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.

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Long-term Functional Outcome and Late Complications of Studer's Ileal Neobladder

Toshiaki Tanaka, Hiroshi Kitamura, Atsushi Takahashi, Naoya Masumori, Naoki Itoh and Taiji Tsukamoto

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

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Objective: The purpose of this study was to evaluate the long-term functional outcome and late complications of Studer's ileal neobladder.
Methods: The study included 57 patients who underwent radical cystectomy and bladder reconstruction with Studer's ileal neobladder, and were followed-up for at least 3 months after surgery. The voiding and storage function, and late complications were evaluated. The times of evaluation after surgery were categorized into periods I (3–23 months), II (24–59 months), III (60–95 months) and IV (⩾96 months).
Results: Daytime and night-time continence rates were 95.6 and 88.6%, respectively. The averages of functional capacity (439 ml), maximum flow rate (15.7 ml/s) and residual urine (35 ml) evaluated in period I were maintained in period IV. Of the 57 patients, intermittent self-catheterization was needed in five (8.8%) due to incomplete emptying or urinary retention. Urethroileal anastomotic stricture was found in two patients (3.5%), who were successfully treated by transurethral intervention. Inguinal hernia was found in seven patients (12.8%), five of whom developed it within 2 years after surgery.
Conclusions: Our results indicate that Studer's ileal neobladder had a favorable long-term functional outcome. Although late complication rates were low, the incidence of inguinal hernia was relatively high, and this was considered as a definite late complication in our study.

Key words: bladder substitutes – urinary diversion – cystectomy – bladder neoplasms – complications

INTRODUCTION

Orthotopic bladder substitutions have become standard for urinary reconstruction after radical cystectomy in patients who do not have neoplastic lesions of the urethra. Several types of orthotopic bladder substitutions have been developed, of which Studer's ileal neobladder is one of the most common procedures (1).

Studer's ileal neobladder is easily constructed and provides unchanged voiding habits with good continence and upper urinary tract preservation, with relatively low rates of complication (2,3), even compared with the intermediate-term results of an ileal conduit (4). However, only a few reports are available on the long-term results of this operation. In this study, we reviewed the clinical outcomes of patients who underwent Studer's ileal neobladder operation and were followed-up for a long time to elucidate whether the voiding function was maintained and to clarify what complications developed in the late period.

For reprints and all correspondence: Toshiaki Tanaka, Department of Urology, School of Medicine, Sapporo Medical University, N-1, W-16, chuo-ku, Sapporo, Hokkaido 060-8543, Japan. E-mail: zappa@pop12.odn.ne.jp

PATIENTS AND METHODS

Between February 1991 and September 2003, 62 patients underwent bladder reconstruction with a Studer's ileal neobladder after radical cystectomy for high risk T1 or Tis and invasive bladder cancer. Indications for this procedure consisted of no evidence of neoplastic lesions of the prostatic urethra of male patients and bladder neck of female patients, which was histopathologically confirmed by biopsy before cystectomy.

We used the original operative procedures for construction of the ileal neobladder reported by Studer et al. (2). However, ureters were implanted in the afferent limb of the ileum with the Le Duc–Camey technique, as previously reported, in all but five patients (3).

Of the 62 patients who received Studer's ileal neobladder, 57 patients who were followed-up for at least 3 months after the operation were analyzed retrospectively. All complications in the periods were reviewed. Continence rates were estimated by the Kaplan–Meier method. The follow-up period was categorized into four groups, depending on the period after surgery: period I consisting of 57 patients who were followed-up from 3 months to 2 years; period II, 40 with follow-up for 2–5 years; period III, 23 patients, for 5–8 years; and period IV,

comprising 13 patients for ⩾8 years. In each period, we evaluated the functional capacity of the neobladder with a frequency/volume chart, the maximum flow rate (Qmax) with conventional uroflowmetry and the post-void residual urine volume (PVR) with catheterization. Changes in these parameters over the periods were statistically examined with the Kruskal–Wallis test. *P*-values <0.05 were considered to be statistically significant.

RESULTS

Patient Characteristics

A total of 53 males (93.0%) and four females (7.0%) were included in this study (Table 1). The mean follow-up period was 57.0 months with a range of 5–136. Patients who were followed-up for ⩾5 years accounted for 40% of the total. More than 90% of patients had invasive disease.

Storage and Voiding Function

Patients achieved 95.6% daytime continence and 88.6% for the night-time, when continence was defined as that with no use of a pad (Fig. 1). Most patients achieved daytime continence within 6 months after the operation. Night-time continence recovered more slowly than that in the daytime. Functional capacity was maintained at 400–500 ml for each period, with no significant change (Table 2). However, two patients developed a neobladder capacity >1000 ml 5 years after the operation. There were no significant changes of Qmax and PVR during the follow-up periods, with the mean rates being maintained at 10–20 ml/s and the mean PVR at <60 ml.

Late Complications

The most frequent complication was transient or long-lasting metabolic acidosis, which had to be continuously treated with potassium/sodium citrate in nine patients (Table 3). Neobladder stones, which were found in seven patients, were successfully treated with endoscopic lithotripsy in all but one patient who had spontaneous passage of a stone. All stones seemed to be formed with a nucleus consisting of mucus and debris from the intestine. A unique late complication was inguinal hernia, which seven patients developed in our study. Most of these patients developed the condition within 2 years after the operation. Because incomplete emptying and urinary retention that resulted in a large amount of PVR (>150 ml) developed during follow-up, five patients needed to undergo clean intermittent catheterization (CIC). No patients had urethroileal anastomotic stricture when starting CIC. Of these patients, two had a poor voiding condition in the early period after the operation. Two other patients gradually developed a poor voiding condition without apparent cause. Urinary retention occurred in one female patient a year after operation, though she had achieved better voiding and continence before this episode. Urethroilael anastomotic stricture was seen in two patients in period I. Balloon dilation or internal urethrotomy under direct vision was effective for management of the stricture. Febrile urinary tract infection occurred in one patient (1.8%) who received Le Duc–Camey ureterointestinal anastomosis. No ureteroileal anastomotic stricture and impaired renal function was observed during follow-up in our series.

Table 1. Patients characteristics ($n = 57$)

Characteristics	
Sex	
Male (%)	53 (93.0)
Female (%)	4 (7.0)
Mean age: years (range)	60.1 (34–75)
Mean follow-up period: months (range)	57.0 (5–136)
Clinical stage: no. of patients (%)	
T0	1 (1.8)
T1	1 (1.8)
Tis	2 (3.5)
T2	35 (61.4)
T3	18 (31.5)

Table 2. Changes in functional capacity, maximum flow rate and post-void residual urine volume after surgery

Periods (months)	I (3–23)	II (24–59)	III (60–95)	IV (96+)	*P*-value
No. of patients	57	40	23	13	
Functional capacity (ml)	439 (109)	447 (115)	509 (270)	405 (153)	0.741
Qmax (ml/s)	15.7 (8.2)	13.7 (7.7)	16.8 (8.0)	16.7 (7.9)	0.636
PVR (ml)	35 (60)	36 (83)	60 (115)	34 (71)	0.386

Values in parentheses are the SD.
Qmax, maximum flow rate; PVR, post-void residual urine volume.
The *P*-value was determined with the Kruskal–Wallis test.

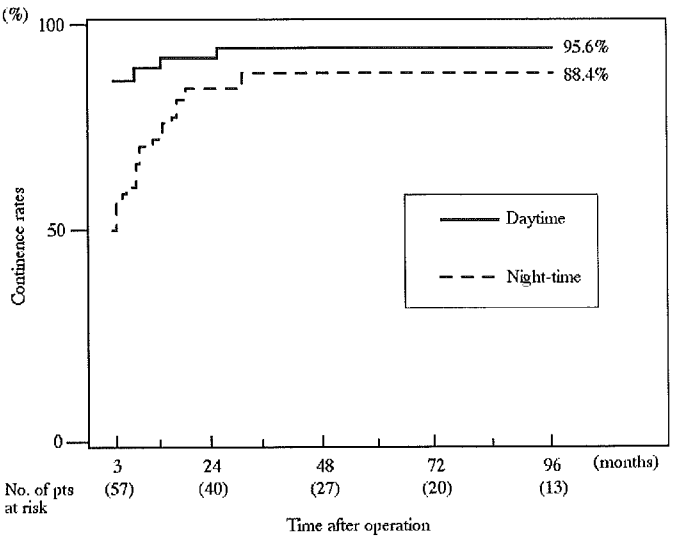

Figure 1. Daytime and night-time continence rates.

Table 3. Late complications

	Overall no. of patients (%)	No. of onsets in each period (months)			
		I (3–23)	II (24–59)	III (60–95)	IV (96+)
Metabolic acidosis	9 (15.8)	4	4	1	0
Inguinal hernia	7 (12.3)	5	1	1	0
Need for intermittent catheterization	5 (8.8)	4	0	1	0
Neobladder calculi	4 (7.0)	1	3	0	0
Upper urinary tract calculi	3 (5.3)	0	1	2	0
Urethroileal anastomotic stricture	2 (3.5)	2	0	0	0
Febrile urinary tract infection	1 (1.8)	1	0	0	0

DISCUSSION

The results of this study indicated that Studer's ileal neobladder maintained favorable voiding and storage functions for many years after the operation. Although the neobladder capacity is insufficient for the first 3 months after operation, it increases to 400–500 ml at 6 months (3,5,6). In this study, the appropriate capacity was maintained even >8 years after the operation. This tendency is comparable with that observed in Studer's series (6,7). However, in our study, two patients developed a capacity of >1000 ml over 5 years after the operation. Periodic assessment with a frequency/volume chart and reinstruction of neobladder management are required to avoid its overextension and too large a storage volume.

Although we did not identify the specific factors, our recommendations for patients to wake up and void at least once in the middle of the night, and to refrain from drinking an excessive amount of water before going to sleep may have contributed to the reduction of incontinence frequency.

Qmax was 10–20 ml/s immediately after the operation, as has been reported by others (8,9), and it was stable in the long term. Urinary retention occurred in one female patient. It was associated with neither anastomotic stricture nor urethral recurrence of carcinoma. Although urinary retention is rare, it occurs more frequently in female patients (10). One of the speculated causes of urinary retention in females is kinking of the urethra (6,7,10), which is probably caused by denervation of the proximal urethra and is considered to be the main cause (10,11). However, neither voiding cystourethrography nor cystourethroscopy revealed such an apparent cause for retention in our patient. Thus the episode was due to other, as yet unknown functional or anatomical causes.

The percentage of our patients who needed intermittent catheterization was 8.8%, which was comparable with that in other reports (9,12). Of those patients, one had a PVR that increased to >150 ml 5 years after the operation. Although a large PVR was reported to be a result of inguinal or incisional hernias (7,10), our patient had neither inguinal nor incisional hernia, and had a functional capacity >800 ml. These findings suggest that overextension is a cause of increased PVR. Mikuma et al. pointed out that in patients with a low Qmax and a high PVR, the anastomosis between the neobladder and membranous urethra was not located at the bottom of the pouch and a cystocele-like change was observed (13). Although that was not confirmed by radiographic examination, in our patient, a cystocele-like change resulting from overextension of the neobladder that occurred several years after the operation might have been involved in the increase of PVR.

The incidence of inguinal hernias was unexpectedly high in this study. Studer et al. reported that the incidence of inguinal or abdominal wall hernias was 7% in their series with a median follow-up period of 30.2 months (5). Our longer follow-up, 57 months, might be related to the difference in the rate from that of others, although we did not find any specific explanations for the incidence. Ichioka et al. reported that 21.3% of patients who underwent radical retropubic prostatectomy developed inguinal hernia. On the other hand, in patients with cystectomy and mainly incontinent urinary diversion in their series, the incidence of inguinal hernias was 5.4% (14). When compared with the rate in radical prostatectomy, the lower rate in their cystectomy series was explained by the increased volume of the abdominal cavity after operation and lesser abdominal pressure provided by the operative procedure so that the peritoneum was left open. However, patients who receive an ileal neobladder need to strain to void. We speculate that this situation has inherent potential to increase to some extent the incidence of inguinal hernias in patients with an ileal neobladder.

CONCLUSIONS

Studer's ileal neobladder had a favorable long-term functional outcome in our study. Although the late complication rate was generally low and all complications were already known to occur, there were several patients who had to undergo CIC for their poor voiding condition resulting in a larger PVR. A unique complication was inguinal hernia, the rate of which was relatively high in our series. This is considered to be one of the definite late complications in patients with an ileal neobladder.

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高齢者の浸潤性膀胱癌の治療：根治性とQOLのバランスをどうとるか

舛森直哉
札幌医科大学医学部泌尿器科講師
市原浩司
札幌医科大学医学部泌尿器科
廣部恵美
札幌医科大学医学部泌尿器科
高橋　敦
札幌医科大学医学部泌尿器科講師
塚本泰司
札幌医科大学医学部泌尿器科教授

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人口の高齢化に伴い，浸潤性膀胱癌を有する高齢者を診察・治療する機会が増加している。膀胱全摘術および尿路変向術は浸潤性膀胱癌に対する標準的な治療法であるが，その侵襲性や合併症発生率は決して低くはない。麻酔手技や手術手技・手術器械・周術期管理の進歩により，高齢者に対しても比較的安全に手術が施行できるようになってきたが，現在においても高齢者に対する手術適応は若年者以上に慎重に決定しなければならない。特に，術後の生活スタイルを規定する尿路変向術の種類は，患者を取り巻く環境や家族構成なども勘案したうえで決定しなければ，逆に患者のQOLを損なうことになりかねない。

最近では，放射線療法と動注化学療法を併用した積極的な膀胱温存の試みもあるが，膀胱温存の明確な適応基準，方法，経過観察法は若年者においても確立してはいない。本稿では，浸潤性膀胱癌を有する高齢者に対する手術療法を中心に，膀胱全摘術および尿路変向術の適応決定や手術の合併症などについて札幌医科大学泌尿器科における成績を交えながら概説する。

札幌医科大学泌尿器科における膀胱全摘術施行症例

1994年から2005年７月までの間，膀胱癌に対して膀胱全摘術を施行した症例は191例であった。平均年齢および高齢者の占める割合は年々増加し，最近の３年間では70歳以上が38%，75歳以上が15%，80歳以上が7.6%を占めていた（**図1**）。以上のように，最近では80歳以上の高齢者に対しても積極的に膀胱全摘術を施行している現状が明らかとなった。検討症例191例中63例（33%）が70歳以上の症例であった。

臨床病期に関しては，70歳以上ではT3/T4あるいはリンパ節・遠隔転移を有する症例の割合が若干高く（**表1**），後述するようにQOLの改善・維持を目的に膀胱全摘術を選択した症例もあった。一方，術前化学療法を施行した症例の割合は加齢とともに減少し，特に75歳以上の症例では１例も施行されていなかった。American Society of Anesthesiologists（ASA）で定めた全

身状態の評価基準[1]の分布については，ASA score 3（重篤な全身疾患を有する）の症例を75歳以上の22%に認めたが，いずれもperformance status(PS)は2以下の症例であった。

尿路変向術の種類としては，症例全体としては回腸導管が70%と最も多く施行されていた。特に70歳以上の症例では89%が回腸導管施行例であった。一方，回腸新膀胱施行例の割合は加齢とともに減少し，75歳以上での施行例はなかった。

各年齢群において手術時間と術中出血量には明らかな差を認めなかったが，同種血輸血率は75歳以上で91%と高い傾向があった。75歳以上の症例における貯血・希釈式自己血の採取率は22%と，75歳未満のそれの48%と比較して低率であったことも背景にあるが，高齢者に対しては躊躇せず輸血を施行している現状が明らかとなった。

術後早期死亡率は1/191（0.5%）であり，死亡例は74歳の女性で感染性心内膜炎による敗血症が死因であった。術後30日以内の早期合併症の発生率は30%であり，major complication（心肺または全身に及ぶ，あるいは，直ちに再手術が必要な合併症）とminor complicationの頻度は，それぞれ6%と24%であった。創部感染症や膿瘍形成の頻度が13%と最も多く，イレウスが12%とこれに続いた。合併症の発生率には年齢群による差はなく，また，高齢者に特徴的な合併症は認めなかった。

高齢者における膀胱全摘術の動向

Hollenbeckら[2]は，1988年から1999年までにSurveillance, Epidemiology and End Results（SEER）Cancer Registryに登録された13,796人の膀胱癌患者の統計において，高齢になるほどAmerican Joint Committee on Cancer(AJCC)病期II～IVの占める割合が増加したことを報告している。このように，高齢者においては浸潤性・進行性膀胱癌患者の占める割合が多いと考えられる。一方，治療内容に関しては，膀胱全摘術の施行率は高齢になるにしたがって減少し，特に85歳以上では，AJCC病期II，IIIのそれぞれ2.5

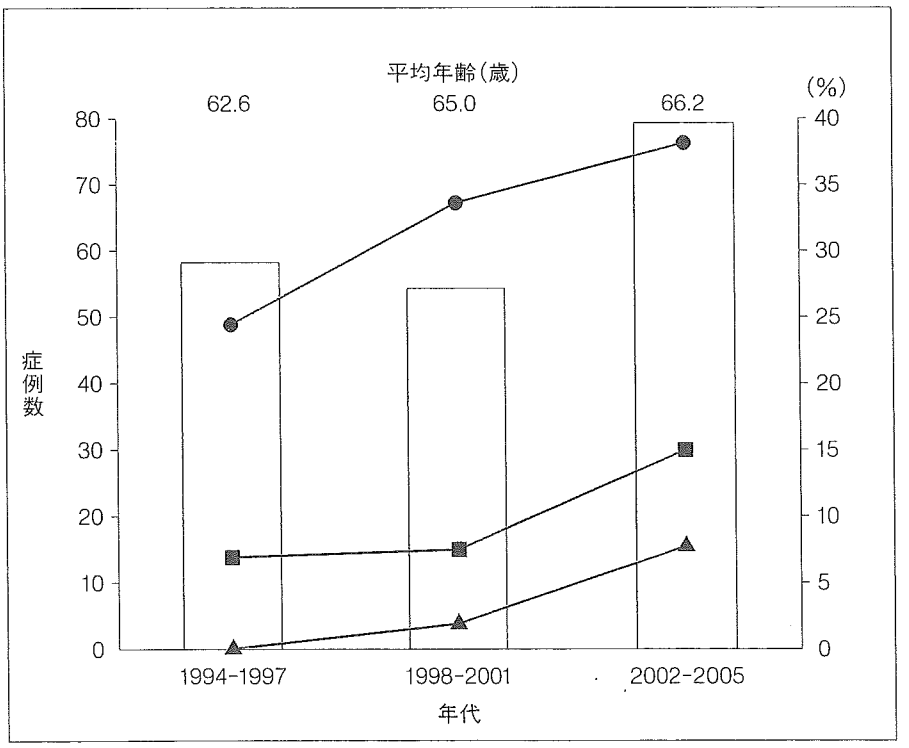

図1　札幌医科大学泌尿器科における膀胱全摘術症例数と高齢者の占める割合の年次推移

●：70歳以上の症例の割合
■：75歳以上の症例の割合
▲：80歳以上の症例の割合

表1　膀胱全摘術施行症例の背景，尿路変向術，手術所見，術後早期合併症

年齢分布	59歳以下 (n=52)	60～64歳 (n=33)	65～69歳 (n=43)	70～74歳 (n=40)	75歳以上 (n=23)
臨床病期					
T2以下	27(52%)	12(36%)	20(47%)	12(30%)	7(30%)
T3/4	20(38%)	15(45%)	19(44%)	26(65%)	12(52%)
N^+/M^+	5(10%)	6(18%)	4 (9%)	2 (5%)	4(17%)
術前化学療法施行	15(29%)	9(27%)	7(16%)	6(15%)	0
ASA score					
1	29(56%)	6(18%)	11(26%)	10(25%)	5(22%)
2	22(42%)	27(82%)	32(74%)	27(68%)	13(57%)
3	1 (2%)	0	1 (2%)	3 (8%)	5(22%)
PS					
0	39(75%)	21(64%)	17(40%)	13(33%)	11(48%)
1	13(25%)	9(27%)	22(51%)	24(60%)	8(35%)
2	0	3 (9%)	4[a] (9%)	3 (8%)	4(17%)
尿路変向術					
回腸導管	27(52%)	18(55%)	32(74%)	34(85%)	22(96%)
回腸新膀胱	20(38%)	12(36%)	11(26%)	3 (8%)	0
リザーバー	5(10%)	1 (3%)	0	0	0
尿管皮膚瘻・腎瘻・その他	0	2 (6%)	0	3 (8%)	1 (4%)
手術時間（中央値，分）	512	440	460	428	425
出血量（中央値，ml）	2,450	2,100	1,910	1,610	1,910
同種血輸血	36(69%)	24(73%)	31(72%)	26(65%)	21(91%)
合併症発生率	13(25%)	10(30%)	11(26%)	16(40%)	7(30%)
major	2 (4%)	3 (9%)	2 (5%)	4(10%)	0
死亡				1	
直腸損傷	1	1			
心合併症[b]			1	1	
肺合併症[c]	1	1		1	
敗血症		3		3	
縫合不全		1			
minor	11(21%)	7(21%)	9(21%)	12(30%)	7(30%)
イレウスなどの消化管合併症[d]	5	3	5	5	4
創部感染症，膿瘍[e]	7	4	6	4	4
吻合部狭窄[f]		1		3	1
ストマ脱出					1
神経麻痺[g]		1		1	

a）1例はPS 4，b）感染性心内膜炎，狭心症，c）術後肺炎，挿管による呼吸管理，ARDS，d）経鼻胃管やイレウス管の挿入を要するイレウス，MRSA腸炎，偽膜性腸炎，e）抗生剤の静脈内投与を要する感染，あるいは外科的処置を要する，f）経皮腎瘻造設を要する，g）腓骨神経麻痺，前腕の感覚麻痺

%，8.8%に膀胱全摘術が施行されたにすぎなかったと報告されている[3]。本邦の全国膀胱癌患者登録データにおいても，80歳以上の症例に対しては膀胱全摘術よりも積極的あるいは消極的な膀胱温存が多く施行されていた[4]。後述するように，治療内容の選択は，臨床病期，高齢者の全身状態や併存する合併症，膀胱全摘術の侵襲性，平均余命，膀胱癌に起因する自・他覚所見の有無などを総合判定した結果と考えられるが，最近の高齢者の全身状態の改善，合併症の良好なコントロールや医学技術の進歩に伴い，今後高齢者に対する膀胱全摘術の適応はさらに拡大することが推測される。したがって，単なる暦年齢のみで手術適応を決定することは困難である。

高齢者の浸潤性膀胱癌に対する膀胱全摘術の目的

浸潤性膀胱癌を有する高齢者に対する膀胱全摘術の目的は，疾患の根治による生存期間の延長および腫瘍に随伴する自覚症状・他覚所見の改善・予防の二つに大別される。

SEERの統計[3]によると，膀胱全摘術が施行された症例の生存のハザード比は年齢群にかかわらずほぼ同様であった。また，膀胱全摘術（一部は膀胱部分切除術）を施行したAJCC病期IIの80歳以上の症例は，待機療法，放射線療法あるいはTUR-BT（transurethral resection of bladder tumor）を選択した症例に比較して疾患特異的生存率および全生存率とも良好であった[2]。癌死のハザード比は，待機療法を1とした場合，膀胱摘除群で0.3，放射線療法で0.56，TUR-BTで0.5であった。Figueroaら[5]は，1,166名の膀胱全摘術施行例を対象とした大規模な検討において，70歳未満と70歳以上の5年無再発生存率は，それぞれ31%と35%であり，両群に有意差を認めなかったことを報告している。膀胱全摘術後の疾患特異的生存率に関しても，70歳未満，70歳以上の5年疾患特異的生存率は，それぞれ54%，49%とほぼ同等であったことが報告されている[6]。本邦においても，西山[7]が膀胱全摘術後平均4.4年の観察期間内の再発率は51歳未満25.6%，51～60歳23.6%，61～70歳25.5%，71～80歳26.9%，81歳以上24.2%とほぼ同率であったことを示しており，高齢者であっても外科治療が可能な場合は若年者と同等の予後が期待できるとしている。同一の病理学的病期内で比較した場合に高齢になるにしたがって再発のリスクが高くなったとのClarkらの報告[8]もあるが，高齢者といえども積極的な外科的治療の施行により生命予後が改善する症例が存在することは明らかである。

根治を目的とする以外にQOLの改善を目指して救済的な膀胱全摘術を施行する場合がある。膀胱癌が原因となった血尿，頻尿，尿意切迫感，下腹部痛などは，患者のQOLを大きく損なう。高齢者のみが対象ではないが，転移を有する浸潤性膀胱癌に対する膀胱全摘術と尿路変向術の意義を検討した当科の検討[9]によると，経過観察中に血尿，頻尿，下腹部痛などの下部尿路症状を呈した割合は，膀胱全摘術施行例では18%（いずれの症例も回腸新膀胱への腫瘍浸潤による症状），未施行例では89%であった。また，生存期間に占める下部尿路症状を有する期間の割合は，膀胱全摘術施行例では3.2%，未施行例では48%であった。積極的な原発巣摘除による局所制御は，QOLの改善や将来的なQOL低下の予防に寄与すると考えられる。

膀胱全摘術が適応となる高齢者とは

以上のように，若年者と同様に高齢者といえども状況が許せば膀胱全摘術が適応となる。一般的に高齢者では種々の合併症を有し，心肺機能が低下していることが多いが，一部には若年者と同様な治療を施行できるfit elderlyが存在することも事実である。しかし，高齢者に対する膀胱全摘術の適応決定の際の明確な基準が存在するわけではない。膀胱全摘術を選択せずに，あるいは，全身状態などの問題から膀胱全摘術が選択できずに経過を観察した高齢者をコントロールとして膀胱全摘術の意義を検討した前向き研究はなく，若年者と同様にASA scoreやPS，合併症の有無や程度，さらには，痴呆の有無や程度などを参考にして手術の可否を決定しているのが現状である。

高齢者における膀胱全摘術の合併症

高齢者に対する膀胱全摘術後の死亡

率や合併症発生率を同一の基準で若年者と比較検討した報告は多くはないが[5,6,10~15]，fit elderlyをさまざまな基準で選択した場合には，その合併症は若年者とほぼ同等であることが報告されている（表2）。当科における検討でも高齢者における特徴的な合併症は認めなかった。一方，高齢者のみを対象とした検討ではないが，術前のASA scoreが3点以上の症例ではmajor complicationsのリスクが5.7倍に増加したことが報告されている[16]。また，根治的な膀胱全摘術を行った症例に比較して，姑息的な膀胱全摘術を行った高齢者における合併症の発生率は明らかに増加する[17]。75歳以上でかつASA score 3以上の症例に対しても膀胱全摘術は安全に施行可能で良好な予後が期待できるとの報告もあるものの[18]，高リスク症例に対しては合併症の発生を念頭においた周術期管理が必要となる。

高齢者に最適な尿路変向術とは

QOLに及ぼす影響を含めて高齢者に最適な尿路変向術を検討した報告はないが，若年者に比較して高齢者では回腸導管が選択されていることが多い[6,7]。正所性新膀胱に比較して手技が

表2　膀胱全摘術の合併症の年齢群別の比較

報告者	報告年	年齢群（歳）	症例数	死亡率（%）	合併症率（%）早期/晩期
Thomas[10]	1982	<65	59	3.4	−
		≧65	41	12.0	
Tachibana[11]	1983	<50	4	0	50.0
		50-59	20	10.0	35.0
		60-69	17	18.0	35.0
		70-79	20	6.0	53.0
		≧80	9	0	67.0
Wood[12]	1987	<70	98	1.0	39.0
		≧70	38	5.3	34.0
Leivovitch[13]	1993	<70	69	4.3	−
		≧70	42	9.5	
Koch[14]	1996	<70	34	−	30.0
		≧70	13		38.0
Figueroa[5]	1998	<70	762	2.0	24.7/22.8
		70-79	352	3.1	32.4/13.3
		≧80	52	0	28.8/5.8
Knap[6]	2004	<70	213	0.9	58.0
		≧70	55	7.2	53.0
Clark[15]	2005	<60	310	1.0	24.0/36.0
		60-69	382	3.0	25.0/30.0
		70-79	312	4.0	37.0/22.0
		≧80	50	0	30.0/14.0
札幌医科大学	2005	<60	52	0	25.0
		60-64	33	0	30.3
		65-69	43	0	25.6
		70-74	40	2.5	40.0
		≧75	23	0	30.4

容易であることが背景にあると考えられる。回腸導管を選択する場合，パウチの交換を含めたストーマの自己管理が可能であることが望ましいが，家族の協力体制が得られればその適応症例は増加する。一方，患者の家庭状況の把握を怠ったり，ストーマケアへの理解が得られない場合は，ストーマ周囲皮膚炎などの障害により患者のQOLを低下させることになりかねない。

正所性新膀胱は高齢者においても安全に施行しうる手技であり[20]，腎機能障害を有さず，術後の排尿管理の重要性などに対する理解が得られれば，今後高齢者に対する適応がさらに拡大することが予測される。Clarkらの報告[15]では，80歳以上の高齢者の36％で正所性新膀胱が作成されていた。また，70歳以上の症例において回腸導管群と正所性新膀胱群の間に合併症の発生率や死亡率に有意差を認めなかったことが示されている。

尿管皮膚瘻は腸管を使用する尿路変向術に比較して手術時間が短かく[15]，術後の合併症の発生も少ないため[20]，全身状態や予後を考慮して選択される。

高齢者における補助的化学療法

生存期間の延長に寄与する術前MVAC療法（メトトレキサート・ビンブラスチン・アドリアマイシン・シスプラチン）の有用性を示したGrossmanらによる報告[21]以来，浸潤性膀胱癌に対する術前化学療法に関心が集まっている。しかし，高齢者に対しては補助化学療法が積極的には施行されていないのが現状である[7,8]。Bamiasら[22]は，転移を有する尿路上皮癌患者に対する全身化学療法の副作用と効果を70歳未満と70歳以上の2群に分類して検討を行っている。MVAC療法の施行サイクル数は70歳未満で4.5回，70歳以上で4.3回と差を認めず，また，高齢群で若干Grade III/IVの白血球減少の頻度が高かったが統計学的な有意差はなかった。奏効率と生存期間に関しても若年群と高齢群で差を認めなかったことから，特に，PS 0/1および10g/dl以上のヘモグロビン濃度を有する高齢者に対しては化学療法の積極的な適応が考慮されると結論している。しかし，高齢者に対する明確な全身化学療法の適応基準は存在せず，さらに，侵襲的な膀胱全摘術と組み合わせた場合の合併症や予後に関する知見はほとんどない。補助化学療法の安全な併用が可能で効果が期待できるfit elderlyの選択基準の確立が必要である。

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詳細は触れなかったが，高齢者におけるリンパ節郭清の意義や範囲など，さらなる検討を要する課題もある。若年者と同様な治療の呈示が可能な高齢者も一部には存在するが，どこまで治療適応を拡大できるかの判断は，知見の少ない現時点では必ずしも容易ではない。疾患の根治やQOLの改善など治療の正の側面と，侵襲性や尿路変向術によるQOLの低下など治療の負の側面のバランスを考慮のうえ，治療方針を決定することが必要である。

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Original article

Removal of more lymph nodes may provide a better outcome as well as more accurate pathology in patients with bladder cancer -An analysis of the role of pelvic lymph node dissection-

Ichiya Honma [1)], Naoya Masumori [1)], Eiji Sato [1)], Toshihiro Maeda [1)], Megumi Hirobe [1)], Hiroshi Kitamura [1)], Atsushi Takahashi [1)], Naoki Itoh [1)], Mitsuharu Tamakawa [2)], Taiji Tsukamoto [1)]

Departments of Urology [1)] and Radiology [2)],
Sapporo Medical University School of Medicine, Sapporo, Japan

Correspondence and Galley proofs: Naoya Masumori, M.D.
Department of Urology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-Ku, Sapporo, 060-8543, Japan
Telephone: +81-11-611-2111 (ext. 3472), Facsimile: +81-11-612-2709, E-mail: masumori@sapmed.ac.jp

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Abstract

Objectives: The diagnostic and therapeutic role of pelvic lymph node dissection (PLND) is still controversial in bladder cancer. The extent of PLND and necessary number of lymph nodes that have to be removed have not been defined. In this study, we examined the role of PLND in patients who underwent radical cystectomy for bladder cancer.

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 between January 1990 and December 2002.

Results: Lymph node metastases were detected in 25 patients (17.1%). The average numbers of nodes removed in node-positive and node-negative patients were 13.9 and 14.2, respectively. Although there was no difference in disease-specific survival in the node-negative patients with between $\geq$ 13 and < 13 nodes removed, significant survival advantage was found in the node-positive patients with $\geq$ 13 nodes removed compared to those with < 13 nodes removed. The patients with $\geq$ 4 positive nodes showed poorer outcome than those with < 4 positive nodes. However, even if the patients had < 4 positive nodes, survival of the patients with < 13 nodes removed was as poor as that of the patients with $\geq$ 4 positive nodes.

Conclusions: In this series, removal of 13 or more pelvic lymph nodes is essential for more accurate pathology to predict the outcomes of patients and contributes to an increased chance of survival.

Introduction

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.[1,2,3] Although it has not been fully documented whether PLND contributes to favorable outcome, recent studies have indicated that PLND provides a survival advantage in node-positive patients.[4,5] On the other hand, the extent of lymph node dissection and the necessary number of nodes to be removed have not been standardized.

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

Materials 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 T1 grade 3 in 2 and muscle invasive cancer in 166 patients. Excluded from the study were 14 patients who underwent non-curative surgery, 3 who died of postoperative complications, 2 who had tumors of non-urothelial origin and 6 whose nodes were inaccurately evaluated. The exclusion left 146 patients who underwent curative cystectomy with PLND and were adequately monitored for the current retrospective review. No patients had a history of pelvic surgery for other malignancies.

Preoperative evaluation included cystoscopy, bimanual examination under anesthesia, excretory urography, abdominal and pelvic CT, and chest x-ray. The patients underwent further evaluation, 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 time of 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 pathological examination. Boundaries of dissection were the circumflex iliac vein inferiorly, pelvic side wall laterally, bladder wall medially and iliac bifurcation superiorly. Thus, 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. Histopathological evaluations were performed by several institutional pathologists. The total numbers of lymph nodes removed and bearing metastasis were recorded for each site separately. Each node with the maximum diameter was sectioned for analysis of metastasis.

Survival time was analyzed from the date of surgery. The end points of 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. They ranged in age from 38 to 79 years (mean; 65). Clinically, 70 patients (47.9%) were diagnosed as having extravesical disease (T3 or more) before cystectomy (Table 1). 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 with T3 or more and/or pelvic adenopathy. Pathologically, 90 patients (61.6%) had tumors confined to the bladder (pT2 or less) and 56 patients (38.4%) had tumors penetrating the bladder wall into perivesical fat or adjacent structures (pT3 or more). Histology of pure urothelial carcinoma (UC) was found in 112 patients (76.7%) and other histological components such as squamous cell carcinoma and adenocarcinoma contained in 34 (23.3%). After surgery, 16 patients (11.0%) with pT3 or more and/or nodal involvement received adjuvant chemotherapy according to the urologists' preference.

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

The median follow-up period of the 146 patients was 35 months, ranging from 3 to 169. The median follow-up of the 91 survivors was 69 months. Distant metastases and/or local recurrence developed in 62 of the 146 patients (42.5%) at a median of 11 months (range 2-71) after cystectomy. Disease-specific survival rates of the node-negative patients at 1, 2 and 3 years were 91.4, 78.3 and 71.0%, respectively. Those of node-positive patients at 1, 2 and 3 years were significantly worse, 60.0, 44.0 and 40.0%, respectively (Fig. 2).

The number of lymph nodes removed did not have a significant impact on disease-specific survival in patients with primary tumors confined

to the bladder (pT0-2, Fig. 3A) or in patients with extravesical disease (pT3/4, Fig. 3B) if they did not have lymph node metastasis. On the other hand, removal of ≥ 13 nodes had a significant survival advantage in node-positive patients (Fig. 3C). The patients with ≥ 4 positive nodes had a poorer outcome than those with < 4 positive nodes (Fig. 4A). However, even if the patients had < 4 positive nodes, survival of those with < 13 nodes removed was as poor as that of the patients with ≥ 4 positive nodes (Fig. 4B). No statistical difference in the primary stage distribution was observed among these three groups (Fig. 4B). The disease specific survival of the patients with lymph node density (the number of positive nodes divided by the number of nodes removed) > 20% was significantly worse than those with lymph node density ≤ 20% (Fig. 4C).

Multivariate analysis demonstrated that the number of nodes removed, the number of positive nodes and pathological stage were independent predictors of disease-specific survival (Table 2).

Discussion

The main objective of PLND is to provide accurate staging of bladder cancer. If pelvic nodal involvement is proven, it should be considered as a manifestation of a systemic disease.[1.2.3] On the other hand, the independent value of PLND for survival in patients with bladder cancer remains controversial, although it is demonstrated that PLND cures some node-positive patients.[4.5]

In the present study, patients with < 4 positive nodes had a statistically significant survival advantage over those with ≥ 4 positive nodes. Similar results were reported by Lerner[9] whose cutoff was 6 positive nodes and Mills[5] and Frank[10] who set the cutoff at 5 positive nodes. Stein[11] also reported that patients with < 8 positive nodes had a statistically significant survival advantage over those with ≥ 8 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 biological nature of the tumor having concomitant systemic spread.

In addition to the number of positive nodes involved, the present study demonstrated that the number of nodes removed had a significant impact on the disease-specific survival in the node-positive patients. Removal of ≥ 13 nodes had a survival benefit even in the node-positive patients. Several recent studies have showed similar results.[4.5] Stein[11] demonstrated that patients with ≥ 15 nodes removed had better recurrence-free survival than those with < 15 nodes removed. Herr[12] reported that excising ≥ 11 nodes from obturator, internal and external iliac nodes to middle common iliac nodes significantly improved survival in node-positive patients. In the present study, even if the patients had < 4 positive nodes, the prognosis of the patients with < 13 nodes removed was as poor as that of the patients with ≥ 4 positive nodes. Thus, removal of an adequate number of lymph nodes is more likely to remove positive lymph nodes and yields accurate nodal staging, whereas limited dissection including only a few negative lymph nodes may leave positive lymph nodes behind.

On the other hand, the number of lymph nodes removed was not related to improved survival in node-negative patients, especially in those having pathologically organ-confined disease in the present study. The South West Oncology Group 8710 showed that the survival advantage conferred by removal of ≥ 10 nodes was found even in node-negative patients.[13] Herr[12] also demonstrated that removal of ≥ 8 nodes resulted in better survival not only in patients with pT2pN0 but also in those with 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. On the other hand, in the node-negative patients with extravesical disease, survival tended to be better in the patients with ≥ 13 removed nodes than in those with < 13 removed nodes. Thus, removal of more pelvic lymph nodes has the potential to contribute to improved survival both in node-negative and positive patients.[14, 15]

This study may be criticized because it was retrospective, with a limited number of cases having only endopelvic LND. The clinical benefit of a more extended area for node dissection advocated by recent studies remains to