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Review Article

Real-time intraoperative diagnosis of lung adenocarcinoma high risk histological features: a necessity for minimally invasive sublobar resection

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Abstract

Recently, peripheral small-sized adenocarcinoma has been increased as lung cancer screening and radiological examination widely performed. Tumor size is one of the determinants of prognostic outcome in clinically node-negative lung adenocarcinoma (ADC). As one of the minimally invasive surgical options for small-sized adenocarcinoma, sublobar resection has been proposed. Two phase III clinical trials have been ongoing to compare prognostic outcome of sublobar resection with that of lobectomy for early stage non-small cell lung cancer. Despite lack of published evidence of clinical trials, sublobar resection has been increased and more important as population of elderly age increase especially in developed countries. However, high risk histological feature such as micropapillary subtype and tumor spread through air space (STAS) was reportedly associated with significantly higher risk of local recurrence after sublobar resection, but not after lobectomy. Surgical-decision making based on frozen section diagnosis of high risk histological features can be useful to prevent local control failure after minimally invasive sublobar resection. To this end, our aim of this article is to review recently published data in this new topic. There is a little evidence demonstrating diagnostic accuracy of high risk histological features on frozen section to date. Available one published data demonstrated that diagnostic accuracy of STAS is higher than that of micropapillary subtype according to previous literature. Also, presence of STAS was more strongly associated with local recurrence in patients who had undergone sublobar resection. Although further investigations are required for validation of the data, STAS diagnosis on frozen section may shed further light on the path forward for intraoperative surgical decision-making regarding minimally invasive surgery.

Keywords: micropapillary, survival, recurrence, lobectomy, sublobar resection

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Introduction

Currently, non-small cell lung cancer (NSCLC) is the most common cause of cancer-related deaths in the world. It has been recognized as one of the major issues in public health. The mortality has been still increasing in both developed and developing countries, despite recent progress in screening and treatment methods [1]. The overall survival rate for all patients diagnosed with NSCLC is approximately 15% [1, 2], which has not changed dramatically despite improved radiological examination as well as introduction of new chemotherapeutic agents. The most common histology is adenocarcinoma (ADC) among NSCLC, which accounts for approximately 50% of cases [2, 3]. In recent years, peripheral small-sized adenocarcinoma has been increased as lung cancer screening and radiological examination widely performed. Approximately 25% of cases are detected at an early-stage [2, 4]. As described in TNM staging system [4], tumor size is one of the determinants of prognostic outcome in early-stage lung ADC, which is currently the primary prognostic factor for disease management. In addition, the incidence in elderly age patients with significant comorbidities has been increasing as population of elderly age increase especially in developed countries [5]. On this background, there must be increased needs of minimally invasive surgery in daily practice. One is minimally invasive approaches including thoracoscopic surgery and robotic surgery, another one is sublobar resection to preserve lung parenchyma. Sublobar resection is considered to preserve postoperative pulmonary function that can cause reduced long-term pulmonary complication such as pneumonia [6].

The new World Health Organization (WHO) classification of lung cancer recommended that lung ADC should be classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive ADC. It also characterized invasive ADC as a heterogeneous mixture of histological subtypes including lepidic (LEP), acinar (ACI), papillary (PAP), solid (SOL), and micropapillary (MIP) subtypes [7]. Particularly, presence of MIP subtype has been shown to be significantly associated with local recurrence only in patients who had undergone sublobar resection [8]. In addition, tumor spread through air space (STAS) that was newly described as a pattern of invasion was reported to strongly correlate to local recurrence after sublobar resection, but not after lobectomy [9]. These data emphasize importance of intraoperative histology-based surgical decision making. However, comparing to studies

investigating oncologically appropriate candidate for sublobar resection with preoperatively available factors among early stage NSCLC patients [10-12], there are less numbers of published data to attempt intraoperative diagnosis of the histological subtype or invasion. To this end, we discuss possibility and utility of intraoperative frozen section diagnosis of histological subtype and STAS in this article.

Importance of high risk histological features in surgical decision-making

Lobectomy with systematic lymph node has been the gold standard for treatment of early-stage lung ADC since when Cahan reported it as "radical lobectomy" [13]. Recently, sublobar resection has been increased as a minimally invasive surgical option for early-stage lung ADC tumors ≤ 2 cm [14, 15]. As previous publication demonstrated, predominant subtypes are associated with survival outcomes in patients with early-stage lung ADC [16-18]. Presence of MIP subtypes is an independent risk factor for local recurrence after sublobar resection [8]. Additionally, STAS is also strongly associated with local recurrence after sublobar resection [9]. From these findings, sublobar resection may be insufficient for aggressive tumors. Also, we may be able to extend surgical resection intraoperatively if MIP subtype or STAS present on frozen section of sublobar resection.

The diagnostic accuracy of frozen section -which is bolstered by the clinical benefits of sublobar resection compared with lobectomy [19] 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 frozen section diagnosis of lung ADC tumors ≤2 cm based on the WHO histological classification system [20]. 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. The patient population was divided into 2 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 frozen section compared with permanent section in identifying histological subtypes and its usefulness in determining extent of additional surgical intervention. Total concordance rate between frozen section and permanent section diagnosis was 84.4%. Additionally, concordance rate can 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 section 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 be a study limitation. While there is a high concordance rate between frozen section and permanent section in the published literature, no concordance rate for histological subtypes of invasive ADC is available; this should be addressed prior to generalizing this conclusion. It was shown that there is the possibility of errors with frozen section diagnosis due to sampling or interpretation since lung ADC usually consists of various histologic subtypes [7]. Therefore, it is generally difficult to predict histological subtype using frozen section diagnosis. In a report of Yeh et al. [21], frozen section diagnosis for micropapillary and solid subtypes had high specificity (94% and 96%, respectively) but low sensitivity (37% and 69%, respectively). They also performed additional analyses and found sampling errors were the major cause of discrepancy between frozen section and permanent section. The most common frozen section errors were overdiagnosing of MIA as invasive ADC. The degree of invasion is often overestimated using frozen section and it is also very difficult to distinguish MIA from LEP predominant invasive ADC using frozen section. On frozen section slides, alveolar spaces are frequently collapsed, which can cause difficulty to evaluate invasion.

STAS is defined as spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to primary tumor [7]. Some studies showed presence of STAS more strongly correlate to higher risk of local recurrence [8, 22, 23]. Remarkably, Kameda et al. reported that the diagnostic sensitivity and specificity of STAS on frozen section were 71 % and 92 %, respectively [24]. These are much higher than those of high grade subtype. STAS thus can be more important histological feature of intraoperative frozen section diagnosis, though further investigations should be required to valid these data.

Bittar et al. [25] investigated histological subtyping of lung ADC according to the IASLC/ERS/ATS classification and suggested that the concordance rate was unsatisfactory mainly because of sampling errors and poor frozen section quality. They also demonstrated 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. [26] reported 98.6% accuracy in histological subtyping using intraoperative frozen section. On the other hand, Liu et al. [20] exclusively investigated small-sized lung nodules that included a considerable number of benign lung nodules and metastatic lung tumors. Herein, we should be aware that diagnostic accuracy can vary depending on proportion of small-sized tumor, technical issues, and level of institution. In the same context, we should reconsider whether FS is representative of whole tumor since lung ADC has remarkable histological heterogeneity. For example, LEP component is often observable on the periphery of invasive

ADC. This may contribute to risk of sampling errors. This is why many pathologists often give a diagnosis of "consistent with adenocarcinoma" to withhold deciding whether the tumor is invasive ADC. The other factor affecting accurate diagnosis of lung ADC histologic subtypes is training level of pathologists. It is important that all patient samples analyzed in these types of studies are also reviewed by well-trained thoracic pathologist before adding these samples to the institutional data set. It was proposed that pathologists be trained to sample at least the largest side of the tumor, when possible, to make a frozen section to represent 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 consisting mostly of LEP subtype is often misdiagnosed as minimally invasive or in situ ADC on frozen section. Although STAS may be more reliably diagnosed on frozen section, sampling error and technical issues including appropriate selection of grossly normal lung parenchyma surrounding tumor and methodology of lung inflation. Despite these issues, investigations of diagnostic accuracy of STAS on frozen section should shed light on clinical application of surgical decision-making based on frozen section diagnosis. If technical details are sophisticated, this approach may result in a lower sampling error rate and can be helpful to determine intraoperatively surgical strategies in the near future.

Conclusions

Although sublobar resection remains a controversial treatment option for stage I lung ADC [27-41], diagnostic accuracy on frozen section in differentiating aggressive tumors that are associated with higher risk of local recurrence among small-sized NSCLC can be improved. Further investigations are required for validation as well as clarification of possible causes for diagnostic discrepancies which may be helpful in generalizing results. Particularly, multi-institutional prospective trials can help valid the accuracy of intraoperative high risk histological features of lung ADC on frozen section. These kinds of studies will also support growing knowledgebase on critical role of real-time diagnosis on FS of lung ADC. Since diagnostic accuracy on frozen section in identifying lung ADC high risk features especially STAS will improve, on-going randomized trials investigating the survival outcome of sublobar resection compared with lobectomy may shed further light on the path forward for intraoperative surgical decision-making based on frozen section.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

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