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Retrospective Study

Genital Sparing Radical Cystectomy in Women: Oncological and Functional Results

Antonio Cisternino, Lorenzo Capone*, Antonio Rosati, Costanzo Latiano, Michelina Croce, Giuseppe Cretì

Department of Urology, Fondazione IRCCS Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Italy

***Corresponding author:** Lorenzo Capone, Department of Urology, Fondazione IRCCS Casa Sollievo Della Sofferenza, via dei Cappuccini, 71013, San Giovanni Rotondo, Italy

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Abstract

Backgrounds: The aim of this study is to report the experience of a high-volume center in the treatment of muscle invasive bladder cancer on "genital sparing" radical cystectomy in female patients, evaluating oncological and functional (urinary and sexual) outcomes, at no less than 46 months follow-up.

Methods: The study was conducted retrospectively between January 2015 and January 2018. 8 female patients underwent radical cystectomy and bilateral pelvic lymphadenectomy with preservation of genital organs and orthotopic urinary neobladder. Inclusion criteria: recurrent T1G3 tumours, recurrent tumours after BCG therapy, T2 and T3a completely resected at endoscopic TURBT. Exclusion criteria: T3b or higher bladder cancer, concomitant CIS and trigone and/or urethra involvement.

Results: Recurrence Free Survival and Overall Survival was 100%. 7/8 (87.5%) maintained complete continence during both day and night, and only 1 patient (12.5%) complained of urinary leakage during the night. The Sandvik Score showed a state of complete continence in 5 patients (62.5%); mild degree in 2 patients; moderate degree of incontinence in one patient (12.5%). One year after surgery the FSFI showed sexual desire in all patients (100%); subjective arousal, achievement of orgasm, sexual satisfaction in 7 / 8 patients (87.5%); sufficient lubrication in 6 / 8 patients (75%). Only one patient (12.5%) complained of dyspareunia during sexual intercourse.

Conclusions: "Genital sparing" cystectomy is a safe treatment from the point of view of oncological radicality and it is advantageous in terms of urinary and sexual function, quality of life, psychological and emotional health of the patients.

Keywords: Bladder cancer; Female patients; Genital sparing cystectomy; Radical cystectomy; Oncologic and functional outcomes

Introduction and Aim of the Study

The bladder cancer ranks seventeenth as the most common neoformation in women, with about 74000 new diagnoses each year worldwide [1]. Radical cystectomy with urinary diversion is still the treatment of choice [2], both for patients with muscle-infiltrating and non-muscle-infiltrating high-risk tumors (patients with multiple recurrences, T1G3 tumor, concomitant CIS, failure of endocavitary BCG therapy). In women it is a true anterior pelvic exenteratio, which consists in the removal of bladder, urethra, fallopian tubes, ovaries and anterior wall of the vagina [2]. Although the procedure guarantees an excellent surgical excision and safety from an oncological point of view, it is very invasive and it is associated with profound alterations from the point of view of urinary function, sexuality and, last but not least, psychologically, especially in young women, who show a subsequent worsening of their quality of life [3,4]. During the years, thanks to an increased focus on functional outcomes in patients undergoing urologic oncologic surgery, improved diagnostic imaging, increased knowledge of the anatomy and function of the female pelvis, and not least improved surgical techniques, they were introduced some less debilitating and invasive treatments for high-risk bladder [5]. Thus, several genital sparing techniques, both male and female,

known as "genital sparing" cystectomy have emerged over the years [6]. The concept of radical cystectomy with pelvic organ sparing arose in the late 1990s and concerned only men. In fact, Spitz and colleagues were the first to propose "genital sparing" cystectomy for the management of non-urothelial tumors in young sexually active men in order to preserve erectile function and fertility [7]. From then on, various Authors proposed several prostate-sparing techniques during radical cystectomy [9-10].

Genital sparing cystectomy in women was only really considered in the early 2000s, mainly due to a slower adoption of orthotopic ileal shunts, despite unanimous concerns about the significant urethral involvement of urothelial cancer and the more advanced state of the disease at diagnosis in women, compared to their male counterparts. After conducting extensive scientific research, it has been found that the urethra can be spared without compromising the oncological outcome and, consequently, many centers successfully performed urethral-sparing radical cystectomy and orthotopic bladder replacement in female patients [11-13]. Similarly, since several Authors have emphasized the low incidence of genital organ involvement in samples of patients undergoing radical cystectomy for urothelial cancer, attention has been drawn to the possible sparing of female genitalia in a highly selected group of patients [14,15]. In recent years, in fact, the marked improvement in therapeutic efficacy in the treatment of bladder cancer led overall survival from disease to rise from 28% in the 1990s to over 59% in the 2000s [16]. Today, 5-year cancer-specific and overall survival in women undergoing radical cystectomy is 70-88 % and 65-83 %, respectively [6]. With increasing survival from bladder cancer, quality of life and sexual function are considered equally important points to pursue, in addition to surgical radicality of course, particularly in young patients diagnosed with bladder cancer and wishing to preserve fertility [4,17]. Identifying patients who are potential candidates for "genital sparing" surgery has become a fundamental element of increasing interest; however, studies considering this topic are few and they are characterized by important limitations, such as the small number of cases, the non-objective and incomplete evaluation of functional and oncological outcomes, and the inclusion of patients with non-orthotopic shunts [3, 17-19].

The aim of this study is to report the experience of a high-volume center in the treatment of muscle-invasive bladder cancer, on "genital sparing" radical cystectomy in female patients, evaluating oncological and functional (urinary and sexual) outcomes at no less than 3 years of follow-up.

Materials and Methods

The study was conducted retrospectively between January 2015 and January 2018, at the Urology Department, IRRCS Casa Sollievo Della Sofferenza, San Giovanni Rotondo (FG). Eight female patients undergoing radical cystectomy and bilateral pelvic lymphadenectomy with preservation of genitalia and orthotopic urinary diversion were considered. The preserved female genital organs were: entire vagina, uterus, fallopian tubes and ovaries. All patients were informed in detail and comprehensively about the procedure, possible complications and consequences of the procedure and signed an informed consent.

Inclusion Criteria and Preoperative Evaluation

Inclusion criteria for surgery were: recurrent T1G3 tumors, tumors recurrent after BCG therapy without concomitant CIS, T2 and T3a tumors completely resected at endoscopic Transurethral Resection Of The Bladder (TURBT) and not involving the bladder trigone and urethra. All patients were carefully evaluated by history (with emphasis on urinary and sexual function), physical examination, bladder ultrasound, cystoscopy and biopsy bladder mapping, to exclude CIS or concomitant dysplasia. All patients were staged by CT abdomen and pelvis with urographic stage and bone scintigraphy, to exclude extension to the perivesical fat (T3b) or lymphnode secondarisms and/or adjacent organs (T4 stage). Patients also underwent gynaecological examination to exclude tumours or papillomas in the cervix or ovaries. Finally, all patients were sexually active and relatively young (under 65 years). Exclusion criteria were: bladder cancer T3b or higher, concomitant CIS and involvement of the trigone and/or urethra. All patients had bowel preparation the day before surgery and received perioperative antibiotic prophylaxis with third-generation cephalosporins.

Open Surgical Technique

The patients were placed in the supine Trendelemburg position with hyperextension of the pelvis, in order to open the area between the umbilicus and the pelvis. After disinfection and preparation of the operating field, an umbilicus-pubic incision was made on the midline and, after dividing the muscular-aponeurotic planes, the peritoneal sac was opened. A lysis of any intestinal-omental adhesions was performed and the intestinal skein was dislocated cranially in order to expose the pelvis. The bladder was mobilized to the lateral walls of the pelvis. The residual urachus was circumscribed, paying attention not to damage the lower epigastric vessels, and removed with the entire bladder. Careful and systematic study was performed to determine the extent of the disease and the possible presence of metastases or massive retroperitoneal lymphadenopathy. At this point the bowel was mobilized from the ascending colon, which was moved medially to obtain access to the right ureter. The mesentery was reversed until the retroperitoneal portion of the duodenum is uncovered. Next, the left colon and sigma were mobilized to the lower pole of the left kidney to gain access the left ureter. The ureters were then isolated at their entry into the bladder, where they were ligated and dissected. The distal margin was sent for extemporaneous histopathological examination to exclude neoplastic involvement.

The umbilical, uterine, superior and inferior bladder arteries were carefully prepared bilaterally. The bladder was mobilized, at which point along the anterior wall of the uterus and by use of an instrument in the vagina, the junction between the cervix and the anterior wall of the vagina was identified. After that, a dissection of the vaginal wall was made at the level of the anteroventral plane of the vagina, at 2 o'clock and 10 o'clock, respectively, as close as possible to the bladder wall, in order to preserve the paravaginal tissue, containing the autonomic nerves reaching the proximal sphincter. The superior and inferior bladder arteries were dissected at their origin, at the level of the hypogastric arteries, while the uterine arteries and vaginal branches directed to the paravaginal tissue were spared. Once the retropubic space was created and opened, the endopelvic fascia was incised very close to the bladder neck to reduce the risk of accidental injury to the paraurethral neurovascular structures, which are crucial for sexual function and continence. The urethra was carefully prepared, exposed and severed, and a sample was sent for extemporaneous histopathological examination. At this point, a careful dissection of the retroperitoneal lymph nodes was performed. The margins of the resection were, cranially, the common iliac artery; laterally, by the genito-femoral nerves; inferiorly, by the Cooper ligament; caudally, by the obturator canal; medially and laterally, by the hypogastric vessels.

Orthotopic Urinary Diversion

A 40 cm ileal segment is isolated 15-20 cm from the ileocecal valve. Intestinal continuity is restored with a latero-lateral anastomosis using mechanical sutures. To reach the membranous urethra, the distal loop (approximately 20 cm in length) is lowered to form a "U". The ileal segment is then opened along the antimesenteric margin. The lower part of the ileal loop is tunnelled posteriorly and anteriorly using a 3/0 V-Loc suture. The proximal loop is folded medially on itself in an inverted U shape and the opposite inner edges are then sutured from side to side to form an upper ileal cup. This is then inverted at the edges of the lower ileal cup so that an oval reservoir can be obtained. The urethrointestinal anastomosis is packed with 6 detached stitches of resorbable 3/0 glyconate monofilament suture on a 20 Ch 3-way neobladder catheter. Uretero-neovesical anastomosis is performed bilaterally using Bracci ureteral catheters as a guide, which are then exteriorized at the level of the left iliac fossa. A hydraulic leak test of the neobladder is performed and a 24 Ch tubular drain is placed in the Retzius excavation at the level of the right iliac fossa. Finally, the abdominal wall is closed.

Robot-Assisted Surgical Technique

Out of the 8 patients who underwent radical genital sparing cystectomy, 3 underwent bladder removal by robotic-assisted laparoscopic technique with Da Vinci X and Xi robot (Ab Medica). During the procedure the patients were placed in supine position with lower limbs abducted, then vaginal, perineal and abdominal disinfection, bladder catheterization with drainage in sterile bag, rectal catheterization for subsequent hydropneumatic test were performed. This was followed by supraumbilical skin incision, abdominal access using the Hasson open technique, opening of the peritoneum under direct vision, positioning of the first optical trocar and induction of pneumoperitoneum at 12 mmHg. The patients were placed in a pushed Trendelemburg position (> 25°), the peritoneal cavity and viscera were inspected to exclude adhesions or metastatic pathology. Two additional 8 mm robotic operative ports were placed approximately 8 centimeters from the optic trocar, approximately 2 centimeters lateral to the rectus abdominis muscle, at the level of the inferior margin of the umbilicus. Two further laparoscopic ports were introduced, one of which was 12 millimeters, 5 centimeters above the anterior superior iliac spine, on the right mid-axillary line for the surgical tractions; another one was 5 millimeters about 2.5 centimeters above the right robotic ports for the surgical aspirator. Finally, the docking of the Da Vinci robot with monopolar curved scissors on the right and bipolar prograsp scissors on the left was performed. The steps of the radical cystectomy were the same as the open surgical approach. At the end of the robotic procedure, a suprapubic incision according to Pfannenstiel was made, the surgical piece previously placed in endobag was removed and the orthotopic padua neobladder (VIP) was packaged.

Post-Operative Evaluation

Patients were evaluated taking into consideration age, Body Mass Index (BMI), American Society of Anesthesiology score (ASA score), hemoglobin and creatinine preoperatively. The surgical outcomes considered were: operative time, hemoglobin and creatinine at discharge, days of hospitalization and perioperative complications according to the Clavien-Dindo classification system [20]. Patients were followed up both functionally and oncologically by outpatient visits quarterly during the first year and semi-annually in the following years. From the oncological point of view, patients were followed at the outpatient clinic dedicated, with a program that includes blood tests, abdominal ultrasound, urinary cytology, CT abdomen and pelvis with urographic phase, urethrocystoscopy and chest X-ray. For the study, the following outcomes were examined as oncological outcomes: recurrence rate (local or metastatic RFS) measured at more than 3 years of follow-up, Overall Survival (OS) at more than 3 years of follow-up and finally anatomopathological outcomes.

Regarding functional outcomes, sexual function was measured by a standardized questionnaire (FSFI) administered both 3 and 12 months after surgery. The Female Sexual Function Index (FSFI-19) [21] is a rapid and effective questionnaire that structures female sexual function into 6 different aspects: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain,

with a score ranging from a minimum of 2 to a maximum of 36. Urinary function, on the other hand, was assessed by the patient's level of continence (daytime and nighttime) and the use of devices for urinary incontinence; the severity of urinary leakage was calculated using the Sandvik score [22]. Finally, the presence of urinary retention with possible need for intermittent urethral catheterization was evaluated.

Results

At Casa Sollievo Della Sofferenza Urology Department, 8 female patients underwent radical "genital sparing" cystectomy between 2015 and 2018 (mean age of patients 57.6 years; range 30 - 65). The clinico-pathological characteristics of the patients, detected before surgery, are shown in Table 1. Regarding the surgical outcomes (Table 2), the mean operative time of the whole procedure, including cystectomy, bilateral pelvic lymphadenectomy and neobladder reconstruction, was 260 minutes (220 - 396 minutes) for open surgery and 318 minutes (258 - 432 minutes) for cystectomy performed with robot-assisted technique. The mean blood loss during surgery was 400 ml (230 - 710 ml). The mean hospital stay of the patients was 18 days (15-24 days) and the hemoglobin and serum creatinine at discharge were 9.3 gr/dL (8.9 - 14.8 gr/dL) and 1.2 mg/dL (0.8 - 1.6 mg/dL), respectively. None of the patients had perioperative complications related to the procedure, such as loss of ileo-ileal anastomosis seal, hemorrhage, loss of neobladder seal. According to the Clavien-Dindo classification of postoperative complications, none of the patients had complications requiring surgery (grade ≥ 3), only one patient had postoperative acute pancreatitis, successfully treated by medical therapy.

PATIENT CHARACTERISTICS	
	Mean (range)
Age (years)	57.6 (30 - 65)
Body Mass Index	26.1 (20 - 30.5)
Preoperative Creatinine (mg/dL)	0.86 (0.72 - 1.1)
Preoperative Hemoglobine (g/dL)	12.7 (11.2 - 14.3)

	No. of patients (%)
Status	
Married	7 (87.5)
Unmarried	1 (12.5)
Menopause	
Premenopausal	4 (50)
Postmenopausal	4 (50)
ASA Score	
I	2 (25)
II	6 (75)
Previous abdominal surgery	
Cesarean section	1 (12.5)
Appendicectomy open	1 (12.5)
Location of the tumor	
Posterior wall	3 (37.5)
Anterior wall	1 (12.5)
Lateral wall	3 (37.5)
Dome of the bladder	1 (12.5)
Pathological type	
Urothelial Carcinoma	7 (87.5)
Other (Embryonal rhabdomyosarcoma)	1 (12.5)
Grading of the tumor	
Low grade	1 (12.5)
High grade	7 (87.5)
Staging TNM	
T2 N0 M0	5 (62.5)
T1 N0 M0	3 (37.5)

Table 1: Patient characteristics.

ONCOLOGIC OUTCOMES	
	Mean (range)
Operative Time (min)	
Open	260 (220 - 396)
Robot-assisted	318 (258 - 432)
Mean Blood Loss (ml)	400 (230 - 710)
Hospital stay (days)	18 (15 - 24)
Postoperative creatinine (mg/dL)	1.2 (0.8 - 1.6)
Postoperative Hemoglobine (gr/dL)	9.3 (8.9 - 14.8)
	No of Patients (%)
Complications	
Clavien Low Grade (0 - 2)	8 (100)
Clavien High Grade (3 -5)	0 (0)
Cystectomy	
Robotic-assisted Cistectomy	3 (37.5)
Open Cistectomy	5 (62.5)
Postoperative Pathologic Stage	
Ta, Tis, T1	3 (37.5)
T2aN0M0	1 (12.5)
T2bN0M0	2 (25)
T3aN0M0	1 (12.5)
T3bN0M0	1 (12.5)
T4	0 (0)
Pathologic nodal stage	
N0	8 (100)
N+	0 (0)
Tumor Grading	
Low Grade	3 (37.5)
High Grade	5 (62.5)
Positive surgical margins	0 (0)
Follow-up 12 months	
Recurrence-free survival	8 (100)
Overall survival	8 (100)
Follow-up 24 months	
Recurrence-free survival	8 (100)
Overall survival	8 (100)
Follow-up 36 months	
Recurrence-free survival	8 (100)
Overall survival	8 (100)

Table 2: Oncologic outcomes.

Oncological Results

Oncological findings are presented in Table 2. Definitive histopathological examination reported urothelial carcinoma in 7 patients of which 3 / 8 patients (37.5 %) had low grade T1 stage, 2 / 8 patients (25 %) had high grade T2 stage and finally 2 patients (25 %) had high grade T3 stage. One patient presented at final histopathological examination with botryoid variant embryonal rhabdomyosarcoma, localized to the bladder and completely excised after surgery (PT2aN0M0). Resection margins were free from neoplastic pathology in all patients, as well as all resected lymphnodes were free of tumor pathology. All patients underwent a follow-up of at least 36 months. No patient during this period developed local recurrence of disease (urethral and/or neovesical), or metastatic recurrence (Recurrence Free Survival 100%) and, finally, overall survival was 100% (Overall Survival 100%).

Functional Results

Out of the 8 patients, 7 (87.5%) maintained complete continence both during the day and night, only one patient (12.5%) complained of urinary leakage during the night with need for use of 1-2 pads. The Sandvik score showed a state of complete continence in 5 patients (62.5%), mild degree of incontinence in 2 patients (25%) without, however, use of devices for urinary incontinence, moderate degree of incontinence in one patient (12.5%) with use of 1-2 absorbent pads during the night. Only one patient, after 6 months, developed a urethra-neovesical stenosis treated by endoscopic surgery, and currently performs intermittent self-catheterization without further problems. No patient had hydronephrosis, urethro-neovesical reflux or deterioration of renal function during the follow-up period.

Out of the 8 patients who underwent surgery, 7 (87.5%) were married, 1 was single (12.5%) but had a stable partner; 4 women (50%) were fertile at the time of surgery, while the other 4 (50%) were already in menopause; all patients were sexually active. As previously mentioned, sexual function was assessed by FSFI-19 administered at 3 months and one year after surgery. One year after surgery, the FSFI showed sexual desire in all patients (100%);

subjective arousal, orgasm achievement, sexual satisfaction in 7/8 patients (87.5%); sufficient lubrication in 6/8 patients (75%). Only one patient (12.5%) complained about dyspareunia during intercourse. All patients were sexually active one year after surgery. Finally, evaluating the result of the tests of the patients at 3 months after surgery and at 12 months after the same, there was an increase in the final score of the test in all patients one year after surgery, as a result of a better sexual wellbeing; these data were also endorsed at the outpatient interview (total FSFI 3 months: 18.3, range 15-21; total FSFI 12 months: 29.1, range 25-33; Table 4) . The functional results are shown in Table 3.

FUNCTIONAL OUTCOMES	
	No of Patients (%)
Continence	
Day-time	8 (100)
Night-time	7 (87.5)
Sandvik Score	
0 (continent)	5 (62.5)
1 - 2 (mild incontinence)	2 (25)
3- 6 (moderate incontinence)	1 (12.5)
8 - 9 (severe incontinence)	0 (0)
12 (very severe incontinence)	0 (0)
Neobladder complications	
Uretral stricture	1 (12.5)
Clean Intermittent Catheterization	1 (12.5)
Female Sexual Function Index (FSFI) at 12 months	
Sexual desire	8 (100)
Sexual arousal	7 (87.5)
Lubrication	6 (75)
Orgasm	7 (87.5)
Satisfaction	7 (87.5)
Pain	1 (12.5)

Table 3: Functional outcomes.

	FSFI 12 month	FSFI 3-month
Patient 1	30	20
Patient 2	32	21
Patient 3	33	17
Patient 4	29	15
Patient 5	25	17
Patient 6	30	21
Patient 7	28	18
Patient 8	26	17
	29.125	18.25

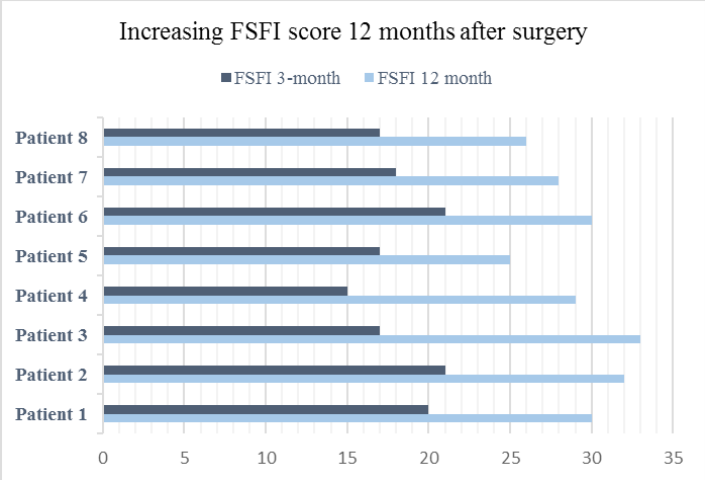

Table 4: There was an increase in the final score of the test in all patients one year after surgery (total FSFI 3 months: 18.3, range 15-21; total FSFI 12 months: 29.1, range 25-33).

Discussion

The main goal of treatment of muscle-invasive urothelial bladder cancer is to eradicate the disease and cure the patient. Achieving an excellent functional and aesthetic result at the expense of oncological radicality is not acceptable. When possible or feasible, however, it is equally important to guarantee the patient the best results from a functional, sexual and psychological point of view, since increasing disease-free survival without improving, as much as possible, the quality of life, is undoubtedly deleterious and counterproductive. The impact of a radical cystectomy in female patients irreversibly modifies the quality of life in several

aspects. First of all, the use of a non-orthotopic urinary diversion has been shown to be debilitating from the point of view of sexual function and "body image". In fact, it has been seen that the diagnosis and treatment of bladder cancer and interstitial cystitis in women are the two pathologies mostly associated with physical decline, mental decay and quality of life, related to social health [23]. Yang and colleagues in 2016 performed a meta-analysis of 29 studies and 3754 patients in order to assess quality of life using validated international scores (FACT, SF-36), in patients undergoing radical cystectomy with continent urinary shunt and incontinent. Researchers found no statistically significant differences in quality of life comparing the different surgical techniques, but subjects undergoing orthotopic continent urinary shunt reported better psychological, emotional, and body-image outcomes [24]. Radical cystectomy is also associated with sexual dysfunction in women for both psychological and anatomical reasons due to the surgery; consequences of cystectomy are significant reduction in vaginal length, injury to the neurovascular bundle of the vagina and clitoris, and removal of the uterus and adnexa [25]. A study conducted in 2004 on 27 patients who underwent radical cystectomy with continent orthotopic urinary diversion found a decreased ability to achieve orgasm in 45% of cases, decreased lubrication in 41%, decreased sexual desire in 37%, and dyspareunia in 22%. After surgery, only 48% of the patients were able to have sexual intercourse. On the other hand, no statistically significant differences were found between sexual function and the different continent orthotopic urinary diversion technique [26]. In 2016, Zahran and colleagues evaluated female sexual dysfunction in women undergoing radical cystectomy in a meta-analysis that considered 11 studies and 361 patients, finding a loss of sexual desire in 49% of patients, dyspareunia in 25%, inability to reach orgasm in 39%, and altered vaginal lubrication in 9.5% [27]. It should be added, moreover, that the focus on quality of life in general, and sexual function in particular, by means of an in-depth interview on the consequences of cystectomy in women with bladder cancer was addressed with only 23 % of women according to a 2018 study by Voigt [28].

Why Sparing the Urethra And Internal Genitalia?

The dogma imposing pelvic exenteratio in women undergoing radical cystectomy was questioned not before the second half of the 1990s, when neoplastic involvement of the urethra and female genitalia in women with muscle-invasive bladder cancer was carefully analyzed. Anatomopathological studies conducted by Stein and colleagues in 1995 and 1998 on bladder specimens demonstrated urethral involvement only when there was neoplastic involvement of the bladder neck [29], or extensive CIS [30]. In the following years, more and more urologists adopted a surgical technique with urethral sparing and orthotopic urinary shunt, demonstrating both its safety from an oncological point of view, and excellent results in terms of spontaneous emptying of the neobladder and quality of life [31]. Only in first half of the 2000s some studies evaluated neoplastic involvement of the female genitalia in patients with muscle-invasive bladder cancer. Groutz et al. in 1999 and Chang et al. in 2002 were the firsts to examine uterine involvement of urothelial carcinoma in patients undergoing cystectomy, reporting 2.7 % (1/37 patients) and 5 % (2/40 patients) incidence, respectively [32,14]. Ali-El-Dein and colleagues in 2004 evaluated the incidence of tumour involvement of the genital organs (uterus, ovaries and vagina) on histopathological specimens from 609 women undergoing radical cystectomy for bladder cancer, reporting a positive rate of 2.6 % (16 / 609 patients) [103]. In the following years other studies have demonstrated the low involvement of female genitalia in patients with high-risk non-muscle invasive or muscle invasive bladder cancer, laying the basis for a "genital sparing" approach to radical cystectomy [33,34].

Currently, in the literature there are few studies that take into account the radical cystectomy "genital sparing" in women and they are also burdened by some bias, such as limited number of cases, short follow-up of patients, heterogeneity in the evaluation of oncologic results. In addition, among the studies that assess functional outcomes, the majority takes into account only the urinary function, which is also undermined by heterogeneity in the definition of incontinence and doesn't use validated scores to estimate the extent of the same. Finally, among the studies that evaluate the functional results, few take into account the sexual function and measure it through validated international questionnaires. Among the first authors to evaluate the oncological and functional results of "genital sparing" cystectomy are Horemblas and colleagues in 2001. They examined 3 patients who underwent radical cystectomy with sparing of the genital organs and, after a follow-up of 36 months, a continence rate of 66% (2/3) was found. Only one patient had to resort to intermittent self-catheterization. No patient had neoplastic involvement of the genital organs [4]. Koie et al. in 2010 reported the oncological and functional results of 30 patients who underwent radical "genital sparing" cystectomy with a follow up of 35.7 months: 1/30 patients had local recurrence, while 6/30 patients died of bladder neoformation within 2 years after surgery. Concerning functional results, only urinary function was considered, intended as day and night continence, which remained preserved in 80% of cases (24/30). The Authors conclude by underlining how "genital sparing" cystectomy is feasible both from the point of view of oncological safety and urinary function [35]. Ali-El-Dein and colleagues in 2013 evaluated 15 patients who underwent radical cystectomy with preservation of the genital organs, reporting oncological and functional outcomes with a follow-up of about 70 months: 2/15 patients showed, at anatomopathological level, a higher stage than the one evaluated preoperatively, 1/15 patients had bone secondarisms 15 months after surgery, and the remaining

12 had no disease recurrence. From the point of view of urinary continence, out of the 13 patients evaluated, 100% (13/13) had preserved daytime urinary continence and 92% (12/13) nocturnal continence. Regarding sexual function, 11 patients were evaluated by FSFI questionnaire, demonstrating higher scores than patients undergoing standard radical cystectomy [36]. Finally, a 2017 systematic review by Veskimae and colleagues identified 15 articles that addressed the oncological and functional outcomes of women undergoing "genital sparing" cystectomy, comparing them with those of patients undergoing standard radical cystectomy with orthotopic urinary diversion. Regarding oncological outcomes, 11 studies were considered and only 7 out of them had a follow-up of ≥ 36 months. Cancer-Free Survival (CSS) was 70-100% and Overall Survival (OS) 65-100% in both groups of patients (genital sparing vs standard). Regarding the functional outcomes, the authors have a great heterogeneity that did not allow a statistical analysis of the subgroups, but a narrative synthesis that shows better results especially in sexual function. The study concludes, once again, that in well-selected patients, radical "genital sparing" cystectomy is comparable to standard radical cystectomy in terms of oncological results, while it is superior in terms of continence and sexual function [6].

The data found in our study are absolutely in line with the international literature with regard to oncological results, demonstrating an Overall Survival (OS) and a Recurrence-Free Survival (RFS) of 100% (8/8 patients) at 36 months of follow-up. This finding is most likely due to the careful selection of patients, through strict inclusion and exclusion criteria, with the ultimate aim of reducing the incidence of patients with more advanced tumor pathology, compared to preoperative evaluation and local or systemic disease recurrence. When we evaluated the urinary and sexual functional results, by means of validated scores and questionnaires (Sandvik score, FSFI), we observed better scores in women undergoing "genital sparing" cystectomy, compared with the data available in the literature of women undergoing standard cystectomy. From the point of view of urinary function, this case report is one of the few that shows results from women who underwent radical cystectomy with ileal neobladder with VIP technique; however, the results are in line with the world literature, showing very high rates of diurnal and nocturnal continence. With regard to sexual function, we noticed not only good results at 3 months after surgery, but also a significant increase in the score itself at 12 months after surgery with 100% of patients sexually active and able to conclude a sexual relationship in a satisfactory manner. We are in agreement with the literature of the sector in identifying anatomical and functional causes at the basis of the best results found. From an anatomical point of view, sparing the vagina, the uterus and the adnexa means providing good support to the neobladder, preventing its posterior dislocation and a consequent angulation of the neobladder-urethral anastomosis. Preserving the uterus, moreover, could prevent a possible enterocele due to the intestine occupying the empty space left by the genital organs. Direct consequence, therefore, would be a lower probability of chronic urinary retention due to a lower percentage of neovesical prolapses. In fact, the vagina, at the apex, is suspended by the uterine-sacral ligament complex, which during a standard radical cystectomy is interrupted; this, added to the lack of adequate posterior support, would lead to neovesical prolapse at the vaginal level [37-39]. Besides, sparing the genital organs, and in particular the vagina, means to spare the neurovascular bundles passing to its sides and, therefore, to safeguard the sexual function, both because the vagina is not shortened and the danger of fistulas between the neobladder and the vagina itself is reduced, and because orgasm and vaginal lubrication stay intact. Last but not least, it should be underlined that in young women this surgical technique would allow the preservation of fertility and therefore the possibility of having children [36,40]. Because of the increased interest in "genital sparing" cystectomy in women, the European Association of Urology (EAU), in its guidelines on muscle-infiltrating bladder cancer, stated that "from an oncological point of view, concomitant malignancy of the gynecological organs is rare and local recurrence after radical cystectomy is infrequent. In premenopausal women, preserving the ovaries will maintain hormonal homeostasis, reducing the risk of cognitive impairment, cardiovascular disease and loss of bone mineral density. Nevertheless, most studies are retrospective and with limited numbers of patients." The EAU therefore recommends that "genital sparing" cystectomy should be considered, not as a reference treatment of bladder cancer, but as an alternative treatment in highly motivated and carefully selected women [2,6,41].

Conclusions

In conclusion, according to our experience, "genital sparing" cystectomy results to be a safe treatment from the point of view of oncological radicality for high-risk non-muscle invasive or muscle invasive bladder cancer and, also, advantageous from the point of view of urinary and sexual function, quality of life and psychological and emotional health of patients. However, it is a treatment reserved to carefully selected female patients who are strongly motivated to preserve fertility and sexual function and who are fully informed about the merits and drawbacks of this procedure.

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