Editorial

# Deciding to trust, coming to believe: sentinel lymph node assessment in lung cancer

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The sentinel lymph node (SLN)—defined as the lymph node that first receives lymphatic drainage from a primary tumor—is the most probable site of early micrometastasis. When the SLN is free of metastatic cells, it is unlikely that cancer has spread to any other, more distant nodes. The clinical impact of SLN assessment has been well documented for breast cancer and melanoma (1,2). Specifically, SLN examination in these malignancies has the advantages of (I) allowing less aggressive nodal dissections and (II) promoting a thorough immunohistochemical analysis of nodes with a peculiarly high risk of metastases (3).

Although the SLN assessment has been advocated for performing a less extensive lymphadenectomy in patients with non-small cell lung cancer (4,5), its use is not yet widespread. In this context, non-selective mediastinal lymph node sampling or complete mediastinal lymphadenectomy remains the standard of care in lung cancer surgery.

The low acceptance level of SLN analysis in lung cancer surgery is attributable to several factors. First, differently from axillary lymphadenectomy for breast malignancies, mediastinal lymph node dissection is a relatively safe procedure that carries a low risk of morbidity. Second, SLN identification rates in lung cancer surgery remain suboptimal (4). In general, SLN mapping requires the peritumoral injection of a tracer that subsequently migrates to the node that lies immediately downstream of the neoplasm. To date, several tracers (e.g., colloidal radioisotopes), injection methods, and detection devices have been investigated in an effort to optimize SLN assessment in lung cancer (6-8). However, there are significant issues that may impact SLN detection rates following radioisotope tracer injection (4)—including the high frequency of anthracotic pigmentation in hilar and mediastinal nodes and the presence of the "shine-through" effect (5,9). Recently, the use of near-infrared (NIR) fluorescence imaging for SLN mapping has been proposed to overcome the drawbacks of radioisotope tracers (10,11). Accordingly, injection of indocyanine green (ICG; dose: >1,000 μg) into the lung via a transpleural peritumoral approach has led to the identification of the SLN in >90% of patients (10). Similar high detection rates have been reported using navigational bronchoscopy-guided ICG marking (12). Importantly, a pooled analysis of patients who underwent either endobronchial or transpleural ICG injection suggested that long-term survival outcomes are achievable (13). After a median follow-up of 45 months, patients with a pathologically-negative SLN did not show nodal recurrences or distant metastases—suggesting that the SLN status may accurately reflect the overall nodal stage of patients with resectable non-small cell lung cancer. Conversely, metastatic nodal disease was invariably accompanied by a positive SLN. Taken together, these results indicate that SLN might serve as a marker to tailor the extension of lymph node dissection in this patient group. Encouragingly, patients with pathologically-negative SLN identified with NIR fluorescence imaging showed a better survival than those with negative nodes identified by traditional mediastinal staging. These results lend further support to the hypothesis that intraoperative SLN mapping may help thoracic surgeons optimize resections and enhance patient selection for adjuvant therapy—ultimately improving outcomes in early-stage lung cancer. However, it is noteworthy that the

SLN mapping protocol implemented by Digesu *et al.* (13) requires a short time period between ICG injection and NIR visualization. During video-assisted thoracoscopic surgery (VATS), transpleural peritumor injection of ICG was performed 5–10 min before removal of tumors having a mean size of 2 cm (10). However, it might be difficult to precisely localize small or deeply located target nodules through VATS (14). Consequently, an incorrect ICG injection technique can compromise the accuracy of SLN detection. Because the current clinical scenario is shifting towards an increasing number of small-sized lung malignancies being detected through low-dose computed tomography screening programs (15), we believe that the aforementioned limitation is not negligible. The use of navigation bronchoscopy could be a potential strategy to overcome this issue, but its availability remains limited. We have recently described the use of image-guided video-assisted thoracoscopic surgery (iVATS) for single-stage localization and removal of small pulmonary nodules in a hybrid operating room (16). Compared with traditional preoperative CT-guided localization, this approach led to a significant shortening of the time interval between lesion location and its subsequent removal (17). Furthermore, we have shown the clinical utility of low-dose ICG injections for NIR marking of lung tumors during iVATS (18). We anticipate that the combined use of iVATS and NIR localization may further improve SLN mapping in patients with lung cancer. Albeit being a pilot study involving a limited number of patients, the results by Digesu *et al.* (13) are encouraging and may pave the way for further clinical investigations on larger samples. We believe that their findings will be invaluable to judge the trustworthiness and clinical relevance of SLN assessment in lung malignancies.

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## Footnote

*Conflicts of Interest*: The author has no conflicts of interest to declare.

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