Letter to the Editor

Lymph node micrometastasis in N stage: a call for more evidence

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We would like to thank Dr. Chen and his colleagues for their interest in and positive comments about our work (1). In lung cancer, even patients with pathological stage I non-small cell lung cancer (NSCLC), who have undergone a radical operation, including total tumor resection and systematic lymphadenectomy, may have recurrence rates between 25% and 40% and 5-year survival rates between 57% and 85% (2). These findings suggest that lymph node micrometastasis (LNMM) (3), consisting of metastases <2 mm that are difficult to detect using routine pathological examination methods, may positively correlate with post-operative recurrence and patient survival.

Stage effect of LNMM in lung adenocarcinoma

The clinical significance of LNMM in patients with lung cancer is a subject of debate. Deng *et al.* (4) using a meta-analysis consisting of eight relevant studies, demonstrated that LNMM had a significantly close relationship with high risk of disease recurrence and poor survival in NSCLC patients. Martin *et al.* found that p-stage I NSCLC patients who had immunohistochemistry (IHC)-positive N2 LNMM had statistically significantly worse survival rates [hazard ratio (HR), 2.04; P=0.017] (5). In the present study, we have further validated their conclusions regarding stage I adenocarcinoma (3), which is the most common type of lung cancer. Several studies have shown that the presence of LNMM was also an independent risk factor for disease recurrence in several tumors, including breast (6,7), colorectal (8), and gastric cancers (9), etc. Therefore, we believe that LNMM may be recognized as a histological finding with prognostic significance for early stage adenocarcinoma.

Although a lot of evidence is available, LNMM has not been included in the 8th tumor/lymph node/metastasis (TNM) staging system for malignant tumors. Additionally, the 2015 World Health Organization's classification of lung cancer stated that LNMM did not qualify as N1, 2, 3, or M1b disease (10). Hence, these current clinical guidelines indicate that LNMM's clinical significance has not received full attention. All of the evidence points to the need for future studies that will focus on whether LNMM can be considered a factor for upstaging.

Prognostic effect

As Dr. Chen mentioned (1), many markers, including histological, genetic, and radiological can be potentially prognostic for early stage lung adenocarcinomas, but their incremental prognostic values over traditional prognostic indicators (such as tumor stage and size) has rarely been discussed. One of the most popular measures in this context is the area under the receiver operating characteristic curve (AUC), often called the 'C statistic' (11), a name derived from its nonparametric estimator, which takes a form of a concordance index (c-index). Suh *et al.* analyzed the incremental prognostic values of computed tomography (CT) characteristics, pathological subtypes, and epidermal growth factor receptor (EGFR) mutations over conventional risk factors as measured by the c-index

for lung adenocarcinoma (12). Prognostic models combining CT characteristics and/or histological subtypes with TNM stage showed higher c-indices (0.763 and 0.767, respectively) than TNM stage-only models (c-index 0.759); however, these differences were not statistically significant (P>0.05).

In this comment, we wished to emphatically discuss two major points that need to be mentioned when the new predictors of post-operative lung adenocarcinoma outcomes: (I) the new predictors should have been tested by C statistical analysis comparing the TNM stage, which would illustrate its value for improving TNM stage and (II) predictors should have been proven as effective indicators for guiding postoperative adjuvant treatment or any other clinical interventions, which need clinical level-one evidence such as randomized controlled trials.

In conclusion, although the concept of LNMM was proposed years ago, more evidence is needed to confirm the potential and significant impact of LNMM in staging for making relevant treatment decisions in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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