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Maximizing Cure for Muscle Invasive Bladder Cancer: Integration of Surgery and Chemotherapy

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Abstract

Context—The optimal treatment strategy for muscle invasive bladder cancer remains controversial.

Objective—To determine optimal combination of chemotherapy and surgery aimed at preserving survival of patients with locally advanced bladder cancer.

Evidence acquisition—We performed a critical review of the published, abstract and presentation literature on combined modality therapy for muscle invasive bladder cancer. We emphasized prospective (level 1) studies combining radical cystectomy and perioperative chemotherapy with curative intent to impact overall and disease-specific survival.

Evidence synthesis—Locally invasive, regional and occult micrometastases at the time of radical cystectomy lead to both distant and local failure, causing bladder cancer deaths. Neoadjuvant and adjuvant chemotherapy regimens have been evaluated as well as the quality of cystectomy and pelvic lymph node dissection.

Conclusions—Prospective randomized clinical trials argue strongly for neoadjuvant cisplatin-based chemotherapy followed by high quality cystectomy performed by an experienced surgeon operating in a high volume center. Adjuvant chemotherapy after surgery is also effective when therapeutic doses can be given in a timely fashion. Both contribute to improved overall survival, however many patients receive only one, or none, of these options, and the barriers to receiving optimal combined systemic therapy and surgery remain to be defined. An aging, comorbid, and often unfit population increasingly affected by bladder cancer pose significant challenges in management of individual patients.

Introduction

Bladder cancer is projected to be responsible for an estimated 70,530 new cancer cases and 14,680 deaths in the United States in 2010.[1] Worldwide, there were an estimated 386,000 cases and 150,000 deaths from bladder cancer in 2008.[2] It is the 4th most common solid tumor in men in the U.S.[1] and represents a major source of health-care expenditures.[3] With surgical treatment, muscle invasive bladder cancer carries a 5-year risk of death ranging from 33-73%.[4]

The natural history of muscle invasive bladder cancer dictates aggressive management with both local and systemic therapy. Until level 1 evidence demonstrated efficacy of neoadjuvant chemotherapy in 2003, the standard for MIBC was unimodal treatment by radical cystectomy with pelvic lymphadenectomy.[4, 5] However, alternative strategies have

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challenged this paradigm in an effort to improve overall survival. The tenets of modern management of muscle-invasive bladder cancer include consideration of combining perioperative chemotherapy with surgery consisting of several key technical requirements. While not a systematic review, we performed a comprehensive review of available literature, including only articles of the highest scientific and epidemiologic quality.

The Case for Integrated Therapy

Although the treatment of organ-confined cancer with radical cystectomy alone can lead to durable results,[4] early dissemination of occult micro-metastases is a significant source of failure. The rates of 5-year recurrence after surgery alone range from 20-30% in pT1 and pT2 disease to 50-90% in pT3-4 disease.[4, 6, 7]

Seeing that the incidence of distant recurrence (20–50%) is greater than that of loco-regional recurrence (5–15%), one may postulate that perioperative systemic therapy is vital in high-risk patients to potentially treat micrometastasis.[8, 9] The combination of Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) demonstrated efficacy in advanced bladder cancer in the 1980s,[10] with subsequent extension to patients in the neoadjuvant setting shortly thereafter.[11] However, even with the gradual accumulation of level 1 evidence supporting the use of perioperative chemotherapy, as outlined below, the actual administration rates remain low.

Data from care patterns during 1997-2003 from the National Cancer Database demonstrates an 11.6% incidence of perioperative chemotherapy usage overall, with 1.2% representing neoadjuvant administration and 10.6% being in the adjuvant setting.[12] In a recent update including 2003 to 2007 from the National Cancer Database, the use of perioperative chemotherapy was reported in over 30% of the patients, with an increase in neoadjuvant chemotherapy utilization from 6% to 13% in that time period.[13] Recent analyses both in the US and in Canada have demonstrated poor utilization of neoadjuvant chemotherapy.[14, 15] Proposed reasons for low uptake include the potential overtreatment of lower risk patients, and surgical delay, which has been hypothesized to affect outcomes, especially in chemotherapy non-responders.[16] The reasoning to avoid overtreatment in organ-confined disease is countered by the rates of clinical understaging, ranging from 31%-61%.[17-20] Staging inaccuracy may further support multimodal therapy, as it has shown increased therapeutic benefit with increasing disease stage. Although many reasons for low uptake in both community and academic centers have been postulated,[12, 21] particularly age and renal dysfunction,[22] the reasons have not been evaluated prospectively, nor have economic considerations been studied in this context. Whether physician compensation plays a role has not been investigated. Further prospective evaluation is needed to better understand the decision process involved.

A prominent concern regarding the administration of chemotherapy is toxicity, which has the potential to both limit overall cisplatin delivery and delay or prevent radical cystectomy. Original investigations of MVAC detailed a significant toxicity-related death rate of 3-4%.[10] Side effects of MVAC are considerable, including: neutropenia, infectious complications, mucositis, gastrointestinal toxicity, and neurologic sequelae.[23] Subsequently, utilization of the alternative regimen of gemcitabine and cisplatin (GC) has had a dramatically improved toxicity profile, with improved tolerability and patient-related acceptance and compliance.[24, 25] With the widespread use of GC, patients experience less toxicity and more patients are able to undergo surgery, in a more timely fashion, following neoadjuvant chemotherapy.[26]

The rationale for integration of systemic and surgical therapy for organ-confined disease has a precedent in other malignancies, including breast cancer. A 4% 10-year overall survival

benefit started the movement to integrate the use of tamoxifen with surgical management of breast cancer,[27] which highlights the translation of a small benefit in overall survival into widespread changes in therapeutic strategy amongst breast cancer specialists. Perioperative chemotherapy is now routinely applied in many stages of breast and colon cancer and may be responsible in part for the improvements in survival seen in the modern era.[28] As the data presented will illustrate, this paradigm of integrated therapy in bladder cancer must be applied to all patients with muscle-invasive disease, including those with organ-confined disease. This methodology will enable optimal curative treatment of patients.

The Case for Neoadjuvant Chemotherapy

The recognition of unimodal therapeutic limitations has ushered in the era of alternative strategy, most importantly, the era of neoadjuvant chemotherapy.[29, 30] While radical cystectomy remains a central management strategy in muscle invasive disease, several studies have demonstrated that the combination of neoadjuvant cisplatin-based chemotherapy with meticulous surgical resection adhering to strict oncologic principles is associated with improved survival compared to surgery alone.[29]

In 2003, a randomized phase III trial conducted by the Southwestern Oncology Group (SWOG-8710) demonstrated a significant survival advantage for clinical stage T2 and T3 patients treated with 3 cycles of MVAC chemotherapy and radical cystectomy compared to surgery alone (77 months vs. 46 months median).[5] The improvement in survival was strongly associated with a complete pathologic response to chemotherapy, with 85% of patients alive at 5 years. Of the patients randomized to the combination arm, 87% received at least one full cycle. On multivariate analysis, improved survival was associated with neoadjuvant chemotherapy (HR 1.39, $p<0.0001$), completion of radical cystectomy (HR 2.88, $p< 0.0001$) and removal of > 10 lymph nodes (HR 2.38, $p< 0.001$). For those patients that satisfied all three of these criteria, the 5-year survival and recurrence free probability were 81% and 91%, respectively.[29] A complete pathologic response to neoadjuvant chemotherapy has been clearly defined as predictive for survival in those receiving multimodal care.[31] Subsequent meta-analyses have confirmed a 5% overall survival advantage in those receiving cisplatin-based neoadjuvant chemotherapy (50% vs. 45%, P =0.016; HR 0.87) and a 14% reduction in bladder cancer specific death.[9, 32] Equally impressive was the relatively low number needed to treat, estimated at 20, which compares favorably to estimates in other unrelated disease groups. Despite this level-1 evidence, adherence to new accepted standards continues to be low.[12]

Similar data from the European Organization for the Research and Treatment of Cancer (EORTC) collaborative study provides robust evidence for the employment of neoadjuvant chemotherapy strategies.[33] A total of 976 clinically staged T2-T4, node-negative patients were accrued and randomized to surgery alone or 3 cycles of cisplatin, methotrexate and vinblastine plus surgery. At 7 years follow-up, the disease-free survival rate was significantly improved in the chemotherapy plus surgery arm (46% vs. 39%). The complete pathological response rate in the chemotherapy arm at cystectomy was 32.5%. Galsky et al recently reported a phase 2 study evaluating the additive sunitinib to gemcitabine and cisplatin for advanced UC.[34] Results demonstrate significant toxicity limiting tolerability of the regimen, despite preliminary activity, with clear implications for the neoadjuvant therapy. Lastly, Messing et al performed a secondary analysis on the SWOG S8710 trial evaluating non-urothelial histology and response to neoadjuvant MVAC.[35] Their results revealed a greater response in this subgroup (HR=0.46, p=0.02) compared to pure urothelial histology, reinforcing the strong recommendation for neoadjuvant therapy in all muscle invasive patients, regardless of histology.

The inclusion of cisplatin in chemotherapy regimens in the neoadjuvant setting has been emphasized as a central component for favorable patient response,[36] predominantly when combined with other agents.[9] Advanced age, poor performance status, and renal dysfunction, as measured by impaired creatinine clearance or GFR, are postulated reasons which may render patients ineligible for cisplatin,[22] although no prospective evaluations have definitively addressed this issue.[37] A multi-institutional prospective study supported by the Bladder Cancer Advocacy Network will aim to shed light on this question. Limited data exists on the proportion of patients who are not eligible for cisplatin based on renal dysfunction. However, a recent report from our institution found that 51% of patients who underwent nephroureterectomy for upper tract urothelial cancer had a preoperative eGFR <60 ml/min/1.73m^2.[38] The high proportion in this patient population, with similar comorbidities and risk factors as those with bladder urothelial cancer, illustrates the imperative for further study. While carboplatin based and non-platinum regimens have been used in patients with advanced urothelial cancer unable to tolerate cisplatin, small, randomized trials suggest that carboplatin is inferior to cisplatin-based regimens.[39-41] Therefore, this population requires a special focus employing tolerable effective regimens.

While the effectiveness of cisplatin-containing regimens is well established, the relative superiority of one regimen over others is difficult to discern without randomized head-to-head comparisons. Additionally, the most common neoadjuvant regimen given today, gemcitabine and cisplatin (GC), was not evaluated in the meta-analysis.[9] The efficacy of GC was demonstrated to be equivalent to MVAC in a randomized phase 3 trial comparing MVAC to GC in patients with metastatic UC.[24] In an analysis of neoadjuvant therapy at our institution comparing a cohort of patients enrolled in a clinical trial with GC to a historical cohort of patients given MVAC, the patients who received GC experienced less chemotherapy-related toxicity.[30] Additionally, patients given GC achieved similar pT0 rates (26% with GC and 28% with MVAC) and long-term disease-specific outcomes. These results reflect a clinical practice with a dedicated neoadjuvant chemotherapy strategy and stand in contrast to those from the Cleveland Clinic experience, in which only 7% of patients achieved a pathologic response with GC and other regimens, not including MVAC.[42] Differences in surgical timing, treatment delay, and neoadjuvant strategy may explain some of the differences observed between these studies. Despite the debate regarding the non-inferiority of GC compared to MVAC, the greater tolerability of GC has supported its use in numerous ongoing neoadjuvant chemotherapy trials testing efficacy of additional novel targeted agents.[43]

The Case for Adjuvant Chemotherapy

Level 1 evidence is less strong for survival benefit of adjuvant chemotherapy, but several surveys of chemotherapy use indicate physicians refer patients for adjuvant chemotherapy more frequently than for neoadjuvant chemotherapy.[12, 13] With respect to data regarding adjuvant therapy, a recent meta-analysis combined data from six randomized controlled trials studying cisplatin-based adjuvant chemotherapy regimens.[44] In the 491 patients analyzed, there was a 25% reduction in risk of all-cause death (HR 0.75, 95%CI [0.60, 0.96], p=0.019) in the patients given adjuvant chemotherapy, with an absolute 3-year survival benefit of 9% (95% CI [1%, 16%]). In the 383 patients with relapse data available, the 3-year absolute disease-free survival benefit was 12% (95% CI [4%, 19%]) with chemotherapy. The effects observed in these studies were limited by compliance with treatment, early termination of studies due to positive preliminary results, and small sample size. Svatek et al. reported outcomes of 932 patients in multiple centers treated off-protocol with varying adjuvant chemotherapy regimens among a total of 3947 patients.[45] Increasing survival benefit of chemotherapy was observed with increasing risk category of the patient, with those patients having the highest risk of disease-specific mortality deriving

the greatest benefit from adjuvant chemotherapy (HR 0.75 [95%CI 0.62, 0.90], p=0.002). A single-institution series of 187 patients, all treated with adjuvant cisplatin-based chemotherapy, documented a median time to recurrence of 3.7 years.[46]

Since the time of the meta-analysis, two randomized trials have attempted to compare standard adjuvant therapy with therapy at the time of relapse; neither trial maintained sufficient accrual to remain open. The EORTC trial, which began in 2001, planned to randomize 660 patients to chemotherapy after surgery versus at the time of relapse; it is no longer open to enrollment[47] and data analysis is pending. In the other trial, reported this year, 142 patients over 7 years were randomized to adjuvant chemotherapy or observation, and there was a significant overall survival benefit in those patients treated immediately with a regimen including paclitaxel, gemcitabine, and cisplatin (5 year OS 60% vs. 31%, p< 0.0009).[48] As this study may suggest, with continued improvements in the ability to give adequate doses of cisplatin, the benefit of adjuvant chemotherapy may begin to match the established benefit of neoadjuvant chemotherapy.

Enthusiasm for administration of adjuvant chemotherapy must be tempered by consideration of patients' ability to receive appropriate chemotherapy after cystectomy. With standardized reporting, our institution found that 64% of patients experienced a complication in the first 90 days after cystectomy, and adjuvant chemotherapy may have been delayed or not offered in up to 30% of patients due to postoperative morbidity.[49] In multiple randomized series, between 23-44% of patients are unable to receive or complete adjuvant chemotherapy according to the planned schedule or timeframe.[17, 46] In a trial of surgery with MVAC chemotherapy, comparing administration of 5 cycles after surgery versus 2 cycles before and 3 cycles after surgery, delivery of MVAC following surgery was problematic.[17] Nine of 70 patients randomized to surgery first never received their adjuvant therapy and in the other arm, 97% received the planned 2 cycles before surgery versus only 77% receiving at least 2 cycles after surgery. With the investigation of additional agents in combination or in place of the standard agents, enabling better patient tolerability or more reliable administration, more significant survival benefits in the adjuvant and salvage settings may be observed.

The Case for Surgical Excellence

While neoadjuvant chemotherapy has been shown to improve survival, radical cystectomy remains an integral component of therapy, to optimize local tumor control. A combined treatment strategy increases the likelihood of achieving no residual tumor (pT0) in the cystectomy specimen, as seen in patients treated with neoadjuvant chemotherapy (MVAC) in the SWOG 8710 trial. Among the 307 randomized patients, 38% of surgical specimens after neoadjuvant chemotherapy were free of disease compared to 15% after cystectomy alone.[5] The absence of disease in the surgical specimen was associated with an improved overall survival advantage with a HR of 2.51 (95% CI 1.47, 4.27; p=0.0008) for patients with residual disease compared to patients with stage pT0.[31] While chemotherapy increases the likelihood of achieving a pT0 specimen, radical cystectomy remains necessary, even after a complete response to chemotherapy, in order to achieve a survival benefit. Relapse occurred in the majority of patients (64%) who refused cystectomy after a complete response to neoadjuvant cisplatin based chemotherapy leading to an additional disease related mortality of 30%.[50] Despite advances in imaging and TUR technique, microscopic disease remains in up to a third of patients that would have otherwise been removed during radical cystectomy.[4] Clearly, chemotherapy alone cannot replace surgery and thus radical cystectomy remains a critical component in the treatment of locally advanced bladder cancer.

Whitmore and Marshall described in their landmark 1964 article the original template for radical cystectomy including dissection up to the crossing of the ureter on the common iliac vessels.[50-52] However, since then, the subject of node dissection template has become highly debated and has been correlated with surgical quality. Recognizing that chemotherapy cannot compensate for poor surgical technique, a high quality radical cystectomy is essential to achieve maximal survival benefit from a combined modality approach. A bilateral pelvic lymph node dissection should be performed, including at a minimum lymph nodes in the obturator, hypogastric, external iliac, and common iliac regions, up to the crossing of the ureter.[53] In patients undergoing radical cystectomy in the SWOG 8710 trial, negative surgical margins ($p=0.0007$) and removal of >10 lymph nodes ($p=0.0001$) were significantly associated with longer survival and decreased local recurrence.[54, 55] In evaluating the optimal target number of nodes to be removed during cystectomy, there is retrospective data supporting improved survival with increasing number of lymph nodes; however, given variations in pathologic analysis, it appears that the operative template may be the most important factor.[56] Further analysis of the SWOG 8710 data suggested that surgeries performed by urologic oncologists and at academic institutions were associated with more extensive lymph node dissections and lower positive margin rates.[55] In experienced hands, the positive soft tissue margin rate should be no greater than 5%.[57] These results, in agreement with other studies,[58-60] suggest that improved outcomes could be achieved by centralizing the treatment of locally advanced bladder cancer at high-volume institutions with surgical expertise.[29]

Robotic assisted surgery is increasingly being incorporated into the management of locally advanced bladder cancer; however, its oncologic efficacy remains to be established, when compared to open surgery. Retrospective data from the International Robotic Cystectomy Consortium (IRCC) have suggested that the positive margin rates and quality of lymph nodes dissection for robotic assisted radical cystectomy (RARC) are similar to the results for large, multi-institutional open radical cystectomy series. After reviewing 513 patients who underwent RARC, they reported a positive surgical margin rate of 6.8%, with age, lymph node involvement, and higher pathologic T-stage as significant predictors of positive margins.[61] However, when comparing the results of a large open radical cystectomy series to these data, positive surgical margins were found in 0% vs 1.5% of patients with organ confined disease and 9% vs 19.8% of patients with extravesical disease, respectively. The importance of achieving a negative surgical margin during radical cystectomy cannot be understated, especially for patients with organ confined disease, as positive margins have been strongly associated with a poor prognosis and increased risk of disease specific death.[57] Furthermore, given the difficulty with preoperative staging and determination of extravesical disease,[62] patients undergoing robotic radical cystectomy may be at higher risk of having a positive surgical margin and worse prognosis.

The oncologic outcomes for robotic assisted radical cystectomy have yet to be determined and current studies have been limited by short followup.[63] Clearly, further studies are needed to properly evaluate the oncologic outcomes of patients undergoing RARC. In order to more definitively evaluate the role of RARC in the treatment of locally advanced bladder cancer, Memorial Sloan Kettering Cancer Center is conducting a randomized trial evaluating the immediate and long term outcomes of RARC and open radical cystectomy.

Conclusion

The body of evidence continues to grow supporting the integration of chemotherapy with the surgical management of muscle-invasive bladder cancer, and urologists must actively collaborate with their medical oncology colleagues to shift current practice patterns. Attention must be paid to the surgical details, including an adequate lymph node dissection

and an approach, which ensures optimal oncologic outcomes. Further understanding regarding the biology and metastatic potential of individuals' tumors may enable us to tailor recommended therapy. Currently, prospective trials are the imperative to fully characterize the benefits of multimodal management.

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