

A Twelve-year Review of Radical Cystectomies in Singapore General Hospital

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Abstract

Introduction: Bladder carcinoma is the tenth most common cancer affecting men in Singapore. This study reviews the complication rates and long-term outcome after radical cystectomy for bladder carcinoma. **Patients and Methods:** A retrospective case-record review of 90 consecutive radical cystectomies in the Department of Urology at the Singapore General Hospital from 1 January 1989 to 31 December 2000 was performed. Patients were included if they were operated for muscle-invasive tumour, high-grade tumour with carcinoma in-situ (CIS), recurring multifocal high-grade tumour, CIS unresponsive to intravesical therapy, or endoscopically uncontrollable tumour. Patients were excluded if they had metastatic disease or non-bladder primary carcinomas. **Results:** The patients were predominantly male (M:F, 80:10) and Chinese (Chinese:Malay:Indian:Others, 70:10:3:7) with a mean age of 64.1 ± 9.9 years (range, 39 to 83 years). Fifty-one patients underwent ileal conduit creation, 36 had ileal neobladder creation, 2 had ureterosigmoidostomies and 1 had Mainz II pouch creation following radical cystectomy. Perioperative mortality was 2.2% ($n = 2$). Early complications constituted 39% ($n = 35$), whilst late complications constituted 14% ($n = 13$) of cases. The mean follow-up was 27.1 ± 29.7 months (range, 1 to 137 months). The mean time to recurrence was 26.0 ± 29.5 months (range, 3 to 137 months). The overall survival was 70%, 43% and 37% at 1, 3 and 5 years, respectively. The disease-free survival was 64%, 35% and 32% at 1, 3 and 5 years, respectively. **Conclusion:** The results of our radical cystectomies for bladder carcinoma are comparable to other established urology units although the morbidity remained significant.

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Key words: Complications, Muscle-invasive bladder carcinoma, Outcome, Risk factors

Introduction

Bladder carcinoma is the tenth most common cancer affecting men in Singapore. It is more common in men with an age-standardised incidence rate of 6.9 per 100,000 per year for men and 1.7 per 100,000 per year for women in Singapore.¹ From 1989 to 2000, 750 new cases of bladder carcinoma were diagnosed and managed in our unit. The majority of bladder carcinomas are superficial. About 20% of superficial disease progress to muscle invasion.² Radical cystectomy is an established treatment option for patients with invasive bladder carcinoma who are surgically fit, while radiotherapy with or without neoadjuvant chemotherapy was used selectively in our department. The earliest radical cystectomy was performed in the 1800s. In 1939, radical cystectomies carried a high mortality rate of 34.5% in Hinman's series of 250 patients.³ In the early eighties, with improvements in surgical techniques and perioperative care, this has decreased to about 1% to 3%.^{4,5} However, complication rates remained high, ranging from 34% to 51% in earlier series.^{6,7}

The aim of this retrospective study was to review the early and late complication rates and long-term outcome following radical cystectomy for primary bladder carcinomas in an Asian population. We also looked at the possible risk factors predisposing to complications from radical cystectomy.

Materials and Methods

The records of 90 consecutive radical cystectomies for bladder carcinoma in the Department of Urology at the Singapore General Hospital over a 12-year period from 1 January 1989 to 31 December 2000 were retrospectively reviewed. These cases were derived from both the records of operations in the department and the histopathology reports from our pathology department.

Inclusion Criteria

Patients were included if they underwent radical cystectomy for muscle-invasive bladder carcinoma, high-grade tumour associated with carcinoma in-situ (CIS),

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rapidly recurring multifocal high-grade tumour, CIS unresponsive to intravesical therapy or endoscopically uncontrollable bladder tumour. Endoscopically uncontrollable bladder tumour referred to those in which the tumour was so extensive that attempted complete transurethral resection of the tumour was not possible.

Exclusion Criteria

Patients were excluded from this review if they had metastatic disease or non-bladder primary carcinomas.

Method

Details of the patients' profile and presenting symptoms were documented. Muscle invasion was demonstrated either histologically from prior transurethral resection specimen or diagnosed from computed tomography (CT) scan of the abdomen and pelvis. All patients had preoperative imaging of the bladder including CT scan of the abdomen and pelvis. A chest X-ray was done to detect pulmonary metastases. Staging was done using the 1997 American Joint Committee on Cancer TNM staging system.⁸ Comorbid status was assessed by the American Society of Anaesthesiologists (ASA) score⁹ and Charlson Comorbidity Index.^{10,11}

Operative Technique

The patients were admitted and underwent bowel preparation using polyethylene glycol a day prior to the surgery. They were informed of the possibility of an ileal conduit creation and intermittent self-catheterisation for ileo-neobladder creation before the operation and given stoma counselling. Preoperative chest physiotherapy, prophylactic intravenous antibiotics (ceftriaxone, metronidazole) on induction, and prophylaxis for deep vein thrombosis were routine practice.

The operative technique and details of the cystectomy have been previously described.¹² A general laparotomy using a lower midline vertical incision was carried out. This was followed by a bilateral pelvic lymphadenectomy and radical cystectomy with frozen section analysis of the distal ureteral and proximal urethral margins.

The operation was completed after the urinary diversion was created. The choice of reconstruction after radical cystectomy depended on several factors, including presence of positive proximal urethral margin, preoperative radiotherapy to the pelvis, poor patient motivation and ability for self-care (including possibility of clean intermittent self-catheterisation), preceding history of renal impairment and hepatic dysfunction or presence of large bowel disease and a poor anal tone.

The first 4 factors are contraindications to orthotopic

bladder reconstruction. Presence of large bowel disease and a poor anal tone are contraindications to uretero-sigmoidostomies. Advance age *per se* is not a contraindication to ileal neobladder creation.^{13,14}

Analysis

Operative mortality was recorded and defined as postoperative death within 30 days of the operation. Complications were divided into early and late. Early and late complications were defined as those arising less than or equal to 3 months and more than 3 months after surgery respectively. Early and late complications were further subdivided into urinary diversion related and non-related causes.

Survival was measured from the date of surgery. The duration of follow-up, time to recurrence and cause of death were documented. The latest status of the patients was obtained through the case notes, telephone calls to the patients or through our electronic medical records. The results were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0. Survival analysis was calculated using the Kaplan-Meier method. Risk factors for postoperative complications were assessed using the Mann-Whitney U and Pearson chi-square tests for nominal and ordinal variables respectively. *P* values of less than 0.05 were considered statistically significant.

Results

Between 1989 to 2000, a total of 90 cases of radical cystectomy for primary bladder carcinoma were performed. Fifty-one patients underwent ileal conduit creation, 36 had orthotopic bladder reconstruction with ileal neobladder creation, 2 had ureterosigmoidostomies and 1 had Mainz II pouch creation following radical cystectomy.

Patient Characteristics

There were more male patients (M:F, 80:10) and the patients were predominantly Chinese (Chinese:Malay: Indian:Others, 70:10:3:7) with a mean age of 64.1 ± 9.9 years (range, 39 to 83 years). The ethnic distribution is similar to the national racial distribution.¹⁵ ASA status scores 1 and 2 constituted 79% of the patient population (*n* = 71). The median serum creatinine level was 102 $\mu\text{mol/L}$ (range, 53 to 542 $\mu\text{mol/L}$). Preoperative imaging of the upper tracts revealed 19% unilateral hydronephrosis and 13% bilateral hydronephrosis.

The indications for radical cystectomy for this series are summarised in Table I. Pathological findings showed that the majority of the cases yielded high-grade (77%) transitional cell carcinoma (91%) and were lymph node negative (77%) (Table II).

TABLE I: INDICATIONS FOR RADICAL CYSTECTOMY

Indication for cystectomy	No.	%
Muscle invasive bladder carcinoma	76	84.4
Rapidly recurring multifocal high-grade tumour	9	10.0
High-grade tumour with CIS, unresponsive to BCG/MMC therapy	4	4.4
Endoscopically uncontrollable tumour	1	1.1

BCG: Bacille Calmette Guerin, CIS: carcinoma in-situ; MMC: mitomycin C

TABLE II: TUMOUR PATHOLOGY

Pathological staging	No.	%
Organ confined (P0-P3a, LN-)	29	32.2
Extravesical (P3b-P4, LN-)	40	44.4
LN+	21	23.3

LN+: lymph node positive, LN-: lymph node negative

Perioperative Results

The mean operation time was 202.8 ± 58.4 min (range, 95 to 375 min). The mean blood loss was 1260.3 ± 1043 mL (range, 500 to 8000 mL) and the mean blood transfusion was 2.0 ± 1.5 units (range, 0 to 7 units). The transfusion rate was 71.1% (64/90). The mean length of hospital stay was 21.9 ± 12.9 days (range, 6 to 59 days).

Complications Following Resection (Tables III & IV)

Mortality

Perioperative mortality was 2.2% (n = 2). The first patient aspirated on the first postoperative day and developed pneumonia. His condition subsequently worsened and he

TABLE III: EARLY POSTOPERATIVE COMPLICATIONS

Complication	Intervention	No.	%
Diversion related			
Ureteroileal leak	PCN drainage	4	4.4
Pyelonephritis	Conservative	3	3.3
Pelvic abscess	Open drainage	2	2.2
EC fistula	Intravenous hyperalimentation	1	1.1
Perinephric abscess	Intravenous antibiotics	1	1.1
Total		11	12.1
Non-diversion related			
Wound infection	Conservative	23	25.6
Pneumonia	Antibiotics	4	4.4
Sepsis	Antibiotics	4	4.4
Intestinal obstruction	Re-operation, adhesiolysis	3	3.3
Burst abdomen	Operative repair	2	2.2
DVT	Anticoagulation	1	1.1
Total		37	41.0

EC: enterocutaneous; DVT: deep vein thrombosis;

PCN: percutaneous nephrostomy

Note: Multiple complications may exist in a patient, therefore the categorical complication rates do not always add up to the total complication rate.

succumbed to multiorgan failure 3 weeks after the operation. The second patient developed methicillin-resistant *Staphylococcal aureus* pneumonia a week after surgery. He subsequently developed fungal sepsis and succumbed to multiorgan failure a month after surgery.

Complications

Early complications constituted 39% (n = 35) whilst late complications constituted 14% (n = 13) of cases. The types

TABLE IV: LATE POSTOPERATIVE COMPLICATIONS

Complication	Intervention	No.	%
Diversion related			
Metabolic acidosis	Intravenous sodium bicarbonate therapy	5	5
Chronic renal failure (CRF)	Conservative, not requiring dialysis	3	3
Renal calculus in solitary kidney, CRF	PCNL	1	1
Ureteric stricture with pyonephrosis	PCN drainage	1	1
Uretero-ileal stenosis	Refashioning of anastomosis	1	1
Ureteric stricture	Ureteroscopic dilatation	1	1
Urethral stricture	Optical urethrotomy	1	1
Bladder neck stenosis	TURBNI	1	1
Total		14	14
Non-diversion related			
Incisional hernia	Repair	3	3
Intestinal obstruction	Laparotomy, adhesiolysis	1	1
Ileo-vaginal fistula	Repair	1	1
Total		5	5

PCN: percutaneous nephrostomy; PCNL: percutaneous nephrolithotripsy; TURBNI: transurethral bladder neck incision

Note: Multiple complications may exist in a patient, therefore the categorical complication rates do not always add up to the total complication rate. The percentages were calculated with the total number of cystectomies (n = 90) as the denominator.

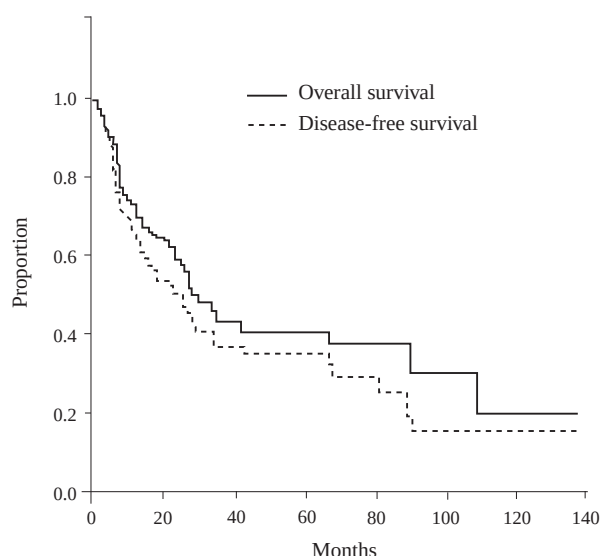


Fig. 1. Overall and disease-free survival.

of complications and their respective intervention are described in Tables III and IV.

Long-term Outcome

The mean follow-up was 27.1 ± 29.7 months (range, 1 to 137 months). The mean time to recurrence was 26.0 ± 29.5 months (range, 3 to 137 months). As shown in Figure 1, the overall survival was 70%, 43% and 37% at 1, 3 and 5 years, respectively. The disease-free survival was 64%, 35% and 32% at 1, 3 and 5 years, respectively.

Discussion

The incidence of bladder carcinoma in Singapore is significantly lower than that in the United States and many European countries but is similar to the rest of Asia.¹⁶ Correspondingly, there are fewer patients with muscle-invasive bladder carcinoma. About 80% of cases present with *de novo* muscle-invasion and the remaining cases are the result of progression from superficial disease, in particular carcinoma in-situ.¹⁷

Our series also showed a significant early postoperative complication rate of 39%. However, the majority (9 out of 11 diversion-related and 35 out of 37 non-diversion-related complications) were minor complications such as superficial wound infections or pneumonia, which do not need open intervention. More serious complications requiring operative interventions such as pelvic abscesses or burst abdomen were far less common.

Infective and medical complications were common complications in the early postoperative period (less than or equal to 3 months) whereas diversion-related complications appeared later in the late postoperative period (more than 3 months). This was due to the fact that anastomotic strictures and other diversion-related

complications take time to develop whilst medical and infective complications are more acute and usually manifest early.

There were fewer late complications. Most of the diversion-related complications did not require operative intervention (9 out of 14 complications) but non-diversion-related late complications required operative intervention. This is probably because the latter complications were structural or mechanical problems (fistula, incisional hernia, adhesions) that did not resolve with medical treatment. A significant proportion of these complications were related to strictures and these problems necessitated operative dilatation or refashioning of the anastomoses.

Our early complication rate of 39% and late complication rate of 25% are comparable to larger contemporary series reported by Figueroa et al¹³ (32% and 12.4%, respectively) and Hautmann et al¹⁸ (39% and 32%, respectively). These two series involved more than 300 radical cystectomies in American and European populations respectively.

The overall survival of 70%, 43% and 37% at 1, 3 and 5 years respectively are comparable to other series in the literature.^{13,14,19,20} The long-term outcome in this review is excellent and significantly better when compared to the outcome after definitive radiotherapy. Holmang et al²¹ showed 5-year crude survival rates of 15% for patients with T2-T3 disease after radiotherapy alone. Mortality rates of 12% to 20% have been quoted during or shortly after irradiation.^{22,23} However, several recent studies have used a combination of cytoreductive transurethral resection and sequential chemoradiotherapy with better results than radiotherapy alone. Arias et al²⁴ reported a 5-year overall survival of 48% and Zapatero et al²⁵ reported 70% clinical complete response rate. However, these studies involved small groups of highly selected patients and long-term results were not available. However, it is important to note that the difference in outcome favouring radical cystectomy over radiotherapy may be partly due to a selection bias as the two groups of patients may not be entirely comparable.

The elderly patients, defined as those aged 70 years and above, were analysed separately from the younger patients, aged below 70 years. We found that there is a higher mortality risk but comparable morbidity risks in the elderly population. Thirty-day mortality was 4.5% ($n = 2$) in the elderly group versus 0% in the younger group. The early (33.3% versus 51.9%) and late (15.9% versus 11.1%) complication rates were comparable in both groups. However, one has to factor in the small study population of 27 elderly patients. The higher incidence of early complications was most likely related to co-morbid conditions, especially ischaemic heart disease and chronic obstructive pulmonary disease, which reduced the cardiopulmonary functional reserve in the elderly. This

resulted in poorer response to the stress of surgery and increased risk of acute coronary events and chest infections. Presence of chronic conditions, such as diabetes mellitus with nephropathy, also impaired wound healing and predisposed to sepsis, chest and wound infections.

The shorter median survival of 8 months (versus 90 months in the younger group, $P < 0.001$) and poorer 5-year overall survival in the elderly (10.6% versus 57.1% in the younger group) were related to the more advanced stage of disease at the time of diagnosis. This led to a higher rate of recurrence and subsequent metastatic spread. This was supported by the short median time to recurrence of 7 months.

Reduction of the early complication rate in this group of patients will entail aggressive optimisation of cardiopulmonary status with the aid of our cardiologists and respiratory physicians and rigorous monitoring and treatment of chronic ailments like diabetes to reduce infective episodes.

The long-term outcome may be improved further by earlier detection of the disease. Radical cystectomy should be offered to our elderly patients as a definitive treatment at an earlier stage and not as a salvage procedure for recurrence or advanced disease after radiotherapy. Age *per se* should not be a contraindication to radical cystectomy.

The survival by stage is shown in Figure 2. The organ-confined group had the best survival, followed by the

extravesical group. As expected, the lymph node positive group yielded the worst survival (log rank, $P < 0.05$).

The possible factors affecting postoperative complications were also analysed (Table V). Univariate analysis showed that a poor preoperative ASA score was a strong predictor of postoperative morbidity ($P < 0.05$). Patient age, sex, race, Charlson Comorbidity Index, preoperative serum creatinine, operation time, intraoperative blood loss and transfusion requirement were not statistically significant factors in this series. Therefore, early assessment by the anaesthetist and meticulous perioperative care may help to decrease the complication rate.

Co-morbid factors denote the presence of co-existing medical conditions but the ASA score factors in their effect on the patient's function. Hence, they are not equivalent variables. The prevailing view by some authors that the presence of multiple co-morbid conditions predisposes to

TABLE V: UNIVARIATE ANALYSIS OF RISK FACTORS FOR COMPLICATIONS

Risk factor	No. with complications/ No. assessable (%)	<i>P</i> value
Age		
<70 years	27/63 (42.9%)	0.153
≥70 years	16/27 (59.3%)	
Sex		
Male	41/80 (51.3%)	0.062
Female	2/8 (25.0%)	
Race		
Chinese	33/70 (47.1%)	0.822
Non-Chinese	10/20 (50.0%)	
ASA score		
<3	30/71 (42.3%)	0.043
≥3	13/19 (68.4%)	
Co-morbidity index		
<3	40/85 (47.1%)	0.573
≥3	3/5 (60.0%)	
Co-morbidity index + age		
<3	16/41 (39.0%)	0.128
≥3	27/49 (55.1%)	
Preoperative renal function		
<200 µmol/L	41/84 (48.8%)	0.463
≥200 µmol/L	2/6 (33.3%)	
Operation time		
<200 minutes	22/44 (50.0%)	0.669
≥200 minutes	20/44 (45.5%)	
Blood loss		
≤1000 mL	27/62 (43.5%)	0.232
>1000 mL	16/28 (57.1%)	
Blood transfusion		
<3 units	33/71 (46.5%)	0.633
≥3 units	10/19 (52.6%)	

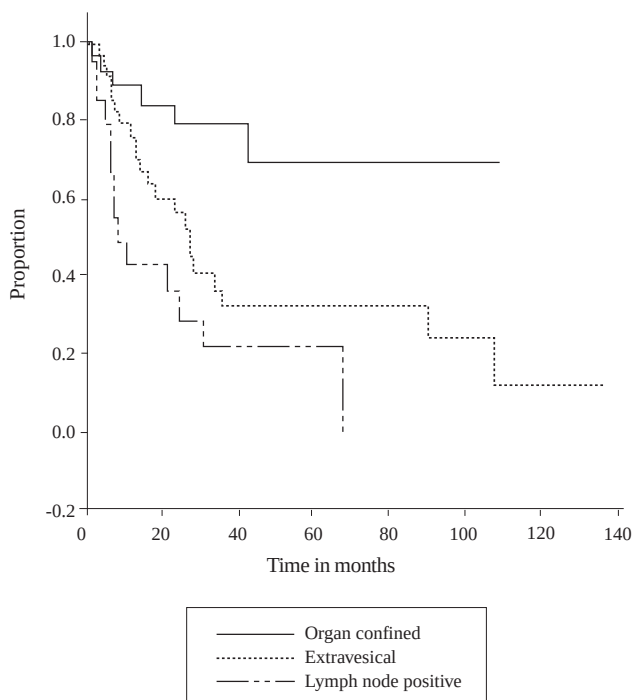


Fig. 2. Survival by stage.

increased postoperative complications was not borne out by our analysis. Stroumbakis et al¹⁴ also showed that the number of co-morbid events was not related to postoperative complications or hospital stay. This is due to a careful selection of patients through meticulous preoperative assessment and anaesthetic management as well as well-controlled co-morbid conditions preoperatively. Increased postoperative complications have also been linked to protein depletion preoperatively as it decreases the rate of wound healing and increases the risks of infection. However, routine intravenous hyperalimentation has not been shown to be of benefit either in reducing mortality or length of stay.⁷

The main limitations of our series are the relatively small number of patients and the retrospective nature of the study. In the earlier part of the series, most of the urologists in the department were performing radical cystectomies but the later years saw most of the procedures performed by a specialised uro-oncology team. The results of this sub-specialisation is still not ready but is expected to improve the outcome.

Conclusion

The results of radical cystectomies for bladder carcinoma in our series have been shown to be comparable to other established urology units with similar perioperative mortality and morbidity rates. Its safety has improved over the years but the morbidity rate remains significant. It is an acceptable option for patients with invasive bladder carcinoma when compared to definitive radiotherapy. As ASA status is a strong prognostic variable, careful preoperative assessment and selection and improved operative techniques and anaesthetic care will minimise morbidity and improve the long-term outcome for these patients.

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