Defining Optimal Therapy for Muscle Invasive Bladder Cancer

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Purpose: We defined an optimal curative strategy for muscle invasive bladder cancer and to determine how best to deliver curative therapy.

Materials and Methods: We reviewed published reports from 1985 to 2006 dealing with the treatment of muscle invasive (stage T2-T4a) bladder cancer. We analyzed all cohort, phase II and randomized phase III studies providing level 1 to 3 evidence impacting survival.

Results: Cisplatin based chemotherapy combined with high quality radical cystectomy and complete pelvic lymph node dissection improves survival over that of cystectomy alone. Surgery quality is an important predictor of survival even in patients receiving chemotherapy. Neoadjuvant chemotherapy is favored over adjuvant chemotherapy because it is better tolerated and more patients are able to receive effective therapy before rather than after surgery.

Conclusions: Neoadjuvant chemotherapy followed by radical cystectomy and complete pelvic lymph node dissection is the optimal curative strategy in most patients presenting with muscle invasive bladder cancer.

Key Words: bladder, bladder neoplasms, cystectomy, drug therapy, neoplasm invasiveness

Muscle invasive bladder cancer (clinical stage cT2-T4a) continues to challenge urologists, medical oncologists and patients facing this devastating disease. Of the 63,210 new cases of bladder cancer diagnosed in 2005 a third invaded the muscularis propria and another 15% to 30% of high grade superficial bladder tumors progress to muscle invasion, usually within 5 years. Unlike many other tumors the death rate from transitional cell carcinoma of the bladder has not undergone a decrease in recent years. In 2005 alone more than 13,000 patients died of invasive bladder cancer.1

Radical cystectomy is the most commonly prescribed treatment in patients with muscle invasive bladder cancer, although bladder sparing programs may be appropriate in a select subgroup of patients. Despite curative intent approximately half of the patients have distant metastases after surgery. After metastases are established few long-term survivors are found, although 60% to 75% of patients have chemotherapy sensitive tumors. It seems logical to introduce chemotherapy at surgery in an attempt to eradicate occult metastases at the earliest opportunity and prevent subsequent metastatic failure. A critical mass of evidence based data now available from mature clinical trials shows that integrating chemotherapy with definitive surgery improves the outcome of muscle invasive bladder cancer and argues for a new treatment paradigm.

We summarized the available literature, addressing the role of combining chemotherapy with cystectomy for muscle invasive bladder cancer. Using the best current evidence we defined an optimal therapeutic strategy capable of curing the most patients presenting with muscle invasive bladder cancer. We also determined how that strategy can best be implemented.

DATA SOURCES

We performed a MEDLINE® search from 1985 to 2006 using the National Center for Biotechnology Information PubMed® Internet site to review the world literature pertaining to the treatment of muscle invasive transitional cell carcinoma of the bladder. We queried PDQ® and The Cochrane Library®. We selected cohort, phase II and randomized phase III studies providing levels 1 to 3 evidence based survival data.2 We also reviewed population and collaborative group studies showing patterns of care to generalize our findings. We began our search in 1985, when effective cisplatin based regimens were first introduced3 and integrated with surgery for invasive bladder cancer4 because, since then, mature data have become available from combined surgery and chemotherapy trials. We also wished to account for current survival results in contemporary cystectomy series.

RADICAL CYSTECTOMY

Radical cystectomy with PLND is the mainstay of treatment for muscle invasive bladder cancer.5 Radical surgery alone provides excellent local control of the primary tumor and it may cure some patients with pelvic and nodal disease. Despite improvements in surgical techniques and perioperative care a sobering analysis of cystectomy series before and after 1985 revealed only modest gains in survival. Table 1 shows comparative 5-year survival rates in contemporary vs historical cystectomy series of 67% vs 60% for pT2, 35% vs 33%
for pT3 and 27% vs 21% for pT4 tumors. Metastatic failure rates of 20% to 30% for pT2, 40% to 60% for pT3 and 70% to 90% for pT4 tumors suggest that treatment in addition to radical cystectomy is needed for all clinical stages even in patients with the most favorable organ confined (pT0-2) and radical cystectomy is needed for all clinical stages even in patients with the most favorable organ confined (pT0-2) and radical cystectomy.

### WHY PERIOPERATIVE CHEMOTHERAPY?

Chemotherapy is now standard practice for localized colon and breast cancer, although it is less effective for these metastatic tumors than for metastatic bladder cancer. MVAC was introduced in 1985 and it became the first successful chemotherapy regimen used for metastatic bladder cancer. Overall response proportions were achieved in 72% of patients, including complete responses in 36%. Because MVAC also produced significant responses in the primary tumor, the regimen was given to patients before cystectomy for muscle invasive bladder cancer.

We found that patients who had down staging (less than pT2) of bladder tumor had a significant 5-year survival advantage over those in whom tumors did not respond (54% vs 12%). Building on these early favorable results, subsequent randomized clinical trials have sought to administer chemotherapy before (neoadjuvant) or after (adjuvant) cystectomy to try to eradicate subclinical disease and improve overall survival.

### NEOADJUVANT CHEMOTHERAPY

Administering chemotherapy before surgery has several advantages. Patients may be better able to tolerate chemotherapy before rather than after the debilitating effects of prior cystectomy. Systemic therapy is initiated sooner for metastatic disease, which is the principle cause of surgical failure. The primary tumor can be evaluated for response, which has major prognostic significance. Also, in patients with tumor shrinkage surgery may be more effective.

Table 2 shows randomized trials of the role of neoadjuvant chemotherapy for invasive bladder cancer. Many earlier trials failed to show a survival benefit in the combined modality arm. However, these studies had inadequate sample size, suboptimal chemotherapy (cisplatin alone), premature closure or inadequate followup. More recently the results of large, well designed trials and several meta-analyses were reported and they shifted the treatment paradigm in muscle invasive bladder cancer in favor of neoadjuvant chemotherapy.

The largest trial of neoadjuvant chemotherapy was performed by the Medical Research Council/European Organisation for Research and Treatment of Cancer. In this trial 976 patients were randomized to CMV or no chemotherapy. Definitive management of the primary tumor included cystectomy and/or RT. Updated results at a median followup of 7 years showed a statistically significant survival advantage in patients receiving neoadjuvant chemotherapy. Unfortunately subset analysis comparing survival after definitive local therapy by surgery or radiation was not done. Although some patients who received radiation were likely cured, it is more likely that more patients were cured by cystectomy.

INT-0080 performed in the United States confirmed the benefits of neoadjuvant chemotherapy. A total of 317 patients with locally advanced bladder cancer (cT2 to T4a) were randomized to 3 cycles of neoadjuvant MVAC, followed by cystectomy vs radical cystectomy alone. Compared to cystectomy neoadjuvant chemotherapy prolonged survival by almost 3 years (range 77 vs 46 months), decreased the risk of death from bladder cancer by 25% and improved overall survival by 5% (p = 0.06). Of the survivors 85% achieved a complete pathological response (pT0) to chemotherapy (38% after MVAC vs 15% after surgery alone, p = 0.001). Age did not affect survival when patients were...
stratified by age younger or older than 65 years. No chemotherapy deaths occurred and MVAC did not impair the ability to proceed with surgery or increase the rate of surgical complications. Patients with locally advanced (cT3 or T4a) disease achieved the most survival benefit from neoadjuvant chemotherapy (65 vs 24 months). However, even patients with clinically staged, organ confined (cT2) tumors had survival time prolonged by 2.5 years (range 105 vs 75 months) after MVAC and cystectomy.

A first meta-analysis of 2,688 patients from 10 randomized trials excluded data from INT-0080 in the United States.\(^\text{12}\) Compared with local therapy alone, neoadjuvant platinum based combination chemotherapy was associated with better overall survival, equivalent to a 13% relative decrease in the risk of death and an absolute survival benefit of 5% (range 45% to 50%) at 5 years (p = 0.016). The survival benefit did not achieve statistical significance when trials using single agent cisplatin were included. A Canadian meta-analysis of 2,605 patients concluded that platinum based combination chemotherapy was associated with a 6.5% absolute improvement in overall survival from 50% to 56.5% (p = 0.006).\(^\text{13}\) Also, a more recent and robust meta-analysis updating results from 11 trials, including INT-0080, comprising a total of 3,005 patients, which represents 98% of all patients in known, eligible, randomized, controlled trials, showed a significant benefit associated with cisplatin based chemotherapy, equivalent to a 5% improvement in overall survival (p = 0.003), a 14% decrease in the risk of death from disease and a 9% improvement in disease specific survival (p < 0.0001) at 5 years.\(^\text{14}\)

Collectively these results strongly support neoadjuvant cisplatin based chemotherapy in patients with muscle invasive bladder cancer. A 5% improved overall survival rate and a 14% decreased risk of death from bladder cancer is significant. Randomized trials show that a 3 to 4-month delay in surgery is not detrimental to overall outcome and survival is improved in all clinical stages of muscle invasive bladder cancer, including 55% to 60% for cT2, 40% to 45% for cT3 and 25% to 30% for cT4. Half of invasive bladder tumors have extravesical disease spread and 10% to 20% have nodal metastases, suggesting that neoadjuvant chemotherapy is also appropriate for clinical stage cT2 tumors.

Given these results, why is the neoadjuvant approach not practiced more widely? There are several reasons. 1) The inaccuracies of clinical staging make the assessment of which patients are destined to have metastasis and who needs systemic therapy to achieve cure less precise, subjecting some patients to needless chemotherapy. 2) The delay in definitive surgery in patients who do not respond to treatment raises concerns regarding compromise of curability. 3) Many urologists simply believe that a 5% gain in overall survival is not great enough to justify giving toxic chemotherapy to all patients before surgery. These and other factors have persuaded many urologists and some medical oncologists to adopt a treatment policy favoring adjuvant chemotherapy based on the pathological risk of relapse.

**ADJUVANT CHEMOTHERAPY**

In patients with pT3-4 and/or N+M0 disease 5-year survival after radical cystectomy is only 25% to 35% at best. As a result, adjuvant chemotherapy has been done in high risk patients in an effort to delay recurrence and prolong survival. Delivery of chemotherapy postoperatively has potential advantages. An adjuvant approach allows the selection of patients at highest risk for surgical failure based on accurate pathological evaluation showing advanced disease in the cystectomy specimen rather than in transurethral biopsy and it avoids overtreatment patients who are estimated to have a reasonable outcome from surgery alone, that is those with tumor confined to the bladder. Surgery is performed without delay, while the acceptable morbidity of cystectomy and improved quality of life due to orthotopic neobladders and continent urinary diversion may favor immediate cystectomy and adjuvant chemotherapy only when justified by the risks of tumor relapse.

Table 3 shows the results of 6 randomized trials of the role of adjuvant chemotherapy after cystectomy.\(^\text{15}\) All of these trials were relatively small, enrolling only 49 to 108 patients. Nonetheless, 2 trials suggest a survival benefit with adjuvant chemotherapy. In the trial by Skinner et al patients with pT3-4a or node positive bladder cancer were randomized to cisplatin, cytoxan and doxorubicin for 4 cycles vs no further treatment after cystectomy.\(^\text{16}\) Median survival was 4.3 years in the adjuvant chemotherapy group vs 2.4 years in the control group (p = 0.006). Criticisms of this trial include selection bias (only 91 of 498 patients deemed eligible were enrolled) and many patients never received the assigned therapy.

Stockle et al randomized similar high risk patients to 3 cycles of methotrexate, vinblastine, doxorubicin/epirubicin and cisplatin or no further therapy after cystectomy.\(^\text{17}\) The study was terminated early with only 49 patients enrolled when interim analysis showed significant improvement in 3-year disease-free survival (63% vs 13%, p = 0.002). Recently reported 10-year survival data from this trial still favored adjuvant chemotherapy over surgery alone for progression-free survival (44% vs 13%, p = 0.002), tumor specific survival (42% vs 17%, p = 0.007) and a trend in overall survival (27% vs 17%, p = 0.07).\(^\text{18}\) A significant benefit was noted in patients with positive lymph nodes who received adjuvant chemotherapy. Only 27% of patients who received chemotherapy had evidence of tumor progression compared to 92% of those treated with cystectomy alone.

The other randomized trials did not show a survival benefit with adjuvant chemotherapy. However, all of these trials had inadequate sample size. Two trials primarily evaluated patients with bladder confined disease, making an incremental benefit from chemotherapy even more difficult to detect. One trial used single agent cisplatin, which is known to be inferior to cisplatin based combinations for advanced disease.

**Table 3. Randomized trials of adjuvant chemotherapy after radical cystectomy**\(^\text{15}\)

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<tr>
<th>References</th>
<th>No. Pts</th>
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<tr>
<td>Skinner et al</td>
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<td>Stockle et al</td>
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<td>Methotrexate, vinblastine, doxorubicin/epirubicin + cisplatin</td>
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<td>Freiha et al</td>
<td>55</td>
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<td>Studer et al</td>
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<td>108</td>
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A single meta-analysis to evaluate the effect of adjuvant chemotherapy for invasive bladder cancer was performed based on 491 patients from 6 trials, representing 90% of all patients randomized and 66% of those in all eligible trials. Although the power of this meta-analysis was limited by small patient numbers, the impact of trials stopped early, patients not receiving allocated treatments or salvage chemotherapy, it suggested a 25% relative decrease in the risk of death in favor of adjuvant chemotherapy over no therapy ($p = 0.02$).

Although the data supporting adjuvant chemotherapy are less compelling than the data supporting neoadjuvant chemotherapy, is it reasonable to extrapolate the results from the neoadjuvant studies to the adjuvant setting? Many oncologists believe that it is, citing large trials in other malignancies that suggest no difference between the 2 approaches. Although no randomized trials have directly compared neoadjuvant and adjuvant therapy for bladder cancer, a trial reported by Millikan et al randomly assigned 140 patients to 2 cycles of neoadjuvant MVAC, followed by cystectomy plus 3 more cycles of adjuvant MVAC, or initial cystectomy, followed by 5 cycles of adjuvant MVAC. There was no significant difference in outcome between the 2 groups with 58% of patients disease-free at a median follow-up of 6.8 years. However, 97% of patients in the neoadjuvant group received at least 2 cycles of chemotherapy, whereas only 77% in the adjuvant group received at least 2 cycles. Adjuvant chemotherapy was planned to begin within 84 days of surgery, although it actually began an average of 103 to 114 days after surgery due to delays in postoperative recovery. In addition, preoperative chemotherapy facilitated complete surgical resection since positive surgical margins were decreased to 2% after chemotherapy compared to 11% in patients undergoing initial cystectomy.

### QUALITY OF SURGERY AND SURVIVAL

Radical cystectomy quality and PLND extent have a major impact on invasive bladder cancer survival. Who performs the surgery, and where and how well it is done matter. Recent studies show that mortality from cystectomy is the surgery, and where and how well it is done matter. Experienced surgeons who frequently perform cystectomy achieve better survival and fewer complications than surgeons who perform an occasional cystectomy. Although acceptable standards for PLND are currently being defined, patients who undergo complete bilateral PLND with dissection of the common iliac, external iliac, obturator and hypogastric nodes have better survival than patients with limited (obturator nodes) or omitted lymph node dissection. An increased number of lymph nodes removed improves survival and decreases pelvic recurrence in patients with node negative and node positive disease. Although node counts vary, the fittest patients. In patients with advanced or metastatic transitional cell carcinoma the combination of gemcitabine plus cisplatin results in comparable response proportions and similar overall long-term survival compared with MVAC but with much less toxicity. Although no randomized trials have directly compared neoadjuvant and adjuvant therapy for bladder cancer, a trial reported by Millikan et al randomly assigned 140 patients to 2 cycles of neoadjuvant MVAC, followed by radical cystectomy and inadequate or no PLND, (52% vs 34%, $p = 0.001$). This cooperative group trial shows that the quality of cystectomy and PLND directly impacts the chances of survival and it is surgeon dependent.

### CHOICE OF CHEMOTHERAPY

Although MVAC is the established effective chemotherapy regimen, significant toxicity limits its perioperative use to the fittest patients. In patients with advanced or metastatic transitional cell carcinoma the combination of gemcitabine plus cisplatin results in comparable response proportions and similar overall long-term survival compared with MVAC but with much less toxicity. Although the data supporting adjuvant chemotherapy are less compelling than the data supporting neoadjuvant chemotherapy, it is reasonable to extrapolate the results from the neoadjuvant studies to the adjuvant setting? Again, best evidence data strongly suggest that neoadjuvant chemotherapy fol-
lowered by radical cystectomy and complete PLND should be adopted as a new treatment paradigm in all patients presenting with muscle invasive bladder cancer. As an overall treatment strategy, the reasons are related to how best to deliver aggressive chemotherapy and surgery to the most patients.

Neoadjuvant chemotherapy is better tolerated and more patients receive adequate numbers of cycles and maximum doses of effective therapy before rather after surgery. Compared to cystectomy alone neoadjuvant chemotherapy improves known risk factors favoring survival, including more patients with tumor-free (pT0) specimens, negative surgical margins and negative lymph nodes. Adjuvant chemotherapy has only been tested in patients with negative surgical margins and it is unlikely to salvage unresected pelvic tumor or grossly positive nodes. Since adjuvant chemotherapy should be started within 8 to 12 weeks after surgery to have an adjuvant effect, many trials show that up to half of proposed patients never received any chemotherapy. Even in the randomized trials only 50% to 70% of patients actually received 3 or 4 cycles of adjuvant chemotherapy. Reasons given for not receiving adjuvant chemotherapy were poor performance status, frequent surgical complications, delayed recovery from surgery, major comorbidities, psychological distress, poor renal function, old age and patient refusal. Patients often need time to recover bowel function, heal anastomoses, reverse protein and calorie malnutrition, adjust their lives to the new urinary diversion and psychologically accept the need for subsequent cytotoxic therapy.

Despite the suggested efficacy of MVAC or MVEC regimens in the adjuvant setting severe toxicity and a treatment related mortality rate of up to 4% cause concern. With the goal of decreasing the toxicity of platinum based chemotherapy Lehmann et al reported the results of a randomized adjuvant trial comparing MVEC with an alternative, less toxic CM regimen. CM was not inferior to MVAC and it was better tolerated. However, these results are questionable since CM has not been shown to be superior to single agent cisplatin and cisplatin alone is ineffective in the perioperative setting. Only 71% of the 327 patients enrolled completed 3 cycles as planned, while 17% stopped treatment early due to toxicity or other reasons, 11% refused treatment and 1% died of chemotherapy related causes. Thus, a third of eligible patients never received adequate or any chemotherapy after surgery.

Another major reason that adjuvant chemotherapy may be difficult to administer to many patients is related to surgical complications. Regardless of the decreased mortality and improved safety of modern cystectomy and urinary diversion, complications are frequent and underreported. The lack of standard criteria on how to report the adverse impacts of surgical morbidity also confounds the feasibility of giving adjuvant chemotherapy. We and others documented 1 or more complications in almost 60% of patients within 90 days of surgery, representing the time frame in which adjuvant chemotherapy should begin. At least a third were major (grades 2 to 4) complications, which often require radiological or another intervention, rehospitalization for medical reasons or are simply associated with failure to thrive, perhaps preventing the timely administration of adjuvant chemotherapy or persuading patients to refuse it altogether due to delayed recovery, poor performance or depressed mental status. A neoadjuvant chemotherapy strategy avoids the problems posed by post-cystectomy complications.

**ELDERLY AND UNFIT PATIENTS**

Bladder cancer is a disease of elderly individuals and it is increasing in frequency as the population ages. The peak age of invasive bladder cancer is 70 years and more than 20% of patients are older than 80 years. With age comes an increased incidence of comorbidities. Elderly patients have an average of 3 diseases. Older patients are less likely to undergo cystectomy or chemotherapy than younger patients despite compelling evidence that cystectomy decreases the risk of death from bladder cancer even in patients of advanced age and many tolerate and derive the same benefit from chemotherapy as their younger counterparts. Although cisplatin may be difficult for older and debilitated patients with borderline renal function to tolerate, drug delivery can be facilitated by hydration, nephrostomy placement to relieve hydronephrosis, adjustment of the initial dose to kidney function rather than to height and weight, and the prophylactic use of growth factors for anticipated neutropenia and anemia.

Unfortunately many elderly and unfit patients receive palliation with less than adequate chemotherapy and radiation as less intrusive (albeit usually failed) therapy, although they may have curable invasive bladder cancer. Fewer than 5% of patients are unable to undergo cystectomy in experienced hands and they should not be excluded from cystectomy simply because of advanced age. If patients cannot receive chemotherapy due to poor renal function or they experience disabling symptoms from local disease, the best treatment option is timely and well performed cystectomy done by an experienced surgeon.

Although cisplatin based regimens are superior to non-cisplatin (carboplatin) regimens, they require adequate renal function and renal function decreases with age. A prospective study in a healthy population showed creatinine clearance less than 50 ml per minute in 12.6% of 60 to 69-year-old patients and in 47.3% of those older than 70 years. Using current formulas to estimate renal function we found in post-cystectomy patients that 28% of all patients and 45% of those older than 70 years were ineligible to receive adjuvant chemotherapy due to impaired renal function. Clearly alternative systemic therapy must be developed for at least a third of patients who are older than 70 years, have poor performance status or impaired renal function and may not be able to tolerate cisplatin based regimens.

Phase II studies have explored the activity of carboplatin plus gemcitabine with and without the taxanes docetaxel and paclitaxel in patients with advanced transitional cell carcinoma. Double and 3-drug regimens are well tolerated and they achieve response rates of 36% to 58%. A combination of paclitaxel, carboplatin and gemcitabine produced an overall response rate of 68% with a complete response in 36% of cases. Although to our knowledge it has not been tested as perioperative therapy, it seems preferable to try one of these alternative regimens in unfit surgical patients with impaired renal function rather than using no chemotherapy.

To appropriately treat elderly and unfit patients with muscle invasive bladder cancer we must also identify more
CONCLUSIONS

Defining optimal therapy in all patients with muscle invasive bladder cancer is an impossible task. Some patients have been cured by transurethral resection or radiation alone and the selection of optimal therapy in a given patient is best individualized. In the majority of patients current data favor neoadjuvant chemotherapy followed by radical cystectomy, including complete PLND, as the optimal curative strategy for muscle invasive bladder cancer. More patients are likely to receive effective chemotherapy before rather than after surgery. All clinical stages of invasive bladder cancer may benefit from this combined strategy. However, a 5% to 6% absolute survival benefit for chemotherapy treated patients is at best a modest improvement and it strongly supports the need for earlier definitive therapy and the development of more effective chemotherapy regimens.

Patients who refuse or are unable to receive neoadjuvant chemotherapy and are at risk for surgical relapse due to extravesical or node positive disease are encouraged to receive adjuvant chemotherapy as tolerated, preferably as part of a clinical trial. Better tolerated and improved drug regimens are needed for patients who are unable to receive cisplatin because of comorbidity or poor renal function. In such patients high quality cystectomy emerges as critical to providing the best chance for decreasing morbidity from disease and preserving survival.

Abbreviations and Acronyms

| CM | cisplatin and methotrexate |
| CMV | CM and vinblastine |
| INT | Intergroup Trial |
| MVAC | methotrexate, vinblastine, doxorubicin and cisplatin |
| MVEC | methotrexate, vinblastine, epirubicin and cisplatin |
| PLND | pelvic lymph node dissection |
| RT | radiation therapy |

REFERENCES


