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The Sentinel Node: Evolution of the Revolution

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The past decade in oncology has been dominated by revolutions in molecular oncology and tumor immunology. The long-term promise of those disciplines has finally begun to bear fruit for more patients, while the volume of data generated through genetic or immunological assays has grown by unprecedented amounts. In the setting of such revolutions, one might wonder what role anatomic staging plays in the evaluation and treatment of cancer patients. Specifically, what does sentinel lymph node mapping add? This edition of *The Cancer Journal* is dedicated to an update on that earlier oncology revolution, sentinel lymph node biopsy. The manuscripts presented make it clear that the procedure continues to have marked relevance to patients today, and will likely be a critically important modality into the future.

As with many revolutions, sentinel node biopsy sprang out of underlying forces that had been present in oncology for a long time. As Dr. Thompson and colleagues make clear, the apparent orderly progression of cancer first to regional lymph nodes and then to distant sites was recognized for some time, and even the idea of a “sentinel” node for a particular primary tumor goes back at least several decades if not further. The spark that changed practice around the world, though, came from Donald Morton and colleagues, who demonstrated a technique that could reliably trace a very specific pathway of drainage from a primary tumor site to a single node or small number of nodes. This had two principal implications: first, the evaluation of regional lymph nodes could be performed with minimal morbidity, and second, the small number of nodes allowed increased scrutiny of those nodes in pathology.

Historically, nodal evaluation was either morbid or inaccurate, or frequently both. Sentinel lymph node mapping has changed that forever. In breast cancer and melanoma, full nodal dissection was a standard in the past, although a controversial standard. Controversial because the vast majority of patients (who have negative lymph nodes) do not benefit from the surgery, except to gain the knowledge of their low-risk status. With sentinel node, the same or more accurate information is available at a minimal cost in terms of morbidity and quality of life. The ability to safely omit a complete node dissection, therefore, was an enormous advance in care.

The other major aspect of the advance, increased scrutiny to the removed nodes, is at times an underappreciated advantage. With a full dissection, some lymph nodes are not found by the pathologist, and the evaluation of the nodes that *are* identified is generally limited to a

single hematoxylin/eosin stained slide. With the multiple sections and immunohistochemical stains that can be performed on sentinel nodes, the accuracy of staging is also enhanced. While this has raised some question about the significance of certain microscopic or “submicroscopic” metastases within sentinel nodes, it has made the reassurance of a negative node more complete. This may mean that in addition to allowing safe omission of complete node dissections in patients with breast cancer and melanoma, it may be possible to spare more patients with truly node-negative colon cancer exposure to chemotherapy, as is being studied by Dr. Bilchik and colleagues.

In other diseases, such as gastric and lung cancer, technical challenges have prevented wide dissemination of the sentinel node biopsy. Advances in technology may enable lymphatic mapping to become more standardized and reliable in those diseases. This would be very useful given the relatively poor outcomes seen in patients judged “node negative” by current, standard evaluations. Drs. Kitagawa and Liptay and their colleagues have reviewed the challenges and opportunities represented by lymphatic mapping in gastric and lung cancer respectively.

Sentinel lymph node biopsy is a multidisciplinary procedure. Accurate performance of the procedure is not merely a matter of the surgeon’s skill; nuclear medicine and pathology are also critical components. In pathology, adequate assessment and appropriate staining are necessary not only to enable identification of metastases, but also to avoid false positive results. Dr. Messina has provided an excellent review of current standards for the process in pathology. Imaging has been the first step of sentinel node mapping throughout much of its history, as noted by Dr. Uren and colleagues. The techniques used for this mapping have increased and improved with advances in technology. These include the use of ultrasound and of novel tracers. While these developments have not yet altered the standard of care in mapping, they may do so in the future making mapping more accurate or feasible in patients who are undergoing minimally invasive surgery, through the use of fluorescent tracers.

The therapeutic effect of sentinel node biopsy, and indeed lymph node dissection, remains controversial. While it is clear in melanoma that regional disease control can be obtained through sentinel node-guided dissection, in breast cancer it appears this may also be achieved in patients with low volume disease by other means including radiation therapy. For overall survival there are impassioned arguments for and against early treatment as guided by sentinel node, as there were for elective node dissection in the past. Dr. Ross has summarized the evidence of therapeutic effect of sentinel node biopsy in melanoma. It is likely this controversy will persist for some time.

Perhaps the most intriguing review in this edition comes from Dr. Cochran and colleagues and deals with the use of the sentinel node to study the biological effects of tumors on the host. Since the sentinel node is on the most direct drainage pathway from the primary tumor, it is the site of most profound influence of the tumor on the normal host defenses. Although it has long been accepted that cancer is immunosuppressive in many cases, our ability to quantify and study this effect, particularly early in the disease process has been limited. Dr. Cochran summarizes the available data demonstrating that the sentinel node is an apt model for examining this phenomenon. It is, essentially, a human model of tumor-derived

immunosuppression. It may also prove an effective way to study methods of reversing that suppression, which may guide therapy in the future.

Overall, while advances in molecular or immune staging of primary tumors will clearly play an increasing role in determining the prognosis and appropriate treatment for cancer patients, the sentinel node should remain a vital source of information for the patient and physician. Indeed, the enhance ability to extract more and more information in analyses makes the ability to select critical points of tumor-host interaction essential. It is a window into the metastatic process unlike any other. I am deeply grateful to the authors of the articles presented in this edition of *The Cancer Journal*. Their extensive efforts and thorough reviews create a wonderful resource for everyone who is interested in finding better ways to evaluate and treat cancer. I have learned a great deal in the process and am excited about the possibilities that are discussed.

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