

**TITLE: Sentinel Lymph Node Biopsy in Melanoma of the Head and Neck**

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## **Introduction**

The incidence of melanoma is rising more rapidly than any other malignancy. The National Comprehensive Cancer Network report that in the year 2007, an estimated 59,940 new cases of melanoma will be diagnosed and about 8119 patients will die of the disease in the United States. They report that although melanoma is the fifth and sixth most common malignancy in men and women, respectively, melanoma ranks second to leukemia in terms of loss of years of potential life, per death. The median age at diagnosis is 45-55 years.

## **Diagnosis**

The history should include details such as bleeding, itching, ulceration, pain. A history of dysplastic nevi or a family history of melanoma should also be sought. Risk factors for melanoma include strong family history, pigmented lesions, multiple clinically atypical moles or dysplastic nevi and inherited genetic mutations. Individuals with an inability to tan and a fair skin that sunburns easily have a greater risk of developing melanoma. Sun exposure may also play a contributing role, however any ethnic group and those without substantial sun exposure can develop melanoma. Unlike other cutaneous malignancies, melanoma has been associated with brief intense exposures of actinic exposure versus chronic exposure.

The physical exam should cover the standard ABCD's, as well as assess for other nevi. Common sites of presentation include sun exposed areas such as the arms and legs, as well as the back for men and the scalp for thin or balding patients. If a family history of melanoma is present, the physical should include all sun shielded areas as well, since melanomas can arise with minimal sun exposure.

- A – Asymmetry
- B – Border irregularities
- C – Color variegation
- D – Diameter (increase or > 6mm)

Any suspicious lesion requires a histologic examination. It is recommended that small lesions undergo *excisional* biopsy with 1-2 mm margins. Exceptions can be made for critical areas where minimal tissue removal is preferable. Excisional biopsy is not recommended for larger lesions due to deformity before diagnosis, and possible alteration of lymph draining patterns that may be needed later for sentinel lymph node mapping. It is also not recommended for lesions on the face. When excision is not performed, a full-thickness incisional or a punch biopsy is recommended to assess the depth of the lesion. Needle and shave biopsies should not be done.

For the *depth* of resection of thin lesions, a deep margin of subcutaneous tissue has been described. For intermediate thickness lesions, depending on the location, deep margins include all the subcutaneous tissue down to the underlying fascia. In the scalp, the galea may be left intact to allow for skin grafting. For melanomas greater than 4-mm in thickness, depending on the location and greatest thickness, resection of the underlying facial muscles as well as the galea and pericranium may be necessary to achieve a safe deep margin. After proper resection has been achieved, the surgeon must determine the status of the surgical margins.

The pathology report should include Breslow thickness, ulceration status, Clark level, as well as deep and peripheral biopsy margin status. Ulceration has been found to be an independent predictor of outcome for primary melanoma and has been incorporated into the AJCC staging system.

## Staging

Both the Clark and Breslow systems are commonly used in the staging of the primary lesion. The Clark stage is based on the tissue level of invasion, and absolute depth may differ depending upon the region of the body involved. The Breslow system is based upon the absolute depth, and has been shown in several studies to be the more reliable factor in predicting outcome. The definition of the levels in each system is given below.

### Clark

Level I Involves only the epidermis

Level II Involves the basal layer and extends into the papillary dermis

Level III Involves the papillary dermis to the boundary of the reticular dermis

Level IV Involves the reticular dermis

Level V Involves the subcutaneous tissues

### Breslow

Stage I < 0.75 mm

Stage II 0.75 – 1.5 mm

Stage III 1.5 – 4.0 mm

Stage IV > 4.0 mm

As with nearly all malignancies, the outcome of melanoma initially depends on the stage at presentation. The National Comprehensive Cancer Network report that, in general, the prognosis is excellent for patients with localized disease and primary tumors 1.0 mm or less in

thickness, with long-term survival achieved in more than 90% of patients. For patients with melanomas greater than 1.0 mm in thickness, survival rates range from 50-90%.

The likelihood of regional nodal involvement increases with increasing tumor thickness. When regional nodes are involved, survival rates are roughly halved. However, within stage III, 5 year survival rates range from 10-60%, depending on factors such as nodal tumor burden. Long-term survival in patients with distant metastases is roughly 10%.

### **AJCC Staging Summary**

Stage 0 – in situ

Stage IA – (low-risk primary), 1.0 mm thick or less without ulceration, Clark level II-III

Stage IB – (intermediate-risk primary), 1.0 mm thick or less with ulceration, or Clark level IV-V

Stage II – (high-risk primary), greater than 1.0 mm in thickness, with any characteristic and clinically negative nodes

Stage III – sentinel node positive, or clinically positive nodes

Stage III – in-transit nodes (In transit metastasis is > 2 cm from primary but not beyond the regional lymph nodes).

Stage IV – distant metastatic disease

## **Treatment**

### **Stage 0**

Surgical excision with 0.5 cm margins. No further workup is needed. No neck dissection or lymph node biopsy is recommended due the low incidence of metastasis.

### **Stage I**

Surgery is the only recommended treatment. For these thin lesions, margins of 1 - 2 cm are acceptable. Minimal workup, including chest x-ray, can be optionally performed to rule out metastasis for IB lesions, as this test is insensitive. Sentinel lymph node biopsy should be encouraged especially in patients with IB disease.

### **Stage II**

Workup for stage II lesions includes optional CXR as with stage IB lesions. Some authors recommend lymph node mapping and a CT metastatic workup in cases such as ulcerative lesions or recurrent disease. The treatment of stage II lesions is probably the most complicated. This difficulty stems from the significant percentage of occult metastasis present with these lesions. While higher stage lesions require more complex and invasive therapies due to their obvious clinical findings, treatment of stage II lesions involves controversial therapies with inherent morbidity to treat a low yet statistically significant percentage of metastasis. The primary therapy for stage II lesions is surgical, with a wide local excision and 2 cm margins. Sentinel lymph node biopsy should be encouraged to look for occult metastasis.

Elective neck dissection has been used frequently in stage II lesions. One of the inherent difficulties with this method is defining the route of lymph drainage. Tumors of the occipital

area and the posterior scalp (separated by a vertical line through the EAC), are considered to drain posteriorly into the postauricular and suboccipital nodes. These lesions should undergo a posterolateral neck dissection. Lesions on the forehead and scalp anterior to the line are believed to drain into the periparotid and upper jugular nodes. A dissection for these lesions should include a parotidectomy and a lateral neck dissection. Lesions which arise on the anterior face generally spread to the submental, submandibular, and deep cervical nodes. A supraomohyoid neck dissection is generally recommended.

Sentinel lymph node biopsy is a relatively new technique, developed in the early 1990s. Recent studies have shown that using a combination of dye and a radioisotope can yield first order lymph nodes in > 95%. These studies have also shown that the status of the sentinel lymph node highly correlates with the metastatic status and overall outcome of the patient. However, many of the current studies cited involve regions other than the head and neck. It has also been shown that a learning curve exists for adequate performance of this procedure. This will be discussed in more detail later.

Myers et al (2004) stated that although elective neck dissection for the clinically negative neck is still an option for patients with intermediate thickness (1–4 mm) lesions, they favor radiotherapy or sentinel lymph node biopsy. In their opinion, the only formal indication for neck dissection in CMM of the head and neck is the presence of clinically or radiographically positive lymphadenopathy.

### **Stage III**

Stage III lesions have clinically positive nodes, have positive sentinel nodes, or harbor in-transit nodal disease. The workup of these lesions includes optional CXR and LDH for occult disease, and a CT of the neck. For clinically positive neck, suspicion of regional metastatic disease, preferably with either fine needle aspiration biopsy or open biopsy of the clinically enlarged lymph node. A CT to evaluate for distant metastasis should be considered. The surgical excision should attempt 2 cm margins. If a node is present distant to a lesion, all in-transit node basins should be addressed. This means for lesions of the temple, cheek, or anterior scalp region, a parotidectomy should be performed. As mentioned before, an appropriate neck dissection, i.e. posterolateral, lateral, or supraomohyoid, should be performed. Radiotherapy has been shown to decrease local recurrence rates. Chemotherapy may be considered.

### **Stage IV**

Workup for these lesions includes CXR, LDH, CT of the abdomen, MRI of the brain, and some recommend a CBC and liver panel. Primary excision with 2 cm margins should be attempted. Radiotherapy for local control should be considered. Chemotherapy for palliation should be considered.

For all types of cancer it is known that occult metastasis may exist in the absence of clinically identifiable disease. In cases such as melanoma, where the presence or absence of these metastases will drastically affect the course of treatment and the prognosis, diagnostic SLNB is often employed. Before sentinel node biopsy was used, the alternatives were neck dissection, which has inherent morbidity, or clinical follow-up. SLNB has the benefit of

allowing for pathologic analysis of the first order lymph nodes while incurring minimal surgical morbidity.

Sentinel lymph node biopsy (SLNB) is based on the principle that the sentinel lymph node is the first node to receive drainage from the primary tumor and is therefore at highest risk for metastasis. This procedure is a staging procedure wherein patients are selected who would potentially benefit from further treatment. Although SLNB for melanoma arising in the head and neck region has been shown to be feasible, long-term follow-up showing that a negative SLNB accurately predicts the absence of microscopic metastasis in the neck is lacking. Therefore, our present use of SLNB is within a prospective protocol designed to address this question. Our protocol includes the following: (1) preoperative lymphoscintigraphy; (2) intraoperative lymphatic mapping with a radiotracer; (3) separation of the SLN from its basin *ex vivo*; and (4) histologic analysis by hematoxylin-eosin and immunohistochemistry of serial sections of the lymph nodes.

The technique of SNLB involves injecting both a radioisotope and a visible dye into the area of the tumor and examining the drainage basin for dye and isotope uptake. The radioisotope is commonly Tc99, which may be injected several hours prior to surgery. Localization of this isotope is carried out intraoperatively by use of a handheld gamma counter. The dye is typically isosulfan blue, which can be injected in the operating room before the start of the procedure. Once the patient is asleep, a dissection of the first order lymph node basin is carried out, which can be guided by the gamma counter. If the radioisotope fails to localize adequately, the isosulfan dye can be tracked to the first set of stained nodes. A node is considered to be a “sentinel node” if it localizes a high amount of isotope, takes up the dye, or both. Morton developed this technique in the early 1990s. Early in the development of the SLNB technique, when only the vital dye technique was employed, the rates of identification of a sentinel node were only 60-80%, even with experienced surgeons. Today, with the combination of both methods, identification of sentinel nodes is commonly reported as 96%, as reported by Gershenwald.

Surgeons who do a sentinel-node biopsy procedure should use the information provided by preoperative lymphoscintigraphy to find and remove every node that has been identified as a definite sentinel node by the nuclear-medicine physician, and should find and check every node that has been reported as a possible sentinel node. This task is made easier and more reliable if both blue dye and radioactive colloid are used as tracers; several studies have now shown that the greatest accuracy is achieved when both agents are used for sentinel-node identification. When doing this surgery, as with the nuclear-medicine physician, the surgeon should recognize that any sentinel node can contain micrometastatic disease—not just the most intensely blue node on inspection or the hottest node on testing with a gamma probe (McMasters et al, 2002). They recommended that all blue nodes and all nodes that measure  $\geq 10\%$  of the *ex vivo* radioactive count of the hottest SLN be harvested and designated as SLNs (McMasters et al, 2001). If every sentinel node is not removed, micrometastatic disease in the regional nodes could remain undetected, which might be detrimental to the patient, who will be given incorrect information on outlook and whose chance of improved survival could be jeopardized.

Thompson et al (2005) describe that the colloid injections should be made as close as possible to the original melanoma site (ie, before excision), and should be truly intradermal and

not subcutaneous if the lymphatic pathways followed by melanoma cells traveling to regional lymph nodes from cutaneous primary sites (ie, in the epidermis and dermis) are to be identified accurately. One pitfall which can occur if sentinel lymph node excision is performed prior to complete excision of the tumor with margin is that the signal from the primary site may be too strong causing one to miss reactivity in a close lymph nodes.

In the SLN mapping technique described by Gershenwald (1999), most patients underwent preoperative lymphoscintigraphy in which  $^{99m}\text{Tc}$ -human serum albumin or  $^{99m}\text{Tc}$ -sulfur colloid was intradermally administered to establish lymphatic drainage patterns and identify those basins at risk for metastatic melanoma. Lymphatic mapping and SLN biopsy were performed after the intradermal administration of 1 to 3 mL of isosulfan blue dye around the intact tumor or biopsy site immediately before the procedure. Patients later also received an intradermal injection of 0.5 to 1.0 mCi of unfiltered  $^{99m}\text{Tc}$ -sulfur colloid 1 to 4 hours before surgery; lymphatic mapping was then performed with the aid of a hand-held gamma counter. The half-life of  $^{99m}\text{Tc}$  is 6 h.

In patients who underwent mapping of more than one basin, the basin with predominant drainage by preoperative lymphoscintigraphy was explored first. An SLN was defined as one that localized blue dye and/or concentrated radiolabeled colloid within a regional nodal basin. Each SLN was excised and submitted for pathologic analysis. All patients underwent wide local excision of the primary melanoma with margins appropriate for tumor thickness.

When micrometastatic disease is identified in a sentinel node, a completion lymph-node dissection of the regional nodes should be done. However, the probability of finding metastatic disease in additional non-sentinel lymph nodes is low (ie, <25% in most series). (McMasters, 2002)

The utility of SLNB has been under investigation since its development, specifically regarding the following areas: 1) How often are SLN's identified, 2) How often are the nodes positive for metastasis, 3) How often are positive nodes not identified by SLNB, and 4) What prognostic or treatment data can be deduced from a positive node?

In the prediction of overall survival, Gershenwald found that 3-year disease-specific survival for a negative biopsy was 96.8%, while a positive biopsy was 69.9%. While it was also found that sentinel nodes were more likely to be positive with increasing Breslow measurements (T1, T2 4.8%; T3 19.2%; T4 34.4%), covariate analysis of tumor thickness, Clark level, and status of SLNB found that the status of the sentinel node was the most significant prognostic factor for survival. Gershenwald also noted that 11% of his patients developed a recurrence following a negative sentinel node biopsy. It was noted that regional recurrence was the primary site. In 80% of the patients that had regional recurrence following negative SLNB, it was found that nodal disease was missed by conventional histologic techniques; and that the application of serial sectioning and immunostaining with S-100 or HMB-45 increases the yield. The benefits of SLN were found not to be limited only to those patients with a positive sentinel node. Those with a negative SLN comprise a favorable patient group with significantly less risk for recurrence.

In a 2005 study by Morton et al on SNB for early stage melanoma, the accuracy of lymphatic mapping and sentinel node biopsy (LM/SNB) was determined by comparing the rates of SN identification and the incidence of SN metastases in the lymphatic mapping/sentinel node biopsy (LM/SNB) group versus the subsequent development of nodal metastases in the regional nodal basin of those patients with tumor-negative SNs. Early morbidity of LM/SNB was evaluated by comparing complication rates between the 2 treatment groups. Trial accrual was completed on March 31, 2002, after enrollment of 2001 patients.

Morton et al (2005) found that the initial SN identification rate was 95.3% overall: 99.3% for the groin, 95.3% for the axilla, and 84.5% for the neck basins. The rate of false-negative LM/SNB during the trial phase, (as measured by nodal recurrence in a tumor-negative dissected SN basin), decreased with increasing case volume at each center: 10.3% for the first 25 cases versus 5.2% after 25 cases. There were no operative mortalities. The low (10.1%) complication rate after LM/SNB increased to 37.2% with the addition of CLND; CLND also increased the severity of complications. Early complications from MSLT-I were uncommon and were not increased by the addition of LM/SNB to treatment of the primary site. Complications of CLND range from those confined to the wound such as seroma, hematoma, or infection to more chronic abnormalities of dysesthesia or lymphedema

They concluded that LM/SNB is a safe, low-morbidity procedure for staging the regional nodal basin in early melanoma. Even after a 30-case learning phase and 25 additional LM/SNB cases, the accuracy of LM/SNB continues to increase with a center's experience. LM/SNB should become standard care for staging the regional lymph nodes of patients with primary cutaneous melanoma.

In a follow-up study in 2006 evaluating SNB vs nodal observation in melanoma, Morton et al found that the staging of intermediate-thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy. Their findings indicated that sentinel-node biopsy has staging and prognostic value in patients with intermediate-thickness melanoma and, when coupled with immediate complete lymphadenectomy, improves survival among patients with a tumor-positive sentinel node. They concluded that in patients with primary melanomas that are 1.2 to 3.5 mm in thickness, sentinel-node biopsy should be preferred to observation.

## **Conclusion**

Many studies have evaluated sentinel node biopsy since it was first described in the early 1990s by Morton. Lymphatic mapping/sentinel node biopsy has been found to be a safe, low-morbidity procedure for staging the regional nodal basin in early melanoma and is becoming the standard of care when evaluating early and intermediate stage melanomas. It is recommended that patients have lymphatic mapping done in conjunction with injection of dye for SLNB. Elective neck dissection has not been found to change outcome if SLNB is negative, but increases morbidity. Discussion of SLNB should be encouraged in patients with stage I and II melanoma.

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## Appendix. AJCC TNM Staging for Melanoma

<b>CLINICAL STAGE GROUPING</b>			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1