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Surrogate Markers for Pulmonary Hypertension May Inform Prognosis in Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide (1). Individuals with lung cancer frequently have comorbidities, including chronic obstructive pulmonary disease (COPD) and cardiovascular disease, which place them at increased risk of pulmonary hypertension (PH) (2). PH is a heterogeneous disease that negatively impacts morbidity and mortality. In patients with lung cancer, the presence of PH may contribute to worse outcomes after surgical resection and, if severe, preclude resection altogether (3). Despite the high prevalence of lung cancer and the potential impact of comorbid PH on treatment decisions, the prevalence of PH in patients with lung cancer is not well defined. Additionally, there is a lack of published data describing the relevance of comorbid PH to the natural history of lung cancer.

In this issue of the *Journal*, Eul and colleagues (pp. 1316–1319) present a retrospective analysis of the prevalence of computed tomography (CT) surrogate markers for PH and their impact on survival in patients with lung cancer (4). In the first part of their analysis, they measured pulmonary artery (PA) and ascending aorta (A) diameter on baseline high-resolution CT in 670 patients with lung cancer. They determined that 43.7% of patients had a mean PA diameter of $\geq$28 mm, and 22.5% had a PA/A ratio of $>$1. These thresholds, particularly PA/A $>$1, have been shown to correlate with mean PA pressure $\geq$25 mm Hg and thus suggest PH (5, 6). A subset of patients ($n = 132$) in this study were evaluated with echocardiography. PA diameter and PA/A were positively correlated with echocardiographic PA systolic pressure (PASP) after adjustment for sex, age, body mass index, tumor type, Union for International Cancer Control tumor–node–metastasis stage, and arterial Po_2. Those with PA/A $>$1 had a mean echocardiographic PASP of 38.6 mm Hg compared with 28.5 mm Hg in the group with PA/A $\leq$1; this finding was statistically significant. Taken together, these findings suggest that patients with lung cancer may have an increased risk of PH.

As the authors point out, a major limitation of the study is the use of noninvasive means to diagnose PH without confirmatory right heart catheterization, which remains the gold standard for diagnosis according to the sixth World Symposium on Pulmonary Hypertension (7). A meta-analysis including 2,134 subjects found a summary sensitivity and specificity of 79% and 83% for mean PA diameter and 74% and 81% for PA/A, suggesting a rate of misdiagnosis of 17–19% (8). The use of Doppler echocardiography to corroborate the presence

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of PH is helpful but still limited. Up to 48% of patients demonstrate Doppler-estimated PASP at least 10 mm Hg greater or less than that obtained with the gold-standard right heart catheterization (9). In patients with advanced lung disease, echocardiography leads to considerable overdiagnosis of PH, with specificity and positive predictive values of 55% and 52%, respectively (10). Future studies using right heart catheterization will be needed to confirm the possible increased prevalence of PH in patients with lung cancer.

In the second part of their analysis, the authors used an adjusted Cox proportional hazards regression analysis to evaluate the impact of PA $\geqslant$28 mm and PA/A $>$1 on progression-free survival (PFS) and overall survival (OS). They found that both markers were associated with significantly reduced PFS and OS. In the group with PA/A $>$1, PFS was 133 days and OS was 207 days, relative to the PFS of 270 days and OS of 568 days in the group with PA/A $\leqslant$1. This analysis was adjusted for sex, age, body mass index, cancer type, Union for International Cancer Control tumor–node–metastasis stage, and P_{O_2}. This effect size is remarkable and may offer meaningful prognostic guidance to clinicians caring for patients with lung cancer. Moreover, they are readily available markers given the standard use of chest CT and/or positron emission tomography–CT in patients diagnosed with lung cancer.

These results must be interpreted with caution, though, as it would be premature to conclude that possible PH causes decreased survival because of the lack of information on specific cause of death and several possible confounders. Cigarette smoking status was not available for most of the patients in this cohort, which is problematic, as it is independently associated with cardiovascular disease. Epidemiologic studies have found that cancer patients diagnosed at age 85 or younger have significantly increased risk of death from heart disease (11). In patients with non–small cell lung cancer, death from cardiovascular disease is the second most frequent cause of death after lung cancer (12). Moreover, left heart disease is more likely to be the etiology of elevated PASP by echocardiogram (13), compared with the much rarer pulmonary arterial hypertension or PH owing to thromboembolic disease or tumor emboli, and has very different treatment implications. Eul and colleagues reported echocardiographic metrics of left heart function, including ejection fraction and ratio of early to late left ventricular filling velocity (E/A ratio), which were similar between groups. However, the absence of echocardiographic features of left heart disease does not rule out clinically significant disease (14).

COPD is an additional possible confounder. Interestingly, PA diameter and PA/A have previously been shown to be associated with increased mortality in patients with COPD (15). It is known that the severity of COPD as measured by FEV_1 is an independent predictor of mortality (16). Both FEV_1 and $D_{L_{CO}}$ were significantly lower in the group with PA/A $>$1. As the authors suggest, it may be difficult to discern if this significant decrease is due to the presence of PH, and they should be commended for examining CT signs of emphysema, which did not differ between the groups. However, further prospective trials will be needed to determine whether it is PH or more severe COPD that predicts increased mortality in patients with lung cancer.

This study offers novel data suggesting possible increased prevalence of PH in patients with lung cancer. Additionally, it suggests meaningful reductions in survival in patients with lung cancer and imaging markers associated with PH. Prospective multicenter studies using right heart catheterization would help to confirm an increased prevalence of PH, and association with mortality, in patients with lung cancer. ■

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