Comment on 'Paediatric nephroblastoma at a South African tertiary hospital: A 21-year retrospective analysis'

To the Editor: I read the article 'Paediatric nephroblastoma at a South African tertiary hospital: A 21-year retrospective analysis'[1] with interest.

The first striking welcome feature was that the first/corresponding author involved many medical students in publishing this article.

Allow me to make certain queries of the corresponding author.

In the abstract, the authors mention favourable preoperative histology, but do not mention the preoperative use of cutting needle biopsy in the article. The histopathological report and tumour staging are available only postoperatively. Surprisingly, the number of patients undergoing surgery was 180 (Table 1), but histopathology has been mentioned for 207 patients (Table 3). How do the authors explain this discrepancy of 27 patients? Did these patients undergo a preoperative cutting needle biopsy? I think the authors should mention *n*=180 as the legend of Table 3, and include only the patients who underwent surgery. The numbers of the high, intermediate and low-risk tumours in Table 3 still add up to 179, 1 less than the total number of patients operated on in the study.

Were there any syndromic patients in the study, or did any patient have a single kidney or horseshoe kidney?

There is no mention of lactate dehydrogenase (LDH) levels in the diagnostics of Wilms' tumour (WT) in the world literature[2] or even Société Internationale d'Oncologie Pédiatrique [International Society of Paediatric Oncology] Paediatric Oncology in Developing Countries (SIOP PODC) protocols to discover the tumour burden. Why was it done in this study?

What do the authors mean when they state, 'negative isotope studies demonstrated skeletal involvement in 143 (69.1%) patients, liver involvement in 128 (61.8%) and clear bone marrow aspirates in 189 (91.3%)'? Isotope studies are not recommended for WT in any of the collaborative group protocols, the only exception being performing pre- and postoperative renal dynamic scans in patients with WT, where the surgeon is contemplating performing nephron-sparing surgery.[3] This helps to learn the pre- and postoperative function of the salvageable kidney. Similarly, bone marrow aspiration is not an integral part of the diagnostics in WT, so why was it performed? In any case, the yield of this investigation has been very poor in this study and, therefore, it is not cost-effective against the background of poor healthcare budgets available in the region.

Referring to Table 1, the six patients with inferior vena cava (IVC) are not to be counted as having metastases. IVC invasion, even if the tumour thrombus reaches the right atrium, is considered a local spread and not metastasis. How many of the patients had multiple-site metastases? How many patients had non-pulmonary, non-hepatic metastases?

Again, referring to Table 1: surprisingly, a diagnostic delay of >2 weeks had a significant impact on survival in the study. A fortnight's delay is common even in high-income countries. Maybe the authors should use receiver operating characteristic (ROC) curves to decide the cut-off delay that results in lower survival.

Again, referring to Table 1: the staging is mentioned for 198 patients, when the number of patients who have been operated on is 180. How do you explain this discrepancy? Are the patients who are known to have stage IV and stage V disease preoperatively included there? With preoperative imaging, one can only know whether the patient has a localised or metastatic disease, and whether the disease is unilateral or bilateral.

Again, referring to Table 1: what was the indication for radiotherapy in 37 patients? The conclusion section does mention that it was administered to advanced cases. The term 'advanced' is not defined in the 'methods' section. What was the breakup of these patients in terms of the region irradiated? How many had flank radiation, whole abdominal radiation and/or pulmonary radiation? It is important to understand that not all stage IV patients need to have flank radiation in cases where the local stage is I or II. Thus, every patient with metastases has an overall stage IV, but the local stage could be I/II or stage III. Only patients with overall stage IV and local stage III would need flank radiation.

Again, referring to Table 1: how did you define a good response to neo-adjuvant chemotherapy (NACT)? If it was as per the reduction of tumour volume on imaging, it is not mentioned in the methods section. In our recently published study, only half of the patients had good responses to NACT; the good response was defined as >40% reduction in tumour volume.[3]

Could you please provide data on 'fast complete responders' and 'late slow responders' from the cohort of patients who had pulmonary metastases alone?

Again, referring to Table 1: did the 18 patients who had a relapse during treatment complete the treatment, or abandon the treatment after the relapse? What was done for 18/132 patients who relapsed after completing the treatment? Were they administered second-line chemotherapy/radiotherapy?

Referring to Table 2, could the authors provide the median (interquartile range) for age for unilateral and bilateral tumours separately?

The median delay of symptoms-to-diagnosis time has been mentioned in both abstract and Table 2 as 30 days. Why did the authors then choose to apply statistics to >2 weeks' delay in Table 1?

Does the survival time in Table 2 refer to survival after the completion of treatment?

Referring to the 'outcome' subsection of the results section, what do the authors mean by the median survival rate throughout the study? The overall survivals (OSs) and event-free survivals (EFSs) are mentioned as available after 2 years, 4 years or 5 years.[1] In the discussion section, 2-year OS has been mentioned as 59.4%. But this is a 21-year study, so the authors could easily mention 5-year and 10-year OSs.

The 'outcome' subsection also mentions that 20 (9.7%) patients defaulted on their treatment and 26 (12.6%) were lost to follow-up, although no significant subsequent impact on survival was observed. The *p*-value mentioned in Table 1 is 0.019, so it shows a significant impact on survival.

What were the 'other areas' in nine patients where relapse happened?

In the subsection 'factors associated with outcome', it is mentioned that the patients with lung metastasis had an 85% higher hazard of

mortality (hazard ratio 1.85; 95% confidence interval 1.15 - 2.95; p=0.010) compared with metastasis to different locations. This seems unusual, and is opposite to the global experience.[4]

In Fig. 1, the authors have depicted an adjusted Kaplan-Meier survival curve for relapse in paediatric patients with WT for different risk stratifications for 90 months (7.5 years). It would have been better if the authors had shown Kaplan-Meier OS and EFS curves for 20 years for unilateral v. bilateral WT, localised v. metastatic WT and for different stages of WT.

Last but not least, may I request the corresponding author to provide raw data. The confidentiality and privacy of the data would be honoured.

Y K Sarin
Department of Pediatric Surgery, Lady Hardinge Medical College, and associated Kalawati Saran Children's Hospital, New Delhi, India
yksarin@gmail.com

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Response to letter regarding 'Paediatric nephroblastoma at a South African tertiary hospital: A 21-year retrospective analysis'

To the Editor: Thank you for allowing us to respond to the letter regarding our article 'Paediatric nephroblastoma at a South African tertiary hospital: A 21-year retrospective analysis.' We appreciate the reader's thoughtful questions and insights, contributing to a more comprehensive discussion of our findings.

We acknowledge the reader's appreciation of our collaboration with undergraduate medical students, and extend our gratitude to Profs David Stones and Jan du Plessis for their support in accessing the database.

Regarding the histological assessments and preoperative use of fine needle aspiration (FNA) and cutting needle biopsy, we clarify that FNAs were routinely performed before initiating chemotherapy. When FNAs were inconclusive, a cutting needle biopsy was performed to aid in diagnosis. This approach ensured accurate preoperative cytological or histological assessment.

The discrepancy between the number of patients undergoing surgery (n=180) and those with histopathological data (n=207) is explained by including preoperative FNAs and cutting needle biopsies. Additionally, some patients defaulted on treatment (n=5) or passed away (n=22) before reaching surgery. We also acknowledge that one patient with anaplastic histology was inadvertently omitted from Table 3, and this should be corrected to n=8 (4.4%).

Concerning syndromic patients, one patient had Denys-Drash syndrome, and another had Beckwith-Wiedemann syndrome. Unfortunately, both patients passed away before completing treatment. We had no patients with a horseshoe or single kidney in this study cohort.

We emphasise that lactate dehydrogenase levels were included in our study as part of our routine biochemical workup for paediatric patients presenting with abdominal distension, rather than as a specific marker for Wilms' tumour.

Concerning the use of isotope studies and bone marrow aspiration, we clarify that these investigations were conducted as part of a broader diagnostic approach for abdominal masses, which includes differential diagnoses such as neuroblastoma and B-cell lymphoma. While not routine for Wilms' tumour, these investigations were valuable in identifying metastases in cases where Wilms' tumour was ultimately diagnosed.

Concerning the site of metastases (single or multiple sites), 67 patients had metastasis, 53 (79.1%) of whom had metastasis at a single site and 14 (20.9%) at multiple sites. The metastasis at single sites included lung (n=32), liver (n=10), marrow (n=3), skeletal (n=1), pleural effusion (n=3), inferior vena cava (IVC) wall infiltration (n=3) and thoracic nodes (n=1).

The metastases at multiple sites included lung and liver (n=7), lung and IVC wall (n=1), lung, liver and IVC wall infiltration (n=2), lung and spleen (n=1), lung and bone marrow (n=1), lung, liver and skeletal (n=1) and lung, liver and lymph nodes (n=1). Non-pulmonary metastases were present in 20 (30.3%) patients, and non-hepatic metastases were present in 45 (67.2%) patients.

We want to clarify the IVC involvement in six patients, as depicted in Table 1. The metastatic breakdown has been provided, and we confirm that these patients had IVC wall infiltration, and the lesions were not IVC thrombi.

We acknowledge the reader's suggestion regarding the impact of diagnostic delay and the need to determine the optimal cut-off for it. Using Youden's index, we found that the cut-off time for experiencing symptoms leading to lower survival was 22 days.

We confirm that patients with metastatic disease were included in the preoperative staging data, and that radiotherapy was primarily administered to patients with local stage III disease or metastases. Unfortunately, specific data on the exact anatomical sites of radiation were not collected.

Our definition of a 'good response' to neoadjuvant chemotherapy was based on clinical and imaging assessments of tumour volume reduction by at least 30 - 50%. However, we acknowledge that further refinement in defining response categories, such as distinguishing between fast and slow responders, would enhance the robustness of future analyses.

Concerning relapsed patients, we confirm that of the 18 who relapsed during treatment, 3 completed treatments, while 1 abandoned therapy. Of those who relapsed post treatment, only 1 abandoned further care, with subsequent management decisions based on individual patient needs such as second-line chemotherapy, radiation, re-resection, or palliation. We are in the process of conducting a dedicated study on relapse patterns, which will provide more detailed insights.

We recognise the need to calculate and present the median age (with interquartile range (IQR)) for unilateral and bilateral tumours separately. In our comparison, we looked at the age at diagnosis (measured in months) for patients with bilateral nephroblastoma (n=12) v. those with unilateral tumours (either left or right, n=195). The median (IQR) age at diagnosis for bilateral tumours was 31 (22 - 39) months, while for unilateral tumours, it was 39 (24 - 64) months. The difference in ages was not statistically significant (p=0.13, based on the Wilcoxon rank sum test), indicating that there was no significant difference in age at diagnosis between bilateral and unilateral cases.

Regarding survival analysis, our study primarily focused on 2-year overall survival (OS), given the increasing loss to follow-up over more extended periods. However, we recognise the value of 5- and 10-year

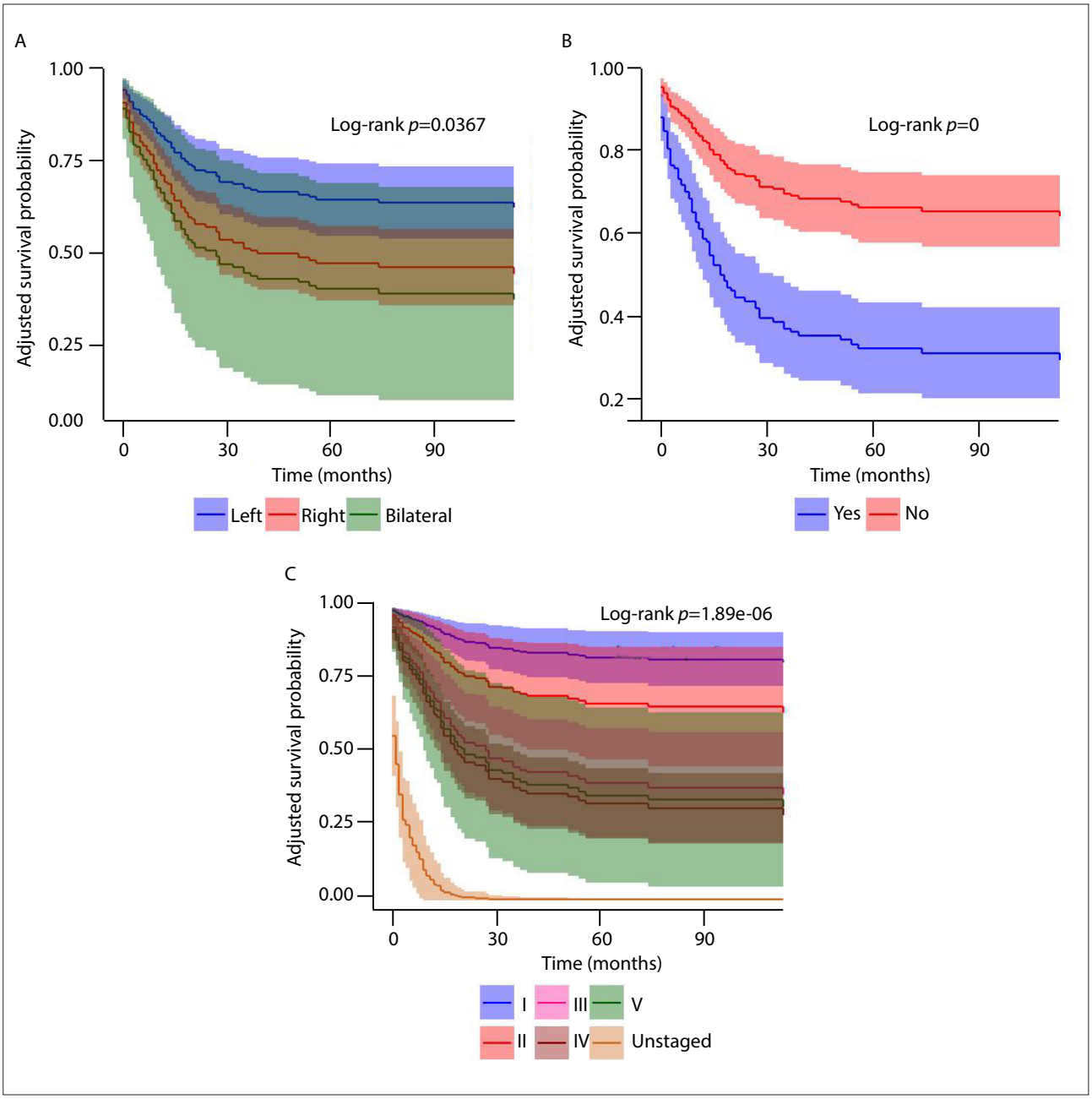

Fig. 1A-C. Subgroup analyses of adjusted survival probability in unilateral v. bilateral disease, localised/single site v. metastatic disease and stage-specific survival. A: Tumour side; B: Metastasis; C: Tumour stage.

OS rates, and will attempt to extract these in future studies. We also acknowledge the inconsistency in reporting treatment default impact, and confirm that treatment default significantly affects survival (p=0.019).

The sites of relapse beyond the lungs and liver included the peritoneum, mediastinum, lymph nodes, pelvis, facial bones, intracranial regions and residual kidney, in a case of bilateral disease.

We recognise that our hazard ratio (HR) for lung metastases seems higher than expected, and may have been affected by our approach of including lung metastases in both the single and multiple metastatic site categories. The initial analysis indicated that patients with lung metastases had an 85% higher risk of mortality (HR 1.85, 95% confidence interval (CI) 1.15 - 2.95, p=0.01) compared with those with metastases in other locations, which contradicts global observations. Therefore, we conducted a re-evaluation to analyse lung metastases separately, both as a single site and as part of multiple metastatic sites, to determine if the original estimate was influenced by classification bias. The updated analysis showed that lung metastases as a single site were not significantly associated with increased mortality risk (HR 0.58, 95% CI 0.31 - 1.08, p=0.088). In contrast, patients with multiple metastatic sites had a significantly higher hazard of mortality (HR 2.29, 95% CI 1.14 - 4.58, p=0.019), confirming that the overall metastatic burden, rather than lung involvement specifically, was the key determinant of prognosis. Additionally, when lung metastases were compared against all other metastases in the dataset, the HR remained non-significant (HR 1.48, 95% CI 0.86 - 2.56, p=0.16). These findings indicate that the previously high HR for lung metastases was likely overestimated owing to the inclusion of multiple-site cases, and that the actual driver of poor survival outcomes was the presence of multiple metastatic sites rather than lung metastases alone.

The reason for choosing 2 weeks for a delayed presentation is that it indicates that the symptoms were not acute but have become chronic, which should be investigated for their persistence. Symptom-to-diagnosis time does not mean that the patient arrived on time. The patient was still being worked up or held up (e.g. transport and passport problems) in the periphery with symptoms, or was wrongly diagnosed elsewhere, and we were only able to diagnose it a month after the onset of symptoms. Survival times are determined from the time of diagnosis, and the median survival rate in this article refers to the OS.

Regarding Kaplan-Meier survival curves, we agree that additional subgroup analyses (e.g. unilateral v. bilateral disease, localised/single site v. metastatic disease, stage-specific survival) would be valuable. These results are shown in Fig. 1A-C, and discussed as follows.

Tumour side

Survival probability was assessed based on tumour laterality, categorised as left (purple), right (brown), or bilateral (green). The log-rank test showed a statistically significant difference in survival between these groups (p=0.0367). Patients with bilateral tumours exhibited the worst survival outcomes, with a more rapid decline in survival probability over time compared with those with unilateral tumours. The curves for left- and right-sided tumours were similar, suggesting that bilateral disease was associated with a poorer prognosis, likely owing to increased tumour burden and treatment challenges.

Metastasis status

The presence of metastatic disease (purple) was associated with significantly reduced survival probability compared with non-metastatic cases (red), with a highly significant log-rank p-value <0.001. Patients without metastasis showed substantially better survival rates over time, whereas those with metastases had a steep and continuous decline in survival probability. These findings highlight the negative prognostic impact of metastatic spread in nephroblastoma, and reinforce the importance of early detection and aggressive management in metastatic cases.

Tumour stage

Survival probability was compared across tumour stages (I - V) and unstaged cases, with a log-rank p-value of <0.001, indicating a significant difference in survival among the different stages. Advanced-stage tumours (likely stages IV and V) showed markedly worse survival, with a steep decline in survival probability, whereas early-stage tumours (I - II) had significantly better outcomes. The unstaged group had variable survival patterns, possibly owing to heterogeneity in disease severity or incomplete staging data. This analysis underscores the tumour stage as the most critical predictor of survival in nephroblastoma, emphasising the importance of early diagnosis and treatment initiation.

These findings confirm that bilateral disease, metastatic spread and advanced tumour stage are all associated with poorer survival outcomes in nephroblastoma. Metastasis and tumour stage have the most pronounced impact on survival, while tumour laterality, though significant, plays a relatively lesser role than metastatic status and stage. These insights highlight the need for aggressive management in advanced and metastatic cases, and support the continued use of staging systems to guide treatment decisions.

Finally, regarding the request for raw data, any request for data access is welcome. It should be made through the editor with an indication of the specific data or analysis required, and for what purpose it will be used.

We appreciate the opportunity to clarify these points, and welcome further constructive discussion.

E Brits
Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa
britse@ufs.ac.za
On behalf of the authors

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