Reply to Letter to the Editor: Renal tumours in children older than 10 years – should we be doing upfront nephrectomy?

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We thank Wanagaru, Stevens and Arul for their comments on our publication on the diagnostic accuracy and clinical utility of pediatric renal tumor biopsy . We wish to provide further data and discussion to refute their suggestion that upfront nephrectomy (UN) should be mandated beyond the age of 12-14 years.

The rationale for advocating neoadjuvant chemotherapy for children with Wilms tumours (WT) is not only to reduce the risk of intra-operative tumour rupture, but also to tailor post-operative treatment based on the response to chemotherapy. This includes potentially downstaging Stage III disease, thereby avoiding the need for post-operative radiotherapy and identification of both low and high risk histological subtypes that add further prognostic information. Conversely, an accurate pre-operative diagnosis of renal cell carcinoma (RCC) can allow for surgical planning, including nephron-sparing surgery for localised disease.

Our recommendation that there is greater value to biopsy children aged 10 years and older is based on both robust epidemiological data and an analysis of our dataset from the SIOP WT 2001 trial. Extrapolating from a single centre's experience of just ten patients is at much greater risk of selection bias, as is using data from SEER, an amalgamated regional registry covering 28% of the United States population[1]. Our analysis of population level data from 896 cases in the English National Cancer Registration and Analysis Service (NCRAS) shows that WT remains the most common renal cancer until the age of 15 years old (Supplementary Figure 3[2]). Not all children are enrolled in clinical trials potentially skewing trial-based datasets. However, a study of UK children enrolled in UKW3 and SIOP WT 2001 trials, which they cite incorrectly as having an inflection point of 14 years, also found that WT ceases to be the most common tumour at 15 years of age[3].

For children aged 15-19 years registered with NCRAS between 2003 and 2014 at least 15/69 (22%) had a tumour where neo-adjuvant chemotherapy is recommended (5 WT and 10 non-

WT). For children 10-14 years this proportion was 42/50 (84%, data from 2006-2015). This is in contrast to children 1-9 years old where WT represents over 90% of all renal cancers[4], and where we showed that a policy of universal biopsy is unlikely to change clinical management in this age group[2].

Finally, we would like to provide additional analyses addressing the possibility of selection bias due to incomplete capture of biopsy reports. As previously reported, there was no significant difference in the proportion of non-WTs for cases where a biopsy report was obtained compared to where it was not[2]. Cases with confirmed UN were overwhelmingly in children under 1 year old (Figure 1). Each of the five children ≥10 years who had UN had a WT. The proportion of older children was slightly higher amongst those without a biopsy report (Figure 1), but this did not meet statistical significance (Kolmogorov-Smirnov Test p=0.47). Moreover 2/10 (20%) children ≥10 years without a biopsy report had an RCC, compared to 5/19 (26%) that did.

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2. Jackson, T. J. *et al.* The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy : Report of the UK experience in the SIOP UK WT 2001 trial. *Pediatr. Blood Cancer* (2019). doi:10.1002/pbc.27627
3. Popov, S. D., Sebire, N. J., Pritchard-Jones, K. & Vujani, G. M. Renal Tumors in Children Aged 10–16 Years: A Report From the United Kingdom Children's Cancer and Leukaemia Group. *Pediatr. Dev. Pathol.* **14,** 189–193 (2011).
4. Pastore, G. *et al.* Malignant renal tumours incidence and survival in European children (1978–1997): Report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **42,** 2103–2114 (2006).

Figure legend

Figure 1: Left panel: histogram of the age at diagnosis for children with a unilateral renal tumour enrolled by a CCLG centre into the SIOP 2001 trial, bin width = 2 months, n= 67, 522 and 167 for upfront nephrectomy, biopsy report found and biopsy report not found respectively. Right panel: empirical density functions corresponding to the histograms in the left panel.