Editorial Commentary

Spread through air spaces-positive T1 lung adenocarcinoma: is lobectomy associated with better outcomes than sublobar resection?

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The gold standard for operative management of early-stage, non-small cell lung cancer (NSCLC) is resection by anatomic lobectomy (1). There exists persistent debate, however, regarding the potential for oncologic equivalence of sublobar resections (wedge or segmentectomy) versus lobectomy for small, peripheral, early-stage NSCLC (2). A parenchymal-sparing resection strategy is appealing, particularly for patients with significant comorbidities, or prohibitively poor lung function that would otherwise preclude resection by lobectomy. Attempts to identify the appropriate cohorts of patients for sublobar resection have included risk stratification by a multitude of factors; including tumor size, histologic subtype, and radiographic characterization (e.g., solid versus ground-glass appearance on cross-sectional imaging), among others (3). The pursuit of parenchymal-sparing options remains at the forefront of investigators' aims to codify oncologic outcomes with extent of surgical resection, yet there persists a lack of certainty regarding which clinicopathologic features contribute to outcome and therefore should be utilized to dictate that operative decision.

To help elucidate this question, Dr. Eguchi and colleagues recently published results from a retrospective analysis of oncologic outcomes for nearly 700 patients who underwent lobectomy or sublobar resection for T1N0M0 lung adenocarcinoma between 1995 to 2014 at Memorial Sloan Kettering Cancer Center (4). Their goal, which was admirably accomplished, was to help elucidate whether lobectomy may be oncologically superior to sublobar resection for patients whose tumors exhibited a specific pattern of invasion by spreading through air spaces (STAS). STAS, a relatively novel histologic characterization of NSCLC, is defined by the presence of tumor cells in air spaces of parenchyma located beyond the edge of the tumor margin. Although this histologic characteristic was described in the context of lung cancer by the World Health Organization guidelines in 2015, STAS has remained somewhat nebulous with respect to its role in formally shaping clinical practice (5). In this study, Dr. Eguchi and colleagues investigated whether the presence of STAS portends a higher risk for locoregional recurrence and lung-cancer specific death in patients undergoing resection when compared to patients without STAS, and the effect of STAS and surgical margin on procedure-specific outcomes.

Eguchi *et al.* obtained data for analysis by screening an institutional lung cancer database, from which nearly 1,500 patients initially met inclusion criteria. Although their final analysis included less than half of those 1,500 patients, their study was strengthened significantly by their stringent propensity-matched scoring, which minimized potential concerns for selection bias. Furthermore, even with a reduction in numbers for the sake of precise propensity score matching, Eguchi *et al.* still had a consortium that was large enough to power the study appropriately. Covariates

were discussed and addressed from the outset, and they were balanced appropriately within each cohort as well as across cohorts. Eguchi's team determined outcomes of interest to be recurrence (which was further stratified as locoregional or distant), and lung cancer-specific mortality. They minimized the potential for subjective error or biased interpretation of pathology by implementing a standard of independent histologic review by multiple thoracic pathologists who were, in turn, blinded to patient outcomes data. Addressing these various areas of potential bias from the outset augmented the strength of their resultant conclusions and highlighted the sophistication of their overall analysis. Ultimately, they concluded that compared with lobectomy, sublobar resection (segmentectomy and wedge) is associated with a significantly higher risk of recurrence and lung cancer-specific death, but only in the patients with STAS. This association was not similarly demonstrated in patients without STAS.

Eguchi *et al.* strengthened the depth of their analysis by looking at the impact of margin-to-tumor ratio on recurrence for patients who underwent sublobar resection. Interestingly, in STAS-negative tumors, a margin-to-tumor ratio of greater than or equal to 1 was associated with a clinically significant lower risk of locoregional recurrence. This risk reduction, however was not evident in the STAS-positive group, i.e., among patients with STAS-positive tumors, the risk of recurrence following sublobar resection was high regardless of the margin-to-tumor ratio. These results suggest that in STAS-positive tumors, a wide margin is still inferior to performing an anatomic lobar resection with respect to lowering risk of recurrence.

A third important component of Eguchi *et al.*'s study focuses on the frozen section analysis of STAS and addresses potential differences in morphologic interpretations therein. Multiple thoracic pathologists were involved in the examination of each specimen to help standardize the histologic evaluation. Ultimately, they determined that STAS was detectable by frozen section with 71% sensitivity and 92% specificity. As mentioned by Eguchi *et al.*, some studies have previously deemed the sensitivity and specificity of STAS detection by frozen section to be unacceptably low for clinical practice, and have concluded that there are insufficient data to support intraoperative detection of STAS as a useful predictive feature for stratifying patients for lobectomy or sublobar resection (6). Not only does Eguchi's group acknowledge these prior claims, they additionally offer potential explanation for the improved sensitivity and specificity in their current study. For example, they propose that inclusion of an adequate amount of nonneoplastic lung parenchyma helps optimize detection of STAS. They also note that evaluation of folded or rugged tissue may produce artifact that interferes with accurate and precise detection of STAS. The improved sensitivity and specificity of frozen section identification of STAS in this study provides helpful rationale for developing future prospective studies for further investigation.

There are several limitations of this study, which are acknowledged and addressed by the study group. For example, there were patients included in whom lymph node staging was not performed. Some of those patients, therefore, may have been miscategorized as early-stage/node-negative in the data analysis, when in fact, N1 disease may have been present, but simply not detected due to inadequate nodal sampling. Had those patients been accurately deemed node-positive, they would have been excluded from the study rather than included in the sublobar cohorts. Appropriate nodal staging of these patients may or may not have had any effect on the study outcomes. The variability of STAS detection is another limitation of this study, however, as discussed above, Eguchi and colleagues addressed this limitation and made efforts to mitigate any variations in histologic examination. Despite these limitations, this study critically addresses an important issue and offers high quality data ascertainment and analysis to derive conclusions that may not only aid in clinical decision-making, but also serve as stimulus for future prospective studies to elucidate these issues.

There have been other recent studies supporting similar conclusions to those rendered by Eguchi's group. For example, Ren *et al.* (7) suggest that STAS is not a prognostic factor in lobar resections, however, they endorse the idea that for sublobar resections, STAS positivity is a significant negative prognostic indicator for both recurrence-free survival and overall survival. Shiono *et al.* also investigated the prognostic impact of STAS in sublobar resections for NSCLC; their group similarly concludes that for overall survival, univariate analysis reveals that STAS was not a prognostic factor in the lobectomy group, but it was a significantly worse prognostic indicator for the sublobar resection group in both univariate and multivariate analyses (8). Chen *et al.* recently published a meta-analysis of 14 studies with similar conclusions regarding the negative prognostic impact of STAS in resected NSCLC (9). The clinicopathologic features and prognostic impact of STAS have been under such heavy scrutiny that some groups have recently developed prognostic models with STAS as

part of their nomogram calibration for predicting 5-year recurrence-free survival and overall survival in patients with NSCLC (10).

The study by Eguchi and colleagues is not only significant in its own right, it raises consideration for future prospective investigations, and suggests a deeper complexity of ways to leverage STAS analysis to improve clinical practice. For example, perhaps it would be useful to investigate correlations of cross-sectional radiographic characteristics with STAS-positivity. If a reliable association exists, it may help preoperatively "screen" for STAS tumors, which could, in turn, potentially increase the sensitivity of frozen section detection by flagging certain tumors for closer scrutiny. Further investigation may reveal certain immunological markers associated with STAS-positivity. If an immunological marker was identified, immunohistochemical staining could possibly be used to help determine STAS-positivity in patients who undergo preoperative tissue biopsy. With respect to therapeutic management of STAS-positive tumors, more information is needed to determine an optimal management strategy. For example, patients undergoing sublobar resection who are found to have STAS-positive tumors on final pathology may have better prognosis with a multimodal management strategy, i.e., with adjuvant therapy, rather than undergoing surgical resection alone. On a larger scale, we clearly need more studies to help understand mechanisms underlying cancer expression and progression—the notion that something like size alone predicts risk of recurrence is likely too simplistic of an interpretation of oncologic behavior.

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Footnote

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

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