Multidisciplinary Approach to Metastatic Melanoma: What Role Should Surgery Play?

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Disclosures

• None
Objectives

• Identify the population of patients in whom surgery for metastatic disease should play a role in their treatment

• Examine the sequence of treatment options, including systemic therapies and surgery, for patients with metastatic disease responding to systemic therapy

• Discuss the morbidity associated with surgery for patients with metastatic disease undergoing concurrent systemic therapy
Case #1

• 59-year-old woman presented in 2015 with left upper quadrant abdominal pain and was found to have metastatic melanoma from an unknown primary
  • Predominant disease in the right lobe of the lung and the spleen
Case #1

• 59-year-old woman presented in 2015 with left upper quadrant abdominal pain and was found to have metastatic melanoma from an unknown primary
  • Predominant disease in the right lobe of the lung and the spleen
  • Initiated on ipilimumab and nivolumab
    • Grade 4 autoimmune hepatitis after two doses
  • Initiated on BRAF/MEK inhibitors
    • Imaging showed response in lung lesion but persistent FDG avidity in the spleen
  • SBRT to spleen followed by IL-2 (two courses, both stopped early for transaminitis)
Surgery for Metastatic Melanoma

Intense FDG avidity in periphery of the spleen surrounding a necrotic mass

FDG = fluoro-deoxyglucose
Case #1

• OR for hand-assisted laparoscopic splenectomy without complications

• Path:
  • SPLEEN WITH METASTATIC MELANOMA, TWO NODULES MEASURING 13.0 AND 0.5 CM GREATEST DIMENSION
  • TUMOR IS CONFINED TO SPLEEN; MARGINS FREE OF TUMOR
  • HILAR ACCESSORY SPLEEN TISSUE
Surgery for Metastatic Melanoma

Before surgery

Most recent imaging
Case #2

• 37-year-old woman with a history of a T1aNx melanoma treated in 2011 presented to ED at 27 weeks of pregnancy with headache and frontal lobe mass
  • Craniotomy revealed metastatic melanoma
  • PET/CT: axillary mass as only other site of disease (biopsy – melanoma)
  • Adjuvant SRS
  • Elective C-section at 34 weeks
    • Placenta without evidence of melanoma
  • Started ipilimumab and nivolumab 2 weeks postpartum, switched to nivolumab monotherapy because of transaminitis
Surgery for Metastatic Melanoma

Before Systemic Therapy

After 6 months of Immunotherapy
Case #2

- OR for left axillary lymphadenectomy

- Path:
  - A. LEFT AXILLARY CONTENTS (LEVELS 1, 2, 3):
    - TWENTY-ONE (21) LYMPH NODES, NEGATIVE FOR MALIGNANCY
    - THE LARGEST NODE IS 2.0 CM AND SHOWS EXTENSIVE FIBROSIS/SCLEROSIS, BUT NO V VIABLE TUMOR IS PRESENT

- Continues on “adjuvant” immunotherapy with single-agent nivolumab with plans to treat for a total of 1 year
Rationale for Surgery in Metastatic Melanoma

• Metastatic melanoma presents in a variety of ways
  • Explosive widespread disease with rapid progression to death
  • Slow-growing oligometastatic disease
• Oligometastatic disease may result from tumor-intrinsic inability to escape cell death or from host-specific immunity
• Surgery has resulted in the highest survival rates for patients with stage IV melanoma
Surgery for Metastatic Melanoma

Overall Survival

Resection
1-year: 77%
3-year: 37%
5-year: 27%

No Resection
1-year: 32%
3-year: 7%
5-year: 3%

A Phase 2 Trial of Complete Resection for Stage IV Melanoma

Results of Southwest Oncology Group Clinical Trial S9430

Progression-free Survival

Median RFS: 5 months

Overall Survival

Median OS: 21 months

RFS = relapse-free survival
Multicenter Selective Lymphadenectomy Trial-1

Median OS: M1a Disease

Surgery +/- medical therapy:
> 60 months
Medical therapy alone: 12.4 months

\[ P = .0106 \]
Response Rates to Modern Systemic Therapies

- Ipilimumab – 15%
- Nivolumab – 40%
- Ipilimumab/nivolumab – 60%
- BRAF/MEK inhibitors – 65%
  - BRAF inhibitor alone – 45%
- T-VEC – 16%

60% to 65% of patients may gain a survival advantage by undergoing surgery in an attempt to eliminate all sites of disease.
Factors Affecting Decision to Operate

• Response to systemic therapy
  • Complete response vs oligoprogression vs true progression
Factors Affecting Decision to Operate

- Response to systemic therapy
  - Complete response versus oligoprogression
- Disease-free interval/tumor doubling time

- OS: DFI > 12 months
  - Surgery: Median OS 17.8 months
  - No surgery: Median OS 9.3 months
  - $P < .0001$

- OS: DFI < 12 months
  - Surgery: Median OS 17.8 months
  - No surgery: Median OS 9.3 months
  - $P = .0326$

Factors Affecting Decision to Operate

- Response to systemic therapy
  - Complete response versus oligoprogression

- Disease-free interval/tumor doubling time

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Median survival (mo)</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 45)</td>
<td>23.1</td>
<td>15.6</td>
</tr>
<tr>
<td>TDT(^a) &lt;60 days (n = 16)</td>
<td>16.0</td>
<td>0</td>
</tr>
<tr>
<td>TDT ≥60 days (n = 29)</td>
<td>29.2</td>
<td>21.6</td>
</tr>
<tr>
<td>TDT &lt;60 days and/or palliative (n = 20)</td>
<td>17.6</td>
<td>0</td>
</tr>
<tr>
<td>TDT ≥60 days and curative (n = 25)</td>
<td>30.6</td>
<td>25.9</td>
</tr>
</tbody>
</table>

\(^a\)TDT, tumor doubling time.

Factors Affecting Decision to Operate

- Response to systemic therapy
  - Complete response versus oligoprogression
- Disease-free interval/tumor doubling time
- Burden of disease
  - Solitary visceral (lung, spleen, adrenal)
  - Oligometastatic
  - Widespread

<table>
<thead>
<tr>
<th>Extent of metastasis</th>
<th>Surgery</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved organ sites (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (242)</td>
<td></td>
<td>17.6 mos</td>
</tr>
<tr>
<td>2 (35)</td>
<td></td>
<td>13.4 mos</td>
</tr>
<tr>
<td>≥3 (14)</td>
<td></td>
<td>4.5 mos</td>
</tr>
</tbody>
</table>
Factors Affecting Decision to Operate

- Response to systemic therapy
  - Complete response versus oligoprogression
- Disease-free interval/tumor doubling time
- Burden of disease
  - Solitary visceral (lung, spleen, adrenal)
  - Oligometastatic
  - Widespread
- Completeness of resection/palliation

![Overall Survival Graph](Image)

Factors Affecting Timing of Surgery

• Single site of disease
  • Upfront surgery
  • Adjuvant therapy: clinical trial or SOC

• Oligometastatic disease
  • All resectable: upfront surgery vs SOC systemic therapy, then surgery
  • Not resectable: SOC systemic therapy, then surgery for good response or oligoprogession

• Widespread disease
  • SOC systemic therapy, then surgery only for palliation

SOC = site of care
Factors Affecting Timing of Surgery


Median OS = 17.1 months
Median OS = 14.7 months
Surgery for Metastatic Melanoma

Other Considerations

- Serum LDH
- Patient performance status
- Extent of surgery
- Morbidity of surgery
  - Pancreatectomy, craniotomy, hepatectomy
  - Splenectomy, small bowel resection, VATS/wedge, adrenalectomy

LDH = lactate dehydrogenase
Conclusions

• Effective systemic therapies have dramatically altered the role that surgery should play in patients with metastatic melanoma.

• Any patient with any response to systemic therapy should be evaluated by a surgical oncologist to consider metastasectomy.

• In the setting of a single resectable asymptomatic metastasis, some patients might undergo surgery followed by systemic therapy.