Describing the 90-day postoperative outcomes after open radical cystectomies and evaluating predictive nomograms at a South African referral centre

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Purpose: Radical cystectomy (RC) is the primary treatment for muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer despite its significant morbidity and mortality rates. There is a need for tools, like nomograms, to help predict mortality following RCs. This study aimed to investigate outcomes and predictive tools (nomograms) in a South African cohort.

Methods: Between January 2014 and April 2022, 89 patients underwent RC at a high-volume centre in South Africa. We described the outcomes of these cases and evaluated the performance of the Aziz and Preoperative Score to Predict Postoperative Mortality (POSPOM) nomograms for predicting 90-day mortality in our population.

Results: Neoadjuvant chemotherapy was administered to 38% of patients, with 41% achieving a complete response. There was a median of 800 ml intraoperative blood loss, and 51.7% required blood transfusions. The median hospital stay post-surgery was ten days. Within one year post-surgery, 79.8% experienced complications, with major complications (Clavien–Dindo III–V) occurring in 15.7% of cases. The 30- and 90-day all-cause mortality rates were 5.6% and 9.0%, respectively. The Aziz nomogram demonstrated moderate predictive accuracy for 90-day mortality (area under the curve [AUC] = 0.749), while the POSPOM nomogram performed less effectively (AUC = 0.635).

Conclusions: This study shows marginally higher complication and mortality rates than high-income countries. The Aziz nomogram shows potential for identifying suitable surgical candidates in this setting.

Keywords: bladder cancer, radical cystectomy, nomogram, complications, predictive

Introduction

Bladder cancer is the tenth most common cancer, excluding nonmelanoma skin cancer. Males are at an increased risk compared to females, as bladder cancer is the sixth most common cancer in men, compared to seventeenth amongst females.¹ The global incidence rate is 9.5 for males and 2.4 for females (age-standardised per 100 000 person-years), whereas the age-standardised mortality rate for both genders is 1.9 per 100 000 person-years.¹

Bladder cancer in Africa differs from reports in developed countries, with predominantly squamous cell carcinoma (SCC) (53–69%, mainly attributable to schistosomiasis) compared to the predominance of urothelial carcinoma (UC) (> 90%) in the developed world.² On average, patients with SCC present 10–20 years younger than those with UC.³ The proportion of SCC depends on schistosomiasis prevalence, and in areas with a low schistosomiasis burden, such as the Western Cape, the proportion of SCC approaches that of developed countries.³ In South Africa, bladder cancer is the ninth most common cancer (6.6 new cases per 100 000 person-years).¹

The current standard curative treatment of non-metastatic muscleinvasive and high-risk non-muscle-invasive bladder cancer is cisplatin-based neoadjuvant chemotherapy, followed by radical cystectomy (RC), pelvic lymph node dissection (PLND), and either a neobladder or urinary diversion.^{3,4} The five-year cancer-specific survival post-RC is around 66%, and the five-year recurrence-free survival is 58%.⁵ An adequate lymph node dissection is associated with an 8% improvement in five-year cancer-specific survival following RC and is generally accepted to be > 10 lymph nodes removed, although the optimal number is not universally agreed on.⁶ The number of lymph nodes counted by pathologists increases artificially when sending lymph nodes as separate specimens instead of *en bloc*, limiting reproducibility.⁷ There is limited evidence of improved outcomes of an extended over a standard PLND.⁶

Despite advances in surgical technique and perioperative care, RC remains a major surgery.89 Complications following RC occur in 58-64% of patients within 90 days of surgery.^{8,9} The most common complications are infections, genitourinary-, gastrointestinal-, and wound-related complications.8 Mortality following RC in large series is reported as 1-3% at 30 days and 2-8% at 90 days.48,10-12 The only South African study reported complication rates of 43-61%, with decreased complications if RC was done laparoscopically, compared to an open procedure.13 The 90-day all-cause mortality rate of 20% was similar in both open and laparoscopic groups and higher compared to large international series.13 The average hospital stay in large studies is 8-15 days, with a shorter stay in robotic-assisted RCs than in open procedures.9,14 More recently, robotic assistance during RC has been shown to maintain oncological equivalence whilst having the following benefits of minimally invasive surgery: a decrease in thromboembolic and wound complications, less blood loss, lower transfusion rates, shorter hospital stays, and earlier recovery from surgery.14-17

The significant complication and mortality rates following RC create the need for tools to predict adverse outcomes and aid patient selection and counselling before RC. Nomograms have been developed and validated to predict 90-day mortality rates following RC; the first was the Isbarn nomogram, followed by the Morgan and Aziz nomograms.¹⁸⁻²⁰ Another validated nomogram for use in RCs is the Preoperative Score to Predict Postoperative Mortality (POSPOM) nomogram, developed from a French cohort of 2.7 million procedures across all surgical fields.²¹ The Aziz nomogram consists of the following variables: clinical nodal and metastatic staging, age, hospital RC volume, and American Society of Anesthesiologists (ASA) score.¹⁹ The POSPOM nomogram consists of age, type of surgery, and various comorbid conditions.²¹ These nomograms' accuracy in predicting postoperative mortality varies between 67% and 78%.^{18,20,22,23}

The following individual variables have been shown to predict adverse outcomes: age > 70 years, ASA score, Charlson Comorbidity Index (CCI), and advanced cancer stage (T3 or greater, or N-positive).8 Several comorbidity scales are used to help select good candidates for RC, with the age-adjusted CCI (aCCI) being the only one to correlate with both cancer-specific and overall survival.²⁴ Current European Association of Urology guidelines highlight the limited use of chronological age in prediction outcomes and recommend using a validated scoring system, like the aCCI.25 Perioperative blood transfusions are independently associated with reduced survival outcomes.²⁶ Bladder cancer may obstruct the ureter(s) or bladder neck, with resultant hydronephrosis. Two recent systematic reviews found that preoperative bilateral hydronephrosis is associated with poorer overall and cancer-specific survival, whereas unilateral hydronephrosis was not associated with adverse outcomes.^{27,28} Gender, body mass index (BMI), preoperative radioand chemotherapy, and the number of transurethral bladder tumour resections are not associated with worse outcomes.8

Another factor incorporated into the Aziz nomogram is the case volume of an institution.¹⁹ The complication and mortality rates decrease as the volume of RCs done at a centre increases, and a minimum of ten RCs per centre per year is recommended. However, there might be an additional benefit if a centre performs more than 20 per year.^{11,12,29}

The reporting of surgical complications has been standardised, and the Clavien–Dindo system is most commonly used in urology. This system grades complications by severity based on the invasiveness of the treatment required to manage the complication (Appendix 1 in *Supplementary material*).³⁰ It is paramount that such a standardised system is used when complications are reported to enable interstudy comparison of complication rates.

There is a need to have accurate local data on patients' demographics, pathological profiles, and markers of adequate surgery, such as lymph node count and negative surgical margins. We also need local complication rates, length of stay, and 90-day mortality rates so patients and healthcare funders can receive accurate information for their treatment decisions. The starting point

of improvement in outcomes is accurate data and identifying the areas where improvements are needed.

This study describes the pathological profile, markers of surgical adequacy, complete response to neoadjuvant chemotherapy, length of stay, one-year complication rate, and 90-day mortality at a high-volume centre in South Africa. Secondarily, we evaluated the performance of the Aziz and POSPOM nomograms for predicting 90-day mortality in our population. The nomograms were evaluated as a pilot project, as the study was not powered to enable formal nomogram validation. See Appendix 2 and 3 in *Supplementary material* for the Aziz and POSPOM nomograms.

Materials and methods

Setting and study design

A record-based retrospective descriptive study was conducted on all consecutive patients who underwent a RC at our centre between January 2014 and April 2022. Tygerberg Hospital is a large referral centre in Cape Town, South Africa. Data was collected from individual electronic hospital records.

Study population and management principles

Indications for RC were non-metastatic muscle-invasive bladder cancer, high-risk non-muscle-invasive bladder cancer, high-volume non-muscle-invasive bladder cancer, stromal tumours of the bladder such as paraganglioma, and BCG failure. Cystectomies done for benign indications were excluded, as were patients with known metastatic disease (M1) before surgery. Patients with locally advanced disease or clinically enlarged lymph nodes at the time of surgery were not excluded. Ileal conduits were performed in all patients, with no neobladders or cutaneous ureterostomies done.

All patients were diagnosed with transurethral resection of a bladder tumour and staged with either a computed tomography (CT) or magnetic resonance imaging (MRI) scan. They were then discussed at a multidisciplinary meeting, and all eligible patients received cisplatin-based neoadjuvant chemotherapy. We aimed to do a complete transurethral resection of all cystoscopically apparent tumours before neoadjuvant chemotherapy, when possible. Patients with locally advanced (T3) tumours, variant urothelial histological types, and non-urothelial tumours were not offered neoadjuvant chemotherapy. Nuclear glomerular filtration rate scintigraphy studies were done for all patients considered for neoadjuvant chemotherapy.

RCs were all done open, and a standard lymph node template was used, with the margins being the ilioinguinal nerve laterally, the bifurcation of the common iliac artery cranially, the ureter medially, and the deep circumflex iliac vein caudally. We did not send separate lymph node packages, but rather *en block* nodal packages, to prevent cutting through lymph nodes containing malignancy and thus compromising oncological outcomes. The prostate was removed in males. In females, the uterus and part of the anterior vaginal wall, including the urethra, were removed. We did not routinely remove the ovaries in females. Indications for male urethrectomies were clinically apparent or histologically proven

prostatic urethral involvement. We did not routinely use frozen sections. Based on surgeon preference, bowel anastomosis was done using staplers or hand-sewn anastomosis. No mechanical or antibiotic bowel preparation was used. We used a Wallace type 1 uretero-ileal anastomosis, with mono-J stents inserted, which we removed at six weeks.³¹

As a training institution, most surgeries were done by senior registrars under consultant supervision. Most of our patients received an epidural with their general anaesthetic and went to an intensive care unit postoperatively. Our practice was to place a wound drain, which was removed when a patient mobilised and if urine was not draining into the wound drain, confirmed by measuring creatinine levels in the drain fluid. We started patients on total parenteral nutrition if they did not tolerate a full oral diet by the fifth postoperative day.

Outcomes and data collected

We collected data on complications during the first year after RC and graded it according to the Clavien–Dindo system. We also recorded the length of hospital stay and 30- and 90-day mortality rates. The complications did not include mortalities that were exclusively due to cancer progression, although these mortalities were included in all-cause mortalities. Other data collected were demographics, risk factors for bladder cancer (smoking, occupation, previous bilharzia, or radiation), and predictors of complications (ASA score and aCCI).

Further, we collected data on neoadjuvant chemotherapy, the presence of hydronephrosis, clinical staging, epidural use, theatre time, blood loss and transfusions, histological malignancy type and stage, and the number of lymph nodes removed and involved by malignancy. The Aziz and POSPOM nomograms were used to calculate each patient's predicted 90-day mortality rate.

Statistical analysis

We described the 90-day mortality as a percentage with corresponding 95% confidence intervals (CI). Continuous variables were described using means with standard deviations (SD) for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. To enable interstudy comparison, we reported the mean and median for the length of stay outcomes and the number of lymph nodes removed. Categorical variables were described with frequencies, percentages, and their corresponding 95% CIs. We performed significance testing for associations between postoperative outcomes and pre- and intraoperative variables where appropriate. We used contingency tables, and the Pearson chi-square and Fisher's exact tests for binary data using STATATM (version 17), with significance levels set at *p*-values of < 0.05.

We evaluated the predictive ability of the Aziz and POSPOM nomograms by constructing a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC) to describe each nomogram's predictive accuracy. Therefore, data were anonymised at the point of data collection. Missing data was treated as missing at complete random, and incomplete records were used in the analysis of fields for which they contained data. A calculation of the percentage of missing data points was done.

Ethical considerations

This study was approved by the Human Research Ethics Committee (HREC) at the Faculty of Medicine and Health Sciences, Stellenbosch University. Ethics reference: S22/10/190. This study was conducted per the Ethical and Good Clinical Practice guidelines of the World Medical Association Declaration of Helsinki (2017) and the South African National Health Act, 2003 (Act 61 of 2003). There was no risk for participants, and all information was depersonalised and stored anonymously to maintain participant confidentiality throughout the study.

Results

The study included 89 patients over the study period, with a yearly average of 10.8 RCs. Data collection showed a missing data level of 2.98%, with 130 out of 4 361 data points missing. The mean length of follow-up was 29.0 months. Of them, 65 (73%) were male and 24 (27%) were female. The mean age was 59 years (SD = 9.9). Most patients (73, 82%) were current or previous smokers. Only two patients (2.3%) had previous schistosomiasis infections, and eight patients (9%) had self-reported occupational exposures to carcinogens. Most patients (81, 91%) presented with macroscopic haematuria as the first symptom. The mean BMI was 26.7 kg/m² (SD = 5.2), and 72 patients (81%) had an ASA score \geq 2. The mean aCCI was 4.24 (SD = 1.3). Unilateral hydronephrosis was present in 22 patients (24.7%) before surgery, while 15 (16.9%) had bilateral hydronephrosis; see Table I.

Neoadjuvant chemotherapy was given to 34 patients (38%), of whom 14 patients (41%) had a complete response with pathological T0 disease at RC. The median volume of blood loss at surgery was 800 ml (IQR 500–1 200 ml), and 46 patients (51.7%) required an intraoperative blood transfusion. The median theatre time, including anaesthetic and preparation time, was 380 minutes (IQR 330–432 min), and most (n = 79/89, 93.3%) received an epidural supplementary to their general anaesthetic. The median lymph node count was nine nodes removed, whilst 39 patients (44%) had more than ten lymph nodes removed. Negative surgical margins were obtained in 77 patients (86.5%); see Table II.

The median length of postoperative hospital stay was ten days (IQR 8–15 days). The risk of any complication was 79.8% (n = 71/89) in the first year of follow-up, and the risk of major (Clavien–Dindo III–V) complications was 15.7% (n = 14/89). This number excludes patients who demised due to cancer progression alone (18 patients, 20.2% at 12 months), who were included in all-cause mortality. The most common major complication was ileal conduit-related complications in five patients. The risk of ileus (defined as not tolerating a full oral diet for five days) was 29% (n = 25/89), and 20% of patients (n = 17/89) required total parenteral nutrition. Ten patients (11.1%) required reoperation under general anaesthesia (grade IIIb). Of those, one was for bowel obstruction, one for a hernia, five for revisions or redo of conduits, and the rest for wound dehiscence; see Table II.

| Table I: Demographics and baseline characteristics | | | | |
|---|---|-----------------|-----------|--|
| Variable | Number with complete data available for variable | Number/ mean | %/SD | |
| Total patients (n) | 89 | 89 | | |
| Age in years | 89 | 58.9 | 10.0 (SD) | |
| Gender | 89 | | | |
| Male | | 65 | 73.0 | |
| Female | | 24 | 27.0 | |
| Macroscopic haematuria as presenting symptom | 89 | 81 | 92.0 | |
| Smoker (former or current) | 89 | 73 | 82.4 | |
| Occupational risk factors | 89 | 8 | 9.4 | |
| Previous bilharzia | 89 | 4 | 4.8 | |
| BMI (kg/m ²) | 81 | 26.8 | 5.2 (SD) | |
| Nuclear medicine glomerular filtration rate (ml/min/1.73 m ²) | 71 | 89.8 | 34.6 (SD) | |
| Haemoglobin (g/dl) | 87 | 10.8 | 2.2 (SD) | |
| ECOG status | 89 | | | |
| 0 | | 26 | 29.2 | |
| 1 | | 49 | 55.1 | |
| 2 | | 14 | 15.7 | |
| 3–5 | | 0 | 0 | |
| ASA score | 89 | | | |
| 1 | | 17 | 19.1 | |
| 2 | | 48 | 53.9 | |
| 3 | | 22 | 24.7 | |
| 4 | | 2 | 2.3 | |
| 5–6 | | 0 | 0 | |
| aCCI | 89 | 4.3 | 1.4 (SD) | |
| Hydronephrosis | 89 | | | |
| None | | 52 | 58.4 | |
| Unilateral | | 22 | 24.7 | |
| Bilateral | | 15 | 16.9 | |
| Clinical T-stage | 89 | | | |
| ТО | | 2 | 2.2 | |
| T1 | | 10 | 11.2 | |
| T2 | | 28 | 31.5 | |
| ТЗа | | 17 | 19.1 | |
| T3b | | 13 | 14.6 | |
| T4a | | 18 | 20.2 | |
| T4b | | 1 | 1.1 | |
| Clinical N-stage | 89 | | | |
| N0 | | 62 | 71.3 | |
| N1 | | 3 | 3.4 | |
| N2 | | 21 | 24.1 | |
| N3 | | 2 | 3.4 | |
| Clinical M-Stage | 89 | | | |
| M0 | | 89 | 100 | |
| M1 | | 0 | 0 | |

aCCI – age-adjusted Charlson Comorbidity Index, ASA – American Society of Anesthesiologists, BMI – body mass index, ECOG – Eastern Cooperative Oncology Group, SD – standard deviation

The 30-day all-cause mortality rate was 5.6%, with the 90-day rate being 9.0%. There was higher mortality among female patients (4/24) compared to males (4/65), but the difference was not statistically significant (p = 0.124). The causes of death at 90 days were cancer progression (n = 5), followed by sepsis (n = 2), and cardiovascular events (n = 1); see Table II.

The histological profile of tumours showed a predominance of UC (75 patients, 84.3%) followed by SCC (nine patients, 10.1%). UC with variant histological patterns were present in 11 patients (12.6%); see Table III.

Table III: Histological profile of bladder tumours

| Histological type | Number (%) | |
|--|------------|--|
| Pure UC | 64 (71.9) | |
| SCC | 9 (10.1) | |
| Adenocarcinoma | 4 (4.5) | |
| Paraganglioma | 1 (1.1) | |
| Variant urothelial patterns | | |
| UC with squamous differentiation: 7 (63.6%) | 11 (12.6) | |
| UC with squamous and sarcomatoid variation: 3 (27.3%) | | |
| UC with squamous and glandular differentiation: 1 (9.1%) | | |
| Total | 89 (100) | |

SCC - squamous cell carcinoma, UC - urothelial carcinoma

The Aziz nomogram showed acceptable predictive accuracy for 90-day mortality, with an AUC of 0.749 (95% CI 0.550 to 0.949, p = 0.021). At a cut-off value of 111 points, the Aziz nomogram had a sensitivity of 75.0% and a specificity of 75.3% for predicting 90-day mortality; see Figure 1. The POSPOM nomogram did not perform well in our cohort, with an AUC of 0.635 (95% CI 0.422 to 0.848, p = 0.209); see Figure 2.

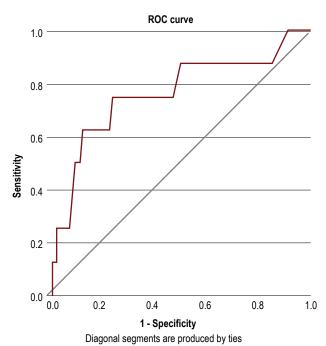


Figure 1: Predictive accuracy of the Aziz nomogram for 90-day mortality

134

Table II: Treatment and outcomes

| Variable | Number with complete data available for variable | Number/average | IQR/SD/% |
|--|--|----------------------------|---|
| Neoadjuvant chemotherapy | 89 | 34 | 38.2 |
| Complete response to chemotherapy (pT0) | 89 | 14 | 15.7 overall 41.2 of those who received chemotherapy |
| Epidural use | 89 | 79 | 88.8 |
| Total theatre time (min) | 83 | 380 (median) | 330–432 (IQR) |
| Blood loss (ml) | 69 | 800 (median) | 500–1 200 (IQR) |
| Intraoperative blood transfusions | 89 | 42 | 47.2 |
| Negative surgical margins | 89 | 77 | 86.5 |
| Number of lymph nodes removed | 83 | 9 (median) 12.5 (mean) | 5–16 (IQR) 10.59 (SD) |
| Lymph node density of N+ patients (number involved/ number removed) | 83 | 51/193 | 26.4 |
| Pathological T-stage | 89 | | |
| pTO | | 18 | 20.2 |
| pT1 | | 14 | 15.7 |
| pT2 | | 17 | 19.1 |
| оТЗа | | 19 | 21.3 |
| PT3b | | 5 | 5.6 |
| bT4a | | 15 | 16.9 |
| bT4b | | 1 | 1.1 |
| Pathological N-stage | 89 | | |
| DN0 | | 70 | 78.7 |
| bN1 | | 13 | 14.6 |
| DN2 | | 6 | 6.7 |
| bN3 | | 0 | 0 |
| Length of hospital stay (days) | 89 | 10 (median) 14.2 (mean) | 8–15.3 (IQR) 10.3 (SD) |
| leus | 89 | 24 | 28.1 |
| Total parenteral nutrition | 89 | 17 | 19.1 |
| Complications (Clavien–Dindo system) | 86 | | |
| Grade I | | 34 | 38.2 |
| Grade II | | 24 | 27.0 |
| Grade IIIa | | 1 | 1.1 |
| Grade IIIb | | 10 | 11.2 |
| Grade IVa | | 1 | 1.1 |
| Grade IVb | | 0 | 0 |
| Grade V | | 1 | 1.1 |
| Risk of major complications (III–V) | | 13 | 14.6 |
| Total (all grades) | | 71 | 79.8 |
| All-cause mortality | 89 | | |
| 30-day mortality | | 5 | 5.6 (95% CI 1.9 to 12.6) |
| 90-day mortality | | 8 | 9.0 (95% CI 4.0 to 17.0) |

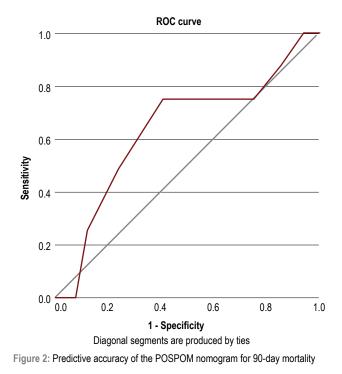
CI - confidence interval, IQR - interquartile range, SD - standard deviation

Discussion

This study aimed to accurately assess and describe the outcomes of RCs at a large training hospital in South Africa and to assess the applicability of predictive nomograms in our population. This study is a large African series reporting outcomes for RCs. It is the first of its kind in many areas, namely reporting the incidence of variant histological patterns, uptake, and complete response to chemotherapy while evaluating two validated nomograms (Aziz and POSPOM).

The overall complication rate in our study (79.78%) appears higher than reported by Hautman et al.⁸ (57.9%) in his series of 1 540 RCs and by Patidar et al.⁹ (64.15%) in his series of 212

135



patients. A recent systematic review from 2021 reported the 90-day complication rate as 58.5% (36.1–80.5%).³² However, it must be noted that the three mentioned studies only recorded complications up to 90 days, whereas we included complications up to one year. Major complications (Clavien–Dindo grade III–V) in our study were 14.61%, which aligns with the 16.9% reported in a systematic review from 2021.³²

One of the main reasons for this study was to have accurate 30- and 90-day mortality rates in our population. We found that our 30- and 90-day mortality rates (5.62% and 8.99%, respectively) were higher than those from the included studies in the 2021 systematic review, which was 2.1% (0.0–3.7%) at 30 days and 4.7% (0.0–7.0%) at 90 days.³² However, our 90-day mortality rate was lower than the 20% in another African study.¹³ This stresses the need for better outcome reporting and implementation of measures to both predict and improve outcomes.

One such prediction tool, the Aziz nomogram, showed promise in our population, with an AUC of 0.749 (p = 0.021). Our study population had a sensitivity of 75.0% and a specificity of 75.3% to predict 90-day mortality, using 111 points on the nomogram as an optimal cutoff, as calculated from the ROC curve. The AUC obtained in our population is similar to those obtained in Aziz's original creation of the nomogram (AUC = 0.788) and a subsequent validation study in Japan (AUC = 0.79).^{19,33}

The other nomogram tested in our study (the POSPOM nomogram) did not perform well, with a non-significant prediction ability (AUC = 0.635, p = 0.209), contrasting with the AUC of 0.78 obtained in a German validation study.²² The difference in predictive ability between the nomograms might be because the POSPOM nomogram does not differentiate between different stages of bladder cancer or the number of cystectomies done per year at a hospital, both of which are included in the Aziz nomogram.

Our study is the first African study to report the uptake and rate of complete response (pT0) to neoadjuvant chemotherapy. All patients were assessed for chemotherapy eligibility, and 38.20% received neoadjuvant chemotherapy, with 41.18% having a complete response and no tumour seen at the final histopathological examination. This aligns with the results of large series neoadjuvant chemotherapy for bladder cancer and denotes an excellent long-term cancer-free survival for patients.³⁴

Our population was younger than reported in most series, with a mean age of 58.93 years being 11 years younger than reported by Osawa et al.³³ in the Japanese validation of the Aziz nomogram. The main risk factor for bladder cancer in our study was smoking, with an 82% smoking prevalence comparable to the 78.81% reported by Zapała et al.⁶

Our series differs from most African series regarding our cohort's paucity of bilharzia exposure. Bilharzia is not endemic to the Western Cape province, which explains why only 4.8% of our patients had previous bilharzia infections. This is reflected in the pathological profile in our series, with only 10.1% SCCs, in contrast to African countries with high schistosomiasis prevalence. In Zambia and Tanzania, SCCs predominate, with 71% and 72% prevalence, respectively.^{2.3}

Our study is also the first African study to report the incidence of variant urothelial histopathological patterns. We found that 12.6% of our cases had variant urothelial patterns, the most common being UC with squamous differentiation (7.9% of total cases). Our centre does not have a formal uropathologist, and it has been shown that many variant patterns go undiagnosed without a dedicated uropathologist. One study showed that the incidence of variant histological patterns increased from 16% to 31% when a dedicated uropathologist examined specimens.³⁵

Surrogate markers of adequate oncological surgery, such as the number of lymph nodes removed and negative surgical margins, are important to audit surgical techniques and decision-making. Removing at least ten lymph nodes during lymph node dissection is generally recommended. Moreover, the mean number in our series was 12.5, with nine as the median number and a range of 0–48 nodes removed. One way to obtain more consistency with the number of nodes removed is to send each nodal packet as a separate pathological specimen.⁶ Negative surgical margins are used as a surrogate for complete removal of the primary tumour and were achieved in 87.5% of cases in a large multicentre study of high-volume institutions.⁶ We achieved a similar and acceptable negative surgical margin rate of 86.52%.

RCs are one of the most invasive and morbid procedures in urology, and our length of stay of ten days (median) and 14.21 days (mean) support this. When counselling patients, it is more appropriate to quote the median value, as this more accurately reflects the "average" length of stay they might expect. However, the mean would be more appropriate for healthcare funding, as there will be a cost to every day in the hospital. Our patients had a 28.09% risk for ileus, with 19.77% requiring total parenteral nutrition. This supports the need for programmes to improve earlier recovery and implement measures leading to shorter hospital stays and fewer bowel-related complications.

There are a limited number of strategies for improvement in patient outcomes in RCs. One strategy might be better patient selection using predictive nomograms. Another strategy to improve postoperative morbidity and earlier recovery is implementing a formal enhanced recovery after surgery (ERAS) programme, such as the ERAS® Interactive Audit System (EIAS) or the ERAS® Implementation Programme (EIP).^{36,37}

Our study had certain limitations, including its retrospective nature, which might have resulted in minor complications being overlooked. However, it is doubtful that any major complications would have been overlooked during data collection. Our study was not adequately powered to enable formal nomogram validation. Furthermore, our study was done at a single centre, and our results might differ from those of the wider South African and African contexts.

Conclusion

The 90-day complication and mortality rate for patients undergoing RCs at a South African referral centre is slightly higher compared to large series in high-income countries. The Aziz nomogram shows promise as a tool to help select patients as good surgical candidates, but it will require further study and validation. Our patients responded well to neoadjuvant chemotherapy, which should be offered to all eligible patients. Negative surgical margins point to an adequate surgical technique. The number of lymph nodes removed varied widely and might result from surgical and pathological factors. The prevalence of variant histological patterns of UC is likely to be underestimated, underlining the need for dedicated uropathological services.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

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References

- gco.iarc.fr [Internet]. Data visualization tools for exploring the global cancer burden in 2022. Lyon: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today. Accessed 23 March 2022.
- Bowa K, Mulele C, Kachimba J, et al. A review of bladder cancer in sub-Saharan Africa: a different disease, with a distinct presentation, assessment, and treatment. Ann Afr Med. 2018;17(3):90-105. https://doi.org/10.4103/aam. aam_48_17.
- Heyns CF, van der Merwe A. Bladder cancer in Africa. Can J Urol. 2008;15(1):3899-908.
- Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-75. https://doi.org/10.1200/JCO.2001.19.3.666.

- Nuhn P, May M, Sun M, et al. External validation of postoperative nomograms for prediction of all-cause mortality, cancer-specific mortality, and recurrence in patients with urothelial carcinoma of the bladder. Eur Urol. 2012;61(1):58-64. https://doi.org/10.1016/j.eururo.2011.07.066.
- Zapała Ł, Ślusarczyk A, Korczak B, et al. The view outside of the box: reporting outcomes following radical cystectomy using pentafecta from a multicenter retrospective analysis. Front Oncol. 2022;1:1-10. https://doi.org/10.3389/ fonc.2022.841852.
- Zehnder P, Moltzahn F, Mitra AP, et al. Radical cystectomy with super-extended lymphadenectomy: impact of separate vs en bloc lymph node submission on analysis and outcomes. BJU Int. 2016;117(2):253-9. https://doi.org/10.1111/ bju.12956.
- Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol. 2010;184(3):990-4. https://doi. org/10.1016/j.juro.2010.05.037.
- Patidar N, Yadav P, Sureka SK, et al. An audit of early complications of radical cystectomy using Clavien-Dindo classification. Indian J Urol. 2016;32(4):282-7. https://doi.org/10.4103/0970-1591.191244.
- Hautmann RE, de Petriconi RC, Pfeiffer C, Volkmer BG. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47. https://doi. org/10.1016/j.eururo.2012.02.028.
- Nielsen ME, Mallin K, Weaver MA, et al. Association of hospital volume with conditional 90-day mortality after cystectomy: an analysis of the National Cancer Data Base. BJU Int. 2014;114(1):46-55. https://doi.org/10.1111/bju.12566.
- Porter MP, Gore JL, Wright JL. Hospital volume and 90-day mortality risk after radical cystectomy: a population-based cohort study. World J Urol. 2011;29(1):73-7. https://doi.org/10.1007/s00345-010-0626-3.
- Cassim F, Sinha S, Jaumdally S, Lazarus J. The first series of laparoscopic radical cystectomies done in South Africa. S Afr J Surg [Internet]. 2018;56(4):44-9. https://doi.org/10.17159/2078-5151/2018/v56n4a2669.
- Catto JWF, Khetrapal P, Ricciardi F, et al. Effect of robot-assisted radical cystectomy with intracorporeal urinary diversion vs open radical cystectomy on 90-day morbidity and mortality among patients with bladder cancer: a randomized clinical trial. JAMA. 2022;327(21):2092-103. https://doi.org/10.1001/ jama.2022.7393.
- Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018;391(10139):2525-36. https://doi.org/10.1016/S0140-6736(18)30996-6.
- Sathianathen NJ, Kalapara A, Frydenberg M, et al. Robotic assisted radical cystectomy vs open radical cystectomy: systematic review and meta-analysis. J Urol. 2019;201(4):715-20. https://doi.org/10.1016/j.juro.2018.10.006.
- Mastroianni R, Ferriero M, Tuderti G, et al. Open radical cystectomy versus robot-assisted radical cystectomy with intracorporeal urinary diversion: early outcomes of a single-center randomized controlled trial. J Urol. 2022;207(5):982-92. https://doi.org/10.1097/JU.00000000002422.
- Isbarn H, Jeldres C, Zini L, et al. A population based assessment of perioperative mortality after cystectomy for bladder cancer. J Urol. 2009;182(1):70-7. https:// doi.org/10.1016/j.juro.2009.02.120.
- Aziz A, May M, Burger M, et al. Prediction of 90-day mortality after radical cystectomy for bladder cancer in a prospective European multicenter cohort. Eur Urol. 2014;66(1):156-63. https://doi.org/10.1016/j.eururo.2013.12.018.
- Morgan TM, Keegan KA, Barocas DA, et al. Predicting the probability of 90-day survival of elderly patients with bladder cancer treated with radical cystectomy. J Urol. 2011;186(3):829-34. https://doi.org/10.1016/j.juro.2011.04.089.
- Le Manach Y, Collins G, Rodseth R, et al. Preoperative Score to Predict Postoperative Mortality (POSPOM): derivation and validation. Anesthesiology. 2016;124(3):570-9. https://doi.org/10.1097/ALN.00000000000972.
- Froehner M, Koch R, Hübler M, et al. Validation of the Preoperative Score to Predict Postoperative Mortality in patients undergoing radical cystectomy. Eur Urol Focus. 2019;5(2):197-200. https://doi.org/10.1016/j.euf.2017.05.003.
- Taylor JM, Feifer A, Savage CJ, et al. Evaluating the utility of a preoperative nomogram for predicting 90-day mortality following radical cystectomy for bladder cancer. BJU Int. 2012;109(6):855-9. https://doi. org/10.1111/j.1464-410X.2011.10391.x.
- Mayr R, May M, Martini T, et al. Comorbidity and performance indices as predictors of cancer-independent mortality but not of cancer-specific mortality after radical cystectomy for urothelial carcinoma of the bladder. Eur Urol. 2012;62(4):662-70. https://doi.org/10.1016/j.eururo.2012.03.057.
- Witjes JA, Bruins HM, Carrión A, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer [Internet]. Arnhem: European Association of Urology;
 2022. Available from: https://d56bochluxqnz.cloudfront.net/documents/ full-guideline/EAU-Guidelines-on-Muscle-Invasive-And-Metastatic-Bladder-Cancer-2022.pdf. Accessed 23 March 2022.
- Kochergin M, Fahmy O, Esken L, et al. Systematic review and meta-analysis on the role of perioperative blood transfusion in patients undergoing radical cystectomy for urothelial carcinoma. Bladder Cancer. 2022;8(3):315-27. https:// doi.org/10.3233/BLC-201534.

- Zhu Z, Zhao J, Li Y, et al. Prognostic value of preoperative hydronephrosis in patients with bladder cancer undergoing radical cystectomy: a meta-analysis. PLoS One. 2019;14(9):e0222223. https://doi.org/10.1371/journal.pone.0222223.
- Oh JJ, Byun S-S, Jeong CW, et al. Association between preoperative hydronephrosis and prognosis after radical cystectomy among patients with bladder cancer: a systemic review and meta-analysis. Front Oncol. 2019;9:158. https://doi.org/10.3389/fonc.2019.00158.
- 29. Bruins HM, Veskimäe E, Hernández V, et al. The importance of hospital and surgeon volume as major determinants of morbidity and mortality after radical cystectomy for bladder cancer: a systematic review and recommendations by the European Association of Urology Muscle-invasive and Metastatic Bladder Cancer Guideline Panel. Eur Urol Oncol. 2020;3(2):131-44. https://doi. org/10.1016/j.euo.2019.11.005.
- 30. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13. https://doi.org/10.1097/01. sla.0000133083.54934.ae.
- Davis NF, Burke JP, McDermott T, et al. Bricker versus Wallace anastomosis: a meta-analysis of ureteroenteric stricture rates after ileal conduit urinary diversion. Can Urol Assoc J. 2015;9(5-6):E284-90. https://doi.org/10.5489/ cuaj.2692.

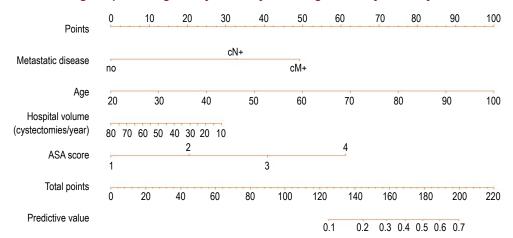
- Maibom SL, Joensen UN, Poulsen AM, et al. Short-term morbidity and mortality following radical cystectomy: a systematic review. BMJ Open. 2021;11(4):e043266. https://doi.org/10.1136/bmjopen-2020-043266.
- Osawa T, Abe T, Takada N, et al. Validation of the nomogram for predicting 90-day mortality after radical cystectomy in a Japanese cohort. Int J Urol. 2018;25(7):699-700. https://doi.org/10.1111/iju.13584.
- Lee HW, Kwon W-A, Nguyen LNT, Phan DTT, Seo HK. Approaches to clinical complete response after neoadjuvant chemotherapy in muscle-invasive bladder cancer: possibilities and limitations. Cancers (Basel). 2023;15(4):1323. https://doi. org/10.3390/cancers15041323.
- Mantica G, Simonato A, Du Plessis DE, et al. The pathologist's role in the detection of rare variants of bladder cancer and analysis of the impact on incidence and type detection. Minerva Urol Nefrol. 2018;70(6):594-7. https://doi. org/10.23736/S0393-2249.18.03175-2.
- Karl A, Buchner A, Becker A, et al. A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: results of a prospective randomized study. J Urol. 2014;191(2):335-40. https://doi. org/10.1016/j.juro.2013.08.019.
- 37. encare.net [Internet]. ERAS® Interactive Audit System (EIAS) or the ERAS® Implementation Program (EIP). Available from: https://encare.net/protocols/?_ gl=1*1eowred*_up*MQ..*_ga*ODA1ODk1NDg5LjE3MjczMzM0ODQ.*_ga_ PGCW0966YT*MTcyNzMzMzQ4NC4xLjAuMTcyNzMzMzQ4NC4wLjAuMA. Accessed 15 August 2024.

Supplementary material

| Appendix 1: | Clavien-Din | do classificat | tion system |
|-------------|-------------|----------------|-------------|
|-------------|-------------|----------------|-------------|

| Grade | Definition |
|-------|---|
| 1 | Any deviations from the standard postoperative course of treatment with only pharmacotherapy with antiemetics, analgesics, diuretics and electrolytes, and physiotherapy being acceptable. Infection of the postoperative wound does not require surgical care. |
| II | Complications require pharmacotherapy with medications other than those listed for grade I complications. Necessary transfusion of red blood cell concentrates or parenteral nutrition. |
| III | Complications requiring surgical, endoscopic, or radiological intervention. |
| Illa | Complications requiring surgical, endoscopic, or radiological intervention without general anaesthesia. |
| IIIb | Complications requiring surgical, endoscopic, or radiological intervention with general anaesthesia. |
| IV | Directly life-threatening complications, including complications associated with the central nervous system, requiring treatment in the intensive care unit. |
| IVa | Single organ failure, including renal failure with the need for haemodialysis. |
| IVb | Multiple organ failure. |
| V | Death of the patient. |

Appendix 2: The Aziz nomogram predicting 90-day mortality following radical cystectomy



Appendix 3: The POSOM nomogram variables with the associated points allocated

The nomogram was accessed online (http://perioperativerisk.com/mortality/) to give the exact predicted postoperative mortality rate.

138