Rama Med J 2009; 32: 54-56

บทบรรณาธิการ

Sentinel Lymph Node (SLN) Biopsy

Lertsithichai P, MD.

Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok Thailand 10400

Sentinel lymph node (SLN) biopsy is an accepted method for evaluating cancer spread to the regional lymphatic system. The use of SLN biopsy has been validated, or studied, on many solid cancers, including those of the thyroid, breast, gastrointestinal system, urogenital system, and skin and subcutaneous tissues (melanoma and squamous cell carcinoma).[1] In breast cancer, where the use of SLN biopsy has been widely validated, the extent of tumor metastasis to the SLNs along with its significance is an outstanding issue. Specifically, the clinical significance of “small volume” tumor involvement of the lymph nodes is unclear.[2]

In the pre-SLN era, “small volume” tumor involvement of the regional lymph nodes, defined as small foci of cancer with overall size no greater than 2 millimeters, including isolated tumor cell metastasis as well, was never an important issue. This was because all lymph nodes in the particular region would be surgically removed. But when small volumes of tumor are found in SLNs, the issue arises as to whether to remove the remaining lymph nodes in that region.

Certain questions must be answered before the issue can be resolved. These include: the frequency or prevalence of small volume lymph node metastasis, both in the SLNs and in relation to the remaining regional nodes; its prognostic significance; and its role in regional and distant cancer recurrence.[3] The following brief discussion aims to stimulate the reader to search the literature further and in greater detail for him- or herself, and is not meant to provide a clear-cut overview of these questions.

To date, these questions remain largely unresolved. The first question, that of the prevalence of small tumor volume lymph node involvement, has been investigated widely, but inadequately. There are several related questions that must be addressed at the same time. How finely should the lymph nodes be sectioned? In the past, when 10 or more lymph nodes were routinely obtained in a regional lymphadenectomy, finely sectioning each lymph node was infeasible. But with only 1 to 3 SLNs, a more detailed pathological examination became a practical possibility. The more finely a node is sectioned, the more likely some cancer cells will be found. There is no consensus on the proper sectioning interval. There are limitations to how finely the sectioning can or should be done, both practically (i.e. related to the methods of sectioning) and theoretically (the distribution of tumor cells in the nodes), but empirical studies are needed to determine the sectioning method with optimum yield for a given

time and financial constraint. What staining methods should be used? What is the prevalence of macro-metastasis (larger than 2 mm.) in the remaining regional lymph nodes in the presence of minimal lymph node metastasis in the SLNs? In other words, what is the "underestimation rate" of SLN micrometastasis? While there are studies addressing all these questions, reliable answers are lacking.

A study in this issue of the Ramathibodi Medical Journal also addressed the prevalence of small volume metastatic disease, but in SLNs that were labeled "negative" by conventional sectioning (at 2 mm. intervals) with hematoxylin and eosin ("H & E") staining. These missed metastases may be termed "occult" metastases. The investigators obtained paraffin-embedded SLN sections from 50 patients for further sectioning at 25 micron intervals. Not surprisingly, small volume metastases were found in some of these nodes. One patient even had a macrometastatic lesion, which was missed on initial H&E examination. But the overall occult metastasis rate, 8% (4/50), was not large, and as expected almost all were small volume metastases. While the clinical significance of these findings can be debated, we can be reasonably assured that, at least by conventional H&E staining, the reported negative SLNs in Ramathibodi Hospital are largely negative even on fine sectioning. More detailed sectioning, e.g. at 15 micron intervals, might not change these conclusions, except to the extent that the presence of isolated cell metastasis can be considered significantly positive. Unfortunately, the present interesting contribution did not and could not address the problem of small volume metastasis in relation to the remaining axillary lymph nodes.

The more troubling aspect of the presence of small volume lymph node metastasis is its prognostic significance and direct influence on subsequent recurrent disease. It has been argued that micro- or even macro-metastatic disease in the lymph nodes has clinical significance only in relation to the overall picture of a particular cancer in an individual patient.[3] It is difficult to argue with this position except that with this attitude no knowledge gained can be generalized across patients. But perhaps this explanation, or some variation of it, is precisely why there are contradictory conclusions from various studies addressing the clinical significance of small volume metastatic disease. Admittedly, all such studies are observational in character, and experimental evidence (randomized controlled trials), or at least large, high quality cohort studies, is needed to conclusively settle the question.

Much of the current evidence is probably pointing towards the prognostic importance of small volume metastasis, specifically micrometastasis. In practice, guidelines are placing micrometastasis, detected by H&E staining, as midway between no pathological metastasis and macrometastasis.[4] Knowledge of the presence of micrometastasis will modify treatment strategy, especially in patients with otherwise favorable prognostic markers. Thus, it is important to know precisely the amount of tumor burden in the regional nodes. And therefore, especially in breast cancer, the presence of micrometastasis in the SLNs should alert the surgeon to the possibility of removing the remaining regional nodes.

If such is the case, should there not be greater effort to detect small volume disease in selected patients? How does one select such patients? The problem is complex, involving economic points of view as well, and requires much more evidence for decision making than is currently available. We need data on the prognostic significance of micrometastasis, but much of the current data were obtained when micrometastasis was not widely recognized, and newer data are plagued by stage migration problems making comparisons between newer and older data lack validity. We should perhaps, to a certain extent, "wipe the slate clean" and use only the best and most

current experimental data to guide our therapeutic decisions. Until such data become available, we should be prudent and offer full regional lymph node dissection to patients with micrometastatic disease, although perhaps not for those with only isolated tumor cell metastasis, but within the framework of conventional detection methods of our pathologist colleagues.

References

1. Leong SPL, Wong JH, editors. Sentinel lymph nodes in human solid cancer. Surg Clin N Am 2000;80:1631-874.
2. Patani N, Mokbel K. The clinical significance of sentinel lymph node micrometastasis in breast cancer. Breast Cancer Res Treat 2009;114:393-402.
3. Weaver DL. The prognostic importance of isolated tumor cell clusters and micrometastases in sentinel lymph nodes. In: Lyman GH, Burstein HJ, editors. Breast cancer: translational therapeutic strategies. New York: Informa Health Care, 2007.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guideline in Oncology: Breast Cancer v.1.2010. URL: http://www.nccn.org/professionals/physician__gls/f__guidelines.asp#site. Accessed Jan 20, 2010.