Retrospective Review of Open versus Laparoscopic Radical Cystectomy for the Treatment of Bladder Cancer: Complications and Oncological Outcome

A MINI DISSERTATION SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

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DECLARATION

I, **Farzana Cassim**, declare that this research report is based on independent work performed by me and neither the whole work nor any part of it has been submitted for another degree to any other university. This work has been presented in part at the proceedings of the biennial conference of the South African Urological Association held in Cape Town in 2014.

Signed:……F. Cassim……

Date: 26 June 2015

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Zubeida, Gasant and the team at Medical Records for assisting me in obtaining as many folders as possible – their help has been invaluable.

And last, but most certainly not least, my wonderful husband, whose love and support has been unbelievable and unwavering.

List of Abbreviations

AUA - American Urology Association

ASA - American Society of Anesthesiologists

BC – Bladder cancer

BCG - Bacillus Calmette Geurin

CIS - Carcinoma in-situ

CSS – Cancer specific survival

CT - Computed tomography (scan)

EAU - European Association of Urology

EUA – Examination under anaesthesia

FACT-G - Functional Assessment of Cancer Therapy - General

IL – Interleukin

LRC - Laparoscopic radical cystectomy

MRC - Medical Research Council

MRI - Magnetic Resonance Imaging

NGT - Nasogastric tube

ORC - Open radical cystectomy

OS – Overall survival

PFS - Progression-free survival

QOL - Quality of life

RC - Radical cystectomy

SIRS - Systemic Inflammatory Response Syndrome

TCC – Transitional cell carcinoma

UC - Urothelial carcinoma

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Part A: PROTOCOL

Title:

Retrospective Review of Open versus Laparoscopic Radical Cystectomy for the Treatment of Bladder Cancer: Complications and Oncological Outcome

A1. Purpose of Study

Radical cystectomy (RC) with extended lymphadenectomy and urinary diversion remains the standard of care for muscle invasive urothelial carcinoma (UC) (2).

Radical cystectomy with ileal conduit or neobladder is currently also accepted as the treatment of choice in the following patients (2):

- Curative or palliative treatment of carcinoma of the bladder
- Muscle-invasive transitional cell carcinoma (TCC)
- High-grade TCC or carcinoma in-situ not responding to intravesical Bacillus Calmette-Guerin (BCG)
- Massive tumour bulk of low-grade TCC (not possible to clear endoscopically)
- Squamous cell carcinoma of the bladder
- Adenocarcinoma of the bladder

Although traditionally performed via laparotomy, laparoscopic and robotic cystectomies have become more common with the popularity of minimally invasive surgery. There is a great deal of data published from various centres

worldwide presenting their experience on this topic (4,5,6,7). There is a definite transition from open to laparoscopic and robotic-assisted RC (7).

Our centre has been performing laparoscopic radical cystectomies (LRC) since 2009. We present our experience with LRC and lymph node dissection, as compared with open radical cystectomy (ORC) and lymph node dissection. We would like to compare the two cohorts in terms of operative complications, post-operative morbidity and mortality, as well as oncological outcomes. This is valuable information to assess laparoscopic radical cystectomy as a reasonable treatment option in our setting. We would like to show that our complications and outcomes are comparable to the global experience. No data regarding this subject has been published for the South African experience to date.

A2. Methodology

Study design:

Retrospective (folder) review of laparoscopic versus open radical cystectomy and lymph node dissection with ileal conduit by a single surgeon at Groote Schuur Hospital (GSH) from 2007 to date.

The patients will be identified from the principal surgeon's database. The folders will be requested from medical records and data collected on the attached data sheet (*Appendix: 2*). Any folder not obtained after 3 requests over a 1-month period will be excluded from the study. All folders must have original Urology notes with operative note and final histology report, anaesthetic record

from the procedure, as well as theatre log sheet. Any folder without all these criteria will be excluded from the study.

In terms of sample size, we expect to review approximately 80-100 folders in total, as this is the number of radical cystectomies that have been performed during the stipulated time frame.

Data will be analysed by a biostatistician using explorative univariate analysis. A Microsoft Excel spreadsheet will be generated, and Stata will be used to analyse the data.

Study population (*inclusion criteria*):

All patients that underwent open and laparoscopic radical cystectomy from 2007 to 2013 have been included in the study. The indications for surgery include:

- Muscle-invasive TCC bladder
- High grade non-muscle invasive TCC bladder not responding to intravesical BCG therapy
- Carcinoma-in-situ not responding to intravesical BCG therapy
- Extensive tumour bulk with inability to clear endoscopically (as assessed by Consultant Urologist)
- Squamous Cell Carcinoma of the bladder
- Adenocarcinoma of the bladder (muscle-invasive)

The patients undergoing LRC were compared to patients undergoing ORC by the same surgeon. The patients were demographically similar. All patients must have been assessed pre-operatively at the Combined Urology Oncology Clinic at Groote Schuur Hospital (LE34) prior to undergoing surgery. These patients were all referred to an Anaesthetic Consultant for assessment prior to surgery as well. Any patients not fulfilling these criteria will be excluded from the study. Patients that underwent LRC converted to ORC for any reason will be reviewed as a separate category. These will be reviewed in terms of reasons for conversion.

Data reviewed:

- Demographics
- Indications for surgery
- Stage of disease (clinical staging vs. post-operative histological staging)
- Margins
- Lymph nodes
- Complications (intra-operative blood loss and post-operative ileus)
- Outcome (duration of hospital stay and mortality within 1 year of surgery)

Specific data analysed:

- Intra-operative blood transfusion requirements
- Duration of surgery
- Post-operative complications as per Clavien Classification (90 days post-op)[3]
- Long-term post-operative complications (90 days – 1 year)

- Pre-operative vs. post-operative staging (ie. Clinical vs. histological)

Literature Review:

- A Medline search will be conducted, looking for the following:
- Open radical cystectomy or laparoscopic radical cystectomy
- Complications of radical cystectomy
- Oncological outcomes after radical cystectomy

A3. Ethics

The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research. Approval will be obtained from the Human Research Ethics Committee at the University of Cape Town (*Appendix: 1*).

A4. Risks

There are no risk factors affecting the patients.

A5. Benefits

As this is a retrospective review, there is no direct benefit to the patients. However, the data obtained may allow us to improve our clinical management of patients with muscle-invasive urothelial carcinoma requiring radical surgery.

A6. Informed consent

As this is a retrospective review, which will not impact on patients that have already undergone surgery, but which will benefit future patients, we ask for a waiver of consent.

A7. Privacy and confidentiality

Patients who have undergone surgery will be identified from the database of the principal surgeon involved in all the cases. Their files will be drawn and the required information will be recorded in an electronic database under a study number or letter. A separate file will be kept linking the study number to the patient. This information will be kept on a computer that needs a code to gain access to it. Only the principal investigator will have access to this computer.

A8. Budget and reimbursement

There is no cost involved with this study. No reimbursement is deemed necessary, as it is a retrospective review.

A9. References

1. EAU Guidelines for Non-Muscle Invasive Bladder Cancer (Ta and T1).
2. EAU Guidelines for Muscle- Invasive and Metastatic Bladder Cancer.
3. Dindo, D, Demartines, N, and Clavien, PA: Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey; Annals of Surgery 2004; 240, 2: pp. 205-213.

4. Gillion, N, et al: Mid-Term Oncological Control after Laparoscopic Radical Cystectomy in Men: A Single Centre Experience; BJU Int 2011; 108: pp. 1180-1184.
5. Ha, US, et al: Laparoscopic versus Open Radical Cystectomy for the Management of Bladder Cancer: Mid-Term Oncological Outcome; Int. J. Urology 2010; 17, 1: pp. 55-61.
6. Jensen, JB, et al: Mini-Laparotomy Approach to Radical Cystectomy; BJU Int 2011; 108: pp. 1125-1130.
7. Khan, MS, et al: A Dual-Centre Cohort Comparison of Open, Laparoscopic, and Robotic-Assisted Radical Cystectomy; The International Journal of Clinical practice 2012; 66, 7: pp. 656-662.

A10. Lay Summary (for Ethics Protocol)

Radical cystectomy with extended lymphadenectomy and urinary diversion remains the standard of care for muscle-invasive urothelial carcinoma. There are other indications for this procedure, as noted in the extended protocol. There has been a worldwide shift to performing minimally invasive surgery where possible. Our centre (Groote Schuur Hospital) has been performing laparoscopic radical cystectomies since 2009. We would like to audit our data and compare it to data obtained from patients undergoing open radical cystectomies by the same surgeon since 2007.

We would like to compare the two procedures in terms of:

- Operative duration
- Intra-operative blood loss
- Peri-operative blood transfusion requirements
- Post-operative complications (using the Clavien Classification)
- Differences in pre- vs. post-operative staging.

Our experience is unique in that we are currently the only centre in the country performing this surgery laparoscopically. We would ultimately like to ascertain whether or not minimally invasive surgery is a reasonable option (in terms of complications and oncological outcome) in our setting.

PART B: LITERATURE REVIEW

B1. INTRODUCTION

Worldwide, bladder cancer is the 9th most common cancer according to the World Cancer Research Fund International in 2012 (1). It is the 12th most common cause of death in South African males, and the 16th most common cause of death in South African females according to the South African Medical Research Council statistics from 2000 (2).

The most common type of bladder cancer is urothelial carcinoma (UC), previously known as transitional cell carcinoma (TCC) (3). Of all the bladder cancers diagnosed, approximately 70% are not muscle-invasive. The majority of these can be managed endoscopically. The risk of progression in 5 years varies from 0.8%-45%, depending on the risk profile of the patient and tumour (4) (Appendix: 3). In patients with superficial high-grade tumours, the risk of progression at 5 years is 54% without BCG instillation, and 10-20% with BCG instillation (induction and maintenance therapy) (4).

Thirty percent of patients require more radical therapy from the time of diagnosis for muscle-invasive disease (4,5). This includes radical surgery, radical radiotherapy, or multimodality treatment and/or bladder-preserving protocols (3,4,5).

Radical cystectomy with extended lymph node dissection and urinary diversion is the standard of care for treatment of localized muscle-invasive bladder

cancer (BC) (3,4). The indications for RC according to the European Association of Urology (EAU) and the American Association of Urology (AUA) are as follows:

- Muscle-invasive bladder cancer
- High-risk and rapidly recurring non-muscle invasive tumours
- BCG-resistant T1G3 TCC or carcinoma in-situ (CIS)
- Extensive low-grade disease that cannot be cleared endoscopically
- Salvage cystectomy post-failure of bladder-preserving measures
- Palliative procedure for pain, haematuria and fistulae

Radical cystectomy has traditionally been performed through open surgery. However, since the advent of laparoscopy and robotic-assisted laparoscopic RC, there has been a worldwide shift towards minimally invasive surgical procedures.

Groote Schuur Hospital is currently the only centre in South Africa performing RC using laparoscopy. We would like to present our data comparing all open and laparoscopic radical cystectomies performed from 2005 – 2013.

B2. OBJECTIVES

There are several aspects that will be reviewed. The basic guidelines governing indications for surgery, surgical options and surgical technique will be explored. We will also be looking at the controversies within these areas of interest.

Other factors to be reviewed include post-operative outcomes. This covers morbidity, mortality and survival outcomes, as well as quality of life issues. Survival outcome, lymph node yield, margin positivity and rate of recurrence are used as surrogate markers for oncological outcomes.

According to the available literature, it appears as though there is no surgical technique that provides oncological superiority to another (4). There does seem to be improved outcomes with regard to blood transfusion requirements, incidence and duration of ileus, wound complications and time to discharge in the laparoscopic group (6,7,8,9). Duration of surgery is shorter in the open surgery group of patients (8,9). The majority of data currently available is from high-volume centres in first world countries. We would like to analyse our data and compare it to outcomes found in these high-volume centres.

B3. METHODOLOGY

Medline and Embase searches were conducted, looking for the following:

- Treatment of muscle-invasive bladder cancer
- Lymph node dissection templates for radical cystectomy
- Extent of surgery during radical cystectomy
- Open radical cystectomy or laparoscopic radical cystectomy
- Complications of open or laparoscopic radical cystectomy
- Oncological outcomes after open or laparoscopic radical cystectomy

Manual searches of the bibliographies of relevant articles were performed. The guidelines of professional associations as well as standard textbooks were consulted.

Inclusion criteria

- Studies looking at open RC
- Studies looking at laparoscopic RC
- Studies comparing open and laparoscopic RC
- Study population greater than 25 patients
- Patients over 18 years of age

Exclusion criteria

- Study population of less than 25 patients
- Paediatric patients (<18 years)
- Robotic-assisted radical cystectomies
- Neobladder as form of urinary diversion

B4. SUMMARY OF THE LITERATURE

B4.1 Current Guidelines

According to the European Association of Urology (EAU) Guidelines, RC with lymph node dissection is the gold standard for the treatment of muscle-invasive BC, as well as for the other indications listed previously. Open radical

cystectomy by means of a mini-laparotomy is still regarded as the primary option according to the guidelines (3,4).

In a recent systematic review by Aboumarzouk, *et al* (10), it was found that patients undergoing LRC had longer operative times, but shorter hospital stay, decreased blood loss, and decreased analgesic requirements. However, due to selection bias and relatively small numbers of patients in the individual studies, this data is not truly statistically significant (11). Tang, *et al* echoed these sentiments in their meta-analysis of LRC versus ORC for bladder cancer. The outcomes were found to be in line with those found by Aboumarzouk, *et al*, with similar shortcomings in the data available, thereby making it difficult to draw definitive statistically significant conclusions (12). It is therefore not possible to accept minimally invasive surgery as standard of care as yet. Laparoscopic radical cystectomy and robotic-assisted radical cystectomy are still considered experimental (11). For the purpose of this literature review, only ORC and LRC will be compared.

Chronological age and American Society of Anaesthesiologists (ASA) scores have been found to be relatively irrelevant in deciding what treatment modality to offer the patient (3,13). A more appropriate consideration is a validated comorbidity index, such as the Charlson Co-morbidity Index, or the Cumulative Illness Rating Scale (*Appendix: 4)*. This allows evaluation of biological age, which has been proven to be more useful in terms of pre-operative risk-stratification. Patients scoring poorly on the co-morbidity indices have a higher

rate of peri-operative outcomes, with poorer all-cause survival rates, and higher rates of complications (14).

B4.2 Extent of Surgery

The basic principles of surgery for the treatment of bladder cancer apply to all surgical methods used. This includes a lymph node dissection (to be discussed in greater detail later), removal of the bladder (and all macroscopic tumour around the bladder), removal of the uterus in females or the prostate and seminal vesicles in males, with or without a urethrectomy (3). Urinary diversion is then performed, which may be by way of a neobladder, or by an ileal conduit. There are other diversion options that have been used in the past, but these are no longer considered to be standard of care.

The decision to perform urethrectomy or not involves taking certain factors into account. Firstly, bladder neck biopsies and prostatic urethral biopsies should be taken during transurethral resection to establish that these areas are clear of tumour (3). Carcinoma in-situ (CIS) being present is not an indication for urethrectomy (4). Secondly, if the diversion type is to be an ileal conduit, certain centres perform routine urethrectomy to avoid the need for long-term surveillance. This is not an absolute indication, as the risk of recurrence in the urethral stump is relatively low: 2.1 – 11.1% post-radical cystectomy with cutaneous diversion, and 0.5 – 4.0% after orthotopic neobladder (3). Routine urethrectomy is not part of the current EAU Guidelines (4).

The type of diversion does not impact on oncological outcomes in any way. The decision should be based on patient factors (including age, body habitus, and willingness to perform clean intermittent self-catheterisation), as well as tumour factors (clear urethral and bladder neck biopsies, and curative cystectomy as opposed to palliative cystectomy). During minimally invasive surgery, the diversion may be performed extra-corporeally in the same manner as is performed during open surgery. The diversion may also be performed intra-corporeally. Intra-corporeal urinary diversion potentially decreases the wound length, but takes longer to perform (average: 180min), with a steep learning curve (15-19).

In terms of prostatectomy and hysterectomy, there are case reports of these organs being spared. This is more the case with the prostate, in order to improve continence, as well as to maintain erectile function. This procedure is accompanied by a nerve-sparing approach and creation of an ileal neobladder (20). It is only possible in tumours that are more than 10mm away from the trigone and bladder neck area, with no urethral involvement and no evidence of prostate cancer (20). The reason for this requirement is for optimal oncological outcomes. These options are currently regarded as experimental and are not routinely recommended as standard of care (4).

B4.3 Pathological Stage

According to the literature (4), optimal pre-operative staging requires assessment of the tumour by way of:

- CT scan for assessment of the upper tracts, lymph nodes, tumour extent and to exclude metastases (4)
- Examination under anaesthesia for presence of a palpable bladder mass (and whether the mass is mobile or fixed) (21-23).
- Cystoscopy and biopsy of the tumour
- Bladder neck and prostatic urethral biopsies
- Random biopsies if warranted

Once the RC has been performed, a true pathological stage can be assigned *(Appendix: 5)*. The rate of stage discrepancy is significant, with up to 11% of patients being over-staged and 33% of patients being under-staged clinically (23). Accurate staging is vital to predict prognosis ***(****Appendix: 6)*, and optimize treatment regimens. Stage has also been found to correlate with risk of peri-operative complications (4).

B4.4 Comparing Surgical Techniques

It is difficult to use the current available literature to compare ORC and minimally invasive techniques. Despite the widespread availability of data comparing the different modalities, as well as several well-conducted systematic reviews, the fact remains that there is definite selection bias between the groups, making direct comparison challenging (8-10). The patients in the minimally invasive groups are, in general, younger and with less co-morbidity. This impacts on intra- and post-operative morbidity.

A significant difference between the 2 techniques is patient positioning. During ORC, the patient is placed in Lloyd-Davis (low lithotomy) position, with mild Trendellenburg (head down) positioning to facilitate the surgery. During LRC, the patient is also placed in Lloyd-Davis position, but the patient needs to be in steep Trendellenburg position. This allows the bowel to fall out of the field of vision, and facilitates optimum angles for the use of the laparoscopic instruments. This positioning may impact on the complication rate. There is higher risk of ocular and facial oedema, as well as raised intra-cranial pressure, raised pulmonary pressures, and impaired venous return to the heart (24,25). The risk of these complications is directly dependent on the duration spent in steep Trendellenburg positioning during surgery.

Overall, the oncological outcomes between the groups have been found to be similar (7,26). These were measured using certain criteria, including: rates of positive margins and lymph node yield. There is inadequate data available to comment on long-term outcomes such as overall survival (OS) and progression free survival (PFS) due to inadequate follow-up times in many studies. However, the implication is that these outcomes are similar when comparing the different surgical treatment groups (7-9,26,27).

Nerve-sparing radical cystectomy is something that is being described more often now. With the advent of minimally invasive techniques, magnification of the surgical field is improved, allowing the surgeon to identify the nerves responsible for erectile function more readily. This theoretically improves

erectile function post-operatively (20). Unfortunately there is not enough data to support this as yet, but it will surely be assessed in the future.

Post-operative morbidity does differ significantly between the groups. Blood loss, rates of ileus, and duration of hospital stay are all less in the LRC group. This comes at the expense of longer operative duration, with a longer learning curve in this group (7-9,12,26,27).

B4.5 Operative Time

The average operative duration in high volume centres for ORC is 260-376min, as compared to 280-445min for LRC (8,12,26,27,30-35). This difference has been found to be statistically significant in multiple studies. The reasons for the difference appear to be multi-factorial, but are largely related to the steep learning curve with LRC.

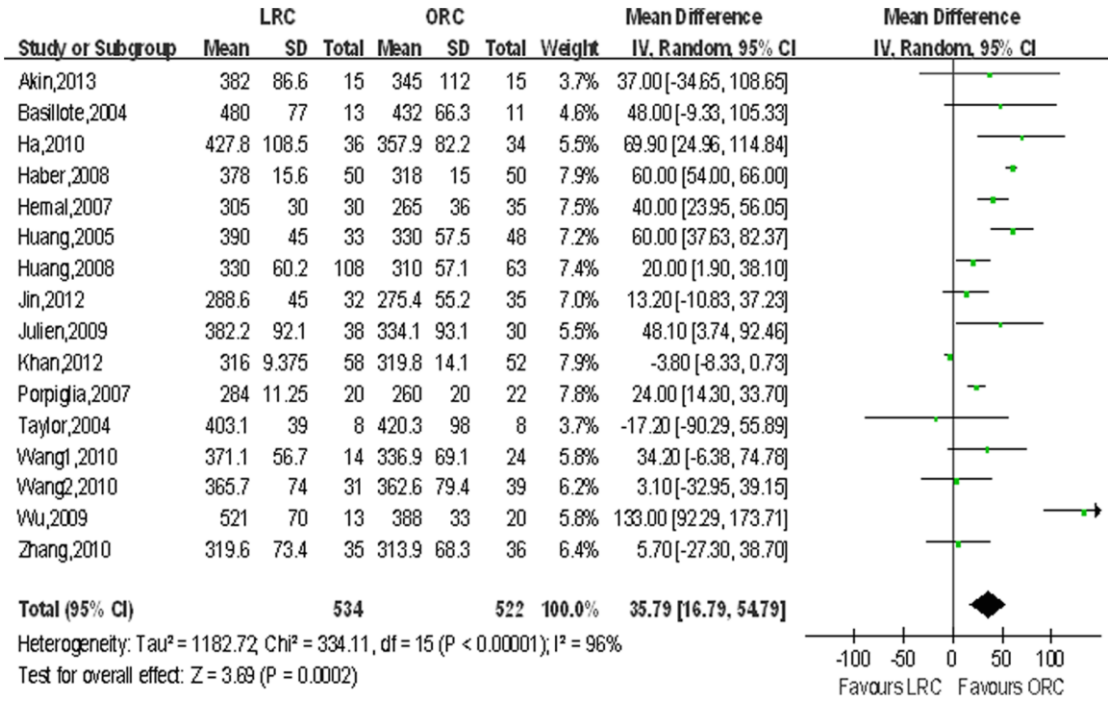

Figure 1. 1 Forest plot and meta-analysis of operative time

Tang K, et al, 2014 (12)

Ideally one would need to compare ORC and LRC in terms of the learning curve. This would entail assessing a single surgeon and comparing ORC and LRC from the very first surgery onward. In this manner one can assess the trend in operative times, thereby assessing the expected improvement in skill level.

Increased operative times lead to increased risks of complications as noted previously. However, once the learning curve has been overcome, the operative time is less of an issue.

B4.6 Complications

Assessing surgical complications has been a topic of discussion for as long as surgeries have been performed. The crucial factors are: which complications to document, how to document them, and how to compare them.

It is clearly essential that one recognizes the complication, and then documents it. It is also vital that one audits the surgeries performed and their complications on a routine basis in order to improve patient care. Without regular monitoring of complications, there is no way to effect change that may improve the surgical technique and overall outcomes for the patient.

Multiple methods have been used in the past to record complications (36). The problems encountered were lack of reproducibility, as well as the arduous filling in of forms that are difficult to interpret. The most recent and effective method of reporting complications, the Clavien-Dindo Classification (Appendix 7), has now been universally accepted by the different surgical fields (37). It has been validated as being easy to use, easy to interpret, and reproducible. It can be used by any member of staff, no matter how junior or senior, with ease and accuracy.

The Clavien-Dindo Classification allows for the reporting of minor and major complications that occur within 90 days after surgery has been performed. The complications are documented and scored based on the intervention required to treat it. The limitations with this system are that it does not take into account

intra-operative complications, nor does it take into account death within 1 year of surgery.

Other methods used to assess post-operative complications include the Martin Criteria. These are a modification of the Clavien-Dindo Classification, so are marred by the same limitations as noted above. Novara (38), et al, found that using the Martin criteria, 13% of patients had Grade 3 to 5 complications in the first 3 months after surgery. The mortality rate was found to be 3% within 3 months. Independent risk factors for high-grade complications included a higher ASA score (39,40), and female gender undergoing orthotopic neobladder formation.

Intra-operative complications are very important to assess. These include the need for transfusion, intra-operative cardiac events, bowel injury, pulmonary complications (related to pneumoperitoneum causing raised intra-thoracic pressures and/or positioning during LRC), to name a few (41). Adequate pre-operative work-up and optimization should allow one to avoid many possible complications. However, with excessive bleeding and atypical positioning of the patient (as noted previously), these complications may still occur.

Cohen, et al (28), used the Patient Safety Indicators (PSI) to assess peri-operative outcomes. These are validated metrics developed by the Agency for Healthcare Research and Quality. They found that the PSI were overall decreased in patients undergoing minimally-invasive RC (LRC and robotic-assisted RC) as compared to those undergoing ORC. This study also showed

that more surgeries are being done on patients in their 8th and 9th decades. These patients are 3X and 5X more prone to significant complications peri-operatively, immaterial of the method used to perform surgery.

Wang, et al (42) noted in a prospective trial that the acute inflammatory response is significantly less in the LRC group. The systemic inflammatory response syndrome (SIRS) response was assessed using IL-6 and interferon levels. These were significantly less in the LRC group. The incidence of a SIRS response was 59% in the LRC group vs. 72% in the ORC group. Duration of the SIRS response was also shorter in the LRC group (1.4 vs. 2.8 days). Targarona, et al (43), looked at laparoscopic surgery in general, and also noted that it is associated with better preservation of the immune response, thereby making one less prone to surgical infection. These studies have been small, but they do lay the foundation for similar studies to be carried out in the future.

Post-operative complications vary from those requiring basic antipyretics or dressings, to death. The spectrum is not dissimilar to those complications occurring with any surgical procedure. Those more specific to or seen more commonly after radical cystectomy include sepsis, bleeding, ileus, wound dehiscence (ORC), bowel obstruction and complications related to the ileal conduit (stenosis, prolapse, para-stomal hernias or anastomotic problems) (3). More serious complications requiring ICU admission, or death, are less common, but do occur. These complications increase in frequency in patients with higher co-morbidity indices (4).

The complications occurring in LRC vs. ORC differ. According to multiple studies, it has been shown that the amount of blood lost and the rate of blood transfusion are significantly lower in the LRC group. Also, there is a lower rate of post-operative ileus, as well as a more rapid return of bowel function in the LRC group. In the ORC group of patients it has been noted that there is a significantly higher rate of wound complications, higher requirements for blood transfusion, increased rate and duration of post-operative ileus, as well as a higher rate of bowel obstruction. Overall hospital stay is longer in the ORC group in most studies (9,15,31,32,38).

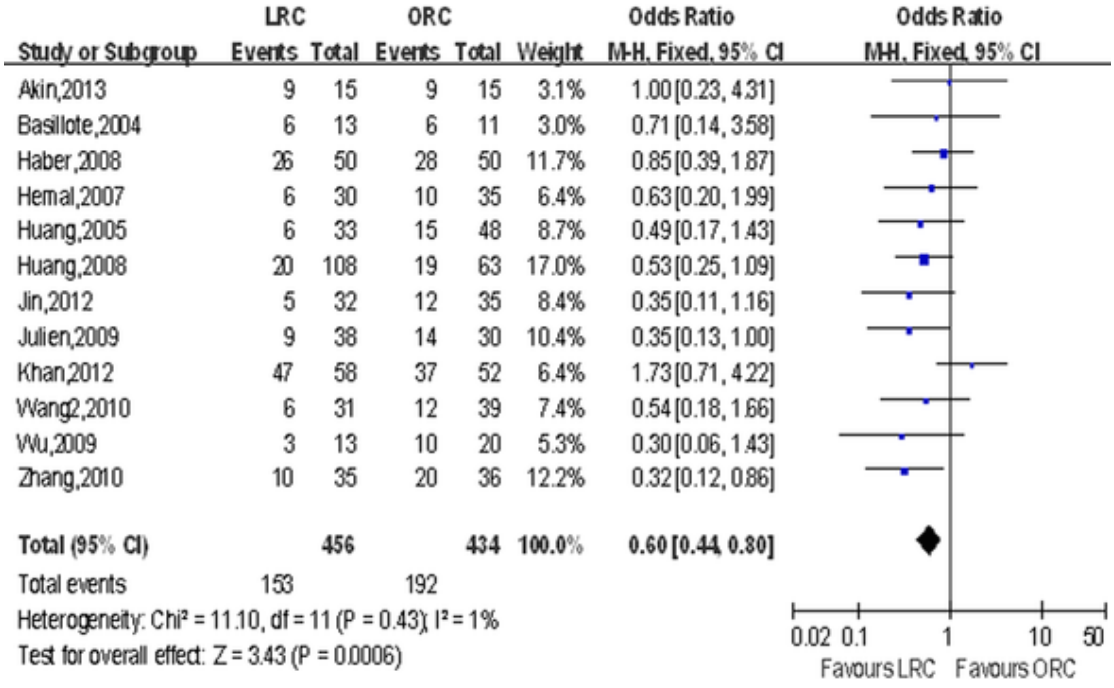

Figure 1. 2 Forest plot and meta-analysis of overall complications

Tang K, et al, 2014 (12)

B4.7 Blood Loss

Blood loss is not unusual during RC. The average expected blood loss is 600ml, with a range of 100ml to 3000ml. The average rate of transfusion is around 30% of patients. The median requirement was 2 units (range of 1-10 units) (44).

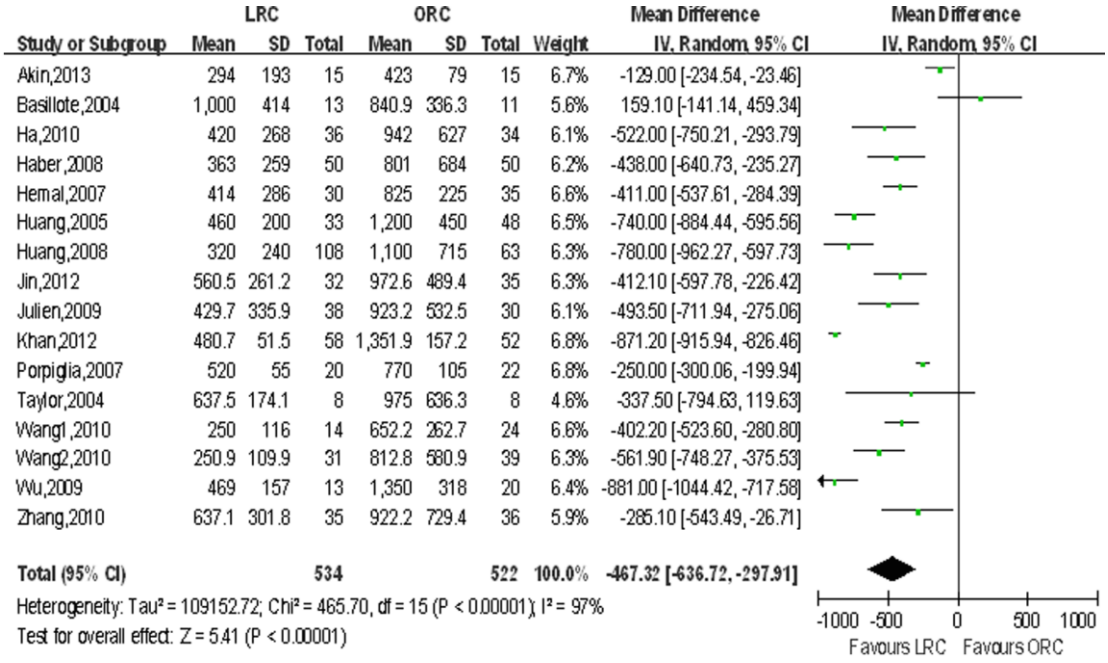

Figure 1. 3 Forest plot and meta-analysis of estimated blood loss (EBL)

Tang K, et al, 2014 (12)

Methods to optimize blood use include the use of pre-operative autologous blood donation, haemodilution techniques, and cell-salvage. None of these methods have been shown to decrease the rate of allogenic blood transfusion, and so their usefulness has been questioned (45).

It therefore becomes clear that meticulous operative technique is much more important in order to prevent blood loss, as opposed to attempting to rectify the problem once it has occurred. Laparoscopic radical cystectomy has, however,

been shown in multiple studies to be superior to ORC in terms of minimizing blood loss (8,9,12,27,30,35).

B4.8 Ileus

The commonest minor complication post-radical cystectomy is ileus. The overall rate of ileus is 18%, as documented by Chang et al (46). Several attempts have been made to decrease the rate of post-operative ileus. Intra-operative insertion of a gastrostomy tube has been advocated (47). This is, however, invasive and does not decrease the rate or duration of post-operative ileus (47). In a systematic review by Ramirez *et al* chewing gum post-operatively was shown to decrease time to bowel action, as well as re-adaptation of the dorso-lateral peritoneal layer intra-operatively (48). In the same review, it was found that certain things increased the risk of patients developing post-operative ileus. These factors include the administration of pre-operative bowel preparation and the insertion of a nasogastric tube peri-operatively (48). Other methods that have been tried in an attempt to decrease the rate of post-operative ileus include intravenous metoclopromide, with removal of nasogastric tube (NGT) on day 1 post-surgery (36).

Multiple studies have shown superiority of LRC to ORC in terms of time to first meal (9,27,30,32). The reasons for this remain unclear. One suggestion has been earlier mobilization that is possible in these patients due to decreased pain from the smaller incisions (12,32). Another suggestion has been that earlier return to normal bowel function is related to the decreased need for narcotic analgesics (12,32).

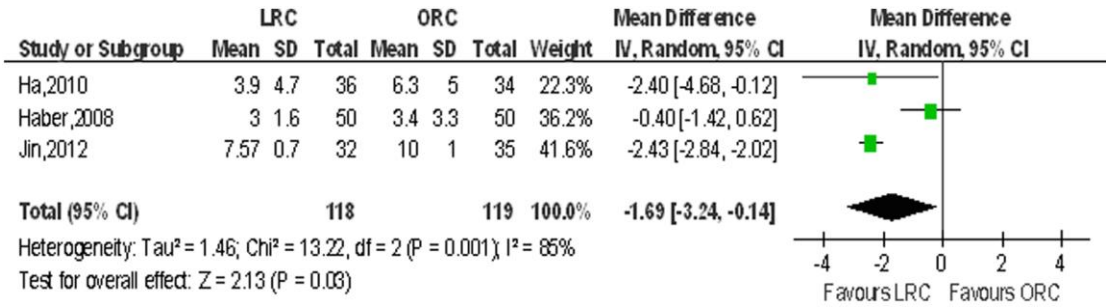

Figure 1. 4 Forest plot and meta-analysis of time to first meal

Tang K, et al, 2014 (12)

B4.9 Positive Margins

Lymph node positivity, extent of lymph node dissection, and rate of positive margins have all been used as surrogate markers for oncological outcome (49,50). These factors impact on PFS, as well as on OS as noted in the data (4).

Positive margins correlate with an increased risk for local recurrence (50). Risk factors for positive margins have been found to include female gender, locally advanced disease, presence of vascular invasion, and mixed histopathology (50). Positive margins were found in 4.2% of patients undergoing RC at Memorial Sloan Kettering Cancer Center in 2007 (50). The rate of local recurrence after RC is 5-15%, with a metastatic risk that is double that of patients with negative margins (4,50). These most commonly occur within the first 2 years after surgery. The prognosis once local recurrence occurs is extremely poor (4-8 months survival).

The limitation of using positive margins as a surrogate marker for oncological outcome is that there are many possible reasons for positive margins.

Tumour extending outside of the bladder is indeed one cause of positive margins in RC specimens. This would impact on the stage of the disease process, and therefore on prognosis and survival outcomes (50). The problem here is that to accurately assess data between ORC and LRC, one would need to compare data stage-for-stage in order to make meaningful comparisons regarding the 2 techniques.

Another cause for positive margins is purely the technical aspect. Again, in order to compare data accurately, one should compare single-surgeon data, including the learning curve period. This allows one to draw meaningful information regarding the 2 techniques from a technical perspective.

The last factor affecting margin positivity is the handling of the specimen by the pathologist. This has been shown to differ slightly from lab to lab, and also from pathologist to pathologist. A dedicated pathologist experienced in the field of Urology would circumvent these issues.

The rate of positive margins, as well as the rate of recurrence amongst the 2 groups has been found to be similar in the literature (9,12,27,30). This implies that neither technique is superior to the other from a technical standpoint as well as from an oncological standpoint.

B4.10 Lymph Node Dissection

It has been well established that lymph node dissection affords the patient improved survival outcomes (4). This is true even if the lymph nodes are found

to be negative for malignancy. Lymph node dissection also allows adequate staging of the patient. It is very difficult to assess lymph node positivity on imaging alone (4). CT and magnetic resonance imaging (MRI) can help, but both have suboptimal sensitivity. Sensitivity with MRI and CT scan is 48-87% (4). Specificity is also poor due to the high rate of enlarged lymph nodes secondary to benign disease (4).

Lymphatic drainage to the bladder is variable, but the primary landing site in the majority of cases is the obturator group of nodes (3). From the mid-common iliac nodes moving more proximally, it is very rare to have skip lesions in terms of lymph node positivity.

The optimal template is yet to be agreed upon. What is for certain is that a standard lymph node dissection is the minimum that should be performed (4). This allows for at least 10 nodes to be sampled. A minimum number of 10 lymph nodes has been found to be associated with improved overall survival in retrospective data (4). This number is also thought to be adequate in terms of lymph node assessment for staging purposes. The probability of missing a positive lymph node if 10 nodes are sampled drops to 26% (49)

Stein and collaborators (51) noted in a review article that cancer-specific survival and disease-free survival improved by 20-25% if more than 16 lymph nodes were sampled. They also noted that if 20 lymph nodes were sampled, then 80% of patients with node-positive disease would be identified. The suggestion in this review articles is to take lymph nodes up to the Inferior

Mesenteric Artery as part of an extended lymph node dissection for optimal clearance. Some centres take the dissection further - up to the para-aortic lymph nodes (52,53).

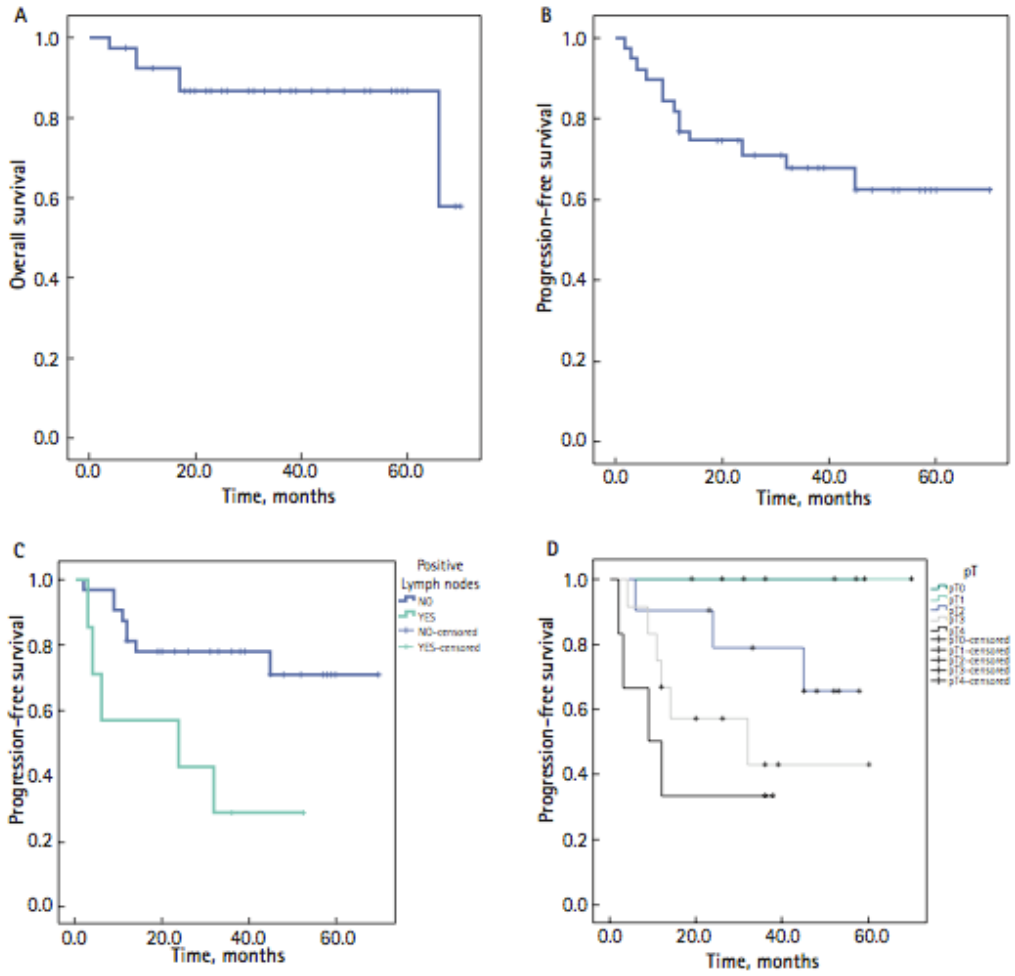

Figure 1. 5 Kaplan-Meier curves (A) for overall survival, (B) for progression-free survival, (C) for progression-free survival stratified by lymph node involvement status (log-rank test, P=0.009) and (D) by pT stages (log-rank test, P=0.011)
Gillion N, et al, 2011 (26)

The standard lymph node template includes the following packets:

- mid-common iliac nodes
- internal iliac nodes
- external iliac nodes
- obturator nodes
- presacral nodes

The boundaries of the standard lymph node dissection are (4,51):

- Superiorly: common iliac vessels (lateral to the ureter)
- Inferiorly: Cloquet's node/Lacunar ligament
- Laterally: genitofemoral nerve
- Medially: ureter and common iliac vessels medial to the crossing ureter
- Floor: Obturator nerve

The centres performing more extensive lymph node dissection do so in order to improve survival. However, the overall benefit vs. risk of increased morbidity secondary to an extensive lymph node dissection has not been proven for any dissection past the level of the bifurcation of the common iliac vessels (4).

The complications of lymph node dissection include (3,4,51):

- Intra-operative vascular and/or nerve damage
- Post-operative formation of a lymphocoele
- Chylous ascites requiring total parenteral nutrition
- Ejaculatory dysfunction in a male
- Lymphoedema of the lower limbs
- Deep vein thrombosis

B4.11 Survival Data

There are many ways in which survival data is reported and analysed. Each method allows one to avoid the limitations encountered by other methods. Data that is analysed includes overall survival, cancer specific survival and progression free survival.

Overall survival is the most robust data that is used to assess efficacy of a treatment modality. This is because OS is a firm end-point, whereby one can assess the chances that a patient will survive in a set time-period. It excludes bias caused by excluding other causes of death, including co-morbidities.

The other survival outcomes used show survival specifically related to the cancer. They do not take into account the general wellbeing of the patient, and whether or not they demised from other causes.

Cancer specific survival (CSS) excludes other causes of death, thereby attempting to assess more accurately the effect of a treatment modality specifically on that type of cancer. The problem with this is that CSS ignores other factors that may cause death, and therefore impact on OS of the patient. These factors may or may not be related to the treatment regimen instituted for that patient.

Progression free survival simply looks at how long a patient survives without progression of the disease process. It does not necessarily mean that the patient is free of disease, nor does it imply increased overall survival. The value of PFS is largely to assess how long a treatment modality may work in controlling a disease process, without necessarily curing it. This may or may not impact on overall survival. It may, however, impact on quality of life.

According to data from Rochon et al (54), and later from Zietman et al (14), comorbidity was found to be independently associated with poorer outcomes.

The data shows that patients with more comorbidities did worse post-operatively in terms of overall mortality and CSS.

Haber and Gill (7) produced some of the first data looking at longer-term follow up after LRC. In 2007, their data looked at 37 patients undergoing LRC that were followed up for a mean of 31 months (Range: 1-66 months). They worked out the 5-year actuarial survival to be: 63% OS, 92% CSS, and 92% recurrence-free survival. This data is comparable to that found in ORC series (55). Subsequently, many other studies have been published showing similar oncological equivalence of LRC compared to ORC. (26,29,35)

Unfortunately there is minimal data comparing survival outcomes between patients having had ORC and those that underwent LRC. This makes it difficult to comment on the differences between the 2 modalities.

The limitations of not having adequate long-term survival data led Puppo and Naselli (11) to categorically state that LRC should still be regarded as highly experimental, and only to be performed in experienced, high volume centres. The reasoning behind this is largely based on the lack of data showing superiority in terms of survival benefit. It is also due to patient selection bias that is noted in the majority of studies that have been published to date comparing ORC and LRC. This sentiment had previously been expressed by Huang and Stein in 2007 (34), and the again by Hautmann in 2009 (56).

B4.12 Quality of Life

None of the above-mentioned modalities assess quality of life issues. Quality of life (QOL) is difficult to assess objectively. The most accurate method is by using validated questionnaires (4,57,58). Several questionnaires exist, for example: Functional Assessment of Cancer Therapy - General (FACT-G), among others (4).

The literature suggests that QOL after LRC is most likely better than after ORC, at least in the short-term. As discussed previously, the immediate post-operative rate of ileus is lower with a shorter time to first meal. Hospital stay is shorter. The risk of wound complications is significantly lower. The risk of bowel obstruction is lower. All of these factors impact on QOL.

Long-term, however, these factors play less of a role. The overall QOL most likely evens out, but is difficult to assess due to the pre-operative patient selection bias. Younger patients, with fewer co-morbidities and less advanced tumours are generally selected for LRC (11). It is therefore difficult to make direct comparisons with ORC in terms of post-operative QOL. There are no randomized prospective studies assessing QOL.

B5. FUTURE RESEARCH

Given that minimally invasive approaches are still regarded as experimental by the current EAU and AUA guidelines, it goes without saying that more data will surely be published in the near future to alter this situation. The challenges with direct comparisons have already been discussed.

However, with growing expertise in LRC, it stands to reason that the selection bias should decrease over time, allowing more meaningful comparisons between ORC and LRC. Also, longer follow-up will allow long-term data to prove the oncological equivalence of LRC as compared to ORC.

There is a paucity of data comparing survival outcomes in LRC and ORC groups. Minimal data is available showing a comparison of morbidity and mortality outcomes between these groups.

QOL issues also need to be addressed in order to optimize patient care. The patient should play an active role in the decision-making process in terms of type of treatment modality, as well as in terms of urinary diversion if radical surgery is the treatment that is chosen. Post-operative and long-term QOL comparisons between the 2 cohorts will need to be reviewed in the future.

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PART: C MANUSCRIPT

TITLE

Retrospective review of open versus laparoscopic radical cystectomy for the treatment of bladder cancer: complications and oncological outcome

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C1. ABSTRACT

C1.1 Objective

Radical cystectomy with extended lymphadenectomy and urinary diversion remains the standard of care for muscle-invasive urothelial carcinoma. Our centre (Groote Schuur Hospital) has been performing laparoscopic radical cystectomies since 2009. We aimed to audit our data regarding complications and oncological outcome and compare it to data obtained from patients undergoing open radical cystectomy by the same surgeon since 2007. The two procedures will be compared in terms of operative duration, intra-operative blood loss, peri-operative blood transfusion requirements, post-operative complications (using the Clavien Classification) and differences in pre- vs. post-operative staging.

C1.2 Patients and Methods

All adult patients (>18 years) that underwent open and laparoscopic radical cystectomy from 2007 to 2013 have been included in the study. Data on demographics, operative time, intra-operative blood loss, post-operative complications (as per Clavien-Dindo Classification), margin positivity, and lymph nodes (number obtained and number of positive nodes) was obtained retrospectively by means of folder review. Extracted data was collected on a Microsoft Excel spreadsheet. Only folders with complete data sets were included for statistical analysis. Patients undergoing laparoscopic radical cystectomy converted to open were analysed on an intention-to-treat basis.

Data was analysed using bivariate statistics and survival analysis was performed to compare mortality rate.

C1.3 Results

Physician's choice of surgical modality was associated with clinical disease staging with 59% of participants who underwent ORC presented with a palpable mass on examination under anaesthesia (EUA) compared to 36% of participants in the LRC arm. This association was confirmed on pathological staging. Participants undergoing ORC experienced shorter operative duration (301 minutes versus 382 minutes; *p-value* < *0.0001*), increased blood loss (1376ml versus 778ml; *p-value* = *0.0023*) and transfusion requirement (2 units versus 0; *p-value* = *0.071*) in contrast to LRC. Post-operative complications were more prevalent in the ORC arm compared to the LRC arm (61% versus 43%) and this trend was reflected in the Clavien classification. The only complication that differed in its occurrence between the two arms was wound complications (18% for LRC versus 44% for ORC) with the main type being sepsis. Patients with a past medical history were at higher risk of experiencing post-operative complications (*p-value = 0.04; Risk Ratio: 1.6*). Margin positivity was comparable between the two arms. A trend was observed when comparing the number of lymph nodes sampled using the two techniques and this trend was maintained irrespective of the area sampled, whereby a higher number of nodes was sampled by the laparoscopic technique in this study (overall *p-value* = *0.07*).

C1.4 Conclusion

Laparoscopic radical cystectomy is associated with longer operative times, decreased blood loss, and equivalent oncological outcomes when compared to open radical cystectomy. Laparoscopic RC is a feasible option in our setting. LRC affords patients a lower risk of requiring transfusion, with minimal risk of post-operative ileus and a lower risk of wound complications. Given the increasing number of laparoscopic procedures being performed at GSH, a prospective trial would be possible in order to confirm these findings.

C2. INTRODUCTION

Worldwide, bladder cancer is the 9th commonest cancer according to the World Cancer Research Fund International in 2012 (1). Cancer of the bladder is the 12th commonest cause of death in South African males, and the 16th commonest cause of death in South African females according to the South African Medical Research Council statistics from 2000 (2).

The commonest type of bladder cancer is urothelial carcinoma (UC), previously known as transitional cell carcinoma (TCC) (3). Of all the bladder cancers diagnosed, approximately 70% are not muscle-invasive (4). The majority of these can be managed endoscopically. The risk of progression of non-muscle invasive urothelial carcinoma in 5 years varies from 0.8%-45%, depending on the risk profile of the patient and tumour grade (4). In patients with superficial high-grade tumours, the risk of progression at 5 years is 54% without Bacillus Calmette-Guérrin (BCG) instillation, and 10-20% with BCG instillation (induction and maintenance therapy) (4).

Thirty percent of patients require more radical therapy from the time of diagnosis for muscle-invasive disease (4,5). This includes radical surgery, radical radiotherapy, or bladder-preserving protocols (3,4,5).

Radical cystectomy (RC) with extended lymph node dissection and urinary diversion is the standard of care for treatment of localized muscle-invasive bladder cancer (BC) (3,4). The indications for RC according to the European Association of Urology (EAU) and the American Association of Urology (AUA) are as follows:

- Muscle-invasive bladder cancer
- High-risk and rapidly recurring non-muscle invasive tumours
- BCG-resistant T1G3 TCC or carcinoma in-situ (CIS)
- Extensive low-grade disease that cannot be cleared endoscopically
- Salvage cystectomy post-failure of bladder-preserving measures
- Palliative procedure for pain, haematuria and fistulae

RC has traditionally been performed by open surgery. However, since the advent of laparoscopy and robotic-assisted laparoscopic RC, there has been a worldwide shift towards minimally invasive surgical procedures.

According to the available literature, it appears as though there is no technique that provides oncological superiority to another in terms of surgical technique used (4). There does seem to be improved outcomes with regard to blood

transfusion requirements, incidence and duration of ileus, wound complications and time to discharge in the laparoscopic group (6,7,8,9). Duration of surgery is shorter in the open surgery group of patients (8,9). The majority of data currently available is from high-volume centres in first world countries.

Groote Schuur Hospital, a tertiary centre serving a mainly indigent population, is currently one of few centres in South Africa performing RC using laparoscopy. We aim to present our data comparing all open and laparoscopic radical cystectomies performed by a single surgeon in order to highlight the possible advantages of performing laparoscopic radical cystectomy (LRC).

C3. PATIENTS AND METHODS

C3.1 Data Collection

Approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. The folders of all patients undergoing open radical cystectomy (ORC) and laparoscopic radical cystectomy (LRC) performed at GSH from 2005-2013 were obtained and retrospectively reviewed. Only patients where all data was available were included in the study.

The data that was collected included demographics, so as to confirm that the cohorts being compared were age-matched. We also compared the prevalence of comorbidities in the two groups, and no statistically significant differences were found. Data pertaining to operative duration (including urinary diversion)

was reviewed, as well as peri- and post-operative complications. Complications were stratified as per Clavien-Dindo Classification. Specific complications that were examined more in-depth included intra-operative blood loss, wound complications, and post-operative ileus. Other factors that were looked at included data on oncological control, such as number of lymph nodes obtained, number of positive lymph nodes, as well as margin positivity. Pre- and post-operative staging data was compared. Survival data was also compared.

C3.2 Surgical Technique

The basic principles of surgery for the treatment of bladder cancer were applied to both surgical methods used. This included a modified extended lymph node dissection (up to the level of the mid-common iliac vessels, excluding presacral lymph node sampling), removal of the bladder (and all macroscopic tumour around the bladder), removal of the uterus in females or the prostate and seminal vesicles in males, with or without a urethrectomy (3). Extra-corporeal urinary diversion was then performed, by way of an ileal conduit.

Positioning differs for ORC as compared to LRC. During ORC, the patient is placed in Lloyd-Davis (low lithotomy) position, with mild Trendellenburg (head down) positioning to facilitate the surgery. During LRC, the patient is also placed in Lloyd-Davis position, but the patient is required to be placed in steep Trendellenburg position. This allows the bowel to fall out of the field of vision, and facilitates optimum angles for the use of the laparoscopic instruments. Steep Trendellenberg positioning may be associated with increased risk of intra-operative complications. These include pulmonary hypertension, cerebral

and facial oedema, and traction on lower limbs with neuropraxia, among others (10,11). No documented cases of these complications were noted in this cohort of patients.

C3.3 Statistical Analysis

Continuous variables were reported using medians and interquartile ranges. Categorical variables were reported as a percentage of the total and proportion of the main subset. Continuous variables were compared by Mann-Whitney U test. Categorical variables were compared between groups by Fisher's exact test. Spearman's correlation coefficients were calculated to assess potential associations between continuous variables. Mortality rate was assessed using the Kaplan-Meier survival analysis. No adjustment for multiple comparisons was used, given the small sample size and the hypothesis-generating nature of the study. Two-sided p-values <0.05 were considered significant. All analyses were performed using GraphPad Prism v5.0 (La Jolla, CA).

C4. RESULTS

C4.1 Participants Characteristics

Seventy five patients underwent radical cystectomy from January 2007 to February 2013 at Groote Schuur Hospital, Cape Town. Of these 75, 40 were operated on using laparoscopic technique and 35 underwent open radical cystectomy. Thirty patients from the laparoscopic arm were included as participants in this study while 32 from the open arm were enrolled as participants. The study is retrospective in its design and as such thirteen patients were excluded based on the lack of data. Ten patients from the

laparoscopic arm and 3 patients from the open arm were excluded. A significantly higher proportion of men underwent laparoscopic surgery when compared to women (83.3% versus 16.7% respectively, p=0.02; Figure 2.1) while the gender balance was approaching symmetry in the open arm (56.3% male versus 43.8% female; Figure 2.1). The mean age of participants included across the two arms did not differ (mean of 61 for laparoscopic surgery and 60 for open surgery). Moreover when classified according to gender and comparing across the two arms, there was no difference in age observed.

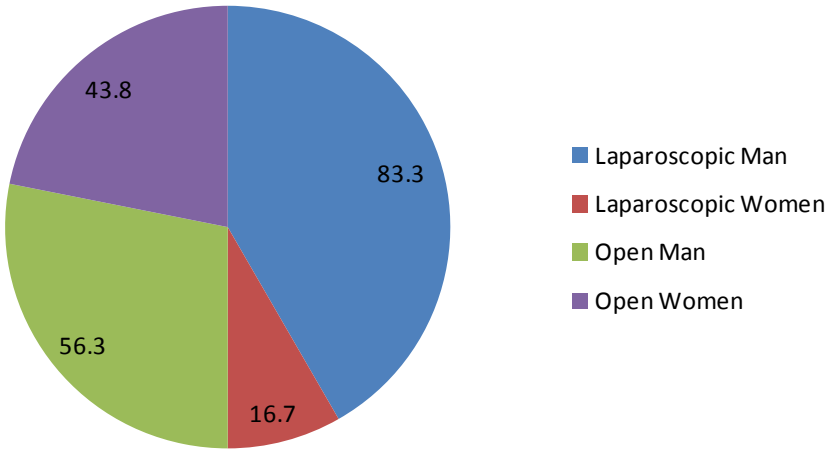

Figure 2. 1 Gender distribution across the two arms of the study

Of the 30 participants included in the laparoscopic arm, 45% presented with comorbidities, while 55% of patients in the open arm had pre-existing conditions. These were mainly medical in nature and the frequency of these reports did not differ significantly across the groups. Two patients in the open group were known with ischaemic heart disease, as opposed to only 1 patient in the laparoscopic group. One patient in each arm had suffered a prior cerebrovascular accident. The leading comorbidity was hypertension.

C4.2 Clinical Staging

On pre-operative screening (ultrasound), there was no difference in the prevalence of hydronephrosis. Every patient referred for radical cystectomy underwent an examination under anaesthesia and a transurethral resection of the bladder tumour. The EUA findings suggest that patients with higher stage disease were more likely to undergo open surgery as opposed to laparoscopic (59% having a palpable mass on EUA in open group versus 36% in laparoscopic group, p=0.08).

C4.3 Intra-operative Parameters

The duration of the two procedures differed significantly with a mean duration of 382 minutes for the laparoscopic intervention as opposed to a mean of 301 minutes for open surgery (Figure 2.2). The duration documented included extra-corporeal formation of an ileal conduit for all cases.

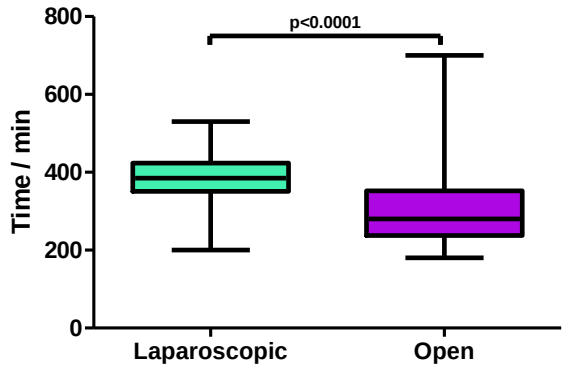

Figure 2. 2 Comparison of duration of laparoscopic and open surgery

A significantly higher volume of blood loss was encountered during the open intervention when compared to the laparoscopic one (1376ml for open versus 779ml for laparoscopic; Figure 2.3A). Of these patients, 38% of participants in the laparoscopic arm required transfusion compared to 64% of patients

undergoing open surgery (p=0.10). Briefly, the median number of units required for transfusion was 0 for the laparoscopic arm compared to 2 for the open arm (Figure 2.3B).

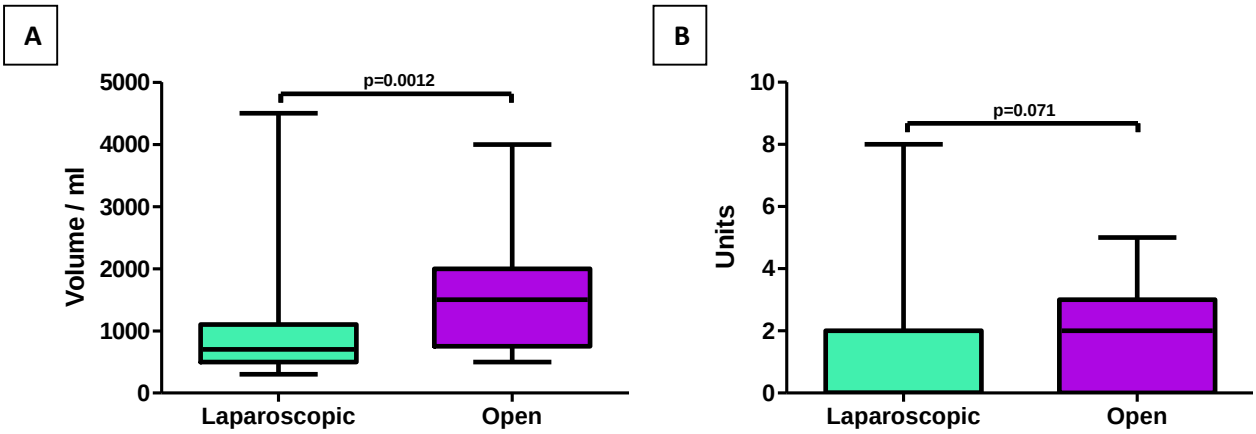

Figure 2. 3 A – Volume of blood loss during intervention. B – Units of blood required for transfusion.

When the proportion of bleeding (>1000ml blood loss) during intervention was compared across the two arms, it was observed that it was a significantly higher in the open arm compared to the laparoscopic group (70% vs. 29% respectively, p=0.05). Three patients experienced intra-operative complications that were not haemorrhagic in nature. A male participant from the laparoscopic group experienced acidosis secondary to hypoventilation and hypocarbia requiring post-operative intubation. The other participant, a male patient from the open group, experienced rectal injury requiring colostomy. One patient in the laparoscopic group also experienced a rectal injury, which was repaired primarily intra-operatively and required no further intervention. There was no

association between the detection of a mass at EUA and intra-operative bleeding. On clinical staging, it was observed that significantly more participants were staged as T1/T2 disease in the laparoscopic arm compared to the open arm (87% versus 43%, p<0.0001; Figure 2.4).

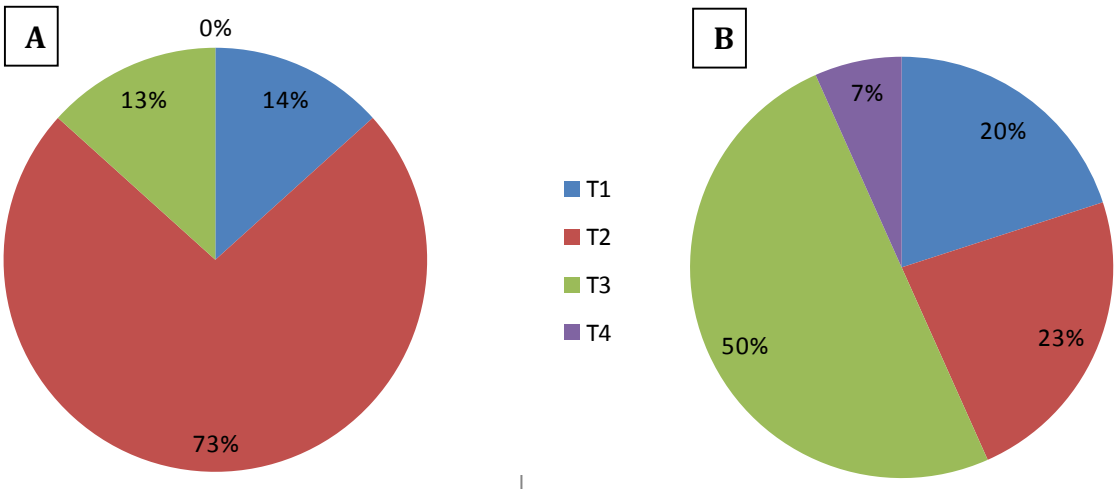

Figure 2. 4 A – Clinical staging for laparoscopic arm. B – Clinical staging for open arm

C4.4 Post-operative complications

More participants reported post-operative complications in the open group when compared to the laparoscopic group (61% for the open group compared to 43% for the laparoscopic group). This difference was however not statistically significant. This trend was confirmed when the degree of complications (Clavien) was compared between the two arms (Figure 2.5).

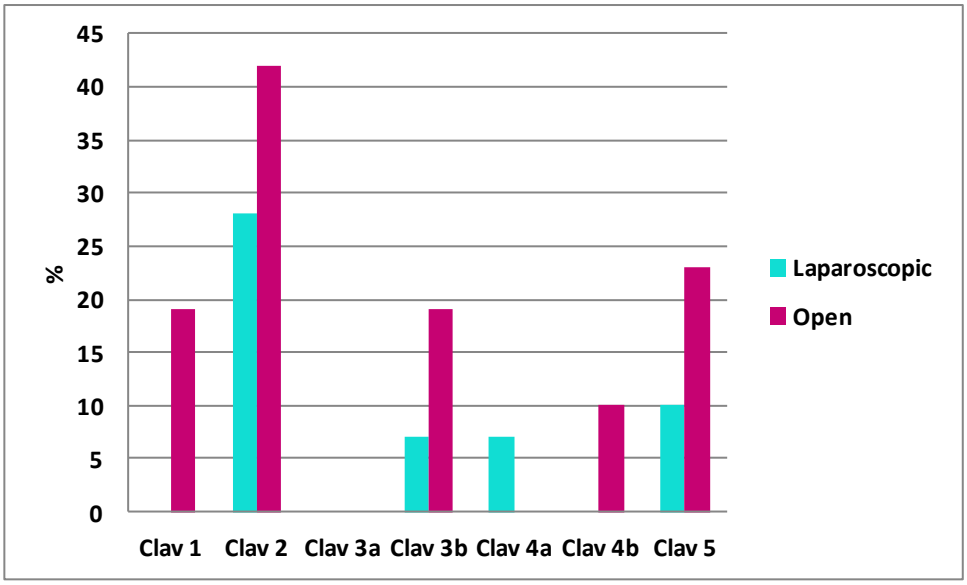

Figure 2. 5 Clavien classifications across two arms

Participants who have reported a past medical history were significantly more at risk (Risk Ratio of 1.6) of experiencing post-operative complications (48% in participants with no medical history as compared to 77% for participants with a past medical history; p=0.04). When investigating further into the nature of the post-operative complications, it was observed that the only complication that differed in proportion between the two arms were those related to wound complications (18% for laparoscopic group versus 44% for the open group; Figure 2.6). The predominant wound complication was sepsis while for the GIT complications, ileus was identified as being the main one.

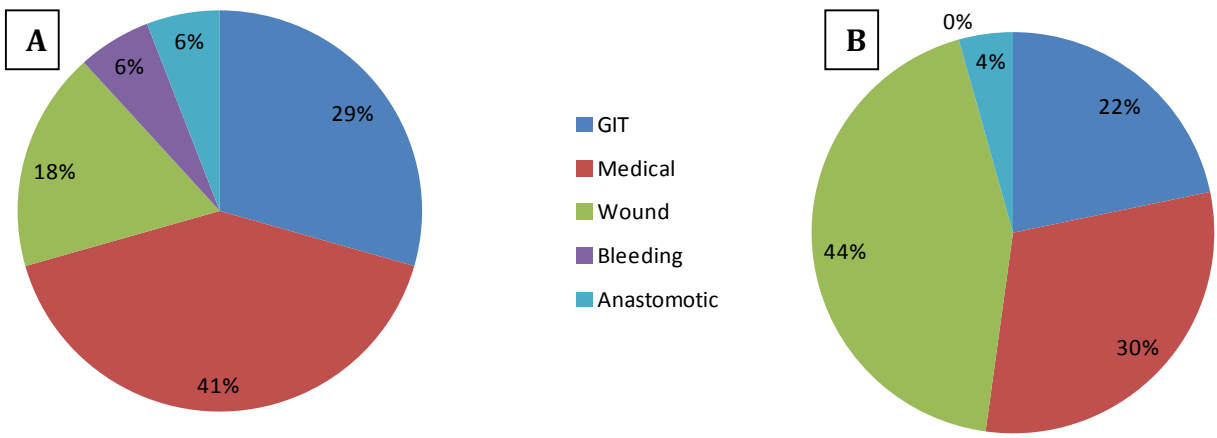

Figure 2. 6 Post-operative complications in A – laparoscopic group, B – open group

There was no association between age of participants and the experience of post-operative complications, and this was irrespective of the type of procedure undergone. Participants with a mass on EUA were more likely to experience overall post-operative complications (60%) when compared to participants with no mass detected on EUA (47%), although this is not the case for wound complications specifically. When looking at the prevalence of post-operative complications among participants who experienced intra-operative complications compared to those who did not experience intra-operative complications, no difference was observed. Following the difference in clinical staging found when comparing the 2 arms (Figure 2.4), the pathological staging of the two groups was compared and this revealed that no differences existed between the two arms (Figure 2.7).

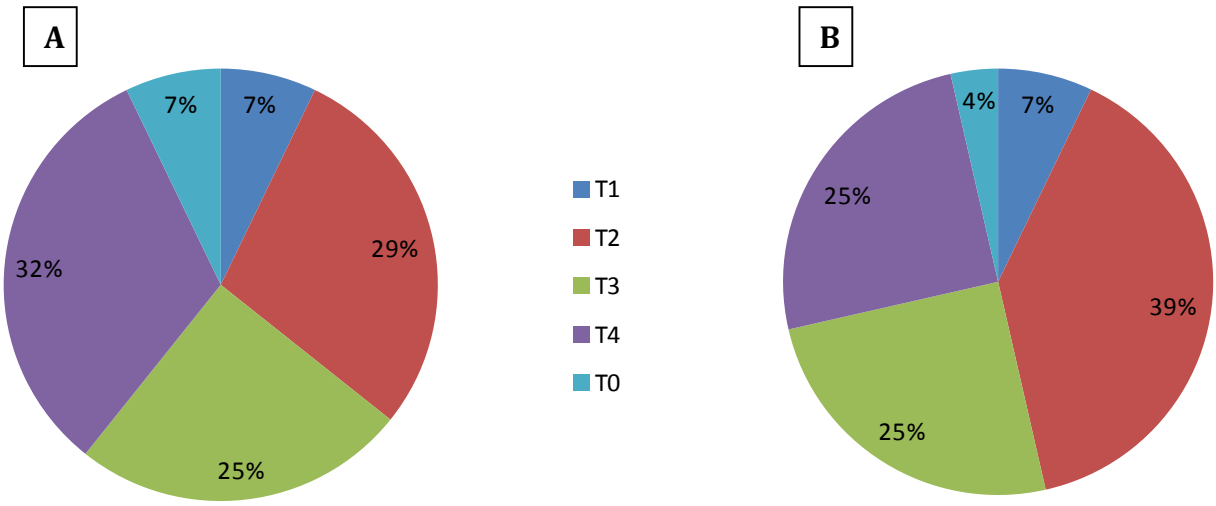

Figure 2. 7 Pathological staging for laparoscopic arm. B – Pathological staging for open arm

C4.5 Oncological outcomes

When comparing margin positivity in the two groups no difference was found (Figure 2.8). However, when comparing disease stage with respect to margin status, while no significant difference was found when looking at clinical staging, an overwhelming trend emerged for the pathological staging where all positive margins were only encountered for stages T3 and T4 disease.

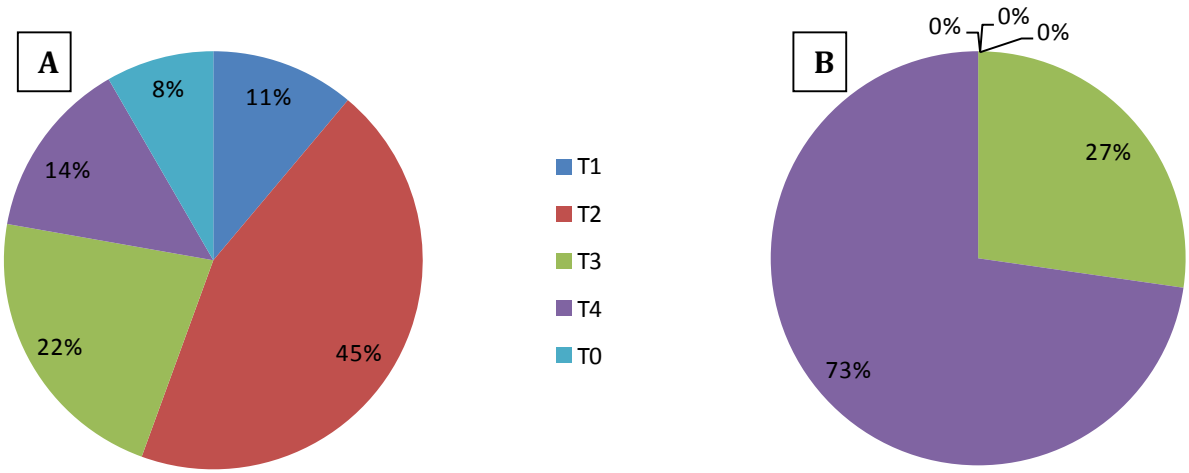

Figure 2. 8 A – Pathological staging for negative margin B – Pathological staging for positive margin

During surgery, irrespective of the technique used, no significant differences were observed across different pathological stages when comparing blood lost during the procedure (Figure 2.9).

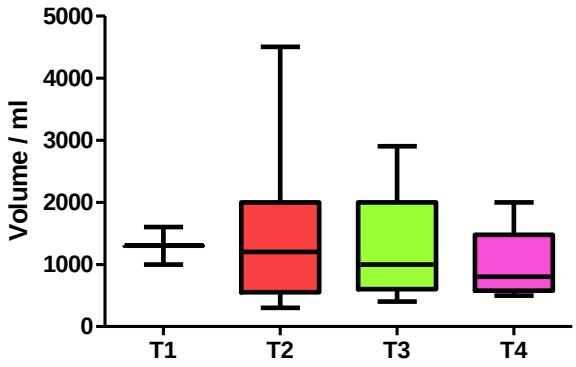

Figure 2. 9 Volume of blood loss across different pathological stages

A trend was observed when comparing the number of lymph nodes sampled using the two techniques and this trend was maintained irrespective of the area sampled, whereby a higher number of nodes was always sampled for laparoscopic technique in this study (Figure 2.10).

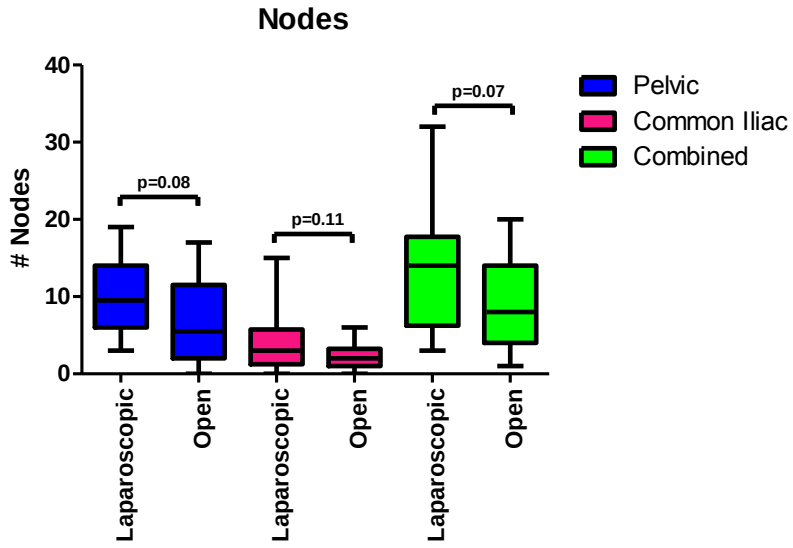

Figure 2. 10 Number of lymph nodes sampled during intervention

Early post-operative mortality rate (one month post-operatively) was comparable between the 2 arms (Figure 2.11), with 6 deaths in the open group and 5 deaths in the laparoscopic group. In terms of long-term survival outcomes, there is minimal difference between the 2 arms, with 56% overall survival in the open arm and 60% laparoscopic arm (Figure 2.11).

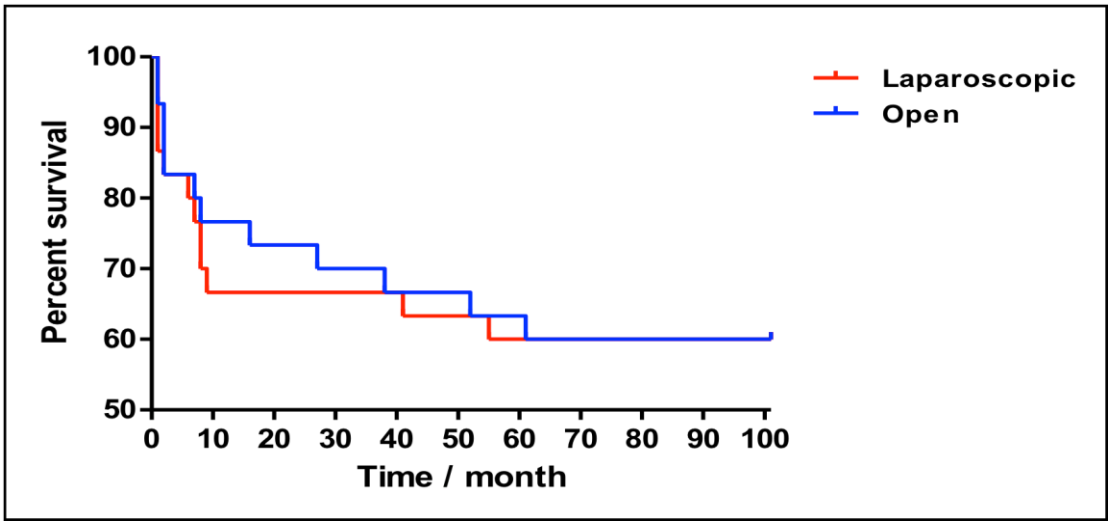

Figure 2. 11 Kaplan-Meier survival estimate comparing LRC to ORC

C5. DISCUSSION

Radical cystectomy is well established as the standard of care for bladder cancer, with open radical cystectomy as the gold standard (4,5). Minimally invasive techniques, including laparoscopic and robotic-assisted laparoscopic radical cystectomy are being described as feasible treatment options on a more regular basis (8,9,12). The proposed reasons for this trend towards minimally invasive surgery include decreased blood loss, with decreased post-operative complications and equivalent oncological outcomes (7,14).

Concerns surrounding laparoscopic radical cystectomy as a truly equivalent technique when compared to open radical cystectomy have been raised due to the lack of good quality evidence to support this (8,13). Comparisons involving unmatched cohorts in terms of the stage of the disease process pose the largest problem when studying the rate of complications, as well as oncological outcomes between the two groups (13).

Our data is comparable to that which has been previously published (13,14,15). We reviewed two age-matched groups of patients undergoing open and laparoscopic radical cystectomy performed by a single surgeon at Groote Schuur Hospital between January 2007 and February 2013. The demographics were similar between the 2 groups, except for the significantly higher proportion of men that underwent laparoscopic surgery when compared to the number of women undergoing LRC. Due to the retrospective nature of the study, it is difficult to assess the reasons for this difference. The difference does, however, compare with worldwide studies where more males than females underwent RC (6,7,9). There was no association found between age or gender and the prevalence of complications. There was also no statistical difference in the prevalence or types of pre-existing co-morbidities between the 2 groups. A difference in clinical staging was observed between the 2 arms, with patients undergoing open surgery being more likely to have a higher clinical stage (59% clinical T3 based on EUA in the open arm versus 36%; p=0.08). This stage bias has been described in multiple previous trials, and is one of the criticisms of studies claiming the superiority of minimally invasive surgery for bladder cancer (8,13).

In this study, we looked specifically at operative time, blood loss, intra- and post-operative complications, as well as oncological outcome (margin positivity and lymph node yield) in order to compare the two modalities.

Operative time was significantly less with open surgery, as has been seen in multiple previous studies (6,16-20). Bleeding was the commonest intra-operative complication. Blood loss and rates of transfusion were significantly lower in the laparoscopic group in our study. This is in line with the current data that is available when comparing these 2 modalities (16-21). The volume of blood loss was not increased by higher stage disease.

Selection bias has been stated to be significant when comparing patients undergoing laparoscopic versus open radical cystectomy. Our results were not dissimilar, in that significantly more patients undergoing laparoscopic RC were Stage T1/T2 disease. However, our findings suggest that this does not necessarily impact on outcomes. The blood loss seen across all participants was greater in the patients with T1/T2 disease as compared to patients with T3/T4 disease. There was no other association with bleeding that could be found to explain this phenomenon.

The predominant post-operative complication globally was ileus, while wound complications were most prevalent in the patients undergoing open RC. None of these differences were statistically significant. Studies from high-volume centres also found these differences, but in these studies, the differences were indeed found to be statistically significant (9,18-20,22). One patient in the open group developed an anastomotic stricture requiring revision of the ileal conduit. This patient also experienced a rectal injury requiring a diverting colostomy. One patient in the laparoscopic group required a relook laparotomy for an anastomotic leak.

The overall prevalence of post-operative complications in both groups in our study was higher in patients with a palpable mass on examination under anaesthesia, as is to be expected. There was also a statistically significant correlation between increased age and increased risk for post-operative complications. This reinforces the findings by Clarke *et al*, which showed that age impacts on post-operative outcomes (23).

The overall survival rates are comparable in the 2 groups. However, given the relatively short follow-up period and the small numbers of participants, it is not possible to accurately comment on overall survival. In terms of early post-operative mortality, it is apparent that the 2 groups have similar 1-month post-operative mortality rates. At least 50% of the patients that died from both groups had palliative cystectomies for advanced disease. Other causes of death included myocardial infarction in patients with pre-existing cardiac dysfunction, sudden death from presumed pulmonary emboli, as well as septic shock. All patients were managed as part of a multi-disciplinary team.

In terms of oncological outcomes, the surrogate markers that were used included positive surgical margins and lymph node yield. Positive margins are clearly undesirable due to incomplete oncological control, as well as the increased risk of early local recurrence. The number of lymph nodes sampled, irrespective of status, has been shown to impact on prognosis and overall survival (27,28). These markers have been used in multiple studies previously, and our findings are in line with those noted in these studies (24-28).

The majority of patients with positive margins had higher stage disease (T3/T4), although it was not found to be statistically significant. The type of surgery performed did not impact on this. In terms of lymph node yield, there was a definite trend towards a higher yield with laparoscopic RC, but it was also found to not be statistically significant. Multiple studies have found that the oncological outcomes using the above-mentioned criteria are similar between the 2 surgical modalities (7,8,9,15,16).

One limitation of this study is the retrospective nature of the study. Unfortunately a large number of folders were not accessible for various reasons. Due to this study design as well as the number of patients lost to follow up, it is not possible to comment adequately on survival outcomes, but from using the available data alone, it is apparent that these outcomes are not affected by the surgical modality used. Other limitations noted included a deficiency in standardised documentation of patient progress reports in terms of time to first meal and time to passing stool. Being a referral centre for advanced BC serving a wide population distribution, several patients were seen at outlying hospitals for follow-up, thereby affecting the number and exact timing of documentation of post-operative complications. Another limitation is the relatively small numbers of participants in the study. The discrepancy in follow-up times between the 2 groups, whereby the open group has a longer follow-up time when compared to the laparoscopic group, is an additional limitation. Also, due to the nature of the disease process, and the stage at which patients present in our setting, it is difficult to always compare these cases without confounding factors being present.

The benefit, however, of assessing data from a single surgeon eliminates possible differences in surgical technique that may be considered to be the cause of differences in complications and outcomes.

C6. CONCLUSION

With this study we are able to conclude that laparoscopic radical cystectomy is associated with a decreased need for blood transfusions. Open radical cystectomy is associated with shorter operative time. The two options are similar in terms of complication rates and oncological outcomes. Laparoscopic radical cystectomy is therefore a feasible option in our setting.

Given the number of patients that have subsequently undergone LRC at GSH since the completion of this study, it is clear that the number of potential participants for a future study may allow for more definitive statements to be made regarding which modality may provide better outcomes. The volume of RC being performed at GSH currently may allow for a prospective study design, thereby producing more robust evidence, which may guide practice in the future.

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PART: D APPENDICES

D1. RESEARCH ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

28 February 2013

HREC REF: 123/2013

Dr F Cassim
Urology
E-26
NGSH

Dear Dr Cassiem

PROJECT TITLE: RETROSPECTIVE REVIEW OF OPEN VERSUS LAPAROSCOPIC RADICAL CYSTECTOMY FOR THE TREATMENT OF BLADDER CANCER; COMPLICATIONS AND ONCOLOGICAL OUTCOME

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 28 February 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

pp T Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28 02 2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	2/5/16

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22/01/2015		
HREC REF Number	123/2013	Current Ethics Approval was granted until	28/02/2016
Protocol title	Retrospective Review of Open Versus Laparoscopic Radical Cystectomy for the Treatment of Bladder Cancer: Complications and Oncological Outcome		
Principal Investigator	FARZANA GASSIM		
Department / Office Internal Mail Address	farzanac@icloud.com		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		80
Total number of records or specimens collected, reviewed or stored since last progress report		—
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report	☐ Yes	☑ No

4. Signature

Signature of PI		Date	22/01/2015

(Note: Please complete the Closure form (FHS018) if the study is completed within the approval period)

D2. DATA COLLECTION SHEET

RECON CLINIC - UROLOGY

PRESENTING SYMPTOMS (duration)

CO-MORBIDITY

PREVIOUS OPERATIONS

DRUGS

ALLERGIES

SMOKING Hx (Pack years)

OTHER RISK FACTORS

INVESTIGATIONS

BLOODS

URINE: MC&S/CYTOLOGY

CHEST X-RAY

US

CT / MRI

IVP

BIOPSY (PIN/PNI)

OTHERS

DRE/ PV / EAU

CYSTOSCOPY

FINAL DIAGNOSIS

PRE-OP STAGE

NEO-ADJUVANT (CHEMO/RAD)

PERFORMANCE STATUS

OPERATION

DATE _____ OPEN/LAPAROSCOPIC _____

LYMPHNODE DISSECTION (Standard /extended)_____

DIVERSION TYPE _____ OPERATING TIME _____

CUTTING TIME _____ BLOOD LOSS _____ BLOOD TRANSFUSION_____

OTHERS _____

COMPLICATIONS

INTRA-OPERATIVE

POST-OPERATIVE

HISTOLOGY

DIAGNOSIS _____

GRADE _____ STAGE _____ LVI _____

PNI/OTHERS _____

MARGINS (Location) _____

LEFT PELVIC NODES (Numbers and status) _____

RIGHT PELVIC NODES (Numbers and status) _____

LEFT COMMON ILIAC NODES (Numbers and status) _____

RIGHT COMMON ILIAC NODES (Numbers and status) _____

URETERAL CUFF MARGINS _____

URETHRAL INVOLMENT _____

OTHERS _____

ADJUVANT TREATMENT (CHEMO/RADIOTHERAPY/HORMONES)

D3. RISK STRATIFICATION

Risk group stratification

Risk group stratification	**Characteristics**
Low-risk tumours	Primary, solitary, Ta, G1 (LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk)
High-risk tumours	Any of the following: • T1 tumour • G3 (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

D4. CHARLSON CO-MORBIDITY INDEX

Calculation of the Charlson Comorbidity Index

Number of points	**Conditions**
1 point	50-60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61-70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins
3 points	71-80 years Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours AIDS

Interpretation

1. Calculate Charlson Score or Index = i

    1. Add comorbidity score to age score

    2. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score.

2. Calculate Charlson Probability (10-year mortality)

    1. Calculate $Y = 10^{(i \times 0.9)}$

    2. Calculate $Z = 0.983Y$ (where Z is the 10-year survival)

D5. PATHOLOGICAL STAGING AND WHO GRADING

2009 TNM classification of urinary bladder cancer(2)

T - *Primary tumour*

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Ta Non-invasive papillary carcinoma

Tis Carcinoma in situ: 'flat tumour'

T1 Tumour invades subepithelial connective tissue

T2 Tumour invades muscle

- **T2a** Tumour invades superficial muscle (inner half)
- **T2b** Tumour invades deep muscle (outer half)

T3 Tumour invades perivesical tissue

- **T3a** Microscopically
- **T3b** Macroscopically (extravesical mass)

T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

- **T4a** Tumour invades prostate, uterus or vagina
- **T4b** Tumour invades pelvic wall or abdominal wall

N - *Lymph nodes*

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)

N2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)

N3 Metastasis in common iliac lymph node(s)

M - *Distant metastasis*

M0 No distant metastasis

M1 Distant metastasis

WHO grading in 1973 and in 2004

1973 WHO grading

Urothelial papilloma

Grade 1: well differentiated

Grade 2: moderately differentiated Grade 3: poorly differentiated

2004 WHO grading

Flat lesions

Hyperplasia (flat lesion without atypia or papillary aspects) Reactive atypia (flat lesion with atypia)

Atypia of unknown significance

Urothelial dysplasia

Urothelial CIS is always high-grade (HG)

Papillary lesions

Urothelial papilloma (completely benign lesion)

Papillary urothelial neoplasm of low malignant potential (PUNLMP) Low-grade (LG) papillary urothelial carcinoma

High-grade (HG) papillary urothelial carcinoma

D6. PROGNOSTIC DATA

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
>8	6	3
Tumour diameter		
< 3 cm	0	0
> 3 cm	3	3
Prior recurrence rate		
Primary	0	0
< 1 recurrence/year	2	2
> 1 recurrence/year	4	2

NON-MUSCLE-INVASIVE BLADDER CANCER (TA, T1 AND CIS)

Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0

Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Probability of recurrence and disease progression according to total score

Recurrence score	**Probability of recurrence at 1 year**		**Probability of recurrence at 5 years**	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	**Probability of progression at 1 year**		**Probability of progression at 5 years**	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)

7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

D7. CLAVIEN-DINDO CLASSIFICATION

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are as follows: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

D8. AUTHOR GUIDELINES FROM JOURNAL OF UROLOGY

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2. Justification of sample size			
3. Participation rate if patients declined study			
4. Inclusion/exclusion criteria			
5. Source and initial number of patients			
6. Randomization method			
7. Blinding techniques			
8. Accrual dates			
9. Identification of transformations or categorization of variables, if done			
10. Justification if outliers were omitted from analysis			
11. Reasons for and analysis of patients withdrawn or protocol deviations			
12. Reporting of time between randomization and start of treatment			
13. Number of subjects who completed treatment(s)			
14. Treatment of missing values			
15. Frequency of side effects			
16. Identification of statistical software			
17. Justification if 1-tailed statistical tests are used			
18. Verification of statistical test assumptions			
19. Identification of all statistical tests with description or references			
20. Median followup time for censored patients			
21. Lost to followup expressed as the proportion of censored patients not evaluated during a specified time			
22. Reporting of the number of patients at risk over time			
23. Confidence intervals for effect sizes			

Recommendations

1. All subgroup analyses and covariate inclusions should be motivated prior to the Results section. Hypotheses which were not established prior to initial analyses should be clearly identified.

2. Variables should be clearly defined, such as specific assays, references for staging, references for validation of survey instruments, etc.

3. Treatment regimens should be described well enough for another study to replicate.

4. It should be clear which statistical test is associated with each p value reported.

5. Rarely used statistical techniques should be described.

6. Medians and percentiles (such as quartiles) are preferred over means and standard deviations (or standard errors) when analyzing asymmetric data, especially when nonparametric statistics are calculated.

7. Fractions (eg, 5/10) should accompany percentages.

8. In randomized clinical trials, consider reporting separate analyses with confounding variables included.

9. If sample sizes differ between groups when patients are randomized, reasons should be provided.

10. Report median survival (using Kaplan-Meier) rather than mean survival if any data are censored.

11. Comparing survival functions (eg, with a log rank test) is more efficient than analyzing particular time estimates (eg, 5-year survival).

12. Use appropriate figures. Scatter plots are useful for illustrating important correlations between variables. If subjects are repeated in a figure (eg, over time), an individual's set of points should be joined with line segments. Different symbols should be used when points are stacked on top of each other. Illustrations of regression lines should be overlaid on raw data. Regression lines should not extend beyond the range of the predictor variable.

13. Confidence intervals are more appropriate than standard errors for comparison of groups.

14. Use appropriate tables. Coefficients and standard errors are useful for interpreting regression predictors. One significant figure beyond the level measured is sufficient for means, standard deviations, standard errors, etc. One decimal place for percentages greater than 1% is sufficient; no decimal

places if the sample size is less than 100. Two significant figures for test statistics and p values are sufficient. Means should generally be accompanied by some measure of their uncertainty, such as confidence intervals or standard errors.

15. Confidence intervals should be reported when possible.

16. When a statistical hypothesis test is not rejected, the actual p value (eg, 0.07) should be reported (if known) rather than omitted or reported as p >0.05.

17. Pay close attention to wording. The word 'correlation' is generally reserved for computing correlation coefficients. The word 'association' is usually preferred. Statistical tests can be nonparametric; data cannot. Studies with negative findings (ie, no difference) may be the result of low statistical power (eg, small sample size), rather than absence of a difference, and this limitation should be made clear. Trends that are not statistically significant should not be identified. A p value is the probability of observing data as extreme as those reported if the null hypothesis of no difference is true. A p value is not the probability of no real effect, nor is it necessarily related to the clinical importance.

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- 3. Manuscript word count is provided.
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- 5. Manuscript does not exceed 3,000 words for Research Article.

• 6. Manuscript does not exceed 500 words for Letter to the Editor.

• 7. Manuscript does not exceed 1,000 words for Opposing Views.

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• 14. Registration number of clinical trial provided.

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• 24. Name of validated system used for reporting complications/outcomes provided.

Updated November 2014