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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References

1. Kakizoe T, Yamaguchi N, Mitsuhashi F, Koshiji M, Oshima A, Ohtaka M. Cancer Statistics in Japan – 2001. Tokyo: Foundation for Promotion of Cancer Research, 2001, p. 38.
2. Schoenberg M. Management of invasive and metastatic bladder cancer. In Walsh PC, Retik AB, Stamey TA, Vaughan ED Jr, editors: Campbell's Urology, 8th edn. Philadelphia: WB Saunders Co, 2002, pp 2803–17.
3. 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;349:859–66.
4. Advanced bladder cancer (ABC) meta-analysis collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927–34.
5. The Japanese Urological Association and Japanese Society of Pathology. The General Rules for Clinical and Pathological Studies on Bladder Cancer, 3rd edn. Tokyo: Kaneharashuppan, 2001.
6. Soloway MS, Soffer M, Vaidya A. Contemporary management of stage T1 transitional cell carcinoma of the bladder. *J Urol* 2002;167:1573–83.
7. van der Meijden A, Sylvester R, Collette L, Bono A, Kate FT. The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer Trials. *J Urol* 2000;164:1533–7.
8. Jichlinski P. New diagnostic strategies in the detection and staging of bladder cancer. *Curr Opin Urol* 2003;13:351–5.
9. *Barentsz JO, Witjes A, Ruijs JHJ.* What is new in bladder cancer imaging. *Urol Clin N Am* 1997;24:583–602.
10. Shvarts O, Han KR, Seltzer M, Pantuck AJ, Belldegrun AS. Positron emission tomography in urologic oncology. *Cancer Control* 2002;9:335–42.
11. Shigyo M, Sugano K, Tobisu K, Tsukamoto T, Sekiya T, Kakizoe T. Molecular followup of newly diagnosed bladder cancer using urine samples. *J Urol* 2001;166:1280–5.
12. Quek ML, Quinn DI, Daneshmad S, Stein JP. Molecular prognostication in bladder cancer – a current perspective. *Eur J Cancer* 2003;39:1501–10.
13. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999;161:1494–7.
14. Dalbagni G, Genega E, Hashibe M, Zhang Z, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001;165:1111–6.
15. 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;19:666–75.
16. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al. Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003;21:690–6.
17. Nishiyama H, Habuchi T, Watanabe J, Teramukai S, Tada H, Ono Y, et al. Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990–2000 in Japan. *Eur Urol* 2004;45:176–81.
18. Takahashi A, Tsukamoto T, Tobisu K, Shinohara N, Satoh K, Tomita Y, et al. Radical cystectomy for invasive bladder cancer: results of multi-institutional pooled analysis. *Jpn J Clin Oncol* 2004;34:14–9.
19. Skinner DG, Stein JP, Lieskovsky G, Skinner EC, Boyd SD, Figueroa A, et al. 25-year experience in the management of invasive bladder cancer by radical cystectomy. *Eur Urol* 1998;33(Suppl 4):25–6.
20. Esrig D, Freeman JA, Elmajian DA, Stein JP, Chen S, Groshen S, et al. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. *J Urol* 1996;156:1071–6.
21. Erckert M, Stenzl A, Falk M, Bartsch G. Incidence of urethral tumor involvement in 910 men with bladder cancer. *World J Urol* 1996;14:3–8.
22. Kakizoe T, Tobisu K. Transitional cell carcinoma of the urethra in men and women associated with bladder cancer. *Jpn J Clin Oncol* 1998;28:357–9.
23. Hickey DP, Soloway MS, Murphy WM. Selective urethrectomy following cystoprostatectomy for bladder cancer. *J Urol* 1986;136:828–30.
24. Lin DW, Herr HW, Dalbagni G. Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. *J Urol* 2003;169:961–3.
25. Hautmann RE, Miller K, Steiner U, Wenderroth U. The ileal neobladder: 6 years of experience with more than 200 patients. *J Urol* 1993;150:40–5.
26. Studer UE, Danuser H, Merz VW, Springer JP, Zingg EJ. Experience in 100 patients with an ileal low pressure bladder substitute combined with an afferent tubular isoperistaltic segment. *J Urol* 1995;154:49–56.
27. Freeman J, Tarter TA, Esrig D, Stein JP, Elmajian DA, Chen SC, et al. Urethral recurrence in patients with orthotopic ileal neobladders. *J Urol* 1996;156:1615–9.
28. Tobisu K, Kanai Y, Sakamoto M, Fujimoto H, Doi N, Horie S, et al. Involvement of the anterior urethra in male patients with transitional cell carcinoma of the bladder undergoing radical cystectomy with simultaneous urethrectomy. *Jpn J Clin Oncol* 1997;27:406–9.
29. Coloby PJ, Kakizoe T, Tobisu K, Sakamoto M. Urethral involvement in female bladder cancer patients: mapping of 47 consecutive cysto-urethrectomy specimens. *J Urol* 1994;152:1438–42.
30. Stenzl A, Draxl H, Posch B, Colleselli M, Falk M, Bartsch G. The risk of urethral tumors in female bladder cancer: Can the urethra be used for orthotopic reconstruction of the lower urinary tract? *J Urol* 1995;153:950–5.
31. Stein JP, Ginsberg DA, Skinner DG. Indications and technique of the orthotopic neobladder in women. *Urol Clin North Am* 2002;29:725–34.
32. Shekarriz B, Pontes JE. Management of poor risk patients with muscle-invasive transitional cell carcinoma of the bladder. *AUA Update Series* 2001;20:90–5.
33. Shekarriz B, Shekarriz H, Upadhyay J, Banerjee M, Becker H, Pontes JE, et al. Outcome of palliative urinary diversion in the treatment of advanced malignancies. *Cancer* 1999;85:998–1003.
34. Nishiyama N, Masumori N, Satoh E, Takahashi A, Itoh N, Tsukamoto T. Role of cystectomy for patients with invasive bladder cancer having metastasis. Hinyoki *Geka* 2003;16:1195–9 (in Japanese).
35. Bochner BH, Herr HW, Reuter VE. Impact of separate versus en block pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. *J Urol* 2001;169:2295–6.
36. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol* 1998;160:2015–20.
37. Leissner J, Ghoneim MA, Abol-Enein H, Thuroff JW, Franzaring L, Fisch M, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol* 2004;171:139–44.
38. Oosterlinck W, Lobel B, Jakse G, Malmstrom P-U, Stockle M, Sternberg C. Guidelines on bladder cancer. European Association of Urology Guidelines. Arnhem (the Netherlands): European Association of Urology, 2001, p.12.
39. Leissner L, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 2000;85:817–23.
40. Weingarter K, Ramaswamy A, Bittinger A, Gerharz EW, Voge D, Riedmiller H. Anatomical basis for pelvic lymphadenectomy in prostate cancer: results of an autopsy study and implications for the clinic. *J Urol* 1996;156:1969–71.
41. Herr HW. Superiority of ratio based lymph node staging for bladder cancer. *J Urol* 2003;169:943–5.
42. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en block pelvic lymphadenectomy: the concept of lymph node density. *J Urol* 2003;170:35–41.
43. Frank I, Cheville JC, Blute ML, Lohse CM, Nehra A, Weaver AL, et al. Transitional cell carcinoma of the urinary bladder with regional lymph node involvement treated by cystectomy. *Cancer* 2003;97:2425–31.

44. Herr HW, Bochner BH, Dalbagni G, Donat M, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002;167:1295–8.
45. Konety BR, Joslyn SA, O'Donnel MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer; analysis of data from the Surveillance, Epidemiology, and End Results Program data base. *J Urol* 2003;169:946–50.
46. Herr HW. Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. *Urology* 2003;61:105–8.
47. Herr HW. Surgical factors in bladder cancer: more (nodes) + more (pathology) = less (mortality). *BJU Int* 2003;92:187–8.
48. Cole CJ, Pollack A, Zangers GK, Dinney CP, Swanson DA, von Eschenbach AC. Local control of muscle-invasive bladder cancer: preoperative radiotherapy versus cystectomy alone. *Int J Radiat Oncol Biol Phys* 1995;32:331–40.
49. Bochner BH, Montie JE, Lee CT. Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. *Urol Clin N Am* 2003;30:777–89.
50. Schuster TG, Smith DC, Montie JE. Pelvic recurrences post cystectomy: current treatment strategies. *Sem Urol Oncol* 2001;19:45–50.
51. Thalman GN, Fleishman A, Mills RD, Burkhard FC, Markwalder R, Studer UE. Lymphadenectomy in bladder cancer. *EAU Update Series* 2003;1:100–7.
52. Westney OL, Pister LL, Pettaway CA, Tu S-M, Pollack A, Dinney CPN. Presentation, methods of diagnosis and therapy for pelvic recurrence following radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 1998;159:792–5.
53. Smith JA Jr, Crawford ED, Paradelo JC, Blumenstein B, Herschman BR, Grossman HB, et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. *J Urol* 1997;157:805–8.
54. Crawford ED, Wood DP, Petrylak DP, Scott J, Coltman CA Jr, Raghaven D. Southwest Oncology Group studies in bladder cancer. *Cancer* 2003; 97(Suppl 8):2099–108.
55. Juffs HG, Moore MJ, Tannock F. The role of systemic chemotherapy in the management of muscle-invasive bladder cancer. *Lancet Oncol* 2002;3: 738–47.
56. 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: a prospective comparative trial. *J Urol* 1991;145:459–64.
57. Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol* 1994;152:81–4.
58. Stockle M, Wellek S, Meyenburg W, Voges GE, Fischer U, Gertenbach U, et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: prognostic impact of lymph node involvement. *Urology* 1996;48:868–75.
59. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996;155:495–500.
60. National Cancer Institute, Bethesda, MD, USA. 2003. http://www.nci.nih.gov/search/clinical_trials/results_clinicaltrials.aspx, accessed October 2003.
61. Martinez-Pineiro JA, Martin GM, Arocena F, Flores N, Roncero CR, Portillo JA, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol* 1995;153:964–73.
62. Malmström PU, Rintala E, Wahlqvist R, Hellström P, Hellsten S, Hannisdal E. Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol* 1996;155: 1903–6.
63. Bassi P, Pagano F, Pappagallo G, Cosciani S, Lembo A, Anselmo G, et al. Neoadjuvant M-VAC chemotherapy of invasive bladder cancer: the G.U.O.N.E. multicenter phase II trial. *Eur Urol* 1998;33(Suppl 1):142.
64. International collaboration of trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party, EORTC Genito-Urinary Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder Norwegian Bladder Cancer Study Group and Club Urologico Espanol de Tratamiento Oncologico (CUETO) group. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomized control trial. *Lancet* 1999;354:533–40.
65. Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer. Nordic Cystectomy Trial 2. *Scand J Urol Nephrol* 2002;6:419–25.
66. Sternberg CN, Yogoda HI, Watson RC, Herr HW, et al. Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the uroepithelium; efficacy and patterns of response and relapse. *Cancer* 1989;64:2448–58.
67. Harker WG, Meyers FJ, Freiha FS, Palmer JM, Shortliffe LD, Hannigan JF, et al. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. *J Clin Oncol* 1985;3:1463–70.
68. Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992;10: 1066–73.
69. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1997;15:2564–9.
70. Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with advanced metastatic urothelial tumors. *J Clin Oncol* 1990;8:1050–5.
71. Loehrer PJ Sr, Elson P, Dreicer R, Hahn R, Nichols CR, Williams R, et al. Escalated dosages of methotrexate, vinblastine, doxorubicin, and cisplatin plus recombinant human granulocyte colony-stimulating factor in advanced urothelial carcinoma: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1994;12:483–8.
72. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T, and the Japanese Urothelial Cancer Research Group. Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). *Jpn J Clin Oncol* 1998;28:497–506.
73. Bellmunt J, Guillem V, Paz-Ares L, Gonzalez-Larriba JL, Carles J, Batiste-Alentorn E, et al. Phase I-II study of paclitaxel, cisplatin and gemcitabine in advanced transitional cell carcinoma of the urothelium. *J Clin Oncol* 2000;18:3247–55.
74. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol* 2001;19:2527–33.
75. Meluch AA, Greco FA, Burris HA 3rd, O'Rourke T, Ortega G, Steis RG, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2001;15:3018–24.
76. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatinum in advanced or metastatic bladder cancer: results of a large randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;17:3068–77.
77. Cohen MH, Rothmann M. Correspondence: Gemcitabine and cisplatin for advanced, metastatic bladder cancer. *J Clin Oncol* 2001;19:1229–31.
78. Hussain SA, James ND. The systemic treatment of advanced and metastatic bladder cancer. *Lancet Oncol* 2003;4:489–97.
79. Bamias A, Aravantionos G, Deliveliotis C, Bafaloukos D, Kalofomos C, Xiros N, et al. Docetaxel and cisplatin with granulocyte-colony stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol* 2004;22:220–8.
80. de Wit R. Overview of bladder cancer trials in the European Organization for Research and Treatment. *Cancer* 2003;97(Suppl 8):2120–6.
81. Montie JE. Against bladder sparing: surgery. *J Urol* 1999;162:452–7.
82. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol* 1987;138:1162–3.
83. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol* 2001;19:89–93.
84. Roosen JU, Geertsen U, Hahn H, Jorgen J, Weinreich J, Nissen HM. Invasive, high grade transitional cell carcinoma of the bladder treated

with transurethral resection – a survival analysis focusing on TUR as monotherapy. *Scand J Urol Nephrol* 1997;31:39–42.
85. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Calabuig C. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term follow-up of a prospective study. *J Urol* 1998;159:95–9.
86. Gospodarowicz MK, Warde PR. A critical review of the role of definitive radiation therapy in bladder cancer. *Semin Urol* 1993;4:214–26.
87. Angulo JC, Sanchez-Chapado M, Lopez JI, Flores N. Primary cisplatin, methotrexate and vinblastine aiming at bladder preservation in invasive bladder cancer: multivariate analysis on prognostic factors. *J Urol* 1996; 155:1897–1902.
88. Scattoni V, Da Pozzo L, Nava L, Broglia L, Galli L, Torelli T, et al. Five-year results of neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy plus radical cystectomy in locally advanced bladder cancer. *Eur Urol* 1995;28:102–7.
89. Galetti TP, Pontes JE, Montie J, Medendorp SV, Bukowski R. Neoadjuvant intra-arterial chemotherapy in the treatment of advanced transitional cell carcinoma of the bladder: results and followup. *J Urol* 1989;142: 1211–5.
90. Jacobs SC, Menashe DS, Mewissen MW, Lipchik EO. Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. *Cancer* 1989;64:388–91.
91. Tester W, Caplan R, Heaney J, Venner P, Whittington R, Byhardt R, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. *J Clin Oncol* 1996;14:119–26.
92. Kachnic LA, Kaufman DS, Heney NM, Althausen AF, Griffin PP, Zietman AL, et al. Bladder preservation by combined modality therapy for invasive bladder cancer. *J Clin Oncol* 1997;15:1022–9.
93. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol* 1998;16:3576–83.
94. Rödel C, Gerhard G, Grabenbauer GG, Kühn R, Papadopoulos T, Dunst J, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002;20:3061–71.
95. Mokarim A, Uetani M, Hayashi N, Sakamoto I, Minami K, Ogawa Y, et al. Combined intraarterial chemotherapy and radiotherapy in the treatment of bladder carcinoma. *Cancer* 1997;80:1776–85.
96. Sumiyoshi Y, Hashine K, Karashima T, Kasahara K, Inoue Y. Preliminary results of bladder preservation by concurrent intraarterial chemotherapy and radiotherapy for muscle-invasive bladder cancer. *Int J Urol* 1998;5: 225–9.
97. Miyanaga N, Akaza H, Okumura T, Sekido N, Kawai K, Shimazui T, et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective pilot study. *Int J Urol* 2000;7:41–8.
98. Tsukamoto S, Ishikawa S, Tsutsumi M, Nakajima K, Sugahara S. An organ-sparing treatment using combined intra-arterial chemotherapy and radiotherapy for muscle-invading bladder carcinoma. *Scand J Urol Nephrol* 2002;36:339–43.
99. Kuczyk M, Turkeri L, Hammerer P, Ravery V. Is there a role for bladder preserving strategies in the treatment of muscle-invasive bladder cancer? *Eur Urol* 2003;44:57–64.
100. Shipley WU, Kaufman DS, Zehr NM, Heney NM, Lane SC, Thakral HK, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002;60:62–8.
101. Montie JE. Editorial comment. *Urology* 2002;60:67.
102. Gospodarowicz M. Radiotherapy and organ preservation in bladder cancer: are we ignoring the evidence? *J Clin Oncol* 2002;20:3048–50.

ELSEVIER

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

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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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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.

REFERENCES

1. Herr HW: Uncertainty and outcome of invasive bladder tumors. Urol Oncol 2: 92–95, 1996.

2. Stein JP, Lieskovsky G, Cote R, *et al:* Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 19: 666–675, 2001.

3. Whitmore WF Jr: Management of invasive bladder neoplasms. Semin Urol 1: 34–41, 1983.

4. Sobin LH, and Wittekind CH: *TNM Classification of Malignant Tumors,* 5th ed. New York, Wiley-Liss, 1997.

5. Mostofi FK, Davis CJ, and Sesterhenn IA: *Histological Typing of Urinary Bladder Tumours,* 2nd ed. New York, Springer, 1999.

6. Thrasher JB, Frazier HA, Robertson JE, *et al:* Does a stage pT0 cystectomy specimen confer a survival advantage in patients with minimally invasive bladder cancer? J Urol 152: 393–396, 1994.

7. Cole CJ, Pollack A, Zagars GK, *et al:* Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. Int J Radiat Oncol Biol Phys 32: 331–340, 1995.

8. Greven KM, Spera JA, Solin LJ, *et al:* Local recurrence after cystectomy alone for bladder carcinoma. Cancer 69: 2767–2770, 1992.

9. Pollack A, Zagars GK, Cole CJ, *et al:* The relationship of local control to distant metastasis in muscle invasive bladder cancer. J Urol 154: 2059–2064, 1995.

10. Schoenberg MP, Walsh PC, Breazeale DR, *et al:* Local recurrence and survival following nerve sparing radical cystoprostatectomy for bladder cancer: 10-year followup. J Urol 155: 490–494, 1996.

11. Tefilli MV, Gheiler EL, Tiguert R, *et al:* Urinary diversion-related outcome in patients with pelvic recurrence after radical cystectomy for bladder cancer. Urology 53: 999–1004, 1999.

12. Herr HW, Bochner BH, Dalbagni G, *et al:* Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol 167: 1295–1298, 2002.

13. Bassi P, Ferrante GD, Piazza N, *et al:* Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 161: 1494–1497, 1999.

14. Gschwend JE, Dahm P, and Fair WR: Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. Eur Urol 41: 440–448, 2002.

15. Dalbagni G, Genega E, Hashibe M, *et al:* Cystectomy for bladder cancer: a contemporary series. J Urol 165: 1111–1116, 2001.

16. Millis RD, Turner WH, Fleischmann A, *et al:* Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol 166: 19–23, 2001.

17. Poulsen AL, Horn H, and Steven K: Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 160: 2015–2020, 1998.

18. Tannenbaum SI, Carson CC, Tatum A, *et al:* Squamous cell carcinoma of urinary bladder. Urology 22: 597–599, 1983.

19. Grignon DJ: Neoplasms of the urinary bladder, in Bostwick DG, and Eble JN (Eds): *Urologic Surgical Pathology.* St. Louis, Mosby, 1997, pp 215–305.

20. Tsukamoto T, Kumamoto Y, Ohmura K, *et al:* Squamous cell carcinoma-assisted antigen in uroepithelial carcinoma. Urology 40: 477–483, 1992.

21. Takai K, Kakizoe T, Tobisu K, *et al:* Clinical significance of the presence of squamous cell carcinoma in transitional cell carcinoma of the urinary bladder. Nippon Hinyokika Gakkai Zasshi 79: 1837–1847, 1988.

22. Yamazaki K, Kumamoto Y, and Tsukamoto T: Expression of squamous cell carcinoma-associated antigen in grade 3 pT1 transitional cell carcinoma of the bladder and prediction of its progression and intravesical recurrence. Cancer 72: 3676–3684, 1993.

23. Serretta V, Pomara G, Piazza F, *et al:* Pure squamous cell carcinoma of the bladder in western countries. Eur Urol 37: 85–89, 2000.

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

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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

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patients undergoing radical cystectomy. However, while about half of patients are cured, the remainder still suffer from local recurrence and distant metastasis within 2–3 years. Thus, in an attempt to improve treatment outcome, many investigators have tried combinations of neoadjuvant or adjuvant chemotherapy with surgery (3–5). Unfortunately, the impact of neoadjuvant or adjuvant chemotherapy on survival remains controversial. Recently, the South Western Oncology Group (SWOG) showed an improvement in overall survival with three cycles of neoadjuvant chemotherapy consisting of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) (6). Furthermore, more recent meta-analysis demonstrated that neoadjuvant chemotherapy provided a significant survival advantage in patients with invasive bladder cancer (7).

In this study, we evaluate outcomes of patients with invasive bladder cancer who underwent radical cystectomy with/without pelvic lymph node dissection in 21 hospitals.

PATIENTS AND METHODS

This study included 518 patients with clinically invasive bladder cancer without regional lymph node or distant metastases (T2–4N0M0). All were treated with radical cystectomy with/without pelvic lymph node dissection at 21 hospitals between 1991 and 1995. Using these data, non-randomized, multi-institutional pooled data were analyzed to evaluate the treatment results of radical cystectomy. Tumors were staged according to the criteria of the 3rd edition of General Rules for Clinical and Pathological Studies on Bladder Cancer of the Japanese Urological Association and Japanese Society of Pathology (8). Urothelial carcinoma was the predominant histological type in all patients. Patients with pure squamous cell carcinoma and adenocarcinoma were excluded from this study. Because the pathology of surgical specimens was not reviewed by central pathologist(s), tumor grade was not included in this analysis.

Almost half of the patients received some type of neoadjuvant and/or adjuvant therapy. The type and dose of the additional therapy depended on each institution's preference.

The overall survival was calculated from the date of operation to death from any cause. The overall survival rate was calculated by the Kaplan–Meier method. The statistical significance of differences was determined by the log-rank test. Spearman's rank correlation test was used to analyze correlations between two factors. A P-value of <0.05 was considered statistically significant. All analyses were performed using StatView 5.0 for Macintosh (SAS Institute, NC, USA).

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. More than two-thirds of the patients were male. The mean age at operation was 65.4 years (range, 33–87 years). Half of the patients had a clinical stage of T2N0M0. Pathological examination revealed that patients with pT2 and pT3 accounted for almost 60% of the total, followed by those with pT1 and lower stages and those with pT4. Nearly 90% of patients received lymph node dissection. Lymph node metastasis was histopathologically proven in 86 patients (16.6%), who accounted for 18.4% of those who received node dissection (Table 2). Its incidence was significantly linked with clinical stage ($P < 0.01$ by Spearman's rank correlation test). The incidence clearly increased with progression of the pathological stage from 5.9% in patients with superficial cancer to 32.5% of those with pT4 ($P < 0.01$ by Spearman's rank correlation test).

Table 1. Patient characteristics

Characteristics		No. of patients (%)
Gender	Male	400 (77.2)
	Female	118 (22.8)
Age (years)	33–87 (mean: 65.4)	
Clinical T classification	T2	271 (52.3)
	T3	178 (34.4)
	T4	69 (13.3)
Pathological T classification	≤pT1	119 (23.0)
	pT2	156 (30.2)
	pT3	152 (29.4)
	pT4	90 (17.4)
Lymph node metastasis	pNx	53 (10.2)
	pN0	379 (73.2)
	≥pN1	86 (16.6)
Additional therapy	No	268 (51.7)
	Yes	250 (48.3)
Type of additional therapy	Neoadjuvant	118 (47.2)
	Adjuvant	85 (34.0)
	Neoadjuvant and adjuvant	47 (18.8)

Neoadjuvant and/or adjuvant therapies were performed for 48.3% of 518 patients together with radical cystectomy (Table 3). Of these, 118 patients (47.2%) received some type of therapy in the neoadjuvant setting. These included systemic chemotherapy for 80 patients, intraarterial chemotherapy for 32, radiation for one and combined systemic chemotherapy and local radiation for five. Among the systemic chemotherapies, MVAC, the most popular regimen for urothelial cancer (9), was frequently used. In the adjuvant setting, systemic chemotherapy was administered most frequently. More than half of the patients received MVAC chemotherapy.

Outcome

The follow-up period ranged from 0.1 to 11.4 years with a median of 4.4 years. The 5-year overall survival rate was 58% for all 518 patients (Fig. 1), 67% for patients with clinical T2N0M0, 52% for those with T3N0M0 and 38% for those with T4N0M0 (Fig. 2). According to pathological stage, the 5-year

Table 2. Relationships among clinical stage, pathological stage and lymph node metastasis

Clinical stage	Pathological stage	No. of patients with radical cystectomy	No. of pathologically node positive patients/no. of patients with node dissection (%)
T2	pT0	26	1/24 (4.1)
	≤pT1	54	4/48 (8.3)
	pT2	110	8/101 (7.9)
	pT3	57	20/53 (37.7)
	pT4	23	6/19 (31.5)
	All	270	39/245 (15.9)
T3	pT0	7	0/4 (0)
	≤pT1	23	2/18 (11.1)
	pT2	41	2/36 (5.5)
	pT3	78	15/71 (21.1)
	pT4	29	9/28 (32.1)
	All	178	28/157 (17.8)
T4	pT0	5	0/5 (0)
	≤pT1	4	0/3 (0)
	pT2	5	2/5 (40.0)
	pT3	17	5/16 (31.2)
	pT4	38	12/36 (33.3)
	All	69	19/65 (29.2)
T2–4	≤pT1	119	7/119 (5.9)
	pT2	156	12/142 (8.4)
	pT3	152	40/140 (28.5)
	pT4	90	27/83 (32.5)

$P < 0.01$ (Spearman's rank correlation test).

Table 3. Type of additional therapy

Type		No. of courses (median)	No. of patients
Neoadjuvant			118
Systemic chemotherapy	MVAC*	1–4 (2)	49
	MEC*	1–4 (2)	13
	CDDP-based chemotherapy	1–2 (2)	18
Local therapy	Intraarterial chemotherapy (CDDP-based)	1–2 (1)	32
	Radiation only		1
Systemic and local therapy	Chemotherapy and radiation		5
Adjuvant			85
Systemic chemotherapy	MVAC	1–4 (2)	48
	CISCA*	1–3 (2)	5
	MEC	1–2 (2)	4
	CDDP-based chemotherapy	1–6 (2)	24
	Others		4
Neoadjuvant and adjuvant			47
Intraarterial→systemic			13
Systemic and radiation→systemic			4
Systemic→systemic			30

*MVAC, methotrexate, vincristine, doxorubicin and cisplatin, (21); MEC, methotrexate, epirubicin and cisplatin, (22); CISCA, cisplatin, cyclophosphamide and doxorubicin.

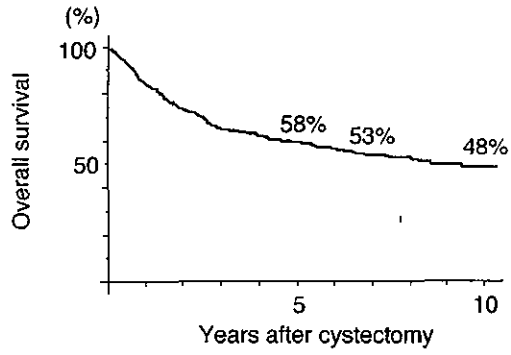

Figure 1. Overall survival rate in all 518 patients.

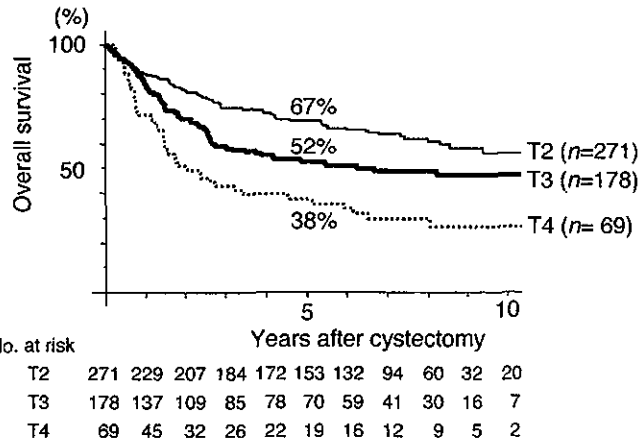

Figure 2. Overall survival rate according to clinical stage. T2 versus T3, $P < 0.01$; T2 versus T4, $P < 0.001$; T3 versus T3, $P < 0.01$ (log-rank test).

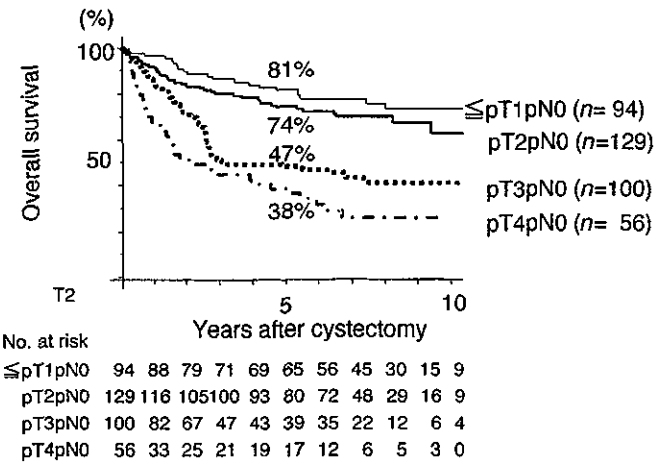

Figure 3. Overall survival rate according to pathological stage. ≦pT1pN0 versus pT3pN0, pT4pN0, $P < 0.001$; pT2pN0 versus pT3pN0, pT4pN0, $P < 0.001$; pT3pN0 versus pT4pN0, $P = 0.02$ (log-rank test).

overall survival rate was significantly higher for patients with pT1 or a lower stage, or pT2 than for those with pT3 or pT4 disease, when those who were pathologically node negative were considered (Fig. 3). Patients who were pathologically proven to be node positive clearly had a lower 5-year overall

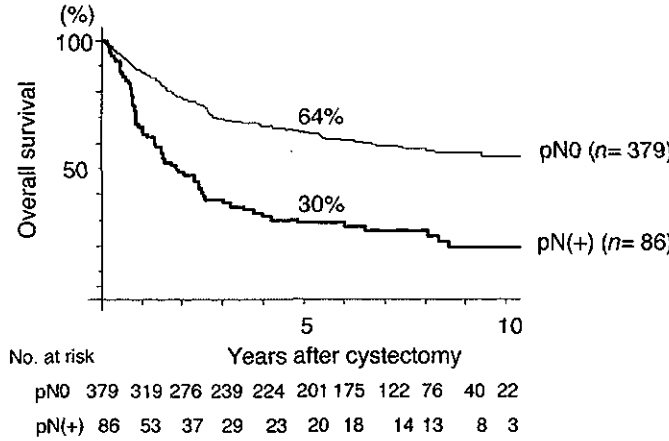

Figure 4. Overall survival rate according to lymph node metastasis. pN0 versus pN(+), $P < 0.001$ (log-rank test).

survival rate (30%) than those who were node negative (Fig. 4, $P < 0.001$ by log-rank test).

Impact of Additional Therapy

When we evaluated whether neoadjuvant chemotherapy could improve survival, there was no significant difference with regard to the 5-year overall survival between patients with and without the therapy (65% versus 56%, $P = 0.13$ by log-rank test) (Fig. 5). Furthermore, neoadjuvant chemotherapy did not influence the overall survival among all clinical stages. Similarly, adjuvant chemotherapy did not improve the prognosis because the 5-year overall survival rates for all patients with and without this therapy were 57% and 56%, respectively. When we investigated the influence of adjuvant chemotherapy on the 5-year overall survival in patients with pT2 or a lower stage without lymph node metastasis, there was no significant difference between patients with and without the therapy. No survival benefit was found for the therapy in patients with pT3 or pT4 without pathologically proven lymph node metastasis. However, the therapy improved the 5-year overall survival in patients with lymph node metastasis, with a significant difference between those with and without it ($P < 0.001$, by log-rank test) (Fig. 6).

DISCUSSION

In this study we evaluated the treatment outcomes of patients with invasive bladder cancer who underwent radical cystectomy with/without pelvic lymph node dissection in 21 hospitals from 1991 to 1995. The study enabled us to analyze the 5-year survival rates of a large volume of patients. The analysis showed that the 5-year overall survival rate for patients with T2N0M0, T3N0M0 and T4N0M0 tumors were 67%, 52% and 38%, respectively. These results are similar to/better than a previous report that the 5-year survival rates were 49% (95% CI: 39–59%) for patients with T2, 25% (95% CI: 10–50%) for those with T3 and 17% (95% CI: 5–45%) for those with T4,

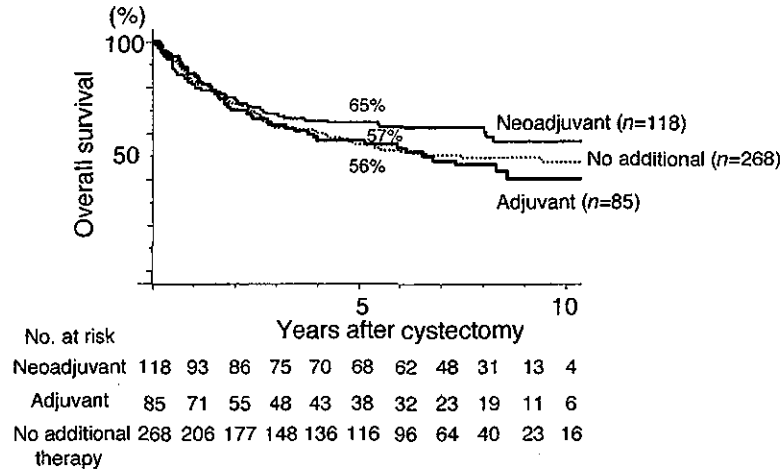

Figure 5. Overall survival rate according to additional therapy. Neoadjuvant versus no additional therapy, $P = 0.13$ (log-rank test); adjuvant versus no additional therapy, $P = 0.72$ (log-rank test).

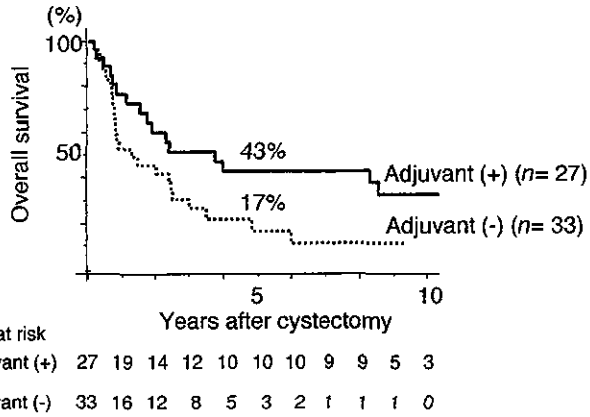

Figure 6. Overall survival rate according to adjuvant therapy in patients with lymph node metastasis. Adjuvant (+) versus adjuvant (–), $P = 0.03$ (log-rank test).

although this report was published 10 years ago (10). Similarly, the analysis according to pathological stage revealed results consistent with those in previous studies showing that the 5-year survival was 76–85% for pT1 or lower stage, 64–84% for pT2pN0, 25–56% for pT3pN0 and 19–44% for pT4pN0 (1,11,12). In Japan, the analysis of 351 patients who underwent radical cystectomy at a single institute showed a similar result (13).

In the present study pathologically proven lymph node metastasis was seen in 18% of patients with lymph node dissection. Some reports indicated that lymph node metastasis was present in 15–34% of patients who underwent radical cystectomy (10,14–16). The variation in the incidence of positive nodes may stem from the heterogeneous profiles of patients, extent of lymph dissection, and the number of lymph nodes removed. Indeed, Leissner et al. (14) reported a correlation between the number of lymph nodes removed (≥16 lymph nodes) and the percentage of patients with positive nodes, especially in locally advanced bladder cancer. Lymph node metastasis is reported to be an independent poor prognostic factor (14–16). Our study supported previous results since the present study also showed that patients with positive nodes had a worse prognosis. Recently, the number of positive lymph nodes, rather than the size, was reported to be associated with death from bladder cancer (15,16). Unfortunately we did not assess the number of lymph nodes in this study. Further study will be necessary to confirm these results. At present it remains controversial whether lymph node dissection has a therapeutic effect or is merely a staging tool. Some investigators advocate extensive bilateral lymphadenectomy as a potentially curative procedure (14,16).

Since the 5-year survival rate with radical cystectomy alone seems to reach a plateau, especially in patients with locally advanced bladder cancer, various trials of additional treatments before and/or after surgery have been carried out (3–5). Unfortunately, it remains undefined whether neoadjuvant or adjuvant chemotherapy with surgery improves the survival (17). However, in the SWOG study, patients with three cycles of neoadjuvant MVAC achieved survival benefit with the median survival of 77 months, as compared with 46 months among patients with surgery alone, although the difference was not significant when it was analyzed by a two-sided stratified log-rank test (6). Furthermore, more recent meta-analysis demonstrated that neoadjuvant cisplatin-based combination chemotherapy provided a survival advantage over a definitive local therapy (7). Our group started a prospective phase III study evaluating the survival benefit of two cycles of MVAC followed by surgery over surgery alone in patients with T2–4N0M0 bladder cancer with the support of the Japanese Clinical Oncology Group.

On the other hand, our retrospective study showed that patients with lymph node metastasis had a survival benefit from adjuvant chemotherapy, although only a small number of patients were included. Some investigators also reported the impact of adjuvant chemotherapy on survival of these patients in retrospective studies (15,16). Furthermore, prospective studies demonstrated a significant survival benefit (18–20). However, these studies were criticized due to their small

numbers of patients, early termination of trials and confusing methodology for analysis. Therefore, the role of adjuvant chemotherapy remains a matter of debate. To evaluate the impact of immediate adjuvant chemotherapy after cystectomy, the European Organization for Research and Treatment of Cancer has launched a large randomized trial that plans to enroll 1344 patients. In the near future its results will tell us whether immediate adjuvant chemotherapy is necessary in high-risk patients.

In summary, our retrospective, multi-institutional analysis showed that radical cystectomy provided an overall survival for patients with clinically invasive bladder cancer similar to that of previous reports. Thus, it is clear that surgery alone will not provide better survival than we have now. Therefore, additional therapy is mandatory to improve the treatment outcome. Further large-scale randomized studies will be needed to clarify the timing and type of additional therapy.

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References

1. Schoenberg M. Management of invasive and metastatic bladder cancer. In Walsh PC, et al., editors. Campbell's Urology, 8th edition. Philadelphia: Saunders, 2002;2803–17.
2. Carrion R, Seigne J. Surgical management of bladder carcinoma. *Cancer Control* 2002;9:284–92.
3. Dreicer R. Neoadjuvant chemotherapy in the management of muscle-invasive bladder cancer. *Semin Urol Oncol* 2001;19:180–85.
4. Lehmann J, Retz M, Stockle M. The role of adjuvant chemotherapy for locally advanced bladder cancer. *World J Urol* 2001;19:133–40.
5. Sternberg CN. Neo-adjuvant and adjuvant chemotherapy of bladder cancer: Is there a role? *Ann Oncol* 2002;13(Suppl 4):273–9.
6. 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;349:859–66.
7. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361:1927.
8. Japanese Urological Association, Japanese Society of Pathology. General Rules for Clinical and Pathological Studies on Bladder Cancer, 3rd edition. Tokyo: Kanehara 2001 (in Japanese).
9. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, et al. Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989;64:2448–58.
10. Paulson DF. Critical review of radical cystectomy and indicators of prognosis. *Sem Urol* 1993;11:205–13.
11. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. *J Urol* 2001;165:1111–6.
12. 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;19:666–75.
13. Kuroda M, Meguro N, Maeda O, Saiki S, Kinouchi T, Usami M, Kotake T. Stage specific follow-up strategy after cystectomy for carcinoma of the bladder. *Int J Urol* 2002;9:129–33.
14. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int* 2000;85:817–23.
15. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. *J Urol* 2003;170:35–41.
16. Frank I, Cheville JC, Blute ML, Lohse CM, Nehra A, Weaver AL, et al. Transitional cell carcinoma of the urinary bladder with regional lymph node involvement treated by cystectomy: clinicopathologic features associated with outcome. *Cancer* 2003;97:2425–31.
17. Juffs HG, Moore MJ, Tannock IF. The role of systemic chemotherapy in the management of muscle-invasive bladder cancer. *Lancet Oncol* 2002;3:738–47.
18. 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: a prospective comparative trial. *J Urol* 1991;145:459–64.
19. Stockle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol* 1995;153:47–52.
20. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996;155:495–9.
21. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T. Efficacy of dose-intensified MEC (Methotrexate, Epirubicin, Cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin). *Jpn J Clin Oncol* 1998;28:497–501.
22. Lynch DF Jr. Preoperative and postoperative adjuvant chemotherapy using CISCA (cyclophosphamide, doxorubicin, and cisplatin) in the treatment of invasive transitional-cell carcinoma of the bladder. *Urol Clin North Am* 1991;18:543–6.

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The Same-Pedicle Concept for Continent Urinary Diversion Using a Yang-Monti Reconfigured Tube

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Key Words

Continent valve · Diversion, urinary · Reservoir, urinary · Yang-Monti tube

Abstract

Objective: To facilitate the anastomosis of a continent valve to the umbilicus or a suitable skin area, we used a reconfigured tube made from the same segment of the intestinal reservoir as that used to construct the urinary pouch. ***Materials and Methods:*** Seven patients underwent continent ileal-pouch formation using a reconfigured ileal tube following cystectomy for bladder cancer. Two irradiated patients and 1 patient with neurogenic bladder underwent continent colon-pouch construction with a reconfigured colon tube. ***Results:*** The average length of the reconfigured ileal tube was 5 cm, while the colon tube was maximally 10 cm long. All procedures were technically straightforward. All the continent pouches functioned well, without catheterization difficulties. ***Conclusions:*** Since the Yang-Monti tube and the pouch are easily mobilized, being based on the same vascular pedicle, and can therefore bridge the gap, making the umbilical anastomosis was greatly facilitated. Sufficient support for the tube is provided by the pouch.

Introduction

An innovative procedure in which a short ileal segment is reconfigured transversally to create a tubular structure for urologic reconstruction was developed by Yang [1] and Monti et al. [2]. Immediately, this was appreciated as a new second-line Mitrofanoff tube for the construction of a continent valve as an alternative to the vermiform appendix. With several advantages (constant availability, minimal loss of bowel, no interference with the mesentery and high mobility of the tube), this technique is actually an excellent alternative to the use of the Mitrofanoff principle [3]. However, it does have one limitation: namely, the tube length is determined by the circumference of the ileal segment. This becomes especially important when the tube is to be used either for a continent ileovesicostomy in obese patients or to bridge the gap between the native bladder and the umbilicus over a long distance. To overcome this problem, a double-length tube can be formed from separate ileal segments [3] or from a continuous ileal segment [4]. Alternatively, a transverse retubularized sigmoid-colon segment is a good choice for the purpose of vesicostomy using an intestinal segment [5].

Another solution to the problem of how to anastomose a continent reconfigured ileal tube to a desirable skin location or to the umbilicus is to implant it into an intestinal segment for augmentation, thus effectively extending it so as to bridge the gap if this is indicated [3]. For this purpose, a reconfigured ileal segment seems to be preferable

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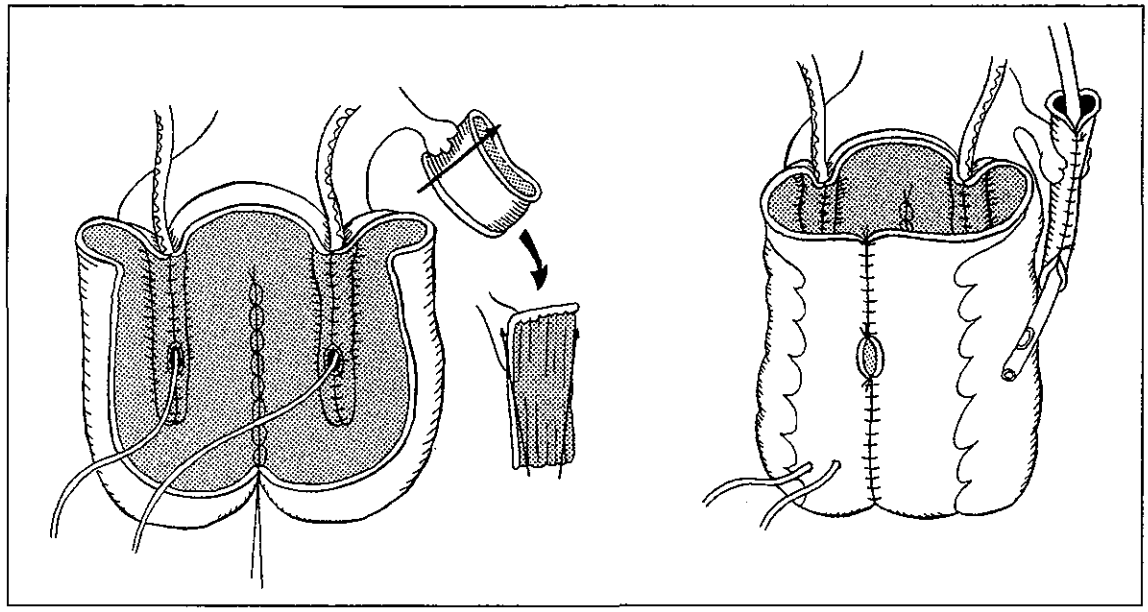

Fig. 1. After ureteral implantation, a short ileal plate is formed by opening a small ileal segment and cutting the edges obliquely. An anterior wall is created with one mucosal hole, and the ileal plate is retubularized to make a cone-shaped tube.

to the appendix because of the proximity of the former to the pouch and the adequate mobility of its vascular pedicle [6]. Having recognized the advantages of the use a reconfigured ileal tube connected to the same mesenteric pedicle as the pouch, we adapted the original idea aggressively to reconstructive surgery of the urinary tract, and we have now evaluated this modified procedure.

Materials and Methods

In 7 patients with an invasive bladder cancer (mean age 52 years, range 38–63), a continent ileal pouch with an umbilical stoma was constructed after radical cystectomy. As shown in figure 1, to construct a continent tube, an additional 3-cm-long segment obtained from the oral end of the pouch was opened longitudinally 1 cm from the mesentery to create an ileal plate, and the side edges of the plate were tailored to form a slim trapezium. The small ileal plate was retubularized over a 14-french catheter in the transverse direction to create a cone-shaped tube, which was divided into a short and a long portion by the mesentery (fig. 1). After ureteric implantation, the end of the long portion was anastomosed to the mucosal hole in the anterior pouch, while the long portion was embedded in a serous-lined tunnel with the transverse suture line of the tube facing the anterior pouch wall (fig.2). Finally, the end of the short portion of the ileal tube was anastomosed to a skin hole made at the bottom of the umbilicus. In 5 of these patients a healthy appendix was present, and we left it in place.

In 2 patients who had undergone pelvic irradiation (57 and 60 years old, respectively), a continent transverse colon pouch was constructed. To make a continent tube, a short colon segment cut from the main colon segment used for pouch construction was reconfigured transversally over a 14-french catheter. The reconfigured tube was implanted submucosally into the anterior pouch, and the distal end was connected to a skin opening at the umbilicus or at a suitable skin location (fig. 3). In 1 patient with a neurogenic bladder due to spina bifida (12 years old), we performed augmentation cystoplasty using a sigmoid colon with construction of a continent umbilical stoma. Since the appendix was used for a Malone antegrade continent enema stoma [7], a short colon segment was taken from the main segment used for the augmentation. This short segment was reconfigured to make a continent tube, which was embedded into a submucosal tunnel created in the augmenting flap (fig. 4). The distal end was connected to a skin opening at the umbilicus.

In the 3 patients in whom a colon segment was used to create a continent tube, the segment was opened at its antimesenteric border, and was thus divided into two portions of equal length by the mesenteric pedicle. For anastomosis to the umbilicus or a suitable skin site, the free end of the reconfigured tube was trimmed to the required length, since we always fixed the pouch wall to the back of the abdominal muscle in order to make the distance short and to avoid angulation and possible kinking of the tube.

Results

The length of the reconfigured ileal tube averaged about 5 cm (4–6 cm) and that of the colon tube about 9 cm (8–10 cm). All tubes provided a sufficient length for implantation either into a serous-lined tunnel in an ileal

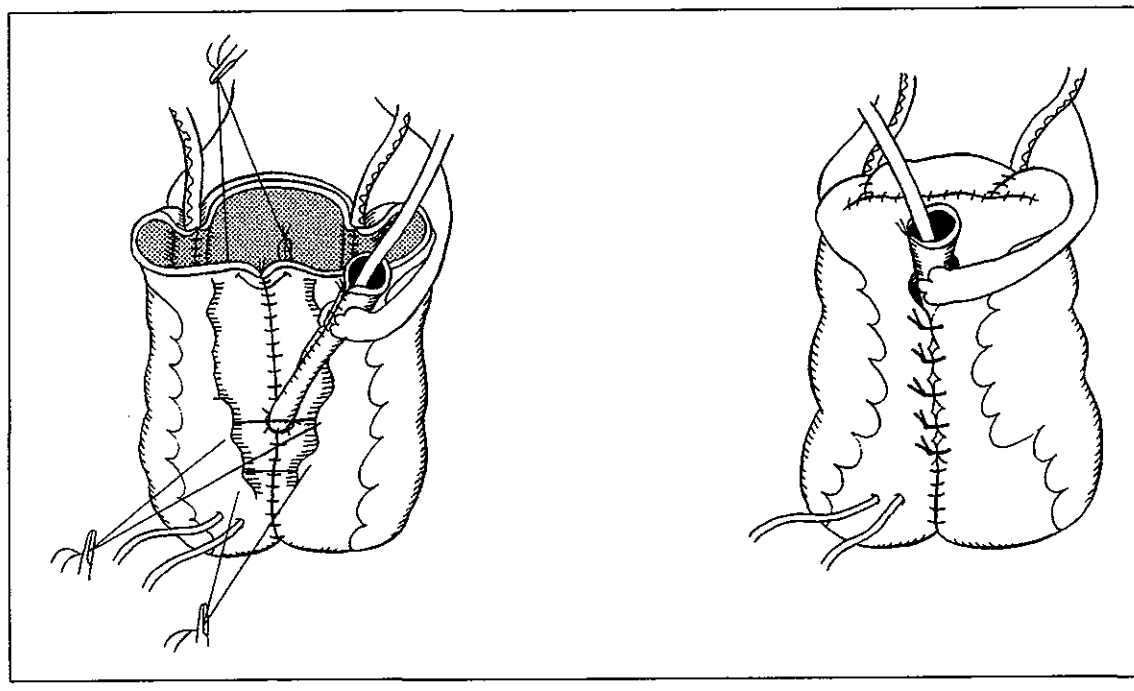

Fig. 2. The tube is anastomosed to the mucosal hole and then embedded into a serous-lined tunnel in the anterior pouch wall. The transverse suture line of the tube faces the pouch wall.

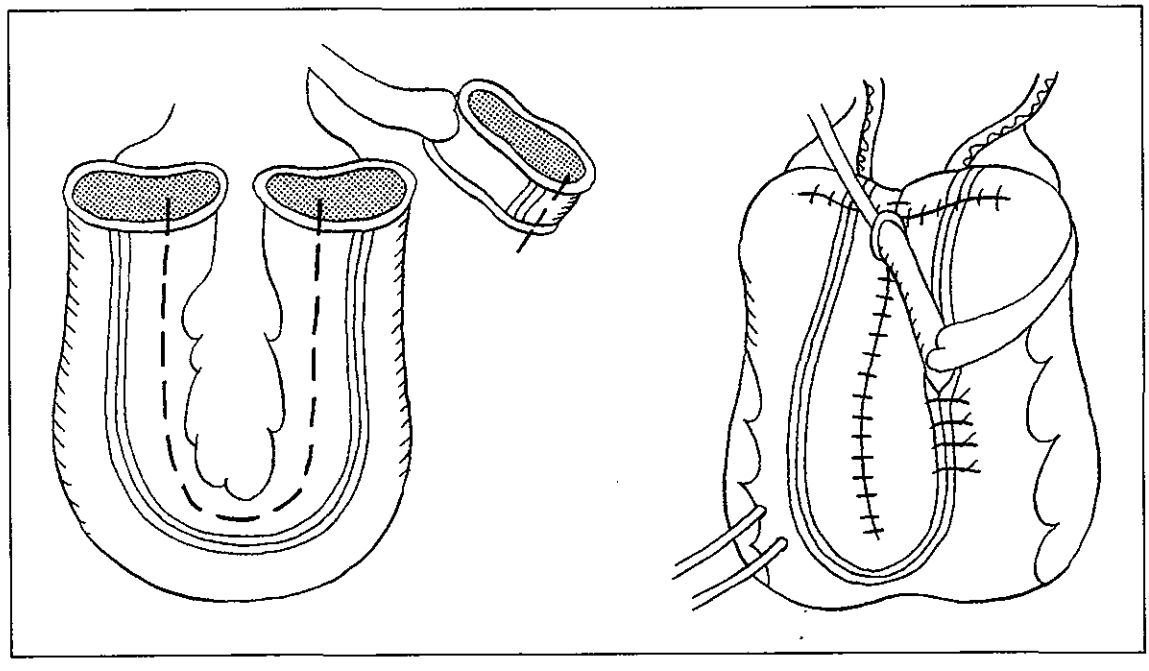

Fig. 3. The transverse colon segment for the pouch and an additional short segment are taken from one and the same pedicle. The retubularized tube made from the short segment is implanted into a submucosal tunnel in the pouch wall.

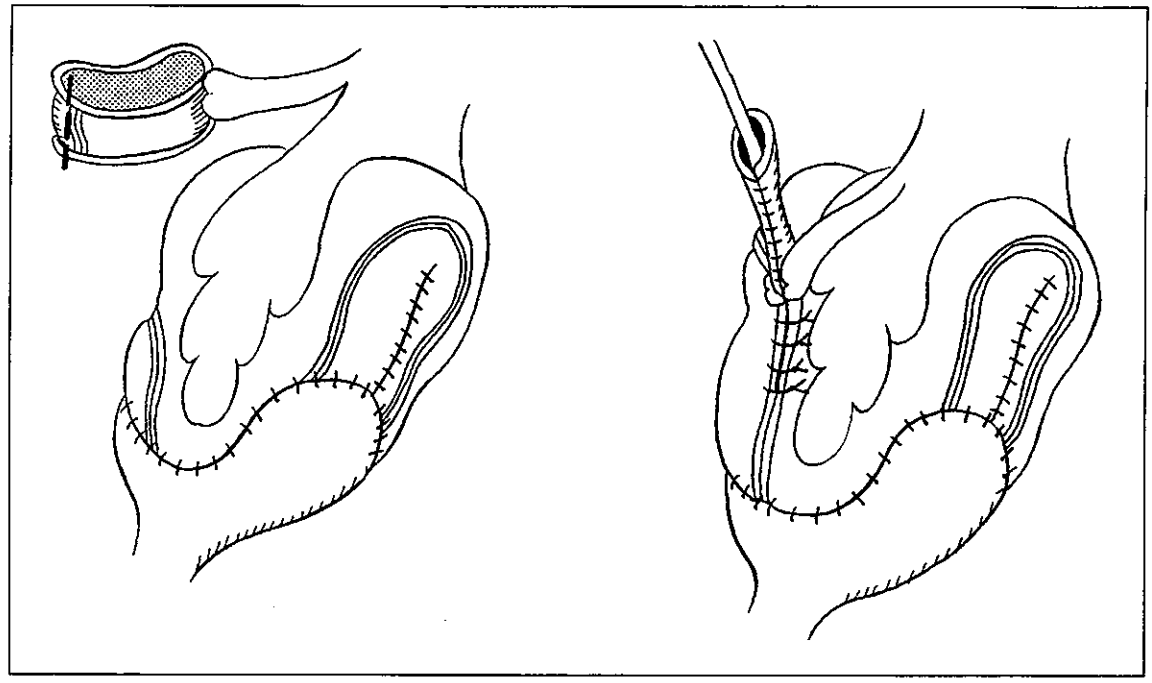

Fig. 4. The native contracted bladder is augmented by a segment of sigmoid colon. An additional short segment isolated from the same pedicle is retubularized and implanted submucosally into the flap augmenting the native bladder.

pouch or into a submucosal tunnel in a colon pouch. The distal end of the tube easily reached far enough to be anastomosed to a hole at the bottom of the umbilicus or in a suitable area of the skin.

With a mean follow-up of 35 (8–56) months, all patients were evaluated by pouchography and intravenous urography 3 and 6 months after surgery. Two patients with a continent ileal pouch died due to cancer progression during the follow-up (8 and 12 months after surgery, respectively). All upper urinary tracts were stable on intravenous urography. All patients could catheterize the pouch easily using a 14-french catheter, and they all had a functional pouch capacity of more than 400 ml at 6 months (range, 400–700 ml). No complications were experienced after construction of the pouch (e.g. stoma-related problems) in any of the patients.

Discussion

Refashioning a small ileal segment transversally to form a Mitrofanoff continent tube was originally described by Yang [1] and Monti et al. [2]. We personally recognized this Yang-Monti method to be geometrically well designed and practically useful, since it could avoid problems inherent in the use of either the appendix or a tapered ileum [6].

However, in general, this technique has been thought of as a second-line Mitrofanoff tube alternative to the vermiform appendix. Only when the appendix was absent or unsuitable for use as a continent tube [3, 8, 9], or when it was planned to use the appendix for a Malone antegrade colonic enema [9], was the Yang-Monti technique applied for the creation of a continent tube.

Although we believe that the mobility of the reconfigured ileal tube on the vascular pedicle is superior to that of the appendix, one limitation of the Yang-Monti technique is the shortness of the tube, which is determined by the circumference of the ileal segment. The values given in the literature for the length of the reconfigured ileal tube are 6–7 cm [3, 9], or 8–13 cm if a colon segment is included [8]. Unfortunately, in our Japanese patients the value is only about 5 cm, not 6–7 cm. Consequently, it could prove difficult for us to bridge the gap between the reservoir and the skin stoma. To overcome this type of problem, other authors have formed a double tube from two retubularized ileal segments joined together (12 cm long) [3] or from a single piece of ileum (10–14 cm long) [4] for ileovesicostomy. A retubularized sigmoid-colon segment (13 cm long) has also been reported to be effec-