



Radical Cystectomy in Female Patients - Improving Outcomes

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Abstract

Purpose of Review To review the methods of improving surgical, oncological, and functional outcomes in women with bladder cancer treated with radical cystectomy.

Recent Findings Orthotopic urinary diversion (ONB) is a safe option for well-selected women as it combines high rates of daytime and nighttime continence with exceptional oncologic outcomes. It is considered safe even for patients with limited lymph node disease and trigone involvement, as long as a preoperative biopsy of the bladder neck or an intraoperative frozen section analysis of distal urethral margin rules out malignant disease. Nerve-sparing techniques have shown promising results. For well-selected patients with early invasive disease, sparing of internal genitalia has proven to be oncologically safe. Yet, generally accepted and evidence-based oncological and functional follow-up schemes for women after radical cystectomy are still lacking.

Summary Properly designed prospective studies are needed with adequate number of participants in order to safely conclude about a broader use of pelvic organ-sparing cystectomy.

Keywords Bladder cancer · Diversion · Outcomes · Radical cystectomy · Women

Introduction

According to epidemiological studies, bladder cancer (BCa) ranks ninth among all malignancies while it is considered to be the 13th most common cause of cancer-related death in the world [1, 2]. With regard to histologic classification, urothelial carcinoma predominates in the developed countries of Europe and North America, with non-urothelial histologies being more common in other regions, such as the Middle East.

Two studies reported that over a period of two decades (1985–2005), the diagnosis of BCa in the USA increased by more than 50%, while from 1975 to 1996 the 5-year survival rate increased by 6% [3, 4]. Similarly, there is a downward

trend of mortality rates among several European nations, with the exception of some eastern European countries [5].

Typically, BCa is diagnosed in older individuals with the mean age of diagnosis being 69 years for men and 71 years for women [6]. In terms of incidence, the diagnosis was found to be three to four times less common in women than in men [7, 8] but at the same time women are more likely to receive a diagnosis of locally advanced disease [6, 8–11].

So far, cigarette smoking has been shown to be the most common risk factor for BCa development [12]. A number of occupational exposures such as dye and petroleum products have also been linked to BCa [13, 14] but to a lesser extent than smoking [15, 16]. It is worth mentioning that even controlled for exposure to smoking and occupational hazards, the diagnosis of the disease is still far more common in men [17].

Interestingly, while female gender is considered to be protective in terms of cancer-specific survival for most types of cancer, this is not the case for women suffering from BCa, since they have been found to experience higher mortality than men [6, 9, 10, 18–20]. One possible explanation could be the aforementioned advanced stage at the time of diagnosis in women, though in a study published by Mungan et al., female patients were shown to have worse outcomes across all stages of the disease when compared to men [11]. During the last decade, several studies trying to shed some light on the

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possible causes of gender disparities reported that women with hematuria are more likely to receive a false diagnosis of urinary tract infection [21], thus missing the opportunity to undergo a prompt and complete hematuria evaluation [22–24]. According to Hollenbeck et al. a subsequent delay in the diagnosis of BCa is clearly associated with a higher cancer-specific mortality [25].

Preoperative Aspects of Orthotopic Diversions in Females

Surgical Considerations

Nowadays, radical cystectomy with bilateral pelvic lymphadenectomy has been established as the gold standard therapy for patients with localized (cT2N0M0) or locally advanced (cT3a–T4a, N0–Nx, M0) BCa, since it provides excellent locoregional control of the disease [26, 27]. It has been more than 150 years since ureterosigmoidostomy was introduced as the first mechanism of urinary diversion following cystectomy [28]. After almost a century, it was replaced by the ileal conduit described by Bricker [29], but it was not until the early 1990s that urologists developed ileal neobladder to allow urine storage and voiding through the native urethra [30, 31]. While it was initially limited to male patients [30], increasing experience and improved understanding of the female pelvic anatomy contributed to orthotopic neobladder becoming an option for many women undergoing radical cystectomy [32–35]. It was of utmost importance that several studies demonstrated the oncological safety of orthotopic diversion in carefully selected female patients, since the fear of cancer cells spreading to the female urethra made that procedure initially unavailable to women [36, 37].

Before proceeding with the operation, the surgeon should have a thorough discussion with the patient in order to decide which type of urinary diversion would yield the best oncological and functional outcomes taking into consideration several patient-centered factors such as biological age, manual dexterity, and history of radiotherapy [38, 39]. Regarding the ideal timeline that should be followed, the operation should take place within 12 weeks from the diagnosis (based on data from the SEER-Medicare database) [40], since any delay could negatively affect long-term survival [41].

Age

As expected, age of the patient plays a major role in the selection of the appropriate urinary diversion technique after radical cystectomy. According to a study published by Aghazadeh et al., advanced age is linked to complications occurring both during the procedure and the following period of recovery [42]. Subsequent studies reported that although disease-

specific survival was similar among different age groups, advanced age was associated with increased burden of postoperative complications [43–45]. The above findings provide an explanation why elderly patients are more often offered ileal conduit as the preferred type of urinary diversion instead of an orthotopic neobladder [27, 46]. In 2010, Stenzl et al. concluded that older patients will finally achieve similar continence rates with their younger counterparts, although this may take longer [47]. Metcalfe et al. reported that younger age is independently associated with better quality of life in patients undergoing radical cystectomy [48]. On the other hand, according to the findings of a recent meta-analysis, advanced age is not an independent parameter affecting quality of life when ileal conduit is compared to orthotopic neobladder [49]. Taken together, it is suggested that the patient selection should be based on surgical fitness and functional status, since biological rather than chronological age seems to be closely related to the final outcome [50, 51].

Manual Dexterity

Every time a surgeon considers one of her or his patients for orthotopic diversion, a thorough discussion about the possible need for clean intermittent self-catheterization (CISC) during the postoperative period is mandatory [52]. Patients should be aware about the efforts required during the rehabilitation period and that they should have sufficient manual dexterity in order to master CIC if needed. In a series of 121 female patients with neobladder substitution, more than half of them required periodic CISC after surgery [53]. Similar results were obtained by one of the largest urethra-sparing cystectomy series to date [37]. All of the above underscore the need for evaluation of manual dexterity before proceeding with the operation, having in mind that most of the patients with muscle-invasive bladder cancer (MIBC) are expected to experience significant mental and physical decline before and after the diagnosis [54].

Anterior Exenteration and Pelvic Lymphadenectomy

Anterior pelvic exenteration is considered to be the standard of care when treating MIBC and recurrent high-grade urothelial tumors [27]. When performed in female patients, the technique involves removal of the bladder, urethra, distal ureters, uterus, fallopian tubes, ovaries, and anterior vaginal wall [27, 37, 55–57].

By definition a radical cystectomy should also include a meticulous bilateral pelvic lymph node dissection (PLND) [27, 58–61]. The extent of PLND is directly related to the perioperative morbidity and survival rates after radical cystectomy [62]. The treating surgeon should also have in

mind that an extended PLND may improve 5-year progression-free survival [58, 63]. Nevertheless, there is no commonly accepted threshold regarding the number of lymph nodes that need to be removed, since there are considerable differences among individuals [59, 62, 64]. Summarizing, an extended PLND is defined as the removal of all lymphatic tissue from the common iliac vessels cranially to the genitofemoral nerve laterally, the circumflex iliac vein and node of Cloquet distally, the hypogastric vessels along with the obturator fossa medially, and presacral nodes posteriorly [65].

Vaginal Sparing Approach

Over the years, efforts to achieve the best possible combination between oncological outcomes and postoperative quality of life have gained increasing attention. The introduction and wide acceptance of orthotopic neobladder has motivated many urologists to experiment on less radical surgical techniques, which are commonly known as pelvic organ-sparing techniques. Historically, pelvic organ-sparing radical cystectomy (POSRC) was initially applied to younger and sexually active men [66]. It was not until the early 2000s that these particular techniques were first used in female patients, after several studies showed that sparing the urethra during RC is oncologically safe [67, 68]. In women undergoing RC, organ-sparing includes preservation of the uterus, anterior vaginal wall, fallopian tubes, and ovaries. It has already been reported that the sparing of the female internal genitalia has a positive impact on postoperative voiding pattern and surgical outcomes following an orthotopic bladder reconstruction [69–73]. Additionally, the preservation of the anterior vaginal wall or interposition of an omental flap between the vagina and the neobladder decreases the risk of a future fistula [52].

Nevertheless, the treating surgeon should never exaggerate with his efforts to achieve a better functional outcome at the expense of oncological results. In several studies including female patients undergoing anterior exenteration, it was found that the local invasion of internal genitalia ranges between 2.7 and 7.5% [74–80]. According to Djaladat et al. [80], the vagina is the most common location of invasion and it is commonly associated with tumors located at the base of the bladder. This means that the surgeon should perform a meticulous preoperative evaluation of the candidate for POSRC and be ready to abandon organ-sparing with the slightest suspicion of pelvic organ involvement, since a positive surgical margin at RC has been associated with a decreased 5-year survival of only 32% [81].

Urethra-Sparing Approach

Since the preservation of the urethra is a prerequisite for an orthotopic bladder reconstruction, a lot of research has been done in order to establish inclusion criteria for candidates for a

urethra-sparing approach. Until the 1990s, en bloc urethrectomy was a common practice for women because of the fear for urethral tumor involvement [82] and the presumption that the remaining urethra in case of partial urethrectomy lacks function [83]. Nowadays, an absolute indication for urethrectomy is a positive urethral surgical margin during RC. Several studies on female population showed that urethral involvement ranges from 2 to 16%, with the major risk factors being location of tumor in the bladder neck and invasion of the anterior wall of the vagina [35, 84, 85]. So far, the use of frozen section analysis intraoperatively has gained wide acceptance as a factor determining whether the surgeon should proceed with the initial plan of orthotopic reconstruction or instead perform a urethrectomy and cutaneous diversion [86–88]. In a study published by Osman et al. in 2012, frozen section analysis had a specificity of 99% and sensitivity of 90% in detecting urethral invasion when compared to the gold standard of the final histopathologic diagnosis [89], which confirms previous findings defining frozen section analysis as a valid method of identifying best candidates for orthotopic urinary diversion [36].

Functional Aspects of Orthotopic Neobladder Reconstruction in Females

Continence-Urinary Retention

The ultimate goal of an orthotopic bladder reconstruction is to provide a low-pressure space for urine storage, which allows the patient to maintain a satisfactory level of daytime and nighttime continence without the need for intermittent catheterization.

Based on data from early studies in female patients with orthotopic neobladder, more than 60% of them were able to void spontaneously after the surgery, while the rates of daytime and nighttime continence were 80% and 65–70% respectively [37, 90–94]. In 2012, Anderson et al. reported that daytime incontinence was associated with preceding hysterectomy, while the severity was closely related to the presence of stress incontinence prior to the surgery [95]. In fact, an analysis of urethral pressure profiles confirmed the hypothesis that patients without hysterectomy, thus with less distortion of pelvic anatomy, experience higher rates of continence when compared to their hysterectomized counterparts [96]. According to Rouanne et al., the only factor predicting daytime incontinence in a population of 41 female patients was found to be the age > 65 years [97]. While more than half of the patients experience nighttime incontinence in the immediate postoperative period [95], many of them are expected to have a significant improvement as the neobladder can store more urine over time [98]. Moreover, nerve-sparing techniques besides yielding better daytime continence rates are directly associated

to an improvement of nighttime continence by 5 to 25% [34, 99, 100].

When it comes to compare POSRC with the classical radical cystectomy, most authors agree that organ-sparing is linked to higher rates of continence [56, 72, 73, 94]. In two large series of patients who were offered an organ-sparing procedure, the rates of both day- and nighttime continence ranged between 80 and 100% [72, 73]. Nevertheless, we should have in mind that in the case of POSRC, most of the patients have an excellent baseline function and are highly motivated, which could be a bias when attempting a direct comparison with the classical RC.

Several studies conducted in animals stressed the importance of preserving the branches of the pudendal nerve and pelvic plexus in order to preserve the mechanism of continence [101, 102]. In 2007, Bhatta Dhar et al. emphasized the need for fine handling of autonomic nerves passing medial to the ureters and crossing the uterine and vaginal arteries as well the paravaginal region [99]. Of equal importance when performing a nerve-sparing cystectomy is the preservation of somatic nerve bundles originating from S2–4 levels of the spinal cord and running in close proximity with the inferior bladder pedicle [103].

One problem that is significantly more common among women with orthotopic neobladder is that of hypercontinence. In 2002, after performing video-urodynamic investigation in a female population with orthotopic neobladder, Ali-el-Dein et al. concluded that hypercontinence should be attributed to anatomical rather than functional reasons [104]. So far, a possible kinking of the vesicourethral anastomosis, strictures in the anastomosis, pouchocele, and dyssynergia of pelvic floor muscles have been proposed as possible mechanisms responsible for hypercontinence. Interestingly, Gross et al. characterized continence as a dynamic process after finding that many of the patients with urinary retention had a previous normal voiding period of 3–6 months. The above findings were attributed to neuropraxia causing denervation of the proximal urethra during the early post-operative period [96]. In a large retrospective study from Egypt, 16% of the study population reported postoperative hypercontinence [105]. On the contrary, there are other studies with much higher rates of hypercontinence among their patients, like that of Bartsch et al. who reported urinary retention affecting 45% of their study population [106]. Such heterogeneity in findings is most likely due to variable assessment of continence via a patient interview instead of using validated questionnaires. Finally, we should mention that several studies focusing on POPRC have reported rates of hypercontinence that range between 0 and 3% [72, 73, 107, 108].

Sexual Function

Sexual dysfunction is a major, although usually overlooked, factor causing significant distress in the lives of cystectomized patients [109–111]. Therefore, it is of utmost importance that the treating surgeon has a thorough discussion on the patient's expectations and on the realistic outcomes after a radical cystectomy [112], since most of sexually active women would like to preserve a good quality of sexual life after the operation [97]. It is self-understood that the surgeon is asked to achieve a balance between excellent oncologic outcomes and preservation of those anatomic structures that would guarantee a satisfactory sexual function.

For reference purposes, sexual dysfunction following RC in female patients is grouped into sexual pain disorders (vulvodynia, dyspareunia, vaginismus) and sexual arousal disorders secondary to devascularization of the clitoris [113]. In 2004, Volkmer et al. [114] retrospectively reviewed the data of 29 female patients with orthotopic neobladder and found that the ability to achieve and maintain lubrication was the function with the greatest decline in the postoperative period as assessed by the use of the Female Sexual Function Index (FSFI) [115]. During the same period, Zippe et al. [116] published the results of a study following up 34 cystectomized women for a median period of 24 months and concluded that the most common complaint was a difficulty in reaching orgasm, while more than half of the participants (52%) complained of significantly decreased sexual satisfaction. Similarly, two subsequent studies reported rates of sexual dysfunction ranging from 46 to 59% [117, 118]. The aforementioned disorders are mainly attributed to a possible injury of the neurovascular bundles which follow a course along the lateral vaginal wall [34, 119] or a severe devascularization of the clitoris during transection of the urethra [119, 120]. According to a study released by Bhatt et al., patients who underwent neurovascular preservation during orthotopic cystectomy reported better results in every aspect of sexual function when compared non-neurovascular preservation counterparts [121]. That means that it is really important to carefully dissect pelvic structures and avoid opening the endopelvic fascia in order to preserve most of the autonomic nervous fibers that are critical for the preservation of both continence and sexual function. Regarding POSRC techniques, Ali-El-Dein et al. showed that genital sparing provides better sexual outcomes without compromising oncological results [73]. Towards the same direction, it has been proposed that when the anterior vaginal wall is removed, a reconstruction should be performed by retubularization of the posterior vaginal wall or by using bowel segments, flaps of rectus abdominis and gracilis, or skin grafts to form a neovagina [114, 122–125]. Of all the above, it is easily understood that although oncologic

outcomes and safety are of paramount importance for these patients, efforts should not be precluded to improve their quality of life.

Risk of Urethral Recurrence

Since the advent of urethra-sparing techniques in women undergoing radical cystectomy, urologists have to confront the challenge of a new population of patients at risk for postoperative urethral recurrence (UR). According to a study published in 2013, male population is at a higher risk of developing UR [65]. This could be partially explained by the fact that the squamous metaplasia, present normally in postmenopausal women even up to the area of the bladder trigone, poses a barrier to the implantation of neoplastic urothelial cells.

A recent meta-analysis on a mixed population (both males and females) of 9498 individuals showed that pathological stage, non-orthotopic diversion, positive urethral margins, male gender, multifocality, and involvement of the bladder neck had a statistically significant positive correlation with the risk for UR [126]. Early series of female patients with orthotopic diversion report UR rates ranging from 0 to 2% [53, 56, 91, 127–129]. In 2012, a large single-institution study showed a UR rate equal to 0.8% after analyzing the data of 121 women with orthotopic neobladder and a median follow-up of 56 months [53]. In one of the largest series to date (1506 individuals) including both male and female patients, Boorjan et al. reported 85 cases of UR, which was three times more common in cutaneous when compared to orthotopic diversion [130]. A large multi-institutional study assessed the risk of UR in a female population of 297 individuals after orthotopic bladder reconstruction and showed that only 2.4% of them developed a UR during the follow-up period [131]. Authors of the same study reported that lymph node metastasis harbors a higher risk for overall but not for UR, confirming the assumption that patients with limited lymph node disease should not be denied the opportunity to receive an orthotopic diversion. Finally, with regard to the time frame and symptomatology, cases of UR most commonly present with discharge and pain [130], while most of them are diagnosed within 3 years after the surgery [132, 133].

Follow-Up

It is common sense that every patient describing suspicious signs and symptoms like urethral bleeding and pain after orthotopic neobladder reconstruction should receive prompt evaluation in order to exclude a possible recurrence of the disease. So far, due to the relative rarity of UR, the urologic community has not reached a consensus as to what a proper follow-up scheme should include [133]. Current literature

describes the urine cytology as the most common screening method for recurrence. According to Varol et al., cytology should be used twice a year for the first 2 years and once a year thereafter [134]. Another protocol suggests the use of urethroscopy, cytology, and urethral washings on a quarterly basis for 2 years and semiannually after that period [135]. Nevertheless, there are authors defying the diagnostic value of cytology in the case of urinary diversion [136], since deciduous and necrotic intestinal cells in the urine could be confused with neoplastic urothelial cells, while the time that the urine remains in the neobladder could also lead to anaplasia of normal urothelial cells. Moreover, it is critical to note that although urethroscopy and biopsy remains the gold standard for the diagnosis of recurrence, the use of urethroscopy as a screening tool on a regular basis is discouraged by many authors, since it does not seem to provide any benefit in terms of survival [133, 134, 137–139].

On the other hand, it is really important that the follow-up plan also includes periodic screening of the upper urinary tract, since 2–9% of patients undergoing radical cystectomy will develop metachronous recurrences after a median period of 24–41 months [140–144]. Although most of the patients are diagnosed with advanced disease predestinating a generally poor prognosis, an early detection in the context of a typical follow-up is associated with significantly higher survival rate [143]. Towards the direction of early diagnosis, most authors recommend periodic cytology [143, 145, 146], while others support the use of IVP at frequent intervals for all patients undergoing RC [147]. As expected, ureterorenoscopy with biopsy is the definitive method for the diagnosis of metachronous upper tract recurrence [148].

Finally, the urologist should also be aware of the medical complications following a radical cystectomy. This means that the follow-up should also include periodic screening for complications of chronic metabolic acidosis [149] as well as assessment for B12 deficiency after the second postoperative year [150].

Conclusions

Radical cystectomy has long since been established as the procedure of choice for muscle-invasive bladder cancer in both male and female patients. The reconstruction of the urinary tract is obviously a challenging process, fruit of the efforts of pioneer surgeons trying to maximize quality of life in this group of patients. So far, several studies confirmed that the orthotopic diversion is a safe option for carefully selected women as it combines high rates of day- and nighttime continence with exceptional oncologic outcomes. It is considered safe even for patients with limited lymph node disease and trigone involvement, as long as a preoperative biopsy of the bladder neck or an intraoperative frozen section analysis of

distal urethral margin rules out malignancy. However, it is really important that every patient besides possessing adequate manual dexterity to perform self-catheterization upon request should also consent to a rather demanding rehabilitation process. Special efforts have been described towards preservation of sexual function, with nerve-sparing techniques yielding promising results. For well-selected patients, sparing of internal genitalia seems to be oncological safe with acceptable results. Nevertheless, we certainly need properly designed prospective studies with adequate number of participants in order to safely conclude about a broader use of POSRC. Finally, a lot of work needs to be done towards establishment of a commonly accepted follow-up scheme in order to allow treating surgeons to be more confident when dealing with their patients during the postoperative period.

Compliance with Ethical Standards

Conflict of Interest Nikolaos Kalampokis, Nikolaos Grivas, Markus Ölschläger, Fahmy Nabil Hassan, and Georgios Gakis each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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