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EDITORIAL

Personal experience with studies of sentinel node biopsy for breast cancer

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In the mid-1970s, I was a fellow in surgical oncology at the University of California, Los Angeles, with Donald L. Morton. At that time, for clinically node-negative melanomas of the mid-trunk, we would perform four elective lymphadenectomies – bilateral axillary and bilateral inguinal. To determine which nodal basin would drain a truncal melanoma, Morton began injecting radioactive gold into the primary tumor which demonstrated that the pattern of gold drainage seen with lymphoscintigraphy could predict the nodal basin most likely to have metastases. Subsequently, with improved lymphoscintigraphy and the use of filtered sulfur colloid (Technetium-99m), we could see individual lymph nodes and lymphatic tracts draining the nodal basin. In the early 1990s, Morton began investigating whether the lymph node first draining the cancer was the node most likely to harbor a metastasis and could, therefore, predict the nodal status for melanoma. He found that a single node could predict axillary status, and he called this lymph node the "sentinel node."

In 1991, we began investigating the sentinel node concept for breast cancer. We tested the feasibility of intraoperative lymphatic mapping and sentinel lymph node biopsy (SNB) for patients with breast cancer. We hoped to eliminate routine axillary lymph node dissection (ALND) for clinically node-negative women without losing staging accuracy by examining only a sentinel node. At the American Surgical Association in 1994, we reported 174 patients with primary breast tumors who underwent sentinel node dissection and a completion axillary dissection[1]. There were 176 cases as two patients had bilateral disease. The sentinel node was identified with injection of 1% isosulfan blue dye alone and no radioisotope and was followed by completion Level I and II ALND. The results of the ALND were then compared to the status of the sentinel node itself. All patients with breast cancer undergoing ALND were included in this study, even in patients, we know now to be inappropriate. A sentinel node was identified in only 114 or two-thirds of the cases. When identified, examination of the sentinel node accurately predicted axillary status in 96% of those patients. In this study, no uniform procedure had yet been devised; hence, patients had different volumes of dye and different time intervals from injection to dissection with different sites of injection. This study is often used to demonstrate that isosulfan blue alone is not an adequate method to identify sentinel nodes. However, the procedure was evolving and being developed in these 174 patients, many of whom had advanced disease with palpable nodes. All patients in whom we injected blue dye were evaluated and the results reported regardless of clinical stage and clinical nodal status. Although this early study showed a low sentinel node identification rate, the technique has been improved so that isosulfan blue alone remains the gold standard.

As we improved the procedure, we learned many things. The injection could not go directly into the tumor nor could it go into a seroma cavity. Patients with advanced disease and palpable nodes were inappropriate

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candidates. Extensive nodal metastases prevent take-up of dye or isotope. We developed and improved the procedure. The mature procedure involved injection of 5 cc of isosulfan blue into the lateral aspect of a primary tumor or seroma cavity wall in patients with non-palpable lymph nodes. Using this technique, we studied 107 consecutive patients, 100 of whom had a sentinel lymph node identified, and in these patients, the accuracy of the procedure was 100%[2]. However, we still had to prove the hypothesis that the sentinel node is the first node to contain metastases and test the validity of the concept that the non-sentinel nodes do not have metastases when the sentinel node is tumor free. A more detailed study was needed. We performed sentinel node biopsy and completion ALND on 157 patients. In these patients, both the sentinel node and non-sentinel axillary lymph nodes were processed with multiple sections and immunohistochemistry (IHC) in an identical manner. In this study, we found that when the sentinel node was negative with hematoxylin and eosin (H and E) and IHC staining, 1087 non-sentinel nodes were tumor free with H and E and only one non-sentinel node showed isolated tumor cells with multiple sections and IHC[3]. Over 4300 nodal sections were examined to find one lymph node with a few scattered tumor cells. This study proved the hypothesis that the sentinel node is the first node to harbor metastases and, if tumor free, then non-sentinel nodes would be tumor free. The study also showed increased the detection of micrometastasis by examining the sentinel node but not by examining non-sentinel nodes.

At this time, we felt that it was safe to abandon ALND for sentinel node-negative patients since the probability of non-sentinel node involvement was extraordinarily low. At ASCO in 1999, we reported the first study of sentinel node biopsy alone without ALND in patients with early breast cancer[4]. Between October 1995 and July 1997, 133 consecutive women with tumors < 4 cm and no palpable axillary lymph node metastases were prospectively studied. A sentinel node biopsy was performed, and an axillary dissection was not performed if the sentinel node was tumor free. Of the 125 women who completed the study and were evaluable, 67 patients with negative sentinel nodes underwent sentinel node biopsy alone without ALND. With a median follow-up of 39 months, there were no local or regional recurrences. Not a single patient developed an axillary metastasis.

Subsequently, Professor Samuel Wells, then president of the American College of Surgeons, formed the American College of Surgeons Oncology Group (ACOSOG). Together, we sought to evaluate the validity of sentinel node biopsy in breast cancer and involve community surgeons in clinical research. I saw no value to randomizing node-negative women to ALND or SNB. Rather than perform such a randomized study of sentinel node-negative women as others were doing, we sought to determine the clinical significance of micrometastases in the sentinel node. At that time, surgeons were completing ALND for patients with sentinel node micrometastases. ACOSOG Z0010, a prognostic study of sentinel node and bone marrow micrometastases in women with clinical T1 or T2 N0M0 breast cancer, was undertaken nationally at numerous centers. In this study, a sentinel node was removed and sent to a central laboratory for the evaluation of multiple sections with IHC. The results of the IHC were blinded to the clinician and to the patients. It was shown among 790 patients that IHC-detected micrometastases or isolated tumor cells in the sentinel node were not clinically relevant[5].

The initial reluctance to perform sentinel node biopsy alone was rapidly overcome for patients whose sentinel node was free of tumor although patients with micrometastases often still underwent ALND, despite the fact that there was no clinical relevance to these small metastases and axillary recurrence was quite rare. After sometime, most surgeons stopped performing ALND for patients with micrometastases. However, the most difficult personal challenge and the greatest controversy occurred with the introduction of ACOSOG Z0011. This study was a prospective randomized study comparing ALND to sentinel node biopsy alone for patients with sentinel node H and E-detected metastases. Controversy surrounded this study and many physicians were against it. Surgeons were reluctant to omit axillary dissection for node-positive women, knowing that involved nodes were likely left behind. Medical oncologists wished to know the number of involved nodes. Radiation oncologists believed that the axilla should be radiated. Surgeons were "certain" that resection was needed.

Despite great opposition, the study randomized 891 patients. In these patients, the performance of an ALND for sentinel node-positive disease did not improve survival[6]. Even though the study was closed early, there was no statistically significant difference seen with results of the two operations – no significant difference in overall survival, disease-free survival, or axillary recurrence. Although the study was initially published with over 6 years median follow-up, a sufficient time to see most axillary recurrences, many clinicians argued that longer follow-up was necessary.

Subsequently, 10-year results were published which showed no advantage to completion ALND for clinically node-negative women whose sentinel node contained metastases and who were managed with breast-conserving therapy, whole breast radiation therapy, and adjuvant systemic treatment[7].

Despite the 10-year results, many surgeons have not yet fully accepted the omission of ALND for sentinel node-positive women treated with breast-conserving therapy and adjuvant systemic therapy. This is not surprising. Acceptance of a less radical procedure is always slow. Early on in my career, I participated in NSABP B06 which compared mastectomy to lumpectomy. Despite the findings of no improvement in survival with mastectomy, lumpectomy was slow to be accepted and, for decades, many centers were not performing lumpectomy and many surgeons felt mastectomy truly improved survival. Axillary dissection for clinically node negative but sentinel node-positive women is very likely to be performed less and less commonly as experience worldwide increases.

The voyage of sentinel node biopsy replacing axillary dissection was often a personal challenge with great animosity and reluctance to believe the results of prospective trials. However, adherence to the scientific method and basic principles of clinical research leads to great improvements in patient management. Axillary dissection will become less commonly used for early breast cancer.

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