

Surveillance strategies after definitive therapy of invasive bladder cancer

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Abstract

Following definitive therapy for muscle invasive bladder cancer, patients remain at risk for local and distant recurrence. Additionally, recurrences can result from formation of new tumours elsewhere in the urinary tract. We review patterns of recurrence and the prognosis associated with recurrence. Optimal surveillance strategies are discussed.

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Bladder cancer is the second most common urologic malignancy after prostate cancer.¹ At the time of initial diagnosis, 19% of patients present with muscle-invasive disease.² In the absence of distant metastatic disease, these patients are most commonly treated with radical cystectomy, pelvic lymphadenectomy and urinary diversion. A select few patients will undergo bladder-preserving protocols. Following treatment, patients can recur with local or metastatic disease as well as with the development of new urothelial tumours in the upper urinary tract or urethra. There is no clear consensus on the optimal schedule of post-treatment surveillance.

Local recurrence

Local recurrence following cystectomy encompasses pelvic soft-tissue involvement and involves pelvic lymph nodes. However, there is not a uniform definition on the proximal extent of the nodes distinguishing local from distant recurrence. Some authors define local recurrence as involvement of the nodes below the iliac bifurcation, whereas others have extended this definition to include the aortic bifurcation.^{3,4} Possible mechanisms of local pelvic recurrence include incomplete resection of the tumour, resulting in grossly or microscopically positive surgical margins, involved unresected lymph nodes beyond the limits of the lymphadenectomy, and intraoperative spillage of tumour cells.³

The frequency at which local recurrence occurs has decreased significantly from the nearly 40% reported in early cystectomy series.^{5,6} More contemporary series report local recurrence rates of 3.9% to 29% (Table 1). Factors associated with local recurrence include pathologic tumour

stage, presence of tumour in regional lymph nodes, extent of lymphadenectomy and use of perioperative chemotherapy.⁴ Patients with extravesical disease are at much higher risk of local recurrence. Rates of local recurrence were 6% to 18% in patients with stage pT1 to pT3a (based on 1992 TNM [tumour, node, metastasis] staging) compared to 51% for those with stage pT3b in a study by Greven and colleagues.⁷ In a long-term analysis of 1054 patients, Stein and colleagues observed an overall local recurrence rate of 7% and rates of 6% and 13% for those with organ-confined and extravesical lymph node negative patients.¹¹ Patients with pelvic lymph node involvement are also at increased risk of local recurrence, with reported rates of 24% to 43%.^{7,8,12,13} Interestingly, in the study by Stein and colleagues, those with lymph node-positive disease demonstrated only a 13% local recurrence rate following cystectomy. Patients in this study underwent a meticulous extended lymphadenectomy extending proximal to the aortic bifurcation. The low rate of local recurrence observed in this study suggests a benefit of extended lymphadenectomy in decreasing pelvic recurrences. Other studies have shown improved local control as well as cancer-specific and recurrence-free survival in patients having more extensive lymphadenectomies.^{14,15}

Time to development of local recurrence is relatively short, with median time being 9 to 18 months and typically less than 12 months.^{7,10,11,16,18} Westney and colleagues, in a review of their institution's experience with local recurrence over 35 years, reported that although 27 of 33 patients (82%) experienced local recurrence within 2 years, the range was from 1 to 72 months.¹⁶ Most patients presenting with local recurrence are symptomatic. In the study by Westney and colleagues, 25 out of 33 patients (76%) had symptoms and in 10 patients (30%) there was a palpable pelvic mass.¹⁶ In the series by Wishnow and Dmochowski, all 10 patients with local recurrence had symptoms.⁸ The most common symptoms are pelvic, perineal, gluteal or hip pain. Bleeding or discharge from the vagina or urethra as well as lower extremity edema are less common symptoms. Asymptomatic local recurrences are detected with axial imaging, most commonly computed tomography (CT) of the abdomen and pelvis. Locally recurrent lesions may be indistinct on CT and some have suggested the superiority of magnetic reso-

Table 1. Local recurrence in contemporary series of radical cystectomy

Publication	Years of study	Local recurrences (%)
Greven et al. ⁷	1977-1986	13/83 (18)
Wishnow and Dmochowski ⁸	1983-1985	10/178 (5.6)
Brendler et al. ⁹	1982-1988	3/76 (3.9)
Schoenberg et al. ¹⁰	1982-1989	5/101 (5)
Stein et al. ¹¹	1971-1997	77/1054 (7)
Volkmer et al. ¹⁸	1986-2006	182/1270 (14.3)
Frazier et al. ²¹	1969-1990	50/531 (9.4)
Cheng et al. ²⁰	1980-1984	63/218 (29)

nance imaging (MRI) in delineation.³ The prognosis associated with local recurrence is, unfortunately, poor. Simultaneous systemic metastases occur in 36% to 64% of patients.^{16,17} Median survival was 7 months in the review by Westney and colleagues, and 4 months in the study by Greven and colleagues.^{7,16} Aggressive treatment with chemotherapy, surgery or radiation, either in combination or alone, does little to alter the outcome, although it does provide significant palliation.¹⁶

Distant recurrence

Most patients who recur following radical cystectomy do so with metastatic disease. The outcomes of patients undergoing radical cystectomy for the treatment of invasive bladder cancer are summarized for several contemporary series in Table 2. Recurrence-free survival ranges from 61.7% to 76% at 5 years and 55.2% to 73% at 10 years. Increasing pathologic stage and lymph node-positive disease are generally associated with higher recurrence rates and worse survival. Table 3 shows the outcomes in several cystectomy series stratified by pathologic stage and lymph node status.

In an analysis of patients undergoing cystectomy at the University of Southern California, over a 25 year period, distant recurrences increased progressively from 13%, in

those with organ-confined lymph node-negative tumours, to 32%, in those with extravesical lymph node-negative tumours. Distant recurrences occurred in 52% of patients with positive lymph nodes. In the Mayo Clinic experience, 10-year metastasis-free survival decreased from 82%, in those with organ confined cancers, to 54%, in those with extravesical disease.²⁰ Metastasis-free survival was 38% at 5 years and 21% at 10 years in patients with positive lymph nodes compared to 81% and 78% in those with negative lymph nodes.

Metastatic disease develops relatively quickly, with 80% to 90% of distant recurrences identified within 3 years.⁴ In a large series from Ulm, Germany, median time to the development of metastatic disease was 13 months. Sites of recurrence were bone in 13.9%, liver in 10.7% and lung in 9.9%.¹⁸ The involvement of other sites, such as brain, peritoneal cavity, skin and vagina, occurs less frequently.⁴ The prognosis of patients with metastatic disease unfortunately remains poor. Combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or gemcitabine and cisplatin (GC) are the current standards however even with these treatments median survival is 13.8 to 14.8 months.^{22,23} Bajorin and colleagues identified Karnofsky performance status of less than 80% and the presence of visceral (lung, liver or bone) metastases as prognostic factors predicting outcome following treatment with MVAC. Median survival for patients with 0, 1 or 2 risk factors was 33, 13.4 and 9.3 months, respectively.²⁴ This data may serve as potential evidence that earlier detection of metastatic disease in the asymptomatic state or with smaller disease burden may result in improved response to treatment.

Urethral recurrence

Recurrent urothelial carcinoma in the retained urethra following cystectomy has historically been shown to occur in only 6% to 10% of patients.^{25,26} Urethral recurrences occur even less frequently in patients undergoing orthotopic as compared to cutaneous urinary diversions. In a large series of 768 men with 397 undergoing orthotopic diversion (median

Table 2. Outcomes of contemporary series of radical cystectomy

Publication	Years of study	% RFS		% CSS		% OS	
		5 years	10 years	5 years	10 years	5 years	10 years
Stein et al. ¹¹	1971-1997	68	60	N/A	N/A	66	43
Volkmer et al. ¹⁸	1986-2006	61.7	55.2	N/A	N/A	N/A	N/A
Dalbagni et al. ¹⁹	1990-1993	N/A	N/A	57	N/A	45	N/A
Cheng et al. ²⁰	1980-1984	76	73	72	67	53	41
Frazier et al. ²¹	1969-1990	N/A	N/A	59	46	48	33

RFS = recurrence-free survival; CSS = cancer-specific survival; OS = overall survival; N/A = not available.

Table 3. Outcomes of contemporary series of radical cystectomy stratified by pathologic stage

Publication	Pathological group	% RFS		% CSS		% OS	
		5 years	10 years	5 years	10 years	5 years	10 years
Stein et al. ¹¹	Organ-confined	80	77	N/A	N/A	74	54
	N-	85	82	N/A	N/A	78	56
	N+	46	44	N/A	N/A	45	37
	Extravesical	46	44	N/A	N/A	37	22
	N-	58	55	N/A	N/A	47	27
	N+	30	30	N/A	N/A	25	17
Dalbagni et al. ¹⁹	Organ-confined	N/A	N/A	N/A	N/A	59-64	N/A
	Extravesical	N/A	N/A	N/A	N/A	26-27	N/A
Cheng et al. ²⁰	Organ-confined	N/A	82	N/A	78	N/A	53
	Extravesical	N/A	54	N/A	47	N/A	23
	N-	N/A	78	N/A	74	N/A	46
	N+	N/A	31	N/A	21	N/A	11
Frazier et al. ²¹	Organ-confined	N/A	N/A	64-82	48-71	N/A	N/A
	Extravesical	N/A	N/A	39	23	N/A	N/A

N- = lymph node-negative; N+ = lymph node-positive; RFS = recurrence-free survival; CSS = cancer-specific survival; OS = overall survival.

follow-up 10 years) and 371 having cutaneous diversion (median follow-up 19 years), Stein and colleagues sought to determine rates and risk factors for urethral recurrence.²⁷ They found a 4% urethral recurrence rate with orthotopic diversions and 8% with cutaneous diversions. The only significant predictor of increased recurrence risk was prostatic involvement. If prostatic stromal involvement was present, the 5-year risk of recurrence rose to 11% in the orthotopic group and 24% in the cutaneous diversion group. The authors recommend the intra-operative frozen section from the urethra at the prostatic apex as the only criterion to determine whether a urethrectomy should be performed. This recommendation is supported by several other studies.²⁶⁻²⁸ A review of several large published series showed low urethral recurrence rates of 0% to 2% in women with a negative intra-operative frozen section of the bladder neck.²⁹ Urethral recurrences occur at a median range of 1.5 to 2.2 years, with most occurring before 5 years.^{26,30-35} Late recurrences can occur with some diagnosed up to 20 years after radical cystectomy.^{26,33} Urethral recurrences are often associated with poor outcomes, with one report showing a median survival of 28 months.³³ Stage at diagnosis was the most important predictor of outcome in that series. Therefore, earlier detection would seem to be important in improving survival outcomes. However, the 2 largest series in the literature found no difference in survival in patients having routine urethral wash cytology compared to those diagnosed based on symptoms.^{33,36} This calls into question the utility of routine urethral wash cytology. Caution must be exercised here, as these series are small and limited by their retrospective methodology. It seems clear that any symptom relative to the retained urethra should be evaluated with endoscopy and wash cytology. Routine scheduled urethral wash cytology may still be reasonable pending

more clear direction from the literature regarding impact on survival outcomes.

Upper tract recurrence

The multifocal nature of urothelial cancer leads to a risk of metachronous upper urinary tract (UUT) recurrence development in patients who have undergone radical cystectomy and urinary diversion for bladder cancer. This risk is relatively low (1% to 9%).³⁷⁻⁴⁰ This low risk is partly due to the high rate of early mortality from bladder cancer. Upper urinary tract recurrence is also often a delayed event and is the most common site of recurrence after 3 or more years of disease-free survival following cystectomy.³⁷⁻⁴⁰ The 3- and 5-year cumulative risks of UUT recurrence has been reported to be 4% and 7%, respectively. Analysis of this data over time showed that the 4% to 6% risk seen at 3 years remained constant for any point in time up to 4 years post-cystectomy.⁴¹ There are reported cases of UUT recurrence found as long as 9 years following cystectomy.^{37,38,40-43} Most UUT recurrences present with symptoms, such as hematuria or flank pain. Only a minority are picked up with routine surveillance imaging.³⁷⁻⁴⁰ In a recent review of published series, 58% to 78% of UUT recurrences presented with symptoms and 22% to 42% were found on surveillance imaging or cytology at a mean of 43 months post-cystectomy.⁴⁶ Urinary cytology detects less than 30% of UUT recurrences when used for routine post-cystectomy surveillance.^{39-41,43} However, in patients with symptoms, such as hematuria, cytology is positive in 80% to 100% of patients with recurrence, thereby making it helpful to confirm the diagnosis.³⁹⁻⁴¹

Multiple risk factors have been studied in an attempt to predict those at higher risk of UUT recurrence post-cystectomy. Pathologic T-stage does not predict for UUT recurrence.^{40,44}

Table 4. Surveillance schedule

	Follow-up schedule (mos)							
	3	6	12	18	24	36	48	60
Organ-confined	X							
Hx + PE	X	X	X	X	X	X	X	X
Routine labs		X	X	X	X	X	X	X
B12, folate	X		X		X	X	X	X
Urine cytology*	X	X	X	X	X	X	X	X
CXR	X	X	X	X	X	X	X	X
CT/MRI abdomen and pelvis			X		X	X		X
Extravesical/N+								
Hx + PE	X	X	X	X	X	X	X	X
Routine labs	X	X	X	X	X	X	X	X
B12, folate			X		X	X	X	X
Urine cytology	X	X	X	X	X	X	X	X
Urethral CXR	X	X	X	X	X	X	X	X
CT/MRI abdominal pelvis	X	X	X	X	X	X	X	X

Hx = history; PE = physical examination; CXR = chest x-ray; CT = computed tomography; MRI = magnetic resonance imaging; Routine labs = complete blood count, electrolytes, creatinine, calcium, liver function tests; * = bagged cytology in patients with ileoconduits; voided cytology in patients with neobladders; catheter cytology in patients with continent cutaneous reservoirs or hypercontinent neobladders; urethral wash is considered optional only.

Beyond 5 years follow-up should consist of annual Hx & PE, routine bloodwork, and cytology with contrast-enhanced CT of the abdomen and pelvis with urography every 2 years.

Tumour involvement of the intramural ureter on final pathology does predict for UUT recurrence, including anastomotic recurrence. Intra-operative positive frozen section analysis of the distal ureteric margin is associated with increased risk of UUT recurrence, however, this is not associated with improved overall survival.^{45,46} Several series show that concomitant carcinoma in situ with muscle invasive disease in the bladder is not associated with UUT recurrence.^{39-41,44} In contrast, in one series of patients undergoing cystectomy for CIS alone there was a higher rate of UUT recurrence than in those with invasive cancer, possibly attributable to a better long-term prognosis and longer period of risk. This longer at-risk interval might increase the risk of UUT recurrence. A large series reviewing risk factors for UUT recurrence found only the presence of associated prostatic urethral involvement to be predictive of subsequent recurrence in the upper tract.⁴² This is to be distinguished from pathologic T4 disease with contiguous prostatic stromal invasion, which was not predictive, probably reflecting reduced survival in these patients and therefore, a shorter at-risk period.⁴⁴ Upper urinary tract recurrences are often advanced at diagnosis and may be associated with a poor prognosis.⁴²

Bladder-preserving protocols

Contemporary bladder-preserving approaches in patients with clinical stage T2-T4a bladder cancer can achieve 5-year survival rates of 50% to 60% and survival rates with an intact bladder of 40% to 45%.⁴⁷ The Massachusetts General Hospital has one of the largest experiences with bladder preservation.⁴⁸ Between 1986 and 1997, 190 patients were treated with bladder preservation based on complete response to transurethral resection (TUR) combined with chemotherapy and radiation therapy. The 5- and 10-year disease specific survival was 74% and 66% for stage T2 and 53% and 52% for stage T3-T4a. The 5- and 10-year disease-specific survival with an intact bladder was 46% and 45%. The pelvic failure rate was 8.4%. With an intact bladder, these patients also continue to be at risk for recurrence of both invasive or non-muscle-invasive bladder cancer. In this series, of the 121 complete responders, 32 (26%) had non-muscle invasive recurrences. Of these 32 patients, 13 (41%) ultimately required cystectomy. This is similar to a large Ottawa series using intra-arterial cisplatin and radiotherapy for bladder preservation.⁴⁹ In this series, 11% (16 of 142 with intact bladders) developed non-muscle-invasive bladder cancer recurrence. These tumours can be managed with transurethral resection of bladder tumour

(TURBT) and intravesical bacillus Calmette-Guérin (BCG) as needed. This risk for subsequent bladder recurrence in the intact bladder necessitates periodic surveillance cystoscopy.

Recommendations

For radical cystectomy

The rationale for post-cystectomy surveillance is that earlier detection of recurrence will allow for timely treatment with improved outcomes. This concept has been questioned recently in a retrospective series of 1270 patients with median follow-up of 59 months (range 0 to 270 months) who all underwent routine surveillance testing following cystectomy.¹⁸ The authors found no difference in survival outcomes whether patients presented with symptoms or had recurrence detected on routine follow-up testing. They hypothesized that symptom-guided follow-up alone may have similar outcomes to surveillance at potentially lower costs. While this hypothesis is provocative, without further confirmation in well-designed prospective trials, it is reasonable for routine surveillance to remain the standard of practice.

The recurrence patterns discussed above indicate that following cystectomy, median time to local and distant recurrence is 12 to 18 months with most patients relapsing within 5 years. Based on the data in Table 3, only 2% to 3% of patients relapsed between 5 and 10 years. To maximize the detection of recurrences, surveillance should therefore be intensive for the first 5 years with particular emphasis on the first 2 years. Patients with extravesical and lymph node-positive disease have significantly higher rates of relapse and warrant the most intensive follow-up. Extended pelvic lymphadenectomy to the aortic bifurcation may help reduce local recurrences and improve cancer-specific survival. However, further evidence from randomized trials is needed to demonstrate its utility and to determine whether it will allow for a modified surveillance protocol. Most UUT recurrences occur beyond 3 years with a median of 43 months. The recurrences therefore occur at a time when risk of local and distant recurrence is decreasing. By virtue of their longer survival, patients at lowest risk of local and distant recurrence are paradoxically at greater risk of UUT recurrence. Routine upper tract imaging is therefore advisable in all patients and should continue long term. Additionally, long-term upper tract imaging will allow for the earlier detection of complications of urinary diversion, such as urolithiasis and hydronephrosis secondary to benign stricture.

Routine scheduled surveillance with the goal of identifying local, distant and upper tract recurrences should include clinical assessment along with physical examination. Imaging

should consist of contrast-enhanced CT of the abdomen and pelvis including delayed urographic images as well as a chest x-ray for surveillance of pulmonary metastases. In patients with elevated serum creatinine, contrast allergy or other contraindications to CT scanning, MRI is an option. As surveillance of the retained urethra does not appear to improve outcome, urethral wash cytology is optional. Upper tract cytology via bagged urine from an ileoconduit or catheterized specimens from continent cutaneous reservoirs as well as voided cytology in patients with neobladders are recommended. Bone and liver involvement can be monitored through serum calcium and liver function tests including alkaline phosphatase levels. It is also reasonable to follow for metabolic complications with serum electrolytes, creatinine, vitamins B12 and folate. Recommendations for post-cystectomy follow-up are summarized in Table 4.

For bladder-preserving protocols

As in patients who have undergone cystectomy, the risk of recurrence in patients treated with bladder-sparing appears greatest in the first few years following treatment and diminishes after 5 years. As such, surveillance following bladder-preserving protocols should follow the same schedule outlined in table 4 with patients with clinical stage T2 disease and those with T3-T4a following the organ-confined and extravesical schema, respectively. Additionally, patients should undergo an initial restaging TUR at 3 months following completion of therapy. Surveillance cystoscopy should then be performed at 3-month intervals for the first year, then every 6 months until 5 years, and annually thereafter.

Conclusion

Patients recurring post-cystectomy for the treatment of urothelial cancer generally have a poor prognosis. Definitive evidence that routine surveillance following cystectomy affects response to treatment and survival is lacking. Nonetheless, it is a generally held oncologic principle that earlier detection of disease at the asymptomatic state positively influences outcome. As such, routine surveillance taking into account a patient's individual risk is justified.

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