Review Article

Standard cystectomy fits all: truth or myth?

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Abstract: Radical cystectomy (RC) with pelvic lymph node dissection (PLND) followed by urinary diversion is the treatment of choice for muscle-invasive bladder cancer (BC) and non-invasive BC refractory to transurethral resection of the bladder (TUR-B) and/or intravesical instillation therapies. Since the morbidity and possible mortality of this surgery are relevant, care must be taken in the preoperative selection of patients for the various organ-sparing procedures (e.g., bladder-sparing, nerve sparing, seminal vesicle sparing) and various types of urinary diversion. The patient's performance status and comorbidities, along with individual tumor characteristics, determine possible surgical steps during RC. This individualized approach to RC in each patient can maximize oncological safety and minimize avoidable side effects, rendering 'standard' cystectomy a surgery of the past.

Keywords: Personalized cystectomy; bladder cancer (BC); urinary diversion; pelvic lymph node dissection (PLND); nerve sparing; seminal vesicle sparing

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Introduction

Bladder cancer (BC) is a significant global health threat (1) with more than 30,000 deaths per year (2). It is also one of the most costly cancers from diagnosis to death (3). Pelvic lymph node dissection (PLND) and radical cystectomy (RC) followed by urinary diversion is established as the gold-standard treatment for BC invading the bladder muscle (MIBC) and for non-muscle-invasive BC refractory to transurethral resection of the bladder (TUR-B) and/or to intravesical instillation therapies such as bacillus Calmette-Guérin (BCG) and mitomycin (4-6). Removal of the bladder, however, leads to significant perioperative and postoperative morbidity, with a 90-day complication rate as high as 50% to 70%, and thus can negatively impact the patient's quality of life (7-9). Performance status (10), biological age, and preexisting comorbidities (best assessed by the Charlson Comorbidity Index (10,11) are important factors affecting the choice of treatment and the risk of complications after surgery. An individualized approach to therapy is therefore necessary in each patient to maximize oncological safety and minimize the risk of avoidable side effects. The keys to achieving these goals are paying close attention to patient selection before surgery and to specific details during surgery, and providing meticulous postoperative care, instruction, and follow-up to help patients cope with their new urinary diversion. Prior to RC, therefore, several factors must be considered in order to maximize each patient's benefit and to reduce potential harm from this demanding surgery.

Is bladder sparing a viable alternative to RC in MIBC?

The goal of bladder preservation in MIBC is to avoid morbidity and potential mortality in RC without compromising oncological outcomes. Several bladder-sparing options exist: TUR-B alone, partial cystectomy, radiotherapy, chemotherapy alone, or multi-modality therapy. Among these options, trimodal therapy involving maximal TUR-B followed by cisplatin-based chemotherapy and radiotherapy is the most widely accepted strategy (12). While bladder sparing is the only option in patients who are unfit for surgery due to medical comorbidities [with poor 4-year overall survival (OS) rates of 30-42% (13-15)], its value in medically operable patients has not yet been

defined due to the lack of randomized controlled trials comparing RC with bladder-sparing therapies. However, the reported 5-year cancer-specific survival (CSS) rates of 50% to 60% (16-18) and 5-year OS rates of 36% to 52% (18-21) are poor when compared to the cystectomy outcomes in centers of excellence reporting 5-year CSS of 83.5% (22) and 5-year OS of 68% (23). Moreover, patients fit for surgery and treated by bladder preservation are rigorously selected, with exclusion criteria such as hydronephrosis, carcinoma in situ (CIS), or impossibility to perform a maximally safe TUR-B, and thus are positively selected compared with the population undergoing primary RC (12). Bladder sparing in medically operable patients, therefore, does not seem to be an equivalent treatment option. In fact, bladder-sparing procedures may only delay RC. Since studies have shown worse survival rates if RC is delayed for more than 3 months (unless the delay was for neoadjuvant chemotherapy) (24,25), prolongation of the interval between diagnosis and RC due to attempted bladder sparing may negatively impact treatment outcome.

Does anesthesia impact outcomes after RC?

One of the key factors affecting optimal outcome following RC is individualized optimization of anesthesia aimed at reducing blood loss, lowering postoperative complications, and improving functional results of orthotopic bladder substitution (26-29). These goals can be achieved mainly through the use of continuous administration of norepinephrine peri- and postoperatively, thus facilitating restrictive deferred intraoperative fluid management (30,31). Additionally, thoracic epidural analgesia leads to a need for minimal opioids peri- and postoperatively, thus accelerating recovery of bowel function and postoperative recovery (29) and reducing postoperative catabolism (32), pulmonary complications due to better diaphragmatic function (27), postoperative stress/inflammatory response, and cardiovascular morbidity in high-risk patients (28,33). It is important, however, to screen patients for contraindications for thoracic epidural analgesia, such as bleeding disorders or anticoagulation, since the possible complications (e.g., neuraxial hematoma and abscess) can be serious, inflicting permanent harm such as paraplegia. If a patient has contraindications for thoracic epidural analgesia, less effective alternatives such as preperitoneal or transversus abdominis plane blocks can be considered (34). In conclusion, individualized anesthesia is part of personalized cystectomy and its importance should not be underestimated.

Is pelvic lymphadenectomy mandatory—and how extensive should it be?

To draw the conclusions first: any kind of PLND is better than none, an extended PLND is better than a limited, but a super-extended has no benefit over an extended PLND (35). Already in 1982 DG Skinner reported that a meticulous PLND can make a difference, namely by decreasing the rate of local recurrence and even achieving a cure in some lymph node (LN)-positive patients (36). However, it is the patient with limited, in most cases microscopic, involvement of a few LNs who has the best chance of long-term survival (36).

Although recent dynamic LN mapping studies revealed that lymphatic drainage of the bladder is complex and individually coined, PLND should be performed bilaterally because cross-over lymphatic drainage is common (40%) (37,38). Roth *et al.* (37) provide strong evidence that a limited PLND (encompassing only the external iliac region and obturator fossa) removes only about 50% of all primary lymphatic landing sites compared to a 90% nodal clearance rate with an extended PLND (up to the mid-upper third of the common iliac vessels and including the areas medial and lateral to the internal iliac vessels). This finding was confirmed by a survival analysis in a cohort of 668 patients operated at two academic urology centers (39). The use of an extended PLND resulted in a more than twofold better 5-year recurrence-free survival rate for patients with ≤ pT3 pN0-2 disease compared to patients in whom the LNs were removed only in a limited field (extended PLND 49%, limited PLND 19%) (39). It could be concluded from this that the higher the proximal template (i.e., the more extended the PLND), the better the outcome. But is it really worthwhile to remove the remaining 8% to 10% of potential lymphatic landing sites located cephalad to the mid-upper third of the common iliac vessels (37)? In fact, a super extended PLND did not show a survival benefit compared to an extended PLND (40) —most probably because the occurrence of positive LNs higher than the endopelvic region is characteristic of systemic disease which cannot be cured by more extended surgery. A superextended PLND is, however, associated with higher morbidity, especially due to the possible harm to sympathetic nerve fibers crossing the bifurcation of the aorta. The mandatory extent of PLND has further been investigated by Roth *et al.* (38). In another dynamic mapping study they could show that the lateral bladder wall does not have lymphatic drainage to the contralateral internal iliac region, which is—on the medial side—another potential spot for harm to the autonomic nerves (38). The latter observation

was confirmed by a patho-anatomical study by Kiss *et al.* (41), who did not find metastases in contralateral internal iliac lymph nodes in unilateral tumors of the lateral bladder wall. Therefore, the location of the tumor within the bladder appears to influence the extent of lymphatic drainage, thus underscoring the need to individually modify the extent of PLND as part of RC.

Should nerve sparing be attempted?

Already in 1982, Walsh and Donker (42) pointed out that preservation of the dorsolateral neurovascular bundle during prostatectomy is important to avoid erectile dysfunction and improve postoperative continence. The significant aggressiveness of BC together with the decades-long limited knowledge regarding the relevant basic neurofunctional anatomy may account for the failure to further evaluate nerve sparing procedures during RC. Autonomic nerves comprised of sympathetic and parasympathetic fibers pass the pelvic plexus (43,44). The parasympathetic system is thought to be responsible for relaxation of the proximal urethra and erectile function, while the sympathetic system controls the tonus of the urethra at rest (42,45-48). Autonomic denervation has been shown to affect the proximal part of the sphincter plexus, causing intrinsic sphincter deficiency (49). Clinical data showing a positive influence of nerve-sparing prostatectomy on erectile function and urinary continence accord with intraoperative findings after electrical stimulation (50). These findings have finally found application in attempts at nerve-sparing during RC as a means of maintaining or improving urinary continence in patients with orthotopic bladder substitution (51). Autonomic nerve sparing, however, not only improves the chance of continence after orthotopic bladder substitution, but also has a positive effect on postoperative erectile function (52,53). While the benefit of autonomic nerve sparing for continence in orthotopic bladder substitution may be greater in the elderly due to their generally weaker urethral sphincter complex, it appears to be even more efficient if performed bilaterally. However, individual factors such as the extent and location of the BC within the bladder, and thus the feasibility of nerve sparing from an oncological point of view, determine if unilateral (on the side contralateral to the tumor) or even bilateral nerve sparing may be attempted.

Should seminal vesicles be preserved?

In men, the role of seminal vesicles in sexual behavior has not yet been documented. However, recent results of mouse experiments suggest that seminal vesicles have a significant effect on the sexual activity of male mice (54). Together with clinical observations that men report stronger sexual desire after seminal vesicle-sparing RC than after removal of the seminal vesicles, this finding raises the question whether seminal vesicle removal at RC should be mandatory. Several reports on simultaneous postero-inferior prostate capsule, vasa deferentia, and seminal vesicle preservation in RC with orthotopic bladder substitution found a postoperative improvement in sexual function and urinary continence (55,56). Minimizing surgical dissection in this manner reduces potential harm to the autonomic nerves, especially the autonomic nerve fibers of the pelvic plexus. The long-term oncological and functional results in these reports (55,56) were excellent (daytime continence and potency rates of up to 95%) and clearly superior to previously reported outcome data from a large series of men undergoing ileal bladder substitution following RC, in which 22% reported having erections without and another 15% with medical assistance (57). However, a meta-analysis of seven prostate-sparing RC series comprising 306 patients with organ-confined (≤ pT2) BC found a systemic recurrence rate twice as high as for standard RC (58). There is controversy therefore regarding the oncological safety of prostate- and/or seminal vesicle-sparing RC. The controversy is even greater because the rate of concurrent prostate cancer and/or occult transitional cell carcinoma (TCC) of the prostate is as high as 48% (59-62), which is especially concerning since local recurrence of BC is lethal in most patients. BC location in the bladder neck or trigone as well as CIS were found to be associated with occult TCC in the prostate (60). As a consequence of the high prevalence of occult prostatic malignancies, RC with removal of the entire prostate but sparing of the seminal vesicles (together with the prostate capsule adjacent to the neurovascular bundle) was introduced. Recently published data show good oncological control and favorable functional outcomes (63). However, maximal local cancer control requires a restrictive selection of patients; patients should not have BC on the side ipsilateral to where seminal vesicle sparing is attempted, or on the trigone/bladder neck. Furthermore, prostate resection biopsies must be free of TCC. For BC located solely in the anterior bladder wall, bilateral seminal vesicle sparing is recommended.

In conclusion, seminal vesicle sparing is an increasingly popular option for individualizing RC to maximally improve postoperative functional outcomes and oncological safety,

especially in patients with a strong desire to preserve libido and potency and with favorable tumor characteristics.

What type of urinary diversion—continent or incontinent?

Careful selection of patients is crucial for successful urinary diversion of whatever type (incontinent, continent cutaneous, orthotopic, rectosigmoid). Age is not a factor affecting whether a diversion can be done or not (64). The choice of urinary diversion depends mainly on performance status and preexisting comorbidities (65). All types of orthotopic bladder substitution by intestinal segment require careful patient selection. Preoperative biopsies from the distal prostatic urethra (male) or the bladder neck (female) should be negative except for CIS, which can be treated postoperatively by BCG instillations (66). Evidence of BC in these biopsies would prohibit sparing of the urinary sphincter from an oncological point of view, which is indispensable in continent orthotopic urinary diversions. Additionally, candidates for orthotopic substitution should be continent, physically and mentally able to adapt to and function with an orthotopic bladder substitute, and must be willing and able to participate in an active postoperative reeducation program and adhere to a strict follow-up regimen (57). A glomerular filtration rate of at least 50 mL/min is mandatory for continent reservoirs since the kidneys must compensate the metabolic acidosis following incorporation of bowel in the urinary tract (67). Candidates for a continent urinary diversion should also have normal liver function (risk of hyperammonemia if the reservoir becomes infected), and should not have undergone any previous major bowel resection in the ileocoecal area (risk of vitamin B12 deficiency) (67-69).

While the ileal conduit and cutaneous diversions are established options for urinary diversion (although both have considerable complication rates), orthotopic bladder substitution is now commonly used in both sexes (65,70,71). The type of urinary diversion does not affect oncological outcome (65). Therefore, factors such as patient comorbidities and tumor characteristics determine the type of urinary diversion, which in turn greatly influences how RC is performed (e.g., nerve sparing, seminal vesicle preservation).

Open or (robot-assisted) laparoscopic cystectomy?

Robot-assisted RC has emerged as an alternative to open RC based on its potential to reduce blood loss, the transfusion rate, and the need for postoperative analgesia, and patients' quicker recovery of bowel function (72-74). Since the first experience with robot-assisted RC was reported in 2003 (75), a number of investigators have reported case series (76-79). However, the absence of long-term oncological and functional outcome data, and a possible selection bias in laparoscopic and robot-assisted laparoscopic RC series make it difficult to compare open versus laparoscopic and robot-assisted laparoscopic RC. Although feasible, laparoscopic and robot-assisted laparoscopic RC is thus still considered experimental (65). Open RC therefore remains the gold standard treatment for MIBC and for non-muscle-invasive BC refractory to TUR-B and/or intravesical instillation therapies due to the thorough characterization of long-term oncological outcomes (80).

Conclusions

Every patient who needs RC must be offered the best possible cancer surgery. This surgery, however, should not be the cause of unnecessary comorbidities. For this reason, each patient should be carefully assessed prior to RC with regard to key factors such as performance status, comorbidities, indications for or against specific procedures, and individual tumor characteristics. During RC close attention must be paid to those surgical details which vary from patient to patient, rendering every cystectomy an individual 'work of art'.

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Footnote

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