Timing cystectomy and perioperative chemotherapy in the treatment of muscle invasive bladder cancer

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Introduction: *The ability of cystectomy to cure patients with muscle-invasive transitional carcinoma of the bladder (TCC) is diminished by the presence of occult micrometatases. Chemotherapy contributes to cure to the extent that it may eradicate these micrometastases. In the absence of methods to preoperatively stage TCC precisely or assess tumor biology, we review the current literature regarding the timing of cystectomy and use of perioperative chemotherapy. Based on this data, we suggest optimal and feasible strategies for treating TCC in a resource-constrained environment.*

Materials and methods: *Systematic reviews of TCC were sought using electronic databases to obtain optimal information about: 1) the relationship between TNM stage and survival, 2) the effect of surgical waiting times on tumor stage and survival outcomes, 3) the benefits of neoadjuvant and adjuvant chemotherapy, and 4) the patients who benefit most from perioperative chemotherapy.*

Results: *Prospective data from the largest contemporary series of patients treated with cystectomy confirmed long-term survival in patients with extravesical and/or lymph node disease of 25%-47% at 5 years and 17%-27% at 10 years. Lymph node involvement was more common in patients with extravesical tumors. Retrospective studies of the effect of delay to cystectomy on outcomes showed higher tumor stage and reduced survival with delay of cystectomy beyond 12 weeks. Two individual patient data meta-analyses, including all currently available randomized controlled trials (RCTs), comparing neoadjuvant and adjuvant chemotherapy to local therapy alone confirmed that overall survival is modestly improved by cisplatin-based combination neoadjuvant chemotherapy. None of these RCTs showed a detrimental effect of delaying cystectomy for this treatment. Tumor status at cystectomy appears to correlate with overall survival.*

Conclusions: *We propose immediate use of neoadjuvant chemotherapy in patients suspected of having extravesical TCC. As most have micrometatastases, immediate surgery is less critical. For patients suspected of having organ-confined TCC, immediate cystectomy is recommended with adjuvant chemotherapy recommendations based on pathological staging. If surgery within 12 weeks is not possible for these patients, neoadjuvant chemotherapy with monitoring of response can be used. Improved preoperative staging and understanding of tumor biology are required to optimize the multimodality treatment of TCC.*

Key Words: bladder neoplasms, cystectomy, neoadjuvant therapy, chemotherapy, adjuvant

Introduction

Bladder cancer is the fifth most common solid tumor and is currently diagnosed in approximately 5000 Canadians per year.[1] Transitional cell carcinomas make up the vast majority of all bladder cancers in Canada. Approximately 1650 Canadians a year will die secondary to their bladder cancer.[1] Thirty percent of patients with bladder cancer present with de novo muscularis propria invasive disease.[2] Between 10% and 20% of patients with superficial bladder cancer progress to muscularis propria invasive disease.[2]

Radical cystectomy and pelvic lymphadenectomy remain the standard of care for patients with resectable

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muscularis propria invasive transitional cell carcinoma of the bladder (TCC) who are surgical candidates, based on age, medical comorbidities, and for patients not ideal candidates or committed to a bladder preservation approach. Surgical and perioperative factors play an extremely important role in patient outcomes.[3-5] Despite the ongoing improvements in surgical technique and perioperative care, survival outcomes continue to be disappointing. Most patients who die from TCC have distant metastases, so suboptimal cure rates with cystectomy are likely due to the presence of occult distant metastases present at the time of surgery.

Improved survival has been observed in patients with metastatic TCC treated with cisplatin-based multiagent chemotherapy in randomized controlled trials (RCTs). This has provided a rationale and prompted the study of perioperative chemotherapy to improve upon the cure rates achieved with cystectomy alone. TCC is an exception amongst the common solid tumors in that the use of chemotherapy prior to surgery (neoadjuvant) is better studied than postoperative (adjuvant) chemotherapy in RCTs. Both strategies have their potential advantages and disadvantages.

The theoretical advantages of neoadjuvant chemotherapy include: 1) *in vivo* chemotherapy sensitivity testing, 2) downstaging of locally advanced tumors thereby facilitating radical cystectomy, 3) no need for post-cystectomy recovery before chemotherapy administration, 4) patients able to receive greater drug dose intensities and cycles and 5) allows earlier treatment of occult metastastases. The theoretical advantages of adjuvant chemotherapy include: 1) earlier radical cystectomy and 2) the availability of pathologic staging to more precisely assess need for perioperative chemotherapy.

Ideally, all patients diagnosed with TCC should receive immediate surgery. However, this is often not practically feasible; and theoretically, immediate surgery may not be as important in all patients. Our objective was to review the most current data providing information about the survival effects of tumor stage, delay of surgery, and use of perioperative chemotherapy; and use this information to generate recommendations for the optimal timing and sequencing of cystectomy and perioperative chemotherapy for patients with TCC.

Materials and methods

Systematic reviews and other sources were used to obtain the best available published articles in the medical literature to address the following questions: What tumor factors predict survival in TCC patients treated with cystectomy? Does delay in cystectomy (for chemotherapy or other reasons) affect tumor stage or survival? Does perioperative chemotherapy improve survival in TCC patients treated with cystectomy? Who benefits from neoadjuvant chemotherapy? Systematic reviews were identified using the MEDLINE (January 1987 to April 2006), CANCERLIT (January 1987 to October 2002) and EMBASE (1986 to 1997) databases searched using a search strategy that included medical subject headings, text words and publication types, namely "bladder neoplasms"; "carcinoma, transitional cell"; "bladder cancer"; and included "surgery", "surgery AND (delay or wait*)", and "drug therapy" for each of the questions respectively. In addition, "randomized controlled trial"; "meta-analysis"; and "systematic review" were used as search terms for the perioperative chemotherapy questions. RCTs or meta-analyses were included in the review if they compared neoadjuvant or adjuvant chemotherapy with a local definitive therapy versus local definitive therapy alone in patients with pT2-T4a, N0 or Nx TCC and provided survival data.

Results

What tumor factors predict survival in TCC patients treated with cystectomy?

Several contemporary cohorts of TCC patients treated with cystectomy have been reported.[6-9] It is beyond the scope of this report to review all of these; however, one series of over 1000 patients treated at one centre in North America was identified.[6] It was the consensus of the authors that this represented the largest and most contemporary series, featured prospective data collection and consistent use of radical cystectomy and lymphadenectomy in all patients and provided optimal and representative data regarding the best possible results achievable with surgery. There were 1054 patients reported with a median follow-up of 10.2 years; a minority of patients also received radiotherapy and/or chemotherapy. The overall survival (OS) for patients with organ-confined disease compared to those with extravesical disease at 5-years was 74% versus 37%, and at 10-years was 54% versus 22%; respectively. The OS for patients without lymph node involvement compared to those with nodal involvement at 5-years was 69% versus 31%, and at 10-years was 49% versus 23%; respectively. In patients with extravesical tumors and/or nodal involvement the 10-year OS ranged from 12%-29%. The risk of nodal involvement correlated with whether the primary tumor was organ-confined (11%) or extravesical (56%).

Does delay in cystectomy affect tumor stage or survival?

The effects of surgical delay in patients with bladder cancer has recently been the subject of a systematic review by Fradet et al.[10] One additional report not included in this review was identified.[11] Five published retrospective studies reported effects on the time from either diagnosis of muscle invasion or last transurethral resection to cystectomy on outcomes.[11-15] Three reports examined the effect of surgical delay of 12 weeks or more on pathological tumor stage.[12-14] All three showed a higher proportion of more advanced tumors at surgery (> pT3 52% versus 81%, pT4 14% versus 31%, and presence of extravesical extension 48.2% versus 84%; respectively). One study examined progression-free survival (PFS) and reported reduced PFS at 5 years (55% versus 34%) also confirmed in multivariate analysis (hazard ratio [HR] for progression 1.62).[13] Two studies examined disease-specific survival (DSS) and both reported reduced DSS in delayed patients (3-year DSS multivariate HR: 1.93 and mean DSS 9.4 versus 6.7 years; respectively).[11,15] One report examined OS and reported reduced 5-year OS in patients delayed 12 weeks or more (44% versus 33%, multivariate HR: 1.7).[11] None of the series reported favorable or neutral effects of surgical delays of 12 weeks or more. These reports are limited by their retrospective nature and intrinsic lack of control of other covariates predicting tumor progression and survival. However, the credibility of the results are enhanced by their consistency, common sense, and the improbability that patients with more aggressive tumors would systematically have delayed surgery in all the reports.

Cystectomy may be delayed to allow administration of neoadjuvant chemotherapy. An individual patient data meta-analysis summarizing all neoadjuvant RCTs has recently been published and updated.[16,17] Although the results of none of these RCTs show statistically significant results individually, none of RCTs studying cisplatin-based combination chemotherapy prior to cystectomy show trends of treatment effect suggesting a detrimental effect of neoadjuvant chemotherapy.[18-23]

Does perioperative chemotherapy improve survival in TCC?

RCTs of neoadjuvant and adjuvant chemotherapy have recently been the subject of individual patient data meta-analyses by the Advanced Bladder Cancer Meta-analysis Collaboration (ABCMC).[16,17,24] Multiple RCTs using single and multi-agent chemotherapy have failed to demonstrate a survival benefit with neoadjuvant chemotherapy.[25] The largest RCT to date was conducted between 1989 and 1995 and was an international collaboration of trialists and involved 976 patients with T2-4a, N0-NX, M0 TCC.[21] Patients were randomized to receive three cycles of neoadjuvant cisplatin, methotrexate and vinblastine or no chemotherapy prior to radical cystectomy or radical external beam radiotherapy. At 7.4 years OS was 6% better in the group receiving this regimen of neoadjuvant chemotherapy. Radical cystectomy and neoadjuvant chemotherapy were associated with a 3.7% operative and 1% mortality rate, respectively. A RCT from the United States and coordinated through the Southwestern Oncology Group (SWOG) enrolled 317 patients between 1987 and 1998 with T2-T4a, N0, M0 TCC and randomized patients to either methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or no chemotherapy prior to radical cystectomy.[19] The median OS among patients undergoing radical cystectomy alone was 46 months versus 77 months among patients assigned to neoadjuvant chemotherapy with radical cystectomy (P = 0.06). At 5 years, 57% of patients in the MVAC treated group were alive versus 43% in the radical cystectomy alone group.

In an updated meta-analyses the ABCMC reported on 3005 patients in 11 RCTs using both single agent and multi-agent neoadjuvant chemotherapy.[17] There was an OS advantage from 45% to 49% at 5 years in the neoadjuvant chemotherapy group (P = 0.022). When only cisplatin-based combination chemotherapy trials were analyzed, OS was improved from 45% to 50% at 5 years in favor of the group receiving neoadjuvant chemotherapy (P = 0.003). Three RCTs using combination chemotherapy reported eight deaths (1.1%) secondary to chemotherapy.[25]

The ABCMC also completed a meta-analysis of individual patient data from adjuvant chemotherapy RCTs.[24] Patients had clinical stage T2-T4a TCC and received radical cystectomy with or without adjuvant chemotherapy. There were no other interventions. Only six RCTs including 493 patients were eligible for analysis.[26-30] Five of these RCTs used combination cisplatin-based chemotherapy and one RCT used single agent cisplatin. There was an OS benefit of 9% at 3 years in the patients that received adjuvant chemotherapy (P = 0.019). However, this analysis has a number of limitations identified by the authors that limit the reliability of its results. The validity of the results is questionable as only 19% of control patients clearly had chemotherapy at relapse, three RCTs were stopped earlier than planned, and individual patient data was unavailable for three unpublished RCTs. Additionally, the power of the analysis was limited

by small numbers of patients and deaths; 900 deaths are required to reliably detect a 9% difference with 80% power and 5% significance.

Who benefits from neoadjuvant chemotherapy?

The ABCMC attempted to examine differential effects of neoadjuvant chemotherapy by patient and tumor factors including age, sex, T and N classification, tumor grade, performance status, and renal function.[16] Only tumor size (diameter > 8cm) was associated with benefit in multivariate analysis (p = 0.008). Four RCTs reported associations of pathological tumor response in cystectomy specimens with survival in multivariable analyses.[25] The most detailed data comes from the most recently completed RCT reported by SWOG.[19] Pathological complete response at cystectomy (pT0) was associated with significantly improved survival in both the control and chemotherapy arms (median survival 11.3 years and not reached, respectively). Any residual disease in the bladder at cystectomy was associated with inferior survival in both the control and chemotherapy arms, although median survival was marginally longer in those who received chemotherapy (2.4 and 3.8 years, respectively). The proportion of pT0 patients in the experimental arm was increased by neoadjuvant chemotherapy compared to the control arm (31.4% versus 11.7%).

Discussion

Invasion of the muscularis propria by transitional cell carcinoma identifies a change in the biology of urothelial cancer from a chronic, benign, recurrent condition to a virulently aggressive neoplasm. The "window of opportunity" for curing patients has often closed by the time muscle invasion is identified, and many patients harbor occult micrometastases that cannot be cured with surgery alone. Extravesical disease is associated with lymph node involvement in over 50% of patients, and the presence of extravesical disease and/or pelvic lymph node involvement signals a dismal prognosis.[6] The caveat to these data is that organ-confined and extravesical status were determined postoperatively and pathologically in this study, and although likely of similar prognostic value preoperatively, the ability to make this distinction within the accuracy of clinical staging is limited.[31,32]

Delay in cystectomy over 12 weeks appears to be associated with higher rates of extravesical disease and thus not surprisingly lower PFS, DSS and OS. Systemic chemotherapy delivered in the neoadjuvant setting has been proven to eliminate micrometastases and contribute to cure in some patients. Neoadjuvant chemotherapy does not appear to be associated with a detrimental effect due to delay of cystectomy despite minimal or no benefit in the majority of patients. Complete pathological response in the cystectomy specimen appears to be a surrogate for the eradication of systemic micrometastases.

Ideally all operable patients diagnosed with TCC and with negative staging studies for distant metastases would have immediate surgery. However, this is often not possible; patients may be subject to delayed diagnosis, treatment delays related to their own health or choices, delays related to access to the health care resources needed for cystectomy, or combinations of these. Optimal use of surgery and perioperative chemotherapy is not only impeded by the inaccuracy of clinical staging of TCC, but also by the inability to assess occult metastases with regard to their presence, volume and chemosensitivity. Notwithstanding these areas of current and future research, we make the following recommendations for stratifying patients to neoadjuvant chemotherapy and triaging them for access to cystectomy. Optimal surgery should include complete transurethral resection prior to cystectomy, and cystectomy with adequate pelvic lymph node sampling (≥ 9 lymph nodes) and negative surgical margins.[33]

Suspected extravesical (pT3, pT4a) or pelvic lymph node positive disease

As neoadjuvant chemotherapy has both local and systemic effects, and has a proven if modest survival benefit, it is recommended that these patients suspected to have extravesical TCC receive treatment with the equivalent of 3 months of a cisplatin-based combination chemotherapy regimen such as, MVAC prior to cystectomy. Although it might seem counterintuitive to delay surgery in patients with more locally advanced disease, most patients with extravesical disease harbor distant metastases and therefore, would not be cured with surgery alone. Alternative chemotherapy regimens with similar or superior activity to MVAC in the metastatic setting, such as gemcitabine-cisplatin or dose intense MVAC with granulocyte-colony stimulating factor are also used perioperatively by some oncologists.[34,35] Cystoscopic monitoring of patients during chemotherapy is not mandatory, but may be of value to identify patients with progressive disease. In such patients, cure with any therapy is unlikely, but alternative chemotherapy or cystectomy may be of value to optimize palliation and clinically detectable disease-free survival. The management of patients

who have had neoadjuvant chemotherapy but have residual disease in their cystectomy specimen is uncertain but their prognosis is known to be poor.[6] Individualized decisions about expectant management or further adjuvant chemotherapy with an alternative regimen to that used neoadjuvantly are reasonable.

Suspected organ-confined (pT1, pT2) disease

Patients with organ-confined TCC should have immediate cystectomy. The reasons for this are threefold. First of all, these patients have a much higher probability of being free of occult distant metastases and therefore, a proportionally higher probability of cure with surgery alone. Second, delay in surgery beyond 12 weeks from diagnosis of TCC appears to be associated with pathological tumor upstaging and worse survival outcomes. Third, as the risk of occult metastases is lower, the risk of receiving unnecessary treatment with neoadjuvant chemotherapy is higher. Pathological staging of these patients allows more precise ascertainment of recurrence risk, although the benefits of adjuvant chemotherapy remain to be precisely defined and are under study in ongoing clinical trials.

Suspected organ-confined disease subject to delayed cystectomy

Efforts should be made to provide cystectomy to patients with suspected organ-confined TCC as soon as possible. Where this is not possible, it is recommended that these patients be offered neoadjuvant chemotherapy as per recommendation above with one proviso. These patients should undergo cystoscopy 6-8 weeks after starting chemotherapy and if progressive disease is observed, proceed directly to cystectomy. Continuing neoadjuvant chemotherapy with a different chemotherapy regimen is not recommended once chemoresistance is observed, as the probability of response is low and there is a possibility of tumor stage progression along with a higher risk of development of metastases if cystectomy is delayed beyond 12 weeks.

Conclusions

Although we agree with others that neoadjuvant chemotherapy may be more beneficial in extravesical advanced TCC,[21] we understand that this has not been definitively shown and is limited in practice by the inaccuracy of clinical staging. Although the delay in cystectomy associated with neoadjuvant chemotherapy does not appear to negatively affect survival outcomes, and in fact appears to confer a modest survival benefit, the quality of life for patients waiting for their cancer surgery is unknown. There is widespread agreement that surgical delays may result in psychological morbidity.[36,37] Further study is required to determine if neoadjuvant chemotherapy impacts on a patients in a negative fashion on their quality of life based upon the additional time to definitive therapy, such as radical cystectomy.

It is appropriate to discuss the risks and potential benefits of neoadjuvant chemotherapy with every patient that has muscle-invasive disease based upon the reported modest OS advantage. However, further stratification is required to minimize or prevent unnecessary systemic therapy for patients that are cured by radical cystectomy alone. Currently the information required to efficiently stratify is unavailable. Whether adjuvant chemotherapy confers a survival advantage is not definitively known given the current data. Although adjuvant chemotherapy may be incorporated into the management of patients at risk for metastases following radical cystectomy, mature data from randomized studies of adjuvant chemotherapy are underway and required to better inform our patients. □

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