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ORIGINAL ARTICLE

The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome

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Abstract

Purpose To assess long-term clinical and oncological outcome in women undergoing radical cystectomy and ileal neobladder reconstruction for invasive bladder cancer. *Methods* From 1995 to 2010, a total of 121 women with clinically organ-confined urothelial carcinoma underwent radical cystectomy with an orthotopic ileal neobladder. Median follow-up was 56 months. Clinical course, functional, pathological, and oncological outcome of these women were analyzed.

Results Seventy-six patients (62.8%) experienced a complication of some type within 90 days of the procedure. 56 patients (46.3%) experienced minor complications, whereas 20 patients (16.5%) experienced major complications. Pathological subgroups included 70 patients (57.9%) with organ confined, lymph node-negative tumors, 24 (19.8%) with extravesical, lymph node-negative disease and 27 (22.3%) patients with lymph node-positive disease. The 5-year overall survival rate in patients with organconfined (\leq pT2, pN0), locally advanced (\geq pT3, pN0), and metastatic disease was 80.2%, 81.9%, and 45.1%, respectively. 4 women (3.3%) experienced a local (pelvic) recurrence. One patient presented with a urethral recurrence (0.8%). Daytime and nighttime urinary continence (0-1 pad) was reported by 82.4 and 76.5%, respectively. Clean intermittent self-catheterization was required by 58.0%. The retrospective study design was the major limitation of the study.

Conclusions Despite a considerable complication rate, radical cystectomy with orthotopic diversion in female patients with bladder cancer may be considered a standard therapeutic option for selected patients with excellent oncological outcome including a low incidence of local and urethral recurrence.

Keywords Cystectomy · Urinary diversion · Transitional cell carcinoma

Introduction

Radical cystectomy including pelvic lymphadenectomy and urinary diversion is extensive surgical procedures and constitutes the treatment of choice for invasive urothelial bladder cancer in men [1]. In addition, continent urinary diversion to the intact urethra in women has passed beyond the experimental stage and has now become a standard procedure at high-volume urological centers during the last 15 years. However, there is still more expertise and longer follow-up in male as compared to female patients [2]. Beside the fact that the incidence of bladder cancer is much lower in women than in men, the lack of long-term data is mainly due to the fact that orthotopic neobladder substitution was regarded as contradicted in females until the early 1990s. The risk of recurrence in the remnant urothelium of the urethra was thought to be higher in women due to the shorter urethral length and the possibility of continuous tumor expansion. In addition, it was hypothesized that the remaining rhabdosphincter was insufficient for providing effective postoperative continence [3]. Recent studies have addressed both of these issues, resulting in a better understanding of the continence mechanism in women as well as a better understanding of

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the risk factors for urethral tumor involvement in women with bladder cancer [4–6]. Consequently, orthotopic lower urinary tract reconstruction was routinely applied in women in the mid 1990s at our institution [7].

Taking these objections into account, the present retrospective study was conducted to analyze long-term functional, oncological, and clinical outcomes of 121 women who underwent radical cystectomy and orthotopic diversion for bladder cancer.

Materials and methods

Patients and methods

From June 1995 to December 2010, 241 women with organ-confined bladder cancer underwent radical cystectomy with subsequent urinary diversion including 50 (20.7%) with ureterocutaneostomy, 70 (29.0%) with ileal conduit, and 121 (50.2%) with ileal neobladder reconstruction. Of the 121 women with orthotopic diversion, 109 (90.1%) had urothelial bladder cancer (UC), 9 (7.4%) suffered from squamous cell carcinoma, and 3 (2.5%) had adenocarcinoma. Patients were followed at 3-month intervals in the first 2 years, 6 month intervals in the years 3 and 4, and annually thereafter. Follow-up included electrolyte panel, uroflowmetry, ultrasonographic assessment of the abdomen including postvoid residual urine, and alternately CT-scan of the abdomen and pelvis. Urethroscopy and biopsy were performed as indicated, that is hematuria and suspicious radiological findings. The data were collected from our computerized neobladder database containing comprehensive clinical and pathological information of all patients at our institution. A retrospective review of charts, outpatient records, and correspondence with local physicians was performed to assess survival data. Long-term functional outcome was analyzed by written inquiry. Comorbidity was assessed using the Charlson Comorbidity Index [8]. The clinical and pathologic data of the patients investigated in this study are given in Tables 1 and 2.

Selection criteria

Patients for orthotopic neobladder were selected according the following contraindications for continent urinary diversion: Impaired renal function (serum creatinine >2 mg/dl), severe hepatic dysfunction, intestinal disease/ tumor manifestation, pre-existing damage of the external urethral sphincter, and impaired cognitive and manual skills for performing clean intermittent self-catheterization (CIC). A general performance status of a minimum of 80% on the Karnofsky scale was thought to be essential for the handling Table 1 Demographic and pathological characteristics

Demographic and pathological characteristics	Totals (%)
No of pts. (%)	121
Median age	61.2
Median months of follow-up (IQR)	56 (IQR 36.0–93.5)
No. CIS	29 (24.0)
No. bladder neck tumor involvement	2 (1.7)
No. trigone area tumor involvement	6 (5.0)
No. tumor multifocality (%)	19 (15.7)
No. recurrent bladder Ca before cystectomy (%)	27 (22.3)
No. high-grade tumors (%)	110 (90.9)
No. soft tissue pos margins (%)	4 (3.3)
No. pathological subgroups:	
Organ confined, lymph node-neg.	70 (57.9)
Extravesical, lymph node-neg.	24 (19.8)
Lymph node-pos.	27 (22.3)
Median No. lymph nodes removed. (range)	19.1 (0-62)
Median No. lymph nodes pos. (range)	2.2 (0-14)
No. neoadjuvant chemotherapy (%)	2 (1.65)
No. neoadjuvant radiation (%)	1 (0.8)
No. adjuvant chemotherapy (%)	20 (16.5)
Charlson score ≥ 3 (%)	27 (23.3)
ASA score ≥ 3 (%)	40 (33.1)
Prior pelvic abdominal radiotherapy (%)	3 (3.6)
Prior pelvic abdominal surgery (%)	69 (56.9)
BMI average (range)	24.0 (15.0-68.0)
BMI >25 (%)	46.0 (38.0)

 Table 2
 Pathological stage and subgroup in 121 women who underwent RC and orthotopic diversion by lymph node involvement

Pathological stage	No. Total (%)	No. LN neg	No. LN pos
No. pT0	14 (11.6)	12	2
No. pTis	12 (9.9)	12	0
No. pT1	18 (14.9)	17	1
No. pT2a	26 (21.4)	21	5
No. pT2b	12 (9.9)	8	4
No. pT3a	23 (19.0)	15	8
No. pT3b	14 (11.6)	9	5
No. pT4	2 (1.7)	0	2
Organ confined ($\leq pT2$)	82 (67.7)	70	12
Extravesical (>pT2)	39 (32.2)	24	15
Total	121 (100)	93	27

of specific problems of orthotopic diversion. Patients with tumor invasion in the urethral margin determined at the intraoperative frozen section analysis were excluded from orthotopic diversion during radical cystectomy. Table 3Highest-gradecomplication per patientaccording to Clavien-Dindoclassification (first 90 days)

Grade	Definition	No. (%)
0	No complication observed	45 (37.2)
1	Any deviation from normal postop course without need for pharmacological treatment (allowed regimes include antiemetics, antipyretics, diuretics, electrolytes, physiotherapy, bedside wound care	22 (18.2)
2	Requiring pharmacological treatment with drugs other than those allowed for grade 1 complications (blood transfusions and total parenteral nutrition also included)	34 (28.1)
3a	Requiring surgical, endoscopic, and radiological intervention with patient not under general anesthesia	9 (7.4)
3b	Same as 3a but requiring general anesthesia	7 (5.8)
4a	Life threatening complication requiring intensive care unit management, single organ dysfunction	2 (1.7)
4b	Same as 4b but involving multiorgan dysfunction	0 (0)
5	Death of patient	2 (1.7)
None		45 (37.2)
Low grade (1-2)		56 (46.3)
High grade (3–5)		20 (16.5)
No. of compl	lications/pt	
0		45 (37.2)
1		44 (36.3)
2		18 (14.9)
3		9 (7.4)
4		2 (1.7)
5 or more		3 (2.5)

Treatment

All patients underwent the surgical procedure previously described by Hautmann [9]. Specific patient preparation and postoperative care was applied as stated previously [1]. Intraoperative frozen section of the proximal urethra was performed in all cases. All adverse events requiring medication or surgical intervention were assessed as a complication. All complications within the first 90 days were recorded, defined, and graded according to an established five-grade modification of the original Clavien system [10] as shown in Table 3 and then were further grouped into categories as outlined in Table 4.

Pathological findings and survival outcomes

Histological grading was performed according to the WHO/ISUP 1999 classification. Pathological staging of the primary bladder tumor was performed according to the TNM classification UICC 2002. The pathological tumor stages were evaluated by assignment to three prognostic groups: organ-confined (\leq pT2, pN0), locally advanced (\geq pT3, pN0), and lymph node-positive (pN+). Lymph

node (LN) density was calculated using the following formula: number of positive LN times 100% divided by the total number of removed LN [11]. Table 2 lists the pathological characteristics of the study cohort.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. Significance was determined by using either the two-sided t-test, the two-sided Mann–Whitney *U*-test, Pearson's χ^2 test, or Fisher's exact test. The Kaplan–Meier procedure with the log-rank test was used for survival statistics. An error probability of p < 0.05 was defined as the significance limit.

Results

Patient's characteristics

Median follow-up was 56 months. The median age at the time of surgery was 61.2 (range, 34–82) years. 33.1% of the patients had a preoperative ASA score of \geq 3; 23.3% had an age-adjusted Charlson-Romano morbidity score of

 Table 4 Incidences of early complications (first 90 postoperative days)

Early complications (first 90 postop. days)	No. total (%)
Gastrointestinal	23 (19.0)
Ileus ^a	10 (8.3)
Intestinal atonia ^b	13 (10.7)
Infectious	44 (36.7)
Sepsis	3 (2.5)
Intraabdominal/pelvic abscess	1 (0.8)
Urinary tract infection	34 (28.3)
Pyelonephritis	6 (5.0)
Wound	12 (10.0)
Fascia dehiscence	1 (0.8)
Incisional hernia	1 (0.8)
Wound healing disorder	10 (8.3)
Genitourinary	15 (12.6)
Urinary stasis	3 (2.5)
Urinoma/urine leakage	8 (6.7)
Renal failure ^c	2 (1.7)
Reflux	2 (1.7)
Cardiac	2 (1.7)
Myocardial infarction	1 (0.8)
Tachyarrhythmia absoluta	1 (0.8)
Pulmonary	2 (1.7)
Pneumonia	1 (0.8)
Respiratory insufficiency	1 (0.8)
Bleeding	4 (3.3)
Thromboembolic	2 (1.7)
Deep leg vein thrombosis	2 (1.7)
Pulmonary embolism	0 (0)
Miscellaneous	11 (9.2)
Lymphocele	11 (9.2)
Neurological	4 (3.3)
Nervus femoralis injury	2 (1.7)
Plexus sacralis injury	2 (1.7)
Percutaneous procedures (% of pt)	3 (2.5)
Reoperations (% of pt)	9 (7.4)

^a Ileus was defined as postoperative nausea or vomiting associated with abdominal distention requiring cessation of oral intake and intravenous fluid support and/or nasogastric tube placement, or the intolerance of oral intake by postoperative day 5 resulting in patient fasting with or without nasogastric tube placement or antiemetic medication administration

^b Intestinal atonia was defined as inability to have a bowel movement by postoperative day 5 with no signs of ileus or small bowel obstruction

^c Renal failure was determined by new acute renal failure or exacerbation of chronic renal deficiency with oliguria (quantified as less than 500 ml/day) and elevated serum creatinine

 \geq 3. The average BMI was 24.1 (range, 15–42), whereas 38% of the patients had a BMI >25. 56.9% of the patient population had prior pelvic abdominal surgery.

Mortality and morbidity

Perioperatively one woman (0.83%) undergoing orthotopic diversion died, following a massive myocardial infarction. 76 (62.8%) patients experienced a complication of some type within 90 days of the procedure: When placing patients into subgroups according the worst complication, 46.3% (56 of 121) had low-grade complications, and 16.5% (20 of 121) had high-grade complications. A mean of 1.6 complications per patient were experienced of those who had any complication. Most common complications were infectious (36.7%), gastrointestinal (19.0%), and genitourinary (12.6%). Percutaneous procedures had to be applied in 2.5% of the patients. The reoperation rate was 7.4%. All events are summarized in Tables 3 and 4.

Using univariate analysis to compare preoperative and intraoperative variables for patients with none, one, or more complications on one hand, or high-grade complications (Clavien \geq 3) on the other hand; neither age (65 years or older) nor comorbidity (ASA \geq 3; Charlson score \geq 3, BMI \geq 25) or prior abdominal surgery were significant predictors of complications.

Pathological variables

Two (1.7%) and six (5%) women had tumor involvement of the bladder neck and the trigone area, respectively. In 2 (1.7%) women intraoperative frozen section analysis revealed tumor involvement in the proximal urethra. In the re-resection of that area further urethral involvement could be excluded. One of these two patients had a history of multifocal and recurrent disease without bladder neck involvement. The other patient had a single muscle invasive and non-recurrent UC located at the right bladder wall. None of the patients had a positive urethral margin on permanent section analysis. Four (3.3%) women had a positive soft tissue surgical margin.

Pathological stage and subgroups

Table 2 shows the pathological staging of all 121 women who received an orthotopic neobladder. Pathological subgroups included 70 patients (57.9%) with organ confined (\leq pT2, pN0), and 24 (19.8%) with extravesical, but lymph node-negative disease (\geq pT3, pN0). 27 (22.3%) had lymph node-positive disease (Tables 1, 2).

The median number of lymph nodes removed was 19 (range, 0–62, IQR 12–26). The median number of positive lymph nodes in those patients with nodal disease was 2 (range, 1–14). The median and mean LN density were 8.0 and 13.7% (range: 2–60%), respectively; 22 (81.5%) and 5 (18.5%) patients exhibited a LN density \leq 20 and >20%, respectively.

Overall survival (OS)

OS in the patient cohort at 5 and 10 years were 72.0 and 55.8%, respectively. Patients with organ-confined LN-negative disease (n = 70) exhibited an OS at 5 and 10 years of 80.2 and 65.1%, respectively. The corresponding results for patients with extravesical but LN negative disease (n = 24) were 81.9 and 70.2%, respectively (p = 0.79). Patients with LN positive disease (n = 27) exhibited significantly lower OS rates at 5 and 10 years of 45.1 and 18.1%, respectively (p < 0.001). However, the 5 years survival rate was not influenced by lymph node density in our study (LN density $\leq 20\%$ (n = 22) vs. $\geq 20\%$ (n = 5), 44.0 vs. 50.0%, p = 0.48).

Thirty-seven (30.6%) women experienced bladder cancer recurrence. Recurrence occurred distant in 33 (27.3%), and locally (pelvic) in 4 (3.3%) patients. One woman presented urethral recurrence (0.8%).

Functional outcome

To evaluate the long-term functional outcome following cystectomy with subsequent ileal neobladder construction, a written inquiry was mailed to all 68 survivors, of whom 50 completed and returned the survey for a 73.5% response rate. Median time from surgery to questionnaire completion was 6.1 years. Good daytime and nighttime urinary continence (0–1 pad) was reported by 82.4 and 76.5%, respectively. Periodic CIC was required by 58.0% to facilitate emptying of the neobladder.

Discussion

As the risk for developing any type of complications in both sexes ranges from 16% to 66%, radical cystectomy with neobladder reconstruction represents a major, complication-prone surgery [12–15]. This wide range of complication rates reported in different studies is mainly explained by the fact that various complications are not surveyed in detail in different standardized reporting systems, and studies are thus difficult to compare. [1]. The overall early complication rate recorded in our study was 62.8%. Notably, high-grade complications occurred in only 16.5% of the patients within 90 days after surgery. 68.9% (82 of 119) of all complications were related to urinary diversion (infectious, gastrointestinal, and genitourinary) not to the cystectomy itself. These findings are analogous with recent studies using the same reporting system in large cystectomy series of both genders. Shabsigh et al. reported an overall 90-day complication rate of 64% in a cystectomy series of 1,142 patients with any type of diversion. They also concluded that 65% of the complications were gastrointestinal, infectious, and genitourinary. However, only 13% were considered to be high-grade complications [15]. Our recent series of over 1,000 neobladders of both genders revealed comparable results to the present femaleonly series with a 90-day overall complication rate of 58% with 22% high-grade complications [1]. This present detailed evaluation of various postoperative complications discloses that cystectomy, and orthotopic urinary diversion in women requires not only experienced skilled performance of the surgical procedure, but additionally multidisciplinary preoperative and postoperative approaches since most of the complications are diversion and not cystectomy related.

Overall survival rates in the present series at 5 and 10 years were 72.0 and 55.8%, respectively. Recurrence occurred distant in 33 (27.3%) and locally in 4 (3.3%) patients. One patient with an organ-confined LN-negative UC without bladder neck or trigone involvement experienced urethral recurrence (0.8%). Our results are in line with recent studies that report on oncological outcomes after orthotopic neobladder reconstruction in female patients [2]. Despite early concerns of an increased risk of urethral recurrence, our study confirms retrospective long-term observations of female patients with primary bladder cancer with an incidence of secondary urethral tumors lower than 4.5% and corresponds to that published in male patients [2, 16–18].

However, most accurate means of predicting urethral involvement and recurrence, and subsequent selection of appropriate patients for neobladder reconstruction is still under debate. Stein et al. prospectively reevaluated the cystectomy specimens of 71 females and reported that tumor localization at the bladder neck and urethra was present in 14 (19%) and 5 (7%) specimens, respectively. All patients with urethral involvement had concomitant bladder neck involvement. However, 9 of 14 (64%) patients with malignancy at the bladder neck had no evidence of tumor involvement of the proximal urethra [19]. In a study by Chen et al. including 115 female patients with invasive bladder cancer, 9 (8%) presented with urethral tumor involvement. While bladder neck involvement was significantly associated with urethral tumor, two patients with urethral involvement did not have bladder neck involvement [20]. In our series, 2 (1.5%) and 6 (5.0%)women had tumor involvement of the bladder neck and the trigone, respectively. Importantly, none of these patients had urethral involvement in the intraoperative frozen section or final histopathological analysis. In 2 (1.5%) women, intraoperative frozen section analysis revealed tumor involvement of the proximal urethra. In the re-resection of that area further urethral involvement could be excluded. None of the patients had a positive urethral margin in final histological analysis or developed a urethral recurrence,

respectively. Interestingly, none of these women had bladder neck involvement. Our study clearly supports the trend that patients with primary tumor localization at the bladder neck or trigone should not be excluded from an orthotopic approach, unless the intraoperative frozen section analysis reveals evidence of malignancy at the distal urethral margin [21, 22]. However, we are aware that in individual cases intraoperative frozen section analysis might be uncertain, that is to differentiate urethral dysplasia from carcinoma in situ.

We noted that 82 and 77% of women were continent during daytime and nighttime, respectively, which is consistent with the findings of previous series of orthotopic neobladder in female patients, which range between 77-90% and 57-86%, respectively [2, 16, 23, 24]. Even though urinary retention requiring CIC is more common in women with long-term rates of 21-61% reported in other series [2, 23, 24], the present CIC rate of 58% deserves our attention and underscores the need to follow voiding patterns carefully in patients with an orthotopic neobladder. The complex pathogenesis of elevated postvoid residual urine or urinary retention requiring CIC is not fully established and might be attributable to both mechanical and neurogenic factors [25]. Ali-El-Dein and colleagues postulated that urinary retention is mainly a result of posterior displacement of the pouch and consecutive urethroileal angulation indicating a mechanical reason, which could be prevented by placing an omentum flap between the vaginal stump and urethroileal anastomosis [26]. However, besides preservation of the urethral support mechanism as well as vagina and uterus, there are indications that rhabdosphincter maintenance and its autonomic nerve supply preserves an effective active relaxation of the proximal urethra and prevents kinking during voiding [27]. To prove real value, well-matched prospective studies are needed to evaluate long-term voiding function and quality of life of women undergoing cystectomy and various types of urinary diversion. However, the goal to achieve good functional results should not compromise the radical nature of this procedure in terms of oncological safety.

A potential limitation of our study is the long timeframe of over 15 years. Obviously the surgical technique and perioperative patient care has been steadily improved and changed over this long time period and may lead to less morbidity and improved functional outcome in a contemporary series.

Conclusion

Neobladder reconstruction in female patients is major procedure that can be performed as safe as in male patients with excellent oncological outcome including a low incidence of local and urethral recurrence. Moreover, female patients with primary tumor localization at the trigone or bladder neck area should not be excluded from an orthotopic approach unless intraoperative frozen section analysis demonstrates malignancy at the distal urethral margin.

Conflict of interest The authors declare that they have no conflict of interest.

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