

**Prognostic Factors in Women**

**with**

**Stage IIIB Cervical Cancer**

Stefanie Hinz MD (Germany) FCOG (SA)

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## **Summary**

This study was designed to identify specific patient and tumour related factors which could be used as prognostic parameters in women with stage IIIB cervical cancer, and to investigate the relationship between these factors and treatment outcome. Primary endpoints were overall survival, disease-free and pelvic recurrence-free survival rates. The data of 99 women was used for this analysis. The presence of hydronephrosis and the level of the pre-treatment haemoglobin were predictors of outcome. A tumour burden system as described by Arthur et al. in 1995 was also found to be useful prognostic tool. Decision trees were created with a three-way regression analysis to guide clinical management of women with stage IIIB cervical cancer. The management options of patients with poor prognostic factors are discussed with special consideration of resource-poor settings.

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## **Chapter One**

### **Introduction**

#### **1.0 Cervical Cancer Incidence with particular reference to South Africa**

Cervical cancer is the commonest cancer cause of death among women in the developing world. In 1990, there were an estimated 360 000 new cases of cervical cancer diagnosed worldwide, 80% of which occurred in developing countries (Pisani et al., 1999).

In 1986, South Africa launched a pathology-based cancer registry, relying on information from 80 private and public laboratories. The total number of cancers reported in South African women was 16 559 in 1986, of which 2 897 (17.4%) were new cases of histologically confirmed cervical cancer (Cancer Registry of South Africa, 1986). In 1992, while the total number of cancers in women increased to 25 143, the proportion of women with newly diagnosed cervical cancer remained the same at 17.8% (n=4 467) (Sitas et al., 1997).

In 1992, the overall crude incidence rate of cervical cancer was 23/100 000 and the Age Standardised Incidence Rate (ASIR) was 30.5/100 000. There were however marked differences in incidence among women in the different population groups. For instance, the ASIR of cervical cancer among black women was 34.6/100 000 with a lifetime risk of developing cervical cancer of 1 in 26 compared to an ASIR of 12.3/100 000 for white women with a 1 in 83 lifetime risk of developing cervical cancer (Sitas et al., 1997). It is acknowledged however, that a significant number of women with cervical cancer die without the diagnosis of cervical cancer ever being made, which suggests that the reported number of cases is an underestimate, and that the extent of the problem is even larger than evidenced by the available statistics (Sitas et al., 1997).

## **1.1 Cervical Cancer Screening**

Cervical cancer is considered a preventable disease by means of organised, population-based cytological screening programs. In South Africa cervical cancer screening is largely opportunistic, and a national policy, which aims to offer three free cervical smears to all women aged 30 years and over, at 10 yearly intervals, was only adopted officially in December 2000. The gap between policy and implementation is large, and it is estimated that only 5-10% of black South African women have been screened in the past 5-10 years (Denny, 2000). The absence of primary prevention strategies for the prevention of cervical cancer is an important reason that cervical cancer remains the commonest cancer cause of death among black women in South Africa.

In addition, the majority of women who develop cervical cancer in South Africa, present with advanced disease. According to a computerised database of all gynaecological cancers seen at Groote Schuur Hospital since 1985, between 47 to 52% of all cervical cancer cases seen at our Unit presented with stage III disease. In contrast, a national survey of patients treated in randomly selected radiation facilities in the United States in 1973 showed that 84% of 697 women diagnosed with cervical cancer presented with stage I or II disease, and only 16% of women suffered from advanced cancer (stage III or IV) (Lanciano et al., 1991).

## **1.2 Treatment of women with Cervical Cancer**

Radiation treatment has been established as the most effective single treatment modality for locally advanced tumours. Radiation facilities in South Africa are limited – six radiotherapy units are attached to tertiary level hospitals, and two smaller units exist in the Eastern Cape. All treatment facilities are located in urban areas, which makes access for the rural population difficult. Financial constraints on the health budget dictate optimal clinical utilization of these facilities in order to benefit a maximum number of patients (Levin et al., 1994).

However, even aggressive radiotherapy for stage IIIB tumours is associated with recurrence rates ranging from 16 to 60% (Lanciano et al., 1992, Kovalic et al., 1991). This wide range of treatment results may be explained by differences in radiotherapy schedules and techniques used (Perez et al., 1988), but is most likely due to tumour or patient related factors. Although the FIGO staging system for cervical cancer strongly predicts survival (Fletcher, 1980, Lanciano et al., 1991), there is a wide range of reported overall and disease-free survival rates as well as local control rates within Stage IIIB. However, it has been difficult to identify factors that consistently predict patient prognosis and results of radiotherapy (Perez et al., 1988, Lanciano et al., 1991 and 1992).

### **1.3 Prognostic factors predictive of treatment outcome**

#### **1.3.1 Tumour related factors**

Several attempts have been made to incorporate patient and tumour parameters as guides for predicting treatment outcomes (Stehman et al., 1991, Logsdon et al., 1999, Lanciano et al., 1991, Perez et al., 1988). In 1991 the Gynecologic Oncology Group published a multivariate analysis of prognostic variables in 626 patients with cervical cancer stage I-IV who were treated with radiotherapy. The authors reported that patient age, performance status, tumour size and lymph node status were significantly associated with progression-free interval (Stehman et al, 1991).

Logsdon and Eifel (1999) reviewed the records of 1096 patients with cervical cancer to define patient, tumour, and treatment factors that influence the outcome of patients with stage IIIB disease. Patients were treated with external beam and intracavitary radiation between 1960 and 1993, and median follow-up time was 134 months. Data analysis revealed poor disease-specific survival for large tumours >8cm in diameter, lower vaginal involvement, the presence of hydronephrosis, bilateral pelvic side wall involvement and lymph node metastasis.

In the United States Lanciano et al. conducted two national surveys of patients who were treated for cervical cancer in 1973 and 1978 (Patterns of Care Study). The participating radiation facilities were selected randomly, and a total of 1558 patients were reviewed. Pretreatment factors and treatment factors were analysed by uni- and multivariate analysis with pelvic control and survival rates as end points of assessment. Lower third vaginal involvement was identified as the least favourable form of pelvic extension. Bilateral pelvic side wall involvement was intermediate in prognosis, whereas unilateral sidewall involvement was the most favourable. The study found that the FIGO staging system for stage III cervical cancer was not predictive of outcome, and that it also accounted inadequately for the variability in the extent of the pelvic disease. The authors recommended separation of stage III disease by means of pelvic tumour extent and vaginal involvement for prospective trials of treatment, to be certain that treatment – and not tumour extent – was responsible for improvements in outcome.

Arthur et al. (1995) made the first attempt to incorporate several tumour parameters into a scoring system with the aim to predict treatment outcomes. The tumour burden scoring system as described by the authors quantifies the anatomical extent of the disease, and total scores > 4 are considered high. Their retrospective analysis included 89 patients with stage IIIB cervical cancer who underwent radiotherapy between 1976 and 1989. The study results supported the view that FIGO stage IIIB can be divided into two prognostic groups of low and high tumour burden with poor loco-regional control and survival rates reported in the latter group.

The “Johannesburg Staging” is a subdivision of Stage IIIB cervical cancer into stage IIIBi (unilateral pelvic sidewall extension) or IIIBii (bilateral pelvic sidewall extension or hydronephrosis). It is used with the intention to define two prognostic subgroups for therapeutic purposes. Experience from the Department of Radiation-Oncology at the University of Witwatersrand indicates that the sub-staging is predictive of treatment outcome (personal communication with Dr J Kotzen).

### **1.3.2 Patient related factors**

Only a few studies have investigated the impact of patient related factors on treatment outcome. Logsdon and Eifel (1999) found parameters associated with poor survival were patient age <40 years, weight loss >10%, and haemoglobin levels <10g/dl before or during treatment.

### **1.4 Survival in women with Cervical Cancer**

In our Radiation Oncology Department at Groote Schuur Hospital 5- year overall survival rates for all patients with stage IIIB cervical cancer undergoing radiotherapy are 29% , and 39% for those who complete curative radiotherapy (Radio-Oncology Database). This means that 60-70% of patients are offered very cost-intensive and potentially hazardous treatment with a poor chance of survival. In addition, major complications (Grade 3 or 4 RTOG) of radiation treatment are in excess of 10% and further impair quality of life in these patients.

Similar survival rates have been reported by other authors: Kovalic et al. (1991) conducted a retrospective analysis of 635 patients with FIGO stage IIB and IIIB carcinoma of the cervix. All patients received definitive radiation therapy (external beam and intracavitary radiation). Overall survival at 5 years was 32% for stage IIIB. The rate of major complications for stage IIIB was 7% at 5 years, 15% at 10 years, and 30% at 15 years.

In the study published by Logsdon and Eifel (1999) 90% of patients with stage IIIB cervical cancer were treated with curative intent, but 8% did not complete their treatment. Seventy-one percent of patients received external beam and intracavitary therapy, and 29% were treated with external beam radiation only. Overall survival rates for all 1096

patients were 32% at 5 years. For patients treated between 1981 and 1993 the rate of major radiation complications was 17%, and there were no deaths from treatment.

In the "Patterns of Care" study Lanciano et al. combined treatment results from selected radiotherapy centres in the United States for the years 1973 and 1978. They analysed a total of 271 patients with stage IIIB disease treated with different radiotherapy regimens and reported a 40% overall survival rate. However, 30% of patients did not receive intracavitary radiation. The overall rate of major complications was 9.5%.

More recently, Arthur et al. published the results of 89 patients with stage IIIB cervical cancer (1995). All patients underwent external beam radiotherapy and brachytherapy between 1976 and 1989. The 5-year overall survival rate was 50.3%.

### **1.5 Alternative treatments to Radical Radiotherapy**

The value of clearly defined prognostic variables, truly predictive of survival, is that they identify patients who are unlikely to be cured by standard radiotherapy. Once identified, these patients could be offered alternative therapies.

Alternative treatment options could include either more aggressive treatment modalities, or, especially in low-resource settings, less aggressive therapy with palliative rather than curative intent for patients with poor prognostic parameters.

With regards to more aggressive treatment, Thomas (2000) reviewed a series of large, well-conducted randomized trials of concurrent chemotherapy with pelvic irradiation in patients with cervical cancer stage IB2 to IVA: five studies showed a consistent 30% to 50% reduction in the risk of death from disease when concurrent chemotherapy was used. However, questions remain as to what constitutes the best chemotherapy dose and schedule, and the benefits of chemoradiation for women with stage III or IV disease have not been clearly defined.

Another approach to more aggressive treatment for high-risk patients would be the use of higher radiation doses. Lanciano et al. (1991) were able to demonstrate a dose response

for in-field pelvic control in stage IIIB cervical cancer. The highest rate of pelvic control was achieved with a paracentral dose (point A) >8500cGy. Major complications were seen in 9.5% of patients, and there was a significant relationship between point A doses and the rate of complications.

Perez et al. (1988) previously examined locoregional tumour control and survival in 1054 patients receiving radiation therapy for cervical cancer. The authors demonstrated a decrease in pelvic recurrence from 42% with point A doses <6000cGy to 18% with point A doses between 7500-9000cGy. Patients with tumour control in the pelvis also had a significantly lower incidence of distant metastases than patients who initially failed to gain tumour control in the pelvis. Although dose intensification is likely to improve the results of radiotherapy for cervical cancer, a concomitant increase in complications can be expected.

Alternatively, where human and financial resources are restricted and access to radiation facilities limited, women with tumour or patient related factors known to be associated with a poor outcome, could be offered palliative rather than radical radiation. This has been practice at the University of Natal where women with advanced stage IIIB cervical cancer are not offered radical radiotherapy.

## **Chapter Two**

### **Methods**

#### **2.0 Overall Aim of the Study**

This study was designed to determine which pre-treatment factors are predictive of a good or poor prognosis in women with a confirmed diagnosis of FIGO stage IIIB cervical cancer.

#### **2.1 Objectives**

The specific objectives of the study are :

1. To identify clinically useful prognostic parameters in stage IIIB cervical cancer
2. To assess treatment outcome in relationship to several prognostic factors
3. To test the predictive power of the tumour burden scoring system (Arthur et al., 1995)
4. To critically evaluate our current treatment approach for stage IIIB cervical cancer in terms of the identified prognostic factors

#### **2.2 Study Group**

From May 1994 to May 1996 a total of 166 women with histologically proven Stage IIIB carcinoma of the cervix were registered at the Combined Assessment Clinic (Gynaecology/Radiotherapy) of Groote Schuur Hospital and included in the study group.

### **2.2.3 Pre-treatment Evaluation of Women with Stage IIIB Cervical Cancer**

All patients underwent pretreatment evaluation consisting of history and physical examination, chest x-ray, renal ultrasound or intravenous pyelogram, and cystoscopy. The individual performance status was documented (European Cooperative Oncology Group / ECOG). Further investigations included a pretreatment full blood count, renal and liver function tests. Patients also underwent computerized axial tomography (CT) scans for radiotherapy planning purposes whenever possible. The patients were jointly evaluated and treated by the dedicated staff of the Departments of Gynaecological Oncology and Radiation Oncology. Staging was performed according to the system of the Federation Internationale de Gynecologie et d'Obstetries (FIGO) (Benedet et al., 2000). Physical findings of the tumours, histology and haemoglobin levels were recorded prospectively for all patients (Table 1). Treatment response and complications were retrospectively extracted from patient files (Table 2).

Tumour burden was estimated using a scoring system as described by Arthur et al. in 1995 (Table 3). In addition, the "Johannesburg Staging" – a subdivision of Stage IIIB disease based on parametrial extension and presence of hydronephrosis was evaluated (Table 4).

### **2.2.4 Inclusion and Exclusion Criteria**

Patients were selected for this study if they satisfied the following criteria:

#### **Inclusion Criteria**

1. Histologically proven primary cervical carcinoma
2. FIGO stage IIIB
3. Completed course of radiotherapy with curative intent  
( $< 2$  weeks treatment delay during radiotherapy course)

### Exclusion criteria

1. Patients receiving treatment with palliative intent were excluded from the analysis. These were patients with :
  - ECOG performance status 3 or 4
  - bilateral hydronephrosis irrespective of renal impairment
  - positive para-aortic lymph nodes
  - pelvic lymph nodes > 5 cm as measured on CT scan
  - cytologically or histologically proven common iliac lymph node involvement above the superior limit of the radiation portals
  - life-threatening co-morbid conditions
2. Prior abdominal surgery related to the cervical carcinoma.
3. Patients lost to follow-up within the first year after treatment

### **2.3 Radiation Treatment**

Radiotherapy ( RT ) with curative intent consisted of whole pelvis RT utilizing a 4-box field technique, 2 (Gy) minimum target dose, 5 times per week for 27 fractions (54 Gy) or 2.2 Gy, 4 times per week for 24 fractions (52.8 Gy). Treatment was on a Cobalt 60 unit or 16mV Linac. AP – PA radiation portals extended from L<sub>5</sub>–S<sub>1</sub> interspace to the lower edge of the obturator foramina, or 2cm below palpable tumour, whichever was lowest. Lateral margins were 1–1.5cm beyond the widest part of the true pelvis. Lateral portals were determined by planning CT scan, but were generally through the midsymphysis pubis anteriorly to S<sub>2-3</sub> posteriorly.

Brachtherapy consisted of a Manchester type manually loaded Radium applicator ( 20 Gy to point A ) until December 1994, and from January 1995 Iridium 192 HDR, 15 Gy to point A in 3 fractions. Midline shielding was not used.

## **2.4 Follow-up**

After radiation treatment patients were followed periodically at 3-monthly intervals for 1 year, then at 6-monthly intervals for an additional 1-2 years, and then yearly. The best clinical response to treatment was recorded from 3 months onwards after completion of radiotherapy. Patients were seen regularly for a minimum of 3 years or until lost to follow-up or death occurred. In some instances information was obtained by letter or telephone contact with the referring physician or the patient.

## **2.5 Recurrence**

Treatment failures were classified as pelvic or distant. When a recurrence was suspected in accessible sites, an attempt was made to confirm it by needle or punch biopsy. Patients with progressive pelvic abnormality on physical examination, or patients with the clinical triad of sciatic pain, hydronephrosis, and leg oedema were considered to have locoregional recurrence even without histological confirmation. Recurrences in any extrapelvic site, including inguinal or paraaortic lymph nodes, were considered distant failures.

## **2.6 Complications**

Major late complications were documented for the purpose of this study and graded according to the current RTOG Radiation Morbidity Scoring Criteria (Cox et al., 1995) : a score of "0" is equivalent to the absence of radiation effects and a score of "5" means that death of the individual occurred as a consequence of radiation. Major complications are defined as grade  $\geq 2$  according to the RTOG classification and require either medical or surgical treatment.

**Table 1:** Information recorded in the pre-treatment evaluation of women with stage IIIB cervical cancer seen at the Combined Assessment Clinic at Groote Schuur Hospital.

<b>Performance status (ECOG):</b>	0 = normal activity 1 = symptomatic but ambulatory 2 = in bed < 50% of the time 3 = in bed > 50% of the time 4 = 100% bedridden
<b>Histology:</b>	Squamous, Adenosquamous, Undifferentiated, Other
<b>Clinical Tumour Diameter:</b>	< 2 cm 2 – 5 cm > 5 cm
<b>Macroscopic Tumour Growth:</b>	Exophytic, Ulcerative, Infiltrative
<b>Parametrial Involvement:</b>	Unilateral parametrium < 50% and contralateral parametrium to pelvic side wall Unilateral parametrium > 50% and contralateral parametrium to pelvic side wall Both parametria to pelvic side wall
<b>Vaginal Involvement:</b>	No involvement One third, two thirds, whole
<b>Hydronephrosis:</b>	None, unilateral, bilateral
<b>Haemoglobin:</b>	Pretreatment haemoglobin Mean haemoglobin level during treatment (including transfused patients)



**Table 4: Johannesburg Staging**

<b>Johannesburg Stage</b>	<b>Parametrial Involvement</b>
Stage IIIB-1	One parametrium involved to pelvic side wall
Stage IIIB-11	Both parametria involved to pelvic side wall or hydronephrosis

## **2.7 Statistical Methods**

Kaplan-Meier curves were generated for overall survival, disease-free survival and locoregional recurrence. Overall survival time was calculated from the date of initiation of therapy to death of the subject or date of last contact. Disease-free survival time and locoregional recurrence-free survival time commenced with the start of treatment and ended with relapse of the disease (local or distant) or at the date of last contact (if disease-free). Patients who did not achieve complete remission were assigned a disease-free and recurrence-free survival time of 0.

Individual patient and tumour characteristics were analysed against overall, disease-free and recurrence-free survival using univariate analysis. Cox-F test was used to assess the association between treatment outcome (survival times) and the individual risk factors. The level of statistical significance was set at  $p \leq 0.05$ .

Multivariate analysis could not be done due to small numbers of patients in some subgroups. Instead, a three-way regression analysis (discriminant analysis) was performed to create decision trees. This method of analysis enables clinical decision-making based on the combination of specific risk factors and the expected treatment outcome.

## **Chapter 3**

### **Results**

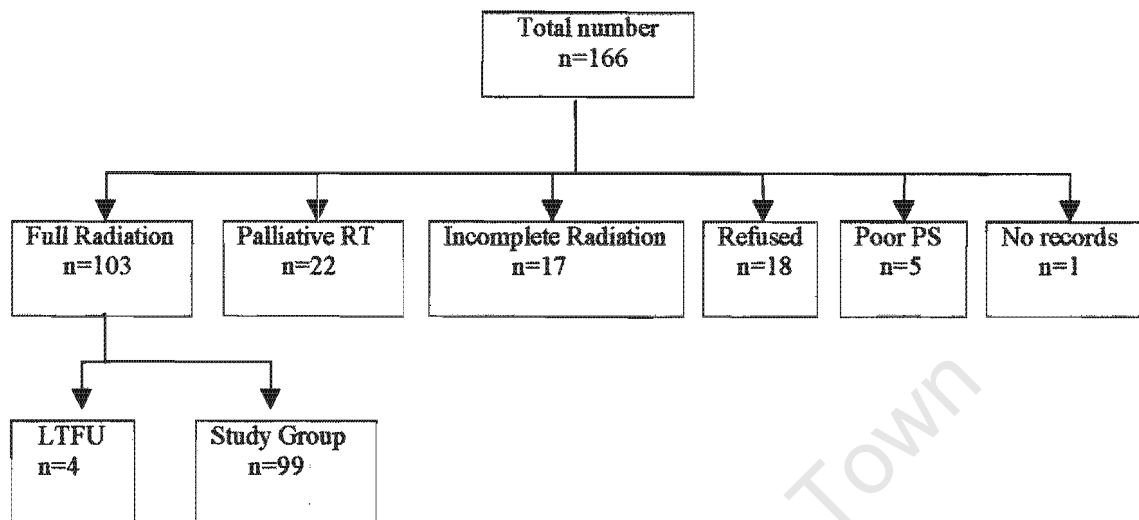
#### **3.0 Study Group**

Between May 1994 and May 1996 166 patients with confirmed primary cervical carcinoma stage IIIB were evaluated at the Combined Assessment Clinic, Groote Schuur Hospital.

Of these 166 women, 63 (38%) were not included in the study for the following reasons: 22 women received palliative radiotherapy only, 17 women defaulted treatment and had to be excluded from this study as they received incomplete radiation therapy or had recurrent interruptions of treatment (>2weeks in total). A further 18 women refused radiation treatment, 5 women were not offered radiotherapy due to an extremely poor performance status and in one case, the patient's hospital records could not be obtained. This left 103 women available for inclusion into the study.

Of the 103 women treated with a full course of curative radiotherapy and who had sufficiently detailed records to allow this retrospective analysis, 4 women were lost to follow-up within the first year of treatment and could not be traced. These 4 women were excluded from the analysis, leaving 99 patients as the final study group.

**Figure 1:** Algorithm of women included and excluded in the study group



### 3.1 Patient characteristics

The median age of the 99 patients in this study was 52.4 years (range 28 - 85 years). Twelve percent of women were less than 40 years old at the time of diagnosis (n=12).

The most common presenting symptom was abnormal vaginal bleeding (n=84/85%). Vaginal discharge and lower abdominal pain were less common (n=13/13%). Only 2% of patients (n=2) were asymptomatic at the time of diagnosis.

Twenty-one percent of patients (n=21) had an initial haemoglobin level of < 9g/dl. Mean haemoglobin levels during treatment were less than 10g/dl in 22% of patients (n=22) (including transfused patients). Ninety-four percent (n=95) were symptomatic but ambulatory, and 5% (n=5) were confined to bed in < 50% of time.

### 3.2 Tumour characteristics

The clinical and physical tumour characteristics are summarized in table 5. The majority of tumours were squamous carcinomas (92%) and most were moderately differentiated (57%). More than half of the tumours showed an exophytic growth pattern and most were more than 5 cm in diameter.

In the majority of cases (72%) there was either bilateral pelvic sidewall involvement or extension of tumour to one pelvic sidewall with more than 50% of the contralateral parametrium involved. In 27% of patients the tumour was found to have spread beyond the upper one-third of the vagina. Unilateral hydronephrosis was documented in just under a quarter of the women in this study group (Table 5).

**Table 5: Tumour Characteristics**

<b>Tumour Characteristics</b>	<b>Number of patients (%)</b>	
<b>Histology :</b>		
Squamous Carcinoma	91	(92)
Adenosquamous Carcinoma	6	(6)
Adenocarcinoma	1	(1)
Other	1	(1)
<b>Tumour Growth :</b>		
Exophytic	55	(56)
Infiltrative	36	(36)
Ulcerative	8	(8)
<b>Tumour Size :</b>		
2 – 5 cm	26	(26)
> 5 cm	73	(74)
<b>Parametrial Involvement :</b>		
Unilateral<50% and contralateral to PSW	28	(28)
Unilateral>50% and contralateral to PSW	22	(22)
Bilateral to PSW	49	(50)
<b>Vaginal Involvement :</b>		
Not involved or less than upper 1/3	72	(73)
More than upper 1/3	27	(27)
<b>Hydronephrosis :</b>		
Present	23	(23)
Absent	76	(77)

### 3.3 Treatment Outcome including Complications

Treatment outcomes and complications are shown in Table 6.

Of the 99 women treated with curative intent, 71 women had a complete response, 19 had a partial response, there was no change in tumour size in 7 women, and 2 women had progressive disease during treatment.

Major complications of radiation therapy were documented in 7 women: 5 of these were bowel related, and 2 were bladder related problems. No deaths occurred as a consequence of treatment complications.

At the time of data analysis (with a mean follow-up time of 30.6 months (range 0 – 73 months)) 42 patients were alive without evidence of tumour. Nine women had died of unrelated diseases, 2 women were alive with evidence of tumour recurrence, and just under half of the women had died as a consequence of cervical cancer (Table 6). Two women were lost to follow-up after 48 and 60 months respectively.

**Table 6: Treatment Outcome and Complications**

<b>Treatment Outcome</b>	<b>Number of patients</b>	<b>(%)</b>
<b>Treatment response :</b>		
Complete response	71	(72)
Partial response	19	(19)
No change	7	(7)
Progressive disease	2	(2)
<b>Mean Hb during treatment :</b>		
> 10g/dl	77	(78)
< 10g/dl	22	(22)
<b>Complications :</b>		
Bowel related	5	(5)
Bladder related	2	(2)
<b>Current Status :</b>		
Alive – no tumour	42	(42)
Alive – with tumour	2	(2)
Dead – unrelated cause	9	(9)
Dead – tumour related	44	(45)
Lost to follow up	2	(2)

### **3.3.1 Overall Survival Rates**

Overall, disease-free and pelvic recurrence free survival rates in relation to various tumour and patient characteristics are shown in Table 7.

Absence of hydronephrosis, pre-treatment haemoglobin levels of more than 9gm%, and a tumour burden score  $\leq 4$  were associated with a statistically significant better overall survival.

However, tumour size, pelvic side wall involvement, mean haemoglobin levels during treatment and the “Johannesburg Staging” were not predictive for overall survival on univariate analysis.

### **3.3.2 Disease-free and Pelvic Recurrence-free Survival Rates**

Absence of hydronephrosis, pre-treatment haemoglobin levels  $>9\text{gm}\%$ , and a tumour burden score  $\leq 4$  were predictive of better disease-free and recurrence-free survival rates. Stage IIIBi of the “Johannesburg Staging” was also associated with significantly better outcome in terms of disease-free and pelvic recurrence-free survival.

Tumour size, pelvic side wall involvement, vaginal tumour extension and mean haemoglobin levels during treatment did not reach statistical significance on univariate analysis.

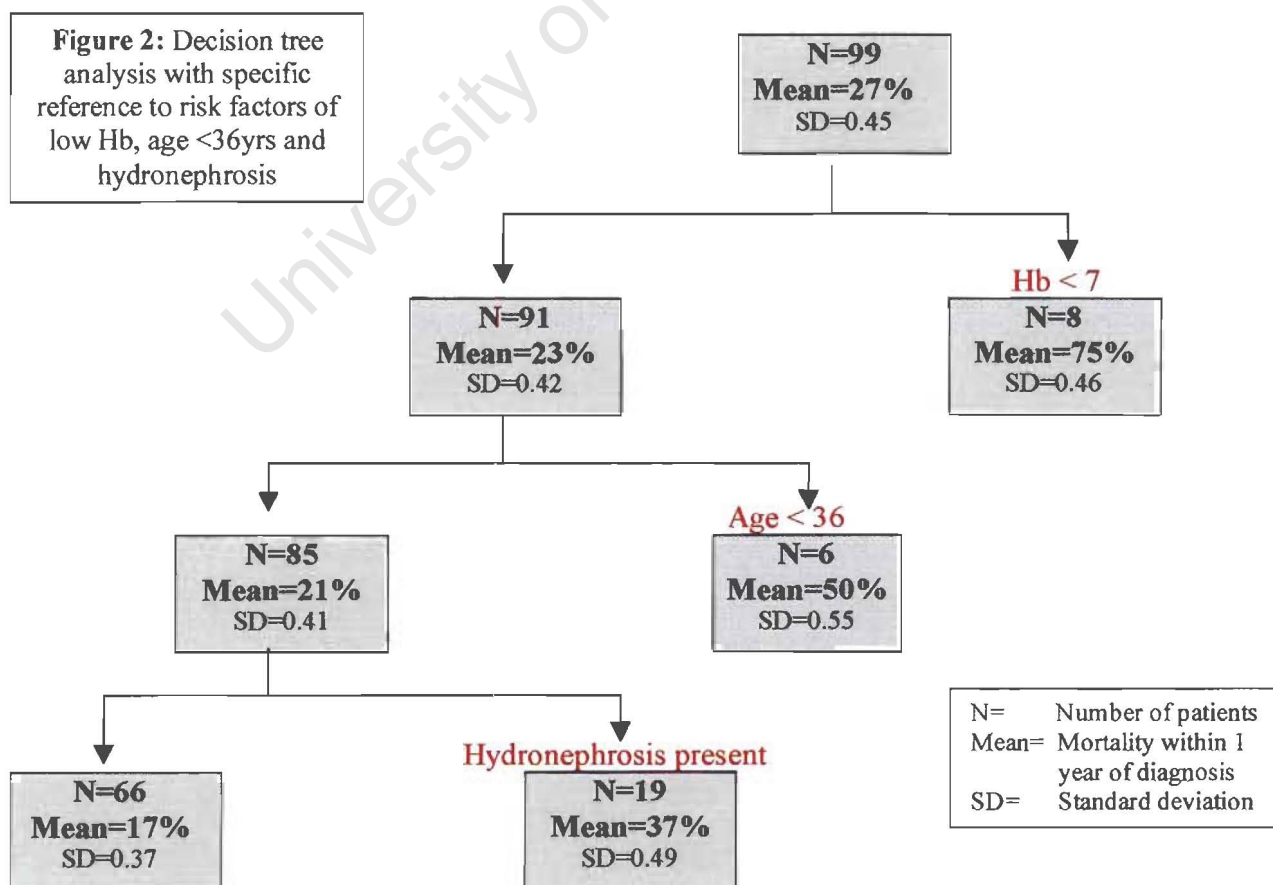
**Table 7: Overall Survival, Disease-Free and Pelvic Recurrence-Free Survival in relation to Tumour and Patient Characteristics**

	Overall Survival Rate* in %	p-value	Disease-Free Survival Rate* in %	p-value	Pelvic Recurrence-Free Survival Rate* in %	p-value
<b>Tumorsize</b>						
2-5 cm	58		64		66	
>5 cm	48	0.075	56	0.097	60	0.25
<b>Pelvic Side Wall Involvement</b>						
Unilateral	52		61		70	
Bilateral	46	0.51	55	0.41	58	0.098
<b>Hydronephrosis</b>						
None	55		64		70	
Unilateral	34	0.012	37	0.047	31	0.0016
<b>Vaginal Involvement</b>						
< 1/3	52		60		64	
> 1/3	40	0.067	50	0.055	52	0.21
<b>Pretreatment Hb</b>						
≥ 9gm%	53		60		68	
< 9gm%	43	0.034	50	0.037	36	0.0017
<b>Mean Hb during treatment</b>						
≥ 10gm%	52		59		67	
< 10gm%	45	0.41	58	0.86	61	0.29
<b>Arthur Score</b>						
≤ 4	60		67		73	
> 4	40	0.014	48	0.014	49	0.0076
<b>Johannesburg Staging</b>						
IIBi	57		63		75	
IIIBii	45	0.35	53	0.041	51	0.0023

\* Survival rates quoted at 36 months

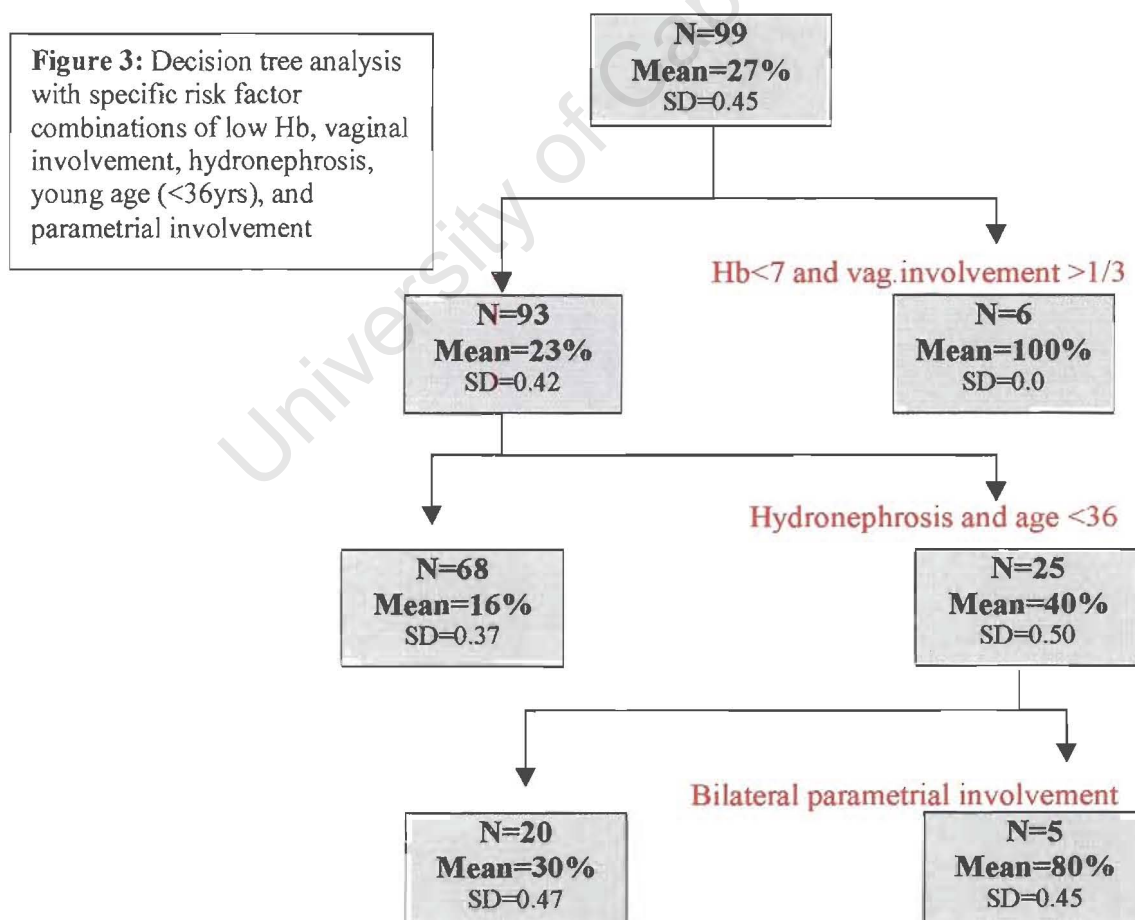
### 3.4.1 Decision Tree 1

For all 99 patients in this study the mean probability of mortality within 1 year of diagnosis was calculated as 27%. Further discriminative analysis showed that this probability rose to 75% for patients with a pre-treatment haemoglobin level of less than 7gm%. For the remaining 91 women with haemoglobin levels above 7gm% the mean probability of succumbing to the disease within 1 year was readjusted to 23%. Amongst these women the chance of dying from the disease within 1 year was increased to 50% for patients aged 36 years or less. After exclusion of these two risk factors (age and low Hb) the mean probability of mortality within 12 months of diagnosis dropped to 21% for the remaining 85 women. However, in the presence of hydronephrosis the probability increased again to 37% for 19 of these women. All 66 patients without any of the three risk factors reduced their chance of mortality to 17% for the first year (or increased their chance of survival beyond the first year to 83%).



### 3.4.2 Decision Tree 2

As in the previous analysis the mean probability of dying from the disease within the first 12 months of diagnosis was determined as 27% for all patients. For women with pretreatment haemoglobin levels below 7gm% and vaginal involvement of more than 1/3 the probability increased to 100% as none of these patients survived the first year. For the remaining 93 patients the chance of demise within 12 months could be readjusted to 23%. Of these, women who were less than 36 years old with evidence of hydronephrosis had an increase of the mean probability to die within the first year to 40%. If, in addition, these women had bilateral parametrial involvement to the pelvic side walls or unilateral extension to one pelvic side wall with >50% parametrial involvement on the opposite side, the probability of demise doubled to 80%. Patients without any of these risk factors had a 84% chance of being alive after 12 months.



## **Chapter Four**

### **Discussion**

#### **4.0 Overview of Results**

This study, which evaluated prognostic factors in women with stage IIIB cervical cancer found:

1. FIGO Stage IIIB cervical cancer is a heterologous group of women which can be divided into 2 prognostic subgroups.
2. Certain patient and tumour-related parameters can be used as prognostic parameters to predict treatment outcome.
3. The tumour burden score (Arthur score) is predictive of overall, disease-free and recurrence-free survival.
4. Patients with low pretreatment haemoglobin levels (<7gm%) and vaginal tumour extension beyond the upper 1/3 have a very poor prognosis.
5. The outcome for young patients (<36yrs) with hydronephrosis and bilateral pelvic side wall involvement is poor.

#### **4.1 Prognostic Factors**

The treatment of locally advanced cervical carcinoma remains a challenging clinical problem. Although aggressive radiotherapy is beneficial in some cases, local control and overall survival rates are still unsatisfactory for the vast majority of patients with Stage III disease. Investigators have reported survival rates of between 25 to 50% for patients treated with radiation therapy alone (Kovalic et al., 1991, Lanciano et al., 1991, Montana et al., 1986). It has become clear that these discrepancies are not only due to different treatment modalities (Kovalic et al., 1991, Lanciano et al., 1991 and 1992), but that intrinsic tumour factors and patient-related factors play an important role (Arthur et al., 1995, Dubben et al., 1998, Perez et al., 1998, Hsu et al., 1998).

Several prognostic factors have been identified that have a profound influence on outcome and prognosis (Perez et al., 1992, Stehman et al., 1991). Some are related to host characteristics (age, performance status, haemoglobin levels), and others are related to the tumour itself (tumour volume, histopathological type, vessel density). Many of the risk factors are interrelated and as a result, it has become difficult to be certain which of several factors are responsible for the patient's overall risk. The variability in treatment success of advanced cervical cancer emphasizes the need for better risk assessment of patients prior to radiation therapy. It is important to identify subgroups of patients with unsatisfactory outcome and attempt to change their prognosis through different treatment approaches.

#### **4.2 Tumour Size**

The volume and local extent of a cancer is a fundamental prognosticator for almost any primary site. This is reflected by the FIGO classification for cervical cancer which correlates increased tumour size and local invasion with a higher staging (Benedet et al., 2000). However, even within a given stage there can be substantial variation in tumour volumes, and the FIGO staging system makes no provision for this. In 1980 Fletcher stressed the importance of tumour volume, and more recently Perez (1998) demonstrated that tumour size is a critical factor in prognosis and therapeutic efficacy of cervical cancer.

There has been no consistent agreement of how to define tumour volume within clinical stage. Kovalic (1991) found that central bulky disease, defined as  $\geq 5$ cm in diameter, was associated with decreased 5-year disease-free survival in both stage IIIB and IIIB patients. Lowrey et al. (1992) reported that tumour size ( $\geq 6$ cm) was an independent predictor of pelvic control, distant relapse, and disease-free survival in stage I or II tumours. In a retrospective analysis of 1178 patients Perez (1992) defined "bulky" tumours as lesions  $\geq 5$ cm and showed that tumour size was directly related to pelvic failure rate and inversely related to disease-free survival.

Assessing tumour size and volume by means of pelvi-rectal examination is “at best an inaccurate estimation of the extent of the disease” (Soeters et al., 1991). Errors of clinical staging have been reported to be as high as 54% and increase with advancing stage (van Nagel et al, 1971). The main areas of error are misinterpretation of parametrial and pelvic side wall involvement. Early surgical studies demonstrated that in many cases, tumours thought to be extending to the pelvic side wall on physical examination, were actually tethered to adjacent structures by scar tissue, possibly from old infection or obstetrical injury (Lohe et al., 1969).

In our own study we distinguished between tumour sizes of  $\geq 5$ cm in diameter or less. Only 26 tumours were thought to have diameters between 2-5cm which may be due to the fact that most patients present with advanced and big tumours, but it may also represent a relative overestimation of tumour size by the examiners as mentioned above. The group of patients with bulky tumours showed a trend towards decreased disease-free survival as well as decreased overall survival rates. However, the difference between the two groups did not reach statistical significance. There was no difference between the groups with regards to locoregional recurrence rates. The lack of statistical significance between the groups could be due to the fact that the “non-bulky” tumour group (< 5cm diameter) contained only a small number of patients (n=26). One could speculate that a more equal distribution of patients between the two groups would result in a significant difference in the survival rates.

The vast majority of studies has found cervical tumour size to be an independent prognostic variable, and in 1994 Stehman and Thomas concluded that “there is a consensus conclusion that size within stage is a significant prognostic factor”.

#### **4.3 Parametrial Involvement**

Several reports have described a strong association between the extent of parametrial involvement and survival rates (Kovalic et al., 1991, Perez et al., 1992, Lanciano et al., 1991). Fyles et al. (1995) compared patients with unilateral pelvic side wall involvement

with either unilateral sidewall/contralateral parametrial involvement or bilateral side wall disease. Outcome was significantly worse in the group with bilateral disease ( $p=0.007$ ).

Kovalic et al. (1991) examined the effect of volume of disease on survival and reported that bilateral parametrial invasion in Stage IIIB cancer decreased the 10-year DFS from 50% for unilateral disease to 34% for women with bilateral disease ( $p=0.006$ ). In the same study the presence of bilateral parametrial disease nearly doubled the rate of pelvic failures compared to unilateral disease, but the difference between the groups did not reach statistical significance ( $p=0.69$ ).

Perez et al. (1998) also found statistically significant better DFS for unilateral disease in comparison with bilateral disease (57% vs 35% 10-year DFS). The analysis of pelvic failure rates showed a 25% pelvic failure rate for unilateral pelvic sidewall extension in contrast to 45% for bilateral involvement.

Our own data showed less locoregional recurrences in patients with unilateral disease compared to women with bilateral pelvic side wall extension ( $p=0.098$ ). We could not demonstrate any differences in disease free survival or overall survival rates between the group with bilateral pelvic side wall involvement and patients with unilateral disease. Similar results have been reported in a study by Hopkins et al. (1993) who analysed the outcome of 113 patients with Stage IIIB disease. He found that the presence of disease to one or both sidewalls did not influence survival. The cumulative 5-year survival was 36% with unilateral disease and 34% with bilateral disease.

The “Patterns of Care” Study was the first multivariate analysis to demonstrate the negative effect of bilateral pelvic side wall involvement on survival and in-field pelvic control (Lanciano et al., 1992). The authors suggested that that the FIGO staging system inadequately accounts for the variability in the extent of pelvic disease within Stage IIIB disease and recommended a separation of Stage III by extent of pelvic side wall involvement for prospective trials of treatment in order to be certain that treatment – and not tumour extent – is responsible for improvement in outcome.

Considering our own results it is likely that the exclusion of patients with bilateral hydronephrosis from the group with bilateral pelvic side wall involvement had a large impact on the survival rates in this group. It has previously been demonstrated that bilateral renal obstruction is a poor prognostic factor (Lee et al., 1994), and inclusion of these patients in other studies may very well be responsible for the demonstrated differences in outcome.

#### **4.4 Vaginal Involvement**

Patients with Stage IIIB cervical cancer can have simultaneous involvement of the vagina. There is a considerable variety of possible tumour extension within the vagina, ranging from no or minimal upper vaginal disease to the involvement of the entire vagina to the introitus. The FIGO staging system makes no provision for this. We identified two groups amongst patients with Stage IIIB disease, and found 27 patients with no vaginal involvement or less than one-third of upper vaginal involved and 72 patients with vaginal tumour spread beyond the upper third of the vagina. The latter group showed a poorer outcome in terms of overall survival ( $p=0.067$ ) with a trend towards decreased disease-free survival rates ( $p=0.055$ ). There was a slightly higher rate of locoregional recurrences in the group with more extensive tumour spread ( $>1/3$ ), but this did not reach statistical significance.

Montana et al. (1986) reviewed 203 patients with Stage III carcinoma of the cervix who received treatment between 1969 and 1980. They reported poorer 5- and 10 year survival rates for Stage IIIA in comparison to Stage IIIB disease (26% vs 35% and 18% vs 30% respectively). Unfortunately, 83% of their patients with Stage IIIA disease received external beam therapy only (31% of Stage IIIB), which may also account for the high rate of locoregional recurrences (42% Stage IIIA and 33% Stage IIIB).

In 1992 Lanciano et al. reported from their "Patterns of Care" Study. Eighteen percent of patients ( $n=289$ ) had Stage III disease. Multivariate analysis revealed a significant

difference in actuarial survival for unilateral versus bilateral pelvic side wall versus lower one-third vaginal involvement for patients with Stage IIIB disease ( $p < 0.001$ ). With the same analysis the authors also demonstrated significant prognostic value of the three parameters with respect to in-field pelvic control : unilateral sidewall involvement had the most favourable prognosis, bilateral sidewall involvement was intermediate in prognosis, and lower-third vaginal involvement was shown to be the least favourable pelvic extension with regards to local recurrence and survival.

The most recent study reporting on the significance of vaginal involvement in Stage IIIB cervical cancer was published by Logsdon et al. in 1999: retrospective analysis of 983 patients treated with curative intent confirmed that poor disease specific survival was correlated with involvement of the lower third of the vagina ( $p = 0.0001$ ). However, 29% of their patients did not receive intracavitary radiation (between 1966 and 1980). To confirm the findings for patients who were offered more modern treatment, a subgroup of 178 patients was re-analysed. The correlation between vaginal involvement and disease-specific survival was weaker but still significant with a p-value of 0.04.

#### **4.5 Hydronephrosis**

It is generally accepted that ureteral obstruction correlates with a poor outcome in patients with cervical cancer (Lee et al., 1994). Hopkins et al. (1993) reported 5-year survival rates of 47% in a group of patients with Stage IIIB disease and normal intravenous pyelogram. When ureteric obstruction was present 29% survived, and when renal failure occurred, all patients were dead of disease by 16 months ( $p = 0.00001$ ).

Logsdon et al. (1999) analysed prognostic factors in Stage IIIB cervical cancer: 25% of patients had unilateral hydronephrosis, 6% had bilateral ureteric obstruction and 69% had a normal pyelogram. The survival rates were generally poorer for patients with evidence of hydronephrosis ( $p = 0.08$ ).

In 1998 Chao et al. (1998) investigated the clinical implications of hydronephrosis and the level of ureteric obstruction. The authors found that, when hydronephrosis resulted from tumour fixation to the pelvic side wall, the progression-free survival did not significantly differ from those patients without hydronephrosis. Patients with hydronephrosis but without tumour fixation to the pelvic side wall had a worse prognosis when compared to the rest of Stage IIIB patients. This was thought to be due to grossly enlarged lymph nodes compressing the ureter.

In our own study the presence of unilateral hydronephrosis proved to be a significant prognostic factor with poor overall survival rates ( $p=0.012$ ), reduced disease-free survival ( $p=0.047$ ) and decreased pelvic recurrence-free survival ( $p=0.0016$ ) in comparison to patients without hydronephrosis. We did not distinguish between levels of ureteric obstruction, and it therefore remains speculative how many patients suffered from ureteric compression secondary to lymphadenopathy.

#### **4.6 Haemoglobin Levels**

It has long been suspected that anaemia during radiotherapy predicts poor outcome. However, it has not been clear whether anaemia leads to an increase in the hypoxic tumour fraction with subsequent decreased radiosensitivity, or whether anaemia at initial presentation is the result of a more aggressive tumour and not an independent predictor of outcome. The significance of raising haemoglobin levels during treatment with red cell transfusions or erythropoetin and the impact on treatment outcome is also unclear.

Takeshi et al. (1998) measured pretreatment haemoglobin levels in 265 women with Stage III cervical carcinoma and reported significant higher survival rates in patients with initial Hb level  $\geq 9\text{g/dl}$  compared to those with a lower Hb ( $53.1\%$  vs  $25\%$ ,  $p=0.0005$ ). This is in agreement with our own study: women presenting with an initial haemoglobin level  $\geq 9\text{g/dl}$  had higher overall survival rates ( $p=0.034$ ), better disease-free survival rates ( $p=0.037$ ), and increased recurrence-free survival rates ( $p=0.0017$ ) in comparison to women with initial Hb levels  $< 9\text{g/dl}$ .

A recent analysis of 983 Stage IIIB cervical cancer patients treated at M.D. Anderson confirmed the prognostic significance of the lowest haemoglobin level during radiotherapy with a reduction in disease-specific survival from 44% to 29% with haemoglobin levels < 10g/dl (Logsdon and Eifel, 1999).

In the only randomized trial of transfusion for anaemia before radiotherapy, Bush (1986) randomized 132 patients with stage IIB and III cervical cancer to red blood cell transfusion versus no intervention. Only patients initially anaemic (Hb 10 to 12.5 g/dl) appeared to benefit from the transfusion. However, the study's conclusion of benefit is undermined by the small patient numbers and the lack of a multivariate analysis to evaluate the impact of other prognostic factors. Furthermore, in contrast to the report of Bush (1986), Vigario et al. (1973) and Evans and Bergsjö (1965) did not find a statistically significant improvement in survival of anaemic patients who were transfused prior to therapy. In our own group of patients we could not demonstrate any survival benefit for patients with haemoglobin levels  $\geq$  10g/dl during treatment in comparison to women with mean Hb levels < 10g/dl. However, we did not separate patients requiring transfusion from those who did not as this was not a primary outcome measure in our study.

In contrast to other studies where patients received transfusions prior to radiotherapy many of our patients only received red blood cell transfusion during their treatment and were generally transfused to maximum Hb levels of 10 g/dl. In addition, it seems that an actual survival benefit may only be seen with maintaining haemoglobin levels at  $\geq$  12g/dl throughout treatment (Vigario, 1973). Grogan et al. (1999) reported a multi-institutional Canadian survey of anaemia and transfusion practice in 605 patients with cervical cancer. In multivariate analysis, average weekly nadir haemoglobin levels during therapy significantly correlated with local control, disease-free survival, and overall survival. The 5-year survival was 74% for patients with an average weekly nadir Hb  $\geq$  12g/dl, 52% for levels 11 to 11.9 g/dl, and 45% for levels < 11g/dl. At each level of haemoglobin, patients who were transfused and attained a higher haemoglobin level had

a survival not significantly different from those at that level spontaneously. The data, however, has limitations as the patients were not randomized, and the number of patients with Hb levels that changed from low to high was relatively small. Any effect of tumour size was not evaluable because of incomplete data.

#### **4.7 Tumour Burden Score**

Although the FIGO staging system for cervical cancer strongly predicts survival (Fletcher, 1980, Lanciano et al., 1991), there still is a considerable variability in outcome. In 1995 Arthur et al. acknowledged that it remains uncertain as to how stage IIIB should be stratified for improved predictability of survival. The authors demonstrated that patients with a low tumour burden score ( $\leq 4$ ) had a significantly better rate of loco-regional control, disease-free and overall survival in comparison with patients who had high tumour burden scores ( $> 4$ ).

We calculated tumour burden scores as described by Arthur et al. (1995) for all our patients and found a significant correlation between high scores and poor recurrence-free survival ( $p=0.0076$ ), disease-free survival ( $p=0.014$ ), and overall survival ( $p=0.014$ ). The tumour burden scoring system could be used to subdivide Stage IIIB into two prognostic groups with the view to a more aggressive treatment approach in patients who score high on the scale ( $> 4$ ).

#### **4.8 Johannesburg Staging**

In a personal communication Dr J Kotzen from the Department of Radiation Oncology at Johannesburg General Hospital suggested the separation of Stage IIIB cervical cancer into unilateral pelvic sidewall involvement (IIIBi) versus bilateral sidewall involvement or hydronephrosis (IIIBii). In his own observations these two groups had a different prognosis with regards to survival and in-field pelvic control.

When we subdivided our patients accordingly we found that the subgroup IIIBi had significantly better pelvic recurrence-free survival ( $p=0.0023$ ), a higher disease-free survival rate ( $p=0.041$ ), and a trend towards improved overall survival ( $p=0.35$ ) in comparison with the group IIIBii.

Lanciano et al. (1991) analysed 289 patients with Stage III disease and reported similar results indicating poor overall survival and higher rates of locoregional recurrence for patients with bilateral pelvic side wall involvement compared to unilateral side wall extension.

In summary, we found that in our group of patients with Stage IIIB cervical cancer the presence of hydronephrosis, pretreatment haemoglobin levels  $< 9\text{g/dl}$ , and Arthur scores  $> 4$  had significant predictive value for poor overall survival and pelvic recurrence-free survival. This analysis further emphasizes the importance of careful assessment of each individual patient within FIGO stage IIIB with regards to the abovementioned prognostic parameters.

#### **4.9 Decision Analysis and Impact on Clinical Management of Women with Cervical Cancer**

Clinical management of these patients can be facilitated by the use of decision trees depending on the specific risk profile of each individual patient. Women with a combination of pretreatment haemoglobin levels below  $7\text{gm}\%$  and more than one-third vaginal involvement had a 100% mortality rate in our study (Figure 2). Although absolute numbers are small ( $n=6$ ), patients with these combined risk factors should rather be considered for palliative care. Whether concurrent chemoradiation would significantly alter mortality in this particular subgroup of women is unknown.

Patients less than 36 years of age with evidence of hydronephrosis had a 50% probability of dying from the disease within the first year of diagnosis. Considering the relative

young age of these patients in combination with a 50% chance of survival beyond the first year, radical radiotherapy seems to be an appropriate approach.

For those women with bilateral parametrial involvement to both pelvic side walls or unilateral extension to one pelvic side wall with more than 50% parametrial involvement on the opposite side, probability of mortality was calculated as 80% within the first year. A 20% chance of survival should be a strong argument for palliation considering that survival will decrease even further after 2 to 3 years.

All remaining women without hydronephrosis, haemoglobin levels above 7gm%, vaginal involvement less than one-third and age >36 years have a 83% chance to survive the first year after diagnosis and should receive maximum therapy.

The Tumour Burden Scoring System (TBS) as described by Arthur et al. (1995) is a simple method to identify “high risk” patients with stage III disease who are characterised by poor treatment response to conventional radiation treatment. This particular subgroup of patients constitutes a therapeutic dilemma because there are no existing guidelines for their management. It may be argued that in a low-resource setting these women should be considered for palliative radiotherapy only. Currently large numbers of patients are competing for the few available radiation facilities in South Africa, and there is considerable pressure on our scarce resources. Offering palliation only to patients with high TBS scores would most certainly result in considerable savings of human and financial resources, but constitutes an ethical dilemma at the same time.

The opposite route would be a more aggressive treatment approach for women with stage IIIB disease and a high TBS. Improvement of pelvic control and survival can be achieved by increasing the dose of radiation. Arthur et al. (1995) found that patients with high tumour burden experienced significantly improved tumour control when doses > 78 Gy were given to Point A. However, radiation complications are the upper limit of acceptability for dose escalation. As a result, other strategies have been investigated in order to improve outcomes for cervical cancer. These include modifications of radiation treatment volumes (Rotman et al., 1995), or radiation fractionation schemes (Thomas,

2000), methods of overcoming the negative impact of tumour hypoxia (Dische et al., 1983), and combination of radiation and chemotherapy as concurrent treatment (Kumar et al., 1995, Tattersall et al., 1995, Souhami et al., 1991).

At present, five randomized clinical trials have been published on the outcome of concurrent chemotherapy with external beam radiation and intracavitary treatment for cervical cancer (Thomas, 2000). All five trials showed a survival benefit for patients receiving chemoradiation ranging between 30% and 50%. In February 1999 the U.S. National Cancer Institute announced that “these five randomized phase III trials show that platinum-based chemotherapy, when given concurrently with radiotherapy, prolongs survival in women with locally advanced cervical cancer, stages IB to IVA.....” and “strong consideration should be given to the incorporation of chemotherapy with radiation therapy...”.

However, there remains uncertainty whether patients with bulky stage IIB, IIIB, and IVA disease benefit from concurrent therapy (Thomas et al., 1998, Morris et al., 1999). In the RTOG trial only 30% of patients had stage III or IVA disease, and in a subset analysis no significant improvement in survival was noted in this subgroup. Thomas et al (1998) also failed to demonstrate a survival benefit for bulky IIIB cancers with concurrent chemotherapy. At present, there remains some doubt that chemoradiation is superior to radiotherapy alone in patients with stage III or IVA disease, and further trials are needed before it can be concluded that benefit exists.

## **Chapter Five**

### **Conclusions**

In patients with stage IIIB cervical cancer the presence of hydronephrosis, the level of the pre-treatment haemoglobin, and the tumour burden score are prognostic factors for the therapeutic outcome.

The presence of specific risk factors can guide the clinician in the selection of patients with poor prognosis.

New treatment strategies like concurrent chemoradiation may improve the therapeutic ratio for this group of women.

In resource-poor settings palliative treatment should be reserved for women with a combination of poor prognostic parameters.

All other women should have access to a full course of aggressive radiotherapy.

## Chapter 6

### Literature

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Figure 4

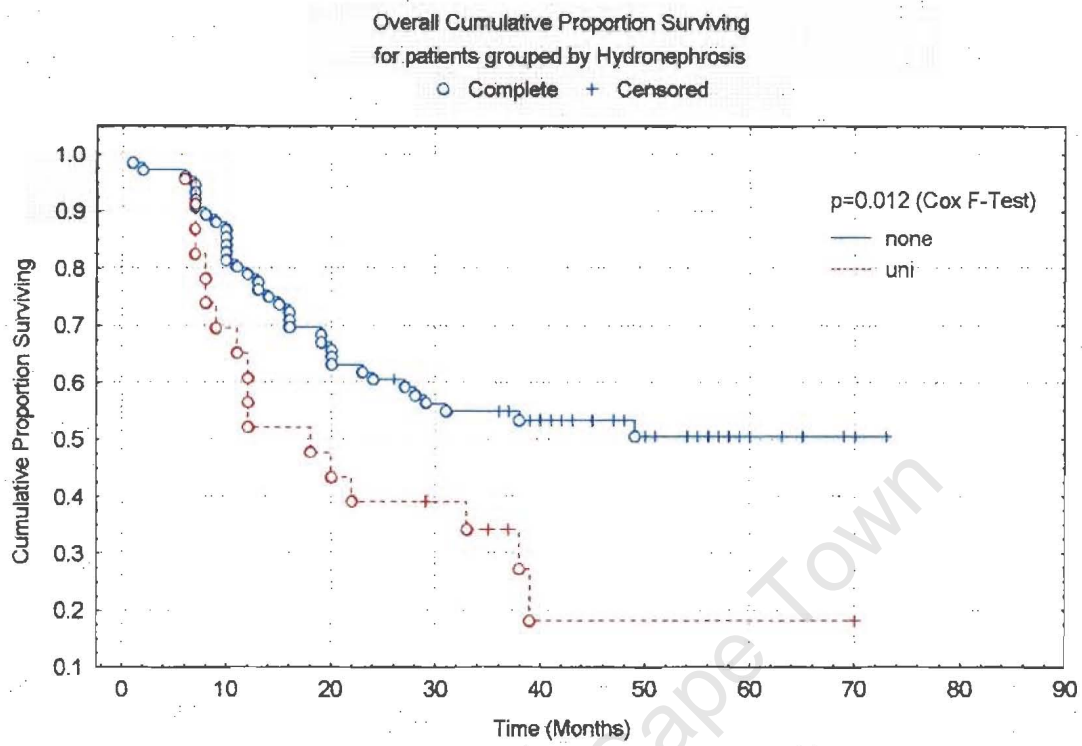


Figure 5

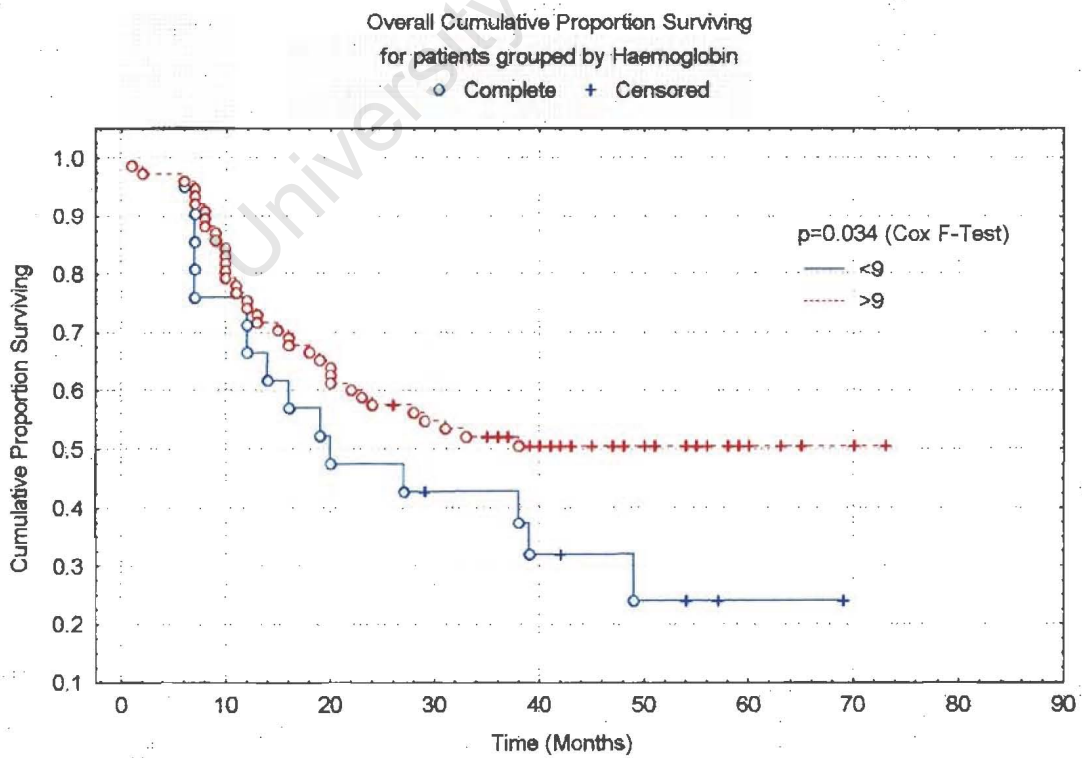


Figure 6

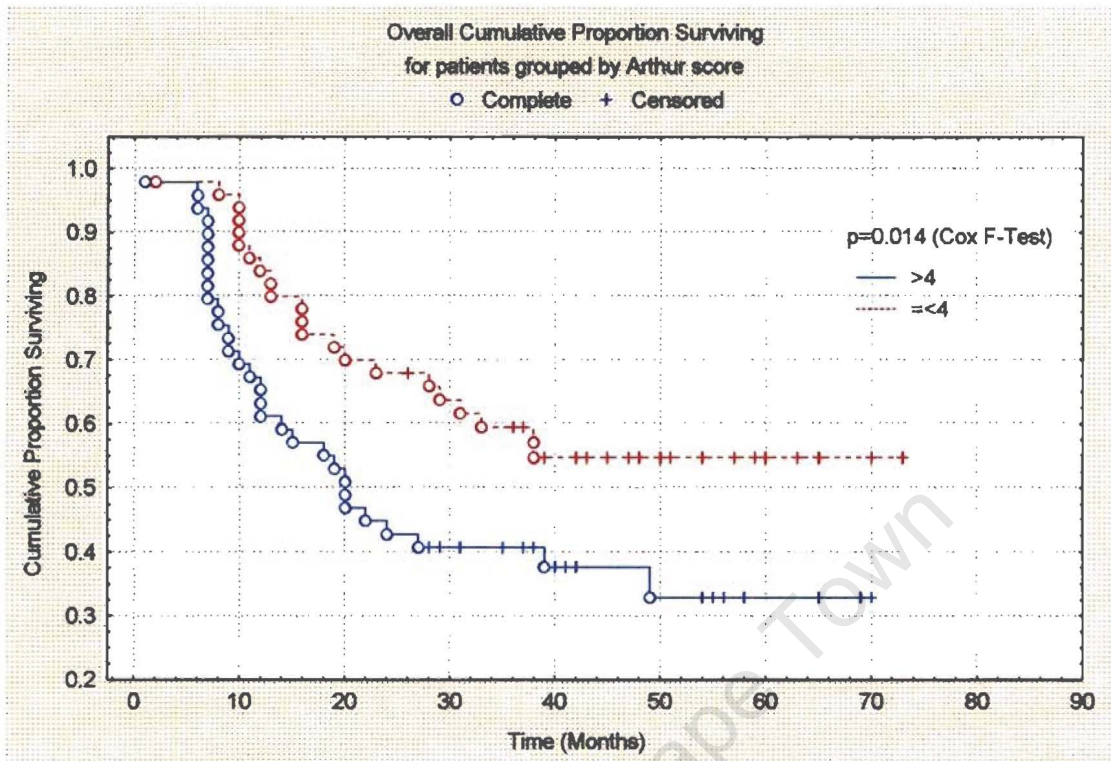


Figure 7

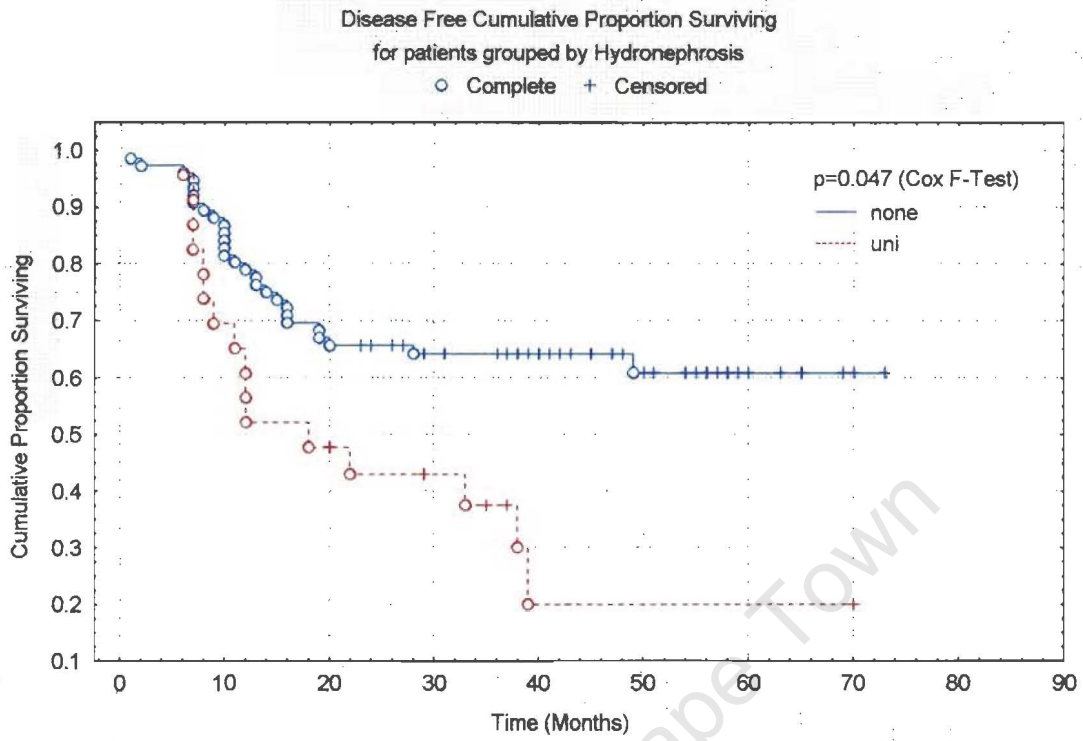


Figure 8

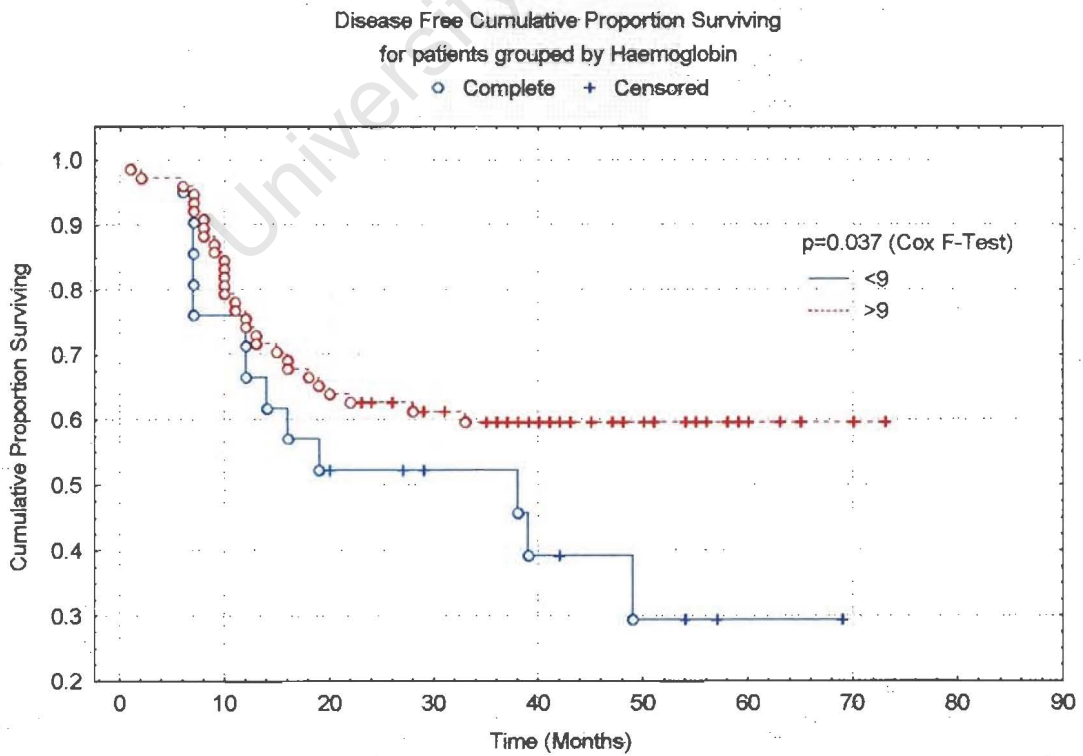


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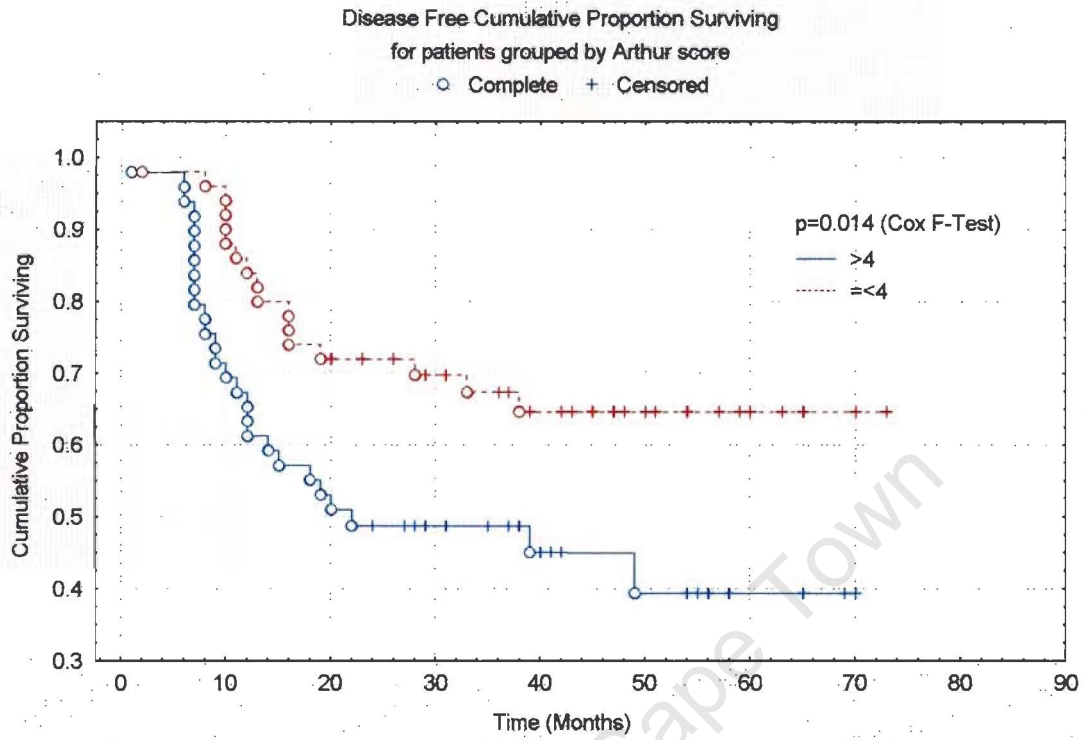


Figure 10

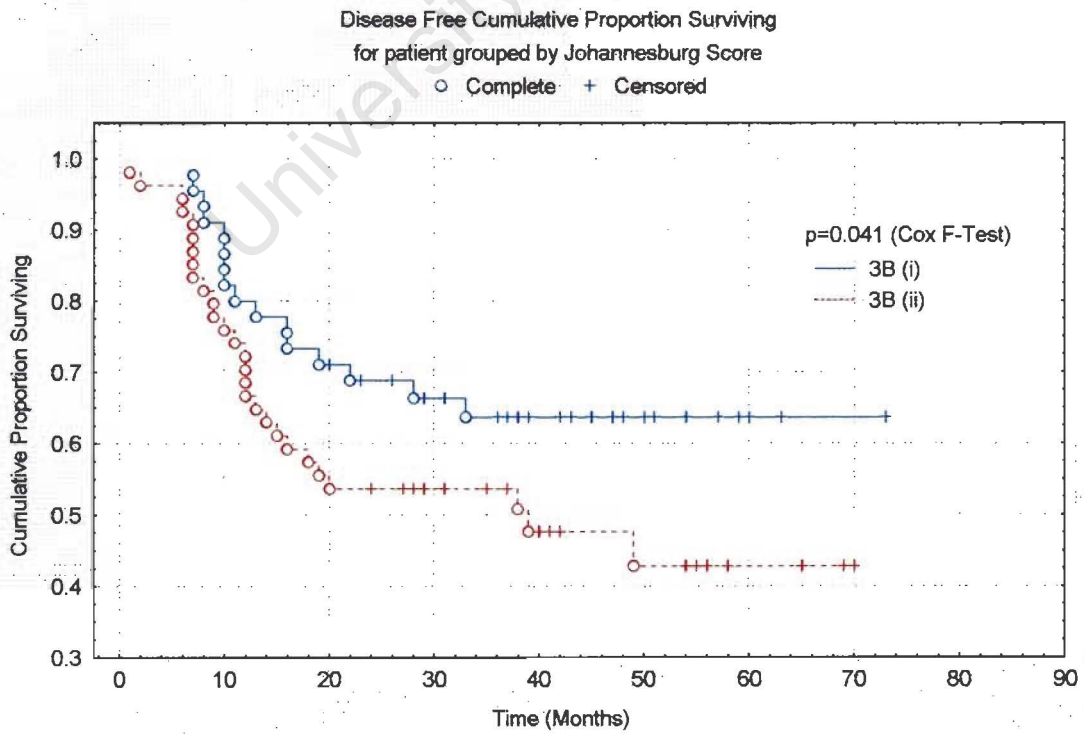


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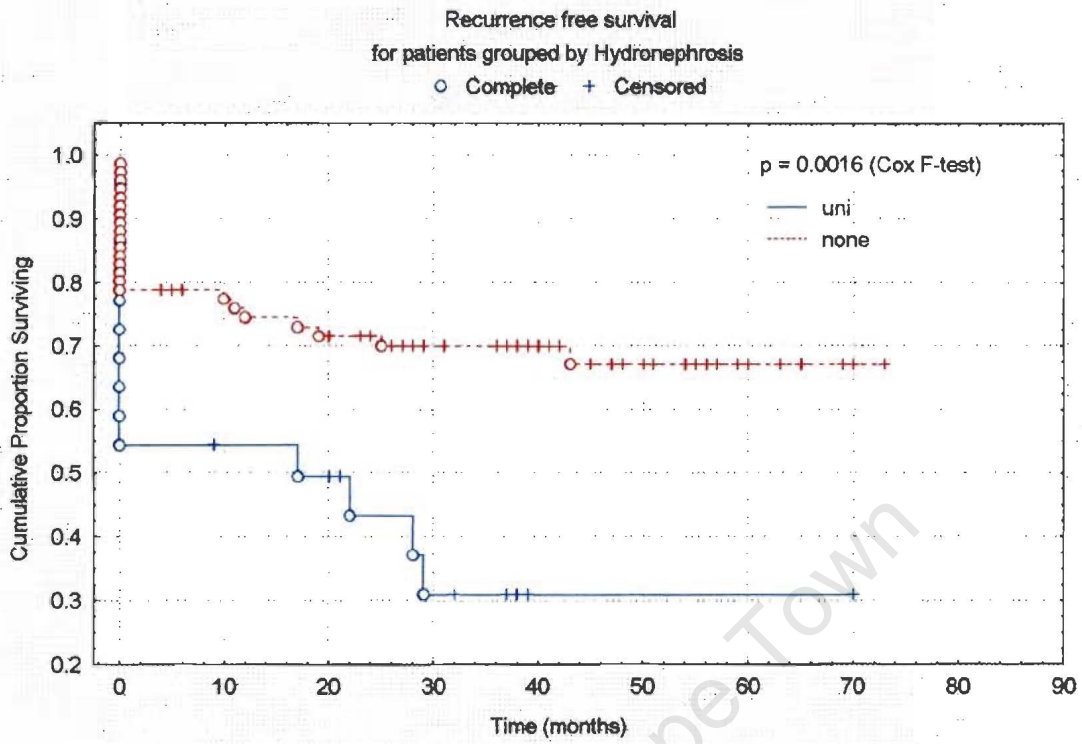


Figure 12

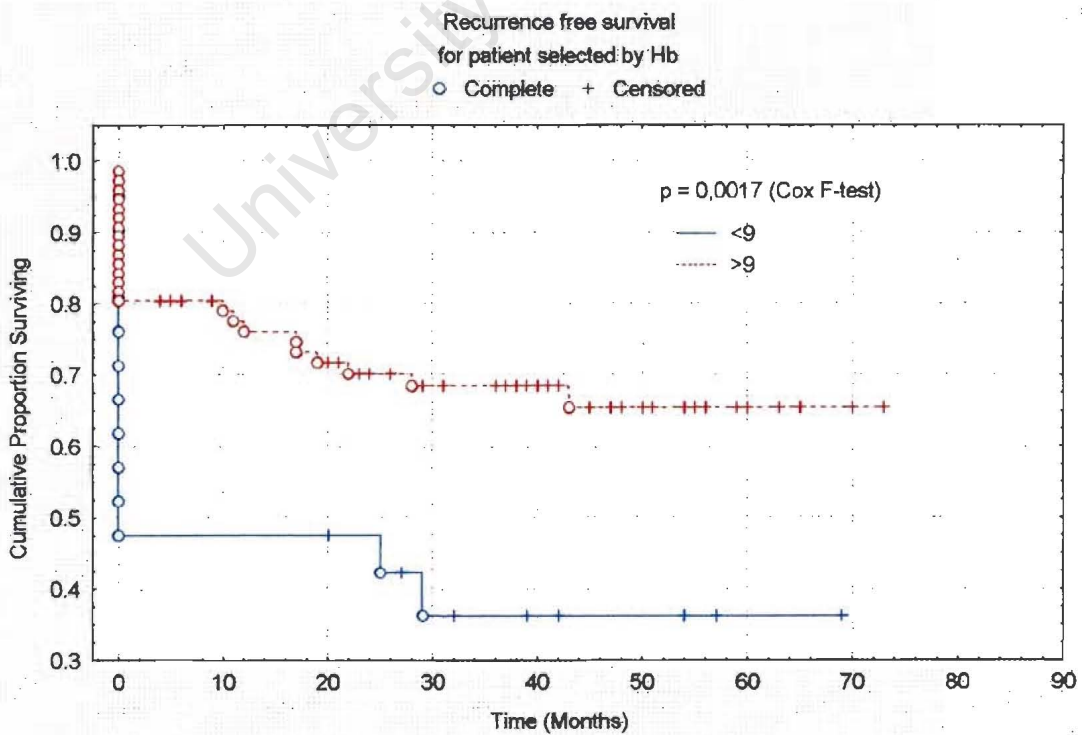


Figure 13

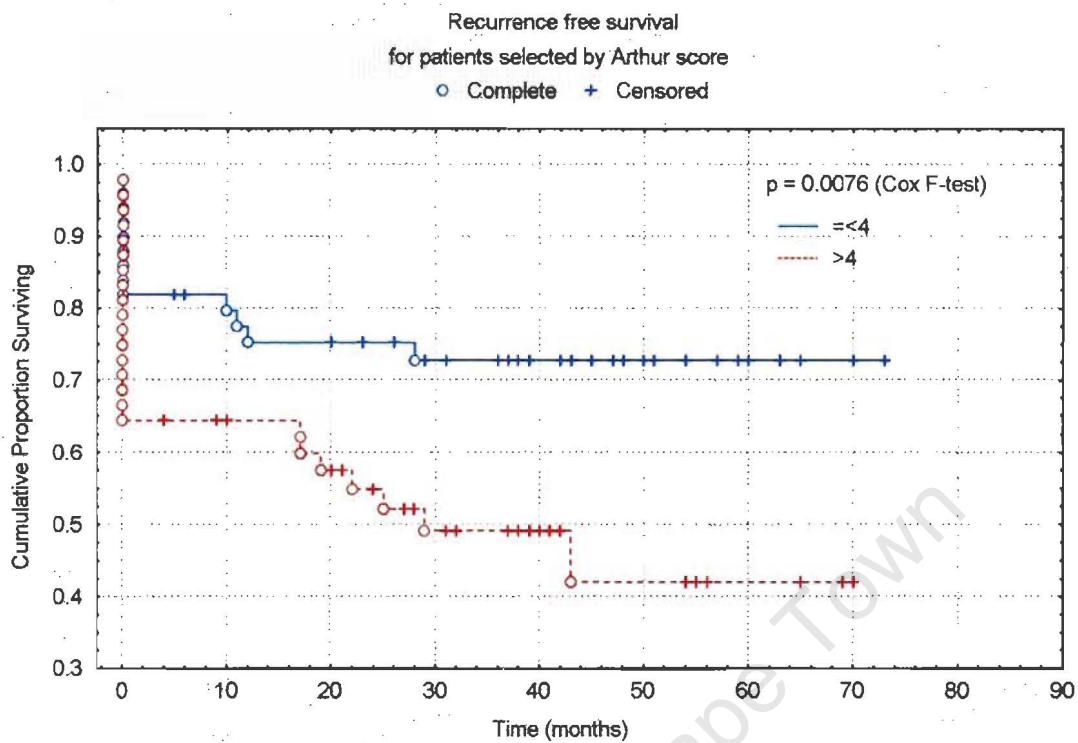
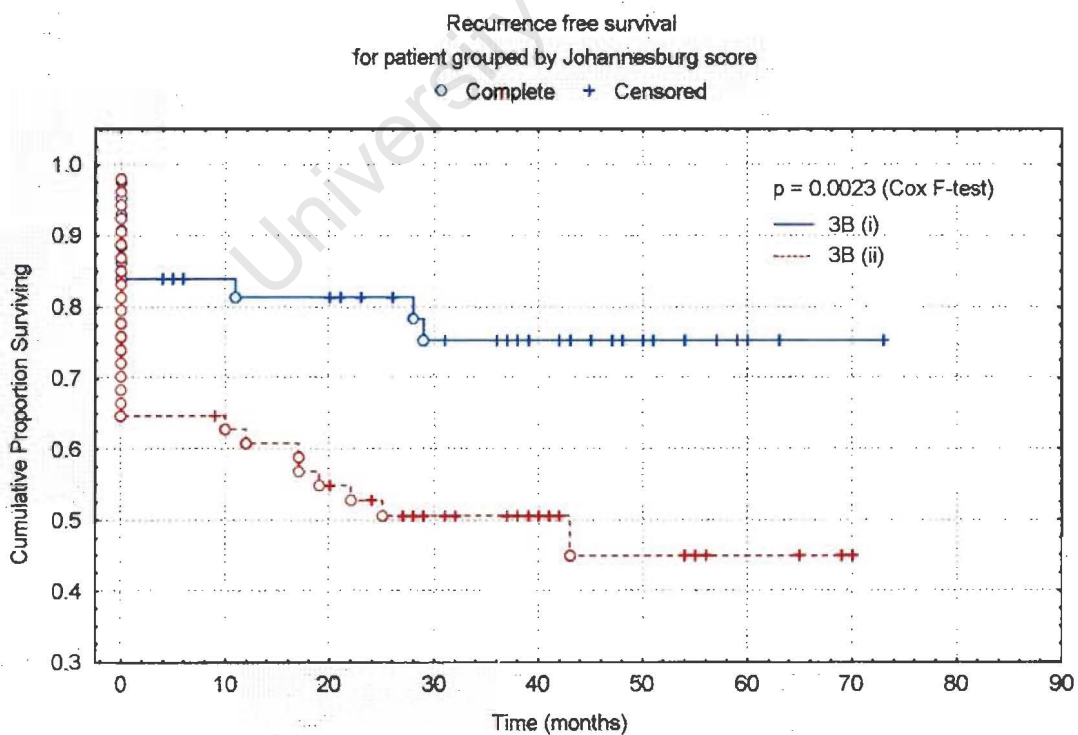


Figure 14



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University of Cape Town