Editorial

Pretreatment identification of micro-metastasis in mediastinal lymph node by endobronchial ultrasound-guided transbronchial needle aspiration for early-stage non-small cell lung cancer—is it time yet?

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The dissemination of malignancy to the locoregional lymph nodes (LNs) impacts the prognosis for most cancer types. However, routine LN histopathological examination will occasionally miss smaller tumor deposits. A case in point is breast cancer. The likelihood of identifying a small (three-cell diameter) metastatic focus of cancer in a regional LN is approximately 1% for early-stage breast cancer (1). Though similar data is not available for LN metastases in lung cancer, it is plausible that a similar situation exists for mediastinal LNs that are removed during lung resection surgery or sampled using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The locoregional recurrence rates for treated early-stage cancer appears to be consistently high between 10–20% (2-5). This problem merits a closer scrutiny.

The term "micrometastasis" (MM) refers to microscopic deposit of malignant cells, less than 2 mm in diameter, separated from the primary tumor (6). The Union for International Cancer Control (UICC) further redefined single tumor cells or cell clusters measuring ≤0.2 mm in the greatest dimension as "isolated tumor cells" (ITCs) because of their different biological behavior and size and thus differentiating them from MM (7). In other words, MM is defined as clusters of tumor cells between 0.2 and 2 mm in the greatest dimension. With the availability of newer techniques such as immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR), our ability to detect MM in LNs has increased many fold (8). However, despite the solid evidence supporting the inadequacy of current hematoxylin & eosin (H&E) staining of LNs (9,10), few, if any, cancer staging systems include the mention of MM. An exception is breast cancer staging in which MM is given the due importance (11).

A thorough review of cancer literature reveals conflicting evidence for the prognostic implications of MM on outcome for most cancers. A reduced three-year disease-free survival and higher risk of recurrence was noted for LN MM-positive Stage I–II colorectal cancer (12). A study by Liefers *et al.* (13) supports the impact of LN MM whereas others disagree (14,15). Inconclusive results are available from the literature on the effect of MM on survival in early gastric cancers (8,16,17). With use of IHC, the detection of MM in LNs with gall bladder cancer has been noted to have an impact on survival (18). Other studies suggested a lack of an effect on survival, albeit with a higher risk of recurrence when MM is detected in regional LNs for surgically resectable esophageal cancers (19,20). Again, there is disagreement among experts (21).

A review of lung cancer literature reveals varying detection range for LN MM in mediastinal LNs, ranging between 10.4% to 80.0% (22). Differences in detection technique and tissue preparation may account for this

wide range. Some authors have used different detection techniques and identified variable detection rates on the same LNs (23). The prognostic implication of LN MM varied with the technique used to identify LN MM (23). Martin *et al*. demonstrated that MM detected by IHC had an effect on prognosis whereas RT-PCR for calretinin did not (23). The work of other authors support this finding (24). IHC carries with it a risk of false-positive results due to cross-reactivity with normal cellular components (24,25). This finding may have clinical implications. For example, Hashimoto *et al*. could only detect negative prognostic impact when the MM was diagnosed by the mutant allele-specific amplification (MASA) method (24). Despite the lack of a standardized and a uniform approach for the detection of LN MM, evidence exists to support its clinical significance. Multiple studies demonstrate MM as a negative prognostic factor (9,23,24,26-35), although other authors disagree (36-38). Adding credence to the assumption that MM impact prognosis is the finding that the more aggressive the primary tumor subtype is, the higher is the risk of MM in the mediastinal nodes (39,40). One common feature that unifies the above-mentioned studies is the observation that these studies recruited patients who underwent surgical resection of the primary lung lesion. There is, however, no reason to believe that outcomes would be any different for those patients undergoing stereotactic body radiation therapy (SBRT). To shed light on the impact of MM on patients not thought to be a surgical candidate, one must first study the feasibility of detecting MM on LN samples obtained by methods other than surgical mediastinal sampling. EBUS-TBNA has become the most widely utilized technique used to sample the mediastinum (41). However, no prior study has used IHC for pan-cytokeratin on EBUS-TBNA LN samples to detect MM before Belanger *et al*. published their current study. The authors collected data retrospectively on EBUS-TBNA done between September 2013 to October 2017. The strength of the study is in its being a real-world study population with patients undergoing EBUS-TBNA for nodal sampling based on current guidelines. This study design increases the likelihood of reproducibility of the data when applied to other larger contemporary patient populations. The authors identified patients with no evidence of cancer metastasis by EBUS-TBNA via H&E staining. Once it was confirmed that these patients did not have N2, N3 and extra thoracic metastatic disease and were candidates for curative therapy, their nodes were then checked for MM using IHC for pancytokeratin. Out of the 44-eligible patients, 3 (6.8%) had MM detected on the sampled nodes. All of these were N2 stations. They further studied the effect of MM on overall survival and progression-free survival. The authors report the positive association between the presence of MM and both overall survival and progression-free survival, both being statistically significant.

The detected rate of MM is much lower than studies that have included surgically resected mediastinal nodes in early-stage lung cancers. The authors attribute the discrepancy to factors such as the effect of a small sample size, possibility of tissue alteration by the effect of the deparaffinization process and possible sampling error. The authors report that the median number of LN stations sampled during the procedure was three stations. It remains unclear if multiple nodes were sampled at each station.

The results of the survival analysis with three patients is less than convincing and clearly points to the need for further studies including larger number of patients with MM. Despite the limited number of patients, the take-home message from this study should be the fact that EBUS-TBNA can be used to detect LN MM in conventional H&E stained disease-negative nodes.

There is good data to suggest that MM occurs in a significant number of surgically resected lung cancer patients and there appears to be evidence to suggest that it impacts disease recurrence rates and progression-free survival. However, no clear studies exist for those undergoing SBRT. There is a lack of data to determine if LN MM would impact overall survival and disease-free survival among those undergoing SBRT. The presence of MM would not explain risk of local recurrence but may explain the risk of regional failure after SBRT. Regional failure, which is defined as disease progression in the mediastinal nodes or hematogenously within the lung, has been strongly linked to overall survival after SBRT (42). These results prompt us to plan for studies to investigate the prognostic impact of LN MM among those treated by SBRT. In addition, this study makes us ponder over some other questions:

- Is IHC (compared to RT-PCR) the ideal way to detect LN MM?
- Should LN samples be routinely tested for MM both for resectable and unresectable cancers?
- Should the presence of MM in LN stations in absence of metastasis on conventional testing alter stage and management?

We feel that mentioning the LN MM status would be

justified and likely supported by the scientific community once the detection techniques are standardized and the impact of LN MM on lung cancer prognosis can be validated in both early and advanced stage lung cancers.

Overall, this study will hopefully infuse more interest and enthusiasm into investigations to study the effect of MM on treatment outcomes for those with early-stage cancer. The 8th edition lung cancer classification does not recommend mentioning MM status or suggest looking for it (43). There have been suggestions to follow breast cancer classification systems and include the LN MM status in lung cancer staging information (44). The substantial recurrence rate after definitive surgical resection among those patients with early-stage lung cancer patients strongly speaks for the need to identify the factors causing cancer recurrence (4,5). LN MM may be one of those. It is high time we considered studying it with a more attentive motive.

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Footnote

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

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