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MINI REVIEW

Challenges for real-time intraoperative diagnosis of high risk histology in lung adenocarcinoma: A necessity for sublobar resection

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Abstract

Recently, the incidence of small, peripheral lung adenocarcinoma has been increasing as lung cancer screening with radiologic examination is more widely performed. Tumor size is one of the determinants of the prognostic outcome in clinically node-negative lung adenocarcinoma. Sublobar resection has been proposed as one of the minimally invasive surgical options for small-sized adenocarcinomas. Despite the lack of robust clinical trial evidence, sublobar resection has become more popular, especially in developed countries where less extensive surgery may be of benefit in a population where the age of the elderly is growing. However, high risk histologic features such as micropapillary subtype and tumor spread through air space (STAS) have been associated with a significantly higher risk of local recurrence after sublobar resection, but not after lobectomy. Surgical decision-making based on frozen section diagnosis of high risk histologic features may be useful to prevent local control failure after sublobar resection. At the present time, there is little evidence to demonstrate the diagnostic accuracy of identifying high risk histologic features on frozen section. One study has so far demonstrated that diagnostic accuracy of identifying STAS is higher than that of identifying the micropapillary subtype. Additionally, the presence of STAS has been found to be more strongly associated with local recurrence in patients who had undergone sublobar resection. Although further investigation is required for validation of this finding, STAS diagnosis on frozen section may shed further light on intraoperative surgical decision-making during sublobar resection. To this end, we review the recently published data on the intraoperative identification of high risk features.

Introduction

At the present time, non-small cell lung cancer (NSCLC) is the most common cause of cancer-related deaths worldwide. The incidence and mortality of NSCLC is still increasing in both developed and developing countries[1] despite the recent progress in diagnostic modalities[2–4] and newly-developed therapeutic drugs.[5–7] The 5-year overall survival rate is approximately 15% across all stages.[1,8,9] Within NSCLC, adenocarcinoma (ADC) is one of the most common histological subtypes.[3,8] The incidence of small, peripheral adenocarcinoma is increasing as lung cancer screening and radiologic examination is more widely performed. Approximately 25% of cases detected at an early-stage are candidates for surgical resection.[8,10] Tumor size and nodal metastasis are well-known prognostic factors in resected early-stage lung ADC[11,12] and one of the major factors that is considered in the treatment strategy. Additionally, given the advancing age of many patients diagnosed with lung ADC, there is a more prevalent risk for significant comorbidities in the aged population.[13] With

this background, there has been a growing need for sublobar resection in order to preserve lung parenchyma in the care of this comorbid population.[14–16] Sublobar resection is considered to preserve postoperative pulmonary function and reduce short- and long-term pulmonary complications including pneumonia.[17,18] On the other hand, prognosis of recurrent NSCLC after surgical resection is still poor.[19] Thus, it is critical to avoid sublobar resection in high risk cases of recurrence, even in early-stage NSCLC patients.

In the new 2015 World Health Organization (WHO) classification of Tumors of the Lung, Pleura, Thymus and Heart,[20,21] lung ADC was further classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive ADC. Invasive ADC is characterized as a heterogeneous mixture of histologic subtypes including lepidic, acinar, papillary, solid (SOL), and micropapillary (MIP) subtypes.[20,21] This histologic subtyping has been shown to well stratify the prognostic outcome in resected early-stage lung ADC.[22–26] In particular, several retrospective studies have demonstrated that the presence of MIP (≥ 5%) subtype was significantly associated with a higher incidence of local recurrence in patients who were treated with sublobar resection (e.g., wedge resection or segmentectomy) for small (≤ 2 cm) lung ADC.[22,27] Thus, MIP and SOL have been categorized as high grade histologic subtypes with a greater risk of recurrence.[26,28] Additionally, Tsao *et al.*[29] documented that patients with stage I–III ADC, who have a MIP subtype, may benefit from adjuvant chemotherapy and have exhibited improved disease-free survival (DFS) rates. The MIP subtype is defined as tumor cells that grow in papillary tufts forming florets that lack fibrovascular cores.[30] Further, tumor cells which spread through air spaces (STAS), a newly described pattern of invasion, is defined as tumor cells extending beyond the tumor edge within the lung parenchyma, has been reported to be a significant risk factor for local recurrence after sublobar resection.[31–33] More recently, STAS was shown to be significantly associated with a poor prognosis in patients who had undergone sublobar resection, but not in patients who had undergone lobectomy in stage IA lung ADC.[34] In addition, some reports demonstrated that the presence of STAS is a unfavorable prognostic factor in lung ADC patients who had underwent lobar resection as well and shows significant relationship to aggressive clinicopathological characteristics (e.g., larger tumor size, nodal metastasis, higher pathologic stage, pleural invasion, and vessel invasion) as well as immunohistochemical features.[35,36] Amongst these, positive correlation of presence of STAS to presence or predominance of SOL or MIP subtypes should be noted.[29,35,36] These findings suggest that STAS may be one of the invasive mechanisms in the MIP and SOL subtypes in resected early-stage lung ADC.

Taken together, the diagnosis of MIP subtype presence or STAS on frozen sectioning during a sublobar resection may augment surgical decision-making and allow for a surgical strategy shift to an anatomic resection. To our knowledge, however, there is dearth of published data demonstrating the accuracy of intraoperative diagnosis of high risk morphology, especially in comparison to the number of studies which investigate appropriate candidates for sublobar resection on the basis of preoperative factors including PET/CT parameters and serum biomarkers.[37–42] There seems to be an unmet need for the intraoperative diagnosis of high risk histologic features in lung ADC, even though ongoing prospective trials are now investigating prognosis comparing patients treated with sublobar resection to those treated with lobectomy in stage IA NSCLC. To this end, we will discuss the utility and accuracy of intraoperative frozen section diagnosis of histologic subtype and tumor STAS.

Utility of high risk morphology in surgical decision-making

Lobectomy with systematic lymph node dissection is the gold standard treatment of early-stage lung ADC since Cahan's report of "radical lobectomy".[43] In 1995, the first randomized control trial revealed that patients who had undergone sublobar resection resulted in significantly higher recurrence rates compared to those who had undergone lobar resection among clinical stage I NSCLC.[44] From this study, higher local recurrence was widely recognized as an appropriate and notable outcome after sublobar resection. In this context, histopathologic studies have been performed to identify appropriate candidates for sublobar resection. Yoshida *et al.* enrolled 50 patients into a prospective study and reported that those with AIS and MIA could have a 100% recurrence-free survival after sublobar resection.[45] These authors also documented that the accuracy of intraoperative frozen section diagnosis for AIS or MIA was excellent (98%). Liu and colleagues demonstrated a good concordance between intraoperative frozen section diagnosis and final pathologic examination for detecting AIS and MIA in lung ADC tumors ≤2 cm.[46] In this retrospective study, the investigators evaluated 803 patients from a single institution diagnosed with clinical stage I peripheral lung ADC ≤3 cm. The patient population was divided into two main groups: one group included 432 patients who had undergone sublobar resection while the other included 371 patients who had undergone sublobar resection plus subsequent completion lobectomy, which was determined based on frozen section results.[46] Total concordance rate in the diagnosis of AIS or MIA tumors between frozen section and permanent section diagnosis was 84.4%. Additionally, tumor size had

a significant influence on the concordance rate. Another retrospective study from China reported that the concordance rate in diagnosis of AIS and MIA was 95.6% among 136 patients with AIS or MIA ≤3 cm.[47] Of note, further histologic subtyping including detection of high grade histology on frozen section was not attempted in both studies.

Can frozen section accurately discriminate tumors with high risk morphology in invasive ADC?

As described above, the accuracy of intraoperative frozen section diagnosis distinguishing AIS or MIA from invasive lung ADC seems satisfied. On the other hand, precise histologic subtyping, in particular detection of high grade histology is generally challenging to date. Errors in sampling and/or interpretation have been reported as major causes of frozen section misdiagnosis as lung ADC usually consists of multiple histologic subtypes.[48] In addition, even a small amount of high-grade histology should be detected because it contributes to an unfavorable prognosis after sublobar resection as above.[31–33] Identification of histologic subtypes is also difficult using cytologic specimens,[49] even though general cytologic diagnosis (adenocarcinoma vs. nonadenocarcinoma) has been reported to be reliable.[50] Yeh *et al*.[51] reported that the frozen section diagnosis of MIP and SOL subtypes had high specificity (94% and 96%, respectively) but low sensitivity (37% and 69%, respectively). Additionally, they demonstrated that the majority of discordance in diagnosis between the frozen section and permanent section was attributed to sampling error. The most common type of diagnostic errors on frozen section was overestimating invasiveness, e.g., misdiagnosis of MIA as invasive ADC.[51] The degree of invasion is often overestimated using frozen section. It is also very difficult to distinguish MIA from a lepidic predominant invasive ADC using frozen section. On frozen section slides, alveolar spaces are frequently collapsed, which can cause difficulty in evaluating invasion.[52] Bittar *et al*.[48] reported that the concordance rate was unsatisfactory mainly due to sampling errors and poor frozen section quality. They also demonstrated a relatively small interobserver discrepancy, thereby suggesting that the main cause of discrepancy between frozen section and permanent section is sampling error. In contrast, Motoi *et al*.[53] reported 98.6% accuracy in histological subtyping using intraoperative frozen section.

STAS is defined as the spread of lung cancer tumor cells into the air spaces in the lung parenchyma beyond the edge of the primary tumor.[31,32,52] Based on the definition of STAS, there may be interobserver disagreement, even if diagnosed by experienced pathologists. Thus, we reviewed the occurrence of STAS and prognostic significance in only pathologic stage I lung adenocarcinoma, focusing on studies with over 100 patients. As shown in Table 1, five reports have documented the prognostic significance of STAS in pathologic stage I lung ADC.[31,54–57] The incidence of STAS ranged from 15% to 56% in pathologic stage I lung ADC. All five reports demonstrated positive correlation of STAS to aggressive pathologic factors including high grade subtypes, pleural invasion, and lymphovascular invasion. Of note, four of five studies showed prognostic significance in patients treated with lobectomy.[54–57] A wide range of occurrence of STAS may suggest difficulty in STAS diagnosis. Some studies showed that the presence of STAS strongly correlates with a higher risk of local recurrence after sublobar resection.[32,33,58,59] Remarkably, Kameda *et al*. reported that the diagnostic sensitivity and specificity of STAS on frozen section were 71% and 92%,

Table 1 Previous studies regarding prognostic significance of tumor spread through air space in resected pathologic stage I lung adenocarcinoma

Author	Patient No.	% Pathologic stage IA	% STAS	Risk factors of STAS	Findings
Toyokawa *et al*. (2018)	276	50%	56%	High grade subtypes, pleural invasion, elevated serum CEA, tumor size ≥ 2.0 cm, higher SUV max on FDG-PET, higher C/T ratio on HRCT	STAS was significantly associated with worse RFS and DSS
Uruga *et al*. (2017)	208	100%	52%	Solid component, vascular invasion, pleural invasion, nodal metastasis	STAS was significantly associated with worse RFS
Dai *et al*. (2017)	383	100%	30%	High grade subtypes	STAS was significantly associated with worse OS and RFS
Shiono & Yanagawa (2016)	318	76%	15%	Stage IB, lymphovascular invasion, pleural invasion, solid nodules on HRCT	STAS was significantly associated with worse OS and RFS
Kadota *et al*. (2015)	411	100%	38%	Lymphovascular invasion, high grade subtypes	STAS was significantly associated with higher CIR in patients treated with sublobar resection

STAS, spread through air space; CEA, carcinoembryonic antigen; SUV max, maximum standardized uptake value; FDG-PET, fluorodeoxyglucose-positron emission tomography; C/T ratio, consolidation-tumor ratio; HRCT, high-resolution computed tomography; OS, overall survival; RFS, recurrence-free survival; CIR, cumulative incidence of recurrence.

respectively.[60] Thus, the identification of STAS may be useful for identifying high risk tumors using intraoperative frozen sections. However, there are specific concerns related to the diagnosis of STAS which may complicate intraoperative diagnosis such as the appropriate selection of "grossly normal" lung parenchyma surrounding tumor, as well as the methodology of lung inflation after resection. It could affect the interobserver difference in diagnosis of STAS on frozen section. In fact, a recent report demonstrated negative predictive value of STAS diagnosis on frozen section was extremely low in 48 cases of resected lung adenocarcinoma, even though the diagnostic sensitivity and specificity of STAS on frozen section was 50% and 100%. It should be noted that there is insufficient published data to support intraoperative detection of STAS.[61] Despite these issues, the frozen section diagnosis of STAS may shed light on the intraoperative surgical decision-making, and thus further investigation is warranted.

Conclusions

If ongoing randomized trials comparing the prognosis between lobectomy and sublobar resection prove noninferiority, the need for accurate frozen section diagnostic evaluation of aggressive tumors may become paramount. Further validation studies are required, particularly multi-institution prospective trials. With this information it may be possible to make real-time surgical decisions using frozen section diagnosis.

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Disclosure

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