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Considerations in the Diagnosis and Management of Pediatric Patients with Favorable Histology Wilms Tumor Who Present with Only Pulmonary Nodules

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Abstract

More than 70% of children with stage IV, favorable histology (FH) Wilms tumor will be relapse-free survivors 16 years after diagnosis. Successful treatment generally includes whole lung radiation therapy and doxorubicin. Such therapy is associated with adverse, long-term effects, including impaired pulmonary function, congestive heart failure, and second malignant neoplasms, especially breast cancer. Cooperative groups have adopted a risk-based approach to the treatment of these patients. It is important to recall the good overall prognosis for this group before recommendations for intensification are made based on preliminary data and in the absence of histological confirmation of persistent malignant disease.

Children with stage IV, favorable histology (FH) Wilms tumor (WT) have a good prognosis. More than 70% are expected to be relapse-free survivors (RFS) 16 years after diagnosis and more than 80% will survive at least 16 years after diagnosis (1). However successful treatment generally includes administration of whole lung radiation therapy (WLRT) and chemotherapy that includes doxorubicin. Such therapy is associated with an increased risk for adverse, long-term effects, including impaired pulmonary function (2, 3), congestive heart failure (4, 5), and second malignant neoplasms, especially breast cancer (6–9).

To avoid these complications, elimination of doxorubicin and/or WLRT would be necessary. deKraker et al.(10) conducted a pilot study in which WLRT was administered only to those stage IV, standard histology (11) patients who did not achieve a complete response (CR) of their pulmonary metastases after pre-nephrectomy three-drug (vincristine, actinomycin D, and doxorubicin) chemotherapy, with or without resection of residual pulmonary nodules. Two-thirds of 36 patients had multiple pulmonary metastases. Twenty-seven of 36 (75%) achieved a CR after six weeks of pre-nephrectomy chemotherapy, and five attained a CR following surgical resection of residual pulmonary nodules. Only four patients required WLRT. Four-year recurrence-free survival (RFS) and overall survival (OS) were 83% (10). These pilot results were the basis for a large, multi-institutional study conducted by the

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International Society of Paediatric Oncology (SIOP) (SIOP 93-01), in which 234 patients with nephroblastoma with or without anaplasia, or malignant rhabdoid tumor of the kidney (one patient), with only pulmonary metastases, received six weeks of pre-nephrectomy three-drug chemotherapy, followed by nephrectomy. One hundred forty-eight (67.3%) of 220 who had complete data achieved CR with combination chemotherapy alone. An additional 37 required surgical resection of one or more pulmonary nodules to achieve CR. The overall five-year event-free survival (EFS) was 73% (OS, 82%). The five-year EFS was 77% (OS, 88%) among those who achieved CR with chemotherapy only, 84% (OS, 92%) among those who required surgical resection of residual nodules to achieve CR, 46% among patients with inoperable pulmonary metastases treated without WLRT, and 50% among those with inoperable pulmonary metastases treated with WLRT (12).

These results were the background for a study initiated by the Renal Tumor Committee of the Children's Oncology Group (COG) in which those stage IV FH patients with pulmonary metastases only who achieved a CR after six weeks of three-drug chemotherapy received no WLRT following nephrectomy (13). In contrast to the SIOP study, only 105 of 296 patients (35.5%) with pulmonary metastases only were in CR after six weeks of chemotherapy, a finding possibly related to the administration of lower cumulative doses of doxorubicin during the pre-nephrectomy chemotherapy period. The four-year EFS for this group of patients was 78%. The median duration of follow-up for those without an event was not reported (13). Those who did not achieve a CR after six weeks of chemotherapy received 12 Gy WLRT, and intensified chemotherapy (Regimen M) that included the addition of cyclophosphamide (cumulative dose – 8800 mg/m²) and etoposide (cumulative dose – 2000 mg/m²)(14). The three-year EFS for this group was 88%. The median duration of follow-up for those without an event was not reported (14).

The COG Renal Tumor Committee recommended that consideration be given to omission of WLRT for the management of patients with stage IV, FH WT whose tumors lack combined loss of heterozygosity (LOH) for 1p and 16q who achieve a CR at week 6, and treatment with Regimen M, which includes WLRT, for those who have not achieved a CR of pulmonary metastases after six weeks of three-drug chemotherapy. These recommendations are based on the preliminary results reported during the previous two (2014 and 2015) Annual Meetings of the American Society of Clinical Oncology, and assume that all residual lesions observed in patients who fail to achieve a CR are malignant and that the observed improvement in EFS among those who did not achieve a CR was the result of treatment with WLRT and intensification of the chemotherapy regimen.

There is literature regarding interobserver variability in the interpretation of chest computed tomography (CT) for evaluating pulmonary nodules and the specificity of chest CT for identifying malignant lung nodules in children with WT and other pediatric malignancies. For example, Wilimas et al. reported that 78 of 202 chest CT scans (38.6%), were read as positive by at least one of three reviewers. Only 46 (22.8%) of the remaining scans were interpreted as negative by all three reviewers (15). McCarville et al. reported the relationship between the radiographic and histologic diagnosis for 81 pulmonary nodules resected from 41 patients with suspected pulmonary metastases. The three experienced pediatric radiologists correctly identified the benign or malignant nature of the nodules in 65%

(39/60), 57% (37/65) and 67% (43/64) of those removed. Lesion size did not predict malignancy, but nodules with a distinct nodule margin were more likely to be classified as malignant by each of the three reviewers (16). Silva et al. reported the results of an evaluation of lung nodules in chest CT scans from 111 of 488 infants and children who underwent chest CT imaging for staging of a non-CNS malignant solid tumor. Twenty-seven underwent nodule biopsy. Seventeen (63%) of the biopsies had benign histology and nine demonstrated malignancy. Three of the six patients with renal tumors who underwent nodule biopsy had benign disease identified in the removed nodule (17). Finally McCarville et al., in an attempt to utilize PET/CT to improve the sensitivity and specificity of interpretation of CT lung nodules in children and adolescents with malignancy, evaluated 75 nodules, 48 of which were malignant, in 25 patients. The images were evaluated blindly by three panels. Panel 1 reviewed chest CTs alone and was comprised of three experienced pediatric radiologists. Panel 2 reviewed PET-CTs alone and was comprised of a physician double-boarded in pediatric radiology and nuclear medicine and two nuclear medicine physicians. Panel 3 reviewed the chest CTs concurrently with the PET-CTs and was comprised of three pediatric radiologists with PET-CT experience. The sensitivity ranged from 60% to 85% for the three panels. Specificity was poor, ranging from 19% to 48%. Sensitivity and specificity were better for lesions > 0.5 cm, with sensitivity of 76% to 87%, and specificity of 36% to 86%. Inter-reviewer agreement was 0.43 for panel 1, 0.22 for panel 2 and 0.33 for panel 3. Twenty-six of 30 (86.7%) biopsied nodules were malignant (18).

There have been fewer studies restricted to children with WT in which the relationship between radiographic and histological findings were evaluated. Meisel et al. reported that lung biopsies were positive for malignancy in 15 of 18 (83%) children with CT only lung nodules (nodules seen only on CT and not on chest radiograph) at the time of presentation of WT (19). Ehrlich et al. reported 13 of 16 (82%) biopsies of solitary CT only lung nodules, and 18 of 26 (69%) of those with multiple CT only lung nodules were positive for malignancy. (20). Verschuur et al. reported that lung nodule biopsies were positive for tumor in 46.4% (13/28) of patients who did not achieve a CR after pre-nephrectomy chemotherapy, but did not report the number, among those that were negative for tumor, that had evidence of completely necrotic or matured tumor (12). Smets et al reported that lung biopsies obtained after treatment with pre-operative chemotherapy were positive for tumor (or necrotic tumor) in 85% (17/20) of patients (21). Some in both of these series were also reported by Berger et al (22). The finding that outcome is better for patients with CT only lung nodules than for those with nodules detectable by plain chest radiograph (19, 21, 23) supports several interpretations, including that some patients with CT only nodules have only benign nodules and that the volume of disease is less among those with CT only nodules compared to nodules identified on plain chest radiograph.

All of the studies of the sensitivity and specificity of chest CT for the diagnosis of malignant nodules in children and adolescents with a variety of solid tumors or only WT have flaws. However the data support the conclusion that, regardless of the experience of the pediatric CT radiologist, a percentage of nodules, whether solitary or multiple, identified on chest CT scans are benign. In the absence of biopsy data from a consecutive series of such patients, it is difficult to estimate exactly what this percentage is. The percentage with malignancy may be as high as 85% and possibly as low as 46.4%. It is clear that not every patient with WT

and pulmonary nodules at initial presentation has stage IV WT. Nodules that are not due to malignant disease, including intrapulmonary lymph node, round atelectasis, granulomatous disease, inflammatory pseudotumor and hamartomas, may or not resolve on follow-up CT (24).

Because a cohort of children with WT and pulmonary nodules includes both those with and those without malignant nodules, the observed EFS is necessarily a weighted sum of the EFS for those with malignant nodules (EFS_m) and the EFS for those with only benign nodules (EFS_b). This model assumes a value for $EFS_b < 100\%$ but $> EFS_m$ to account for intra-abdominal relapses related to the renal tumor. If one defines the proportion of patients who have only benign nodules as p , assumes that relapse is extremely uncommon more than four years after diagnosis, a value for the four-year EFS_b for those with only benign nodules, and a value for the four-year EFS_m for those with malignant nodules, one can estimate the number surviving at four years for the cohort with various values for p as:

$$N_s(t = 4 \text{ years}) = p * N * EFS_b(t = 4 \text{ years}) + (1-p) * N * EFS_m(t = 4 \text{ years}),$$

where N_s is the number surviving at four years, t = time, N is the total number of individuals in the cohort, EFS_b is the assumed four-year EFS for those with only benign lesions, and EFS_m is the assumed four-year EFS for those with malignant lesions. If all relapse-free members of the cohort have a minimum follow-up of four years, one can approximate the observed four-year EFS (EFS_o) as:

$$EFS_o = N_s/N$$

Solving these equations for various values of p , assuming the value of 85% for the four-year EFS_b , and values of 65%, 70%, and 75% for the four-year EFS_m , yields the following graph (Figure 1):

Figure 1 illustrates the impact that various proportions of benign nodules will have on the observed four-year EFS for a group of “slow incompletely responding” patients. The “slow incompletely responding” patients will have an observed four-year EFS that will appear to improve as the proportion of patients in the cohort with benign nodules increases.

This figure illustrates the problem of interpreting the results of the COG Renal Tumor Committee studies. In the study reported in 2014 (14), the investigators suggested that the improved outcome, compared to the historical control, was related to treatment with the more intensive Regimen M. However the observed three-year EFS of 88% is consistent with the proportion of benign nodules being 0.6 if the four-year EFS for the malignant nodules is 75%. Restriction of the protocol to those patients lacking combined LOH at 1p and 16q biases the baseline outcome for the COG study patients to a more favorable four-year EFS (25). By contrast, the reported four-year EFS for those patients who achieved a CR was 78% and the four-year overall survival was 95%, suggesting that unirradiated patients who relapse may be retreated successfully, although the median follow-up of this cohort was not reported.

The model suggests that the recommendation for intensification of therapy for those patients who lack LOH at 1p and 16q may be premature, as the observed “improved” outcome may

reflect enrichment of the “slow incompletely responding” group with patients who have benign nodules. The recommended intensification will add the new risks related to treatment with cyclophosphamide, of a substantial risk for azoospermia among males (26), and, related to treatment with etoposide, of treatment-related leukemia (27, 28) among all participants.

The treatment of pediatric patients with stage IV FH WT is very successful, although the lack of specificity of the diagnosis of malignant nodules using more sensitive modalities, such as chest CT, complicates both the treatment of these patients and the interpretation of clinical trials asking therapeutic questions in this population. Great care must be exercised in recommending adoption of more intensified treatment regimens in a population lacking biopsy proven malignant disease in the presence of radiographic evidence of persistent pulmonary nodules after initial treatment with chemotherapy. Exposure of significant numbers of patients to the additional toxicities of cyclophosphamide and etoposide is not justified in the absence of adequately analyzed data demonstrating an unambiguous, statistically significant improvement in both RFS and overall survival in this group of patients.

Finally the difficulty in interpreting the results of the current COG studies suggests that uniform definitions of malignant pulmonary nodules using chest CT that are shown to have good sensitivity and specificity, as well as low intra- and inter-observer variability, are needed (29). Histological confirmation of the nature of those nodules identified as benign or malignant on the basis of chest CT is necessary if these problems of diagnostic imaging accuracy are to be overcome. Limiting histological confirmation to a subset of patients is inherently biased and will neither improve our understanding of the reasons for discrepancies between chest CT and histological findings, nor restrict administration of intensified therapy to those patients who truly have persistent malignant disease.

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Figure 1.

Relationship between observed event-free survival and the proportion of residual pulmonary nodules that are benign for various values of the event-free survival of patients with malignant nodules.