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Libni J. Eapen
The Ottawa Hospital Cancer Centre

Edward Jones
British Columbia Cancer Agency

Wassim Kassouf
Centre Universitaire de Santé McGill

Carole Lambert
Hôpital Notre-Dame

Scott C. Morgan
The Ottawa Hospital Cancer Centre

See next page for additional authors

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Libni J. Eapen, MD;[1] Edward Jones, MD;[2] Wassim Kassouf, MD;[3] Carole Lambert, MD;[4] Scott C. Morgan, MD;[1] Madeleine Moussa, MD;[5] Robert Nam, MD;[6] Matthew Parliament, MD;[7] Laurie Russell, MD;[7] Fred Saad, MD;[8] D. Robert Siemens, MD;[5] Luis Souhami, MD;[3] Ewa Szumacher, MD;[6] Scott Tyldesley, MD;[2] Yan Xu, MD;[1] Ingrid Zbieranowski, MD;[6] Rodney H. Breau, MD;[1] Eric Belanger, MD;[1] Peter Black, MD;[2] Eric Estey, MD;[7] Julie Bowan, MD;[9] Bishwajit Bora, MD;[9] Michael Brundage, MD;[10] Peter Chung, MD;[11] Neil Fleshner, MD;[11] Andrew Evans, MD;[11] Glenn Bauman, MD;[12] Jonathan Izawa, MD;[12] Chris Davidson, MD;[5] Fadi Brimo, MD[3]

[1]The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada; [2]BC Cancer Agency, BC, Canada; [3]McGill University Health Centre, Montreal, QC, Canada; [4]Notre-Dame Hospital, Montreal, QC, Canada; [5]Queen's University, Kinston, ON, Canada; [6]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [7]Cross Cancer Institute, Edmonton, AB, Canada; [8]Université de Montréal, Montreal, QC, Canada; [9]Sudbury Cancer Centre, Sudbury, ON, Canada;[10]Kingston Cancer Centre, Kingston, ON, Canada; [11]Princess Margaret Hospital, Toronto, ON, Canada; [12]London Cancer Centre, London, ON, Canada

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See related article on page 95.

Abstract

Introduction: We aimed to enumerate the rate of pelvic recurrence following radical cystectomy at university-affiliated hospitals in Canada.

Methods: Canadian, university-affiliated hospitals were invited to participate. They were asked to identify the first 10 consecutive patients undergoing radical cystectomy starting January 1, 2005, who had urothelial carcinoma stages pT3/T4 N0-2 M0. The first 10 consecutive cases starting January 1, 2005 who met these criteria were the patients submitted by that institution with information regarding tumour stage, age, number of nodes removed, and last known clinical status in regard to recurrence and patterns of failure.

Results: Of the 111 patients, 80% had pT3 and 20% pT4 disease, with 62% being node-negative, 14% pN1, and 27% pN2; 57% had 10 or more nodes removed. Cumulative incidence of pelvic relapse was 40% among the entire group

Conclusions: This review demonstrates a high rate of pelvic tumour recurrence following radical cystectomy for pT3/T4 urothelial cancer.

Introduction

The current gold standard management for locally advanced urothelial bladder cancer consists of neoadjuvant chemotherapy, followed by radical cystectomy with pelvic node dissection and neo-bladder reconstruction, as appropriate.[1,2] This combination addresses the loco-regional pelvic disease and the systemic micrometastatic tumour burden. Unfortunately, cure rates have remained static for over two decades, reflecting the lack of more effective systemic treatment and a continuing problem with pelvic tumour eradication.[3] We report the results of a Canadian academic centre survey designed to enumerate the proportion of patients developing pelvic tumour recurrence following contemporary cystectomy.

Methods

In 2011, 17 university-affiliated cancer clinics across Canada were invited to participate in this effort. Specifically, each centre was asked to identify a trio of investigators comprised of a pathologist, urologist, and radiation oncologist. Following ethics approval, the pathologist generated a chronologically accurate list of consecutive patients undergoing cystectomy for bladder cancer starting January 1, 2005. To be eligible for the study, the following criteria had to be met: 1) primary urothelial carcinoma with or without any admixed other histologies (no other primary histologies such as squamous, adenocarcinoma, or small cell were included); 2) no known hematogenous metastases or nodal involvement above the iliac bifurcation; 3) surgery performed with curative intent and no gross residual disease; 4) neoadjuvant or adjuvant chemotherapy was permitted; 5) only pT3/T4 N0-2 stages. The first 10 consecutive cases meeting these criteria, regardless of whether the subsequent clinical outcome was fully known or not, constituted the required patient sample from each institution. It was the expectation that this method of case selection from each hospital's surgical pathology chronological record would minimize case selection bias.

Abstracted clinical data included birthdate, date of radical cystectomy, pathological stage, number of removed lymph nodes recorded in the pathology report, date of last clinical contact, and last known clinical status. Defining any hematogenous spread or nodal disease above or at L5 as distant metastases (DM) and any pelvic soft tissue or nodal disease below L5 as pelvic recurrence (PR), the eventual clinical status was categorized as: 1) no tumour recurrence; 2) pelvic recurrence only (with date); 3) distant metastases only (with date); 4) distant metastases and pelvic recurrence regardless of whether identified simultaneously or not; and 5) pelvic tumour status unknown. The anonymized individual patient data sheets were collated centrally for compilation and analysis. Arithmetic proportions of patients developing pelvic recurrence with or without distant metastases were tabulated and cumulative incidence calculations were performed to compute the risk of developing pelvic relapse.

Results

Eleven university-affiliated cancer clinics (Vancouver, Edmonton, London, Kingston, Ottawa, Princess Margaret, Sunnybrook, McGill, CHUM, Saint John, and Sudbury) from five provinces participated.

Ten centres from five provinces provided data on 111 patients (Table 1). Age ranged from 43.9–92.7 years, (mean/median 69.6/70.9 years). T stage was pT3 in 81 patients (pT3a=39, pT3b=41, pT3NOS=1) and pT4 in 30 (pT4a=27, pT4b=2, pT4NOS=1). N stage was N0 in 62 patients, N1 in 14, N2 in 27, and Nx in 8. The median number of nodes dissected was 11 and ranged from 0–67. With regard to nodes, 26.6% had more than 15 nodes resected; 21.1% had 11–15 resected; 26.6% had 6–10 resected; 22.9% had 5 or less resected. Median time to last followup was 15 months, and ranged from 0–87 months. PR occurred in 34.2% of patients; 51.4% had no PR. Pelvic status was unknown in 14.4%, but these were considered as having no PR. Of the 38 patients with PR, 25 (65.8%) developed DM and 13 (34.2%) had only PR. Fig. 1 shows the 40% pelvic recurrence rate when calculated as cumulative incidence.

Table 1. Patient characteristics and recurrence status

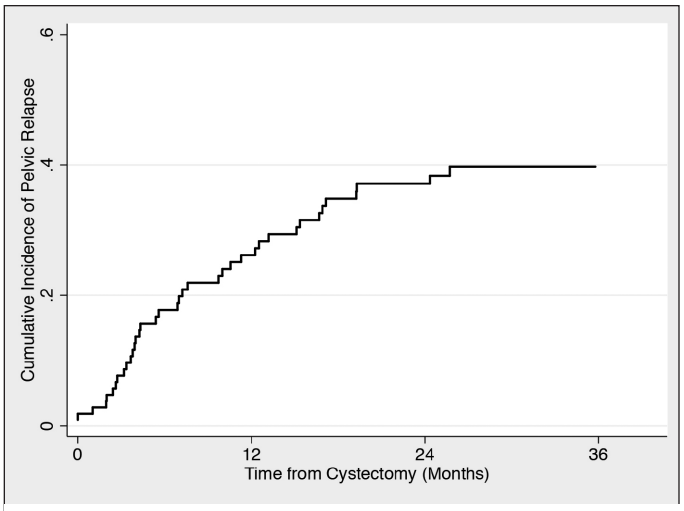
Characteristics	N (%)
Age	
<65	31 (27.9)
≥65	79 (71.2)
Unknown	1 (0.9)
Node status	
pN0	62 (55.9)
pN1	14 (12.6)
pN2	27 (24.3)
Unknown	8 (7.2)
Pathologic stage at cystectomy	
pT3a	39 (35.1)
pT3b	41 (37.0)
pT3NOS	1 (0.9)
pT4a	27 (24.3)
pT4b	2 (1.8)
pT4NOS	1 (0.9)
Nodes removed	
<10	52 (46.9)
≥10	57 (51.4)
Unknown	2 (1.8)
Recurrence status at followup	
None	36 (32.4)
Pelvic only	13 (11.7)
Distant only	22 (19.8)
Pelvic and distant	25 (22.5)
Unknown	15 (13.5)

Discussion

Starting with Whitmores' emphasis on the nodal dissection component of a radical cystectomy in 1962[4] to examination of planned perioperative adjuvant radiotherapy in the 70s and 80s, Skinners' compilation of the large, single-institutional testament to comprehensive, meticulous surgical technique through the 90s,[5] and calibrated further by Herrs' elucidation of the importance of resected node counts in 2003,[6] these strategies have addressed the all-important matter of pelvic tumour eradication in bladder cancer. In a 2007 comprehensive review, Cagiannos et al tabulated contemporary post-cystectomy pelvic recurrence rates ranging from 3.9–29%.[7] These numbers have significantly underestimated the actual occurrence of loco-regional failures due to: 1) dilution by reporting overall rather than per T stage recurrence rates; 2) calculation of simple proportions rather than cumulative incidence risk; 3) requirement of biopsy confirmation; 4) discounting pelvic failure if accompanied or preceded by systemic metastases; and 5) relative inattention to pelvic imaging following the development of distant disease. These detriments to accurate risk determination are compounded by the known insensitivity of pelvic imaging in the context of subcentimetric tumour deposits.

Two experiences published in 2005 and 2012 define the scope of this ongoing pelvic control issue. The SWOG trial of neoadjuvant chemotherapy featured a 32% biopsy-proven crude simple pelvic relapse rate in T3/T4 patients.[8] The MRC trialists' report of the long-term results of the seminal European neoadjuvant chemotherapy trial yielded a 49% loco-regional relapse rate.[9] While documenting the high intrapelvic recurrence rates, both these trials also demonstrate that although overall survival is improved by 5%, neoadjuvant chemotherapy does not have a discernible impact on pelvic tumour control.

The 40% pelvic relapse rate in this cross-Canada study is in concert with the experiences detailed above. Unfortunately, it is likely that even this high risk is an underestimate, given that we used the conservative assumption



Month	0	12	24	36
At risk (events)	110 (25)	46 (10)	27 (3)	19 (0)

Fig. 1. Cumulative incidence of pelvic recurrence following cystectomy of 110 patients; number of patients at risk and events occurring per 12-month period at bottom of graph.

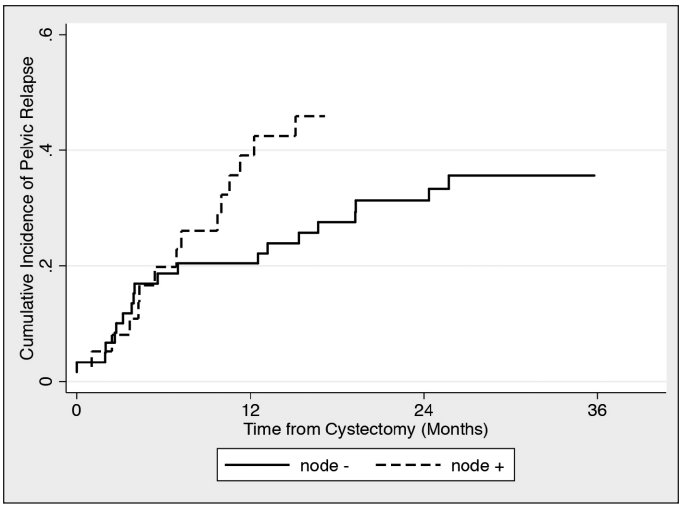


Fig. 2. Cumulative incidence of pelvic recurrence following cystectomy of 110 patients; subgroups defined by nodal status at time of surgery.

that patients in whom pelvic tumour status was unknown were free of tumour.

The strength of our data is two-fold. Firstly, the data is a random snapshot of outcomes. By virtue of the patient retrieval strategy used, the selection biases that can occur when measuring outcomes in patients selected for participation in a clinical trial or abstracting data from cultivated institutional patient data sets is reduced. Secondly, and likely most importantly, the sole and simple object of this exercise was to enumerate pelvic relapse in unselected patients undergoing contemporary surgery at widely dispersed academic institutions. This is in contrast to the general literature, wherein pelvic control is not the prime focus of published reports.

Weaknesses of this data set are the relatively small number of cases audited at each centre (10), the limited rigour in determining pelvic tumour status in those patients for whom it was deemed "unknown" from the readily available documentation, and omission of surgical margin status. The latter two are a reflection of the practicalities of a multicentre survey.

Whereas enumeration defines the magnitude of the problem, understanding causation requires unraveling the interplay between the culprit clinical, surgical, and pathological factors. In this Canadian patient cohort, node positivity predicted for higher PR (Fig. 2), while the number of lymph nodes resected appeared to not materially influence

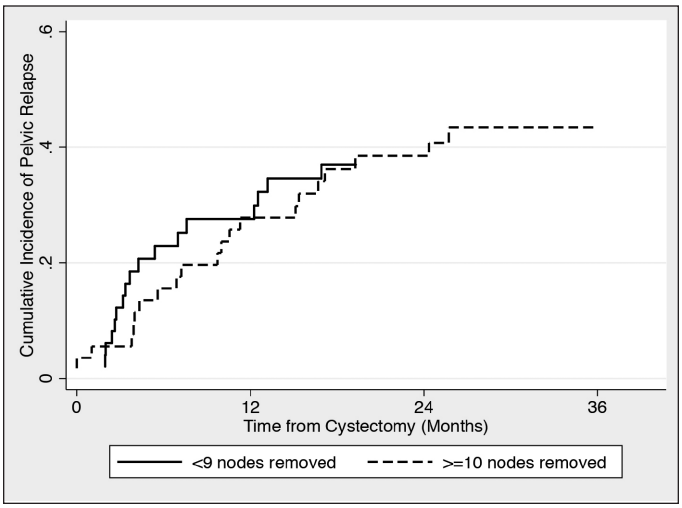


Fig. 3. Cumulative incidence of pelvic recurrence following cystectomy of 110 patients; subgroups defined by number of nodes removed.

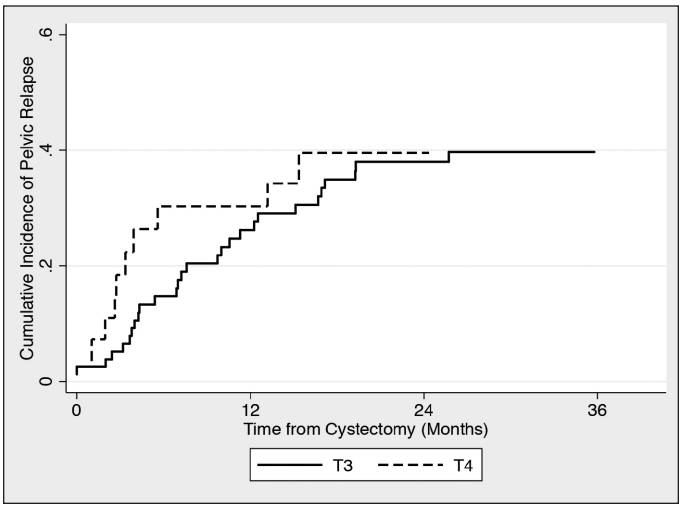


Fig. 4. Cumulative incidence of pelvic recurrence following cystectomy of 110 patients; subgroups defined by pathological tumour stage.

PR (Figs. 3 and 4). This latter observation is at odds with what currently comprises a cardinal aspect of radical cystectomy, whereby still more extensive nodal clearance is being advocated and investigated.[10,11] Lymph node counts, be they absolute or proportional, are vulnerable to variations in retrieval from the resected specimen. Additionally, the relatively small number of patients and the possibility that patients with node-positive disease are more likely to manifest metastatic disease, thus reducing the clinical probability of identifying PR, likely explain this anomalous result.

Our data must not be misconstrued as minimizing the importance of adequate nodal dissection. Christodouleas has validated, extramurally, the robustness of assigning post-cystectomy patients to low-, intermediate- and high-risk categories on the basis of pathological stage, numbers of resected lymph nodes, and margin status.[12] The soundness of this model has been further corroborated by Froehner[13] and Ku[14] This stratification of PR risk accounts for tumour-related parameters. Other factors can be considered as being patient- or treatment-related. Given that, by definition, all patients undergoing curative radical cystectomy had to be sufficiently well-suited in terms of medical condition and performance status to undergo the surgery, it is unlikely that other patient variables have contributed to the probability of PR. Treatment factors include the use of neo or adjuvant chemotherapy, thoroughness of the operation, and case volume issues that speak to the surgical team's experience. As noted previously, randomized trial data show that administering chemotherapy to these patients does not reduce PR rates. While nodal status is unequivocally a tumour parameter, resected nodal counts definitely and margin status possibly also reflect surgical rigor. That all these patients underwent surgery at academic hospitals with cancer clinic affiliations speaks to the likely sufficient patient volumes and requisite surgical expertise.

In the final analysis, this high rate of PR cannot be attributed to any unfortunate case mix or singular compromise of accepted bounds of contemporary surgical management. Rather, it is almost certainly a reflection of the true rates of pelvic failure revealed when the singular focus of the study is the number of pelvic relapses.

The approach of discounting pelvic recurrence if it coincides with or succeeds distant metastases speaks to a perspective that relegates loco-regional failure to the status of being an unfortunate, but clinically unimportant event. This derives from the fact that the majority of patients with pelvic relapse also develop distant disease. However, it remains the clinical reality that: 1) essentially, no patient with pelvic failure can be salvaged, rendering the magnitude of the pelvic relapse problem an absolute ceiling on surgical curability; 2) in the 15% minority of patients who develop isolated pelvic relapse, the clinical outcome is determined by local and not distant disease; and 3) patients with recurrent tumour in the pelvis can and do experience significant morbidity that is poorly palliated, whether or not distant disease coexists.

This study was undertaken because of the clinical perception that PR remains a significant problem following curative surgery in pT3/T4 urothelial bladder cancer, an issue that is not readily discernible in the uro-oncological literature. The multi-institutional data presented corroborates this materially high risk of loco-regional failure following contemporary radical cystectomy in advanced-stage presentation and emphasizes the need to address the issue definitively. Pelvic control is a necessary, but insufficient requirement for cure. Giving it the focus it warrants will enable uro-oncologists to elucidate the optimal, nuanced amalgam of surgery, radiotherapy, and systemic therapies that maximizes the cure potential for the individual bladder cancer patient.

In North America, the NRG clinical trials group[15] has opened a randomized trial examining adjuvant radiotherapy and similar studies are being launched in France, Asia, and the U.K. This is the currency of clinical investigation into the treatment of all other solid malignancies that has yielded ever-improving local, regional, and systemic control, a scenario that can be realistically anticipated for bladder cancer as well.

Competing interests: Dr. Eapen has received grants/honoraria from Abbott and AstraZeneca; and has participated in numerous clinical trials. Dr. Kassouf has received grants/honoraria from Amgen, Astellas, and Janssen; and is also the recipient of a Research Scholar Award from the FRSQ. Dr. Lambert has received grants/honoraria from Ferring and has participated in clinical trials for Ferring and Janssen. Dr. Morgan has been an Advisory Board member for Accuray, Bayer, Janssen, and Sanofi; has received grants/honoraria from Abbvie and Astellas; and has participated in clinical trials for Bayer and Janssen. Dr. Siemens has participated in clinical trials for Amgen, Astellas, Ferring, and Janssen. Dr. Tyldesley has received grants/honoraria from Amgen, Bayer, and Janssen. Dr. Black has been an Advisory Board member for Abbvie, Amgen, Astellas, Biocancell, Cubist, Janssen, Novartis, and Sitka; has been on Speaker Bureaus for Abbvie, Janssen, Ferring, Novartis, and Red Leaf Medical; has received grants/honoraria from Pendopharm; has participated in clinical trials for Amgen, Astellas, Ferring, Janssen, and Roche; and has received research funding from GenomeDx, iProgen, Lilly, and New B Innovation. Dr. Bowen has been an Advisory Board member for Astellas and Janssen; and has received grants/honoraria from AstraZeneca. Dr. Evans has been an Advisory Board member for Omnyx Digital Pathology. Dr. Bauman has received grants/honoraria from Sanofi and has participated in clinical trials for Sanofi. Dr. Izawa has received grants/honoraria from Abbott, AstraZeneca, Astellas, Janssen, Sanofi, and Pfizer. Dr. Chung has received grants/honoraria from Sanofi and has participated in clinical trials for Abbvie. The remaining authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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Correspondence: Dr. Libni Eapen, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; leapen@toh.on.ca