

Editorial

Preoperative Pathological Diagnosis of Lung Cancer: Is It Always Necessary?

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The incidence of resectable non-small cell lung cancer (NSCLC) has increased over the past several decades. In 2009, in Japan, over 30000 patients underwent surgical resection of NSCLC, three times the number from 20 years earlier.¹⁾ This increase is due, in part, to demographic changes in an aging society and earlier disease detection with computed tomography (CT) imaging. However, a breakthrough in the outcome of treatment for NSCLC has yet to occur. The best treatment option to date is precise diagnosis and surgical resection in the early stages.

Chest CT with computer-aided diagnostics has advanced to detect smaller suspicious pulmonary nodules in cases of suspected lung cancer.²⁾ 2-¹⁸Fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) is also instrumental in evaluating the malignancy of pulmonary nodules.³⁾ Despite the benefits that such imaging brings, however, pathological or cytological examination is still the mainstay for diagnostic confirmation of lung cancer. The sensitivity of CT scans in detecting pulmonary nodules >5 mm in diameter is close to 100%.⁴⁾ However, CT imaging is limited in distinguishing benign inflammatory nodules from malignant nodules. Furthermore, FDG-PET cannot always compensate for this limitation in CT diagnosis, because active inflammatory foci appear as hot spots like malignant neoplasms.⁵⁾ Thus, specificity in diagnosing malignant pulmonary nodules by CT combined with FDG-PET remains around 80%.⁶⁾

Biopsy techniques are classified as either excisional or

incisional, based on the extent of the resection. Excisional biopsy is a surgical procedure performed by macroscopically and completely resecting the lesion; incisional biopsy is a technique for retrieving part of the lesion during surgery or with forceps or needle. Lung cancer with centrally located lesions has long been diagnosed by transbronchial biopsy through bronchoscopy.⁷⁾ That is, incisional biopsies have been routinely performed for patients suspected of lung cancer.

In most patients who die of malignant disease, metastasis occurs by lymphatic and/or hematogenous dissemination. The first step in the development of distant metastasis is the destruction of the basement membrane, where carcinoma in situ starts to invade stromal lymphatic vessels or capillaries. Neovascularization by tumor cells is regulated by complex factors, such as vascular endothelial growth factor (VEGF)⁸⁾ and Notch,⁹⁾ which promote the process, and e-cadherin¹⁰⁾ and extracellular matrix,¹¹⁾ which inhibit it. After tumor invasion is established, free cancer cells start to circulate in the blood or lymphatic system and can then implant in distant organs. Incisional biopsy procedures directly damage both tumor and surrounding tissue, initiating a route by which cancer cells can invade.

The question of whether incisional biopsy increases the risk of recurrence in breast cancer^{12,13)} and melanoma^{14,15)} remains controversial. One study showed that patients with malignant melanoma who underwent incisional biopsy developed distant metastasis more frequently than those who underwent excisional biopsy.¹⁴⁾ Another study bearing on the possible relationship between biopsy and metastasis found that, in patients with nasopharyngeal carcinoma, the 5-year survival rate was significantly higher if radiotherapy was administered within 14 days after incisional biopsy rather than after 14 days.¹⁶⁾ This implies that a shorter interval between an incisional biopsy and radiotherapy might favorably influence results.

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Received: January 17, 2012; Accepted: March 12, 2012
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No evidence of tumor seeding via the bronchial lumen caused by transbronchial lung biopsy has been reported to date. However, the local recurrence of lung cancer in an airway cannot be distinguished from the iatrogenic spread of the neoplasm. We have speculated that tumor seeding might start via lacerated capillaries, lymphatic vessels, and/or airway tracts. In a previous study,¹⁷⁾ we retrospectively analyzed whether preoperative bronchoscopic biopsy worsened postoperative survival rate and found that stage I NSCLC had a significantly higher recurrence rate if it was preoperatively diagnosed pathologically by transbronchial biopsy rather than not diagnosed preoperatively. This difference was still significant even if the patients were stratified by other clinicopathological risk factors by propensity score. However, the difference between biopsied and non-biopsied groups was not present if the disease was advanced (i.e., stage II or III).¹⁷⁾

CT-guided percutaneous needle biopsy might disrupt the microenvironment in early lung cancer as much as other biopsy methods. On the one hand, tumor implantation around the needle tract in the chest wall is very rare after percutaneous needle biopsy.^{18,19)} On the other hand, one report indicated that the risk of pleural dissemination in patients with stage I lung cancer—especially p-Stage IB with subpleural lesions—was significantly higher in patients who underwent needle biopsies rather than other types of biopsies, even after its having been adjusted for other risk factors.²⁰⁾

Circulating tumor cells (CTCs) have also become more easily examined. Previously, CTCs were often detected in patients with advanced NSCLC, indicating worse prognosis in terms of survival.^{21,22)} Manipulation during lung cancer surgery could cause the release of CTCs.²³⁾ Thus, we hypothesize that incisional biopsy of NSCLC might allow cancer cells to reach circulating blood. In addition, these studies of CTCs suggest that patients with solitary, small, indeterminate pulmonary nodules suspected of having clinical stage I NSCLC might undergo tumor biopsy and subsequent resection at the same time. Some articles have described the yields of thoracoscopic biopsies for indeterminate pulmonary nodules.^{24,25)} These biopsies may be advantageous over bronchoscopic and percutaneous needle biopsies in terms of reducing the risk of tumor dissemination. On the other hand, more precise imaging could further reduce the risk of thoracoscopic biopsies.

Another challenge in diagnostics is locating and retrieving small intrapulmonary nodules via thoracoscopy. For this challenge, preoperative percutaneous placement of a hook wire with the aid of CT²⁶⁾ has been widely ac-

cepted. Several other techniques have also been used, including CT-guided coil injection around the lesion²⁷⁾ and the use of a tactile sensor.²⁸⁾

In conclusion, nonsurgical biopsies performed to determine the pathological diagnosis of lung cancer are crucial in determining treatment strategy, especially in advanced NSCLC. Nonetheless, we might reconsider the need for preoperative biopsies in early stage NSCLC, given that current biopsy techniques may worsen postoperative survival.

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