Review

Reconstruction of the urinary tract after cystectomy for transitional cell carcinoma of the bladder

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Abstract: Transitional cell carcinoma (TCC) in the urinary tract is characterized by the development of multiple tumors in time and space. When cystectomy is performed, urinary tract is reconstructed by various options including a neobladder using patient's own intestine anastomosed to the urethra. This procedure assures normal voiding from the urethra even after cystectomy. Use of the urethra for preserving urethral voiding and function of a neobladder are reviewed from viewpoints of carcinogenesis and quality of life after cystectomy. Incidence of subsequent urethral cancer arising after cystectomy is relatively high, however, if high risk patients are appropriately excluded, a neobladder can be constructed safely from the oncologic standpoint and patient's quality of life.

Key words: Bladder cancer; renal pelvic cancer; ureteral cancer; urethral cancer; urinary diversion; neobladder.

Introduction. Mucosal surface of the urinary tract, i.e., renal pelvis, ureter, bladder and the greater part of the proximal urethra, is covered with urothelium or transitional cell epithelium being composed with three to seven cell layers thick.[1] Typical structure is composed with basal cells, intermediate cells and superficial cells. Superficial cells have the binucleated, flat, large characteristic shape being called umbrella cells.[1] Luminal surface of the umbrella cells is covered with asymmetric unit plasma membrane which is effective to protect the tissue from high osmotic pressure of the urine.[2]

More than 90% of cancers arising in the urinary tract are transitional cell carcinomas (TCC), the rest are squamous cell carcinomas and adenocarcinomas. Multiple tumor development in the entire urinary tract in time and space is a well-known biological phenomenon of TCC, particularly in the bladder.[3] Ureteral and urethral involvement of TCC needs serious consideration when cystectomy is necessary and urinary reconstruction is indicated. This phenomenon is explained as a result of "field cancerization"[4)-7)] in which the entire urothelium from the renal pelvis to the urethra is susceptible to carcinogens flowing down in the urine. On the other hand, TCC cells can be implanted to other sites of the urothelium,[8] so called "implantation". These two mechanisms make it difficult to determine whether a recurrent tumor represents an inadequately treated initial one, or implantation of cancer cells, or the effects of multifocal carcinogenesis. Molecular analysis of multiple cancers in the bladder or multiple cancers developed in the upper urinary tract and the bladder tells us as one possibility that those multiple cancers are monoclonal origin indicating the implantation of cancer cells from the original tumors.[9)-12)] It is likely that all of these mechanisms are relevant. In fact, Akaza *et al.*[13] reported the biphasic pattern of recurrences of the bladder cancers after transurethral resection (TUR), which may indicate the combination of early implantation and late new growth.

Urinary reconstruction after cystectomy has been conducted historically by uretero-sigmoidostomy, ileal conduit, cutaneous continent reservoir requiring self-catheterization and an orthotopic neobladder anastomosed to the urethra. An orthotopic neobladder assures normal voiding from the urethra. Each procedure has relation to cancer development in the reconstructed

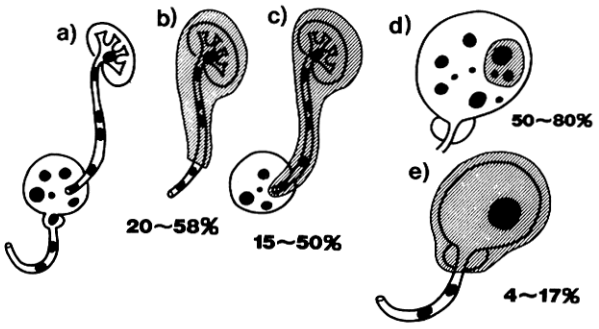

Fig. 1. Schematically illustrated multiple development of cancers in the urinary tract. The extreme left a) indicates a case having renal pelvic, ureteral, bladder and urethral cancers simultaneously. b) When ordinary nephrectomy is performed for the renal pelvic and/or ureteral cancer, subsequent ureteral cancer in the remaining ureter is 20-58%. c) Even though total nephroureterectomy is performed, subsequent bladder cancer occurs in 15-50%. d) When superficial bladder cancers are resected by transurethral procedure, subsequent bladder cancers arising in the normal appearing bladder mucosa are 50-80%. e) After complete removal of the bladder and prostate, incidence of subsequent urethral cancer is 4-17% (Ref.3)).

Table I. Pathological findings of the subsequently and concurrently resected urethras

	No. Cases
Subsequently resected urethra	
Coexistence of papillary and *in situ* ca	3
Ca *in situ*	5
Papillary ca	3
Invasion to the corpus spongiosum and cavernosum	7
Concurrently resected urethra	
No cancerous tissue	17
Small foci of ca in the corpus spongiosum	1
Small area of dysplasia	1

urinary tract.

In this review, urinary reconstruction will be discussed in relation to cystectomy from the standpoints of multiple, tumor development in the entire urinary tract and the function of a neobladder.

Carcinogenesis in the urinary tract. *Characteristic patterns of transitional cell carcinoma (TCC).* TCC can be classified as papillary carcinoma, nodular carcinoma and carcinoma *in situ* (CIS) according to their gross and microscopic configuration. Papillary carcinomas usually develop in multiple forms and frequently recur elsewhere, however, these tumors usually remain superficial confining to the mucosal layer, and the prognosis of patients, even treated conservatively, is generally fair. On the other hand, nodular carcinomas are usually deeply invasive when first observed, and the clinical outcome, even after cystectomy, is poor. CIS is a flat lesion with or without reddy velvet-like appearance of the mucosal surface, and although initially CIS is confined to the mucosal layer, CIS easily starts to invade to the submucosal or deeper muscular layer. TCCs are a mixture of these three basic patterns.[15]

Multiple development of TCC in the urinary tract. Multiple development of TCC in the entire urinary tract has been well documented. For example, renal pelvic, ureteral, bladder and urethral cancers are sometimes observed in a single case (Fig. 1a). When ordinary nephrectomy is performed for the renal pelvic and/or ureteral cancer, TCC arising in the remnant ureter, i.e. about one third of the lower part of the ureter, is reported in 20-58% (Fig. 1b). Consequently, the established state of the art operation for TCC of the renal pelvis and/or ureter is total nephroureterectomy indicating removal of the kidney, total ureter with resection of the small part of the bladder. Even such an operation is performed, however, a 15 to 50% incidence of subsequent TCC in the bladder is reported (Fig. 1c). When superficial papillary TCC of the bladder is treated by transurethral resection (TUR), the subsequent development of tumors having a similar nature in the normal-appearing bladder mucosa is reported to be 50-80% (Fig. 1d). After cystoprostatectomy (removal of the bladder and prostate) for bladder cancer in men, a 4-17% incidence of cancer in the remaining urethra is reported[16] (Fig. 1e). In female patients, involvement of the urethra in relation to bladder cancer is reported to be 1.4-36%.[17]

These data should be taken into consideration when we perform nephroureterectomy (removal of the kidney and ureter) or cystectomy and for the follow-up plans of the upper and lower urinary tract and the contralateral urinary tract assuming them as a single unit from the renal pelvis to the urethra.

Selection of urinary reconstruction in relation to carcinogenesis. When a patient is indicated for cystectomy as the treatment of invasive bladder cancer, basically three different options of selecting 1 of 3 types of urinary reconstruction are provided to the patients and families as information: (1) an ileal conduit, (2) a cutaneous continent reservoir requiring self-catheterization, or (3) an orthotopic neobladder anastomosed to the urethra to ensure urethral voiding. Presently, type (2) is not commonly used because patients do not choose this type of reconstruction mainly because type (2) seems to be intermediate of types (1) and (3). From the carcino-

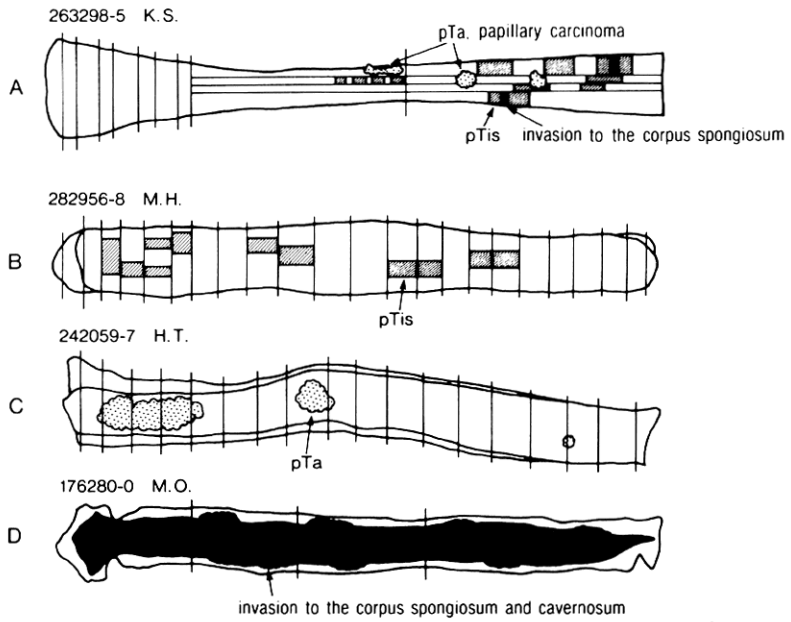

Fig. 2. Typical pathological findings in the resected urethra. Prostatic side is at left and meatus of urethra is at right side. Each specimen was examined by vertical or horizontal sections as indicated (Ref. 18). pTis indicates carcinoma *in situ* on the surface of the urethral mucosa. pTa indicates papillary superficial cancer without submucosal invasion.

geneic standpoint, an orthotopic neobladder anastomosed to the urethra is the biggest issue to be discussed. In male bladder cancer patients, urethral recurrence of TCC after cystoprostatectomy is reported to be 4-17% (Fig. 1e). In our series of patients analyzed by Tobisu *et al.*,[18] of 169 male patients who underwent cystectomy for bladder cancer, 18 (10.6%) demonstrated subsequent urethral cancer within 5 years after cystectomy. Risk factors for subsequent urethral cancer were analyzed in terms of the grade, stage, number, size, location and gross pattern of bladder cancers in the cystectomized specimens. Significant risk factors in bladder cancer relevant to the later development of cancer in the retained urethra were papillary cancers, multiple cancers, and tumors in the bladder neck, prostatic urethra and prostatic gland. On the other hand, 19 patients with concomitant CIS and/or multiple tumors in the bladder compatible to the above-mentioned risk factors underwent simultaneous prophylactic urethrectomy with cystectomy in the same observed period. Of them, 17 (89%) of 19 had no pathological lesion in the resected urethra (Table I). As is indicated in Fig. 2, pathological findings observed in the urethra subsequently resected after cystectomy were versatile but the urethra simultaneously resected with cystectomy exhibited almost no pathological lesions. Possible reason to explain this extreme difference may be that the urine stream is preserved in the latter cases until simultaneous removal of the bladder, prostate and urethra (cystoprostatourethrectomy). To support this hypothesis, urethral cancer development is not commonly observed and is not a serious problem for patients who undergo repeated TUR for multiple, frequent recurrences in the bladder. This hypothesis together with above mentioned risk factors for urethral cancer development in relation to bladder cancer supports our idea to reconstruct the urinary tract by anastomozing the neobladder to the urethra. Regarding urethral cancer after cystectomy, male patients are carefully analyzed, however, the incidence and characteristics of urethral involvement in female patients with bladder are not well documented. One reason for the very few amount of data may the principle of routine urethrectomy together with cystectomy is well established in female patients because the female urethra is short and easy to remove with the bladder. A 1.4% incidence of urethral involvement was observed during follow-up cystoscopy in 293 female patients with bladder cancer.[19] A few studies of bladder cancer were reported urethral involvement in cystourethrectomy specimens.[20,21] We reviewed 47 consecutive step-sectioned cys-

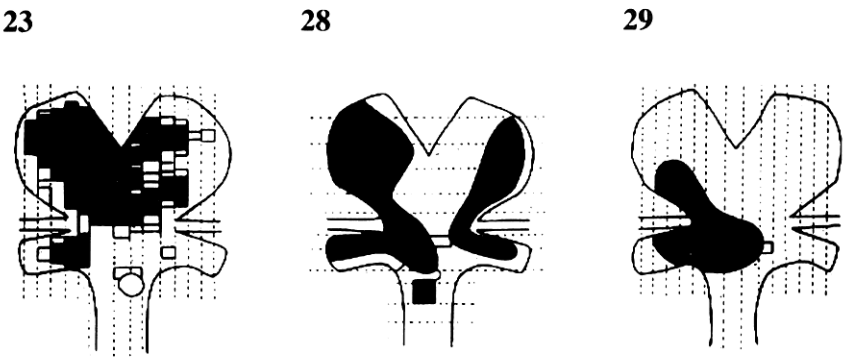

Fig. 3. Urethral involvement in 47 cystourethrectomy specimens in female bladder cancer (Ref.17)). Bladders are sagittally opened and lower part of the diagram indicates the urethra.

tourethrectomy specimens of bladder cancer in female patients to determine the incidence and characteristics of bladder cancer with the involvement of the urethra.[17] Of the 47 cases, 10 (23%) were papillary, 9 (21%) papillonodular that is intermediate between papillary and nodular carcinoma and 18 (42%) nodular carcinoma, and 6 (14%) primary or secondary CIS. There were 23 cases (54%) of invasive carcinoma of more than stage pT1 and 27 (63%) were grade 3 lesions. Urethral cancer was observed in only 3 cases (Fig. 3): 1 stage pT4, grade 3 papillonodular carcinoma developed widely in the bladder and, overriding the bladder neck and proximal urethra, stage pTa, grade 2 papillary cancer, was detected, while in 2 with nodular invasive lesions of the bladder including bladder neck, urethral cancer was detected either as a direct invasive extension via urethral CIS or as an intralymphatic spread without urethral mucosal change. These findings indicate the necessity for prophylactic urethrectomy in cases of papillary or papillonodular carcinoma encroaching on the bladder neck, and nodular invasive carcinoma infiltrating the bladder neck and trigone. Based on those analyses, by only removing the bladder, we successfully treated the first female bladder cancer patient by a neobladder anastomozing to the retained urethra.[22] Later, a large series of orthotopic neobladder for female bladder cancer patients including our series of patients were reported.[23]

Ureteral involvement in association with bladder cancer such as in a manner of spread of CIS is well documented. Consequently, it is a routine to examine the proximal end of the ureters by frozen section during cystectomy whether there is any CIS or cancerous lesions in the cut end of the ureters. Margin-free ureters must be used for ileal conduit or various forms of neobladder. In addition to this, when urinary tract is reconstructed after cystectomy via ileal conduit or neobladder, the incidence of appearing subsequent cancers in the remaining renal pelvis and/or ureter is reported to be 2-4%.[24] Bilateral involvement of the renal pelvis and ureter (synchronous or metachronous) occurs in 2-5%[25] of sporadic cases. Although the possibility is low, we have to be careful and always bear in mind this possibility.

Reconstruction of the urinary tract after cystectomy. Reconstruction of the urinary tract, particularly after cystectomy, must be planned from the two points, i.e., carcinogenic nature of remaining urinary tract, and postoperative function of the urinary tract and quality of life (QOL) of patients.

History. In 1852, Simon[26] performed the first continent urinary diversion in a patient with ectopic bladder using ureterorectal anastomosis. In 1911, Coffey[27] reported a physiologic implantation of the ureters to the sigmoid colon and in 1913, Lamoine[28] reported the first use of the true rectal bladder i.e., implanting both ureters to the rectum using the rectum as a bladder. Since 1913 ureterosigmoidostomy, implanting both ureters to the sigmoid colon, has been utilized as a major means of continent urinary diversion. With increased clinical experience, problems associated with ureterosigmoidostomy, such as recurrent pyelonephritis due to ureteral reflux, hyperchloremic acidosis, and the possibility of later colonic cancer development,[29] have become apparent. Development of mainly adenocarcinoma, occasionally TCC has been reported near the site of anastomosis between the ureters and sigmoid colon. Leadbetter[30] reported 45 cases arising cancer after ureterosigmoidostomy during 50 years. Physical irritation by fecal stream is thought to be one reason and the risk of developing this sort of cancer in patients who underwent ureterosigmoidostomy is 500 times higher than nor-

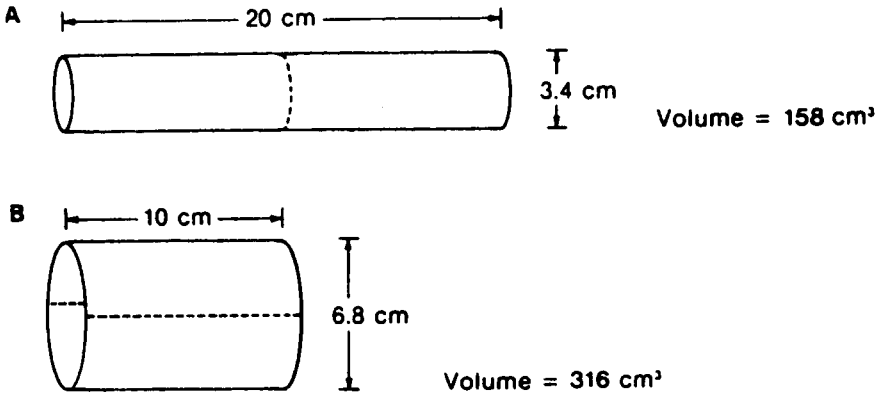

Fig. 4. Comparison of calculated capacities of (A) an intact 20 cm tube having 3.4 cm diameter and of (B) same segment opened lengthwise and folded upon itself (Ref. 38)).

mal controls.[31] This risk is evaluated as 5% for 6-50 years after ureterosigmoidostomy. Hydronephrosis appearing in patients who underwent ureterosigmoidostomy must be carefully checked bearing in mind the possibility of carcinoma near the ureteral anastomoses. In 1950, Bricker[32] first reported reconstruction of the urinary tract using an ileal conduit. This technique is widely accepted as the major procedure for urinary tract reconstruction. In 1951,[33] Couvelaire 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[34] used an isolated U-shaped ileum anastomosis to the urethra as a continent urinary diversion in more than 150 patients. Unfortunately, nocturnal incontinence due to increased pressure of the ileal segment resulting from ileal peristalsis occured. For a long time this type of procedure was used sporadically. In 1982, Kock *et al.*[35] reported on their pioneering use of a detubularized ileal segment i.e., opening the lumen of ileal tube and to use it as a ileal plate, a continent reservoir. With this breakthrough, an almost explosive interest in continent urinary reconstruction using cutaneous and urethrally anastomosed forms occurred throughout the world.

Theoretical considerations. The neobladder procedure involved postcystectomy construction using a segment of the patient's own intestine to form a new almost natural-like bladder. Ideally this neobladder must achieve high compliance, i.e., low pressure in neobladder, continence, and nonrefluxing reservoirs that allow adequate capacity and preservation of upper urinary tract function. The purpose of bladder replacement with an internal reservoir is not to improve survival of patients after cystectomy for bladder cancer but to improve quality of life. The status of continence and upper urinary tract function are evaluated by a normal micturition pattern, 24-hour continence, serum creatinine levels, and intravenous pyelography. QOL and functional comparison among various procedures of urinary tract reconstruction[36),37] have been reported.

The basic principles of a neobladder, including configuration of reservoir, accommodation, viscoelasticity and contractility have been thoroughly reviewed by Hinman[38] from the standpoints of physics, mathematics, and hydraulics. The configuration, and studies of the volume of the reservoir (height × radius^2) showed that the detubularized, folded pouch had almost twice the volume of the original ileal segment (Fig. 4). Interestingly, accommodation, volume to mural tension and viscoelasticity or compliance depend on the physical characteristics of the reservoir wall, and contractility depends on the motor functions of the bowel.

The clinical success of a neobladder is principally related to its reservoir geometry. The selected bowel segments are opened (detubularized) along the antimesenteric border and refashioned into various shapes, such as a U, S, M or W resembling to the shape of alphabet. Different reservoir shapes produce different characteristics in length and location of selected bowel, radius, and volume of the reservoir.

Quality of life after reconstruction of the urinary tract. Ileal conduit is the time-honored procedure since 1950[32] and significant number of patients underwent this surgery all over the world. In principle, this surgical procedure needs to apply urine-collecting pouch to the stoma where the distal end of ileal conduit is anastomosed to the skin. This pouch must be changed to the new one every 5 to 10 days. Patients must discard the

urine from pouch when it is full, 5-6 times a day. If the urine extravasates to the space between the stoma and pouch, severe dermatitis around the stoma occurs. Unexpected urine leakage may sometimes occur from the stoma. Renal pelvic stones may arize. These are the main clinical issues associated with ileal conduit. With neobladder, when successfully constructed, patients can enjoy almost normal life by voiding the urine from the urethra even after cystectomy. However, this procedure is relatively new compared to ileal conduit, we have only 10 to 15 years observation period after construction. About 10-15% of patients suffer from incontinence, particularly while sleeping, and approximately 10-15% of patients cannot void necessitating intermittent self-catherization indicating to introduce a catheter from the urethra to the neobladder. As a long-term sequelae, stone formation in the neobladder is known and hyperchloremic acidosis by absorbing the electrolytes in the urine stored in the neobladder, or excretion of calcium resulting in osteoporosis, particularly elderly female patients are also known. Consequently, both procedures have characteristic merits and demerits, respectively.

In summary, urinary reconstruction after cystectomy should be considered from the carcinogenic standpoint and the function of reconstructed urine flow route.

As was stated earlier, the variety of cancerous changes observed in the 18 patients with urethral recurrence is in sharp contrast to the simultaneously resected urethras of 19 patients with almost no cancerous changes (Table I, Fig. 2). The shedding of cancer cells from malignant urethral tissue by urine flow appears to be an important mechanism when considering the very low incidence of urethral recurrence in the large numbers of patients who undergo repeated transurethral resections for multiple papillary bladder cancers (unpublished). Shed bladder cancer cells spilled in the urethra during cystectomy procedure are left intact in the remnant urethra because there is no urine flow after cystectomy. They are harvested in the urethra during the months or years after cystectomy. This mechanism may explain the difference shown in Table I. In addition, recent molecular evidence[9)-12)] indicates that the implantation of cancer cells may provide an explanation for the multiple development of TCC in the urinary tract.

For a support of this hypothesis, we are seeking molecular evidence to prove the same molecular changes in the bladder cancer and the urethral cancer. However, we are so far unsuccessful to obtain appropriate specimens to analyze. Should this be the case, subsequent urethral cancer development may not be a hindrance to neobladder construction when patients at high risk for urethral cancer are excluded.

Conclusion. Urinary reconstruction after cystectomy for bladder cancer has a long history. Modern surgical technique revolutionalized the procedure of reconstructions using patient's own intestine for a neobladder. Theoretical consideration must be added to construct the neobladder from the standpoints of the function of neobladder, selection of the bowel, shape and size of the reservoir in terms of length and radius. At the same time, when neobladder is anastomosed to the urethra to assure voiding from the urethra after cystectomy, carcinogenic risk factors of developing subsequent cancers in the urethra both in male and female patients must be seriously considered. In this respect, contribution from Japan was great as was reviewed in this article. QOL and cure of the disease are two most important factors when cystectomy is indicated for a patient with bladder cancer. Highest QOL and/or function of the neobladder and the lowest risk of the subsequent carcinogenesis must be compromised reasonably for each patient.

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