Micrometastases in Sentinel Lymph Nodes: Few Data Make for Hard Decisions

By Karen Rowan

Over the past 10 years, breast cancer researchers have debated the tricky question of what to do when a pathologist finds micrometastases or isolated tumor cells in the sentinel lymph node. Their conflicting opinions have left many physicians questioning whether to proceed with the axillary lymph node dissection (ALND), which removes all remaining axillary lymph nodes, or to skip the operation and spare the patient its potential side effects.

A group of Dutch researchers recently came down on one side of the debate. Published in the August 13 issue of the New England Journal of Medicine, their study found that patients with micrometastases left untreated had a substantially higher 5-year risk of recurrence than did node-negative patients, who also did not receive adjuvant therapy.

“In patients with micrometastases in the sentinel node, we advise complete [ALND],” said Vivianne C. Tjan-Heijnen, M.D., Ph.D., head of the division of medical oncology at Maastricht University Medical Center in The Netherlands, who presented the data from the New England Journal of Medicine study at the annual meeting of the American Society of Clinical Oncology (ASCO). Tjan-Heijnen pointed out that in this study, even among patients whose primary tumors had favorable characteristics, such as being smaller than 3 cm, and even including patients given adjuvant therapy, the risk of axillary recurrence was about 5% for women with micrometastases, compared with 1% for those who had ALND or axilla radiotherapy.

The sentinel lymph node, which is the first node that lymph fluid enters after draining from the breast, is the most common site of breast cancer metastasis, and patients who are node negative—meaning that the biopsy turns up no cancer in the sentinel node—have a better prognosis than those who are node positive. Under present U.S. guidelines, patients with micrometastases, which range from 0.2 mm to 2.0 mm, are considered to be node positive, and some experts say they should be treated as all other node-positive patients. Their biopsy should be followed by an ALND.

However, in about 40%–60% of node-positive patients, no cancer will be found in any other axillary nodes. That means, say some experts, that the ALND can be safely avoided altogether in some patients.

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Answers to this confounding question do not seem to be forthcoming—trials done thus far are retrospective and the results are mixed. And existing imaging techniques do not hold hope for revealing cancers this tiny. So physicians and patients may be left to weigh the cost and benefits of proceeding with ALND for some time.

Debate Arises

Until the 1990s, surgeons routinely removed all the axillary lymph nodes during the operation to remove the primary tumor. The lymph nodes were then dissected and a pathologist reviewed one or two slices of tissue from several nodes, looking for evidence of metastasis. But after the nodes were removed, patients faced a lifelong risk of developing lymphedema and the near-crippling loss of mobility that can accompany it. ALND can also injure nerves and lead to shoulder dysfunction, all of which can critically affect a patient’s quality of life.

But later in the decade, the introduction of sentinel lymph node biopsy began to change practice. In a 1994 article in Annals of Surgery, researchers led by Armando E. Giuliano, M.D., professor at the John Wayne Cancer Institute in Santa Monica, Calif., reported that they had developed a technique to perform lymphatic mapping and that they had used sentinel lymph node biopsy to predict with 95% accuracy whether cancer was present in the rest of the axillary nodes. In this procedure, a pathologist can review many slices of tissue from each of the two or three sentinel nodes, increasing the chances of finding any small clumps of cancer. The research continued to evolve and in 1998, scientists led by David Krag, M.D., professor at the University of Vermont, published the results of a larger, multicenter validation study in The New England Journal of Medicine. They found that the sentinel lymph nodes accurately predicted the status of the axillary lymph nodes in 97% of cases. Over the following decade, conducting an ALND only in
patients who were sentinel node positive became common practice.

The question of how to treat patients with micrometastases then became critical. In a 1999 report in Cancer, Paul Hermanek, M.D., professor at the University of Erlangen in Germany, pointed out that advances in pathological techniques had led to an increase in the identification of micrometastases and isolated tumor cells (which are defined as growths smaller than 0.2 mm) and called for research into the clinical importance of these growths. Since then, some studies have attempted to answer the question, but conclusive results have eluded researchers.

“It remains unclear what to do when we find isolated tumor cells or micrometastases,” said Gary Lyman, M.D., a medical oncologist at Duke University, Durham, N.C.

With ALND, the physician has a better idea of how many nodes are affected, and “there is a linear correlation between the number of lymph nodes affected and the risk of death. It’s an overwhelming prognostic factor,” he said. The only way to know if other lymph nodes are involved is to do the complete dissection, and that information is important to physicians because it helps answer questions during the treatment, Lyman said.

But although the standard of care is to perform ALND on all node-positive patients, it is certainly reasonable to not remove the rest of the nodes in situations where the patient is truly at low risk for further involvement, he said.

Recent findings supporting that view came from a study led by Karl Y. Bilimoria, M.D., a surgical resident at the Feinberg School of Medicine at Northwestern University in Chicago. Bilimoria’s study, which appeared in the Journal of Clinical Oncology in June, showed that 21% of 97,314 node-positive women in the National Cancer Data Base did not undergo ALND and that women treated at non-National Cancer Institute-designated hospitals were more likely to not undergo ALND. Among women with micrometastases in the sentinel node, 45% did not undergo ALND. The researchers also found that axillary recurrence and survival were not statistically significantly worse for patients who had undergone sentinel lymph node biopsy alone than for those who also undergone completion ALND. And although the authors wrote that their retrospective study had limitations, they concluded that “completion ALND does not appear to benefit patients with microscopic nodal disease.”

Arguing against that view are the findings from the recent Dutch study. Those researchers, led by Maaike de Boer, M.D., at the Maastricht University Medical Center in The Netherlands, found that patients with either isolated tumor cells or micrometastases who did not receive adjuvant therapy had substantially reduced 5-year survival compared with that of node-negative patients who also did not receive adjuvant therapy (77.2% versus 85.7% for patients with isolated tumor cells; 75.9% versus 85.7% for patients with micrometastases). Further, the researchers found that patients with micrometastases who did not receive adjuvant therapy had substantially reduced disease-free survival compared with that of patients who did receive adjuvant therapy (75.9% versus 87.9%). The work was based on a total of 2,707 patients: 856 with node-negative disease who did not receive systemic adjuvant therapy, 856 with either isolated tumor cells or micrometastases who also did not receive adjuvant therapy, and 995 with isolated tumor cells or micrometastases who did receive adjuvant therapy. The results support the argument that sentinel lymph nodes that are affected only minimally are still important prognostic factors.

But Stephen Edge, M.D., at the Roswell Park Cancer Institute, Rochester, N.Y., disagrees with the findings from the Dutch study, which counted patients with isolated tumor cells as node positive. Despite their conclusion that isolated tumor cells are associated with a 50% higher chance of death within 5 years, “there is large body of conflicting evidence in the literature” about the clinical importance of isolated tumor cells, he said. In the U.S., ASCO and the National Comprehensive Cancer Network guidelines advise physicians that isolated tumor cells have minimal prognostic importance and should not be used to guide treatment decisions.

One potential solution to the dilemma facing oncologists would be a way to determine which patients with micrometastases are at higher risk and therefore should have a full ALND. Edge said that a test developed by Kimberly Van Zee, a surgical oncologist at Memorial Sloan–Kettering Cancer in New York, could help. In 2003, Van Zee developed a nomogram that could help physicians determine a node-positive patient’s risk for further lymph node involvement. Published in the Annals of Surgical Oncology, the nomogram includes nine criteria, such as the size of the primary tumor, the estrogen receptor status, and the number of positive sentinel lymph nodes.

Van Zee said that the nomogram gives physicians a way around the limitations of their own experiences with patients. “Clinicians’ assumptions about lymph node involvement tend to be lower than the reality,” she said. Because so many patients will not have further lymph nodes that are affected, doctors can lose their perspective that a substantial number of women will have more nodes affected.

Van Zee said that the data from Bilimoria’s study of the National Cancer Data Base, showing that almost half of women with micrometastases did not undergo ALND, make her nervous.

“I find it just remarkable. We just kind of whole-hog adopted it without proof that it’s safe to not do [ALND],” she said. She had hoped her nomogram would steer physicians toward performing more ALNDs, but instead it seems to have had the opposite effect.

The debate over what to do about micrometastases in the sentinel nodes is complicated by different approaches to treatment in different countries. Edge pointed out that in the Dutch study, patients with micrometastases were treated differently than they would be in the U.S., where all women who have estrogen receptor–positive cancer—even those who are node negative—are given endocrine adjuvant therapy. The important conclusion from the Dutch report is that isolated tumor cells and micrometastases are important to prognosis, he said; it’s that chemotherapy should be considered for these women.

“This paper hasn’t answered the question of prognostic significance,” Edge said. “For that, we need large numbers of patients in a prospective study.”

Whether such a study is even possible remains doubtful. There was a National
Cancer Institute–funded clinical trial specifically designed to answer this question, said Edge. The prospective trial was set up to randomize node-positive patients to either receive ALND or not receive it. “It was a great trial,” he said. But after 4 years, it had accrued only 500 patients, and it needed 2,000. Doctors wouldn’t put their patients on it, he said, and the trial was closed in 2004. “It was a really sad story.”