

Orthotopic genital sparing radical cystectomy in pre-menopausal women with muscle-invasive bladder carcinoma: A prospective study

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ABSTRACT

Introduction: Invasive cancer bladder is a life-threatening disease that is best treated with radical cystectomy and a suitable urinary diversion. The aim of this study was to evaluate the oncological outcome, voiding and sexual functions after genital sparing radical cystectomy with orthotopic bladder reconstruction in pre-menopausal women with bladder cancer.

Materials and Methods: 18 pre-menopausal women who underwent radical cystectomy and orthotopic urinary diversion with preservation of genital organs were included for this study. The patients were followed-up clinically and radiologically to assess their oncological outcome in addition to their voiding and sexual function.

Results: Mean age of the patients was 37.8 years, and the median follow-up after surgery was 70 months. One patient was lost to follow-up at 12 months post-operatively. The surgery was completed as planned in all patients, with a mean operative time of 290 min and an average blood loss of 750 mL. 14 patients were able to void satisfactorily, being continent day and night, while four patients needed clean intermittent catheterization. Sexual life remained unchanged in 15 cases, while three patients reported dyspareunia. Till the last follow-up, there was no local recurrence while distant metastases were detected in three cases, two of whom died.

Conclusions: Genital sparing cystectomy is a valid option for managing carefully selected women with muscle-invasive bladder cancer with good functional and sexual outcomes.

Key words: Genital-sparing cystectomy, invasive cancer bladder, radical cystectomy

INTRODUCTION

Muscle invasive cancer bladder is ideally treated with radical cystectomy followed by a suitable urinary diversion. In women, radical cystectomy entails *en block* excision of the bladder, urethra, distal ureteral segments, draining lymph nodes and most of the internal genital organs, including the uterus, ovaries and anterior vaginal wall.^[1]

This major surgery has a negative impact on the patient's psychology and their quality of life. Over the years, the technique has been modified in selected patients through preserving the urethra, allowing orthotopic urinary diversion^[2] and, more recently, through preserving the internal genital organs.^[3] Genital-sparing cystectomy is based upon studies confirming that genital organ involvement in women with bladder cancer is rare.^[4-6]

This technique is especially important in young women, aiming at maintaining sexual life and fertility. It is also expected to provide a better support to the urethra,

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minimizing the incidence of post-operative incontinence and neobladder prolapse.^[7] Although the concept is not new, studies reporting the outcome of this technique are still infrequent and mainly report the outcome in elderly post-menopausal women suffering from urothelial and not squamous cell carcinoma.^[3,8,9]

In Egypt, squamous cell carcinoma is encountered in nearly 75% of urinary bladder cancers, mostly due to the high prevalence of bilharzial infestation, while it constitutes 5–15% of cases in non-endemic areas. Characteristically, shistosomiasis-related bladder cancer usually affects young patients with a rapidly growing muscle-invasive tumor that necessitates radical cystectomy. Distant metastases are usually uncommon.^[10-12]

Therefore, our aim was to prospectively evaluate the outcome of orthotopic genital-sparing cystectomy performed in pre-menopausal, sexually active women suffering from muscle-invasive bladder carcinoma.

MATERIALS AND METHODS

Between January 2006 and January 2010, 135 female patients presented to us with a bladder mass. All patients were evaluated clinically and radiologically with abdominal ultrasonography, abdomino-pelvic CT scan and chest X-ray in addition to cystoscopy and biopsy from the tumor, the trigone and bladder neck area and ending with bimanual examination under general/spinal anesthesia.

Patient selection

68 of these patients underwent radical cystectomy, either genital sparing (18 cases) or non-genital sparing (50 cases). Genital-sparing cystectomy (18 cases) was chosen for pre-menopausal, sexually active women with organ-confined, low-stage (T2bN0M0 or less), low-grade (G1 or GII), unifocal muscle-invasive tumors away from the bladder neck area and posterior bladder wall. Malignant infiltration of the internal genital organs was excluded, both clinically and radiologically, with abdomino-pelvic computed tomography (CT) and transvaginal ultrasonography. Pre-operative patients' characteristics are given in Table 1. These 18 patients were included for this study which was approved by the Ethics Committee in our institute. In addition, informed consent was taken from all patients.

Surgical management

Genital-sparing cystectomy entails *en block* excision of the bladder, tumor, distal ureters and regional lymph node, sparing the female internal genital organs.^[3,7-9] The superior and inferior vesical vessels are ligated and transected at their origin from the internal iliac vessels. The peritoneum covering the vesico-uterine pouch is incised to develop the plane between the uterus posteriorly and the bladder anteriorly, ligating and then transecting the paravaginal

dorsomedial bladder pedicle close to the bladder wall. At the bladder neck-paravaginal area, dissection is kept close to the bladder neck. The urethra is transected just distal to the bladder neck, which is identified by the balloon of Foley catheter after ligating the deep dorsal venous complex [Figure 1]. Orthotopic bladder substitute is then created using the Hautmann ileal neo-bladder technique^[13] with anti-refluxing ureteral anastomosis using a serous-lined extramural tunnel technique as described by Abol-Enein and Ghoneim.^[14]

Post-operatively, the ureteral stents are removed on the 7th day and Foley' catheter on the 14th day after a pouchogram. The patients then start toilet training and learn to void by pelvic floor relaxation without abdominal straining and are instructed to void every 2 and 4 h during the day and night times, respectively. The patients are allowed to start sexual intercourse 3 months post-operatively, but are advised to use an intrauterine device for contraception in the initial 3 years.

Follow-up

The patients were followed every 3 months during the initial 2 years, every 6 months for the next 3 years and then annually for life. Voiding pattern was assessed every 3 months, both clinically and sonographically. Clinical evaluation included reporting day and night continence and voiding frequency while sonographic evaluation included periodic measurement of pouch capacity and post-voiding residual urine, in addition to assessment of the upper urinary tracts. A urodynamic study was not routinely performed, unless there was an abnormal voiding pattern.

Oncological evaluation included abdomino-pelvic CT and chest CT every 6 months for 5 years and then annually, while a bone scan was performed annually. Sexual function was assessed through patients' discussion to report dyspareunia, sexual desire and orgasmic feelings. Female sexual index was not used because of socio-cultural traditions in addition to absent documented translation into our native language.

RESULTS

The study included 18 women with a mean age of 37.8 years (range 32–43 years) and a median follow-up of 70 months after surgery (range 39–95 years). One patient was lost to follow-up at 12 months post-operatively. The surgery was completed as planned in all patients, with a mean operative time of 290 min (range 270–330 min) and an average blood loss of 750 mL (range 600–1100 mL). The early post-operative course was uneventful.

Post-operative histopathological examination of the specimen demonstrated that the tumor was squamous cell carcinoma in 13 patients and muscle-invasive urothelial carcinoma in five patients. There was no invasion of the perivesical fat and distal ureters, bladder neck and internal

Table 1: Patients' characteristics and outcomes

Patients	Age	Pre-op stage	Histo-pathology	Voiding pattern	Metastases	Sexual life	Follow-up
1	35	T2aN0M0	Sq CC	Spontaneous	NED	Norm	95
2	37	T2aN0M0	Sq CC	Spontaneous	NED	Dysp	90
3	39	T2bN0M0	Sq CC	Spontaneous	NED	Norm	88
4	36	T2aN0M0	TCC	CIC, incon/night	NED	Norm	83
5	32	T2bN0M0	Sq CC	Spontaneous	NED	Norm	78
6	40	T2aN0M0	Sq CC	Spontaneous	NED	Norm	76
7	41	T2bN0M0	TCC	Spontaneous	Yes and died	Norm	75
8	35	T2aN0M0	Sq CC	CIC incon/night	NED	Norm	73
9	37	T2bN0M0	TCC	Spontaneous	Yes and died	Norm	70
10	42	T2bN0M0	Sq CC	CIC	NED	Dysp	67
11	39	T2aN0M0	Sq CC	Spontaneous	NED	Norm	65
12	36	T2aN0M0	TCC	Dropped off follow-up			
13	39	T2bN0M0	Sq CC	Spontaneous	NED	Norm	57
14	43	T2bN0M0	Sq CC	Spontaneous	NED	Dyspa	53
15	41	T2aN0M0	TCC	Spontaneous	NED	Norm	50
16	37	T2bN0M0	Sq CC	Spontaneous	NED	Norm	46
17	35	T2aN0M0	Sq CC	CIC	Yes and alive	Norm	40
18	37	T2bN0M0	Sq CC	Spontaneous	NED	Norm	39

NED=No evidence of disease, Pre-op stage=Pre-operative stage, CIC=Clean intermittent catheterization, Norm=Normal, Dysp=Dysparunia, Sq CC=Squamous cell carcinoma, TCC=Transitional cell carcinoma

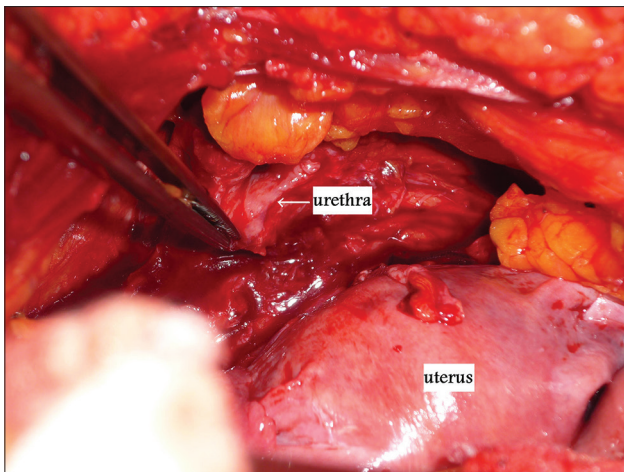


Figure 1: The field after cystectomy with preservation of the female genital organs

genital organs were tumor free. Lymph nodes metastases were detected in two cases.

Voiding function

After catheter removal, 14 patients were able to void satisfactorily, being continent day and night, with a median pouch capacity of 320 mL (range 220–400 mL) and a median rate of five voids per day (range 3–7) and two voids per night (range 1–3), demonstrating minimal post-voiding residual urine of <50 mL.

The remaining 4 patients had a median pouch capacity of 340 mL (range 260–500 mL) with post-voiding residual urine

of >100 mL (range 120–230 mL), and these patients required clean intermittent catheterization three times daily to completely evacuate the bladder. They were continent by the day time, but two of them reported night time incontinence, needing pads. None of our patients developed upper urinary tract deterioration or pouch–vaginal fistula. One patient had a stone in the pouch 27 months post-operatively, which was managed endoscopically.

Sexual life

15 patients had an unchanged sexual life, practicing sexual intercourse at a once-weekly average rate with normal orgasms. Three patients complained of dysparunia that was managed with indomethacin 100 mg suppository on demand.

Oncological outcome

Till the last follow-up visit, there were no local recurrences in the urethral stump or in the spared genital organs in any patient. Distant metastatic disease occurred in three patients at 10, 16 and 20 months post-operatively. These patients had an average tumor size of 5.2 cm, and two of them had lymph node metastases in the resected specimen. They were managed with chemotherapy and two of them died of metastatic disease, while one showed partial response to chemotherapy with no progression of the metastases. 14 patients were still alive, with no evidence of local or distant metastases, while one patient was lost to follow-up at 12 months post-operatively but was disease free at the time of the last visit. Patients' outcomes are given in Table 2.

Table 2: Post-operative findings and patients outcome

Patients	Post-op. Stage	Voiding pattern	Metastases	Sexual life	Follow-up (months)
1	T2aN0M0	Spontaneous	NED	Normal	95
2	T2aN0M0	Spontaneous	NED	Dysparunea	90
3	T2bN0M0	Spontaneous	NED	Normal	88
4	T2aN0M0	CIC, incon/night	NED	Normal	83
5	T2bN0M0	Spontaneous	NED	Normal	78
6	T2aN0M0	Spontaneous	NED	Normal	76
7	T2bN1M0	Spontaneous	Yes and died	Normal	75
8	T2aN0M0	CIC incon/night	NED	Normal	73
9	T2bN0M0	Spontaneous	Yes and died	Normal	70
10	T2bN0M0	CIC	NED	Dysparunea	67
11	T2aN0M0	Spontaneous	NED	Normal	65
12	T2aN0M0	Dropped of follow-up			
13	T2bN0M0	Spontaneous	NED	Normal	57
14	T2bN0M0	Spontaneous	NED	Dysparunea	53
15	T2aN0M0	Spontaneous	NED	Normal	50
16	T2bN0M0	Spontaneous	NED	Normal	46
17	T2aN1M0	CIC	Yes and alive	Normal	40
18	T2bN0M0	Spontaneous	NED	Normal	39

Pts=Patients, Post-op. Stage=Post-operative stage, CIC=Clean Intermittent Catheterization, NED=No evidence of the disease, incon/night=Incontinent/night

DISCUSSION

For several decades, radical cystourethrectomy was considered the gold standard treatment for women with invasive bladder cancer in spite of significant post-operative urinary and sexual dysfunction. With growing interest in quality of life issues, the procedure has been modified in selected patients by sparing the urethra, allowing orthotopic diversion,^[13,15,16] and more recently by sparing the internal genital organs, allowing a better sexual life.^[3]

In this series, we report our experience in orthotopic genital-sparing cystectomy to manage sexually active pre-menopausal women with bladder carcinoma. The technique was based on reports of infrequent genital organ involvement in women with bladder cancer. Groutz *et al.* found uterine involvement in only one of 37 patients with bladder urothelial tumors.^[17] Ali-El-Dein *et al.* also reported an only 2.6% incidence of concomitant genital organ involvement by bladder cancer with a 0% rate of concomitant primary genital cancer among 609 female radical cystectomies.^[4] Salem *et al.* reported the outcome of 29 women undergoing radical cystectomy with internal genital organ preservation, and they noted that none of them had late ovarian, vaginal or uterine recurrence at the last follow-up.^[6]

These data encouraged the preservation of genital organs in selected women undergoing radical cystectomy. In 2008, Kulkarni *et al.* reported a series of 14 female patients with orthotopic genital-sparing cystectomy. Patients' age ranged

from 45 to 72 years, and all of them had transitional cell carcinoma. In their series, there was no reported urethral recurrence, although one patient died of metastases and another of pelvic recurrence.^[3] In 2010, Koie *et al.* reported a series of 30 female bladder cancer patients who underwent cystectomy with preservation of the gynecologic organs. The median follow-up period was 35.7 months, during which time one patient had local recurrence and six patients died of bladder cancer. However, the study was retrospective and the tumor was urothelial carcinoma in 29 patients and leiomyosarcoma in one patient.^[8] More recently, Ali-El-Dein *et al.* reported a prospective study of 15 cases with a mean age of 42 years who underwent genital-sparing cystectomy with a mean follow-up of 70 months. They reported no recurrence in the retained genital organs, although two patients developed local recurrence and bony metastasis 3–4 months post-operatively and a third patient developed bony metastasis 15 months post-operatively.^[9]

In our series, the technique was performed to manage pre-menopausal women and the tumor histopathology was squamous cell carcinoma in most of them (72% of cases), mostly as one of the sequelae of bilharzial infestation. *Shistosoma hematobium* is causally related to bladder squamous cell carcinoma, mostly through chronic inflammation and irritation in addition to some carcinogens such as nitrosamines; unfortunately, it is endemic in upper Egypt where our institute is located.^[18] The disease characteristically affects young patients who are still sexually and socially active, and the tumor is usually nodular and located in the dome or posterior or

lateral bladder walls.^[19] Further, it usually presents at a locally advanced muscle-invasive stage, although metastasis is relatively uncommon.^[20] Therefore, the technique of orthotopic genital-sparing cystectomy is a suitable option in this group of patients as it eradicates the tumor while keeping the functional aspects.

In an attempt to balance between radicality and functional issues, our selection criteria included only pre-menopausal, sexually active women who presented with low-grade, low-stage tumors away from the bladder neck area, trigone and posterior bladder wall. Internal genital organ involvement was also clinically and radiologically excluded.

Hautmann's pouch^[13] was chosen as a bladder substitute, aiming at configuration of an oval-shaped, low-pressure reservoir with a capacity of at least 150 mL with antirefluxing ureteral anastomosis using the serous-lined extramural tunnel technique.^[14] Using this technique, none of our patients demonstrated prolapse, pouch vaginal fistula or upper urinary tract deterioration with stable overall serum creatinine level throughout the study period. Day and night time continence was achieved in 100% and 88% of cases, respectively. It is suggested that genital organ sparing during cystectomy may aid in post-operative continence through preserving the urethral support mechanism. It may also significantly decrease the risk of post-operative pouch vaginal fistula and pouch prolapse,^[7,17] which may lead to angulation of uretero-intestinal anastomosis and pouch herniation through the anterior vaginal wall.^[21]

Oncologically, none of our patients had urethral or genital organ recurrence till the last follow-up visit, while distant metastases were reported in three cases. Sexual relations were unchanged in 15 patients with normal orgasmic feelings. In their series, Ali-El-Dein *et al.*^[9] also reported a better sexual function in patients with genital-sparing cystectomy than in others without genital preservation. The limited dissection at the region of the bladder neck and anterior vaginal wall possibly has a positive impact on patients' sexual life through preserving the autonomic nerve fibers, which are important to maintain vaginal lubrication. These fibers are mostly injured where they pass between the ureters and the cervix and also in the paravaginal/bladder neck area.^[22] At these areas, caution should be exercised to carefully dissect close to the bladder neck and to transect the dorsomedial bladder pedicles close to the bladder.

Using the Female Sexual Function Index (FSFI) questionnaire, Bhatt *et al.*^[23] assessed female sexuality in 13 patients after orthotopic cystectomy, which was nerve sparing in six and non- nerve sparing in seven patients, indicating no significant difference in the post-operative FSFI scores in the nerve-sparing group, while there was a significant decline in the score in the non-nerve-sparing group.

From the clinical and social points of view, this technique maintains reproductive ability, avoids early menopause and allows a better sexual function without compromising tumor radicality, with an expected overall positive impact on patients' life. Moreover, preserving the genital organs in addition to orthotopic diversion help to keep body image.

However, the study is limited because of the small number of patients and the relatively short follow-up period. Also, none of our patients became pregnant till the last follow-up visit. Therefore, we think it is too early to have an accurate long-term assessment of the oncological and functional outcome of this technique, and further studies with a larger sample size and a longer follow-up are still needed.

CONCLUSIONS

Genital-sparing cystectomy is a valid modality to manage selected women with muscle-invasive bladder cancer without compromising their quality of life. However, careful patient selection, meticulous operative technique and close follow-up are still mandatory to standardize this line of management.

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Conflicts of interest

There are no conflicts of interest.

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