



# Pleural Invasion in Non-small Cell Lung Cancer: An Important Characteristic during Clinical Decision-Making

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Pleural invasion is an important sign of malignancy for peripheral non-small cell lung cancer (NSCLC), which can upstage NSCLC from stage T1 to stage T2. Pleural invasion has been also characterized as a high-risk factor in NSCLC, which may determine the application of adjuvant therapy for early stage NSCLC because it has been found to significantly affect the survival of patients with early stage NSCLC after surgery.<sup>1</sup> Moreover, significantly worse survival has been observed in patients with pleural invasion (stage T2 disease) compared with patients with the same stage T2 disease but with no pleural invasion, indicating that pleural invasion was an innate characteristic of invasiveness of NSCLC.<sup>2</sup> Recently, Kanzaki et al.<sup>3</sup> conducted an interesting study to analyze the risk factors for late recurrence after surgery among NSCLC patients who achieved 5-year disease-free survival. By including a total of 1275 patients, they found that pleural invasion was an independent risk factor for late recurrence and a poor prognostic factor for both recurrence-free survival (RFS) and overall survival (OS), suggesting that pleural invasion could have a significant impact on the risk of late recurrence and its negative impact on recurrence

for NSCLC after surgery seemed to be long-lasting (more than 5 years). As a result, it is important to put more emphasis on comprehensive research regarding the significance of pleural invasion in NSCLC.

First, it seemed important to identify the status of pleural invasion in NSCLC, especially during surgery. A previous study utilized computed tomography (CT) to predict the presence of pleural invasion and found that pleural tags on CT scan could increase the accuracy of early diagnosis of pleural invasion, with an accuracy rate of 71%.<sup>4</sup> Moreover, in our previous study, we also investigated potential factors correlated to pleural invasion comprehensively by including a total of 403 patients for analysis. We found that CT features, such as distance to visceral pleura and pleural indentation, could significantly predict the status of pleural invasion; other characteristics, such as elderly age, adenocarcinoma, and poor tumor differentiation, were also found to be novel biologic factors correlated to pleural invasion in early-stage NSCLC.<sup>5</sup> Furthermore, it is of great value to intraoperatively make pathological diagnosis of pleural invasion so as to guide the extent of resection for early stage NSCLC on the table. Previous studies also used Victoria Blue, Gomori's aldehyde-fuchsin, or Weigert's resorcin-fuchsin, and even elastic staining assays to aid intraoperative diagnosis of pleural invasion.<sup>6</sup> However, the accuracy of intraoperative diagnosis of pleural invasion should be further improved.

Second, with the wide application of sublobar resection for early stage NSCLC, it is important to figure out the optimal extent of lung resection in early stage NSCLC with pleural invasion. A previous study<sup>7</sup> compared the effect of lobectomy and sublobar resection in treating early stage NSCLC with pleural invasion and found that the cumulative incidence of cancer-specific death was significantly lower in the lobectomy group compared with the sublobar resection group (5-year: 34% versus 45%,  $P = 0.04$ ), indicating that

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lobectomy should remain as the prior option for early stage NSCLC with pleural invasion. Moreover, in our previous study,<sup>8</sup> we included a total of 1993 patients with small-sized NSCLC and with pleural invasion (stage IB disease) and found that lobectomy was associated with better survival compared with sublobar resection [hazard ratio (HR) 1.41;  $P = 0.011$ ] while it was comparable to segmentectomy in treating early stage NSCLC with pleural invasion (HR 1.41;  $P = 0.735$ ), suggesting that either lobectomy or segmentectomy could serve as an option for treating stage IB NSCLC ( $\leq 3$  cm) with pleural invasion. Interestingly, our study also found that adjuvant chemotherapy may not bring survival benefit for early stage NSCLC with pleural invasion after surgery. Therefore, the optimal extent of lung resection for early stage NSCLC with pleural invasion remains to be further defined and investigated by conducting well-designed prospective randomized controlled trials.<sup>9</sup>

Finally, besides its negative impact on early recurrence,<sup>10</sup> pleural invasion has also been proven to have significant unfavorable impact on late recurrence (more than 5 years) as presented by Kanzaki et al.<sup>3</sup> Moreover, pleural invasion was also significantly correlated with poor RFS and OS. Similarly, Koike et al. also found that pleural invasion was a risk factor for both RFS and OS of NSCLC after surgery.<sup>11</sup> Therefore, for early stage NSCLC with pleural invasion, 5 years without recurrence seemed insufficient to indicate a cure of lung cancer and 5-year follow-up time seemed not enough for these patients. Instead, prolonging the follow-up time over 5 years should be emphasized for NSCLC with pleural invasion after surgery, even at early stage.

In conclusion, pleural invasion as an important sign of malignancy and aggressiveness in NSCLC could have significant unfavorable impact on the risk of both early recurrence and late recurrence. In addition, it should remain an important characteristic for clinical decision-making throughout the diagnosis, treatment, and follow-up of early stage NSCLC.

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