

Review Article

Radical Cystectomy and Orthotopic Bladder Substitution Using Ileum

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Over the past decade, continent urinary diversion, especially orthotopic bladder substitutions, has become increasingly popular following radical cystectomy for bladder cancer. The ultimate goal of orthotopic bladder substitution is to offer patients the best quality of life, similar to that of patients with native bladders. To achieve that purpose, surgeons should be familiar with the characteristics of good candidates for neobladders, the possible intraoperative and postoperative problems related to the surgery, and the solutions to these problems. Postoperative surveillance and instructions given to the patients also contribute to successful, functional results. Here, we reviewed the indications, pitfalls, and solutions for orthotopic bladder substitutions and the patients' quality of life after surgery. When performed properly, orthotopic continent diversion offers good quality of life with few long-term complications. Therefore, we believe it is the best option for the majority of patients requiring cystectomy.

Key Words: Cystectomy; Quality of life; Urinary bladder; Urinary bladder neoplasms; Urinary diversion

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INTRODUCTION

Radical cystectomy (RC) and urinary diversion have been the standard treatment of high-grade, invasive transitional cell carcinoma of the bladder. Ideal urinary diversion after RC should be the safest for cancer control, have the fewest complications, and provide the easiest adjustment for patients' lifestyle, thereby supporting the best quality of life (QoL). Over the past decades, since the introduction of orthotopic bladder substitution (OBS) by Camey and Le Duc in the late 1970s, orthotopic urinary diversion has been increasingly performed in both sexes.

Today, the proportion of cystectomy patients receiving a neobladder has increased to 50% to 66% at large-volume institutes [1-3]. In this article, we review the published results regarding OBS using ileum, which is the most commonly performed procedure for continent urinary diversion, specifically focusing on the indications, preoperative and intraoperative considerations, possible problems and solutions, and postoperative QoL of the patients.

PATIENT SELECTION: INDICATIONS AND CONTRAINDICATIONS

Appropriate patient selection for OBS is one of the keys to success. All cystectomy patients are possible candidates for a neobladder. Nowadays, although contraindications for OBS are fewer than in the past, it is important to identify patients in whom OBS may be less ideal (Table 1). Before determining the urinary diversion method, surgeons should consider the patient's preferences and general performance status, renal and hepatic function, primary tumor stage and location, and the need for adjuvant therapy.

The primary patient factor for OBS is the patient's desire for a neobladder. The patient should have a certain motivation to tolerate the initial, and sometimes lasting, inconveniences of nocturnal incontinence associated with a neobladder [4]. If patients lack the motivation to understand the new voiding techniques that will be required postoperatively, OBS is not desirable. Thus, the ileal conduit is preferred in patients with inadequate intellectual capacity, dexterity, or physical conditions that impede self-

TABLE 1. Contraindications for orthotopic bladder substitution using ileum

Absolute	
Permanently compromised renal function: serum Cr > 2 mg/dl or GFR < 40-50 ml/min	
Severe hepatic dysfunction	
Inadequate intellectual capacity, dexterity, or mobility	
When simultaneous urethrectomy is indicated on the basis of primary tumor	
Relative	
Compromised intestinal function, especially inflammatory bowel disease	
Recurrent urethral stricture	
Noncompliance of patient to indefinite follow-up	

catheterization.

OBS is contraindicated in patients with permanently compromised renal function or severe hepatic dysfunction. OBS is absolutely contraindicated in patients with a glomerular filtration rate of less than 40-50 ml/min or serum creatinine greater than 2 mg/dl as a result of long-standing obstruction or chronic renal failure [5]. However, some patients with significant creatinine elevations due to bladder cancer can recover sufficient renal function to allow OBS if the obstruction is relieved. In this situation, placement of percutaneous nephrostomy before surgery may give more accurate information on true renal function. Severe hepatic dysfunction is also a contraindication to OBS because absorption of ammonia from the urine into the portal circulation markedly increases postoperatively through the intestinal mucosa of the neobladder, leading to hyperammonemia. In addition, OBS is relatively contraindicated in patients with compromised intestinal function, particularly inflammatory bowel disease.

OBS is also absolutely contraindicated in patients who are candidates for simultaneous urethrectomy on the basis of their primary tumor [6,7]. Similarly, OBS is relatively contraindicated in patients with significant benign urethral pathology, such as recurrent urethral strictures. Although prostate tumor involvement in male patients and bladder neck involvement in female patients are risk factors for urethral recurrence [8,9], OBS is possibly indicated, provided that intraoperative frozen section analysis of the urethral margin is without evidence of tumor [9-11].

With accumulated experience in the OBS procedure, advanced tumor stage is not an absolute contraindication for OBS. In a proportion of patients with locally advanced or node-positive disease, long-term survival can be achieved with a low incidence of pelvic recurrence (range, 10-13%) through RC and thorough pelvic lymph node dissection [12-14]. Thus, OBS can be performed in these patients with anticipated good results. Furthermore, it was reported that even in the presence of recurrent disease, most patients can achieve normal neobladder function until death [14]. However, if tumor involvement to adjacent organs or extensive lymph node involvement is suspected, an ileal

conduit rather than OBS is preferable for prompt adjuvant therapy [15].

Notably, old age is not a contraindication for OBS. Older patients, as part of the informed consent, need to be aware that they have a greater incidence of enuresis or nocturnal incontinence than do younger men, but age by itself should not be a contraindication. In this context, physiologic rather than chronologic age must be taken into consideration [7].

INTRAOPERATIVE CONSIDERATIONS

1. Positive urethral margin and lymph node metastasis

If the tumor is located near the bladder neck in females or involves the prostatic urethra in males, intraoperative frozen section analysis of the distal urethral margin may be necessary. Because a positive urethral margin warrants total urethrectomy, all patients should be informed that diversion to the skin via an ileal conduit may be necessary owing to unexpected tumor extent, and an appropriate stoma site should be marked on the abdominal wall beforehand.

The incidence of lymph node metastasis at RC has been reported to be 14% to 32% [16-19]. Although intraoperative frozen section analysis for removed lymph nodes is not our routine practice, we do frozen section analysis in cases of palpable or grossly enlarged lymph nodes. If the results reveal positive lymph nodes, we do frozen section analysis for all lymph node specimens removed through meticulous lymph node dissection. In our practice, OBS can be performed in patients with minimal nodal disease, whereas ileal conduit is preferable in patients with extensive lymph node involvement for prompt adjuvant therapy.

2. Ureterointestinal anastomosis: refluxing or nonrefluxing?

One of the important goals of urinary diversion is preservation of renal function. The necessity of reflux prevention at a ureteroileal anastomosis is controversial [3,7,20-22]. Advocates for antireflux anastomosis reported that, on the basis of animal experiments, refluxing anastomosis was more commonly associated with reflux and pyelonephritis and subsequent renal function deterioration [23]. However, previous studies have shown that the need for reflux prevention differs depending on the urinary diversion method. Although conduits are not always low-pressure systems [24,25], often due to obstruction at the level of the fascia immediately superficial to the external oblique muscle, OBS is associated with consistently low intra-reservoir pressure through bowel detubularization [26] and simultaneous pressure increases in the neobladder, abdomen, and renal pelvis during the Valsalva maneuver [21]. Meanwhile, many studies have reported that the risk of anastomosis stricture is significantly higher in nonrefluxing techniques than in direct refluxing anastomosis [2,21,22,27]. Hautmann et al reported that simple end-to-side, freely refluxing anastomosis to an afferent limb of a low-pressure

orthotopic reconstruction, in combination with regular voiding and close follow-up, has the lowest overall complication rate [4]. Consistent with these reports, we have reported no significant difference in functional or radiographic changes between the refluxing and nonrefluxing types of OBS [28], and although reflux was more common in refluxing anastomosis in postoperative voiding cystourethrography, the development of reflux after RC does not significantly alter renal function regardless of its severity [29].

Integrating the published results and our experience, we believe that freely refluxing ureteroileal anastomosis is a safe and easy method for OBS.

3. Short mesentery

Tension-free anastomosis between a neobladder and the distal urethra may be difficult in patients with a short mesentery. In this situation, anastomosis can be performed under a more flexed position to minimize tension. If this is not enough, dissecting the mesentery to a more proximal site or making multiple, small incisions in the mesentery can lengthen the mesentery. Several investigators have suggested neourethral tube modification methods for adding extra length to reach the urethra. For example, Rawal et al reported a modification of the Studer neobladder method, the 'pitcher pot' ileal neobladder, which is the formation of a tube or neourethra by use of a part of the ileal wall, consequently providing extra length for anastomosis without tension [30]. However, note that this method is associated with urinary retention and an obstructive voiding pattern.

4. Ureteral stents and cystostomy

Placement of a ureteral stent at a ureteroileal anastomosis depends on the surgeon's preference. Most surgeons use a ureteral stent at a ureteroileal anastomosis and then remove the stent with the Foley catheter after cystography at 2-3 weeks postoperatively. In our experience, a ureteral stent is not necessarily needed in refluxing anastomosis, whereas it is helpful to prevent anastomosis obstruction in antirefluxing anastomosis.

Placement of a cystostomy into the neobladder is useful for postoperative manual irrigation and monitoring of the voiding pattern after Foley catheter removal. However, in our experience, use of a large-sized (22-24 Fr) double-lumen catheter or nephrostomy catheter without cystostomy is enough.

POSTOPERATIVE PROBLEMS AND SOLUTIONS

1. Postoperative ileus

Ileus following RC is one of the most frequent postoperative complications that cause delayed recovery and increased hospital stay [31-34]. Ileus was noted in 4-23% of patients undergoing RC [32-35]. Chang et al reported that increased blood loss during surgery and the presence of major complications were significant predictors for ileus [32]. Several

perioperative managements should be considered to reduce postoperative ileus. Because the perception of pain is an acknowledged promoter of ileus [36], adequate intraoperative and postoperative pain control is important. Hypovolemia during surgery is also associated with an increased risk of postoperative ileus [31,32]. Thus, timely and adequate hydration with colloids or blood transfusions is crucial after exenteration, when blood loss exceeds 10% of the estimated total blood volume [37]. Additionally, early postoperative provision of artificial nutrients, in the form of both total parenteral nutrition and enteral nutrition, has shown beneficial effects in preventing postoperative ileus [37].

Although nasogastric tubing is helpful intraoperatively to obtain bowel decompression, routine postoperative nasogastric decompression may be unnecessary. For example, recent studies have shown that bowel resection can be performed safely without postoperative nasogastric tubing both in general surgery cases and in radical cystectomy [35,38]. Two meta-analyses including over 4,000 cases concluded that routine postoperative nasogastric decompression was unnecessary and was associated with a higher incidence of pulmonary complications than selective nasogastric decompression [39,40]. Meanwhile, two recent studies reported that gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion [41,42].

2. Urinary tract infection

Contrary to normal urothelium, which has inhibitory action against bacterial adherence, bowel epithelium lacks inhibitory action against bacterial adherence. It has been reported that about 51-67% of patients with orthotopic neobladder have a positive urine culture [43-45]. Compared with other types of urinary diversion, few studies have investigated urinary tract infection (UTI) in patients with orthotopic neobladder. In a study by Wullt et al, *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* were frequently detected pathogens, and bacterial colonization was strongly correlated with residual urine [44]. However, all patients in this study were asymptomatic. In another study by Wood et al, the overall rate of UTI was 39%, and 12% of patients had urosepsis [43]. The authors suggested that prophylactic antibiotics are recommended in patients with recurrent UTI but that treating a positive urinary culture in the absence of specific voiding symptoms is not advocated. As such, the need for antibiotic treatment and the clinical significance of bacteriuria in patients with OBS are controversial. In our experience at the Asan Medical Center, the most frequent uropathogens associated with perioperative pyelonephritis and febrile UTI are *Enterococcus faecalis*, followed by methicillin-resistant *Staphylococcus aureus*. Because *Enterococcus* species are mostly susceptible to ampicillin, we use prophylactic antibiotics for 4 weeks postoperatively.

After RC, patients with neobladders commonly have chronic bacteriuria, which is fairly steady over many years

[43,44,46,47]. Although ileal neobladders lack the native immunologic defenses of the native bladder mucosa and bacterial colonization may progress to invasive tissue-level infection, all investigators recommend against long-term prophylactic antibiotic therapy for patients with asymptomatic bacteriuria to reduce the development of drug-resistant species and to minimize cost and drug-related adverse effects. Additional studies are needed so that conclusions can be made regarding UTI in patients with orthotopic neobladder.

3. Urinary continence

Continence after OBS is affected by multiple factors, including the size and configuration of the neobladder, urethral length, patient age and mental status, intact pelvic nerve supply to the rhabdosphincter, completeness of voiding, and the presence or absence of bacteriuria [48-50]. Continence improves over time during the initial 6 to 12 months postoperatively as the compliance of the diversion increases [46,48]. In addition, after surgery, patients learn to void by performing a Valsalva maneuver in coordination with relaxation of the pelvic floor, resulting in spontaneous voiding to empty the diversion. Daytime continence is achieved earlier than nighttime continence [2]. At postoperative 1 year, the overall rate of daytime continence, defined as totally dry or the use of 1 pad per day, is approximately 85% to 90% [1,47,50-53]. Regarding the relationship between neobladder configuration and continence, Nesrallah et al found that at 3 to 6 months postoperatively, daytime incontinence and enuresis were more common in elongated ileal neobladders than in spherical neobladders but the results were the same by 1 year in both groups [53]. In that study, at 1 year, spherical neobladders tended to enlarge to a greater capacity and to have a higher prevalence of postvoid residual urine volume over 100 ml and a greater need for catheterization [53]. Thus, surgeons should be careful to not make the initial volume of a spherical neobladder too large. On the other hand, decreased functional urethral length after surgery [48] or decreased urethral sensitivity at the membranous urethra in men [54] was reported to be associated with daytime incontinence. Daytime continence rates may decrease 4 to 5 years postoperatively, partly because of decreased tone of the urethral sphincter with advanced age [55]. Persistent severe incontinence after OBS may be treated by periurethral collagen injection [56] or definitive placement of a urethral sling or artificial urinary sphincter.

In contrast with daytime continence, some degree of nocturnal leakage is a constant finding in most reports despite a technically sound operation [48]. Most series report a prevalence of nighttime leakage of 20% to 50% even after 1 year postoperatively [57-60]. Similar to daytime incontinence, nighttime incontinence resolves as the functional capacity of the neobladder increases. Rates of complete nighttime continence without any pads are reported to be 45% to 65% [60,61]. In a study based on urodynamic study [58], patients with enuresis had higher pressures, max-

imal volumes, postvoid residual urine volumes, and rates of positive urine culture, as well as lower maximal urethral pressures, flow rates, and compliance, than did those without enuresis by univariate analysis. However, in the multivariate analysis, only the amplitude of uninhibited contractions and increased postvoid residual volume were associated with enuresis [58]. Increased age was associated with a higher rate of enuresis in some series [51], whereas in other reports, age was not correlated [58]. For treatment of nighttime incontinence, patients are instructed initially to limit their fluid intake after the evening meal, to void before going to sleep, and to set an alarm clock to awaken and void once or twice during the night. Several studies reported that the use of imipramine hydrochloride 25 mg at bedtime decreases nighttime leakage in up to 25% of patients [57,58]. However, nighttime continence can ultimately be achieved with improvement of the patient's voiding pattern.

4. Incomplete voiding (hypercontinence)

After OBS, incomplete emptying and so-called hypercontinence requiring clean intermittent catheterization (CIC) is observed in 4% to 25% of males [44,50,62] and in 0% to 53% of females with neobladders [63,64]. Thus, voiding dysfunction after OBS is more common in women than in men. Although the cause of this finding is unclear, many studies have suggested that the primary cause of hypercontinence in female patients is formation of a "pouchocoele" from lack of posterior support of the neobladder, which leads to angulation and obstruction of the neobladder-urethra junction [64-67]. Additionally, several factors such as an elongated bladder neck, the neobladder outlet not located at the most caudal portion of the reservoir, a dysfunctional bladder neck, inadequate pelvic floor relaxation, and excessive reservoir volume are suggested to be the cause of hypercontinence [62,65,67].

Although CIC is the best method for treatment of hypercontinence, compliance of male patients is low compared with female patients. In our experience, high doses of an alpha-blocker can bring subjective symptom improvement, but reduction of residual urine volume is rare. To reduce postoperative hypercontinence, patients should clearly understand the principle that lowering outlet resistance is crucial for complete emptying. Because increasing intra-abdominal pressure only is not enough for voiding, instruction on pelvic floor relaxation through biofeedback, regular voiding to prevent overdistention, and regular follow-up is essential [68]. In patients who do not respond to conservative management, cystoscopic evaluation to exclude the presence of stricture is necessary. In addition, if hypercontinence is associated with fixed sphincter tone on urodynamic study, partial sphincterotomy may be helpful. In females, techniques to prevent pouchocoele formation include urethral suspension, placement of the omentum into the space posterior to the pouch, and suspension of the vaginal fornices to the Cooper ligament [69,70].

5. Mucus production

The bowel mucosa secretes mucus made up of a glycoprotein core [71], and about 35 g/day of mucus is produced in continent urinary diversions [72]. Therefore, from the first postoperative day, indwelling catheters must be carefully irrigated to prevent initial mucous buildup within the neobladder [46,73]. Because a sudden increase in mucous production may be an early sign of urinary infection [74], it is worthy of notice. Patients with good voiding and complete emptying usually pass the mucus spontaneously in the urine, whereas patients with incomplete emptying and those performing CIC may need to irrigate the neobladder to remove the retained mucus.

Ileal mucosa incorporated into urinary diversion appears to atrophy over time when exposed to urine [75]. However, it takes more than 4 years for ileal mucosa to lose its absorptive and secretive functions and acquire the function of a urinary reservoir [48,76]. Thus, during the period for structural and ultrastructural changes to the ileal mucosa, regular monitoring of the voiding pattern and complete emptying is necessary. Once a large mucous plug is formed, no drug treatment may be effective, and manual evacuation through a large resectoscope sheath is most beneficial [77]. Patients experiencing recurrent mucous retention should be instructed in periodic catheter irrigation and mucous evacuation, and oral or instillation therapy with *N*-acetylcysteine or urea is helpful in these patients [71,72,78].

6. Metabolic problems

Metabolic complications of OBS are common but are generally not severe. However, when renal function is insufficient or deteriorated, metabolic abnormalities can be

problematic. Postoperative deterioration in renal function is most commonly associated with obstruction or infection [79]. Meanwhile, the more ileum that is used for reservoir construction, the higher the incidence of postoperative metabolic acidosis.

After urinary diversion, altered drug metabolism should be considered. Particularly, chemotherapeutic agents used in the treatment of bladder cancer require attention. Because methotrexate toxicity in patients with ileal conduits had been reported [80,81], patients with OBS who are receiving chemotherapy should be monitored closely and should stay well hydrated; the reservoir should be drained during treatment. Additionally, preservation of the terminal ileum is important to prevent vitamin B₁₂ deficiency, which increases with age and declining renal function. Because chronic vitamin B₁₂ deficiency is insidious and may result in irreversible neurologic and hematologic sequelae, long-term monitoring for vitamin B₁₂ is necessary [82].

PATIENT'S QoL

The optimal form of urinary diversion after RC in terms of patient QoL remains controversial. To date, more than 30 articles have compared the impact of different types of urinary diversion on patient QoL (Table 2), whereas no studies have examined QoL among different types of OBS. A major obstacle in assessing patient QoL after urinary diversion is the lack of a universal definition of the term "quality of life," which may differ between cultures, countries, and study groups. In addition, a patient's QoL is largely dependent on measurement modalities (open or structured face-to-face interview, telephone interview, proxy rating, self-

TABLE 2. Overview of studies that assessed health-related QoL after radical cystectomy and NB or IC

References	Year	No. of patients	Instrument			Time of QoL assessment	Main findings
			Name	General or disease-specific	Validated		
Dutta et al [83]	2002	NB (49)	SF-36 &	General	Yes	2.7 yr	No differences in SF-36 (multivariate analysis)
		IC (23)	FACT-G	General			
Hara et al [85]	2002	NB (48)	SF-36	General	Yes	NB - 46 mo IC -131 mo	No differences in any scale score, all patients generally satisfied with overall health QoL
		IC (37)					
Sogni et al [86]	2008	NB (32)	QLQ-C30 &	General (cancer)	Yes	42 mo	No differences in elderly (≥75 yrs) patients
		IC (53)	QLQ-BLM	Specific (bladder cancer)			
Hobisch et al [87]	2001	NB (69)	QLQ-C30 &	General (cancer)	Yes	NB - 28.3 mo IC -55.5 mo	NB better in all domains, NB with more travel + Leisure + more likely to recommend to friend
		IC (33)	Self-designed questionnaire	Specific (urinary diversion)			
Porter et al [89]	2005	-	Systematic review of the literature			-	Evidence III/B (retrospective, cross-sectional) in most studies. Any form of urinary diversion is not superior to another in QoL outcomes
Gerharz et al [90]	2005	-	Systematic review of the literature			-	Evidence III/B (retrospective, cross-sectional) in most studies. Any form of urinary diversion is not superior to another in QoL outcomes

QoL: quality of life, NB: neobladder, IC: ileal conduit, FACT-G: Functional Assessment of Cancer Therapy-General, QLQ-C30: EORTC instruments QoL questionnaire C30, QLQ-BLM: QLQ-muscle-invasive bladder cancer module

report, etc) [4] and the QoL questionnaire itself (validated questionnaire or not, generic or cancer-specific or bladder cancer-specific QoL instruments, etc). To minimize these limitations and to evaluate QoL appropriately, it is crucial that a neutral third party be used to carry out the studies and questionnaires with validity and reliability.

Obviously, patients with neobladders have enhanced cosmesis and the potential for normal voiding function with no abdominal stoma and no need for a stomal appliance. However, the assumption that OBS provides better QoL than ileal conduit diversion is not supported by the results of previous studies. In a study comparing QoL between ileal conduit and OBS with 2 validated questionnaires, the RAND 36-Item Health Survey (SF-36) and the Functional Assessment of Cancer Therapy-General (FACT-G), young age and neobladder type were associated with higher QoL scores in 5 of the 9 SF-36 domains, but such significance favoring neobladder was not observed in the multivariate analysis with adjustment for age [83]. In this study, there were no significant differences in QoL between the two groups on the FACT-G. Similarly, no difference was observed in other studies comparing QoL between ileal conduit and orthotopic neobladder by use of the SF-36 questionnaire [84,85] and EORTC instruments QoL questionnaire C30 (QLQ-C30) and QLQ-muscle-invasive bladder cancer module (QLQ-BLM) [86]. To date, the superiority of OBS has been shown in only one study by Hobisch et al [87] in which patients with neobladders scored significantly better on the QLQ-C30 in all functional domains (role-physical, role-emotional, cognitive, and social) than did patients with conduits. However, a systematic review of the published literature [88-90] was insufficient to conclude that any form of urinary diversion is superior to another on the basis of QoL outcomes.

In fact, patients with an ileal conduit may discover that life with an ileal conduit is better than anticipated in terms of satisfaction, whereas patients with OBS may be dissatisfied if they anticipate the internal reservoir to function as well as the original bladder [48]. Thus, regarding patient satisfaction and QoL, it is important that the clinician provide a detailed explanation about the physical and lifestyle changes that occur after OBS. We believe that with this detailed preoperative education and discussion, most patients undergoing OBS can enjoy good QoL and have an improved self-image without an external urostomy appliance.

CONCLUSIONS

Orthotopic bladder substitution following cystectomy can provide excellent outcomes in patients who are highly motivated and carefully selected. To achieve this goal, surgeons should be familiar with possible pitfalls and their solutions as well as with adequate operative technique. When performed properly, orthotopic continent diversion offers good QoL with few long-term complications. Therefore, we believe it is the best option for the majority of patients requiring cystectomy.

Conflicts of Interest

The authors have nothing to disclose.

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