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Review Article

Treatment of Invasive Bladder Cancer: Lessons from the Past and Perspective for the Future

Taiji Tsukamoto, Hiroshi Kitamura, Atsushi Takahashi and Naoya Masumori

Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan

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Radical cystectomy with lymphadenectomy is the gold standard for treatment of invasive bladder cancer. However, the treatment alone does not always provide a satisfactory result for the disease extending outside the bladder. In this review we discuss several clinical issues in the diagnosis and treatment of this invasive disease. Although the quality of diagnostic imaging modalities has improved, they are still not sensitive enough for the staging of the disease, especially for early invasive disease. In addition, lack of serum markers hinders appropriate monitoring of patients with the disease. Regarding the surgical aspect of lymphadenectomy, the area of its dissection, the standard number of nodes retrieved and the method of pathological examination should be established so that the clinical benefits of surgery can be more clearly defined. Neoadjuvant chemotherapy for invasive disease is promising for improvement of survival of patients. A chemotherapy regimen as effective as, but less toxic than, MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) has been reported and several phase III clinical trials have been launched to determine the benefits of adjuvant or neoadjuvant chemotherapy with newly developed agents. However, we still lack a chemotherapy regimen more effective than MVAC, which is the most crucial issue in the treatment of this invasive disease. An alternative option for such disease may be bladder preservation with transurethral resection of tumor followed by chemoradiotherapy. However, patients who are indicated for this treatment may be limited to those with early invasive disease having certain favorable clinical and pathological features.

Key words: bladder cancer – invasive – surgery – chemotherapy – radiation

INTRODUCTION

Bladder cancer is the second most common genitourinary cancer. In Japan, 12 000 patients are newly diagnosed as having this disease and 5000 patients die of it per year (1). It is usually divided into superficial and invasive diseases. The former is defined as that confined to the mucosal or submucosal layer of the bladder. In the latter, cancer cells invade the muscle layer or extend beyond it. The superficial disease found in two-thirds of patients with bladder cancer is basically managed by the transurethral resection of the bladder tumor (TUR-Bt), with or without adjuvant intravesical treatment with chemotherapy or bacille Calmette-Guerin, and thus the bladder can be preserved. The clinical course of the superficial disease is favorable with 5-year cause-specific survival higher than 95%. However, the invasive disease found in one-third of patients with bladder cancer usually has an unfavorable clinical course with a 5-year survival of 50–60%. Thus, treatment of the invasive disease remains a challenge for us (2).

The standard treatment for invasive bladder cancer is radical cystectomy with lymphadenectomy. This treatment is indicated for patients who have a clinically invasive disease but not pelvic lymph node or distant metastases. However, there are several pitfalls in this standard management of the disease. First, not all patients are indicated for radical cystectomy with lymphadenectomy followed by urinary diversion or reconstruction because of the invasive nature of surgery. Surgery is generally contraindicated for some patients with medical complications such as cardiovascular disease. More importantly, there is a group of patients who do not achieve full benefit from surgery alone. Many studies have been performed to decide whether treatments in addition to surgery alone provide a better

For reprints and all correspondence: Taiji Tsukamoto, Department of Urology, Sapporo Medical University School of Medicine, Minami 1-Jo, Nishi 16-chome, Chuo-Ku, Sapporo 060-8543, Japan. E-mail: taijit@sapmed.ac.jp

clinical course or survival for such patients. Unfortunately, there is still little clinical evidence that clearly demonstrates clinical benefit of treatments added to surgery, since either the numbers of patients in past studies were small or the studies were retrospective. Recently, however, the efficacy of neoadjuvant chemotherapy prior to radical cystectomy was demonstrated by both an excellent clinical randomized study that recruited many participants and a meta-analysis (3,4). Many more clinical trials are now under way which will evaluate the efficacy of current modalities of treatment.

We overview in this review what we have learned from past and present studies on this invasive disease and consider the future of its treatment.

The grading and staging system of the disease in this article is based on the General Rules for Clinical and Pathological Studies on Bladder Cancer based on the TNM Classification of Malignant Tumours (Fifth edition) (5), unless otherwise indicated.

DILEMMA IN CLINICAL STAGING AND LACK OF SERUM MARKERS IN INVASIVE BLADDER CANCER

TUR-Bt is the standard procedure to detect invasion of cancer cells into the muscle layer of the bladder. Invasive bladder cancer can be verified by TUR-Bt only when its specimens contain the bladder muscle tissue. Thus, resection must be deep enough to obtain muscle tissue, otherwise, the extent of bladder cancer cannot be accurately known. In addition, even when the specimens contain bladder muscle tissue, damage caused by the resection itself does not always allow surgical pathologists to stage them accurately. Indeed, understaging of TUR specimens can often occur in patients with clinically non-muscle invasive disease who undergo radical cystectomy (6). This is particularly common in T1 G3 disease (7). Deep resection of all visible tumors in the bladder is a cornerstone for diagnosis and treatment of invasive bladder cancer.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) are widely used modalities for staging of invasive bladder cancer. However, they do not necessarily allow us to achieve accurate staging of the disease. In particular, an early muscle-invasive disease cannot be distinguished from a superficial one by CT or MRI (8). For this purpose, TUR-Bt is still the most reliable method for staging. When patients have a tumor large enough to be detected by CT or MRI, however, staging of the disease becomes more reliable. Barentsz et al. (9) showed that the accuracy of CT ranged from 40 to 92% (mean, 74%) and that MRI accuracy was 10–30% higher than CT. In terms of imaging diagnosis of lymph node metastasis, both imaging modalities achieve similar accuracy. However, minimal disease of the node, which is found in 10–30% of invasive disease depending on the extent of the primary lesion, cannot be accurately detected by CT or MRI, because their false negative rates are as high as 40% (10). Even positron emission tomography achieves only a 67% detection rate of node disease (10). Thus, at this time, urologists should integrate all information available from clinical and TUR-Bt-findings, and those obtained from imaging diagnosis, to determine the clinical stage of patients with the disease.

It is unfortunate that bladder cancer does not have a 'serum marker' that can reflect the clinical course of patients and monitor the response to treatment, like prostate-specific antigen for prostate cancer. Efforts so far have been mainly towards developing methods for detecting new lesions in the bladder rather than monitoring the response to treatment or the clinical course. We now have various methods that can be used for screening high-risk patients with superficial disease or for detecting early recurrence of the disease in the bladder. Indeed, markers for urine protein and chromosomal or gene alterations have become available (8,11). In addition, various oncogenes, tumor-suppressor genes, microvessel density and angiogenic inhibitors are available as tissue markers (12). Although these markers potentially allow us to retrospectively stratify patients with invasive disease who are likely to respond to a specific treatment such as chemotherapy, they cannot be used as convenient serum markers reflecting disease status at a given time. Thus, what we really need in the treatment of invasive bladder cancer is a serum marker on which we can rely for determining the treatment policy.

RADICAL CYSTECTOMY WITH LYMPHADENECTOMY AS THE GOLD STANDARD FOR TREATMENT OF INVASIVE BLADDER CANCER

Radical Cystectomy With or Without Urethrectomy

Radical cystectomy is the gold standard for treatment of invasive bladder cancer. This procedure includes bilateral pelvic lymphadenectomy in addition to removal of the bladder, seminal vesicles and prostate with perivesical fat in male patients. In female patients, the bladder with perivesical fat, urethra, anterior wall of the vagina, uterus and ovary are removed together with lymphadenectomy. Many studies have reported that favorable long-term survival is achieved for patients with pathologically organ-confined disease (13–18). Five-year overall survival rates by pathologic stage after radical cystectomy are summarized in Table 1. Although the rate for patients with organ-confined disease (pT2N0) is higher than 60%, it decreases to 30–50% in those with locally advanced diseases (pT3N0 and pT4N0) or lymph node involvement. Thus, the curability of bladder cancer by radical cystectomy primarily depends on the pathologic stage of the primary tumor and pathological status of the lymph nodes. Indeed, Dalbagni et al. (14) reported that only the pT stage and previous chemotherapy were significant factors for disease-specific survival in Cox's proportional hazards analysis, and the survival prognosis for non-organ-confined disease was significantly worse than that for organ-confined disease. Involvement of the prostatic stroma has a significant effect on survival, but prostatic ductal or urethral involvement does not (19,20). Esrig et al. (20) reported that 5-year overall survival rates of patients with

Table 1. Five-year overall survival rates of patients with invasive bladder cancer following radical cystectomy according to pathologic stage

Authors	Year	No. of patients	pT2N0	pT3N0	pT4N0	N (+)
Bassi et al. (13)	1999	369	63/53*	33	28	15
Dalbagni et al. (14)	2001	300	64	31	30	–
Stein et al. (15)	2001	1054	77/64†	49	44	31
Madersbacher et al. (16)	2003	507	62‡	40‡	49‡	26
Nishiyama et al. (17)	2004	1113	84/69§	59	43	35
Takahashi et al. (18)	2004	466¶	74	47	38	30

*pT2N0/pT3aN0 in TNM classification, 1978 Edn.
†pT2N0/pT3aN0 in TNM classification, 1987 Edn.
‡Data suggested by figure.
§pT2a/2b.
¶48% of patients received neo- and/or postadjuvant chemotherapy.

urethral tumors, ductal involvement and stromal invasion were 74%, 67% and 36%, respectively.

When radical cystectomy is attempted, urethrectomy is indicated only for male patients with urethral involvement of the disease. Thus, recurrence of the disease in the urethra is always considered whenever the urethra is left intact. The incidence of recurrence in the retained male urethra ranges from 4 to 14% (21,22). Urethral washing cytology has been recommended for early detection of recurrence in the urethra. Indeed, the procedure has high sensitivity and specificity in detecting early disease (23). However, a recent study raised a question about the procedure as a routine test, since early detection of the urethral disease may not guarantee patients a favorable survival outcome (24). The aggressive biological nature of bladder cancer generally affects survival more strongly than urethral recurrence. This issue should be confirmed by studying a larger number of patients.

Interestingly, the rate of urethral recurrence in patients who underwent orthotopic neobladder construction was reported to range between 2 and 6% (22,25,26), which was lower than the rate for those with cutaneous urinary diversion (27). In other words, urine flow potentially contributes to prevention of recurrence in the urethra. However, diffuse carcinoma in situ (CIS) extending to the prostatic urethra is a sign of high risk for synchronous anterior urethral involvement (28). Therefore, prophylactic urethrectomy is recommended for patients with this risk factor, and an orthotopic neobladder is basically contraindicated for such patients.

In female patients, radical cystourethrectomy has been the standard procedure. Coloby et al. (29) reported that 6% of female patients who underwent radical cystourethrectomy had urethral involvement. All of them had grade 3 disease with adjacent CIS, located in the bladder neck. In a study by Stenzl et al. (30), urethral involvement was found in 2% of female patients with bladder cancer (including superficial disease), and a risk factor for the involvement was simultaneous disease in the bladder neck. Thus, they recommended that most of the urethra should be left intact for orthotopic urinary diversion when patients did not have any cancerous changes or atypia in the bladder neck in transurethral biopsy before cystectomy or frozen sections of the distal end of the urethra at cystectomy. To date, however, there has been no report of urethral recurrence after orthotopic neobladder construction in women (31).

Radical cystectomy with lymphadenectomy is indicated for patients with clinical stages T2-4N0M0. When patients clinically have node metastasis in the pelvis or distant metastasis, they are believed not to benefit from this treatment alone. However, symptoms caused by locally advanced disease such as gross hematuria, difficulty on urination, urgency and pain on urination often cause conspicuous deterioration of the quality of life (QOL) of patients. Palliative cystectomy is an optional treatment for a relief of those symptoms, since palliative urinary diversion alone does not always improve patients' QOL (32,33). Indeed, even in our small series of such patients, some had the chance to benefit from cystectomy in terms of maintenance of their QOL and survival, although the selection of candidates for the treatment was biased (34).

Pelvic Lymphadenectomy

Pelvic lymphadenectomy is an integral part of treatment for patients with invasive bladder cancer. It provides accurate extension and staging of the disease, information that is valuable for prediction of the clinical course. Indeed, as shown in Table 1, the disease status of pelvic lymph nodes is surely one of the critical determinants for survival. Lymphadenectomy is believed to have a therapeutic role as well for a very limited burden of node metastasis in some patients, depending on the extent of node dissection. This issue will be discussed later.

Before reviewing staging and the therapeutic role of lymphadenectomy, we will discuss how extensive lymphadenectomy should be. Unfortunately, there is no consensus on the extent of lymphadenectomy. Limited pelvic lymphadenectomy consists of node dissection in the areas of the external iliac artery and vein, the internal iliac artery and vein and the obturator nerve on both sides (Fig. 1). It removes all lymph nodes that are regarded as the 'regional lymph nodes' of bladder cancer defined by the TNM classification. The conventional or

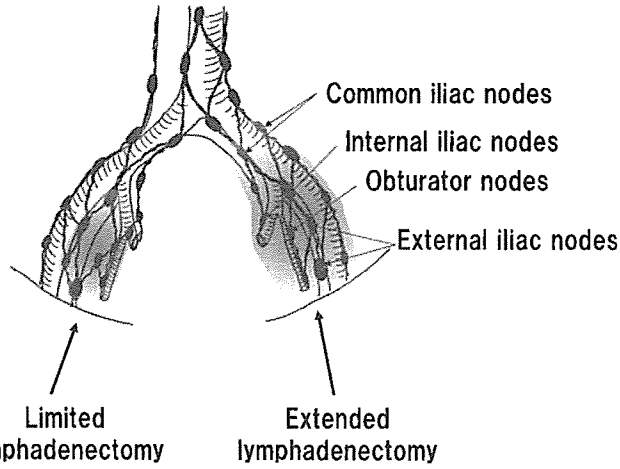

Figure 1. Areas of the extended and limited pelvic lymphadenectomies.

extended type is defined as that removing the bilateral common iliac lymph nodes as well as regional lymph nodes. There are some differences in the dissection areas for conventional or extended lymphadenectomy according to the studies (35–37). For example, Bochner et al. (35) defined conventional (or standard) lymphadenectomy as removal of the distal common iliac (or the mid-common iliac) nodes together with the regional lymph nodes. Poulsen et al. (36) regarded lymphadenectomy as the 'extended type', when they removed the common iliac lymph nodes together with the regional lymph nodes. However, in another study, removal of lymph nodes above the level of the aortic bifurcation and those located in the presacral area together with the regional lymph nodes was included in 'extended lymphadenectomy' (37). Thus, we should be careful in interpreting results for extended lymphadenectomy when this may represent a different area of dissection in each study.

Although lymphadenectomy is included in the surgical procedure for radical cystectomy, there is some controversy over whether limited or extended lymphadenectomy should be performed. The guidelines on bladder cancer of the European Association of Urology recommend limited lymphadenectomy, although they refer to recent studies that show the benefit of the extended type (38). This is partly because lymph node metastases are found more frequently in the regional lymph nodes than in the common iliac or presacral ones, and also metastasis beyond the regional lymph nodes is regarded as disseminated disease. The lack of an established adjuvant chemotherapy for patients who are node positive is another explanation for the limited type to be recommended.

As for staging and prognostic indicators, extensive lymphadenectomy retrieving 16 lymph nodes or more was reported to detect a higher proportion of pathologically proven node metastases in those with pT3 and pT4 cancer, although this was not the case in those with pT2 or less (39). Poulsen et al. (36) compared the incidence of lymph node metastasis in limited lymphadenectomy with that in the extended type. They found that the incidence was higher in patients with the extended type, although it was more prominent when the disease was pathologically confined to the bladder or was less extensive. How many lymph nodes should be retrieved by lymphadenectomy for accurate diagnosis of node metastasis? In the study by Poulsen et al. (36), extended lymphadenectomy retrieved a larger number of lymph nodes than the limited type. The extended lymphadenectomy recovered 23–25 nodes, ranging from 9 to 67, and the limited type recovered 5–14, with a range of 5–30. A postmortem study suggested that removal of approximately 20 nodes may be the reference number of nodes for retrieval by limited pelvic lymphadenectomy (40). It can be expected that node metastasis will be found more frequently with an increase in the number of nodes retrieved. According to the study of Leissner et al. (39), 60% of node-positive patients had, at most, 15 nodes retrieved. To detect more than 80% of patients who are node positive, at most 23 nodes should be removed (39). A similar number of nodes, around 20, was also reported to detect 80% of node-positive patients (41).

It is well known that the number of positive nodes strongly affects the survival of patients with invasive disease who undergo radical cystectomy with pelvic lymphadenectomy. Indeed, two recent large series clearly confirmed this (42,43). Stein et al. (42) showed that patients with eight positive nodes or less had a clearly better prognosis than those with more than eight. Frank et al. (43) also reported that the number of positive nodes was a significant prognostic parameter. In their study, patients with more than five positive nodes had a significantly worse prognosis than those with five or less. Since the number of positive nodes may depend on the number of lymph nodes removed by lymphadenectomy, the absolute number does not necessarily indicate an accurate prognosis. Thus, the concept of the ratio of positive nodes per total number of nodes removed or the positive-lymph node density was introduced and this ratio has been reported to be more predictive of the prognosis of patients in two studies (41,42). These studies demonstrated that patients with a ratio of 20% or greater definitely had a lower survival rate than those with ratios less than 20%. While the ratio of 20% remains to be confirmed by future studies, it can be applicable in the clinical setting, in particular in the case of limited lymphadenectomy, which recovers a smaller number of nodes than the extended type.

Finally, there is still the question of whether the number of lymph nodes retrieved affects the prognosis of the patient. In other words, does retrieval of a greater number of lymph nodes achieve a more favorable clinical outcome?

There are few studies that compare survival of patients who received extended lymphadenectomy with that of those who received regional or limited lymphadenectomy. The study of Poulsen et al. (36) showed that patients with disease confined to the bladder wall and negative nodes achieved a higher survival rate when the limit of lymphadenectomy was extended (Table 2). Unfortunately, it was not a randomized study, and it used historical controls, so it may not be possible to extrapolate their conclusion. However, several recent studies have emphasized the survival benefit of extended lymphadenectomy. Leissner et al. (39) reported that patients who had 16 or

Table 2. Impact of the extent of lymphadenectomy and number of lymph nodes retrieved on survival

Study	Pathological stage	End-point	Comments
Poulsen et al. (36)	≤T2	RFS	Extended LAD is higher than limited LAD.
	≤T2N0	RFS	Extended LAD is higher than limited LAD.
Leissner et al. (39)	all stages	DSS	16 L/N retrieved or more is higher than 15 or less.
		DFS	16 L/N retrieved or more is higher than 15 or less.
	≤T2N0	DFS	16 L/N retrieved or more is higher than 15 or less.
	T3N0	DFS	No difference between 16 L/N retrieved or more and 15 or less.
	N+ (1–5 positive L/N)	DFS	16 L/N retrieved or more is higher than 15 or less.
Herr (44)	T2-4N0	DSS	8 L/N or more retrieved is higher than 7 or less.
	T2-4N+	DSS	11 L/N retrieved or more is higher than 10 or less.

RFS, recurrence-free survival; LAD, lymphadenectomy; DSS, disease-specific survival; DFS, disease-free survival; L/N, lymph nodes.

more lymph nodes removed by extended lymphadenectomy achieved cancer-specific and disease-free survivals significantly higher than those who had 15 or less removed. Even when patients were subcategorized according to several pathological stages, significantly higher disease-free survival was confirmed. Similar results were reported in other studies, all of which suggested that the number of lymph nodes recovered by lymphadenectomy and thorough pathological study of them affected the outcomes of patients (44,45). Interestingly, using the Cox proportional hazards model, Herr (46) indicated that the number of lymph nodes examined was one of the significant risk factors for both survival and local recurrence in node-negative patients. Even in node-positive patients, the number of lymph nodes retrieved similarly affected these outcomes. Finally, based on personal and others' experience, Herr (47) suggested that complete lymphadenectomy along with securing a wider margin around the bladder and more thorough examination of surgical specimens by pathologists contributed to improvement of outcomes in patients with invasive bladder cancer.

Although recent studies have suggested that extended lymphadenectomy may be more beneficial than the limited type for staging accuracy and survival benefit, as indicated earlier, this issue remains to be determined in a prospective, randomized study.

Local Recurrence

Local recurrence of cancer in the pelvis after definitive surgical treatment for patients with invasive disease is a greatly frustrating problem both for patients and physicians. Its development potentially compromises not only survival but also the QOL of patients. Local recurrence may not produce any symptomatic findings in the early stage but eventually causes bowel obstruction and pain due to involvement of various nerves, both of which strongly affect the QOL of patients. For physicians, that there is no effective treatment for such lesions is a devastating problem. Before the era of modern imaging diagnosis, many small lesions recurring in the pelvis were not precisely detected if they did not produce specific signs and symptoms. However, the current use of CT allows us to more frequently detect even small lesions of recurrence in the pelvis. Accurate diagnosis and specific treatment of such lesions is a matter for debate in daily practice, in particular when they are not associated with distant metastasis.

A recent study indicated that local recurrence was much more frequent than previously believed (48). Recurrence with or without concurrent distant metastasis was found in 5–20% of patients who received radical surgery, depending on their clinical and pathological features (49). In patients with pT3 or pT4 disease, the rate of local recurrence or systemic recurrence was reported to be around 30% (50). Although pathological stage and lymph node status were suggested to be risk factors for local recurrence, recent studies indicate that it may be avoided by meticulous radical cystectomy and extended lymphadenectomy (44,51).

Once local recurrence develops, its clinical course is generally pessimistic. Westney et al. (52) reported that the survival interval from diagnosis of local recurrence was less than one year with treatments currently available. Unfortunately, there have been no studies suggesting any specific treatments that can clearly reduce the rate of local recurrence after cystectomy. Whether or not neoadjuvant and adjuvant chemotherapy regimens currently available and newly developing are effective for reduction of the rate remains to be determined.

BENEFITS AND PITFALLS OF CHEMOTHERAPY ADJUNCTIVE TO RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER

Adjuvant and Neoadjuvant Chemotherapy

As indicated earlier, radical cystectomy with lymphadenectomy alone cannot achieve satisfactory survival for patients with pT3, pT4 and node-positive disease. Patients with such diseases need additional treatments for improvement of their survival. Preoperative irradiation, which was tried in the early

Table 3. Current clinical trials for adjuvant chemotherapy for invasive bladder cancer (60)

Title of ongoing clinical trials	Status of trial	Protocol ID
Phase II study of adjuvant gemcitabine, cisplatin, and amifostine in patients with completely resected locally advanced bladder cancer	Active	UCCRC-9193
Phase II study of adjuvant paclitaxel, ifosfamide, carboplatin and gemcitabinein patients with high-risk transitional cell carcinoma of the urothelium	Active	TULCC-RM-002
Phase III randomized study of adjuvant cisplatin and gemcitabine versus observation in patients with transitional cell cancer of the bladder at high risk after radical cystectomy	Active	ITNRC-CU02.00447ST/97
Phase III randomized study of immediate versus deferred adjuvant chemotherapy after radical cystectomy in patients with stage III or IV transitional cell carcinoma of the urothelium	Active	EORTC-30994

Table 4. Randomized phase III trials of neoadjuvant chemotherapy

Authors	Year	No. of patients	Chemotherapy	Survival benefit
Martinez-Pineiro et al. (61)	1995	122	Cisplatin versus control	No significant difference
Malmström et al. (62)	1996	325	Cisplatin + doxorubicin versus control	Chemotherapy > control (in patients with T3-4)
Bassi et al. (63)	1998	206	MVAC versus control	No significant difference
MRCA-Advanced Bladder Cancer Working Party (64)	1999	976	CMV versus control	No significant difference
Sherif et al. (65)	2002	317	Cisplatin + methotrexate versus control	No significant difference
Grossman et al. (3)	2003	317	MVAC versus control	MVAC > control

MRCA, Medical Research Council; MVAC, methotrexate + vinblastine + doxorubicin + cisplatin; CMV, cisplatin + methotrexate + vinblastine.

1980s, finally turned out not to have advantage for survival in a randomized study conducted by the Southwest Oncology Group (SWOG) (53,54). Since then, along with progress in clinical efficacy of cisplatin-based combination chemotherapy for metastatic bladder cancer, many chemotherapeutic regimens have been studied for this purpose. Unfortunately, until very recently, only non-conclusive results were reported. In addition, the timing of chemotherapy adjunctive to cystectomy, neoadjuvant or adjuvant, has not been established.

Adjuvant and neoadjuvant chemotherapies have their own advantages and disadvantages (55). The advantages of adjuvant chemotherapy consist of accurate stage diagnosis, more appropriate selection of patients based on pathologically identified risk factors for recurrence, and no delays in performing cystectomy. On the other hand, its disadvantages include the lack of a marker lesion for assessment of the response to chemotherapy, no chance to preserve the bladder, relative delay for treatment of micrometastases and difficulties in giving chemotherapy with a planned dose intensity and treatment cycle. In the daily clinical setting, many patients seem to receive adjuvant chemotherapy when the disease pathologically extends beyond the bladder or have margin-positive status of the cystectomy specimen. However, no published studies have proved any definite benefit of adjuvant chemotherapy for long-term disease-free and overall survivals, although several investigators have conducted randomized trials (56–59). Currently, the adjuvant phase II and III protocols using newly developed drugs and their combinations are under investigation (Table 3) (60).

Advantages of neoadjuvant chemotherapy include information about the response to chemotherapy that may predict future clinical course, possible treatment of micrometastases without delay and potential preservation of the bladder if the disease responds well to chemotherapy (55). Another advantage is that patients may better tolerate chemotherapy in a neoadjuvant setting than in an adjuvant one.

Disadvantages of neoadjuvant chemotherapy are the negative sides of each advantage of adjuvant chemotherapy, which include less accurate staging of the primary tumor, no identifiable pathological risk factors and unavoidable chemotherapy not beneficial for patients with a low risk for recurrence.

As with adjuvant chemotherapy, many randomized trials of neoadjuvant chemotherapy have been conducted over the last 10 years to determine whether the chemotherapy improved survival (3,61–65). Unfortunately, there have been no reports that clearly demonstrate any survival benefit of chemotherapy in the neoadjuvant setting before the study conducted by the SWOG (Table 4). The group reported in 2003 that three cycles of MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) neoadjuvant chemotherapy followed by radical cystectomy provided patients with invasive disease a median interval of survival longer than that with cystectomy alone (3). Even when patients were stratified according to age and stage, the survival benefit was predominant in those who received neoadjuvant chemotherapy. The study concluded that neoadjuvant chemotherapy can be offered to patients with invasive disease who need radical cystectomy. Hopefully, there will be additional successful trails that support the results of the SWOG.

Table 5. Phase II and III studies of chemotherapy using paclitaxel and/or gemcitabine (55,60,80)

Phase	Title of trial	Protocol ID
II	RS of induction paclitaxel, cisplatin and XRT versus fluorouracil, cisplatin and radiotherapy followed by consolidation chemoradiotherapy or radical Cx and adjuvant gemcitabine, paclitaxel and cisplatin in patients with operable stage II or III bladder cancer	RTOG-0233
II	Study of adjuvant gemcitabine, cisplatin and amifostine in patients with completely resected locally advanced bladder cancer	UCCRC-9193
II	Study of adjuvant paclitaxel, ifosphamide, carboplatin and gemcitabine in patients with high-risk transitional cell carcinoma of the urothelium	TULCC-RM-002
II	Study of cisplatin, ifosphamide and paclitaxel in patients with unresectable or metastatic urothelial tumors	MSKCC-95031
II	Study of gemcitabine and paclitaxel in patients with advanced or recurrent urothelial cancer	SWOG-S0028
II	Study of neoadjuvant carboplatin, paclitaxel and gemcitabine followed by concurrent cisplatin and XRT in patients with locally advanced or recurrent carcinoma of the urothelium	SWOG-S0121
II	Study of neoadjuvant gemcitabine, paclitaxel, carboplatin followed by observation or immediate Cx in patients with stage II or III transitional cell cancer of the urothelium	SWOG-S0219
II/III	RS of gemcitabine and carboplatin versus methotrexate, carboplatin and vinblastine in previously untreated patients with transitional cell cancer of the urothelium who are ineligible for cisplatin-based chemotherapy	EORTC-GU-30986
III	RS of adjuvant cisplatin and gemcitabine versus observation in patients with transitional cell cancer of the bladder at high risk after radical Cx	ITNRC-CU02.00447ST/97
III	RS of cisplatin and gemcitabine with or without paclitaxel in patients with stage IV transitional cell carcinoma of the urothelium	EORTC-30987

RS, randomized study; XRT, radiation; Cx, cystectomy.

The predominant benefit of neoadjuvant chemotherapy before radical cystectomy is supported by a recent meta-analysis summing up 11 randomized, potentially eligible studies of neoadjuvant chemotherapy (4). This analysis, including survival data for a total of 2492 patients, showed a 9% relative reduction in the risk of death with neoadjuvant chemotherapy. Furthermore, the platinum-based chemotherapy in the neoadjuvant setting achieved significantly improved overall survival that was characterized by a 13% relative reduction in risk of death, 5% absolute benefit at 5 years and improvement of overall survival from 45% to 50%. The author concluded that the platinum-based combination chemotherapy showed a significant survival benefit although platinum alone did not contribute to improved survival of patients. In Japan, a randomized phase III study of two cycles of MVAC neoadjuvant chemotherapy followed by radical cystectomy, compared with cystectomy alone for T2-T4aN0M0 bladder cancer is being conducted by the Japan Clinical Oncology Group.

Currently, the SWOG is conducting a phase II study of neoadjuvant chemotherapy consisting of gemcitabine, paclitaxel and carboplatin followed by observation or immediate cystectomy in patients with stage II or III transitional cell cancer of the urothelium (SWOG-S0219) (60). The aim of this study is to evaluate the effectiveness of the new combination chemotherapy.

More Effective Regimens of Chemotherapy in Adjuvant and Neoadjuvant Settings

At this moment, there are no adjuvant and neoadjuvant chemotherapy regimens more effective than MVAC, although several clinical trials with new agents are being carried out. Even for patients with advanced or metastatic disease, MVAC is still the standard regimen. Indeed, among many combination chemotherapy regimens that were studied, MVAC (66) and CMV (cisplatin, methotrexate and vinblastine) (67) achieved the highest overall response and CR rates. Randomized trials for metastatic urothelial cancer showed that MVAC was superior to the single agent cisplatin (68,69) and CISCA (cisplatin, cyclophosphamide and doxorubicin) (70). There is no randomized trial comparing MVAC with CMV. Although MVAC is one of the most effective chemotherapy regimens for advanced or metastatic diseases, it is associated with substantial toxicity, including leucopenia, culture-negative fever at the time of granulocytopenia, mucositis and renal failure (54). Furthermore, an escalated dosage of MVAC was associated with significant toxicity but had no apparent benefit over standard MVAC with regard to the complete response rate and survival (71). Interestingly, a combination of methotrexate, epirubicin and cisplatin was reported to achieve a response rate comparable to MVAC in patients with metastatic urothelial cancer but had milder intensity and less frequent toxicity (72). Unfortunately, the survival benefit was not reported.

New regimens using new chemotherapeutic agents have recently been studied for locally advanced or metastatic disease. Bellmunt et al. (73) demonstrated that a combination of cisplatin, paclitaxel and gemcitabine achieved 28% complete and 50% partial response rates for patients with previously untreated, locally advanced or metastatic urothelial cancer. In this phase II trial, the main nonhematologic toxicity was grade 2 and grade 3 asthenia, found in 37% and 8% of patients, respectively. Grade 3/4 neutropenia was found in 55% of patients and thrombocytopenia with the same grades occurred

Table 6. Results of combined treatment for bladder preservation in muscle-invasive disease

Authors	Year	No. of patients	TUR	Chemotherapy	XRT	%CR	% bladder preservation survival (years)	% overall survival (years)
Tester et al. (91)	1996	91	Yes	MCV	Yes	75	60 (4)	62 (4)
Kachnic et al. (92)	1997	106	Yes	MCV	Yes	66	66 (5)	52 (5)
Shipley et al. (93)	1998	61	Yes	MCV	Yes	61	36* (5)	48 (5)
Rödel et al. (94)	2002	398	Yes	Either cisplatin or carboplatin ± 5-FU,	Yes	72	42† (5)	45 (5)
				or no chemotherapy			27† (10)	29 (10)
Mokarim et al. (95)	1997	35	Yes	IAC (cisplatin + doxorubicin)	Yes	74	74 (5)	77 (5)
Sumiyoshi et al. (96)	1998	21	Yes	IAC (pirarubicin + cisplatin)	Yes	91	91 (5)	91 (5)
Miyanaga et al. (97)	2000	42	No	IAC (MTX + cisplatin)	Yes	93	84 (3)	63 (5)‡
Tsukamoto et al. (98)	2002	23	Yes	IAC (cisplatin ± MTX)	Yes	78	78 (5)	46 (5)

TUR, transurethral resection; XRT, external beam radiation therapy; CR, complete response; MCV, methotrexate, cisplatin and vinblastine; IAC, intraarterial chemotherapy; MTX, methotrexate.
*Percent alive with intact bladder.
†Including patients with high-risk T1 cancer.
‡For patients with preserved bladder.

in 22%. Overall, febrile neutropenia was seen in 22% of patients, and one toxic death occurred because of neutropenic sepsis. A similar combination of paclitaxel, carboplatin and gemcitabine also achieved a favorable result with 32% complete and 36% partial responses (74). The incidence of side effects was comparable to that reported by Bellmunt et al. (73). Febrile neutropenia was observed in 1.4% and no patients died of drug-related toxicity. In the study of Meluch et al. (75), 47% of patients who were previously treated with platinum-based chemotherapy responded to combination therapy using paclitaxel and gemcitabine. The side effects in their study consisted of grade 3/4 leukopenia (46%), thrombocytopenia (13%) and anemia (28%). One of 54 patients died of treatment-related sepis.

Finally, von der Maase et al. (76) reported a randomized study of gemcitabine plus cisplatin (GC) versus MVAC, which demonstrated that GC provided response and survival rates similar to MVAC and less intensive toxicity than MVAC. However, Cohen and Rothman (77) criticized the result reported by von der Maase who recommended GC instead of MVAC for advanced or metastatic urothelial cancer. Thus, a further large scale study will be needed to confirm the current results (78). Another recent multicenter, randomized phase III study consisting of more than 200 patients with inoperable or metastatic urothelial cancer reported that MVAC was significantly superior to a combination of docetaxel and cisplatin (DC) in terms of median time to progression and median survival (79). Although MVAC produced hematologic toxicity more frequently than DC, support with granulocyte-colony stimulating factor reduced its frequency when compared with that of MVAC without such support in previous studies.

Thus, several new agents or their combinations may be promising in the treatment of patients with advanced or metastatic disease because of their less toxic nature. This may be advantageous when a regimen with a combination of several agents is used in the adjuvant or neoadjuvant setting. However, at this moment, we have no chemotherapy regimen that clearly exceeds the clinical efficacy of MVAC. In addition, no advantage has been proved in the adjuvant or neoadjuvant setting.

Currently, various phase II and III trials of chemotherapies using paclitaxel and/or gemcitabine are in progress (Table 5) (54,55,80). Their objective is to find the most effective and least toxic combination for patients with advanced or metastatic disease and also for those with neoadjuvant or adjuvant chemotherapy. It is also valuable to evaluate other anti-cancer drugs such as gefitinib, irinotecan or bortezomib, although the long-term results of such studies have not been disclosed to date. The efficacy of the drugs is being studied in phase II trials (60).

BLADDER PRESERVATION IN THE TREATMENT OF INVASIVE BLADDER CANCER

Bladder-sparing strategy is basically considered when patients are poor risks for radical cystectomy. However, a recent trend is for the treatment to be indicated also when it seemingly controls invasive disease without compromising the 'cure' of the disease. Needless to say, the QOL of the patient with the bladder preserved is definitely better since urinary diversion is avoided. However, it is of concern that a later tumor developing in the preserved bladder may increase the risk of cancer uncontrollable by treatment modalities currently available (81).

While superficial bladder cancer can be completely resected by TUR-Bt, a well-defined and non-penetrating tumor is also resectable even in muscle-invasive disease. Herr (82) reported a 5-year survival of 70% in treatment of T2 bladder cancer with TUR-Bt. The 10-year disease-specific survival rate of patients who received TUR-Bt as definitive treatment for cancer of this stage was reported to be 76% and the bladder preservation rate 57% (83). In contrast, Roosen et al. (84) reported a 5-year sur-

vival of <30% in patients with T2 cancers who were treated with TUR-Bt. Solsona et al. (85) found that 41% of patients treated with radical TUR-Bt for invasive disease were alive with bladder preservation in a follow-up at 5 years and 22% of those at 10 years. Thus, TUR-Bt alone for muscle-invasive disease is controversial. However, when TUR-Bt is combined with other modalities, it may achieve more favorable results, which will be discussed later.

External-beam radiation therapy (XRT) is planned for patients with high risks who are not good candidates for radical cystectomy, since its curative capability has not been clearly proved (81). The radiosensitivity of transitional cell carcinoma is low and XRT alone offers local control inferior to that obtained with cystectomy (81,86). XRT as a single-modality therapy is not usually recommended in the USA or Japan, partly because of control of bleeding, and relief of pain, bladder irritability and urinary frequency are crucial for patients with invasive bladder cancer. Systemic chemotherapy alone has the same efficacy as XRT (87). Scattoni et al. (88) reported that only half of clinical complete responders achieved a pathological complete response. Another monotherapy for bladder-sparing treatment of invasive disease is intra-arterial chemotherapy in which a larger dose of chemotherapeutic agents may be delivered to the tumor with less toxicity (2). Unfortunately, the pathological complete response rate, which is mandatory for bladder preservation, was reported to be less than 50% (89,90). Thus, it is clear that every monotherapy fails as an appropriate single treatment modality for bladder preservation in patients with invasive disease.

This situation has led to the next stage where combination treatments consisting of TUR-Bt, XRT and systemic chemotherapy have been tried, and are seemingly more effective in selected patients (Table 6) (91–98). A combination of intra-arterial chemotherapy with concurrent XRT demonstrated good local control (95–98). The main purpose of their combination is to increase radiosensitivity by chemotherapeutic agents. Furthermore, systemic chemotherapy in combination can eradicate occult metastases that have already developed in as many as 50% of T2-3 patients who have T2-3 disease at the initial presentation (99). In most studies, however, radical cystectomy was performed even when the initial bladder sparing treatment produced a complete response. In other words, survival data were based on patients who were treated not by bladder-sparing treatment alone but by protocol treatment including cystectomy. In addition, in studies with long-term outcomes, 30–60% of complete responders eventually developed new tumors in the bladder even if the patients underwent combination treatment with bladder preservation (91,93,100). Patients might not have died of this new cancer, because they would not have developed it if the bladder had been removed initially (101).

Nevertheless, the results of a recent large, long-term study by Rödel et al. (94) are intriguing. It included almost 400 patients with high-risk T1 and invasive disease, and followed-up those surviving for more than 5 years (Table 6). They reported that TUR-Bt followed by chemotherapy with XRT or XRT alone achieved a 72% complete response rate and 42% 10-year disease-specific survival, and that the bladder could be preserved in more than 80% of survivors. In addition, chemotherapy with XRT produced more favorable results than XRT alone. Based on the results of this study together with those of other studies, Gospodarowicz (102) commented that 'these results certainly offer hope and indeed opportunity for bladder preservation in a significant proportion of patients who currently undergo cystectomy'. However, it should be cautioned that not all invasive diseases are indicated for bladder preservation. Indeed, Rödel et al. (94) stated that 'ideal candidates for this treatment were patients with early-stage and unifocal tumors in whom a microscopically or at least visibly complete TUR-Bt was accomplished'. Thus, appropriate selection of patients and confirmation of complete TUR are crucial for applying this treatment modality.

Unfortunately, to date, there have been no randomized studies that directly compare radical cystectomy with bladder-sparing treatment. A current pilot phase I/II study at the University of Michigan of concurrent gemcitabine and radiotherapy after aggressive TUR has shown good patient tolerance, preserved bladder function and favorable results (101). Furthermore, phase III randomized studies of radical radiotherapy with or without carbogen and niaciamide, and standard volume radiotherapy versus reduced volume radiotherapy with or without synchronous fluorouracil and mitomycin in patients with locally advanced bladder cancer have been initiated in the UK (60).

At present, although some patients with invasive disease can be managed with bladder-sparing treatment, the indication for the treatment may be limited to those with favorable clinical and pathological features. In addition, once the initial bladder-sparing treatment fails, immediate radical surgery is mandatory.

CONCLUSIONS

In summary, radical cystectomy is still the most effective and reliable treatment for invasive bladder cancer. Neoadjuvant chemotherapy may contribute to improvement of survival of patients with organ-confined and locally advanced disease, but more clinical studies are necessary to confirm this. Although new chemotherapeutic regimens and new methods of cancer therapy are expected to be more effective and less toxic than MVAC, there are no such regimens at this time. Various clinical studies are under way, and will give us valuable information in the near future. Bladder preservation should be basically indicated when poor general condition does not allow cystectomy in patients with invasive disease. Some, but not all, patients with invasive disease may be managed with bladder-sparing treatment when they have favorable clinical and pathological features and the bladder tumor can be completely resected.

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ELSEVIER

LOCAL RECURRENCE AFTER RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER: AN ANALYSIS OF PREDICTIVE FACTORS

ICHIYA HONMA, NAOYA MASUMORI, EIJI SATO, AKIO TAKAYANAGI, ATSUSHI TAKAHASHI, NAOKI ITOH, MITSUHARU TAMAGAWA, MASA-AKI SATO, AND TAIJI TSUKAMOTO

ABSTRACT

Objectives. To examine which clinicopathologic parameters predict clinically detectable local recurrence after radical cystectomy. Local recurrence after radical cystectomy for invasive bladder cancer was infrequently observed until 20 years ago because of the lack of adequate diagnostic tools. The recent development and use of pelvic computed tomography has allowed us to detect local recurrence more precisely. However, only a few studies have investigated the rate and pattern of local recurrence in the computed tomography era.

Methods. This retrospective review included 145 patients with muscle-invasive bladder cancer treated with radical cystectomy, regional pelvic lymph node dissection, and urinary diversion between January 1990 and December 2001. The development of local recurrence and/or distant metastasis was analyzed as the endpoint using univariate and multivariate analyses.

Results. Local recurrence developed in 27 (18.6%) of the 145 patients at a median of 8 months after cystectomy. Of the 27 patients, 8 had local recurrence alone and 19 had concurrent distant metastasis. Distant metastasis without local recurrence developed in 34 patients (23.4%). Univariate and multivariate analyses revealed that Stage pT3-T4 and pathologic pelvic lymph node involvement were statistically significant factors predicting clinical failure, local recurrence, and/or distant metastasis. However, a concomitant squamous cell carcinoma component in the specimen was the only independent predictor of local recurrence alone in both univariate and multivariate analyses.

Conclusions. Only the finding of a concomitant squamous cell carcinoma component in the specimen was an independent predictor of local recurrence in patients treated with radical cystectomy. UROLOGY **64:** 744–748, 2004. © 2004 Elsevier Inc.

Radical cystectomy with pelvic lymph node dissection (PLND) is a standard surgical procedure for muscle-invasive bladder cancer, with a 5-year survival rate of approximately 60%. However, one third of the patients treated by cystectomy die of the disease, mostly of metastatic tumor spread.[1,2] Thus, distant metastasis has been considered the main reason for clinical failure after cystectomy. However, the actual rates and frequent sites of clinically detectable local recurrence have been infrequently examined because recurrence was considered rare before the development of computed tomography (CT). Although the current availability of CT has allowed us to detect local recurrence that has aggressive behavior with a poor prognosis more frequently, only a few studies have reported the rates and patterns of clinically detectable local recurrence after cystectomy in detail.

In this study, we retrospectively reviewed patients who underwent definitive surgery for invasive bladder cancer after 1990 when CT was routinely used as a part of clinical staging and follow-up. The clinical and pathologic factors possibly predicting local recurrence were analyzed using univariate and multivariate analyses,

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From the Departments of Urology, Radiology, and Laboratory Medicine (Pathology), Sapporo Medical University School of Medicine, Sapporo, Japan

Reprint requests: Naoya Masumori, M.D., Department of Urology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-Ku, Sapporo 060-8543, Japan

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as were the rate and pattern of local recurrence after radical cystectomy.

MATERIAL AND METHODS

A total of 160 consecutive patients underwent radical cystectomy and regional PLND with or without chemotherapy for muscle-invasive bladder cancer from January 1990 to December 2001 at Sapporo Medical University Hospital. Ten patients who underwent noncurative surgery with positive surgical margins, three who died of postoperative complications, and two who had tumors of nonurothelial origin were excluded, leaving 145 patients who underwent curative cystectomy and were adequately monitored for the current retrospective review.

The preoperative evaluation included cystoscopy, transurethral resection of bladder tumor, bimanual examination under anesthesia, excretory urography, abdominal and pelvic CT, and chest x-ray. The patients underwent additional evaluations, including bone scan and chest CT, if clinically indicated. Bladder cancer was histopathologically diagnosed by transurethral resection in all patients before cystectomy. No patients investigated in this study had distant metastasis at the time of the initial diagnosis.

Radical cystectomy and regional PLND were performed using a standard technique.[3] PLND included the internal iliac, external iliac, and obturator lymph nodes. The boundaries of dissection included the circumflex iliac vein inferiorly, pelvic side wall laterally, bladder wall medially, and iliac bifurcation superiorly. Prophylactic urethrectomy was not usually done. Concurrent urethrectomy was preserved for male patients with a histologically proven tumor on the prostatic urethra. Anterior pelvic exenteration was done in the women who selected urinary diversion other than an orthotopic ileal neobladder.

The tumor was staged and graded according to the 1999 TNM classification[4] and the World Health Organization system,[5] respectively. In addition to the depth of tumor invasion and degree of nodal involvement, vascular invasion, lymphatic invasion, and the presence of a squamous cell carcinoma (SCC) component were determined histologically. Because no statistically significant survival benefit was reported in patients with pT0 compared with those with a pathologic stage identical to the original clinical stage,[6] the histopathologic analysis was done according to the specimens from transurethral resection in patients with Stage pT0.

After cystectomy, patients with pT2 or lower without nodal involvement were followed up at 6 to 12-month intervals with physical examination, hemogram, serum chemistry profiles, chest x-ray, and CT of the abdomen and pelvis. Patients with pT3 or greater and/or lymph node involvement were followed up at 3 to 6-month intervals. Clinical failure was defined as the appearance of local recurrence and/or distant metastasis. Local recurrence was defined as recurrence in the pelvic soft tissue or pelvic lymph nodes detected with imaging studies. Involvement of lymph nodes above the level of the iliac bifurcation and inguinal lymph nodes was classified as distant metastasis. When local and distant metastases were found within a given 3-month period, they were considered concurrent recurrence.

The survival time and time to clinical failure were analyzed from the date of surgery. The endpoints of the univariate and multivariate analyses were local recurrence and/or distant metastasis. Survival estimates were constructed using the Kaplan-Meier method. The log-rank test was used to evaluate the statistical significance of differences in the univariate analysis. For multivariate analysis, the Cox proportional hazards model was used.

TABLE I. *Clinical and pathologic stage and tumor histologic type*

Characteristic	Patients (%)
Clinical stage	
T2	70 (48.3)
T3	44 (30.3)
T4	31 (21.4)
Pathologic stage	
T0	17 (11.7)
T1-Tis	28 (19.3)
T2	41 (28.3)
T3	39 (26.9)
T4	20 (13.8)
Histologic type	
UC	107 (73.8)
UC + SCC component	25 (17.2)
UC + AC	6 (4.1)
UC + undifferentiated carcinoma	3 (2.1)
Pure SCC	4 (2.8)

KEY: UC = urothelial carcinoma; SCC = squamous cell carcinoma; AC = adenocarcinoma.

RESULTS

Of the 145 patients, 116 were men and 29 were women. The median follow-up period of the 145 patients was 25 months (range 3 to 153). The median follow-up of the 89 survivors was 56 months. Patient age ranged from 38 to 79 years (mean 65). Simultaneous urethrectomy was performed for 37 men and 26 women. An ileal conduit was performed in 67 patients (46.2%), an orthotopic ileal neobladder in 50 (34.5%), continent cutaneous diversion in 22 (15.2%), a colonic conduit in 4 (2.8%), and cutaneous ureterostomy in 2 (1.4%). Clinically, 75 patients (51.7%) were diagnosed with extravesical disease (T3 or greater) before cystectomy (Table I). Twelve patients had pelvic adenopathy on CT. Neoadjuvant chemotherapy was given to 59 patients (40.7%), most of whom had Stage T3 or greater and/or pelvic adenopathy.

Pathologically, 86 patients (59.3%) had tumors confined to the bladder (pT2 or less), and 59 patients (40.7%) had tumors penetrating the bladder wall into the perivesical fat or adjacent structures (pT3 or more; Table I). The histologic type was pure urothelial carcinoma in 107 patients (73.8%) and urothelial carcinoma associated with other histologic components in 34 (23.4%). Most of the mixed histologic types consisted of urothelial carcinoma with an SCC component, which was found in 25 patients (17.2%). Nodal involvement was detected in 25 patients (17.2%). Sixty-eight patients (46.9%) had either vascular and/or lymphatic invasion. The number of lymph nodes retrieved by regional PLND ranged from 2 to 42 (median 12). No statistically significant difference was found in

TABLE II. *Anatomic location of 108 recurrences and metastases in 65 patients*

Site	No. of Sites (%)
Local	
Pelvic soft tissue	14 (9.7)
Pelvic lymph node	8 (5.5)
Pelvic soft tissue + pelvic lymph node	5 (3.4)
Distant	
Bone	20 (14.0)
Distant lymph node	17 (11.7)
Lung	15 (10.3)
Liver	12 (8.3)
Other	10 (7.0)
Urinary tract	
Upper urinary tract	3 (2.1)
Urethra	4 (4.9)*
Total	108

* *Percentage of 82 patients without urethrectomy.*

the number of nodes retrieved between patients with nodal involvement and those without it (mean ± standard deviation 14.2 ± 5.2 versus 13.9 ± 7.1). Fifteen patients (10.3%) with pT3 or more and/or nodal involvement received adjuvant chemotherapy according to the urologists' preference.

Local recurrence developed in 27 (18.6%) of the 145 patients at a median of 8 months (range 2 to 71) after cystectomy. Of these, 8 (6 men and 2 women; 29.6%) had local recurrence alone without distant metastasis. Concurrent distant metastasis was found in 19 patients (70.4%), including 7 with nodal involvement above the bifurcation of the iliac vessels, 5 in bone, 5 in the liver, 3 in the lung, and 2 with peritoneal seeding. Distant metastasis without local recurrence developed in 34 patients (23.4%) at a median follow-up time of 11 months (range 1 to 47). The disease recurred in the upper urinary tract in 3 patients (2.1%). Of the 82 patients who did not undergo urethrectomy, 4 (4.9%) had urethral recurrence. The disease-free survival rate of the 145 patients at 1, 2, 3, and 5 years was 73.8%, 60.6%, 56.8%, and 54.3%, respectively.

Table II summarizes the 108 sites of recurrent or metastatic lesions in 65 patients. The anatomic location of local recurrence was the pelvic soft tissue in 14, pelvic lymph nodes in 8, and both of them in 5. CT demonstrated the exact location of the pelvic soft-tissue recurrence, which was soft tissue in front of the anterior rectal wall in 15 patients, behind the pubic bone in 3, and at the presacral area in 1. Of these 19 patients, 12 (63.2%) had extravesical disease pathologically. Regional pelvic lymph node recurrence was observed in the obturator node in 6 patients, obturator and internal iliac nodes in 3, internal and external iliac nodes in 3, and external iliac node in 1 patient. Of the 13 patients, 4 (30.7%) had nodal metastasis in the regional PLND. The most common site of distant metastasis was bone followed by distant lymph nodes.

Because recurrence in the urethra or the upper urinary tract implies a biologic character different from local recurrence and metastasis, the patients with such recurrence were not defined as having clinical failure. Univariate and multivariate analyses revealed that pT3-T4 and nodal involvement correlated significantly with clinical failure (Table III). However, a concomitant SCC component or pure SCC in the specimen was the only independent predictor of local recurrence, especially in the soft tissues, by univariate and multivariate analyses. Neither pT3-T4 nor nodal involvement had any impact on the development of local recurrence.

COMMENT

Before the CT era, local recurrence after radical cystectomy for invasive bladder cancer was rarely detected. However, Cole *et al.*[7] demonstrated that local recurrence is much more frequent than previously believed. In contemporary series, the rate of local recurrence after radical cystectomy has ranged between 5.0% and 16.4%, depending on the pathologic stage (Table IV).[2,8–12] Local recurrence generally occurs within the first 2 years after cystectomy. In our series, the time to recurrence after cystectomy was shorter than 1 year. Although improvements have been made in the treatment of bladder cancer, long-term survival after local recurrence is extremely rare because of its aggressive behavior. Therefore, it is necessary to understand the exact rate of local recurrence using a contemporary modality such as CT and to clarify the risk factors for it.

Many studies have evaluated the prognostic variables of survival after radical cystectomy. It has been reported that the pathologic disease stage and pelvic node involvement are important predictors of disease-free survival.[13–15] The results of our study also demonstrated that the pathologic stage and nodal involvement were statistically significant predictors of clinical failure. Complete extended PLND has been suggested to improve the prognosis of patients with invasive bladder cancer. Millis *et al.*[16] and Poulsen *et al.*[17] reported that long-term survival was achieved even in node-positive patients, and, therefore, bilateral complete PLND was mandatory. With respect to local recurrence, many investigators have reported that the pathologic stage is an important prognostic factor, just as for distant metastasis.[8,9] Moreover, Herr *et al.*[12] reported that local control was improved when more lymph nodes, at least nine, were excised,

TABLE III. *Univariate and multivariate analyses of parameters predicting clinical failure and local recurrence*

			Local Recurrence					
	Clinical Failure		Total		Pelvic Lymph Nodes		Soft Tissue	
Parameter	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Neoadjuvant chemotherapy (with vs. without)	0.771	0.909	0.733	0.801	0.924	0.772	0.770	0.853
Concomitant SCC component or pure SCC (without vs. with)	0.361	0.812	0.003	0.018	0.096	0.190	0.004	0.026
Grade (G1-G2 vs. G3)	0.074	0.732	0.284	0.464	0.069	0.131	0.160	0.384
Pathologic stage (≤T2 vs. >T2)	<0.0001	<0.0001	0.169	0.553	0.173	0.893	0.010	0.168
Nodal involvement (negative vs. positive)	<0.0001	0.018	0.955	0.866	0.097	0.286	0.144	0.484
No. of retrieved lymph nodes (>10 vs. ≤10)	0.644	0.533	0.778	0.726	0.209	0.374	0.876	0.685

Key: SCC = squamous cell carcinoma.
Data presented as P values.

TABLE IV. *Local recurrence rates and prognostic factors in contemporary series*

	Local Recurrence Rate (%)			
		Concurrent Distant Metastasis		
Reference	Total (%)	No	Yes	Prognostic Factor
Stein *et al.*[2]	NA	7.3 (77/1054)	NA	NA
Greven *et al.*[8]	15.7 (13/83)	NA	NA	Pathologic stage (T3-T4)
Pollack *et al.*[9]	13.2 (30/228)	NA	NA	Pathologic stage (T3-T4)
Schoenberg *et al.*[10]	5.0 (5/101)	1.0 (1/101)	4.0 (4/101)	NA
Tefilli *et al.*[11]	16.4 (33/201)	NA	NA	NA
Herr *et al.*[12]	15.8 (51/322)	NA	NA	No. of retrieved lymph nodes (<8)
Present study	18.6 (27/145)	5.5 (8/145)	13.1 (19/145)	Concomitant SCC component/pure SCC

Key: NA = not available; SCC = squamous cell carcinoma.
Data in parentheses are number of cases per number of analyzed patients.

despite the existence of clinical nodal involvement. In our study, 8 patients (5.5%) had local recurrence alone without distant metastasis and 19 patients (13.1%) had local recurrence with concurrent distant metastasis. These results are similar to those reported by others.[2,8–12] The most frequent site of local recurrence in the soft tissue and pelvic lymph nodes was the anterior rectal wall and obturator nodes, respectively. Although cystectomy and PLND were performed according to the standard surgical technique, it is possible that subtle differences existed in the surgical procedures among surgeons, although such assessment would be quite difficult. Incomplete excision of the bladder pedicle, perivesical fat, and pelvic lymph nodes may result in local recurrence. However, the pathologic stage, number of nodes retrieved, or nodal involvement did not contribute to local recurrence. Thus, other biologic parameters may be involved in the development of local recurrence, as described below.

Multivariate analysis using Cox's proportional hazard model showed that only a concomitant SCC component or pure SCC was an independent predictor of local recurrence alone. High-grade urothelial carcinoma is often associated with an SCC component. In addition, less-differentiated urothelial carcinoma is often difficult to distinguish from SCC histopathologically and biologically.[18–20] Our previous study revealed that some of the grade 3 urothelial carcinoma immunohisto-

chemically expressed SCC-associated antigen.[20] Thus, the SCC component may be linked with aggressive malignant potential.[21] Yamazaki *et al.*[22] reported that the expression of SCC-associated antigen in grade 3 pT1 urothelial carcinoma of the bladder was related to more frequent progression and intravesical recurrence. Serretta *et al.*[23] reported on 19 consecutive cases of pure SCC of the bladder that were not related to bilharziasis or spinal cord injury. Because 12 of the 19 patients died of locoregional recurrence, they concluded that SCC of the bladder prefers locoregional, rather than metastatic, spread. Thus, the existence of an SCC component may have a great impact on the development of local recurrence.

Although tumor spillage and incomplete excision of the tumor at cystectomy are definitely critical for local recurrence, the malignant potential of the cancer cells may play an important role in its development as well. Therefore, careful follow-up and aggressive adjuvant therapy should be considered for patients with these factors.

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Radical Cystectomy for Invasive Bladder Cancer: Results of Multi-institutional Pooled Analysis

Atsushi Takahashi[1], Taiji Tsukamoto[1], Ken-ichi Tobisu[2], Nobuo Shinohara[3], Kazunari Sato[4], Yoshihiko Tomita[5,*], Shu-ichi Komatsubara[6], Osamu Nishizawa[7], Tatsuo Igarashi[8], Hiroyuki Fujimoto[9], Hayakazu Nakazawa[10], Hideki Komatsu[11], Yoshiki Sugimura[12], Yoshinari Ono[13], Masao Kuroda[14], Osamu Ogawa[15], Yoshihiko Hirao[16], Tadashi Hayashi[17], Tomoyasu Tsushima[18], Yoshiyuki Kakehi[19], Yoichi Arai[20], Sho-ichi Ueda[21] and Masayuki Nakagawa[22]

Departments of Urology, [1]Sapporo Medical University School of Medicine, [2]Shizuoka Cancer Center Hospital, [3]Hokkaido University Graduate School of Medicine, [4]Akita University School of Medicine, [5]Niigata University Graduate School of Medicine and Dental Sciences, [6]Niigata Cancer Center Hospital, [7]Shinshu University School of Medicine, [8]Chiba University Graduate School of Medicine, [9]National Cancer Center Hospital, [10]Tokyo Women's Medical University School of Medicine, [11]Toranomon Hospital, [12]Mie University Faculty of Medicine, [13]Nagoya University Gradate School of Medicine, [14]Nissei Hospital, [15]Kyoto University Graduate School of Medicine, [16]Nara Medical University, [17]Japan Red Cross Wakayama Medical Center, [18]Okayama University Graduate School of Medicine and Dentistry, [19]Kagawa University Faculty of Medicine, [20]Tohoku University Graduate School of Medicine, [21]Kumamoto University School of Medicine and [22]Kagoshima University School of Medicine, Japan

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Background: We report the outcome of radical cystectomy for patients with invasive bladder cancer, who did not have regional lymph node or distant metastases, at 21 hospitals.
Methods: Retrospective, non-randomized, multi-institutional pooled data were analyzed to evaluate outcomes of patients who received radical cystectomy. Between 1991 and 1995, 518 patients with invasive bladder cancer were treated with radical cystectomy at 21 hospitals. Of these, 250 patients (48.3%) received some type of neoadjuvant and/or adjuvant therapy depending on the treatment policy of each hospital.
Results: The median follow-up period was 4.4 years, ranging from 0.1 to 11.4 years. The 5-year overall survival rate was 58% for all 518 patients. The 5-year overall survival rates for patients with clinical T2N0M0, T3N0M0 and T4N0M0 were 67%, 52% and 38%, respectively. The patients with pT1 or lower stage, pT2, pT3 and pT4 disease without lymph node metastasis had 5-year overall survivals of 81%, 74%, 47% and 38%, respectively. The patients who were node positive had the worst prognosis, with a 30% overall survival rate at 5 years. Neoadjuvant or adjuvant chemotherapy did not provide a significant survival advantage, although adjuvant chemotherapy improved the 5-year overall survival in patients with pathologically proven lymph node metastasis.
Conclusions: The current retrospective study showed that radical cystectomy provided an overall survival equivalent to studies reported previously, but surgery alone had no more potential to prolong survival of patients with invasive cancer. Therefore, a large-scale randomized study on adjuvant treatment as well as development of new strategies will be needed to improve the outcome for patients with invasive bladder cancer.

Key words: multi-institutional pooled analysis – radical cystectomy – invasive bladder cancer

INTRODUCTION

Radical cystectomy has been considered the standard curative treatment for invasive bladder cancer all over the world (1,2). Recent improved surgical techniques in addition to development of perioperative care and anesthesia have reduced morbidity and mortality. Furthermore, advances in orthotopic urinary tract reconstruction have improved the quality of life of

*Present address: Yamagata University School of Medicine

For reprints and all correspondence: Taiji Tsukamoto, Department of Urology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-Ku, Sapporo 060-8543, Japan. E-mail: taijit@sapmed.ac.jp