

# Bilateral Wilms' Tumour: An international comparison of treatments and outcomes

Authors: Henry Drysdale<sup>1</sup>, David Fawcner-Corbett<sup>1</sup>, Zubrina Solomon<sup>2</sup>, Olivia Cundy<sup>1</sup>, Jerome Loveland<sup>2</sup>, Jenni Perrin<sup>4</sup>, Rosemary Lane<sup>4</sup>, Neil Price<sup>4</sup>, Lofty-John Chukwuemeka Anyanwu<sup>3</sup>, Shaun Wilson<sup>1</sup>, Kokila Lakhoo<sup>1</sup>

Affiliations: <sup>1</sup>Departments of Paediatric Surgery and Oncology, University of Oxford, Oxford, UK; Department of Paediatric Surgery, <sup>2</sup>University of Witwatersrand, Johannesburg, South Africa; <sup>3</sup>Department of Surgery, Aminu Kano Teaching Hospital and Bayero University Kano, Nigeria; <sup>4</sup>Department of Paediatric Surgery, Starship Children's Health, Auckland, New Zealand.

Corresponding Author: Henry Drysdale, [henry.drysdale1@nhs.net](mailto:henry.drysdale1@nhs.net)

Competing Interests: No authors have any competing interests to declare

Key Words: Wilms' Tumour, Nephroblastoma, International health, Paediatric Oncology, Global Surgery

# Abstract

## *Introduction:*

Wilms' tumour is the most common childhood renal malignancy, with 5-10% of cases presenting bilaterally <sup>1</sup>. However, there is currently no consensus between centres on optimal management of bilateral Wilms' tumours. This is an international multi-centre case series comparing management and outcomes of bilateral Wilms' tumours between low-income centres (LIC) and high-income centres (HIC).

## *Methods:*

Patients with bilateral Wilms' tumour were identified from four tertiary referral centres internationally. Data were collected on baseline characteristics, disease status, treatment used and clinical outcomes. Results were compared between individual centres as well as between groups of low-income centres (LIC) and high-income centres (HIC).

## *Results:*

Data were collected for forty patients. Most patients received preoperative chemotherapy (n=38, 95%). The most common surgical procedures were bilateral nephron-sparing surgery (n=10, 25%) and nephrectomy with partial nephrectomy (n=20, 50%). Ten-year survival after treatment was as follows: LIC's n = 13 (65%); HIC's n = 20 (100%) (p = 0.0104).

## *Discussion:*

Ten-year survival was significantly higher in HIC's. Our results show this may be caused by patient factors such as later presentation with more advanced disease in low-income centres. This comparative case series is the first to report on a large number of cases from multiple international centres, and to compare key outcomes.

# Introduction

Wilms' tumour represents the most common renal malignancy of childhood, accounting for 90% of paediatric renal cancers, and around 7% of all childhood malignancy<sup>1</sup>. It affects one in 10,000 children under 15 years old globally <sup>1,2</sup>, with the majority of cases occurring in children under five years old <sup>3</sup>. In 10% of cases, Wilms' tumour is associated with an underlying congenital syndrome, such as Denys-Drash, Beckwith-Wiedemann and Wilms tumour-aniridia (WAGR) syndromes <sup>4</sup>.

Through collaborative studies the prognosis of Wilms' tumour has significantly improved in recent decades; overall five-year survival rates have risen from 54% in the 1960s to over 80% reported in more recent clinical trials led by the National Wilms Tumour Study group (NWTs), the United Kingdom Children's Cancer Study Group (UKCCSG) and the Societe Internationale D'oncologie Pediatrique (SIOP) <sup>5 6,7,8</sup>. However, the majority of cases in these studies are unilateral presentations, so the results have limited applicability to bilateral Wilms' Tumour. Furthermore, despite greatly improved outcomes for Wilms' tumour in high-income centres, outcomes for low-income centres remain poor, with reported survival rates in settings such as sub-saharan Africa of less than 50% <sup>9 10</sup>.

Around 5-10% of all cases of Wilms' tumour are bilateral: these are mostly synchronous presentations, although around 1% of unilateral presentations will develop subsequent contralateral disease (metachronous presentation). The prognosis of bilateral Wilms' tumour remains significantly worse than for unilateral tumours of a similar stage and histology, both in terms of overall survival and long-term renal function <sup>11</sup>, with a recurrence rate of 8.2% in bilateral cases treated with partial nephrectomy, compared with 1.5-2.5% in unilateral cases. In the NWTs-5 study, 4-year event-free survival was 56% for bilateral Wilms' tumour, and 85% for unilateral Wilms' tumour <sup>12</sup>. Effectively treating bilateral Wilms' tumour is a challenge. Where tumour removal may be the primary aim for unilateral Wilms' tumour, treating bilateral Wilms' tumour requires a balance between adequate tumour removal to achieve a low recurrence rate, and maintenance of good long-term renal function despite removing renal tissue bilaterally. Other challenges to treatment include the tension between upfront biopsy for diagnosis, which carries a 3%

risk of tumour spread <sup>13 14</sup>, and primary resection, which is associated with increased morbidity and does not allow for tissue diagnosis prior to surgery. Over the past few decades, the management of bilateral Wilms' tumour has evolved to include a combination of radical and nephron-sparing surgical techniques, neoadjuvant chemotherapy regimens and supplemental radiotherapy, with renal transplantation reserved for cases that ultimately require bilateral nephrectomy, or those that progress to develop end stage kidney disease.

There is great diversity in the management of bilateral Wilms' tumour between different centres and a paucity of large studies to provide treatment guidance <sup>15</sup>. Where studies of bilateral Wilms' tumour exist with good sample sizes <sup>11</sup>, they do not include patients recruited from a range of developed and developing centres, so these international comparisons cannot be made <sup>16</sup>. International comparison is especially important when comparing new treatment guidelines in the developing world, with the majority of treatment guidelines being developed in European or American studies.

Given the lack of large international studies on the treatment of bilateral Wilms' tumour, this project sought to collect data from a number of international tertiary hospitals from both high-income centres (UK, New Zealand) and low-income centres (South Africa, Nigeria). This is a large-scale multi-centre collaborative case series, using data collected over twenty years (1996-2016) from four large centres managing unilateral and bilateral Wilms' tumour (John Radcliffe Hospital, Oxford, UK; Starship Children's Hospital, Auckland, NZ; The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, SA; Aminu Kano Teaching Hospital and Bayero University Kano, Nigeria). This study aims to compare management strategies and outcomes for bilateral Wilms' tumour between low- and high-income centres. This is the largest study on bilateral Wilms' tumour comparing centres with different incomes, and as such provides a unique insight into the treatment of this paediatric tumour, on a global scale.

# Methods

## Setting

South Africa is classified as a middle-income country <sup>17</sup>, however medical management and health infrastructure varies enormously across provinces. Two low-income centres in Johannesburg, Charlotte Maxeke Johannesburg Academic (CMJAH) in Parktown, and Chris Hani-Baragwanath Academic Hospital (CHBAH) in Soweto, have an estimated total drainage population of 17.3 million people, 3.5 million of whom are under the age of 16 <sup>18</sup>. These are the only two government-funded hospitals that offer access to paediatric surgery, renal transplantation and associated support care facilities, in Johannesburg and the surrounding areas. Oncology patients are managed by a multidisciplinary team including paediatric surgery, oncology, and radiation oncology, with paediatric intensive care support available.

Aminu Kano Teaching Hospital is situated in the city of Kano, Northwestern Nigeria, and has a catchment area of 21 million people. It provides tertiary health care to Kano and neighboring states. Here between 10 to 15 new cases of Wilms' tumor are seen in a year, although there have been only 4 bilateral Wilms' cases in the last 10 years. Aminu Kano Hospital can provide chemotherapy and surgical treatment, but not radiation therapy. Patients pay out of pocket, as they do not have any health insurance. This has posed a challenge, as the rate of treatment abandonment is high.

Oxford Children's Hospital, on the John Radcliffe Hospital site, is a tertiary referral centre for Wilms' tumour in the UK, serving a population of 3 million children in the Thames Valley area. Here six to eight new cases of unilateral Wilms' tumour are treated per year, and around two new cases of bilateral Wilms' tumour. Both unilateral and bilateral cases are managed with a multidisciplinary team involving paediatric oncology, paediatric radiology and paediatric surgery.

New Zealand has a population of 4.8 million spread over a country 1,600km long, with one third living in the greater Auckland region. Starship Children's Hospital in Auckland is New

Zealand's only standalone children's hospital. Starship provides secondary care for children in the Auckland region and tertiary/quaternary care for the whole country (including renal replacement and transplant). Childhood cancer is managed collaboratively within a National Network; there are two major treatment hubs, Christchurch Hospital and Starship. At Starship oncology is treated in a multi-disciplinary team and has a strong focus on recruitment into international collaborative studies.

## Data Collection

Following ethical approval in each centre, cases of bilateral wilms' tumour were retrospectively identified by means of clinical coding systems (UK/SA/Nigeria) or cancer registries (NZ). In Oxford, cases were identified between January 2003 and October 2016. In Johannesburg, cases were identified between January 2003 and December 2013. In Auckland, cases were identified between April 1996 and July 2016. In Kano, cases were identified between December 2012 and January 2016. All cases of bilateral wilms' tumour treated at these centres were included.

A case note review was performed by individuals in each of the four centres using a data collection form. The following data points were collected for each patient: date of diagnosis, age at diagnosis, local disease staging, presence of metastatic disease, chemotherapy regime used, date of surgery, surgical procedure carried out, histology of tumour, recurrence of disease, overall outcome. All results were collected into a password protected central database (Microsoft Excel v16.32). They were then compared as individual centres, as well as grouped for comparison of low-income (Johannesburg and Nigeria) and high-income (Oxford and Auckland) centres.

## Statistical analysis

Statistical analysis and presentation of results was performed using Prism (Graphpad Inc v7.0). Data that was not normally distributed is reported as a median with the interquartile range. Statistical tests performed included: Mann-Whitney for time to surgery and age of diagnosis; Chi-squared for presence of metastasis; and Kaplan Meier survival curves statistics using a log-rank (Mantel-Cox) test. A p-value of <0.05 was considered statistically significant.

# Results

## Patient demographics

Data were collected for a total of forty patients across the four centres: Oxford, n=3; New Zealand, n=17; Nigeria, n=3; South Africa, n=17. Patients were diagnosed between 1996 and 2016. Median age at initial diagnosis was 26 months overall [interquartile range (IQR) 15-43 months]. Median age of diagnosis was comparable for high-income centres, 24 [IQR 13-44] months, and for low-income centres 34 [IQR 21-41] months ( $p=0.26$ ).

All bilateral Wilms' tumour patients are stage V by definition, however data for local tumour staging (stages I - III) for each kidney were also collected. As all patients included had bilateral disease, there are two data points per patient for local tumour staging. In this study the presence of metastases was considered separately from local tumour staging. Local tumour staging distribution across all centres, using tumour stage confirmed post-operatively for each kidney, was as follows: stage I, n = 19 (24%); stage II, n = 16 (20%); stage III, n = 31 (39%); unrecorded, n = 14 (17%). Median local tumour stage at diagnosis was III for low-income centres and II for high-income centres. Metastases were present in 9 cases (23%) across all centres. There was no statistically significant difference in the incidence of metastasis at diagnosis when comparing high-income and low-income centres (3 vs 6,  $p=0.47$ ,  $\chi^2=0.53$ ).

Tumour histology was recorded as favourable or unfavourable, where unfavourable histology is defined by the presence of anaplasia in at least one kidney per patient. The distribution of tumour histology was as follows: favourable histology n = 33 (82.5%), unfavourable histology n = 4 (10%). For the Nigerian patients, data on favourable and unfavourable histology were not available (n=3, 7.5%). Of the patients with unfavourable histology, two were from a high-income centre (NZ) and two were from a low-income centre (SA).

Median year of diagnosis was 2010 for both high- and low-income centres. Median length of follow-up was 49 months (IQR 37-79) for low-income centres, and 93 months (IQR

57-117) for high-income centres. Full patient demographics for low- and high-income centres are given in table 1.

**Table 1: Patient demographics**  
*[attached separately]*

## Chemotherapy

Chemotherapy treatment plans were based on trials by major Wilms' Tumour research groups, namely SIOP (Societe Internationale D'oncologie Pediatrique), National Wilms Tumor Study (NWTs), United Kingdom Children's Cancer Study Group (UKCCSG), and the Children's Oncology Group (COG). Specifically, treatment was based on the following trials: SIOP Wilms' tumour 2001, SIOP 9, UKW3, NWTs5, AREN0534, AREN03B2.

The majority of patients received preoperative chemotherapy (n=38, 95%). Based on the above trials, the following chemotherapy regimens were used: Vincristine and actinomycin D (n=24); Vincristine, actinomycin D and doxorubicin (n=14). High-income centres used a third chemotherapy agent (doxorubicin) in the majority of cases (n=14, 78%), whereas the low-income centres invariably used only two chemotherapy agents (vincristine and actinomycin, n=20, 100%). Mean duration of chemotherapy for the NZ patients was 13 weeks. Mean duration of chemotherapy for the Oxford patients was 6 weeks. The duration of pre-operative chemotherapy for all Nigerian patients was 4 weeks. The duration of pre-operative chemotherapy for all South African patients was 6 weeks.

There was no statistically significant difference in the time to surgery when comparing high income and low income centres (median 69 [51-92] days vs 63 [33-109] days, p=0.79).

## Surgery

Surgical treatments used across the four centres were as follows: Bilateral nephron sparing surgery (n=10, 25%); Nephrectomy and partial nephrectomy (n=20, 50%); Bilateral nephrectomy (n=3, 7.5%); Unilateral radical nephrectomy (n=4, 10%); None (patient died) (n=3, 7.5%). The distribution of surgical procedures between low- and high-income centres is shown in figure 1. Nephrectomy with partial nephrectomy was the most common



procedure for patients with stage II or stage III disease. The distribution of surgical procedures for the highest local tumour stage per patient is given in figure 2.

Of the patients with unilateral radical nephrectomy, none received surgical treatment for the other kidney. All patients were treated with postoperative chemotherapy. Three patients were alive with disease at follow-up, and one patient died.

***Figure 1: Distribution of surgical procedures between high- and low-income centres***  
***[Attached separately]***

***Figure 2: Distribution of surgical procedures by highest local tumour stage per patient (stages I, II, III and unrecorded)***  
***[Attached separately]***

## Outcomes

10-year overall survival across the four centres (n=40 cases) was 83%. 10-year survival by centre was as follows: Oxford n = 3 (100%); New Zealand n = 17 (100%), South Africa n = 11 (65%); Nigeria n = 2 (67%). These are shown in figure 3. Survival after treatment when compared by high- and low-income centres was as follows: high-income centres n = 20 (100%); low-income centres n = 13 (65%) (p = 0.0104). A Kaplan-Meier curve showing 10-year survival for high- and low-income centres is given in figure 4.

10-year survival by local disease stage was as follows: stage I, 100%; stage II, 71%; stage III, 82%; unrecorded stage, 86%. 10-year survival was n=9 (82%) for low local disease stage (stages I and II) and n=18 (82%) for high-stage disease (stage III) (P=>0.99, fisher's exact test). Overall 10-year survival post-treatment for each disease stage is given in figure 5. 10-year survival for low- and high-income centres grouped by disease stage is given in figure 6.

Overall 10-year survival was n=9 (90%) for bilateral nephron sparing surgery and n=18 (90%) for nephrectomy with partial nephrectomy (P=>0.99, fisher's exact test). Overall 10-year survival for each surgical procedure is given in figure 7. 10-year survival for low- and high-income centres grouped by surgical procedure is given in figure 8.

Seven patients died within 10-year follow-up: three patients from South Africa died before surgery, however the mode of death was undetermined. Three South African patients died from neutropenic sepsis after treatment. One patient from Nigeria died after treatment: this patient re-presented 2 years after completion of the post op chemotherapy, with a left chest recurrence and features of an intracranial space-occupying lesion, and died during that admission.

***Figure 3: 10-year overall survival by centre***

***[Attached separately]***

***Figure 4: Kaplan-Meier survival curve comparing low- and high-income centres***

***[Attached separately]***

***Figure 5: 10-year overall survival post-treatment, grouped by disease stage***

***[Attached separately]***

***Figure 6: 10-year survival for high- and low-income centres, grouped by disease stage***

***[Attached separately]***

***Figure 7: 10-year overall survival post-treatment, grouped by surgical procedure***

***[Attached separately]***

***Figure 8: 10-year survival for high- and low-income centres, grouped by surgical procedures***

***[Attached separately]***

## Discussion

In this study, data were collected on 40 patients with bilateral Wilms tumour from 4 centres internationally across a 20 year period. The majority of patients were diagnosed early across all centres, however the median age at diagnosis varied between high- and low-income centres (24 months for high-income centres and 34 months for low-income centres). Median local tumour stage was higher for low-income centres (3 vs 2), however there was no statistically significant difference in the incidence of metastases for low- vs high-income centres (6 vs 3,  $p=0.47$ ).

Our study period spanned 20 years, during which time the trials informing treatment were developed and findings implemented. Patients were included with a range of dates of diagnosis between 1996 and 2016: this is a potential limitation of the study, as the treatment for bilateral Wilms' tumours evolved during this time. However, this is a common limitation of bilateral Wilms' tumour studies: international studies with comparable numbers of participants span between ten and forty years <sup>19 20 21</sup>.

The difference in choice of chemotherapy regimens between centres is a reflection of the fact that high-income centres based treatment on UKCCSG, SIOP, COG and NWTs trials; whereas low-income centres based their treatment exclusively on SIOP trials which specifically excluded a third chemotherapy agent (doxorubicin). This difference in treatments may not have contributed to the difference in survival rates observed: a retrospective analysis of the SIOP trial data has suggested that preoperative chemotherapy regimens which include doxorubicin are non-inferior to those including vincristine and actinomycin D alone in terms of survival rates for patients with stage II and III Wilms' tumours <sup>22</sup>.

Choice of definitive surgical treatment also varied between high- and low-income centres. The favoured procedure in low-income centres was nephrectomy with contralateral partial nephrectomy (n=11, 55%). Bilateral nephron sparing surgery was more common in high-income centres (7 vs 3). This may have been driven by the higher stage of disease at presentation in low-income centres (median 3 in low-income centres vs 2 in high-income centres) with large tumours that completely replaced the involved kidney, precluding nephron sparing surgery as an option. Our analysis of frequency of surgical procedure by low- and high-stage disease supports this: nephrectomy with partial nephrectomy was a more common surgical procedure than bilateral nephron sparing surgery in those patients with local stage III disease (12 vs 5).

Overall 10-year survival was statistically significantly higher in high-income centres compared with low-income centres (100% vs 65%,  $p=0.0104$ ), which may reflect the earlier diagnosis of patients in high-income centres (24 months for high-income centres and 34 months for low-income centres). Our data suggest do not show significant associations between overall survival and surgical procedure, local disease stage or presence of metastatic disease at diagnosis, suggesting the difference in mortality rates

observed between low- and high-income centres is unlikely to have been caused by these factors. However, our results for these analyses may have been non-significant due to low patient numbers. In larger studies of unilateral Wilms' tumour, it is well described that mortality increases with overall disease stage, however there remains a paucity of large studies describing the effect on mortality of local disease stage or metastatic disease in bilateral Wilms'. It is also known that lymph node involvement is associated with lower event-free survival in large studies of patients with unilateral Wilms' <sup>23</sup>, however it is not known whether this association translates to metastatic bilateral Wilms'. One study from the National Wilms' Tumor Study Group includes 188 patients with bilateral Wilms' tumour, however only 16 of these had metastatic disease <sup>24</sup>, so again the relationship between metastatic bilateral Wilms' and mortality can not be inferred here. Overall the impact of local disease stage and metastatic disease on survival rates in bilateral Wilms' tumour remains an area in need of further study.

This study showed that low-income centres had higher rates of mortality from bilateral Wilms' tumour than high-income centres, despite the fact that one of the low-income centres (SA) had access to key resources such as specialist paediatric surgery, radiation oncology and paediatric intensive care. This suggests that the difference in mortality observed is unlikely to be driven by differences in medical infrastructure, and more likely caused by patient factors such as later presentation with advanced disease.

# Conclusion

Bilateral Wilms Tumour is a rare condition, and thus case series and international comparisons are often limited. This comparative case series is the first study to report on a large number of cases from multiple international centres, and to compare key outcomes between high- and low-income centres. Our findings highlight differences in chemotherapy choices, surgical treatment and overall survival between low- and high-income centres: key findings that warrant further investigation. Overall, this study shows that differences in mortality observed may be related to patient-specific factors in centres with different incomes, rather than differences in medical infrastructure between these centres. This study also demonstrates that such trends can only be established by means of international collaboration. Future studies should build on current work, such as the Global Paediatric Surgery Network, in order to monitor and continue to improve the treatment of children with bilateral Wilms' tumours.

# Acknowledgements

D.F-C receives funding from a British Association of Paediatric Surgeons / Royal College of Surgeons of England fellowship and a Wellcome Trust Doctoral training fellowship at the University of Oxford.

We acknowledge the contribution of Mr Vipul Upadhyay, who was instrumental in initiating and supervising the collection and presentation of the data from New Zealand that is used in the current paper. These data were presented at the RACS Annual Scientific Congress conference in 2017, in a presentation entitled "Twenty year experience of synchronous bilateral Wilms tumour at Starship Children's Hospital." We also acknowledge the contribution of Dr Jane Skeen, consultant oncologist at Starship Children's Hospital, who treats all cases of bilateral Wilms' tumour in that centre.

New Zealand data contributions were supported by the New Zealand Children's Cancer Registry (NZCCR) database.

# References

1. Hamilton, T. E. & Shamberger, R. C. Wilms tumor: recent advances in clinical care and biology. *Semin. Pediatr. Surg.* **21**, 15–20 (2012).
2. Breslow, N., Olshan, A., Bruce Beckwith, J. & Green, D. M. Epidemiology of Wilms tumor. *Med. Pediatr. Oncol.* **21**, 172–181 (1993).
3. Breslow, N. E., Bruce Beckwith, J., Perlman, E. J. & Reeve, A. E. Age distributions, birth weights, nephrogenic rests, and heterogeneity in the pathogenesis of Wilms tumor. *Pediatr. Blood Cancer* **47**, 260–267 (2006).
4. Scott, R. H., Stiller, C. A., Walker, L. & Rahman, N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *J. Med. Genet.* **43**, 705–715 (2006).
5. Tongaonkar, H. B. *et al.* Wilms' tumor: An update. *Indian J. Urol.* **23**, 458–466 (2007).
6. Mitchell, C. *et al.* Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: Results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. *Eur. J. Cancer* **42**, 2554–2562 (2006).
7. Pritchard-Jones, K. *et al.* Treatment and outcome of Wilms' tumour patients: an analysis of all cases registered in the UKW3 trial. *Ann. Oncol.* **23**, 2457–2463 (2012).
8. Pritchard-Jones, K. & Pritchard, J. Success of clinical trials in childhood Wilms' tumour around the world. *Lancet* **364**, 1468–1470 (2004).
9. Njuguna, F. *et al.* Wilms Tumor Treatment Outcomes: Perspectives From a Low-Income Setting. *J Glob Oncol* **3**, 555–562 (2017).
10. Israels, T. *et al.* Survival of children with a Wilms tumor in Blantyre, Malawi. *Pediatr. Hematol. Oncol.* **35**, 196–202 (2018).
11. Ehrlich, P. *et al.* Results of the First Prospective Multi-institutional Treatment Study in Children With Bilateral Wilms Tumor (AREN0534). *Annals of Surgery* vol. 266 470–478 (2017).
12. Grundy, P. E. *et al.* Loss of Heterozygosity for Chromosomes 1p and 16q Is an Adverse

Prognostic Factor in Favorable-Histology Wilms Tumor: A Report From the National Wilms Tumor Study Group. *Journal of Clinical Oncology* vol. 23 7312–7321 (2005).

13. Irtan, S. *et al.* Evaluation of needle biopsy as a potential risk factor for local recurrence of Wilms tumour in the SIOP WT 2001 trial. *European Journal of Cancer* vol. 116 13–20 (2019).
14. Irtan, S. *et al.* Risk factors for local recurrence in Wilms tumour and the potential influence of biopsy – The United Kingdom experience. *European Journal of Cancer* vol. 51 225–232 (2015).
15. User, I. R. *et al.* Management of bilateral Wilms tumor over three decades: The perspective of a single center. *J. Pediatr. Urol.* **11**, 118.e1–118.e6 (2015).
16. Brodie, K. E. & Cost, N. G. An Update on Current Treatment Options for Pediatric Genitourinary Tract Tumors. *Current Treatment Options in Pediatrics* **2**, 1–9 (2016).
17. Dell, A. J. & Kahn, D. Geographical maldistribution of surgical resources in South Africa: A review of the number of hospitals, hospital beds and surgical beds. *S. Afr. Med. J.* **107**, 1099–1105 (2017).
18. Website. Census 2015. [www.statsa.gov.za](http://www.statsa.gov.za).
19. Hadley, G. P., Mars, M. & Ramdial, P. K. Bilateral Wilms' tumour in a developing country: a descriptive study. *Pediatric Surgery International* vol. 29 419–423 (2013).
20. Millar, A. J. W. *et al.* Bilateral Wilms' tumors: a single-center experience with 19 cases. *Journal of Pediatric Surgery* vol. 40 1289–1294 (2005).
21. Aronson, D. C., Slaar, A., Heinen, R. C., de Kraker, J. & Heij, H. A. Long-term outcome of bilateral Wilms tumors (BWT). *Pediatr. Blood Cancer* **56**, 1110–1113 (2011).
22. Pritchard-Jones, K. *et al.* Omission of doxorubicin from the treatment of stage II–III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. *The Lancet* vol. 386 1156–1164 (2015).
23. Kieran, K. *et al.* Lymph node involvement in Wilms tumor: results from National Wilms Tumor Studies 4 and 5. *J. Pediatr. Surg.* **47**, 700–706 (2012).
24. Hamilton, T. E. *et al.* The Management of Synchronous Bilateral Wilms Tumor: A Report from



the National Wilms Tumor Study Group. *Ann. Surg.* **253**, 1004 (2011).

**Table 1 - Demographics**

<b>Patient demographics (n=40)</b>		<b>Low-income centres</b>	<b>High-income centres</b>
Median age at diagnosis (months, IQR)		34 (21-41)	24 (13 - 44)
Median follow-up (months, IQR)		49 (37-79)	93 (57-117)
Local tumour stage	I	4	15
(Number of tumours)	II	11	5
	III	18	13
	Unknown	7	7
Presence of metastases	IV	6	3
(Number of patients)			
Histology per patient (Number of patients)	Favourable	15	18
	Unfavourable (anaplasia)	2	2
	Data unavailable	3	0
Median year of diagnosis		2010	2010

***Table 1: Patient demographics for high- and low-income centres***

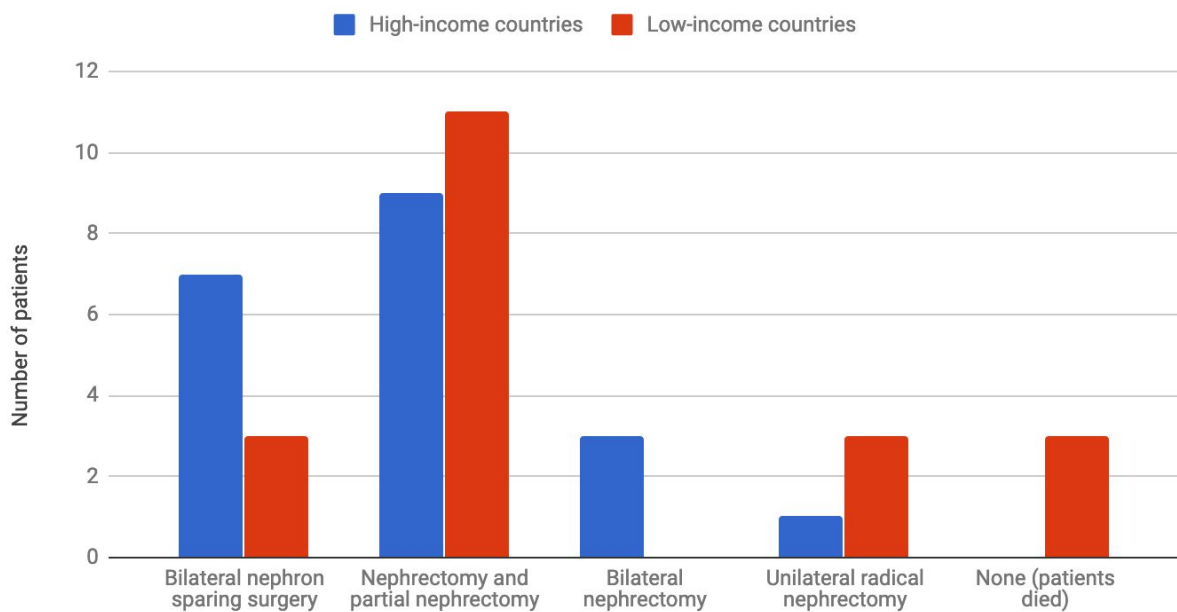
**Table 2 - Chemotherapy**

	Low-income centres	High-income centres
Vincristine and Actinomycin D (number, percentage)	n=20, 100%	n=5, 25%
Vincristine, Actinomycin, and Doxorubicin	n=0, 0%	n=13, 65%
Mean duration of chemotherapy (weeks)	6	12

**Table 2: Chemotherapy used and mean duration of chemotherapy for low- and high-income centres**

**Figure 1 - Surgical procedures for high- and low-income centres**

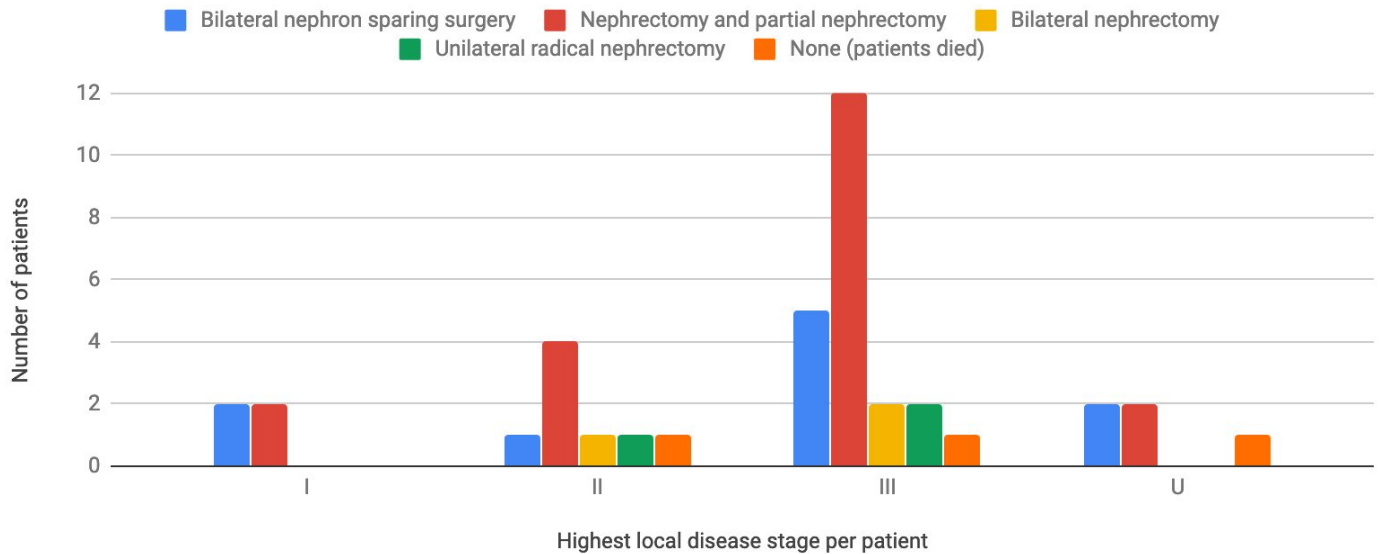
Distribution of surgical procedures between high- and low-income countries



**Figure 1: Distribution of surgical procedures between high- and low-income centres**

**Figure 2 - staging vs surgical procedure**

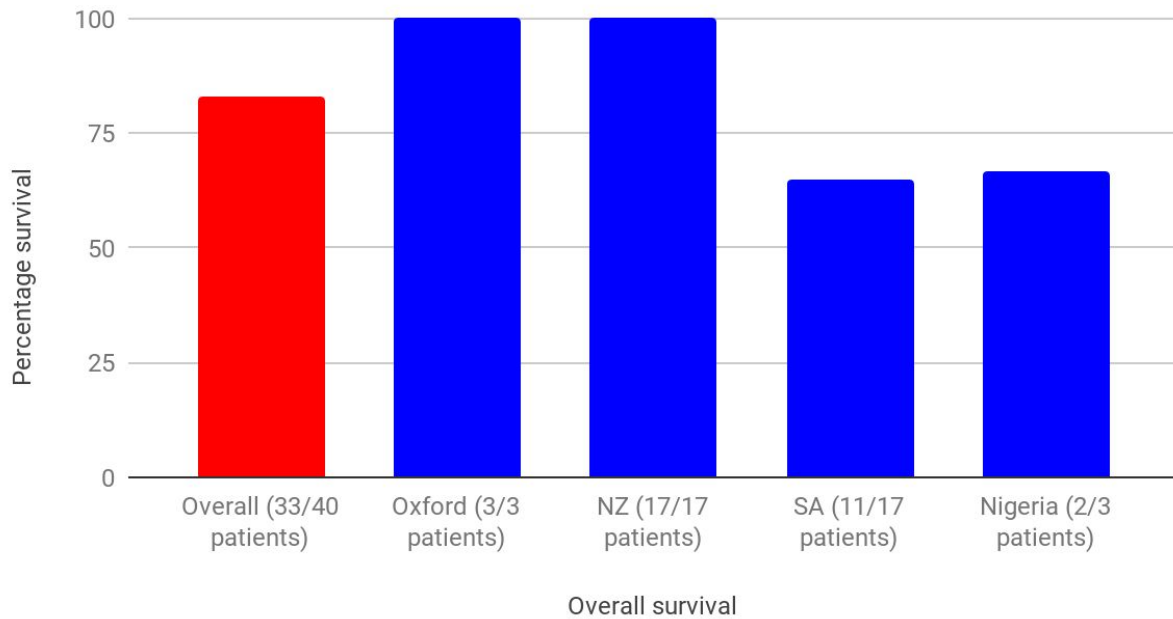
Frequency of surgical procedures grouped by highest local disease per patient



**Figure 2: Distribution of surgical procedures by highest local tumour stage per patient (stages I, II, III and unrecorded)**

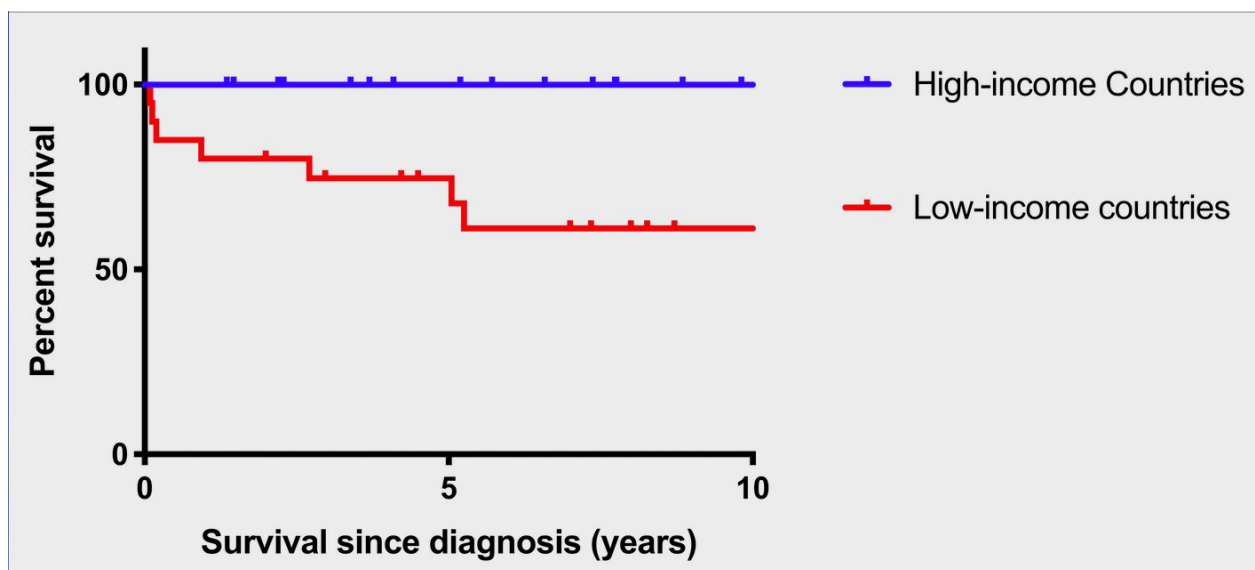
**Figure 3 - 10 year overall survival post-treatment**

Overall survival at 10 years, by centre



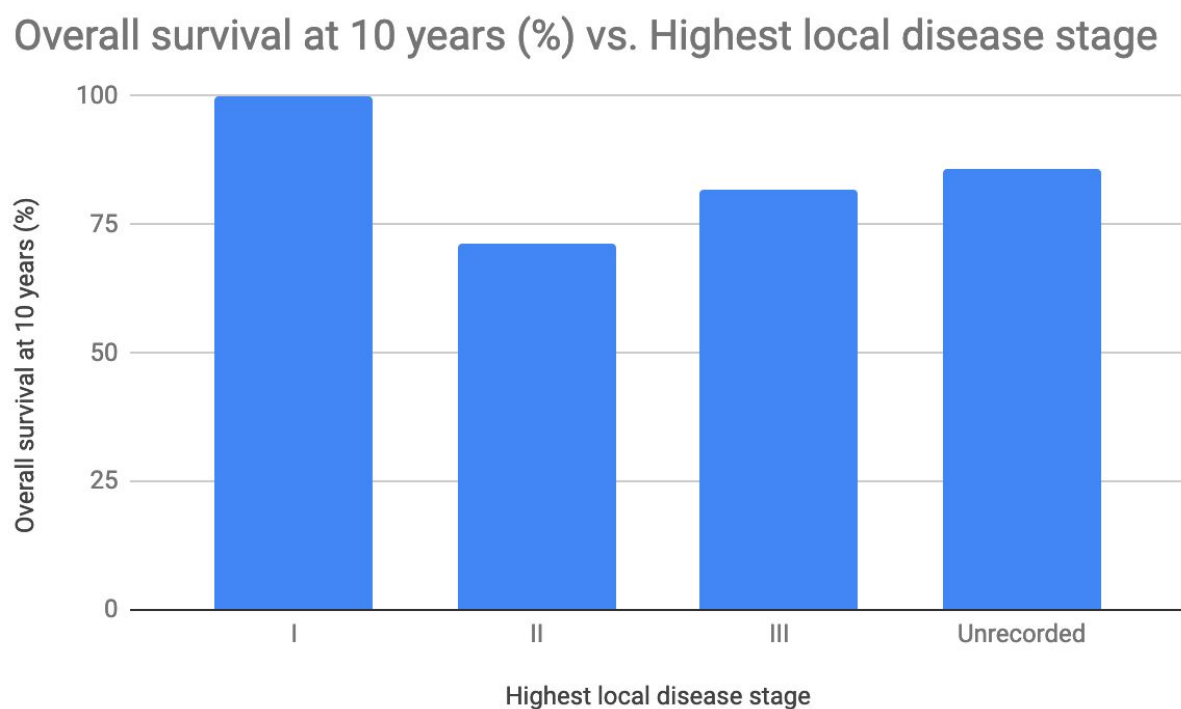
**Figure 3: 10-year overall survival post-treatment, grouped by centre**

**Figure 4 - KM survival plot**



**Figure 4: Kaplan-Meier survival curve comparing low- and high-income centres (censored cases marked as perpendicular ticks)**

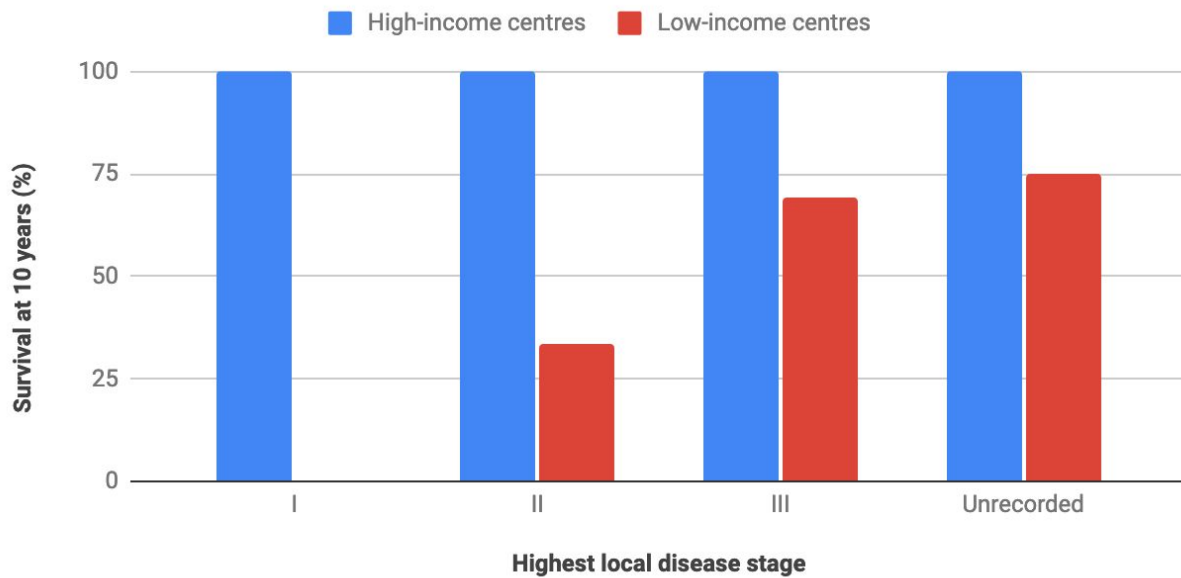
**Figure 5 - 10-year survival grouped by highest local disease stage**



***Figure 5: 10-year overall survival post-treatment, grouped by highest local disease stage***

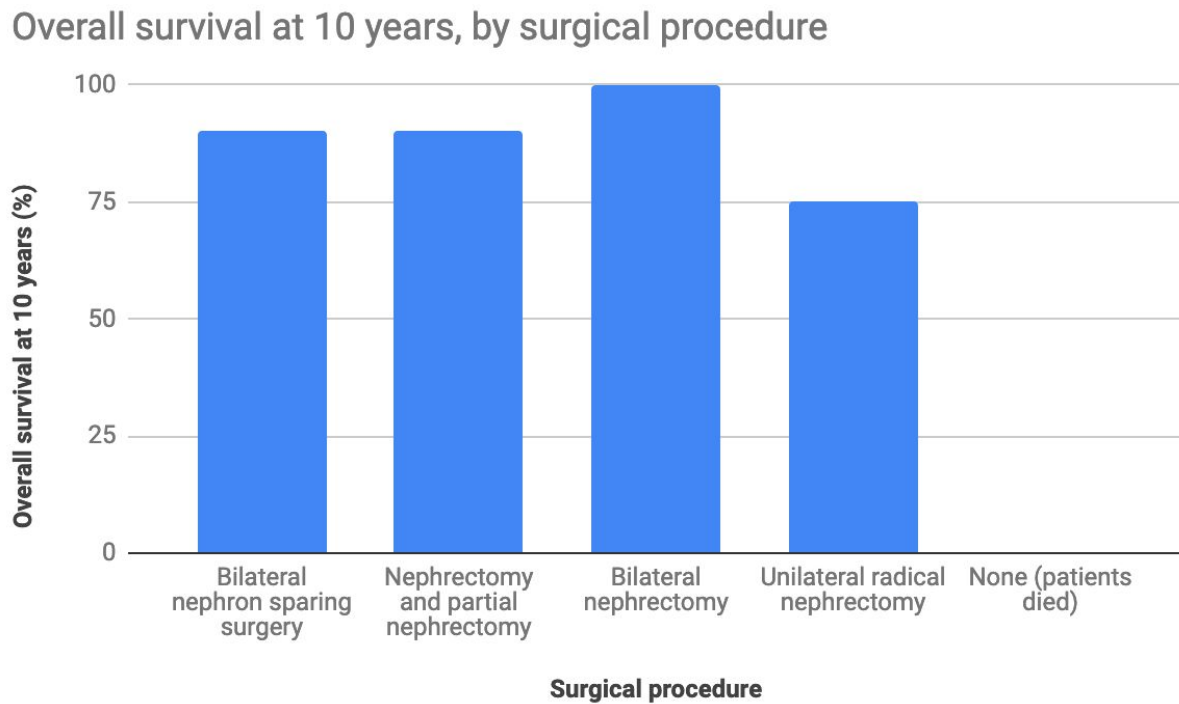
**Figure 6 - 10-year survival grouped by highest local disease stage**

Survival at 10 years for low- and high-income centres, grouped by highest local disease stage



**Figure 6: 10-year survival for high- and low-income centres, grouped by highest local disease stage**

**Figure 7 - 10-year survival grouped by surgical procedure**

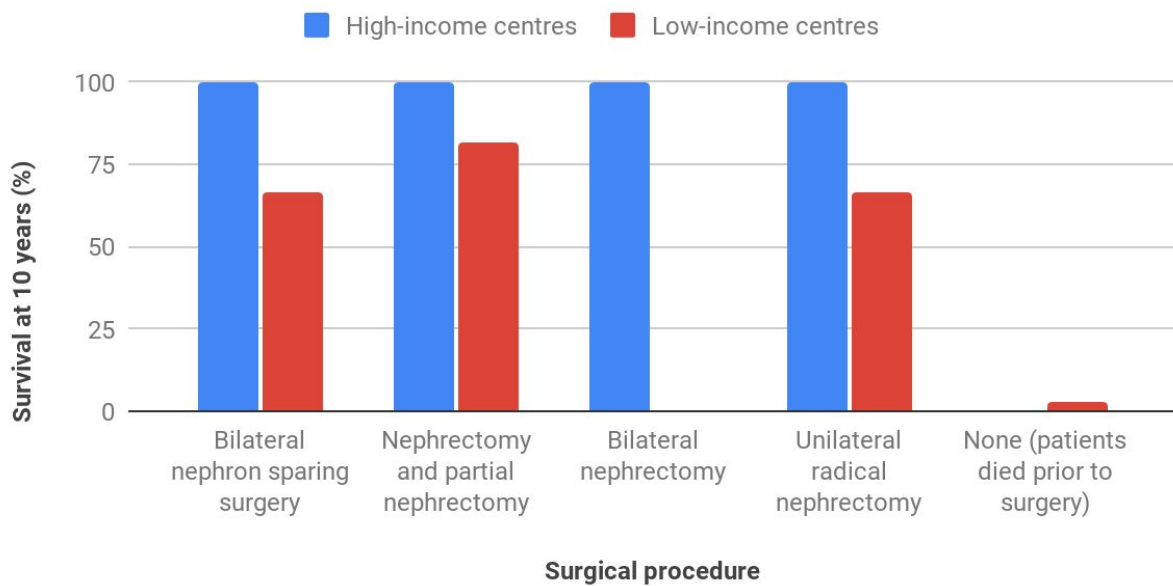


**Figure 7: 10-year survival for high- and low-income centres, grouped by surgical procedure**



**Figure 8 - 10-year survival for high- and low-income centres, grouped by surgical procedure**

Survival at 10 years for high- and low-income centres, grouped by surgical procedure



**Figure 8: 10-year survival for high- and low-income centres, grouped by surgical procedures**