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Leow, J.J., Catto, J.W.F. orcid.org/0000-0003-2787-8828, Efstathiou, J.A. et al. (8 more authors) (2020) Quality indicators for bladder cancer services : a collaborative review. European Urology, 78 (1). pp. 43-59. ISSN 0302-2838

https://doi.org/10.1016/j.eururo.2019.09.001

Quality Indicators for Bladder Cancer Services: A Collaborative Review

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Keywords**:** Urothelial carcinoma of bladder; Bladder cancer; Neoplasms of bladder; Quality of care; Quality indicators

Abstract

Context**:** There is a lack of accepted consensus on what should constitute appropriate quality-of-care indicators for bladder cancer.

Objective**:** To evaluate the optimal management of bladder cancer and propose quality indicators (QIs).

Evidence acquisition**:** A systematic review was performed to identify literature on current optimal management and potential quality indicators for both non–

muscle-invasive (NMIBC) and muscle-invasive (MIBC) bladder cancer. A panel of experts was convened to select a recommended list of QIs.
***Evidence synthesis*:** For NMIBC, preoperative QIs include tobacco cessation counselling and appropriate imaging before initial transurethral resection of bladder tumour (TURBT). Intraoperative QIs include administration of antibiotics, proper safe conduct of TURBT using a checklist, and performing restaging TURBT with biopsy of the prostatic urethra in appropriate cases. Postoperative QIs include appropriate receipt of perioperative adjuvant therapy, risk-stratified surveillance, and appropriate decision to change therapy when indicated (eg, unresponsive to bacillus Calmette-Guerin). For MIBC, preoperative QIs include multidisciplinary care, selection for candidates for continent urinary diversion, receipt of neoadjuvant cisplatin-based chemotherapy, time to commencing radical treatment, consideration of trimodal therapy as a bladder-sparing alternative in select patients, preoperative counselling with stoma marking, surgical volume of radical cystectomy, and enhanced recovery after surgery protocols. Intraoperative QIs include adequacy of lymphadenectomy, blood loss, and operative time. Postoperative QIs include prospective standardised monitoring of morbidity and mortality, negative surgical margins for pT2 disease, appropriate surveillance after primary treatment, and adjuvant cisplatin-based chemotherapy in appropriate cases. Participation in clinical trials was highlighted as an important component indicating high quality of care.
***Conclusions*:** We propose a set of QIs for both NMIBC and MIBC based on established clinical guidelines and the available literature. Measurement of these QIs could aid in improvement and benchmarking of optimal care of bladder cancer.

***Patient summary*:** After a systematic review of existing guidelines and literature, a panel of experts has recommended a set of quality indicators that can help providers and patients measure and strive towards optimal outcomes for bladder cancer care.

1. Introduction

Bladder cancer (BC) is a common malignancy that is managed by most urologists and many other medical professionals. It is a heterogeneous disease with variable outcomes. Relevant organisations have published guideline recommendations regarding the care of patients with BC [1–8]. However, the outcomes from BC treatments vary widely [9,10], suggesting that differences exist in health care delivery and guideline compliance. Given these findings, patient and caregiver surveys report concerns reflecting variations in service provision and outcomes [11–13]. There is a lack of consensus regarding appropriate quality-of-care indicators for managing BC.
A quality-of-care indicator should be based upon accepted standard of care evidence-based practice. It should be measurable to allow clinicians, administrators, and payers to track, report, and improve outcomes. Feedback

using quality indicators should then drive organisational behaviour to improve outcomes and may serve as criteria for approval of centres of excellence. Such metrics are increasingly recorded in clinical registries, aiming to assist in delivering high-quality care while also facilitating patients' choice and reimbursement incentives, and creating novel research datasets [14,15]. For example, to support a culture of quality improvement, National Health Service Scotland established a steering group to develop quality performance indicators as a proxy measure of quality care for BC (see http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx). Clinical audit data now exist for patients diagnosed between April 2014 and March 2017 [16], although it is uncertain how these indicators are currently used within the UK. In the USA, the Oregon Urology Institute developed electronic clinical quality measures to help urologists submit mandated outcome reports, obtain necessary reimbursements, and importantly avoid penalties [17].

Over the past decade, BC care has seen an increase in the creation of evidence through quality research. This has led to more solid understanding of the biology and clinical management of BC. Our aim is to systematically review the evidence-based practices for the management of both non–muscle-invasive and muscle-invasive disease, and to recommend quality indicators. Clinicians, policy makers, and payers may consider these to influence better practices for BC patients. Patients may also benefit by being better equipped to ensure their own high-quality care.

2. Evidence acquisition

2.1. Materials and methods

A comprehensive search of the published literature, assessed through a publication date of February 2019, was performed using the following query terms: ("Urinary Bladder Neoplasms"[Mesh] OR "Bladder malignancy") AND ("quality indicators" OR "Quality of care"). This yielded a total of 53 peer-reviewed articles (Fig. 1). Relevant references within each article were also evaluated. Seven articles were excluded as they were either not in English or judged not relevant to the topic. Additionally, all 1310 references from the aforementioned guidelines [1–8] were screened and reviewed. The scope of this paper is limited to that of non–muscle-invasive and muscle-invasive disease; therefore, literature related to metastatic disease was not evaluated.

The systematic review of contemporary literature combined with the experience of the authors provided the basis for the following recommendations on which quality indicators should exist for optimal BC services. We used a structured, consensus-driven, modified Delphi method including a combination of e-mails to debate proposals based on evidence and expert opinions from the project team and agreed to define the following indicators. We used a two-thirds threshold to determine consensus.

3. Evidence synthesis

Our proposed quality indicators relate to non–muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), as well as general aspects of BC management.

3.1. Quality indicators for NMIBC

3.1.1. Preoperative

3.1.1.1. Tobacco cessation counselling

At the time of diagnosis, patients should be counselled to discontinue tobacco smoking. Retrospective studies have found that smoking increases the risk of tumour recurrence and progression [18,19] and reduced the efficacy of bacillus Calmette-Guerin (BCG) immunotherapy [20]. Although the association between smoking cessation and cancer-specific or all-cause mortality is less clear [21,22], we recommend that clinicians counsel patients for cessation of smoking, given the known beneficial effects on non-BC–related outcomes such as preventing cardiovascular events and second tobacco-related primary malignancies. Preoperative tobacco cessation also reduces anaesthetic complications.

To drive appropriate care, physicians should be incentivised to include this as part of their preoperative management. For example, in the USA, urologists may use a separate billing code for up to a 10-min discussion on the importance of and practical steps towards tobacco cessation. Counselling can direct patients to pharmacotherapy or referral to a tobacco cessation specialist for cognitive behavioural therapy.

3.1.1.2. Appropriate counselling

Treatment and surveillance should be based on patient's risk of recurrence and progression. For patients who are known to have BC and are on follow-up, the following will apply. The European Organization for Research and Treatment of Cancer Genito-Urinary Cancer Group has developed a scoring system and risk tables to predict recurrence and progression in patients with NMIBC depending on patient and disease characteristics, including the number and size of tumours, recurrence rate, stage, grade, and the presence of concomitant carcinoma in situ (CIS) [23,24]. However, the patient cohort used to develop this scoring system did not include patients with CIS alone, and the patients did not receive a second transurethral resection of bladder tumour (TURBT) or maintenance BCG. Another scoring model for patients who received BCG was developed by the Club Urológico Español de Tratamiento Oncológico (Spanish Urological Oncology Group), which also considers patient age and gender [25]. These scoring systems can guide treatment and surveillance protocols, and allow for prognostication of patients.

3.1.2. Intraoperative

3.1.2.1. Administration of perioperative antibiotics

The best evidence (level 2B) on the role of pre-TURBT antibiotics come from two historical randomised trials published in 1988 [26] and 1993 [27], consisting of 91 and 61 patients, respectively, randomising patients to preoperative antibiotics compared with placebo. Both trials revealed a nonsignificant decrease in the incidence of postoperative bacteriuria with the use of antibiotic prophylaxis. Delavierre et al's [27] trial found a 0% incidence of symptomatic urinary tract infections (UTIs) in both arms. Experts have concluded that "there is moderate to low-grade evidence suggesting that antibiotic prophylaxis is not necessary in TURBT" [28]. Importantly, there were no subgroup analyses according to the presence of risk factors for postoperative infection (eg, immune-compromised state, tumour size, and length of surgery). The panel for European Association of Urology (EAU) guidelines on urologic infections concluded with a weak recommendation that it would be appropriate to use antibiotic prophylaxis for patients undergoing TURBT who had a high risk of suffering postoperative sepsis. A short guide on how best to use antibiotic prophylaxis in urologic procedures has been provided [29]. It has also been shown that adherence to EAU guidelines on prophylactic antibiotics reduced antibiotic usage without increasing the postoperative infection rate and lowered the prevalence of resistant uropathogens [30].

The best practice policy statement on urologic surgery antimicrobial prophylaxis of the American Urological Association (AUA) [31] is to administer perioperative antibiotics in an adequate dose based on patient weight within 60 min of the surgical incision and discontinuing these 24 h after surgery. Additionally, intraoperative redosing should occur after two antibiotic half-lives to ensure sufficient antimicrobial serum levels until the incision is closed. The duration of TURBT typically does not exceed 2 h.

The Global Prevalence of Infections in Urology (GPIU) study is currently the only study registering health care–associated urogenital tract infections in urology patients, in an on-going surveillance protocol that can help deliver data on adequate empirical antibiotic therapy in hospitalised urology patients according to guideline recommendations [32], and may report data on post-TURBT sepsis in the future.

3.1.2.2. Proper conduct of TURBT—adequate and safe

A systematic approach is necessary during TURBT to achieve the goal of safe and complete bladder tumour resection, via either a fractioned or an en bloc strategy [33]. A widely accepted surgical principle for TURBT is to achieve adequate resection with detrusor muscle identified [33]. The presence of detrusor muscle in the specimen is considered a surrogate indicator of resection quality and is mandatory (except for TaG1/LG tumours); its absence is associated with a significantly higher risk of residual disease, early recurrence, and tumour

understaging [34]. Submitting the base separately to prove no residual disease (completeness of TURBT) and/or to confirm the presence of muscle is recommended and can avoid cautery artefact. It is also critical to document the number, location, and size of bladder tumours, for example, using a bladder diagram. The use of a checklist is also recommended [35–37].
A properly conducted TURBT should also be safe. The surgeon should aim to avoid bladder perforation and repeated interventions for haemostasis. These surgical outcomes should be maintained prospectively in an outcome database; complications should be categorised using a standard classification scheme such as the Clavien-Dindo classification, with specific outcome data collected for the rate of perforation and return to the operating room for haemostasis. The use of image-guided TURBT with narrow-band imaging or blue light/fluorescence-guided “photodynamic diagnosis” with 5-aminolevulinic acid or hexyl aminolevulinate [38–40] may be considered a future quality indicator if conclusively proven to be superior to conventional TURBT.

3.1.2.3. Restaging TURBT
The indications for re-resection TURBT include (1) incomplete initial TURBT, (2) no muscle in specimen from initial TURBT and not Ta low grade, and (3) T1 tumours. Residual disease after resection of T1 tumours has been seen in up to 55% of patients [41]. Without restaging TURBT, there is a high likelihood of understaging, as muscle-invasive disease is detected by second resection of initial T1 tumour in up to 25% of cases, which rises to 45% if there was no muscle in the initial resection [42].
In a meta-analysis of published trials comprising 3556 patients with T1 tumours, 61% of patients had residual disease and 15% subsequently were found to upstage to T2 disease [43]. Among the subgroup of T1 tumours with muscle present, the prevalence of residual disease was 58% and that of understaging was 11%. This underscores the necessity of restaging TURBT in T1 disease even if muscle was present in the initial TURBT.

As for the timing for restaging TURBT, as per EAU guidelines, we recommend that this should be performed within 2–6 wk of the initial TURBT and should include resection of the primary tumour site. This is based on level 3 retrospective evidence, which demonstrated longer recurrence- and progression-free survival among those who underwent a second resection performed 14–42 d after initial resection compared with that performed 43–90 d after [44].

The pathology results of the restaging TURBT reflect the quality of the initial TURBT [9,45], and recording it in a prospectively maintained database is critical.

In summary, our proposed indicators related to the performance of an adequate and safe TURBT are as follows:

1. Percentage of patients with muscle present in specimen from initial TURBT (excluding TaLG disease).
2. Percentage of patients meeting indications who undergo restaging TURBT.

3. Percentage of patients with muscle present in specimen from restaging TURBT.

3.1.3. Postoperative

3.1.3.1. Immediate instillation of intravesical chemotherapy
Immediate instillation of intravesical chemotherapy (eg, gemcitabine and mitomycin C [MMC]) within 24 h of TURBT has been shown to significantly reduce 5-yr recurrence rate by 14% (from 59% to 45%) compared with TURBT alone [46]. The recent SWOG S0337 study demonstrated a similar reduction in 4-yr recurrence rates by 12% (from 47% to 35%) [47]. This is due to the intravesical chemotherapeutic agent destroying circulating tumour cells after TURBT, preventing tumour cell implantation, and chemoablating residual tumour cells at the resection site and small overlooked tumours [48,49].

There is no recommendation on which chemotherapeutic agent to use since MMC, epirubicin, pirarubicin, and gemcitabine have all shown a beneficial effect [46,50,51], with no head-to-head randomised comparisons.

Despite guidelines from various organisations, adoption of this practice is low due to logistical reasons and safety concerns. A population-based study of 32 068 patients who underwent TURBT in over 300 US hospitals showed that only 53.1% of hospitals used MMC, and at these hospitals, MMC was used in 6.1% of procedures [52].

Our proposed quality indicator is the percentage of patients who received immediate post-TURBT instillation of intravesical chemotherapy, excluding those with contraindications (eg, incomplete resection, suspected perforation, and significant haematuria).

3.1.3.2. Intravesical BCG utilisation for intermediate- or high-risk NMIBC with appropriate duration of maintenance BCG
Guidelines recommend that the following groups of patients should be offered postoperative intravesical induction followed by maintenance BCG therapy to reduce the risk of tumour recurrence or progression:

1. Intermediate-risk disease (not high or low risk as defined by the following: primary, solitary, Ta low grade, <3 cm, no CIS).
2. High-risk disease (newly diagnosed CIS, T1, and high-grade disease).

The duration of maintenance BCG for patients who completely respond to the 6-wk course of induction BCG depends on their initial risk stratification (intermediate risk: 1 yr; high risk: 3 yr).
Our proposed quality indicator is simply the percentage of intermediate- and high-risk NMIBC patients who were counselled and subsequently *initiated* BCG. Given that some patients subsequently are unable to tolerate the local or

systemic symptoms associated with intravesical BCG therapy, which is then appropriately discontinued, our proposed indicator does not intend to measure the duration or dose of maintenance BCG therapy. The ability to maintain patients on BCG after induction is likely reflective of higher-quality care and better ability to rescue continued maintenance.
The dose of BCG should be prioritised as such [53]. Full-strength BCG must be offered to high-risk NMIBC, high-grade T1, and CIS patients receiving induction therapy. If this was not possible (eg, due to BCG shortage), then these high-risk patients can be given a reduced one-half or -third dose, as supported by several trials showing similar outcomes [54–56] and a phase 3 trial showing no difference in progression or survival rates [57].
Additionally, we recommend measuring the initiation of BCG as a quality indicator because the duration of maintenance BCG (1 vs 3 yr) is controversial in the context of the global supply constraint of BCG [58–60]. We have summarised the various intravesical therapeutic options for NMIBC patients in various scenarios (Table 1) and suitable alternatives, particularly during BCG shortage. A review by Abufaraj et al [58] provided a list of valid strategies. The National Comprehensive Cancer Network guidelines for BC version 3.2019 also concurred that the priority for BCG treatment should be given to patients with high-risk NMIBC (cT1 high grade or CIS) [53].

3.1.3.3. Appropriate frequency of surveillance based on stage/grade of BC
For all patients, guidelines recommend cystoscopic surveillance 3 mo after TURBT (Table 2). For low-risk patients, if the first post-TURBT surveillance cystoscopy is negative, guidelines recommend cystoscopy at 12 mo followed by yearly for 5 yr. For intermediate-risk patients, if the first post-TURBT surveillance cystoscopy is negative, guidelines recommend cystoscopy at 3–6-mo intervals until 5 yr and yearly thereafter. For high-risk patients, if the first post-TURBT surveillance cystoscopy is negative, guidelines recommend cystoscopy every 3 mo for 2 yr, every 6 mo thereafter until 5 yr, and yearly thereafter. Upper tract imaging should be performed yearly.
Our proposed quality indicators are as follows:

1. Accurate documentation of risk stratification into low-, intermediate-, or high-risk disease.
2. Appropriate intervals between cystoscopic surveillance.
3. Appropriate assessment of the upper urinary tract for high-risk patients.

As it may be more complicated to track tumour recurrences, its subsequent management, incorporating patient preferences and choices, we have decided to omit that from our consideration as a suitable quality indicator.

3.2. Quality indicators for MIBC

3.2.1. Preoperative

3.2.1.1. Administration of perioperative antibiotics

The aforementioned GPIU study [32] may report data on posturologic surgical sepsis in the future. As for the current prevalence of infectious complications after cystectomy, it is worth mentioning data from a large population-based study of 57 554 patients in the USA from 2003 to 2013, which revealed a 90-d rate of 11.9% for UTIs and 1.8% for pyelonephritis [61]. This is similar to 2003–2013 clinical chart review data from 1133 radical cystectomy patients at USC Institute of Urology; 151 UTIs were recorded in 123 patients (11%) during the first 90 d postoperatively, with 21/123 (17%) having multiple infections and 25 (20%) having urosepsis [62]. Another retrospective study has suggested the benefit of discharging patients home on antibiotic prophylaxis following a postoperative urine culture obtained during hospitalisation, showing significant differences in the rates of documented UTIs (12% in the prophylactic antibiotic group vs 36% in the no antibiotic group, $p < 0.004$) and readmission for urosepsis (2% in the antibiotic group vs 17% in the no antibiotic group, $p = 0.02$) [63].

The AUA's best practice policy statement on urologic surgery antimicrobial prophylaxis [31] is to administer perioperative antibiotics in an adequate dose based on patient weight within 60 min of the surgical incision, and discontinuing these 24 h after surgery. Additionally, intraoperative redosing should occur after two antibiotic half-lives to ensure sufficient antimicrobial serum levels until the incision is closed. This may be interpreted to include open, laparoscopic, or robot-assisted urologic surgical procedures.

We suggest the following quality indicators: (1) timely administration and discontinuation of appropriate antibiotics; (2) rates of UTIs; (3) rates of surgical skin infections as classified by the National Surgical Quality Improvement Program, in accordance with the need for intervention, for example, bedside alternative removal of surgical stiches, image-guided drainage of deep infections, take-back to operating room for infection-related complications, etc., and should be classified according to the Clavien-Dindo classification as per EAU recommendation; and (4) rates of readmissions from urosepsis after radical cystectomy (Table 3).

3.2.1.2. Evidence of multidisciplinary care

For any patient with newly diagnosed ≥cT2 MIBC, we advocate for multidisciplinary care to consider curative treatment options prior to choosing the best approach based on patient's comorbidity status, tumour characteristics, and patient preferences [3]. This will likely improve utilisation of neoadjuvant chemotherapy, but also allow for collaborative discussion of bladder-sparing options in appropriate candidates. Clinically appropriate candidates may include those who desire to retain their bladders and those with significant comorbid conditions that preclude them from undergoing major extirpative surgery (ie, radical cystectomy).

Given that practice patterns differ widely [64], tracking referral rates to medical or radiation oncologists may under-represent utilisation of multidisciplinary care. Patients may be discussed at a multidisciplinary urology tumour board meeting prior to a referral being initiated. Therefore, we propose to track the percentage of patients with newly diagnosed ≥cT2 MIBC who were discussed at a multidisciplinary meeting.

3.2.1.3. Receipt of neoadjuvant chemotherapy

As part of a multidisciplinary approach, eligible patients should be offered neoadjuvant cisplatin-based combination chemotherapy prior to radical cystectomy. The latest meta-analysis of 15 randomised trials consisting of 3285 patients demonstrated a significant overall survival benefit with cisplatin-based neoadjuvant chemotherapy compared with local treatment alone (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.79–0.96) [65]. Modern chemotherapeutic regimens such as gemcitabine/cisplatin have shown similar pT0/pT1 rates as the combination of methotrexate, vinblastine, doxorubicin, and cisplatin in the most recent retrospective series and meta-analysis [65,66]. Despite this, the use of neoadjuvant chemotherapy in patients undergoing radical cystectomy is limited, with as few as 17% of patients with T2 or greater disease receiving treatment, even at academic centres [67,68]. A National Cancer Data Base (NCDB) analysis of patients with no prior malignancy who ultimately underwent radical cystectomy for ≥cT2/cN0/cM0 MIBC between 2006 and 2010 revealed that the use of neoadjuvant chemotherapy has increased from 10.1% in 2006 to 20.8% in 2010 [69]. This relatively low proportion—despite level 1 evidence supporting its use—may be due to patient factors (eg, advanced age, comorbidity status, cisplatin eligibility), nonclinical factors (eg, lack of insurance, lower income), and conflicting real-world retrospective data on its survival benefit [70]. It has also been demonstrated that important baseline differences exist between patients from the SWOG-8710 trial and those in general urologic practice; in a study evaluating the effectiveness of neoadjuvant chemotherapy using the NCDB (2004–2012), there was no clear survival advantage.

To determine quality of care, it will be important to measure and track the utilisation of neoadjuvant chemotherapy for clinically eligible ≥cT2 MIBC with urothelial cell carcinoma histology.

3.2.1.4. Time from TURBT to radical cystectomy <12 wk in patients proceeding directly to surgery

It is a widely accepted surgical principle to limit the delay from initial TURBT to definitive extirpative radical cystectomy to <12 wk, due to the risk of disease progression with more advanced pathologic stage and poorer survival outcomes [71–74]. If patients are not considered for or have declined neoadjuvant chemotherapy, delaying surgery beyond 12 wk is associated with a significant risk of nodal metastasis [75]. A recent SEER-Medicare analysis found that similar delays in radical cystectomy increased overall mortality, regardless of the use of neoadjuvant chemotherapy [76].

3.2.1.5. Utilisation of trimodal therapy as a bladder-sparing alternative for appropriate candidates

As part of a multidisciplinary approach, eligible patients should be offered trimodal therapy (TMT) [2,6,8,77]. TMT is a suitable bladder-sparing alternative for patients newly diagnosed with cT2-T3 MIBC, in particular those with favourable factors such as maximal visibly complete TURBT, absence of hydronephrosis, primary urothelial carcinoma [78], unifocal tumours <6 cm in size, absence or limited CIS, as well as good bladder and bowel function [79]. After multidisciplinary discussion, these patients should be presented the options of radical cystectomy versus bladder-sparing TMT [77,80]. Of note, in new trials such as the SWOG/NRG 1806 intergroup phase 3 trial (Clinicaltrials.gov Identifier: NCT03775265), patients with unilateral hydronephrosis are eligible as long as their glomerular filtration rate is $\geq$25 ml/min.

Especially among those in whom radical cystectomy is contraindicated, who refuse cystectomy, or who elect bladder preservation after informed decision making [81], TMT represents a viable treatment option with curative intent [79,80]. Indicators of quality TMT include the following: (1) receiving a repeat maximal TURBT by the treating institution, which is safe but ideally visibly complete; (2) receipt of concurrent radiosensitising chemotherapy given level 1 evidence (BC 2001) and receipt of definitive dose radiotherapy (RT; 64–65 Gy with conventional fractionation and 55 Gy with moderate hypofractionation); (3) treatment assessment response with cystoscopy/rebiopsy; (4) lifelong cystoscopic surveillance since NMIBC recurrence can occur in up to 25% of patients; and (5) receipt of salvage cystectomy for muscle-invasive recurrences and/or if otherwise indicated in cystectomy candidates [79,82,83]. It underscores the importance of a multidisciplinary approach.

On top of the percentage of patients being referred to and seen by a radiation oncologist, we recommend tracking the actual utilisation rate of TMT for MIBC in appropriate candidates as a quality indicator. The challenge is to identify who these appropriate candidates are, which we have listed above. If TMT is pursued, the following may be tracked: (1) repeat maximal TURBT prior to chemoradiation, (2) utilisation of concurrent radiosensitising chemotherapy, (3) dose of RT, (4) complete response rates, (5) frequency of cystoscopic surveillance, and (6) rates of salvage cystectomy.

3.2.1.6. Preoperative counselling with stoma marking

Preoperative education of patients about to undergo major extirpative surgery for MIBC is important, particularly since they will be coping without their native bladders postoperatively, with either continent or noncontinent urinary diversion. The patient's abdomen should be evaluated, and the optimal site of stoma should be marked prior to surgery. This provides an opportunity to select the optimal site, reducing postoperative problems such as leakage, peristomal dermatitis, and difficulty with self-care. A randomised controlled trial has been found that a preoperative standardised stoma education programme improves patients' ability

to independently change a stoma appliance postoperatively, as measured by the Urostomy Education Scale, a reliable tool to evaluate urostomy self-care skills after cystectomy [84,85]. Postoperative stoma care is also important for both incontinent ileal conduits and continent neobladders [86].
We propose measuring and tracking the percentage of patients referred to an enterostomal therapist or a specialist urology nurse clinician before radical cystectomy as a surrogate quality indicator for adequate preoperative counselling with regard to urinary diversion.

3.2.1.7. Surgical volume of radical cystectomy
Multiple studies have shown the relationship between surgical volumes of major complex surgical procedures with improved surgical outcomes [87–89]. This is also the case with radical cystectomy. A meta-analysis in 2011 found a significant association between high-volume hospitals and lower mortality (pooled odds ratio [OR] 0.55, 95% CI 0.44–0.69) [90]. The systematic review also identified two studies showing a beneficial effect of surgeon volume on mortality (OR 0.55 and 0.64). A recent systematic review has also revealed fewer complications among cystectomies performed by higher-volume providers [91]. Proponents of centralisation typically cite these volume-outcome studies and have even proposed certain volume standards for high-risk surgical procedures, for example, the Leapfrog initiative in the USA [92]. Even though the Leapfrog volume thresholds do not specifically include radical cystectomy, its beneficial effect on radical cystectomy outcomes has been demonstrated, with Leapfrog volume status (higher volume) found to be inversely related to mortality ($p = 0.03$), intra- ($p = 0.04$) and postoperative ($p = 0.04$) complications, as well as the likelihood of blood transfusion ($p < 0.001$) [93]. A similar effort was seen in the UK with the introduction of the “Improving Outcomes Guidance” (IOG) in 2002, which recommended that radical surgery for prostate cancer and BC should be provided by teams serving populations of >1 million and carrying out a cumulative total of ≥50 operations annually. A study evaluated all radical cystectomies performed in England from 2003 to 2014 ($N = 15\ 292$), and found that, compared with the IOG-noncompliant group, the IOG-compliant group had improved median survival time (4.07 vs. 5.41 yrs), lower 30-d (2.9% vs 2.1%) and 90-d (7.2% vs. 5.2%) mortality rates, shorter length of stay (16 vs 14 d), and decreased reintervention rates (33.6% vs 30.0%, all $p < 0.01$) [94].
Since higher surgical volume may be considered a surrogate marker of better overall quality of care [89,95–99], we recommend its use as a quality indicator. However, the cut-off used may vary regionally, depending on the density of available specialists and other demographic factors.

3.2.1.8. Enhanced recovery after surgery protocols/pathways in place
Radical cystectomy remains a morbid procedure with complication rates as high as 67% even in the care of experienced surgeons [100]. Aspects of a patient’s perioperative care can be optimised to improve outcomes for such a major and complex oncologic surgical procedure. Enhanced recovery pathway principles

that underlie enhanced recovery after surgery protocols extend across pre-, intra-, and postoperative phases of an MIBC patient's surgical care. This includes preoperative avoidance of a formal bowel preparation, preoperative use of carbohydrate loading to decrease postoperative insulin resistance, judicious intraoperative use of fluids and blood transfusion, early mobilisation postoperatively, early resumption of normal diet, and optimal postoperative pain management centred around avoidance of narcotics [101–104].

3.2.2. Intraoperative

3.2.2.1. Adequacy of lymphadenectomy

Lymph node status is the best surrogate for long-term recurrence-free and overall survival after radical cystectomy [105]. A well-performed lymphadenectomy is associated with improved local control rates, curative potential, and reasonable morbidity profile postoperatively. Numerous studies have been performed to evaluate the anatomic extent of pelvic lympadenectomy and how nodal metastases are distributed during radical cystectomy. A higher number of dissected lymph nodes have been shown to correlate with improved survival rates [106]. At minimum, a "standard" lymphadenectomy should be performed; this entails removal of all lymphatic tissue around the common iliac, internal and external iliac, and obturator packets bilaterally, and is recommended as such in all guidelines.

In terms of the minimum numbers of lymph nodes required, the AUA/Society for Urologic Oncology guidelines recommend that at least 12 lymph nodes be evaluated [3]. The EAU guidelines refrained from mandating a number, but state that "removal of at least 10 lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for overall survival in retrospective studies" [107–109].

Both surgical and nonsurgical factors can greatly influence nodal counts, and these include anatomic extent of the template and the number of packets submitted to pathology [110–112].

Two phase 3 randomised trial have evaluated the impact of different pelvic lympadenectomy templates on survival. The recently published German trial (LEA AUO AB 25/02) randomised 401 patients with locally resectable T1G3 or T2-T4aM0 urothelial carcinoma of bladder patients to limited (obturator, and internal and external iliac nodes) versus extended lymph node dissection (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 regard to recurrence-free survival (5-yr recurrence-free survival 65% vs 59%; HR 0.84 [95% CI 0.58–1.22]; $p = 0.36$), cancer-specific survival (5-yr cancer-specific survival 76% vs 65%; HR 0.70; $p = 0.10$), and overall survival (5-yr overall survival 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%, $p = 0.04$) [113]. The other trial, SWOG-1011, completed accrual but results are pending (Clinicaltrials.gov Identifier: NCT01224665).

On this basis, our recommendation is that patients undergoing radical cystectomy should (at least) receive a standard template pelvic lymphadenectomy, and we advocate for this to be a quality indicator.

3.2.3. Postoperative

3.2.3.1. Prospective standardised monitoring of morbidity and mortality
A critical component of quality surgical care is the existence of an audit-based mechanism of tracking postoperative complications in a standardised and prospective manner. We recommend using the Clavien-Dindo classification.
A population-based study of 36 773 radical cystectomies in the USA from 2004 to 2010 revealed a 90-d mortality rate of 3.7% [114]. Inpatient mortality rate has been found to be 1.7% among 10 027 radical cystectomies done from 2008 to 2013 in the USA [115]. This is comparable with the 30-d mortality rate of 1.58% reported among 2537 cystectomies performed from 2014 to 2015 in the UK, as reported in an analysis of the British Association of Urological Surgeons' cystectomy audit [116]. We recommend using a 30-d mortality rate after elective radical cystectomy of <2% as a quality indicator.
The mortality rates among older patients aged >80 yr [117,118] would be expectedly higher. It has been found that mortality rates in the salvage radical cystectomy setting were similar to the primary setting, that is, 2.2% [119].

3.2.3.2. Negative surgical margins for pT2 disease
In a meta-analysis of 38 384 BC patients across 36 studies, it was found that 4354 patients had positive surgical margins (11.3%). Positive surgical margin status was found to be significantly associated with poorer recurrence-free, cancer-specific, and overall survival [120]. Achieving negative surgical margins is a key aim for radical cystectomy, and the rate may reflect surgical practice. High-volume centres typically report lower margin rates. For example, in the Memorial Sloan-Kettering Cancer Center series of 1655 radical cystectomies from 1985 to 2005, 858 patients (54%) demonstrated organ-confined disease (≤pT2) and all of these patients (100%) had negative surgical margins. Of note, positive surgical margin status in the perivesical soft tissue was an independent predictor of metastatic progression and increases the probability of disease-specific death [121]. Pang et al [101] reported similar data from Sheffield. In 455 consecutive radical cystectomies, the soft tissue margin rate was 2.4%, of which all were in T3–4 cancers (0% rate for T2). Every safe effort with wide excision should be undertaken to obtain negative surgical margins during cystectomy, and this should be considered a quality indicator at surgery.

3.2.3.3. Offer adjuvant chemotherapy to patients with high-risk disease (≥pT3 and/or pN+) who did not receive neoadjuvant chemotherapy
Guidelines strongly recommend adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and//or pN+ disease if no neoadjuvant chemotherapy has been given. This rationale is to eradicate micrometastatic

disease. This is based on meta-analyses demonstrating overall survival and disease-free survival benefit [122]. Strength of recommendation has been strong despite a lack of high-quality level 1 evidence, as trials have generally failed to complete accrual.
Consideration can be given to adjuvant chemotherapy following TMT as well, as was standard in most RTOG/NRG trials [6,119,123].

3.3. Quality indicators for general aspects of BC services
These quality indicators are not limited to NMIBC or MIBC (Table 4).

3.3.1. Appropriate imaging for patients newly diagnosed with BC
Diagnosis of a bladder tumour is typically confirmed visually during flexible cystoscopy. The next step prior to initial TURBT will be appropriate imaging. Guidelines recommend that patients should undergo cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI) with a delayed urogram phase prior to the initial TURBT. In patients unable to receive either, options include noncontrast CT or MRI, grey-scale or contrast-enhanced ultrasonography of the kidneys, or retrograde pyelogram. This is to identify metachronous lesions in the upper urinary tract, which occurs in 1.8–2.6% of cases [124,125].
For systemic staging, we recommend chest imaging with at least plain x-ray. When the chest x-ray is equivocal or an abnormality is identified, or in selected high-risk patients, a CT thorax is indicated. For selected high-risk patients, including high-grade or clinically muscle-invasive cancers, and for those with tobacco smoking exposure (past/present), we recommend CT thorax imaging (regardless of the stage of cancer) due to the competing risks of lung cancer, particularly if patients are undergoing concurrent imaging of the abdomen and pelvis. Low-grade NMIBC does not require chest imaging if there is no clinical suspicion. We do not recommend routine CT brain or bone scan unless specific symptoms (eg, bone pain) or signs (eg, focal neurology deficit) indicate these sites as potential metastases, or neuroendocrine variant histology was identified [126]. To put it in context, based on a recent Nationwide Inpatient Sample (1998–2007) retrospective analysis of 7543 patients, the most common metastatic sites for BC were lymph nodes (25%), bone (24%), urinary tract (23%), lung (19%), liver (18%), and brain (3%) [127]. However, this study is limited by the use of claims to identify metastatic site, with expected variability in the use of imaging modalities.

3.3.2. Participation in clinical trials
Clinical trials evaluate how to prevent, detect, or treat disease [128]. For BC, the benefits of participating in clinical trials include access to the latest tools for early detection of de novo or recurrent bladder tumours, and the most advanced therapeutic options and techniques available to best treat BC. There are currently 148 trials in the USA [129] and 84 in the UK [130]. When a treatment facility can

actively recruit patients for such trials, it reflects well on the variety of options available for patients.

3.3.3. Composite scores that have been developed and evaluated so far

Disease characteristics remain the main determinant of survival, but high-quality surgical technique and optimal perioperative care are mandatory to achieve survival benefits in patients with favourable pathology. Quality of surgical performance has traditionally been linked to survival outcomes. However, survival may not always reflect quality of care because adverse outcomes can still result from “nonmodifiable” factors, complexity of the procedure, severity of pathology, and associated patient comorbidities. Composite measures that combine multiple quality indicators into a single score have improved the reliability of assessment of performance [131]. Such measures are crucial for comparative effectiveness research.

Currently, there are three composite scores, mainly developed for robot-assisted radical cystectomy (RARC), but most aspects apply to open surgery as well. These may be considered as suitable quality indicators for MIBC care.

Cystectomy Assessment and Surgical Evaluation (CASE) evaluates the surgical technique for cystectomy in an objective way based on expert consensus on what defines surgical proficiency [132]. Eight domains of the CASE included pelvic LND, development of the periureteral space, lateral pelvic space, anterior rectal space, control of the vascular pedicle, anterior vesical space, control of the dorsal venous complex, and apical dissection.

The Quality Cystectomy Score (QCS) evaluates the global surgical care that patients receive with some outcomes that are directly related to surgical technique, based on the following criteria: preoperative (administration of neoadjuvant chemotherapy), operative (operative time <6.5 h and estimated blood loss <500 cc), pathologic (negative soft tissue surgical margins and lymph node yield ≥20), and postoperative (no high-grade complications, readmission, or noncancer-related mortality within 30 d). QCS was categorised as follows: one star—achieving two or fewer criteria or mortality within 30 d; two stars—meeting three or four criteria; three stars—meeting five or six criteria; and four stars—meeting seven or all criteria. A high QCS was found to be significantly associated with better recurrence-free, cancer-specific, and overall survival [133].

The Pelvic Lymphadenectomy Appropriateness and Completion Evaluation tool evaluates the intraoperative completeness and appropriateness of pelvic LND following RARC [134].

The rates of neoadjuvant chemotherapy, LND, and positive margins for MIBC have been evaluated as a composite “Bladder Cancer Quality Score (BC-QS)” using data from the NCDB (2004–2014) for 48 341 patients treated at 1200 facilities [135]. Improved BC-QS performance was significantly associated with lower 30-, 90-d, and overall mortality (adjusted OR 0.78 [0.64–0.96], OR 0.84 [0.72–0.97], HR 0.86 [0.81–0.92]). This is an easy-to-capture metric correlating to pertinent short- and long-term survival outcomes, making it an attractive validated quality indicator for policymakers and payers to measure hospital quality. The Fox-Chase group had evaluated receipt of neoadjuvant

chemotherapy, timely treatment within 3 mo, adequate LND (≥10 nodes), and continent urinary diversion as quality indicators, similarly using the NCDB, which tended to occur in academic high-volume institutions; however, this was not correlated to survival outcomes [98].
The above list of quality indicators for BC services has been endorsed by the EAU.

4. Conclusions

In summary, we propose a set of quality indicators for both NMIBC and MIBC that are measurable across the pre-, intra-, and postoperative phases of a patient's journey. These quality indicators are based on the latest evidence-based clinical practice widely accepted in the urologic community. If utilised correctly to drive clinician and organisational behaviour, this set of quality indicators can be impactful and improve bladder cancer outcomes.

Author contributions: Jeffrey J. Leow had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Catto.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Leow, Trinh.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: Trinh.
Supervision: Trinh.
Other: None.

***Financial disclosures*:** Quoc-Dien Trinh certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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Fig. 1 – PRISMA flowchart.
ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; AUA = American Urological Association; EAU = European Association of Urology; ICUD = International Consultation on Urologic Diseases; MIBC = muscle-invasive bladder cancer; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; NMIBC = non–muscle-invasive bladder cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SIU = Société Internationale d'Urologie; SUO = Society for Urologic Oncology.

Figure 1. PRISMA flow chart

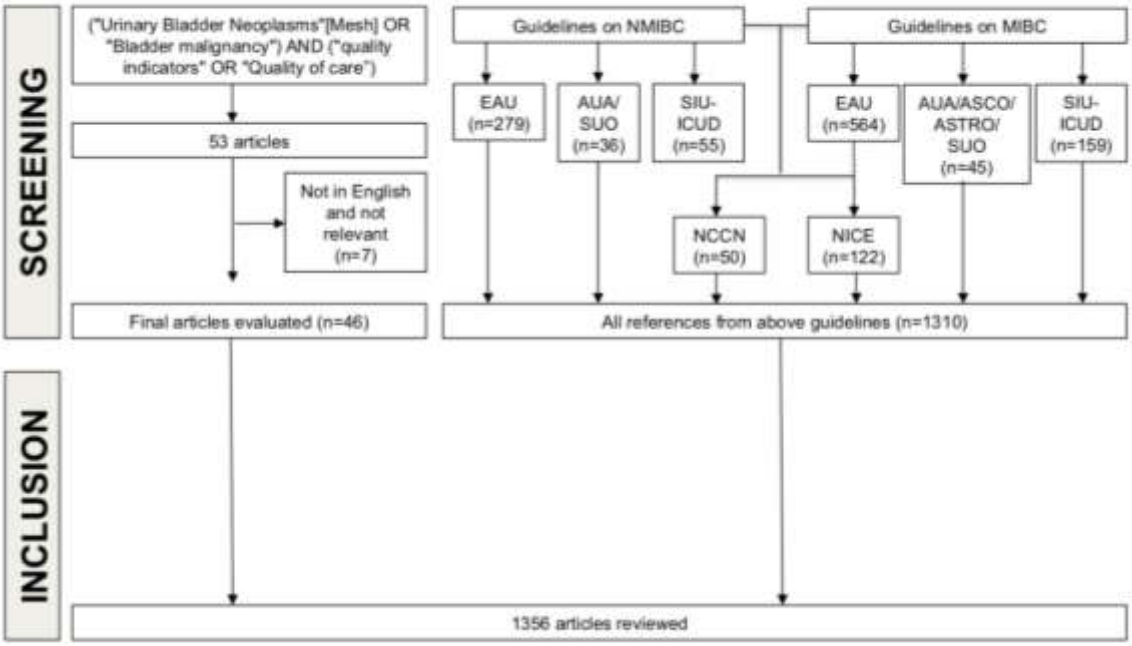

Figure 1

Tables

Table 1 – Post-TURBT intravesical therapeutic options for patients with non–muscle-invasive bladder cancer when BCG is available, in shortage, or absent, and for other alterative options

	Recommendation when BCG is available	Recommendation during BCG shortage [a]	Recommendation during absence of BCG	Other options
High-risk disease				
Induction	Full-strength BCG × 6 once-a-week cycles	• Full-strength BCG × 6 once-a-week cycles (priority is for BCG-naïve patients) • If not available, then consider reduced one-half or one-third dose, if feasible.	• Intravesical gemcitabine [136,137] • Intravesical mitomycin [138]	"Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates."
Maintenance	• Full-strength BCG with 3 yr of maintenance (3-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 mo)	• Consider 1/3 dose BCG and limit dose to 1 yr. • Maintenance therapy should not be given	• Mitomycin [b] (monthly maintenance up to 1 yr) • Epirubicin [139,140] • Valrubicin [141] • Docetaxel [142] • Sequential gemcitabine/docetaxel • Gemcitabine/mitomycin	

			[143,144]
Intermediate-risk disease			
Induction and maintenance	Intravesical BCG for 1 yr (6 weekly and 3 weekly at 3, 6, and 12 mo) or intravesical chemotherapy for up to 12 mo	Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy (eg, mitomycin, gemcitabine, epirubicin, or docetaxel) instead of BCG	
Low-risk disease			BCG should not be used.

BCG = bacillus Calmette-Guerin; NCCN = National Comprehensive Cancer Network; TURBT = transurethral resection of bladder tumour.

[a] Recommendations from American Urological Association, American Association of Clinical Urologists, Bladder Cancer Advocacy Network, Society of Urologic Oncology, the Large Urology Group Practice Association, and the Urology Care Foundation in 2019 (available at: https://www.auanet.org/practice-resources/bcg-info/bcg-shortage-notice; last accessed 7 May 2019).

[b] As per NCCN guidelines for bladder cancer v3.2019, there were two separate meta-analyses of randomised trials showing no differences in risk of recurrence between BCG and mitomycin [145], although BCG may show more favourable outcomes from maintenance regimens [146].

Table 2 – Recommended quality indicators for non–muscle invasive bladder cancer (NMIBC)

Aspect of NMIBC care	Recommended quality indicator	Level of evidence	Grade of recommendation
Preoperative			
Counselling	At the time of diagnosis, patients should be counselled to discontinue tobacco smoking	2	B
Risk stratification and surveillance counselling for patients with NMIBC	Use of EORTC and CUETO scoring systems to risk stratify patients known to have NMIBC and on surveillance follow-up	2	B
Intraoperative			
Antibiotic prophylaxis	Administer perioperative antibiotic prophylaxis prior to TURBT.	2	B
Conduct of TURBT	• Percentage of patients with muscle present in specimen from initial TURBT (excluding TaLG disease) • Percentage of patients meeting indications who undergo restaging TURBT • Percentage of patients with muscle present in specimen from restaging TURBT	2	B
Restaging TURBT	Restaging TURBT should be performed within 2–6 wk of the initial TURBT and include resection of primary tumour site	3	B
Postoperative			

Intravesical therapy	• Percentage of patients who received immediate post-TURBT instillation of intravesical chemotherapy, excluding those with contraindications (eg, incomplete resection, suspected perforation, significant haematuria) • Percentage of intermediate- and high-risk NMIBC patients who were counselled and subsequently *initiated* BCG	2	B
Appropriate frequency of surveillance based on stage/grade of bladder cancer	• Accurate documentation of risk stratification into low-, intermediate-, or high-risk disease • Appropriate intervals between cystoscopic surveillance • Appropriate assessment of the upper urinary tract for high-risk patients	2	B

BCG = bacillus Calmette-Guerin; CUETO = Club Urológico Español de Tratamiento Oncológico; EORTC = European Organization for Research and Treatment of Cancer; TURBT = transurethral resection of bladder tumour.

Table 3 – Recommended quality indicators for muscle-invasive bladder cancer (MIBC)

Aspect of MIBC care	Recommended quality indicator	Level of evidence	Grade of recommendation
Preoperative			
Administration of perioperative antibiotics	• Timely administration and discontinuation of appropriate antibiotics • Rates of urinary tract infection • Rates of surgical skin infections as classified by the National Surgical Quality Improvement Program, in accordance with the need for intervention (eg, bedside alternative removal of surgical stiches, image-guided drainage of deep infections, take-back to operating room for infection-related complications, etc.) and should be classified according to the Clavien-Dindo classification as per EAU recommendation • Rates of readmissions from urosepsis after RC	2	B
Evidence of multidisciplinary care	Percentage of patients with newly diagnosed ≥cT2 MIBC who were discussed at a multidisciplinary meeting	2	B
Receipt of neoadjuvant chemotherapy	Utilisation of neoadjuvant chemotherapy for clinically eligible ≥cT2 MIBC with urothelial cell	1	A

	carcinoma histology		
Time from TURBT to radical cystectomy <12 wk in patients proceeding directly to surgery	Percentage of newly diagnosed MIBC patients, who are eligible/fit for cystectomy, who experienced a delay of >12 wk from TURBT to radical cystectomy	3	C

Utilisation of TMT as a bladder-sparing alternative for appropriate candidates	• Percentage of patients being referred to and seen by a radiation oncologist
	• Actual utilisation rate of TMT for MIBC in appropriate candidates (see text for suggested criteria for appropriate candidates)
	• If TMT is pursued, the following may be tracked:
	  ○ Repeat maximal TURBT prior to chemoradiation
	  ○ Utilisation of concurrent radiosensitising chemotherapy [a]
	  ○ Dose of RT
	  ○ Complete response rates
	  ○ Frequency of cystoscopic surveillance
	  ○ Rates of salvage cystectomy
		2	B

Preoperative counselling with stoma marking	Percentage of patients referred to an enterostomal therapist or a specialist urology nurse clinician before radical cystectomy	2	B
Surgical volume of radical cystectomy	*Note*: Since higher surgical volume may be considered a surrogate marker	2	B

	of better overall quality of care, we recommend its use as a quality indicator; however, the cut-off used may vary regionally, depending on the density of available specialists and other demographic factors		
ERAS protocols/pathways in place	Percentage of patients undergoing radical cystectomy who are placed on ERAS protocols/pathways		
Intraoperative			
Adequacy of lymphadenectomy	Percentage of patients undergoing radical cystectomy who receive (at least) a standard template pelvic lymphadenectomy		
Postoperative			
Prospective standardised monitoring of morbidity and mortality	30-d mortality rate after elective radical cystectomy of <2%	2	B
Negative surgical margins for pT2 disease	Percentage of patients undergoing radical cystectomy who have negative soft tissue surgical margins on final histopathology	3	C
Adjuvant chemotherapy for select high-risk patients	Percentage of high-risk disease (≥pT3 and/or pN+) who did not receive neoadjuvant chemotherapy who were offered adjuvant chemotherapy postoperatively	2	B

EAU = European Association of Urology; ERAS = Enhanced recovery after surgery; RC = radical cystectomy; RT = radiotherapy; TMT = trimodal therapy; TURBT = transurethral resection of bladder tumour.

[a] Utilisation of concurrent radiosensitising chemotherapy is based on level 1 evidence (BC 2001 trial by James et al [82]).

Table 4 – Recommended quality indicators for general aspects of bladder cancer services

General aspects of bladder cancer care	Recommended quality indicator	Level of evidence	Grade of recommendation
Appropriate imaging for patients newly diagnosed with bladder cancer	• Percentage of newly diagnosed MIBC patients who obtained chest imaging with either chest XR or CT thorax • Percentage of newly diagnosed bladder cancer patients who have cross-sectional imaging of upper urinary tract (eg, CT, MRI, or US)	2	B
Participation in clinical trials	Availability of clinical trials to bladder cancer patients who are treated at a particular healthcare facility	4	C

CT = computed tomography; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; US = ultrasound; XR = x-ray.