
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%

Submitted for publication February 20, 2006.

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TABLE 1. *Survival after radical cystectomy according to pathological (pT) stage⁶*

References	No. Pts	% pT0*	% Operative Mortality	% 5-Yr Survival		
				pT2	pT3	pT4
Richie	134	8	8.5	40	20	—
Braedel	174	—	4	51	25	18
Mathur	58	7	3	77	33	29
Skinner	197	10	2	64	44	36
Montie	99	10	9	69	57	—
Giuliani	202	—	12	56	19	0
Totals	864	9	7	60	33	21
Roehrborn	280	—	2	63	36	24
Pagano	261	9	2	57	15	21
Wishnow	188	5	1	79	46	33
Waehre	227	25	—	61	36	29
Vieweg	686	8	2	58	22	15
Stein	633	6	3	72	48	33
Dalbagni	284	10	—	59	29	25
Studer	507	—	4.5	74	52	36
Grossman	154	15	0.6	75	—	28
Totals	3,220	12	2.2	67	35	27

* No residual tumor in cystectomy specimen.

for pT3 and 27% vs 21% for pT4 tumors.⁶ 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 node negative (N0) invasive tumors.⁷ In 2006 we can do better.

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.³ 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.⁸ 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.

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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.⁹ 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.⁶ 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.¹⁰ 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.¹¹ 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

TABLE 2. *Randomized trials of neoadjuvant chemotherapy⁶*

Trial	No. Pts	Chemotherapy	Primary Treatment	Survival Benefit
Medical Research Council/European Organisation for Research and Treatment of Ca ¹⁰	976	CMV	Cystectomy +/-or RT	Yes
INT-0080 ¹¹	317	MVAC	Cystectomy	Yes
Nordic-1	325	Cisplatin + doxorubicin	Cystectomy/RT	Yes
Nordic-2	317	MC	Cystectomy	No
Spain	122	Cisplatin	Cystectomy	No
Australia/United Kingdom	255	Cisplatin	RT	No
MA General Hospital/Radiation Therapy Oncology Group	123	CMV	Cystectomy + RT/cystectomy	No
Italy	171	MVEC	Cystectomy	No
Egypt	194	Carboplatin, methotrexate + vinblastine	Cystectomy	No

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.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% ($p = 0.006$).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.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 sur-

vival. 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 over treating 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.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.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.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%, $p = 0.07$).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 cystectomy¹⁵

References	No. Pts	Chemotherapy	Survival Benefit
Skinner et al	102	Cyclophosphamide, doxorubicin + cisplatin	Yes
Stockle et al	49	Methotrexate, vinblastine, doxorubicin/epirubicin + cisplatin	Yes
Freiha et al	55	CMV	No
Studer et al	91	Cisplatin	No
Bono et al	93	CM	No
Otto et al	108	MVEC	No

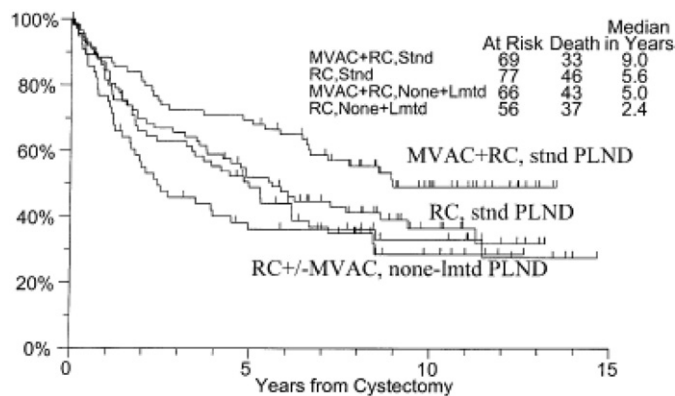
A single meta-analysis to evaluate the effect of adjuvant chemotherapy for invasive bladder cancer was performed based on 491 patients from 6 trials, representing 90% of all patients randomized and 66% of those in all eligible trials.¹⁵ Although the power of this meta-analysis was limited by small patient 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.¹⁹ There was no significant difference in outcome between the 2 groups with 58% of patients disease-free at a median followup 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 higher at low vs high volume hospitals (3.1% vs 0.7%).²⁰ Experienced surgeons who frequently perform cystectomy achieve better survival and fewer complications than surgeons who perform an occasional cystectomy.²¹ 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.²² Although node counts vary widely due to other uncontrolled factors, we found on multivariate analysis of a prospective study that only the surgical extent of node dissection (limited vs standard or extended) was associated with significant differences in node yields.²³

Even more compelling evidence of the importance of surgical quality was provided by an analysis of INT-0080 in the United States involving multiple institutions and surgeons.²⁴ Negative surgical margins and 10 or more lymph nodes removed were associated with better overall survival



Overall survival by treatment group. *RC*, radical cystectomy. *Stnd*, complete PLND. *None-Lmtd*, no or limited PLND.

independent of patient age, pathological stage, nodal status and whether chemotherapy was given. These surgical factors also predicted pelvic relapse, which is a death knell in most patients. Of the patients 15% had local recurrence and all eventually died of disease. Local recurrence developed in 68% of cases with positive surgical margins compared to 6% with negative margins, while high vs low volume urologists had a positive margin rate of 4% vs 14%. The figure shows that despite chemotherapy patients with the best overall 5-year survival received neoadjuvant MVAC, followed by quality radical cystectomy and complete PLND, compared to patients who underwent 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.²⁵ Although to our knowledge the gemcitabine plus cisplatin combination has not been tested in randomized perioperative trials, the favorable toxicity profile has led to its wider and accepted use before and after cystectomy. Single agent cisplatin or carboplatin based regimens are inferior to combined cisplatin regimens and no data support their routine use in the perioperative setting. New agents are being investigated in novel sequential dose-dense and other regimens in an effort to improve activity and tolerability in surgical patients.

DEFINING OPTIMAL THERAPY

Optimal therapy for muscle invasive bladder cancer aims to prevent local recurrence, decrease the probability of metastases and improve survival. Current evidence shows that these goals are best achieved by an integrated approach combining cisplatin based chemotherapy with high quality radical surgery. How can effective chemotherapy best be integrated with radical cystectomy? Again, best evidence data strongly suggest that neoadjuvant chemotherapy fol-

lowed 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 than 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.²⁶ Even in the randomized trials only 50% to 70% of patients actually received 3 or 4 cycles of adjuvant chemotherapy.¹⁵ 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.²⁷ CM was not inferior to MVEC 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. We²⁸ and others²⁹ 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 patients³⁰ despite compelling evidence that cystectomy decreases the risk of death from bladder cancer³¹ even in patients of advanced age³² and many tolerate and derive the same benefit from chemotherapy as their younger counterparts.³³ 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.³⁴ Fewer than 5% of patients are unable to undergo cystectomy in experienced hands³⁵ 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.³⁶ 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.³⁷ 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.³⁸ 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.³⁹ 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

precisely those who are at greatest risk for death from bladder cancer and who are likely to have a successful recovery after surgery with and without chemotherapy.⁴⁰ Better assessments of comorbidity as well as the ability to predict the response to chemotherapy using gene expression profiles are steps toward future risk adjusted individualized therapy for invasive bladder cancer.⁴¹

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

- Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A et al: Cancer statistics, 2005. *CA Cancer J Clin* 2005; **55**: 10.
- Sackett DL, Rosenberg WM, Gray JA, Haynes RB and Richardson WS: Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71.
- Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR et al: Preliminary results of M-VAC for transitional cell carcinoma of the urothelium. *J Urol* 1985; **133**: 403.
- Scher HI, Yagoda A, Herr HW, Sternberg CN, Bosl G, Morse MJ et al: Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. *J Urol* 1988; **139**: 470.
- Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S et al: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001; **19**: 666.
- Galsky MD, Herr HW and Bajorin DF: The integration of chemotherapy and surgery for bladder cancer. *J Natl Compr Cancer Netw* 2005; **3**: 45.
- Volkmer BG, Kuefer R, Bartsch G, Straub M, de Petriconi R, Gschwend JE et al: Effect of a pT0 cystectomy specimen without neoadjuvant therapy on survival. *Cancer* 2005; **104**: 2384.
- Schultz PK, Herr HW, Zhang Z-F, Bajorin DF, Seidman A, Sarkis A et al: Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. *J Clin Oncol* 1994; **12**: 1394.
- Teramukai S, Nishiyama H, Matsui Y, Ogawa O and Fukushima M: Evaluation for surrogacy of end points by using data from observational studies: tumor downstaging for evaluating neoadjuvant chemotherapy in invasive bladder cancer. *Clin Cancer Res* 2006; **12**: 139.
- Hall RR: Updated results of a randomized controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle invasive bladder cancer. *Proc Am Soc Clin Oncol* 2002; **21**: 178A.
- Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; **349**: 859.
- Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Advanced Bladder Cancer Meta-analysis Collaboration. Lancet* 2003; **361**: 1927.
- Winquist E, Kirchner TS, Segal R, Chin J and Lukka H: Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004; **171**: 561.
- Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. *Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol* 2005; **48**: 202.
- Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. *Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol* 2005; **48**: 189.
- Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P et al: The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: results of a prospective comparative trial. *J Urol* 1991; **145**: 459.
- Stockle M, Meyenburg W, Wellek S, Voges GE, Rossman M, Gertenbach U et al: Adjuvant polychemotherapy of non-organ confined bladder cancer after radical cystectomy revisited: long term results of a controlled prospective study and further clinical experience. *J Urol* 1995; **153**: 47.
- Lehmann J, Franzaring L, Thuroff J, Wellek S and Stockle M: Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. *BJU Int* 2006; **97**: 42.
- Millikan R, Dinney C, Swanson D, Sweeney P, Ro JY, Smith TL and Logothetis C: Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. *J Clin Oncol* 2001; **19**: 4005.
- Elting LS, Pettaway C, Bekele BN, Grossman HB, Cooksley C, Avritscher EB et al: Correlation between annual volume of cystectomy, professional staffing, and outcomes. *Cancer* 2005; **104**: 975.

21. Joudi FN and Konety BR: The impact of provider volume on outcomes from urological cancer therapy. *J Urol* 2005; **174**: 432.
22. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE and Bajorin DF: Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002; **167**: 1295.
23. Bochner BH, Cho D, Herr HW, Donat SM, Kattan MW and Dalbagni G: Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. *J Urol* 2004; **172**: 1286.
24. Herr HW, Faulkner JR, Grossman HB, Natale RB, DeVere White R, Sarosdy MF et al: Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004; **22**: 2781.
25. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T et al: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005; **23**: 4602.
26. Droz JP, Cukier J, Beurton D, Terdjman S, Theodore C and Amiel JL: Adjuvant chemotherapy of infiltrating bladder cancer: a feasibility trial. *J Urol (Paris)* 1985; **91**: 435.
27. Lehmann J, Retz M, Wiemers C, Beck J, Thuroff J, Weining C et al: Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, doxorubicin and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). *J Clin Oncol* 2005; **23**: 4963.
28. Donat SM, Herr HW, Dalbagni G and Bochner BH: Incidence and risk factors of post-operative complications in patients undergoing radical cystectomy. Unpublished data.
29. Knap MM, Lundbeck F and Overgaard J: Early and late treatment-related morbidity following radical cystectomy. *Scand J Urol Nephrol* 2004; **38**: 153.
30. Schrag D, Mitra N, Xu F, Rabbani F, Bach PB, Herr H et al: Cystectomy for muscle invasive bladder cancer: patterns and outcomes of care in the Medicare population. *Urology* 2005; **65**: 1118.
31. Clark PE, Stein JP, Groshen SG, Cai J, Miranda G, Lieskovsky G et al: Radical cystectomy in the elderly: comparison of survival between younger and older patients. *Cancer* 2005; **103**: 546.
32. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Underwood W 3rd, Montie JE et al: Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. *Urology* 2004; **64**: 292.
33. Bamias A, Efstathiou E, Mulopoulos A, Gika D, Hamilos G, Zorzou MP et al: The outcome of elderly patients with advanced urothelial carcinoma after platinum-based combination chemotherapy. *Ann Oncol* 2005; **16**: 307.
34. Prout GR, Wesley MN, Yancik R, Ries LAG, Havlik RJ and Edwards BK: Age and comorbidity impact surgical therapy in older bladder carcinoma patients. *Cancer* 2005; **104**: 1638.
35. Herr H, Lee C, Chang S, Lerner S and Bladder Cancer Collaborative Group: Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: a collaborative group report. *J Urol* 2004; **171**: 1823.
36. Duncan L, Heathcote J, Djurdjev O and Levin A: Screening for renal disease using serum creatinine: who are we missing? *Nephrol Dial Transplant* 2001; **16**: 1042.
37. Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G et al: Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006; **107**: 506.
38. Galsky MD: The role of taxanes in the management of bladder cancer. *Oncologist* 2005; **10**: 792.
39. Hussain M, Vaishampayan U, Du W, Redman B and Smith DC: Combination paclitaxel, carboplatin, and gemcitabine in an active treatment for advanced urothelial cancer. *J Clin Oncol* 2001; **19**: 2527.
40. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Khuri SF, Henderson WG et al: Identifying risk factors for potentially avoidable complications following radical cystectomy. *J Urol* 2005; **174**: 1231.
41. Takata R, Katagiri T, Kanehira M, Tsunoda T, Shuin T, Miki T et al: Predicting response to methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy for bladder cancers through genome-wide gene expression profiling. *Clin Cancer Res* 2005; **11**: 2625.