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REVIEW

Current status of laparoscopic and robot-assisted nerve-sparing radical cystectomy in male patients

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Abstract During radical cystectomy (RC), the neurovascular bundles are easily removed or damaged, leading to varying rates of incontinence and erectile dysfunction. The nerve-sparing technique was developed to preserve urinary and erectile function. The adoption of laparoscopic and robot-assisted technology has improved visualization and dexterity of pelvic surgeries, thus facilitate the nerve-sparing technique. Although nerve-sparing RC is technically similar with nerve-sparing radical prostatectomy, there are still some anatomical differences. There are mainly three different types of nerve-sparing techniques. Pelvic lymph node dissection (PLND) is another important factor to influence erectile function and urinary continence. Nerve-sparing laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) may be an optimal treatment choice in well-selected younger patients with low-volume, organ-confined disease. We should attempt to do, whenever possible, a nerve-sparing cystectomy at least on oneside. However, due to the need of a well-refined surgical technique, nerve-sparing LRC and RARC is now being performed only by experienced urological surgeons.

1. Introduction

Radical cystectomy (RC) with neobladder reconstruction still represents the first choice of treatment for both muscle-invasive and high-risk non-muscle invasive bladder cancer. In recent years, minimally invasive surgery such as laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) are performed more commonly at many centers with the technological advancements. The safety and

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potential advantages in terms of blood loss, analgesic requirements, improved cosmesis and quick recovery of LRC and RARC compared to open RC (ORC) have been well established [1—3]. At present, the ultimate goal of LRC and RARC is to remove the tumor completely while still maintaining erectile function and urinary continence at the same time.

During RC, particularly ORC, the neurovascular bundles are easily removed or damaged. Varying rates of continence and erectile function have been described after RC in the literatures as the degree of injury to the neurovascular bundles differed from technique to technique [4—6]. RC was then modified on the basis of this information to avoid injury to the neurovascular bundles and thus better preserve erectile function and urinary continence in patients undergoing this operation.

Although nerve-sparing RC has been proposed in the 1980s, progress of this procedure actually remained limited over the years [7]. However, nerve-sparing radical prostatectomy (RP), which is widely applied for more than 20 years, has achieved a consolidate position in routine clinical practice of every urologic unit [8]. Whether the nerve-sparing technique in prostatectomy could be applied in RC is still controversial. Firstly, the innervations of the neobladder after RC is different from original bladder after RP. Secondly, the voiding pressure of neobladder is much lower than original bladder as the former does not have detrusor muscle. In addition, the pelvic lymph node dissection (PLND) is much more extensive during RC than RP, thus higher branches of pelvic plexus may be injured. Moreover, as urothelial carcinoma is considered to be a potential lethal disease, nerve-sparing surgery may compromise the oncological safety.

Nevertheless, the adoption of laparoscopic and robot-assisted technology has improved visualization and dexterity of pelvic surgeries. Several studies with varying results after nerve-sparing LRC have been published [8—10]. Herein we review the current available literatures concerning the anatomic basis, nerve-sparing techniques, and therapeutic effects of nerve-sparing LRC and RARC in male patients. We aim to clarify the rational nerve-sparing techniques and establish the proper patient selection criteria.

2. Evidence acquisition

A literature search was performed in February 2016, using the PubMed and the Web of Science databases. The following terms and their combinations were searched in Title/Abstract: "nerve-sparing", "laparoscopic", "robot-assisted", "radical cystectomy" and "male". Case reports and non-English articles were excluded. Full text case series and their references were reviewed.

3. Evidence synthesis

3.1. New insights of the anatomical basis of nerve-sparing radical cystectomy

In 1982, Walsh and Donker [11] suggested that erectile dysfunction (ED) was caused by damage to the neurovascular bundles (NVB), which supply the corpora cavernosa. In 1983, Walsh et al. [12] found that the branches of pelvic nerve plexus which dominate corpora cavernosa locate laterally of the prostate capsule and Denonvillier's fascia. They spread along the post lateral part of the prostate and the urethra, the anterior wall of the rectum. These delicate nerves spread along with the blood vessels supplying prostate, seminal vesicle, bladder neck and urethra, and together they form the NVBs which are embedded in the dense fibrous connective fat tissue [12]. NVBs play an important role in erectile function and urinary control. By using cadaver models, Costello et al. [13] further detailed the precise anatomy of the NVBs because of their close relationship to the prostate and seminal vesicles. They identified three functional components of the NVBs. The first posterior and posterolateral component runs within Denonvillier's fascia and the pararectal fascia and innervates the rectum. The second lateral component supplies the levator ani. The third component cavernosal nerves and prostatic neurovascular supply, originally described by Walsh and colleagues [11,12], lie along the posterolateral surface.

Takenaka et al. [14] confirmed that branches of the hypogastric nerve and the pelvic splanchnic nerve are likely to interdigitate at multiple levels, showing spray-like arrangement without clear bundle formation. In addition, Lunacek et al. [15] demonstrated that during the growth of the prostate, the cavernous nerves running along the prostate are displaced more anteriorly and spread, thus forming a concave shape (like a "curtain") of the NVBs. Therefore, dissection of the NVBs has to start anteriorly to preserve all the nerve fibers that are spread along the surface of the lateral lobes of the prostate.

Although nerve-sparing RC is technically similar with nerve-sparing RP, there are still some anatomical differences. During RC, the lateral portion of each bladder vascular pedicle is stapled with a vascular staple load, and a second staple load is used to divide the proximal portion of the posterior pedicle. Clips and athermal dissection are used to divide the distal portion of the posterior pedicle, staying close to the seminal vesicles, thereby avoiding undue damage to the erectile nerves that are in close proximity lateral to the seminal vesicles [9,16]. In addition, a more extended PLND should be performed in RC compared with RP, and the erectile nerves are at risk of injury when the lymph nodes in the presacral and internal iliac area are being removed [17].

3.2. Different techniques of nerve-sparing radical cystectomy

There are mainly three different types of nerve-sparing techniques. Their main features and relative reports are described below (Table 1).

3.2.1. Nerve-sparing cysto-vesicle prostatectomy (NS-CVP)

This technique, adopted according to that initially described by Schlegel and Walsh [18] in 1987, includes the "en bloc" removal of bladder, prostate and seminal vesicles only leaving the NVBs intact. This is the most commonly used nerve-sparing procedure which was mainly carried out by a transperitoneal approach, using a combined ante-

Table 1 Functional outcomes of different techniques of nerve-sparing radical cystectomy.

Study	Technique	Patients	Follow-up	Urinary continence		Recovery of erectile function
				Daytime	Night time	
Kessler *et al.*, 2004 [5]	NS-CVP	Bilateral: $n = 38$ Unilateral: $n = 218$ Non: $n = 75$	24 months	Attempted NS: 96% Non NS: 88%	Attempted NS: 88% Non NS: 74%	Bilateral: about 58% Unilateral: about 32% Non: about 12%
Colombo *et al.*, 2015 [8]	NS-CVP CS-S SS-CP	35 36 19	24 months	88.6% 97.2% 94.7%	57.1% 83.3% 63.2%	Satisfactory erectile function rate (IIEF-5 $\geq$ 22) 28.6% 91.6% 84.2%
Canda *et al.*, 2012 [19]	NS-CVP	Bilateral: $n = 19$ Unilateral: $n = 1$ Non: $n = 1$	About 6 months	11 (73.3%) fully continent, 4 (26.6%) mild incontinence[a]	3 (20%) good, 4 (26.7%) fair and 8 (53.3%) poor[a]	—
Jacobs *et al.*, 2015 [21]	NS-CVP	20	37 months	At 12 months, average urinary function compared with baseline decreased by 13 $\pm$ 30 points		Average sexual function at 12 months, decreased by 23 $\pm$ 30 points
	CS-C	20	41 months	Decreased by 28 $\pm$ 33 points		Decreased by 1 $\pm$ 11 points
Ong *et al.*, 2010 [23]	SS-CP	Bilateral: $n = 14$ Unilateral: $n = 17$	18 months	27 out of 29 evaluable patients (93%)	19 out of 29 evaluable patients (66%)	15 out of 19 evaluable patients (79%) remained potent

NS-CVP, nerve-sparing cysto-vesicle prostatectomy, CS-S, capsule-sparing cystectomy, SS-CP, seminal-sparing cysto-prostatectomy; IIEF, International index of erectile function.

[a] Only 15 patients were available for postoperative urinary continence evaluation.

retrograde bladder dissection in combination with an inter fascial prostatectomy [8].

Kessler et al. [5] assessed factors influencing urinary continence and erectile function after RC and ileal orthotopic bladder substitution in 381 consecutive male patients. These patients were classified into three groups, without attempted nerve-sparing ($n = 75$), attempted bilateral nerve-sparing ($n = 38$) and attempted unilateral nerve-sparing ($n = 218$). After 2 years of follow-up, 58% patients in bilateral nerve-sparing group could achieve recovery of erectile function, 32% in unilateral nerve-sparing group, whereas only 12% in without attempted nerve-sparing group. This study also demonstrated that attempted nerve sparing and age younger than 65 years are associated with improved urinary continence [5]. Another study by Colombo et al. [8] reported 35 patients underwent NS-CVP, and their functional outcomes showed that 88.6% patients could achieve complete daytime urinary continence, and 28.6% patients could achieve satisfactory erectile function at 24 months after surgery. Canda *et al.* [19] reported 21 male patients underwent robot-assisted nerve-sparing RC with bilateral PLND and intracorporeal urinary diversion for BCa, 15 were available for postoperative urinary continence evaluation (four died and two were lost to follow-up). Among those, 11 (73.3%) were fully continent and four (26.6%) had mild urinary incontinence during the daytime. Therefore, daytime urinary continence seems to be very promising in male patients, although the follow-up is currently very limited in this study. On the other hand, for nighttime continence outcomes, three (20%) had good, four (26.7%) had fair and eight (53.3%) had poor UI. Patients with preoperative erectile function (IIEF score >7, $n = 11$) were instructed to use oral phosphodiesterase type 5 (PDE-5) inhibitors after removal of the urethral catheter postoperatively. However, only one patient used an oral PDE-5 inhibitor and clearly benefited from its use. Most of the present patients had a decreased libido postoperatively. Additionally, the follow-up is limited; therefore it is not easy to comment on postoperative erectile functional outcomes. The authors suggested that in longer term follow-up increased use of PDE-5 inhibitors and an increase in libido will result in better functional outcomes reflected by increased IIEF scores [19].

3.2.2. Capsule-sparing cystectomy (CS-C)

This technique, described by Colombo et al. in 2001 [20], includes a preliminary transurethral resection of prostate (TURP) and then entire removal of the bladder while leaving the prostate capsule, vas deferens, seminal vesicles and NVBs intact. Biopsies of bladder neck and prostatic urethra were obtained at the time of previous transurethral resection of bladder tumors. TURP is carried out together

with systematic prostate biopsies before RC in order to exclude prostate cancer [8].

Colombo et al. [8] reported 36 patients underwent CS-C, and their function outcomes showed that 97.2% patients could achieve complete daytime urinary continence, and 91.6% patients could achieve satisfactory erectile function at 24 months after surgery. Another randomized controlled trial by Jacobs et al. [21] compared CS-C *vs.* NS-CVP, with 20 patients in each cohort. Neither sexual function nor urinary continence could achieve significant differences between the two groups.

3.2.3. Seminal-sparing cysto-prostatectomy (SS-CP)

This procedure was firstly described by Puppo et al. [22] in 2008 and subsequently by Ong et al. [23] and Hautmann et al. [4] in 2010. The main steps include a blunt extraperitoneal antegrade dissection between the posterior bladder wall and the seminal vesicles up to the ejaculatory ducts and a retrograde intrafascial prostatectomy. With this procedure, seminal vesicles, vas deferens and NVBs were left intact into the pelvis.

Colombo et al. [8] reported 19 patients underwent SS-CP, and their functional outcomes showed that 94.7% patients could achieve complete daytime urinary continence, and 84.2% patients could achieve satisfactory erectile function at 24 months after surgery. Ong et al. [23] reported 31 patients (17 unilateral and 14 bilateral) underwent SS-CP. At last follow-up (median 18 months), 27 out of 29 evaluable patients (93%) had daytime continence and 19 out of 29 (66%) had nighttime continence. In terms of postoperative potency, 15 out of 19 evaluable patients (79%) remained potent. Hautmann et al. [4] reported nine patients underwent SS-CP, and four out of nine patients maintained spontaneous complete tumescence, and five patients had partial tumescence using sildenafil as a successful erectogenic aid.

3.3. The influence of PLND on erectile function and urinary continence

In the male, the inferior hypogastric plexus, or pelvic plexus, is responsible for the mechanisms of erection, ejaculation, and urinary continence [17]. The pelvic plexus lies within a fibrofatty, flat, rectangular, sagittally oriented plate between the bladder and the rectum [13]. PLND might be extended into this area. So, PLND is another important factor to influence erectile function and urinary continence. The pelvic plexus and particularly the erectile nerves are at risk of injury in a standard PLND during the medial dissection in the area of the internal iliac area and towards the bladder wall. A more extended PLND may damage branches of the pelvic plexus providing the cavernous nerves which contribute to erectile function. During extended PLND, the nerves are also at risk of injury at their origin in the presacral area and medial to the common iliac vessels [17]. In fact, significantly better recovery of erectile function was reported in men with negative lymph nodes compared to those with positive lymph nodes [5].

Studies have shown that extended PLND provides additional survival benefits for patients with pT3-4 disease, but not for patients with $\leq$pT2 disease [24]. In addition, super extended template up to the inferior mesenteric artery dose not provide survival benefit compared with extended PLND [25]. Nerve-sparing RC is usually restricted to $\leq$ cT2 patients, for whom standard PLND is enough. So para-aortic lymph nodes and presacral lymph nodes should not be removed during nerve-sparing RC, unless there is suspected lymphatic metastasis or palpable lymph nodes during surgery.

3.4. Surgical skills for nerve-sparing radical cystectomy

Many of the NVBs fibers are microscopic and cannot be identified during surgery. Those nerves are located postero-lateral to the seminal vesicles and very close to their tips. Gentle dissection of the seminal vesicles during RC may reduce the risk of injury to these nerves and, in consequence, may improve postoperative potency rates [26]. A high intrafascial release of the NVB is performed with a strict athermal technique using Hem-o-Lok clips and metal clips for hemostasis. It is important to not accidentally transect the NVBs during dissection close to the vesicles and the base of the prostate, where the dissection is in close proximity to the NVBs [16].

In addition to a nerve sparing technique, the management of the urethral sphincter mechanism at surgery is of utmost importance. The less damage done to tissue related to the sphincteric mechanism, the more likely patients will be continent. For rapid achievement of continence after surgery, the urethral supporting structures and a maximum of membranous urethral length should be preserved [5].

3.5. Surgical indications for nerve-sparing radical cystectomy

According to the above considerations, the nerve-sparing technique is important for both preservation of sexual function and urinary continence. Men with good erectile function and preferring to preserve their potency after RC may be candidates for preservation of NVBs. However, nerve-sparing RC requires dissection close to the bladder, exposing patients to the risks of positive surgical margins, which may compromise tumor control. Thus, patient selection is critically important when performing nerve-sparing cystectomy. The risks and benefits of nerve sparing should be assessed according to preoperative sexual function and disease burden.

Firstly, age plays a significant role in the recovery of erectile function after RC. Schoenberg et al. [27] demonstrated that the overall potency of their cohort was 47%. After broken down by decades, men in their 40s, 50s, 60s, and 70s had potency rates of 62%, 47%, 43%, and 20%, respectively. Kessler et al. [5] also showed significantly better effects of the open nerve-sparing approach on men younger than 65 years compared with those who were older. Patient with a younger age may achieve better outcomes in term of sexual function. In addition, the clinical tumor stage should be restricted within T2 without evidence of disease at bladder neck and a negative urethral margin at the time of surgery is mandatory. Thirdly, we should exclude patients probably with prostate cancer. Prostate specific antigen (PSA) $<$ 4.0 ng/mL with normal digital rectal examination (DRE) and normal transrectal ultrasound (TRUS) are required. Additional pre-operative criteria include sexually

potent before surgery and suitable for orthotropic neobladder.

With the purpose of preservation of sexual function, rectal function, and improving urinary continence in patients with or thotopic bladder substitutes, we should attempt to perform at least one side nerve-sparing cystectomy [28]. Unilateral nerve-sparing should be considered on the non-tumor-bearing side. Bilateral nerve-sparing may be considered in patients with high risk non-muscle invasive disease or invasive tumors at anterior wall or dome of the bladder [28].

4. Conclusion

Nerve-sparing RC is beneficial for both preservation of sexual function and urinary continence according to current studies. Nerve-sparing LRC and RARC may be an optimal treatment choice in well-selected younger patients with low-volume, organ-confined disease. We should attempt to do, whenever possible, a nerve-sparing cystectomy at least on one side. However, due to the need of a well-refined surgical technique, nerve-sparing LRC and RARC is now being performed only by experienced urological surgeons.

Conflicts of interest

The authors declare no conflict of interest.

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