

# Open radical cystectomy: still the gold standard for muscle invasive bladder cancer

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## Abstract

**Introduction** Muscle invasive bladder cancer is an unforgiving disease, and if untreated, it leads to death within 2 years of the diagnosis in >85 % of the patients. Long-term oncologic efficacy remains the ultimate standard that all procedures have to be measured by. In the past decades, open radical cystectomy (RC), extended pelvic lymph node dissection (PLND), and urinary diversion have been established as the gold standard. In the last few years, however, growing attention has been set on robotic-assisted radical cystectomy (RARC).

**Results** Even in the very long term, open RC has good oncological results and if an ileal neobladder is performed excellent functional results. Follow-up of patients after open RC exceeds more than a decade which is unsurpassed by any other technique. Its outcomes have been proven to be durable and cost-effective. Least perioperative complications as well as best oncological and functional results can be achieved if open RC and urinary diversion were performed in a high-volume hospital by high-volume surgeons and an experienced team.

**Conclusions** Despite upcoming new technologies such as RARC, open RC following extended (PLND) remains the gold standard treatment for high-grade muscle invasive bladder cancer.

**Keywords** Open radical cystectomy · Muscle invasive bladder cancer

## Introduction

Bladder cancer is the ninth most common cancer worldwide. More than 330,000 new cases are diagnosed each year, and more than 30,000 suffer death each year. At present, approximately 30 % of patients have already muscle invasive disease [1]. Muscle invasive bladder cancer (MIBC) is an unforgiving disease, and if untreated, it leads to death within 2 years of the diagnosis in >85 % of the patients [2].

Despite upcoming new technologies, open radical cystectomy (RC) following extended pelvic lymph node dissection (PLND) remains the gold standard treatment for high-grade MIBC and for non-muscle invasive bladder cancer refractory to TUR-B and intravesical instillation therapies [3, 4].

Although morbidity and mortality of RC have significantly decreased over the past years, removal of the bladder still leads to significant peri- and postoperative complications with complication rates within the first 90 days after surgery of 50–64 % [5–7] irrespective of the surgical approach. Anyhow, an aggressive surgical treatment provides the best long-term survival rates and lowest local recurrence rates [8, 9] and thus has to be standard of care. Several important patient-dependent factors, such as performance status, biological age, and preexisting comorbidities [10–12], are affecting the choice of treatment and the risk of postoperative complications and outcome. Anyhow, best functional and oncological results surely can be achieved if RC and urinary diversion were performed in a high-volume hospital with at least 40–50 cases annually by high-volume surgeons and an experienced team [13].

## Surgical technique

Standard technique of RC includes removal of the bladder (including the perivesical fat) along with the prostate and seminal vesicles in men and the uterus, tubes, and ovaries in

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women [14–16]. Over the last years, several modifications of this standard technique have been developed mainly to improve postoperative continence in patients with an orthotopic bladder substitute and sexual function.

#### *Nerve sparing*

Whenever possible, without compromising oncological outcome, nerve sparing should be performed at least on one - the non-tumor-bearing- side. In men, nerve sparing means preservation of the neurovascular bundles dorsolateral to the prostate as well as more cranially in the angle between the prostate, bladder base, and seminal vesicle by ligation and division of the dorsomedial pedicle close to the seminal vesicles [17]. In women, the dorsomedial pedicle is transected close to the bladder wall further on the side of attempted nerve sparing, and the vaginal wall dissection at the cervical level is in the anteroventral plane of the vagina, that is, at the 2 or 10 o'clock position [14].

It has been shown that the attempt of nerve sparing—in addition to other factors such as age at surgery and careful preparation of tissue related to the sphincter mechanism [17]—is an important factor influencing continence after RC and ileal orthotopic bladder substitution [17–19]. In men, nerve sparing also appears to safeguard erectile function by preserving parasympathetic fibers passing the plexus pelvis [20–22]. Anyhow, nerve sparing is not only of utmost importance in terms of better functional results of subsequent orthotopic bladder substitution or better recovery of sexual function, but also as a means to avert potential problems of defecation [23].

#### *Seminal vesicle sparing*

The primary goal of seminal vesicle sparing RC was to improve the functional outcomes for urinary continence and potency. In younger patients and patients with a strong desire to preserve libido and potency, this is of special interest. Due to the better exposure of the vesicoprostatic angle (between the bladder wall, seminal vesicles, and base of the prostate) sparing of the neurovascular bundles and the pelvic plexus is made easier [24]. In a mouse experiment, Birkhauser et al. [25] showed that seminal vesicle sparing may also positively influence sex drive, and so the authors stated that this should be an additional incentive to question the need for standard seminal vesicle removal during RC. Ong et al. [26] report in their study a rate of complete daytime continence of 93 % and of nighttime continence of 66 % after a median follow-up of 18 months in patients who received seminal vesicle sparing at least on one side.

In other series investigating prostate sparing RC, daytime and nighttime continence rates (>90 % and >80 %, respectively) are even more encouraging [27].

Potency rates after seminal vesicle sparing were 79 % in the above-mentioned series [26] with half of the patients needing medical aid. These potency rates are superior to the previous reported 22.4 and 15.4 % without and with medical assistance, respectively, in a large series by Studer et al. [28]. However, oncological safety of prostate and/or seminal vesicle sparing is still under debate because of the high rate—up to 48 %—of concurrent urothelial carcinoma in the prostatic duct or adenocarcinoma of the prostate in patients with MIBC [29–32]. In about 40 % of RC specimens, prostate cancer is incidentally detected of which approximately 20 % are clinically significant. Data on seminal vesicle involvement are scarce; however, in a recent trial in 24.5 % of radical prostatectomy specimen, extraprostatic disease (not necessarily into the seminal vesicles) has been found [33]. This high number has to be kept in mind if considering seminal vesicle sparing. Despite favorable functional outcomes after prostate and/or seminal vesicle sparing RC, the indication has to be made conservatively and based on oncological concerns.

#### *Uterus sparing*

If no tumor can be found in the trigone or the dorsal or lateral bladder wall, the uterus and ovaries can be spared. This might improve continence due to the better preservation of the autonomic nerves which run closely along the lateral aspect of the cervix uteri. However, these women have to be strictly selected because of the fact that in the female pelvis, there is no anatomical barrier between the posterior bladder wall and the anterior vaginal wall. The lymphatic drainage which runs from the bladder neck to the internal iliac lymph nodes along the lateral vaginal walls exposes women to a higher risk of continuous or lymphatic tumor spread or by continuity [34].

Although a rare condition, concomitant tumors of the vagina or the cervix uteri are found in 5–6 % of the patients [35, 36] and thus have to be kept in mind.

#### *Lymph node dissection*

Two-thirds of the patients with MIBC and lymph node (LN) metastases (pN+) who receive a RC and PLND will die from cancer [9]. On the other hand, Skinner has shown that 30 % of patients with only a few LN metastases can be cured by a meticulous LN dissection [37]. Already more than 30 years ago but still up to date, Skinner stated that it is the patient with limited or even microscopic LN involvement who profits the most from a meticulous PLND [37].

Given that both RC and PLND are important hallmarks in surgical treatment, there still is controversy regarding the extent of the PLND template—especially the proximal boundaries.

As Roth et al. [38] showed in their multimodal LN mapping study crossover lymphatic drainage can be seen in 40 % of patients, thus PLND should always be performed bilaterally.

Further, limited PLND only in the external region and the obturator fossa would remove only 50 % of all primary lymphatic landing sites. This is significantly less compared to a 90 % nodal clearance when an extended PLND is performed [38]. In a survival analysis of two academic centers, 5-year recurrence-free survival was significantly better when extended PLND was performed compared to limited PLND (49 vs. 19 %, respectively) in patients with  $\leq pT3pN0-2$  disease [39]. As a logical consequence, one might conclude that the higher the proximal border of the PLND, the higher the survival rates. On this background, Zehnder et al. [40] examined in their comparative RC series whether an additional survival advantage could be achieved by expanding the template to the inferior mesenteric artery (IMA) takeoff. Surprisingly, they found similar survival and recurrence rates in pT2–3 cN0 cM0 BC patients receiving a meticulous extended PLND up to the mid-upper third of the common iliac vessel as compared to a super-extended template up to the IMA. This is most probably because the occurrence of LN metastases higher than the endopelvic region is characteristic of systematic disease which cannot be cured by extensive surgery [12]. This was the first time it could be shown that more is not always better in PLND for BC. As a consequence, PLND up to the mid-upper third of the common iliac vessels seems to provide local and systemic oncological control and should be considered standard treatment in all patients undergoing RC.

In the future, individualized PLND might be an option in a highly selected group of patients with strictly unilaterally localized bladder cancer. In this highly selected group, Roth et al. [38] showed in their mapping study and Kiss et al. confirmed in their pathoanatomical study that no lymphatic drainage to the contralateral internal iliac region—a region of special interest in nerve sparing—can be found.

So in conclusion, any kind of PLND is better than none, an extended is better than a limited, but a super extended has no explicit benefit over an extended PLND as this might represent systemic disease [12, 41].

## Oncological outcomes

Long-term survival after RC for MIBC depends on several histopathological parameters as well as on variables such as patient-related factors, extent of PLND, treatment delay or hospital and surgeon operative case load.

The follow-up time of open RC exceeds more than a decade which is unsurpassed by any other surgical modality whether laparoscopic or robotic RC. Long-term oncologic efficacy remains the ultimate standard that all procedures have to be measured by. In large single-center and multicenter series, 5-year recurrence-free (RFS) and 5-year cancer-specific survival rates (CSS) vary between 58–68 % and 59–66 %, respectively [8, 9, 42]. Hautmann et al. [43] reported 10-year overall survival (OS) in a surgery-only group (without neoadjuvant or adjuvant chemotherapy) of 44 % which is comparable to Stein's reported 10-year OS rates in a mixed cohort including also chemotherapeutically treated patients [9] (Table 1). When stratified into subgroups, long-term survival is best in patients with organ-confined, pathologically LN-negative disease, followed by patients with extravesical, yet LN-negative disease. Finally, patients with LN metastases have the poorest long-term outcome [8, 9, 44, 45].

## Robotic-assisted radical cystectomy

After successful adoption of minimally invasive techniques in kidney surgery and prostate surgery which is widely used and even has completely replaced open surgery in some places, in the last few years growing attention has been set on robotic-assisted radical cystectomy (RARC). In 2010, 13 % of all cystectomies in the US were already performed robotically assisted [46], and numerous reports have

**Table 1** Oncological outcomes and lymph node status of open RC

Series	Madersbacher et al. [8]	Stein et al. [9]	Hautmann et al. [43]	Shariat et al. [42]	Ghoneim et al. [3]
Patients ( <i>n</i> )	507	1054	1100	888	2720
CSS (%)	—	—	67	66	—
RFS (%)	73 <sup>a</sup>	68	66	69	56
RFS 10 years (%)	50 <sup>a</sup>	68	66	52	50
OS (%)	62 <sup>a</sup>	69	44	—	—
Median follow-up (months)	45	122	38	39	43
pN+ (%)	24	24	18	23	20

CSS cancer-specific survival, OS overall survival, RFS recurrence-free survival

<sup>a</sup> In organ-confined LN-negative patients

documented the feasibility and equal or even improved perioperative outcomes compared to the open approach [47–49], although a selection bias toward younger and fitter patients with more favorable pathological features is evident in trials investigating oncological or functional outcome in patients receiving RARC. In a recently performed prospective randomized single-center trial by Bochner et al. [50], non-inferiority of perioperative outcome after RARC was shown in a carefully selected, rather low-risk group of patients, compared to open RC in an experienced high-volume cancer center. They found complication rates out to 90 days after surgery of 62 and 66 % in the RARC and open RC arms, respectively. Furthermore, they found similar quality of life 3 and 6 months after surgery in both arms as well as equal costs. Although, as mentioned above, again there was a clear selection bias toward low-risk patients, this trial failed to confirm previously reported patient benefits of RARC.

The CORAL trial is an early phase randomized three-arm trial with a small sample size concentrating on early complication rates, with major drawbacks [51]. 164 patients were assessed for the trial, but only 60 patients were randomized. This fact raises the concern of selection bias that the other 100 patients were higher-risk patients which would have possibly negatively influenced the outcome of the trial. Furthermore, in our opinion, according to the data presented in the CORAL trial, the conclusion that conventional laparoscopy offers the best results is not valid due to the fact that 15/20 patients of the laparoscopy group had to be converted to open RC or RARC.

In a systematic review, the RARC Pasadena Consensus Panel stated that RARC can be performed safely, although there is a lack of solid high-quality data [52].

Anyhow, and this is probably most important, real long-term data on oncological and functional outcomes of RARC in a significant number of patients are not available to date. Although Raza et al. [53] report in the largest multiinstitutional series on long-term oncological outcome after RARC to date—702 patients recruited in 37 institutions—rather encouraging results with 5-year RFS, CSS, and OS of 67, 75, and 50 %, respectively, in a well selected group of patients in which 62 % were staged  $\leq pT2$ . Despite these data of similar outcomes for RARC compared with open RC, the true oncologic effectiveness will not be determined until well-designed randomized controlled trials on long-term outcomes are available [54]. This even more in light that other groups found different recurrence patterns after RARC with a frightening high rate of peritoneal carcinomatosis in more than every fifth patient with recurrence after RARC [55]. In this interesting study, the authors detected no differences in local recurrences within 2 years of surgery in open RC and RARC (23 and 18 %, respectively), but they found that distant

recurrences are more frequent (23 vs. 15 %, respectively) and most importantly, they found peritoneal carcinomatosis in 21 % of recurrences after RARC compared to 8 % after open RC, although the distribution of pathologic stage was unbalanced between the groups in favor of RARC.

Another important aspect that has to be kept in mind nowadays is the costs of the surgical procedure. Although some cost analyses even suggest a benefit in favor of RARC over open RC [56], the lion's share of cost analyses demonstrates an increase in total costs for RARC [46, 50, 57].

In a recently performed systematic review—again by the RARC Pasadena consensus panel—the group concluded that oncologic and functional data from RARC remain immature, and long-term studies are needed. Although cumulative analyses demonstrated that LN yields and positive surgical margins (PSM) rates were similar between RARC and open RC, conclusive long-term survival outcomes for RARC are limited [58]. Perhaps the upcoming prospective RAZOR (randomized open vs. robotic cystectomy) trial [59] helps to light up the question whether RARC is really able to compete with open RC. Although feasible and in some areas even with encouraging results, RARC is still considered experimental [4]. In our opinion for a new surgical procedure it is not enough to be just feasible. It has to be at least equal regarding oncological safety compared to the standard procedure. Above that, it has to have major advantages for the patients to favor it over a well-established surgical procedure. The mistakes of 30 years ago should not be repeated by minimal invasive surgeons. Therefore, open RC still remains the gold standard in patients with high-grade muscle invasive bladder cancer and for non-muscle invasive bladder cancer refractory to TUR-B and intravesical instillation therapies [3].

## Urinary diversion

The choice of urinary diversion depends on different factors and requires careful selection of patients. The choice of urinary diversion not only depends on patients' preference and performance status or comorbidities but is also influenced by the training and experience of the surgeon and the availability of specially trained staff to assist with perioperative management and patient education [60]. In so-called RC pioneering institutions, orthotopic reconstruction is performed in 39–76 % of patients and has become the procedure of choice [60]. This, however, is not reflective of the daily routine in most urological departments. The ileal conduit continues to be the most common form of urinary diversion and occurs in up to 80 % of procedures in the US [61], and this might be influenced by robotic surgery as the urinary diversion is another complex surgical part of the intervention. Indeed,

**Table 2** Functional outcomes of open RC and OBS

Series	Studer et al. [28]	Abol-Enein and Ghoneim [69]	Hautmann et al. [70]	Stein et al. [71]
Patients ( <i>n</i> )	482	450	363	209
Women ( <i>n</i> )	40	97	0	40
Daytime continence (%)	92	93	84	87
Nighttime continence (%)	79	80	66	72
Hyper-continen <sup>a</sup>	7	—	4	25
Follow-up (months)	32	38	57	33

<sup>a</sup> Patients dependent on intermittent self-catheterization or indwelling catheter

there is a justified fear that due to the more demanding surgical procedure, continent urinary diversions will lose out to the much less demanding ileal conduit in the era of RARC. There is still ongoing debate which type of urinary diversion offers the best quality of life [62, 63], and the choice has to be tailored for each patient because the literature is insufficient to recommend one form of diversion over another.

Long-term functional results of ileal orthotopic bladder substitution after open RC are excellent and well documented (Table 2). In men, daytime and nighttime continence can be achieved in 92 and 76 % of cases, respectively [17]. In women, a higher percentage of incontinence and chronic urinary retention are reported [64]. In one of the largest series of orthotopic bladder substitution in women, however, continence during the day and night was reported in 95 and 86 %, respectively, with 16 % experiencing chronic urinary retention [65].

Real long-term functional results of ileal orthotopic bladder substitution after RARC are very sparse. There are only a few results published to date, and the number of patients included is small. Canda et al. [66] report daytime continence rates in 73 and 20 % nighttime continence rates following intracorporeally performed robotic ileal orthotopic bladder substitution in a group of 21 male patients. The two female patients who were included in the trial showed severe urinary incontinence during day and night. Those results are clearly inferior to continence rates after open ileal orthotopic bladder substitution. In addition, the group from USC which has probably the largest experience in RARC recently presented rather discouraging functional results of robotic intracorporeal orthotopic neobladders with complete continence rates of only 17 % after a median follow-up of 9.4 months [67].

Another important issue of urinary diversion following RARC is that the diversion is mostly performed extracorporeally which leads to major limitations such as devascularized long ureters which probably might lead to a higher number of strictures in the upcoming years [68].

## Conclusions

Muscle invasive bladder cancer is a potentially life-threatening disease, and every patient who receives an RC must be offered surgery according to the best possible oncological principles. In the hands of a dedicated and experienced uro-oncological surgeon working hand in hand with an experienced team, open RC including a meticulous PLND, negative surgical margins and whenever possible preservation of the autonomic nerves remains still the gold standard to achieve the best possible oncological and functional results for the patients.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** Ethical committee review was not required as the manuscript is a review of the published literature.

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