Partial cystectomy for muscle-invasive bladder cancer: a review of the literature

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Abstract: The radical cystectomy (RC) for muscle-invasive bladder cancer is one of the most morbid and complex urologic procedures performed today. To avoid these complications, the partial cystectomy (PC) has been offered as an alternative in carefully selected patients as a means of achieving equal oncologic efficacy with less morbidity. Selection criteria should include solitary tumors without concomitant carcinoma in situ (CIS) and amenable to resection with 1–2 cm margins in a normally functioning bladder. In addition to the standard work-up, random bladder and prostatic biopsies may be performed. The PC can be performed through an open, laparoscopic, or robot-assisted approach, each with acceptable outcomes. A number of techniques have been developed to identify and resect the tumor completely with negative margins, while preventing tumor spillage within the abdomen. While there are no randomized trials, single institution series have demonstrated acceptable oncologic outcomes in appropriately selected patients. Therefore, offering PC in the appropriate candidate, including those patients who do not accept or are unfit for the associated morbidity of a RC, represents an acceptable alternative.

Keywords: Urothelial carcinoma; partial cystectomy (PC); bladder preservation therapy; radical cystectomy (RC)

Introduction

There will be approximately 80,470 new bladder cancer cases and 17,670 related deaths in 2019, making it the most expensive and morbid of the urologic malignancies to treat (1). For patients who have disease invading the muscle-wall of the bladder, radical cystectomy (RC) is the gold standard of care. However, the RC is one of the most morbid and complex urologic procedures performed today. Even from the most experienced centers, complication rates are reported as high as 58–77% within the first 30 days, with readmission rates in 27% of patients (2-5). To avoid these complications, the partial cystectomy (PC) with bilateral pelvic lymph node dissection has been offered as an alternative in carefully selected patients. Data suggests that between 5% and 10% of patients meet certain selection

criteria for undergoing a PC (6). Interestingly, despite comprising 7–10% of all cystectomies performed within the United States, only 2.8% were performed for muscle invasive disease (7,8). This article will review the body of literature regarding patient selection, surgical technique, and oncologic outcomes for the PC.

Selection of surgical candidates

Selection of the appropriate surgical candidate is critical to the oncologic success of a PC. Early series exploring the role of PC in muscle invasive bladder cancer were marked with high recurrence rates and poor oncologic control. However, more recent series from Memorial Sloan Kettering Cancer Center (MSKCC) and MD Anderson developed more strict criteria, including solitary tumor that would allow for 2

cm margins, no carcinoma in situ (CIS), and no history of bladder tumors in other locations (6,9). Highlighting the importance of selection, the MSKCC study found that 33% of patients with CIS had a local recurrence, versus 9% for those without. Fifty-six percent of multifocal tumors had a recurrence versus 8% with solitary tumor. They found that tumor location was not a predictor of recurrence or survival, although they did note that tumors along the posterior wall trended towards worse outcomes.

MD Anderson, likewise, reported on their experience, but used more strict criteria in offering PC, specifically in those patients with solitary tumor without concomitant CIS and amenable to resection with 2 cm margins and without need for ureteral reimplantation in a normally functioning bladder. Urachal tumors were excluded. They also performed random bladder biopsies in 58% of patients and prostatic urethral biopsies in 31% of men. They found that with these more strict selection criteria, there was a recurrence rate of 41%.

In selecting patients, some groups recommend a restaging TURBT with random bladder and prostatic urethral biopsies to rule out concomitant CIS (10). Furthermore, an examination under anesthesia should be performed to ensure that there is no palpable mass, which would indicate clinical stage T3b and represent a relative contraindication to PC. Patients with significant voiding dysfunction or a small capacity bladder would also be inappropriate candidates for surgery. One group suggested grade should be considered when offering surgery, specifically those patients with high-grade disease (11). However, as our understanding of bladder cancer has advanced, it is now well understood that tumors that progress to muscle-invasion are by nature high grade.

Variant histology should also be considered in patient selection. There is no data specifically analyzing those patients with variant histology undergoing a PC. Certainly, for patients with histologic evidence of micropapillary, plasmacytoid, and sarcomatoid differentiation, an RC is the treatment of choice. These are known to be particularly aggressive, and as such PC would be contraindicated. While considered less aggressive relative to the variants mentioned above, squamous or adenocarcinoma differentiation may still be more likely to progress in comparison to those tumors with pure urothelial carcinoma. As such, it is uncertain whether a PC would provide adequate oncologic outcomes.

Bladder tumors within diverticula also represent a clinical situation in which a PC may be considered. The incidence of such tumors ranges from 0.8% to 14.3%, with the most common histologic type being urothelial carcinoma (12,13).

As there is no muscle in a bladder diverticula, these tumors may pose a greater risk of progressing to extravesical disease. And while transurethral resection may be feasible in some non-invasive tumors, PC represents a good alternative.

Urachal adenocarcinoma is also amenable to a PC. These tumors occur in less than 1% of all bladder cancer and 10% of all primary bladder adenocarcinomas (14). As such there are only single institution series and case reports within the available literature to suggest how to diagnose and treat these patients appropriately. However, in general, because by definition a urachal adenocarcinoma has to occur at the dome of the bladder, most patients are surgical candidates.

Preoperative work-up

All patient should undergo the standard work-up for muscle-invasive bladder cancer, just as they would for a RC. This includes labs (CMP and CBC), cross-sectional imaging of the abdomen and pelvis with intravenous contrast, as well as chest imaging with either a CT or chest X-ray. If there is concern for bone metastasis then a bone scan should also be performed. Random bladder biopsies may also be performed priory to surgery to exclude multifocal disease and/or CIS.

Special consideration should be taken in the diagnosis and management of urachal tumors as it can be difficult to distinguish between urachal and non-urachal bladder adenocarcinomas. While various criteria have been established to aid in this differentiation, a practical approach was developed by MD Anderson. The clinicopathologic features required for a diagnosis include an enteric-type adenocarcinoma in the midline of the bladder, location within the bladder wall, sharp demarcation between tumor and normal urothelium, and exclusion of a primary adenocarcinoma located elsewhere that has spread secondarily to the bladder (15). Urachal cancers may express detectable serum levels of carcinoembryonic antigen (CEA), CA125, and cancer antigen (CA) 19-9, especially in the setting of peritoneal carcinomatosis (16,17). These markers should be drawn and may be followed for monitoring of disease response.

Operative technique

Prior to surgery, the surgeon should discuss the possibility that intraoperative findings may necessitate abandoning the PC, in favor of proceeding with an RC. The surgeon must also reiterate the fact that RC remains the gold standard, and that long-term oncologic outcomes may not be equivalent even in a carefully selected patient. The

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following discussion on operative technique will highlight the major steps involved in the surgery, with a focus on open, robotic, and laparoscopic approaches.

Open PC

The surgical technique for an open PC has been well described in the literature and begins by placing the patient in the supine position with small degree of flexion. A midline incision is made from the pubic symphysis to the level of the umbilicus. Dissection is carried down through the fascia, after which the peritoneum is opened and space of Retzius developed. If further exposure is required, then the vascular pedicle can be divided on one side. The colon is mobilized on each side along the white line of Told to expose the retroperitoneum. The ureters are identified and swept medially. A retractor of the surgeon's choice is then placed. At this point, a bilateral pelvic lymph node dissection should then be performed, with the same limits as a RC. This includes the aortic bifurcation proximally, Cooper's ligament distally, the genitofemoral nerve laterally, and the bladder medially. After the lymph node dissection, the bladder tumor is then resected. The bladder is opened away from the site of the tumor, preferably on the anterior bladder wall. The tumor is identified intravesically and then excised with a 1 to 2 cm margin. Alternatively, a flexible cystoscope can be inserted to identify the location of the tumor, and the cystotomy can be made over the light of the cystoscope. Specimens should be sent for frozen section to confirm negative margins. Next, the bladder is closed in two layers and filled to confirm the closure is water tight. A closed-suction drain is placed and the abdominal incision is closed.

The open surgical approach for urachal adenocarcinoma proceeds in much the same way as for urothelial carcinoma. However, because the urachus may be involved with tumor anywhere along its course, an *en bloc* resection of the entire urachus as well as umbilicus is required.

Robotic PC

When performed from a robotic approach, the patient is placed in low lithotomy position. After insufflation of the abdomen, the camera port is placed 2 cm above the umbilicus. Additionally, flanking paramedian robotic instrument ports and a far left robotic instrument port are placed. A 12 mm air seal port is placed in the right flank. This is the same configuration as is utilized in a robotic RC (18). Once the ports are placed, a simultaneous flexibly cystoscopy is performed using CO_2 (pneumovesicum). By

using pneumovesicum, instead of saline irrigant, spillage of tumor cells can be prevented once the bladder is opened. Moreover, some will instill mitomycin C in the bladder prior to docking the robot to decrease the risk of tumor seeding (19). Using dual vision screens and the light from the cystoscopy as a guide, the surgeon at console can score the bladder with a monopolar scissor (20). It should be mentioned that the light source can be difficult to see with robot assisted laparoscope due to washout from the intraabdominal light source. To avoid this, the light from the laparoscope can be dimmed. The cystoscope can then be removed or remain in until an incision is made into the healthy part of the bladder, at which time a urethral catheter is placed. Whenever possible, the bladder is left attached to the anterior abdominal wall to maximize visualization (21). However, some cases may require mobilization to find a safe area to make the cystotomy. The tumor and 1–2 cm surrounding bladder margin is then excised using monopolar scissors. An alternative to the scissors for excision of the tumor while using the robot is the EndoWrist One™ Vessel Sealer. During the excision, the indwelling foley catheter can be intermittently attached to suction to avoid spillage. The specimen is then immediately placed in the specimen bag for later removal. The bladder defect is closed in 2 layers with barbed suture and a bilateral pelvic lymphadenectomy is performed (22).

In order to prevent positive surgical margins, better identification of the tumor edges is required. Kim *et al.* incorporated technology first used in laparoscopic gastrointestinal surgery of polyps and colon cancer (23). They used endoscopic India ink inside a Deflux needle to tattoo a 1 cm outer margin around the bladder tumor. Then, they performed a robotic PC, opening the bladder, identifying the tattooed margins, and excising the tumor. Hockenberry *et al.* used near-infrared fluorescence through the robotic lens without an injectable contrast agent (24). By switching to fluorescence imaging, the white light from the cystoscope illuminated green, allowing for easier marking of the margins for resection, while still maintaining the surrounding field of vision. Alternatively, intra-tumor injection of indocyanine green (ICG) can be utilized to localize the bladder lesion to facilitate partial bladder resection with negative margins, as reported in abstract form and reviewed by Pathak *et al.* (25,26). Manny *et al.* has used fluorochrome, ICG, to identify the sentinel lymph node packets during our pelvic lymph node dissection (27,28). In the study evaluating the efficacy of detecting the sentinel nodes, ICG was cystoscopically injected into the tumor. Then, then during the pelvic lymph node dissection,

node packets containing fluorescent nodal material by near-infrared fluorescence were sent for pathologic exam.

Laparoscopic PC

Similar to that of a laparoscopic RC, the patient is placed in lithotomy position (29). After insufflation of the abdomen, a camera port is placed 2 cm above the umbilicus. Two 12-mm flanking, paramedian ports are then placed, followed by a fourth and fifth 5 mm port 2.5 cm anterior and medial to the anterior superior iliac spine (30). The remainder of the operation proceeds in much the same way as previously described using the robotic approach.

A complete resection can be more challenging from a laparoscopic approach. This holds especially true for urachal tumors, as the port configuration must be able to access the entire length of the urachus. As a result, Wadhwa *et al.* described their laparoscopic technique specific to urachal tumors, with modifications based on tumor size (21). In their description, the anatomic boundaries of resection included resection of the tumor, resection of the peritoneum lateral to the medial umbilical ligaments, the posterior sheath of the rectus muscle of the abdomen to the arcuate line and the muscle fibers of the rectus muscle below it, the extraperitoneal fat in the space of Retzius, and the urachus up to the umbilicus superiorly, sparing the umbilical skin. Ports are placed in the standard fashion, with the camera port 3 cm cephalad to the umbilicus. For tumors less than 5 cm, an antegrade approach is taken. The anterior abdominal wall peritoneum is incised lateral to the medial umbilical ligament on either side, at the level of the inguinal canal and directed cephalad toward the umbilicus. The lateral incisions meet in the midline at the level of the umbilicus. The urachus is then disconnected from the umbilical skin and placed on tension to allow dissection of the entire urachus with the overlying peritoneum, keeping to the previously mentioned boundaries of dissection. This dissection is carried caudally, entering the space of Retzius, thus mobilizing the bladder off the anterior abdominal wall. A cystotomy is made 1.5 cm away from where the tumor is visualized, allowing for inspection of the inner surface of the bladder. The tumor is resected *en bloc* and the bladder is repaired in standard fashion. For tumors greater than 5 cm, a retrograde approach is utilized. With this approach, they began as before, making the lateral peritoneal incisions. However, instead of proceeding antegrade with urachal mobilization, they instead developed the space of Retzius while keeping the tumor attached to the anterior abdominal wall. A posterior wall cystotomy was made to visualize the tumor, The tumor was subsequently resected, placed in an Endocatch bag, and then placed on tension to aid in dissecting out the urachus in a retrograde fashion towards the umbilicus.

Oncologic outcomes

There are no randomized controlled trials comparing PC to RC. However, a number of retrospective studies and case series suggest that in the appropriately selected patients, a PC may be an acceptable alternative (*Table 1*). Series out of Memorial Sloan Kettering and MD Anderson both suggested adequate outcomes over a decade ago, which in effect renewed interest in the PC (6,9).

In Holzbeierlein *et al.*, 115 patients underwent PC, of which 58 were for primary bladder tumors of non-urachal origin. Their cohort consisted of predominantly clinical stage T2 unifocal disease without CIS. Of note, there were patients with CIS and multifocal disease. The majority of patients received neoadjuvant chemotherapy as part of a bladder sparing protocol. At a mean follow-up of 33.4 months, 40 patients (69%) had no evidence of disease. There was a local recurrence in 11 patients (19%). Seven patients had superficial disease managed with TURBT. An RC was attempted in the four with locally advanced disease, but two were considered unresectable at time of surgery. Twelve patients (21%) developed metastatic disease after PC. There was a 10% complication rate with no perioperative deaths and a median hospital stay of 6 days. At 5 years, 43 patients (74%) are alive with an intact bladder. Most importantly, this group evaluated the various risk factors for disease recurrence, and provided recommendations for selecting appropriate patients.

Kassouf *et al.* examined 37 patients undergoing PC, of which none had CIS or multifocal disease. At a mean follow up of 72.6 months, 19 patients (51%) were disease free. Nine patients (24%) had a superficial recurrence that was managed with transurethral resection. Nine patients (24%) had advanced recurrence of either muscle-invasive disease or metastasis. 18 patients (49%) had an intact bladder with no disease after 62 months. Calculated 5-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival were 67%, 87%, and 39%.

Another group reported on their findings shortly after these two series were published. Smaldone *et al.* analyzed data on 25 patients with either T2 or HGT1 unifocal disease without CIS (10). As part of their protocol, they gave all patients preoperative radiotherapy localized to the abdominal wall, a single intraoperative dose of intravesical thiotepa before tumor excision, and 6 weeks of intravesical

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Table 1 Summary of retrospective reviews and case series evaluating oncologic efficacy of partial cystectomy

Retrospective study/case series	No. patients	Study design	Oncologic outcomes	Mean follow-up (months)
Holzbeierlein *et al.* (9)	58 PC	Inclusion criteria: primary bladder tumor of non-urachal origin	5-year advanced RFS: 67%; 5-year OS: 69%	33.4
Kassouf *et al.* (6)	37 PC	Inclusion criteria: (I) solitary tumor; (II) absence of CIS; (III) 2 cm surgical margin; (IV) not requiring ureteral reimplant	5-year RFS: 39%; 5-year DSS: 87%; 5-year OS: 67%	72.6
Smaldone *et al.* (10)	25 PC	Inclusion criteria: (I) solitary, urothelial tumor; (II) absence of CIS; (III) negative surgical margin. Protocol: (I) pre-operative radiation (25 Gy); (II) 6 weeks of BCG post-operatively	5-year RFS: 62%; 5-year DSS: 84%; 5-year OS: 70%	45.3
Golombos *et al.* (31)	29 PC	Included urothelial and variant histology (adenocarcinoma, squamous, neuroendocrine, micropapillary, myxoid)	5-year RFS: 68%; 5-year OS: 79%	37.0
Koga *et al.* (32)	46 PC	Inclusion criteria: (I) intravesically circumscribed tumor; (II) bladder neck and trigone uninvolved; (III) no residual tumor or only NMIBC at restaging after chemoradiation. Protocol: (I) pre-operative radiation (40 Gy); (II) pre-operative cisplatin (2 cycles)	5-year MFS: 100%; 5-year DSS: 100%	45 (median)
Knoedler *et al.* (33)	167 RC; 86 PC	1:2 matched case-control study comparing PC to RC	RC: 10-year MFS: 66%; 10-year DSS: 63%; 10-year OSS: 36%. PC: 10-year MFS: 61%; 10-year DSS: 58%; 10-year OS: 36%	74.4
Capitanio *et al.* (34)	5670 RC; 1573 PC	Matched case-control study from SEER database comparing PC to RC in patients with T1-4, N0-2, M0 disease	RC: 5-year DSS: 65.8%; 5-year OS: 50.2%. PC: 5-year DSS: 76.4%; 5-year OS: 57.2%	77.0; 64.0
Herr *et al.* (35)	17 RC; 15 PC	(I) Patients underwent 4 cycles of neoadjuvant MVAC; (II) Case-control comparing RC to PC for those patients who were rendered T0 after chemotherapy	RC: 10-year MFS: 65%. PC: 10-year MFS: 73%	120 (median)
Sternberg *et al.* (36)	39 RC; 13 PC	(I) Patients underwent 3 cycles of neoadjuvant MVAC; (II) Inclusion criteria for PC: complete or partial response to MVAC, solitary lesions, no CIS, good capacity bladder; (III) RC selected based on lack of chemotherapy response	RC: 5-year OS: 46%. PC: 5-year OS: 69%	45 (median); 88 (median)

PC, partial cystectomy; RC, radical cystectomy; RFS, recurrence-free survival; MFS, metastasis-free survival; DSS, disease-specific survival; OS, overall survival; NMIBC, non-muscle invasive bladder cancer; MVAC, methotrexate, vincristine, doxorubicin, cisplatin.

BCG therapy postoperatively. Sixty-four percent of patients received a pelvic lymphadenectomy. With mean follow up of 45.3 months, 5-year recurrence-free, disease-specific, and overall survival rates were 62%, 84%, and 70%, respectively. Three patients (12%) had non-muscle-invasive recurrence, two patients (8%) had muscle invasive recurrence, two patients (8%) had locally advanced recurrence, and one patient (4%) had metastatic recurrence. There were two major perioperative complications, but no perioperative deaths.

The largest robotic PC series was recently published by Golombos *et al.* (31). This group identified 29 patients who underwent robotic PC as definitive management of a primary bladder tumor. With a median follow-up of 37 months, the 5-year OS and RFS rates were 79% and 68%, respectively. Seven patients (24%) had a recurrence, three of which were local and four of which were regional or distant. Two local recurrences were managed with TURBT because there was no muscle invasion. The third local recurrence was

muscle-invasive, and thus managed with a cystectomy.

Using the most stringent criteria, Koga *et al.* reported on selective bladder-sparing protocol (32). Patients underwent a debulking TURBT with random biopsy, and were subsequently considered for PC if they had intravesically circumscribed tumors ≤25% of the bladder area and no involvement of the bladder neck or trigone. They then underwent radiation and two cycles of cisplatin, before being restaged 4–6 weeks later. To qualify as a PC candidate, the restaging TURBT must show no evidence of disease or small amounts of non-muscle invasive disease. Of their initial cohort of 183 patients, 65 met criteria, of which 46 actually underwent PC. Seven patients developed intravesical recurrence, all of which was superficial. Five-year CSS for this cohort was 100%.

Knoedler *et al.* performed a matched-control analysis comparing PC to RC (33). Patients undergoing partial PC, like the previously mentioned studies, had a single bladder tumor without associated CIS. In this analysis, 167 RC patients were matched in a 2:1 fashion to 86 PC patients. They were matched based on age, gender, pathological stage and receipt of neoadjuvant chemotherapy. It was unclear whether they were originally matched based on multifocality and absence of CIS. And as expected on analysis, patients undergoing PC were less likely to have multifocal bladder tumors on final pathology as compared to RC (15.1% *vs.* 32.9%). 38% of patients who underwent a PC developed an intravesical recurrence. Five percent of PC patients experienced a pelvic recurrence. At a mean follow-up of 6.2 years, 81% of patients maintained an intact bladder. Most significant, no differences existed between PC and RC with regard to 10-year metastasis free survival (61% *vs.* 66%), cancer-specific survival (CSS) (58% *vs.* 63%), or overall survival (36% *vs.* 36%).

A second study examined the SEER database, comparing overall survival and cause-specific survival in patients treated with PC versus those treated with RC (34). In this analysis, Capitanio *et al.* performed three separate analyses. The first was of the entire cohort of 7,243 who had pT1-4N1-2M0 disease and underwent either PC or RC. They repeated the comparison between PC and RC after matching in a 1:4 ratio for tumor grade, pT stage, pN stage, age, race, and year of surgery. A second matched analysis was performed after adding the number of removed lymph nodes to the matching criteria. In the first analysis, the OS and CSS estimates at five years were 57.2% and 76.4% for PC patients, respectively, and 50.2% and 65.8% for RC patients, respectively (P<0.001). In the second analysis, the OS and CSS estimates were 56.0% and 73.5%

for PC patients, respectively, and 50.9% and 67.5% for RC patients, respectively (P=0.03; and P<0.001 for both). When the number of removed lymph nodes was included in the third analysis, the 5-year OS and CSS estimates were 57.2% and 70.3%, respectively, for PC patients and 54.6% and 69.2%, respectively, for RC patients.

With regard to the application of neoadjuvant chemotherapy, there is little literature to guide management. Herr *et al.* reported on a group of 60 patients who achieved cT0 after receiving MVAC chemotherapy followed by TURBT (35). Fifteen of these patients subsequently underwent PC and 17 underwent RC. The 10-year metastasis free survival was 73% for those who underwent PC, and 65% for those who underwent RC. Furthermore, 53% of patients in the PC group had intact bladders. Sternberg *et al.* performed a similar analysis, evaluating 104 patients with muscle invasive disease who underwent TURBT after MVAC chemotherapy (36). Thirteen patients with history of a solitary lesion and either a complete or partial response underwent PC. Thirty-nine patients underwent RC. Five-year survival for PC was 69% compared to 46% for RC.

Many of these series report on recurrences after PC. They are often categorized as either intravesical or extravesical (metastatic). Intravesical disease can further be classified as either superficial, non-invasive or invasive/ locally advanced. Much of the literature reports use of transurethral resection in those patients who presents with recurrent superficial disease. However, a salvage cystectomy should be recommended in those with muscle-invasive or locally advanced disease. A small group of patients will also present with disease having metastasized. These patients often had either positive lymph nodes from surgery, or micrometastatic disease at time of presentation. While it seems logical to offer RC after muscle-invasive recurrence, there is no data to provide guidance on the best treatment for superficial disease. The question of whether these patients would benefit from RC rather than repeat resections remains unanswered.

Complications

Of the published reports discussed, only three provide the associated complication rates. Holzbeierlein *et al.* reported 6 complications (10%), of which only one would be considered a major complication (9). In Smaldone *et al.*, there were two major complications requiring intervention (8%) out of the 25 patients treated with PC (10). Specifically, one patient required re-exploration, and another required percutaneous drainage of lymphocele.

Golombos *et al.* reported two perioperative complications (6.9%) and 5 (17.9%) complications within 90 days of surgery, all of which were minor (31). Nevertheless, a comparison of reported complications after RC reveals that the morbidity associated with a PC is notably less. Indeed, a review by Shabsigh *et al.* found that of 1,142 patients undergoing RC, there was a 64% total complication rate and 13% major complication (3). Therefore, offering PC in an appropriately selected patient who does not accept or cannot tolerate the associated morbidity of an RC, represents an acceptable alternative.

Conclusions

PC with a bilateral pelvic lymph node dissection can be offered to the appropriately selected surgical candidate. While only 5–10% of patients with muscle invasive bladder cancer would be considered good candidates, it remains underutilized as many are concerned with compromising oncologic success. More recent literature has demonstrated that in the short-term, acceptable oncologic outcomes are achievable. Clinicians must keep in mind, however, that this is an alternate approach. The most definitive and durable, long-term outcomes remain with RC. As the literature is comprised of only case series and retrospective studies, there Level 1 evidence is lacking in this respect. Additional work must be done to further elucidate the most appropriate candidates, as well as the roles and timing of chemotherapy and radiation in a more comprehensive bladder sparing approach.

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Footnote

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