Surgery for Metastatic Cancer

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Surgery and Stage IV Cancer

• Surgery as palliation
• Surgery for diagnosis
• Surgery as therapy
  – Stage IV cancer is a systemic illness, surgery is a local therapy
  – Surgery is fraught with morbidity and mortality
  – Risk/Benefit ratio is too high
Increasing frequency of surgery

- Number of metastasectomies increasing for many cancers
- Nationwide inpatient sample was used from 2000-2011.

Decreasing mortality

- Inpatient mortality trends, meanwhile, are decreasing

Rationale

• Immunologic benefit of decreased tumor burden

• Resection to NED status

• Medical therapies may select out resistant mutants
Tumor-induced Immunosuppression

- Some evidence that patients with intact tumors are immunosuppressed.
  - Immune tolerance of host to tumor antigens
  - Genetic changes in tumor cells create immune privilege
  - Lack of activation to tumor antigens
  - Dysfunction of tumor-reactive lymphocytes
  - Immune suppression by tumor-secreted factors

Tumor immune suppression in breast cancer

- Campbell et al examined immune function in 84 patients with breast cancer compared to 26 healthy controls.

- They found that both CD4 and CD8 cells were significantly lower in the breast cancer patients.

- Post-operative immune function studies were not performed.

Reversible Immunosuppression?

- Danna et al used a mouse model to compare mice with no tumor, intact metastatic tumor, and excised primary tumor.

- They found the mice with tumors were immunosuppressed but returned to baseline with excision of primary mammary carcinoma.

- Conclusion: Data supports potential of immunotherapy after removal of primary tumor.

Objectives

• In the following slides we will review evidence for and against surgery for some common and some less common primary cancer sites

• Review the role of metastasectomy

• Review the role of primary tumor excision

• Review the role of surgery in concert with medical therapies.
Melanoma

- Melanoma is variable in its metastatic presentation
- Single site metastatic disease may be unique (poorly performing cancer cells? or Host immune protection?)
- Tumor-specific antibody titers have been correlated with post-metastasectomy survival (evidence of the immune response to metastasectomy\(^1\)).
- Regardless of the mechanism, resection has yielded the highest survival rates for stage IV melanoma

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# Volume of Data

<table>
<thead>
<tr>
<th>Authors/Study</th>
<th>Institution</th>
<th>Total Patients</th>
<th>M1 Overall</th>
<th>Any type of surgery</th>
<th>Curative Surgery</th>
<th>Palliative/Incomplete Surgery</th>
<th>No surgery</th>
<th>Prospective Trials</th>
<th>M1A</th>
<th>M1B</th>
<th>M1C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Pts</td>
<td>med OS</td>
<td>1/2/3/4/5 yr OS</td>
<td>Pts</td>
<td>med OS</td>
<td>1/2/3/4/5 yr OS</td>
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<td><strong>Prospective Trials</strong></td>
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<td>1/2/3/4/5 yr OS</td>
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<td>med OS</td>
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<tr>
<td>Howard et al.</td>
<td>MSLT1 (2012)</td>
<td>291</td>
<td>161 15.8</td>
<td>4 yr = 20.8%</td>
<td>130</td>
<td>6.9 4 yr = 7.0%</td>
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<td>6</td>
<td>12.4 4 yr = 0%</td>
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<tr>
<td>Morton et al.</td>
<td>MMA/T (2007)</td>
<td>496</td>
<td>496 32-39</td>
<td>5 yr = 40-45%</td>
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<td>Sosman et al.</td>
<td>SWOG (2006)</td>
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<td>77 21.0</td>
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<td>1/2/3/4/5 yr OS</td>
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<td>med OS</td>
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<tr>
<td>Essner et al.</td>
<td>JWCI (2004)</td>
<td>260</td>
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<td>5 yr = 25.0%</td>
<td>96</td>
<td>13.0 5 yr = 0%</td>
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<td>Meyer et al.</td>
<td>Erlangen, Ger (2000)</td>
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<td>75 17 - 18 5 yr = 17.8 - 20.0%</td>
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<td>5 yr = 0 - 16.7%</td>
<td>26</td>
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<td>1/2/3/4/5 yr OS</td>
<td>Pts</td>
<td>med OS</td>
<td>1/2/3/4/5 yr OS</td>
<td>Pts</td>
<td>med OS</td>
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<tr>
<td>Howard et al.</td>
<td>MSLT1 (2012)</td>
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<td>22</td>
<td>9.1 4 yr = 14.3%</td>
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<td>Petersen et al.</td>
<td>Duke (2007)</td>
<td>1738</td>
<td>318</td>
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<td>20.0 5 yr = 4%</td>
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<td>Neumayer et al.</td>
<td>MSKCC (2007)</td>
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<td>1420</td>
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<td>Andrews et al.</td>
<td>Moffitt (2006)</td>
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<td>86 35.0</td>
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<td>Essner et al.</td>
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<td>46</td>
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<td>Meyer et al.</td>
<td>Erlangen, Ger (2000)</td>
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<td>130 11 - 14</td>
<td>5 yr = 10.2 - 15.2%</td>
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<td>Loo et al.</td>
<td>IRLM (2000)</td>
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<td>Pillai et al.</td>
<td>JWCI (1998)</td>
<td>45</td>
<td>45 23.1</td>
<td>5 yr = 15.6%</td>
<td>46</td>
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<td><strong>M1C</strong></td>
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<td>med OS</td>
<td>1/2/3/4/5 yr OS</td>
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<td>med OS</td>
<td>1/2/3/4/5 yr OS</td>
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<tr>
<td>Faries et al. (Liver)</td>
<td>JWCI (2014)</td>
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<td>58 24.8</td>
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<td>Howard et al. (All)</td>
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<td>Reddy et al. (Pancreas)</td>
<td>Johns Hopkins (2009)</td>
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<td>11 14.0</td>
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<td>Mitterodorf et al. (Adrenal)</td>
<td>MDACC (2008)</td>
<td>154</td>
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<td>Collinson et al. (Adrenal)</td>
<td>Sydney (2008)</td>
<td>186</td>
<td>23 16.0</td>
<td>61/39/-/-</td>
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<td>Fife et al. (Brain)</td>
<td>Sydney (2004)</td>
<td>686</td>
<td>205 8.7 - 8.9</td>
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<td>446</td>
<td>2.1 - 3.4</td>
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<tr>
<td>Wood et al. (Solid organs)</td>
<td>JWCI (2001)</td>
<td>838</td>
<td>60 27.6</td>
<td>/-/-/-/24%</td>
<td>16</td>
<td>8.4 5 yr = 0%</td>
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<td>Rose et al. (Liver)</td>
<td>JWCI/Sydney (2001)</td>
<td>923</td>
<td>24 28.0</td>
<td>/-/-/-/29</td>
<td>24</td>
<td>28.0 /-/-/-/29</td>
<td>899</td>
<td>6.0 5 yr = 4.0%</td>
<td>-</td>
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<tr>
<td>Hight et al. (Adrenal)</td>
<td>JWCI (1999)</td>
<td>83</td>
<td>27 25.7</td>
<td>-</td>
<td>9</td>
<td>9.2</td>
<td>-</td>
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<tr>
<td>Agrawal et al. (GI)</td>
<td>MSKCC (1999)</td>
<td>68</td>
<td>68 14.9</td>
<td>67/45/-/-/38</td>
<td>49</td>
<td>6.9 22/-/-/-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pillai et al. (GI)</td>
<td>JWCI (1996)</td>
<td>124</td>
<td>60 48.9</td>
<td>5 yr = 41%</td>
<td>45</td>
<td>48.9 5 yr = 41%</td>
<td>55</td>
<td>5.7 5 yr = 0%</td>
<td>-</td>
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</tbody>
</table>


Patient selection

• Response to prior therapy is becoming a more and more important factor – especially in light of more effective immune therapies for melanoma

• Complete resectability

Patient selection

- Tumor doubling time/disease free interval
- Response to neoadjuvant chemotherapy
- Ability to achieve NED status
- Overall patient performance status
Adrenocortical Carcinoma

- ACC is a rare cancer with a poor prognosis
- More than 25% present with metastatic disease
- After an R0 resection, survival is about 74 months with 16-50% 5-yr survival but with 40% patients recurring or developing metastases
- Repeat R0 resection is the best known treatment
Adrenocortical Carcinoma

- Schulick and Brennan reviewed 113 patients treated for ACC and 107 had surgery with 47 undergoing 2nd resection.

Complete re-resection: 5-yr OS 57%, incomplete: 0%

Sarcoma

- Once metastatic, soft tissue sarcomas are generally associated with a short survival interval.
- Retrospective series have demonstrated the feasibility of resection for limited metastases, specifically in the lungs and liver.
- Pulmonary resection – selection criteria include primary tumor control, no extrapulmonary disease, medical health, and disease completely resectable.
- 3-year survival data ranges from 23-54%.

GIST

- Gastrointestinal stromal tumors (GIST) is a unique subset of sarcoma.
- Therapy for GIST has been changed due to success with tyrosine-kinase inhibition, with imatinib being the original agent.
- Patients with metastatic, recurrent, or locally advanced GIST are treated with imatinib and can experience profound responses.
- However drug resistance is frequently encountered and the role of surgery is unclear.
Surgery for GIST responding to imatinib

- A randomised trial from China, asked the question of the role of and timing of surgery.
- While they fell short of accrual goals, they randomized 19 patients to surgery between 3 and 12 months of imatinib and 22 patients to continued imatinib therapy.

Surgery for GIST responding to imatinib

• While they fell short of accrual, they demonstrated a survival benefit to surgery for patients responding to imatinib.
• This result is in line with a recent retrospective analysis of 239 European patients undergoing metastasectomy with median OS of 8.7 years for RO/R1 resection and 5.3 years in R2 resection.

Neuroendocrine Tumors (NETs)

- Incidence of NETs has markedly increased over several decades
- Hepatic involvement associated with significant morbidity
- Several treatment options, but no proven optimal therapy

Hepatic cytoreduction produces excellent survival outcomes in metastatic NETs

• All patients were treated surgically:
  – Hepatic resection (78%)
  – Ablation alone (3%)
  – Resection + ablation (19%)

• Median follow-up of 43.3 months

• Excellent survival outcomes seen in patients with isolated liver disease

Combination therapy results in a superior disease-specific survival


Combination vs. surgery alone → p=0.03

Combination vs. S-LAR alone → p=0.02

Combination vs. neither therapy → p<0.01
Colorectal Cancer

• Metastatic disease from colorectal cancer is a common target for metastasectomy
• Up to 50% of patients will experience liver metastases
• Patients with liver mets can be cured

• Median survival for stage IV patients is 18 months. With complete resection that increases to 40 months with operative mortality less than 5%
Colorectal Cancer

- Adapted from Ito et al review of hepatic metastasectomy
- Hepatic metastasectomy is a safe treatment

Patient Selection

- Selection of the right patients may be the single most important factor in outcomes. This is precisely what makes trials so difficult.

<table>
<thead>
<tr>
<th>TABLE 2. Clinical Risk Score (CRS): Prognostic Scoring System for Hepatic Colorectal Metastases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node-positive primary tumor</td>
</tr>
<tr>
<td>Disease-free interval less than 12 mo between colon resection and appearance of metastases</td>
</tr>
<tr>
<td>Size of largest lesion &gt;5 cm</td>
</tr>
<tr>
<td>More than one tumor</td>
</tr>
<tr>
<td>Carcinoembryonic antigen &gt;200 ng/dl</td>
</tr>
</tbody>
</table>

*One point assigned for each positive criterion. Sum of points is CRS.

- This simple scoring system was derived from large studies
- Outcomes based on 0-2 or 3-4 points.

Adjuncts to Resection

- Microwave ablation is another common modality
- MSKCC review of microwave experience of 176 patients included 80% colorectal liver mets but HCC and cholangiocarcinoma as well\(^1\)
- Demonstrated a local recurrence rate of 17% and was higher in tumors \(>3\text{cm}\)\(^1\)
- Colorectal patients had a 4-year OS of 58%\(^1\)
- 4 centers pooled data on 288 patients received ablation AND resection for a combined 37% 5-yr OS\(^2\)

2. Evrard S, et al. Combined ablation and resection (CARe) as an effective parenchymal sparing treatment for extensive colorectal liver metastases. *PLOS One* 2014;9(12):
Use and Timing of Chemotherapy

- Response to chemotherapy is a critical indicator of success in patients undergoing systemic treatment first.
- Downstaging is certainly possible from 12-47% with favorable survival rates.

### TABLE 3. Results of Downstaging Chemotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Chemotherapeutic Agent</th>
<th>N (%) Converted to Resectable</th>
<th>5-yr Survival</th>
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</thead>
<tbody>
<tr>
<td>Bismuth et al</td>
<td>330</td>
<td>5-FU, Leucovorin, Oxaliplatin</td>
<td>53 (16%)</td>
<td>OS: 40%</td>
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<tr>
<td>Adam et al</td>
<td>701</td>
<td>5-FU, Leucovorin, Oxaliplatin</td>
<td>95 (13.5%)</td>
<td>OS: 35–60%</td>
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<tr>
<td>Clavien et al</td>
<td>23</td>
<td><em>Flouxuridine</em></td>
<td>6 (26%)</td>
<td>—</td>
</tr>
<tr>
<td>Adam et al</td>
<td>1104</td>
<td>5-FU + oxaliplatin (70%), 5-FU + irinotecan (7%), 5-FU + both (4%)</td>
<td>138 (12.5%)</td>
<td>OS: 33%</td>
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<tr>
<td>Kemeny et al</td>
<td>49</td>
<td><em>Flouxuridine</em>, Oxaliplatin, Irinotecan</td>
<td>23 (47%)</td>
<td>(Median f/u 26 mo, median OS: 39.8 mo)</td>
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<tr>
<td>Alberts et al</td>
<td>42</td>
<td>5-FU, Leucovorin, Oxaliplatin (FOLFOX4)</td>
<td>17 (40%)</td>
<td>(Median f/u 22 mo, median OS (all patients): 26 mo)</td>
</tr>
<tr>
<td>Barone et al</td>
<td>40</td>
<td>5-FU, Leucovorin, Irinotecan</td>
<td>19 (47.5%)</td>
<td>OS: 62%, DFS: 46%</td>
</tr>
</tbody>
</table>

*Administered via hepatic arterial infusion (HAI). 5-FU, fluorouracil; DFS, disease-free survival; f/u, follow up; mets, metastases; OS, overall survival.
Non-curative resection of primary

- While a synchronous resection has been shown to be safe, this is avoided if the patient cannot be rendered NED.
- There has been significant interest in resection of the primary in the setting of unresectable metastatic disease for palliation AND survival benefit – all retrospective.
- Canadian cohort study of stage IV colorectal patients underwent primary resection (944) or not (434).
- Median OS was 10.6 vs. 3.0 months for resected primaries (p<0.0001).
Non-curative resection of primary

• The Dutch Colorectal Cancer Group is enrolling in a clinical trial (CAIRO 4) to answer this question.
• Patients will be enrolled and treated with chemotherapy (5-FU based with bevacizumab) or randomized to surgery within 4 weeks of randomization.
• ClinicalTrials.gov ID: NCT01606098
Breast Cancer

• Multiple reports of long-term survival for metastasectomy for isolated sites

• Difficult to select patient who benefit from surgery in an era where systemic therapies can also be very successful

• Long-term survival rates in resected patients make surgery an option to keep in mind for metastatic breast cancer
Management of Primary Tumor in Stage IV Breast Cancer

- 6 randomized controlled trials are underway to answer this question. 2 have reported preliminary results.

<table>
<thead>
<tr>
<th>Country</th>
<th>Trial number</th>
<th>Accrual period</th>
<th>N</th>
<th>Initial therapy</th>
<th>Radiotherapy</th>
<th>Primary endpoint</th>
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<tr>
<td>India</td>
<td>NCT00193778</td>
<td>2005–2012</td>
<td>350</td>
<td>Adriamycin, cytoxan, 5-FU</td>
<td>If indicated</td>
<td>Time to progression</td>
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<td>Japan</td>
<td>JCOG 1017</td>
<td>2011–2016</td>
<td>410</td>
<td>Systemic therapy</td>
<td>Not addressed</td>
<td>Survival</td>
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<tr>
<td>USA and Canada</td>
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<td>2011–2016</td>
<td>880</td>
<td>Systemic therapy</td>
<td>Per standards for stage I–III</td>
<td>Survival</td>
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<tr>
<td>Turkey</td>
<td>NCT00557986</td>
<td>2008–2012</td>
<td>281</td>
<td>Surgery</td>
<td>For breast conservation</td>
<td>Survival</td>
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<tr>
<td>Netherlands</td>
<td>NCT01392586</td>
<td>2011–2016</td>
<td>516</td>
<td>Surgery</td>
<td>For positive margins or palliation</td>
<td>2-year survival</td>
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<td>Austria</td>
<td>NCT01015625</td>
<td>2010–2019</td>
<td>254</td>
<td>Surgery</td>
<td>Per standards for stage I–III</td>
<td>Survival</td>
</tr>
</tbody>
</table>
1. Soran A, et al. Early follow-up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (Protocol MF07-01)clinicaltrials.gov ID: NCT00557986
Management of Primary Tumor in Stage IV Breast Cancer

1. Soran A, et al. Early follow-up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (Protocol MF07-01) clinicaltrials.gov ID: NCT00557986
Management of Primary Tumor in Stage IV Breast Cancer

N=350

Renal Cell Carcinoma

• RCC is another cancer with solid data to support surgery in the setting of metastatic disease
• Slightly different from metastasectomy, the benefit seems to be from resection of the primary tumor in the setting of metastatic disease.
• This is demonstrated in 2 RCT

Conclusions

• There is a role for surgery in the face of stage IV cancer.

• Patient selection is the key

• Ongoing studies should provide better data

• Future studies will incorporate immune treatments
Renal Cell Carcinoma

- RCC is another cancer with solid data to support surgery in the setting of metastatic disease.
- Slightly different from metastasectomy, the benefit seems to be from resection of the primary tumor in the setting of metastatic disease.
- This is demonstrated in 2 RCT

Thank You