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CORR Insights®: How Are Indeterminate Pulmonary Nodules at Diagnosis Associated with Survival in Patients with High-Grade Osteosarcoma?

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Where Are We Now?

The characterization of indeterminate pulmonary nodules (IPNs), often defined as nodules less than 1 cm in diameter, remains problematic in children and adults during cancer staging. Small nodules are common in healthy children as well as adults; they are seen in the lungs of approximately one-third of children undergoing CT for trauma [7, 8]. Tsoi et al. [10], in their retrospective analysis of 431 patients with high-grade osteosarcoma or spindle cell sarcoma of bone, help elucidate the importance of small pulmonary nodules found on staging chest CT. The authors showed that IPNs have a substantial risk of being synchronous metastatic pulmonary disease and/or a harbinger of future metastasis.

Although this study [10] found that patients with IPNs had poorer survival, another study with a similar design did not show a survival difference between patients with IPNs and those without lung nodules [4]. This outcome difference may be explained by some features of the study by Ghosh et al. [4], including a smaller sample size of 30 patients with IPNs in 104 patients or possibly the longer follow-up time of up to 14 years. Nonetheless, the current study [10] affirms the overarching theme of multiple prior investigations, namely that detailed IPN characterization on CT has limited utility in distinguishing benign from malignant sub-centimeter pulmonary nodules [1, 4, 5, 6, 9]. The nodule size cutoff for the risk of metastasis has been debated, with no clear answer in the setting of osteosarcoma or other solid extrapulmonary malignancies. Some studies suggest a lower risk of malignancy in nodules less than 5 mm [1, 5] while others do not [6, 9]. Of note, in Tsoi et al.'s [10] analysis, they were able to downgrade the tumors of 19% (16 of 84) of patients originally judged to have IPNs at outlying centers, using an expert review for features of pleural tags or fissural lymph nodes. This critical distinction may have classified benign nodules less than 5 mm in size out of the IPN group, allowing for a greater discrimination of outcomes between the no-metastasis group and the IPN group. The final proportion of patients with IPNs, 16% of the total number, was slightly lower than that in other reports (21% to 33%) [4, 5, 6], possibly because of this secondary nodule classification. An awareness of the key features of small-nodule benignity is important for the radiologist and the oncologist alike.

Another interesting detail from the current study [10] is that IPN mineralization was associated with improved overall survival in the univariate analysis, but this was not confirmed in the multivariate analysis, which means it may have been a function of confounding variables. Other investigators likewise found no relationship between nodule calcification and the risk of malignancy [4, 6]. This is in

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contradistinction to the findings of Brader et al. [1], who specifically investigated IPNs in children with osteosarcoma and found a higher likelihood of malignancy in those with calcified nodules. The effect of patient age on the balance between the possibility of calcified granulomas or other benign lung conditions and the possibility of malignant calcified osteoid in metastatic nodules is unknown. The importance of this specific feature in osteosarcoma staging remains unresolved and probably depends on the patient's geographic environment, tumor grade or subtype, and age.

Based on the work of Tsoi et al. [10], surgeons and multidisciplinary oncology care teams should pay close attention to describing pulmonary nodules when performing staging chest CT. Patients with IPNs may have worse overall and metastasis-free survival than patients without pulmonary nodules and require close imaging follow-up to monitor for disease progression. These data should be clearly communicated to the patient and may inform treatment decision-making, including if and when to pursue pulmonary nodule resection.

Where Do We Need To Go?

Although common themes can be drawn between this current study [10] and prior investigations [1, 4, 5, 6, 9], more consistency in the definitions of benign, indeterminate, and metastatic pulmonary nodules in osteosarcoma is needed. Imagers are very accurate when confident in a malignant nodule determination, but even in those scenarios, the exact criteria remain incompletely articulated [6]. Imaging criteria, in both children and adults, need to be established and then easily adopted by general radiologists. Expert review in a quaternary-care oncology setting is ideal, but most CT images will be interpreted by general radiologists, who are more familiar with the classic teachings of pulmonary nodules that have a risk of primary lung cancer than they are with osteosarcoma.

Even in the most expert hands (or eyes), the current CT imaging parameters available to radiologists can only be used to refine the discrimination of benign, indeterminate, and malignant nodules to a certain point. We may, in fact, be approaching a point of limited returns with modern high-resolution anatomic CT imaging. Positron emission tomography may play a larger role in the characterization of small lung nodules in the future, but it has the limitations of spatial resolution and difficulty in accurately assessing nodules less than 5 mm in diameter [3]. The rapidly expanding field of artificial intelligence may hold greater promise for a more-accurate prediction of metastatic disease. One recent investigation in children with osteosarcoma used a computerized texture analysis to differentiate benign and malignant pulmonary nodules [2]. Higher mean attenuation and larger effective diameter assessed with the automated three-dimensional texture analysis were better predictors of malignancy than a conventional assessment of attenuation and diameter, especially in small, noncalcified nodules.

How Do We Get There?

Additional multi-institutional studies of a wider group of children and adults with osteosarcoma are needed to confirm the outcome stratification of pulmonary nodules shown by Tsoi et al. [10] in high-grade osteosarcoma or spindle cell sarcoma of bone. A clear lexicon of benign nodules (pleural tags and fissural lymph nodes [also called perifissural nodules]), IPNs, and presumptive metastatic nodules in osteosarcoma using modern, thin-section chest CT is needed, an effort that could be led by the American College of Radiology Imaging Network or the Children's Oncology Group. If IPNs can be strictly defined and reproducibly can show there is an intermediate risk of disease progression in the no-metastasis and metastasis groups, refined treatment algorithms can be formulated. Risk stratification in the group of IPNs is especially challenging and may be beyond the capabilities of an anatomic assessment with high-resolution CT. Newer advanced imaging techniques, including molecular imaging and artificial intelligence, may ultimately hold the keys to greater accuracy in osteosarcoma staging in the setting of IPNs.

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