

Reply to Dr. R. Dong et al. and Dr. G. Fan et al,

We thank the Lancet Oncology editors for the opportunity to reply to the letters from Fan and Dong. We interpret that they are asking us to comment on the following topics:

- 1: whether having a diagnostic biopsy should influence surveillance strategy, considering a potential risk of relapse related to biopsy;
- 2: that a prospective trial is needed to confirm if earlier detection of relapses corresponds to improved clinical post-relapse outcomes;
- 3: that low and middle-income countries may have limited surveillance capability, because of less resources, which may influence post relapse survival rates. Portable ultrasound and chest X-ray are easy to use and relatively cheap in comparison with CT scan.

We are fully aware that in some countries renal tumour biopsy is mandatory or strongly recommended prior to commencing chemotherapy. The potential association with an increased risk of relapse due to tumour seeding has been considered. In recent data from UK, biopsy was not significantly associated with increased risk of local relapse, but the results were borderline.¹ Currently much work is ongoing within the SIOP-RTSG analysing data from previous protocols to obtain more robust data about the clinical utility and risk of biopsy, which can be transferred to clinical recommendations.^{2,3} Hence, our manuscript focused on surveillance and mode of detection of relapse as potential risk factors for post-relapse survival and we did not include biopsy status in the analyses. Unless more convincing data emerge, we recommend that patients undergoing a diagnostic biopsy should follow the standard surveillance.⁴

We strongly agree that a prospective trial is needed to establish the clinical benefits and harms (eg, false positive findings) of different surveillance strategies. We quote our manuscript 'Randomised clinical trials are needed to assess different surveillance regimens...'.⁴ In our study we present the best available evidence on the largest cohort of Wilms tumour. We flag up that these data are retrospective cohort data, thus 'low' in the evidence hierarchy and encourage to perform surveillance trials (also within other areas of paediatric solid tumours). The main challenges in conducting such a trial are: 1) a large sample is needed to detect a significant clinical difference between alternative surveillance regimens as the relapse event rate is low, 2) funding bodies prefer to support trials of novel therapeutic strategies rather than surveillance, and 3) it could be a challenge to obtain parents' support to enrol their child in a randomised trial of differing intensities of surveillance.

The authors allude to the unsatisfactory survival rates for children with Wilms tumour in low income countries, pointing to the limited surveillance program as a possible reason. However, there is much evidence emerging that poor survival rates can be improved by prospective studies that aim to increase adherence to a therapeutic standard which is adapted to the health care setting. We agree that a program based on portable ultrasound and chest X-rays is the most pragmatic, more child friendly and can be applied in a variety of resource settings but also acknowledge that the setting in low income countries can be different from countries participating in the RTSG-SIOP protocol. However, considering the shortage of drugs commonly used at relapse (ie, etoposide, alkylating agents, carboplatin, often requiring

intensive supportive care facilities), which are responsible for improved outcome of relapsed patients over the past years,⁵ it is less likely that a more comprehensive surveillance regimen of relapsing tumour would lead to better outcome.

Jesper Brok, Kathy Pritchard-Jones and Filippo Spreafico.

References

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3: The diagnostic accuracy and clinical utility of paediatric renal tumour biopsy – the SIOP UK WT 2001 experience. Jackson T, Williams R, Brok J, et al. Submitted and to be presented at the annual *SIOP 2018 meeting* in November, Kyoto, Japan.

4: Brok j, Lopez-Yurda M, Tinteren HV Relapse of Wilms' tumour and detection methods: a retrospective analysis of the 2001 Renal Tumour Study Group-International Society of Paediatric Oncology Wilms' tumour protocol database. *Lancet Oncol* 2018; 19(8): 1072-81.

5: Spreafico F, Pritchard Jones K, Malogolowkin MH, et al. Treatment of relapsed Wilms tumors: lessons learned. *Expert Rev Anticancer Ther* 2009; 9(12): 1807-15.