Published in final edited form as:

Urology. 2011 April ; 77(4): 878–883. doi:10.1016/j.urology.2010.08.065.

Oncological and Functional Outcomes of Radical Cystectomy and Orthotopic Bladder Replacement in Women

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Abstract

OBJECTIVE—To report oncological and functional results in women undergoing radical cystectomy and orthotopic bladder replacement.

MATERIALS AND METHODS—The charts of all women undergoing bladder replacement after radical cystectomy at UCSF through April 2008 were reviewed. Pathologic characteristics, survival (overall and disease-specific), and urinary functional outcomes are reported. Survival was estimated using Kaplan-Meier methods, and Cox proportional hazards regression analyses were performed to determine factors associated with incontinence, retention, and mortality.

RESULTS—Fifty-six women with a mean follow-up of 35 months were analyzed. The cancer recurrence rate was 32%. Kaplan-Meier estimated 5-year recurrence-free, cancer-specific, and overall survival were 54%, 57%, and 47%, respectively. Pathologic lymph node status (HR 14.2, $P < .001$) and age at diagnosis (HR 1.7, $P = .04$) were the only clinical or pathologic characteristics significantly associated with survival. The overall continence rate (no pads) was 57%. Hypercontinence occurred in 24% of patients.

CONCLUSIONS—With careful patient selection and usage of urethral frozen section, rates of local recurrence are low. Overall rates of incontinence (43%) and hypercontinence (24%) are similar to those previously reported. When pathologically organ-confined, women have an excellent disease-specific survival. Orthotopic bladder replacement is a safe and effective form of urinary diversion after radical cystectomy in women.

Radical cystectomy remains the standard therapy for muscle-invasive or recurrent high-grade urothelial carcinoma of the bladder.¹ Orthotopic bladder replacement or neobladder reconstruction (ONB) after radical cystectomy was initially reserved for men given concerns for poor functional and oncological results in women. However, with advancements in understanding of the female rhabdosphincter² and refinements in surgical technique, ONB has become increasingly common in female patients.

Although ONB after radical cystectomy has been shown to have similar oncological results when compared with other urinary diversion types in men,^{3–5} sufficient validation of ONB in women is limited. Prior case series have reported 5-year survival at 62–83% and recurrence rates of 25–29%, with mean follow-up ranging from 29–103 months.^{6–8} Data regarding functional outcomes of incontinence and hypercontinence range from 34–44% and 35–61%, respectively, but are subject to differing definitions.^{6–8} Postoperative maximum urethral closure pressure and neobladder pressure at capacity are urodynamic predictors of

incontinence in men,⁹ but neobladder function is less well-described in women. Little is also known about clinical and pathologic predictors of functional outcomes.

The aim of this study was to add to the literature describing the oncological and functional outcomes in women undergoing radical cystectomy and bladder replacement and to determine whether there are clinical and pathologic predictors of better functional outcomes.

MATERIAL AND METHODS

Patients

Institutional Review Board approval to collect clinical, pathologic, and follow-up data on consenting patients was obtained as part of the UCSF Urologic Oncology Database. All female patients who underwent radical cystectomy with ONB at UCSF from 1994 to April 2008 were identified for retrospective chart review. All patients underwent the procedure as treatment for neoplastic disease. To be eligible, women had to be fit for major surgery, have clinically organ-confined disease, and be willing and able to perform self-catheterization. Although patients were counseled that any preoperative incontinence may worsen after surgery, no woman was excluded from undergoing ONB because of preoperative urinary function.

Preoperative staging included bimanual examination, chest X-ray, computed tomography or magnetic resonance imaging of the abdomen and pelvis, and bone scintigraphy. Patients were not excluded from ONB based on the location of the primary tumor within the bladder, but rather on intraoperative assessment frozen section analysis at the time of surgery. Postoperatively, patients were followed every 3 months within the first year, every 6 months for 2 years, and annually thereafter. Oncological surveillance included physical examination, urine cytology, and cross-sectional imaging; endoscopy was performed to evaluate abnormal symptoms or signs (ie, hematuria), findings on urinalysis, or assessment of exfoliating cells. Disease recurrence was defined as pathologic or radiographic evidence of cancer after cystectomy. Local recurrence was defined as disease occurring within the pelvis. Functional outcomes after ONB were ascertained by patient interview during office visits, phone interview, and by examination of the medical record. Day- and night-time urinary incontinence was defined as the daily use of any pads. Hypercontinence was defined as the need for any catheterization daily. Patients were advised to catheterize if postvoid residual urine volume was >150 mL.

Surgical Technique

Radical cystectomy was performed through a low-midline incision, with en bloc resection of the bladder and anterior vaginal wall. The uterus and ovaries were excised selectively based on patient age, hormonal status, and the extent of the cancer. Bilateral pelvic lymph node dissection was performed, extending proximally to the bifurcation of the common iliac arteries. Intraoperative frozen section of the urethral margin was obtained. Conduit or other continent diversion was performed if a negative margin could not be achieved. ONB was performed using a segment of terminal ileum as described by Studer or Hautmann.¹⁰⁻¹² Based on our initial experience, a few modifications have been made. The maximum extent of vagina was preserved as far as permissible based on anatomy and tumor location. The reconstructed vagina was suspended to the sacrospinous ligaments, and omentum was interspersed between the vagina and the neobladder when available.

Statistical Analyses

Disease-specific and all-cause mortality were assessed. Bladder cancer-specific mortality was defined as death with known pelvic recurrence or distant metastases. Bladder cancer–

specific recurrence-free survival was estimated using Kaplan-Meier methods. Cox proportional hazards regression analysis was used to determine predictors of disease-specific survival, incontinence, and retention. Because of the strong association of lymph node status with survival, adjusted hazard ratios were calculated for each covariate in the univariable model. The alpha value was set at 0.05 for all analysis and 95% confidence intervals were calculated in the Cox regression models. Analysis was performed using Stata version 11.0 (StataCorp, College Station, TX).

RESULTS

Study Subjects

A total of 56 women with a mean age of 61 years (range 31-81) and a mean follow-up of 35 months (range 2-113) were included for analysis. Thirty-five (63%) women underwent bladder reconstruction as described by Studer and Zingg¹² and 21 (37%) as described by Hautmann et al.¹⁰ Hysterectomy was performed before or at time of cystectomy in 51 (91%) patients, with the remaining 5, desiring future fertility, having the uterus left in situ. At UCSF, all patients with suspicion of extravesical extension of tumor on preoperative imaging are referred for consideration of neoadjuvant therapy. Neoadjuvant chemotherapy was administered in 5 (9%) women, and none received preoperative radiation therapy. Adjuvant chemotherapy was administered in nine (16%) patients and adjuvant radiation in three (5%).

Pathologic Characteristics

The histology of the tumors in the current series was predominantly urothelial carcinoma (80%), as shown in Table 1. One patient underwent radical cystectomy for primary cervical squamous cell carcinoma. The pathologic T-stage of the cohort is also shown in Table 1. Twenty-seven percent of the women had pathologic extravesical extension of tumor. Of the 12 women with pathologic T0, Ta, and T1 disease, 6 had clinical T2 disease at the time of transurethral resection, 1 had clinical Tis disease, and 5 had recurrent T1 tumors refractory to intravesical agents.

The mean number of lymph nodes removed was 19 (range 3-45), and 11 (20%) subjects were found to have lymph node-positive disease. In those women with positive lymph nodes, an average of 20% of the nodes contained cancer. The proportion of subjects with positive lymph nodes varied with pathologic tumor stage (Table 1). Despite negative intraoperative frozen section margins, the final pathologic urethral margin was positive for cancer in four (7%) cases, and at least one of the ureteral margins was positive in four (7%) cases.

Oncological Outcomes

In total, 18 (32%) patients developed disease recurrence—5 (9%) local, 15 (27%) distant, and 2 (4%) with both local and distant recurrence. In the 2 women who developed both local and distant recurrence, 1 patient recurred in the vagina and liver, and the other patient recurred in the pelvic sidewall and lung. Mean time to recurrence was 28 months (range 3-76). Of the 4 patients with positive urethral surgical margins, there were no local recurrences and 1 distant recurrence (spine). Of the 4 patients with positive ureteral margins, 2 patients recurred—both in the renal pelvis (at 24 and 58 months).

Survival was estimated by Kaplan-Meier methods, as seen in Figure 1. Recurrence-free, cancer-specific, and overall 5-year survival was 54%, 57%, and 47%, respectively. For patients with lymph node-negative disease at cystectomy, cancer-specific and overall 5-year survival was 75% and 60%, respectively. Univariate regression analysis (Table 2) found

lymph node status as the only clinical indicator significantly correlated with cancer-specific survival (HR 14.2, 95% CI 4.6–43.8, $P < .001$). After adjusting for lymph node status, age at diagnosis was a significant predictor of bladder cancer-specific survival (HR 1.7, 95% CI 1.0–2.7, $P = .04$). This suggests that lymph node status is a confounder of the association between age and bladder cancer-specific mortality.

Functional Outcomes

At last follow-up, 32 (57%) women remained completely continent. Of the 24 subjects who continued to use pads, 18 provided information about the number of pads used (Table 3), and most women (66%) required only 1 or 2 per day (Table 3). Two (3%) women developed vaginal fistulae as the etiology for their incontinence, and three (5%) women who were initially incontinent ultimately gained complete continence (at 3, 48, and 72 months). Hypercontinence occurred in 13 (24%) women. Two initially voided but developed the need for catheterization after 6 months, and only one who had initial hypercontinence improved to normal voiding. No clinical or pathologic factors were significantly associated with continence or hypercontinence.

Separate analyses of oncological and functional outcomes were completed using only patients with greater than 9 months follow-up, and results were not significantly different from those presented here before (data not shown).

COMMENT

ONB after radical cystectomy has been established as an accepted form of urinary diversion for men. In women, ONB has become increasingly common, with the accumulation of evidence showing its oncological safety and functional efficacy.⁶⁻⁸ Here, we report on a cohort of 56 women who underwent radical cystectomy with ONB for malignant disease.

Oncological characteristics and outcomes in this study are similar to the limited number of similar series previously reported. Eighty percent of subjects had urothelial carcinoma, which is the most common histology in the United States.^{6,8} A study from Egypt had primarily squamous cell carcinoma, likely reflecting the prevalence of Bilharzial disease in that region.⁷ In our series, 27% of women had pathologic stage T3 disease and 20% had lymph node-positive disease. The recurrence rate of 32% is consistent with other studies, which range from 28–36%.⁶⁻⁸ Lymph node status at cystectomy and age at diagnosis were the only clinical or pathologic variables that predicted recurrence or survival. In this series, 5-year estimated recurrence-free, cancer-specific, and overall survival of 54%, 57%, and 47% are similar to that reported by others.^{6-8,13}

There has been significant debate about the risk of urethral recurrence after ONB in women, given the much shorter urethra compared with men. Early investigations reported urethral involvement of bladder cancer in women to be as high as 36% and recommended urethrectomy with cystectomy as the standard of care.¹⁴ More recently, retrospective studies reported lower rates of urethral involvement and that precystectomy evidence of tumor at the bladder neck could distinguish patients at risk of urethral recurrence.¹⁵⁻¹⁷ In a recent review of the literature, Stein et al found that approximately 50% of women with bladder neck tumors had urethral disease, making this a risk factor but not an absolute contraindication for ONB.¹⁸ More importantly, intraoperative frozen section has been shown to provide an accurate assessment of extension into the urethra.¹⁹ At UCSF, women with bladder neck tumors are not excluded from ONB if intraoperative frozen section of the urethral margin is negative. In this series, 7% of patients had a positive permanent urethral surgical margin, despite uniformly negative frozen sections. However, none of these patients had local recurrence. In fact, no patient had urethral recurrence. These findings suggest that women

with negative intraoperative urethral frozen sections can safely undergo ONB after radical cystectomy without undue risk of urethral recurrence, including those with bladder neck tumors.

The primary advantage of ONB after radical cystectomy, compared with ileal conduit or other continent cutaneous diversions, is the potential for near-normal voiding function and retained body image by voiding from the native urethra.²⁰ However, functional outcomes after ONB in women are not as well-defined as in men. We found a similar rate of incontinence (43%) compared with previous reports, and among our patients with urinary leakage, 66% used only 1 or 2 pads per day. Our rate of incontinence was meant to be inclusive, using the intentionally broad definition of the use of any pads daily. Granberg et al, using the same definition, reported day- and nighttime incontinence rates of 10% and 43%, respectively.⁶ Stein et al reported questionnaire-driven rates of 23% and 34% for “frequent leakage or no urinary control whatsoever” during daytime and nighttime, respectively.⁸ Our hypercontinence rate of 24% is lower than reported figures ranging from 35-61%,^{6,8} but we continue to counsel patients preoperatively of the potential need for self catheterization. In general, approximately 35 cm of ileum (Studer and Zingg¹²) and 60 cm (Hautmann et al¹⁰) neobladders were harvested in this series, which are both smaller lengths of bowel than originally described. We believe that a smaller capacity reservoir may be responsible, in part, for this lower retention rate. However, this may come with an initially higher risk of incontinence in the first few months after surgery. We also did not observe an increase in hypercontinence with time, as has been reported previously in a study done primarily in men.²¹ Women are counseled both preoperatively and postoperatively about techniques of voiding and are monitored closely with assessments of postvoid residual urine volume.

The etiology of incontinence or hypercontinence after ONB is unclear but is likely multifactorial and related to patients’ baseline urinary function, surgical technique during urethral reconstruction, and postoperative changes to pelvic musculature. Multiple mechanisms for hypercontinence have been proposed, including downward migration of the neobladder-urethra angle.^{22,23} To address this, technical modifications, such as anterior fixation or posterior elevation of the neobladder, have been proposed, with varying success.^{22,24,25} We did not identify any clinical or pathologic variables significantly related to post-ONB urinary function. It seems clear, however, that rates of incontinence after ONB in women are higher than daytime (2-8%) and nighttime (20-24%) rates in men.³⁻⁵ Further study, as well as modification and refinement of surgical technique, in women undergoing ONB are needed to achieve better results.

Data regarding health-related quality of life after cystectomy and ONB were not available in our cohort. Although Gilbert et al published general results of the Bladder Cancer Index in 2007,²⁶ the actual questionnaire was not made available until just recently.²⁷ Using The Bladder Cancer Index, its creators reported superior urinary *function* in patients undergoing ileal conduit diversion compared with ONB, but urinary *bother* was equivalent in both groups.²⁸ However, their cohort consisted primarily of men (81%), and the survey awaits further external validation.

There are several limitations to this study, including those inherent to the retrospective design. In addition, women were treated over a lengthy period by several surgeons, and therefore they represent a heterogeneous cohort. We did not analyze whether a nerve-sparing operation was performed because its impact on continence is controversial. There are also shortfalls to obtaining functional outcomes by physician interview.²⁹ Finally, assessment of functional outcomes is partly limited by varying length of follow-up. No incontinent women

developed continence with prolonged follow-up. However, it is possible that the risk of hypercontinence was underestimated in women with short follow-up.

CONCLUSIONS

This study expands upon a small but growing body of literature regarding women undergoing ONB after radical cystectomy. With careful patient selection and usage of urethral frozen section, rates of local recurrence are low. Overall rates of incontinence (43%) and hypercontinence (24%) are similar to those reported previously. When pathologically organ-confined, women experience excellent long-term disease-specific survival. This study reaffirms that ONB is a safe and effective form of urinary diversion.

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Figure 1. Kaplan-Meier estimated recurrence-free and overall survival are shown in (A) and (B), respectively. Estimated cancer-specific survival stratified by lymph node status is shown in (C).

Table 1

Pathologic data

	Frequency (%)	No. With +LN
Histology*		
Cervix-SCC	1 (2)	0
LEL	3 (5)	0
SCC	6 (11)	2
SSC	2 (4)	1
UC	44 (80)	8
T stage		
T0	6 (11)	0
Ta	1 (2)	0
Tis	12 (22)	1
T1	5 (9)	0
T2	16 (29)	3
T3	15 (25)	6
T4a	1 (2)	1

* SCC, squamous cell carcinoma; LEL, leioepithelial-like; SSC, small cell carcinoma; UC, urothelial carcinoma.

Table 2

Analysis of predictors of bladder cancer–specific mortality

Predictor	Univariable			Adjusted (by LN Status)		
	HR	(95% CI)	P value	HR	(95% CI)	P value
Age at diagnosis (per decade increase)	0.8	(0.5-1.1)	.16	1.7	(1.0-2.7)	.04*
Year of surgery (per year increase)	1.0	(0.9-1.1)	.94	1.0	(0.9-1.2)	.98
TCC histology (vs other)	0.7	(0.2-2.1)	.49	2.2	(0.6-8.6)	.26
Pathologic stage (vs Ta, TIS, T1)			.003*			.60
T2	1.6	(0.4-7.2)	.53	1.6	(0.3-9.3)	.61
T3/T4	8.0	(2.1-30.6)	.002*	2.6	(0.4-18.0)	.33
Lymph node Pos (vs neg)	14.2	(4.6-43.8)	<.001*	—	—	—

UC, urothelial carcinoma.

Table 3

Functional outcomes in women undergoing cystectomy and orthotopic neobladder construction

Characteristic	No. (%)
Initial retention *	12 (21)
Retention *	13 (23)
Initial incontinence *	27 (48)
Incontinence *	24 (43)
Day	9
Night	2
Both	13
Pads/day [†]	
1	5 (28)
2	7 (39)
3	1 (6)
4	0 (0)
5	5 (28)

*
n = 56.[†]
n = 18.