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**WILMS' TUMOUR OUTCOMES AT  
RED CROSS CHILDREN'S  
HOSPITAL 1979-2003**

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# FOREWORD

The first patient with Wilms' Tumour to be entered onto the Children's Cancer Registry at the Red Cross Children's Hospital was a 19-month-old girl. She was admitted in December 1966 with a left-sided Wilms' tumour. She was given dactinomycin and radiotherapy pre-operatively and then came to nephrectomy, after which she received further radiotherapy. She relapsed with a pulmonary metastasis three years later. This was removed at thoracotomy and she was treated by Cyril Karabus with vincristine and dactinomycin for the next 18 months. When she was lost to follow up nine years later in 1980, she remained alive and disease free. Three hundred and twenty six patients with Wilms' Tumour have followed in her footsteps. Most of them are also survivors.

This thesis should stand as a tribute to Cyril Karabus and his successors, Paddy Hartley and Farieda Desai, who have delivered quality care to several generations of children suffering from both malignancies and haematological disorders.

While modern multimodal cancer therapy has yielded results of which we can be rightfully proud, it remains an ongoing responsibility to audit those outcomes. Where we fall short of the high standards set by international cooperative groups, we must be ready to scrutinise our deficiencies and look

for solutions. That was the brief I set for myself and I hope that it has been achieved.

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# ABBREVIATIONS

BWT	Bilateral Wilms' Tumour
BWS	Beckwith-Wiedemann syndrome
CT	Computed Tomography
EFS	Event Free Survival
FH	Favourable Histology
GPOH	German Society for Paediatric Haematology and Oncology
Gy	Gray (a unit of measure of absorbed radiation dose)
IE	Ifosfamide and Etoposide
ICE	Ifosfamide, Carboplatin and Etoposide
IVCT	Inferior vena cava tumour thrombosis
NWTS	National Wilms' Tumor Study
NWTSG	National Wilms' Tumor Study Group
OS	Overall Survival
PTT	Partial Thromboplastin Time
RCCH	Red Cross Children's Hospital
RFS	Relapse Free Survival
SIOP	International Society of Paediatric Oncology
UFH	Unfavourable Histology
UKCCSG	United Kingdom Children's Cancer Study Group
UWT	Unilateral Wilms' Tumour
WT	Wilms' Tumour
VOD	Veno-occlusive disease

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# **ABSTRACT**

## **BACKGROUND**

In Africa Wilms' tumour frequently presents with advanced disease. This study reports our results over 25 years using the National Wilms' Tumor Study Group approach of primary surgery, in the form of nephrectomy, followed by chemotherapy. A small number of these tumours are bilateral and here surgery has evolved from simple nephrectomy into the use of nephron-sparing techniques.

## **METHODS**

A retrospective analysis was performed on all patients diagnosed with Wilms' tumour between January 1979 and December 2003. Treatment was according to National Wilms' Tumor Study Group protocols. For unilateral Wilms' tumour primary surgery, where possible, was followed by adjuvant chemotherapy with vincristine and dactinomycin. Doxorubicin was added for stage III and IV tumours. Other drugs were used for unfavourable histology, and radiotherapy was reserved for local stage III tumours and pulmonary metastases. Patients with bilateral Wilms' tumours underwent initial bilateral biopsy, neoadjuvant chemotherapy and tumourectomy. Where indicated, nephrectomy (partial or complete) involved using ice dam topical cooling and vascular control, and in one case bench surgery and extensive renal reconstruction with orthotopic autotransplantation. Revision tumourectomy was utilized on three occasions for recurrence in areas of

nephroblastomatosis. Radiotherapy was reserved for pulmonary metastases and palliation.

## RESULTS

There were 188 children with unilateral Wilms' tumour and 20 with bilateral Wilms' tumour. Among those with unilateral Wilms' tumour fifty seven (30.3%) were stage I, 33 (17.6%) were stage II, 60 (31.9%) were stage III and 38 (20.2%) were stage IV. Twenty-four patients (12.8%) had unfavourable histology. Fifteen of the bilateral Wilms' tumours had a synchronous presentation, one with liver metastases at diagnosis, and five were metachronous. Nephroblastomatosis was identified in 18 of the 20 patients (90%) with bilateral Wilms' tumour.

One hundred and forty five patients are alive and disease free, 23 to 318 months from diagnosis. The estimated 5-year overall survival for all unilateral Wilms' tumours was 78.3%; 82.8% for favourable histology and 47.3% for unfavourable histology. Among those with favourable histology, estimated 5-year overall survival was 94.6% for stage I, 96.2% for stage II, 78.4% for stage III and 54.2% for stage IV. There was no difference in overall survival between those favourable histology stage III tumours that were operable and those deemed inoperable. Intra-operative spillage was uncommon (8%), and did not increase local relapse rate. Survival of stage IV disease has not improved over the last decade.

Among those with bilateral Wilms' tumours, 11 are alive free of disease one to fifteen years after completing treatment, all with well-preserved renal function. Nine have died (two of unrelated disease), including six of the seven with spread outside the kidney. All three with unfavourable histology are alive, as are four of the five with a metachronous presentation. Survival for bilateral Wilms' tumour has improved markedly in the last decade.

## **CONCLUSIONS AND RECOMMENDATIONS**

National Wilms' Tumor Study Group protocols employed in a South African setting with highly competent and experienced surgical care, produced results for non-metastatic favourable histology unilateral Wilms' tumour comparable to those of the National Wilms' Tumor Study Group. For bilateral Wilms' tumours appropriate chemotherapy together with conservative (nephron-sparing) and innovative surgery produced good results with preservation of adequate renal function in nearly all cases.

We can seek to improve outcomes via better risk stratification with molecular markers, new adjuvant chemotherapy regimes for high risk tumours and novel surgical approaches to improve nephron-sparing in bilateral Wilms' tumour. Improving results in Stage IV patients may depend as much on earlier diagnosis, as on advances in therapeutics.

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# CHAPTER ONE:

## BACKGROUND

Wilms' tumour (WT) or nephroblastoma is one of the paediatric embryonal tumours. It was named for Max Wilms, a German surgeon of the nineteenth century who wrote a monograph on the subject in 1899. <sup>1</sup> The tumour arises from the primitive kidney or metanephric blastema and in its classic form consists of three elements; blastema, stroma and an epithelial component.

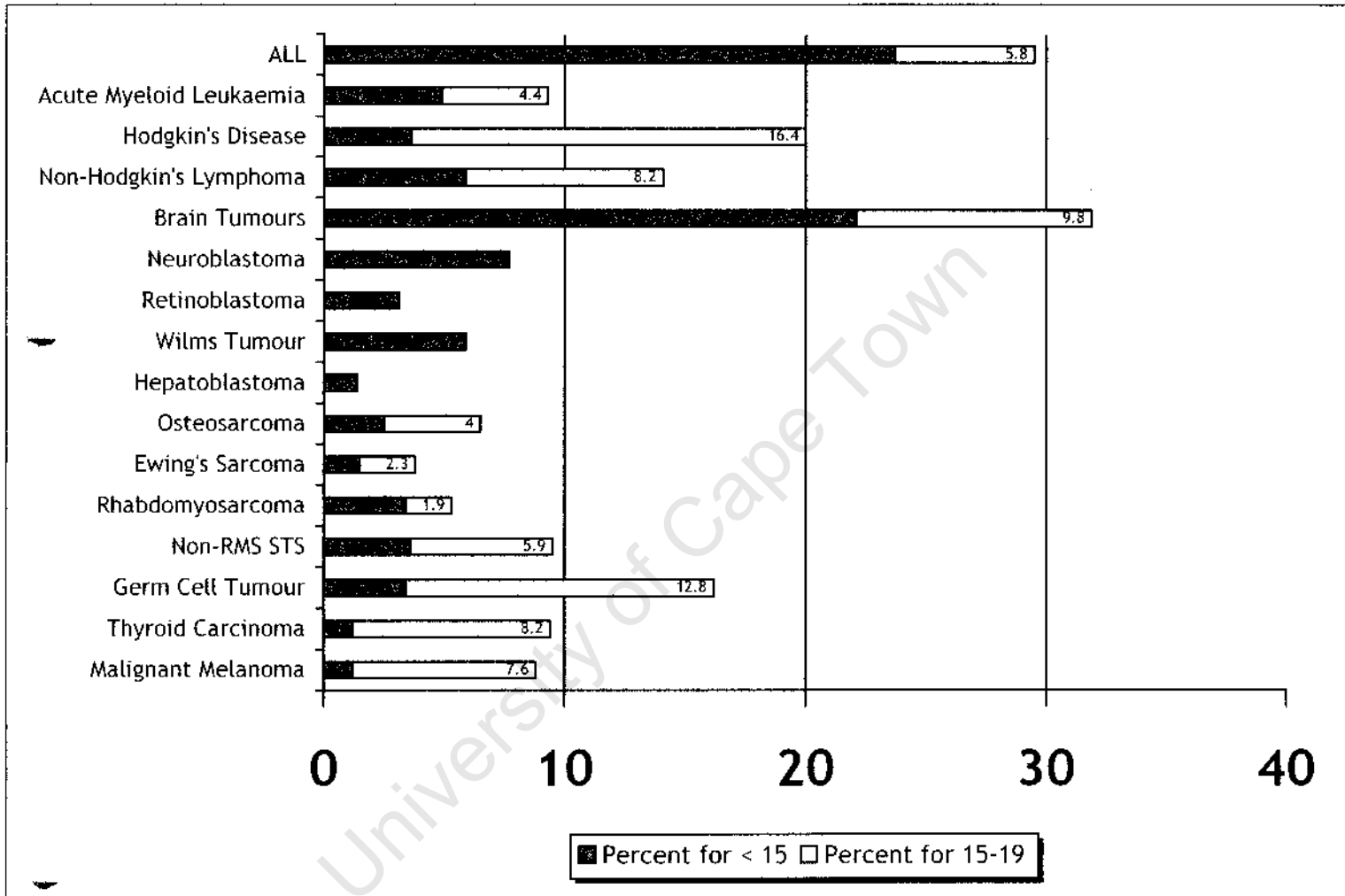
WT is the most common childhood renal tumour. In North America it is the fourth commonest malignancy among children under the age of fifteen. <sup>2</sup> Only acute lymphoblastic leukaemia, brain tumours and neuroblastomas occur more frequently [figure 1]. The annual incidence of WT in the United States among children under fifteen between 1975 and 1995 was 7.6 per million. <sup>3</sup>

WT has been found to be slightly more common among blacks than whites. Annual incidence per million 0-19 year olds in the United States between 1990 and 2001 was 7.6 for blacks and 6.9 for whites. For neuroblastoma the annual incidence per million was 7.4 for blacks and 9.1 for whites. <sup>2</sup>

Accurate population-based figures for South Africa are not available. Figures from the South African Children's Cancer Study Group reveal that WT is the third most common cancer registered (personal communication: GW

# FIGURE 1

**Distribution of specific cancer diagnoses for children (0 to 14 years) and adolescents (15 to 19 years), 1992 to 2001.**



Percent distribution by International Classification of Childhood Cancer diagnostic groups and subgroups for younger than 15 years and 15 - 19 years of age (all races and both sexes). ALL = acute lymphoblastic leukaemia; RMS = rhabdomyosarcoma; STS = soft tissue sarcoma. (Incidence data are from the Surveillance, Epidemiology, and End Results program, National Cancer Institute).

Reference: Gurney JG, Bondy ML. Epidemiology of Childhood Cancer. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*, 5<sup>th</sup> ed. Philadelphia: Lippincott Williams at Wilkins, 2006:3.

Wessels). Using data from STATS SA Census 2001 <sup>4</sup> we can estimate that the annual incidence per million among 0 to 14-year-olds in the Western Cape is 7.3 for WT and 4.6 for neuroblastoma.

Mean age at diagnosis is approximately 3.5 years for unilateral WT (UWT), with a median of 35 months for boys and 42 months for girls. <sup>5</sup> Bilateral Wilms' tumour (BWT) typically occurs at a younger age, <sup>6</sup> with a median of 23 months for boys and 28.5 months for girls. There is a slight female preponderance with a male:female ratio of 0.92:1 for UWT and 0.6:1 for BWT. <sup>5</sup>

About 10% of children with UWT <sup>7</sup> and 20-28% of those with BWT <sup>8, 9, 10</sup> have recognised malformations. These may be isolated urogenital abnormalities such as cryptorchidism, hypospadias, double collecting system and horseshoe kidney, <sup>11</sup> or recognizable phenotypic syndromes. These syndromes can be divided into those characterised by overgrowth such as Beckwith-Wiedemann syndrome (BWS), <sup>12</sup> isolated hemihypertrophy or Perlman syndrome, and those not associated with overgrowth such as aniridia, WAGR syndrome (WT, aniridia, ambiguous genitalia, and mental retardation) <sup>13, 14</sup> and Denys-Drash syndrome (WT, ambiguous genitalia and mesangial sclerosis with proteinuria). <sup>15</sup> These syndromes have in common abnormalities of the short arm of chromosome 11 (11p) involving either the WT1 gene (aniridia or Denys-Drash syndrome) <sup>16</sup> or the WT2 gene (BWS). WT1 mutations are also found in 2% of phenotypically normal children with WT. <sup>17</sup> WT1 encodes a transcription factor that is crucial to normal kidney and

gonadal development. It acts as a tumour suppressor gene by decreasing the expression of growth associated genes such as Insulin-like growth factor 2.<sup>18</sup> WT2 encodes a growth factor, probably Insulin-like growth factor 2, whose increased expression results in BWS and WT.

Additional tumour suppressor genes have been identified on the long arm of chromosome 16 (16q) and the short arm of chromosome 1 (1p). Loss of heterozygosity at these loci occurs in association with some cases of WT, and confers an adverse prognosis.<sup>19</sup> Mutations of the p53 tumour suppressor gene also carry a poor prognosis,<sup>20</sup> although there is some dispute as to whether they cluster with advanced stage or anaplastic histology.<sup>18</sup>

Recently, overexpression of genes on the long arm of chromosome 1 (1q) was also identified as a potential marker for poor prognosis and relapse.<sup>21</sup>

Despite the number of genes involved in the development of WT, hereditary WT is uncommon, with only 1% to 2% of patients having a positive family history.<sup>18</sup> Affected family members are usually siblings or cousins. BWT is seldom familial, though one pair of sisters was described in 1967.<sup>22</sup>

WT arises in the kidney and metastasizes by way of vascular invasion to the liver, the lungs, and rarely the central nervous system. Stage I tumours are confined within the capsule of the kidney, Stage II tumours have penetrated the capsule but without local spread outside the kidney and Stage III tumours have local extrarenal spread (this includes extension into the inferior vena cava) or lymph node involvement. Metastatic disease is

designated Stage IV. Most patients in the developed world are low stage at diagnosis. The third National Wilms' Tumour Study Group trial (NWTS-3) reported a stage distribution as follows: stage I 47%, stage II 21%, stage III 21% and stage IV 11%.<sup>23</sup> Advanced stage carries a poor prognosis. Four-year OS for stages I through IV reported by the fourth National Wilms' Tumour Study Group trial (NWTS-4) were 95.6%, 91.1%, 90.9%, and 80.9% respectively.<sup>24</sup>

Synchronous BWT represent 4-7% of all WT,<sup>25</sup> and are designated stage V. They usually present at a younger age than UWT;<sup>6</sup> age over three years at diagnosis carries a poor prognosis.<sup>26</sup> About 1% of UWT go on to develop contralateral disease or metachronous BWT. More than 95% of these second tumours develop within five years.<sup>27</sup> The risk is increased in children under the age of 12 months with nephrogenic rests at diagnosis.<sup>28</sup>

Nephrogenic rests are persistent clusters of embryonal cells representing microscopic malformations of the developing kidney.<sup>29</sup> They are found in about 1% of infant autopsies and are usually absent by the age of four months.<sup>30</sup> They may be intralobar, which are frequently associated with mutations or deletions of WT1, or perilobar, which typically occur in the overgrowth syndromes. Incipient or dormant rests may regress or become sclerotic. Alternatively, they may become hyperplastic, some going on to become neoplastic and develop WT.<sup>31</sup> Nephrogenic rests are seen in 90% of synchronous BWT and 94% of metachronous BWT.<sup>30,32</sup> About 70% of children

with synchronous BWT in NWTS series have multiple nephrogenic rests or nephroblastomatosis."

Apart from clinical stage, prognosis is most influenced by histology. Favourable histology (FH) tumours consist of one or more of the three components that make up the typical triphasic histology. These are epithelial elements, blastema or stroma. Blastema rich tumours tend to be invasive but often respond well to chemotherapy,<sup>33</sup> whereas epithelial rich tumours and the rhabdomyomatous variant (where the tumour cells resemble muscle cells) are usually less aggressive but respond less well to chemotherapy.<sup>34'35'36</sup> Unfavourable histology (UFH) is designated anaplastic. Anaplasia is defined by the presence of enlarged polyploid nuclei with hyperchromasia and a high mitotic index within the tumour sample. It occurs in about 5% of UWT and about 10-15% of BWT, more commonly in older than younger children.<sup>37</sup> Anaplasia may be focal or diffuse, the latter being recognised as much more adverse.<sup>38'39</sup> Nuclear unrest, characterized by an increase in nuclear size without an increase in mitoses, is not associated with a worse outcome than FH.<sup>40</sup>

A number of paraneoplastic syndromes have been associated with WT.<sup>41</sup> The most common is hypertension due to tumour production of renin. This is seen in up to 25% of WT,<sup>25</sup> and may be sufficiently severe to cause cardiomyopathy.<sup>42</sup> There have been a few reports of polycythaemia due to elevated erythropoietin,<sup>43</sup> Cushing's syndrome due to ectopic ACTH<sup>44</sup> and hypercalcaemia as a result of parathyroid hormone or prostaglandin

overproduction.<sup>45</sup><sup>46</sup> Acquired von Willebrand disease has also been described,<sup>47</sup> and is thought to be due to tumour production of antibodies to the von Willebrand factor. Tumours that produce these paraneoplastic effects are typically well-differentiated (FH)<sup>48</sup> and may be of low stage.

The first successful nephrectomy for WT was performed by Thomas Jessop in 1877 on a two-year-old boy at the Leeds General Infirmary.<sup>49</sup> Until the 1950s management was surgical with cure only a possibility for local tumours. The addition of adjuvant therapy in the form of chemotherapy and radiotherapy has introduced the possibility of cure for metastatic WT, and greatly improved the prognosis for non-metastatic disease. The use of dactinomycin was pioneered by Sidney Farber<sup>50</sup> in Boston during the mid-1950s, and vincristine,<sup>51</sup><sup>52</sup> doxorubicin<sup>53</sup> and cyclophosphamide were introduced during the years that followed. Radiotherapy was used for the first time in 1916,<sup>54</sup> but only became routine postoperative treatment at the Boston's Children's Hospital<sup>55</sup> during the 1940s. The development of treatment protocols eventually led to the formation of large multicentre trials under the auspices of the International Society of Paediatric Oncology (SIOP) and the National Wilms' Tumor Study Group (NWTSG).<sup>56</sup><sup>57</sup>

The five studies of the NWTSG were conducted between 1969 and 2002. The central philosophy of the NWTSG is that all operable tumours should be treated primarily with total nephrectomy before adjuvant treatment in the form of radiotherapy and chemotherapy. The major findings of each trial<sup>58</sup> were carried forward into the next study in order to achieve the goal of

maximising survival while minimising toxicity. The first study of the NWTSG (NWTS-1, 1969-1973)<sup>59</sup> demonstrated that stage I patients could be treated without renal bed radiotherapy, and that stage II and III patients fared better with the combination of vincristine and dactinomycin compared to either drug alone. The second study (NWTS-2, 1974-1978)<sup>53</sup> demonstrated that six months of vincristine and dactinomycin was as effective as 15 months of therapy for stage I tumours, and that the addition of doxorubicin improved the relapse-free survival for stage II to IV tumours. The third study of the NWTSG (NWTS-3, 1979-1986)<sup>23</sup> showed that FH stage I tumours could be successfully treated with a 10-week regimen of vincristine and dactinomycin without radiotherapy. Patients with stage II FH WT treated with vincristine and dactinomycin achieved similar results as those who also received doxorubicin or renal bed radiotherapy. Patients with stage III FH tumours were given vincristine and dactinomycin with or without doxorubicin, and were also randomised to 10 or 20 Gray (Gy) of radiotherapy. Similar results were achieved for those who received doxorubicin and 10 Gy as those who received 20 Gy alone, but there were more relapses in the group who received 10 Gy alone. Long term follow up, however, indicates no difference in overall survival (OS) between those receiving doxorubicin and 10 Gy of radiotherapy and those receiving 10 Gy alone. Thus, the use of doxorubicin for stage III FH WT is associated with decreased relapse but there is no conclusive evidence that it improves survival.<sup>60</sup> Patients with stage IV FH WT received renal bed radiotherapy and 12 Gy of whole lung irradiation, and were randomised to vincristine, dactinomycin and doxorubicin with or without cyclophosphamide. The

addition of cyclophosphamide did not confer a survival advantage over the three-drug regime.

The fourth study of the NWTSG (NWTS-4, 1986-1993) compared "pulse-intensive" regimens using single doses of dactinomycin and doxorubicin to the traditional regimens using divided doses, and studied a reduction in treatment duration from 15 to six months for stage II to IV FH tumours.<sup>61</sup>

There was no significant difference in outcome for either of these randomisations and cost analysis<sup>62</sup> showed a massive saving using the shorter "pulse-intensive" regimens. The fifth study (NWTS-5, 1995-2002) utilized regimens whose efficacy had been established by its predecessors and preliminary results suggest that it now provides a reasonable standard of care for the treatment of patients with FH WT.<sup>25</sup> Its primary goal was the identification of biologic prognostic markers for FH WT such as loss of heterozygosity at chromosomes 1p and 16q<sup>19</sup> and telomerase expression.<sup>63</sup> A second objective was to examine the use of surgery only for stage I FH WT weighing less than 550 grams in patients under the age of two years. This randomisation was terminated early based on predefined stopping rules because of an excess number of relapses in the trial arm, but all the patients who relapsed were salvaged. Consequently observation without chemotherapy remains a treatment consideration for this group of patients." The design and outcome of the first four NWTS trials are detailed in **Appendix 1**.

As a result of these efforts current OS rates approach 90%.<sup>6</sup> The fourth study of the NWTSG (NWTS-4) reported four-year OS for Stage I through IV of 95.6%, 91.1%, 90.9% and 80.9% respectively.<sup>24</sup> However the 4-year OS for diffusely anaplastic tumours (stage II to IV) was only 52.2% in NWTS-3 and NWTS-4.<sup>65</sup> This is in spite of the fact that treatment was intensified with renal bed radiotherapy and doxorubicin, as well as cyclophosphamide and etoposide.

STOP protocols utilise neoadjuvant chemotherapy followed by surgery.<sup>66,67</sup> The histology of the resected specimen then helps to dictate further chemotherapy and radiotherapy.<sup>68,69,70</sup> Advocates argue that this limits surgical complications by shrinking tumours (which may be of particular importance with advanced disease in developing world settings) and allows for stratification based on tumour response to chemotherapy. This in turn minimises the number of children requiring intensive treatment in the form of cardiotoxic anthracyclines or renal bed irradiation.<sup>72,73</sup> Architects of NWTSG protocols<sup>74</sup> argue that the optimal approach is primary surgery, which allows accurate assessment of original stage and histology, with appropriate stratification of treatment. In early NWTS trials inoperable tumours were staged by imaging and treated accordingly, but this group fared poorly and subsequent trials treated all inoperable tumours with Stage III protocols.<sup>75</sup> STOP protagonists suggested that this might lead to over treatment and the second United Kingdom Children's Cancer Study Group (UKCCSG) WT Trial (UKW2) provided some data to support this.<sup>76</sup> In this trial inoperable tumours fared better than Stage III tumours, suggesting that at

least some of them must have been Stage II. The only randomised trial to directly compare pre-operative chemotherapy and primary surgery was the third UKCCSG WT Trial (UKW3).<sup>77</sup> The investigators experienced considerable difficulty accruing patients for this randomisation. They found a lower proportion of Stage III tumours and less tumour spill or rupture in the pre-operative chemotherapy cohort. There was no significant difference in the relapse rate or survival between the cohorts.

There are few reported series of WT from Africa. Hadley et al<sup>78</sup> reported on 78 black South African children from KwaZulu-Natal with WT. They noted a high proportion of advanced local and metastatic disease (53% were stages III and IV) as well as generally poor outcomes. In addition, treatment was compromised by a high incidence of nutritional and infective co-morbidity. Of the 78 children, eight declined treatment or absconded and 16 died during or prior to pre-operative chemotherapy. Only 54 (69%) came to nephrectomy, 31 primarily and 23 after chemotherapy with or without radiotherapy. Long-term survival of this cohort was not reported. A more recent study by the same group<sup>79</sup> reported a 63% OS for a cohort of 67 patients with large tumours (all resected specimens weighed more than one kilogram). This group, like many others in Africa<sup>80</sup> and other parts of the developing world, utilised protocols based on the STOP approach. This strategy is aimed at facilitating surgery in the setting of advanced disease, and minimising surgical complications.

Zhaghloul et al<sup>81</sup> confirmed a high proportion of advanced disease (51% were stages III and IV) in a series of 112 children in Egypt. Using NWTSG-based protocols, with primary surgery followed by chemotherapy, they reported good results for non-metastatic tumours (10 year actuarial survival of 94% for stage I, 86% for stage II and 71% for stage III).

Ekenze et al<sup>82</sup> also utilised primary surgery followed by chemotherapy for 42 Nigerian children, 83.3% of whom had stage III or IV disease. There was a high rate of abandonment (in part because families are unable to afford the chemotherapy which is self-funded) and a high rate of relapse. OS was only 40%.

We have also utilised a NWTSG-based approach for UWT for many years. Tumours deemed operable, even in the face of pulmonary metastases, were resected prior to the initiation of chemotherapy. Where the surgeons felt that the tumour could not be resected safely, neoadjuvant chemotherapy was administered and the patient reviewed at four to six weeks with a view to surgery. The current WT protocol employed by the Red Cross Children's Hospital (RCCH) Oncology Service is designated 5981 and is based on NWTSG-5 protocols. See **Appendix 2**.

There are some advocates of partial nephrectomy instead of total nephrectomy for favourable risk UWT.<sup>83'84'85</sup> Partial nephrectomy was used off protocol for 37 UWT patients in SIOP93-01 /GPOH.<sup>86</sup> These patients had a relapse-free survival not inferior to the much larger group treated with total

nephrectomy. Nonetheless, total nephrectomy with palpation of the contralateral kidney to exclude bilateral disease<sup>87</sup> remains the mainstay of treatment. Beckwith-Wiedemann syndrome<sup>88</sup> is an exception to this rule since these patients are at risk of both metachronous tumours and non-malignant renal disease. Renal anomalies such as horseshoe and single kidney also mandate partial nephrectomy, and it should be considered where contralateral nephroblastomatosis is established on imaging prior to surgery.

Radiotherapy for WT has two principal applications - to the renal bed following surgery and for pulmonary metastases - and has also been used for metastases or relapsed disease in the liver or central nervous system. Renal bed radiotherapy is utilised for locally advanced tumours. Radiation dose has diminished from 18 - 40 Gy based on age in the 1970s<sup>58</sup> to 10.8 Gy on NWT5-5. Where there has been pre-operative rupture or peri-operative spill beyond the flank, irradiation of the whole abdomen is advocated.<sup>89</sup>

Approaches to lung metastases vary. The NWTSG advocates that pulmonary metastases visible on chest xray should be treated with whole lung irradiation. FH WT with pulmonary lesions identified on computed tomography (CT) scan only on NWT3-3 and NWT4-4 were treated either as stage IV tumours or by local stage at the investigator's discretion.<sup>90</sup> Event free survival (EFS) for the 53 treated with three drugs (vincristine, dactinomycin and doxorubicin) and pulmonary radiotherapy was 89% compared to 80% for those treated with chemotherapy by local stage only.

The difference was not statistically significant but the study was underpowered because the sample size was too small. Those treated with pulmonary radiotherapy had fewer pulmonary relapses but more deaths attributable to lung toxicity.

Considering FH stage IV patients treated on NWTs-4 and NWTs-5, 231 had pulmonary metastases on chest xray and 186 had pulmonary lesions on CT scan only.<sup>91</sup> There was an inferior relapse free survival (RFS) for those treated with vincristine and dactinomycin compared to those who also received doxorubicin, regardless of whether they received pulmonary radiotherapy or not. This suggests that small lesions require more intensive chemotherapy than that used for low stage tumours, but perhaps less treatment than for traditional metastatic disease. The current recommendation is that lesions identified on CT scan only do not automatically receive radiotherapy but should be biopsied with a view to intensifying therapy if they do not resolve after six to eight weeks of chemotherapy. Future NWTs trials will likely abandon chest xray appearance as a way of stratifying pulmonary metastases.<sup>92</sup> All pulmonary metastases visible on CT scan will be treated with three-drug chemotherapy, reserving radiotherapy for non-responders with biopsy-proven tumour deposits.

The major clinical challenge in BWT is the preservation of functioning renal tissue while achieving cure with the minimum of therapy-related morbidity.<sup>93'94'95'96</sup> This may be particularly difficult with delay in

presentation and advanced local disease, when there is a poor response to chemotherapy or when a nephrectomy has already been done as in metachronous presentation. In addition, management is frequently complicated by the presence of multiple nephrogenic rests or nephroblastomatosis. Even on biopsy, hyperplastic rests are difficult to distinguish from and may transform into WT.<sup>31 '97</sup> Fortunately, nephroblastomatosis is easy to follow up on serial imaging and does respond to chemotherapy.

Early work clearly demonstrated that biopsy followed by neoadjuvant chemotherapy was superior to surgical reduction at diagnosis.<sup>98</sup> It then became increasingly clear that the first procedure after neoadjuvant chemotherapy should be partial rather than total nephrectomy. The use of partial nephrectomy or tumourectomy for BWT in NWTs-4<sup>9</sup> was associated with a local recurrence rate of only 8.2%; 16% if the margins were histologically positive and 6.3% if they were negative. Seventy two percent of these kidneys were salvaged. A more recent report advocated an extremely conservative approach: macroscopic tumour was resected with no attempt to obtain clear microscopic margins in a series of 14 cases of BWT.<sup>99</sup> Renal salvage techniques included the use of longitudinal incisions with reconstruction of the renal pelvis. Thirteen of the fourteen are alive and disease free with no patients in chronic renal failure; the sole death was a patient with anaplastic histology.

While emphasis is increasingly placed on nephron-sparing surgical approaches, it should be remembered that most deaths occur as a result of progressive disease, and usually in the first two years after diagnosis.<sup>25</sup> Cure rates of 70-80% have been reported for BWT; ,8 9,100,101,102the 4-year OS for stage V tumours in NWTS-5 was 81.7%.<sup>61</sup> For synchronous BWT, outcome is influenced by local stage with stage I and II tumours faring better than those that are stage III. <sup>103</sup> Results for metachronous BWT have been reported as inferior<sup>103</sup> or comparable<sup>100</sup> to synchronous BWT. There appears to be a better outcome if the time to development of the second tumour is less than 18 months.<sup>27</sup>

Long-term complications seen in WT survivors include renal impairment, cardiomyopathy and second malignancies. Renal impairment typically presents with proteinuria and / or hypertension culminating in renal failure in 0.25% to 0.6% of UWT and between 3.8% and 11.5% of BWT.<sup>01 4,105</sup> Renal failure develops in 50-74% of cases with Denys-Drash syndrome, usually within five years. Appropriate management of these children entails bilateral nephrectomy, with transplantation being offered after a disease free interval of one to two years.<sup>106</sup> By contrast the patients with WAGR syndrome and those with isolated genitourinary abnormalities, usually present late with renal failure.<sup>14,105</sup> Survivors of UWT should be closely followed up with serial blood pressure and urinalysis but they can be reassured about the risk of renal failure. In a study of forty WT patients who were followed up for a mean of 8.8 years, two had proteinuria, but all had normal blood pressures and the mean GFR was 100ml/min/1.73m<sup>2</sup>.<sup>107</sup>

Twenty five percent of WT patients treated with doxorubicin develop some form of cardiac abnormality on echocardiogram. <sup>108</sup> The incidence of cardiac failure for WT patients treated on NWTS protocols was 1.7% over the fifteen years from diagnosis, <sup>109</sup> 50% occurring within 8 years. The risk is increased from 1% to 5.4% for those who also received pulmonary radiotherapy.

Fifteen years after WT diagnosis, the cumulative incidence of second malignancy was 1.6% in a large series of patients treated on NWTS protocols. <sup>110</sup> There were 43 second malignancies, including 9 leukaemias, 4 lymphomas, 3 brain tumours and 13 sarcomas. This was somewhat lower on SIOP studies, where a cumulative incidence of 0.65% was reported. <sup>111</sup> There was consensus that the use of radiotherapy and anthracyclines place these patients at greater risk of second malignancy.

Veno-occlusive disease (VOD) is an entity that presents with thrombocytopenia, hepatomegaly with jaundice, ascites and weight gain. In a United Kingdom study it occurred in 1.4% of those WT patients treated with vincristine and dactinomycin, and none of those treated with vincristine alone <sup>112</sup> lending support to the belief that it is caused by dactinomycin. It occurs shortly after chemotherapy administration and the highest reported incidence was 8% on the SIOP-9/GPOH trial. <sup>113</sup> Patients who suffer isolated thrombocytopenia after dactinomycin administration may be at higher risk of VOD, but it is not clear to what degree this is prognostic. <sup>112</sup> An episode of VOD mandates a reduction in the dactinomycin

dose. Treatment is supportive and fortunately there is negligible long-term morbidity.

As with much of modern paediatric oncology, the success of WT therapy has led investigators to focus on two areas of study. Firstly, increasing intensity of therapy for high-risk disease in an effort to improve results, and secondly, decreasing intensity for standard and low risk disease in order to minimise toxicity.

Ifosfamide, carboplatin and etoposide (ICE) is an extremely myelosuppressive regimen that is now being widely used for poor risk relapsed WT (**UFH**, early relapse and extra-pulmonary relapse). Overall survival of up to 63.6%<sup>114</sup> has been reported but this has still to be validated in large trials. Other agents such as anti-angiogenesis factors, irinotecan, oxaliplatin and histone deacetylase inhibitors are under consideration as relapse therapies.<sup>92</sup> High dose chemotherapy (using such combinations as melphalan, thiotepa, etoposide, cyclophosphamide and ifosfamide) with autologous stem cell rescue has also been utilized but it has a low rate of success in patients who have not already achieved complete remission with intensive chemotherapy.<sup>115,116</sup> This implies that these patients may incur considerable additional toxicity from autologous transplant without much added benefit.

An example of a decreased intensity regimen would be the use of vincristine only for adjuvant chemotherapy, in order to avoid dactinomycin-induced

VOD. One arm of NWTS-5 made provision for the use of vincristine only for children less than two years of age with tumours smaller than 550g. <sup>64</sup> This arm was terminated early because of an increased relapse rate but all these relapses were salvaged, and consideration is being given to repeating this randomisation. STOP is also contemplating using vincristine only for younger children since there seems to be no increase in the relapse rate under the age of four years. <sup>86</sup>

This thesis describes our experience with WT at the Red Cross Children's Hospital (RCCH) over 25 years between 1979 and 2003. <sup>117,118</sup> In analysing this data we consider how we have measured up to the exacting standards set by the NWTSG. Our challenge is to maximise cure and minimise toxicity. Are there patients with low risk disease who could receive less treatment? Can we identify patients with FH tumours who are at higher risk for relapse and could benefit from intensified treatment? How can we improve results for those with high-risk disease such as metastatic tumours, anaplasia and relapsed disease?

## CHAPTER TWO:

### METHODS

The study was retrospective; the records of all patients diagnosed with WT at RCCH between January 1979 and December 2003 were reviewed. Details of presentation, histology and management were extracted from patient records.

Patients were assessed at diagnosis and primary surgery was undertaken where possible. All patients were staged radiographically with chest xray and ultrasound abdomen and, since 1986, CT scan of the abdomen and chest. Tumours deemed inoperable, including all BWT, were subjected to fine needle aspiration biopsy to prove the diagnosis, and then given pre-operative chemotherapy. The patient was then re-imaged after four to six weeks with a view to definitive surgery. UWT were assigned a local stage of III regardless of findings at that operation whereas BWT were staged to the local stage of each side on imaging and/or biopsy. After surgery all patients with unilateral stage III disease received renal bed radiotherapy, and those with pulmonary metastases on chest xray received pulmonary radiotherapy.

Chemotherapy protocols were based on those of the NWTSG, NWTs-1 through NWTs-5.<sup>89</sup> RCCH WT protocols are designated 5 (denoting WT), two digits (denoting year of inception) and 1 (denoting the number of new protocols for WT that year - usually only one). Hence the latest is 5981,

which was first used in 1998. The protocol in use in 1979 was 5974, and since that time there have been four modifications: 5811, 1891, 5921 and 5981. These protocols are set out in **Appendix 2**.

Duration of chemotherapy protocols changed over time, varying from 15 months initially, to 18 weeks (all stage I and FH stage II) and 24 weeks (all other stages) currently. All patients received vincristine and dactinomycin. Patients with stage III and IV tumours also received doxorubicin -  $300 \text{ mg/m}^2$  until 1998, and  $5 \text{ mg/kg}$  (equivalent to  $150 \text{ mg/m}^2$ ) since 1999. Before 1989 stages II to IV received 20 Gy renal bed irradiation. Subsequently, only those with local stage III received renal bed radiotherapy (currently 10.8 Gy in six fractions), and those with pulmonary metastases visible on chest xray received pulmonary radiotherapy (currently 12 Gy in eight fractions). Patients with pulmonary metastases visible on CT scan only were treated with vincristine, dactinomycin and doxorubicin. Those patients whose metastases resolved were not given pulmonary radiotherapy. The protocol did not require biopsy of persistent lesions prior to pulmonary radiotherapy.

From the outset, all patients with UFH received vincristine, dactinomycin, doxorubicin ( $300 \text{ mg/m}^2$ ) and cyclophosphamide. Stage I patients with UFH were excluded from this in 1989 and now receive only vincristine and dactinomycin. Since 1999, stage II-IV tumours with diffuse anaplastic histology have been treated with vincristine, doxorubicin ( $7.5 \text{ mg/kg}$  equivalent to  $225 \text{ mg/m}^2$ ), cyclophosphamide and etoposide. Stage II-IV tumours with focal anaplasia have been treated with vincristine,

dactinomycin and doxorubicin (5 mg/kg equivalent to 150 mg/m<sup>2</sup>). All stage II to IV UFH tumours received renal bed radiotherapy.

Management of BWT differed in a number of respects. At the outset, transperitoneal exploration with bilateral renal biopsies and lymph node sampling was performed prior to commencement of chemotherapy. Since 1999 this has been replaced in some cases by percutaneous biopsy.

Vincristine, dactinomycin and doxorubicin were used in all cases. Since 1999 cyclophosphamide and etoposide have been added for diffuse anaplasia or poorly responding tumours that are not amenable to surgery at review.

Laparotomy was usually planned two to three months after initiating treatment with excision of tumour from the kidney with the least involvement. If this left a viable functioning kidney the contralateral kidney was examined and removed if extensively involved. In the last decade we have been more surgically conservative, and if there was hope of some salvage, another biopsy was done, the extent of the tumour marked with titanium clips, and more chemotherapy given. Surgical exploration and tumourectomy or partial nephrectomy was then performed two to three months later. All attempts were made to avoid bilateral nephrectomy.

Extensive bilateral nephroblastomatosis prevented partial nephrectomy or tumourectomy in two cases. These children were treated with three drugs only and achieved complete remission. Both suffered local relapses which were successfully excised, and are alive and disease free.

Surgical techniques for BWT varied over the study period and changed considerably over the last decade. Up to 1993 partial nephrectomy and tumourectomy was done by conventional techniques with vascular pedicle clamping for short periods of time. Since then surgical techniques have included ice dam topical cooling of the kidney, as well as vascular control with tumourectomy or partial nephrectomy performed under bloodless conditions using diathermy, or more recently the ultrasonic scalpel. Two steridrapes stuck together with a slit cut for the vascular pedicle acts as a dam. The patient is insulated with packing swabs and after full mobilization of the renal tumour the plastic dam is placed, the pedicle clamped and the kidney immersed in slush ice. After a five to eight minute wait (depending on kidney size) excision of the tumour commences. Heparin is not given. Cross-clamp time was usually less than 30 minutes; in only one of our cases was there evidence of any degree of acute tubular necrosis following surgery.

On one occasion bench surgery and orthotopic autotransplantation was required for a very extensive tumour with rhabdomyomatous change not responding to chemotherapy. The whole kidney was removed and flushed with EuroCollin's organ preservation solution prior to the tumour excision and reconstruction of the pelvicalyceal system. When this was completed the kidney was placed in the renal fossa with re-anastomosis of the vessels and ureter. This patient has had a recurrence of tumour in the opposite kidney away from previous resection sites within an area of biopsy-proven nephroblastomatosis. This was successfully excised and he remains a long-

term survivor despite tumour having had to be extracted from the renal pelvis at revision surgery.

Metachronous tumours were given preoperative chemotherapy and then tumourectomy was performed. Local renal bed radiotherapy was avoided completely for BWT. Radiotherapy was reserved for pulmonary metastases and local palliation.

Patients with UWT or BWT who relapsed were treated with surgery, local and pulmonary radiotherapy (depending on site), as well as a variety of chemotherapeutic regimens. These regimens changed over time and included vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, etoposide and carboplatin.

EFS and OS were estimated by the method of Kaplan and Meier.<sup>119</sup> EFS and OS times were calculated in months for each patient. Cases were assigned a censor code as follows: those who relapsed (EFS) or died of disease (OS) were uncensored (code = 0) because their outcome was known; survivors and patients who died of unrelated disease were censored (code = 1).<sup>119</sup>

Survival analysis was then performed using Statistica 7.1 (Statsoft, Inc. 1984-2005). Survival curves for different subgroups were compared using the logrank test. This is the most widely used method of comparing two or more survival curves.<sup>119</sup> It is used to test the null hypothesis that there is no difference between two or more groups in the probability of an event (death or relapse) at any time point.<sup>120</sup> The logrank test provides a p-value

for the differences between the groups offering a statistical, though not necessarily clinical, assessment of the factor's impact. <sup>121</sup> We assigned a p-value of  $< 0.05$  as significant.

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# CHAPTER THREE:

## RESULTS

### PATIENT CHARACTERISTICS

208 children were diagnosed with WT during the 25-year study period.

One hundred and eighty eight had UWT. There were 77 males and 111 females representing a male:female ratio of 2:3. Age at diagnosis ranged from 0.24 to 12.87 years. The median age at presentation was 39.2 months. There were 24 white patients (12.8%), 85 mixed-race patients (45.2%) and 79 black patients (42%).

Of the twenty patients with BWT, 15 were synchronous (7.2% of the total) and five metachronous (2.4% of the total). Five of the fifteen synchronous BWT patients were male and ten female representing a male:female ratio of 1:2. Age at diagnosis ranged from 0.6 to 7.9 years. The median age was 23.9 months. There were five white patients (33.3%), three mixed-race patients (20%) and seven black patients (46.7%).

Most presented with an abdominal mass or distension (76.9%). Abdominal pain occurred in 52 patients (25%). There was macroscopic haematuria in 19 (9.1%) and microscopic haematuria in 44 (21.1%). Forty-two patients (20.2%) were hypertensive at diagnosis, thirty-two of those with UWT (17%) and ten

of those with BWT (50%). Two of the UWT patients, and three of those with BWT, presented with hypertensive cardiomyopathy.

There was only one other WT-related paraneoplastic phenomenon. This was seen in a patient with a stage I FH WT who presented with hypertensive cardiomyopathy. She had an elevated red cell count of  $6.11 \times 10^{12}/l$  (normal  $3.9-5.1 \times 10^{12}/l$ ) with a relatively normal haemoglobin of 9.4 g/dl and a low mean corpuscular volume of 55 fl. Red cell distribution width was 27% (normal 11.6-14.8%) and iron deficiency was confirmed by iron studies: iron 4.1  $\mu\text{mol}/l$  (normal 7.1-17.9  $\mu\text{mol}/l$ ), total iron binding capacity 61  $\mu\text{mol}/l$  (normal 17.9-71.6  $\mu\text{mol}/l$ ) and saturation 6.7% (normal 20-55%). We believe this patient had excessive erythropoietin production<sup>122</sup> but we were not able to secure a pretransfusion specimen for testing. No patients presented with hypercalcaemia or Cushing's syndrome. Routine partial thromboplastin time (PTT) testing has been undertaken for several years. Only one child had a prolonged PTT but was found to have normal von Willebrand factor activity.

Weight for age was below the 3<sup>rd</sup> centile in 41 patients (19.7%). There were three cases of renal failure; two with elevated urea and creatinine and normal urine output, and one with a massive tumour, raised urea and normal creatinine, and oliguria (urine output < 0.5 ml/ kg/ hour). Two of these three patients had unilateral tumours, representing 1% of all UWT.

Thirteen patients, all with UWT, had associated abnormalities. These included five with urogenital abnormalities, four with hemihypertrophy, three with aniridia, and one with Beckwith-Wiedemann syndrome. There was one instance of familial WT. A WT patient with a normal phenotype, whose sibling had WT and renal dysplasia, was found to have a deletion of chromosome 11. There were four patients with unrelated syndromes (Alagille syndrome, Moebius syndrome, Chondrodysplasia punctata and Ectodermal dysplasia). None of the BWT patients had associated abnormalities.

## **UNILATERAL WILMS' TUMOUR**

Fifty-seven children were stage I (30.3%), 33 were stage II (17.6%), 60 were stage III (31.9%) and 38 were stage IV (20.2%). Inferior vena cava tumour thrombosis (IVCT) was present at diagnosis in 11 cases (5.9%), five with extension into the right atrium.

Stage IV disease constituted 8.3% of the tumours among white patients, 17.6% of the tumours among mixed-race patients and 26.6% of the tumours among black patients. Of these 38 patients with metastatic disease, 34 (89.4%) had lung metastases. Six of these 34 patients also had liver metastases, and three others had isolated liver metastases. One had central nervous system metastases. There were 22 patients with FH UWT who had lung metastases. Twelve of these could be seen on chest xray, and 10 could only be appreciated on CT scan.

Characteristics of the UWT are shown in **Table 1**, and those of the stage IV UWT patients are shown in **Table 2**.

Of the 137 tumours operable at diagnosis, 118 were weighed. Seventy-five (63.6%) weighed more than 550g and 24 (20.3%) weighed more than one kilogram. For purposes of comparison with NWTs-3, 79 (66.9%) had tumours larger than 500g. Of the 28 operable stage III tumours that were weighed, 23 (82.1%) exceeded 550g and 10 (35.7%) weighed more than one kilogram.

There were 24 patients (12.8%) with UFH. Thirteen (6.9%) had diffuse anaplasia and 11 had focal anaplasia. Only one stage I patient had UFH; a patient with a small focal anaplastic tumour. Fifty-four-and-a-half percent of the patients with focal anaplasia and 23% of those with diffuse anaplasia had stage IV disease. UFH was seen in 29.2% of white patients, 8.2% of mixed-race patients and 12.7% of black patients. Twenty-four patients (12.8%) had nephroblastomatosis.

Rhabdomyomatous elements were noted in the histology of 20 cases (10.6%). Twelve of these patients underwent primary surgery and eight were deemed inoperable and received three drug chemotherapy. Six of these eight (75%) demonstrated a reduction in tumour volume facilitating nephrectomy. One came to nephrectomy without a reduction in tumour volume and one patient died of disease. There were 34 other **FH** tumours that were inoperable at diagnosis. Thirty-two were evaluable for response to chemotherapy because two were lost early (one to default and one to

disease). Twenty-nine of these cases (90.6%) demonstrated a reduction in tumour volume facilitating surgery. One came to nephrectomy without a reduction in tumour volume and the other two died without coming to definitive surgery.

## **BILATERAL WILMS' TUMOUR**

Of the 15 synchronous cases, 13 presented with the tumours confined to the kidneys (local stage I or II), one had liver metastases (stage IV) and one had ruptured at diagnosis (stage III). On histological examination, 13 were considered favourable (five triphasic, one mixed and seven blastemal), and two had diffuse anaplasia. All but two had nephroblastomatosis seen on biopsy or in the resected specimens. Rhabdomyomatous change was noted in three of those with FH.

The five metachronous tumours presented an average of 32.8 months after initial diagnosis (range 20 to 50 months). Three were originally stage I, and two stage II. Histologically, one patient had focal anaplasia, three were triphasic and one blastemal; all had nephroblastomatosis.

Characteristics of the BWT are shown in **Table 3**.

## **PATIENT OUTCOMES**

One hundred and forty five patients are alive and disease free. Length of follow-up varies from 23 to 318 months with a mean of 130 months, and 123

are more than five years from diagnosis. Thirteen patients were lost to follow up less than five years from diagnosis. All were in complete remission following surgery and all but one had completed chemotherapy. Fifty patients have died, 33 as a result of disease, three due to treatment-related complications (two with anthracycline-induced cardiomyopathy and one with chemotherapy-induced acute myeloid leukaemia), three from infection (gastroenteritis, adenoviral pneumonia and myocarditis) and one from an unknown cause. Ten patients were lost to follow up with active disease; nine of them following relapse. All are presumed dead.

## **UNILATERAL WILMS' TUMOUR**

Estimated 5-year OS for the whole group was **78.3% [figure 2]; 82.8%** for FH tumours and 47.3% for UFH tumours ( $p = 0.0013$ ) **[figure 3]. Estimated 5-year EFS (representing relapse or death from any cause) for the whole group was 72.5% [figure 4]; 76.8% for FH tumours and 42.9% for UFH tumours ( $p = 0.0006$ ) [figure 5].**

Estimated 5-year OS for **FH tumours by stage was 94.6% for stage I, 96.2% for stage II, 78.4% for stage III, and 54.2% for stage IV ( $p = 0.00001$ ) [figure 6].**

The estimated 5-year EFS by stage for **FH tumours was 87% for stage I, 80.6% for stage II, 78.4% for stage III, and 50.9% for stage IV ( $p = 0.0016$ ) [figure 7].**

Outcomes for UWT by stage are shown in **Table 1.**

In the group of patients with FH stage **III** tumours, the estimated 5-year OS was 74.4% for those that had primary surgery ( $n = 31$ ), compared to 85% for

those that were deemed inoperable (n = 20) and had pre-operative chemotherapy (p = 0.55) **[figure 8]**.

Three of the 11 patients with inferior vena cava tumour thrombosis (IVCT) had primary surgery. Eight were deemed inoperable and received chemotherapy initially. Ultimately, surgery was carried out in nine cases, three of these on cardiopulmonary bypass. Two patients died early as a result of thromboembolism and vascular decompensation. Six are alive and disease free, and three died of progressive disease or following relapse. These patients did poorly compared to the whole group; estimated 5-year OS for the 10 **FH** tumours with IVCT was 60% (p = 0.035) **[figure 9]**.

Thirteen of the 29 patients with FH stage IV tumours did poorly. Seven patients failed to achieve remission and seven relapsed, only one of whom survived. When stage IV FH patients were analysed in cohorts, the estimated 5-year OS for 1984-1993 was 62.9%, compared to 50% for 1994-2003 (p = 0.39) **[figure 10]**. FH patients with lung metastases detected on chest xray did as well as those whose metastases were appreciated on CT scan only. There were five survivors out of 10 in the chest xray-positive group, and six survivors out of 12 in the CT scan only group.

Considering the small group of patients with stage I to **IV UFH**, those with focal anaplasia fared as poorly as those with diffuse anaplasia; estimated 5-year OS was 54.5% and 40.3% respectively (p = 0.47) **[figure 11]**. The single stage I patient with UFH had focal anaplasia and is alive and disease free.

Six of the 11 patients with focal anaplasia were stage **IV** compared to only three of the 13 patients with diffuse anaplasia. Four of the five deaths among those with focal anaplasia occurred in stage IV tumours.

Neither nephroblastomatosis nor rhabdomyomatous histology conferred a poorer outcome, with estimated 5-year OS of 82.6% ( $p = 0.7$ ) **[figure 12]** and 78.9% ( $p = 0.92$ ) **[figure 13]** respectively. Of the 20 patients with rhabdomyomatous histology, 40% were inoperable with a 75% response rate to chemotherapy. This was comparable to the 90.6% response rate seen among other **FH** tumours that were inoperable at diagnosis.

When the patients were analysed by race, there is a trend that does not achieve statistical significance for white patients to do better than mixed-race and black patients. Estimated 5-year OS was 91.3%, 81.8% and 70.6% respectively ( $p = 0.08$ ) **[figure 14]**. However, when metastatic disease was excluded, there was no difference between the groups. Estimated 5-year OS was 90.5%, 86.5% and 83.4% respectively ( $p = 0.79$ ) **[figure 15]**. **Table 2** shows that a higher proportion of black children (26.6%) had metastatic disease compared to mixed-race (17.6%) or white children (8.3%), and that nearly one quarter (23.8%) of black stage IV patients had **UFH**. Estimated 5-year OS for black children with stage IV disease was 35.4% compared to 60% for mixed-race children ( $p = 0.13$ ) **[figure 16]**. Notably, when UFH tumours were excluded from analysis, the estimated 5-year OS was still lower for black FH stage IV patients at 47.6% compared to 61.5% for mixed-race FH stage IV patients ( $p = 0.36$ ) **[figure 17]**. Both the white children who

presented with stage IV disease had focal anaplasia and are alive and disease free.

There was no difference in outcome between children treated in the second decade and the last decade. Estimated 5-year OS and EFS was 80.3% and 73.1% for 1984-1993 and 75.1% and 70.9% for 1994-2003 ( $p = 0.45$  and  $0.96$ ) [figures 18 and 19].

Thirteen patients failed to achieve remission despite the use of IE (ifosfamide and etoposide) and ICE (ifosfamide, carboplatin and etoposide) in two of these cases respectively. Relapse occurred in 33 children of whom 20 were still receiving chemotherapy. The remaining 13 relapsed two months to three-and-a-half years after completing therapy, only four of them more than two years off treatment. Of the 175 patients who achieved remission, the rate of relapse by stage was as follows: stage I 12.3%, stage II 18.2%, stage III 17.5%, stage IV 35.7%. The number of relapses by stage is shown in **Table 1**. The commonest site of relapse was pulmonary, occurring in 18 cases. There were eight local relapses, two liver relapses and five relapses at multiple sites. Eight patients (24.2%) had UFH, and two patients (6.1%) had nephroblastomatosis. Twelve patients received no active treatment and one received palliative radiotherapy. The remaining twenty were treated with chemotherapy; IE in five cases and ICE in one.

Survival was better for stage I and II patients who relapsed (eight of 13) than for those who were stage III and IV (one of 20). There were more

survivors after pulmonary relapse (five of 18) than local relapse (two survivors out of eight). Only one of the eight patients with UFH who relapsed survived. Five of the 13 (38.5%) who relapsed off treatment are alive and disease free. By contrast only four of 20 (20%) who relapsed on treatment were survivors **[figure 20]**. Only two of the ten patients treated for refractory or relapsed disease with IE or ICE were survivors.

## **BILATERAL WILMS' TUMOUR**

Of the 15 synchronous cases, seven (46.6%) are alive and disease free, six died of disease and two patients died free of disease; one as a result of anthracycline-induced cardiomyopathy, and one from pneumonia. While on treatment or after completion of chemotherapy five developed metastases; two pulmonary, two hepatic and one extensive extra-renal hilar node involvement. All of these patients died, as did the patient who presented with liver metastases. Four of the survivors have had local recurrences in the kidney in areas of nephroblastomatosis away from previous resection sites. All four underwent successful revision tumourectomy.

Three of the five metachronous cases had their original nephrectomies elsewhere. One patient developed an isolated pulmonary metastasis seven months after completing treatment for a stage I WT. This was removed and four months after completing three-drug chemotherapy, she was referred to our centre with a small tumour in an area of nephroblastomatosis in the contralateral kidney. This was removed by tumourectomy. Three other patients were treated with biopsy, further chemotherapy and

tumourectomy. These four patients are alive and free of disease, with preserved renal function. The fifth patient who had also come from another hospital presented late with an obstructive uropathy of the remaining kidney requiring nephrostomy. He responded poorly to three-drug chemotherapy, and was given palliative radiotherapy after an unsuccessful attempt to remove the tumour.

Reviewing the whole group, 11 of 20 are alive free of disease - three of nine (33%) from the first fifteen years (1979-1993), and eight of 11 (70%) from the last decade (1994-2003). Nine have died, seven of disease and two free of disease (anthracycline-induced cardiomyopathy and pneumonia). Six of the seven with extra-renal spread died; the one survivor had a lung metastasis successfully resected. All three patients with UFH are alive.

Estimated 5-year OS was 48.5% for synchronous BWT and 80% for metachronous BWT ( $p = 0.3$ ) [figure 21]. Estimated 5-year OS for synchronous BWT improved from 34.3% in the first fifteen years (1979-1993) to 62.5% in the last decade (1994-2003) ( $p = 0.42$ ) [figure 22].

## COMPLICATIONS OF TREATMENT

Complications of treatment were relatively few.

Renal function after treatment was closely monitored. One patient with UWT has chronic renal failure. She was treated with local radiotherapy for a

relapsed tumour and developed radiation nephritis. She does not require dialysis. Two of the eleven surviving BWT patients have a degree of renal impairment, but none have required dialysis or transplantation. Three had isotope GFR assessment after completion of surgical intervention, and the other eight patients had GFR calculated from serum creatinine, height and the Schwartz constant ( $k=38$ ), and these ranged from 78 to 162 ml/min/1.73m<sup>2</sup>. Only two of these were below 90 ml/min/1.73m<sup>2</sup>; these being 85 ml/min/1.73m<sup>2</sup> and 78 ml/min/1.73m<sup>2</sup> respectively.

One hundred and thirty one patients received anthracyclines initially or at relapse, the cumulative dose ranging from 45 mg/m<sup>2</sup> to 440 mg/m<sup>2</sup>. Of these, 83 received a cumulative dose over 250 mg/m<sup>2</sup>; three of them exceeding 350 mg/m<sup>2</sup>. Three of the 131 (2.3%) patients developed cardiomyopathy. Of the two who died of cardiomyopathy, one received 300 mg/m<sup>2</sup> and the other 430 mg/m<sup>2</sup> as well as pulmonary radiotherapy. The third patient received 300 mg/m<sup>2</sup> and is alive on antifailure treatment.

Twelve patients received ifosfamide for resistant disease or at relapse, the cumulative dose ranging from 18 g/m<sup>2</sup> to 72 g/m<sup>2</sup>, with a mean of 38.25 g/m<sup>2</sup>. One patient developed nephrogenic diabetes insipidus and Fanconi's syndrome after 36 g/m<sup>2</sup> and subsequently died of disease. There are only three survivors - 65.2 to 152.6 months from diagnosis - all with normal renal tubular reabsorption of phosphate.

One patient developed veno-occlusive disease after dactinomycin, and one infant suffered a brief unexplained apnoea after vincristine and dactinomycin.

One patient developed a secondary malignancy. She was a five-year-old girl with a stage II anaplastic UWT, who was diagnosed with secondary acute myeloid leukaemia three-and-a-half years after completing treatment that included doxorubicin, etoposide and renal bed radiotherapy. The leukaemia cells had the typical translocation involving the MLL gene on the long arm of chromosome 11 that is associated with the use of topoisomerase inhibitors such as etoposide. The family declined further treatment and she was palliated.

Complications of surgery occurred in 41 of 188 (21.8%) UWT patients, and three of 20 (15%) BWT patients. There was rupture or spillage as defined by the NWTSG (beyond the flank) in 12 UWT (6.4%), and local spillage in five UWT, but none in the BWT. All those with NWTSG-defined spillage were treated as stage III tumours with vincristine, dactinomycin and doxorubicin as well as renal bed irradiation (10-20 Gy). Of the 122 FH UWT that were operable, 10 (8.2%) had NWTSG-defined spillage. In this group there were no local relapses but two pulmonary relapses, and no difference in estimated RFS between those with spill (80%) and those without (84.1%) ( $p = 0.66$ ) [figure 23]. Of interest is that of the five patients who experienced local spillage - all were treated with vincristine and dactinomycin, and one before 1989 with renal bed radiotherapy - there were three relapses - one

local and two pulmonary. The patient with local relapse was salvaged with three drugs and renal bed radiotherapy.

Post-operative small bowel obstruction occurred in 20 cases (9.6%), including two cases of volvulus, two cases of intussusception and three closed loop obstructions. There were three episodes of wound sepsis, two cases of wound dehiscence and one patient had major bleeding during surgery (defined as more than 50ml/kg of blood loss). This patient was not tested for acquired von Willebrand disease.

University of Cape Town

**TABLE 1**

**Unilateral Wilms' Tumour:  
Patient Characteristics and Outcome by Stage**

	<b>TOTAL</b>	<b>STAGE I</b>	<b>STAGE II</b>	<b>STAGE III</b>	<b>STAGE IV</b>
<b>PATIENTS [%]</b>	188	57 [30.3]	33 [17.6]	60 [31.9]	38 [20.2]
Black [% of total]	79	17 [21.5]	10 [12.7]	31 [39.2]	21 [26.6]
Mixed-Race [% of total]	85	32 [37.6]	15 [17.6]	23 [27.1]	15 [17.6]
White [% of total]	24	8 [33.3]	8 [33.3]	6 [25]	2 [8.3]
<b>TUMOUR WEIGHT</b>					
Inoperable	41	0	0	23	28
Operable	137	57	33	37	10
Operable (weighed)	118	49	31	28	10
Weight < 550g		22	15	5	1
Weight 550-999g		22	10	13	6
Weight > 1000g		5	6	10	3
<b>HISTOLOGY</b>					
Favourable Histology	164	56	28	51	29
Focal Anaplasia	11	1	1	3	6
Diffuse Anaplasia	13	0	4	6	3
<b>OUTCOME</b>					
Achieved remission	175	57	33	57	28
Relapse	33	7	6	10	10
Local	8	3	1	1	3
Lung	18	2	3	7	6
Liver	2	1	0	1	0
Multiple	5	1	2	1	1
Alive Disease Free [%]	134 [71.3]	52 [91.2]	26 [78.8]	39 [65]	17 [44.7]
Died of Disease	41	3	4	15	19
Lost / Unrelated death	13	2	3	6	2

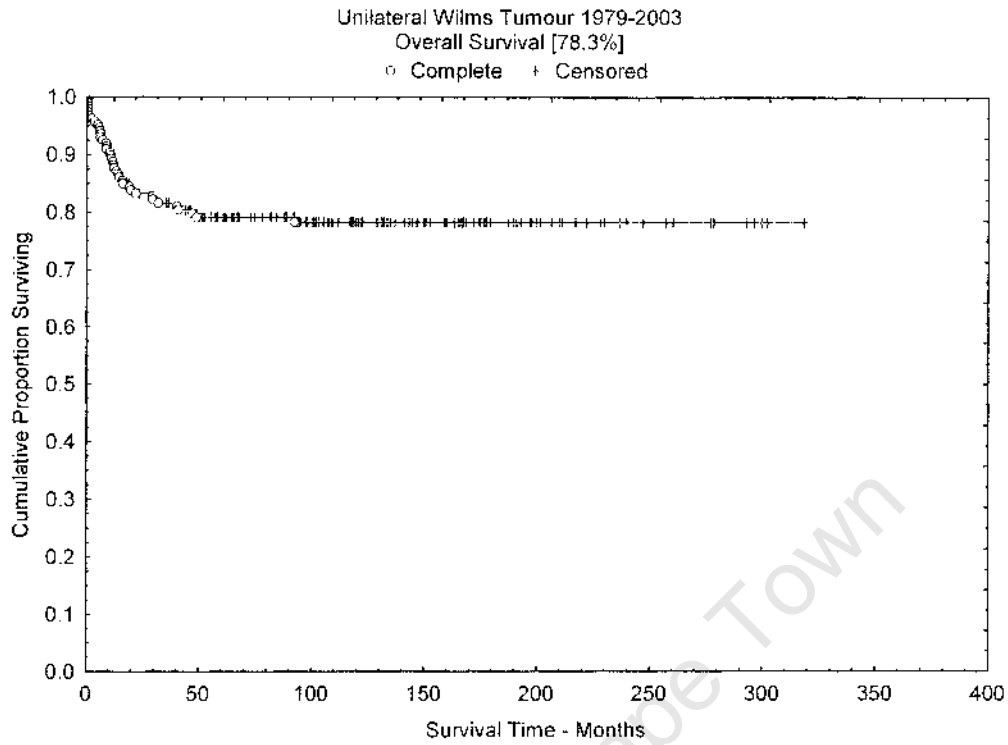
**TABLE 2****Stage IV Unilateral Wilms' Tumour:  
Patient Characteristics and Outcome**

	<b>TOTAL</b>	<b>Black</b>	<b>Mixed-Race</b>	<b>White</b>
<b>% by Race</b>				
Stage IV WT	38	21	15	2
All UWT	188	79	85	24
% of Stage IV WT	20.2%	26.6%	17.6%	8.3%
<b>HISTOLOGY</b>				
Favourable Histology	29	16	13	0
Focal Anaplasia	6	4	0	2
Diffuse Anaplasia	2	1	2	0
<b>COHORT</b>				
1979-1983	1	0	1	0
1984-1993	18	11	7	0
1994-2003	19	10	7	2
<b>METASTATIC SITE</b>				
Lung	28	14	13	1
Liver	3	2	1	0
Liver and Lung	6	4	1	1
Brain	1	1	0	0
<b>OUTCOME</b>				
Achieved Remission	27	15	11	2
Relapse	10	7	3	0
Alive Disease Free	17	6	9	2
Died of disease	19	13	6	0
Lost	2	2	0	0

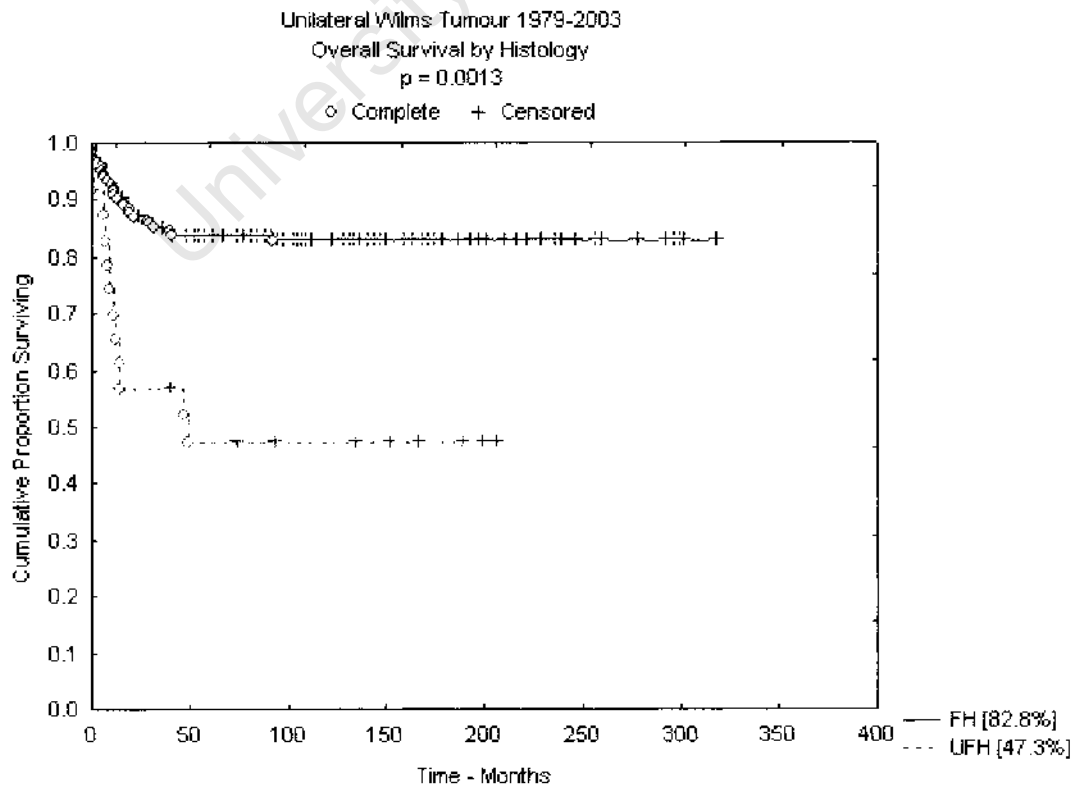
**TABLE 3****Bilateral Wilms' Tumour:****Patient Characteristics and Outcome**

	<b>TOTAL</b>	<b>Metachronous</b>	<b>Synchronous</b>
<b>LOCAL STAGE</b>			
Stage I	12	2	10
Stage II	6	2	4
Stage III	2	1	1
<b>HISTOLOGY</b>			
Favourable Histology	17	4	13
Focal Anaplasia	1	1	0
Diffuse Anaplasia	2	0	2
<b>OUTCOME</b>			
Achieved remission	14	4	10
Relapse	7	0	7
Local	4	0	4
Lung	2	0	2
Multiple	1	0	1
Alive Disease Free [%]	11 [55.0]	4 [80.0]	7 [46.7]
Died of Disease	7	1	6
Unrelated death	2	0	2

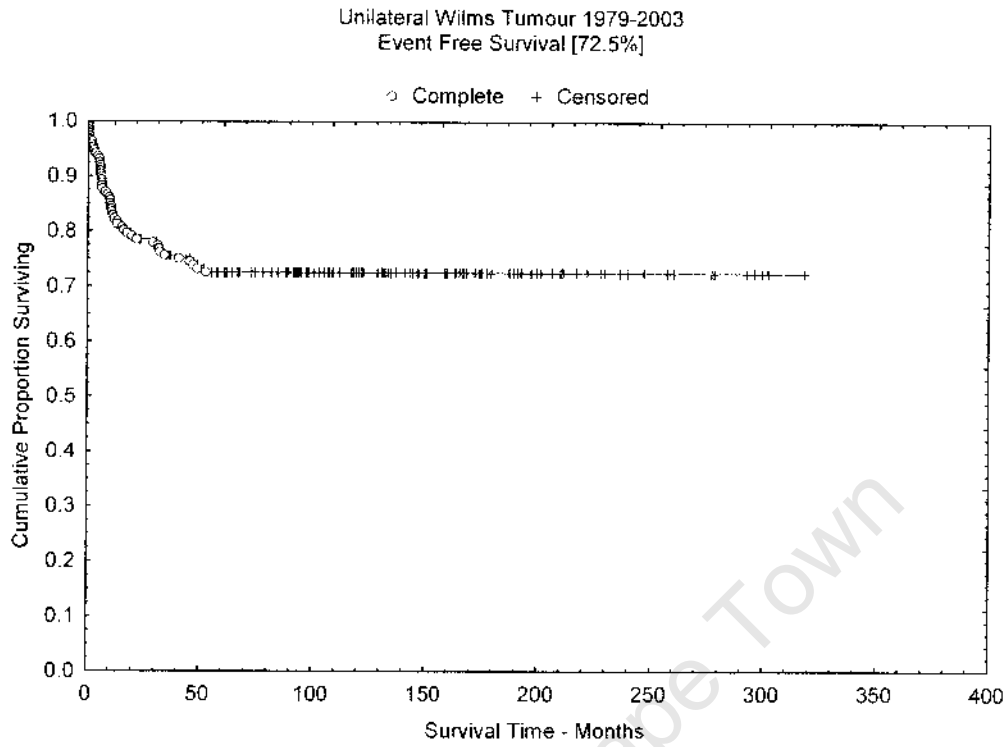
**FIGURE 2**



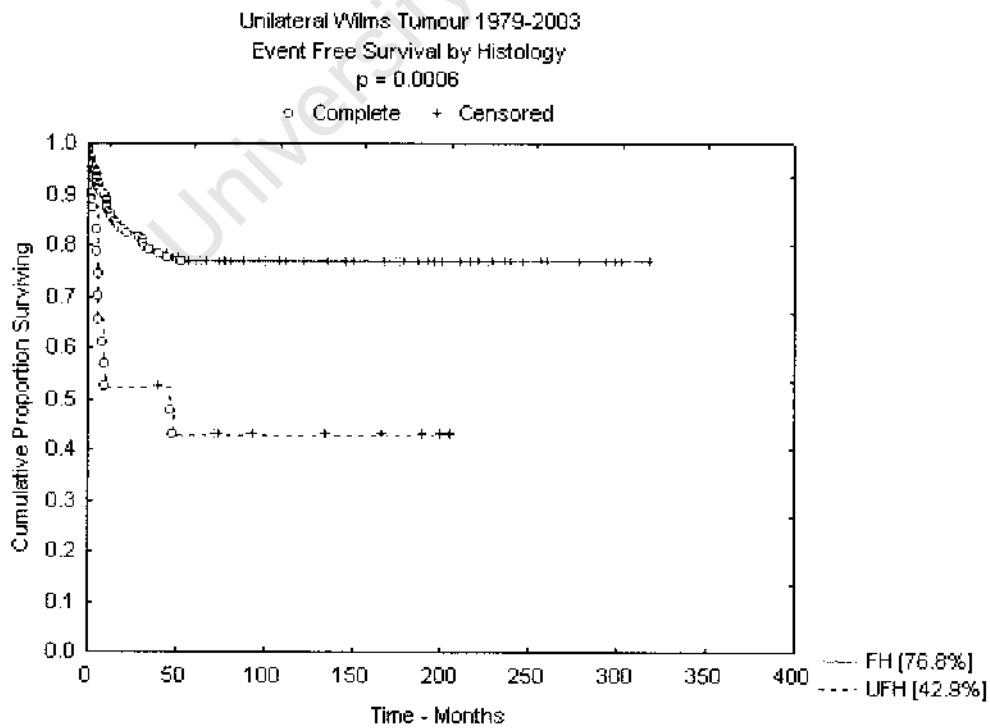
**FIGURE 3**



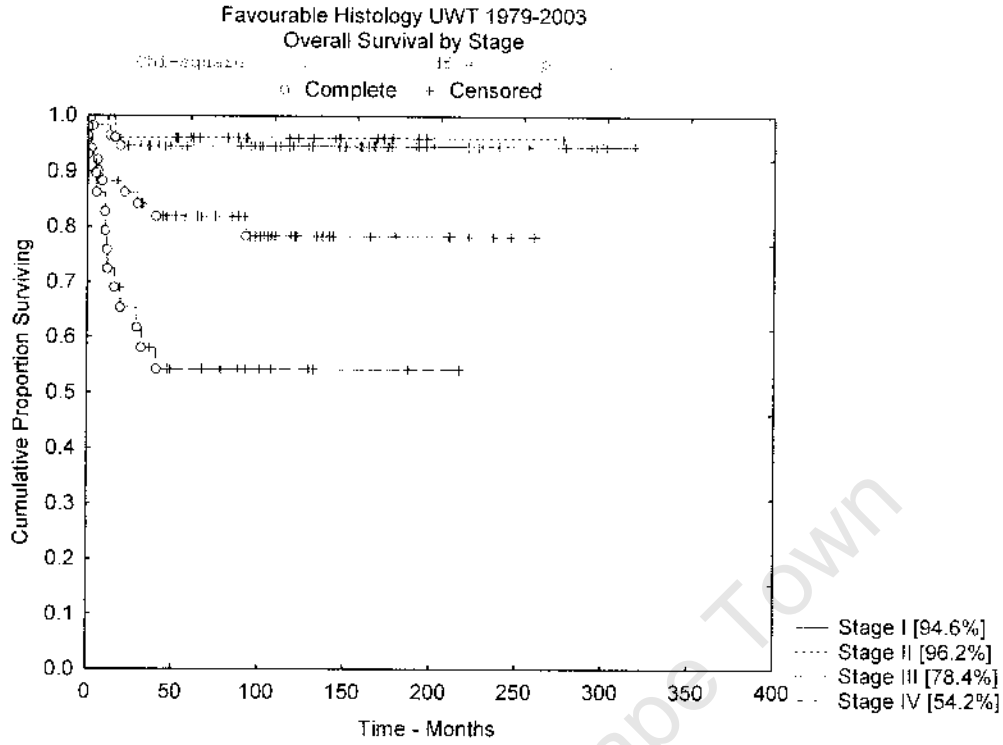
**FIGURE 4**



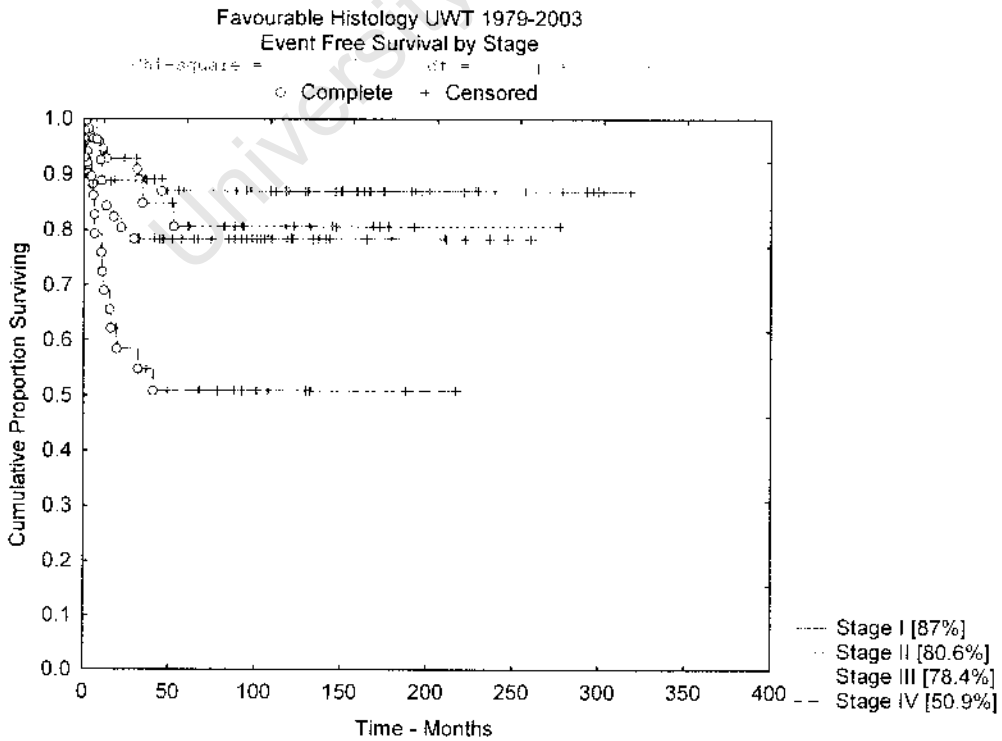
**FIGURE 5**



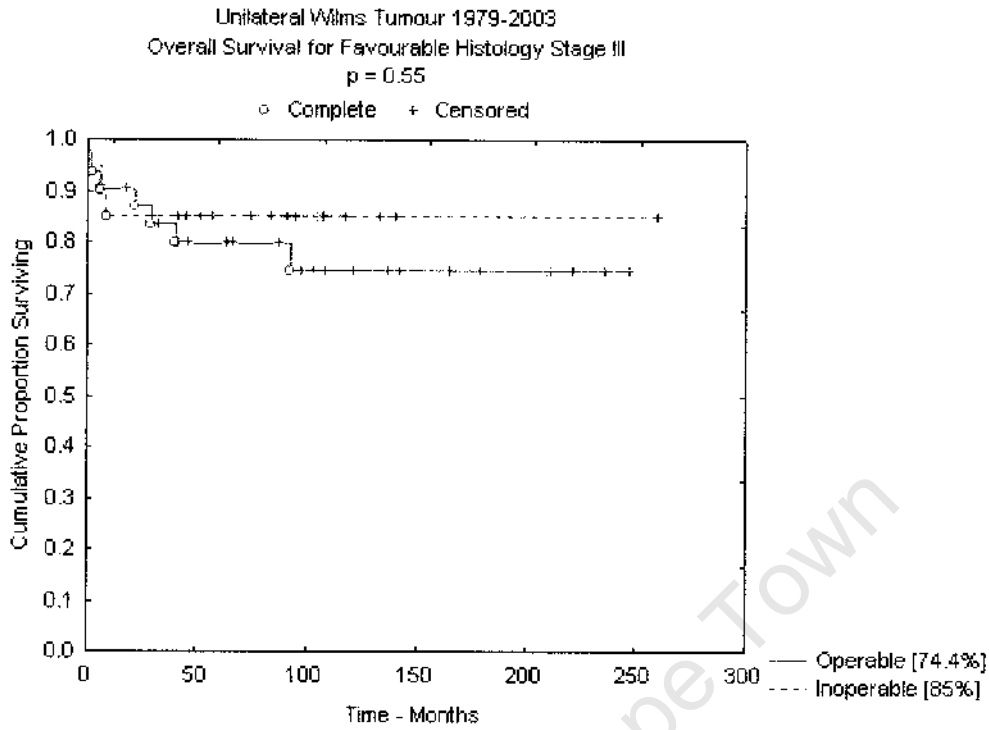
**FIGURE 6**



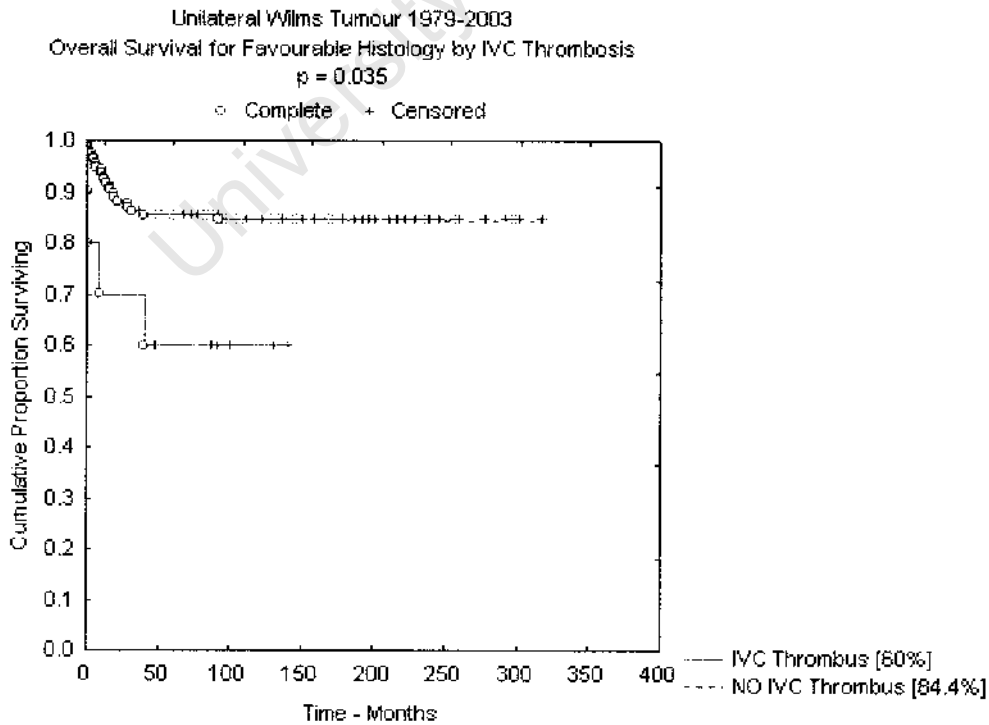
**FIGURE 7**



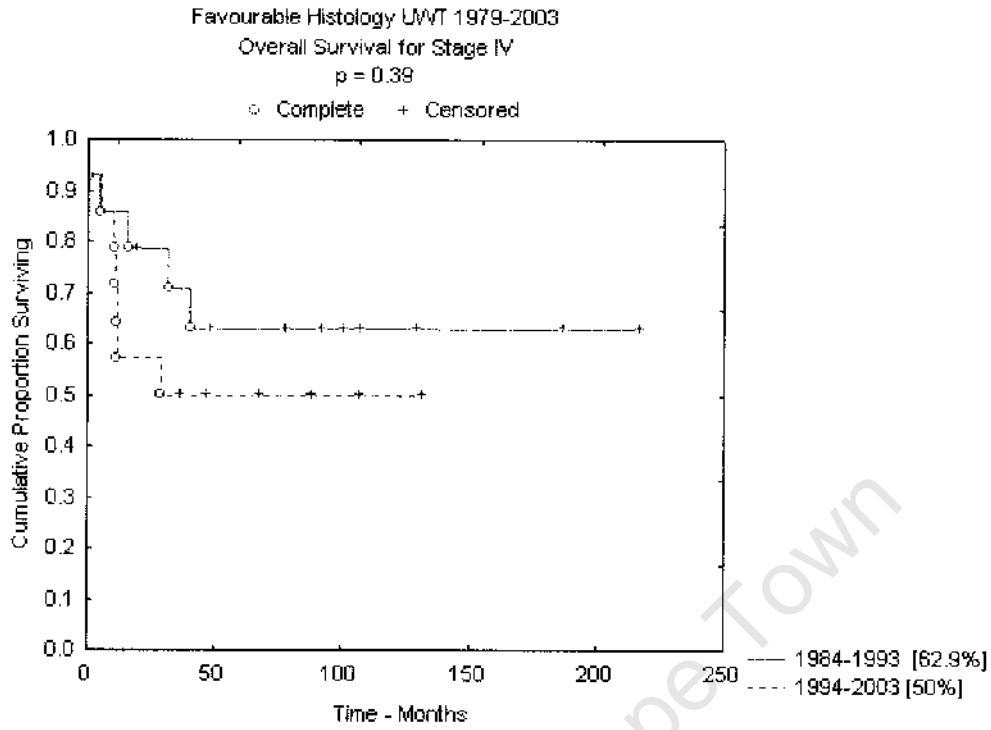
**FIGURE 8**



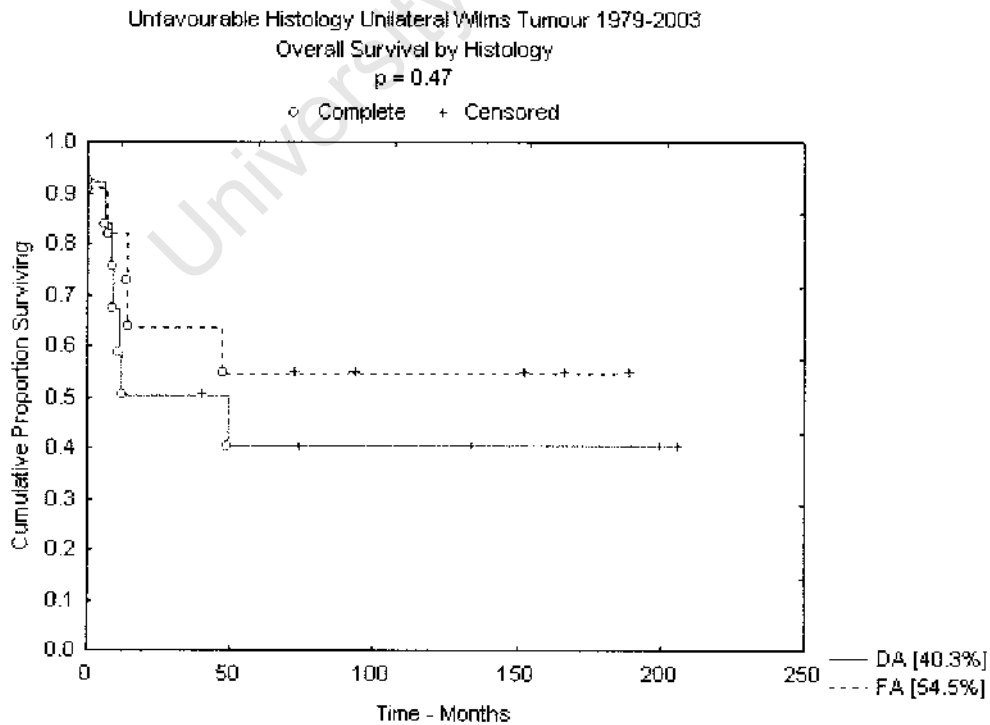
**FIGURE 9**



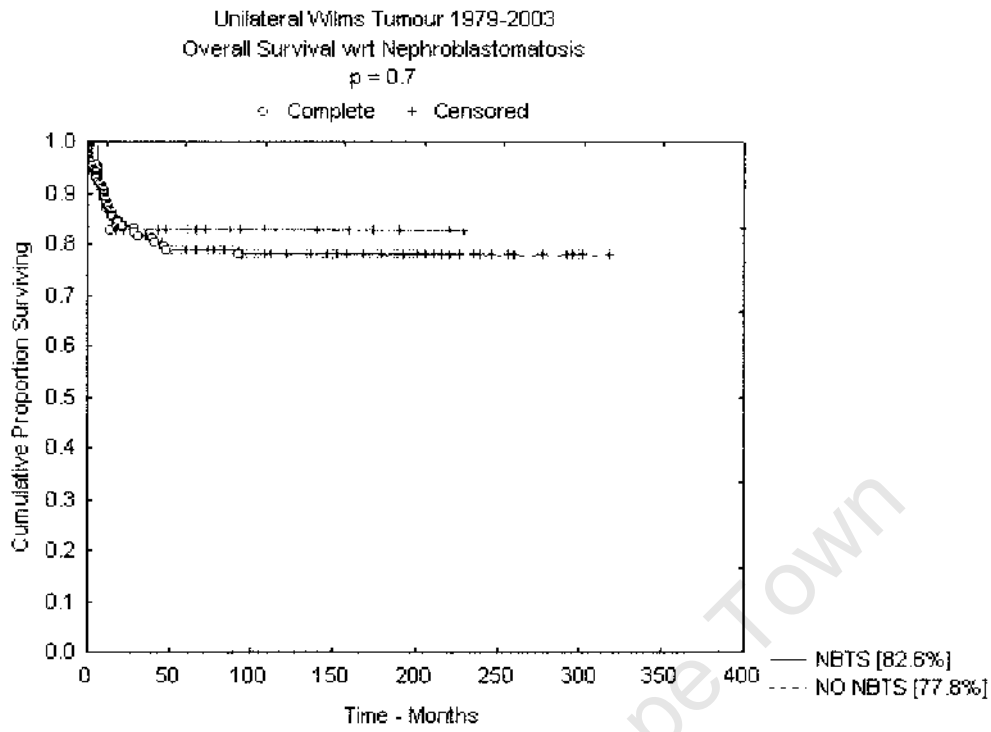
**FIGURE 10**



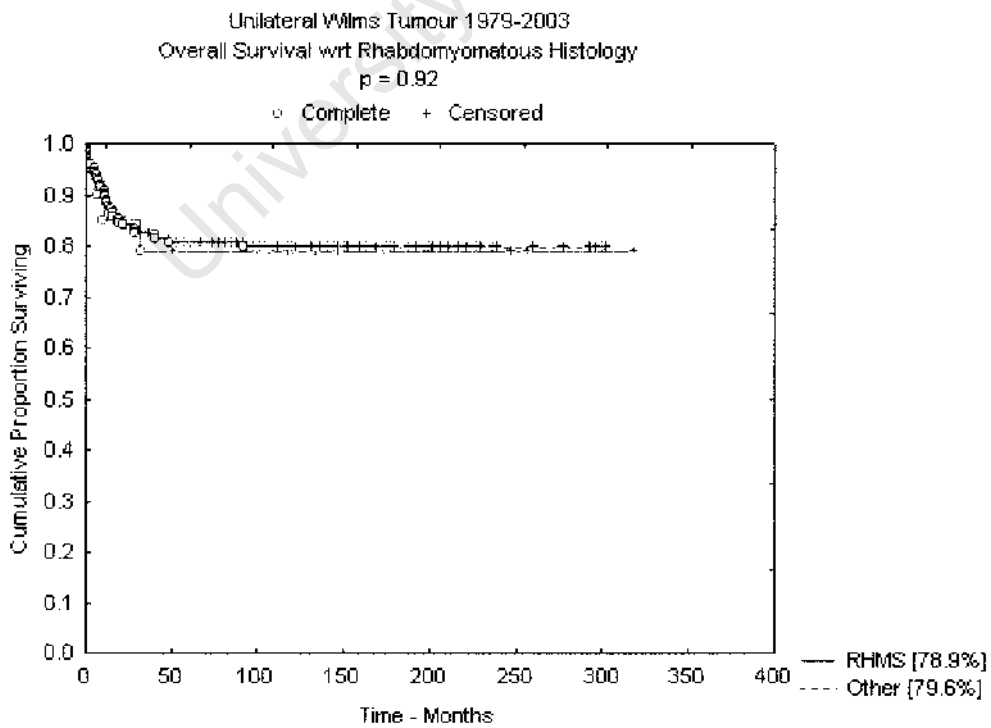
**FIGURE 11**



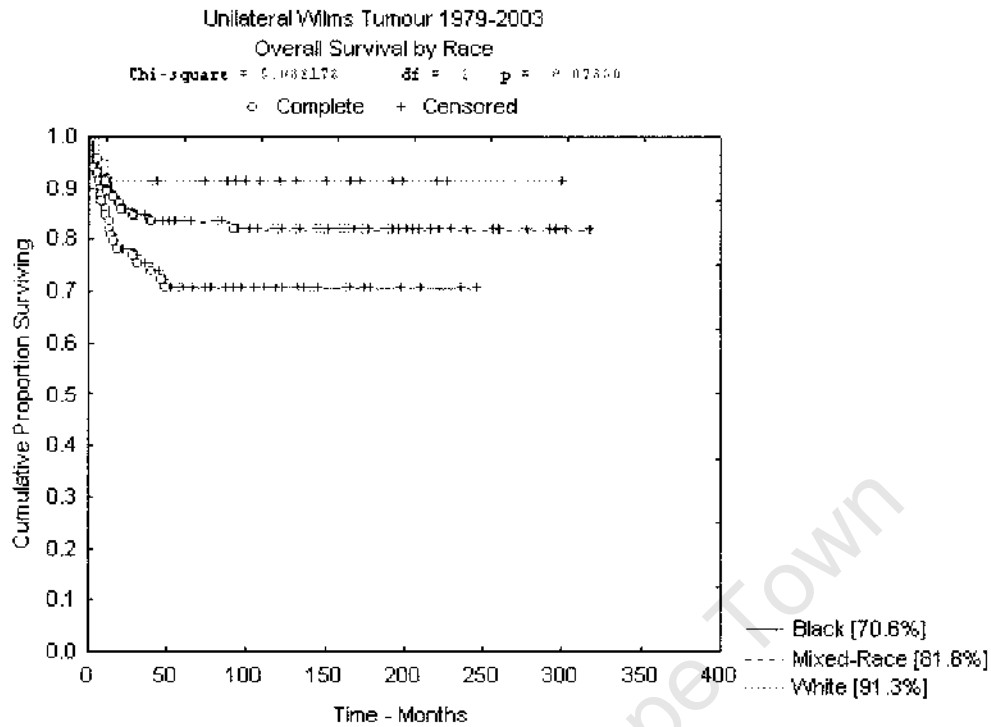
**FIGURE 12**



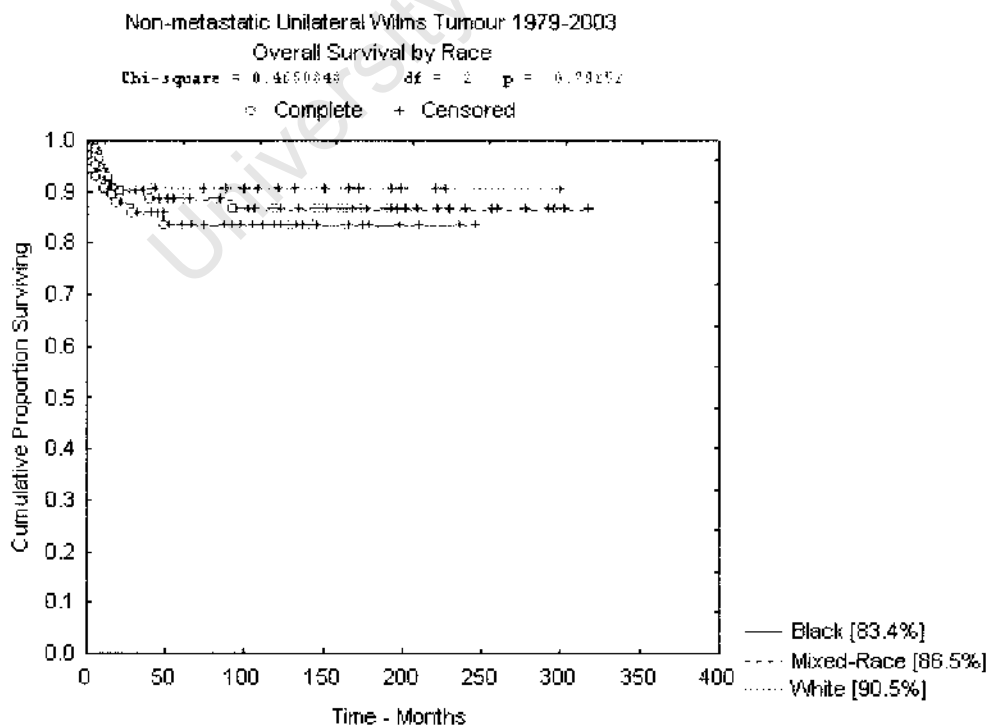
**FIGURE 13**



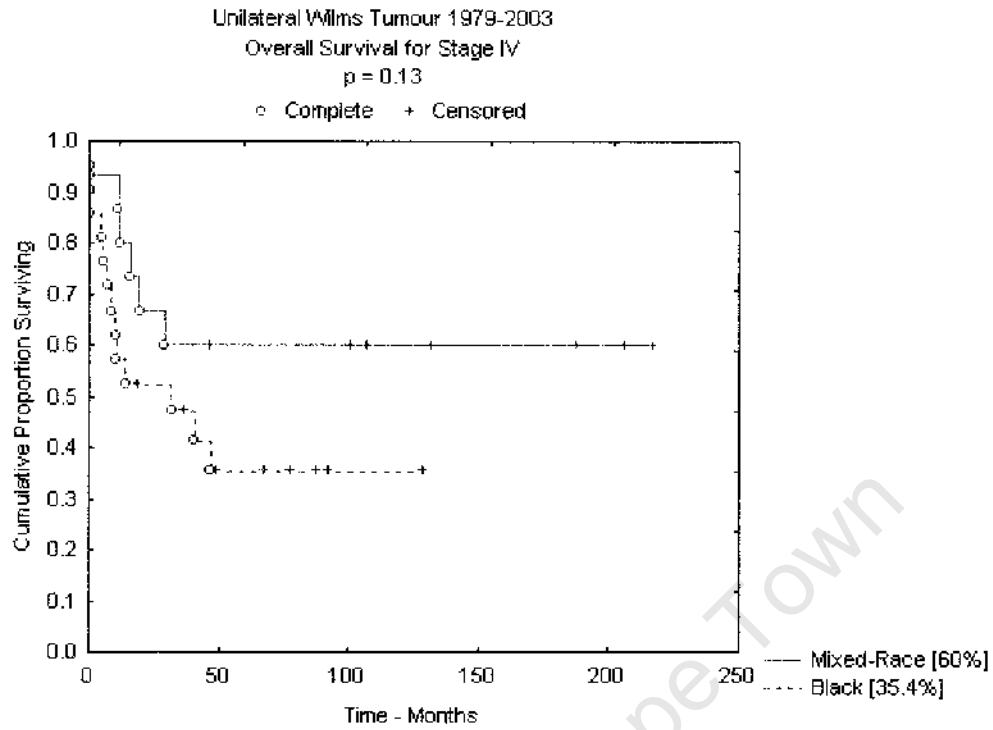
**FIGURE 14**



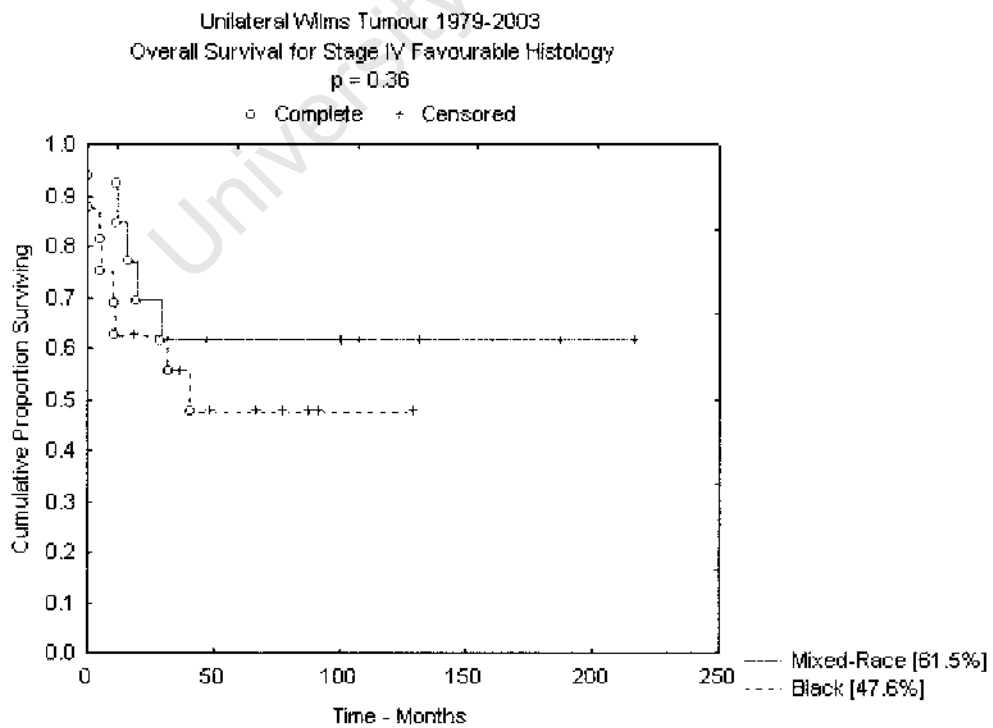
**FIGURE 15**



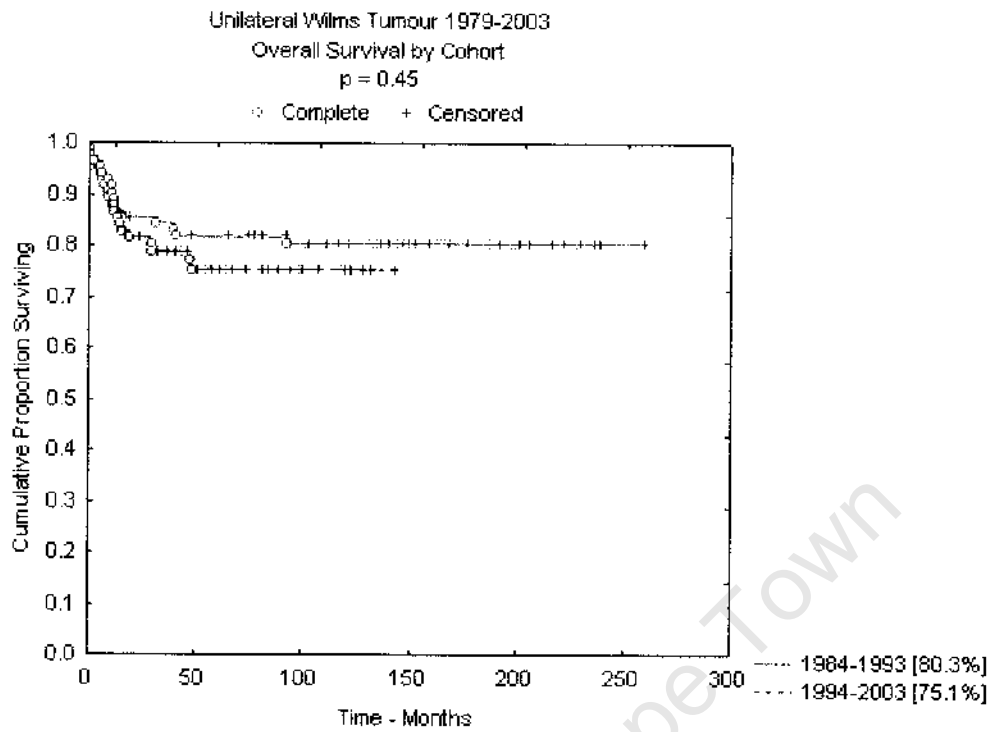
**FIGURE 16**



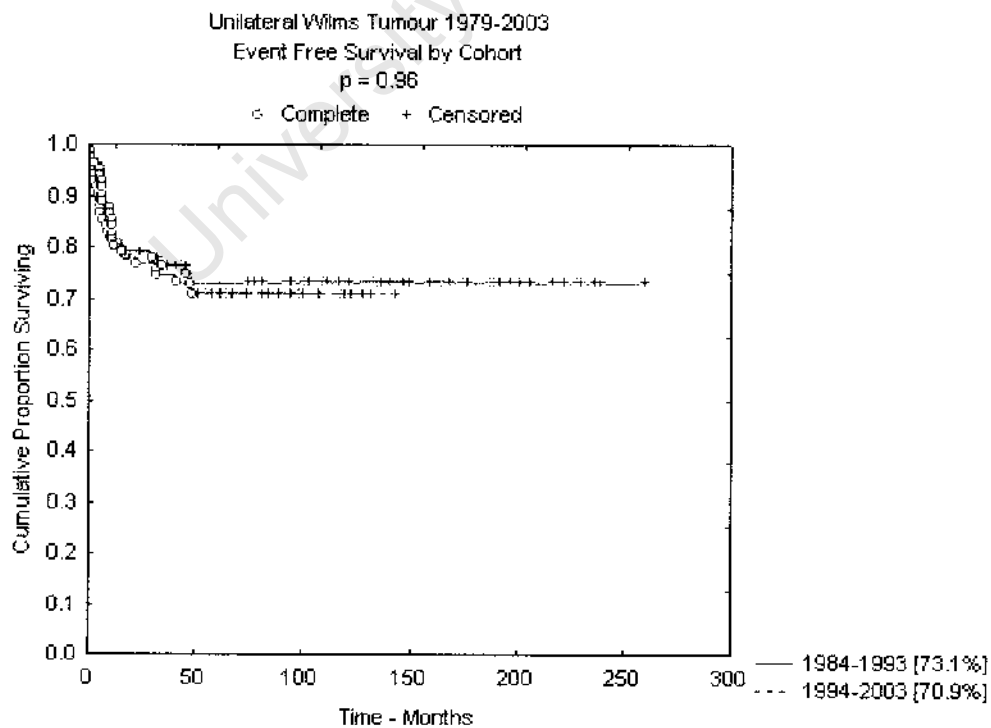
**FIGURE 17**



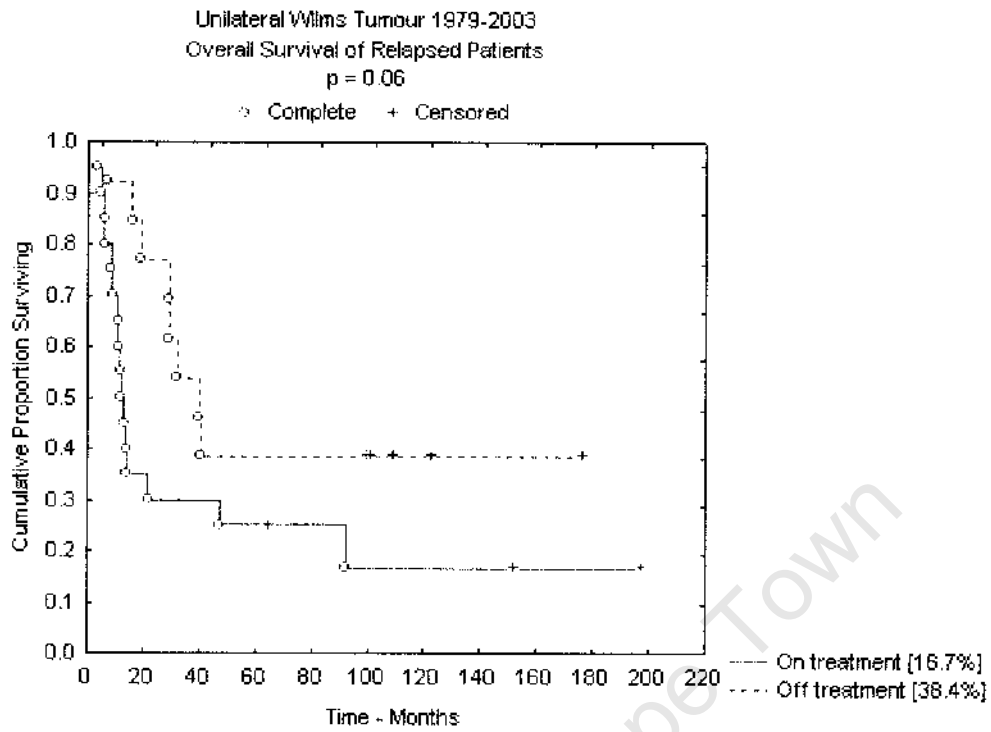
**FIGURE 18**



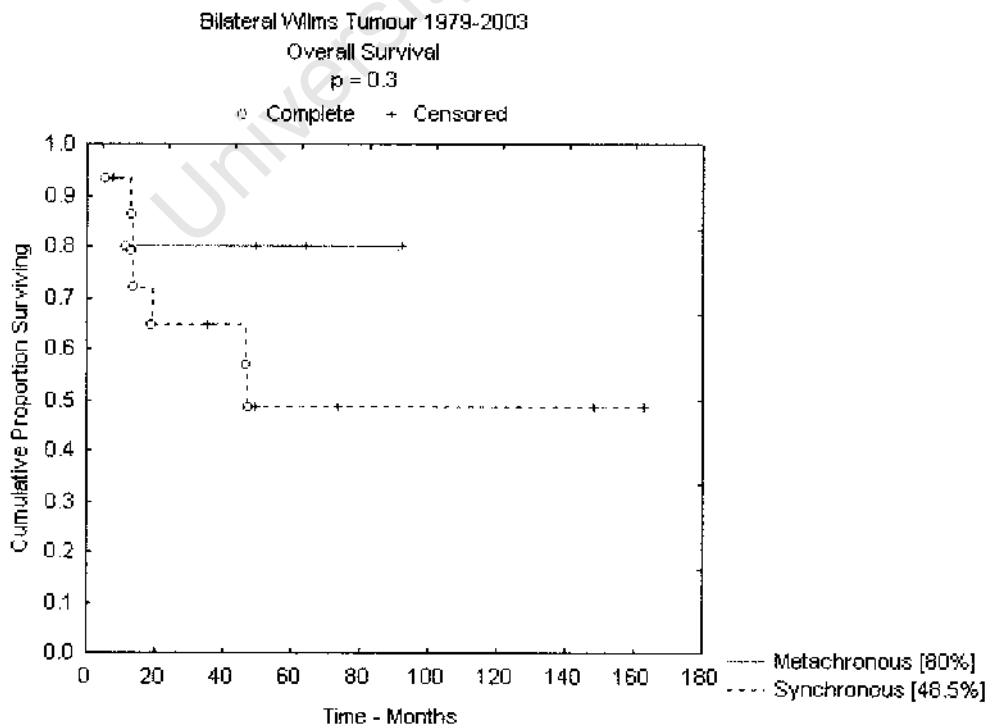
**FIGURE 19**



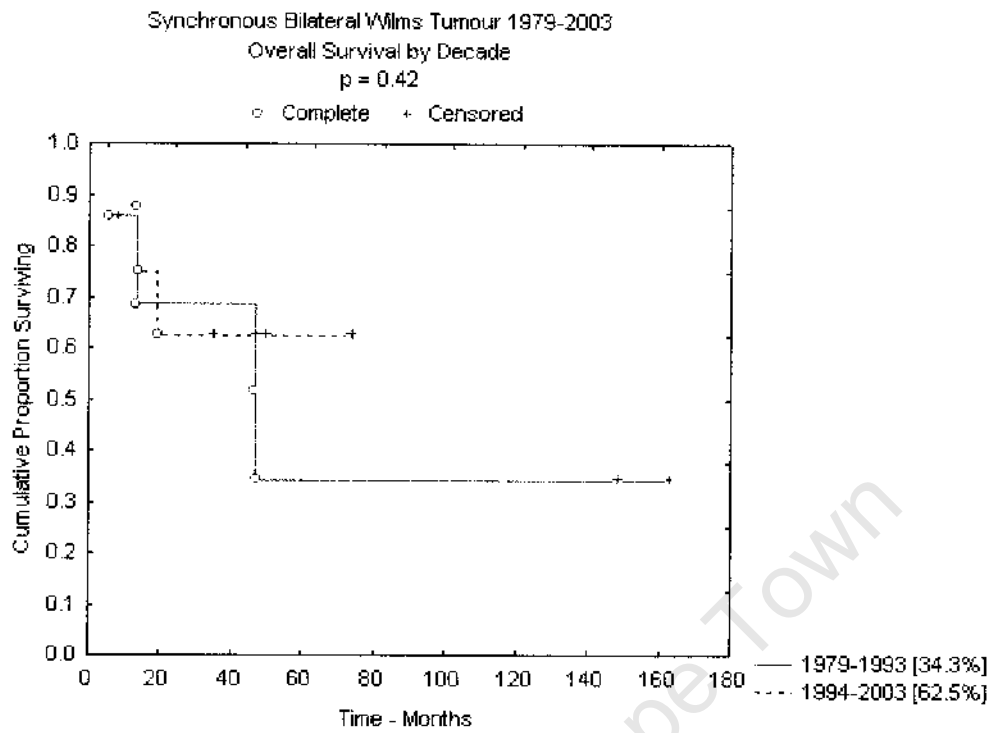
**FIGURE 20**



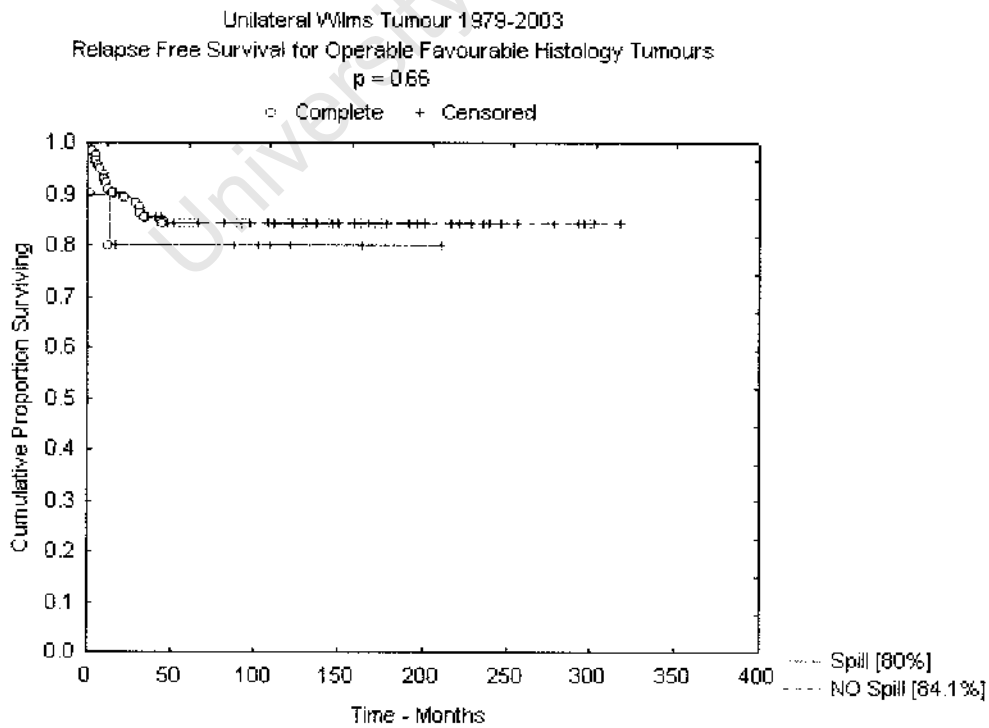
**FIGURE 21**



**FIGURE 22**



**FIGURE 23**



## CHAPTER FOUR:

# CONCLUSIONS AND RECOMMENDATIONS

## CONCLUSIONS

### UNILATERAL WILMS' TUMOUR

How does our cohort compare with larger reported series such as those of NWTSG? The mild predominance of female patients is unusual, but the age distribution is typical with a median of 39.2 months - median age of presentation in NWTSG series is 36.5 months for boys and 42.5 months for girls.<sup>6</sup> Poor nutrition was a common problem. At least 20.7% of our children were below the 3<sup>rd</sup> centile of weight for age - the true figure may be higher because 20.3% of the operable tumours weighed more than one kilogram.

There were 13 patients with abnormalities known to be associated with WT, including urogenital abnormalities, hemihypertrophy, aniridia and Beckwith-Wiedemann syndrome (BWS). This finding supports current recommendations for WT surveillance in these patients.<sup>123,124</sup> There is consensus that children with hemihypertrophy, aniridia and BWS should be followed with three monthly ultrasound until the age of five years, and for a further two years in the case of BWS.

More patients had advanced disease than those on NWTSG studies; 31.9% of our patients were stage III and 20.2% stage IV compared to 21% and 11% respectively of NWTSG-3.<sup>62</sup> There were also larger tumours; 66.9% of our patients had tumours larger than 500g compared to 49% of the patients on NWTSG-3.<sup>125</sup> Moreover, 63.6% were more than 550g, a weight below which tumours are associated with a good prognosis especially in children younger than two years of age.<sup>64</sup> There were more anaplastic tumours (12.8%) in our series than in NWTSG-3 (3.9%).<sup>62</sup>

NWTSG currently reports a 4-year OS for patients with FH WT that approaches 90/0.<sup>6</sup> Four-year OS for stages I through IV reported by NWTSG-4 was 95.6%, 91.1%, 90.9%, and 80.9% respectively.<sup>24</sup> Five year OS for FH WT reported by SIOP-9 was 90%:<sup>126</sup> 100% for stage I; 88% for stage II and 85% for stage III.<sup>72</sup> Hence our results are comparable for non-metastatic WT (OS for FH tumours by stage was 94.6% for stage I, 96.2% for stage II, 78.4% for stage III), but disappointing for patients with stage IV disease (OS of 54.2%). Significantly recent stage IV patients (1994-2003) did no better than those in earlier years (1984-1993).

What factors may be playing a role here? Historical data from NWTSG-2 showed that more than half the patients with Stage IV FH WT were cured with vincristine and dactinomycin alone.<sup>127</sup> Absence of pulmonary radiotherapy from the treatment regime of the first UKCCSG WT trial (UKW1) was implicated as the cause for the disappointing OS of 65% for stage IV tumours.<sup>128</sup> Our patients were adequately treated with vincristine,

dactinomycin and doxorubicin, as well as pulmonary radiotherapy for metastases visible on chest xray. The most likely explanation for our poor results is that delay in diagnosis resulted in advanced presentations that were more difficult to cure.

Favourable histology patients with CT-only lung metastases did as well as those with chest xray metastases, despite not all receiving pulmonary radiotherapy, and this is consistent with NWTS data. It is worth noting that 5.2% of the 2498 patients on NWTS-5 had CT-only pulmonary metastases. Of these 129 cases, 42 were biopsied, and 11 (26.2%) were histologically benign.<sup>129</sup> The authors concluded that pulmonary metastases only visible on CT scan and not responding to first-line chemotherapy should be biopsied before changes are made to the therapeutic regime.

In our series inoperable stage III tumours fared no better than those who underwent nephrectomy prior to chemotherapy. This is an important check on patient selection for surgery. Inclusion of too many patients who would have been stage I or II at primary surgery might result in the group of inoperable stage III tumours having better results. This would also mean that a significant number of patients might have been over treated. Tumour size was not an obstacle to resection with 35.7% exceeding one kilogram. The incidence of IVCT (5.9%) was comparable to that reported by NWTSG (4%)<sup>130</sup> and the third UKCCSG WT Trial (8.1%).<sup>131</sup> Reported OS for these patients varies from 33% to 70/0.<sup>132, 133</sup> Pre-operative chemotherapy resulted in

significant tumour shrinkage allowing definitive surgery to be performed in most children. This was the case in our series (OS of 60%).

The results of our UFH are surprising in that focal anaplasia fared as poorly as diffuse anaplasia. NWTS-3 and 4 reported a 4-year OS of 52.2% for stage II to IV tumours with diffuse anaplasia.<sup>65</sup> The OS for a small group of children with focal anaplasia was 100%. In our series, the larger number of stage IV tumours among those with focal anaplasia (54.5%) probably accounts for their poor outcome. Preliminary results of NWTS-5 suggest that two drugs may be inadequate adjuvant treatment for stage I anaplastic tumours<sup>134</sup> but we had only one stage I tumour with UFH - a patient with focal anaplasia who is alive and disease free.

Hadley et al<sup>78</sup> reported poor prognosis for black patients in South Africa with WT, and noted a high proportion of advanced local and metastatic disease, as well as nutritional and infective co-morbidity. The same group published a series of 67 black patients, all of whom had tumours larger than one kilogram after neoadjuvant chemotherapy." In only 13% of these could UFH be invoked to explain the poor response to chemotherapy. Our results show that black patients with non-metastatic disease do as well as other patients. Metastatic disease was seen more frequently in black patients and conferred a very poor prognosis. In part this is explained by a higher proportion of stage IV tumours with UFH, but even black children with FH metastatic disease fared worse than their mixed-race counterparts. Once

again, delay in diagnosis with advanced presentation is the likely explanation.

The risk of recurrence in WT is approximately 15%.<sup>135</sup> Lungs, liver, contralateral kidney and renal bed are the commonest sites, and risk factors include advanced stage, UFH, advanced age at diagnosis, tumour size, and lymph node involvement. In addition, spillage or pre-operative rupture has been demonstrated to be a risk factor for local recurrence,<sup>136</sup> and nephroblastomatosis has been cited as an independent risk factor for both relapse<sup>137</sup> and contralateral disease.<sup>28</sup> Most recurrences occur within two years and almost all within four years.<sup>138</sup> In our series, UFH and high stage were associated with increased relapse. All relapses occurred within four years, only 12% of them beyond two years. Nephroblastomatosis occurred more frequently in our series (12.8%) than the 4.5% reported in the literature,<sup>125</sup> but did not confer additional risk of relapse. Spill or rupture was also not associated with increased risk of local relapse.

Post-relapse survival on NWTS-2 and NWTS-3 was best for tumours of low stage and FH, pulmonary relapse, and those relapses occurring more than 12 months after diagnosis,<sup>139</sup> and this was our experience. Survival is superior in those patients not already treated with doxorubicin and radiotherapy.<sup>136</sup>

In the literature, rhabdomyomatous change is associated with a poor response to chemotherapy<sup>34</sup> but a generally favourable outcome when treated by surgery.<sup>36</sup> However, the response rate among our patients with

rhabdomyomatous histology was comparable to that of other patients with FH WT, as was the survival.

The rate of surgical complications was low in our series. NWTSG-defined intra-operative spillage or rupture occurred in 8.2% of operable FH UWT; less frequently than the 15.2% reported by NWTSG-5<sup>140</sup> but more frequently than the 2.8% incidence reported by SIOP-9.<sup>141</sup> At 9.6%, the frequency of small bowel obstruction was comparable to the 6.9% reported by NWTSG-3<sup>142</sup> but clearly higher than the 3.7% reported by SIOP-9.<sup>141</sup> All other complications were negligible.

The incidence of renal failure among survivors (0.5%) was comparable to the 0.25% reported by NWTSG for UWT.<sup>104</sup> Cardiomyopathy occurred in 2.3% of our patients treated with doxorubicin, marginally higher than the 1.7% reported by NWTSG.<sup>109</sup> All three patients developed cardiomyopathy after cumulative doses at or above 300mg/m<sup>2</sup>. The maximum dose in current use (for anaplastic tumours) is 225mg/m<sup>2</sup>. There was only one second malignancy, yielding a 0.5% incidence that is comparable with both NWTSG and STOP data.<sup>110,111</sup>

In conclusion, NWTSG protocols employed in a South African setting with appropriate surgical expertise, produced comparable results for non-metastatic FH WT. Results for metastatic disease and UFH were poor.

In a recent review of WT treatment Giulio D'Angio concluded that there is very little to choose between primary surgery and pre-operative chemotherapy in the face of modern, expert care.<sup>143</sup> He advocates early surgery where circumstances allow, and our results show that this is possible outside of a developed world setting.

## **BILATERAL WILMS' TUMOUR**

Synchronous BWT comprised 7.2% of our series and metachronous BWT 2.4%, and they presented at a younger age than those with UWT (median of 23.9 months). All but two (both synchronous BWT) had multiple nephrogenic rests or nephroblastomatosis, and two of the synchronous BWT had diffuse anaplasia (13.3%). This is entirely consistent with NWTSG data. Unusually, there were no associated congenital abnormalities or syndromes.

In our series, neither UFH nor metachronous presentation was associated with a poorer prognosis. However, when extra-renal disease developed, this was associated with reduced survival. Multicentricity and nephroblastomatosis was an almost universal finding, and all but two were local stage I or II. Survival improved considerably between the first fifteen years (34.3% for 1979-1993) and the last decade (62.5% for 1994-2003).

The prime goal in the management of patients with BWT is to provide effective curative treatment while at the same time preserving sufficient functioning renal tissue for normal growth and development.<sup>144</sup> This should commence with early clinical diagnosis and for those presenting with

ostensibly unilateral disease, a very close look at the contralateral kidney with biopsy of any suspicious areas. Pre-operative imaging is increasingly accurate<sup>145</sup> but should not replace careful visualization of the contralateral kidney.<sup>146</sup> Any nephroblastomatosis in a resected tumour should alert the physician to be particularly diligent in follow-up and monitoring. Where nephroblastomatosis is identified pre- or intra-operatively, there may be a place for nephron-sparing surgery in a selected group of infants with well-circumscribed UWT, and the NWTSG has recommended that such an approach should be formally studied.<sup>28</sup>

With metachronous presentation there is only one kidney remaining and some attempt at nephron-sparing surgery is almost always indicated. The alternative is leaving the patient free of disease but anephric requiring renal transplantation with all the consequences of lifelong immune suppression and drug toxicity. With synchronous BWT, the current recommendations for treatment are biopsy followed by neo-adjuvant chemotherapy and then renal salvage procedures (partial nephrectomy or tumourectomy).<sup>9</sup> Nephron-sparing is not advocated in the face of diffuse anaplasia,<sup>147</sup> nor in cases of Denys-Drash syndrome.<sup>15</sup> Patients can be considered for transplant when they have achieved two years of disease-free survival after treatment, though this may be reduced to one year if there is a living-related donor.<sup>15</sup>

A number of innovations have facilitated nephron-sparing surgery. In-situ topical cooling or perfusion with preservation solution allows careful and

extensive dissection and reconstruction without loss of renal function from ischaemia. <sup>148</sup> In most cases the cross clamp-time is relatively short and topical cooling with ice is sufficient. The use of the ultrasonic scalpel facilitates dissection as it cuts so well in a wet environment, with the residual preserved part of the kidney remaining in ice while the tumour is resected. The Cavitron ultrasonic surgical aspirator has been used to good effect in some centres. <sup>148</sup> Using loop magnification, vascular structures can be identified and sutured and the pelvicalyceal system, if involved, repaired. The renal artery and vein are usually large as they have supplied a large tumour and this allows for considerable mobilization of the kidney making surgical access and orthotopic positioning, as well as vessel reanastomosis, easier, particularly if there was tumour shrinkage with chemotherapy.

Bench surgery with autotransplantation <sup>149</sup> can be performed in exceptional circumstances as demonstrated in one of our cases. Ex-vivo perfusion does have the disadvantage, however, of making it very difficult to visually discriminate between tumour, nephroblastomatosis and normal renal tissue. Multiple frozen section biopsies may be required but can also be difficult for the histopathologist to interpret. In-situ cold perfusion with organ preservation solution is an alternative to bench surgery providing for longer cross-clamp times without renal injury. It still has the disadvantage of loss of tissue definition.

Tumours arising in areas of nephroblastomatosis tend to respond to chemotherapy and this was our experience. Two patients with extensive nephroblastomatosis achieved complete remission with chemotherapy only, a phenomenon that has been described in a child with Beckwith-Wiedemann syndrome.<sup>150</sup> One patient with extensive rhabdomyomatous change had a poor response to chemotherapy, and this phenomenon has been reported in the literature.<sup>35</sup> After successful bench surgery and subsequent contralateral tumourectomy, he suffered a recurrence of tumour, but remains a survivor with good renal function after further nephron-sparing surgery.

The use of radiotherapy for BWT has diminished over time; 57% of patients on NWTS-2 and -3<sup>8</sup> received renal or renal-bed irradiation, compared to 42 of the 196 kidneys (21.4%) registered on the renal salvage procedure arm of NWTS-4.<sup>9</sup> This supports our decision to avoid radiotherapy; its use could come at the cost of reduced renal function and significant survival advantage has not been demonstrated.

A particularly difficult area is that of progressive or non-responding BWT. In NWTS-4 these tumours achieved an OS of only 66.8%.<sup>102</sup> Notably, only a small percentage had anaplastic histology or rhabdomyomatous change. In the event of a poor response to neoadjuvant chemotherapy early biopsy and early resection is recommended, and nephron-sparing techniques may not be feasible. Some workers have even advocated the use of brachytherapy (local treatment with radioactive implants) for these tumours."

Other than cardiomyopathy and second malignant neoplasms, renal failure is the commonest source of morbidity in BWT survivors. The risk of renal failure increases with the loss of more than 50% of renal mass. <sup>111</sup>

Consequently, with the changing nature of treatment, the rate of renal failure in BWT has decreased from 16.4% in NWTs-1 and -2 to 9.9% in NWTs-3 and 3.8% in NWTs-4. <sup>104</sup> The absence of significant renal impairment among our survivors is proof of the success of nephron-sparing surgery, but all ~~should have~~ should have systematic follow-up of blood pressure, urine protein and renal

## RECOMMENDATIONS

Further advance in the management of WT depends on a number of factors. Firstly, better risk stratification using new molecular markers <sup>151</sup> may improve our ability to identify tumours that require more intensive therapy. Loss of heterozygosity at chromosomes 1p and 16q has been shown to be an adverse prognostic factor for FH WT <sup>19</sup> and increased telomerase expression is associated with increased risk of relapse, <sup>63</sup> though not with decreased survival. Gene expression profiling using micro array technology <sup>152,153</sup> appears to hold some promise in selecting out those FH tumours that are destined to relapse. Secondly, new chemotherapeutic regimes may improve the outcome of patients with relapsed or refractory disease. For both of these we are largely dependant on the research efforts of the large North American (NWTSG) and European (STOP) collaborations. Thirdly, surgical innovations will likely form the focus of our efforts to improve the outcome

of BWT. Tumours not responding to chemotherapy remain a challenge but the proportion of such tumours may be smaller if nephron-sparing techniques improve.

Success for us at RCCH will be determined by our ability to maintain current standards of medical and surgical care, and incorporate newly proven techniques into our treatment regimens as they become available.

Decreasing the intensity of adjuvant chemotherapy for low risk tumours (young patients with small low stage tumours) awaits results from the latest NWTSG trial, because we have experienced very little in the way of treatment-related morbidity in this group. Despite the introduction of more intensive chemotherapy regimes such as IE and ICE, we are not achieving better results among patients with metastatic and anaplastic disease.

Future success may lie with biological therapies such as monoclonal antibodies and small molecule enzyme inhibitors, but expense will likely limit their availability to most of our patients. In the final analysis, achieving better outcomes for our stage IV patients may depend as much on improved surveillance with earlier diagnosis, as on advances in treatment regimes.

Part of our responsibility as oncologists is to train young doctors to recognize paediatric malignancy in the community setting and impart this knowledge at the coalface to their nursing colleagues. In addition it behoves us to help prepare future generations of paediatric oncologists and surgeons to carry the torch of caring for children with cancer.

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# APPENDIX ONE

## National Wilms' Tumour Studies:

### Design and Major Outcomes

SUR	surgery
XRT	renal bed radiotherapy
VCR	vincristine 1.5-2 mg/m <sup>2</sup>
AMDx5	dactinomycin 15 mcg/kg x 5
AMDx1	dactinomycin 45 mcg/kg x 1
DOXO	doxorubicin total dose from 120 to 300 mg/m <sup>2</sup>
CPM	cyclophosphamide 10 mg/kg x 3
w	weeks
m	months
DFS	disease free survival
OS	overall survival
RFS	relapse free survival

## NWTS-1 [1969-1973]

### Stage I

Arm						
A	SUR	XRT	AMDx5	< 2 years	DFS 90%	OS 97%
				> 2 years	DFS 77%	OS 97%
B	SUR		AMDx5	< 2 years	DFS 94%	OS 94%
				> 2 years	DFS 58%	OS 91%

### Stage II and III

Arm					
A	SUR	XRT	AMDx5	DFS 57%	OS 67%
B	SUR	XRT	VCR	DFS 55%	OS 72%
C	SUR	XRT	VCR + AMDx5	DFS 81%	OS 86%

### Stage IV

Arm						
A			SUR	XRT	VCR + AMDx5	OS 83%
B	PreOp VCR		SUR	XRT	VCR + AMDx5	OS 29%

### CONCLUSIONS

XRT provides no additional benefit for stage I patients (equal OS)  
 VCR + AMDx5 better than VCR or AMD alone for stage II and III patients  
 Preoperative VCR for stage IV patients unsuccessful

## NWTS-2 [1974-1978]

### Stage I

Arm			
E1	SUR	VCR + AMDx5 [6m]	RFS 88%
E2	SUR	VCR + AMDx5 [15m]	RFS 88%

### Stage II - IV

Arm			
C	SUR	XRT VCR + AMDx5 [15m]	all stages stage IV RFS 62% RFS 43%
D	SUR	XRT VCR + AMDx5 + DOXO [15m]	all stages stage IV RFS 77% RFS 59%

### CONCLUSIONS

Shorter arm as effective for stage I patients  
DOXO improves survival for stage II to IV patients, especially those with FH

## NWTS-3 [1979-1985]

### Stage I

Arm			
L	SUR	VCR + AMDx5 [10w]	RFS 89% OS 95.6%
EE	SUR	VCR + AMDx5 [6m]	

### Stage II

Arm			
DD1	SUR	VCR + AMDx5 + DOXO [15m]	RFS 91.1%
DD2	SUR	XRT (20Gy) VCR + AMDx5 + DOXO [15m]	
K1	SUR	VCR + AMDx5 [15m]	
K2	SUR	XRT (20Gy) VCR + AMDx5 [15m]	

### Stage III

Arm			
DD1	SUR	XRT (10.8Gy) VCR + AMDx5 + DOXO [15m]	RFS 82% OS 90.9% 3 relapses of 70
DD2	SUR	XRT (20Gy) VCR + AMDx5 + DOXO [15m]	
K1	SUR	XRT (10.8Gy) VCR + AMDx5 [15m]	7 relapses of 61
K2	SUR	XRT (20Gy) VCR + AMDx5 [15m]	3 relapses of 68

### Stage IV and Unfavourable Histology

Arm			
DD	SUR	XRT (20Gy) VCR + AMDx5 + DOXO [15m]	RFS 79% OS 80.9%
J	SUR	XRT (20Gy) VCR + AMDx5 + DOXO + CPM [15m]	

### CONCLUSIONS

Shorter arm as effective for stage I patients  
XRT and DOXO provide no additional benefit for stage II patients  
XRT (10 Gy) only results in increased relapse for stage III ... No change in OS  
CPM did not improve stage IV results but did improve results for UFH

## NWTS-4 [1986-1994]

**Stage I** RFS 89%      OS 95.6%

Arm

EE	SUR	VCR + AMDx5 [25w]
EE-4A	SUR	VCR + AMDx1 [18w]

### Stage II

Arm

K	SUR	VCR + AMDx5 [22w]	RFS 82.3%	OS 97.8%
	SUR	VCR + AMDx5 [66w]	RFS 88.2%	OS 96%
K-4A	SUR	VCR + AMDx1 [18w]	RFS 86.4%	OS 95.6%
	SUR	VCR + AMDx1 [60w]	RFS 88.9%	OS 98.7%

### Stage III

Arm

DD	SUR	XRT (10Gy)	VCR + AMDx5 + DOXO [26w]	RFS 93.3%	OS 97%
	SUR	XRT (10Gy)	VCR + AMDx5 + DOXO [65w]	RFS 91.4%	OS 94%
DD-4A	SUR	XRT (10Gy)	VCR + AMDx1 + DOXO [26w]	RFS 91.8%	OS 98%
	SUR	XRT (10Gy)	VCR + AMDx1 + DOXO [54w]	RFS 89.5%	OS 95.4%

### Stage IV

Arm

DD	SUR	XRT (10Gy)	VCR + AMDx5 + DOXO [26w]	RFS 82.4%	OS 91.2%
	SUR	XRT (10Gy)	VCR + AMDx5 + DOXO [65w]	RFS 93.4%	OS 100%
DD-4A	SUR	XRT (10Gy)	VCR + AMDx1 + DOXO [26w]	RFS 82.8%	OS 85.3%
	SUR	XRT (10Gy)	VCR + AMDx1 + DOXO [54w]	RFS 78.4%	OS 90.9%

### Overall

AMDx5 regimes	RFS 90.5%
AMDx1 regimes	RFS 89.4%

Short regimes	RFS 83.7%
Long regimes	RFS 88.2%

### CONCLUSIONS

Single dose as effective as divided dose AMD

6 months as effective as 15 months for stages II to IV

## APPENDIX TWO

### Wilms' Tumour protocols used at Red Cross Children's Hospital 1979 - 2003

#### 5741 [1974-1980]

##### Stage I

###### Surgery

Week 0 Nephrectomy

###### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-8	Vincristine	1.5 mg/m <sup>2</sup>	weekly [8]
Week 6, 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [6]
Week 12, 24, 36, 48, 60	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

##### Stage II

###### Surgery

Week 0 Nephrectomy

###### Radiotherapy

Week 1 1800-4000 rads to renal bed

###### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-8	Vincristine	1.5 mg/m <sup>2</sup>	weekly [8]
Week 6, 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [6]
Week 12, 24, 36, 48, 60	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

##### Stage III and IV

###### Surgery

Week 0 Nephrectomy and accessible tumour resection

###### Radiotherapy

Week 1 1800-4000 rads to renal bed

###### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-8	Vincristine	1.5 mg/m <sup>2</sup>	weekly [8]
Week 6, 18, 30, 42, 54	Doxorubicin	20 mg/m <sup>2</sup>	daily x 3 [5]
Week 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [5]
	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

In addition for Stage IV consider XRT to metastases and/or surgical removal if accessible.

## 5811 [1981-1988]

### Stage I

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 12, 24	Dactinomycin	15 mcg/kg	daily x 5 [3]
Week 12, 24	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [4]

### Stage II

#### Surgery

Week 0 Nephrectomy

#### Radiotherapy

Week 1 2000 rads to renal bed (reduce for age)

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [6]
Week 12, 24, 36, 48, 60	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

### Stage III

#### Surgery

Week 0 Nephrectomy and accessible tumour resection

#### Radiotherapy

Week 1 2000 rads to renal bed (reduce for age)

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 18, 30, 42, 54	Doxorubicin	30 mg/m <sup>2</sup>	daily x 2 [5]
Week 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [5]
	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

### Stage IV and Unfavourable Histology (All Stages)

#### Surgery

Week 0 Nephrectomy and accessible tumour resection  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 Up to 3500 rads to renal bed  
Consider XRT to metastases

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 18, 30, 42, 54	Doxorubicin	30 mg/m <sup>2</sup>	daily x 2 [5]
	Cyclophosphamide	10 mg/kg	daily x 3 [5]
Week 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [5]
	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]
	Cyclophosphamide	10 mg/kg	daily x 3 [5]

## 5891 [1989-1991]

### Stage I (Favourable or Anaplastic Histology)

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 12	Dactinomycin	15 mcg/kg	daily x 5 [2]
Week 12	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [2]

### Stage II (Favourable Histology)

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [6]
Week 12, 24, 36, 48, 60	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

### Stage III and IV (Favourable Histology)

#### Surgery

Week 0 Nephrectomy and accessible tumour resection  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 1000 rads to renal bed (reduce for age)  
Consider XRT to metastases

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 18, 30, 42, 54	Doxorubicin	30 mg/m <sup>2</sup>	daily x 2 [5]
Week 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [5]
	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]

### Stage II to IV (Unfavourable Histology)

#### Surgery

Week 0 Nephrectomy and accessible tumour resection  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 2000 rads to renal bed  
Consider XRT to metastases

#### Chemotherapy

Week 0	Dactinomycin	15 mcg/kg	daily x 5
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup>	weekly [10]
Week 6, 18, 30, 42, 54	Doxorubicin	30 mg/m <sup>2</sup>	daily x 2 [5]
	Cyclophosphamide	10 mg/kg	daily x 3 [5]
Week 12, 24, 36, 48, 60	Dactinomycin	15 mcg/kg	daily x 5 [5]
	Vincristine	1.5 mg/m <sup>2</sup>	on days 1 + 5 of Actino [10]
	Cyclophosphamide	10mg/kg	daily x 3 [5]

## 5921 [1992-1997]

### Stage I (Favourable or Anaplastic Histology)

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0, 3, 6, 9, 12, 15	Dactinomycin	45 mcg/kg	[6]
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup> [Max 2mg]	weekly [10]
Week 12, 15	Vincristine	2 mg/m <sup>2</sup> [Max 2mg]	[2]

### Stage II (Favourable Histology)

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0, 3, 6, 9, 12 ... to 51	Dactinomycin	45 mcg/kg	[18]
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup> [Max 2mg]	weekly [10]
Week 12, 15 ... to 51	Vincristine	2 mg/m <sup>2</sup> [Max 2mg]	[14]

### Stage III and IV (Favourable Histology)

#### Surgery

Week 0 Nephrectomy when feasible  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 10.8 Gy to renal bed for local Stage III  
Consider XRT to metastases

#### Chemotherapy

Week 0, 6, 12, 18 ... to 48	Dactinomycin	45 mcg/kg	[9]
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup> [Max 2mg]	weekly [10]
Week 12, 15 ... to 51	Vincristine	2 mg/m <sup>2</sup> [Max 2mg]	[14]
Week 3, 9	Doxorubicin	45 mg/m <sup>2</sup>	[2]
Week 15, 21, 27 ... to 51	Doxorubicin	30 mg/m <sup>2</sup>	[7]

### Stage II to IV (Unfavourable Histology)

#### Surgery

Week 0 Nephrectomy when feasible  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 10.8 Gy to renal bed for local Stage III  
Consider XRT to metastases

#### Chemotherapy

Week 0	Dactinomycin	45 mcg/kg	
Week 1-10	Vincristine	1.5 mg/m <sup>2</sup> [Max 2mg]	weekly [10]
Week 12, 15 ... to 51	Vincristine	2 mg/m <sup>2</sup> [Max 2mg]	[14]
Week 3, 6, 9 ... to 51	Cyclophosphamide	10 mg/kg	daily x 3 [17]
Week 6, 12, 18 ... to 48	Dactinomycin	45 mcg/kg	[8]
Week 3, 9	Doxorubicin	45 mg/m <sup>2</sup>	[2]
Week 15, 21, 27 ... to 51	Doxorubicin	30 mg/m <sup>2</sup>	[7]

## 5981 [1998-2003]

### Stage I (Favourable or Anaplastic Histology) Stage II (Favourable Histology)

#### Surgery

Week 0 Nephrectomy

#### Chemotherapy

Week 0, 3, 6, 9, 12, 15, 18	Dactinomycin	45 mcg/kg	[7]
Week 1-10	Vincristine	0.05 mg/kg [Max 2mg]	weekly [10]
Week 12, 15, 18	Vincristine	0.067 mg/kg [Max 2mg]	[3]

### Stage III and IV (Favourable Histology) Stage II to IV (Focal Anaplasia)

#### Surgery

Week 0 Nephrectomy when feasible  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 10.8 Gy to renal bed for local Stage III  
Consider XRT to metastases

#### Chemotherapy

Week 0, 6, 12, 18, 24	Dactinomycin	45 mcg/kg	[5]
Week 1-10	Vincristine	0.05 mg/kg [Max 2mg]	weekly [10]
Week 12, 15, 18, 21, 24	Vincristine	0.067 mg/kg [Max 2mg]	[5]
Week 3, 9	Doxorubicin	1 mg/kg	[2]
Week 15, 21	Doxorubicin	1.5 mg/kg	[2]

### Stage II - IV (Diffuse Anaplasia)

#### Surgery

Week 0 Nephrectomy when feasible  
Consider surgical removal of metastases if accessible

#### Radiotherapy

Week 1 10.8 Gy to renal bed for local Stage III  
Consider XRT to metastases

#### Chemotherapy

Week 0, 6, 12, 18, 24	Doxorubicin	1.5 mg/kg	[5]
Week 1-2 ... 4-8 ... 10-11	Vincristine	0.05 mg/kg [Max 2mg]	“weekly” [9]
Week 12-13	Vincristine	0.067 mg/kg [Max 2mg]	weekly [2]
Week 18, 24	Vincristine	0.067 mg/kg [Max 2mg]	[2]
Week 3, 9, 15, 21	Cyclophosphamide	14.7 mg/kg	daily x 5 [4]
Week 6, 12, 18	Cyclophosphamide	14.7 mg/kg	daily x 3 [3]
Week 3, 9, 15, 21	Etoposide	3.3 mg/kg	daily x 5 [4]