

Optimal timing of chemotherapy and cystectomy

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F1000 Medicine Reports 2010, **2**:48 (doi:10.3410/M2-48)

The electronic version of this article is the complete one and can be found at: <http://f1000.com/reports/medicine/content/2/48>

Abstract

Radical cystectomy with pelvic lymphadenectomy is the standard treatment for muscle-invasive bladder cancer. However, the high recurrence rates and high death rate from metastases after radical cystectomy for locally advanced bladder cancer emphasize the high risk of occult distant disease. To improve patient survival, multimodal therapy whereby chemotherapy and surgery are used in concert with each other is necessary. The preponderance of data suggests that neoadjuvant chemotherapy offers patients a clear – albeit small – survival advantage, whereas the data for adjuvant chemotherapy are less convincing. Currently, trials to improve the results of such neoadjuvant therapy using biologic targets in conjunction with cytotoxic regimens are under way.

Introduction and context

Radical cystectomy with extended pelvic lymphadenectomy is the mainstay of treatment of muscle-invasive urothelial carcinoma of the bladder (UCB) [1]. However, in a number of patients, especially those with high-risk disease, such as pathologic stage T3 or T4, and those with lymph node metastases, surgery alone is not sufficient. Five-year overall survival rates for patients with pT3a, pT3b, pT4, and pN⁺ treated with surgery alone are 78%, 62%, 50%, and 35%, respectively [1]. It is believed that micrometastases present at the time of cystectomy [2] contribute to subsequent local and distant recurrences and mortality from UCB. As a result, both neoadjuvant and adjuvant chemotherapy clinical trials have been conducted in order to improve the clinical outcomes of this group of patients.

Neoadjuvant chemotherapy has several potential advantages. It has the potential of treating micrometastases that could be present at the initial diagnosis of UCB [2]. In addition, many patients tolerate chemotherapy better when it is given prior to radical cystectomy. Patients with locally advanced disease or bulky unresectable disease can be downstaged with neoadjuvant chemotherapy, and this could render surgery technically feasible. On the

other hand, opponents of this paradigm suggest that it is difficult to assess the true pathologic stage of disease on the basis of clinical factors (such as grade and stage from TURBT [transurethral resection of bladder tumor] and bimanual physical examination before) and that, as a result of such an assessment, some patients could receive unnecessary chemotherapy. In fact, up to one-third of the cases can be incorrectly staged prior to radical cystectomy.

Several trials have studied neoadjuvant chemotherapy in a randomized fashion. The largest trial was an international collaboration [3] in which 976 patients with clinical stage T2 to T4a UCB were randomly assigned to radical cystectomy or radiotherapy with or without neoadjuvant chemotherapy (methotrexate, vinblastine, cisplatin, and folinic acid residue). Patients treated with chemotherapy had a median survival of 44 months compared with 37.5 months for upfront cystectomy. In addition, 3-year overall survival was improved by 5.5% with chemotherapy (from 50% to 55.5%). This study did have confounders: radiotherapy was used in almost half of the patients (instead of radical cystectomy), and no adriamycin was used. In addition, patients had a short follow-up of 4 years. More recently, Grossman *et al.* [4]

presented results from the Southwest Oncology Group (SWOG) 8710 trial of 307 patients with clinical stage T2 to T4a UCB randomly assigned to radical cystectomy with or without neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, and cisplatin). In that study, patients treated with combination therapy had higher pT0 rates (38% versus 15%), improved median survival (77 months versus 46 months), and improved 5-year overall survival (57% versus 43%) compared with patients treated with surgery only ($P = 0.06$ by a two-sided stratified log-rank test). In 2005, the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration conducted a large meta-analysis of 11 neoadjuvant chemotherapy clinical trials that included 3005 patients. That study showed that neoadjuvant platinum-based chemotherapy resulted in a significant survival benefit (hazard ratio [HR] = 0.86, $P = 0.003$) with a 13% reduction in risk of death and a 5-year absolute reduction of disease-specific mortality of 9% and overall mortality of 5% [5].

Adjuvant chemotherapy (given immediately after surgery) is another option. The advantage is that the pathology is ascertained and the stage is accurately assessed, allowing better selection of patients for chemotherapy. In theory, this would minimize the number of patients who receive unnecessary therapy. On the other hand, surgery and its associated potential complications could prevent some patients from receiving adjuvant chemotherapy in a timely fashion. Of the 10 or so trials performed to date, only 3 have shown a benefit to adjuvant chemotherapy. Skinner *et al.* [6] randomly assigned 91 patients with stage pT3 to T4, N0 to N2 UCB to surgery with or without adjuvant chemotherapy (mainly with cisplatin, adriamycin, and cyclophosphamide) and found that the median overall survival rate was higher for patients treated with chemotherapy (4.3 years versus 2.4 years). Stöckle *et al.* [7,8] randomly assigned 49 patients with stage pT3b to T4a, N0 to N2 UCB to radical cystectomy with or without chemotherapy with MVAC or MVEC (epirubicin instead of adriamycin) and on an updated intention-to-treat analysis [9] showed a median progression-free survival of 66.9 months and a median overall survival of 35.1 months for the adjuvant chemotherapy group (compared with 11.6 months and 20.4 months, respectively, for the surgery-only group). Freiha *et al.* [10] randomly assigned 50 patients with stage pT3b to T4, N0 to N2 UCB to surgery with or without adjuvant CMV (cisplatin, methotrexate, and vinblastine) chemotherapy and noted that progression-free survival was higher in patients treated with chemotherapy (37 months versus 12 months). The ABC Meta-analysis Collaboration also

performed a meta-analysis for adjuvant chemotherapy that included six clinical trials with 491 patients. Although that analysis showed a 25% relative reduction in mortality (HR = 0.75, $P = 0.019$) and 3-year absolute reduction in mortality of 9% in patients treated with adjuvant therapy, the power of the meta-analysis is limited since those trials were generally small and underpowered to investigate small differences in survival, some trials were stopped early, some patients did not receive salvage therapy, and others did not receive their allocated treatment [11].

Recent advances

More recently, trials that include large numbers of patients have been launched. A group from Italy recently reported their results on adjuvant versus salvage (given at the time of clinical relapse) chemotherapy (with gemcitabine and cisplatin) after radical cystectomy in patients with pT2G3 to T4 N0 to N2 disease and found that 3-year overall survival rates were 48% with adjuvant chemotherapy and 67% with salvage chemotherapy, and these rates were not statistically different [12]. Unfortunately, that trial closed early because of poor accrual and reported on only 194 patients instead of the planned 610. The EORTC (European Organization for Research and Treatment of Cancer) 30994 trial (NCT00028756) randomly assigned patients to receive early (within 90 days of cystectomy) versus delayed (at the time of clinical relapse) chemotherapy using MVAC, dose-dense MVAC, or GC (gemcitabine plus cisplatin), and the final results are awaited.

Millikan *et al.* [13] reported on a trial in which 140 patients with stage T2 with lymphovascular invasion or stages cT3 to T4a were enrolled. One group received two cycles of neoadjuvant MVAC, followed by surgery, and then three more cycles of MVAC, and the second group received five cycles of MVAC only after surgery. Overall survival was not different between the two strategies, suggesting that the sequence of chemotherapy in relation to surgery might not be as important as the fact that multimodal therapy is needed.

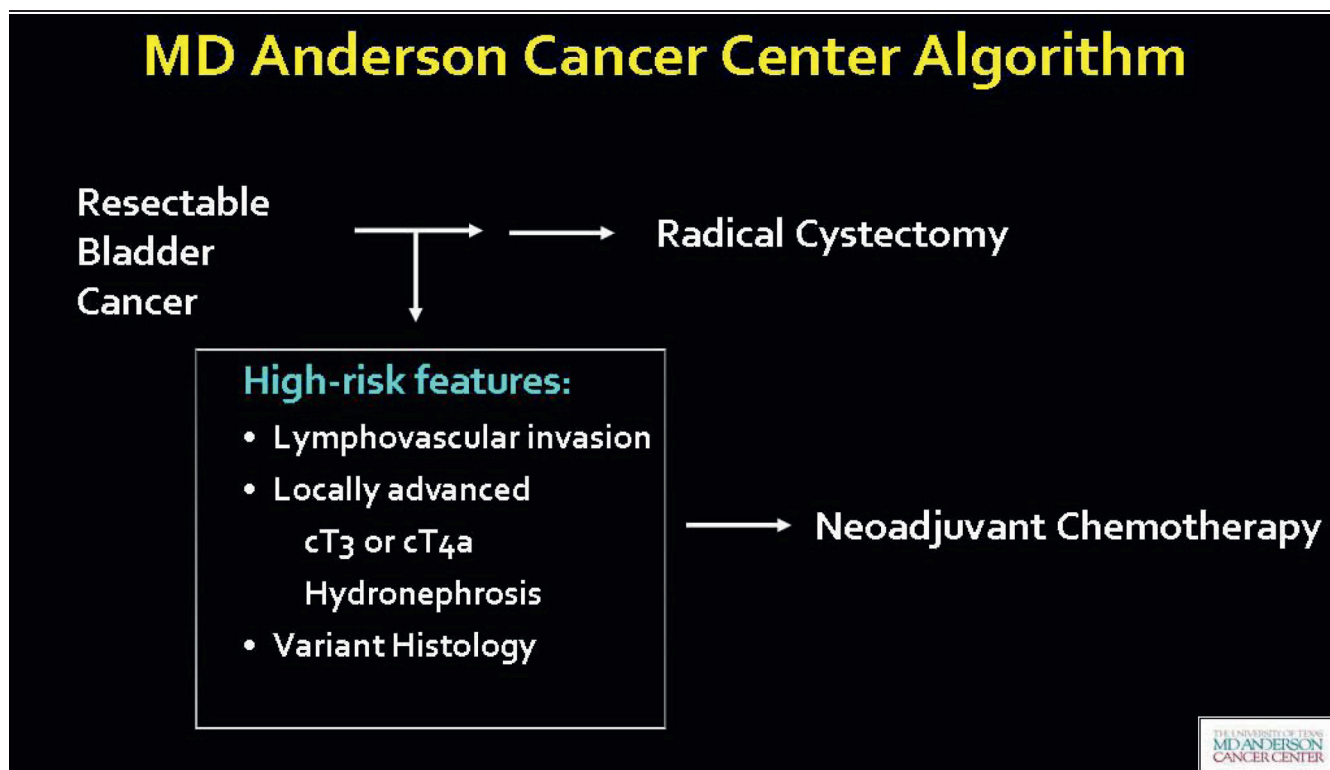
Several trials with the aim of improving survival in patients with high-risk non-metastatic UCB are currently ongoing. Erlotinib is currently being used prior to radical cystectomy in two phase II clinical trials in patients with muscle-invasive but resectable disease. The first trial (NCT00749892) is studying the pT0 rate after radical cystectomy as a primary endpoint, and the second trial (NCT00380029) aims at investigating the gene expression changes noted at radical cystectomy after a 1-month treatment with erlotinib. A pilot trial

of neoadjuvant dasatinib (NCT00706641) was recently started and aims to study feasibility in 25 patients who will undergo radical cystectomy after 4 weeks of dasatinib. In addition, two phase II trials are currently enrolling patients with muscle-invasive UCB and treating them with gemcitabine/cisplatin/sunitinib prior to radical cystectomy. The aim of the first trial (NCT00859339) is to assess the pT0 rate, whereas the second trial (NCT00847015) aims to assess the pT0 rate along with regimen safety. In a recent clinical trial of adjuvant MVAC [14] (NCT00005047), patients were randomly assigned on the basis of p53 staining status in radical cystectomy specimens. Patients who had altered p53 status (defined as nuclear immunoreactivity of greater than 10%) were randomly assigned (stratified by age, grade, stage, and p21 status) to either three cycles of MVAC or observation, whereas patients with normal p53 underwent observation. Owing to a lack of efficacy, accrual for this study has stopped early (only 114 patients with positive p53 underwent random assignment).

Implications for clinical practice

Although the current data suggest that neoadjuvant chemotherapy should be standard practice, this paradigm has been slow to be adopted, even in the US; a recent report suggests that only 11.6% of eligible patients receive chemotherapy (10.4% adjuvant therapy and 1.2% neoadjuvant therapy) [15]. This is partly due to the desire of patients to avoid overtreatment. Thus, currently, at MD Anderson Cancer Center, we prefer to use a risk-adapted approach (Figure 1) to patients with muscle-invasive UCB by selecting patients who are at high risk of death from disease to receive neoadjuvant chemotherapy. Patients who are at low risk, defined as clinical stage CIS (carcinoma *in situ*), Ta, T1, or T2 only (in the absence of lymphovascular invasion, non-urothelial or variant histology, and hydronephrosis), are offered upfront cystectomy. Clearly, however, future focus should be on improving the preoperative selection criteria for chemotherapy, using both clinical and molecular methods, in order to appropriately allocate patients to chemotherapy. Encouraging clinicians to

Figure 1. The MD Anderson Cancer Center algorithm for management of surgically resectable bladder cancer



Risk-adapted approach to patients with muscle-invasive bladder cancer by selecting patients who are at high risk of death from disease to receive neoadjuvant chemotherapy. Patients who are at low risk, defined as clinical stage CIS (carcinoma *in situ*), Ta, T1, or T2 only (in the absence of lymphovascular invasion, non-urothelial or variant histology, and hydronephrosis), are offered upfront cystectomy.

participate in well-designed trials is paramount to fast accrual, quick completion, and ultimately the success of these trials.

Abbreviations

ABC, Advanced Bladder Cancer; HR, hazard ratio; MVAC, methotrexate, vinblastine, adriamycin, and cisplatin; UCB, urothelial carcinoma of the bladder.

Competing interests

The authors declare that they have no competing interests.

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Evaluated by Ashish Kamat 5 May 2010