

Supratrigonal cystectomy: Last line treatment for radiation-induced hemorrhagic cystitis

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Summary

Introduction: Hemorrhagic cystitis is defined by the presence of hematuria, lower urinary tract symptoms and cystoscopy findings indicative of underlying urothelial damage. It is common in patient with prior radiotherapy for pelvic malignancies. The severity of the bleeding can vary from a mild to a severe hematuria refractory to conservative therapy and with a continuous need for transfusions. Treatment can be challenging not only by the lack of clear guidelines but also the multiple comorbidities of these patients. Urinary diversion with or without cystectomy should be reserved for those who failed all the previously available therapy, because of the morbidity/mortality associated with this type of procedure. Supratrigonal cystectomy can be an option in patients with intense fibrosis of the pelvic region. The purpose of this article is to present the results of our institution with supratrigonal cystectomy with urinary diversion as a last line treatment for radiation-induced hemorrhagic cystitis.

Materials and methods: We retrospectively analyzed 17 patients who underwent supratrigonal cystectomy and bladder mucosa fulguration with urinary diversion for refractory radiation-induced hemorrhagic cystitis in our institution from January 2010 to December 2020.

Results and discussion: Median patient age at time of cystectomy was 69 years and 64.7% (11) were females. The most common etiology was prior radiation therapy for gynecologic malignancies (11-64.7%). All the patients had prior therapy with bladder irrigation and fulguration. Besides that, 29.4% (n = 5) received intravesical therapy with formalin, 11.8% (n = 2) hyperbaric oxygen therapy and 5.9% (n = 1) prior urinary diversion. Median time between radiation therapy and cystectomy was 65 months. Median ASA score of 3, median preoperative hemoglobin was 9,6mg/dl and 10.5 mg/dl at time of discharge after surgery. Ileal conduit was used in 52.9% (9), cutaneous ureterostomy in 41.2% (7) and ureterosigmoidostomy in 5.9% (1).

Majority of patients (10-58.8%) did not require any blood transfusion during surgery or during their stay. Clavien-Dindo complications grade III or higher occurred in 29,4% (5). Median hospital stay postoperative was 12 days. No mortality was reported in the 30 days after surgery. Median follow-up after cystectomy was 28 months, with a 1-year survival of 93.3% (14 of 15) and 3-year survival of 83.3% (10 of 13). There was no difference in the presence of postoperative complications or overall survival between the types of urinary diversion.

Conclusions: This represents one of the largest series on cystectomy in hemorrhagic cystitis, that we found to this date.

Supratrigonal cystectomy is a valid option as a last line treatment for radiation-induced hemorrhagic cystitis, reducing the

risks associated with simple cystectomy in patients with prior pelvic radiation.

KEY WORDS: Radiotherapy; Supratrigonal cystectomy; Cystitis; Ileal conduit; Hematuria.

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INTRODUCTION

External beam radiotherapy is used as a treatment for several pelvic cancers, such as prostate cancer, rectal cancer and gynecological cancers. The main objective of radiation therapy is to deliver high doses of radiation to target organs while reducing to the least possible, the injury to surrounding organs.

Radiation-induced hemorrhagic cystitis is a well-known complication of pelvic radiation, affecting 5-10% of patients submitted to pelvic radiotherapy. This late complication can appear after 6 months and up to 20 years after radiation (1). Nevertheless, severe hematuria occurs in less than 5% of cases (2).

Radiation induces mucosal edema and inflammation, leading to telangiectasias, submucosal hemorrhage and interstitial fibrosis. Subendothelial proliferation, edema and medial thickening progressively deplete blood supply to urothelium, resulting in endarteritis obliterans causing acute and chronic ischemia. These changes promote the development of revascularization with superficial, fragile vessels that have an increased tendency to bleed, being responsible for uncontrollable hematuria.

Hemorrhagic cystitis is defined by the presence of hematuria, lower urinary tract symptoms and cystoscopy findings indicative of underlying urothelial damage, such as erythema, edema or telangiectasias (3, 4).

Despite being a known entity, its treatment remains a challenge for most urologists, mainly because of the lack of clear guidelines and the multiple comorbidities of these patients.

Several treatments have been proposed, such as bladder irrigation, transurethral bladder fulguration, intravesical instillations, hyperbaric oxygen therapy, internal iliac embolization and, in extreme/refractory cases, cystectomy with urinary diversion (3, 5).

In addition to bladder injury, the desmoplastic reaction of the surrounding tissues and organs, a consequence of pre-

vious radiation, renders surgical planes challenging to identify and dissect, increasing the risks of involuntary damage to adjacent organs. Furthermore, ureteral and bowel segments affected by radiation can increase the risks and possible complications associated with urinary diversion (6). The usage of supratrigonal cystectomy can be a valid solution in patients where the dissection of the posterior plane of the bladder cannot be safely achieved (7, 8). There is a lack of data on the outcomes of these patients when submitted to cystectomy, and even fewer report the outcomes of supratrigonal cystectomy (8, 9). Consequently, the aim of our study was to evaluate the clinical outcomes, complications, and efficacy of supratrigonal cystectomy in managing refractory hematuria associated with radiation-induced hemorrhagic cystitis at our center.

MATERIALS AND METHODS

We conducted a retrospective observational single-center study, including 17 patients who underwent supratrigonal cystectomy for radiation-induced hemorrhagic cystitis at our institution from January 2010 to December 2020. All patients underwent supratrigonal cystectomy with urinary diversion after the failure of conservative measures. Patient charts were reviewed, and clinicopathological variables recorded included age at cystectomy, etiology for hemorrhagic cystitis, previous therapies, ASA score, hemoglobin value pre-operative and at time of discharge, operative time, intraoperative blood loss, length of postoperative hospitalization, perioperative (within 30 days of surgery) complications, 30 and 90-day mortality and overall survival. Postoperative complications were graded according to the Clavien-Dindo classification (10). Survival was estimated as the time from cystectomy to death using the Kaplan-Meier method. Data analysis was performed using SPSS® software version 25.0 (IBM Corp., Armonk, NY, USA) and a p-value < 0.05 was considered statistically significant.

RESULTS

After screening for the patients submitted to cystectomy after radiotherapy, we identified 17 patients who had a supratrigonal cystectomy for intractable hematuria associated with radiation-induced hemorrhagic cystitis. The median age of the patients at the time of cystectomy was 67 years (IQR 58.5, 82.5), 11 (64.7%) patients were females and the median time between radiotherapy and cystectomy was 65 months (IQR 35, 182). The most common cause of hemorrhagic cystitis was radiotherapy for gynecological cancer (64.7%), followed by radiotherapy for prostate cancer (23.5%). All the patients had previous treatment with bladder irrigation and endoscopic fulguration. In addition, (29.4%) received intravesical treatment with formalin, hyperbaric oxygen therapy (11.8%), and previous urinary diversion with bilateral nephrostomy tubes (5.9%). The median ASA was 3 and the median preoperative hemoglobin was 9,6 g/dL (IQR 9, 10.55) (Table 1). All the patients underwent a supratrigonal cystectomy with urinary diversion, with Bricker ileal conduit being the most used in 52.9% (9 out of 17), followed by cuta-

Table 1. Clinical and demographic features of patients undergoing supratrigonal cystectomy.

Median Age (IQR) years	67 (58.5, 82.5)
Gender	
· Female	11 (64.7%)
· Male	6 (35.3%)
Etiology	
· External Beam Radiotherapy for Prostate Cancer	4 (23.5%)
· Radiotherapy for gynecological cancer	11 (64.7%)
· Radiotherapy rectum cancer	2 (11.8%)
Median time between Radiotherapy and Cystectomy (IQR), months	65 (35-182) months
Previous treatment	
· Bladder irrigation	17 (100%)
· Endoscopic Fulguration	17 (100%)
· Formalin	5 (29.4%)
· Hyperbaric Oxygen Therapy	2 (11.8%)
· Urinary Diversion	1 (5.9%)
Median ASA	3
Median hemoglobin pre operation (IQR), g/dl	9.6 (9, 10.55)

neous ureterostomy in 41.2% (7 out of 17) and one patient had a ureterosigmoidostomy. At least 7 patients (41.2%) required one or more blood transfusions, during surgery or during their postoperative hospital stay. Median intraoperative blood loss was 300 ml (IQR 125, 500) and the median time from surgery to discharge from the hospital was 12 days (IQR 10, 17.5), with a median hemoglobin of 10.5 g/dL (IQR 10.15, 10.85) at the last blood sample during hospitalization. In terms of complications, 5 (29.4%) patients presented with a Clavien-Dindo complication grade III or higher in the first 30 days after surgery. The most common complications of any grade were gastrointestinal, namely, ileus requiring a nasogastric tube insertion and wound infections. The patient with a complication grade IV had abdominal abscess and kidney failure, requiring surgical drainage and transfer to an Intensive Care Unit. There were no deaths in the first 30 days after surgery (Table 2).

Table 2. Perioperative outcomes.

Median intraoperative blood loss (IQR), ml	300 (125, 500)
Median length of stay (IQR) days	12 (10.0, 17.5)
Median hemoglobin at time of discharge (IQR), g/dl	10.5 (10.15, 10.85)
Median follow-up after cystectomy (IQR), months	28 (16, 36)
Urinary diversion	
· Bricker Ileal conduit	9 (52.9%)
· Cutaneous Ureterostomy	7 (41.2%)
· Ureterosigmoidostomy	1 (5.9%)
Complications	
· Gastrointestinal (Ileus, intestinal anastomosis dehiscence)	4 (23.5%)
· Urinary (urinary leak, stenosis urinary anastomosis)	3 (17.7%)
· Infectious (Wound infection, abdominal collection, sepsis)	3 (17.65%)
Clavien Dindo - grade III or higher	
· IIIa	1 (5.9%)
· IIIb	3 (17.7%)
· IV	1 (5.9%)

Figure 1.
Overall survival of patients undergoing cystectomy with urinary diversion for refractory hemorrhagic cystitis.

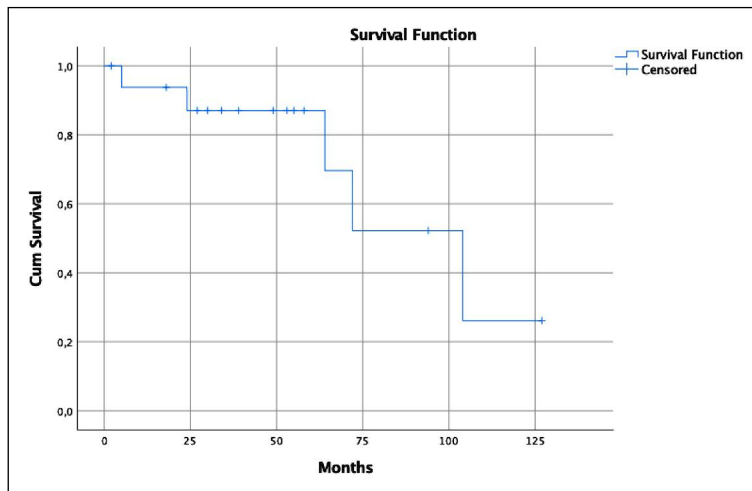
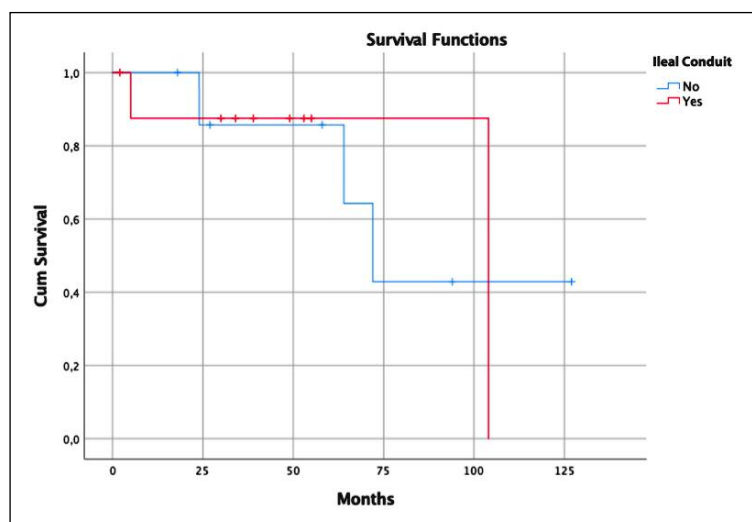


Figure 2.
Overall survival of patients undergoing cystectomy with urinary diversion for refractory hemorrhagic cystitis stratified by usage or not of ileal conduit.



Median follow-up after surgery was 28 months (IQR 16, 36), with a 93.3% (14/15) and 83.3% (10/13) survival rate, at one and three years of follow-up, respectively (Figure 1). The sole first-year mortality occurred 36 days postoperatively due to sepsis.

Subgroup analysis comparing ileal conduits to cutaneous ureterostomies revealed no statistically significant differences in complication rates ($p = 0.64$), length of hospitalization ($p = 0.81$), or overall survival ($p = 0.96$) (Figure 2).

DISCUSSION

Our study sought to evaluate the results of supratrigonal cystectomy in patients with refractory radiation-induced hemorrhagic cystitis. We considered refractory hematuria as gross hematuria that did not respond to conservative measures and first-line treatments, and with constant need for blood transfusions. We were able to identify 17

patients who underwent supratrigonal cystectomy over a ten-year span in our institution.

Hemorrhagic cystitis is a well-known adverse effect of pelvic radiation, despite this, its management is still a challenge. Patients presenting with macroscopic hematuria after any form of radiation treatment should undergo a diagnostic evaluation, to rule out other causes. A population-based study compared the incidence of bladder cancer in a group of patients with localized prostate cancer that underwent external beam radiotherapy or radical prostatectomy, and the results show that patients treated with radiotherapy are at an increased risk of developing a bladder cancer (11).

Radiation-induced hemorrhagic cystitis should initially be managed with conservative measures, such as hydration and, when needed, catheterization with a large-bladder catheter to treat possible retention and allow clot evacuation. In refractory cases, cystoscopy with electrofulguration or laser therapy can be used to control suspected hemorrhagic lesions. When the previous procedures were not successful in controlling the hematuria several intravesical agents have been studied such as, alum salts, aminocaproic acid, hyaluronic acid, and formalin. The latter presents high treatment efficacy with a single instillation but at cost of significant morbidity. In line with the intravesical agents, hyperbaric oxygen therapy has been intensively studied, showing a high percentage of complete responses with a low rate of complications (12, 13). A phase II/III clinical trial (RICH-ART) also reported improvement in other urinary symptoms related with radiation and an improvement in bladder tissues changes induced by radiotherapy, after hyperbaric oxygen therapy (14). In cases of severe and life-threatening hematuria transarterial embolization provides an alternative to more invasive procedures, mainly in older and frailer patients, showing a success rate above 80% (15, 16). Urinary diversion without cystectomy

has also been proposed, with the objective of avoiding contact of urine components with the bladder mucosa, however, this raises concerns about the leftover bladder, with up to 50% of the patients experiencing complications and 25% requiring cystectomy (17, 18). A recent study comparing urinary diversion alone against urinary diversion with supratrigonal cystectomy in benign diseases did not identify concomitant cystectomy as a predictor of increased morbidity, discouraging the use of urinary diversion alone in patients with increased risk of bleeding or infection of the remaining bladder (19).

Linder *et al.* published the biggest series on cystectomies on patients with hemorrhagic cystitis, reporting severe complications (Clavien III or IV) in 42% and 16% 90-day mortality rate. One and three-year survival rates of the remaining patients were 84% and 52%, respectively (8). Series accounting for cystectomies for bladder cancer report 1.5% and 2.7% mortality rates at 30 and 90-day, respectively

(20). In our series we found 5 (29.4%) patients with severe complications (Clavien III or IV) and no fatalities in 30-days after surgery. Survival outcomes of our cohort showed 93.3% survival one year and 83.3% three years after surgery. In our series the population was younger, and no patients underwent surgery in an emergency setting, nevertheless, the median hemoglobin was lower (9.6 vs 10.2 g/dL) and the median ASA scores were the same.

Urinary diversion alone (nephrostomy, intestinal conduit or cutaneous ureterostomy) is one of the possibilities of treatment in patients with hemorrhagic cystitis, working by preventing bladder distension and rupture of vessels, as well as, decreasing the exposure of the bladder urothelium to urokinase, increasing the possibility of successful hemostasis (2, 21). Bilateral nephrostomies are valid options, considering the advanced age, comorbidities and past radiotherapy of these patients, all factors that can affect the outcomes of more invasive procedures. Nevertheless, up to 25% will need further cystectomy, for complications associated with the leftover bladder or for intractable symptoms (17). In our series, only 5.9% (1) of our patients had nephrostomies tubes placed before cystectomy, possibly because of the elective setting the procedures were done and concomitant complaints such as fistula and pain.

When deciding the type of urinary diversion in patients who underwent cystectomy for radiation cystitis, one of the main problems is the tissue devascularization related to radiotherapy, increasing the risk of complications with uretero-enteric anastomosis (8, 22). While ileal conduits remain the standard, cutaneous ureterostomy emerges as a viable option in these frail population. A systematic review comparing ileal conduit and cutaneous ureterostomy in bladder cancer patients published by *Korkes et al.* showed that cutaneous ureterostomy was associated with a reduction in surgery time, lower transfusion rate, less blood loss, shorter hospital stay and reduced intra and post-operative complications (23). *Suzuki et al.* reported similar perioperative results between ileal conduit and cutaneous ureterostomy, however the latest was associated with an increased risk of pyelonephritis and renal deterioration (24). In our series we found no significant difference in early complications, length of stay or mortality when comparing ileal conduit and cutaneous ureterostomy. The type of urinary diversion should be carefully chosen for each patient and according to surgeon experience and intraoperative findings.

Radiotherapy is responsible for inducing fibrosis and extensive adhesions, between the bladder and the rectum, but also between the bladder and the symphysis and pubic rami, increasing the difficulty of the surgery. Kim and Steinberg reported an increased risk of complications in patients who had cystectomy after pelvic radiation, with 39% of the patients in the irradiated group having complications that required an invasive surgical or radiologic intervention, compared with 9% of the group without previous radiotherapy (22). Similar results were reported in other studies (8). In our series, the severe complications requiring intervention had a lower incidence (29.4%), possibly because of the less complexity of the surgery, requiring less dissection and mobilization of structures, thereby slightly reducing operative time and blood loss. When the dissection of posterior planes is difficult due to

fibrosis, we chose to use a supratrigonal approach with fulguration of the remaining bladder, with the objective of decreasing the morbidity of this surgery in such a frail population, by decreasing dissection and slightly reducing operative times (25). In these situations, it is important to exclude the presence of urothelial neoplasm, not only due to the risk of seeding after opening of the bladder, but also for the sub-optimal oncological treatment.

Our study should be viewed in the context of certain limitations. It was conducted in a single institution and had a small sample size. As well as, the retrospective nature of this study impacts the risk of underreporting, mainly minor complications. As such, the number of complications after discharge could be underreported.

Nevertheless, with the paucity of data on patients submitted to cystectomy for hemorrhagic cystitis our study represents one of the largest series published, providing important insights into the management of this challenging condition (8, 26, 27). Despite the encouraging results compared with previous studies, this procedure should remain a last resort for patients with intractable hematuria. The decision between the type of procedure and urinary diversion should be made by the surgeon and according to the intraoperative findings.

CONCLUSIONS

Radiation-induced hemorrhagic cystitis is a severe complication of pelvic radiation that often necessitates invasive interventions. In cases of intractable hematuria unresponsive to conservative treatments, immediate and effective management is crucial. Our findings support supratrigonal cystectomy as a viable last resort option, with acceptable perioperative morbidity and, possibly, reduced risks compared with simple cystectomy in patients with prior pelvic radiation. This approach provides a practical solution for

DECLARATIONS

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Authors' contributions: JAP, study concept, data analysis and interpretation, manuscript original drafting; DVB, data collection and interpretation, manuscript drafting; ML, study concept, data analysis and manuscript reviewing; PC, data interpretation and manuscript reviewing; RG, data interpretation and manuscript reviewing; BJP, manuscript drafting and reviewing; PP, data collection and interpretation, manuscript drafting; CR, study conception and design, data analysis and manuscript reviewing. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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managing this challenging condition while balancing safety and efficacy. Future studies with larger cohorts and prospective designs are needed to further optimize management strategies for this challenging condition.

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