MELANOMA IN FOCUS

Current Developments in Melanoma

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Sentinel Lymph Node Biopsy and Completion Lymph Node Dissection in Melanoma

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H&O When is sentinel lymph node biopsy indicated in melanoma?

MR It should be stated at the outset that the major motivation for studying the role of sentinel lymph node biopsy (SLNB) in the initial management of newly diagnosed primary melanoma was the need to improve both regional disease control and melanoma-specific survival in patients with regional lymph node metastases. Studies performed globally supported the hypothesis that minimally invasive, targeted lymph node biopsy could accurately identify clinically occult (microscopic) regional lymph metastases (early stage III disease). It was also determined that treating the disease at a microscopic stage could prevent the development of clinically palpable lymph node metastases (more-advanced stage III disease), which in turn could improve long-term disease control and survival outcomes. These same studies also demonstrated that the strongest independent predictor of decreased melanoma-specific survival in patients with stage I/II melanoma was sentinel lymph node positivity. As a result, SLNB—also referred to as "sentinel lymphadenectomy"—was embraced for its role in both therapy and staging.

The most common indication for SLNB in melanoma is newly diagnosed primary melanoma with a thickness of at least 0.8 mm (rounded up from 0.75 mm) and clinically normal regional lymph node basins. These tumors are classified in the eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system as clinical stage I/II disease, with the tumor stages ranging from T1b to T4b (AJCC stages IB-IIC). The overall risk for sentinel lymph node involvement is approximately 20% (ranging from 8% to 55%), and increases as the tumor stage increases in an almost linear fashion. In addition, we may selectively perform SLNB in patients with category T1a (<0.8 mm) disease if at least 2 or 3 mitotic figures are identified on histologic examination, or if another adverse pathologic sign—such as lymphovascular invasion or an extensively involved deep margin on the biopsy specimen—is present. The risk for the presence of microscopic disease in the sentinel lymph nodes is greater in this subgroup of patients with relatively thin melanomas than in most of the remaining patients with stage T1a disease. In such cases, the risk for finding sentinel lymph node positivity is somewhere between 8% and 12%, similar to what we find in patients with tumors in the T1b to T2a category. Generally, the SLNB is performed in the same surgical setting as the formal wide excision used to treat the primary tumor. Together, these procedures represent the current standard of care for this patient population.

The preceding criteria have been established and promoted as practice guidelines by expert consensus panels, including the American Society of Clinical Oncology, the Society of Surgical Oncology, and the National Comprehensive Cancer Network. Although these guidelines represent the current standard of care, it should be noted that the overall chance of finding sentinel node positivity is approximately 20%, meaning that 80% of the stage I/II patients who undergo this procedure are found to have no microscopic lymph node involvement and therefore are subjected to the cost and morbidity of a potentially unnecessary surgical procedure. Therefore, interest has emerged

in establishing noninvasive methods of predicting the presence or absence of microscopic nodal disease. Predictive models of clinicopathologic features combined with a novel gene expression profile of the primary tumor have been developed. Prospective evaluation of these promising predictive models is currently ongoing to determine if we may be able to recommend SLNB more selectively.

Other "soft" criteria exist for indicating when to consider SLNB. For example, we sometimes conduct a second SLNB in someone who was previously treated for melanoma and later has a local recurrence. A prior SLNB does not preclude the accurate performance of another procedure, which may reveal a lymphatic drainage pattern different from that found in the earlier SLNB.

H&O What are the standard techniques used for SLNB?

MR Most commonly, a dual-modality approach is used, in which a visible blue dye (isosulfan blue or methylene blue) and a radioactively labeled compound, such as technetium ^{99m}Tc sulfur colloid or technetium ^{99m}Tc tilamocept, are combined. The agents are injected into the biopsy site or just adjacent to the tumor, where they are taken up by the dermal lymphatics. Injection of the radioactive agent allows us to identify the location of the sentinel lymph node transcutaneously with a handheld gamma detection probe before the incision is made. The blue dye facilitates visual detection as it accumulates in the sentinel nodes.

In anatomic regions where the lymphatic drainage pattern is likely to be unpredictable or ambiguous, such as the head and neck or the trunk, we routinely perform lymphoscintigraphy (a lymphatic scan) preoperatively. This technique provides an anatomic roadmap of the pattern of lymphatic drainage, so that the surgeon knows which lymph node basin or basins to examine in the operating room. The same radioactive material is injected that is used for SLNB. Because lymphoscintigraphy can be done on the same day as surgery, the radioactive component has already been taken care of, and only the blue dye needs to be injected in the operating room.

H&O Have any recent advances been made in SLNB technique?

MR SLNB is an elegant procedure that works well with the agents that we already have, so it has been difficult to improve it further. Some surgeons are using compounds containing fluorescein for internal SLNB identification during laparoscopy for cervical, uterine, or gastric cancer, but these are not used in melanoma. In addition, a magnetic compound called Magtrace (Endomagnetics) has been approved for use in breast cancer and is currently being studied in melanoma. Magtrace can be visualized when it accumulates in lymph nodes, and it also produces a magnetic field that is detectable with a handheld probe.

The indications for completion lymph node dissection have been something of a moving target.

H&O When is completion lymph node dissection indicated?

MR The indications for completion lymph node dissection (CLND) have been something of a moving target. Until recently, the consensus standard of care was to perform a formal CLND routinely as a second surgical procedure after a positive sentinel lymph node had been found. The rationale for this approach was to remove other nodes in the same basin that might contain additional microscopic disease, so as to prevent progression from microscopic to macroscopic (clinically palpable) disease. Additional positive nodes (non-sentinel nodes) are seen in an approximate average of 15% to 20% of cases, with a widely ranging incidence that depends on a constellation of clinicopathologic features (discussed below). Because only patients with additional microscopically involved nodes can derive benefit from a formal dissection, and because the procedure entails costs and morbidity, researchers have been interested in determining what role routine CLND plays in disease outcome beyond what is achieved by SLNB. To address these concerns formally, 2 prospective, randomized trials—MSLT-2 and DeCOG-SLT—randomly assigned patients with a positive sentinel node to CLND or to observation that included surveillance with ultrasound of the nodal basin. Both trials showed no melanoma-specific survival advantage with CLND. A recent update of DeCOG-SLT, with a few additional years of follow-up, further supported the original results. The MSLT-2 trial did, however, demonstrate significant improvement in regional disease control with CLND. A plausible explanation of why improved regional disease control did not translate into improved melanoma-specific survival is found in this same study. MSLT-2 showed that the presence of additional positive nodes (non-sentinel

node involvement) was the most powerful predictor of eventual distant disease recurrence and therefore poor survival outcome; the finding of additional positive nodes identified a subset of patients whose disease, because of unfavorable biology, was not treatable by surgical resection. In other words, most of the patients participating in these trials likely derived any surgery-related survival benefits from the SLNB itself, with CLND adding little if any survival advantage. A limitation of both these trials is that they were biased toward relatively low-risk patients because the treating physicians were not inclined to enroll patients at high risk for additional positive nodes. Despite this limitation, neither of the studies provides even a hint of improvement in survival with CLND.

These trials have been practice-changing; we no longer routinely perform CLND after SLNB in most situations. We still consider CLND in certain high-risk patients, however, such as those with a relatively thick primary tumor, multiple positive sentinel nodes, or a large burden of microscopic disease in the sentinel nodes, for the purpose of improving regional disease control. All these factors are predictors of the presence of additional positive nodes in the same basin (see below), and therefore of regional basin failure. The guidelines from the National Comprehensive Cancer Network give us leeway to offer CLND on a selective basis. Other clinical situations in which CLND might be offered arise when a patient lacks access to active surveillance programs that include ultrasound of the index nodal basin(s), or when a patient who could benefit from systemic adjuvant therapy is unable to tolerate predicted side effects because of underlying comorbidities.

H&O What are the risks and disadvantages of CLND?

MR We see both short- and long-term surgical morbidities. Potential short-term morbidities include seromas, hematomas, surgical site infections, and localized numbness in the surrounding area of skin; the numbness is permanent in some cases. The most worrisome long-term side effect is lymphedema.

The location of the nodal basin is relevant to the risk. Surgical morbidity is most frequent with groin dissection and least frequent with neck dissection; morbidity with axillary dissection is somewhere in between. As a result, we lower our threshold for CLND in the neck and raise it for CLND in the groin.

Another disadvantage of performing CLND is that the use of this procedure tends to delay the initiation of recently approved effective systemic adjuvant immunotherapy or BRAF/MEK-targeted therapy. We have some data suggesting that the early initiation of adjuvant therapy is important in terms of preventing disease recurrence. If CLND is deemed important for regional disease control, one way around this problem is to administer a couple of cycles of adjuvant therapy before CLND to patients who are likely to have additional positive nodes.

H&O How often does CLND reveal metastasis to non-sentinel nodes?

MR The risk depends on how many sentinel lymph nodes are removed, the thickness of the primary tumor, and the volume of disease in the sentinel node. The more sentinel nodes we remove, the less likely we are to find additional positive nodes, so that is a negative predictive factor—meaning we are less likely to find additional involved nodes. Thicker primary tumors and sentinel nodes with larger volumes of microscopic disease are positive predictive factors. If the predicted risk for additional positive nodes is higher than the predicted risk for distant disease, I strongly recommend that CLND be considered.

H&O How have advances in adjuvant therapy altered the approach to CLND?

MR An important question that remains is how effective adjuvant therapy might be for treating residual microscopic lymph node disease in patients who do not undergo CLND. The reason is that the randomized trials of targeted therapy and immunotherapy that led to the approval of these agents in melanoma—specifically, COMBI-AD, CheckMate 238, and KEYNOTE-054—mandated that all patients receive CLND after detection of a positive sentinel node. All these trials were performed before we had the survival results of the CLND trials described above. If we assume that the effect on residual microscopic disease in the lymph nodes is the same as the effect in treating distant micrometastatic disease, we should observe a 50% reduction in clinical nodal failure. A subsequent adjuvant therapy trial, CheckMate 069, evaluated the use of combination checkpoint blockade vs single-agent checkpoint inhibition in node-positive patients, whether they had clinical or microscopic nodal involvement (NCT01927419). This trial did not mandate CLND in patients with microscopic node-positive (sentinel lymph node–positive) disease, but it did mandate a formal therapeutic node dissection for patients with gross or palpable nodal disease. Long-term results of this trial should provide interesting insights into the effectiveness of adjuvant immunotherapy in controlling regional disease in those patients who did not undergo CLND.

H&O What important studies are ongoing or would you like to see conducted?

MR There was talk about conducting a trial in patients with head and neck melanoma because they were underrepresented in the 2 CLND trials. Conducting SLNB can be tricky in these patients because the lymphatic drainage patterns are ambiguous and the sentinel lymph nodes are often in difficult locations, such as near the facial or spinal accessory nerves. Most studies show a slightly elevated false-negative rate in such cases, which increases the likelihood that microscopic disease will be left behind. A specific trial has never been conducted, however, and I would still like to see these patients studied.

An important area of study is the use of gene expression profiling to improve our ability to prognosticate in patients with a positive sentinel node in terms of risk for distant recurrence of disease. A couple of profiles are being studied that may be linked to a reduced likelihood of recurrence, in which case patients could be spared the toxicity of adjuvant therapy. The addition of gene expression profiling to standard clinicopathologic features has the potential to provide a better assessment of the risk for recurrence. The tests that are being examined are DecisionDx-Melanoma from Castle Biosciences and MelaGenix from NeraCare.

H&O What advances can we look forward to in the treatment of patients with regional lymph node metastases?

MR Although the widespread appropriate use of SLNB has significantly reduced the number of patients in whom resectable advanced regional (stage III) lymph node metastases develop, we still encounter this clinical scenario with some frequency in a highly heterogeneous group of patients. The current usual scenarios include the following: patients who present with locally advanced primary disease and synchronous palpable nodal disease, those with metastatic lymph node disease without a known primary tumor, those who were not offered SLNB despite being candidates, those with recurrent disease who did not receive a CLND and either did or did not receive systemic adjuvant therapy, and finally, lymph node metastases that develop in a small number of patients after they have been appropriately treated with wide excision alone for T1a melanomas. Outcomes in these groups are relatively poor despite treatment with the current standard of up-front lymphadenectomy followed by systemic adjuvant therapy. As a result, they have been the focus of novel neoadjuvant strategies in which effective systemic therapy is initiated for 8 to 12 weeks before formal surgical resection, which is followed by a formal postoperative adjuvant phase. As mentioned earlier, one of the many potential benefits of such an approach is avoiding delay in initiating systemic therapy.

Regarding the use of neoadjuvant therapy in patients with advanced (clinically palpable) but resectable stage III regional lymph node metastases, the most important study to date has been a pooled analysis of 6 trials from the International Neoadjuvant Melanoma Consortium, recently published in *Nature Medicine*. This analysis, which encompassed 192 patients, found a pathologic complete response (pCR) in 40% of patients receiving immunotherapy and 47% of patients receiving BRAF/MEK-targeted therapy. The major finding of the study was that a pCR serves as a surrogate for improvement in long-term outcome, which is most pronounced in patients who achieve a pCR after immunotherapy. The goals of subsequent ongoing trials are to improve the pCR rate, identify biomarkers for pCR as well as immunotherapy resistance, and look at the possibility of limiting the extent of surgery or completely avoiding surgery in the context of pCR. In addition, a fundamental proof-of-concept randomized trial of standard up-front surgery followed by adjuvant therapy vs a neoadjuvant approach with the same systemic treatment is actively accruing patients. The goal is to solidify a new standard paradigm of care for patients with advanced regional disease.

Disclosure

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Suggested Readings

Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563-585.

Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376:2211–2222.

Gershenwald JE, Andtbacka RH, Prieto VG, et al. Microscopic tumor burden in sentinel lymph nodes predicts synchronous nonsentinel lymph node involvement in patients with melanoma. *J Clin Oncol*. 2008;26(26):4296-4303.

Gershenwald JE, Ross MI. Sentinel-lymph-node biopsy for cutaneous melanoma. *N Engl J Med*. 2011;364(18):1738-1745.

Leiter U, Stadler R, Mauch C, Hohenberger W; German Dermatologic Cooperative Oncology Group. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT) a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2016;17:757–767.

Leiter U, Stadler R, Mauch C, Hohenberger W; German Dermatologic Cooperative Oncology Group. Final analysis of DeCOG-SLT trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. *J Clin Oncol*. 2019;37(32):3000-3008.

Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med*. 2021;27(2):301-309.

Mulder E, Dwarkasing JT, Tempel D, et al. Validation of a clinicopathological and gene expression profile model for sentinel lymph node metastasis in primary cutaneous melanoma. *Br J Dermatol*. 2021;184(5):944-951.