Sentinel Lymph Node Biopsy in Melanoma of the Head and Neck

Camysha Wright, MD
Faculty Advisor: Shawn Newlands, MD, PhD, MBA
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Department of Otolaryngology
The University of Texas Medical Branch at Galveston
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Melanoma

- Almost 30% of all melanomas arise in the head and neck
- Although melanoma is the fifth and sixth most common malignancy in men and women, respectively, it ranks second to leukemia in terms of loss of years of potential life, per death.
- The median age at diagnosis is 45-55 years
Melanoma

- 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.
Predisposing Factors

- Risk factors for melanoma include:
  - strong family history
  - pigmented lesions
  - multiple clinically atypical moles or dysplastic nevi
  - Individuals with an inability to tan and a fair skin that sunburns easily have a greater risk of developing melanoma.

- Sun Exposure
  - Age, frequency, severity of exposure may play a role (brief intense actinic exposure)
  - Any ethnic group and those without substantial sun exposure can develop melanoma.

- Familial Melanoma / DNS
  - Family members have almost 50% chance of developing melanoma
  - Lesions may be multiple and in sun shielded areas
Diagnosis

- **History**
  - Family History
  - Sun exposure
  - Bleeding, pain

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

- **Histology**
  - H&E
  - S-100, HMB-45 (more specific markers for melanin)
Biopsy

Excisional
- Recommended for small lesions
- Margins of 2mm

Full thickness Incisional
- For larger lesions *(due to deformity before diagnosis)*
- Lesions on face
- Does not alter draining lymphatics *(may be needed later for sentinel lymph node mapping)*

- Punch
  - Same as incisional

- Shave
  - Contraindicated

- Needle
  - Contraindicated
Biopsy

- 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.
Staging

- 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.
Clark staging

- Based upon histologic level of invasion
- Level I – Epidermis only (in situ)
- Level II – Invades the papillary dermis, but not to the papillary-reticular interface
- Level III – Invades to the papillary-reticular interface, but not into the reticular dermis
- Level IV – Into the reticular dermis
- Level V – Into subcutaneous tissue
Breslow staging

- Based upon absolute depth of invasion
- Stage I – < 0.75 mm
- Stage II – 0.76 – 1.5 mm
- Stage III – 1.51 – 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:

- 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%.
Primary Tumor (T)

TX  Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
T0  No evidence of primary tumor
Tis  Melanoma in situ
T1  Melanoma ≤ 1.0 mm in thickness with or without ulceration
T1a  Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
T1b  Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
T2  Melanoma 1.01–2 mm in thickness with or without ulceration
T2a  Melanoma 1.01–2.0 mm in thickness, no ulceration
T2b  Melanoma 1.01–2.0 mm in thickness, with ulceration
T3  Melanoma 2.01–4 mm in thickness with or without ulceration
T3a Melanoma 2.01–4.0 mm in thickness, no ulceration
T3b Melanoma 2.01–4.0 mm in thickness, with ulceration
T4  Melanoma greater than 4.0 mm in thickness with or without ulceration
T4a Melanoma > 4.0 mm in thickness, no ulceration
T4b Melanoma > 4.0 mm in thickness, with ulceration
AJCC Cancer Staging Manual, Sixth Edition – Melanoma

T4b

Ulceration

Epidermis
Papillary dermis
Reticular dermis
Subcutaneous tissue

>4 mm
Regional Lymph Nodes (N)

NX    Regional lymph nodes cannot be assessed
N0    No regional lymph node metastasis
N1    Metastasis in one lymph node
N1a   Clinically occult (microscopic) metastasis
N1b   Clinically apparent (macroscopic) metastasis
N2    Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
N2a   Clinically occult (microscopic) metastasis
N2b   Clinically apparent (macroscopic) metastasis
N2c   Satellite or in-transit metastasis without nodal metastasis
N3    Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)
Distant Metastasis (M)

MX  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
M1a Metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b Metastasis to lung
M1c Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
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<tr>
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<tr>
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</tr>
<tr>
<td>Stage IV</td>
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</tr>
</tbody>
</table>

**Note:** Clinical staging includes microstaging of the primary melanoma and clinical/radiological evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
### PATHOLOGIC STAGE GROUPING

<table>
<thead>
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<th>Stage</th>
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<td>Stage IIIB</td>
<td>T1–4b</td>
<td>N1a</td>
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<td>T1–4a/b</td>
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<td>N3</td>
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</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

*Note: Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.*
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
Staging

- 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%.
Treatment – Stage 0

- Labs
  - None
- Radiology
  - None
- Excision
  - 0.5 cm margin
- Adjunctive Therapy
  - None
Treatment - Stage I

- Labs
  - None
- Radiology
  - CXR (optional for IB)
  - Possible Lymphoscintigraphy
- Excision
  - 1-2 cm margins
- Adjunctive Therapy
  - Possible SLB (especially for IB lesions)
Treatment - Stage II

- Labs
  - None
- Radiology
  - Possible CXR
  - Possible Lymphoscintigraphy
- Excision
  - 2 cm margins
- Adjunctive Therapy
  - Possible elective neck dissection
  - Possible sentinel lymph node biopsy
  - Possible elective radiation
Elective neck dissection had been used frequently in stage II lesions. One of the inherent difficulties with this method was 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 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.
# Neck Dissection

## Location of Nodes

<table>
<thead>
<tr>
<th>Location</th>
<th>Neck dissection</th>
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<tbody>
<tr>
<td>A. Submental</td>
<td>Parotidectomy, Levels II, III and IV</td>
</tr>
<tr>
<td>B. Submandibular</td>
<td>Retroauricular, suboccipital, Levels II, III, IV and V.</td>
</tr>
<tr>
<td>C. Preauricular</td>
<td>Level I, II and III.</td>
</tr>
<tr>
<td>D. Jugular Chain</td>
<td>Levels (I), II, III, IV and V.</td>
</tr>
<tr>
<td>E. Occipital</td>
<td>Levels II, III, IV and V.</td>
</tr>
<tr>
<td>F. Posterior Cervical</td>
<td></td>
</tr>
<tr>
<td>G. Retroauricular</td>
<td></td>
</tr>
<tr>
<td>H. Jugulodigastric</td>
<td></td>
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<tr>
<td>I. Supraclavicular</td>
<td></td>
</tr>
</tbody>
</table>
Treatments - Stage III

- Stage III lesions have clinically positive nodes, have positive sentinel nodes, or harbor in-transit nodal disease.
- Labs
  - LDH
  - For clinically positive neck, fine needle aspiration biopsy or open biopsy of the clinically enlarged lymph node
- Radiology
  - CXR
  - CT neck
  - Possible CT abdomen, MRI brain
- Excision
  - 2 cm margins
  - Remove in-transit lymphatic basins
  - Neck dissection directed by site
    - Posterolateral vs. Lateral vs. Supraomohyoid
- Adjunctive Therapy
  - Probable radiotherapy
  - Possible chemotherapy
Treatment - Stage IV

- Labs
  - CBC, LFT’s, LDH

- Radiology
  - CT Chest, Abdomen, Pelvis
  - MRI brain

- Excision
  - 2 cm margins
  - Remove in-transit lymphatic basins
  - Neck dissection directed by site
    - Posterolateral vs. Lateral vs. Supraomohyoid

- Adjunctive Therapy
  - Radiation therapy
  - Consider chemotherapy as part of a clinical trial
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.
Sentinel Lymph Node Biopsy

- Used to determine nodal status in low-risk tumors
- Allows for limited surgical morbidity.
- Has prognostic value for patient outcome
- Multivariate analysis has shown that positive SLNB predicts survival more accurately than depth
Sentinel Lymph Node Biopsy

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.
Sentinel Lymph Node Biopsy

- 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. 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%.
Surgery of Melanoma of the Head and Neck.

- EBM rating: D
- Expert opinion, MD Anderson
- 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.
A patient with a 3-mm-thick melanoma located in the temple area, with adenopathy in the parotid gland.

In this case, the incision is designed to allow continuity of resection with the primary lesion, given its close location to the first echelon (A).

The primary lesion is removed initially with a 2-cm margin, with a depth of resection carried down to the superficial temporal fascia.

(B) A superficial parotidectomy is performed that identifies and preserves the facial nerve and each of its branches. The white arrow indicates the main trunk of the facial nerve where it divides at the pes anserinus.

A selective neck dissection is performed to remove the contents of levels II, III, and IV, and spare all the no lymphatic structures.
The approach for a 2.3-mm melanoma located on the posterior scalp for which the incision of the neck is tailored to include the primary lesion (A).

In this case, a posterolateral neck dissection is performed to remove the suboccipital and retroauricular nodes in addition to levels II-V.

(B) Upon completion of the dissection, the trapezius muscle (*) is identified and the spinal accessory nerve (arrowhead) followed inferiorly to the trapezius muscle, which it innervates. The arrow indicates the internal jugular vein.
(A,B) Preoperative lymphoscintigraphy scan of a patient with a 1.6-mm CMM of the skin overlying the left malar area.

One milliliter of technetium-99 labeled sulfur colloid is injected around the periphery of the biopsy scar in a 4-quadrant fashion.

Using a gamma camera with a low-energy, high-resolution collimator, dynamic images of the head and neck are taken 15 minutes after injection and every 30 minutes thereafter until the SLN is visualized.

At this point, transmission images of the head and neck are obtained.
Two hours before the anticipated time of operation, the patient is taken to the nuclear medicine suite, and technetium-99labeled sulfur colloid is injected around the periphery of the lesion in a 4-quadrant fashion.

The patient is then taken to the operating room and transcutaneous localization of the SLN is performed with the handheld gamma probe (A).

This information, in addition to the preoperative lymphoscintigraphy, is used to determine the type of incision.

Isosulfan blue (0.2–0.5 mL) is injected within the area to be removed to avoid permanent tattooing (B), the primary lesion is removed first to decrease background counts (C-D).
In this patient, a subplatysmal skin flap is elevated (A, arrows) and the greater auricular nerve (B, arrow) preserved as it passes over the sternocleidomastoid muscle.

The sentinel lymph node is identified either by concentration of radiolabeled colloid with the hand-held gamma probe (C) or by direct visualization of the blue dye-stained node.

Each SLN is resected and ex vivo counts recorded.

If the SLN cannot be directly identified because of its small size, encasement in fibro fatty tissue, or other factors, the complete lymph node level is excised and the SLN identified ex vivo.

They performed a comprehensive neck dissection that included all the predicted lymph nodes at risk. (D)
Multi-Institutional Melanoma Lymphatic Mapping Experience: The Prognostic Value of Sentinel Lymph Node Status in 612 Stage I or II Melanoma Patients.


- EBM rating: C
- Retrospective analysis
- Compared the effect of pathologic sentinel lymph node (SLN) status with that of other known prognostic factors on recurrence and survival in patients with stage I or II cutaneous melanoma
- Reviewed the records of 612 patients with primary cutaneous melanoma who underwent lymphatic mapping and SLN biopsy between January 1991 and May 1995 to determine the effects of:
  - tumor thickness, ulceration, Clark level, location, sex, and SLN pathologic status on disease-free and disease-specific survival.
In the 580 patients in whom lymphatic mapping and SLN biopsy were successful, the SLN was positive by conventional histology in 85 patients (15%) but negative in 495 patients (85%).

Gershenwald found that 3-year disease-specific survival for a negative biopsy was 96.8%, while a positive biopsy was 69.9%.

Use of S-100 or HMB-45 increased the diagnostic value and was thought to lower the false negative rate.
Multi-Institutional Melanoma Lymphatic Mapping Experience: The Prognostic Value of Sentinel Lymph Node Status in 612 Stage I or II Melanoma Patients.
Multi-Institutional Melanoma Lymphatic Mapping Experience: The Prognostic Value of Sentinel or II Melanoma Patients.

- Concluded that lymphatic mapping and SLN biopsy is highly accurate in staging nodal basins at risk for regional metastases in primary melanoma patients and identifies those who may benefit from earlier lymphadenectomy.

- Pathologic status of the SLN in these patients with clinically negative nodes is the most important prognostic factor for recurrence.
Sentinel Node Biopsy or Nodal Observation in Melanoma.

- EBM rating: A
- Prospective, multicenter, international trial MSLT-1
- Patients with a primary cutaneous melanoma were randomly assigned to:
  - wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or
  - to wide excision and sentinel-node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy
Sentinel Node Biopsy or Nodal Observation in Melanoma.

- Patients were stratified according to
  - Breslow thickness (1.20 to 1.79 mm vs. 1.80 to 3.50 mm) and
  - Tumor site (arm or leg vs. other site) of the primary melanoma.

- Some patients were unable to continue in the study because of relocation, insurance problems, or other illness.
Sentinel Node Biopsy or Nodal Observation in Melanoma.

- Among 1269 patients with an intermediate-thickness primary melanoma, the mean (± SE) estimated 5-year disease-free survival rate for the population was 78.3 ± 1.6% in the biopsy group and 73.1 ± 2.1% in the observation group.

- Five-year melanoma-specific survival rates were similar in the two groups (87.1 ± 1.3% and 86.6 ± 1.6%, respectively).

- In the biopsy group, the presence of metastases in the sentinel node was the most important prognostic factor; the 5-year survival rate was
  - 72.3 ± 4.6% among patients with tumor-positive sentinel nodes and
  - 90.2 ± 1.3% among those with tumor-negative sentinel nodes.
The incidence of sentinel-node micrometastases was 16.0% (122 of 764 patients), and
The rate of nodal relapse in the observation group was 15.6% (78 of 500 patients).
The corresponding mean number of tumor-involved nodes was 1.4 in the biopsy group and 3.3 in the observation group, indicating disease progression during observation.
Among patients with nodal metastases, the 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed.
Concluded that the staging of intermediate-thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel-node biopsy provided important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy.
Sentinel Node Biopsy for Early Stage Melanoma in MSLT-I, an International Multicenter Trial.

- EBM rating: A
- Prospective, multicenter, international trial MSLT-1
- After each center achieved 85% accuracy of SN identification during a 30-case learning phase, patients with primary cutaneous melanoma (≥1 mm with Clark level ≥III, or any thickness with Clark level ≥IV) were randomly assigned in a 4:6 ratio to
  - WE plus observation (WEO) with delayed CLND for nodal recurrence, or to
  - WE plus LM/SNB with immediate CLND for SN metastasis

- MSLT-I study design.
- All patients are followed up for disease-free and melanoma-specific survival.
The accuracy of LM/SNB was determined by comparing the rates of SN identification and the incidence of SN metastases in the 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wide Excision Only (n = 782)</th>
<th>Lymphatic Mapping and Sentinel Node Biopsy (n = 1191)</th>
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<tr>
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<tr>
<td>Female</td>
<td>352 (45.0%)</td>
<td>494 (41.5%)</td>
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<td>Male</td>
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<td>697 (58.5%)</td>
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<td>543 (45.6%)</td>
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<td>Trunk</td>
<td>298 (38.1%)</td>
<td>455 (38.2%)</td>
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<td>Breslow</td>
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<td>Mean ± SD</td>
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<td>2.49 ± 1.83 mm</td>
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<tr>
<td>Median</td>
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<td>1.90 mm</td>
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<td>III</td>
<td>319 (40.7%)</td>
<td>517 (44.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>429 (54.9%)</td>
<td>630 (54.4%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>34 (4.4%)</td>
<td>44 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>233 (29.8%)</td>
<td>344 (28.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>487 (62.3%)</td>
<td>742 (62.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>62 (7.9%)</td>
<td>105 (8.8%)</td>
<td></td>
</tr>
</tbody>
</table>

*χ². NS, not significant; SD, standard deviation.
 Sentinel Node Biopsy for Early Stage Melanoma in MSLT-I, an International Multicenter Trial.

- 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.

Wound separation, hematoma, and infection were more common after graft repair than after primary closure.

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 did not evaluate the complications of delayed CLND in the WEO arm, but stated would expect a possibly higher incidence of chronic lymphedema or dysesthesia because nodal tumor burden is higher.
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.
Sentinel Lymph Node Biopsy

Conclusions

- It is recommended that patients have lymphatic mapping done in conjunction with injection of dye for SLNB
- LM/SNB is a safe, low-morbidity procedure for staging the regional nodal basin in early melanoma
- 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 IB and II melanoma
Gershenwald, Jeffrey; et al. “Patterns of Recurrence Following a Negative Sentinel Lymph Node Biopsy in 243 Patients With Stage I or II Melanoma.” *Journal of Clinical Oncology*. 16 (6), 1998: pp 2253-60.


Bibliography