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Do Patients Benefit from Routine Follow-up to Detect Recurrences After Radical Cystectomy and Ileal Orthotopic Bladder Substitution?

Gianluca Giannarini^a, Thomas M. Kessler^a, Harriet C. Thoeny^b, Daniel P. Nguyen^a,
Claudia Meissner^a, Urs E. Studer^{a,*}

^a Department of Urology University of Berne, Inselspital, Berne, Switzerland

^b Institute of Diagnostic, Interventional and Paediatric Radiology, University of Berne, Inselspital, Berne, Switzerland

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Abstract

Background: The need for and intensity of follow-up to detect disease recurrence after radical cystectomy (RC) for transitional cell carcinoma (TCC) remains a matter for debate.

Objective: To determine whether diagnosis of asymptomatic recurrence after RC by routine follow-up investigations confers a survival benefit versus symptomatic recurrence.

Design, setting, and participants: Retrospective analysis of 479 patients with nonmetastatic bladder TCC receiving no neoadjuvant chemotherapy/radiation therapy and prospectively followed with a standardised protocol for a median 4.3 yr (range: 0.3–20.9) after RC at an academic tertiary referral centre.

Intervention: RC and extended pelvic lymph node dissection with ileal orthotopic bladder substitution.
Measurements: Cancer-specific survival (CSS) and overall survival (OS) probability for asymptomatic and symptomatic recurrent patients were estimated using the Kaplan-Meier method. The effects of age, nerve-sparing surgery, pathologic tumour stage, lymph node status, adjuvant chemotherapy, mode of recurrence diagnosis, and recurrence site on survival were assessed with multivariable Cox regression models.

Results and limitations: Of the 174 of 479 patients (36.3%) with tumour recurrence, 87 were diagnosed by routine follow-up investigations and 87 by symptoms. Routine follow-up mostly detected lung metastases and urethral recurrences, while symptoms were predominantly the result of bone metastases and concomitant pelvic/distant recurrences. Of 24 patients with urethral recurrences, 13 had carcinoma in situ (CIS). Of these, 12 were successfully managed with urethra-sparing treatment, and 6 are still alive with no evidence of disease. Most other recurrent long-term survivors had lung and extrapelvic lymph node metastases. Cumulative 5-yr survival rates of the entire cohort were 69.8% (95% confidence interval [CI], 65.5–74.3%) for CSS and 61.9% (95% CI, 57.4–66.7%) for OS. In multivariable analysis, mode of recurrence diagnosis and site of initial recurrence were the only independent predictors of CSS and OS. Patients with recurrences detected by routine follow-up investigations and with secondary urothelial tumours as site of recurrence had a slightly but significantly higher survival probability.

Conclusions: Patients diagnosed with asymptomatic recurrences during our routine follow-up after RC had a slightly higher survival than patients with symptomatic recurrences. Routine follow-up appears particularly effective in early detection of urethral CIS, which can be treated conservatively. In addition, the predominance of lung and extrapelvic lymph node metastases in survivors may justify the use of routine cross-sectional imaging.

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* Corresponding author. Department of Urology, University of Berne, Anna-Seiler-Haus, Inselspital, CH-3010 Berne, Switzerland. Tel. +41 31 632 3641; Fax: +41 31 632 2180.
E-mail address: urology.berne@insel.ch (U.E. Studer).

1. Introduction

Radical cystectomy (RC) with extended pelvic lymph node dissection (PLND) is the standard treatment for nonmetastatic (N0, M0) muscle-invasive and high-risk non-muscle-invasive transitional cell carcinoma (TCC) of the bladder [1,2]. Despite advances in patient selection, surgical techniques, and adjuvant and neoadjuvant therapies, disease recurrence remains substantial, even in large-scale series, affecting approximately one-third of patients within 10 yr after surgery [3–7]. Once recurrence has occurred, prognosis is dismal.

Recurrence patterns of bladder TCC after RC are poorly predictable [8,9]. A major concern regarding regular surveillance after RC is whether it can anticipate diagnosis of recurrence and, if so, whether it positively affects long-term survival. The present retrospective study examines the potential of routine follow-up investigations to detect recurrence and whether early detection improves the oncologic outcome in bladder TCC patients undergoing RC and extended PLND with ileal orthotopic bladder substitution.

2. Patients and methods

2.1. Patients

Between April 1985 and January 2009, 554 consecutive patients underwent RC and extended PLND with ileal orthotopic bladder substitution for primary bladder TCC. All patient data were evaluated retrospectively from a prospectively collected database (Table 1).

To ensure a well-defined population, we excluded 75 patients meeting the following conditions: neoadjuvant chemotherapy or radiation therapy (RT), salvage RC, incomplete clinical or pathologic data, follow-up time <3 mo, and irregular follow-up. The remaining 479 patients were the objects of this study. Our analysis included patients with ileal orthotopic bladder substitute, because for these patients, a prospective and standardised surveillance protocol has been used for >20 yr at our institution.

2.2. Treatment

Indications for RC over the entire study period were T2 or higher tumours, primary multifocal T1G3 tumours with or without carcinoma in situ (CIS), and unifocal T1G3 tumours with or without CIS refractory to or early recurrent after endovesical bacillus Calmette-Guérin (BCG). All tumours were preoperatively staged as NOMO based on findings at physical examination, bimanual palpation, chest x-ray, intravenous urography (IVU), computed tomography (CT) scan of the abdomen/pelvis, and bone scan. In addition, as a prerequisite for orthotopic bladder substitution, biopsies of the paracollicular prostatic urethra (males) and of the bladder neck (females) had to be negative for concomitant carcinoma.

Extended PLND was performed, applying the template described previously [10]. Briefly, all lymphatic, connective, and fatty tissue within the following boundaries was removed: (1) anterolaterally, genitofemoral nerve; (2) distally, femoral canal; (3) proximally, crossing of ureter with common iliac artery; (4) inferiorly, obturator muscle and floor of the obturator fossa down to internal iliac vessels; and (5) medially, bladder side wall. Tissue medial to internal iliac vessels was also removed.

Nerve sparing was attempted whenever possible—unilaterally on the non-tumour-bearing side for unilateral tumours and bilaterally for

Table 1 – Clinical and pathologic characteristics of the study cohort (n = 479)

Age at surgery, median [IQR], yr		65.7 (58.4–71.4)
Gender, No. (%)	Male	439 (91.6)
	Female	40 (8.4)
Nerve-sparing technique, No. (%)	None	80 (16.7)
	Unilateral	301 (62.8)
	Bilateral	98 (20.5)
Pathologic tumour stage (TNM 2002), No. (%)	pTa/Tis	11 (2.3)
	pT1	100 (20.9)
	pT2	181 (37.8)
	pT3	156 (32.6)
	pT4	31 (6.5)
Pathologic tumour grade (WHO 1973), No. (%)	G1	2 (0.4)
	G2	21 (4.4)
	G3	456 (95.2)
Pathologic lymph node status, No (%)	Negative	366 (76.4)
	Positive	113 (23.6)
Lymph nodes removed per patient, median [IQR], No.		25 (18–33)
Positive lymph nodes removed per patient, median [IQR], No.		2 (1–5)
Adjuvant chemotherapy*, No. (%)		42 (8.7)
Type of follow-up scheme, No. (%)	Original	227 (47.4)
	Revised	252 (52.6)
Follow-up time, median [IQR], yr		4.3 (1.8–8.3)
IQR = interquartile range; Tis = carcinoma in situ; WHO = World Health Organisation.		
* Including one patient with adjuvant radiochemotherapy; percentages may not equal 100 due to rounding.		

tumours located at the bladder dome or anterior bladder wall or for T1G3 tumours with or without CIS. The surgical technique is described elsewhere [11].

Bladder TCC was confirmed histologically in all cases by an experienced uropathologist. The 2002 TNM classification and 1973 World Health Organisation system were used to stage and grade all specimens. Final pathologic stage and grade were defined as the highest stage and grade in transurethral resection or RC specimen, whichever was higher. Adjuvant cisplatin-based chemotherapy (combined with either methotrexate, vinblastine and adriamycin, or gemcitabine) was offered within 3 mo after RC to patients with pT3b or higher and/or pN+ (excluding patients with two or fewer positive nodes with micro-metastases).

2.3. Follow-up protocol

Patients were followed according to a prospective protocol (generally at our institution, a few by referring urologists). Based on our previous findings on recurrence patterns after RC [12], the original follow-up scheme was replaced in January 1999 by a risk-oriented protocol (Fig. 1). Some investigations, such as blood tests, urinalysis/urine culture, kidney ultrasound, and postvoid residual urine, were primarily performed for functional reasons.

Patients complaining between scheduled visits of symptoms suspicious for recurrence were immediately evaluated by appropriate imaging.

Patterns of initial recurrence were categorised as pelvic recurrence (tumour recurring in soft tissue within the exenteration bed or lymph node metastases within the dissection template), distant recurrence (any metastases in viscera, bone, or lymph nodes outside the pelvic field), concomitant pelvic and distant recurrence (tumour diagnosed at both locations within a 2-mo period), or secondary urothelial tumour (upper urinary tract and urethra), whichever came first. In all cases, at least one site of recurrence was documented cytologically or histologically. After diagnosis of recurrence, patients were fully evaluated for concomitant

Type of investigation	Months after surgery						Years after surgery																				
	3	6	12	18	24	30	36	42	48	54	60	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine dip stick and culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests (basic) (Hb, Cl, creatinine, AP, VBGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests (complete) (Hb, Na, K, Cl, Ca, P, Mg, BUN, creatinine, GOT, γ -GT, LDH, AP, VBGA, folate, B12 vitamin)			X				X		X					X								X					X
PSA (only in case of prostate cancer)	X		X					X					X									X					X
Chest x-ray		X	X	X	X	X	X	X	X	X	X																
Bone scan (only if \geq pT3 or pT1-4 pN+)		X																									
CT scan of abdomen/pelvis (only if \geq pT3 or pT1-4 pN+)		X																									
IVU with tomography (only if previous ureteral tumour or Tis in distal ureter on frozen section analysis or previous multifocal bladder tumour pTa/T1)		X	X	X	X	X	X	X	X	X	X																
Urine cytology after forced diuresis		X	X	X	X	X	X	X	X	X	X					X											
Urethral barbotage cytology		X	X	X	X	X	X	X	X	X	X																
Kidney ultrasound	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Postvoid residual urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Micturition protocol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Voiding questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Fig. 1 – Surveillance protocol incorporating oncologic, functional, and metabolic investigations for regular follow-up of patients treated with radical cystectomy, extended pelvic lymph node dissection, and ileal orthotopic bladder substitution for transitional cell carcinoma at our institution since 1985. After 1999, chest x-ray was less intensive and computed tomography scans of the abdomen/pelvis and bone scans were performed only in pT3 or higher and/or pN+ patients; intravenous urography was limited to 5 yr postoperatively.
 AP = alkaline phosphatase; BUN = blood urea nitrogen; Ca = calcium; Cl = chloride; CT = computed tomography; GOT = glutamic-oxaloacetic transaminase; Hb = haemoglobin; IVU = intravenous urography; K = potassium; LDH = lactate dehydrogenase; Na = sodium; P = phosphorus; PSA = prostate-specific antigen; VBGA = venous blood gas analysis; γ -GT = gamma-glutamyltransferase.

lesions at other locations. If distant recurrence involved multiple sites, the site diagnosed first at a single follow-up investigation or deemed responsible for the heralding symptom was termed the site of initial recurrence. Serious recurrence-related complications were also recorded.

Based on site and extent of recurrence as well as patient comorbidities, therapy consisted of chemotherapy, external-beam RT, brachytherapy, endocavitary BCG, surgery, or no active treatment.

2.4. Outcome measures

Outcome measures were tumour recurrence rate, patterns of recurrence, rate of serious recurrence-related complications, and survival rate. Cancer-specific survival (CSS) was calculated as time from RC to date of death from progressive bladder TCC; overall survival (OS) was calculated as time from RC to date of death from any cause. Living patients without recurrence were censored at date of last follow-up; patients dying before recurrence were censored at time of death.

2.5. Statistical analysis

Differences were assessed with the Mann-Whitney, χ^2 , or Fisher exact test, as appropriate. Multivariable Cox regression models were built to investigate the simultaneous effect of relevant clinical and pathologic factors on survival in patients diagnosed with recurrence. Tested covariables were age, nerve-sparing status, pathologic tumour stage, pathologic lymph node status, adjuvant chemotherapy, mode of recurrence diagnosis (follow-up vs symptoms), site of initial recurrence, and follow-up scheme (original vs revised). All reported *p* values are two-sided; statistical significance was set at 0.05. Statistical analyses were performed in collaboration with the Department of Mathematical Statistics, University of Bern, Switzerland, using SAS v.9.1 software (SAS Institute, Cary, NC, USA).

3. Results

Of the 479 patients followed, 187 (39%) had extravesical disease (pT3/T4), and 113 (23.6%) had pN + . Median follow-up time after RC was 4.3 yr (range: 0.3–20.9; Table 1).

3.1. Rate and time pattern of recurrence

Of the 479 patients studied, 174 (36.3%) experienced recurrence, 87 being diagnosed at routine follow-up and 87 by symptoms. Median time between RC and diagnosis of recurrence was 0.9 yr (interquartile range [IQR]: 0.5–1.7), 1 yr (IQR: 0.6–1.8) for asymptomatic recurrences, and 0.7 yr (IQR: 0.4–1.6) for symptomatic recurrences (*p* = 0.19). Approximately 90% of recurrences were diagnosed within the first 3 yr after RC.

3.2. Anatomical patterns of recurrence (Fig. 2)

3.2.1. Pelvic recurrence

Of the 174 patients studied, 12 (6.9%) had isolated pelvic recurrence (Table 2). Diagnosis was made by routine follow-up investigations in four (33.3%) patients and by symptoms in eight (66.7%) patients (Table 3). Asymptomatic pelvic recurrence was detected in all four cases by CT scan. Of the patients with symptomatic recurrence, three complained of pelvic/hip pain and one each of abdominal pain, diarrhoea, lower-limb oedema, voiding failure, and haematuria.

3.2.2. Distant recurrences

Of the 174 patients studied, 106 (60.9%) had distant recurrence. The most frequent sites of metastases were bone and lung (Table 2). In 31 (29.2%) of these patients, there were multiple metastatic sites. Diagnosis was made by routine follow-up investigations in 50 (47.2%) patients and by symptoms in 56 (52.8%). Asymptomatic distant recurrences were detected by chest x-ray in 24 patients, by CT scan in 14 patients, by bone scan in 5 patients, by physical examination in 4 patients, and through blood tests (ie, liver and renal function tests) in 3 patients. Of those patients with symptomatic recurrence, 33 complained of bone pain, 7 of flank pain, 7 of dyspnoea/cough/haemoptysis, 4 of nausea/vomiting/asthenia, 4 of headache/dizziness, and 1 of abdominal pain. Although bone metastases were predominantly symptomatic, lung recurrences were not (Table 3).

3.2.3. Concomitant pelvic and distant recurrences

Of the 174 patients studied, 18 (10.3%) had concomitant pelvic and distant recurrence. The most frequent sites of distant metastases were bone and lung (Table 2). Diagnosis was predominantly made by symptoms (Table 3). Asymptomatic recurrences were detected locally in two cases by CT scan and distantly (lung) in one case by chest x-ray. All symptomatic patients had complaints from pelvic recurrence (pelvic/hip pain in eight patients, abdominal pain and lower-limb oedema in each of three patients, and constipation in one patient).

3.2.4. Secondary urothelial tumours

Of the 174 patients studied, 38 (21.8%) had a secondary urothelial tumour—14 (8%) in the upper urinary tract and 24 (13.8%) in the urethra. Concomitant distant metastases were present in four (11%) of these cases. Secondary urothelial tumours were usually detected by routine follow-up investigations (30 out of 38, 79%). In particular, urethral recurrences were detected by urethral barbotage cytology in 21 out of 24 (88%) patients (Table 3) and were CIS in 13 out of 21 (62%) patients. Of these 13 patients, 12 (92%) were successfully managed with urethra-sparing treatment (ie, endourethral BCG), and 6 (46%) are still alive with no evidence of disease after a median observation time of 6.2 yr (range: 2.3–16.2) from RC.

3.3. Serious recurrence-related complications

No serious complications resulting from tumour recurrence occurred. Reservoir function was maintained, even in one patient with covered reservoir erosion by lymph node metastases.

3.4. Survival rate

Cumulative 5-yr survival rates of the entire cohort were 69.8% (95% confidence interval [CI], 65.5–74.3%) for CSS and 61.9% (95% CI, 57.4–66.7%) for OS (Fig. 3). Of the 174 recurrent patients, 144 died from bladder cancer and 8 from other causes. Twenty-two recurrent patients were still alive

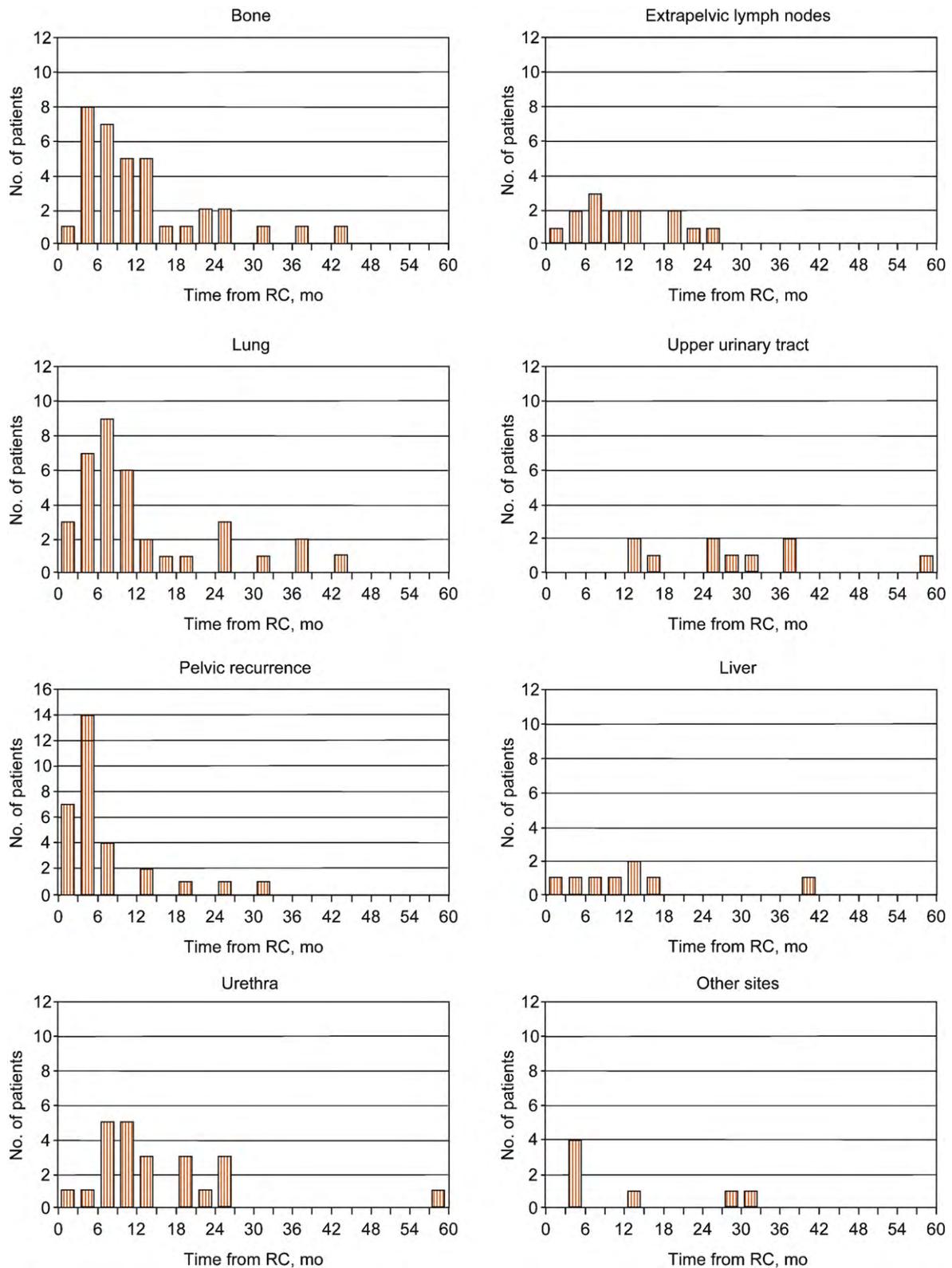


Fig. 2 – Number of patients diagnosed with disease recurrence (n = 174) after radical cystectomy according to site of initial recurrence: bone (n = 38), lung (n = 36), pelvis (n = 30), urethra (n = 24), extrapelvic lymph nodes (n = 16), upper urinary tract (n = 14), liver (n = 8), and other sites (brain, penis, peritoneal carcinosis, muscle; n = 8). Recurrences were detected at >5 yr in 11 patients only (data omitted). RC = radical cystectomy.

Table 2 – Distribution of tumour recurrences by single site*

Site of initial recurrence	n	All patients with recurrence, % (n = 174)	All patients operated, % (n = 479)
Pelvic	12	6.9	2.5
Pelvic and distant:	18	10.3	3.6
Bone	8	4.6	1.7
Lung	5	2.9	1
Liver	3	1.7	0.6
Extrapelvic lymph nodes	1	0.6	0.2
Peritoneal carcinosis	1	0.6	0.2
Distant:	106	60.9	22.1
Bone	38	21.8	7.9
Lung	36	20.7	7.5
Extrapelvic lymph nodes	16	9.2	3.3
Liver	8	4.6	1.7
Brain	4	2.3	0.8
Penis	2	1.2	0.4
Peritoneal carcinosis	1	0.6	0.2
Muscle (leg)	1	0.6	0.2
Secondary urothelial tumours:	38	21.8	7.9
Upper urinary tract	14	8	2.9
Urethra	24	13.8	5

* In case of multiple sites of distant recurrence, the site diagnosed first at a single follow-up investigation or deemed responsible for the heralding symptom was termed the site of initial recurrence.

at last follow-up. The site of initial recurrence in these patients was lung ($n = 7$), urethra ($n = 6$), extrapelvic lymph nodes ($n = 3$), upper urinary tract ($n = 3$), bone ($n = 2$), and pelvis ($n = 1$).

The only independent predictors of CSS and OS in multivariable analysis were mode of recurrence diagnosis and site of initial recurrence. Patients with recurrence detected at routine follow-up and patients with secondary urothelial tumours as site of initial recurrence had significantly higher CSS and OS (Table 4).

4. Discussion

Ideally, an effective surveillance protocol following curative cancer treatment should detect recurrence in asymptomatic

patients during early disease stages, when treatment options can be delivered to achieve longer survival with lower morbidity compared to symptomatic cases. Follow-up can also identify and manage complications related to the initial treatment or tumour recurrence and provide reassurance and guidance to patients [13]. These considerations hold particularly true for patients with invasive bladder TCC after RC because of the aggressive nature of their disease.

The need for and the duration, intensity, and impact on long-term survival of regular surveillance have been evaluated for several malignancies [14–19]. Most studies found no survival benefit for regular versus no/nonregular follow-up.

The effect of the various investigations used to diagnose recurrence in postcystectomy patients on long-term oncologic outcome is largely unknown. In our series, the mode of recurrence diagnosis had a statistically significant, albeit small, effect on survival. Patients in whom recurrences were diagnosed by routine follow-up investigations had a slightly higher survival probability than those with symptomatic recurrences. This finding was maintained in a post hoc analysis, excluding patients with secondary urothelial tumours, which could reflect de novo primary tumours rather than true recurrences (data not shown).

Our results contrast with those of the only other study on the issue [20], which reported no survival benefit for asymptomatic versus symptomatic recurrence in 444 patients followed for approximately 6 yr after RC. Differences in patient inclusion criteria, patient characteristics, follow-up scheme, and pattern of recurrences may account for this discrepancy. In our series, the pattern of recurrences may explain why the outcome of patients with recurrences diagnosed by routine follow-up is somewhat better than that of symptomatic recurrent patients. Lung metastases and secondary urothelial tumours were usually detected at

Table 3 – Mode of recurrence diagnosis according to the site of initial tumour recurrence (n = 174)

Site of recurrence	Mode of diagnosis of recurrence	
	Routine follow-up, n	Symptoms, n
Pelvic	4	8
Bone*	5	33
Lung*	29	7
Extrapelvic lymph nodes	10	6
Liver	4	4
Brain	0	4
Penis	2	0
Peritoneal carcinosis	0	1
Muscle (leg)	0	1
Pelvic and distant*†	3	15
Upper urinary tract	9	5
Urethra*	21	3
Total	87	87

* $p < 0.01$.

† Often with bone metastases.

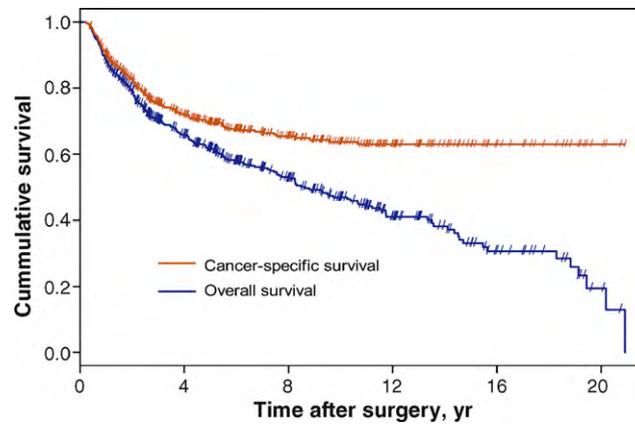


Fig. 3 – Survival probability of the 479 patients treated with radical cystectomy, extended pelvic lymph node dissection, and ileal orthotopic bladder substitution.

routine follow-up, while bone metastases and concomitant pelvic and distant recurrences (often the result of bone lesions) were predominantly symptomatic. Indeed, soft tissue metastases respond better to chemotherapy than bone metastases [21]. Moreover, most urethral recurrences were diagnosed by routine barbotage cytology, and most were noninvasive. We have previously shown what we confirm herein, namely, that low-stage urethral recurrences durably respond to conservative treatment with endourethral BCG perfusion in >80% of patients, averting the need for urethrectomy with consequent sacrifice of the bladder substitute [22]. Whether this good outcome reflects the efficacy of treatment or a rather benign natural history of disease remains unknown.

Besides the potential oncologic value of routine follow-up, it is mandatory for patients with any form of urinary diversion, especially for those receiving orthotopic bladder substitution [23]. We previously showed that meticulous surveillance promotes excellent long-term functional results (high urinary continence rate, optimal voiding pattern, preservation of upper urinary tract function, no irreversible metabolic derangements) [24,25].

Finally, our routine follow-up protocol entailed no serious recurrence-related complications. Patients may also have benefited from the regular psychological support provided by physicians and nurses during follow-up visits.

Our study is not without limitations. First, to fully assess the value of oncologic surveillance, a randomised

Table 4 – Multivariate analysis in recurrent patients (n = 174) after radical cystectomy assessing cancer-specific survival and overall survival

Outcome variable	HR	95% CI	p value
CSS:			
Recurrences diagnosed by routine follow-up vs symptoms	0.65	0.46–0.91	0.013
Secondary urothelial tumours vs other recurrence sites	0.40	0.25–0.65	<0.001
OS:			
Recurrences diagnosed by routine follow-up vs symptoms	0.66	0.48–0.92	0.015
Secondary urothelial tumours vs other recurrence sites	0.46	0.30–0.71	<0.001

HR = hazard ratio; CI = confidence interval; CSS = cancer-specific survival; OS = overall survival.

Table 5 – Proposed protocol for oncologic follow-up after radical cystectomy, extended pelvic lymph node dissection, and ileal orthotopic bladder substitution for transitional cell carcinoma based on the site and timing of recurrences

Type of investigation	Months after surgery									
	6	12	18	24	30	36	42	48	54	60
IVU with tomography/CT (only if previous, concomitant, or multifocal bladder tumour pTa/T1)	–	x	–	x	–	x	–	–	–	–
CT scan of chest/abdomen/pelvis (only if ≥pT3 or pT1–4 pN+)	x	x	x	–	–	–	–	–	–	–
Chest x-ray (only if no chest CT)	x	x	x	x	–	x	–	–	–	–
Bone scan (only if pT3 or higher or pT1–4 pN+)	x	x	x	–	–	–	–	–	–	–
Urine cytology after forced diuresis (upper tract)	x	–	x	–	x	–	x	–	x	–
Urethral barbotage cytology	x	x	x	x	–	x	–	–	–	–

IVU = intravenous urography; CT = computed tomography.

comparison between patients participating in versus patients not participating in a regular follow-up protocol should be conducted. Such a comparison would, however, raise ethical concerns, because half of the patients in such a study would be excluded from follow-up without robust evidence that surveillance is ineffective. In our series, all patients with symptomatic recurrences had previously been regularly monitored and thus may also have profited from previous follow-up investigations. A substantial survival benefit cannot be expected, as there was not much time between the consultations to develop major tumour progression or severe recurrence-related complications.

Second, our analysis was restricted to patients receiving ileal orthotopic bladder substitution. The rate and pattern of recurrences may be somewhat different for subjects undergoing other forms of urinary diversion because of patient selection, more advanced disease, or less stringent follow-up. Thus, our findings may not apply to all cystectomy patients.

Third, our follow-up scheme may not have been optimal. A higher diagnostic yield and better survival could perhaps be achieved by intensifying CT exams, anticipating bone scans, replacing chest x-ray with CT scans and IVU with CT urography. The possible advantages of these alternatives must be weighed against their higher costs and radiation-induced toxicity [26]. Moreover, considering the sites and timing of the recurrences in our patients, follow-up investigations should be rather frequent in the early postoperative period. This led us to introduce some modifications to our current follow-up scheme (Table 5). However, its usefulness remains to be proven because long-term cancer control rates are comparable across contemporary cystectomy series of major institutions applying various surveillance protocols, and we too have been unable to achieve better outcome with the more recent risk-oriented protocol than with the original one (data not shown). Finally, whether urine cytology after forced diuresis is a valid alternative to IVU or CT scan is still unknown, warranting prospective comparative studies [27].

Our data suggest that urethral barbotage cytology and imaging exams to detect soft tissue metastases are the most useful investigations to be included in a follow-up protocol after RC and ileal orthotopic bladder substitution.

5. Conclusions

Patients in whom recurrences after RC and ileal orthotopic bladder substitution are diagnosed by routine follow-up investigations have a slightly higher survival probability than patients with symptomatic recurrences. Regular surveillance is particularly effective in detecting urethral, usually noninvasive recurrences, which can be treated conservatively and are associated with good prognosis. Moreover, the predominance of lung and extrapelvic lymph node metastases in long-term survivors may justify the use of routine cross-sectional imaging. Finally, routine follow-up is associated with no serious recurrence-related complications.

Author contributions: Urs E. Studer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Giannarini, Studer.

Acquisition of data: Giannarini, Thoeny, Nguyen, Meissner.

Analysis and interpretation of data: Giannarini, Kessler, Studer.

Drafting of the manuscript: Giannarini, Kessler, Thoeny.

Critical revision of the manuscript for important intellectual content: Studer.

Statistical analysis: Giannarini, Kessler.

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Supervision: Studer.

Other (specify): None.

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