

University of Cape Town

Retrospective Review of Radical Cystectomies at GSH 1993-2007

By

Prenevin Govender

Student number GVNPRE007

A MINI DISSERTATION SUBMITTED
IN FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE
MMed (UROLOGY)

Supervisor: Dr Dick Barnes

Division of Urology

Groote Schuur Hospital

Faculty of Health Science

University of Cape Town

Date of re-submission May 2010

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Acknowledgements

Thank you to Dr Dick Barnes for supervising me in this project. His ideas, insight and suggestions have been invaluable. A special word of thanks must go to Diederick Duijewis who spent many hours helping me with the data capture.

Further gratitude is expressed to the following people:

Mrs Adri Winckler (Post graduate office)

Mr N Weeder (Records, GSH)

Gina and Rachmat (Microfilms, GSH)

Mrs L Burke (Departmental Secretary, Division of Urology, GSH)

Mrs Mohamed (Department of Radio-Oncology)

Mrs Petersen (Stomatherapy)

Mr Henri Carrara (Biostatistician)

List of Acronyms and abbreviations

TCC- Transitional cell carcinoma

SCC- Squamous cell carcinoma

TNM- Tumour, node, metastasis

TUR- Transurethral resection

CIS- Carcinoma-in-situ

BCG- Bacillus Calmette Guerin

PLND- Pelvic lymph node dissection

ABSTRACT

Objective

To look at the epidemiology of patients needing this procedure, clinical presentation and investigation, pathology, complications related to the procedure, adjuvant and neoadjuvant treatment, and survival.

Method

This is a retrospective review of radical cystectomies done at Groote Schuur Hospital from October 1993 to March 2007. Surgical Research Committee and Ethics committee approval was obtained. 105 Patient case notes in folders and on microfilms were reviewed. In addition, records kept by the stomatherapy and oncology departments were examined. Patients and their family were contacted telephonically, in instances where the information in the folder was lacking. The vast majority (93/105 or 89%) of patients had Transitional cell carcinoma (TCC). 5/105 Patients had Adenocarcinoma (5%) and 3/105 patients had Squamous cell carcinoma (3%). For the purposes of this study, I will be looking specifically at the group of patients who had TCC.

Results

The mean age of patients undergoing this procedure, was 63 years (Range 45-78 yrs). The median age was 66 years. The majority of patients were Coloured (64/93 or 69%). Very few Black patients underwent this procedure (4/93 or 4%). The majority of patients were male (77/93 or 83%), smokers (69/93 or 74%) and presented initially with macroscopic haematuria (77/93 or 83%). 80/93 (86%) Patients had high grade disease. On pathological staging of these tumours (TCC), 45/93 (48%) had extravesical disease (pT3A or greater). It must be noted that in 6/93 (6%) patients, no comment is made on the pathological stage. 10/93 (11%) Patients had radical cystectomies for clinically non-muscle invasive TCC. Of these patients, 5/10 (50%) had muscle-invasive TCC on pathological staging, and 4/10 had extravesical disease (pT3A or greater). 20/93 (22%) patients with TCC had lymph nodes

positive for malignancy. 12/77 (16%) Of men who had radical cystectomies, had associated incidental prostate cancer. Intra-operative complications were primarily related to massive bleeding (2/93 or 2%), stoma-related difficulties (2/93 or 2%) and rectal injury (2/93 or 2%). Early post-operative complications were varied, but included wound dehiscence (8/93 or 9%), upper GI bleed (3/93 or 3%), DVT (3/93 or 3%), ureteric anastomotic leaks (2/93 or 2%) and stoma-related complications (1/93 or 1%). In addition, 2 rectal injuries manifested as enteric fistula in the first week post-operatively. Most late post-operative complications were related to adhesive small bowel obstruction (4/93 or 4%) and local recurrence (2/93 had pelvic recurrence, 2/77 men had urethral recurrence and 1/16 females had a vaginal recurrence). One ureteric anastomotic stricture was seen (1/93 or 1%). 2/93 (2%) of patients received neoadjuvant chemotherapy prior to radical cystectomy and 8/93 (9%) patients received adjuvant chemotherapy. 5/93 (5%) patients received radical radiotherapy as primary treatment, but then required salvage cystectomy at a later date. 51/93 (55%) Deaths have been documented. 22/93 (24%) Patients are known to still be alive. The following statistics apply to the 73/93 patients whose status is definitively known. The mean survival is 36 months (3 years). The median survival is 32 months (2.67 years).

Conclusions

Patients requiring this procedure are predominantly elderly coloured or white males. Very few black patients and a minority of females required radical cystectomy. A positive smoking history was a very common association. The vast majority of patients present with macroscopic haematuria. Our results show, there is a risk of understaging the patient (5/10 or 50% of patients with presumed non-muscle invasive disease had muscle invasion on pathological staging). Our series of patients with TCC was marked by a high rate of extravesical disease (45/93 or 48%), and 20/93 (22%) had positive lymph nodes. This is strong evidence that we are not operating on our patients early enough. Future goals must include attempts at earlier detection.

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CHAPTER 1: LITERATURE REVIEW

Radical cystectomy is the standard of care for patients with muscle-invasive bladder cancer in the absence of metastatic disease. It includes prostatectomy in the male patient, and anterior exenteration in the female, coupled with pelvic lymphadenectomy. (1)

1. Epidemiology of Bladder cancer

63210 new cases of bladder cancer were diagnosed in the United States in 2005. It is almost three times more common in men than women. In men, it is the fourth most common cancer after prostate, lung and colorectal cancers. In women, it is the ninth most common cancer. There were approximately 13180 bladder cancer deaths in 2005 in the United States. They account for 3% of all cancer deaths in men and 1.5% in women. (2)

Bladder cancer can occur at any age. However, it is generally a disease of middle-aged and elderly people. The median age at diagnosis is 69 years in males, and 71 years in females. (3)

2. Aetiology and Risk Factors for Bladder Cancer

Factors known to be causally related to the development and progression of transitional cell carcinoma include:

1. Cigarette Smoking
2. Occupational Exposure Risk Factors
 - A. Aniline dyes used in Clothing Industry
 - B. Acrolein used in Rubber and Textile Industries
 - C. Combustion gases and soot from coal
3. Analgesic abuse

4. Pelvic Irradiation
5. Cyclophosphamide (1)

Squamous cell carcinoma has been related to chronic cystitis and other infections, especially Schistosomiasis. (1)

Adenocarcinoma may be related to the urachus, or may be a secondary originating from the gastrointestinal tract. (1)

Genes known to be implicated in the development of transitional cell carcinoma include:

- P21 RAS oncogene (Chromosome 9p)
- TP53 (Chromosome 17p)
- Retinoblastoma gene (Chromosome 13q) (1)

Cigarette smoking

Cigarette smokers have up to a four-fold higher incidence of bladder cancer than do people who have never smoked. (14, 15) This risk correlates with the number of cigarettes smoked, the duration of smoking and the degree of inhalation of smoke. (21) Former smokers have a reduced incidence of bladder cancer compared with active smokers. (16) However, it takes nearly 20 years to reduce this risk down to baseline. (21) Other forms of tobacco use are associated with only a slightly higher risk for bladder cancer. (15) The evidence regarding increased risk with passive smoking is less clear. It has been shown, however, that spouses of long-term cigarette smokers are at increased risk. (17) Various compounds have been looked at as potentially being responsible for the increased risk of bladder cancer. These include, nitrosamines, 2-naphthylamine and 4-aminobiphenyl. In addition, increased urinary tryptophan metabolites have been demonstrated in cigarette smokers. (40) There is very variable risk of developing bladder cancer in patients with seemingly similar exposure. Much attention has been focused on why this may be the case. 4-Aminobiphenyl has specifically been looked at. Acetylation of

this compound initiates a detoxifying pathway. (21) It has been shown that slow acetylators are more susceptible to development of bladder cancer. (41) Further study has been directed at the enzymes N-Acetyltransferase 1 and 2. Investigators have confirmed that in bladder cancer patients, slow acetylator genotypes predominated. (42, 43) The glutathione transferases are another enzyme family important in the detoxification of carcinogens. Decreased activity of these enzymes is associated with an increased risk of bladder cancer. (44) The cytochrome P450 1A2 enzyme demethylates aromatic amines resulting in activation of potential carcinogens. Excessive inducibility and activity of this enzyme may predispose to greater carcinogen activation and thus increased risk of bladder cancer. (45)

3. Pathology

Histological subtypes of Urothelial Carcinomas include:

1. Transitional Cell Carcinoma (TCC)
 - Compromises more than 90% of cases
2. Squamous Cell Carcinoma (SCC)
3. Adenocarcinoma

TCC is graded as:

- Papillary urothelial tumours of low malignant potential
- Low grade urothelial carcinoma
- High grade urothelial carcinoma (4)

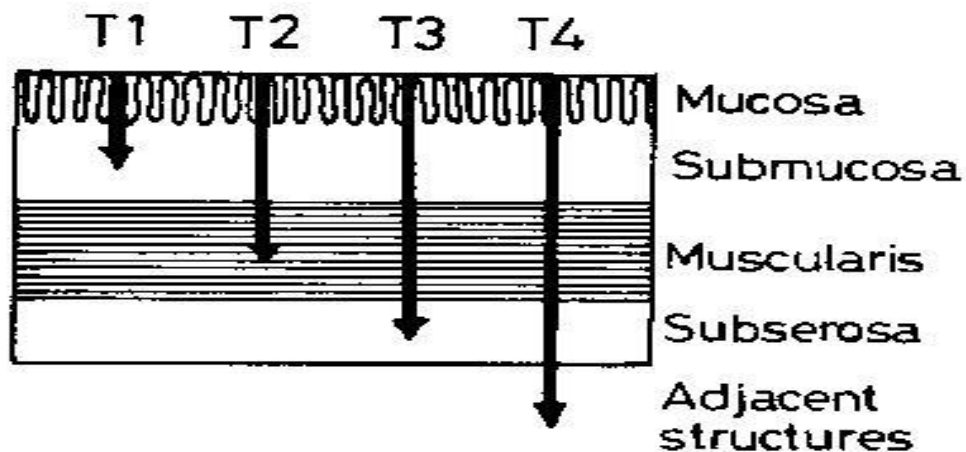
Staging is done according to the TNM classification. Muscle-invasive bladder cancer is T2 and higher.

TABLE 1: 1997 AJCC-UICC TNM Staging

Ta	Papillary, epithelium confined
Tis	Flat carcinoma in situ
T1	Lamina propria invasion
T2a	Superficial muscularis propria invasion
T2b	Deep muscularis propria invasion
T3a	Microscopic extension into perivesical fat
T3b	Macroscopic extension into perivesical fat
T4a	Cancer invading pelvic viscera (e.g., prostatic stroma, vaginal wall, rectum, uterus)
T4b	Extension to pelvic sidewalls, abdominal walls, or bony pelvis
N0	No histologic pelvic node metastases
N1	Single positive node ≤ 2 cm in diameter, below common iliacs
N2	Single positive node 2-5 cm in greatest diameter or multiple positive nodes
N3	Positive nodes >5 cm in diameter
Nx	Nodal status unknown
M0	No distant metastases
M1	Distant metastases documented
Mx	Distant metastases status uncertain

(5)

FIGURE 1: Diagrammatic illustration of Pathological stage



(39)

4. Clinical Presentation

Painless haematuria is the most common presenting symptom. It occurs in about 85% of patients. (6) Some patients may present with frequency, urgency and dysuria. With this history, carcinoma-in-situ should be looked for as a possible cause. Rarer presentations may include:

- Flank pain from ureteric obstruction
- Pelvic mass
- Lower extremity oedema
- Symptoms of advanced disease e.g. weight loss
- Symptoms of metastases e.g. bone pain

5. Investigation

- a. Ultrasound of the kidneys, ureter and bladder or an Intravenous Pyelogram
- b. Flexible cystoscopy
- c. Urine cytology

6. Clinical Staging

- a. Bimanual examination under anaesthesia
 - If tumour is palpable on bimanual examination before resection, it is usually infiltrating into the deep muscle or perivesical tissues (21)
 - If a mass is present after trans-urethral resection, the chance of extravesical extension is considerable. (21)
 - The teaching at our institution is:
 - No mass: T0-T1
 - Thickening: T2a

Mobile mass: T2b,T3a or b

Fixed mass: T4b

(46)

b. TUR

- Tumour resected with deep biopsies of muscle

7. Management

A. Radical Cystectomy

The gold standard of treatment for muscle-invasive bladder, in the absence of metastases, is radical cystectomy. This includes bilateral pelvic lymphadenectomy. (1) Survival after radical cystectomy is related to pathological stage as seen in Table 2.

TABLE 2: Percentage Disease-Specific Survival by Pathologic Stage after Radical Cystectomy with and without Pelvic Lymph Node Metastasis: Selected Series (1980-1999)

<i>Selected Series</i>	<i>No. of Patients</i>	<i>P2</i>	<i>P3</i>	<i>P4a</i>	<i>N+</i>
Mathur	58	72	40	29	NA
Montie	99	62	57	75	NA
Giuliani	202	75	19	0	NA
Skinner	197	64	44	36	44
Malkowicz	160	76	NA	NA	NA
Wishnow	71	~80	NA	NA	NA
Waehre	227	79	36	29	22
Schoenberg	101	84	56	NA	48
Ghoneim	1026	66	31	19	23
Bassi	369	63	33	28	15

(1)

Patients with organ-confined, muscle-invasive bladder cancer (pT2) had better long-term outcomes than patients with disease extending beyond the bladder (pT3 and 4a).

There are also indications for radical cystectomy in non-muscle invasive bladder cancer. The rationale behind this is as follows:

- Despite local therapy, many cases of high-grade non-muscle invasive bladder cancer progress to invasion and thus increased risk of death (8)
- In Carcinoma-in-situ (CIS) patients who fail BCG therapy, there is a 50% chance of disease progression and potential for disease specific mortality (9)
- Early (<3 months) failure for T1 tumours after BCG therapy is associated with an 82% progression rate (10)

- Each occurrence of T1 tumour is associated with a 5-10% chance of metastasis (11)

These arguments suggest a role for early radical cystectomy.

B. Pelvic Lymphadenectomy

The rationale of doing a pelvic lymphadenectomy is that it provides:

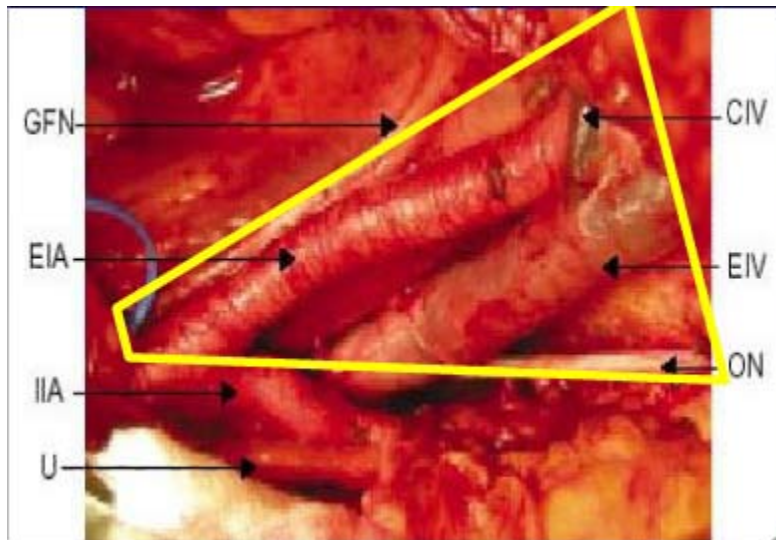
- accurate pathological staging
- prognostic information
- patients who may benefit from adjuvant chemotherapy

In addition, it doesn't significantly increase the complication rate of radical cystectomy. The risk of developing pelvic lymph node metastases is related to the pathological stage of disease. With pT2, the risk is 10-30%, while pT3 disease is associated with a risk of 30-65%. The obturator and external iliac nodes are the groups most commonly involved, with the common iliac and presacral nodes less commonly involved. (34)

The anatomical limits of the standard pelvic lymph node dissection (PLND) are as follows:

- Lateral limit- Genitofemoral nerve
- Cephalad limit- External iliac artery and vein dissected up to the bifurcation of the common iliac artery
- Caudal limit- Endopelvic fascia
- Medial limit- Bladder

FIGURE 2: Standard Pelvic Lymph Node Dissection



GFN- Genitofemoral nerve

EIA- External iliac artery

IIA- Internal iliac artery

U- Ureter

CIV- Circumflex iliac vein

EIV- External iliac vein

ON- Obturator nerve

(47)

Current research suggests that an extended PLND improves survival in both lymph node-negative and limited lymph node metastatic disease. (36) An extended PLND includes tissue along the common iliacs up to the aortic bifurcation. It also includes pre-sacral, distal para-aortic and para-caval lymph nodes. (35)

FIGURE 3: Before extended pelvic lymph node dissection



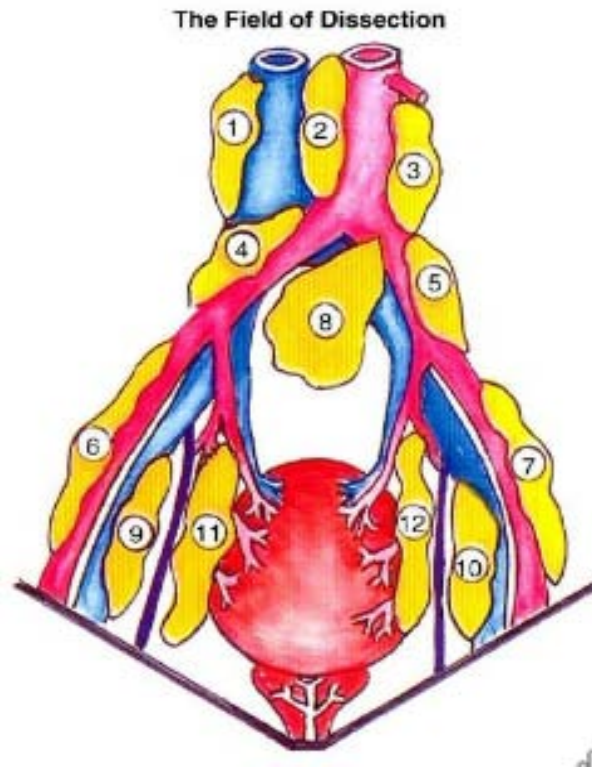
(39)

FIGURE 4: After extended pelvic lymph node dissection



(39)

FIGURE 5: Field of dissection for an extended pelvic lymph node dissection

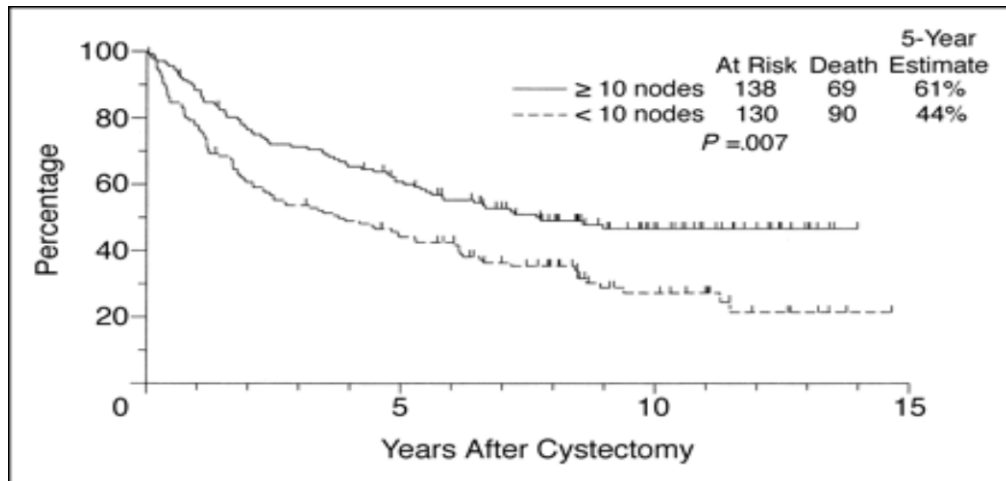


- 1-paracaval nodes
- 2-interaortocaval nodes
- 3-para-aortic nodes
- 4-right common iliac nodes
- 5-left common iliac nodes
- 6-right external iliac nodes
- 7-left external iliac nodes
- 8-presacral nodes
- 9-right obturator nodes
- 10-left obturator nodes
- 11-right internal iliac nodes
- 12-left internal iliac nodes

(47)

It has been shown that the lymph node yield can be increased by dissecting and submitting separate lymph node packets. (37) This is important as it has been shown that the number of lymph nodes removed has prognostic value i.e. the more nodes removed, the better the prognosis. (38)

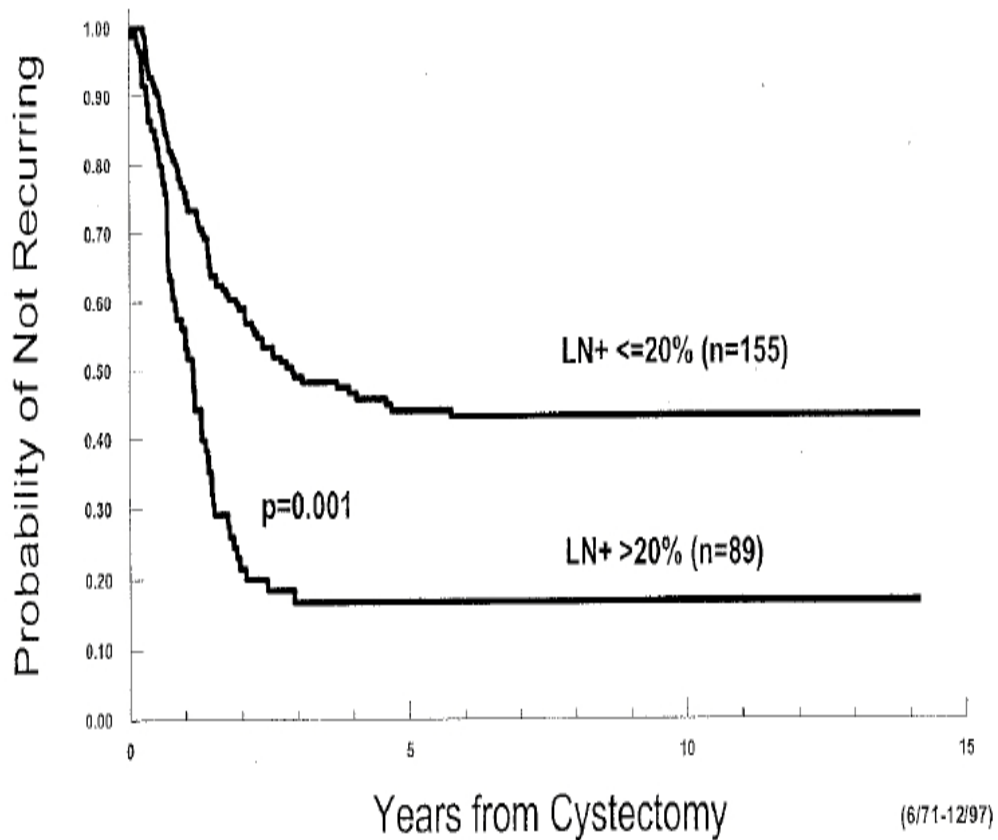
FIGURE 6: Survival related to number of lymph nodes removed



(48)

The number of positive lymph nodes in the specimen also has prognostic value. More than 8 positive nodes was associated with a 10 year recurrence-free survival of 10% vs 8 or fewer nodes which was associated with a 40% survival. (32) This has led on to the concept of lymph node density, which is the total number of positive nodes divided by the total number of extracted nodes. As seen in figure 8 below, a lymph node density of 20% or less was associated with a 43% 10yr recurrence-free survival whereas a density of greater than 20% was associated with only a 17% survival. (32)

FIGURE 7: Recurrence-free survival in 244 patients with lymph node positive disease stratified by lymph node density (20% or less vs greater than 20%)



(32)

C. Neoadjuvant Chemotherapy

This approach involves administration of chemotherapy prior to radical cystectomy. Advantages include:

- Demonstration of chemosensitivity
- Potential downstaging of the tumour
- Treatment of micrometastases while patient is not debilitated by major surgery.

There are, however, disadvantages to this approach. These include:

- Reliance primarily on clinical as opposed to pathological staging, which can result in both under- and over-treatment
- Delay in undergoing radical cystectomy > 3 months associated with worse prognosis (1)

TABLE 3: Stratified and unstratified survival analysis of patients who received neoadjuvant M-VAC + cystectomy vs cystectomy alone

Variable	Median Survival		P Value [‡]
	M-VAC and Cystectomy	Cystectomy Alone	
	<i>months</i>		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75	
T3 or T4a	65	24	

[‡] There were 90 deaths in the combination-therapy group after a median follow-up of 8.7 years. There were 100 deaths in the cystectomy group after a median follow-up of 8.4 years. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

[†] The log-rank test was used to calculate P values.

(13)

Current evidence suggests that neoadjuvant chemotherapy + cystectomy provides better long term survival than cystectomy alone. This was demonstrated in a landmark study by Vogelzang (as shown in Table 3), where neoadjuvant MVAC was used and compared with cystectomy alone.

D. Adjuvant Chemotherapy

This approach is used in patients with evidence of advanced disease (either presence of positive lymph nodes or locally advanced disease) following radical cystectomy and pelvic lymphadenectomy. The chemotherapy is given so as to reduce the risk of local recurrence or distant metastatic relapse. As these patients have been pathologically staged, there is less likelihood of over-treating them (As compared to patients who have been clinically staged).

Disadvantages of this approach include:

- Delay in administration of systemic chemotherapy (due to recovery time required following cystectomy)
- Difficulty in assessing tumour response, in the absence of radiographically visible disease
- Patients may not be fit for chemotherapy because of major surgery (1).

The evidence suggests that with locoregional disease and pelvic lymph node involvement, cisplatin-based adjuvant chemotherapy may provide a survival advantage. (12)

E. Radiation Therapy

Preoperative radiotherapy was commonly performed prior to radical cystectomy until the 1980's. The rationale behind this approach was that it was thought to treat local micrometastases. Randomized data suggests that in patients with T3 disease, local control may be improved by pre-operative radiotherapy, but a survival advantage has been difficult to demonstrate. (1)

CHAPTER 2: AIM OF STUDY

To do a retrospective audit of the radical cystectomies done at Groote Schuur Hospital between October 1993 and March 2007, looking specifically at:

1. The spectrum of age, gender and race of patients requiring this procedure
2. Number of smokers vs non-smokers who required this procedure.
3. Clinical presentation initially
4. Type of imaging
 - Presence or absence of Upper tract dilatation
 - Presence of concurrent Upper tract tumours
 - Diagnosis of bladder lesion
5. Pathology
 - Clinical vs Pathological staging
 - Ureteric involvement
 - Lymph node involvement
 - Upper tract cancer
 - Incidence of associated Prostate cancer
6. Incidence and spectrum of complications related to procedure
 - Intra-operative
 - Post-operative
 - Early
 - Late
7. Patients receiving chemotherapy (Number & Indications)
 - Neoadjuvant
 - Adjuvant
8. Patients receiving radiotherapy
 - As primary treatment, and then requiring salvage cystectomy
 - Post-operatively
9. Mortality and Survival

CHAPTER 3: MATERIALS AND METHODS

Surgical and Ethics committee approval was obtained in writing. 105 Patient case notes were reviewed. Both patient folders and microfilms were used from the Medical Records department at Groote Schuur. Data was obtained predominantly from the Urology folder within the patient folder, but the patient registration form, anaesthetic notes and pathology result sheet were also used. This data was captured in Microsoft Excel. All the relevant data on some patients could not be obtained from the folder. The pathology department aided us in obtaining some, but not all the data needed. In the results section, patient numbers will be indicated in brackets (n). Demographic data was recorded as per the Groote Schuur classification noted in the patient registration form. Information was supplemented by the Radio-Oncology folders and Stomatherapy records. Where necessary, patients and their family were contacted telephonically in order to gather further information.

CHAPTER 4: RESULTS

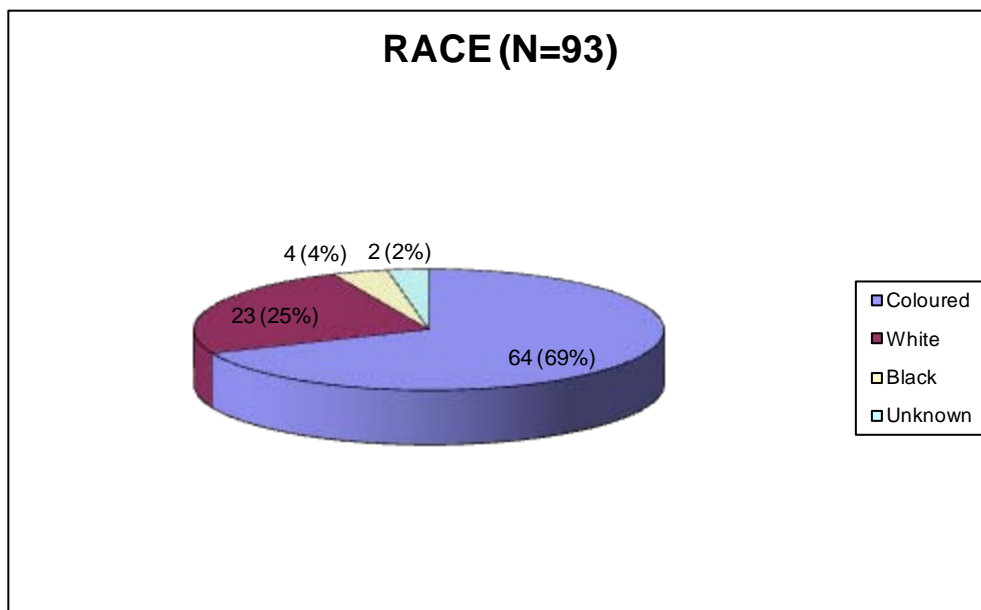
For the purposes of this study, I will look specifically at the cohort of patients who had radical cystectomy for TCC (93/105 patients or 89%). There were 5/105 (5%) patients who had Adenocarcinoma, 4/105 (4%) patients had Squamous cell carcinoma, and in 2/105 (2%) patients, it was not documented what histological type was present.

1. Socio-economic data

The mean age of patients undergoing this procedure was 63 yrs (Range 45-78 yrs). The median age was 66 years.

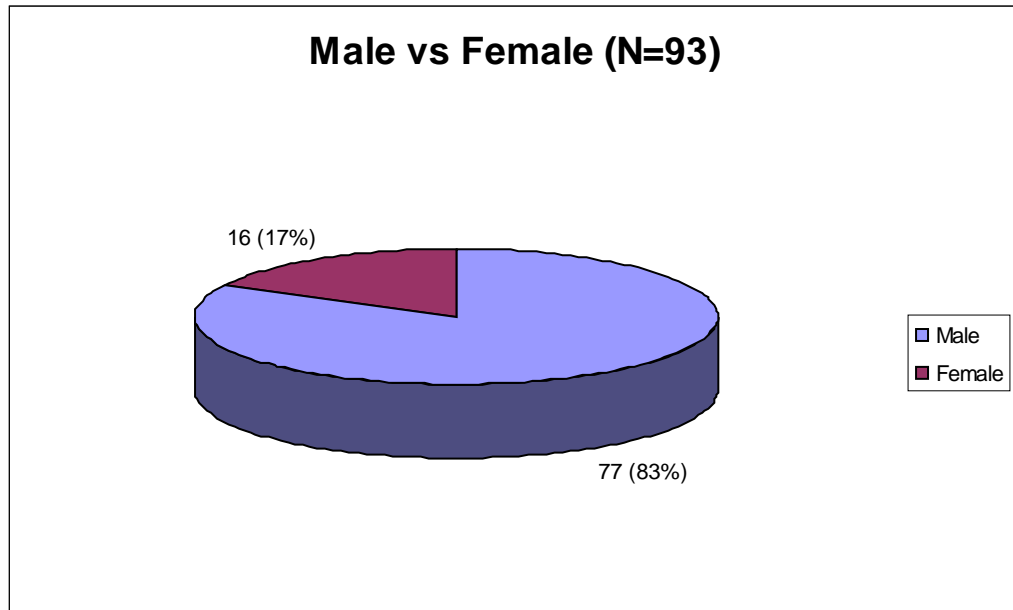
The majority of patients were Coloured (64/93 or 69%). 23/93 (25%) Patients were White. Only 4/93 (4%) patients who underwent this procedure were Black. In 2/93 (2%) patients, a race classification was not applied. Racial classification was according to what was applied by Groote Schuur, and was taken directly from the hospital folder

FIGURE 9: Racial composition of study group



The majority 77/93 (83%) of patients were male. 16/93 (17%) Patients were female.

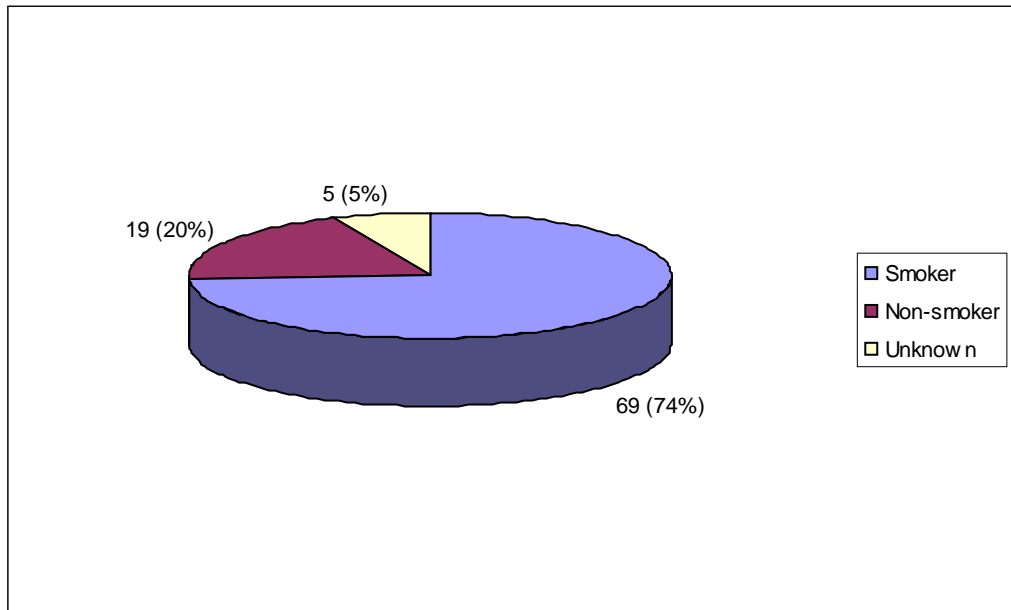
FIGURE 10: Gender composition of study group



2. Smoking

The majority of patients who underwent radical cystectomy for TCC, were smokers 69/93 (74%) . In 5/93 (5%) patients, it was not documented whether they were smokers or not. For the purposes of this study, someone who was an ex-smoker for greater than 20 years was categorised as a non-smoker. In patients who were recorded as ex-smokers, but no time period was specified, they were categorised as smokers.

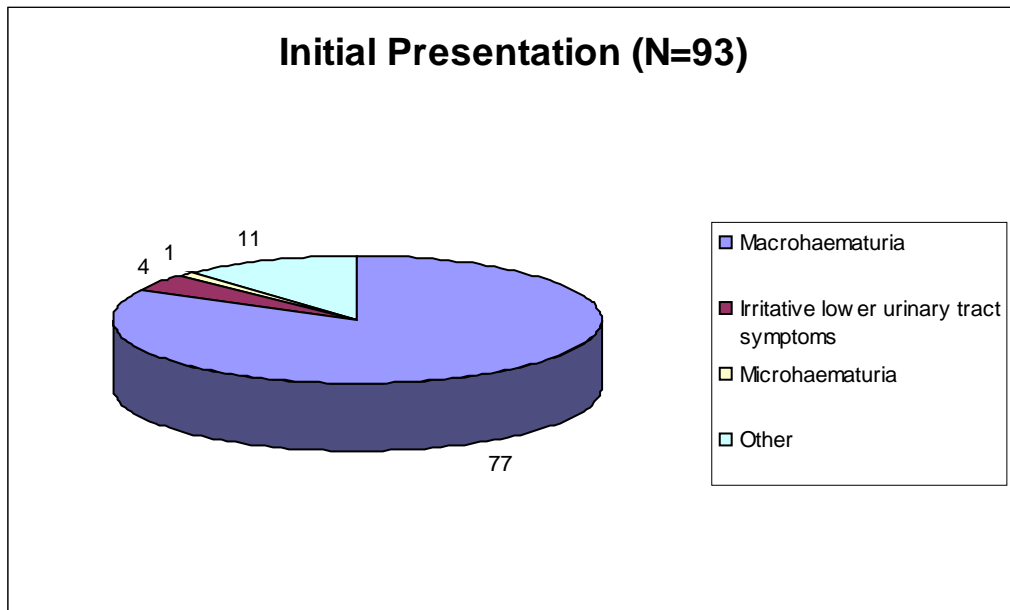
FIGURE 11: Smokers vs Non-smokers(N=93)



3. Initial Presentation

The majority of patients presented initially with macroscopic haematuria 77/93 (83%). Some patients presented with irritative lower urinary tract symptoms (4/93 or 4%). Only 1/93 (1%) patients presented with microscopic haematuria.

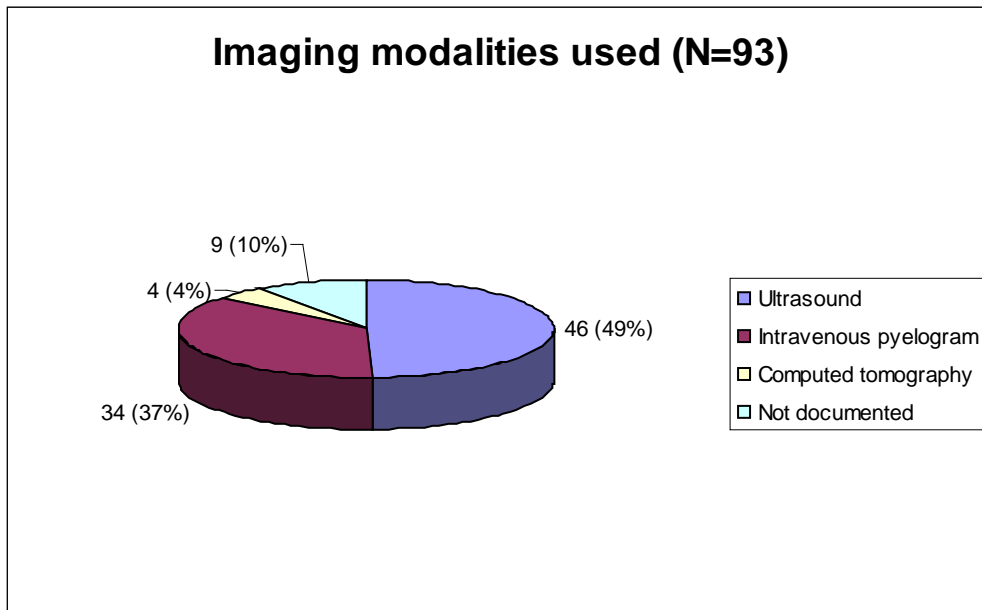
FIGURE 12: Initial presentation of patients requiring radical cystectomy



4. Imaging

Imaging modalities used were Ultrasound, Intravenous pyelogram or Computed Tomography.

FIGURE 13: Imaging modalities used



These imaging modalities told us whether there was hydronephrosis, and gave us a clinical suspicion of bladder tumour

FIGURE 14: State of upper tracts

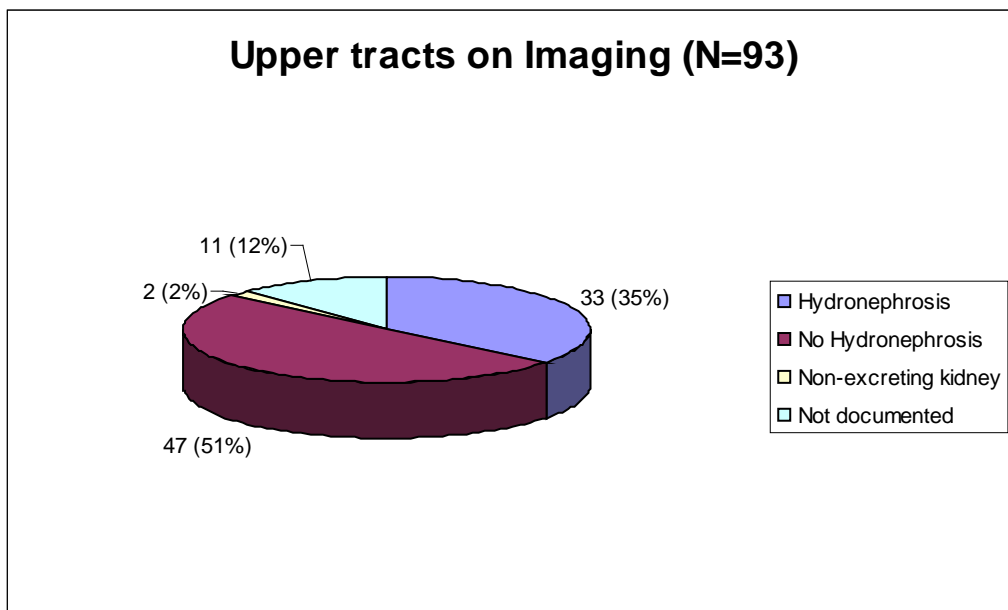
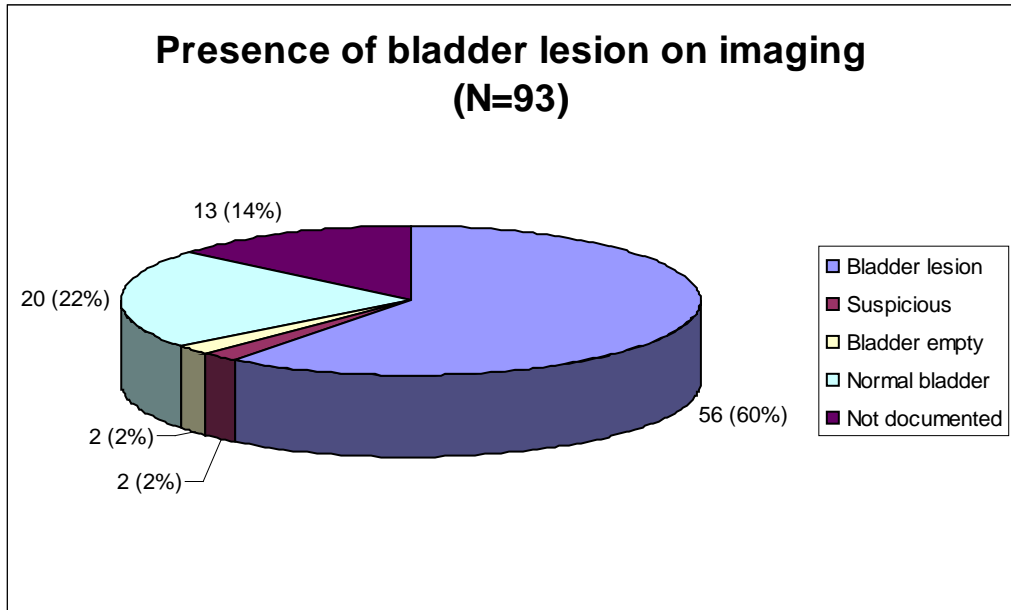
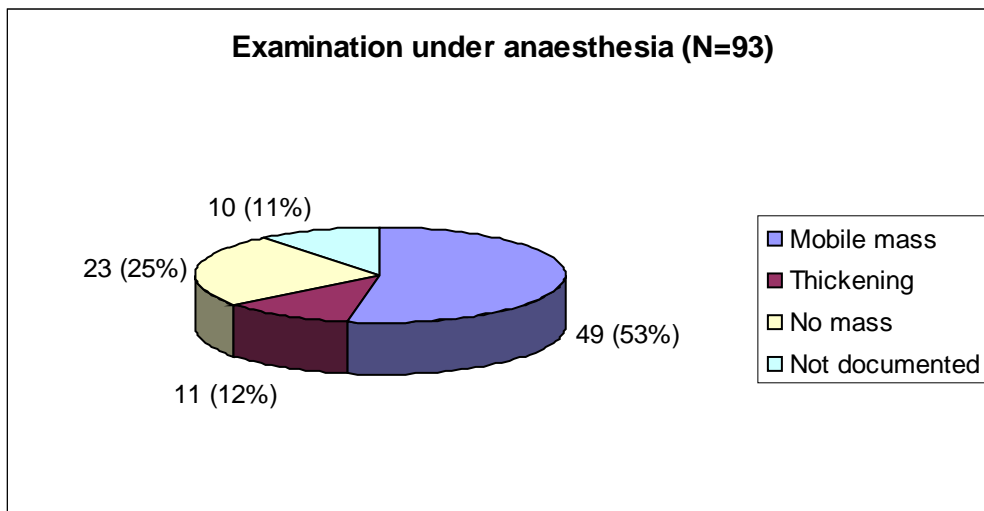


FIGURE 15: Presence/Absence of bladder lesion on imaging (U/S, IVP and CT)



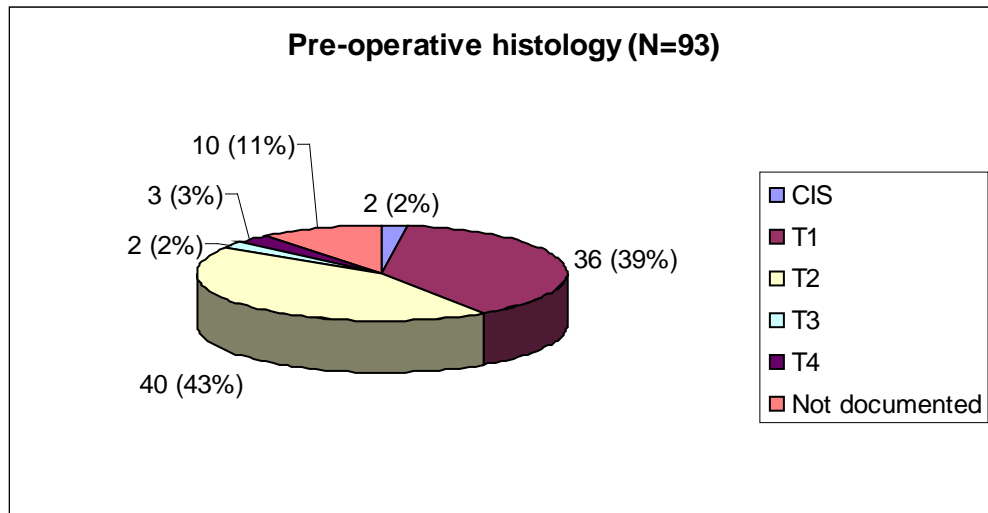
5. Clinical Staging

FIGURE 16: Examination under anaesthesia



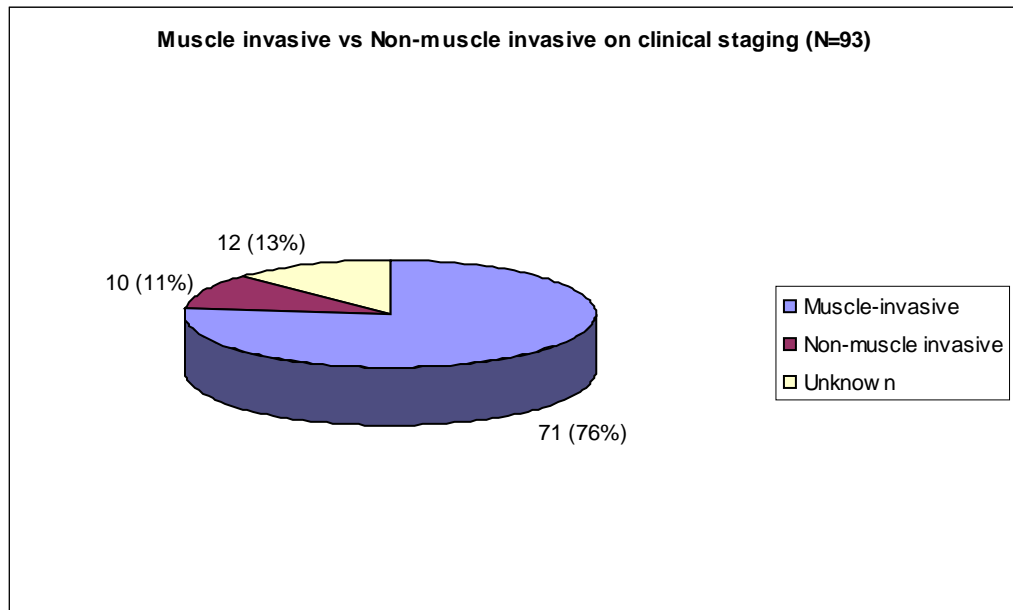
49/93 (53%) Patients had a mobile mass on bimanual examination under anaesthesia, while 11/93 (12%) patients had a thickening noted on bimanual examination under anaesthesia.

FIGURE 17: Pre-operative histology



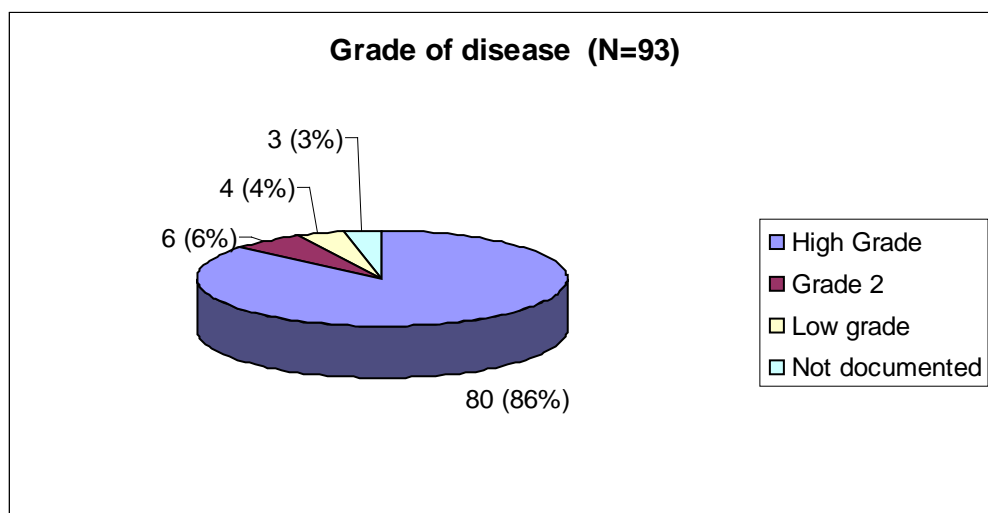
The distribution of pre-operative histology is demonstrated in Figure 17. The pre-operative histology was used in conjunction with the bimanual examination under anaesthesia to clinically stage the patients into non-muscle invasive, and muscle-invasive disease.

FIGURE 18: Muscle-invasive vs Non-muscle invasive disease on clinical staging



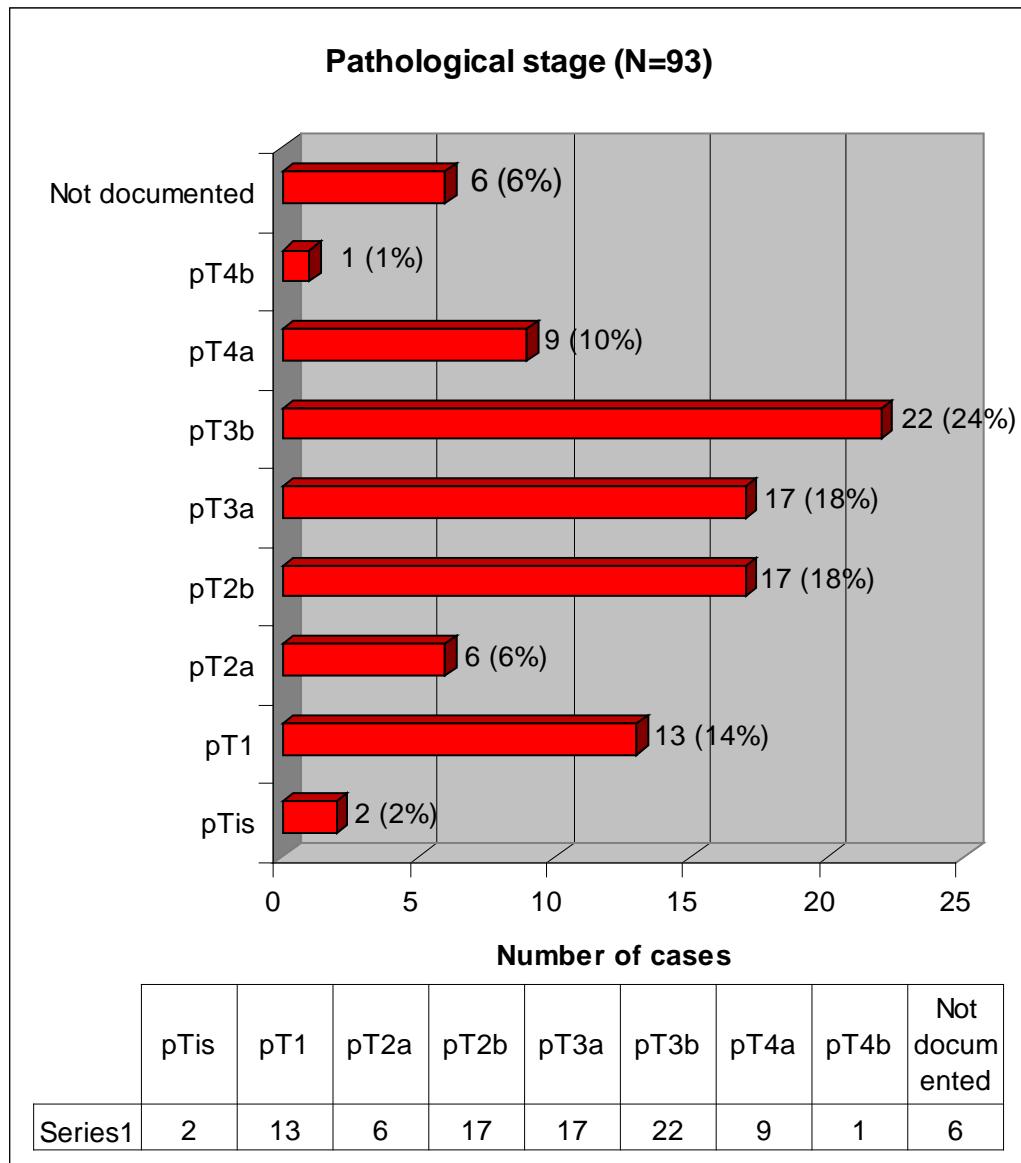
6. Pathology

FIGURE 19: Grade of disease on Radical cystectomy specimen



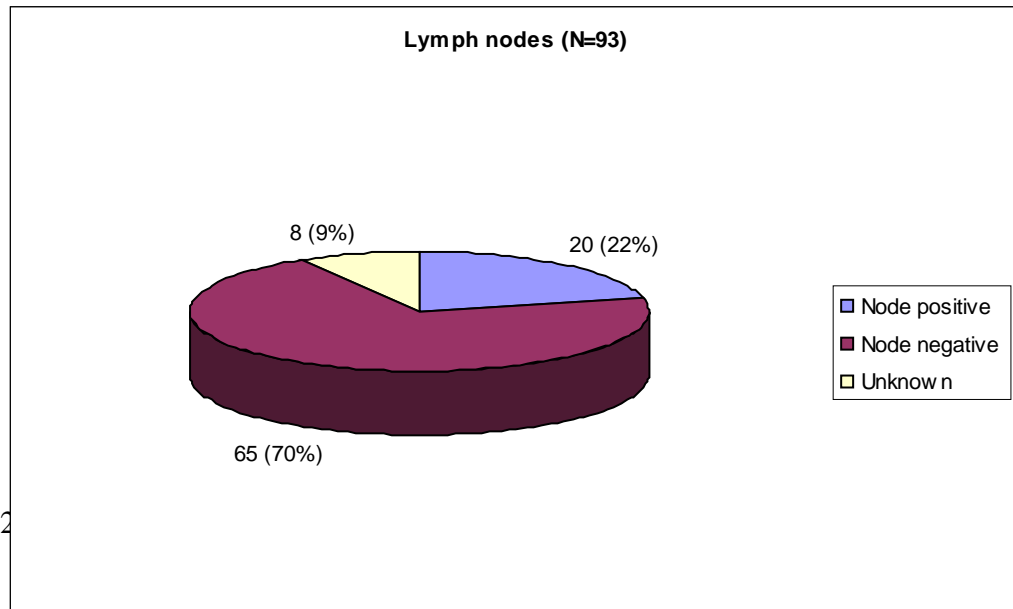
The vast majority (86%) had high grade disease. The grading system has changed from when the study period started, hence some G2's seen.

FIGURE 20: Pathological stage of Radical cystectomy specimen



On pathological examination of the distal ureters, 1/93 (1%) patients had dysplasia in a ureters, 2/93 (2%) patients had Carcinoma-in-situ of the distal ureters, and 11/93 (12%) patients had TCC of the distal ureters.

FIGURE 21: Patients with/without lymph node metastases



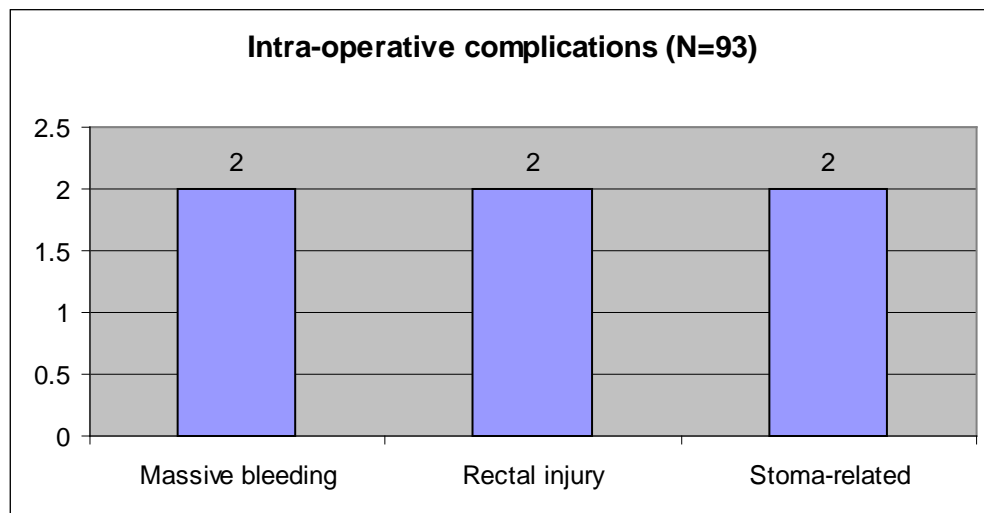
20/93 (22%) Patients had nodes positive for TCC at the time of radical cystectomy. If one stratifies these patients for stage, 1/20 (5%) was pT1, 1/20 (5%) was pT2b, 6/20 (30%) were pT3a, 7/20 (35%) were pT3b, 4/20 (20%) were pT4a and 1/20 (5%) was pT4b. Put another way, 18/20 (90%) of patients who were node-positive, also had disease which had extended beyond the bladder wall.

Of the 77 men who underwent radical cystectomy for TCC, 2/77 (16%) had associated adenocarcinoma of the prostate. They were generally of small volume and low Gleason score. In 1/12 (8%) patients, the Gleason score was 3+4/10. All the other patients were of lower Gleason score.

8. Complications

Intra-operative complications were primarily related to massive bleeding (>5units packed red blood cells transfused), stoma-related difficulties and rectal injury.

FIGURE 22: Intra-operative complications



For the purposes of this study, early post-operative complications were defined as occurring within 2 weeks of radical cystectomy. 8/93 (9%) Patients had wound dehiscence. 3/93 (3%) Patients had deep venous thromboses. 3/93 (3%) Patients had upper gastro-intestinal bleeds. 3/93 (3%) Patients had uretero-intestinal anastomotic leaks. 2/93 (2%) Patients developed an enteric fistula. 2/93 (2%) Patients had a prolonged ileus requiring total parenteral nutrition. 1/93 (1%) Patients had breakdown of their stoma and required their ileal conduit to be redone.

For the purposes of this study, late post-operative complications were defined as occurring greater than 2 weeks post radical cystectomy. 4/93 (4%) Patients developed adhesive small bowel obstruction. In terms of local recurrence, 2/93 (2%) patients developed pelvic recurrence, 2/77 (3%) male patients developed

urethral recurrence and 1/16 (6%) female patients developed a vaginal recurrence. 1/93 (1%) Patients developed a uretero-intestinal anastomotic stricture and 1/93 (1%) patients developed a parastomal hernia.

9. Chemotherapy

2/93 (2%) Patients received neoadjuvant chemotherapy prior to radical cystectomy. Unfortunately, only 1 of the 2 Oncology folders could be traced. This patient had a high grade TCC involving the trigone and bladder neck region. There was no muscularis propria in the specimen, and on ultrasound, there was left hydronephrosis. He received 3 cycles of Methotrexate, Vinblastine and Cisplatin. His radical cystectomy was done approximately 2 weeks post his 3rd cycle of chemotherapy. His final histology was pT1N0. He was contacted telephonically on the 7/02/2010, and is alive and well (Survival 39 months or 3.25 years).

8/93 (9%) Patients received adjuvant chemotherapy. 1/8 (13%) Patients received 4 cycles of Methotrexate, Vinblastine and Cisplatin. 5/8 (63%) Patients completed 3 cycles of Methotrexate, Vinblastine and Cisplatin. 1/8 (13%) Patients developed pyelonephritis after his 1st cycle of Methotrexate, Vinblastine and Cisplatin, and was not given the other 2 cycles as the time period between 1st and 2nd cycles would have been too great. The oncology folder for 1/8 (1%) patients was not traceable. Of the 7/8 patients who have records, 5/7 (71%) received adjuvant chemotherapy for positive lymph nodes. 2/7 (29%) Patients received chemotherapy for non organ-confined disease (pT3a and pT3b). 1/8 (13%) Patients had a performance status of 0, 3/8 (38%) patients had a performance status of 1, 3/8 (38%) patients had a performance status of 2, and 1/8 (13%) patients was of unknown performance status. Of the 8/93 (9%) patients who underwent adjuvant chemotherapy, there have been 3 confirmed deaths. These patients survived for 51 months (4.25 years), 22 months (1.83 years) and 18 months ((1.5 years) respectively. 2/8

(25%) Patients have been confirmed (telephonically) to still be alive. These patients have survived for 55 months (4.58 years) and 40 months (3.33 years) respectively. The status of the other 3/8 (38%) patients is unknown, despite looking at the hospital folder, oncology folder and attempts to contact them or their family have failed.

10.Radiotherapy

5 patients received radical radiotherapy as primary treatment, but then required salvage cystectomy at a later date. Records were available for 3/5 (60%) patients. All received 6 weeks of radiotherapy, 5 fractions per week. The time between completion of radiotherapy and radical cystectomy was 5 months, 5 months and 16 months respectively.

There was 1 confirmed death. This patient survived 102 months (8.5 years) post cystectomy. 1 Patient has been confirmed (telephonically) alive. He has survived 135 months (11.25 years) post cystectomy. The status of the other 3 patients is unknown, despite looking at their hospital records, oncology folder, and attempts to contact them telephonically have failed.

11.Survival

For the purposes of this study, the survival data will be analysed up to and including July 2009. It is difficult to definitively comment on survival as some patients have been lost to follow up. 51/93 (55%) Deaths have been documented. 22/93 (24%) Patients are known to still be alive. These patients have either been telephonically contacted, or have been to collect stoma bags. The status of the remaining 20/93 (22%) patients is unknown. Efforts to ascertain their status included:

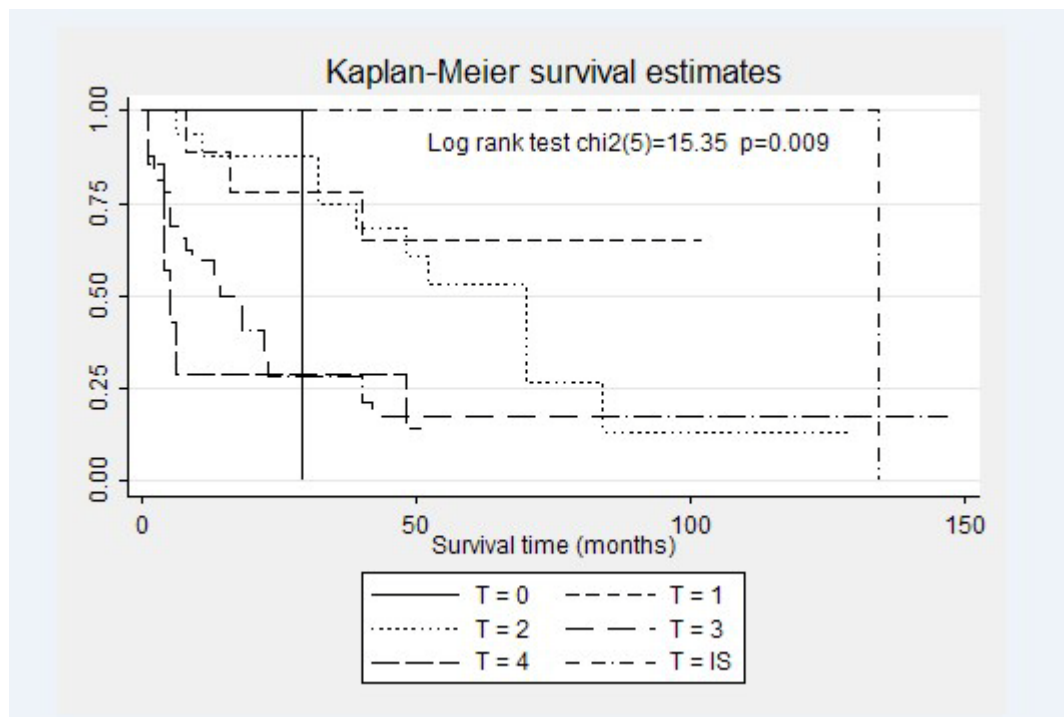
- Reviewing the hospital folders

- Reviewing the oncology folders, where available
- Liasing with stomatherapy and looking at their records, including telephoning the day hospitals where the patients should have been receiving their stoma bags
- Telephoning the patients and their families directly

Of these 24 patients, 13 have had their stomatherapy records archived, which means they have not collected stoma bags for at least the past five years. They are presumed dead, but this is not known for sure, and if indeed they have demised, the dates are unknown.

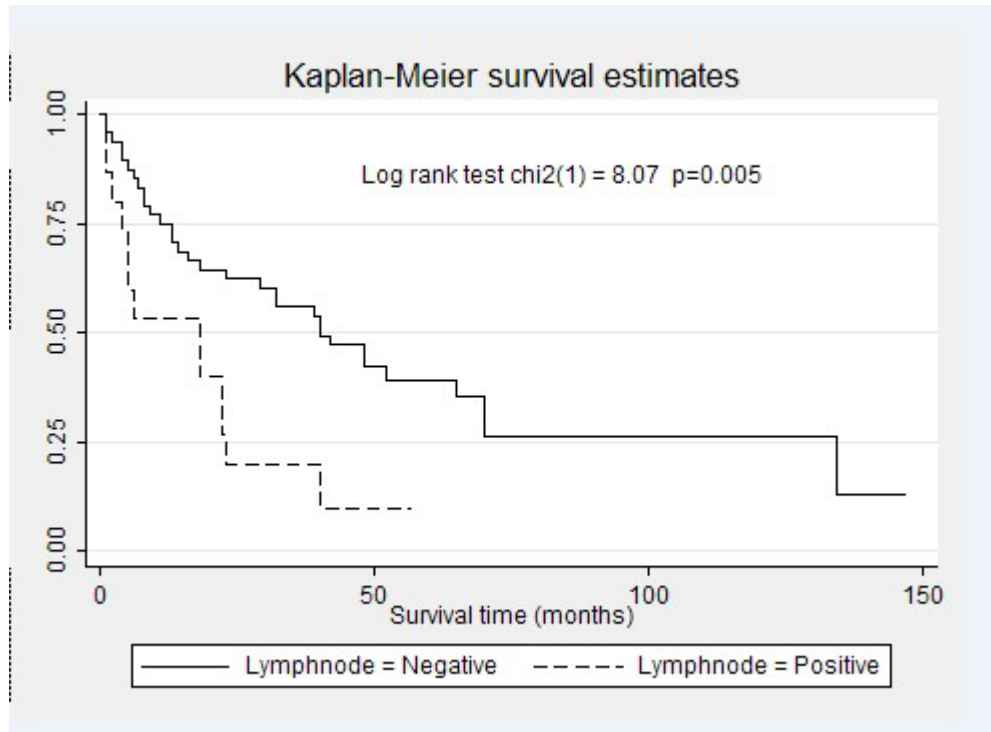
The following statistics apply to the 73/93 patients whose status is definitively known. The mean survival is 36 months (3 years). The median survival is 32 months (2.67 years). 2/73 (3%) Patients died in the first month after their surgery. The longest survivor has survived for 147 months (12.25 years), and is still alive.

FIGURE 23: Kaplan Meier graph of survival according to T stage



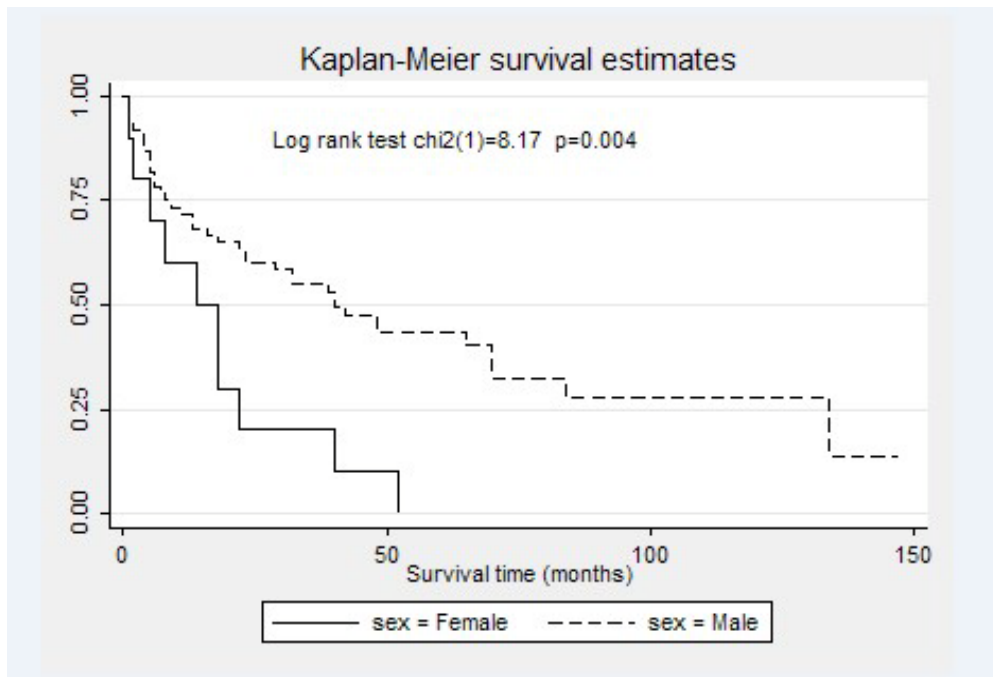
Survival in months according to Tumour stage is represented in the above Kaplan Meier graph. From our data it is quite clear that survival is related to stage, and with increasing tumour stage, survival decreases.

FIGURE 24: Kaplan Meier graph of survival according to lymph node status



Survival in months according to nodal status is represented in the above Kaplan Meier graph. From the above data, it is clear that in patients with positive lymph nodes, survival is markedly poorer when compared to patients who were node negative. This difference in survival is statistically significant.

FIGURE 25: Kaplan Meier graph of survival according to sex



Survival according to sex is demonstrated in the above Kaplan Meier graph. In our study population, females had a poorer survival than males. This difference was statistically significant.

CHAPTER 5: DISCUSSION

Radical Cystectomy is done predominantly for muscle-invasive bladder cancer, and is a major operation associated with both intra- and post-operative complications. Patients in our series who required this procedure were predominantly elderly coloured or white males. Very few black patients and a minority of females required radical cystectomy. We can't be sure why this is the case. Possible theories include:

- Increased exposure to carcinogens eg. Smoking and industrial carcinogens, amongst Coloured and White males
- Genetic basis for protective effect amongst the black population
- Black population under-represented at Groote Schuur (perhaps related to our drainage area?)
- Female gender protective?

Further study is needed to prove or disapprove these theories. Hollenbeck et al. from the University of Michigan have published a study on "Racial differences in treatment and outcomes among patients with early stage bladder cancer." (49) They used the Surveillance, Epidemiology, and End Results (SEER)-Medicare data for the years from 1992 through 2002. In this database, there were 14271 white patients, and only 342 black patients. However, they note that black patients are at increased risk of death, although the reasons for this are unclear. (49)

A positive smoking history was a very common association. This association is well proven in the literature, with cigarette smokers having up to a fourfold higher incidence of bladder cancer than people who have never smoked. (14, 15) Risk correlates with number of cigarettes smoked and duration of

smoking. Ex-smokers have a reduced incidence of bladder cancer compared with active smokers. Reduction down to baseline, however, can take up to 20 years. (16) In our study, it was difficult to assess ex-smokers specifically, as the notes were not accurate enough. For the purposes of this study, if it was specified that a patient was an ex-smoker for greater than 20 years, they were classified as non-smokers. However, in the majority of patients, no time was documented as to how long the patient was an ex-smoker, and they were thus classified as smokers. In every contact we have with our patients, we would do well to warn them of the dangers of smoking and the benefits of stopping. These benefits would be not just in terms of reducing the risk of bladder cancer, but cardiovascular benefits as well. The evidence regarding increased risk in passive smokers is less comprehensive, but an association has been demonstrated. (17)

The vast majority (77/93 or 83%) of patients presented with macroscopic haematuria. At some stage, they will have had microscopic haematuria. With education of healthcare professionals and routine dipstix testing, we could potentially identify patients at an earlier stage of disease and thus get better results from our surgery. In addition, we may be able to offer patients less invasive forms of management. Experience and anecdotal evidence in our Haematuria Clinic, however, has shown us that the yield of bladder cancer patients from microscopic haematuria, is very low. In our study, only 1/93 (1%) patients presented with microscopic haematuria. Further study and analysis would answer questions of cost-effectiveness. It has been demonstrated that a delay in cystectomy of even 12 weeks is associated with poorer survival. (23) We don't have the data in our study to prove patients were delayed in receiving definitive surgery from time of presentation and therefore had inferior outcomes as a result of this. The reasons for this are many:

- Heterogenous population of patients e.g. some patients were sent directly from other hospitals or private, some patients were initially managed endoscopically, some patients received radical radiotherapy, some patients received neo-adjuvant chemotherapy etc.

- Poor record keeping e.g. The duration of macroscopic haematuria was not recorded on numerous occasions.

However, it is logical that we should diagnose and treat these patients as soon as possible. We have therefore instituted the Haematuria Clinic at Groote Schuur in an effort to make a more rapid diagnosis. Patients may be referred directly. They are seen, an ultrasound is done, and they have flexible cystoscopy. This is all done on one afternoon by a consultant urologist. A patient suspected to have bladder tumour is prioritised to have a transurethral resection as soon as possible. The histology from the resection is requested as urgent, and once the decision has been made for a radical cystectomy, the procedure is usually done within 4 weeks.

Ultrasound is the imaging investigation we most commonly employ (46/93 patients in our series or 49%). Intravenous pyelography as well as computed tomography scanning were also used. Our practice has changed over the 14 years this series covers. Almost all patients are now evaluated with an Ultrasound.

The reasons for this are:

- It is quick
- Non-invasive
- No use of contrast
- Gives us good information on the state of the upper tracts.

Computed tomography scanning and intravenous pyelograms are rarely done in our practice. In the First World, the majority of patients have a computed tomography scan of the abdomen and pelvis. Proponents say that this modality improves the accuracy of staging by:

- Assessing the extent of the primary tumour
- Presence/Absence of pelvic and para-aortic lymphadenopathy
- Presence/Absence of visceral metastases (18,19)

Opponents say that all staging studies including computed tomography (with the possible exception of transurethral ultrasonography), appear to be inaccurate in determining the presence or absence of microscopic muscle invasion and minimal extravesical tumour spread. (20) As regards the diagnosis of the primary bladder tumour, imaging modalities alone were not sensitive enough. A bladder lesion was picked up in 56/93 (60%) of patients who had imaging prior to radical cystectomy. Therefore, cystoscopy is still mandatory in evaluating patients in the bladder cancer age range with haematuria. (21)

Patients with abnormal findings on imaging or cystoscopy, are further evaluated with an examination under anaesthesia as well as transurethral resection of the tumour. This allows us to make a histological diagnosis as well as clinically stage them. However, as our results show, there is a significant risk of understaging the patient. 10/93 (11%) Patients had radical cystectomies for clinically non-muscle invasive transitional cell carcinoma. Of these patients, 5/10 (50%) had muscle-invasive transitional cell carcinoma on pathological staging, and 4/10 had extravesical disease (pT3A or greater). 2/10 (20%) Patients had positive lymph nodes.

This phenomenon is well recognised internationally. Understaging occurs most frequently in patients who have high-grade and intermediate-stage tumours. Approximately 1/3 of these patients are understaged and 10% are overstaged.(22) The greatest danger of clinically understaging a patient, is treating them as a non-muscle invasive tumour when they do in fact have muscle invasion. It is thus mandatory to repeat the transurethral resection if there is no muscle in the initial specimen and the patient has high-grade disease. In addition, there is a trend to repeat the cystoscopy and do biopsies at

6 weeks in the presence of high-grade disease, even if there is adequate muscle in the specimen with no invasion of tumour. Likewise, in patients with high-grade non-muscle invasive disease (T1G3) and/or Carcinoma-in-situ (CIS) who fail Bacillus-Calmette-Guerin (BCG) therapy, there is low threshold for doing early Radical Cystectomy. This is because patients with carcinoma-in-situ who fail BCG therapy, have a 50% chance of disease progression and potential for disease-specific mortality. (9, 24) Early (3 months) failure for T1G3 tumours after BCG is associated with an 82% progression rate. (10, 25) In addition, up to 50% of patients with presumed non-muscle invasive disease, who undergo cystectomy will be found actually to have muscle-invasive disease (8) and up to 15% will already have micrometastases. (25) There is thus a very real chance of missing an opportunity for cure, and operating on patients too late. Ongoing efforts at improving the staging of our patients, is being made. Research worldwide into improving imaging techniques and modalities is being done. In addition molecular techniques, to detect a variety of related gene products is under way.

The vast majority of patients (93/105 or 89%) had Transitional cell carcinoma. This correlates with international experience. (21) 5/105 (5%) of our patients had adenocarcinoma. Generally though, they account for less than 2% of primary bladder cancers. (27, 28) 4/105 (4%) had squamous cell carcinoma (SCC). The prevalence of SCC is very variable. It accounts for only 1% of bladder cancers in England, 3-7% in the US, but as many as 75% in Egypt. (28, 29, 30) Our patients had predominantly high-grade disease (80/93 or 86%)

49/93 (53%) Patients were pathologically staged as having extra-vesical disease (pT3a or greater). Our positive lymph node rate was 22% (20/93). When one considers that for the duration of the study period, we were only doing node sampling for staging purposes, the proportion of patients with node positive disease may well have been considerably greater. We are currently doing an extended lymph node dissection, and the international literature

seems to indicate that this can improve outcome. (31, 32, 33) The above data shows that we are operating on patients at an advanced stage. Efforts are being made to try and change this pattern and help our patients at an earlier stage.

These include:

- Education of healthcare professionals with our ongoing Undergraduate teaching programme
- Streamlining the system so that patients have access to specialised services faster (Our Urology Outpatient waiting period has been drastically reduced to approximately 2 weeks)
- Creation of the Haematuria clinic
- Prioritising bladder cancer patients in terms of theatre bookings as well requesting histology as urgent.

Associated Carcinoma of the Prostate was found in 12/77 (16%) of the Radical Cystectomy specimens in our male patients. The vast majority were of low Gleason score and have not proven to be clinically significant. Our rate is a little lower than that found in international series, but their experience in the clinical insignificance of the lesions has been similar.

Intra-operative complications were primarily related to bleeding. Massive blood loss (defined as requiring 5 or more units of packed red blood cells) was only recorded in 2/93 (2%) patients. Rectal injury was identified in 2 patients (2) intra-operatively. 1 patient was primarily repaired and the other underwent a colostomy. In addition, 1 missed rectal injury manifested as an entero-cutaneous fistula in the first post-operative week. This patient underwent a colostomy. Extreme difficulty with the stoma was encountered in 2 patients. 1 patient needed the stoma to be redone 3 times before the surgeons were satisfied, and difficulty was encountered in 1 patient in getting the stoma to the skin. Contemporary reviews state that catastrophic haemorrhage is rare, but can occur during cystectomy. In addition, rectal injury occurs in not more than

1 %. Radical cystectomy is associated with a mortality rate of 1-2%. (1) In this series, there has not been any intra-operative mortality.

Post-operative complications are divided into early (<2 weeks post surgery) and late (>2 weeks). Early complications that were seen include:

- Wound dehiscence 8/93 (9%)
- Upper GI bleed 3/93 (3%)
- Prolonged urine leak 3/93 (3%)
- Deep vein thrombosis 3/93 (3%).
- Stoma complications 1/93 (1%)
 - 1 patient needed the conduit to be redone because of breakdown
- 2/93 (2%) Patients had a prolonged ileus requiring total parenteral nutrition. Although often not documented, post-operative ileus is a very common problem following Radical Cystectomy

With the above knowledge in my mind, Groote Schuur Urology have implemented uniform protocols in an effort to prevent these complications.

- A review of wound closure techniques was presented at an academic meeting. Very close attention is now paid to the technical aspects of the abdominal closure.
- All patients receive sucralfate while in ICU, and cimetidine in the ward, post-operatively until they are tolerating a full ward diet. There is some evidence to suggest the use of Cimetidine to prevent post-surgical stress ulceration. (50, 51) However, this is for intravenous and not oral use. In addition, antacids have been shown to be more effective, cheaper and safer than cimetidine. (52)
- All patients are placed on Heparin 5000u subcutaneously 8-hourly from day 1 post-operatively. Leg stockings are applied and patients are

encouraged to mobilise early. Contemporary series show that post-operative pulmonary embolism is rare (2%). (1)

- In addition, we give all patients a positive end expiratory pressure bottle to blow on in order to prevent post-operative atelectasis.

Late post-operative complications seen were:

- Pelvic recurrence 2/93 (2%)
- Urethral recurrence in males 2/77 (3%)
- Vaginal recurrence 1/16 (6%)
- Adhesive small bowel obstruction 4/93 (4%)
- Uretero-ileal anastomotic stricture 1/93 (1%)

Contemporary series record an anastomotic stricture rate of 3%. (1) In this study, the patient with uretero-ileal obstruction was due to recurrent disease. He was treated with an indwelling nephrostomy tube. Special mention should be made of the pelvic recurrence rate of 2/93 (2%) which is very low, especially considering that many of these patients were operated on at an advanced stage of disease. Urethrectomy is not routinely done at our institution. However, there is a risk of recurrence, urethral washings are done on follow up, and any patient with urethral bleeding is urgently evaluated.

Neo-adjuvant chemotherapy was given to 2/93 (2%) patients and adjuvant chemotherapy was given to 8/93 (9%) patients. These 2 approaches have been discussed at length in the preceding literature review. At Groote Schuur, 3 cycles of adjuvant Cisplatin, Methotrexate and Vinblastine (CMV) chemotherapy is favoured for extravesical as well as nodal disease. Although not regarded as the standard of care, the above regimen is considerably less toxic than one with Adriamycin added. In addition, due to cost constraints, Gemcitabine is not available.

Median survival was 36 months (3 years). Median survival was 32 months (2.67 years). Survival was related to stage. With increasing pathological stage, survival decreased. This is well recognised in international series. (1, Table 2)

Extravesical disease is associated with a poor outcome when compared to organ-confined disease. Lymph node positive disease has a very poor prognosis. Although mean survival for lymph node positive disease was 15 months, the median survival was only 6 months. In our study population, females did significantly worse than males in terms of survival. 9/11 (82%) Females had extravesical disease and 3/11 (27%) had positive lymph nodes. This may explain the poorer survival outcomes seen in females in our study population.

CONCLUSIONS

- Radical cystectomy at our institution is needed predominantly for white and coloured patients
- The vast majority of patients are male
- Most patients were smokers
- Ultrasound is used for evaluating the upper tracts, and while it may diagnose a bladder lesion, it has a very poor sensitivity for this purpose
- Cystoscopy is thus mandatory in a patient with suspected bladder cancer
- There is a significant risk of clinically understaging the patient
- Wound dehiscence, upper gastrointestinal haemorrhage and deep vein thrombosis were some of the commonest complications seen, and steps have been taken to address these.
- The risk of local recurrence after Radical Cystectomy is low
- Survival is related to the stage of disease and the status of the lymph nodes:
 - Extravesical disease has a poor prognosis
 - Lymph node disease has an extremely poor prognosis
- In our study population, females had a poorer survival outcome

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