

Putting guidelines into practice: has the era of perioperative chemotherapy arrived?

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In the current landscape of bladder cancer management, marked survival differences exist between non-muscle invasive, muscle invasive and metastatic disease (5-year survival 95%, 50% and 6%, respectively) (1). The rationale for a multi-modal approach to muscle-invasive bladder cancer (MIBC) is to maximize curative treatment outcomes and prevent progression to metastatic disease. For surgical management, radical cystectomy is the definitive treatment option. Peri-operative chemotherapy offers additional benefit in disease free interval and overall survival (2), however utilization rates continue to be relatively low worldwide. The study by Booth *et al.* is a large population-based analysis of time trends in use of peri-operative chemotherapy for MIBC in Ontario, Canada (3).

The extensive variation in practice patterns may be partly due to a lack of consensus regarding the optimal sequence of treatment. Consensus international guidelines (4-6) recommend neo-adjuvant chemotherapy for MIBC based on level 1 evidence from meta-analyses, which demonstrate an improvement in overall survival by about 5% (7-9). Although similar effects are also evident in some trials of adjuvant chemotherapy, smaller sample sizes, variability in study design and inconsistent results make these data less robust (10). There are some data suggesting progression-free survival benefit in adjuvant *vs.* delayed post-operative chemotherapy, but no difference in overall survival (11). To date, there has been no direct comparison between neo-adjuvant and adjuvant chemotherapy.

From a practical perspective, neo-adjuvant chemotherapy may be more easily delivered in a prescribed, planned schedule in the lead up to radical cystectomy. Additional benefits include downstaging of disease with increased chance of T0 stage at resection, potentially leading to greater ease of surgery. Improved prognostication based on histology at time of cystectomy has also been demonstrated (12). This approach also avoids delays and failure to undergo adjuvant treatment, which can occur due to slow post-operative recovery and return to baseline performance status, as well as unexpected post-operative complications.

Conversely, there may be clinical rationale to progress immediately to resection and subsequently consider adjuvant treatment. This approach may mitigate against concerns regarding the delay to cystectomy, which has repeatedly been found to decrease overall survival (13). Additionally, radical cystectomy can potentially demonstrate histopathological factors including nodal status and extravesical extension, which are associated with higher risk of recurrent or metastatic disease, thereby justifying the risks and morbidity of chemotherapy. On the other hand, accurate pathological staging at the time of resection may also identify patients with favorable features who may derive less benefit and therefore avoid adjuvant chemotherapy. The decision to proceed straight to definitive surgical management also captures patients who may have otherwise had delay or been unfit for surgery due to chemotherapy toxicities.

In addition to the controversy regarding the timing of chemotherapy in relation to cystectomy, other factors that may limit its usage include patient fitness and preferences as well as clinician preferences. In an effort to understand these factors further, Booth *et al.* conducted a retrospective analysis of 5,582 cystectomy patients treated in Ontario over a 20-year period from 1994–2013 (3). Such a substantial collection of data allows for comprehensive analysis of practice patterns in the field of MIBC treatment. Primary outcomes evaluated the rate of perioperative chemotherapy utilization, as well as referral to medical oncology. This article builds on previous work establishing trends from 1994–2008 (14) and compares contemporary results from 2009–2013.

In this study, the use of pathology reports from time of cystectomy added a level of data integrity to the identification of cases. These were then correlated with billing records for medical oncologists and chemotherapy codes within a 16-week perioperative time frame. This process likely captured the majority of cases who received neoadjuvant or adjuvant chemotherapy, and in itself was no mean feat. However, this may have unintentionally excluded cases in which an informal oncology opinion was sought, including in multidisciplinary meetings (MDMs).

In terms of their primary endpoint, Booth *et al.* demonstrated a significant increase in perioperative chemotherapy utilization, with an OR of 5.17 for patients undergoing radical cystectomy in 2009–2013 compared to the earlier timeframe. A significant trend was seen towards increased peri-operative referral to medical oncology in the contemporary era (from 12% in 1994–1998 to 32% in 2009–2013). For patients seen pre-operatively, there was also a substantial increase in the use of neoadjuvant chemotherapy (from 5% in 1994–1998 to 19% in 2009–2013).

Post-operatively, node positivity at cystectomy was correlated with a higher referral rate to medical oncology and a greater than three-fold increase in the prescription of adjuvant chemotherapy. This is a change in practice that has been reported by other groups (15), and the authors acknowledged the potential influence of previous papers and release of consensus guidelines. Whilst this demonstrates an encouraging trend, the overall rate remains low and further highlights the need to identify factors preventing appropriate uptake of perioperative chemotherapy.

In this paper, confounders such as age, geographic location, socioeconomic status, medical comorbidities, and volume of surgical experience per clinician have been taken into account. The authors acknowledged potential bias due to inability to evaluate lack of treatment based on patient factors,

including preference for surgical treatment alone, or social factors including financial difficulty or absence from work. Data on performance status and creatinine clearance were also not available, two factors which would identify patients in whom cisplatin containing regimes or any perioperative chemotherapy may have been deemed inappropriate.

Within the limitations of a retrospective study, Booth *et al.* identify multiple factors that may contribute to the disparity in practice and referral patterns. An assessment of referral rate adjusted for volume of cases per surgeon and hospital district intriguingly implies significant practitioner-based variability. This may provide a valuable opportunity to target further interventions towards improving referral rates at low-outlying centers. Given this established dataset, a potential continuation of this project could involve an intervention surrounding education patterns and streamlined referral processes to optimize patient referrals from surgeon to medical oncologist.

When reporting on their secondary objective, Booth *et al.* discuss the utilization of MDM discussion to identify patients who would benefit from perioperative treatment. Participation in the MDM process has been found to increase rates of referral and perioperative chemotherapy uptake, and development of a robust MDM program in health networks may be one systemic approach which increases capture of appropriate cases in a timely fashion (16). The identification of a subgroup of patients who may have received further treatment if referred to medical oncologists is perhaps the most novel aspect of this paper. This highlights the need for a system to identify cases at initial diagnosis and ensure timely referral and treatment. Whilst not all cases treated with cystectomy may be appropriate for perioperative chemotherapy, sophisticated analysis has found that 51% of cases in this series may have obtained benefit, indicating that many may have missed out.

The current treatment landscape in non-metastatic bladder cancer is changing, with improved understanding of the biology on a cellular and genetic level (17). Through genomic sequencing, specific genes have been identified which may assist in the identification of patients most likely to benefit from neo-adjuvant chemotherapy (18). Clinical trials are also currently underway to assess the use of immunotherapy agents as adjuncts to surgical management (clinicaltrials.gov identifier NCT02450331, NCT01435356) (19), and results of these studies are eagerly awaited.

The data presented by Booth *et al.* comprehensively narrates the story of a population wide shift in treatment patterns and approach to MIBC, and mirrors observations

of similar practice changes in other studies. Whilst there are many exciting developments in the field, we have the current ability to improve the application of best practice treatment in a multidisciplinary, patient centered approach. It is crucial to ensure that patients who may benefit from perioperative chemotherapy are provided with the opportunity to discuss available options and make informed treatment decisions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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