Perspective

Omitting pulmonary radiotherapy in selected stage IV nephroblastoma patients with pulmonary metastases

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The appropriate treatment approach of pulmonary metastases in children with nephroblastoma is controversial. One of the distinctions between the approaches lies in the indication of pulmonary radiotherapy. Some collaborative groups have advocated the routine use of pulmonary radiotherapy for metastases detected on conventional pulmonary X-ray, whereas other collaborative groups have adopted a strategy based on the response to a neoadjuvant three-drug regimen (1,2).

The results of A. Verschuur and colleagues' report in *The Journal of Clinical Oncology* show for the first time that pulmonary radiotherapy may be safely omitted in most of the nephroblastoma patients with pulmonary metastases, in a large collaborative protocol (3). They stated that pulmonary radiotherapy may be restricted to selected patients with unresectable pulmonary metastases - still remaining after primary chemotherapy - and to all patients with high risk histology - regardless of the degree of response- during first-line treatment, and to cases suffering from a pulmonary relapse (3,4). It should, however, be taken into account that the currently considered blastemal type nephroblastoma was not specifically regarded as high risk histology in the SIOP 93-01 trial. Therefore, the data as reported in the manuscript will need to be confirmed in the next SIOP trials in which the blastemal predominant type is considered high risk (5).

To omit pulmonary radiation therapy in rapidly and completely responding metastatic patients, was an original idea of the lately deceased dr. Jan de Kraker, who was one of the most dedicated experts in the field of Wilms tumors (1,6). His passion was not only to cure patients, but also to take care of late effects of treatment in the survivors. Especially in children with Wilms tumor, late toxicity from treatment is of interest because of the excellent long-term survival. The rationale for omitting pulmonary radiotherapy for the majority of patients is based on avoiding the severe late effects of treatment, like reduced total lung capacity, interstitial pneumonia, growth abnormalities, second malignant neoplasms, valvular cardiac disease and congestive heart failure (7-11). Besides late toxic effects of local thoracic radiation, scattered radiation to surrounding organs also causes late toxicity, like radiation to the pancreas leading to diabetes mellitus (12-14). Unfortunately, Verschuur *et al*. did not specifically address the radiation dose, which has been shown to be an important determinant in relation to late toxicity.

The modern therapeutic attitude to omit pulmonary radiotherapy in early complete responders - initially born within the SIOP trials and studies - is now shared within the Children's Oncology Group (COG) protocol as well. The *in vivo* responsiveness of tumor cells to a given drug represents the scientific mainstay of administering initial chemotherapy in the SIOP trials. Likewise, American colleagues were able to integrate this to a certain content in their trials. Together with the application of pre-operative chemotherapy in bilateral disease, this underscores the cooperation between the SIOP and COG renal tumor study groups.

Interestingly, the SIOP 93-01 study was mainly based on conventional pulmonary X-ray imaging for the detection of lung metastases. Currently, in practice in most children CT scans of the lungs are being performed, for central revision purposes (15). Still, it remains important to keep the results

of the current study in mind in order to avoid unnecessary irradiation given the excellent outcome in well-responding stage IV patients with pulmonary metastases.

The authors hypothesize that the type of anthracyclines - although not independent - may have contributed to the better outcome of patients with pulmonary metastases treated in GPOH centers. Since the current protocols are using doxorubicin only, it may be difficult to prove this hypothesis in the current trials.

For the future, it will be interesting to better understand the biological basis underlying the speed and degree of tumor response (slow incomplete responders versus rapid complete responders), and together with the initial metastatic tumor burden, to incorporate these elements in the decision making process to treat or not with additional pulmonary radiotherapy or with doxorubicin. Molecular studies in stage IV pulmonary metastasized nephroblastoma patients may unravel the clinical heterogeneity and could guide future patient-targeted and risk-based radiation treatment decisions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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