18 Questions and Concerns of Robotic Approaches to Bladder Cancer Surgery

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Introduction

It is projected that 56,000 men and 18,000 women will be newly diagnosed with bladder cancer in 2012, and approximately 15,000 individuals with bladder cancer will die from their disease [1]. Bladder cancer is the eighth leading cause of death in men and the fourth most common cancer, with transitional cell carcinoma comprising 90 % of these cases. While the incidence of new cases in males has been stable since 2004, the incidence of bladder cancer in women has been steadily increasing (0.3 % per year) [1].

Most new cases of bladder cancer arise in patients >70 years of age, and though approximately 80 % of newly diagnosed cases are non-muscle invasive, as many as 70 % may recur after treatment and up to 25 % will progress to muscle invasive disease [2]. Open radical cystectomy with lymphadenectomy is the gold standard therapy for any patient with muscle-invasive bladder cancer and non-muscle invasive cancer that is high risk or refractory to intra-vesicular therapy. And while open radical cystectomy has witnessed a decrease in associated morbidity and mortality over the years, there remains a high rate of complications, exceeding 60 % in some large series [3, 4]. The mortality rate has been reported to be approximately 3 % [5, 6]. With hopes of decreasing cystectomy-related morbidity and recovery time, there is growing interest in the use of minimally invasive approaches to radical cystectomy, specifically with employment of the surgical robot.

Robot Gaining Ground

The introduction of the Intuitive Surgical da Vinci robot in laparoscopic pelvic surgery has changed the way many surgeons think about operations in this area. First used in radical prostatectomy, the three-dimensional visualization with endo-wrist tools providing six degrees of movement and tremor dampening has allowed the rapid adoption of a minimally invasive technique that had otherwise been limited to expert laparoscopists. It has gained such widespread acceptance in radical prostatectomy, that it is now the most used surgical technique for removal of the prostate. Though still somewhat controversial, several studies have shown equivalent if not better outcomes with use of the robot compared to open surgery when evaluating intra and perioperative parameters for radical prostatectomy, as well as continence, potency,

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quality of life, and most importantly long-term oncologic outcomes [7].

Given the positive experience with prostatectomy, the robot has been employed to perform a number of other urologic procedures including nephrectomy, partial nephrectomy, and even microsurgical procedures with equivalent success [8, 9]. With the higher degree of maneuverability provided by the newer da Vinci models, the robot has solidified its utility in the surgical armamentarium of urologists. However, with the added complexity, larger anatomic scope, and more commonly aggressive disease seen in muscle-invasive bladder cancer, the use of the robot in radical cystectomy has been approached more cautiously.

The first report of robot assistance in radical cystectomy came from Beecken et al. [10] who performed the operation including an intracorporeal urinary diversion in 8.5 h. This was shortly followed by Menon et al. [11] who reported on a series of 17 patients. These and more recent studies confirmed feasibility of the procedure and suggest possible advantages to robot-assisted radical cystectomy (RARC) including decreases in pain, blood loss, hospital stay, and time to recovery. However, there remain concerns that implementation of this minimally invasive, technically challenging approach will lead to unnecessarily long operating times, increased positive surgical margins due to decreased tactile feedback, and decreased lymph node yields due to operation in an enclosed space. This would undoubtedly result in sub-par oncologic outcomes compared to open surgery. In this chapter, we seek to analyze the current literature to address a few of the issues and controversies surrounding the acceptability of robotic assistance for the performance of radical cystectomy.

Pelvic Lymph Node Dissection: Does Robot-Assisted Pelvic Lymphadenectomy Allow for Adequate Diagnostic and Therapeutic Efficacy?

The most common sites for metastasis in patients with bladder cancer are to the pelvic lymph nodes, with approximately 25 % of patients having lymph node metastases at diagnosis [5, 12]. It has been well established that removal of these nodes improves survival with a decreased rate of local recurrence. A "standard" LND (obturator fossa posteriorly, genitofemoral nerves laterally, hypogastric vessels distally, to bifurcation of common iliac proximally and including node of Cloquet and tissue around deep circumflex vein) has been traditionally accepted as adequate in the treatment with cystectomy [13, 14]. However, more recent studies have reported that as many as 31 % of patients with lymph node positive disease will have metastases outside the range of a "standard" LND; metastasizing to levels above the bifurcation of the aorta and to presacral nodes [12, 15, 16]. Skinner [17] showed that an "extended" LND (standard dissection plus nodes extending to aortic bifurcation and pre-sacral region) resulted in improved long-term survival in patients with lymph node positive disease. Since that time there has been an increasing body of evidence to support a survival benefit in patients undergoing more extensive LND [13, 18–21]. Given the apparent survival benefits of an "extended" LND, and the evidence that it can be performed without increasing the morbidity of the procedure, several authors have recommended that "extended" LND be a necessary component of the management for muscle-invasive bladder cancer [16, 22–24].

Without time consuming additional port placement and redocking procedures, robot-assisted laparoscopy is limited by a fixed camera port position, with subsequent constraints on the direction and field of view not encountered with open surgery. Similarly the robotic arms, despite their high level of dexterity, have limited travel (25 cm) which may prevent access throughout the pelvis. Some have argued that this theoretical mobility and vision restriction would compromise lymphadenectomy such that an "extended" LND is not feasible. This alone could likely result in poorer oncologic outcomes compared to standard open techniques and present an argument against the use of a robotic approach to bladder cancer.

Menon et al. [11] published the first series of RARC with lymphadenectomy on 17 patients revealing feasibility and safety. The initial reports from robot-assisted cystectomy with LND series

Table 18.1 Lymph node yield from "extended" pelvic lymph node dissection

References	Number of patients (RC vs. OC)	Mean nodes RC (range)	Mean nodes OC (range)	Complications from ePLND
Abraham et al. [81]	10	22.3 (13–42)		NR
Wang et al. [43]	33	17 (6–32)		0
Woods et al. [26]	27	12.3 (7–20)		0
Guru et al. [34]	100	21		0
Gamboa et al. [58]	41	25 (4–68)		3
Guru et al. [49]	26	25.5 (13–56)		1
Lavery et al. [82]	15	41.8 (18–67)		0
Pruthi et al. [41]	100	19 (8–40)		NR
Nix et al. [32]	41 (21 vs. 20)	19 (12–30)	18 (8–30)	NR
Richards et al. [33]	70 (35 vs. 35)	16 (11–24)	15 (11–22)	NR
Kauffman et al. [83]	85	19 (0–56)		NR
Khan et al. [59]	50	17 (9–28)		1
Schumacher et al. [36]	14	32 (19–52)		5
Davis et al. [30]	11	43 (19–63)	4 (0–8)[a]	NR

Results from various trials reporting lymph node yields from extended pelvic lymph node dissection from robot-assisted radical cystectomy alone or comparison to open cystectomy
There were no statistically significant differences for lymph node yields in the studies that directly compared OC versus RC
[a]Nodes removed during second-look open LND following robotic extended LND
RC robot-assisted radical cystectomy, *OC* open cystectomy

mostly performed dissections within the boundaries of "limited" (obturator region) and "standard" LND templates [25]. However, more recently studies have explored the acceptability and feasibility of robotic "extended" LND. Table 18.1 shows a list of studies that have performed robot-assisted "extended" LND. When evaluated, the robot-assisted LND only added an additional 30–45 min of operation time and was not associated with increased morbidity/mortality [26–28]. In general, the lymph node count has been the only measure by which to compare the adequacy of the node dissection. However, it is an imperfect measure since the number of lymph nodes counted is dependent on both the manner in which the specimens are submitted to pathology and the technique used by the pathologist [29, 30]. Despite its drawbacks, lymph node yields in a range of 10–20 have been shown to confer a survival benefit in several open series [13, 18–21, 31]. By comparison, all robotic series noted in Table 18.1 were able to obtain mean lymph node counts of greater than 16 with only a few studies having counts less than 10 nodes. Notably, in two separate prospective randomized trials comparing open and RARC, lymph node yields were not statistically different while employing identical anatomic lymphadenectomy templates [32, 33].

An additional small, but provocative study by Davis et al. [30] looked directly at the number of lymph nodes leftover by robot-assisted "extended" LND through the use of a second look open LND. A total of 11 patients underwent robot-assisted LND by a single surgeon, and each robotic LND was immediately followed by a second-look open LND by a different team of surgeons to extract any leftover nodal tissue. The mean lymph node yield was 43 (range 19–63) with a median of 93 % of all lymph nodes retrieved removed by the robotic technique. Interestingly, the newer da Vinci S system allowed for even higher retrieval rates with a range of 83–100 % of all lymph nodes removed robotically compared to 70 and 75 % in each of the two procedures using the older da Vinci machine.

Surgeon learning and experience with the robotic platform may also be an important factor affecting lymph node yield. Of concern, Guru et al. [34] found a significant increase in lymph node yield over time which plateaued at the 30th case. Similarly, Hayn et al. [35] found that lymph node yield increased 73 % when surgeons had performed >50 RARC's compared to those who had performed <30 cases. On the other hand, several other studies found no change in lymph node yields with increasing experience/volume [27, 36, 37]. Therefore, available data on the effects of early experiences with RARC on lymph node yield remains controversial.

Given the abundance of reports including two small randomized trials, it appears that robot-assisted extended lymphadenectomy up to the aortic bifurcation is technically feasible and safe, yielding lymph node counts on par with open surgery. With the varied initial results, further evaluation of the surgical learning curve is needed to determine whether early experience with RARC sacrifices acceptable lymph node yields. However, it appears that, when using lymph node counts as a surrogate for the extent of lymph node dissection (LND), robot-assisted lymphadenectomy does not represent an inferior surgical intervention compared to open lymphadenectomy, and, all other factors being equal, we would expect similar long-term oncologic outcomes.

Positive Margin Rate: Can the Robot-Assisted Approach Match or Improve on the Open Approach?

Whereas there exists some controversy on lymph node yield as a surrogate for adequate surgical resection, it is well established that the completeness of the primary resection plays a critical role in oncologic outcomes following treatment for bladder cancer. A positive surgical margin at time of radical cystectomy has been shown to be an independent predictor of disease recurrence, metastatic progression, and cancer-specific mortality [19, 38–40]. The overall positive margin rates in large series of open radical cystectomy have ranged from 4 to 9 %, with slightly higher rates in advanced disease [19, 38–40]. As a result of such studies and the importance of surgical margins in patient survival, Herr et al. [19] recommended a surgical benchmark of less than 10 % positive surgical margin rate for all cystectomies and less than 15 % positive margin rate for advanced (≥pT3) disease.

Though the use of the surgical robot can improve visualization with the 3D, 10× magnifications available with the stereoscopic laparoscope, questions arise as to whether visual cues alone are sufficient for determining the extent of surgical resection. Some argue that the lack of tactile sensation may compromise the ability to assess the level of tumor extension, particularly with pT3/pT4 disease, thus leading to a higher rate of positive margins. Are surgical margin rates similar between robotic versus open cystectomies? Does the stage of the tumor have an effect?

Table 18.2 shows a list of the robot-assisted cystectomy studies and their rates of positive surgical margins. The overall incidence of positive surgical margins at the time of robot-assisted radical cystectomy has ranged from 0 to 7.2 %, with most of the studies showing an overall positive surgical margin rate <10 %, which meets the standard set by series of open radical cystectomy. However, the data raises concern for the rates of positive surgical margins in more advanced disease. There also exists the potential for significant unaccounted for selection bias in many of these retrospective and/or nonrandomized reports. Early studies that reported 0 % positive margins often did not report the breakdown of organ confined versus more advanced disease and, these being early experiences, may have bias toward selecting patients with less aggressive disease for RARC. More recently, however, there have been reports which include significant numbers of patients with pT3/pT4 disease. In one of the larger multi-institutional trials, Hellenthal et al. [40] used the IRCC database to show an overall positive margin rate of 6.8 % in 513 patients undergoing robot-assisted radical cystectomy. However, the positive margin rate increased to 16.6 % when considering pathologic stage ≥pT3; a rate slightly above the standard suggested by Herr et al. [19]. Patients in this study with pT4 disease were found to have a positive margin rate of 39 %. Another larger retrospective study by Guru et al. [34] showed an overall

Table 18.2 Rates of positive surgical margins from trials of robotic and open cystectomy

References	Number of patients (RC vs. OC)	Total PSM RC: *n* (%)	Total PSM OC: *n* (%)	PSM in pT3/T4 RC: *n* (%)	PSM in pT3/pT4 OC: *n* (%)
Beecken et al. [10]	1	0			
Menon et al. [11]	17	0			
Hemal et al. [78]	24	0			
Rhee et al. [70]	30 (7 vs. 23)	0	0	0	0
Galich et al. [42]	37 (13 vs. 24)	0	3 (12.5)	0	3 (20)
Wang et al. [43]	54 (33 vs. 21)	2 (6)	3 (14)	2 (22)	3 (25)
Guru et al. [34]	100	7 (7)		7 (13)	
Richards et al. [33]	70 (35 vs. 35)	1 (3)	3 (9)	1 (7)	2 (13.3)
Ng et al. [44]	187 (83 vs. 104)	6 (7.2)	9 (8.7)	6 (19)	9 (20.5)
Nix et al. [32]	41 (21 vs. 20)	0	0	0	0
Hellenthal et al. [40]	513	35 (6.8)		31 (17)	
Pruthi et al. [41]	100	0		0	
Khan et al. [59]	50	1 (2)		1 (7)	
Schumacher et al. [36]	45	1 (2.2)		1 (10)	
Nepple et al. [45]	65 (36 vs. 29)	2 (6)	2 (7)	2 (12)	2 (17)
Davis et al. [30]	11	0		0	

The total number of positive margins is shown followed by the rate of positive surgical margins in patients with non-organ-confined disease (pT3/pT4)
n number of patients, *PSM* positive surgical margins, *RC* radical cystectomy, *OC* open cystectomy

positive surgical margin rate of 7 % for 100 patients undergoing RARC, with the positive margin rate increasing to 13 % in the patients with advanced disease. Pruthi et al. [41] found no positive margins in a cohort of 100 patients undergoing RARC. However, when looking at the patient population included in the trial, most of the patients (87 %) had pathologic stage ≤pT2.

Several nonrandomized comparisons have been performed comparing open and RARC but these are generally single-institution case series with surgeon preference governing which patients received an open vs. robot-assisted approach [33, 42–45]. As seen from the data in Table 18.2, overall positive margin rates were actually slightly higher in the open group, though in most studies this did not reach statistical significance [33, 42–45]. This trend persists when only pT3/pT4 patients were analyzed. However, these differences again did not reach statistical significance and the studies were not powered to detect these differences [33, 42, 44, 45]. Though some series had similar stage breakdown between cohorts [42, 44, 45], they may have suffered from other unaccounted selection bias. Others clearly were early robot experiences with a significant bias toward more difficult cases being performed open [43]. The only published prospective randomized trial comparing open and robotic was reported by Nix et al. [32]. The patient populations did not differ with respect to pathologic stage, and there were no patients in either cohort that had positive surgical margins. Though the absolute number of patients was relatively low and there were a disproportionate number of patients with ≤pT2, this last study would suggest non-inferiority of robot-assisted radical cystectomy compared to open surgery in pT2 or lower disease when possible bias is controlled for by randomization. However this study was not powered to detect difference in positive margin rates between groups and hence additional studies with that specific endpoint in mind are required to truly answer that question.

While a direct comparison of positive margins to open cystectomy is important, there is also the need to assess changes in positive margin rates over time as surgeons are progressing on their learning curves. Similar to lymph node yields, if there were a significant increase in positive

Table 18.3 Medium-length follow-up reports of oncologic outcomes following robot-assisted radical cystectomy

References	Number of patients	Mean follow-up	Overall survival (%)	Recurrence-free survival (%)	Disease-specific survival (%)
Dasgupta et al. [57]	20	23 mo	95	90	95
Pruthi et al. [41]	100	21 mo	91	85	94
Kauffman et al. [83]	85	18 mo	79	71	85
Nepple et al. [45]	36	12 mo	68	72	75
Martin et al. [84]	59	36 mo	69	71	72

margins during early robotic experiences, it may be irresponsible to implement use of the robot since positive margins result in substantial consequences to oncologic outcomes [19, 38–40]. While Guru et al. [34] found a significant decrease in positive margin rate from their first to fourth cohort, other studies found no change in positive margin rate with increasing surgeon experience/volume [27, 36, 37]. Therefore, the available data on the effect of RARC on positive margins (both compared to open and along surgeons' learning curves) is controversial. All training surgeons must remember the oncologic principles of radical cystectomy and prioritize their operation to maximize patient outcomes.

It is important to remember that measures of positive margins, in addition to lymph node yields, are only surrogates for oncologic outcomes. The true measure of oncologic efficacy of a procedure is the effect on overall and disease-free survival. Unfortunately, there is limited long-term follow-up among patients undergoing RARC so discussion is therefore limited to short and medium-term follow-up. Table 18.3 shows results from a few studies reporting oncologic outcomes following RARC. However, the follow-up time across studies ranged from 1 to 3 years. While the overall survival, disease-specific survival, recurrence-free survival rates are promising and deemed comparable to results from an open series by Stein et al. [5], they do not allow for adequate comparison due to limited follow-up periods and bias toward performing RARC on patients with less aggressive disease.

Currently, we are left with comparisons to historical controls, case series, one small randomized trial, and studies with limited follow up to assess (1) the ability to obtain an adequate resection with the surgical robot and (2) the long-term oncologic efficacy of this approach. From the data available for stage T2 or lower disease, it appears that a number of groups have shown the ability to match or even improve on historically acceptable positive margin and lymph node yield rates. For more advanced disease, the data are not as clear since many of the cohorts had positive margin rates greater than 15 %. There is currently an ongoing large multicenter randomized trial which should be able to more definitively assess this concern. Until then, and until more studies report on the long-term follow-up after RARC, patient selection for robot-assisted radical cystectomy should be made carefully, and one should abide by the surgical benchmarks from studies of ORC [19] that serve as surrogates for optimizing long term oncologic outcomes.

Should Urinary Diversions Be Performed Intracorporeally for Robot-Assisted Cystectomy?

Surgeons employing a pure laparoscopic approach to radical cystectomy have demonstrated the feasibility of intracorporeal (IC) urinary diversion, but this was never widely adopted due to the technical challenges. In fact, purely laparoscopic intracorporeal urinary diversion was associated with significantly more complications along with higher blood loss, longer operative times, and increased time to ambulation and oral intake when compared to extracorporeal (EC) urinary diversion [46]. Despite these short comings, the smaller incisions, decreased bowel exposure, and reduced tissue manipulation creates the potential for decreased pain, decreased fluid imbalances with perhaps subsequent advantages in time to bowel function return and overall recovery. Does the use of the surgical robot improve results of intracorporeal diversion compared to a pure laparoscopic approach? Have the theoretical advantages been demonstrated?

The first robot-assisted radical cystectomy (RARC) involved an intracorporeal urinary diversion [10]. The total operating time was 8.5 h, but the blood loss was only 200 ml and the reservoir was considered functionally and oncologically excellent at 5 months follow-up. Another early attempt at RARC with IC diversion by Balaji et al. [47] included three patients all of whom had operative times greater than 10 h, but similarly had nominal mean blood loss of 250 ml and good postoperative functional outcomes at 2 months.

Since these early attempts, there has been continued interest with reports of additional small series showing promising results. Pruthi et al. [48] compared the perioperative outcomes among 12 patients undergoing RARC and IC to 20 patients receiving RARC and EC diversion during the same period. The overall operative time was significantly longer in patients who underwent the IC diversion; 5.3 h versus 4.2 h in the EC cohort, but not as substantial as that seen in the earliest reports. There was, however, no difference in mean blood loss, time to return of bowel function, time to discharge, or the number of complications. A benefit of the IC method was evidenced by a significantly decreased narcotic requirement in the group receiving an IC diversion.

Recently, Guru and colleagues [49] published data on their initial experience with IC conduit diversion in which they found no difference in operative times compared to EC diversion. A total of 26 patients underwent RARC; the first 13 patients received an EC diversion and the last 13 an IC conduit diversion. There was no difference in overall operative time. The difference in diversion times alone trended toward but did not reach significance (159 min for IC versus 120 min EC, $P = 0.058$). The groups did not differ in number of complications or other perioperative parameters (mean blood loss, lymph node yield, time to oral feeds, and length of hospital stay), and the mean time for IC diversion decreased over sequential case number which suggests a rapid learning curve. Lastly, Smith et al. [50] reported on a multi-institution, multi-surgeon experience with RARC with regard to operative outcomes. There were 227 patients in the study with a mixture of EC and IC diversions performed. The 30-day complication rate was 30 % with 7 % major complications. Multivariate analysis showed that the type of diversion was not associated with postoperative complications.

Unfortunately, there is a lack of evidence comparing IC versus EC while subdividing for type of urinary diversion. This is an important consideration because different types of urinary diversion represent different levels of difficulty and pose a risk for different associated complication rates and operative times when performed intracorporeally. Lee et al. [51] compared RARC with EC versus ORC and found significantly longer operative times in RARC with EC for ileal conduit and orthotopic neobladders, but not for continent cutaneous diversions. This study supports the variability in operative time as a function of diversion type during RARC. Additional studies are needed to determine which (if any) diversion types confer an unsuitable risk to patient outcome if performed intracorporeally.

Current assessment suggests that in experienced hands there is a place for intracorporeal urinary diversion in the armamentarium of urologists, with some evidence for improvement in pain and non-inferiority across other measures. However, inferences should be made with caution as these studies were not randomized trials and therefore were subject to selection bias that accompanies early attempts with new procedures; patients tended to be younger with fewer comorbidities or a lower stage disease in order to optimize tolerability to a potentially prolonged procedure. We currently believe that the potential advantages of the intracorporeal method have not been fully demonstrated and thus, except in the most expert hands, do not outweigh the associated disadvantages or potential complications.

Furthermore, longer studies and follow-up are required to confirm that other complications such as stricture rate are not adversely affected.

Does Restriction of Movement in an Enclosed Pelvis During Robot-Assisted Radical Cystectomy Result in Increased Ureteral Skeletonization and Stricture Formation?

Proponents of minimally invasive surgery cite that one of the advantages over open surgery is that there are fewer surgical-related complications [52]. However, a theoretical concern exists that robot-assisted radical cystectomy (RARC), with its lack of tactile feedback and limited workspace, may lead to excessive tissue skeletonization and devascularization resulting in an increased frequency of delayed complications, specifically ureteral–intestinal anastomic strictures. Anastomotic strictures are a well-known occurrence in open radical cystectomy with urinary diversion with an overall incidence ranging from 2 to 4 % [53–56], but have been reported as high as 10 % [4, 53]. While it is not fully known why ureteral anastomotic strictures develop, there are number of factors thought to play a role: tissue ischemia, tissue tension, inflammation from urinary leak, and/or suturing errors. While studies have sought to determine risk factors for stricture formation [53, 55, 56], the results remain inconclusive and/or controversial over the extent any of these play in stricture formation.

With RARC in addition to the potential issues related to ureteral skeletalization, there exists particular concern on the ability to fully mobilize the left ureter allowing for a tension free anastomosis. The rate of ureteral anastomotic stricture formation reported among the various RARC series has ranged from 1.5 to 10 % [44, 57–59]. This is similar to the reports from large series of open radical cystectomy. Thus, early data may suggest that RARC has similar stricture rates as ORC.

However, the emerging use of intracorporal urinary diversion (a diversion limited to minimally invasive surgery) could theoretically play a role in decreasing the relative risk of stricture formation in RARC compared to ORC. It has been proposed [36] that urinary diversion performed extracorporally may be a risk factor in stricture formation due to increased mobilization required for the appropriate tissue exposure required for suturing. With this in mind, perhaps employment of more intracorporeal diversions will decrease tissue mobilization and subsequently the incidence of ureteral strictures associated with urinary diversion. Evidence to support this theory comes from studies performing RARC with extracorporeal diversions that reported stricture rates from 8 to 10 % [49, 57, 59] which are at the high end of the range for ORC. Further, Guru et al. [49] compared the two types of diversion in their series and found a 7.9 % stricture rate in the extracorporeal group and 0 % in their intracorporeal group. However, a stricture rate of 7.3 % was reported in a group of patients undergoing intracorporeal diversion which may argue against this theory [58]. However, this study did not perform a comparison to patients undergoing open surgery, so it is hard to assess the relative difference in stricture rates between open and robotic approaches. Overall, definitive conclusions are limited because of the small sample sizes, few direct comparisons, and highly variable stricture rates regardless of the diversion type reported in different studies.

Perhaps the greatest hindrance to full realization of the risk of stricture formation in RARC is the lack of long-term follow-up. To date, many of the studies of RARC have either been (1) feasibility studies or (2) reports on the perioperative and short-term outcomes following the procedure. Thus, many of the current studies likely did not follow patients long enough to report on stricture formation since studies of ORC have shown stricture formation can occur at a time point ranging from 8.8 months [54] to 1 year [4]. This is an area that will need close monitoring and more studies employing long-term follow-up to determine whether this technology confers increased or unique complications or whether perhaps provides an opportunity to reduce the complication risks associated with ORC. As of this time it does not appear that there is a significant increase risk of stricture formation with RARC compared to open cystectomy, though availability of additional data in the future may shed more light on this issue.

Does Robot-Assisted Radical Cystectomy Confer Increased Risk of Direct Tumor Spread from Tumor Spillage or Port Site Recurrence?

In addressing oncologic outcomes between robot and open radical cystectomy, in addition to issues related to positive margins and extent of lymph node dissection, one must also address concerns about aspects of the robotic technique that may generate risks for cancer recurrence not realized in open surgery; specifically, the possibility for port site metastases or increased local recurrence secondary to local spread from tumor spillage in a closed abdomen.

One concern that directly arises from the issue of minimally invasive surgery is the risk of port site metastasis, especially with highly aggressive tumors. The exact etiology of port site metastases is unknown and so any effort to confidently prevent occurrence in RARC is difficult. Some authors have proposed different methods to prevent port site metastases in patients with bladder cancer including the use of meticulous dissection, the use endobags for specimen extraction [60], avoiding specimen morcellation, and ensuring adequate seal of laparoscopy trocars to prevent chimney effect of a pneumoperitoneum [61]. Regardless of the method employed, this concern has failed to become reality as only one case of port site metastasis has been reported in the literature [61], occurring at 10 months. Similarly, studies employing minimally invasive surgery for colorectal, uterine, and other urologic malignancies have shown no or minimal incidence of port site metastases [62–64].

Another concern, given the closed peritoneal space and additional access sites from laparoscopic ports, is that a robotic approach may be more susceptible to spillage-related cancer recurrence. Urothelial cell carcinoma is known to be aggressive with numerous descriptions from open surgery reporting local spread from spillage or access tracts including suprapubic and percutaneous nephrostomy tubes. Thus, meticulous effort to avoid urine spillage has become a requirement in open surgery. Proposed techniques to avoid spillage of urine during robot-assisted radical cystectomy (RARC) include meticulously avoiding puncture of the bladder, carefully clipping the ureters before dissection, and ensuring adequate stapling, clipping, or suturing of the urethral stump [65]. Similarly, most studies publishing their RARC technique have also reported their efforts toward preventing urine leak/tumor spillage. To date, no studies have reported local disease recurrence secondary to documented seeding from tumor spillage. Pruthi et al. [41] reported an inadvertent bladder puncture intraoperatively but noted no urine spillage at the time and did not report any local recurrence from suspected seeding from tumor spillage in any of their patients at a mean follow-up of 21 months. However, with accrual of additional data, the true risk of tumor spillage and local recurrence will become clear.

With lack of good data surrounding documented spillage or use of laparoscopic ports causing local recurrence in RARC overall local recurrence rates may serve as a surrogate. Looking at the studies with longest follow-up, there does not appear to be a change in local recurrence rates over 1–2 year observed follow-up [66–68] suggesting that techniques and caution employed during surgery are preventing this concern from rising to clinical significance.

Is There a Learning Curve Associated with RARC, and If So, Are Patient Outcomes Sacrificed During Early Surgeon Experiences?

Like any new technology, the surgical robot will only gain universal acceptance as a treatment modality for cystectomy if it can be incorporated safely and efficiently into the practice of established surgeons. It is of utmost importance that the oncologic standards of this operation be upheld regardless of technical approach, because such an oversight would unquestionably sacrifice patient outcome and survival [19]. As we've noted in the preceding sections, in many instances, based upon various criteria, RARC appears to be as good as and in some cases superior to ORC. However, much of this work comes from high volume centers experienced with the use of the robot. Are these results replicable by less experienced surgeons? Is there a learning curve associated with RARC? If so, will the initial use of RARC by surgeons lower on their learning curves sacrifice patient outcomes?

One might make the assumption that more experience and familiarity with any procedure results in better patient outcomes. Unfortunately, quantitation of how much experience is required to effectively perform a RARC is difficult because the heterogeneity of the patients as well as the surgeons' prior experience can play a significant role. There is also no definitive variable that can be used to judge the effectiveness of the procedure. We have previously noted the mixed results seen in evaluating the learning curve by looking at lymph node yields and positive margin rates. Factors that have been evaluated in relation to experience/volume that we will discuss here include the operating time and complication rates.

Operative Time

The ability to withstand anesthesia and the overall physical stresses of an operation are serious considerations when deciding if a patient is a candidate for surgery. This is particularly true for patients with bladder cancer who tend to have serious illnesses with multiple comorbidities. Therefore, it is imperative to limit the length of surgery for all patients in order to reduce possible risks associated with an operation. The use of minimally invasive surgery generates its own risk-conferring variables; specifically, the use of steep Trendelenburg positioning and carbon dioxide to induce pneumoperitoneum, which is itself a time-dependent stressor. These factors can cause serious strain on patients, especially those with poor lung function. Radical cystectomy regardless of surgical approach should have the goal of minimizing operative times to minimize the risk of surgical-related complications.

The initial studies of robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversions reported operative times as long as 10 h [10, 47], far surpassing the average 4.3 h open cystectomy at that time [69]. This was very disconcerting and caused question of the appropriateness of robotic surgery.

Several studies have since published on operative times between open and robot-assisted radical cystectomy at their institutions. While initial trials reported a significantly longer operative time in patients undergoing RARC compared to ORC (even with extracorporeal diversion) [42, 43, 70], more recent published studies demonstrate a trend toward decreasing operative times comparable to that of ORC [30, 35, 58].

Several studies seeking to specifically address the learning curve in RARC have reported improvement in operative times with increased experience. Schumacher et al. [36] divided 45 patients into 3 cohorts to assess their learning curve with RARC and found a significant decrease in mean operative times over the 3 cohorts. Similarly, Hayn et al. [35] used the IRCC to assess the outcomes of 496 patients undergoing RARC by 21 different surgeons at 14 different institutions and found a significant decrease in operative time when surgeons had performed >50 RARCs compared to those who performed <30. Guru et al. [34] analyzed the learning curve from 100 consecutive patients, while Richards et al. [37] used data from their first 60 patients undergoing RARC; both studies showed a trend toward decreased operative times (just missing statistical significance). Guru et al. [34] also showed a plateau for operative time occurring at the 16th case but all the surgeons were fellowship trained in robotic surgery, likely shifting the learning curve. Unfortunately, these studies employed multiple surgeons so the learning curve is more of a facility-based learning curve with respect to procedure volume rather than an individual learning curve generalizable to all Urologists. There is a report of a single-surgeon experience from Pruthi et al. [27] who used data from their initial 50 patients divided into 5 cohorts. They found a decrease in operating time that plateaued after the 20th case. Again, however, this surgeon was seasoned in robot-assisted prostatectomy, so familiarity with the robot likely lowered his plateau. Despite the drawbacks to this work, one might expect continued improvement in operative times during the first 15–20 cases for a well-experienced robotic surgeon, but perhaps as many as 50 cases may be required to approach more optimum efficiency for a more robot-naïve surgeon.

Lastly, while there may be an increase in operative time during early surgeon experience with RARC, it may be comforting to note that perioperative complication rates following RARC have not been significantly greater than ORC and actually have shown a trend toward fewer complications in some studies (discussed in detail below). This suggests that differences in operative time to date have not been responsible for increasing complications in patients undergoing RARC. Further, studies of complications following RARC have found no association between operative time and complication rate [50, 71]. However, interpretation of these data should be made with caution and full awareness that early studies with robotic surgery have tended to select for patients with fewer comorbidities to ensure optimal ability to handle any increased stress from the procedure. As surgeons gain more experience with RARC (and with decreasing operative times), one could expect to see a more widely distributed patient population undergoing the procedure from which more generalizable conclusions can be drawn.

Complications

An important concern when addressing the learning curve with RARC is the effect of initial experiences on postoperative complications. Theoretically, one might speculate that robot-naïve surgeons may be more likely to have surgical complications simply from lack of comfort/knowledge of the subtleties of the procedure. While Richards et al. [37] found a significant decrease in their complication rates over 60 patients, other studies failed to show a change in complication rates over time [27, 34]. Interestingly, Schumacher et al. [36] reported a trend toward fewer complications over time and actually found a significant decrease in the number of late complications (>30 days). Therefore, again, there is controversy regarding the presence of a significant learning curve when the presence of complications is used as a surrogate for effectiveness.

Another factor affecting the learning curve for a RARC is the surgeon's prior experience with any robotic surgery, including prostatectomy and/or nephrectomy. One might think that familiarity with the technology would allow more rapid advancement through the learning curve with RARC. Hayn et al. [72] used the IRCC database to assess the outcomes of 496 patients undergoing RARC by 21 different surgeons at 14 different institutions. The surgeons were divided into four groups based on previous robot-assisted radical prostatectomy (RARP) experience (<50, 51–100, 101–150, >150). There was a significant association between more robotic experience and (1) decreased operative time, (2) decreased EBL, (3) increased lymph node yield, and (4) increased pathologic stage. In fact, there was a 20 % decrease in operative time and a 31 % increase in lymph node yield when surgeons had performed 51–100 RARPs compared to <50 RARPs. Interestingly, this trend toward better outcomes was witnessed only between the first two groups of surgeons. There was actually a detrimental effect on these operative parameters when surgeons had performed 101–150 and >150 RARPs. Further, this worsening trend did not disappear when the authors controlled for pathologic stage of disease. The authors hypothesized that surgeons with very large RARP experience may not have had the time for or interest in open radical cystectomy, while surgeons with less RARP experience may have more open cystectomy experience due to different subspecialization. Thus, the possibility that surgeons with less RARP experience have more experience with open radical cystectomy would likely have granted them the advantage in early experience with RARC.

When assessing the feasibility and practicality of incorporating a new technique/procedure into surgical practice, one must consider the benefits versus potential harm to the patient. In RARC, it is important to assess whether a patient's perioperative and oncologic outcomes are sacrificed when physicians are early in their learning curve. Unfortunately, the evidence from the studies noted above is not conclusive. While there appears to be a consistent decrease in operative time, other critical parameters in predicting patient outcomes following RARC have varied. Of most concern is the association some studies have shown between initial surgeon experiences and a higher rate of positive surgical margins, higher complication rates, and fewer lymph nodes removed. These variables are significant predictors of morbidity and mortality and must not be ignored. Thus, further investigation with well-controlled trials is needed to better characterize the learning curve associated with RARC. Characterization of this learning curve is important because it would determine the acceptability of this technology's universal implementation and help set realistic expectations for surgeons attempting to master this technique.

Are the Costs Associated with the Use of Robotic Technology Greater than Open? If So, Is It Too Substantial to Warrant Its Use?

Bladder cancer has the highest lifetime treatment costs per patient [73]. With rising healthcare costs and widespread pressure to reduce expenditures, a discussion of robot versus open radical cystectomy would not be complete without considering the differences in cost associated with the two techniques. For radical cystectomy there are costs associated with the operation, including anesthesia time, surgeon fee, instrument costs, and with the robot a significant acquisition and maintenance fee [74]. How this robotic equipment cost factors into the average procedural cost is highly dependent on hospital volume. There are also hospitalization related costs which can include medications, blood transfusions, and daily room cost which is directly related to length of stay. Follow-up, including imaging, laboratory tests, and physician time will also contribute. Finally, complication-related costs are something that have not always been addressed but are critical to take into account. Konety et al. [75] presented evidence that post-cystectomy complications can drastically impact hospital charges imparting a cumulative effect on charges mostly through extended length of hospital stay. They report that a single complication can increase the charges for treatment by $15,000 [75].

Several groups have attempted to analyze the cost difference, taking some or all of these factors into account. Smith et al. [76] analyzed the fixed and variable costs, further subcategorized by operating room and hospital costs, between 20 robotic and 20 open radical cystectomies. Overall, there was a higher financial cost of $1,640 associated with robotic versus open surgery. This higher cost of robotic surgery was largely due to differences in operating room costs ($1,634 more for RARC) driven primarily by the amortized acquisition cost of the robot itself as well as maintenance fees and the increased average operative time. However, comparison of hospital costs favored RARC because of a shorter average hospital stay and decreased transfusion requirements. They did not take into account differences in complications or analgesic needs postoperatively because in earlier work, they had noted similar values for these parameters [27]. This study also did not specific the type of urinary diversion used which can greatly impact length of surgery, thus influencing costs. Interestingly, each day of hospitalization represented a loss of $658, while each hour in the operating room represented $1,902. Thus, decreasing operative times as a result of increased surgeon experience and refinement of technique may make RARC a more cost-effective procedure. These data suggest that the cost differential ratio between hospital stay and operative time is approximately 1:3 meaning that hospital stay would have to come down by 3 days to compensate for each hour of increased operative time.

With the operative time, length of stay, and complication rates being such significant driving forces in cost related to radical cystectomy, any increased cost associated with using a robot in the operating room has the potential to be completely offset by improvements in these areas. Martin et al. [77] did consider procedure-associated complications in their analysis of costs when they compared 14 open to 19 robot-assisted cystectomies. All cases were assumed to use ileal conduit diversions. Costs were divided into direct (surgeon fees, purchase and maintenance of robot, anesthesia fees, operating room costs, length of stay, and blood transfusion costs) and indirect costs (complications and their associated treatments and readmissions up to 30 days postoperatively). There was a 16 % higher direct cost of RARC (driven by operating room costs) that was offset by the 60 % less expensive hospitalization costs. This resulted in a 38 % overall decreased cost of the robot approach [74, 77]. The authors reported that complications and readmission rates are major drivers of differences in cost.

Similarly, Lee et al. [51] performed cost analysis of RARC and ORC while including costs resulting from complications and readmissions for up to 90 days postoperatively. In contrast to the previous two studies, Lee et al. [51] stratified costs by type of urinary diversion. The investigators found higher direct costs for RARC (which included surgeon fee, per-case cost of robot, disposable instruments, utilization cost, and anesthesia cost) but this higher cost was offset by lower indirect costs (length of stay and complication-associated costs). The investigators found that length of hospital stay was the most significant driving factor in offsetting the costs of RARC. However, upon subcategory analysis, the higher direct cost of RARC was only offset for ileal conduit (IC) and continent cutaneous diversions (CCD), not for orthotopic neobladders (ON). As a result, the authors concluded that RARC would be most cost efficient in patients receiving IC, but less advantageous for CCD or ON (probably because they are more complex diversions resulting in longer operating times). Further, the complication rates were equivalent between ORC and RARC groups but trended toward fewer complications in RARC resulting in an indirect cost difference that favored RARC. These data suggest that the high costs associated with RARC may be offset if fewer complications and a shorter length of hospital stay are seen.

As with other suggestions and conclusions made in this chapter, it is again important to keep in mind the likelihood of patient selection bias that is present in early studies with RARC; specifically, that the difference in complications and operative times could be a result of different patient comorbidities or disease severity prior to the operation rather than a direct result of RARC versus ORC [59, 71]. Variations in hospital policy, insurance reimbursement rates, and geographic region will also affect calculated cost effectiveness. The studies discussed here would suggest that the high costs associated with acquisition and maintenance of a robot can be offset by shorter hospital stays and decreased complications as compared to ORC. However, until more studies are performed across a range of institutions and geographic regions, with better controlled patient populations, extrapolations from these studies should be made critically and cautiously and specific to every institution's financial structure, case volume, and surgeon experience. An ongoing multi-institutional randomized study comparing robotic and open radical cystectomy should provide answers to some of these questions.

Are There Benefits of Robot-Assisted Radical Cystectomy That Are Not Realized in Open Radical Cystectomy That Would Make RARC a Superior Option in the Treatment of Bladder Cancer?

In prior sections we have addressed different controversies surrounding robot-assisted radical cystectomy by providing evidence that suggests non-inferiority compared to open radical cystectomy—the gold standard treatment of bladder cancer. However, if RARC is to be widely implemented, we would hope to see specific advantages as well. Several potential benefits have been suggested including decreased blood loss, decreased length of hospital stay, decreased complications, and faster recovery.

Table 18.4 Comparison of perioperative parameters following robotic and open radical cystectomy

References	Number of patients (RC vs. OC)	EBL RC (range)	EBL OC (range)	mean LOS RC: *n* (range)	mean LOS OC: *n* (range)	Complications RC: *n* (%)	Complications OC: *n* (%)
Rhee et al. [70]	30 (7 vs. 23)	479[a]	1,109	11	13	NR	NR
Galich et al. [42]	37 (13 vs. 24)	500 (100–1,000)[a]	1,250 (300–10,200)	8 (4–23)[b]	10 (6–35)	2 (15.4)	4 (16.7)
Wang et al. [43]	54 (33 vs. 21)	400 (100–1,200)[a]	750 (250–2,500)	5 (4–18)[b]	8 (5–28)	7 (21)	5 (24)
Ng et al. [44]	187 (83 vs. 104)	460 (161–759)[a]	1,172 (256–2,088)	5.5 (3–28)[b]	8 (3–60)	37 (44.6)[c]	64 (61.5)
Nix et al. [32]	41 (21 vs. 20)	258[a]	576	5.1	6	7 (33)	10 (50)
Richards et al. [33]	70 (35 vs. 35)	360 (260–600)[a]	1,000 (500–2,000)	7 (6–9)[b]	8 (7–15)	21 (60)	23 (65.7)
Nepple et al. [45]	65 (36 vs. 29)	675[a]	1,497	7.9	9.6	NR	NR

EBL estimated blood loss in milliliters, *LOS* length of hospital stay in days
[a]Mean EBL of RC significantly less than OC
[b]Mean LOS RC significantly less than OC
[c]Number of complications following RC significantly less than OC

Perioperative Parameters

The first reports of robot-assisted radical cystectomy provided evidence that this technique offers decreased intraoperative blood loss compared to open cystectomy. Menon et al. [11] reported a mean blood loss of 150 ml, while Hemal et al. [78] reported a mean of 100 ml. This is very appealing when compared to a study during the same time period of open cystectomy [79] which sought to decrease the amount of blood loss associated with the procedure; despite all attempts the mean blood loss was still 600 ml with a third of patients requiring transfusion [79]. Other studies of ORC have shown mean blood loss from 1,000 to 1,300 ml [3, 80]. Similarly, Table 18.4 shows various studies comparing RARC to ORC, with significantly decreased blood loss associated with RARC across studies.

These studies also show a benefit in length of hospitalization with mean length of stay ranging from 5 to 11 days for RARC and 8 to 13 days for ORC (Table 18.4). Though the data are promising, it is important to realize that these trials were not randomized and likely were subject to selection bias in an attempt to minimize difficulty and complications while attempting a new surgical technique.

The first randomized trial comparing ORC to RARC was reported by Nix et al. [32] who compared the perioperative differences between the two techniques and reported significantly less blood loss, time to flatus, time to bowel movements, and less inpatient narcotic needs. They found no difference in hospital stay between groups. However the study was not adequately powered to answer all of these questions. Overall, these studies point toward improved perioperative outcomes with RARC compared to ORC.

Complications

Postoperative complications are a well-known consequence of radical cystectomy. And while we previously addressed complications following RARC during initial surgeon experience, we have yet to directly compare complications between open and robotic approaches. However, until recently, such comparisons have been limited because of a lack of standardized reporting system. With the more widespread reporting of complications using the Clavien system, comparison of complication rates between RARC and ORC has become more feasible. A large series of open radical cystectomy from Memorial Sloan-Kettering Cancer Center reported complication rates using the Clavien system [3]. They found that 64 % of patients experienced a complication within 90 days of ORC. The authors discussed that their complication rate was higher than previously reported with ORC but that this was likely due to the detailed nature of the Clavien system and extension of reporting out to 90 days.

Though the Clavien system can help standardized comparisons across studies, not all groups have reported using this method. One study that employed the Clavien classification was by Ng et al. [44], reporting that patients undergoing ORC had significantly higher rates of overall and major complications at 30 days. And, though the overall complications were not different at 90 days between these groups, there were still significantly more major complications in the ORC group. This study suggests that RARC could possibly result in fewer major complications; however, since this was a nonrandomized trial, it is unclear whether patient selection bias contributed to differences in complication rates. The only randomized trial comparing RARC and ORC from Nix et al. [32] also used the Clavien system and found no differences in the complication rates between RARC and ORC, but the study was not powered to detect differences in complication rates. Other comparison studies not using the Clavien system have reported variable complication rates ranging from 15 to 60 % (Table 18.4) [32, 33, 42–44], with several showing no differences in the overall complication rates between RARC and ORC [33, 42, 43]. With variations in reporting and the concern for selection bias, the true effect of RARC on postoperative complications is still undetermined and requires further study using standardized reporting systems.

Recovery

Lastly, with the less invasive nature of the robotic approach, some theorize a faster long-term recovery. This is a difficult parameter to assess, but two studies have looked at timing to initiation of chemotherapy to address this. Nix et al. [32] compared 21 patients undergoing RARC to 20 undergoing ORC and found a significant difference in the time to adjuvant chemotherapy initiation; 6.7 weeks in RARC versus 8.8 weeks in ORC which they attributed to quicker time to recovery after surgery. Pruthi et al. [41] studied 100 patients undergoing RARC, 18 of which required adjuvant chemotherapy with a mean time to initiation of 7.2 weeks. The authors compared their results to an age-matched cohort of 20 patients undergoing ORC at their institution and found a mean time to chemotherapy initiation of 10.2 weeks. With the need for good overall health and functional status before initiation of chemotherapy, the decreased time to initiation provides some preliminary evidence that RARC may confer a more rapid recovery. But again, the speedier recovery in some patients may be related to selection bias and baseline performance status. Since the choice of adjuvant chemotherapy is also not based on uniform criteria, time to such therapy may be influenced by a variety of factors. This further confounds the use of the variable of time to adjuvant chemotherapy as an outcome variable outside of a controlled study. However, these data do suggest that patients undergoing RARC may recover more quickly than those undergoing ORC. This will certainly benefit those needing to go onto adjuvant chemotherapy.

In conclusion, it appears that robotic approaches may hold significant promise in improving certain outcomes while ensuring adequate cancer control from a complex procedure such as radical cystectomy. Early data indicate that several concerns pertaining to the use of robotic surgery such as adequacy of resection, adequate node dissection, and complication rates are not of substantial merit. There appear to be some potential benefits to RARC in reduction of blood loss, reduced length of stay, and even decreased complication rates. Additional data that will become available from large cohort studies and ongoing randomized trials will further help clarify these issues and delineate the role of robotic surgery as applied to radical cystectomy.

Editors' Commentary

Erik P. Castle and Raj S. Pruthi

Robotic techniques in bladder cancer surgery must continue to duplicate the surgical principles of open radical cystectomy with regard to the extirpative portion of the procedure, the ability to perform adequate lymphadenectomy, and the urinary diversion. While the potential benefits of robotics for radical cystectomy are well defined, the universal acceptance of this technique has been met with some resistance because of concerns about unique issues and complications surrounding the application of robotic surgery. The authors provide a thoughtful and evidence-based examination of the potential areas of concerns ranging from oncologic efficacy to perioperative complications to the learning curve and costs. Those initiating a robot-assisted radical cystectomy program are strongly encouraged to understand these potential concerns and be sure to evaluate and address such issues when applying robotics to their own clinical practice.

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