Is Surgery for Melanoma Obsolete?

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Disclosures

- Dr. Sondak is a compensated consultant for Array, Genentech, Merck, Novartis, Pfizer and Provectus

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PRIMARY CUTANEOUS MELANOMA

It Still All Starts With Surgery

**TUMOR**
- Tis: In situ
- T1: ≤1.0 mm
- T2: 1.1-2.0 mm
- T3-4: >2.0 mm

**SURGERY**
- 0.5 cm excision
- 1 cm excision
- 1-2 cm excision
- 2 cm excision

NCCN Guidelines for Cutaneous Melanoma
### Evidence Based Guidelines for Sentinel Lymph Node Biopsy

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mm (T1cN0)</td>
<td>No SLN Bx*</td>
</tr>
<tr>
<td>1-4 mm (T2-3cN0)</td>
<td>Recommend SLN Bx</td>
</tr>
<tr>
<td>&gt;4 mm (T4cN0)</td>
<td>SLN Bx May Be Recommended</td>
</tr>
<tr>
<td>Any positive nodes (TanypN+)</td>
<td>Complete LN dissection</td>
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</table>

* Selected patients with melanomas <1 mm may be considered for SLN Bx

Sentinel node biopsy reliably predicts recurrence and death at 5 and 10 years for intermediate thickness primary melanomas.

Cox model (adjusted for all other prognostic factors: age, gender, primary site, Breslow, Clark level and ulceration):

LN pos vs. neg hazard ratio: 2.32, 95% CI (1.62, 3.32), P<0.0001
MSLT-1 RANDOMIZED TRIAL FINAL ANALYSIS

Relapse-Free Survival
Intermediate Thickness 1.0-4.0 mm

Sentinel node biopsy decreases recurrence by preventing nodal relapse

Cox model (adjusted for all other prognostic factors: age, gender, primary site, Breslow, Clark level and ulceration):

SNB vs. WEX hazard ratio: 0.75, 95% CI (0.61, 0.90), P=0.0028

DOI: 10.1056/NEJMoa1310460
Sentinel node biopsy improves melanoma-specific survival for node-positive patients with intermediate thickness primary melanomas.

Cox model (adjusted for all other prognostic factors: age, gender, primary site, Breslow, Clark level and ulceration):

SNB vs. OBS hazard ratio: 0.55, 95% CI (0.37, 0.82), P=0.0029

10-year
- SNB Pos: 41.4 ± 5.1 %
- OBS Nodal Recurrence: 63.1 ± 4.2 %
Sentinel node biopsy identifies the overwhelming majority of patients who would require a complete node dissection anyway, with a low rate of nodal failure in sentinel node-negative patients (<4%).

Moffitt Recommendation 2017

• What are the indications for sentinel lymph node biopsy?

*Thin melanomas* (<1 mm Breslow)

Selecting patients with melanomas <1mm for SLN Bx should be **personalized** based on likelihood of long-term survival to benefit from the information, the relative risk of the procedure, and the yield of positive SLN (5% or more for a patient at low risk from the procedure, 10% or more for a patient at slightly higher risk). SLN Bx is **not indicated** for patients with cutaneous melanomas <0.8 mm (<0.75 mm) in the absence of very specific criteria.
Evidence Based Indications for Sentinel Lymph Node Biopsy

**TUMOR**

- <1 mm (T1cN0)

**SURGERY**

- No SLN Bx unless:
  - Obvious residual tumor >1mm
  - Ulcerated primary
  - Thickness ≥0.8mm plus either:
    - Mitotic rate >0
    - Patient <70 years of age
  - Positive deep biopsy margin
  - Clark's level IV-V
  - Regression

Selecting patients with melanomas <1mm for SLN Bx should be personalized based on likelihood of long-term survival, yield, and risk of the procedure.
A Question for the Ages

To dissect or not to dissect
That is the question
Are We Asking The **Right** Question?

- Does *everyone* with a positive sentinel lymph node need a completion lymph node dissection?
- Does *anyone* with a positive sentinel lymph node need a completion lymph node dissection?
- **How do we identify who really needs a completion lymph node dissection?**
Why Is A Node Dissection Useful?

• To achieve durable regional control with the least morbidity in patients for whom sentinel node biopsy alone will not...
Regional Recurrence After Sentinel Node Biopsy Without Lymphadenectomy

Retrospective review of selected patients undergoing observation after a positive SLN biopsy

Selected patients undergoing nodal observation had more nodal recurrences (31%) than patients undergoing CLND (13%, P<0.002) after a median follow-up of only 23 months.

<table>
<thead>
<tr>
<th></th>
<th>Nodal recurrence only</th>
<th>Systemic recurrence only</th>
<th>Regional disease as component of recurrence</th>
<th>Nodal disease as component of recurrence</th>
<th>Systemic disease as component of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (15)</td>
<td>20 (6)</td>
<td>34 (20)</td>
<td>26 (16)</td>
<td>21 (13)</td>
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<tr>
<td></td>
<td>13 (8)</td>
<td>89 (27)</td>
<td>65 (20)</td>
<td>23 (7)</td>
<td>90 (27)</td>
</tr>
</tbody>
</table>

*CLND* completion lymph node dissection

A significant percentage of regional nodal recurrences will occur more than 2 to 3 years after initial surgery.
Regional Recurrence After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy


![Graph showing probability of nodal recurrence-free survival over years after randomization.](image-url)
Regional Recurrence After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy

Disease-Free Survival After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – MSLT-2

Why Is A Node Dissection Useful?

• To achieve durable regional control with the least morbidity in patients for whom sentinel node biopsy alone will not
Completion lymph node dissection after a positive sentinel node biopsy has lower morbidity than “watch and wait” with LND at recurrence.

Faries et al. *Ann Surg Oncol* 2010;17:3324
Why Is A Node Dissection Useful?

• To achieve durable regional control with the least morbidity in patients for whom sentinel node biopsy alone will not

• To provide additional staging information that improves prognostication and facilitates adjuvant therapy decision-making
Non-sentinel Node Metastases Are Worse Than Sentinel Node Metastases

• “Among node-positive melanoma patients, presence of a positive non-SLN is a highly significant poor prognostic sign, even after considering the total number of positive nodes and volume of disease in the SLN. CLND after a positive SLN provides this important prognostic information.”

Non-sentinel Node Metastases Are Worse Than Sentinel Node Metastases

Bigger Node Metastases Are Worse Than Smaller Node Metastases
Why Is A Node Dissection Useful?

• To achieve durable regional control with the least morbidity in patients for whom sentinel node biopsy alone will not
• To provide additional staging information that improves prognostication and facilitates adjuvant therapy decision-making
• To qualify patients for clinical trials
• All patients must have a full lymphadenectomy
• Sentinel node-positive patients with one positive sentinel node from a non-ulcerated primary are only eligible if completion lymph node dissection finds metastasis to at least one non-sentinel node (stage IIIAN2a).

**SWOG 1404**

- Resected stage IIIAN2a/B/C or IVA patients
  - Pembrolizumab 3 mg/kg Q3 weeks x 1 year
  - High-dose IFN x 1 year
Why Is A Node Dissection Useful?

- To achieve durable regional control with the least morbidity in patients for whom sentinel node biopsy alone will not...
- To provide additional staging information that improves prognostication and facilitates adjuvant therapy decision-making.
- To qualify patients for clinical trials.
- To improve survival?
Sentinel node biopsy followed in all cases by completion lymph node dissection improves melanoma-specific survival for node-positive patients with intermediate thickness primary melanomas.

Cox model (adjusted for all other prognostic factors: age, gender, primary site, Breslow, Clark level and ulceration):

SNB vs. OBS hazard ratio: 0.55, 95% CI (0.37, 0.82), P=0.0029

10-year
- SNB: 41.4 ± 5.1%
- OBS: 63.1 ± 4.2%
This survival benefit does not even begin to be evident until well after 2 years post-sentinel node biopsy and increases as time goes on.
Distant Metastasis After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – DeCOG

Distant Metastasis After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – MSLT-2

Survival After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – DeCOG

Leiter et al. Lancet Oncol 2016;17: 757
Survival After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – MSLT-2

Survival After Sentinel Node Biopsy Without Lymphadenectomy

Prospective randomized trial of nodal observation vs CLND after a positive SLN biopsy – MSLT-2

How Do We Answer The Big Question?

• Does everyone with a positive sentinel lymph node need a completion lymph node dissection? **NO!**

• Does anyone with a positive sentinel lymph node need a completion lymph node dissection? **Absolutely!**

• How do we identify who really needs a completion lymph node dissection?
My Recommendation (June) 2017

- What is the role of completion lymph node dissection (CLND) after a positive sentinel node biopsy?

**Therapeutic LND is indicated for all** patients with clinically detected positive nodes, and **CLND remains the standard of care recommendation** for patients after a positive SLN biopsy. With careful selection, some SLN positive patients do well without CLND, so **nodal observation is an appropriate alternative** for informed patients willing to comply with a careful surveillance regimen.
My Selection Criteria (June) 2017

- Who do I feel most comfortable observing after a positive sentinel node biopsy?

  ✓ T1 or T2a primary Melanoma <1 mm or 1-2 mm without ulceration
  ✓ N1a or N2a(2) One or at most 2 positive SLNs
  ✓ Limited tumor burden Unifocal disease, met maximum dimension <0.2 mm

  ✓ Patient not highly motivated for clinical trial
  ✓ Patient whose SLN biopsy I did!
My Recommendation (June) 2017

• What is the appropriate follow-up regimen after a positive sentinel node biopsy without CLND?

Regional nodal ultrasonography by an experienced team Q4 months x 3 years then Q6 months x 2 years then annually for a total of 10 years

PET-CT annually

Brain MRI????
My Speculation (June) 2017

- What do I think will change these recommendations?

Not MSLT-2 trial results!

Availability of a clinical trial of systemic therapy for patients with a positive SLN but no CLND

More data regarding the impact of neoadjuvant systemic therapy before therapeutic LND lessening the adverse impact of nodal recurrence
There had been no significant improvement in overall survival for metastatic melanoma in three decades.
Surgery for Selected Patients with Metastatic Melanoma
Effective Therapy for a Select Few

One-year survival 71%
Long-term survivors 15%

Sosman et al. Cancer 2011;117:4740
So in this modern era of effective systemic therapy for melanoma, can we effectively employ systemic therapy first before surgery?
Moffitt Recommendation 2017

• What is the role of completion lymph node dissection (CLND) after a positive sentinel node biopsy?

Therapeutic LND is indicated for all patients with clinically detected positive nodes, and CLND remains the standard of care recommendation for patients after a positive SLN biopsy. Although early results show some SLN positive patients do well without CLND, we must be sure long-term recurrence and death rates are not adversely impacted.
Even After Two Randomized Trials, No Consensus Yet

• “If this aggregate of data is insufficient to extinguish the enthusiasm for immediate completion lymph node dissection, then it is unclear what more is required. These results should be construed as practice changing.”

• What more is required?

Long term follow-up!

MSLT-1 RANDOMIZED TRIAL FINAL ANALYSIS

Melanoma-Specific Survival Node-Positive
Intermediate Thickness 1.0-4.0 mm

DOI: 10.1056/NEJMo1310460
Melanoma-specific Survival by Stage

These represent huge improvements over 2010!
Not Happening Anytime Soon!
Surgery is NOT Obsolete

- Neoadjuvant therapy using BRAF + MEK targeted therapy for BRAF mutant patients with stage IIIC/IV resectable tumors will become routine.
- Upfront therapy using anti-PD1 ± ipilimumab for BRAF wild-type patients with stage IIIC/IV resectable tumors is next, but many patients may never actually need an operation!
- There will still be a role for adjuvant therapy after surgery for many cases of resectable stage III or IV disease!
Surgery is NOT Obsolete

• Neoadjuvant therapy using BRAF + MEK targeted therapy for BRAF mutant patients with stage IIIC/IV resectable tumors will become routine

• Neoadjuvant therapy using anti-PD1 ± ipilimumab for BRAF wild-type patients with stage IIIC/IV resectable tumors is next, but many patients may never actually need an operation!

• “Surgical gene therapy” will be useful for selected patients with multiple unresectable metastases treated with targeted therapy or immunotherapy in whom most tumors are stable/regressing but one or two are growing