Unexpected Early Oncologic Mortality after Open Radical Cystectomy for Bladder Cancer: Who Is to Be Blamed?

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Keywords

Urinary bladder neoplasms · Cystectomy · Neoplasm recurrence · Oncologic mortality

Abstract

Purpose: To investigate prevalence and variables associated with early oncologic mortality (EOM; within ≥ 30 to ≤ 90 days) of open radical cystectomy (RC) for bladder cancer. The unexpected rapidity of tumour recurrence and the huge metastatic burden of these patients drew us to analyse this cohort. **Methods:** We reviewed our RC database. All 1,487 patients were treated with curative intent between January 1986 and December 2008. Imaging for staging was done by CT (chest) and CT or MRI (abdomen). Clinical and histopathological variables were recorded until death to determine whether disease- or treatment-related factors were associated with mortality. **Results:** There were 93 deaths within 90 days of surgery. Twenty-four patients died from early progression to high volume disseminated metastatic disease. Group 1: unresectable tumours, which were never free of disease. Group 2: resectable tumours, considered tumour-free after RC. Group 1 is characterized by local tumour spread and a low distant failure rate. Group 2 has a low local and a high distant failure rate. **Conclusions:** Disease related (advanced tumour stage, positive soft tissue surgical margins (+STSM),

non urothelial histology, unresectable tumours, atypical occult metastasis), rather than technical factors, had the leading role in EOM. Understaging was universal.

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Introduction

Perioperative mortality of open radical cystectomy (RC) for bladder cancer (BC) defined as death within 30 days of surgery or prior to hospital discharge has decreased from nearly 20% before 1970 to approximately 2% in most contemporary series. When perioperative mortality is defined as death within 60 or 90 days after surgery, mortality rates increase to 2.4 and 3.9% [1, 2]. In a most recent report, Groeben et al. [3] have detailed in-hospital outcomes after RC for BC in the United States and Germany from 2006 to 2014.

To the best of our knowledge the contribution of early oncologic mortality (EOM), defined as death between ≥ 30 and ≤ 90 days after RC to perioperative mortality has never been studied systematically, although every high-volume BC surgeon has encountered similar cases. It is also surprising that almost all Kaplan-Meier plots on cancer-specific survival or disease-specific survival start with an immediate steep decline. Occasionally EOM is followed

Table 1. Unexpected EOM (>30 till ≤90 days) after open RC for margin positive (R1/R2) or locally advanced or unresectable BC: Group 1

Name	Age, years	Gender	Year	Preoperative stage	Histology	RCX specimen	NAC	Postoperative course	CSS, days
<i>Local recurrence</i>									
S.K.	78	Male	2000	pT1 cN0 cM0	UC G2	pT4b (rectum) cN0 cM0 G3	R2 none	Huge local recurrence, ileus	65
K.M.	71	Female	1986	pT2a cN0 cM0	UC G3	pT4b pN0 cM0 G3 R2	None	Huge local recurrence, ileus	71
T.J.	46	Male	1990	pT2a cN0 cM0	UC G3	pT4b pN2 cM0 G3 R2	None	Local recurrence, penile inflt. invasion pelvic bones	60
J.S.	44	Female	2005	pT2a cN0 cM0	UC G4	pT4b pN3 cM0 G3 R2	None	Local recurrence, diffuse liver mets	46
S.M.	80	Male	1999	pT4a cN0 cM0	UC G3	pT4a pN2 cM0 G3 R2	None	Local recurrence	31
H.M.	18	Male	1995	Embr. rhabdomyosarcoma, IV, yM0, pul	Embr. rhabdomyosarcoma	Stage IV (penetrating abdominal wall)	Adriamycin ×4 ifosfam. DTIC	Local and pulmonary progression	75
A.H.	65	Male	1987	pT3a cN0 cM0	UC G3	pT4b pN0 cM0 G3 R2	MVAC ×2	Local recurrence, ileus sepsis	57
K.D.	55	Male	1998	pT2a cN0 cM0	UC G3	pT3b pN1 cM0 G3 R2	None	Local recurrence, ileus	82
K.R.	68	Female	2003	pT4b ycN0 cM0	UC G2	pT4b pN2 cM0 G3 R1	Gem-Cis ×4	Huge local recurrence	43
<i>Pulmonary, hepatic</i>									
R.R.	68	Male	1990	pT2a cN0 cM0	UC G3	pT4b pN2 pM1 (lymph) G3 R2	None	Paraneoplastic thrombosis lethal pulmonary embolism	63
V.E.	74	Female	1999	pT2a cN0 cM0	UC G3	pT4a cN2 cM1 (pul) G3 R2	None	Pulmonary mets	44
M.W.	69	Male	1990	pT4a cN0 ycM0	UC G3	pT4b pN3 cM1 G3 R1	EC ×6	Total liver necrosis sepsis	30
EOM, early oncologic mortality; BC, bladder cancer; NAC, neoadjuvant chemotherapy; CSS, cancer specific survival.									

by queries regarding diagnosis, staging, indication, surgical skill and breach of oncologic principles. We also sought to investigate possible factors contributing to EOM.

Methods

Patient Population

Between January 1986 and December 2008, 1,487 patients underwent RC for malignant tumours of the bladder at our institution with curative intent. Patient characteristics were entered into a prospectively maintained institutional review board-approved database. Data was collected from the patient or the treating urologists to document the course of the disease. Neoadjuvant chemotherapy (NAC) was not routinely offered to patients, but we had patients referred for RC who had NAC in the referring institution. Patient characteristics are presented in Tables 1 and 2 and are available in previous publications of our RC/urinary diversion series [4]. Study inclusion criteria were as follows: (1) primary BC treated with open RC with the intent to cure (cNO, cMo) and NAC responders (ycN0, ycM0). (2) All perioperative mortalities defined as death within 90 days of surgery were identified. Medical records of these patients were reviewed to determine the cause of death, any precipitating intraoperative or postoperative factors, predisposing comorbidities, and management of early postoperative complications that could have contributed to mortality. (3) Concomitant surgical procedures, intraoperative findings and choice

of urinary diversion were also recorded to determine whether disease-related or treatment-related factors were associated with EOM. Exclusion criteria were (1) presence of untreated metastasis (mts) prior to RC or other primaries or distant mts at diagnosis; (2) perioperative non-oncologic complications leading to death.

Patient-Related Variables

Clinical staging was initially determined by the treating physician and was verified by the investigators in all 1,487 patients. Staging was performed within 8 weeks before surgery and included ultrasound, intravenous pyelogram, cystoscopy, transurethral tumour resection, bimanual examination under anaesthesia, CT of the chest, CT or MRI of the abdomen and pelvis. Patients were defined as cNO, when all pelvic LN were <8 mm and abdominal LNs <10 mm in maximum diameter. All surgical specimens were examined under a standardized pathologic protocol. Tumour staging and grading were standardized to the American Joint Committee on Cancer and World Health Organisation recommendations respectively. Initial precystectomy clinical and final post cystectomy pathologic stages were compared to determine tumour upstaging. A positive soft tissue surgical margin (+STSM) was defined as the presence of tumour at inked areas of soft tissue on the RC specimen.

Clinical Outcomes and Analysis

Patients with +STSM, locally advanced or unresectable pT4 (R1, R2), pN-any, who were never free of disease were assigned to Group 1. Patients with resectable disease (R0) formed Group 2. Cause of death was prospectively entered into the institutional database, verified by chart review and corroborated by death certifi-

Table 2. Unexpected EOM (≥ 30 till ≤ 90 days) after open RC for advanced but resectable BC (R0): Group 2

Name	Age, years	Gender	Year	Preoperative stage	Histology	RCX specimen	NAC	Postoperative course	CSS, days
<i>Local recurrence</i>									
R.H.	74	Male	1997	pT2a cN0 cM0	UC G3	pT4a cN0 cM0 no PLND	CIS + 45 Gy	Local recurrence, ileus	88
<i>Neurological, metabolic, gastrointestinal</i>									
K.H.	56	Male	1988	pT2a cN0 cM0	UC G3 + neuroendocrine	pT4b pN1 cM0 G3 neuroendocrine	MVAC $\times 2$	Paraplegia, fracture Th12	70
B.K.	69	Male	1991	pT3a cN0 cM0	UC G3	pT3a pN1 cM0 G3	None	Path.fract.fem., hyperCa. untreat	60
K.W.	72	Male	1999	pT1 cN0 cM0	UC G3 + small cell	pT4b pN3 cM1 (perit, N) G3	None	Perit. Carcinomatosis, ileus	58
B.H.	69	Male	1998	pT2a cN0 cM0	UC G2	pT3b pN2 pM1 (lymph) G3	None	LN extensiv, progressive	84
S.H.	66	Male	1995	pT3b cN0 cM0	UC G3	pT3b pN0 cM0 G3	None	LN mets, cava compression, RLND: intestinal necrosis	32
<i>Brain metastasis</i>									
P.H.	58	Male	2000	pT2a cN0 cM0	UC G3	pT3b pN2 cM0 G3	None	Brain mets, brachiofac. paresis	31
W.A.	63	Female	2008	pT1 cN0 cM0	Carcinosarcoma G3	pT4a pN0 cM0 G3	None	Brain mets, stupor	75
P.H.	68	Male	1996	pT4a cN0 cM0	UC G3 + neuroendocrine	pT4a pN0 cM0 G3	None	Brain mets, epileptic seizure	53
D.H.	42	Male	1993	pT2a cN0 cM0	UC G3	pT4a pN2 cM0 G3	None	Brain mets, epileptic seizure	30
<i>Pulmonary/bone metastasis</i>									
N.G.	64	Male	2007	pT2a cN0 cM0	UC G3	pT3b pN0 cM0 G3	None	Pulmonary + bone mets	51
W.W.	75	Male	2003	pT3b cN0 cM0	UC G3 + neuroendocrine	pT4a pN1 cM0 G3 neuroendocrine	Rad. chemo	Pulmonary mets	85
EOM, early oncologic mortality; BC, bladder cancer; NAC, neoadjuvant chemotherapy; CSS, cancer specific survival.									

cates. The causes of death were classified into 6 categories – pulmonary, thromboembolic, neurological, gastrointestinal, hepatic and metabolic. Early mortality in cases with neurological, pulmonary, hepatic and metabolic death was easy to classify. It was more difficult to assign the local recurrence (LR) cases of the R2 group. They were classified as EOM when the disease diameter (≥ 10 cm) and the rapidity of growth were the leading symptom of EOM.

The primary outcome of interest was EOM, defined as any oncology-related mortality within ≥ 30 and ≤ 90 days after RC. We choose this time frame as a cut off for EOM, so that mortality was most likely related to oncologic disease severity rather than to the surgical technique or surgical complications.

Results

i. A total of 1,487 patients, with complete data were included into the study. There was a perioperative mortality of 5.2% (≤ 90 days). EOM developed in 24 patients (1.6%).

ii. Fifteen of the 24 EOM patients with clinically organ confined disease had non-organ confined pathological stage. Eleven patients were pT4b. Twelve patients were never free of disease (Group 1) and 12 were (Group 2) free of disease. Pathological upstaging of the T-category oc-

curred in 19 out of 24 patients. When LN involvement was categorized as upstaging, 14 out of 24 patients were upstaged. There was no pathological down staging.

iii. Patients with asymptomatic, very rare or atypical mts escaped the primary clinical staging. An example are the 4 patients with brain mts in Group 2 (Tables 2, 3). Four out of the 24 patients had non-urothelial BC.

iv. Our analysis shows that all LR occurred when there was extra vesical disease at RC. In Group 1, out of 12 patients, 8 had a frozen pelvis at the time of surgery (versus 2/12 in Group 2) and 9 out of 12 patients in Group 1 versus only 1 out of 12 in Group 2 were with an LR. In 7 patients, the LR was the first and only failure without distant mts. Three EOM patients had synchronous local and distant failure.

v. The metastatic pattern of the 2 groups was different. While both had a comparable pN+ rate (7/12 in Group 2 vs. 8/12 in Group 1), Group 1 is characterized by local tumor spread (LR 9/12) and a low distant failure rate (3/12). Group 2 has a low LR rate of 1 out of 12 patients and a distant failure rate of 9 out of 12 patients (Table 3).

vi. In none of our EOM patients, breaching of oncologic surgical principles (entry into the bladder or urine

Table 3. Unexpected EOM (≥ 30 till ≤ 90 days) and pattern of failure after open RC in locally advanced, margin positive (R1/R2), or unresectable (Group 1) versus resectable (R0), BC (Group 2). (>1 feature may apply per patient)

	Group 2 (R0; <i>n</i> = 12 patients)	Group 1 (R2; <i>n</i> = 12 patients)
pN+	7	8
pN1	3	1
pN2	3	5
pN3	1	2
pN0	5	4
pN+ complications	3	2
Frozen pelvis	2	8
Peritoneal carcinomatosis	1	–
Local recurrence	1	9
Distant failure	9	5
Brain mts	4	–
Liver mts	–	2
Pulmonary mts	2	2
Bone mts	3	1
Metabolic	1	1

EOM, early oncologic mortality; RC, radical cystectomy; BC, bladder cancer.

leakage from the urethra or the ureters) could be demonstrated.

vii. Reasons for suboptimal/no NAC were Toxicity (patient A.H.) and patient refusal (P.H., W.W., K.W.)

Discussion

In our series, 24 out of 93 patients with perioperative mortality had EOM (1.6%). Previous series of open RC for BC, including our own, did not report EOM systematically [4]. This is most likely because EOM was not evaluated and misclassified into categories like gastrointestinal, sepsis, and so on. The surgical morbidity database of the MSKCC database reports only on 1 out of 1,142 patients who died of disease progression during ≤ 90 days [5]. In Bern, 35 out of 507 patients died within 3 months after surgery, and reasons for death were tumour related in 12 and non-tumour related in 23 [6]. In contrast to EOM, more information is available on early oncologic failure (EOF) defined as any disease relapse within 3 months of RC [7]. The Mayo Clinic Cystectomy Registry excluded 72 of the 2,438 patients because of development of metastatic disease within 30 days of surgery [8]. Hussein et al. [9] sought to investigate the prevalence and variables associated with EOF following robot-assisted

RC EOF developed in 5% of their patients. The lack of similar open reports of EOF in the open RC literature limits any comparison with RARC.

In the largest study on the STSM status, it was a powerful predictor of outcomes after RC. The recurrence-free survival probabilities of patients with positive versus negative STSM were 21 vs. 63% at 5 years after RC [10]. Our Group 1 patients were never free of disease and all had positive STSM. As opposed to Group 1, all Group 2 patients were free of disease after RC, albeit 7 had occult lymph node mts. Only 1 patient developed an LR and the distant failure rate was 9 out of 12 patients.

In an autopsy study, the pattern of mts in advanced BC has been analysed by Wallmeroth et al. [11]. The frequency of mts increased with local tumour extension and was higher in patients treated by RC than in patients without RC. For pT4 patients it was 89 vs. 79% respectively. The most frequent sites of mts were regional lymph nodes, liver, lung, bone and peritoneum in 90, 47, 45, 32 and 19% respectively. This corresponds to the pattern of our Group 2.

Clinical staging is the main determinant governing decision making. We found, that the level of agreement between clinical and pathological staging for EOM patients was only 10% for the primary tumour alone (T-stage) and 40% when lymph node involvement was considered upstaging (N-stage). Our rates of stage discrepancy are below the error range of clinical staging reported in the literature, which are between 27 and 62% [12, 13]. Reasons for that are, that in some of our patients in Group 2 the location of the mts escaped conventional staging examinations (f.i. the 4 patients with brain mts) and was only symptom driven. The key driver for EOM in Group 1 was the high upstaging rate to pT4b resulting from a frozen pelvis. Our experience with 11 out of 24 patients being upstaged pT4b underscores that conventional imaging techniques scan have a limited role in staging BC patients. In a recent meta-analysis, Gandhi et al. concluded that MRI for $<T4b$ versus pT4b sensitivity exceeded the estimated accuracy for clinical staging and should be considered potentially superior to the current standard for clinical staging [14, 15].

Strengths of our study are the homogeneity of this large single-centre series and the completeness of staging and follow-up. All patients were treated by high-volume surgeons under standardized conditions in terms of indications for surgery, operative characteristics, postoperative care, analysis of complications and comorbidity. There are several limitations to our study, especially the limitations that are inherent to retrospective analyses.

The study period spans almost 25 years and the data in the present study may not represent current practice patterns. However, 769 of the patients were treated in the 1990s and 718 in the year 2000 or thereafter, which may limit the relevance of such issues.

What could have been done better for these 24 patients? What could be done better for similar patients in 2019?

The majority of our patients were treated before the NAC era. Furthermore our institutional treatment protocol for BC till 2009 was “surgery only,” and our 10 year OS, disease-specific survival and cancer-specific survival rates of 44.3, 66.8 and 65.5% [4] compare favourably to any NAC series [16]. However, in 2019, potential improvements for a treatment of this type of disease are on the horizon. At the 2019 AUA there was a report on neoadjuvant pembrolizumab and Cis platin chemo therapy for MIBC. The pathologic non-muscle invasive rate ($\leq pT1$, NO, MO) was 61%, the $pT0$ rate was 44.4%. These rates warrant further study [17].

Our high upstaging proportion of patients with clinically localized disease to advanced or metastatic disease must be accepted.

Positron emission tomography combined with CT is increasingly used in clinical practice and its exact role continues to be evaluated.

All of our Group 1 patients had unanticipated findings of bulky/metastatic disease at the time of a planned curative RC. The clinical outcome and optimum management of these patients is unclear [18, 19]. Guzzo et al. [20] evaluated the clinical outcome of patients who had an aborted attempt at curative RC for intraoperative findings of

metastatic disease. Sixty per cent of their patients died within the study period, 31% are alive with progression/persistent disease, and 9% are NED. The authors conclude when metastatic disease is discovered at RC, completing the RC should be considered [20]. Until clinical staging improves and is supported by genomic data we believe that an attempt of RC as primary treatment should be offered to Group 1 patients.

Conclusions

EOM is not negligible (1.6%). High-risk tumours including non-urothelial BC, advanced pathological tumour stage, positive STSM, unresectable tumours, tumours with atypical mts (brain) that escape the conventional staging examinations, and a dramatic upstaging rate, but not surgical technical related factors (entry into the bladder, urine leakage from urethra, or ureter) have the leading role in EOM after open RC.

Statement of Ethics

All human subjects provided written informed consent with guarantees of confidentiality. Institutional review board approved protocol number is URO-CX-1/2009.

Disclosure Statement

The authors declare that they have no conflict of interest to disclose.

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