Review

The importance of maximal TURBT in trimodality therapy for muscle-invasive bladder cancer (MIBC)

Bladder Cancer
Vol. 11(2): 1–8

DOI: 10.1177/23523735251346569
journals.sagepub.com/home/blc

Chris Ho-Ming Wong[1], Ivan Ching-Ho Ko[1], David Ka-Wai Leung[1], Brian Siu[1], Steffi Kar-Kei Yuen[1] and Jeremy Yuen-Chun Teoh[1,2,3]

Abstract

Trimodality therapy (TMT), consisting of maximal transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiotherapy, has emerged as a bladder-sparing alternative to radical cystectomy for select patients with muscle-invasive bladder cancer (MIBC). While each component of TMT plays a critical role, maximal TURBT is foundational to its success. This review examines the importance of maximal TURBT in optimizing oncological outcomes in TMT, discusses its technical nuances, and explores the evidence supporting its role in achieving durable local control and improving survival outcomes in MIBC.

Keywords

TURBT, maximal TURBT, muscle invasive bladder cancer, trimodal therapy, bladder preservation

Received: 3 January 2025; accepted: 15 May 2025

Introduction

Muscle-invasive bladder cancer (MIBC) remains one of the more aggressive and challenging urological malignancies to manage. Despite advancements in diagnostic pathways and heightened clinical awareness, nearly one in four bladder cancer cases is muscle invasive at the time of diagnosis.[1] Traditionally, these patients have been treated with radical cystectomy (RC) combined with pelvic lymph node dissection.[2] However, the significant morbidity associated with RC, coupled with a growing interest in bladder preservation strategies, has fueled increasing attention toward trimodality therapy (TMT). TMT consists of maximal transurethral resection of bladder tumor (TURBT), followed by chemoradiotherapy.[3] Maximal TURBT lies at the core of TMT, serving as both a diagnostic and therapeutic intervention. It aims to achieve maximal tumor debulking while creating an optimal foundation for subsequent chemoradiotherapy.[4] This review examines the pivotal role of maximal TURBT in TMT for MIBC, with a focus on its technical considerations, oncological importance, and the evidence supporting its integration into bladder-preservation strategies.

Overview of trimodality therapy strategies

Trimodality therapy (TMT) represents a bladder-preserving approach for MIBC and serves as a viable alternative for patients who are either medically unfit for radical cystectomy (RC) or prefer to avoid bladder removal.[5] Advocates of TMT propose that it offers survival outcomes comparable to RC in carefully selected patients.[6] TMT involves three sequential components: maximal TURBT, concurrent chemotherapy, and radiotherapy.[7] Maximal TURBT aims to achieve complete or near-complete tumor resection, serving as the foundation for subsequent therapies. Concurrent chemotherapy is administered to enhance the radiosensitivity of the tumor and to address potential micrometastases.[8] Radiotherapy is then delivered to eradicate microscopic disease within the bladder, completing the multimodal approach.

TMT can be delivered through either a split-course regimen or a continuous-course regimen, with each approach tailored to the patient's clinical circumstances. In the split-course regimen, induction chemoradiotherapy is administered

[1]S.H. Ho Urology Centre, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China
[2]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China
[3]Department of Urology, Medical University of Vienna, Vienna, Austria

Corresponding author:
Jeremy Yuen-Chun Teoh, S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR.
Email: jeremyteoh@surgery.cuhk.edu.hk

after maximal TURBT, followed by response evaluation with cystoscopy and cross-sectional imaging. Patients who achieve a complete response proceed to consolidative chemoradiotherapy,[9] while partial or non-responders are directed to radical cystectomy without significant delay. This approach minimizes the risk of treatment delays, which are known to negatively impact oncological outcomes.[10,11] In contrast, the continuous-course regimen involves delivering the full course of chemoradiotherapy upfront, with disease evaluation performed upon completion. Advocates of this method suggest that it increases the likelihood of bladder preservation by avoiding interruptions in treatment.[12]

Techniques in maximal TURBT

In both TMT protocols, maximal TURBT remains the cornerstone of treatment. Maximal TURBT refers to the thorough debulking of visible tumor prior to initiating chemoradiation. However, to date, there is no universally accepted definition of completeness in maximal TURBT.[13] The assessment of completeness often relies on the clinical judgment of the operating urologist rather than on imaging evidence obtained postoperatively. In general, it involves the resection of the primary tumor along with any satellite lesions and suspicious areas identified during the procedure.[14]

While TURBT is a critical component of TMT, it is not without complications. The risks associated with TURBT vary and was quoted at 4–10%.[15] This underscores the importance of technical precision and thorough preoperative counseling. General anesthesia (GA) with neuromuscular blockade is recommended for performing a complete TURBT, as it offers significant advantages. First, patients with MIBC often have extensive disease, which can result in prolonged operative times in certain cases. Procedures performed under spinal anesthesia may need to be prematurely terminated if the anaesthetic effect begins to wane, potentially leading to an incomplete resection. Second, GA minimizes the risk of obturator reflex activation, which can cause unintentional bladder wall perforation during tumor resection. By utilizing GA, the likelihood of achieving a safe and complete TURBT is maximized.

Intraoperatively, the use of bipolar cautery is preferred over monopolar cautery. Although rare, transurethral resection (TUR) syndrome can still occur during TURBT, particularly in patients with advanced or large tumors requiring prolonged resection times. Careful and meticulous surgical technique is essential. Ideally, resection should commence at the edge of the tumor, with adjacent normal urothelium clearly visualized to reduce the risk of inadvertent bladder perforation. Special attention should be given to minimizing complications, such as bladder perforation, as these can delay subsequent chemoradiation therapy in the context of TMT. It should be highlighted that while maximal TURBT is performed here in to enhance long term outcomes, being overly aggressive in resection should not be encouraged. Resecting through muscle into the perivesical fat – which obviously poses the danger of fill thickness bladder perforation – should not be the routine practice.

Overall, maximal TURBT remains a critical step in TMT protocols, and its success depends on careful preoperative planning, optimal anesthesia selection, and meticulous surgical technique to minimize complications and ensure timely progression to subsequent therapies.

The role of maximal TURBT on TMT response rates

The oncological efficacy of maximal TURBT remains incompletely defined, as no head-to-head trials have directly compared outcomes between patients treated with and without maximal local tumor control prior to chemoradiation. Consequently, our understanding of its oncological benefits is primarily derived from non-randomized studies. The most notable advantage of maximal TURBT lies in its association with an improved likelihood of achieving a complete response (CR) following TMT.

A pooled analysis of Radiation Therapy Oncology Group (RTOG) studies, involving 468 patients, utilized multivariate regression analysis and found that maximal TURBT significantly improved complete response rates.[16] Similarly, the landmark Massachusetts General Hospital (MGH) series demonstrated superior CR rates in patients who underwent maximal TURBT compared to those with incomplete resections (84% vs. 58%).[17] Earlier studies echoed these findings, showing that patients with no residual tumor after maximal TURBT had a markedly higher likelihood of achieving CR—up to 20% more—thereby reducing the need for immediate cystectomy.[18,19]

The role of maximal TURBT in facilitating pathological regression has also been supported by evidence from cystectomy series. Post-cystectomy specimen reviews revealed that up to 15% of patients had already achieved complete pathological response before surgery,[20] underscoring the potential therapeutic impact of maximal TURBT in reducing tumor burden.[21] In fact, even in cases that maximal TURBT appear not feasible at initial resection (for example, in the presence of multifocal extensive disease), it is also noteworthy to re-attempt a maximal resection after neoadjuvant chemotherapy (NAC). As NAC brings about potential pathological regression, the resection could be made technically feasible. Combining the effect of both NAC and maximal TURBT, the likelihood of a pathological CR could hopefully be maximized. Overall, these findings collectively highlight the importance of maximal TURBT in solitary or in combination to improve the likelihood of CR and enhancing the efficacy of bladder-sparing treatment strategies.

Can maximal TURBT impact on the long term oncological outcomes in patients receiving TMT?

Regarding long-term oncological efficacy, the benefits of maximal TURBT appear less definitive. The MGH series demonstrated improved disease-specific survival (DSS) and overall survival (OS) in patients who underwent maximal TURBT compared to those with incomplete resections.[17] However, in the same series, while the higher complete response (CR) rates associated with maximal TURBT translated into improved DSS in univariate analysis, this benefit was not sustained in multivariate regression analysis. Across multiple studies, advanced tumor stage (T stage) consistently emerges as a significant prognostic factor, raising the question of whether the observed benefits of maximal TURBT in TMT response rates are confounded by less aggressive tumor biology.

In a large-scale retrospective cohort of 757 patients undergoing TMT,[14] incomplete TURBT was more frequently observed in patients with advanced T stages (T3-T4), compared to those with T2 disease (47% vs. 9.1%). This suggests that maximal TURBT is inherently associated with a subgroup of patients with organ-confined disease, potentially confounding its perceived benefits. These findings highlight the complexity of interpreting the oncological impact of maximal TURBT, as it may reflect both the technical achievement of resection and the biological characteristics of the tumor.

The extent of TURBT being a surrogate for assessing tumor extent in TMT

While the long-term oncological benefit of maximal TURBT on DSS remains the subject of debate, it is appropriate to evaluate its role in identifying the best candidates for TMT. Critics have argued that the completeness of TURBT may be confounded by the aggressiveness of the tumor; conversely, one could argue that an incomplete TURBT serves as a predictor of poor response to TMT. Existing studies have demonstrated that advanced T4 disease and the presence of carcinoma in situ (CIS) are adverse factors associated with non-responsiveness to chemoradiation.[22] On the other hand, multifocal disease, which had been shown to be one of the a risk factors for recurrences, should also be taken into account when maximal TURBT is contemplated.

Moreover, several trial protocols have required a maximal TURBT as a prerequisite for inclusion in TMT,[23,24] supporting its importance in stratifying patients for bladder-preserving approaches. A maximal TURBT not only serves as a therapeutic modality but also plays a critical role in identifying patients who are most likely to benefit from TMT, ensuring that bladder preservation strategies are pursued in well-selected individuals with favorable tumor characteristics.

The role of maximal TURBT on bladder preservation

Moving on to long-term bladder preservation beyond initial TMT, it is crucial to evaluate whether maximal TURBT is associated with longer duration of intact-bladder. The MGH study reported that the overall bladder-intact DSS over 15 years was approximately 40%, with maximal TURBT emerging as an independent factor associated with better bladder-intact DSS (HR = 0.72). When stratified by the era of treatment (before 1995, 1996–2004, and beyond 2004), it was observed that long-term bladder-intact rates were higher in the more modern era. While there can be many contributing factors that varied between eras, for instance, a difference in number of cT2 cases or the portion of patients with hydronephrosis within the cohorts, one of the postulations for this temporal improvement could be that advancement in surgical techniques enhanced quality of endoscopic equipment, and the hence the increasing adoption of complete tumor resection as a standard practice.[25]

Over the years, there has also been a growing international consensus on standardizing the preoperative assessment, procedural steps, and documentation involved in TURBT.[26,27] This has likely contributed to optimizing the quality and completeness of TURBT, improving outcomes for patients undergoing TMT. Furthermore, advancements in other components of TMT—including radiation therapy and chemotherapy—have also played a significant role in improving bladder preservation rates.[21] The introduction of three-dimensional conformal radiotherapy, intensity-modulated radiotherapy (IMRT), and more effective chemotherapy agents has enhanced the efficacy of TMT protocols, contributing to better long-term bladder-intact survival for TMT candidates. These improvements underscore the importance of a multidisciplinary approach and evolving techniques in achieving durable bladder preservation and favorable oncological outcomes.

Challenges and limitations

A significant challenge in establishing the efficacy of maximal TURBT lies in the difficulty of acquiring high-quality level 1 evidence.[28] The Selective Bladder Preservation Against Radical Excision (SPARE) trial, a phase II feasibility study conducted in the UK, aimed to randomize MIBC patients to bladder preservation treatment versus radical cystectomy. However, the trial was terminated in 2010 due to poor patient accrual. Several factors contributed to this outcome, including the complexity of implementing multiple treatment modalities, the limited

pool of patients who were eligible for either treatment arm, and patient reluctance to have their therapeutic pathway determined by randomization.[29]

These challenges highlight the logistical and ethical difficulties of conducting randomized controlled trials (RCTs) in this setting. Given these barriers, it is highly unlikely that a head-to-head trial comparing TMT with RC will be conducted in the future. Similarly, prospective randomized evidence specifically investigating the role of maximal TURBT within TMT protocols is also unlikely to emerge. As a result, our understanding of the oncological and bladder-preserving benefits of maximal TURBT will continue to rely on retrospective analyses, observational studies, and pooled data from non-randomized series. While these data provide valuable insights, they underscore the need for careful interpretation given the inherent limitations of non-randomized evidence.

TURBT is a highly variable skill, with outcomes often dependent on the surgeon's experience and level of expertise. Variability in surgical proficiency can significantly influence the quality of resection and, consequently, the oncological and functional outcomes for patients. Systematic reviews on TURBT have highlighted the importance of surgical quality and the need for active measures to ensure quality control. Standardization of technique, adherence to procedural guidelines, and appropriate training are critical to optimizing outcomes and minimizing variability.[30]

The risks of complications associated with TURBT should not be underestimated. Among these, bladder perforation is one of the most detrimental events and must be avoided at all costs. Studies have reported bladder perforation rates as high as 10%,[31] depending on tumor characteristics, surgical technique, and surgeon experience. While conservative management with urethral catheter drainage is sufficient in over 80% of cases, the associated morbidities—including prolonged hospital stays, delayed subsequent treatment, and potential extravesical tumor spread[32]—cannot be overlooked. These risks underscore the importance of meticulous surgical technique, proper patient selection, and comprehensive preoperative planning to minimize complications and maximize the therapeutic benefits of TURBT.

The theoretical risk of tumor cell dissemination during maximal TURBT is an important consideration and warrants discussion. To date, there is no conclusive evidence linking TURBT to systemic dissemination of tumor cells. Autoneiwicz et al. investigated this phenomenon by analyzing RT-PCR or RNA from blood samples collected during TURBT and found no increase in the number of PCR-positive transcripts, suggesting that TURBT itself does not significantly promote tumor cell spread.[33] However, in a small-scale study involving seven MIBC patients undergoing TURBT, venous blood from the inferior vena cava was collected intraoperatively, and it was observed that the number of circulating tumor cells (CTCs) increased during the procedure.[34] The clinical significance of this finding remains unclear and unproven, as no direct correlation with oncological outcomes has been established. While TURBT should not be avoided based on these preliminary findings, it is important to acknowledge that the potential risk of tumor cell dissemination cannot be entirely dismissed. Further research, particularly larger-scale studies, is necessary to better understand the implications of CTCs during TURBT and whether they have any meaningful impact on long-term outcomes. Until then, surgeons should remain aware of this theoretical risk but continue to prioritize the complete resection of tumors, given its critical role in bladder cancer management.

An alternative TMT protocol

While maximal TURBT remains a cornerstone of bladder-sparing therapy, there is a growing body of counterarguments challenging its universal necessity. In an exploratory prospective study, Shi et al. enrolled MIBC patients into an alternative protocol that prioritized chemotherapy first, followed by response reassessment using cystoscopic biopsy and multiparametric MRI, without performing maximal TURBT upfront.[35] The study reported a respectable 3-year overall survival (OS) rate of 88.4% for patients in the bladder-sparing cohort. Based on these findings, the authors advocated for a more selective approach to offering maximal TURBT in MIBC patients. This alternative protocol highlights the potential role of modern imaging and biopsy techniques to stratify patients for bladder preservation without necessitating maximal TURBT in all cases. However, while these findings are promising, further validation through larger studies and longer follow-up is necessary to establish whether this approach can reliably replicate the outcomes of traditional TMT protocols.

Future directions alongside maximal TURBT to optimize TMT

The use of MRI before and after maximal TURBT

Multiparametric MRI (mpMRI) is gaining increasing popularity in the management of MIBC, offering potential advancements in diagnostic accuracy and clinical decision-making. Developed in 2018, the Vesical Imaging-Reporting and Data System (VIRADS) stratifies the risk of muscle invasion by bladder tumors into five categories.[36] Validation studies of mpMRI have demonstrated promising sensitivity, ranging from 0.73 to 0.92. Systematic reviews exploring diagnostic accuracy reported a pooled sensitivity of 0.83 for the VIRADS system. A cutoff of VIRADS-3 or 4 has been proposed as a clinical threshold for identifying muscle-invasive disease.[37,38] There are several ways in

which mpMRI can be incorporated into the care pathway for MIBC. For example, imaging can be performed prior to TURBT to assess the extent of disease. In cases with aggressive features—such as overt extravesical extension, involvement of the ureteric orifice, multifocal disease, or tumors located in anatomically challenging sites—mpMRI can help identify patients less likely to benefit from maximal TURBT. For these cases, early radical surgery may be a more appropriate option, sparing patients from an incomplete resection and its associated risks. By providing detailed anatomical and functional information, mpMRI can not only refine clinical staging but also guide treatment planning, enabling a more tailored approach to MIBC management. As its role in bladder cancer continues to evolve, mpMRI has the potential to complement traditional diagnostic and therapeutic workflows, particularly in challenging cases where maximal TURBT is unlikely to achieve optimal outcomes.

However, the advocates of early mpMRI in the management of MIBC has perhaps taken it even further, with the latest BladderPath RCT. Using TTCT (Time to correct treatment) as the primary outcome (on the basis that deferment in diagnosing MIBC and enacting the associated treatment would be associated with inferior oncological outcomes), the authors compared between mpMRI without TURBT vs conventional TURBT, and reported that the MRI arm was able to come with a shorter TTCT (Median being 53 versus 98 days), and concluded that incorporating MRI in all of the patients with the suspicion of MIBC prior TURBT would be beneficial.[39] There are certainly limitations, to our belief, on this conclusion. The benefit of early MRI could only be established if 1) an MRI could done early enough with delay and 2) resection without the information from an MRI is more likely to result in understaging T2+. First, it ought to be highlighted that the above was concluded form a UK based trial. Whether MRI can be arranged timely in a non-trial setting, and in non-UK regions remain in doubt. For instance, even in the more resources abundant region of the Nordic, it was reported that MRI wait times still ranged between 8–12 weeks on average.[40] Even though recent technological advances from artificial intelligence are bringing hope to reduce interpretation times and improve scan prioritization,[41] it would seem still far off to actualize the benefit of pre-TURBT MRI on each and every bladder cancer patient. Moreover, the conclusion of the limitation of TURBT understanding MIBC was mostly drawn from historical cohorts where conventional TURBT was practised. It was not uncommon that resection was only performed on a "biopsy basis". It would be far too early to conclude whether maximal TURBT or improved enbloc resection would still suffer from this inheritant weakness.

Aside from assessing disease extent prior resection, mpMRI can also be utilized in different timepoints in TMT. In fact, mpMRI has attained reasonable diagnostic accuracy for disease relapse. A retrospective study of mpMRI and multidetector CT (MDCT) on bladder cancer relapse showed that the area under curve (AUC) for mpMRI on relapse detection was 0.91 (which outperformed MDCT at 0.71).[42] It allows for a sensible detection of recurrences or residual disease, and could give additional information in order to differentiate residual disease or relapse from post-treatment inflammation changes. Potential time points when performing an MRI can be beneficial in TMT include defining the maximal-ness of a pre-therapy TURBT, disease evaluation in between a split course TMT, or surveillance following the completion of TMT (especially in equivocal cases).

Optimizing maximal TURBT by en bloc resection technique

Recently following an increased amount of evidence that suggests the vital role of en bloc (ERBT) TURBT in achieving a complete resection of bladder tumors,[43,44] the idea of following the principle of an enbloc resection in MIBC during TURBT has also come into the spotlight. While ERBT can be achieved with different energy sources or techniques, the caveat of the procedure is that it abides to the core principle of cancer surgery by removing the tumor in one piece. In MIBC with predominant larger tumor sizes, an ERBT may be more beneficial than conventional piecemeal TURBT by ensuring a maximal resection. Even if an one-piece extraction of the tumor cannot be done after a resection (and that the tissue needed to be fragmented in pieces for retrieval), a better resection quality can be ensured. This forms for basis of a modified ERBT. A modified ERBT advocates the removal of tumors as en bloc as reasonably possible. Relatively easier cases may still allow an enbloc resection of the entire tumor. Moderately difficult cases may require a piecemeal resection of the exophytic part, followed by the enbloc resection of the tumor base. Understandably, this is far from a case-approach-fits-all scenario. Evidences in this regard were limited and the potential benefits were mostly based on postulations. MIBC cases were certainly more challenging, requiring the input from experienced oncological or neurological urologists, and would still come at the risks of bladder perforation. One of the major benefits form enbloc TURBT which is the avoidance of floating tumor cells and their subsequent re-implantation was also not valid in the setting of MIBC. All in all, even if the most challenging cases where piecemealing cannot be avoided, one may still follow the principles of ERBT, by defining the margins of the tumor, identifying normal urothelial and detrusor, and working from periphery to central.[45] In this way, a maximal TURBT can be better performed and facilitated. This also potentially reduces the need of a re-resection after initial staging and before the initiation of systemic chemoradiation, ultimately smoothens the care pathway for TMT.

The interplay of maximal resection and biomarkers in predicting treatment outcomes

Researchers have been actively exploring biomarkers to predict treatment responses following TMT. Certainly and only understandably, a maximal resection - compared to a standard - does share comparable effect of obtaining tissue for histological confirmation. However, it should be highlighted here that obtaining a tissue at the time point most imminently precedes systemic therapy – just as the cases of maximal TURBT - may bring benefit to allow for the specimen being sent for further genomic analysis, the results of which may bring hope predicting treatment response.[46] Among different genomic markers being described, Kamran et al. reported that somatic mutations in *ERCC2*—a DNA damage repair (DDR) gene—were strongly correlated with improved bladder-intact DSS (HR = 0.15, 95% CI = 0.06–0.37; $P = 0.03$) and overall survival (OS) (HR = 0.33, 95% CI = 0.15–0.68; $P = 0.04$).[47] These findings underscore the potential utility of *ERCC2* mutations as predictive biomarkers for favorable outcomes in bladder-preserving strategies. More broadly, genomic DDR mutations are common in MIBC. Previous studies have demonstrated a strong association between DDR mutations and enhanced responses to chemotherapy and immune checkpoint inhibitors.[48,49] This has sparked interest in leveraging these mutations to guide personalized treatment approaches.

The RETAIN BLADDER phase II trial was a notable example of integrating biomarkers in selecting MIBC patients for surveillance (bladder sparing) versus cystectomy. It was a non-inferiority trial including patients having received methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) for either bladder sparing or radical surgery. Specimen from pre-NAC TURBT was sent for the analysis of *ATM*, *ERCC2*, *FANCC*, with mutation positive patients having cT0 following NAC entering surveillance protocol. While the primary end point of 2 year metastasis free survival (MFS) was not met, up to 48% of patients were metastasis-free with an intact bladder.[50] This brings both hopes and sparked the much needed discussion on the room of further refinement in this sort of bladder sparing protocol, in order to avoid any type of local therapy. The potential fascinating role of biomarker on the management of MIBC was also demonstrated in the PURE-01 trial, in which pembrolizumab was administered prior to RC for T2-4aN0M0 MIBC. The overall ypT0 and < T1 rates were 37% and 55% respectively.[51] Noteworthily, TURBT tissue pre-therapy was utilized for DNA extraction and tumor biomarker analysis, and it was found that higher tumor mutational burden (TMB) was associated with better pathological response (HR 1.06, 95% CI 1.01–1.13 for ypT0 endpoint) regardless of histology (UC or variant histology), and that outstanding responders had been identified. In the future we could be expecting an increased adoption of immune checkpoint inhibitors in MIBC as part of bladder conservative strategies. This suggests an potential pivotal role of maximal TURBT, in tumor debulking, obtaining tissue for DNA analysis in order to best select and prepare the patients for bladder conservative treatment. There are other several ongoing clinical trials are investigating the role of genomic biomarkers in optimizing bladder-conserving strategies. For example, the Alliance A031701 trial and the HCRN GU 16–257 trial aim to evaluate how these markers can inform decisions regarding bladder preservation versus radical interventions. These efforts represent a promising step toward precision medicine in MIBC, with the potential to refine patient selection and improve outcomes in bladder-sparing therapies.

Conclusion

Maximal TURBT remains a cornerstone of trimodality therapy for MIBC. Urologists should consider prioritizing achieving complete or near-complete tumor resection, leveraging advanced imaging and surgical techniques when necessary, to maximize bladder preservation and improve survival outcomes. Ongoing advancements in imaging modalities and risk stratification tools hold promise for further enhancing the effectiveness of maximal TURBT in the management of MIBC.

ORCID iDs

Chris Ho-Ming Wong https://orcid.org/0000-0003-1795-1198
Steffi Kar-Kei Yuen https://orcid.org/0000-0002-9956-1558

Ethical considerations

Ethics approval is waived for the review nature of the publication with no patient data involved.

Author contributions

WCHM: conceptualization, writing of the manuscript; BS, ICHK, DKWL, YKK: literature search and review, revision of article; JTYC: conceptualization and supervision

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

There is not data generated form the production of this manuscript.

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