Multimodality therapy for locally advanced esophageal cancer

Are we making progress?

Surgical Progress

- Marked reduction in operative morbidity and mortality
- Introduction of Minimal-Access approaches for complex esophageal cancer resections
- Significantly better functional outcomes
Early Diagnosis and Treatment for Stage 0-1 Esophageal Cancer

- Understanding the biology of Barrett’s
- Surveillance and early diagnosis of dysplasia and cancer in the Barrett’s population
- Ablation techniques for Barrett’s with dysplasia
- Endoscopic Resection techniques for T1a esophageal cancer

However, most patients present with Stage III disease and this will continue to be the case for the foreseeable future.
Survival for Stage III Patients, Historical

Disease-Free Survival

Survival for Stage III Patients treated with Neoadjuvant Therapy and Surgery, 1994-2013

Axis Title

Surgery Only
ChemoRT Only

All Neoadj + Surgery
Surgery Only
ChemoRT Only

32%
Survival for Pathologic Complete Responders

![Graph showing survival rates for pathologic complete responders (path CR) and non-pathologic complete responders (non-CR)].

CROSS Trial
NEJM 366:2074, 2012

- Weekly carboplatin (dose titrated to achieve AUC of 2 mg/ml/minute) and paclitaxel 50 mg/m² BSA) x five weeks with concurrent XRT (41.4 GY)
- Low toxicity with excellent tolerability, compliance and completion rate
- No additional operative mortality or morbidity seen in the neoadjuvant group

Updated in Lancet Oncol 16:1090, 2015
Ochsner Neoadjuvant for Locally Advanced Esophageal Cancer

Ochsner Cross Regimen
89 patients

Ochsner Pre-Cross 160 pts

Ochsner Neoadjuvant for Locally Advanced Esophageal Cancer

Ochsner Cross Regimen

Ochsner Pre-Cross

CROSS NEJM
Based on this data, one can conclude that we are making incremental progress. Currently, a patient newly diagnosed with carcinoma of the esophagus or EG junction can expect a 40-50% chance of long-term survival with multimodality therapy.

However, we still have a long way to go....
Patterns of recurrence in the CROSS trial

- Overall Recurrence Rates for surgery only vs. neoadjuvant groups:
  - Locoregional: 34% vs. 14% (p<0.001)
  - Peritoneal carcinomatosis: 14% vs. 4% (p<0.001)
  - Hematogenous: 35% vs. 29% (p=0.025)

J Clin Oncol 10:385, 2014

Ideas for next steps:

- Intensify neoadjuvant chemotherapy?

- Evaluate neoadjuvant chemotherapy-in-progress and switch to non-cross resistant regimen if no response is seen with 1st regimen?

- For non-responders/node + patients after neoadjuvant, give postop adjuvant chemotherapy?

- Add targeted therapy?
Next Steps? (cont)

• Intensify neoadjuvant chemotherapy?
  • Add a third agent? (may increase toxicity)
  • Give 2-3 cycles before concurrent chemoRT?
  • In lieu of XRT?

University of Miami Experience

• 232 locally advanced eso cancer patients receiving neoadjuvant chemo only (no XRT)
• 27 patients (11.7%) achieved a path CR and enjoyed a 10 year OS of 74%
• 115 patients (49.6%) achieved a path partial response with 10 yr OS of 67%
• 10 yr OS for all 232 patients was 52%
University of Miami Neoadjuvant for Locally Advanced Esophageal Ca

<table>
<thead>
<tr>
<th>CHEMO ONLY</th>
<th>Path CR</th>
<th>Path PR</th>
<th>Non-responder</th>
<th>All</th>
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<td># patients</td>
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<td>232</td>
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<td>10 yr surv rate</td>
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<td># 10 yr survivors</td>
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<tr>
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<td># patients</td>
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<td>33</td>
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Next steps? (cont)

- Evaluate neoadjuvant chemotherapy-in-progress and switch to non-cross resistant regimen if no response is seen with 1st regimen?
  - Do we really have non-cross resistant therapy?
### Level 1 Data for Preoperative Chemoradiation (NCCN)

<table>
<thead>
<tr>
<th>Paclitaxel and carboplatin</th>
<th>Fluorouracil and cisplatin</th>
<th>Fluorouracil and oxaliplatin (FOLFOX)</th>
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### CALGB 80803: PHASE II RCT OF PET SCAN-DIRECTED COMBINED MODALITY THERAPY IN ESOPHAGEAL CANCER

<table>
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<tr>
<th>mFOLFOX6 q 2 weeks for 3 cycles</th>
<th>Carbo AUC 2 and taxol 90 mg/m2 d 1 and 8 q 3 weeks for 2 cycles</th>
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**PET scan response (> 35% reduction in metabolic activity)?**

Responders continue the primary chemotherapy during XRT; non-responders cross over to the alternate regimen during XRT

**Surgical Resection**
Next Steps? (cont)

- For non-responders/node + patients after neoadjuvant, give postop adjuvant chemotherapy?
  - Recent analyses show that even partial response to neoadjuvant improves survival, measuring PR by downstaging from clinical to surgical path stage or evaluating the % residual viable cancer in the surgical path specimen
  - Persistence of + nodes in the surgical path specimen clearly an adverse prognostic indicator
  - What would be the best adjuvant chemo???

Next steps? (cont)

- Add targeted therapy?
  - VEGF inhibition (ramucirumab)
  - Checkpoint inhibitor (pembrolizumab)
Summary

- Incremental, significant progress has been made with the introduction of multimodality therapy, for patients with stage III esophageal cancer

- ‘Cure’ (5 year survival) rates for stage III esophageal cancer are now in the 40-50% range

- Eliminating systemic recurrence is the biggest current challenge we face
Survival for Stage III Patients treated with Neoadjuvant Therapy and Surgery

Disease-Free Survival

- All: 42%
- SCC: 32%
- ACA: 28%