

Outcome of Surgical Intervention for Bladder Carcinoma

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Abstract: ***Background:** Despite advances in medical oncology, radiation therapy, and molecular and cell biology, the mainstay in the management of bladder cancer continues to be surgery. **Methods:** The authors reviewed the literature regarding the endoscopic diagnosis and management of bladder cancer as well the role of partial and radical cystectomy. **Results:** Cystoscopy and transurethral resection are required to diagnose and stage bladder cancer. The indications for random bladder biopsies, prostatic urethral biopsy, and re-resection of the tumor bed are examined. The results and complications of endoscopic resection in the management of Ta, T1, and T2 or greater bladder cancer are reported. The roles of partial cystectomy, radical cystectomy, extent of lymphadenectomy, and indications for urethrectomy are also examined. The results and complications of radical cystectomy for the management of T2, T3, T4, and N+ bladder cancer are reported. **Conclusions:** Surgery remains a critical element in the management of bladder cancer. Improvements in surgical technique, urinary reconstruction, and multimodal therapy continue to improve the prognosis and quality of life of patients with transitional cell cancer of the bladder.*

Keywords: bladder cancer, urothelial cancer, intravesical

1. Introduction

Despite advances in medical oncology, radiation therapy, and molecular and cell biology, surgery continues to be the mainstay of the management of bladder cancer. The initial assessment, diagnosis, and staging of bladder cancer are determined with cystoscopy. Therapy of the more common superficial bladder cancer is by cystoscopic transurethral resection (TUR), with intravesical cytotoxic chemotherapy and immunotherapy being used almost exclusively in an adjuvant setting. Surgery continues to be an important part of the management of invasive bladder cancer, used either in the more classical approach (i.e., radical cystectomy and urinary diversion) or as a component of a combined-modality bladder-sparing approach (ie, aggressive TUR with radiation and chemotherapy). This review focuses on the critical principles and controversies in both the endoscopic and open surgical approaches to superficial and invasive bladder cancer.

2. Material and Methods

The literature search was performed on PubMed, Medline and Google scholar, chosen because they are reliable and easy to read. The reference lists of the articles retrieved were examined to capture any other potentially relevant article. The search was restricted to articles published between 2000 and 2022 to acquire all the scientific knowledge about neurologic bladder, which grew fast in this period.

3. Results

Endoscopic Approaches to Bladder Cancer

The majority of patients who are diagnosed with bladder cancer present with either hematuria or irritative voiding symptoms. The initial diagnosis of bladder cancer is usually suspected following flexible cystoscopy performed under local anesthesia by a urologist as part of an assessment of

these symptoms. Although the gross appearance of the tumor is a guide to the probable tumor type and stage, a definitive diagnosis is established by formal transurethral tumor resection under either general or regional anesthesia. At the time of cystoscopy, an inspection of the bladder is performed documenting the number, location, size, and appearance of each of the tumors on a standard bladder template. As bladder cancer is a field disease of the urothelium, it is not unusual to find more than one tumor. In fact, the size and number of tumors are almost as important as the grade and stage in predicting tumor recurrence in the future. [1, 2] Following tumor mapping, a larger cystoscope/resectoscope (24F to 26F or mm in circumference) is introduced into the bladder and the tumors are resected. It is important that the initial resection includes the underlying smooth muscle muscularis propria to allow for proper tumor staging. After tumor resection, additional biopsies may be obtained of any abnormal appearing areas since these may be carcinoma in situ, which has important prognostic and therapeutic implications. The need for random biopsies of areas of the bladder that appear normal in order to assess for a field change is controversial. In general, most studies indicate that in patients with 1 to 2 bladder tumors, additional random bladder biopsies yield little important additional information and are probably unnecessary. [3] An obvious exception is for patients with a positive urine cytology in whom no obvious tumor is found. These patients require careful assessment of the renal collecting systems and ureters with selective ureteral washings for cytology and bilateral retrogrades, as well as random bladder biopsies and a TUR biopsy of the prostatic urethra.

Appearance Suggesting a Superficial Tumor (Ta)

When the suspected diagnosis is superficial bladder cancer (based on the appearance of the tumor), consideration should be given to administering an immediate postoperative single intravesical dose of 40 mg of mitomycin C. In a randomized, controlled trial performed in Europe, a single postoperative intravesical administration of mitomycin C decreased the

recurrence rate at 3 months from 55% to 40%.6 Mitomycin C is presumed to act on the tumor cells that are released at the time of TUR by preventing their implantation and growth in deepithelialized areas created by the surgery.

Appearance Suggesting an Invasive Tumor (T1 or Greater)

When the suspected diagnosis is invasive bladder cancer (based on the appearance of the tumor), it is reasonable to perform a more limited resection to obtain sufficient tissue, including deep muscle, in order to establish a diagnosis since the majority of these patients will go on to have a radical cystectomy. However, in most cases, we attempt to completely resect the tumor for two reasons. First, a tumor that *appears* to be invasive may in fact be a superficial T1 tumor, and second, an aggressive TUR to remove as much visible tumor as possible is an important component of any bladder-sparing approach, which may be a therapeutic option for the patient. [7, 8] Following gross resection of the tumor, we perform biopsies of the tumor bed and submit these separately for pathologic assessment of the completeness of the resection. In the past, we routinely performed prostatic urethral biopsies since urethral involvement indicates an increased risk of local recurrence, suggesting the need for urethrectomy at the time of cystectomy. [9] Recent data suggest that urethral recurrence is not a problem if continent urinary diversion to the urethra is performed and a frozen section margin from the tip of the prostate is negative. Following completion of the tumor resection, a careful bimanual examination is needed to assess for any residual mass and to determine if the bladder and tumor mass are mobile or fixed to the pelvic sidewall. Patients in whom the mass is fixed to the sidewall (cT4b) are at increased likelihood to be inoperable or have positive margins at the time of surgery. This patient subgroup may benefit from preoperative chemotherapy. [10, 11]

Complications of Transurethral Resection of Bladder Tumor

The size of the tumor and the aggressiveness of the resection determines the postoperative management and risk of complications following a transurethral resection of bladder tumor (TURBT). The majority of patients who have a resection of a small superficial tumor can be discharged without a catheter on the day of surgery. A patient who undergoes an extensive resection down to perivesical fat may require 24 to 48 hours of hospitalization with a Foley catheter remaining in the bladder for 4 to 7 days. The most common complication of TURBT is bleeding that requires clot irrigation with a reoperation rate of <2%. Intraperitoneal bladder perforation requiring emergency laparotomy is rare, occurring in <1% of patients. [12]

The Role of Re-resection

On occasion, the pathologist will have difficulty determining whether the tumor has invaded the muscularis propria. As this is important in determining therapy, these patients need to undergo a re-resection of the base of the tumor. Indeed, an argument has been made that all patients should undergo a second-look cystoscopy and TURBT. In a referral setting, 79% of patients initially diagnosed with superficial bladder tumors were found to have residual tumor at second-look cystoscopy. Upstaging from superficial to invasive bladder

cancer occurred in 29% of patients, and management was changed based on the results of the re-resection in 33% of patients. [13] We currently perform office cystoscopy on all patients referred for evaluation of bladder cancer, even if a prior resection was performed elsewhere. However, we re-resect only those with unusual or unexpected findings. We recommend routine re-resection of all patients with high-risk superficial bladder cancer (Ta grade III, T1 grade II-III) as it is in this group that different findings most commonly alter management.

The Role of Laser and Other Endoscopic Modalities

TUR of bladder tumors and transurethral resection of the prostate (TURP) use the same electrosurgical technology. Considerable progress has been made in developing new, less invasive therapies for benign prostatic hyperplasia in order to decrease the morbidity associated with TURP. Unfortunately, few of these technologies have been translated to the endoscopic management of bladder tumors. The neodymium: yttrium aluminum garnet (Nd: YAG) and holmium YAG laser have been used for the treatment of benign prostatic hyperplasia and bladder tumors. In general, lasers work effectively to destroy tumors. However, lasers are not useful in situations where pathologic assessment of the tumor is necessary. Because pathologic assessment is important in most circumstances surrounding the management of bladder cancer, these modalities have not flourished. Recently, a new device has been introduced that uses bipolar current for TUR, thus improving hemostasis and allowing the use of saline for electrosurgery.

Our preliminary experience with this device suggests that the technology offers improvements with enhanced safety and decreased blood loss while allowing for adequate pathologic assessment. [14] Several reports have suggested that the sensitivity of cystoscopy to detect dysplasia and carcinoma in situ can be improved by instilling 5-aminolaevulinic acid into the bladder and then examining protoporphyrin IX fluorescence under blue and white light. However, this technology has not spread beyond select research centers. [15, 16]

Results of TURBT: Tumor Control

TURBT effectively provides tissue for the diagnosis and staging of bladder cancer. The effectiveness of TURBT as a therapy of bladder cancer is primarily dependant on the biological behavior of the bladder tumor rather than the surgical resection itself. Thus, small, solitary, low-stage and low-grade (Ta grade I-II) tumors are effectively excised and have a low recurrence rate following TURBT, whereas T1 grade III tumors recur frequently (60%) despite the fact that they are completely excised. [17-19] Clearly, patients with these high-risk tumors have the most potential to benefit from adjuvant intravesical therapy. In the case of invasive tumors (T2 or greater), the limitations of endoscopic resection are 3-fold. First, complete resection of the tumor is difficult because of extension into and through the muscle wall. Second, the field defect is not treated; therefore, there is a high risk of tumor recurrence (or a new occurrence) elsewhere in the bladder. Third, muscle-invasive bladder cancer is associated with a significant rate of metastatic disease that is neither evaluated nor treated by local surgery within the bladder. [8, 12, 13, 17-21] Endoscopic resection

alone of select T2 tumors can provide long-term control. The recent summary experience reported at one institution showed a 10-year disease-specific survival of 76%. [22] However, because of the limitations noted above, bladder-sparing approaches for invasive bladder cancer generally combine radiation and chemotherapy.

Open Surgical Management

Radical cystectomy is the most common treatment for invasive bladder cancer in the United States. This approach allows wide excision of the bladder, the surrounding structures, and the draining lymph nodes. Current improvements in surgical technique, urinary reconstruction, and perioperative care have decreased surgical morbidity and mortality and have improved patient quality of life.

Partial Cystectomy

Fewer partial cystectomies are performed today due to the development of improved techniques for TUR of bladder tumors and improved understanding of the natural biology of bladder tumors. Partial cystectomy provides certain intrinsic advantages attractive to patients and physicians alike, including sparing potency in men, leaving a functioning natural reservoir, allowing a full thickness resection of the tumor, and allowing the ability to sample the pelvic nodes. However, the major disadvantage is that the field defect is not treated, thus leading to high tumor recurrence rates ranging from 40% to 80% in some series. [23, 24] The high tumor recurrence rate has not only potentially life-threatening consequences for the patient, but also the added burden of requiring frequent cystoscopic (ie, uncomfortable, labor intensive, and costly) follow-up and often adjuvant intravesical therapy. Less than 10% of patients with invasive bladder cancer are candidates for a partial cystectomy. The lesion should be an initial occurrence and should be solitary with no associated carcinoma in situ (random bladder biopsies are required to confirm this). The tumor must be located in a part of the bladder that allows for complete resection with clean margins and preservation of an adequate bladder capacity. In essence, this excludes patients with lesions around the trigone where the ureteral orifices and bladder neck are in close proximity. Patients with lesions on the dome of the bladder and tumors located in diverticula are good candidates for partial cystectomy. At the time of surgery, the tumor is excised from the bladder with a 2-cm margin (confirmed by frozen section), and the bladder is then closed in two layers with absorbable sutures. Intraoperatively, care must be taken to prevent spillage of urine due to the risk of tumor cell implantation in the surgical wound. Long term complications include decreased bladder capacity and tumor recurrence.

Radical Cystectomy

The most common indication for radical cystectomy is a muscle-invasive (T2 or greater) bladder tumor without evidence of distant metastasis. Additional indications include recurrent high-grade T1 or Ta bladder carcinoma despite repeated endoscopic resection and adjuvant intravesical chemotherapy (these patients have a high risk of disease progression) and multiple recurrences of low-grade Ta bladder cancer that cannot be controlled by periodic endoscopic resection. The surgery is performed through a lower midline incision (although perineal cystectomies and

laparoscopic cystectomies have been described). [25-27] A complete pelvic lymph node dissection is performed. In men, the bladder, peritoneal covering, perivesical fat, lower portion of the ureters, prostate, seminal vesicles, the distal portion of the vasa deferentia, and possibly the urethra are removed. The urinary tract is reconstructed with either an ileal conduit, a continent cutaneous diversion, or a neobladder. In women, the bladder, peritoneal covering, perivesical fat, lower portion of the ureters, uterus, ovaries, fallopian tubes, and possibly the anterior vaginal wall and the urethra are removed. In a fashion similar to that used in men, the urinary tract is reconstructed with either an ileal conduit, a continent cutaneous diversion, or a neobladder.

Lymphadenectomy

Bilateral pelvic lymphadenectomy is important for the staging and treatment of invasive bladder carcinoma. [28] This entails removing the fibrolymphatic tissues surrounding the iliac vessels in the pelvis. The margins of dissection are proximally from the common iliac artery (some would say the aortic bifurcation) to the circumflex iliac vein distally and laterally from the genitofemoral nerve superiorly to the pelvic floor inferiorly. Care must be taken to correctly identify and preserve the obturator nerve as it emerges from the medial border of the psoas muscle. [29] There is some controversy as to how extensive the lymph node dissection should be, whether it should be obtained en bloc or submitted separately, whether the node dissection has any therapeutic as opposed to just prognostic value, and whether cystectomy in the face of positive lymph nodes provides any survival advantage. Several recent reports have clarified some of these issues. Herr and colleagues examined whether the number of nodes removed would affect outcomes after radical cystectomy. [30] These investigators found that a minimum of 9 nodes needed to be examined to accurately assess nodal status. They also found that survival improved in both node-positive and node-negative patients as the number of nodes removed increased. Although it cannot be concluded from this report that the extent of the node dissection generated the improved survival (because of multiple confounding influences such as adjuvant treatment decisions and more accurate staging), it is likely that it was a contributing factor. The same investigators evaluated the impact of submitting nodes en bloc or as separate packages and suggested that submitting nodes as separate packages not only is easier but also optimizes the evaluation and number of the lymph nodes retrieved. [30, 31] There is no doubt that a pelvic lymphadenectomy has significant prognostic importance. Patients with positive nodes are clearly at increased risk of failure and are candidates for adjuvant chemotherapy, which has the potential to provide a survival advantage (again, a controversial issue). [30, 32] Whether the node dissection itself provides a survival advantage in patients with positive nodes is less clear. Certainly, some studies indicate that lymphadenectomy, in combination with radical cystectomy, can cure a small fraction of node-positive patients. [32] The subset of patients benefiting most from lymphadenectomy and cystectomy in the face of positive nodes appear to be those with a low-stage primary tumor. Based on this information, we proceed with radical cystectomy when we discover positive nodes (either grossly or on frozen section) at the time of surgery in the following circumstances: (1) when the patient has

substantial local symptoms from the tumor, (2) when the local stage of the tumor is low, and (3) when cystectomy can be performed easily with minimal morbidity to the patient (to allow for prompt initiation of chemotherapy). We are reluctant to perform continent urinary diversion to the urethra in these circumstances due to the risk of pelvic recurrence and the necessity for subsequent therapy.

Urethrectomy

Over the past 10 years, the indications for total urethrectomy at the time of cystectomy have undergone substantial modification. The overall risk of urethral recurrence after cystectomy is approximately 10%. [33] Historically, urethrectomy was performed in patients with multifocal tumors, diffuse carcinoma in situ, and prostatic urethral involvement. More recent studies have identified prostatic stromal invasion or diffuse carcinoma in situ of the prostatic urethra as the primary risk factor, conferring a 25% to 35% risk of urethral recurrence. [34] Two studies have found a less than 5% incidence of urethral recurrence in patients undergoing ileal neobladder replacement despite the postoperative identification of prostatic stromal involvement.

[35] Based on these two large series, we no longer perform routine preoperative prostatic urethral biopsies prior to cystectomy, but instead we rely on frozen section analysis of the urethral margin to decide whether to proceed with neobladder construction or perform a urethrectomy and continent cutaneous diversion. In patients who are not candidates for a neobladder and have known prostatic stromal involvement by tumor, we perform an en bloc urethral resection. For patients who have had a cutaneous diversion and are discovered on final pathology to have prostatic stromal involvement, we recommend a delayed urethrectomy after they have completed adjuvant chemotherapy. In women, a classical radical cystectomy includes removal of the urethra and anterior vaginal wall since case series have reported urethral and vaginal involvement by transitional cell carcinoma in approximately 13% of cystectomies. [36, 37] However, careful histological studies have documented a low incidence of urethral tumor involvement (0% to 20%) in the absence of tumor at the bladder neck. Currently, in women who are candidates for neobladders, we perform cystoscopy and preoperative bladder neck biopsies combined with intraoperative frozen section of the bladder neck margin prior to proceeding with neobladder construction. [36, 37] We routinely resect the urethra and anterior vaginal wall in women who are not candidates for a neobladder.

Management of the Ureter

A small subgroup of patients (1% to 9%) are found to have carcinoma in situ at the distal ureteral margin at the time of frozen section during a cystectomy. Resection of sufficient ureter to obtain a negative margin may result in substantial ureteral shortening. In such a situation, the ureter may no longer reach the necessary distance into the pelvis to perform a tension-free anastomosis to an orthotopic neobladder. Certain continent diversions (eg, the Studer pouch and the modified Hautmann neobladder) have long afferent limbs that can bridge moderate ureteral gaps. [38, 39] In cases where we are unable to obtain a margin clear of

carcinoma in situ and the patient has good ipsilateral renal function, we will cut the ureter "comfortably" short and perform the urinary diversion. Several studies have shown a low incidence of ipsilateral tumor recurrence in these circumstances. [40, 41]

Choosing a Urinary Diversion

Once the bladder is removed, the urologist is challenged in selecting the appropriate urinary diversion. Several urinary diverting procedures are described in the medical literature. These procedures can be divided into incontinent (ileal conduit and cutaneous urostomy) and continent procedures. The continent procedures can be further subdivided into cutaneous reservoirs (in which the reservoir is connected to the abdominal skin requiring intermittent catheterization) and orthotopic neobladders (in which the reservoir is connected to the urethra). The gold standard in incontinent diversions is the ileal conduit, which is a simple and safe method of diverting the urine, but continuously draining stoma can affect the quality of life of some patients. This disadvantage has led to the development of several continent reconstructive procedures. Each form of diversion has its intrinsic advantages and disadvantages. The urologist must analyze a variety of elements before selecting the optimal procedure for that patient. We favor orthotopic neobladders in properly selected patients with continent cutaneous diversion followed by ileal conduit as second and third choices. [42, 43]

The Role of Cystectomy in Locally Advanced Bladder Cancer

Less than 50% of patients with locally advanced or node-positive bladder cancer will survive if treated by surgery (cystectomy) alone. Several large trials of combination chemotherapy administered prior to surgery have suggested a survival benefit with the neoadjuvant approach. [10, 11] The patient group demonstrating the most benefit in terms of long-term survival are those who have an excellent response to the chemotherapy. In the M. D. Anderson trial, 40% of the patients had no evidence of tumor in the specimen at the time of cystectomy (good responders) after 2 cycles of MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) chemotherapy. [10] Only 12% of these "good responders" had a subsequent relapse. Of the patients with persistent viable pelvic nodal disease after 2 cycles of chemotherapy (poor responders), 86% subsequently died of progressive bladder cancer. Surgery appears to be providing important consolidation after chemotherapy even in patients who have a clinical complete response. In a study from the Memorial Sloan-Kettering Cancer Center, 30% of patients with a clinical complete response to chemotherapy were found at surgery to have unsuspecting residual disease, and only 1 of 12 patients with major responses to chemotherapy but who refused surgery were alive at 3 years. [44] Based on these data, we recommend 2 to 3 cycles of preoperative MVAC chemotherapy to patients with locally advanced bladder cancer whom we believe to be unresectable at the time of examination under anesthesia. Additionally, we recommend radical cystectomy to the group achieving a complete or substantial partial response. Patients who do not achieve a good clinical response are likely to be unresectable or progress rapidly despite surgery. We recommend second-line chemotherapy to this poor-prognosis patient group.

Complications of Radical Cystectomy and Urinary Diversion

Radical cystectomy is considered to be a major surgical procedure. As a result, various complications may occur during both the early and late postoperative period. It is important to know not only the complications, but also the factors that can increase or decrease the risk for complications following a radical cystectomy. Important preoperative variables include age, sex, American Society of Anesthesiologists score, preoperative hemoglobin, smoking history, prior abdominal surgeries or external-beam radiation therapy, and type of diversion. The patient who has a standard radical cystectomy with ileal conduit or cutaneous ureterostomy usually requires 5 to 7 days of hospitalization, while the patient undergoing continent urinary diversion may require 7 to 10 days of hospitalization. Important intraoperative and postoperative variables include estimated blood loss, operative time, transfusion requirement, pathologic tumor stage, the need for surgical intensive care unit admission, and postoperative hemoglobin level. Overall, the rate of minor complications for patients undergoing radical cystectomy is approximately 30%. The risk for a major complication with this procedure is about 5%, and the mortality rate is approximately 1% to 3%. [45-49]

Results of Radical Cystectomy: Tumor Control

The significant improvements in clinical outcomes over the past 25 years can be attributed to advances in surgical technique and in medical and anesthetic care. Overall recurrence-free and survival rates vary among institutions. However, higher pathological stage and increased lymph node status are generally associated with increased recurrence rates and worse cancer specific survival. Overall, a patient undergoing a radical cystectomy for invasive bladder cancer has an approximate 60% to 70% 5-year disease-free survival rate. Subdivided, this percentage can increase to greater than 70% for organ-confined lymph node-negative bladder tumors and can decrease to 40% to 50% for those patients with non-organ-confined lymph node-positive bladder tumors. In a review of the literature, this latter group consistently demonstrates higher rates for recurrence and worse survival compared to those with organ-confined disease. [28, 50-55]

4. Conclusions

Surgery remains a critical element in the management of bladder cancer. Cystoscopy and TURBT serve to diagnose and stage bladder cancer. Contemporary management of bladder cancer is directed by disease stage and grade. TURBT in combination with intravesical therapy effectively manages most superficial bladder cancers (Ta/T1) and select invasive tumors. Radical cystectomy, including lymphadenectomy, is the primary modality for the management of clinically localized invasive bladder cancer (T2/T3). Improvements in surgical technique, urinary reconstruction, and multimodal therapy continue to improve the prognosis and quality of life of patients with transitional cell cancer of the bladder.

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