Sentinel Lymph Node Biopsy Still Provides No Benefits for Patients With Melanoma

INTRODUCTION

The procedure of sentinel lymph node biopsy (SLNB) is based on an outdated and flawed concept of melanoma spread, namely the "incubator hypothesis," first put forward in 1892 by an English surgeon named Herbert Snow, who proposed that melanoma cells always implicate the nearest lymph glands, which he called "traps." His belief that the melanoma cells would rest in the lymph nodes for a time led him to recommend elective node dissection before the nodes become palpable.[1] For over a century, the complete lymph node dissection (CLND) became the standard of care for melanoma treatment, despite randomized trials since 1977, which showed no survival benefit.[2,5–7]

In 2003, Ackerman stated eloquently that the belief in the "incubator hypothesis" is unfounded,[3] and he stressed that lymph nodes are not "traps," but rather "filters" which sample cells as they pass into the circulation.

Subsequently, there has been much more evidence against the "incubator hypothesis" and support for the opposing view, known as the "marker hypothesis," whereby metastasis occurs simultaneously through lymphatic and hematogenous routes.[4]

The first large trial to give strong evidence against the "incubator hypothesis" was published in 2014, being the final 10-year follow-up report of the Multicenter Selective Lymphadenectomy Trial I (MSLT-1). This landmark trial failed to demonstrate a significant difference in the overall survival rate or in the melanoma-specific survival rate for patients who were SLNB-positive and went on to have CLND.[8]

Unfortunately, however, in their reporting of the results, the authors chose to focus on terms such as "disease-free survival" in a postrandomization subgroup of patients. Despite these claims being clearly shown to be a result of lead time bias and inappropriate subgroup analysis,[9] patients continued to be told that SLNB and CLND confer survival benefits, and the rates of these surgeries did not decrease at most centers.

Then in 2017 came the most powerful evidence so far against the "incubator hypothesis" when the results of the multicenter selective lymphadenectomy trial II (MSLT-II) were released and conclusively demonstrated that immediate CLND did not increase overall or melanoma-specific survival compared with observation and delayed CLND, even among patients with melanoma and positive sentinel nodes.[10] These results proved once and for all that SLNB followed by CLND has no survival value.

Yet, rather than sounding the death knell for SLNB, the enthusiasm for SLNB by its supporters continues unabated, if not stronger than ever.

The support for SLNB today is based on the following 2 claims; its purported value as "the most powerful prognostic marker for melanoma patients" and by extension, its value in "accurately staging" patients, and its necessity for patients to access the new immunotherapy drug trials.

Both of these claims are based on false premises.

The oft-repeated claim that SLNB is the most powerful prognostic criterion is mostly based on the authors of MSLT-1 comparing HR for Breslow thickness (BT) of 1-mm increments to the HR for SLNB survival.[8]

However, as we have explained previously,[11,12] hazard ratios should not be compared in this way, and in fact, if we use this logic, the data suggest that BT is a better indicator than lymph node status in predicting overall death from melanoma when different increments rather than 1 mm are used.

Recently, a retrospective cohort study assessed prognostic value of SLNB status versus BT on the 5-year overall survival rate in 896 patients who underwent SLNB for primary cutaneous melanoma. The authors concluded that "SLNB status does not provide

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additional prognostic information beyond BT. Practitioners should acknowledge the limited prognostic and therapeutic value of SLN biopsy when engaging patients in shared decision making."[13]

This study was highlighted in a systematic review, which listed SLNB as an example of medical overuse in dermatology.[14,15]

Other univariate markers of prognosis for melanoma include BT, ulceration, and gene expression profiling. These are noninvasive being derived from the primary tumor not the regional lymph nodes.

Multivariate analysis, area under the curve (receiver-operating characteristic) analysis has shown that the prognostic ability of SLNB can be matched and indeed surpassed by a pooling of data or indeed just the use of BT from the primary tumor alone.[14]

The other frequent claim that SLNB is "necessary for accurate staging" is also based on a false premise.

It has been shown repeatedly, including by MSLT-1, that only 15%–20% of melanoma patients have a positive SLNB, meaning it will be negative for most patients.

Therefore, most patients with melanoma will have a negative SLNB, and most deaths from melanoma therefore occur in patients with a negative SLNB.

The test-performance characteristics of SLNB are in fact, quite poor. The 10-year data from MSLT-1 showed that, of 179 sentinel node-positive patients, 69 (39%) died of melanoma. Of the 759 SLNB-negative patients, 119 (15.6%) died of melanoma. This translates to a sensitivity of 36% and a positive predictive value of 38% for the SLNB, which are very poor characteristics for any diagnostic test.

Therefore, why should physicians continue to recommend this test for their melanoma patients, if it will be negative for at least 80% of them, and, even when positive, 61% of these patients will still be alive after 10 years?

Consider what benefit will an individual patient with superficial melanoma gain from SLNB? Most patients diagnosed with melanoma are afraid and are not interested in theoretical staging curves for research purposes.

They simply want an estimate of their prognosis and any treatment that may treat their cancer. A further operation of sentinel lymph node biopsy will not help either of these concerns, but it will put them at 6% risk of lymphedema, in addition to other morbidities.[10]

Our individual patients will obtain adequate prognostic information from BT and from high-resolution ultrasound of their nodal basins, and we know that sentinel node status is highly correlated with BT.[16]

The important question is what additional prognostic information is provided by SLNB above and beyond the clinical and pathological features of the tumor and do they outweigh the cost (around €10,000 in Spain from 2007 to 2010 and $14,000 to $18,000 in the United States in 2018) and morbidity of the procedure (6% incidence of lymphedema).[17,18]

The second main justification for SLNB as a staging procedure is that it is required for patients to be stratified and entered into trials of new drugs for the prevention of melanoma progression.

The paradox seen in the current entry criteria for melanoma trials is that intermediate-thickness melanoma patients with a positive SLNB will be entered into trials while patients with thick melanomas, who on Breslow alone, have a worse prognosis, with a negative SLNB will be excluded. Currently, the trials proposed by the SLNB/pharmaceutical lobby do not contain a wing of non-SLNB patients who by BT or multivariate analysis have a similar prognosis.

The proponents of SLNB now say that SLNB is justified and necessary for all melanoma patients with a BT of 1 mm or more or for BT greater than 0.8 mm with ulceration. The justification they give is that the new immunotherapy drugs have reduced the rate of relapse-free survival, and some have even prematurely used the word "cure."

This claim is unjustified based on the current evidence and is mostly based on the following study:

Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma.

G.V. Long et al. *N Engl J Med* 2017;377:1813–23.

This pharmaceutical company sponsored article covers all melanoma stages between III A–C, and only 18% of enrolled patients had stage IIIA disease. All had completion lymphadenectomy. It is heavily skewed to more advanced or unresectable melanoma cases and also to the subgroup who are BRAF mutation positive. These patients are clinically completely different to the microscopic disease SLNB recognizes, and therefore, the trial patients do not reflect most melanoma patients who will be subjected to SLNB and immunotherapy if positive. And the overall survival results did not reach the nominated significance level.

Given the high rate of significant morbidity and 1% mortality of some regimens, it is imperative to choose patients with a high risk of recurrence and death for adjuvant trials.

In the above-mentioned trial alone, 64% of patients in the treatment arm experienced adverse effects, which required dose reduction or discontinuation of the drugs.

Most physicians and patients would agree that patients with advanced metastatic melanoma should be given the immunotherapy drugs, to delay recurrence and improve relapse-free survival.

The big question is whether patients with early disease, with no lymph node disease detectable clinically or by ultrasound, will benefit from immunotherapy and therefore whether SLNB is a necessary procedure, given all its deficiencies and shortcomings.

For more than a century, surgeons considered that CLND was the standard of care for melanoma patients and continued to perform the surgery, despite lack of evidence for its efficacy in overall survival. After the introduction of SLNB, CLND was standard of care in SLNB-positive patients.

The definitive study that finally convinced surgeons in melanoma centers to stop performing CLND in SLNB-positive patients was MSLT-II because this was a good-quality, randomized controlled trial with a "placebo" arm where SLNB-positive patients were observed for recurrence.

Unfortunately, the same study design using a placebo arm in early melanoma or IIIA melanoma patients who have microscopic disease only (SLNB positive) has not yet been performed for immunotherapy drugs, but it is essential for this to occur. Otherwise, how is the public and the medical community to know the truth about the efficacy of immunotherapy in patients with early melanoma?

There are serious negative consequences to the indiscriminate and non–evidence-based use of SLNB and immunotherapy drugs in all patients with early melanoma. In addition to the adverse effects of the drugs, there is a huge financial cost to both patients and taxpayer of the drugs, and this is compounded when the cost of SLNB is added.

If SLNB is NOT the most powerful predictor of prognosis,[11,12] then patients should receive the drugs based on other prognostic criteria, such as BT or ultrasound evidence of lymphatic involvement.

Research to improve ultrasound monitoring of lymph nodes is underinvestigated and is underutilized in many countries. In experienced hands, high-resolution ultrasound can now detect very small melanoma deposits in lymph nodes (1- to 2-mm size), and melanoma-specific survival is not compromised in patients who do not undergo SLNB.[19]

In addition, research funds should now be channeled into improving the prognostic data from the new gene profiling technologies, which are already available.

As physicians, our duty is to first do not harm. Our patients deserve information based on honest informed consent and therapy that is properly based on high-quality evidence.

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