Editorial

Intraoperative subtyping of lung adenocarcinoma: an unmet need

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Early-stage non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is currently the most common cause of cancer-related death throughout the world and is a challenging management problem for clinicians. Despite recent advances in screening modalities and treatment methods, there is still an expected increase in mortality in both developed and developing countries (1,2). The overall survival rate for all patients diagnosed with NSCLC is approximately 15% (2,3), which has not changed despite improvements in imaging techniques and introduction of new chemotherapeutic agents. Among NSCLC, the most common histology is adenocarcinoma (ADC), which accounts for approximately 50% of cases (3,4). In developed countries it is detected at an early-stage only in 25% of cases. The outcome of early-stage lung ADC depends on tumor size, which is currently the primary prognostic factor for disease management.

A new classification of early-stage lung ADC

According to the new International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) classification, lung ADC should be classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), or invasive ADC. Both AIS and MIA are considered very low-risk histologies for recurrence or metastasis after complete resection. According to its predominant histological components, invasive ADC was subdivided into lepidic (LEP), acinar (ACI), papillary (PAP), solid (SOL), and micropapillary (MIP) subtypes with presence of each histological subtype reported in 5% increments and 4 variants [invasive mucinous ADC (MUC), colloid ADC (COL), fetal ADC, and enteric ADC] (5). The vast majority of invasive ADC is heterogenous with several histological subtypes presenting simultaneously.

Importance of histological subtyping in surgical decision-making

The current gold standard for treatment of early-stage lung ADC is lobectomy with systematic lymph node dissection while sublobar resection is proposed as a treatment option for lung ADC tumors ≤2 cm (6,7). It has been shown that predominant subtypes are associated with survival outcomes in patients with early-stage lung ADC (8-10). Based on disease-free survival (DFS), 3 histological grades were identified: low (AIS, MIA), intermediate (LEP, ACI, PAP), and high (SOL, MIP). The 5-year DFS of patients with low-, intermediate-, and high-grade histologies were 100%, 86.1%, and 50.2%, respectively (11). Presence of MIP or SOL subtypes is associated with local recurrence in patients who have undergone limited resections, regardless of predominant histologic subtype (12,13). These results suggest that limited resection may not be sufficient for aggressive tumors. When selecting patients for sublobar resection

it is important to distinguish AIS and MIA from invasive ADC intraoperatively. In this group, patients diagnosed with AIS and MIA had 100% 5-year DFS and they may be the ideal candidates for sublobar resection. By contrast, patient diagnosed with aggressive subtypes (MIP and SOL) may require more extensive surgical interventions with lymph node dissection and/or adjuvant therapy.

The diagnostic accuracy of frozen section (FS)—which is bolstered by the clinical benefits of sublobar resection compared with lobectomy (14) and favorable 5-year DFS of patients diagnosed with AIS and MIA—has made it an ideal method for surgeons when selecting candidates eligible for sublobar resections. A recent study by Liu *et al.* investigated the accuracy of intraoperative FS diagnosis of lung ADC tumors ≤2 cm based on the IASLC/ERS/ATS classification system (15). In this retrospective study Liu *et al.* evaluated 803 patients from Fudan University Shanghai Cancer Hospital database who were diagnosed with clinical stage I peripheral lung ADC ≤3 cm. Patient population was divided into two main arms for this study. One arm included 432 patients who had undergone sublobar resection while the other arm included 371 patients who had undergone sublobar resection plus subsequent complementary lobectomy, which was determined based on FS results. Patients diagnosed with adenomatous hyperplasia (AAH)/AIS/MIA had undergone sublobar resection whereas patients diagnosed with invasive ADC had undergone sublobar resection followed by lobectomy. The aim of the study was to evaluate the accuracy of FS compared with final pathology in identifying histological subtypes and its usefulness in determining extent of additional surgical intervention. Total concordance rate between FS and permanent section (PS) diagnosis was 84.4%. Additionally, concordance rate was 95.9% when AAH, AIS, and MIA were classified together as a low-risk group. Of the 803 patients with stage I peripheral lung ADC ≤3 cm in this study, there were 431 (53.7%) ground glass opacity (GGO) cases with a diagnosis of AAH, AIS, or MIA, which was significantly higher than other cohorts from different regions of the world.

Can frozen sections predict histological subtypes of lung ADC accurately?

The validity of this study is strengthened by the large number of patients and effective study design; however, data from only a single institution may prove to be a study limitation. While there is a high concordance rate between FS and PS in the published literature, no concordance rate for histological subtypes of invasive ADC is available; this should be addressed prior to generalizing this conclusion. The possibility of errors with FS diagnosis due to sampling or interpretation exists since lung ADC usually consists of various histological subtypes (13). Therefore, it is often difficult to predict histological subtypes using FS diagnosis. In Yeh *et al.* (13), we showed that FS diagnosis of MIP and SOL subtypes had high specificity (94% and 96%, respectively) but low sensitivity (37% and 69%, respectively). We also performed additional analyses and found that sampling errors were the major cause of discrepancy between FS and PS. The most common FS error was overdiagnosing of MIA as invasive ADC. Degree of invasion is often overestimated using FS and it is also very difficult to distinguish MIA from LEP predominant invasive ADC using FS. On FS slides, alveolar spaces are frequently collapsed, which can make evaluation of invasion quite problematic.

Trejo Bittar *et al.* (16) investigated histological subtyping of lung ADC according to the IASLC/ERS/ATS classification and suggested that the concordance rate was unsatisfactory mainly due to sampling errors and poor FS quality. They also demonstrated relatively small interobserver discrepancy, thereby suggesting that the main cause of discrepancy between FS and PS is sampling error. By contrast, Liu *et al.* (15) investigated exclusively small-sized lung nodules, which included a considerable number of benign lung nodules and metastatic lung tumors. Thus, one should be aware that diagnostic accuracy can vary based on proportion of cases that are difficult to diagnose and size of study population. In the same context, we should reconsider whether FS is representative of the whole tumor since lung ADC has remarkable histological heterogeneity. For example, LEP component is often observable on the periphery of invasive ADC, which contributes to higher sampling errors. Many pathologists often give a diagnosis of either "consistent with ADC" or "ADC, unable to specify invasiveness" in order to withhold deciding whether or not the tumor is invasive ADC. The other factor affecting accurate diagnosis of lung ADC histological subtypes is the training level of pathologists. It is important that all patient samples analyzed in these types of studies are also reviewed by well-trained thoracic pathologists prior to adding them to the institutional dataset. We propose that pathologists be trained to sample at least the largest representative part of the tumor, when possible, to make a FS that is representative of the whole tumor.

An unresolved clinical necessity

As described above, sampling error is largely affected by tumor heterogeneity, which depends on tumor size and subtyping. For example, invasive ADC that is LEP predominant is often misdiagnosed as AIS or MIA on FS. To this end, we are now investigating diagnostic accuracy for tumor spread thorough air space on FS, which has emerged as an unfavorable prognostic factor (17,18). This approach may result in a lower sampling error rate and may help us determine intraoperatively surgical strategies in the near future.

Summary

Although sublobar resection remains a controversial treatment option for stage I lung ADC, diagnostic accuracy of FS in differentiating AAH, AIS, and MIA from invasive ADC should be studied further and improved upon. Further investigation is required to determine possible causes for diagnostic discrepancies; interobserver disagreement may also be helpful in generalizing results. Future multi-institutional prospective studies can help improve the accuracy of intraoperative diagnosis of lung ADC on FS. These types of studies will also contribute to the growing knowledgebase on the critical role FS plays in real-time diagnosis of lung ADC histological subtypes. Although diagnostic accuracy of FS in identifying lung ADC histological subtypes will improve, on-going randomized trials investigating survival outcome of sublobar resection compared with lobectomy may shed further light on the path forward for surgeons.

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Footnote

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