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ORIGINAL RESEARCH

Describing postoperative complications and the perioperative associations of curative surgery for renal cell carcinoma at a South African centre

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Background: Adverse events after renal oncological surgery have a marked impact on the postoperative course with many identifiable determinants. However, data are mainly from American and European centres, and it is uncertain whether the same risk factors for adverse events apply in the South African or wider African context. We provide an accurate description of postoperative complications and assess the potential perioperative associations.

Methods: A retrospective cohort study was done by reviewing records of patient who received curative surgery for either confirmed or suspected renal cell carcinoma (RCC). The primary outcome was to assess the complication rate during the first year after surgery and describe postoperative complications according to the Clavien–Dindo (CD) classification system. Patient demographics, comorbidity and operative data were considered to have a potential association with complications. A multivariable logistic regression analysis assessed variables with statistically significant associations.

Results: We collected data from 107 patients. The complication rate was 29%, with most complications (83.9%) being of low grade. The remainder (16.1%) experienced high-grade complications and no mortalities were noted. Surgical approach (favouring laparoscopy) (p = 0.025), presence of perioperative transfusions (25.2%; p < 0.001) and perioperative blood loss (50–500; > 1 000 ml; p < 0.001) all showed a significant association with postoperative complications. Following the multivariable logistic regression, only blood loss > 1 000 ml maintained significance.

Conclusion: Overall, complication rates and severity were low. However, there is room for improvement in increasing the amount of minimally invasive procedures, and implementing a formal postoperative recovery plan such as the enhanced recovery after surgery (ERAS) programme.

Keywords: renal cell carcinoma, South Africa, Clavien–Dindo classification, radical nephrectomy, partial nephrectomy

Introduction

Renal cell carcinoma (RCC) has an insidious onset and wide variations in pathology, clinical course and response to treatment.[1] Globally, RCC constitutes 2.2% of all cancers and is shown to be the seventh most common malignancy in the developed world.[2,3] It is the third most common urological malignancy with the majority of RCC worldwide and in South Africa being diagnosed incidentally.[4,5]

Surgical resection in the form of either radical or partial nephrectomy remains the gold standard in curative treatment.[6,7] The RENAL nephrometry score is used to assess the suitability of performing partial nephrectomy. But more importantly, it is used as a means of standardising tumour complexity, with the goal of comparing outcomes.[8] Curative surgery for RCC is regarded as major surgery, where monitoring and reporting of complications and outcomes are paramount to improve treatment safety and efficacy.[6,9] Current surgical approaches include open as well as pure- and robotic-assisted laparoscopic radical and partial nephrectomy. The surgical management approach is determined by taking patient, surgeon and tumour factors into consideration.[10] Open nephrectomy is still the standard of care at regional level in South Africa. This is despite the proven benefits of laparoscopic surgery, such as lower estimated blood loss and postoperative pain and shorter hospital stay.[11,12] Robotic-assisted partial nephrectomy has only become available in the public health sector in South Africa in May 2022. Postoperative complications have been reported in only two studies from Africa, and no study has been published with complications as the main focus.[11,13]

When considering the demography of patients with RCC in South Africa as reported to the National Cancer Registry (NCR), there is a predominance of white patients (50%), followed by black (28%), coloured (14%) and Asian/Indian (6%).[14] This might not reflect the true epidemiology for RCC, due to the differences in reporting of cases to the NCR by private and public laboratories.[14] A previous study from our institution showed a predominance of patients of mixed ancestry, which reflects the demography of the local referral population.[5] There is, however, consensus regarding the histopathological profile, with clear cell RCC being the most prevalent by far.[5,14] In addition, while the South African epidemiology of RCC has been well documented, primary data describing postoperative complications and potential determinants thereof, are still lacking.[5] Potential associations with postoperative complications in curative treatment for RCC are multiple, including tumour characteristics, laterality of tumour, age, gender, comorbidity index and surgical approach (Table I).[12,15]

Postoperative complications following surgical procedures is an important measure of outcomes and have shown to bear a

Table I: Tumour pathology

Histological subtypes	Frequency (%) *n* = 92
Clear cell	62 (57.9)
Papillary type	18 (19.6)
Mixed type 1 and 2	1 (0.9)
Chromophobe	11 (10.3)

significant risk for mortality.[6] The Clavien–Dindo (CD) classification system is the most widely used model, devised to report adverse postoperative events and defines any deviation from the expected postoperative course as a complication (Table II).[16] Reported complication rates following partial nephrectomy are 27–36%, while following radical nephrectomies, these are 10–30%.[7,12,17] Locally-reported complication rates are higher (80%); however, the majority (90.2%) were low grade.[11]

This study was done to shed light on the operative outcomes of more than 100 nephrectomies conducted in a tertiary institution in South Africa, to accurately describe complications according to the CD classification system and to identify potential perioperative associations of these complications.

Materials and methods

Setting and study design

A retrospective review of adult patients who received curative surgery for RCC between August 2016 and July 2021 at Tygerberg Hospital, Cape Town, South Africa, was conducted. Data were collected by accessing individual electronic medical records. The Western Cape database for medical records, the Enterprise Content Management (ECM), National Health and Laboratory Services (NHLS) system and the Picture Archiving and Communication System (PACS) were used. The retrospective data were supplemented by telephonic interviews of patients to complete data sets.

Study population and management principles

All patients older than 18 years with confirmed or suspected RCC who underwent partial or radical nephrectomy between August 2016 and July 2021, at the specified institution, were deemed eligible for inclusion. We did not exclude patients with eventual benign histology which included patients with suspected pathology on imaging and patients with histologically confirmed disease. Management steps of patients with suspected RCC, taken at the institution include doing cross-sectional imaging (CT or MRI) for staging. Preoperative biopsies are not routinely done. In non-metastatic and oligometastatic (< 3 metastases) disease, curative surgery will be offered. In patients with T4 disease (other than due to adrenal invasion) or widespread metastases, no nephrectomy will be done unless symptoms necessitate it; however, N-status is not an exclusion. No immune checkpoint inhibitors or tyrosine kinase inhibitors (TKIs) are available at this stage. Operative approaches in line with the standard of care in the state sector nationally, included open and laparoscopic surgery.

The management of these patients involves a multidisciplinary process which is individualised according to the imaging evidence and histological profile of disease. The decision of partial nephrectomy instead of radical nephrectomy was at the discretion of the attending surgeon. Surgical entry was also surgeon dependent. Open and laparoscopic surgical approaches included flank, subcostal, chevron incision, and both retro- and transperitoneal. All partial nephrectomies were done via extraperitoneal flank approach.

Outcome and data collection

We collected data on the presence or absence of any complications arising during the first year after surgery, classified according to the CD classification system. Other data collected included demographic factors such as age and gender, Charlson Comorbidity Index (CCI), body mass index (BMI), smoking status, presence of diabetes mellitus (DM), as well as preoperative haemoglobin levels and renal function. Data on surgical approach, type of procedure and transfusion rates, as well as tumour factors such as RENAL nephrometry score and tumour pathology, were also collected. The data were accessed via ECM, specifically departmental in-patient notes, anaesthetic notes and surgical notes. To identify potential complications, postoperative surgical follow-up notes were perused and supplemented by telephonic interviews where patients were lost to follow-up.

Table II: Clavien–Dindo classification system

Grade	Frequency (%)	Description
I	15 (48.4)	Conditions including any deviation from expected postoperative course. The treatment required to fall in this grade classification is limited to basic pharmacotherapy such as analgesia, anti-emetics and electrolytes. This also include postoperative wound infections not requiring surgical intervention.
II	11 (35.5)	Complications requiring pharmacotherapy with medications other than those listed for grade I complications. The need for transfusion of red blood cell concentrate or parenteral nutrition.
III		Complications which require radiological, endoscopic or surgical intervention.
IIIa	1 (3.2)	The description for grade III without the need for general anaesthesia.
IIIb	4 (12.9)	The description for grade III with the need for general anaesthesia.
IV	-	Life-threatening complications necessitating intensive care.
IVa	-	Single organ failure, which includes renal failure with a need for dialysis.
IVb	-	Multiple organ failure.
V	-	Patient demise.

Statistical analysis

All categorical variables are presented as frequencies and percentages, while continuous variables are represented by mean, interquartile range (IQR) and standard deviation (SD). Where appropriate, binary transformation of categorical variables were performed to assess significance of association with postoperative complications. Microsoft Excel was used to describe and summarise the data.

Significance testing for associations between postoperative outcomes and patient, tumour and operative variables, was performed. We used contingency tables, the Pearson Chi^2 and Fisher's exact tests where the data was converted to binary representation. For continuous variables, paired (two-tailed) t-tests were done using STATA™ (version 12) and *p*-values of < 0.05 were deemed significant. We incorporated those variables with statistically significant associations in a multivariate logistic regression analysis.

Results

Patient profile and operative details

In total, 107 patients had received curative therapy for RCC at Tygerberg Hospital between August 2016 and July 2021. Of these, 51% (55) were men. The mean age at surgery was 57.7 years (SD = 12.15). Of the surgeries performed during this time, 81.3% (87) were radical nephrectomies with the remaining 18.7% (20) being partial nephrectomies. None of the patients had more than one surgery. The open surgical approach was used in 90% (96) of the cases, while 10% (11) used the laparoscopic approach. The complication rate for open surgery was 32.3% (31); however, no postoperative complications were noted with the laparoscopic approach ($p < 0.001$). Intraoperative blood loss ranged from 50–2 000 ml (median = 300 ml).

The majority of patients (68.2%) were classified as American Society of Anesthesiologists (ASA) class II, while the least common classification was ASA class III (26.17%). This relatively low prevalence of comorbidities is also reflected in the CCI (mean = 4.16; SD = 1.85). There was a predominance (69%) of overweight patients (BMI > 25 kg/m^2; mean = 29.59; SD = 7.55) and while the minority of patients were non-diabetic (24.5%), 60% of the cohort were smokers. Overall, 79.4% (85) of patients had normal renal function (eGFR > 60 ml/min/1.73 m^2) and the presence of anaemia was 17.8% (19) and 20.6% (22) for males and females, respectively. In terms of clinical tumour staging, T1 was the most prevalent at 45.7% (49). The second most prevalent, representing equal percentages of the cohort, were stages T2 and T3 (22.4%).

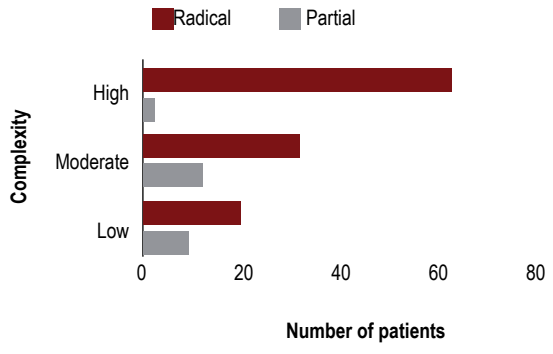

Figure 1: RENAL nephrometry scores for radical and partial nephrectomy

Considering that 14% (15) of the surgeries were carried out on benign conditions, the most frequent tumour pathology was clear cell subtype (57.9%; 62). Previously classified as type 1 and 2, the papillary subtype was found in 19.6% of the cohort (Table I).[18] While most of the surgeries in this study were radical nephrectomies (81.3%; 87), close to 20% of the surgeries were conducted as partial nephrectomies which are often guided by the RENAL nephrometry score. The RENAL nephrometry scores portrayed in Figure 1 are classified into low, moderate and high complexity surgeries. The number of specific procedures conducted in relation to the RENAL nephrometry score depict the expected reluctance to conduct partial nephrectomies on tumours of high complexity. The average length of follow-up was 11.3 months. Patient demographic, tumour and operative data are summarised in Table III.

Complications

The overall complication rate was 29%, while 71% of patients reportedly did not experience any complications. Table II shows the classification of the complications according to the CD classification system. Most complications (83.9%; 26) were low grade (grade I–II) and did not necessitate surgical intervention. Only five patients experienced high-grade complications (IIIa – 3.2%; IIIb – 12.9%) which required surgical, endoscopic or radiological treatment under general anaesthesia. No CD grade IV complications were reported, and no mortalities (grade V) were noted. The most common complications observed included postoperative pain (32.3%), wound or systemic infection (19.35%) and abdominal hernia (16.1%). Other complications included postoperative lymphocoele (6.4%) and constipation (6.4%). Only three patients experienced intraoperative complications which were managed at the time of the primary surgery.

Associations with postoperative complications

We observed statistically significant associations (according to parametric measurements) between the postoperative complication rate and several variables. This included length of hospital stay ($p = 0.0086$), surgical approach ($p = 0.025$), the need for perioperative transfusions (25.2%; $p < 0.001$), and perioperative blood loss > 1 000 ml ($p < 0.001$). The operative approach was a significant factor in predicting postoperative complications, with less complications associated with laparoscopic surgery. Poor preoperative renal function (GFR =< 60 ml/min/1.73 m^2; $p = 0.056$) and the laterality of surgery ($p = 0.172$) showed a trend toward an association with the presence of postoperative complications. Statistical assessment of patient variables (Table III) which were not associated with postoperative complications include age, gender and other comorbid factors such as BMI, CCI and ASA. Specific risk factors such as DM and smoking were not significantly associated with postoperative complications. The multivariate regression analysis showed sustained significance of intraoperative blood loss of > 1 000 ml after the covariates of perioperative transfusion

and operative approach were controlled for (p = 0.002) (Figure 2). However, the significance of transfusion and laparoscopic vs open approach was lost after controlling for blood loss. This, however, does not negate the benefit seen in the laparoscopic approach, but rather stresses the importance of preventing intraoperative haemorrhage.

Table III: Association of demographic and descriptive characteristic with complication rate (n = 107)

Variable	Mean	Median	SD	*p*-value
Age	57.7	58	12.15	0.3284
CCI	4.16	4	1.83	0.5882
BMI	29.59	28	7.55	0.7537
Length of stay	5.16	4	5.13	0.0086
Variable		**Total (%)**		***p*-values**
ASA				0.312
I		5 (4.7)		
II		73 (68.2)		
III		28 (26.2)		
IV		1 (0.9)		
Diabetes		26 (24.5)		0.220
Smoking		65 (60.7)		0.424
Kidney affected				0.172
Right		49 (45.8)		
Left		58 (54.2)		
Surgical approach				0.025
Laparoscopic		11 (10.3)		
Open		96 (89.7)		
Perioperative transfusion		27 (25.2)		< 0.001
Renal function				0.056
Poor		22 (20.6)		
Normal		85 (79.4)		
Anaemia				
Male		19 (17.8)		0.895
Female		22 (20.6)		0.746
Type of operation				0.911
Total		87 (81.3)		
Partial		20 (18.7)		
Clinical stage				0.958
1		49 (45.8)		
2		24 (22.4)		
3		24 (22.4)		
4		2 (1.9)		
Benign		5 (4.7)		
Blood loss (ml)				
1 500 >/> 1 000		(4.6)		< 0.001
2 000 >/> 1 500		(4.6)		0.024

SD – standard deviation, CCI – comorbidity index, BMI – body mass index, ASA – American Society of Anesthesiologists

Discussion

The description of postoperative complications of curative surgery for RCC is limited in the South African context. With respect to specific complications, our data set aimed not to address qualitative descriptions of postoperative complications, but rather the level of invasiveness needed to treat the complication according to the CD classification system.[16] This method of reporting is currently endorsed by the European Association of Urology (EAU). Importantly, only complications deemed to be a direct consequence of surgery were included. The potential role of intraoperative complications and timeline-specific complications are not considered in this system and have recently been identified as a limitation of the CD classification system by the EAU.[19]

We noted higher rates of low-grade (grade I and II) complications and observed that overall complication rates were lower in our cohort compared to other South African studies.[11] However, this is also seen in comparison to studies done in developed countries, and while our rates of complications are increased in comparison to another African study, our sample size was twice as large. Salako et al.[13] noted a 19% prevalence of complications in a Nigerian study comprising 51 patients. South African literature reports a 75% complication rate in 196 patients, with 59.7% being low grade (grade I and II).[20] Another South African study[11] reported that mild complications according to the CD classification system were predominant, where 90.2% constituted low-grade complications, but with a total of six fatalities reported. Our prevalence of complications were slightly lower than described in an American study where there was a 37% complication rate.[6]

Our results support the significantly improved postoperative outcomes of laparoscopic surgery compared to open surgery.[10] Furthermore, our lack of complications in laparoscopic procedures bears significance in light of recent literature, where complications of laparoscopic surgery was found to be 22.3% in a Polish study comprising 112 patients.[10] A decrease in rate and severity of postoperative complications was shown with laparoscopic surgery in a comparative study done by Xu et al.[17] The apparent lack of complications observed at our institution may be due to the small sample size of 11 patients receiving laparoscopic surgery. However, other reasons include surgeon experience, drawn from our laparoscopic living kidney donor programme, improved intraoperative vision, the benefit of the pneumoperitoneum and less tissue trauma.[17] Our study results mimic the aforementioned South African studies where laparoscopic surgery has shown to have a significant impact on improving postoperative care.[20]

We also assessed whether the variables in our review were associated significantly with the presence or absence of

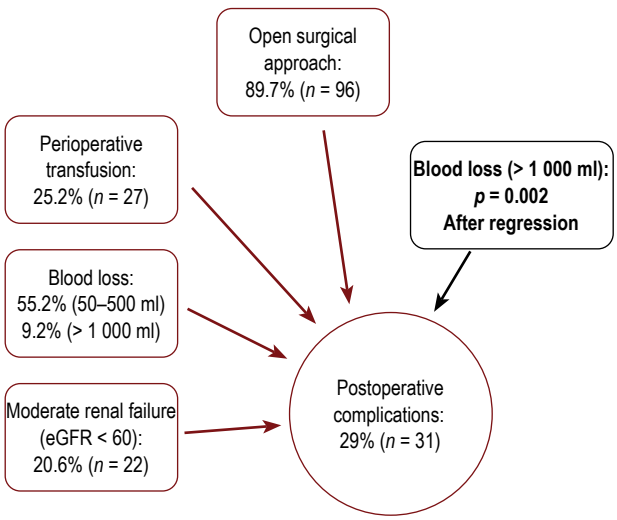

Figure 2: Factors significantly associated with postoperative complications prior to, and after regression

postoperative complications. Renal compromise (moderate: eGFR < 60) prior to surgery did not show significant association with complication rates (p = 0.056). This may be influenced by the small sample size and confounding factors such as intraoperative fluid shifts, blood loss and anaesthetic agents.[21] Our data show that all patients with poor kidney function who experienced complications underwent open surgery. However, even with the overall benefits held by laparoscopic surgery, the literature highlights risks to the kidney involved with abdominal insufflation causing a reduction in renal perfusion. Therefore, preoperative renal function may still prove clinically significant.[21] There is an increased risk of prolonged hospital stay in patients experiencing postoperative complications.[22] This is to be expected and is a likely explanation for the statistical significance found in our data. Patients experiencing postoperative complications while still an in-patient will usually result in a longer stay.

Intraoperative blood loss (> 1 000 ml) and perioperative transfusion were each independently associated with complication rates. In our study, 40.7% (11) of those 27 patients receiving transfusions experienced complications. While significance of transfusion was lost in the regression analysis, the risks of blood transfusions have been well established and should still be considered. These include systemic infection, immune modulation and systemic inflammatory response syndrome (SIRS).[23] In an American study assessing the effects of anaemia, blood loss and transfusion, there was still an independent significance of transfusion in postoperative mortality shown after adjusting multiple variables in a regression analysis.[24] This association is dose dependant and it has been found that patients with the least risk of operative morbidity are at higher risk of postoperative complications were they to be transfused.[23]

Our multivariate logistic regression analysis also confirmed the significance of blood loss in our study. This is likely linked to perioperative transfusion and it is thought that a larger sample size would have increased the accuracy of assessing these variables. This sentiment is highlighted in the aforementioned South African study where there was a significant association between intraoperative blood loss (50–2 000 ml) and transfusion (p < 0.001).[11] However, the significance of this on postoperative complications was not assessed. The previously cited American study also found a significant association (p < 0.001) between perioperative bleeding and long-term mortality after regression analyses.

It is postulated that right-sided nephrectomies, with the difficulty of a short renal vein on the right, might be associated with more complications as opposed to left-sided surgeries. However, in our study left-sided nephrectomies had a higher complication rate, with a trend towards statistical significance (p = 0.172). In donor nephrectomies, the left-sided kidney is usually preferred, as the right renal vein is shorter than the left, which results in a more difficult venous anastomosis.[25] In radical nephrectomies, the left-sided renal vein has two more branches, compared to the right, and the colon needs to be more extensively mobilised, which might be reasons for more complications. Our study was underpowered for this specific outcome and it would be worthwhile studying in larger cohorts.

While laparoscopic surgery has steeper learning curves, our study shows a significant improvement in perioperative outcome compared to open surgery.[12] Other minimally invasive approaches, such as robotic-assisted laparoscopy have the potential to further decrease complication rates should these be implemented in the South African public healthcare setting. Robotic technology has shown improved outcomes in overall complication rates and warm ischaemic time in partial nephrectomy.[26]

There is no formal enhanced recovery after surgery (ERAS) programme at the study institution, although many of the ERAS components are followed to varying degrees. It is postulated that full implementation of the programme might further decrease postoperative complications, as a systematic review concerning its implementation in the urology setting indicated that success in the programme is related to adherence to the ERAS components.[27]

Study limitations

Our study was limited by the retrospective nature of data collection which inherently limits the variables considered in the study to those documented historically. This method is also subject to confounding variables and there may be other factors involved with postoperative complications that were not measured. The sample was also collected from one institution which may have limited the size and the generalisability of the results. The complications were reported according to the CD classification system and, therefore, is inherently subject to limitations of not reporting intraoperative complications and looking at complications at various time periods.[19]

Conclusion

We demonstrated that the most common postoperative complications seen in patients receiving partial or radical nephrectomy are low grade (CD grade I and II), with no life-threatening complications and no fatalities reported in our series. Our observations of significant perioperative variables associated with postoperative complications show that intraoperative blood loss, perioperative transfusion and surgical approach bear significance in predicting postoperative complications. However, after multivariate regression analysis, only blood loss maintained significance, while recognising the effect of laparoscopy on minimising blood loss. These findings shed light on the effectiveness of tertiary care within a South African context and where optimisation is necessary. We suggest that the combination of optimising patient variables prospectively, expanding access to minimally-invasive surgery and effective postoperative care planning will decrease the prevalence of postoperative complications.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval and consent to participate

While the retrospective nature of this study constitutes minimal risk research, ethical approval from the Health Ethics Research Committee (HREC) of Stellenbosch University (Ref U21/08/135) was obtained. Informed consent was wavered by the Health Ethics Research Committee (HREC) of Stellenbosch University. This comes in light of the practical difficulty presented by obtaining individual informed consent from over 100 patients. Furthermore, due to the malignant nature of the disease and data being collected over a span of 8 years, patients may have demised subsequent to the operation and can therefore not consent to the retrieval of information. However, where telephonic interviews were necessary for supplementing data, verbal informed consent was obtained. This study was conducted in accordance with the Ethical and Good Clinical Practice guidelines of the World Medical Association Declaration of Helsinki (2013), as well as the National Health Act, 2003 (Act No 61 of 2003).

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