

## Benefit of Sentinel Lymph Node Mapping in Non-Small Cell Lung Cancer

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The presence or absence of lymph node metastasis is a key prognostic indicator in non-small cell lung cancer (NSCLC). Mediastinal lymph node dissection (MLND) is an effective therapeutic procedure when carried out in patients with nodal metastasis. On the other hand, MLND is not therapeutic and may even be harmful for patients without lymph node metastasis.

The sentinel lymph node (SLN) concept is when the lymphatic flux from a primary tumor first flows into the SLN before flowing into the more distal lymph nodes. If this concept is correct, when metastasis is not found in a SLN, it most likely will not be present in the more distal nodes. Although the benefit of SLN mapping and biopsy remains controversial, in recent years it has gained acceptance as a way to avoid the complications of lymph node dissection. It has become a common procedure in the treatment of breast cancer and melanoma.<sup>1,2</sup> Although there is also evidence of the existence of SLNs in NSCLC,<sup>3,4</sup> SLN mapping is not widely used in the treatment of NSCLC because 1) special precautions are required to minimize exposure when a radioisotope is used as the tracer for SLN mapping; 2) when blue dye is used as the tracer, it is often difficult to detect within thoracic lymph nodes due to anthracosis; and 3) major complications comparable to the arm edema seen in breast cancer or the lymph edema and nerve injury seen in melanoma are not seen with MLND. To address these issues, new techniques are being developed by groups at several institutions, including our own.<sup>3</sup> However, they remain purely experimental. The potential benefit of SLN mapping in NSCLC is that it will enable surgeons to more precisely stage the cancer. More sensitive techniques can then be employed on a limited amount of tissue to detect occult micrometastases with less cost and effort.<sup>4</sup> In ad-

dition, SLN mapping can be applied to video-assisted thoracic surgery (VATS) for NSCLC, enabling surgeons to avoid non-therapeutic and technically difficult MLND often carried out with traditional open surgery.

The SLN concept was initially considered only in the context of surgical treatment. More recently, it has also been considered in the context of the pathophysiology of cancer, especially tumor immunity. For example, the numbers of dendritic cells — an antigen-presenting cell population thought to play key roles in the initiation of antigen-specific T-cell proliferation — are reportedly lower in SLNs than in other lymph nodes, not only in breast cancer and melanoma<sup>5,6</sup> but also in NSCLC.<sup>7</sup> This is not a surprising finding. It is well known that tumor cells release a variety of cytokines and other biologically active materials.<sup>8,9</sup> These various mediators must flow into the SLN, making it easy to imagine that they influence the immune response to tumor cells there, for instance via a reduction in dendritic cell number. This suggests that tumors prepare SLNs for metastasis via an immunosuppressive mechanism. Lymph nodes are known to play a crucial role in the host immune defense against tumor progression. For instance, T-cell responses — i.e., the proliferation of T cells and the generation of cytotoxic and killer-augmenting T cells — are induced within lymph nodes, especially the SLN, depending upon the immunological properties of the tumor cells. Small numbers of tumor cells are thus able to be rejected in the lymph node. Eventually, however, the immune system is defeated and metastasis occurs. This makes the SLN a kind of battle front and the primary barrier to tumor progression. Thus, while MLND can be acceptable from the viewpoint of practical surgery for NSCLC, from an immunological viewpoint, the lack of non-metastatic regional lymph nodes after surgery for NSCLC might diminish the host defense against infectious lung diseases, or even against NSCLC.

The definition of pathological lymph node metastasis is very important in NSCLC, as TNM staging is based in part on the status of nodal metastasis, and the treatment

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strategy after lung resection is mainly based on TNM stage. For certain organ sites, especially the breast, extensive discussion of new methods of SLN imaging has led to new descriptors for lymph node metastasis in the 6<sup>th</sup> edition cancer staging manual of the American Joint Committee on Cancer (AJCC). In this edition, new terms for the minimal cellular involvement that are detected using immunohistochemistry or polymerase chain reaction (PCR) technology are proposed for breast cancer. Isolated tumor cells (ITCs) are defined as single tumor cells or small cell clusters  $\leq 0.2$  mm in diameter, which are usually detected only by immunohistochemical or molecular methods. These may be verified by HE staining. ITCs are classified as pN0. Micrometastases are defined as being  $> 0.2$  mm but  $\leq 2.0$  mm in diameter and are classified as pN1. An absence of histologically detectable regional lymph node metastasis with positive molecular findings (RT-PCR) is also classified as pN0. Unfortunately, unlike breast cancer, ITCs and micrometastases have not yet been clearly defined and classified for NSCLC. But applying the aforementioned definitions to NSCLC, Marchevsky et al. reported that NSCLC patients with ITCs or micrometastases in N1 have survival rates similar to breast cancer patients classified as pN0.<sup>10</sup> By comparison, several other investigators have reported that survival times among NSCLC patients with micrometastases detected immunohistochemically are no better than those among patients with nodal metastases detected by conventional histological examination.<sup>11,12</sup> The clinical significance of the difference between ITCs and micrometastases is thus controversial in NSCLC, and further investigation will be required to resolve these issues. If we are to forgo MLND based on nodal status, a precise diagnosis based on a clear definition of nodal metastasis is crucial.

The clinical significance of survival rate is absolutely paramount when considering the surgical treatment of NSCLC. We therefore agree that MNLD is an acceptable treatment for resectable NSCLC, as it is difficult to demonstrate a clear advantage of forgoing MLND in cases of pathological stage I NSCLC, especially on the basis of survival rate. However, we hope that surgeons will bear in mind the biological significance of non-metastatic lymph nodes to the host immune defense. We believe not only in the clinical benefit but also the immunological benefit of forgoing non-therapeutic MLND based on the

results of SLN mapping, and hope that SLN mapping will become a practical procedure in the treatment of patients with stage I NSCLC in the future.

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