with long-term follow-up (see Table 1). Although TaG1 and TaG2 disease has lower progression and cancer death rates, T1G3 has much higher rates, which is one of the reasons why early radical cystectomy is recommended for the disease.[22] Even when the disease is treated by TUR-Bt, postoperative intravesical treatment with BCG and careful observation of the clinical course are mandatory.

CIS is another type of superficial bladder cancer. Most of the disease is found in association with papillary or solid high-grade disease. Primary CIS defined clinically as bladder cancer without any visible tumor by cytoscopy. The final diagnosis is only made with histopathological examination. Intravesical BCG treatment can eradicate cancer cells in the bladder in more than 70% of patients with the disease. The 5-year recurrence-free rate is 60%. However, the rate of progression to muscle-invasive or metastatic disease is significant.

How do we detect early disease?

Usual presentation and detection

Urinalysis, urine cytology, and cystoscopy are well accepted as the standard methods for detecting bladder cancer (Fig. 2). Even if urinalysis reveals microscopic hematuria, however, it is unclear whether the hematuria is derived from bladder cancer. Moreover, hematuria in bladder cancer may be intermittent. Cytology has high specificity but the diagnostic value is far from satisfactory, particularly for low grade or Ta superficial bladder cancer. Cytoscopy can identify most superficial disease, but it sometimes fails to detect a small or flat lesion. Its greatest disadvantage is that it is an invasive diagnostic procedure. Thus, flexible fiberscopy is the current procedure of choice as it provides a clear intravesical view with less invasiveness. In this context, novel specific markers for bladder cancer are expected.

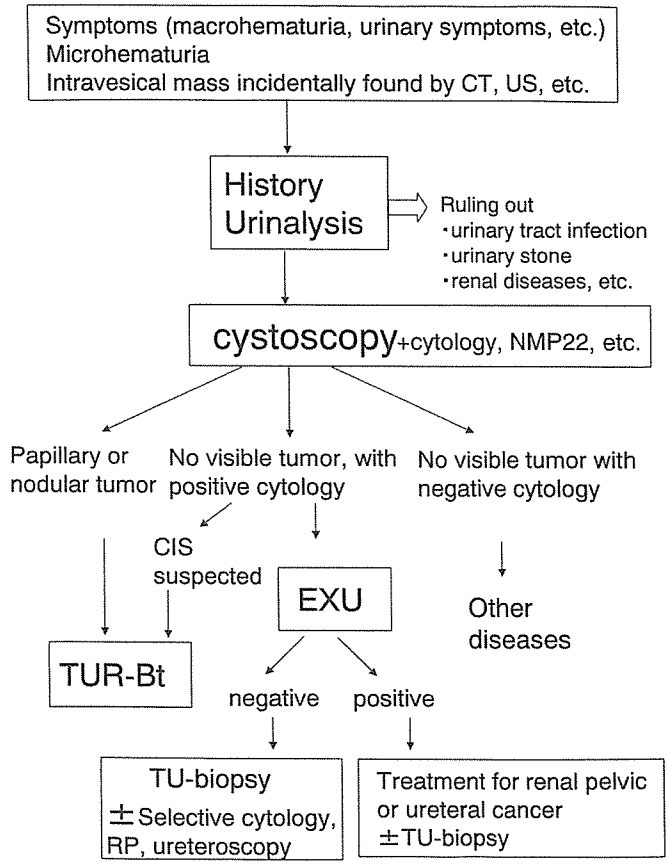

Fig. 2. Algorithm for diagnosis of bladder cancer. *EXU*, excretory urography; *TUR-Bt*, transurethral resection of bladder tumor; *TU-biopsy*, transurethral biopsy; *RP*, retrograde pyelography

Innovative methods for detection

Commercially available molecular markers

Several urinary markers for bladder cancer have been investigated in recent years. Unfortunately, no serum marker is as yet available for clinical use.

Bladder tumor antigen (BTA)stat, BTA TRAK, nuclear matrix protein (NMP)22, fibrinogen degenerative product (FDP), ImmunoCyt, and fluorescence in situ hybridization (FISH) (UroVysion) tests for bladder cancer have been approved by the U.S. Food and Drug Administration.[23,24] Bladder tumor antigen (BTA) is a human complement factor H-related protein that is similar in structure and function to human complement factor H.[25,26] The BTAst at test (Mentor, Santa Barbara, CA, USA) is an immunoassay using two monoclonal antibodies recognizing two epitopes on human complement factor H-related protein.[27] It is a one-step, qualitative, immunochromatographic assay whereas BTA TRAK (Polymedco, Cortlandt Manor, NY, USA) is a quantitative two-step enzyme-linked immunosorbent assay (ELISA).[24] When the role of BTAstat was compared with that of BTA TRAK in detection of bladder cancer, BTAstat was reported to have higher specificity and lower sensitivity.[28] Which test is better remains to be determined, although with BTA TRAK there is slightly higher sensitivity in high-grade tumors.[29,30]

NMP22 (Matritech, Newton, MA, USA) is a nuclear mitotic apparatus protein involved in the distribution of chromatin to daughter cells. It is located in the nuclear matrix in all cell types and is released from the nuclei of tumor cells during apoptosis.[29] The NMP22 test is an immunoassay that detects complexed and fragmented forms of the nuclear mitotic apparatus protein in urine.[31] This protein has an up to 25-fold-greater intracellular concentration in bladder cancer cells than in normal urothelium and is released in soluble form during apoptosis.[32]

FDP is released into the circulation and is detectable in the urine of patients with bladder cancer.[33] Bladder cancer cells produce vascular endothelial growth factor (VEGF), an angiogenic factor involved in the maintenance and induction of vascular endothelial cells, which increases the vessel wall permeability of blood and plasma proteins such as plasminogen, fibrinogen, and other clotting factors.

Recent assay systems that use monoclonal antibody immunoassays to detect FDP consistently achieve overall sensitivities ranging from 68% to 83%.[33–35] The urinary FDP level tends to become higher in patients with cancer as grade and stage increase, although its utility in the detection of CIS remains unproved.[35] Although inflammatory conditions of the urinary tract generate detectable amounts of FDP in urine, the FDP levels are far lower than those in urine of patients with bladder cancer. However, FDP does not seem to have additional value over cytology for recurrent disease.[24]

ImmunoCyt (DiagnoCure, Sainte-Foy, QC, Canada) is a test combining cytology with an immunofluorescence assay using three antibodies: 19A211 against a high molecular weight form of carcinoembryonic antigen, and M344 and LDQ10 against mucins, which are expressed in bladder cancer but not in normal epithelium.[36] Pfister et al.[37] performed a multicenter study and reported that the ImmunoCyt test improved the diagnostic accuracy of cytology in daily practice. The sensitivity of ImmunoCyt for low-grade and low-stage cancer is controversial.[38,39] However, Toma et al.[39] performed comprehensive analysis of several urine markers for noninvasive bladder cancer and concluded that ImmunoCyt in combination with conventional cytology offered better sensitivity than other tests.

Fluorescence in situ hybridization (FISH) is a technique that uses fluorescently labeled DNA probes to assess the centromeres of chromosomes 3, 7, 17, and 9p21 (p16/CDKN2A). FISH can detect genetic alterations in the urine sediments of patients with urothelial carcinoma.[40,41] UroVysion (Abbott Laboratories, Downers Grove, IL, USA), a multicolored FISH probe set developed to detect bladder cancer, has significantly higher sensitivity than cytology, while maintaining the high specificity of cytology and low sensitivity for Ta tumors.[41,42] FISH also appears to be useful for monitoring the response to intravesical treatment in patients with superficial bladder cancer.[42] However, the meticulous technique necessary hampers its wide application in the clinical setting.

Several studies show that a combination of these tests offers superior sensitivity. To date, however, none of these assays has been shown to replace cystoscopy or provide substantial, additional information for making the diagnosis of recurrent bladder carcinoma.

Other markers under investigation

The urine markers that are commercially available now are somewhat limited in clinical use by low sensitivity and specificity. Various newer markers have been investigated because more-sensitive, more-specific, and less-invasive methods for detecting cancer are desired.

The hyaluronic acid (HA)-hyaluronidase (HAase) test is based on an enzyme-linked immunosorbent like-assay.[43] HA is a nonsulfated glycosaminoglycan made of repeating disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine.[44] Lokeshwar et al.[45] reported that HA levels are three- to fivefold elevated in tissue extracts of bladder cancer when compared with the levels in normal tissues. It is suggested that HA is synthesized mostly by stromal fibroblasts of cancer, and that the cancer cells activate these fibroblasts to synthesize high levels of HA.[44] HAase, an endoglycosidase, degrades HA into small fragments that promote angiogenesis. Hautmann et al.[46] reported the expression of HA and HAase in bladder cancer tissue and indicated that patients with bladder cancer were positive for the HA-HAase test because of secretion of HA and HAase in urine. The overall sensitivity and specificity are 91.2% and 84%, respectively.[26]

Survivin is a member of the inhibitor of apoptosis protein (IAP) family. This gene is overexpressed in various human malignancies, including cancers of the lung, colon, pancreas, prostate, and breast, but not in normal adult tissues.[47,48] It is a protein with a single baculoviral IAP repeat (BIR) domain and a COOH-terminal ring domain and can inhibit apoptosis by binding to caspases 3 and 7.[49] Survivin expression has been associated with features of biologically aggressive disease, resistance to therapy, and poor clinical outcome in patients with various malignancies.[48] Some investigators have reported that survivin expression in urine specimens has high sensitivity (64%–100%) and efficiency (93%–100%) for the diagnosis of bladder cancer.[50–52]

The telomeric repeat amplification protocol (TRAP) assay can detect and measure the activity of telomerase, an enzyme helping to synthesize telomeres and maintain chromosomal ends.[53] The overall sensitivity of the TRAP assay is between 70% and 86%, although the false-positive rate of 21%–76% is not negligible.[54,55] Recent studies suggested that by using the reverse transcriptase-polymerase chain reaction (RT-PCR) for the mRNA of human telomerase reverse transcriptase (hTERT), the assay has a sensitivity between 74% and 92% and specificity between 70% and 93%.[56–58]

Microsatellites are inherited short tandem repeat DNA sequences that are widely interspersed through the genome with low mutation rates unique to individuals.[58] Mutations of the gene can lead to loss of heterozygosity and/or microsatellite instability[59] and can be useful as markers of neoplasia. The microsatellite assay is performed by PCR using DNA primers for a panel of various microsatellite markers.[60,61] Although this assay has high sensitivity and high specificity, it is a very complex and expensive technique. Blunt-end single-strand DNA conformation polymorphism (blunt-end SSCP) analysis is also useful for diagnosis of bladder cancer by detecting loss of heterozygosity (LOH) on chromosome 9 in urine samples.[62]

Cytokeratins (CKs) are intermediate filament proteins specific for epithelial cells. CK18, CK19, and CK20 were found to be overexpressed in urothelial cancer cells. CYFRA21-1, an ELISA assay for detecting fragments of CK19, is a promising test with sensitivity of 76.2% and specificity of 84.2%.[63]

Lewis X antigen belongs to the Lewis system, occurring in secretions and serum lipoproteins.[64] Papilloma and urothelial cancer cells, but not normal adult urothelial cells, express this antigen, regardless of the blood group, secretory status, and grade and stage of the tumor.[48] The test for

Table 2. Sensitivity and specificity of urinary markers in the detection of bladder cancer: summary of recent reviews

Marker	Assay	Sensitivity	Specificity
Cytology	Cytology	16%–100%	62%–100%
BTAstat	Qualitative immunoassay	24%–89%	52%–93%
BTA TRAK	Quantitative immunoassay	57%–79%	45%–95%
NMP22	ELISA	47%–100%	56%–95%
FDP	Immunoassay	52%–81%	75%–96%
ImmunoCyt	Fluorescence immunocytochemistry	50%–100%	69%–90%
UroVysion	FISH	73%–92%	92%–100%
HA-HAase	ELISA-like	70%–100%	73%–84%
Survivin	Immunoassay	64%–100%	93%–100%
Telomerase	TRAP, RT-PCR	7%–100%	24%–99%
Microsatellites	PCR	72%–97%	89%–100%
CYFRA21-1	ELISA	74%–99%	67%–100%
Lewis X	Immunoassay	80%–89%	80%–86%

BTA, bladder tumor antigen; NMP, nuclear matrix protein; ELISA, enzyme-linked immunosorbent assay; FDP, fibrinogen degenerative protein; FISH, fluorescence in situ hybridization; HA, hyaluronic acid; TRAP, telomeric repeat amplification protocol; RT-PCR, reverse transcriptase-polymerase chain reaction
Sensitivity and specificity were summarized by data from references 23, 24, 67, and 68

Lewis X antigen has high sensitivity, but its specificity has not been promising, with reported rates between 32.8% and 86.4%.[39,64–66]

What modality is most suitable for detecting bladder cancer?

The sensitivities and specificities of various biomarkers, including urine cytology, are far from satisfactory in studies analyzing a single voided urine sample (see Table 2). Glas et al.[67] meta-analyzed studies evaluating urine markers, BTA, BTAstat, BTA TRAK, NMP22, telomerase, and FDP. However, they had no data to evaluate specific test combinations and concluded that none of the markers was sensitive enough to be recommended for daily practice. The sensitivity and specificity can be more satisfactory with a combination method using two or more urine markers and/or two or more consecutive urine samples. However, such multitest methods are expensive. Although the newer tests may potentially be more sensitive and specific, clinical studies on a larger number and more heterogeneous population of patients are needed to determine the sensitivity and specificity.[68] Therefore, cystoscopy is still the standard method for detecting bladder cancer. Recently, fluorescence endoscopy using intravesical application of 5-aminolaevulinic acid or its hexyl-derivative ester has been reported to have high sensitivity and reasonable specificity, especially for flat urothelial high-risk lesions that can be missed by conventional white-light cystoscopy.[69] Cystoscopy with less invasiveness, high sensitivity, and high specificity should be developed, and time- and cost-effective urinary and serum markers for bladder cancer with high sensitivity and high specificity are anticipated.

How do we manage early disease?

Standard treatment

TUR-Bt is the standard treatment for superficial bladder cancer. The surgery is also an important diagnostic method, providing histologic type, tumor grade, pathological T stage, and type of tumor invasion. Primary, low-grade, and low-stage Ta cancers progress less frequently to muscle-invasive disease, whereas disease associated with high-grade, T1, or concomitant CIS has a greater risk for progression, as indicated earlier. Multirecurrent, multifocal, or grade 2 disease tends to have an intermediate risk between these types.[70] Radical cystectomy for superficial disease is sometimes indicated for patients with high-grade T1 disease or multifocal disease uncontrolled by TUR-Bt or intravesical chemotherapy or BCG therapy.

Intravesical chemotherapy

The goal of intravesical therapy is to decrease recurrence, prevent progression, and eradicate residual disease after TURBt. In particular, the mechanical dispersion during TUR-Bt may cause cancer cells to be implanted in the mucosa of the bladder. Therefore, intravesical chemotherapy is recommended to start immediately after the TUR-Bt. A recent meta-analysis by Sylvester et al.[18] showed that a single immediate intravesical instillation of epirybicin, mitomycin C, thiotepa, or pirarubicin decreased the risk of recurrence after TUR-Bt in 39% of patients. No difference in efficacy of agents was found among these agents. However, Koga et al.[71] conducted a prospective randomized study of prophylactic intravesical instillation of epirubicin for superficial bladder cancer and concluded that 19 instillations in the year after TUR-Bt were more effective than 9 done in the first 3 months after surgery. As indicated earlier, Hinotsu et al.[20] reported that intravesical

chemotherapy tended to be more effective in reducing the hazard for recurrence in the early phase, i.e., during the first 500 days after operation. Thus, intravesical chemotherapy continuing for more than a year is not supported by more than a dozen clinical studies.

Inravesical BCG treatment

It is generally assumed that BCG-induced antitumor activity is critically dominated by a local nonspecific immunological reaction reflecting the activity of immunocompetent cells.[72,73] Furthermore, current insights of the mode of action of BCG, ranging from its introduction into the bladder to killing of residual tumor cells, have revealed a complex sequence of processes.[73] After adhering to the bladder epithelium and passage through the glycosaminoglycan layer, BCG is internalized and processed by professional antigen-presenting cells and cancer cells. The modified gene expression of these professional cells causes the secretion of particular cytokines and presentation of BCG antigens via HLA class I and II to CD8+ and CD4+ T cells, respectively. Upregulation of the Th2 response may occur and adversely affect the functioning of the Th1 response, inducing recruitment and maturation of cytotoxic effector cells.

Intravesical BCG treatment remains the most effective treatment for eradication and prophylaxis of recurrence of superficial bladder cancer, including CIS and residual papillary tumors after TUR-Bt.[74] For papillary tumors, the treatment provides an approximately 30% absolute advantage, whereas that of chemotherapy is 15% over TUR-BT alone.[48] For CIS, the advantage was 35% for the BCG treatment with an overall risk of progression of 14% for a group with a median follow-up of 2.5 years.[75] Davis et al.[76] reported 10-year estimates of progression-free survival of 55%, 77%, and 62% for patients with CIS or high-grade Ta tumors, and T1 tumors, respectively, when intravesical BCG treatment was used. However, 30%–50% of cancers either fail to respond or relapse within the first 5 years of treatment. In other words, it remains unclear whether BCG actually alters the natural history of the disease to prevent ultimate progression and improve survival.[70] In addition, application of intravesical BCG treatment in the clinical setting is somewhat limited by local toxicity such as vesical irritability, demonstrated by dysuria and frequency, and hematuria. Furthermore, it may cause febrile systemic toxicity in 3.9% of patients.[77] When multiple organ failure is suspected, chemotherapy with appropriate antimicrobial agents for tuberculosis should be started immediately. Allergic complications involving arthritis, migrating joint pain, or skin rashes are uncommon.[77,78]

Other bladder-sparing surgical treatments

Photodynamic therapy

Photodynamic therapy (PDT) aims at inducing a cytotoxic reaction in cancers in which a photoreactive chemical compound or photosensitizer has already accumulated.[79] Increased accumulation of the photosensitizer in cancer cells might allow more selective destruction of malignant cells after light exposure and reduce damage to adjacent normal tissue.[80] Although previous studies used porphyrin mixtures, which tended to cause long-term skin hypersensitivity and damage the detrusor muscle of the bladder, ALA and HAL, precursors of the photosensitizer protoporphyrin IX (PpIX), offer less toxicity for PDT. Marti et al.[81] evaluated the accumulation and location of PpIX under different conditions of ALA or HAL instillation and showed that topical bladder administration of HAL for 2h followed by 2h of resting time resulted in the most intense accumulation of PpIX among several conditions. However, most recent studies of PDT used ALA, one of the most promising photosensitizers.[79] Two large studies using ALA achieved 29%–52% recurrence-free rates at 24–36 months without severe side effects.[82,83] A report on a phase 1 study of PDT using sequential mitomycin C and ALA suggested that recurrence occurred in 56% of the patients at 24 months after PDT without significant toxicity.[83]

Laser therapy

The neodymium:YAG laser has been the most widely used instrument. Small, papillary bladder cancer is a good candidate for laser therapy because it may not need a histopathological diagnosis. This therapy can be performed on an outpatient basis and may require only local anesthesia to perform.[84] Unfortunately, the limited number of rather old studies hampers the extensive use of the treatment in the clinical setting.[85,86]

Chemoprevention and alternative therapies

Overexpression of cyclooxygenase (COX)-2 inhibitors, nonsteroidal antiinflammatory drugs, has been observed in various cancers, including colorectal, non-small-cell lung, gastric, breast, cervical, prostate, and bladder cancers.[87–89] COX-2 is frequently upregulated in urothelial cancers and the extent of its expression is correlated with the presence of CIS and the grade and stage of the disease,[90,91] but COX-2 is highly expressed in noninvasive cancer (CIS or Ta), and strong expression is found in T1 and muscle-invasive diseases.[92] Nevertheless, piroxicam, a mixed COX-1/2 inhibitor, was reported to reduce tumor volume in 12 of 18 dogs with muscle-invasive bladder cancer.[93] A clinical study on chemoprevention of bladder cancer by oral intake of COX-2 inhibitors is currently underway.

Nutrition and diet potentially reduce new bladder cancer formation.[70] Recent excellent reviews indicated that dietary vitamin E and vitamin E supplements may protect against the development of bladder cancer, although further studies are needed to confirm this indication.[94–96] Vitamins A and C probably have no promising effect for prevention of bladder cancer. Folate intake is not associated with bladder cancer risk.[96] The effect on cancer prevention of total fluid consumption is still controversial. Lowering saturated fat and the overall calorie intake may reduce the risk of bladder

cancer, although there are only a limited number of investigations and a lack of prospective studies.[93] Smoking cessation provides the most convincing evidence for prevention of bladder cancer. Cigarette smoking cessation would result in decreases of bladder cancer development of 50% in males and 23% in females.[96] With time elapsed from quitting smoking, the occurrence rate for bladder cancer continues to fall most rapidly during the first 3 to 4 years.[70] Although it has not yet been clarified that quitting smoking can alter the actual recurrence rate, smoking cessation is recommended to all patients with bladder cancer, especially those with recurrent superficial disease.

Conclusions

During the past 10 years, evidence has accrued on molecular pathways of bladder cancer. However, the molecular mechanisms of recurrence of the disease and progression into muscle-invasive disease are not fully understood. With such understanding, we could more appropriately select candidates for intravesical chemotherapy and BCG treatments. Although innovative diagnostic markers for detection of bladder cancer have been developed, the diagnostic accuracy and specificity not only of cytology but also of other commercially available makers are still far from the level where cystoscopy would not be needed.

Recurrences associated with progression into muscle-invasive disease are found in approximately 10% of patients with superficial bladder cancer, even though the primary cancer is completely managed. Adjuvant intravesical treatment after TUR-Bt that reduces or prevents progression into muscle-invasive disease should be investigated. Thus, we need more basic as well as translational research and clinical trials for better detection and management of superficial bladder cancer and prevention of its recurrence and progression into muscle-invasive disease.

Acknowledgment This work is, in part, supported by a grant-aid of Clinical Research of Cancer by the Ministry of Health, Labour and Welfare.

References

1. Witje JA, Debruyne FMJ (2005) Natural history and initial management based on prognostic factor. In: Vogelzang NJ, Scardino PT, Shipley WU, et al (eds) Comprehensive textbook of genitourinary oncology, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 449–451
2. Tsukamoto T, Kitamura H, Takahashi A, Masumori N (2004) Treatment of invasive bladder cancer. Lessons from the past and perspective for the future. Jpn J Clin Oncol 34:295–306
3. Epstein JI, Amin MB, Reuter VE, Mostofi FK, the Bladder Consensus Conference Committee (1998) The World Health Organization/International Society of Urological Pathology consensus classification of urothelial neoplasms of the urinary bladder. Am J Surg Pathol 22:1435–1448
4. Donat SM (2003) Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin N Am 30:765–776
5. Holmang S (2000) Follow-up of patients with noninvasive and superficially invasive bladder cancer. Semin Urol Oncol 18:273–279
6. Cote RJ, Lerner SP, Datar R (2005) Molecular biology and prognostic markers in bladder cancer. In: Vogelzang NJ, Scardino PT, Shipley WU, et al (eds) Comprehensive textbook of genitourinary oncology, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 385–401
7. Wu X-R (2005) Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer 5:713–725
8. Wolff EM, Liang G, Jones PA (2005) Mechanism of disease: genetic and epigenetic alterations that drive bladder cancer. Nat Clin Prac Urol 2:502–510
9. Cappellen D, De Oliveira C, Ricol D, et al (1999) Frequent activating mutations of FGFR3 in human bladder cancer and cervix carcinomas. Nat Genet 23:18–20
10. Billerey C, Chopin D, Aubriton-Lorton MH, et al (2001) Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors. Am J Pathol 158:1955–1959
11. Jebar AH, Hurst CD, Tomlinson DC, et al (2005) FGFR3 and Ras gene mutations are mutually exclusive genetic events in urothelial carcinoma. Oncogene 24:5218–5225
12. Orlow I, LaRue H, Osman I, et al (1999) Deletions of the INK4A gene in superficial bladder tumors: association with recurrence. Am J Pathol 155:105–113
13. Hartmann A, Zanardo L, Bocker-Edmonston T, et al (2002) Occurrence of chromosomal 9 and p53 alterations in multifocal dysplasia and carcinoma *in situ* of human urinary bladder. Cancer Res 62:809–818
14. Sidransky D, Frost P, Von Eschenbach A, et al (1992) Clonal origin of bladder cancer. N Engl J Med 326:737–740
15. Harris AL, Neal DE (1992) Bladder cancer-field versus clonal origin. N Engl J Med 326:443–447
16. Hafner C, Knuechel R, Stoehr R, Hartmann A (2002) Clonality of multifocal urothelial carcinomas: 10 years of molecular gnetic studies. Int J Cancer 101:1–6
17. Habuchi T (2005) Origin of multifocal carcinomas of the bladder and upper urinary tract: molecular analysis and clinical implications. Int J Urol 12:709–716
18. Sylvester RJ, Oosterlinck W, van der Meiden APM (2004) A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 171:2186–2190
19. Duggan BJ, Gray SB, McKnight JJ, et al (2004) Oligoclonality in bladder cancer: the implication for molecular therapies. J Urol 171:419–425
20. Hinotsu S, Akaza H, Ohashi Y, Kotake T (1999) Intravesical chemotherapy for maximum prophylaxis of new early phase superficial bladder carcinoma treated by transurethral resection. Cancer (Phila) 86:1818–1826
21. Heney NM, Ahmed S, Flanagan M, et al (1983) Superficial bladder cancer: progression and recurrence. J Urol 130:1083–1086
22. Herr WH, Soganni PC (2001) Does early cystectomy improve the survival of patients with high risk superficial bladder tumor? J Urol 166:1296–1299
23. Simon MA, Lokeshwar VB, Soloway MS (2003) Current bladder cancer tests: unnecessary or beneficial? Crit Rev Oncol Hematol 47:91–107
24. van Rhijn BWG, van der Poel HG, van der Kwast TH (2005) Urine markers for bladder cancer surveillance: a systematic review. Eur Urol 47:736–748
25. Kinders R, Jones T, Root R, et al (1998) Complement factor H or a related protein is a marker for transitional cell cancer of the bladder. Clin Cancer Res 4:2511–2520
26. Saad A, Hanbury DC, McNicholas TA, et al (2002) A study comparing various noninvasive methods of detecting bladder cancer in urine. BJU Int 89:369–373
27. Friedrich MG, Hellstern A, Toma MI, et al (2003) Are false-positive urine markers for the detection of bladder carcinoma really wrong or do they predict tumor recurrence? Eur Urol 43:146–151
28. Babjuk M, Kostirova M, Mudra K, et al (2002) Qualitative and quantitative detection of urinary human complement factor H-related protein (BTA stat and BTA TRAK) and fragments

of cytokeratins 8, 18 (UBC rapid and UBC IRMA) as markers for transitional cell carcinoma of the bladder. Eur Urol 41:34–39
29. Ellis WJ, Blumenstein BA, Ishak LM, et al (1997) Clinical evaluation and the BTA TRAK assay and comparison to voided urine cytology and the Bard BTA test in patients with recurrent bladder tumors. Urology 50:882–887
30. Heicappell R, Wettig IC, Schostak M, et al (1999) Quantitative detection of human complement factor H-related protein in transitional cell carcinoma of the urinary bladder. Eur Urol 35:81–87
31. Giannopoulos A, Manousakas T, Mitropoulos D, et al (2000) Comparative evaluation of the BTAstat test, NMP22, and voided urine cytology in the detection of primary and recurrent bladder tumors. Urology 55:871–875
32. Hoffman M (1993) The cell's nucleus shapes up. Science 259:1257–1259
33. Schmetter BS, Habicht KK, Lamm DL, et al (1997) A multicenter trial evaluation of the fibrin/fibrinogen degradation products test for detection and monitoring of bladder cancer. J Urol 158:801–805
34. Johnston B, Morales A, Emerson L, et al (1997) Rapid detection of bladder cancer: a comparative study of point of care tests. J Urol 158:2098–2101
35. Tsihlias J, Grossman HB (2000) The utility of fibrin/fibrinogen degradation products in superficial bladder cancer. Urol Clin N Am 27:39–46
36. Fradet Y, Lockhart C (1997) Performance characteristics of a new monoclonal antibody test for bladder cancer: ImmunoCyt. Can J Urol 4:400–405
37. Pfister C, Chautard D, Devonec M, et al (2003) ImmunoCyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study. J Urol 169:921–924
38. Feil G, Zumbragel A, Paulgen-Nelde HJ, et al (2003) Accuracy of the ImmunoCyt assay in the diagnosis of transitional cell carcinoma of the urinary bladder. Anticancer Res 23:963–967
39. Toma MI, Friedrich MG, Hautmann SH, et al (2004) Comparison of the ImmunoCyt test and urinary cytology with other urine tests in the detection and surveillance of bladder cancer. World J Urol 22:145–149
40. Sarosdy MF, Schellhammer P, Bokinsky G, et al (2002) Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer. J Urol 168:1950–1954
41. Skacel M, Fahmy M, Brainard JA, et al (2003) Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. J Urol 169:2101–2105
42. Kipp BR, Karnes RJ, Brankley SM, et al (2005) Monitoring intravesical therapy for superficial bladder cancer using fluorescence in situ hybridization. J Urol 173:401–404
43. Lokeshwar VB, Block NL (2000) HA-HAase URINE TEST. A sensitive and specific method for detecting bladder cancer and evaluating its grade. Urol Clin N Am 27:53–61
44. Fraser JRE, Laurent TC, Laurent UB (1997) Hyaluronan: its nature, distribution, functions and turnover. J Intern Med 242:27–33
45. Lokeshwar VB, Öbek C, Soloway MS, et al (1997) Tumor associated hyaluronic acid: a new sensitive and specific urine marker for bladder cancer. Cancer Res 57:773–777
46. Hautmann SH, Lokeshwar VB, Schroeder GL, et al (2001) Elevated tissue expression of hyaluronic acid and hyaluronidase validates the HA-Haase urine test for bladder cancer. J Urol 165:2068–2074
47. Ambrosini G, Adida C, Altieri DC (1997) A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med 3:917–921
48. Altieri DC (2001) The molecular basis and potential role of survivin in cancer diagnosis and therapy. Trends Mol Med 7:542–547
49. Tamm I, Wang Y, Sausville E, et al (1998) IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. Cancer Res 58:5315–5320
50. Smith SD, Wheeler MA, Plescia J, et al (2001) Urine detection of survivin and diagnosis of bladder cancer. JAMA 285:324–328
51. Shariat SF, Casella R, Khoddami SM, et al (2004) Urine detection of survivin is a sensitive marker for the noninvasive diagnosis of bladder cancer. J Urol 171:626–630
52. Weikert S, Christoph, Schrader M, et al (2005) Quantitative analysis of survin mRNA expression in urine and tumor tissue of bladder cancer patients and its potential relevance for disease detection and prognosis. Int J Cancer 116:100–104
53. Liu BCS, Loughlin KR (2000) Telomerase in human bladder cancer. Urol Clin N Am 27:115–123
54. Rahat MA, lahat N, Gazawi H, et al (1999) Telomerase activity in patients with transitional cell carcinoma: a preliminary study. Cancer (Phila) 85:919–924
55. Cassel A, Rahat MA, Lahat N, et al (2001) Telomerase activity and cytokeratin 20 as markers for the detection and follow-up of transitional cell carcinoma: an unfulfilled promise. J Urol 166:841–844
56. Ito H, Kyo S, Kanaya T, et al (1998) Detection of human telomerase reverse transcriptase messenger RNA in voided urine samples as a useful diagnostic tool for bladder cancer. Clin Cancer Res 4:2807–2810
57. Fukui T, Nonomura N, Tokizane T, et al (2001) Clinical evaluation of human telomerase catalytic subunit in bladder washings from patients with bladder cancer. Mol Urol 5:19–23
58. Melissourgos N, Kastrinakis NG, Davilas I, et al (2003) Detection of human telomerase reverse transcriptase mRNA in urine of patients with bladder cancer: evaluation of an emerging bladder tumor marker. Urology 62:362–367
59. Brentnall TA (1995) Microsatellite instability. Shifting concepts in tumorigenesis. Am J Pathol 147:561–563
60. Sourvinos G, Kiwanis I, Defaces D, et al (2001) Genetic detection of bladder cancer by microsatellite analysis of p16, RB1, and p53 tumor suppressor genes. J Urol 165:249–252
61. Sepira D, Parrela P, Gallucci M, et al (2001) Sensitive detection of transitional cell carcinoma of the bladder by microsatellite analysis of cells exfoliated in urine. Int J Cancer 95:364–369
62. Shigyo M, Sugano K, Fukayama, N, et al (1998) Allelic loss on chromosome 9 in bladder cancer tissues and urine samples detected by blunt-end single-strand DNA conformation polymorphism. Int J Cancer 78:425–429
63. Nisman B, Barak V, Shapiro A, et al (2002) Evaluation of urine CYFRA 21-1 for the detection of primary and recurrent bladder carcinoma. Cancer (Phila) 94:2914–2922
64. Planz R, Striepecke E, Jakse G, et al (1998) Use of Lewis X antigen and deoxyribonucleic acid image cytometry to increase sensitivity of urinary cytology in transitional cell carcinoma of the bladder. J Urol 159:384–388
65. Cordon-Cardo C, Reuter VE, Lloyed KO, et al (1988) Blood group-related antigens in human urothelium: enhanced expression of precursor, LeX, and LeY determinants in urothelial carcinoma. Cancer Res 48:4107–4112
66. Friedrich MG, Hellstern A, Hautmann SH, et al (2002) Clinical use of urinary markers for the detection and prognosis of bladder carcinoma: a comparison of immunocytology with monoclonal antibodies against Lewis X and 486p3/12 with the BTA STAT and NMP22 tests. J Urol 168:470–474
67. Glas AS, Roos D, Deutekom M, et al (2003) Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 169:1975–1982
68. Eissa S, Kassim S, El-Ahmady O (2003) Detection of bladder tumours: role of cytology, morphology-based assays, biochemical and molecular markers. Cur Opin Obstet Gynecol 15:395–403
69. Jain S, Kockelbergh RC (2005) The role of photodynamic diagnosis in the contemporary management of superficial bladder cancer. BJU Int 96:17–21
70. O'Donnell MA (2002) New therapeutic strategies for non-muscle-invasive (superficial) bladder cancer. AUA Update Ser 22:10–15
71. Koga H, Kuroiwa K, Yamaguchi A, et al (2004) A randomized controlled trial of short-term versus long-term prophylactic intravesical instillation chemotherapy for recurrence after transurethral resection of Ta/T1 transitional cell carcinoma of the bladder. J Urol 171:153–157
72. Alexandroff AB, Jackson AM, O'Donnell MA, et al (1999) BCG immunotherapy of bladder cancer: 20 years on. Lancet 353:1689–1694
73. Bevers RFM, Kurth KH, Schamhart DHJ (2004) Role of urothelial cells in BCG immunotherapy for superficial bladder cancer. Br J Cancer 91:607–612

74. O'Donnell MA (2005) Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. Urol Clin N Am 32:121–131
75. Sylvester RJ, van der Meijden APM, Lamm DL (2002) Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients in patients with superficial bladder cancer: a meta analysis of the published results of randomized clinical trials. J Urol 168:1964–1970
76. Davis JW, Sheth SI, Doviak MJ, et al (2002) Superficial bladder carcinoma treated with bacillus Calmette-Guerin: progression-free and disease-specific survival with minimum 10-year followup. J Urol 167:494–500
77. Lamm DL, Stogdill VD, Stogdill BJ, et al (1986) Complications of bacillus Calmette-Guerin immunotherapy in 1278 patients with bladder cancer. J Urol 135:272–274
78. Rischmann P, Desgrandchamps F, Malavaud B, et al (2000) BCG intravesical instillations: recommendations for side-effects management. Eur Urol 37(suppl 1):33–36
79. Jichilinski P, Leisinger HJ (2001) Photodynamic therapy in superficial bladder cancer: past, present and future. Urol Res 29:396–405
80. Berger AP, Steiner H, Stenzl A, et al (2003) Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single-center study. Urology 61:338–341
81. Marti A, Jichlinski P, Lange N, et al (2003) Comparison of aminolevulinic acid and hexylester aminolevulinate induced protoporphyrin IX distribution in human bladder cancer. J Urol 170:428–432
82. Waidelich R, Stepp H, Baumgartner R, et al (2001) Clinical experience with 5-aminolevulinic acid and photodynamic therapy for refractory superficial bladder cancer. J Urol 165:1904–1907
83. Skyrme RJ, French AJ, Datta SN, et al (2005) A phase-1 study of sequential mitomycin C and 5-aminolaevulic acid-mediated photodynamic therapy in recurrent superficial bladder carcinoma. BJU Int 95:1206–1210
84. Pietrow PK, Smith JA (2001) Laser treatment for invasive and noninvasive carcinoma of the bladder. J Endourol 15:415–418
85. Beisland HO, Seland P (1986) A prospective randomized study on neodymium-YAG laser irradiation versus TUR in the treatment of urinary bladder cancer. Scand J Urol Nephrol 20:209–212
86. Beer M, Jocham D, Beer A, et al (1989) Adjuvant laser treatment of bladder cancer: 8 years' experience with the Nd-YAG laser 1064 nm. Br J Urol 63:476–478
87. Fosslien E (2000) Molecular pathology of cyclooxygenase-2 in neoplasia. Ann Clin Lab Sci 30:3–21
88. Howe LR, Subbaramaiah K, Brown AM, et al (2001) Cyclooxygenase-2: a target for the prevention and treatment of breast cancer. Endocr Relat Cancer 8:97–114
89. Turini ME, DuBois RN (2002) Cyclooxygenase-2: a therapeutic target. Annu Rev Med 53:35–57
90. Pruthi RS, Derksen E, Gaston K, et al (2004) Rationale for use of cyclooxygenase-2 inhibitors in prevention and treatment of bladder cancer. Urology 64:637–642
91. Shirahama T (2000) Cyclooxygenase-2 expression is up-regulated in transitional cell carcinoma and its preneoplastic lesions in the human urinary bladder. Clin Cancer Res 6:2424–2430
92. Ristimaki A, Nieminen O, Saukkonen K, et al (2001) Expression of cyclooxygenase-2 in human transitional cell carcinoma of the urinary bladder. Am J Pathol 158:849–853
93. Mohammed SI, Bennett PF, Craig BA, et al (2002) Effects of the cyclooxygenase inhibitor, piroxicam, on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. Cancer Res 62:356–358
94. Moyad MA (2003) Bladder cancer prevention. Part I: What do I tell my parents about lifestyle changes and dietary supplements? Curr Opin Urol 13:363–378
95. Kakizoe T (2003) Chemoprevention of cancer: focusing on clinical trials. Jpn J Clin Oncol 33:421–442
96. Zeegers MPA, Kellen E, Buntinx F, et al (2004) The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. World J Urol 21:392–401

ELSEVIER

REMOVAL OF MORE LYMPH NODES MAY PROVIDE BETTER OUTCOME, AS WELL AS MORE ACCURATE PATHOLOGIC FINDINGS, IN PATIENTS WITH BLADDER CANCER—ANALYSIS OF ROLE OF PELVIC LYMPH NODE DISSECTION

ICHIYA HONMA, NAOYA MASUMORI, EIJI SATO, TOSHIHIRO MAEDA, MEGUMI HIROBE, HIROSHI KITAMURA, ATSUSHI TAKAHASHI, NAOKI ITOH, MITSUHARU TAMAKAWA, AND TAIJI TSUKAMOTO

ABSTRACT

Objectives. To examine the role of pelvic lymph node dissection (PLND) in patients who underwent radical cystectomy for bladder cancer. The diagnostic and therapeutic role of PLND is still controversial in bladder cancer. The extent of PLND and the necessary number of lymph nodes to remove have not been defined.

Methods. This retrospective review included 146 patients with refractory superficial and muscle-invasive disease treated with radical cystectomy, regional PLND (internal iliac, external iliac, and obturator nodes) and urinary diversion from January 1990 to December 2002.

Results. Lymph node metastases were detected in 25 patients (17.1%). The average number of nodes removed in the node-positive and node-negative patients was 13.9 and 14.2, respectively. Although no difference was found in disease-specific survival in the node-negative patients when stratified by the number of nodes removed (13 or more versus less than 13), a significant survival advantage was found in the node-positive patients with 13 or more nodes removed versus less than 13 nodes removed. The patients with four or more positive nodes had a worse outcome than those with less than four positive nodes. However, even if the patients had less than four positive nodes, the survival of patients with less than 13 nodes removed was as poor as that of the patients with four or more positive nodes.

Conclusions. In this series, the removal of 13 or more pelvic lymph nodes was essential for more accurate pathologic examination to predict patient outcome and contributed to an increased chance of survival. UROLOGY **68:** 543–548, 2006. © 2006 Elsevier Inc.

Radical cystectomy with pelvic lymph node dissection (PLND) is a standard surgical procedure for muscle-invasive bladder cancer. It is known that lymph node metastasis in patients with bladder cancer is an unfavorable prognostic factor.[1–3] Although it has not been fully documented whether PLND contributes to a favorable outcome, recent studies have indicated that PLND provides a survival advantage for node-positive patients.[4,5] However, the extent of lymph node dissection and the necessary number of nodes to remove have not been standardized.

We retrospectively reviewed patients who underwent radical cystectomy with PLND for bladder cancer at our institute after 1990 when computed tomography (CT) was routinely used as a part of clinical staging and follow-up. We analyzed the rate of pathologic nodal involvement, survival according to the number of positive nodes and/or removed nodes, and clinicopathologic factors predicting for survival of node-positive patients in this study.

This study was supported in part by a Grant-in-Aid for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan.

From the Departments of Urology and Radiology, 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. E-mail: masumori@sapmed.ac.jp

Submitted: July 3, 2005, accepted (with revisions): March 23, 2006

0090-4295/06/$32.00
doi:10.1016/j.urology.2006.03.049

MATERIAL AND METHODS

A total of 171 consecutive patients underwent radical cystectomy and regional PLND with or without neoadjuvant chemotherapy for refractory superficial and muscle-invasive bladder cancer from January 1990 to December 2002 at Sapporo Medical University Hospital. The indications for cystectomy were refractory Tis in 3, high-risk Stage T1 grade 3 in 2, and muscle-invasive cancer in 166 patients. Excluded from the study were 14 patients who underwent noncurative surgery, 3 who died of postoperative complications, 2 who had tumors of nonurothelial origin, and 6 whose nodes were evaluated inaccurately. The exclusions left 146 patients who underwent curative cystectomy with PLND and were adequately monitored for the present retrospective review. No patient had a history of pelvic surgery for other malignancies.

The preoperative evaluation included cystoscopy, 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 had distant metastasis at the initial diagnosis.

Radical cystectomy and regional PLND were performed using a standard technique.[6] PLND included the internal iliac, external iliac, and obturator lymph nodes. Each area of nodes was separately removed as a packet and provided for pathologic examination. The boundaries of dissection were the circumflex iliac vein inferiorly, pelvic side wall laterally, bladder wall medially, and iliac bifurcation superiorly. The common iliac lymph nodes were not removed.

The tumor was staged and graded according to the 1999 TNM classification[7] and the World Health Organization system,[8] respectively. Several pathologists at our hospital performed the histopathologic evaluations. The total number of lymph nodes removed and bearing metastasis was recorded for each site separately. Each node was sectioned at the maximal diameter for analysis of metastasis.

The survival time was analyzed from the date of surgery. The endpoints of the univariate and multivariate analyses were death from bladder cancer. Survival estimates were constructed using the Kaplan-Meier method. The log-rank test was used to evaluate the significance of differences in the univariate analysis. For multivariate analysis, Cox's proportional hazards model was used.

RESULTS

Of the 146 patients, 119 were men and 27 were women. The mean patient age was 65 years (range 38 to 79). Clinically, 70 patients (47.9%) were diagnosed as having extravesical disease (Stage T3 or worse) before cystectomy (Table I). Preoperative CT demonstrated suspected metastasis on the pelvic lymph nodes in 11 patients. Neoadjuvant chemotherapy was given to 54 patients (37.0%), most of whom had Stage T3 or worse and/or pelvic adenopathy. Pathologically, 90 patients (61.6%) had tumors confined to the bladder (pT2 or less) and 56 (38.4%) had tumors penetrating the bladder wall into the perivesical fat or adjacent structures (pT3 or worse). Histologic features of pure urothelial carcinoma were found in 112 patients (76.7%); other histologic components such as squamous cell carcinoma and adenocarcinoma were found in 34 (23.3%). After surgery, 16 patients (11.0%) with Stage pT3 or worse and/or nodal involvement received adjuvant chemotherapy according to the urologists' preference.

TABLE I. *Clinical and pathologic stages and tumor histologic features*

Variable	Patients (n)
Clinical stage	
T1/Tis	5 (3.4)
T2	71 (48.6)
T3	43 (29.5)
T4	27 (18.5)
Pathologic stage	
T0	19 (13.0)
T1/Tis	30 (20.6)
T2	41 (28.1)
T3	37 (25.3)
T4	19 (13.0)
Histologic feature	
Urothelial carcinoma	112 (76.7)
Urothelial carcinoma + other histologic component	28 (19.2)
Other histologic component	6 (4.1)

Data in parentheses are percentages.

Pathologic pelvic lymph node metastasis was found in 25 patients (17.2%). Of the 25 patients, 12 had single nodal involvement (pN1) and 13 had two or more positive nodes (pN2). Metastasis of the obturator node was found in 12 patients, internal iliac node in 12, and external iliac in 8. Of the 11 patients with suspicious pelvic adenopathy on preoperative pelvic CT, 6 had positive nodes but 5 had negative nodes. The number of lymph nodes retrieved by regional PLND ranged from 2 to 42 (mean 14.0). No difference was found in the number of nodes retrieved between the node-positive and node-negative patients (14.2 $\pm$ 5.2 versus 13.9 $\pm$ 7.1). Neither neoadjuvant chemotherapy (14.1 $\pm$ 5.5 with neoadjuvant therapy and 14.0 $\pm$ 7.1 without neoadjuvant therapy, $P = 0.671$) nor patient age (15.4 $\pm$ 6.1, 13.2 $\pm$ 7.3, and 13.5 $\pm$ 5.6 for those younger than 60, 60 to 69, and 70 years or older, respectively, $P = 0.053$) influenced the number of nodes removed. In addition, no difference in the number of nodes removed was observed among the five staff surgeons (data not shown). The number of lymph nodes removed was up to 17 in 80% of the node-positive patients (Fig. 1).

The median follow-up period of the 146 patients was 35 months (range 3 to 169). The median follow-up of the 91 survivors was 69 months. Distant metastases and/or local recurrence developed in 62 (42.5%) of the 146 patients at a median of 11 months (range 2 to 71) after cystectomy. The disease-specific survival rate of the node-negative patients at 1, 2, and 3 years was 91.4%, 78.3%, and

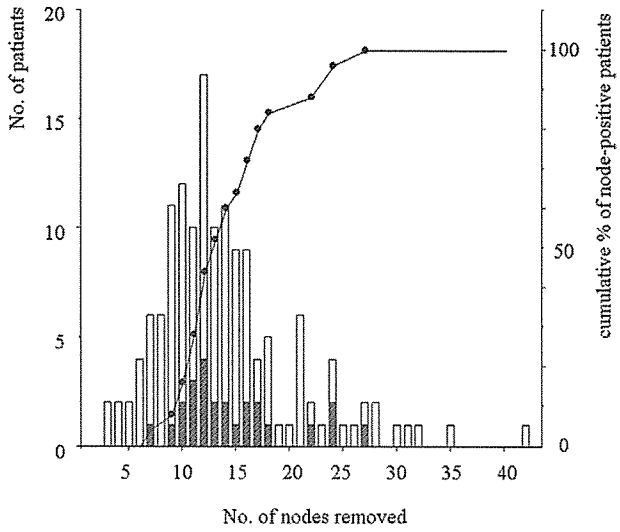

FIGURE 1. *Distribution of node-negative and node-positive patients stratified by number of nodes removed and cumulative percentage of node-positive patients according to number of nodes removed. White bars indicate number of node-negative patients; black bars, number of node-positive patients. Plots and line indicate cumulative percentage of node-positive patients according to number of lymph nodes removed.*

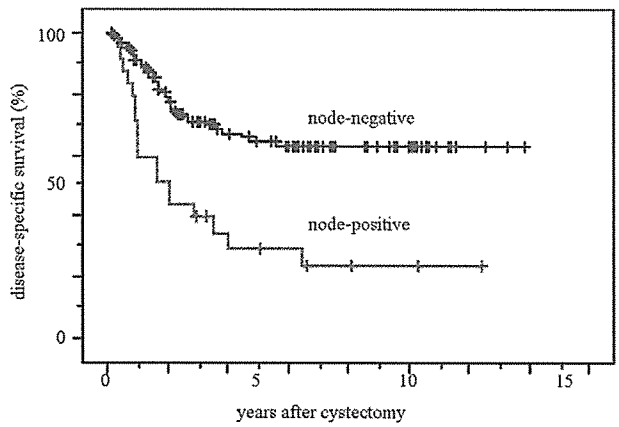

FIGURE 2. *Disease-specific survival of 146 patients stratified by nodal status. Node-positive (n = 25) versus node-negative (n = 121) patients (*P *<0.0001, log-rank test).*

71.0%, respectively. The disease-specific survival rate at 1, 2, and 3 years for the node-positive patients was significantly worse at 60.0%, 44.0%, and 40.0%, respectively (Fig. 2).

The number of lymph nodes removed did not have a significant impact on the disease-specific survival of patients with primary tumors confined to the bladder (pT0-T2; Fig. 3A) or in patients with extravesical disease (pT3/4; Fig. 3B) if they did not have lymph node metastasis. In contrast, removal of 13 or more nodes resulted in a significant survival advantage for node-positive patients (Fig. 3C). The patients with four or more positive nodes had a poorer outcome than did those with less than

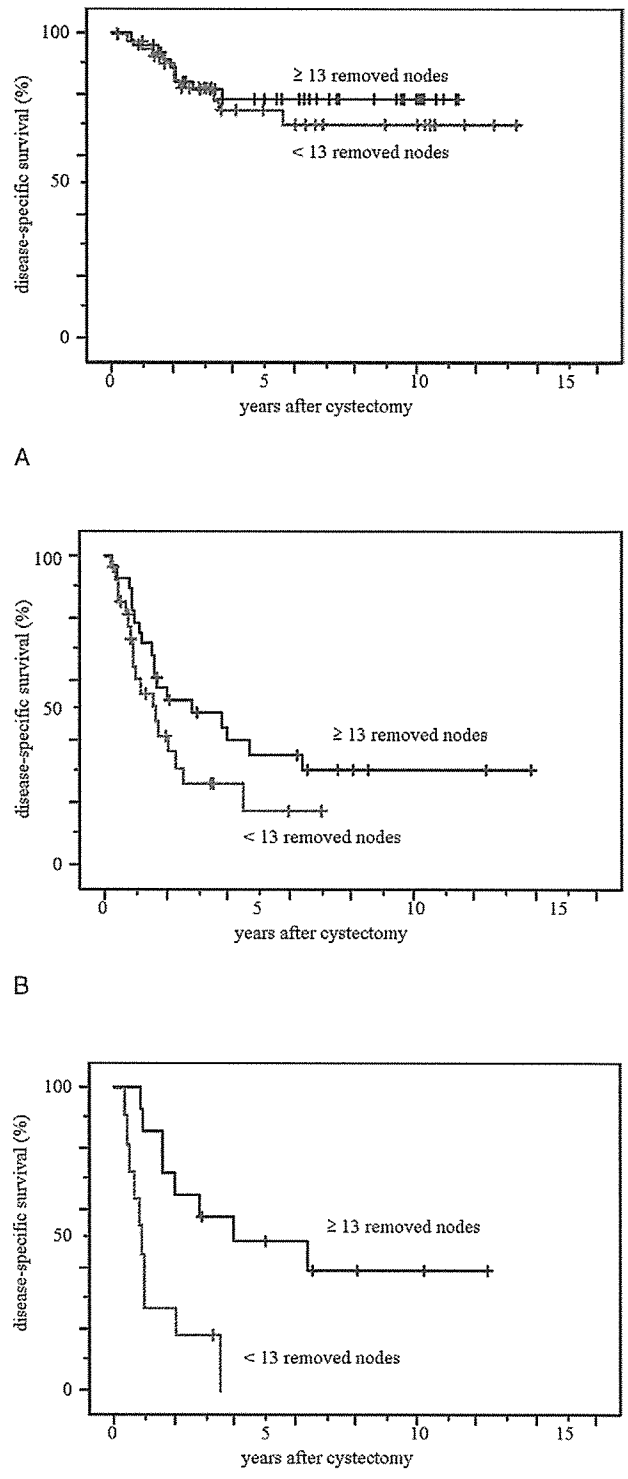

FIGURE 3. *Disease-specific survival according to number of nodes removed. (A) Patients with pathologically organ-confined tumor and negative nodes (pT0-T2, pN0); number of nodes removed was 13 or more (n = 46) versus less than 13 (n = 44;* P *= 0.604). (B) Patients with pathologically extravesical tumor and negative nodes (pT3-T4, pN0); number of nodes removed was13 or more (n = 28) versus less than 13 (n = 28;* P *= 0.113). (C) Node-positive patients (pN+) with 13 or more (n = 14) versus less than 13 (n = 11) nodes removed (*P *= 0.002). All* P *values determined by log-rank test.*

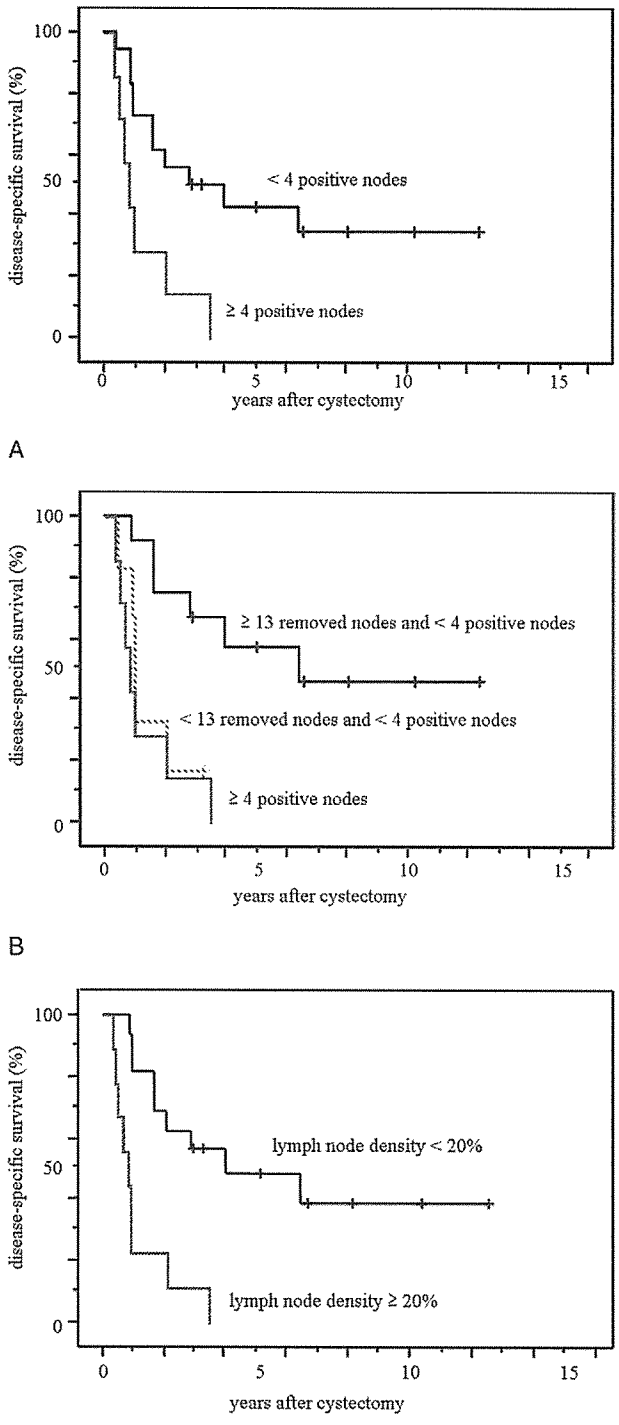

FIGURE 4. *Disease-specific survival of node-positive patients. (A) According to number of positive nodes: four or more (n = 7) versus less than four (n = 18;* P = *0.003). (B) According to combination of numbers of nodes removed and positive nodes: 13 or more nodes removed and less than 4 positive nodes (n = 12) versus less than 13 nodes removed and less than 4 positive nodes (n = 6;* P = *0.016), and less than 13 nodes removed and less than 4 positive nodes (n = 6) versus 4 or more positive nodes (n = 7;* P = *0.499). (C) According to lymph node density: 20% or more (n = 9) versus less than 20% (n = 16;* P = *0.0001). All* P *values determined by log-rank test.*

four positive nodes (Fig. 4A). However, even if the patients had less than four positive nodes, the survival of those with less than 13 nodes removed was as poor as that of the patients with four or more positive nodes (Fig. 4B). No significant difference in primary stage distribution was observed among these three groups (Fig. 4B). The disease-specific survival of the patients with a lymph node density (number of positive nodes divided by number of nodes removed) greater than 20% was significantly worse than for those with a lymph node density of 20% or less (Fig. 4C).

Multivariate analysis demonstrated that the number of nodes removed, number of positive nodes, and pathologic stage were independent predictors of disease-specific survival (Table II).

COMMENT

The main objective of PLND is to provide accurate staging of bladder cancer. If pelvic nodal involvement is proven, it should be considered a manifestation of a systemic disease.[1–3] However, the independent value of PLND for survival in patients with bladder cancer remains controversial, although it has been demonstrated that PLND cures some node-positive patients.[4,5]

In the present study, patients with less than four positive nodes had a statistically significant survival advantage compared with four or more positive nodes. Similar results were reported by Lerner *et al.*,[9] whose cutoff was six positive nodes, and Mills *et al.*[5] and Frank *et al.*,[10] who set the cutoff at five positive nodes. Stein *et al.*[11] also reported that patients with less than eight positive nodes had a statistically significant survival advantage compared with those with eight or more positive nodes. Thus, radical surgery with PLND provides benefits for some patients with nodal disease, especially those who have micrometastasis to a few nodes. The poor outcomes of patients with many positive nodes may imply the inherent aggressive biologic nature of the tumor with concomitant systemic spread.

In addition to the number of positive nodes involved, the results of the present study have demonstrated that the number of nodes removed has a significant impact on disease-specific survival in node-positive patients. The removal of 13 or more nodes had a survival benefit even in the node-positive patients. Several recent studies have had similar results.[4,5] Stein *et al.*[11] demonstrated that patients with 15 or more nodes removed had better recurrence-free survival than did those with less than 15 nodes removed. Herr *et al.*[12] reported that excising 11 or more nodes from the obturator, internal and external iliac nodes, and middle common iliac nodes significantly improved survival in

TABLE II. *Multivariate analysis of parameters predicting disease-specific survival in node-positive patients*

Parameter	Multivariate *P* Value	Hazard Ratio	95% Confidence Interval
Histologic feature (pure UC vs. other histologic component ± UC)	0.6897	1.279	0.382–4.279
Grade (G1-G2 vs. G3)	0.4450	1.936	0.355–10.550
Pathologic stage (≤T2 vs. ≥T3)	0.0132	8.205	1.553–43.343
Removed nodes (≥13 vs. <13)	0.0008	9.363	2.526–34.704
Positive nodes (<4 vs. ≥4)	0.0115	4.944	1.431–17.085
Adjuvant chemotherapy (with vs. without)	0.6164	1.344	0.423–4.274

Key: UC = urothelial carcinoma.

node-positive patients. In the present study, even if the patients had less than four positive nodes, the prognosis of the patients with less than 13 nodes removed was as poor as that of the patients with four or more positive nodes. Thus, removal of an adequate number of lymph nodes is more likely to remove positive lymph nodes and yield accurate nodal staging, and limited dissection, including only a few negative lymph nodes, may leave positive lymph nodes behind.

In contrast, the number of lymph nodes removed was not related to improved survival in the node-negative patients, especially those with pathologically organ-confined disease in the present study. The Southwest Oncology Group study 8710 showed that the survival advantage conferred by the removal of 10 or more nodes was found even in node-negative patients.[13] Herr *et al.*[12] also demonstrated that removal of eight or more nodes resulted in better survival, not only in patients with Stage pT2pN0, but also in those with Stage pT3-pT4pN0. The low probability of occult nodal metastasis in organ-confined disease may make it difficult to elucidate the therapeutic role of PLND in our small study. However, the node-negative patients with extravesical disease tended to have better survival if they had had 13 or more removed nodes than if they had had less than 13 nodes removed. Thus, removal of more pelvic lymph nodes has the potential to contribute to improved survival in both node-negative and node-positive patients.[14,15]

This study could be criticized because it was retrospective, with a limited number of patients undergoing only endopelvic lymph node dissection. The clinical benefit of a more extended area for nodal dissection advocated by recent studies remains to be determined.[16,17] Although no agreement has been reached on the boundary of lymph node dissection, previous studies have demonstrated that 10% of single metastases involved the common iliac nodes[17] and nodal metastases in patients with multiple nodal metastases were found in the common iliac and extrapelvic nodes, such as paracaval, aortocaval, and para-aortic nodes.[18] Because preoperative assessment of nodal status is difficult even using modern imaging modalities, complete lymph node dissection is necessary for accurate nodal staging of bladder cancer. In addition, the most effective therapy for metastatic nodes might be complete surgical dissection. Thus, it is mandatory to remove as many pelvic lymph nodes as possible for accurate staging, prognosis, and radical treatment.

CONCLUSIONS

The results of our study have shown that removal of 13 or more lymph nodes has a significant impact on disease-specific survival in node-positive patients. Adequate PLND provides accurate nodal staging and important pathologic information for prognosis in node-positive patients.

REFERENCES

1. 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.
2. Dalbagni G, Genega E, Hashibe M, *et al:* Cystectomy for bladder cancer: a contemporary series. J Urol **165**: 1111–1116, 2001.
3. 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.
4. 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.
5. Mills 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.
6. Whitmore WF Jr: Management of invasive bladder neoplasms. Semin Urol **1**: 34–41, 1983.
7. Sobin LH, and Wittekind CH: *TNM Classification of Malignant Tumors*, 5th ed. New York, Wiley-Liss, 1997.
8. Mostofi FK, Davis CJ, and Sesterhenn IA: *Histological Typing of Urinary Bladder Tumours*, 2nd ed. New York, Springer, 1999.
9. Lerner SP, Skinner DG, Lieskovsky G, *et al:* The rationale for en bloc pelvic lymph node dissection for bladder cancer patients with nodal metastasis: long-term results. J Urol **149**: 758–765, 1993.
10. Frank I, Cheville JC, Blute ML, *et al:* Transitional cell carcinoma of the urinary bladder with regional lymph node

involvement treated by cystectomy. Cancer 97: 2425–2431, 2003.

11. Stein JP, Cai J, Groshen S, *et al:* Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: the concept of lymph node density. J Urol 170: 35–41, 2003.

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. Herr HW, Faulkner JR, Grossman B, *et al:* Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 22: 2781–2789, 2004.

14. Leissner J, Hohenfellner R, Thuroff JW, *et al:* Lymphadenectomy in patients with transitional cell carcinoma of the bladder; significance for staging and prognosis. BJU Int 85: 817–823, 2000.

15. Konety BR, Joslyn SA, and O'Donnell M: 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 169: 946–950, 2003.

16. Thalmann GN, Fleichmann A, Mills RD, *et al:* Lymphadenectomy in bladder cancer. EAU Update Series 1: 100–107, 2003.

17. Leissner J, Ghoneim MA, Abol-Enein H, *et al:* Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol 171: 139–144, 2004.

18. Abol-Enein H, El-Baz M, Abd El-Hameed MA, *et al:* Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study—a single center experience. J Urol 172: 1818–1821, 2004.

Evaluation for Surrogacy of End Points by Using Data from Observational Studies: Tumor Downstaging for Evaluating Neoadjuvant Chemotherapy in Invasive Bladder Cancer

Satoshi Teramukai,[1] Hiroyuki Nishiyama,[2] Yoshiyuki Matsui,[2] Osamu Ogawa,[2] and Masanori Fukushima[1]

Abstract **Purpose:** In clinical cancer trials for evaluating neoadjuvant chemotherapy, tumor downstaging is frequently used as a surrogate end point for overall survival. We evaluated the surrogacy of tumor downstaging using data from a follow-up observational study in bladder cancer.

Experimental Design: A total of 586 patients (from 32 Japanese hospitals) who underwent radical cystectomy for invasive bladder cancer (clinical T2 to T4) between 1990 and 2000 were analyzed. We considered changes over time in clinical stage at diagnosis and pathologic stage at cystectomy as a surrogate end point, and survival time after cystectomy as a true end point. First, we developed a new criterion for tumor downstaging. Second, we statistically evaluated surrogacy for the criterion using Prentice's criteria.

Results: To develop the criterion of end points based on tumor downstaging, we selected the best classification among all possible classifications in an attempt to separate prognosis for patients. The hazard ratios after adjustment for prognostic factors in the intermediate effect patients and the poor effect patients were 1.9 (95% confidence interval, 1.0-3.7) and 5.0 (95% confidence interval, 2.6-9.8), respectively, compared with that in the good effect patients. The conditions for correlation and conditional independency of Prentice's criteria were satisfied approximately. Neoadjuvant chemotherapy has a statistically significant tumor downstaging effect, whereas there was no difference on survival between treatment groups.

Conclusions: The tumor downstaging effect could be an appropriate intermediate end point for screening novel neoadjuvant chemotherapy for invasive bladder cancer. The dataset from follow-up studies were useful for evaluating the surrogacy of end points.

Appropriate surrogate end points are critical for developing new therapies through evaluation of biological activity. The surrogate end point is a test, measurement, score, or some other similar variable that is used in place of a clinical event in the design of a trial, or in summarizing results from it. Used because the variable is believed to be correlated with the clinical event of interest and because of its perceived utility in yielding detectable treatment differences (1). In clinical cancer trials, overall survival is considered to be the most reliable and definitive true end point. However, surrogate end points such as tumor burden outcomes including objective tumor effect, disease-free survival, and progression-free survival, or biomarkers including prostate-specific antigen have been widely used because trials with the true clinical outcome are often longer and larger. In a recent analysis for oncologic drugs in the U.S., 68% (39 of 57) of the regular approvals and all of the 14 accelerated approvals were based on end points other than overall survival in the last 13 years (2). To use a valid and reliable surrogate end point in cancer clinical trials, we should evaluate the surrogacy of end points on a case-by-case basis because the adequacy as a surrogate end point is highly dependent upon the type and/or stage of cancer, and other available therapies.

For statistical validation of surrogate end points, Prentice (3) proposed the validity criterion that a valid between-group analysis of the surrogate end point also constitutes a valid analysis of the true clinical end point. Freedman et al. (4) showed that these criteria were not straightforward to verify by hypothesis testing. Recently, Buyse et al. (5) have proposed two new measures, termed "relative effect" and "adjusted association." However, to explore the validity of a surrogate end point by these measures, we have to combine information from several randomized clinical trials testing the effect of a treatment on both the surrogate and the true end points (6). In practice, we rarely have information about both end points from even single randomized clinical trials before designing a feature clinical trial for new agents. Such situations have motivated us to assess the surrogacy of end points using

Authors' Affiliations: [1]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital and [2]Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Received 7/24/05; revised 9/17/05; accepted 10/10/05.

Grant support: Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, and Technology of Japan.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Satoshi Teramukai, Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, 54 Shogoin Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Phone: 81-75-751-4768; Fax: 81-75-751-4732; E-mail: steramu@kuhp.kyoto-u.ac.jp.

doi:10.1158/1078-0432.CCR-05-1598

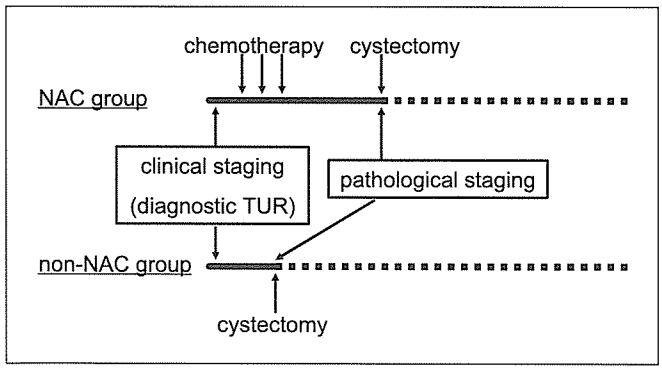

Fig. 1. Schema of treatment group comparison.

available information other than randomized studies. In clinical trials for evaluating neoadjuvant chemotherapy in bladder cancer, "tumor downstaging" is frequently used as a surrogate end point for overall survival. Clinical staging with transurethral resection (TUR) is very important in treatment planning and prognosis. However, the reliability of TUR staging is a problem. The disparity between clinical and pathologic staging may be caused by repeat TUR, i.e., TUR effect, and measurement error (7). We developed a new criterion of tumor downstaging effect and evaluated the surrogacy of tumor downstaging using data from a follow-up observational study in invasive bladder cancer.

Patients and Methods

A total of 1,131 patients who underwent radical cystectomy for invasive bladder cancer between 1990 and 2000 at 32 Japanese hospitals were retrospectively registered (8). The information that was collected from the medical records included age, gender, histology, clinical staging, and pathologic staging according to the tumor-node-metastasis classification (9), and the presence of perioperative systemic chemotherapy. In the present study, 586 patients who have clinical stage T2 to T4, N0, M0, transitional cell carcinoma, and who were less than 80 years old were included.

Figure 1 shows a schema of treatment group comparison. The patients were divided into two treatment groups, i.e., neoadjuvant chemotherapy (NAC) group and no neoadjuvant chemotherapy (non-NAC) group. After the clinical staging was done based on diagnostic TUR, chemotherapy followed by radical cystectomy was done in the NAC group, and only cystectomy was done in the non-NAC group. More precise pathologic staging was done at the time of cystectomy.

Statistical analysis. Prentice's criterion for evaluating the surrogacy of end points is a set of four conditions as follows (3, 5, 10):

PC1: $f(T|Z) \neq f(T)$ so the treatment affects the distribution of T,
PC2: $f(S|Z) \neq f(S)$ so the treatment affects the distribution of S,
PC3: $f(T|S) \neq f(T)$ so the surrogate affects the distribution of T,
PC4: $f(T|S, Z) = f(T|S)$ so that conditionally on S, T is independent of Z.

where, for example, $f(T|Z)$ is the conditional distribution of the true end point T given the treatment assignment Z, and S is the surrogate end point. In the present study, the treatment Z is set to 0 for non-NAC group and 1 for NAC group. The candidate surrogate end point S is a tumor downstaging effect based on the difference between clinical stage and pathologic stage and the true end point T is overall survival after cystectomy. Therefore, in this setting, the PC1 means that neoadjuvant chemotherapy must affect overall survival, PC2 means that neoadjuvant chemotherapy must affect tumor downstaging, PC3 means that tumor downstaging must be correlated with overall survival, and PC4 means that tumor downstaging must fully capture the net effect of neoadjuvant chemotherapy on overall survival.

The survival curves were estimated with the Kaplan-Meier method. The Cox proportional hazards model was used to estimate hazard ratios (HR) after adjustment for covariates. All statistical analyses were done by using SAS version 8.02 (SAS Institute, Inc., Cary, NC).

Results

A total of 586 patients [481 men (82%) and 105 women (18%)], with a mean age of 65.2 years (range, 33-80 years), were treated with radical cystectomy with bilateral lymph node dissection. Out of 586 patients, 183 patients (31%) were treated with neoadjuvant chemotherapy. As the neoadjuvant chemotherapy, methotrexate, vinblastine, doxorubicin, and cisplatin, was used in 43% of patients and used for 1.5 cycles on average. The other patients were treated with the modified cisplatin-based regimens including methotrexate, epirubicin and cisplatin; and cisplatin, cyclophosphamide, and doxorubicin; and cisplatin, adriamycin, and methotrexate, as well as other miscellaneous regimens (11-15). The distributions of prognostic factors in treatment groups were as follows: mean patient age was 65.8 years (SD, 8.8) and 63.7 years (SD, 8.6)

Table 1. Hazard ratios by clinical stage and pathologic stage

Clinical stage	Pathologic stage (95% CI)				
	P0/1	P2a	P2b	P3	P4
All cases					
T2	1	1.9 (0.9-4.1)	2.4 (0.9-6.1)	4.3 (1.8-10.3)	11.1 (4.2-29.5)
T3/4	1.5 (0.6-3.6)	2.2 (0.9-5.5)	4.6 (2.2-9.7)	5.3 (2.6-10.7)	5.3 (2.5-11.6)
Non-NAC group					
T2	1, $n = 59$	2.2 (0.9-5.6), $n = 81$	2.7 (0.9-8.0), $n = 30$	4.9 (1.7-14.0), $n = 22$	14.4 (4.5-45.9), $n = 11$
T3/4	2.6 (0.8-8.5), $n = 26$	2.2 (0.7-7.1), $n = 24$	5.5 (2.1-14.1), $n = 43$	6.2 (2.5-15.3), $n = 80$	5.3 (1.9-14.7), $n = 27$
NAC group					
T2	1, $n = 27$	1.3 (0.3-6.0), $n = 18$	2.6 (0.3-23.5), $n = 3$	3.4 (0.6-21.1), $n = 4$	11.0 (1.2-103), $n = 2$
T3/4	1.0 (0.3-3.5), $n = 40$	2.5 (0.6-10.4), $n = 13$	3.7 (1.1-12.3), $n = 20$	3.9 (1.2-12.2), $n = 40$	5.5 (1.7-18.2), $n = 16$

in the non-NAC and NAC groups, respectively. The patient proportion of positive lymph node involvement was slightly higher in the non-NAC group (17.4%) than in the NAC group (14.2%), but that of clinical T3 or T4 was much higher in the NAC group (70.5%) than in non-NAC group (49.6%). Proportions of receiving postoperative chemotherapy were similar in both groups, i.e., 23.1% in the non-NAC group, 23.0% in the NAC group.

Development of tumor downstaging effect criterion. We estimated HRs on the overall survival after cystectomy by 10 combinations of clinical and pathologic stage after adjustment for age, lymph node involvement, and adjuvant chemotherapy (Table 1). The estimated HRs by treatment group were similar to that in all cases. First, the 10 combinations were ordered according to the size of HR [1, T2 to P0/1 (HR, 1); 2, T3/4 to P0/1 (HR, 1.5); 3, T2 to P2a (HR, 1.9); 4, T3/4 to P2a (HR, 2.2); 5, T2 to P2b (HR, 2.4); 6, T2 to P3 (HR, 4.3); 7, T3/4 to P2b (HR, 4.6); 8, T3/4 to P3 (HR, 5.3); 9, T3/4 to P4 (HR, 5.3); 10, T2 to P4 (HR, 11.1)] in all cases. Second, we selected the best classification among all possible classifications in an attempt to separate the prognosis of patients with respect to the Akaike's information criteria. The total number of examined classifications was 45—9 for two categories (good/poor) and 36 for three categories (good/intermediate/poor). For example, the examined classifications were 1 (good) versus 2 to 10 (poor), 1 to 2 versus 3 to 10,..., 1 to 9 versus 10 for two categories, and 1 (poor) versus 2 (intermediate) versus 3 to 10 (poor), 1 versus 2 to 3 versus 4 to 10, 1 versus 2 to 4 versus 5 to 10,..., 1 to 8 versus 9 versus 10 for three categories.

As a result, patients were classified into three categories, i.e., good effect (1, T2 to P0/1), intermediate effect (2-5, T2 to P2a/2b or T3/4 to P0/1/2a), and poor effect (6-10, T2 to P3/4 or T3/4 to P2b/3/4). Survival curves according to the tumor downstaging effect were shown in Fig. 2A. The HRs in the intermediate effect patients and the poor effect patients were 1.9 [95% confidence interval (CI), 1.0-3.7] and 5.0 (95% CI, 2.6-9.8), respectively, compared with that in the good effect patients after adjustment for age, lymph node involvement, and adjuvant chemotherapy. The risks by tumor downstaging effect were similar between treatment groups (Fig. 2B and C).

Statistical evaluation for surrogacy of the end point. It is obvious that to fulfill the PC3 condition, tumor downstaging must be correlated with overall survival because we selected the tumor downstaging in such a way that the patients can be classified based on their overall survival. To verify the PC4 condition that tumor downstaging must fully capture the net effect of neoadjuvant chemotherapy on overall survival, it is usually stated that the coefficient corresponding to treatment effect corrected for tumor downstaging is required to be equal to zero. The HRs between treatment groups by tumor downstaging effect, pooled HR and their 95% CIs were estimated after adjustment for age, lymph node involvement, and adjuvant chemotherapy (Table 2). The estimated pooled HR was 1.06 (95% CI, 0.77-1.47) when stratifying by tumor downstaging effect. Although the nonsignificance of the test in which HR = 1 does not prove the PC4 condition, it was suggested that PC4 might be plausible in this study because the pooled HR was close to 1.

As the data is not from randomized trials, strictly speaking, the inference for treatment comparison is not valid and thus

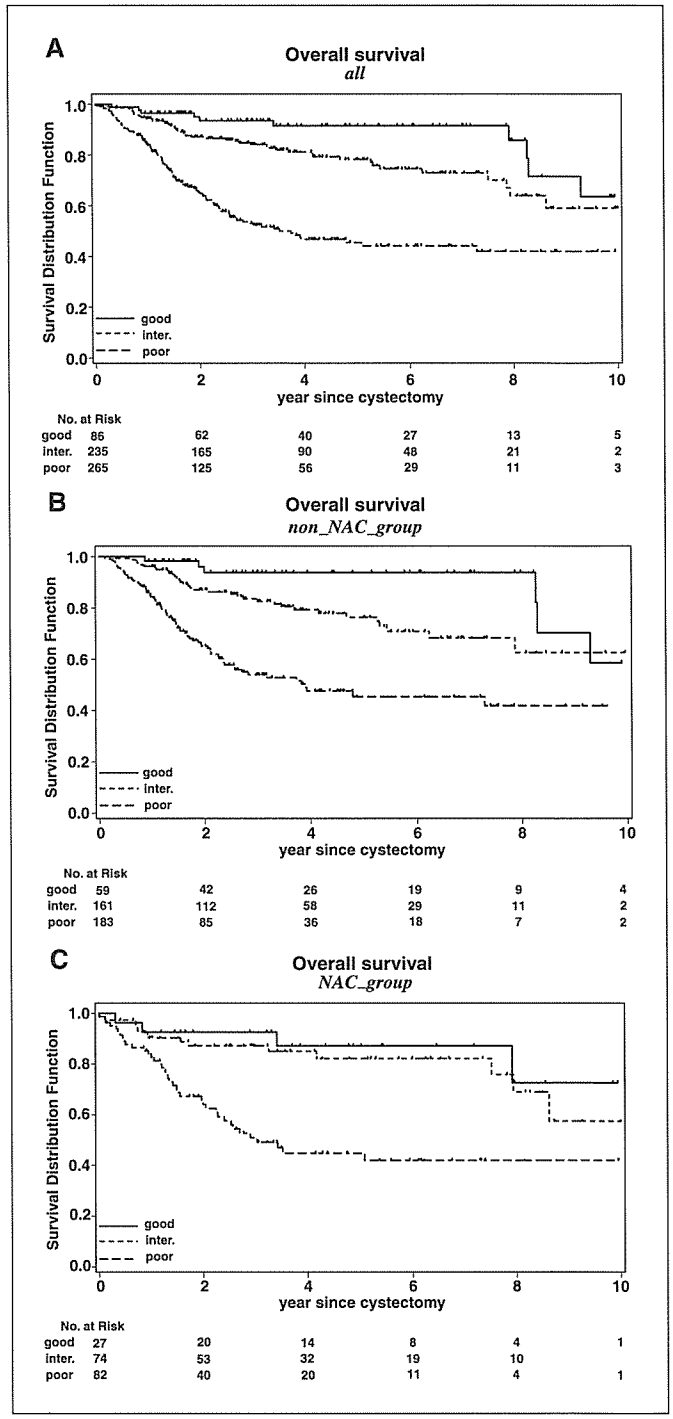

Fig. 2. Survival curves according to tumor downstaging effect in all patients (*A*), in the nonneoadjuvant chemotherapy group (*B*), and in the neoadjuvant chemotherapy group (*C*).

the PC1 and PC2 conditions cannot be evaluated. However, we attempted to verify the PC1 and PC2 conditions after adjustment for the confounding factors. For evaluating PC2, we used the Cochran-Mantel-Haenszel statistic with rank score, i.e., the stratum-adjusted Wilcoxon test, because of imbalance of clinical stage distribution among treatment groups. The effect of neoadjuvant chemotherapy on tumor downstaging effect was statistically significant (χ^2 = 16.1, P = 0.001; Table 3).

Table 2. Overall survival HRs for NAC over non-NAC, according to tumor downstaging effect

Tumor downstaging effect	No. of patients		HR (95% CI)
	NAC	Non-NAC	
Good	27 (15%)	59 (15%)	1.32 (0.37-4.74)
Intermediate	74 (40%)	161 (40%)	0.76 (0.40-1.45)
Poor	82 (45%)	183 (45%)	1.17 (0.79-1.73)
Pooled, stratified by tumor downstaging effect	183	403	1.06 (0.77-1.47)

To evaluate the PC1 condition, we compared the overall survival between treatment groups by clinical stage. In clinical stage T2, the treatment effect was not statistically significant (HR, 0.87; 95% CI, 0.44-1.70) after adjustment for age, lymph node involvement, and adjuvant chemotherapy. Similarly, in clinical stage T3 or T4, the treatment effect was not statistically significant (HR, 0.98; 95% CI, 0.67-1.43).

Discussion

In this study, we proposed a new tumor downstaging criterion based on prognosis in invasive bladder cancer patients for evaluating neoadjuvant chemotherapy. Objective tumor response has been a widely accepted measure of cancer chemotherapy activity. According to international standards, including WHO criteria (16) and Response Evaluation Criteria in Solid Tumors (17), patients were usually classified into either responders (complete response or partial response) or non-responders (no change or progressive disease). The objective tumor response can be assessed even in single-arm studies, however, in the NAC group of the present study, overall survival had no difference between responders and non-responders for neoadjuvant chemotherapy (adjusted HR, 1.09; 95% CI, 0.59-2.03; Fig. 3). Therefore, objective tumor response might not be a valid surrogate end point for evaluating neoadjuvant chemotherapy in invasive bladder cancer.

Some investigators defined the criterion for tumor downstaging (7, 18). However, few data were available with regard to clinical staging and pathologic staging for patients who were treated with or without neoadjuvant chemotherapy, and no definite criterion has been developed based on the prognosis of patients. In the present study, the HRs among clinical stages were different even on the same pathologic stage, especially on $P_{0/1}$ and P_{2b} in the non-NAC group (Table 1). This suggests that unmeasurable components, including the clinician's subjective judgment on clinical stage, might reflect different prognoses. With regard to tumor downstaging in invasive bladder cancer, it is questionable to generalize the findings to other cancers because downstaging can occur without chemotherapy when the tumor is removed by the diagnostic TUR (7). In addition to the TUR effect, misclassification for staging system, called staging error, have to be considered. In the present study, a proportion of good downstaging effect was 29% even in the non-NAC group. This means that a control group is essential for evaluating therapies in invasive bladder cancer if the tumor downstaging effect is used as an end point of clinical trials.

We statistically evaluated the surrogacy of the end point using data from a follow-up observational study. Prentice's criterion was useful for that purpose, especially for the evaluation of PC3 (correlation) and PC4 (conditional independency). In the present study, the PC3 and PC4 conditions were satisfied approximately. Although the study is not a randomized trial, it is suggested that the neoadjuvant chemotherapy affects tumor downstaging, i.e., PC2 (tumor downstaging benefit) is acceptable, but the treatment does not affect overall survival, i.e., PC1 (survival benefit) is unacceptable. We gave an actual example of hypothetical situations from other articles (5, 10), which showed that the PC2 does not imply the PC1. As another actual case, a randomized trial for locally advanced bladder cancer concluded that the survival benefit of neoadjuvant chemotherapy was of borderline statistical significance ($P = 0.06$), whereas the tumor downstaging effect was statistically significant ($P = 0.001$; ref. 7). Do the inconsistent results between PC1 and PC2 depend on the differences of statistical power for evaluating these conditions? We calculated the power of two kinds of statistical tests, i.e., Wilcoxon rank-sum test for tumor downstaging effect and log-rank test for overall survival, based on our data. If the expected proportions of downstaging effect are 0.50 (good), 0.39 (intermediate), and 0.11 (poor) in the NAC group and 0.29 (good), 0.55 (intermediate), and 0.16 (poor) in the non-NAC group from the data in clinical stage T2, a sample size of 96 in each group will have 80% power to reject the null hypothesis using a Wilcoxon rank-sum test with a 0.05 two-sided significance level (19). On the other hand, if the expected 5-year survival probability in the non-NAC group is 0.5, 0.6, and 0.7 and HR is 0.87, a corresponding sample size in each group will be 1,595, 2,004, and 2,683, respectively, using a 0.05 level two-sided log-rank test for equality of survival curves (20). The difference of statistical power is critical for evaluating the PC1 and PC2 conditions. In two recently published studies, the survival curves for patients treated with neoadjuvant

Table 3. Tumor downstaging effect of treatment according to clinical stage

Clinical stage	Treatment	Tumor downstaging effect			Total
		Good	Intermediate	Poor	
T2	NAC	27 (50%)	21 (39%)	6 (11%)	54
	non-NAC	59 (29%)	111 (55%)	33 (16%)	203
T3/4	NAC	0	53 (41%)	76 (59%)	129
	non-NAC	0	50 (25%)	150 (75%)	200

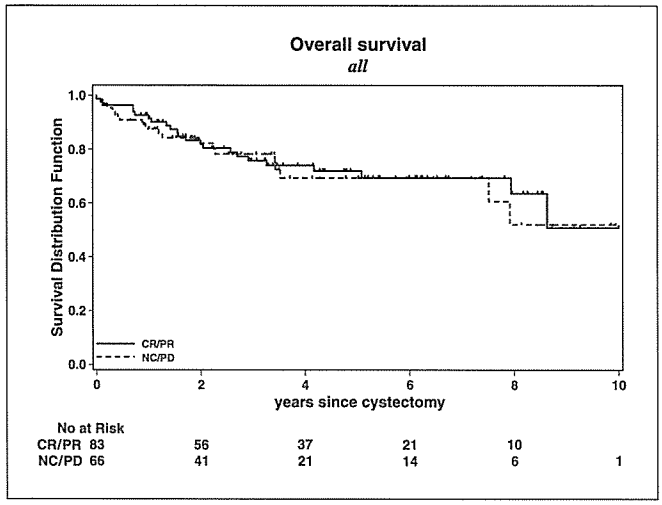

Fig. 3. Survival curves according to tumor response (CR/PR versus NC/PD). CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

methotrexate, vinblastine, doxorubicin, and cisplatin was superior for patients treated with cystectomy alone, with a HR of 0.74 (95% CI, 0.55-0.99) in a randomized trial (7, 21), and platinum-based combination chemotherapy showed a survival benefit with a HR of 0.87 (95% CI, 0.78-0.97) in a meta-analysis of individual patient data (22). The HR which we assumed to calculate the power might be plausible from these results. However, an important question for implementing neoadjuvant chemotherapy for patients with invasive bladder cancer remains, i.e., how do we select the appropriate patients for combination therapy (23).

Buyse et al. (5, 6) have emphasized that we have to combine information from several randomized clinical trials testing the effects of treatment on both surrogate and true end points to explore the validity of a surrogate end point. In practice, we must assess the surrogacy of a candidate end point without data from a randomized trial because the primary objective of a randomized trial will often be to evaluate survival benefit, hence, if the survival benefit were known to be true, then one would have to question the value of conducting such a study. Nonetheless, the purpose of the evaluation of surrogacy should be restricted to find out "appropriate intermediate end points" (10). Fleming et al. (24) also pointed out that surrogate end points can be useful in phase 2 screening trials for identifying whether a new intervention is biologically active and for guiding decisions about whether the intervention is promising enough to justify a large definitive trial with clinically meaningful outcomes. The basic premise is that we cannot predict a treatment effect on the true end point from the effect on the surrogate end point. In conclusion, the tumor downstaging effect could be an appropriate intermediate end point in phase 2 trials for screening novel neoadjuvant chemotherapy in invasive bladder cancer. The dataset from follow-up studies were useful for evaluating the surrogacy of end points.

Acknowledgments

We thank the hospitals associated with Kyoto University, Nara Medical University, and Nagoya University for providing clinical data.

References

1. Meinert CL. Clinical trials: design, conduct, and analysis. Oxford: Oxford University Press; 1986. p. 304.
2. Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003;21:1404–11.
3. Prentice RL. Surrogate end points in clinical trials: definition and operational criteria. Stat Med 1989;8: 431–40.
4. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med 1992;11:167–78.
5. Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. Biometrics 1998;54:1014–29.
6. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000;1:49–67.
7. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
8. Nishiyama H, Habuchi T, Watanabe J, 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.
9. Fleming ID, Cooper JS, Henson DE, et al., editors. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven; 1997. p. 241–3.
10. Berger VW. Does the Prentice criterion validate surrogate endpoints? Stat Med 2004;23:1571–8.
11. Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403–7.
12. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T. 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;28:497–501.
13. Sternberg JJ, Bracken RB, Handel PB, Johnson DE. Combination chemotherapy (CISCA) for advanced urinary tract carcinoma. A preliminary report. JAMA 1977;238:2282–7.
14. Oshima S, Ono Y, Fujita T, et al. Three-drug combination chemotherapy for advanced urothelial tract carcinoma. Cancer Chemother Pharmacol 1987;20: S20–3.
15. Matsui Y, Nishiyama H, Watanabe J, et al. The current status of perioperative chemotherapy for invasive bladder cancer: a multiinstitutional retrospective study in Japan. Int J Clin Oncol 2005;10:133–8.
16. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47:207–14.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
18. Splinter TAW, Scher HI, Denis L, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. J Urol 1992;147:606–8.
19. Kolassa JE. A comparison of size and power calculations for the Wilcoxon statistic for ordered categorical data. Stat Med 1995;14:1577–81.
20. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Stat Med 1982;1:121–9.
21. Raghavan D. Chemotherapy and cystectomy for invasive transitional cell carcinoma of bladder. Urol Oncol 2003;21:468–74.
22. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003;361:1927–34.
23. Millikan R, Siefker-Radtke A, Grossman HB. Neoadjuvant chemotherapy for bladder cancer. Urol Oncol 2003;21:464–7.
24. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.

International Journal of Urology (2006) **13**, 703–706

Original Article

5-year interval change in voiding function of orthotopic ileal neobladder

YOICHI ARAI[1], ATSUSHI TAKEDA[1], YOJI TAKI[2], YUSAKU OKADA[3] AND OSAMU OGAWA[4] AND THE TOHOKU-KYOTO URINARY RECONSTRUCTION STUDY GROUP*

[1]*Department of Urology, Tohoku University Graduate School of Medicine, Sendai,* [2]*Department of Urology, Toyooka Public Hospital, Toyooka,* [3]*Department of Urology, Shiga University of Medical Science, Otsu, and* [4]*Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan*

Aim: We report the 5-year interval change in voiding function of orthotopic ileal neobladder.
Methods: Voiding function was evaluated at two points with an interval of 5 years in 49 patients with orthotopic ileal neobladder. The first and second surveys were performed in May, 1998 (1998 survey) and in April 2003 (2003 survey), respectively. Median age at operation was 67 years, ranging 47–77. Median follow-up times at the first and the second surveys were 19.5 months (range, 3–87) and 67.5 months (range, 62–145), respectively.
Results: There was no significant change in daytime continence status between the 1998 and 2003 surveys. More than 95% never or only occasionally suffered daytime incontinence in the two surveys. On the other hand, 15 (34.1%) and 14 (31.8%), respectively, experienced night-time incontinence, despite regular voiding during the night. When voiding patterns were analysed, 11 patients (23.4%) sometimes or often performed catheterization because of difficulty in urinating or incomplete emptying of the neobladder in the 1998 survey. Three patients (6.4%) were unable to void and required regular catheterization. In the 2003 survey, however, such poor voiders increased to nine (19.1%), although the difference was not significant. During the study period of 5 years, there was no change in renal function.
Conclusions: Continence status, either at daytime or at nighttime, was stable during the study period. The number of the patients who needed regular catheterization tended to increase, suggesting deterioration of voiding function with time. Careful long-term follow up is warranted.

Key words neobladder, urinary reconstruction, voiding function.

Introduction

The orthotopic neobladder enables patients to void through his or her own urethra. Thus, the neobladder is potentially capable of providing better quality of life for cystectomy patients. To date, many forms of bladder substitute have been reported, all giving comparable results.[1–5]

Correspondence: Yoichi Arai MD, Department of Urology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
Email: yarai@uro.med.tohoku.ac.jp

Received 5 September 2005; accepted 15 November 2005.
*Yoichi Arai, Atsushi Takeda, Masanori Kato; Tohoku University Graduate School of Medicine, Sendai. Yoji Taki, Hideo Takeuchi; Toyooka Public Hospital, Toyooka. Akito Tearai; Kurashiki Central Hospital, Kurashiki. Tatushiro Okabe; Shiga Medical Center for Adult Diseases, Moriyama. Teruo Konami; Otsu Municipal Hospital, Otsu. Mieko Miyakawa; Shimada Municipal Hospital, Shimada. Mutsushi Kawakita; Kobe City General Hospital, Kobe. Asaki Soeda; Nishi-Kobe Medical Center, Kobe. Yoshihiko Wakabayashi, Yusaku Okada; Shiga University of Medical Science, Otsu. Arata Higashi, Osamu Ogawa; Kyoto University Hospital, Kyoto.

There have been only a few reports on longitudinal functional outcome of neobladder creation.[6–9] We previously reported voiding function of ileal neobladder in both men and women.[6,7] The survey was performed in 1998. In 2003, 5 years after the initial survey, the second survey was performed for the same patients. We herein present the 5-year interval change in voiding function of orthotopic ileal neobladder.

Materials and methods

From November 1990 through February 1998, 71 patients underwent Hautmann bladder substitution in Kyoto University Hospital, Shiga University of Medical Science, and their affiliated hospitals. Among them, voiding function was evaluated at two points with an interval of 5 years in 49 patients, who comprised the study population. There were 43 men and six women, and median age at operation was 67 years old, ranging 47–77. Of these patients, 46 underwent simultaneous radical cystectomy. The three remaining patients underwent simultaneous unilateral nephroureterectomy and cystectomy for primary invasive ureteral cancer in the ureterovesical junction. All patients gave their full consent and were informed about other

options for urinary reconstruction. Patients were monitored at regular intervals of 3–6 months. Serum electrolytes, blood urea nitrogen and creatinine measurements, were performed at 3 months and then annually. Uroflowmetric study and postvoid residual urine measurements were performed arbitrarily.

The first and second surveys were performed in May, 1998 (1998 survey) and in April 2003 (2003 survey), respectively. Therefore, at the second survey, follow-up time was at least 5 years or longer. Median follow-up times at the first and the second surveys were 19.5 months (range, 3–87) and 67.5 months (range, 62–145), respectively. We questioned the patients regarding voiding behavior and continence, need for self-catheterization, voiding posture, incontinence, and the need for a pad to manage incontinence. If a patient wore a sanitary pad only for precautionary reasons or had only occasional spotting, he was regarded as continent. Statistical analyses were made using Wilcoxon or χ^2-test and $P < 0.05$ was considered statistically significant.

Results

The data on voiding function in the 1998 and 2003 surveys are shown in the Table 1. Since the study was retrospective, data were not available in some patients in each parameter. When voiding patterns were analysed, 11 patients (23.4%) sometimes or often performed catheterization because of difficulty in urinating or incomplete emptying of the neobladder in the 1998 survey. Three patients (6.4%) were unable to void and required regular catheterization. In the 2003 survey, however, nine (19.1%) were unable to void and needed regular catheterization, although the difference was not significant ($P = 0.174$). Of these nine patients, eight were male and one was female, thus there was no difference in the need for regular catheterization between the male and female: 18.6% and 16.7%, respectively. With regard to posture at voiding, 23 (52.3%) voided in a regular standing position in the 1998 survey. Eighteen patients (40.9%) preferred a sitting position while voiding, of whom 13 (29.5%) only voided in a sitting position. At the

Table 1 Voiding function of ileal neobladder patients

	1998 survey		2003 survey		*P*-value
	Number of patients	(%)	Number of patients	(%)	
Difficulty on urination†					0.174
None	28	(60.9)	25	(54.3)	
Yes	15	(32.6)	12	(26.1)	
Inability to void	3	(6.5)	9	(19.6)	
Need for catheterization†					0.301
Never	33	(70.2)	30	(63.8)	
Sometimes	5	(10.6)	4	(8.5)	
Often	6	(12.8)	4	(8.5)	
Routine catheterization	3	(6.4)	9	(19.1)	
Posture at voiding†					0.277
Standing position only	23	(52.3)	19	(43.2)	
Sitting position only	13	(29.5)	10	(22.7)	
Sitting position, sometimes	5	(11.4)	6	(13.6)	
Inability to void	3	(6.8)	9	(20.5)	
Daytime incontinence†					0.798
Never	38	(82.6)	37	(80.4)	
Occasionally	6	(13.0)	6	(13.0)	
Sometimes	0	(0.0)	1	(2.2)	
Always	2	(4.3)	2	(4.3)	
Night-time incontinence†					0.978
None	16	(36.4)	18	(40.9)	
None, if voided at night	13	(29.5)	12	(27.3)	
Yes, despite regular voiding at night	14	(31.8)	13	(29.5)	
Always	1	(2.3)	1	(2.3)	
Voiding frequency during night-time†					0.956
0	2	(5.6)	2	(5.6)	
1	18	(50.0)	19	(52.8)	
2	12	(33.3)	10	(27.8)	
3 or more	4	(11.1)	5	(13.9)	
Use of pads during daytime†					0.724
No	37	(90.2)	36	(87.8)	
Yes	4	(9.8)	5	(12.2)	
Use of pads during night-time†					0.499
No	21	(52.5)	24	(60.0)	
Yes	19	(47.5)	16	(40.0)	

†Data are not available in some patients.