Review

Orthotopic neobladder after cystectomy for bladder cancer

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Abstract: More than 90% of bladder cancer is composed of transitional cell carcinoma (TCC), being characterized by the development of multiple tumors in the entire urinary tract over time. When cystectomy is conducted, the urinary tract must be reconstructed by various procedures, which can include an orthotopic neobladder using the patient’s own intestine formed into a spherical shape anastomosed to the urethra. Using this procedure, patients can void urine from their own urethra even after cystectomy. The incidence of subsequent urethral cancer arising after cystectomy is known to be relatively high; however, if patients with a high risk of urethral recurrence are appropriately excluded, a neobladder can be safely provided for patients. Orthotopic neobladder use is reviewed from an oncological viewpoint and the patient’s quality of life after cystectomy for bladder cancer.

Keywords: bladder cancer, transitional cell carcinoma, cystectomy, urethral cancer, neobladder

Introduction

Transitional cells cover almost the entire mucosa of the urinary tract, including the renal pelvis, ureter, bladder, and the greater part of the proximal urethra. Approximately 90% of cancers arising in the urinary tract are transitional cell carcinoma (TCC), with the remainder mostly comprised of squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Of these, bladder cancer is most common, being the ninth most common cancer worldwide.

When surgery is planned for TCC in the urinary tract, concurrent and subsequent tumor development in the remaining urinary tract is a well-known biological phenomenon of TCC, particularly in the bladder.1) Nephroureteral and urethral involvement of TCC should be considered seriously when cystectomy and reconstruction of the urinary tract are indicated for bladder cancer.

These biological phenomena are caused by a result of “field cancerization”,2)–5) in which transitional cells covering the urinary tract are exposed to urinary carcinogens. Another explanation is due to "implantation"6)–10) in which TCC cells spread to other sites in the urinary tract from the original tumor. These two potential mechanisms make it difficult to identify whether recurrent tumors that develop after surgery are due to insufficient surgery to remove the original tumor, implantation of the original cancer cells to another mucosal surface, or new growth due to multifocal tumor development.

Molecular analysis of p53 mutation patterns in bladder cancers or multiple subsequent cancers in the bladder arising after treatment of upper urinary tract tells us that these multiple cancers are monoclonal in origin, indicating the implantation of cancer cells from the original tumors.7)–10) It is likely that all of these mechanisms are mutually relevant. A biphasic pattern of recurrence of bladder cancers after transurethral resection (TUR) has been reported, indicating the combination of early implantation and late new growth.11)

Reconstruction of the urinary tract after cystectomy has been conducted historically by ureterosigmoidostomy, ileal conduit, cutaneous continent reservoir requiring self-catheterization, and most recently using an orthotopic neobladder anastomosed to the urethra. Each procedure has specific benefits and risks. This review will discuss reconstruction of the urinary tract after cystectomy in terms of tumor

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development in the urethra and the function of a neobladder both in males and females.

**TCC in the urinary tract in terms of carcinogenesis**

**Clinical patterns of TCC, particularly in the bladder.** TCC appears in the urinary tract as papillary carcinoma (Fig. 1), nodular carcinoma (Fig. 2), and carcinoma in situ (CIS, Fig. 3) according to the gross configuration by endoscopy and microscopic patterns. Papillary carcinomas usually develop in multiple forms in the entire urinary tract; however, these tumors usually remain in the superficial layer of the urinary tract, *i.e.*, confined to the mucosal or submucosal layer, which is associated with good prognosis. In contrast, nodular carcinomas usually develop as deeply invasive in the muscular layer or subserosal area, and the prognosis of patients is poor even after radical cystectomy. CIS does not appear in tumorous development. It appears like a flat region or with the mucosal surface having occasionally a red velvet-like appearance on endoscopy. CIS, although initially confined to the mucosal layer, easily starts to invade to the submucosal or deeper muscular layers and prognosis is poor. TCCs are a mixture of these three basic patterns.

Tumors were examined using the TNM Classification of Malignant Tumours\(^\text{12}\) by the International Union Against Cancer. Stage was described as a combination of Tumors (T1–4), Nodes (N1–3), and Metastases (M0–1). When clinically examined, a lowercase letter c is added as cT2N1M0, and when examined pathologically, lowercase p is added as pT2N1M0.

In bladder cancer, T1 is separated into Ta indicating a papillary protruding tumor without
submucosal invasion and Tis indicating a flat mucosal lesion without submucosal invasion, which indicates CIS in the above description, and simple T1 indicates tumors invading the submucosa.

**Multicentric tumor development of TCC in the urinary tract.** The characteristic nature of multiple TCCs developing in the whole urinary tract has been well documented (Fig. 4). Rarely, however, we sometimes see a patient with simultaneous tumors in the renal pelvis, ureter, bladder, and urethra (Fig. 4a). When ordinal nephrectomy (removal of the kidney) is performed for renal pelvic and/or ureteral cancer, approximately one-third of the lower ureter is left inside the body. The incidence of subsequent TCC arising in the remnant ureter is reported to be 20–58% (Fig. 4b; the shaded area indicates the range of nephrectomy). Consequently, the established state of the art surgery for TCC of the renal pelvis and/or ureter is total nephroureterectomy, i.e., removal of the kidney, total ureter together with resection of a small part of the bladder with the ureteral end (so-called bladder cuff).

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**Fig. 3.** Carcinoma *in situ* (CIS). Left side: histology of CIS; middle: severe dysplasia; right side: mild dysplasia.

**Fig. 4.** Multicentric tumor development of TCC in the urinary tract. Black lesions indicate original tumors arising somewhere in the urinary tract and red lesions indicate subsequent, recurrent tumors.
However, a 15–50% incidence of subsequent TCC in the bladder has been reported (Fig. 4c; shaded area indicates total nephroureterectomy with bladder cuff). When superficial papillary TCC of the bladder is treated by TUR (Fig. 4d; shaded area indicates removal of three tumors by TUR), subsequent papillary TCC arising in the normal appearing bladder mucosa is reported to be 50–80% (Fig. 4d).

To prevent ectopic recurrences of bladder cancer after TUR, intravesical instillation of chemotherapeutic drugs such as mitomycin and doxorubicin or instillation of Bacillus Calmette–Guérin (so-called BCG instillation) is effective. With cystoprostatectomy (resection of the bladder and prostate, shaded area in Fig. 4e) for bladder cancer in men, 4–17% of patients experience subsequent urethral cancer. In female patients, involvement of the urethra in relation to bladder cancer is reported to be 1.4–36%.13)

From these data, we have to pay close attention to the whole urinary tract assuming it as a single unit from the renal pelvis to the urethra, including the contralateral unit of the upper urinary tract, when we perform nephroureterectomy or cystectomy for TCC.

**Oncological consideration for use of the urethra to assure normal voiding after cystectomy.** The length of the urethra is different between males, approximately 30 cm, and females, approximately 5 cm. Therefore, separate oncological considerations must be done in male and female patients when we plan an orthotopic neobladder to assure voiding from the urethra.

In male bladder cancer patients, urethral recurrence of TCC after cystoprostatectomy is 4–17% (Fig. 4e).1) In our series of patients at the National Cancer Center Hospital between 1963 and 1987, of 169 male patients who underwent cystoprostatectomy for TCC of the bladder, 18 (10.6%) exhibited subsequent urethral cancer within 5 years after cystoprostatectomy.14) Risk factors for subsequent urethral cancer were analyzed in terms of the tumor grade and stage, number, size, location in the bladder, and gross pattern such as papillary and/or nodular cancer in step-sectioned cystoprostatectomy specimens. Cystoprostatectomy specimens, including the bladder, prostate, and bilateral ends of the ureters, were examined by step-sectioning indicating serial vertical sections of approximately 1 cm width to examine both tumorous tissue and normal appearing mucosa. Significant risk factors identified from these 169 patients for the later development of cancer in the retained urethra were papillary cancers, multiple cancers, and tumors arising in the bladder neck, prostatic urethra, and prostatic gland. Of these, 28 patients later demonstrated bloody discharge from the urethra, and subsequent urethrectomy was performed in these patients. The pathology of these 28 patients is illustrated in Table 1. Typical pathological findings in the subsequently resected urethra are illustrated in Fig. 5.12)

In other series at the National Cancer Center Hospital between 1963 and 1987, 19 patients underwent simultaneous prophylactic urethrectomy, namely cystoprostatectourethrectomy. These 19 patients seemed to be at very high risk of developing subsequent urethral cancer, having wide-spread concomitant CIS and/or multiple tumors in the bladder compatible with the above-mentioned risk factors.14) In total, 17 (89%) of the 19 patients had no pathological lesions in the resected urethra (Table 1). Observed pathological findings in the subsequently resected urethra due to bloody discharge from the

| Subsequently resected urethra          | No. Cases |
|---------------------------------------|-----------|
| Coexistence of papillary and carcinoma in situ (CIS) | 3         |
| Carcinoma in situ (CIS)               | 5         |
| Papillary carcinoma                   | 3         |
| Invasion to the corpus spongiosum and cavernosum | 7         |
| Concurrently resected urethra         |           |
| No cancerous tissue                   | 17        |
| Small foci of carcinoma in the corpus spongiosum | 1         |
| Small area of dysplasia               | 1         |

Table 1. Pathological findings of the urethra subsequently resected after cystoprostatectomy (upper half of the table) and concurrently resected urethra with cystoprostatectomy because of high-risk factors for bladder cancer (lower half)
retained urethra after cystoprostatectomy and the concurrently resected urethra were quite in contrast (Table 1, Fig. 5). A possible explanation for this extreme difference may be that the urine stream is preserved in the concurrently resected cases until simultaneous removal of the bladder, prostate, and urethra (cystoprostatourethrectomy). However, in patients who underwent subsequent urethral resection, the urethra was not used for passing urine after cystoprostatectomy. During the cystoprostatectomy procedure, cancer cells may have spilled into the urethra during surgical handling of the bladder and prostate, and these cells may have subsequently implanted into the urethral mucosa.

Further supporting evidence for this idea is that urethral cancer development is very rarely observed and is not a serious clinical issue for patients who undergo repeated TUR for multiple, frequent recurrences in the bladder. In these cases, again, urine flow is kept through the urethra and cancer cells cannot implant into the urethral mucosa because of the strong urine stream.

In female bladder cancer patients, compared with male patients, however, pathological issues have not had special attention paid to them, because bladder cancer is less common in women than in men at a ratio of 1:3. In addition, the female urethra is short, so cystourethrectomy is a state-of-the-art surgery for female bladder cancer patients. Consequently, the incidence and characteristics of urethral involvement in female bladder cancer patients have not been well documented. A 1.4% incidence of urethral involvement was reported during follow-up cystoscopy in 293 female bladder cancer patients. A few studies of bladder cancer reported urethral involvement in cystoprostatectomy specimens.

We reviewed 47 consecutive cases of female bladder cancer treated at the National Cancer Center Hospital between 1970 and 1990, who were analyzed by step-sectioning of the cystourethrectomy specimens. Of the 47 cases, 10 (23%) had multiple papillary cancers, 9 (21%) had papillomodular carcinoma with an intermediate pattern between papillary and nodular carcinoma, 18 (42%) had nodular carcinoma, and 6 (14%) had primary or secondary wide-spread CIS. Twenty-three cases (54%) exhibited more than pT1 stage indicating invasive carcinoma, and 27 (63%) were grade 3 tumors. Of
these 47 cases, urethral involvement was observed in only 3 cases (Fig. 6). In 1 case, stage pT4, grade 3 papillonodular carcinoma developed widely in the bladder, and overriding the bladder neck and proximal urethra, together with stage pTa, grade 2 papillary cancer (No. 23 in Fig. 6). In 2 cases (Nos. 28 and 29 in Fig. 6) with nodular invasive carcinoma of the bladder including the bladder neck, urethral cancer was observed either separate invasive carcinoma in the urethra or an intralymphatic spread without urethral mucosal change. These findings strongly suggested the necessity for prophylactic urethrectomy in cases of multiple papillary or papillonodular carcinoma encroaching to the bladder neck, and nodular invasive carcinoma infiltrating the bladder neck and trigone.

**Reconstruction of the urinary tract after cystectomy**

Reconstruction of the urinary tract, particularly after cystectomy, must be planned from two aspects, 1) the oncological nature of the remaining urinary tract, and 2) the handling of urine after cystectomy from the standpoint of quality of life (QOL) of patients.

**History of urinary diversion.** Simon\(^{18}\) in 1852 performed the first continent urinary diversion in a patient with ectopic bladder by implanting both ureters onto the rectum. In 1911, Coffey\(^{19}\) reported implantation of the ureters to the sigmoid colon. Since 1913, ureterosigmoidostomy, implanting both ureters to the sigmoid colon, has been utilized as a major method of continent urinary diversion. After surgery, both feces and urine are defecated from the anus. With increased clinical experience, problems associated with ureterosigmoidostomy such as repeated pyelonephritis due to ureteral reflux of dirty urine, hyperchloremic metabolic acidosis due to the absorption of urine from the sigmoid-mucosa and the possibility of later colonic cancer development,\(^{20}\) have become well-known. Development of adenocarcinoma, occasionally TCC, has been reported near the site of anastomosis between the ureters and sigmoid colon. Leadbetter Jr. et al.\(^{21}\) reported 45 cases of sigmoid colon cancers after ureterosigmoidostomy during 50 years. Physical irritation caused by fecal and urinary stream was presumably one reason, and the risk of developing this kind of cancer in patients who underwent ureterosigmoidostomy was estimated to be 500 times higher\(^{22}\) than normal controls.

When hydronephrosis appears in patients with ureterosigmoidostomy, urologists must carefully check the possibility of the development of ureteral end carcinoma. In 1950, Bricker\(^{23}\) first reported reconstruction of the urinary tract using an ileal conduit. This surgical procedure to reconstruct the urinary tract after cystectomy has been widely accepted as a major procedure until now (Fig. 7).

In 1951, Couvelaire\(^{24}\) reported the first clinical use of bladder substitution, a kind of neobladder from the present meaning, through an anastomosis of the isolated ileum to the urethra. In 1985, Camey\(^{25}\) used an isolated U-shaped ileum anastomosed to the urethra as a continent urinary diversion in more than 150 patients. Patients suffered from nocturnal incontinence due to the increased inside pressure of the ileal segment due to the physiological peristalsis of the ileum. For a long time, this type of procedure was used sporadically. In 1982, Kock et al.\(^{26}\) reported the use of a detubularised ileal segment as a pouch together with opening the lumen of the ileum.

![Fig. 6. Three cases of urethral involvement in 47 cystourethrectomy specimens in female bladder cancer.\(^{13}\) Bladders were opened sagitally and examined using a step-sectioning. The lower part of the diagram indicates the urethra.](image-url)
to the skin from where intermittent self-catherization was required. Patients do not need to use a pouch applied to the skin like Bricker's procedure, *i.e.*, cutaneous continent reservoir.

In line with the increased number of prostatectomies for the treatment of prostate cancer in the United States and Europe, instead of anastomosis between the urethral stump and urinary bladder after prostatectomy, anastomosis of the urethral stump with a neobladder constructed using various parts of the patient’s own bowel collected almost explosive interest among urologists for continent urinary diversion after cystectomy for bladder cancer. Ideally, the neobladder must achieve high compliance, *i.e.*, low pressure, large capacity, continence, and nonrefluxing ureteral implantation, *i.e.*, keeping normal kidney function by preventing urine backflow from the reservoir to the kidneys. The status of continence and kidney function were evaluated by the pattern of micturition, continence status during 24 hours, serum creatinine levels, and intravenous pyelography or enhanced CT. QOL and functional comparison among various procedures of urinary tract reconstruction have been reported.27,28)

**Theoretical considerations.** The basic principles of a neobladder, including configuration of the reservoir, accommodation, viscoelasticity, and contractility have been thoroughly reviewed by Hinman Jr.29) from the standpoints of physics, mathematics, and hydraulics. The configuration and studies of the volume of the reservoir (height × radius²) exhibited that a detubularized, folded pouch had almost double the volume of the original ileal segment (Fig. 8).

To avoid an increase in the inside pressure by intestinal peristalsis, detubularization, namely, opening of the intestinal segment along the antimesenteric border is very effective. According to Laplace’s law (Box 1), a detubularized bowel refashioned into a spherical reservoir will have a larger radius, enabling it to contain high volumes at lower intraluminal pressures.

**Box 1. Laplace's law for a spherical reservoir**

\[
P = \frac{2TW}{R}
\]

where, \(P\) indicates pressure, \(T\); tension, \(W\); wall thickness, and \(R\); radius of the reservoir.

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![Fig. 7. Ileal conduit.](image)

Approximately, 15 cm of ileal segment was isolated and the proximal end closed by suturing. The distal part of the ileal segment was anastomosed to the skin of right lower abdomen where a stoma was constructed. Urine comes out to this stoma and is collected by applying a pouch.

![Fig. 8.](image) Comparison of theoretical capacity of: (A) an intact 20 cm intestinal tube with 3.4 cm diameter; and (B) the same segment opened lengthwise and folded upon itself.29) The volume is doubled in (B). (used with permission)
pressures. The ileum, ileocecum, sigmoid colon, and so forth were refashioned into various shapes, including ones resembling the letters U, S, M, or W.

**QOL of patients after ileal conduit and neobladder**

**QOL of patients after reconstruction of the urinary tract.** The ileal conduit (Fig. 7) is a time-honored procedure since 1950, and significant numbers of patients have undergone this surgery all over the world. Principally, Bricker’s ileal conduit needs a connection of a urine-collecting pouch to the stoma, where the distal part of the ileal conduit is anastomosed to the right-lower abdominal skin. This pouch must be changed for a new one every 5–10 days. Patients must discard the urine from the pouch when it is full, 5–6 times a day. If the urine flows into the space between the stoma and pouch, severe dermatitis occurs around the stoma. Unexpected urine leakage may sometimes occur from the stoma and clothes may be contaminated. In addition, renal pelvic stones and pyelonephritis may arise. In spite of these complications inherent to an ileal conduit, patients can enjoy an almost normal life including swimming, dancing, and a variety of daily activities.

With a neobladder, when successfully constructed, patients can enjoy an almost normal life by voiding urine from the urethra even after cystectomy. Avoiding patients with a high risk of urethral recurrences listed in our previous paper for male patients, we successfully reconstructed the urinary tract for male patients using this procedure. For female bladder cancer patients, as stated previously, cystourethrectomy was routine at that time. More than that, neobladder construction for female patients was contraindicated because the female urethra is short and if a neobladder is anastomosed to the short urethra, patients may suffer from total incontinence resulting in very poor QOL postoperatively. We doubted this concept and the exclusion of patients with a high risk of urethral recurrence, and after examining the anatomical structure of the female urethra we successfully treated a female bladder cancer patient using an orthotopic neobladder (Figs. 9 and 10). To the best of our knowledge, this was the first case reported in the world (Table 2). The patient enjoyed normal micturition from the urethra after cystectomy. Later, Stenzl et al. reviewed the female neobladder cases.

**Functional outcomes of an orthotopic neobladder, particularly in women and recent progress.** Functional outcomes of interest include urinary function, sexual function, bowel function, metabolic function, and QOL of patients. In terms of urinary function, in one review, daytime incontinence was approximately 20%, nighttime incontinence 20%, and hypercontinence (patients cannot void and use intermittent self-catheterization) 10–
20%. Another review reported total continence rates as 22.3–63.2% at 12 months postoperatively. Daytime continence rates varied from 21.4% to 99.0% at 3–48 months postoperatively. Sexual function favorably recovered in patients who undergo pelvic organ preserving surgery. Concerning bowel function, Erber et al. reported that patients undergoing neobladder formation had a higher risk of experiencing ileus postoperatively than those undergoing ileal conduit formation (14.8% vs. 5.5%). As for metabolic function, urine contains elevated concentrations of $K^+$, $H^+$, and $Cl^-$! These ions absorbed in exchange for $Na^+$ and bicarbonate from the blood stream, resulted in hyperchloremic, hypokalemic metabolic acidosis, and salt-losing syndrome. This phenomenon was related to the intestinal segment used. The terminal ileum experiences more mucosal atrophy in the long term, which means a reduced risk of this kind of metabolic acidosis. As for QOL, an orthotopic neobladder is a good alternative to an ileal conduit in suitable patients who do not want a stoma and are motivated to comply with neobladder training after surgery.

Precluding factors for orthotopic neobladder are:

1) Before cystectomy, careful evaluation is necessary to avoid urethral recurrence after neobladder construction such as biopsies of bladder neck and prostatic urethral.

2) Sphincter muscle function should be evaluated before orthotopic neobladder construction to avoid urinary incontinence after surgery.

3) Compared with an ileal conduit, a neobladder needs an additional 1–2 hours operating time to construct the spherical neobladder. These factors should be discussed between patients and attending doctors before operation.

Serious discussions with patients and physicians are naturally required before surgery. According to progress in surgical techniques, robotic surgery is being introduced rapidly into the field of urology. The “gold standard” treatment for high-grade, high-stage bladder cancer is radical cystectomy with extended lymph node dissection and urinary diversion, including ileal conduit, continent urinary reservoir, and orthotopic neobladder. For every step in these procedures traditional surgery is now being replaced by robotic surgery.

From the middle of the 19th century, reconstruction of the urinary tract, especially after cystectomy for bladder cancer, has been a major issue for urologists worldwide. QOL of patients who undergo cystectomy is the main issue, and various procedures have been trialled, as stated in this review.

Neobladder construction is an important solution for this issue. Even in the era of robotic surgery, creation of a neobladder will survive as an important option for bladder cancer patients, both male and female, from the standpoint of QOL.

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Profile

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