Sentinel Lymph Node Biopsy in Cutaneous Melanoma—Should Not be Considered Standard of Care

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**Sentinel Lymph Node Biopsy**

- **SLNBx** is a Diagnostic, not a Therapeutic technique.
- Identifies the first node draining the area where the melanoma is located.
- Uses radioactive and/or blue dye to locate the node.
Lesions of the trunk may drain to more than one nodal basin.

In a study of 281 truncal melanomas 86 (31%) had multiple nodal basin drainage. 56 (20%) had at least 1 + SLN.

In 19 of the 86 pts (20%) pathology in one basin did NOT predict pathology in the other basins.
The Argument For Sentinel Lymph Node Biopsy in Melanoma

- The purpose of SLNBx is as a screening tool to detect clinically occult lymph node metastasis.

- Patients with positive SLNBx then go on to completion lymph node dissection to remove all nodes in the lymph node basin in order to resect any other possible metastatic disease.

HOWEVER....
NO TRIAL TO DATE HAS DEMONSTRATED AN INCREASE IN SURVIVAL FROM EITHER SENTINEL LYMPH NODE BIOPSY OR ELECTIVE LYMPH NODE DISSECTION

SLNBx in melanoma should not be considered the standard of care, but rather a investigational modality best suited to continued evaluation in randomized controlled trials to demonstrate its effectiveness.
An old debate revisited...

- SLNBx followed by Completion Node Dissection (CND) is essentially a two step approach to Elective Lymph Node Dissection (ELND)

- ELND is the prophylactic removal of all nodes in the draining basin to remove subclinical disease.

- ELND is usually compared against radical lymphadenectomy after nodes become clinically positive.

- ELND has been proven in multiple trials to have no survival benefit to patients with melanoma.

Medalie, Ackerman British Journal of Dermatology 2004; 151: 298-307
Elective Lymph Node Dissection

2001- Meta-analysis of the 3 RCTs comparing ELND to no treatment or delayed dissection

- No statistically significant difference in survival at 5 years between patients undergoing ELND and delayed or no treatment.

Meta-analysis of included randomized controlled trials comparing immediate lymph node dissection (treatment group) vs delayed or no lymph node dissection (control group) for mortality at 5 years. OR indicates odds ratio; CI, confidence interval; and WHO, World Health Organization.
MSLT-1: The Multi-center Selective Lymphadenectomy Trial

- Multi-national study of 1269 patients with intermediate depth (1.2mm to 3.5mm) primary cutaneous melanoma
- All patients underwent wide local excision
- Pts randomized to SLNBx (764) with completion lymphadenectomy for +SLN vs Observation (500) with radical lymphadenectomy for clinically + nodes
MSLT-1
No difference in melanoma specific survival with SLNBx vs Observation

![Graph showing melanoma-specific survival with SLNBx vs Observation]

- **Biopsy (96 events)**: 87.1%
- **Observation (69 events)**: 86.6%

**No. at Risk**
- Observation group: 500  446  338  177  73  9
- Biopsy group: 769  694  507  255  106  8

*P = 0.58*
If SLNBx does not increase survival, shouldn’t it at least help with prognosis?

- Melanoma specific 5 year survival
  - 90% in SN negative patients
  - 72% in SN positive patients
Prognostic information from SLNBx is practically useless.

- Individual patients are not going to be helped much by knowing their 5 year survival is 90 vs 72%.
- Oncologists have nothing to offer, regardless of prognosis.
- Without effective treatment options prognosis is irrelevant.
Interferon α has no impact on survival

- Meta-analysis of 9 IFN-α trials for stage II-III melanoma
- No overall survival benefit for treatment or the subgroups of high or low dose INF.
- 30% delay in relapse rate with high dose INF - but no impact on overall survival.
Morbidity of High Dose INF-α
Benefits and risks of high-dose interferon- 2b therapy

Benefit
- Delaying time to relapse: Median of 1 year improvement
- Being proactive: Varies with individual pt

Risk
- Decreased performance status: Virtually all patients
- Severe fatigue: 21%-24% of patients
- Severe muscle aches: 17% of patients
- Depression (mild to moderate): 40%-72% of patients
- Suicidal ideation: 0%-10% of patients
- Grade 3-4 hepatotoxicity: 27%-29% of patients
- Frequent monitoring, blood draws etc

In one study only 25% of enrolled patients received 80% or more of their calculated interferon dose.

“Among patients destined to recur, a year’s worth of HD IFN treatment can delay the time of recurrence, although for half of these patients this delay will be less than 1 year. However, the overall chance of recurrence and the overall survival is not improved. This means that, if the patient is destined to relapse and die of melanoma, HD IFN does not affect this nor does it significantly delay the time of death.”

The Oncologist, Vol. 10, No. 9, 739-742, October 2005
Systemic Adjuvant Therapy Does NOT Increase Survival

- Meta-analysis of 4 levemisole trials shows no improvement in survival
- No benefit with vaccines (9 trials)
- No benefit with chemotherapy (10 trials)
Isolated Limb Perfusion

- Does NOT Increase Survival or improve distant metastasis
- May decrease loco-regional recurrence rates or delay recurrence (10 to 17 months)
- Needs additional study
In Conclusion

- SLNBx for melanoma shows no benefit in overall mortality.
- There likely is benefit in select subgroups:
  - Pts with 1.2-3.5 mm melanomas with + nodes who go on to CND.
- SLNBx for “prognosis” is problematic because there are no effective agents to try and improve prognosis.
- SLNBx should be performed only in the setting of clinical trials until its efficacy in improving survival is established or the development of adjuvant therapy which could be administered on the basis of improving a defined prognosis.
Unanswered Questions

TNM Classification for Clinical Staging of Malignant Melanoma

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<tr>
<td>T1</td>
<td>≤ 1.0 mm</td>
<td>A: without ulceration</td>
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<tr>
<td>T1</td>
<td>B: with ulceration or Clarks’ level IV or V</td>
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<tr>
<td>T2</td>
<td>1.01-2.0 mm</td>
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<td>≥4.0 mm</td>
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<tr>
<td>N1</td>
<td>One lymph node</td>
<td>A: micrometastasis*</td>
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<td>B: macrometastasisb</td>
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<td>N2</td>
<td>2-3 lymph nodes</td>
<td>A: micrometastasis*</td>
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<td></td>
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<td>B: macrometastasisb</td>
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<td></td>
<td></td>
<td>C: in-transit met(s)/satellite(s) without metastatic lymph nodes</td>
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<td>N3</td>
<td>4 or more metastatic lymph nodes, matted lymph nodes, or combinations of in-transit met(s)/satellite(s), or ulcerated melanoma and metastatic lymph node(s)</td>
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<table>
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<tr>
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<td>Distant skin, sub-Q, or lymph node mets</td>
<td>Normal LDH</td>
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<tr>
<td>M2</td>
<td>Lung mets</td>
<td>Normal LDH</td>
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<tr>
<td>M3</td>
<td>All other visceral or any distant mets</td>
<td>Normal LDH</td>
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<td>Elevated LDH with any M</td>
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MSLT II and Sunbelt Melanoma Trial

- Evaluating need for completion lymphadenectomy in select patients with + SLNBx
- RT-PCR for detection of sub-microscopic metastasis in SLN and evaluation of need for completion lymphadenectomy in sub-microscopic disease.
TAKE HOME POINT

SLNBx in Melanoma will likely become the standard of care-

But SLNBx in Melanoma does NOT IMPROVE SURVIVAL