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Optimising surveillance for relapse of Wilms' tumour

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Wilms' tumour is the most common kidney cancer in children worldwide and, in developed countries, overall survival exceeds 90% at 5 years.¹ Although only a minority (around 15%) of patients with Wilms' tumour relapse, salvage therapy for these children is challenging, requiring highly intensive treatments that are only effective for approximately half of patients.^{2,3} Survivors of relapse can have lifelong health problems and are at risk of secondary malignant neoplasms from toxic therapeutic regimens, which mandate improved therapy with cell-specific activity and fewer off-target sequelae.⁴ A clearer understanding of the biology that drives resistance to multimodal therapies for Wilms' tumours and earlier clinical detection of its relapse are principles emphasised in cooperative groups that treat pediatric cancers.^{5,6}

In their Article⁷ published in *The Lancet Oncology*, Jesper Brok and colleagues report the relapse pattern of Wilms' tumour and critically analyse the methods used for its detection until now, whether through routine surveillance imaging or upon evaluation of clinical symptoms arising between scheduled visits. The authors offer a novel algorithm to optimise early detection of Wilms' tumour relapse, which could improve salvage rates and streamline use of precious health-care resources. As is proposed in their Article, personalising surveillance protocols might reduce unnecessary exposure to radiation from frequent and repeated CT scanning of patients who are at low risk of relapse, which could help to ease the stress placed on patients and their families during this angst-provoking and uncertain time.

Brok and colleagues suggest that current International Society of Paediatric Oncology (SIOP) radiographic surveillance modalities are insufficiently sensitive or timed to detect the aggressive and symptom-producing forms of relapse that arise between scheduled follow-ups, but conclude that existing techniques and timelines are sufficient to detect the more indolent and asymptomatic forms of relapse. Notably, these mapping data could enhance guidelines for imaging surveillance according to risk of relapse. For example, as mentioned in the Article, cases that are at increased risk of relapse should have stricter and shorter imaging schedules with more sensitive modalities, such as high-resolution CT scans or MRI, as opposed to abdominal sonography and plain radiographs, which have been the most commonly used methods until now. Conversely, patients who are at low risk of relapse, and arguably have a more indolent biology if such an event occurs, can be followed up according to existing protocol timelines and with simpler, less expensive imaging modalities.

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Brok and colleagues report that relapse was detectable on clinical examination in only 31% of cases, which highlights the need to refine current surveillance protocols, with respect to both imaging sensitivity and specificity and interval duration. Furthermore, given that 80% of relapse events occurred within the first 2 years after nephrectomy, an opportunity exists to intensify surveillance during this early window for patients with high-risk clinical and biological variables and then to relax protocols for the next 3 years for those with more favourable features. Predictably, early relapse cases (ie, occurring within the first 2 years) predominantly had high-risk histology and more advanced stage disease at presentation, whereas children treated for bilateral disease or in the context of a Wilms' tumour-predisposing syndrome typically relapsed later. Tumours with larger volumes and those in older children also tended to relapse earlier than smaller tumours in younger children.

Children diagnosed with symptomatic relapse between scheduled surveillance imaging had inferior overall survival when compared with those with asymptomatic events detected through routine monitoring, and the risk of post-relapse death was increased (hazard ratio 1.85, 95% CI 1.24–2.74; $p=0.0027$) in the former subgroup, both of which are novel and important findings. Moreover, relapse within 6 months after nephrectomy was also associated with an increased risk of treatment failure and ultimate death (hazard ratio 1.63, 1.15–2.31; $p=0.0062$).

In summary, this important study emphasises the profound need for improvements (with regards to sensitivity and timeliness) in radiographic detection of relapsed disease involving specific and predictable organ sites and in knowledge of the underlying biology that fuels treatment failure. Existing surveillance protocols for Wilms' tumour are arbitrarily standardised to monitor all patients with the same type of imaging and interval duration. The data reported by Brok and colleagues might help to shape new methods of monitoring that account for biology, histopathology, stage and age at presentation, and ongoing genomic predisposition. A prospective trial is needed to evaluate novel surveillance protocols and determine whether early detection of relapsed Wilms' tumours corresponds with improved outcomes.⁶ This study lays the groundwork to optimise detection of relapsed Wilms' tumour that could improve survival from its current dismal and unpredictable odds.

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