sub-standard lymphadenectomy despite the evidence and the guideline recommendations (49).

With regard to the available evidence, standard pelvic LND should be the absolute minimum to be performed during RC, but extended LND might be beneficial until proven otherwise. Adequacy of LND is proposed as another essential quality of care indicator for the management of MIBC.

Enhanced recovery after surgery (ERAS)

ERAS programs are based on multimodal and interdisciplinary protocols in order to standardize perioperative care and improve postoperative recovery and surgical outcomes of the patients(50,51). First described in colorectal surgery (52-54), ERAS programs have become crucial for uro-oncologic surgeries in recent years (55). For RC, accompanied by perioperative complications in up to two-thirds of the cases (56), ERAS strategies are of utmost interest. Therefore, the ERAS society established specific guidelines extrapolated from protocols of other specialities in order to transfer approved knowledge to this field (57). ERAS regimes are composed of multimodal domains, which may vary slightly between the different protocols and institutions. In general, they combine multiple preoperative (e.g., patient education, optimization of medical conditions, bowel preparation, carbohydrate loading), intraoperative (e.g., thrombosis and antimicrobial prophylaxis, avoidance of narcotic analgetics, optimized fluid management) and postoperative elements (e.g., ileus prevention, multimodal analgesia, early enteral nutrition and mobilization) (57-59). With the aim to aggregate variating results from previous studies, Tyson and Chang conducted a systematic review on ERAS strategies for RC in 2016 (60). They found a lower overall complication rate, shorter in-hospital length of stay (LOS), faster recovery to normal bowel function, and lower 30-d readmission rate for the ERAS group. However, no difference was found regarding the overall readmission rate (60). Another systematic review published 2020 by Williams *et al.* reported comparable results. Accordingly, the

authors found reduced LOS and postoperative complication rates for implementing ERAS strategies to RC (61). Moreover, accounting for the inter-provider variation of the programs, they described the avoidance of nasogastric tubes and the use of local anaesthesia as individual ERAS components to be associated with reduced LOS (61).

Even though ERAS protocols may not be uniform between institutions yet, their general implementation has been shown to accelerate postoperative re-convalescence while reducing complications rates, in-hospital stay and overall costs of RC. Therefore, we propose the inclusion of ERAS strategies in the perioperative management of patients undergoing RC as another key factor to ensure and compare the quality of this procedure.

Smoking cessation counselling

Cigarette smoking is the strongest modifiable risk factor for the carcinogenesis of BC (62-66). For non-muscle-invasive BC, several studies showed that ongoing smoking leads to worsened prognoses with disease-recurrence up to two-fold (67-71). For MIBC, the impact of continued cigarette consumption on survival outcomes after RC and on the efficacy of chemotherapy is gaining evidence.

A recently published systematic review from Cacciamani *et al.*, including 17 studies comprising 13,777 patients, showed that ongoing smoking subsequently to RC increases risks of overall mortality (HR =1.21, 95% CI: 1.08–1.36; P=0.001), cancer-specific mortality (HR =1.24, 95% CI: 1.13–1.36; P<0.00001), and disease recurrence (HR =1.24, 95% CI: 1.12–1.38; P<0.0001) (72). Moreover, the authors demonstrated superior pCR rates (HR =0.47, 95% CI: 0.29–0.75; P=0.001) for non-, respective never-smoking patients after NAC compared to smokers (72). Comparable results were found in a recent prospective study (n=167) showing a significant association of current smoking with decreased odds of pCR [odds ratio (OR) 0.34, 95% CI: 0.13–0.85] and an increased probability of pathological non-response (OR =2.49, 95% CI: 1.02–6.06) after NAC (73). Therefore, there is an urgent need to educate smoking patients on these effects and offer cessation interventions as early as possible, starting at diagnosis (74,75). Indeed, the time of cancer diagnosis is a "teachable moment" for lifestyle changes (76), and cancer patients are more likely to stop smoking than patients without a cancer diagnosis (77,78).

The beneficial effect of smoking cessation on the prognosis of MIBC has been investigated in several studies. Rink *et al.* showed in a retrospective study of 1,506 patients treated with RC that smoking cessation over ten years significantly decreases the risks of overall mortality (HR =0.69; P=0.012), cancer-specific mortality (HR =0.42; P<0.001), and disease recurrence (HR =0.44; P<0.001) (79). Moreover, several prospective studies investigating the potential effect of smoking cessation in MIBC patients are still ongoing. For example, the multicenter randomized STOP-OP trial (Intensive Smoking and Alcohol Cessation Intervention in Bladder Cancer Surgery Patients, NCT02188446) used a smoking cessation specific programme (Gold Standard Programme), which combines a 6-week behavioural education with pharmacotherapeutic strategies (i.e., nicotine replacement) (80). Besides, shorter programs (i.e., Come & Quit, crash courses, brief intervention) are available and also effective. These programs should be promoted to obtain the highest rate of smoking cessation in patients who suffer from bladder cancer (80).

Since there is evidence for improved cancer-specific and general survival outcomes through smoking cessation, we advocate pro-active smoking cessation counselling provided by health care providers along the treatment process of MIBC for every actual smoker as another quality indicator for clinical practices.

The Bladder Cancer Quality Score (BC-QS)

A retrospective study using the National Cancer Database (NCDB) evaluated NAC, LND, and STSM as potential quality indicators for BC treatment in 48,341 patients who underwent RC and led to a composition of the BC-CS. Interestingly, better performance in this score was associated with a significantly lower 30-day, 90-day, and overall mortality of patients after RC (adjusted OR =0.78, 95% CI: 0.64–0.96; OR =0.84, 95% CI: 0.72–0.97 and HR 0.86, 95% CI: 0.81–0.92, respectively) (17). These findings may support the relevance of the proposed indicators for an optimized care-taking of MIBC patients. Moreover, combining separate indicators into simply applicable scoring systems may increase the application in clinical practices and facilitate quality measurements and comparison. Additionally, composite measures through scores improve both the reliability of quality measurements and predicting hospital performances (81).

Conclusions

Providing optimal care for MIBC patients remains

Table 2 Quality of care indicators for the management of MIBC perioperatively to RC

Time	Quality indicator	Recommendation	Technique/extent/regime
Preoperative	Utilization of NAC	Provide NAC to all clinically eligible MIBC (≥T2) patients prior to RC	Cisplatin-based combination therapies
Intraoperative	Performance of an adequate LND	Perform LND during every RC for improved disease control and accurate nodal-staging	At least by following a standard pelvic template; potentially extended
Postoperative	Proportion of negative soft tissue surgical margins	Ensure negative soft tissue margins on final pathological specimen	Reasonable wide surgical excision; secured by intraoperative frozen section consultation when in doubt
Along the treatment	Implementation of ERAS programs	Standardize perioperative care by providing ERAS strategies to all patients undergoing RC	Following multimodal and interdisciplinary protocols as proposed by the ERAS society
	Provision of smoking cessation advice	Offer pro-active cessation counselling to all smokers along the treatment process for BC	Behavioral education and pharmacologic strategies (i.e., nicotine replacement, benzodiazepines for withdrawal symptoms); Short-term interventions and established programs (i.e., the Gold Standard Program, Come & Quit, Crash courses, etc.)

NAC, neoadjuvant chemotherapy; MIBC, muscle-invasive bladder cancer; RC, radical cystectomy; LND, lymph node dissection; ERAS, enhanced recovery after surgery.

challenging, and a large variety of treatment outcomes indicates the need of establishing disease-specific quality measurements. We propose five key indicators for the perioperative quality management of MIBC that include the use of NAC with cisplatin-based combination regimes in eligible patients, performance of at least a standard pelvic template LND, avoidance of positive STSM, implementation of ERAS strategies, and offering smoking cessation counselling to every active smoker. Both the adherence and measurement of these indicators would allow for an improvement of care-taking, survival, and comparability of performances. Combining these factors into simple-to-capture scores could increase application rates and would allow for a validated metric correlation of expectable survival outcomes and hospital quality (*Table 2*).

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Footnote

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