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ORIGINAL ARTICLE

Patterns of local recurrence after radical cystectomy in a contemporary series of patients with muscle-invasive bladder cancer

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Abstract
Purpose To describe the epidemiology, clinical features, and prognostic factors of local recurrence (LR) in a large case series of patients treated by radical cystectomy (RC) for bladder cancer.
Methods A retrospective study was conducted on 903 patients treated in a single tertiary reference center. All cases of LR were identified. Descriptive analysis was performed on the clinical features, evolution, and overall mortality of these patients. Prognostic factors of LR were assessed using the Mann–Whitney test for continuous variables and the χ^2 test for categorical variables.
Results Fifty-three patients were diagnosed with LR during follow-up (5.9 %). One patient had concomitant distant metastasis. Pain was the most frequent symptom leading to diagnosis. Mean time interval from RC to LR was 14.4 ± 13 months (1–64) with 50 % of cases diagnosed in the first postoperative year. Overall median survival of patients diagnosed with LR was 9 months [95 % confidence interval (6–11)]. Advanced pathological stage (T3 or T4) and lymph-node invasion were associated with increased LR rate in univariate and multivariate analysis. Presence of squamous cell carcinoma (SCC) was associated with a poorer prognosis after LR compared to pure urothelial carcinoma ($p = 0.04$). None of the parameters tested was associated with time interval between RC and LR diagnosis.
Conclusions LR is not uncommon, favored by high pathological stage (T3/T4), and has a very bad prognosis, particularly when SCC is present. LR must be carefully tracked during follow-up after RC, and optimal management of these cases remains to be determined.

Keywords Bladder cancer · Local recurrence · Epidemiology · Retrospective study

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Introduction

Radical cystectomy (RC) is recommended as the first-line treatment for muscle-invasive bladder cancer without metastasis at the time of diagnosis, or in case of failure of intravesical therapy for high-grade tumors [1]. In these cases, cancer-specific survival rate is mainly influenced by tumor stage and lymph-node status and is estimated as 66 % at 5 years in contemporary series.

Recurrence after RC occurs mostly in the first 24 months of follow-up, but can be diagnosed up to 10 years after surgery. Recurrence sites are classified as distant (bones, lungs, brain) or local (pelvic or urethral) [1]. Local recurrence (LR) after RC can involve pelvic soft tissue, pelvic regional lymph nodes, or both [2]. LR is commonly associated with a poor prognosis [3], and its management is based on a combination of surgery and chemotherapy on an individual basis [4]. Although LR is not uncommon and represents a challenge for physicians, the literature dealing with this specific evolution of the disease remains scarce. Our goal was to describe the incidence, clinical features, and outcome of LR after RC for muscle-invasive bladder cancer in a contemporary series.

Table 1 Patient characteristics of the study cohort

Patient characteristics	LR group ($N = 53$)	Non-LR group ($N = 850$)
Age [mean ± SD (range)]	64 ± 10 (37–86)	64.9 ± 10.2 (34–89)
Follow-up [mean ± SD (range)]	23.2 ± 15 (4–80)	52.2 ± 42 (1–374)
Sex		
Male	43	100
Female	10	750
ASA score		
ASA 1	14	255
ASA 2	32	486
ASA 3	7	109
ASA 4	0	0
Clinical stage at diagnosis		
<T4	50	816
≥T4	3	34
Type of urinary diversion		
Bricker	21	292
Camey 1	5	113
Camey 2	4	91
Coffey	1	3
Cutaneous ureterostomy	2	16
Z-Neobladder	20	330
Other	–	5
Lymph-node status on definitive pathological examination		
Negative	25	649
Positive (unilateral)	15	135
Positive (bilateral)	10	52
Number of positive lymph nodes		
One	10	78
Two or more	15	99
Unknown lymph-node status	3	14
Pathological stage		
pT0	–	87
pTa	–	27
pT1	2	85
pT2a	–	109
pT2b	3	106
pT3a	5	106
pT3b	12	115
pT4a	19	108
pT4b	2	39
CIS only	–	68
Associated CIS	14	368
Surgical margins		
Positive (urethra)	5	43
Positive (ureter)	1	32
Negative	47	775
Tumor grade		
0	–	87
1	–	8
2	2	67
3	51	685
Unknown	–	3
Histological type		
Urothelial carcinoma	47	726
Squamous cell carcinoma	4	26
Both	2	8
No tumor/other	–	90
Adjuvant chemotherapy		
None	21	508
MVAC	13	100
Carboplatin[a] + gemcitabin	2	24
Other	10	146
Missing data	7	74

SD standard deviation, *ASA* American association of anesthesiology, *MVAC* methotrexate, vinblastine, doxorubicin, and cisplatinum, *CIS* carcinoma in situ

[a] or cisplatin

Materials and methods

Patients

A retrospective study was conducted in a tertiary reference center. Data were extracted from a prospectively held local database registering preoperative and postoperative data for every patient treated by RC. Between 1990 and 2009, 903 patients (802 men and 101 women) were treated by RC for invasive bladder cancer in our unit. For the present study, we reviewed data for all the patients who presented isolated LR during follow-up. Isolated LR was defined by pelvic soft tissue invasion or pelvic lymph-node invasion on CT scan, confirmed if necessary by biopsy guided by imaging, with no secondary lesions on pulmonary CT scan, bone scan, or magnetic resonance imaging (MRI). Follow-up in our unit usually includes axial imaging (by CT scan or MRI) and clinical examination at 3, 6, 12 months in most of cases and every 6/12 months (depending on T stage and nodal status), as recommended [1]. Patients treated more than 15 years ago had intravenous urography X-ray and chest X-ray instead of axial imaging.

Pathological assessment

A genitourinary pathologist examined all of the RC specimens according to standard pathological procedures.

Table 2 Details about diagnosis, locations, and treatment about local recurrence

Local recurrence (LR) details	Number of cases
Symptoms leading to diagnosis (number of patients)	
No symptoms (pre-planned CT scan or MRI)	7
Lumbar pain	21
Pelvic pain	14
Abdominal pain	10
Leg pain	9
Fistula	6
Alteration of performance status	6
Venous compression	3
Mean time interval between RCP and LR diagnosis months, mean ± SD (range)	14.4 ± 13 (1–64)
Recurrence sites (number of patients)	
Pelvic lymph nodes	14
Pelvic soft tissue	34
Retroperitoneum	5
Treatment for local recurrence[a]	
Chemotherapy	
Methotrexate + vinblastine + doxorubicin + cisplatin (MVAC)	10
Paclitaxel + gemcitabine	6
Carboplatin + gemcitabine	2
Cisplatin + gemcitabine	5
Gemcitabine	1
Vinblastine + carboplatin	1
Etoposide + cisplatin	1
5FU + navelbin	2
5FU + cisplatin	2
Radiation therapy	
Pelvic tissue	10
Pelvic lymph nodes	6
Retroperitoneum	2
Surgery	
Colpectomy	2
Conversion for neobladder to bricker	2
Double J stent or nephrostomy	5
Uretrectomy	2

[a] 12 patients had both radiation therapy and chemotherapy. Ten patients received no treatment

Limited sections of the ureter and urethra were taken in all cases. In cases of anterior exenteration, resection limits were also taken from the uterus and vagina. In cases of gross invasion of the peripelvic fat, the specimens were stained in the suspicious areas for better examination of the limits. Pathologists considered limits as positive if urothelial carcinoma (invasive, as well as carcinoma in situ) was found on the limits, independent of the size. The pathological staging was systematically updated according to the 2002 TNM criteria.

Data collection

Data collected from the centralized database were preoperative characteristics (age at the time of RC, American society of anesthesiologists (ASA) score, medical history of bladder tumor management before RC), preoperative clinical stage (defined as T4 or not T4), preoperative lymph-node status on pulmonary and abdominal CT scan, preoperative aspect of upper urinary tract (tumor, dilatation, not available), intraoperative and pathological results [urinary diversion mode, intervention duration, type of lymph-node removal (pelvic lymph-node dissection basically included the external iliac, ilio-obturator, and internal iliac regions and was noted as "extended" when more regions were removed), tumor type, T stage and grade, definitive lymph-node status, invasion of distal ureteral frozen section, urethral invasion, presence of prostate cancer (Gleason, pT stage)], and type of adjuvant chemotherapy. Data concerning follow-up were time interval between RC and LR diagnosis, overall, and specific survival.

Statistical analysis

Quantitative and qualitative data were compared using the Mann–Whitney test and the χ^2 test, respectively; p values of <0.05 were considered as statistically significant. Influence of symptoms at diagnosis of LR (present/absent), tumor stage, tumor type [squamous cell carcinoma (SCC) or urothelial carcinoma (UCC)], lymph-node status (positive or negative), and adjuvant treatment after LR diagnosis on overall survival was studied by log-rank analysis. Influence of pathological data (tumor stage, surgical margins) and adjuvant chemotherapy on time interval between surgery and LR was also studied by log-rank analysis. All statistical analyses were conducted with XLStat 2010 for Windows (Addin Soft, Paris, France).

Results

Fifty-three patients (5.9 %) were diagnosed with LR during follow-up. Patient characteristics are presented in Table 1. No patient had metastatic disease at the time of LR diagnosis except one case of cutaneous metastasis of a locally extended tumor. In one case, a radical nephroureterectomy was associated with RC. Patients had positive margins on urethral section underwent subsequent urethrectomy immediately after RC within the same procedure.

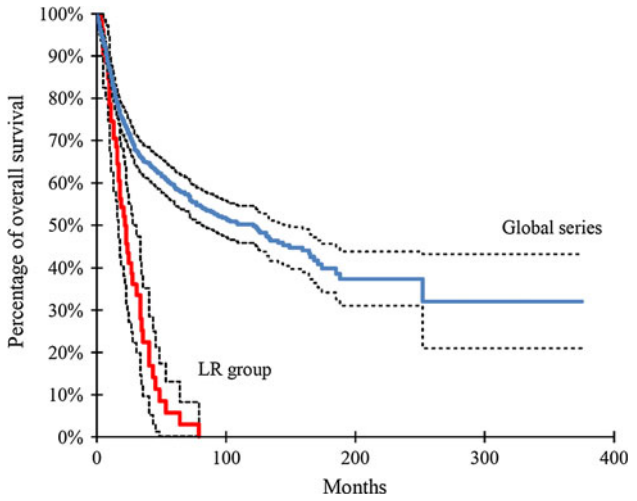

Fig. 1 Kaplan–Meier analysis of overall survival. *Blue line* represents the survival curve for all patients included in this series, who where M0 at the time of cystectomy. *Red line* represents survival of the local recurrence (LR) group. *Dotted lines* are 95 % confidence intervals

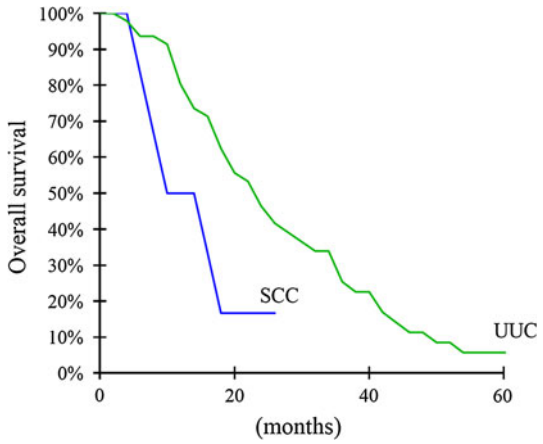

Fig. 2 Overall survival of the squamous cell carcinoma (SCC) group ($N = 6$) and urothelial cell carcinoma (UCC) group ($N = 47$). *SCC* squamous cell carcinoma, *UCC* urothelial cell carcinoma

LR diagnosis was made on CT scan examination for all patients. Symptoms that led to the diagnosis of LR were multiple (Table 2), but only four patients presented with isolated pelvic pain. Mean time interval from RC to LR was 14.4 ± 13 months (1–64). 50 % of cases occurred in the year following RC and 98 % within the first 5 years after RC.

Univariate analysis showed that only definitive pathological stage (T3 or T4) and lymph-node invasion were associated with an increased risk of LR (both $p < 0.0001$). Presence of squamous cell carcinoma (SCC) at pathological examination and positive surgical margins was associated with an increased rate of LR but without statistical significance ($p = 0.056$ and $p = 0.076$, respectively). Age, preoperative chemotherapy, preoperative radiation therapy, tumor grade, and type of urinary diversion were not associated with increased rate of LR. After multivariable analysis, only pathological stage and lymph-node invasion remained associated with LR ($p < 0.0001$ and $p = 0.008$, respectively).

Overall median survival of patients diagnosed with LR was 9 months [95 % confidence interval (6–11)], and 46/53 patients had died from bladder cancer after diagnosis at last follow-up (Fig. 1). In 15 cases, death was indirectly linked to bladder cancer; one died after acute renal failure, four after septic shock, one after acute myocardial infarction, one after pulmonary embolism, one after another non-urothelial neoplasia, and eight because of peritoneal carcinomatosis. In the remaining 31 cases, patients died because of bladder cancer as stated in our database (without further details) presumably from distant metastatic disease or treatment complication. At all, 31 patients diagnosed with LR had a subsequent diagnosis of distant metastasis, within the next 6 months in 20/31 cases. No parameter was correlated with survival after LR except histological type of bladder tumor. Indeed, presence of SCC at pathological examination was associated with a poorer prognosis after LR ($p = 0.04$, Fig. 2). None of the variables tested was associated with time interval between RC and LR diagnosis in univariate or multivariate analysis.

Discussion

LR after RC for muscle-invasive bladder cancer occurred in 5.9 % in our series, in line with results provided by others [1, 5, 6]. As already stated in previous reports, few patients have concomitant distant metastasis at the time of LR diagnosis. Hence, if detection of distant metastasis or urinary tract recurrence remains crucial during follow-up after RC, particular attention should be paid to the fact that LR can occur before these events and must be considered as a possible evolution of the disease by itself.

A specific search for LR should be carried out in the early years after radical surgery. Indeed, the time interval between RC and LR has been reported to be usually inferior to 3 years [2] and maximal in the first year [5]. Our results are consistent with these data, since the mean interval between RC and LR in our series was 14.4 months. Particular attention should be paid to the postoperative CT scans in the early postoperative period to detect signs of LR. Some authors have attempted to compare the performance of CT scan, transrectal ultrasound (TRUS), transabdominal ultrasound, and MRI for LR diagnosis, underlying the effectiveness of TRUS. In case of doubtful standard imaging, PET/CT can be used but data are yet published about its ability to detect LR. Hence, we

recommend routine CT scans at regular intervals after surgery. CT scan is probably also useful in case of symptoms suggesting LR, mainly pain (Table 2).

Identification of predictive factors of LR should be useful to adjust follow-up and postoperative imaging for patients at high risk of LR. Several studies have tried to identify such risk factors in the past, leading to controversial results [5]. Pathological stages (T3–T4) have been assessed as a risk factor for LR by some authors, but only in limited case series. Moreover, to be reliable, these data must be integrated into multivariable models in order to take into account multiple confounding factors (type of surgery, surgical margins, preoperative chemotherapy, tumor type, etc.). Presence of SCC at pathological examination has been previously proposed as risk factor for LR in one limited case series of 145 patients and not confirmed in our study in multivariable analysis. Our analysis confirms that T3/T4 stages are associated with LR, together with lymph-node invasion. Due to the small number of patients having LR in our study, no subgroup analysis was however possible to determine whether lymph-node invasion is a risk factor for local lymph-node recurrence and whether T3/T4 status is a risk factor for pelvic soft tissue recurrence, or both. Furthermore, due the fact that LR recurrence was diagnosed via CT scan, the distinction between pelvic soft tissue and lymph-node recurrence is not perfect. To our knowledge, no other factor has been clearly identified as a risk factor for LR after RC. In particular, modern surgical approaches such as laparoscopic or robotic-assisted RC seem to lead to comparable rates of LR according to a recent review on the topic [7].

Even if the prognosis of LR is overall poor, we were able to show that the presence of SCC (even if not linked to increased LR rate) was associated with a worse outcome after LR. These data are consistent with a previous study on 20 patients having non-bilharzial bladder SCC [8]. Nine patients (45 %) had LR, shortly interval after surgery, and seven died, suggesting a different natural history for SCC with a particularly aggressive pattern. Hence, pathological examination of specimens following radical cystectomy should be very careful in determining the presence or not of associated SCC, possibly using specific markers [9]. Recently, Mitra et al. [10] have attempted to assess predictive factors of survival after recurrence, but without specifically focusing on LR, so that the data exposed in their work cannot be compared to ours.

Although our work is based on a large, rather homogeneous dataset, some limitations may apply. First, this study is retrospective and comes from a single institution. Then, since the data come from a large period of time, we were not able to adjust our data to the type of urinary diversion or the use of preoperative chemotherapy, which have evolved over years. Moreover, we were not able to assess precisely the number of invaded lymph nodes, which could be a risk factor for LR (especially pelvic lymph-node recurrence). Furthermore, in our series, 20 patients out of 46 had subsequent diagnosis of distant metastasis in the first 6 months after LR diagnosis. These data, partly explaining the poor prognosis of our series, suggest that an important part of patients diagnosed with LR have already microscopic distant metastasis. On the other hand, if our experience led us to consider clinical examination and regular CT scans as the cornerstones of LR diagnosis, the heterogeneity of our series cannot allow us to provide any recommendation about management of LR cases. Our work thus should now be followed by a prospective study about the management of these patients, which are challenging cases even for high caseload institutions.

Conclusion

In this study, LR after RC for bladder cancer was not uncommon, appeared before metastatic disease evolution and was associated with a poor prognosis. LR was mainly asymptomatic and sometimes revealed by abdominal or pelvic pain. Hence, this particular, deadly challenging evolution of the disease must be specifically targeted during follow-up, especially during the first years following RC. Presence of SCC carcinoma at pathological examination is a critical issue that must be carefully assessed to potentially anticipate LR.

Conflict of interest None.

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