Metastasectomy for Melanoma
What’s the Evidence and When Do We Stop?

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Disclosures

• Dr. Sondak is a compensated consultant for Provectus, Merck and Navidea

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Surgery For Metastatic Melanoma
Why? Who? When?
TREATMENT OF METASTATIC MELANOMA

Don Morton’s Top 3 Recommended Treatments

Surgery
Surgery
Surgery

Department of Cutaneous Oncology
Stage IV Immunotherapy Algorithm
Society for Immunotherapy of Cancer Consensus Statement on Tumour Immunotherapy for Cutaneous Melanoma

Stage IV Immunotherapy Algorithm
Society for Immunotherapy of Cancer Consensus Statement on Tumour Immunotherapy for Cutaneous Melanoma

1. All patients should be evaluated for resection before and after immunotherapy treatment

SURGERY FOR METASTATIC MELANOMA

Reasons For Resurgence Of Interest

• Improvements in imaging allowing better selection of patients
• Availability of minimally invasive approaches
• Decreased morbidity and mortality after major surgery
• Reports of long-term survival after resection
• Failure of nonsurgical treatments to improve overall survival for patients with metastatic melanoma
Metastatic Melanoma Can Itself Metastasize!
METASTATIC MELANOMA

How Many Patients Are Long-term Survivors Without Surgery?

• National Cancer Database 5-year survival in stage IV melanoma (1998) **13.8%**

• Clearly, there are more 5-year survivors than most surgeons (or oncologists) would expect

• Therefore, long-term survival is not proof that surgery caused the outcome
  ▪ Is there a selection bias?
  ▪ Do surgeons select patients who would have lived a long time anyway?

Chang et al, Cancer 1998; 83:1664
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What’s The Secret?

Selection
Selection
Selection
SURGERY FOR METASTATIC MELANOMA

Selection Bias in Past Studies

• Retrospective studies are characterized by significant selection and referral bias
• Prospective randomized trials of adjuvant therapy are biased as well!
  ▪ Must be able to undergo (afford) surgery
  ▪ Must be able to survive surgery
  ▪ Must be rendered disease-free by surgery
  ▪ Must be healthy (wealthy) enough to get referred
  ▪ Must recover from surgery in time to enroll
  ▪ Must be willing to accept randomization, placebo
  ▪ No prior treatment for metastatic melanoma allowed
SWOG-9430
Prospective Evaluation of Surgery for Metastatic Melanoma

- Patients registered to the study BEFORE surgery, once the decision had been made that the patient was potentially resectable
- Any site(s) of disease allowed
- Any prior therapy allowed, and any postoperative adjuvant therapy allowed per physician choice
- Evaluated the resectability rate, outcome
SWOG-9430

Results

- 77 patients entered from 18 SWOG institutions, 1996-2005
- 3 had no evidence of metastatic melanoma at surgery, 2 had only stage III disease
- 8 were unresectable or incompletely resected
- 64 patients (82%) were resected free of disease
  - 61% skin/soft tissue/lymph nodes; 13% lung, 8% liver, 5% CNS, 27% other visceral sites
  - 1 patient had a nonfatal postoperative pulmonary embolus
  - 18 received adjuvant therapy (8 IFN, 7 radiation)

Sosman et al, Cancer 2011;117:4740
SWOG-9430
Progression-free Survival After Resection

Sosman et al, Cancer 2011;117:4740
SWOG-9430
Overall Survival After Resection

Sosman et al, Cancer 2011;117:4740
How Do Results Of Past Medical Therapies Compare?

• 2100 melanoma patients on 70 cooperative group phase II trials of were evaluated for progression-free and overall survival

• Median PFS 1.7 months; PFS6 14.5%
  • Median PFS 6 months; PFS6 50%

• Median survival 6.2 months; OS12 25.5%
  • Median survival 21 months; OS12 71%

Korn et al, J Clin Oncol 2008;26:527
How Do Results Of Modern Medical Therapies Compare?

- 790 melanoma patients on 2 multinational phase III trials of ipilimumab ± vaccine or DTIC were evaluated for PFS and OS
- Ipilimumab arms median PFS <3 months; PFS6 20-30%
  - Median PFS 6 months; PFS6 50%
- Median survival 10-11 months; OS12 45%
  - Median survival 21 months; OS12 71%

How Do Results Of Modern Medical Therapies Compare?

- 587 melanoma patients on 2 multinational phase III trials of BRAF inhibitors vs DTIC were evaluated for PFS
- Targeted therapy arms median PFS 5.2 months; PFS6 ~47%
  - Median PFS 6 months; PFS6 50%

Hauschild et al, Lancet 2012; 380:358
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Do Surgeons Select Patients Who Would Have Lived A Long Time Anyway?

- Long disease-free interval from primary tumor (or absence of a known primary)
- No or limited regional nodal metastasis
- Primary site well controlled, no in-transit or satellite metastases
- Metastases confined to one or two organs and only one or a few per organ
- Metastases relatively small in size
- Normal LDH level?
SURGERY FOR METASTATIC MELANOMA

Other Important Candidates

• Patients with multiple metastases treated with systemic therapy (especially immunotherapy) with complete resolution of all but a few progressing tumors

• Patients with multiple metastases treated with systemic therapy (especially targeted therapy) with control of all but a few progressing tumors
What Percent Of Stage IV Patients Are Candidates For Resection?

Initial treatment of 291 patients on MSLT-1 who developed stage IV recurrence

<table>
<thead>
<tr>
<th>Treatment for stage IV recurrence</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Surgery only</td>
<td>43</td>
<td>15</td>
</tr>
<tr>
<td>Surgery, then SMT</td>
<td>85</td>
<td>55</td>
</tr>
<tr>
<td>SMT, then surgery</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>SMT only</td>
<td>130</td>
<td>45</td>
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</table>

*SMT* systemic medical therapy

What Percent Of Stage IV Patients Are Candidates For Resection?

Initial treatment of 70 consecutive patients who developed stage IV recurrence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic medical therapy</td>
<td>55 pts</td>
<td>79%</td>
</tr>
<tr>
<td>Complete resection</td>
<td>6 pts</td>
<td>9%</td>
</tr>
<tr>
<td>Partial resection</td>
<td>9 pts</td>
<td>12%</td>
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</tbody>
</table>

Wevers and Hoekstra, Ann Surg Oncol 2013;20:2352
How Do The Outcomes of Surgery and Medical Therapy for Stage IV Melanoma Compare?

How Do The Outcomes of Surgery and Medical Therapy for Stage IV Melanoma Compare?


SMT = Standard Medical Therapy
Limited (Resectable) Metastatic Disease

Resect or Observe or systemic therapy, then repeat scans [duration not specified], if negative for other disease then resect

Evidence-based guidelines for when and how long potentially resectable patients should be observed or treated, and whether this strategy of deferring surgery improves outcomes or decreases morbidity, are lacking at this time.
How Good Must Medical Therapies Be Before We Move Away From Surgery?

- Are there modern treatment regimens that provide superior results in unselected patients to what surgery provides in highly selected patients, and if so what does that imply?

  82% complete response rate, median PFS 6 months, median OS 21 months

How Good Must Medical Therapies Be Before We Move Away From Surgery?

82% complete response rate, median PFS 6 months, median OS 21 months


Dabrafenib plus trametinib for BRAF mutant melanoma
How Good Must Medical Therapies Be Before We Move Away From Surgery?
82% complete response rate, median PFS 6 months, median OS 21 months

Adjuvant stage IV NED anti-PD-1 antibody relapse data with 18 months of follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1 (Nivo 1mg/kg)</th>
<th>Cohort 2 (Nivo 3mg/kg)</th>
<th>Cohort 3 (Nivo 10 mg/kg)</th>
<th>All Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse event</td>
<td>3/12</td>
<td>2/10</td>
<td>3/11</td>
<td>8/33</td>
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</tbody>
</table>

Weber et al, Proc ASCO 2013
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Looking to the Future

• Improved algorithms for following high-risk stage II and III melanoma patients are needed to identify patients most likely to benefit from metastasectomy

• Neoadjuvant therapy using targeted therapy for BRAF mutant patients with unresectable or borderline resectable tumors

• Neoadjuvant therapy using anti-PD1 for BRAF wild-type patients with unresectable or borderline resectable tumors?

• “Surgical gene therapy” for patients with multiple metastases treated with targeted therapy in whom most tumors are stable but one or two are growing
  • Experience in GIST tumors treated with imatinib showed benefit for eliminating these resistant tumors while continuing effective therapy for the other metastases