# Significance of IASLC/ATS/ERS classification for early-stage lung adenocarcinoma patients in predicting benefit from adjuvant chemotherapy

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Non-small cell lung cancer (NSCLC) is currently the leading cause of cancer-related deaths worldwide and represents an incredibly challenging problem for clinicians. Despite advances in methods of detection and treatment, there is an expected increase in mortality in both developed and developing countries (1,2). The most common histologic subtype is adenocarcinoma (ADC), which accounts for approximately 50% of NSCLCs (3,4). In developed countries it is detected at an early-stage only in 25% of cases. The current gold standard for treatment of early-stage lung ADC when there are no significant risk factors is lobectomy. Despite recent progress and development of surgical techniques and minimally invasive approaches, approximately 40% of lung ADC patients experience tumor recurrence and death following complete resection (3,4). While meta-analysis has confirmed survival benefits for patients with pathologic stage II or IIIA lung ADC who have undergone adjuvant chemotherapy following surgical resection (5), there is still controversy over the role of chemotherapy in pathologic stage I patients. Additionally, its role in combination with surgery versus radiotherapy has yet to be elucidated.

In 2011, the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) recommended a new classification system to characterize invasive lung ADC based on predominant histologic subtype [lepidic (LEP), acinar (ACN), papillary (PAP), solid (SOL), and micropapillary (MIP)] with presence of each histologic subtype reported in 5% increments (6). The majority of invasive ADCs are heterogenous with several histologic subtypes presenting simultaneously (7). It has been shown that predominant subtypes are associated with survival outcomes in patients with early-stage lung ADC (8,9). Solid predominant tumors are associated with higher incidence of early recurrence at distant sites in addition to having worse prognosis among stage I lung ADC patients (10). Presence of MIP subtype is an independent risk factor for local recurrence only for patients who have undergone limited resection, regardless of predominant histologic subtype (11). Although it has been shown that histologic subtypes can be used to stratify surgically resected patients into prognostic groups, its value in determining the survival benefit of chemotherapy has yet to be established.

A recent article by Tsao *et al.* investigated the implications of the new lung ADC classification system on clinical outcomes following adjuvant chemotherapy (12). This retrospective study evaluated patients with stage I-III NSCLC selected from the LACE-Bio database composed of 4 large cohorts—this includes the International Adjuvant Lung Cancer Trial (13), JBR.10 (14), Adjuvant Navelbine International Trialist Association (15), and Cancer and Leukemia Group B/Alliance for Clinical Trials in Oncology (16). Of the 3,533 patients accrued, 575 lung ADC patients were selected and stratified based on pathologic stage: 310 (53.9%) stage I, 179 (31.1%) stage II, and 86 (15.0%) stage III. Histology of each case was reviewed according to the IASLC/ATS/ERS classification and stratified based on

predominant histologic subtype. Prognostic value of each subtype was investigated by comparing outcomes between the adjuvant chemotherapy arm and the no-chemotherapy arm. Results revealed that MIP/SOL predominant patients showed significantly worse overall survival (OS) (P=0.05), disease-free survival (DFS) (P<0.01), and lung cancer-specific DFS (P<0.01) compared with other subtype predominant groups. Micropapillary/solid predominant lung ADC was also significantly predictive of whether a patient will benefit from adjuvant chemotherapy for disease-specific survival but not OS (OS: HR, 0.71; 95% CI, 0.51–0.99; interaction P=0.18; DFS: HR, 0.6; 95% CI, 0.42–0.81; interaction P=0.01). There was no significant survival benefit for patients with other lung ADC subtypes. Moreover, survival benefit from adjuvant chemotherapy was more apparent in patients with either stage II or III lung ADC.

The validity of this study is strengthened by the large number of patients selected from multiple institutions and 4 pivotal prospective trials, and bootstrap analysis. A limitation to this study is only 1 slide was evaluated to stratify patients into histologic subtype groups. Nevertheless, MIP predominant subtype in this LACE-Bio study accounted for 7% of all patients, which is comparable with previous literature (17). Another limitation includes use of a heterogenous patient population for pathologic stage and adjuvant chemotherapy regimens employed. Influence of these factors on overall outcome is difficult to assess, especially given that the underlying mechanism directly responsible for the benefit of adjuvant chemotherapy remains unknown.

Understanding that MIP/SOL predominant lung ADC is significantly predictive of whether a patient will benefit from adjuvant chemotherapy for disease-specific survival but not OS is of interest to clinicians. The MIP/SOL predominant tumor group also revealed a higher response rate to first-line chemotherapy compared with the low- and intermediate-grade subtype predominant groups (18).

On the contrary, Zhang *et al.* reported that platinum-based adjuvant chemotherapy had a negative impact on SOL predominant lung ADC patients after resection and a negative EGFR-TKI response after recurrence (19). Additionally, SOL predominant lung ADC was predicative of worse EGFR-TKI response in patients with recurrent lung ADC with an EGFR mutation (20). However, these results are drawn from 2 retrospective studies that utilized relatively small sample sizes.

Due to the limited information available from published studies investigating this area and study limitations, implications of histologic subtypes on survival benefit from adjuvant chemotherapy still remains controversial. A comprehensive approach that includes examination of driver mutation status and expression of chemoresistance-related proteins and genes may provide useful information. Unfortunately, the mechanism of cytotoxic agents is not fully understood and chemotherapeutic strategy, according to expression of these proteins, is not well established. Resistance to chemotherapeutic agents may depend on several mechanisms including drug delivery, drug metabolism, DNA repair, and resistance to apoptosis (21,22). Among these, metabolic enzymes, such as excision repair cross-complementation group 1 (ERCC1), thymidylate synthase (TS), and β-tubulin, were reportedly associated with response to platinum-agents, pemetrexed, and taxane, respectively (23). Basic and translational studies may also further identify the extent of benefits gained from adjuvant chemotherapy in MIP/SOL predominant lung ADC cases. Understanding the underlying mechanism will allow us to identify whether histologic subtype or another molecular pathway is responsible for this benefit. This discovery could lead to development of more appropriate individualized therapeutic strategies for selecting candidates for adjuvant chemotherapy.

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## Footnote

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

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