Barrett’s Esophagus and Esophageal Cancer: Update on Surgical Management

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Esophageal Cancer

- 6th most common cancer worldwide
- Endemic to certain areas:
  - Asia, SE Africa, N France
  - Squamous cell carcinoma is most common
- In US it is 4% of all cancers: 15,560 new cases and 13,940 new deaths in 2007
- In US and Europe, adenocarcinoma is now the predominant type forming >70% of all cases

Risk Factors for Squamous Cell Carcinoma

- Smoking: 5-fold risk
  - risk decreases significantly after cessation
- Alcohol: 5-fold risk
- Combined smoking & alcohol: 25-100 fold risk
- Male sex: 5-fold risk
- African American race: 5-fold risk
- Living in an endemic area

Risk Factors for Adenocarcinoma

- GERD and Barrett’s Esophagus
  - 62% of esophageal adenocarcinoma is associated with BE
- Smoking: risk does not decrease after cessation
- Alcohol: modest risk
- Male sex
- Age: over 50
- Caucasian race
- High BMI

GERD and Barrett’s Esophagus

• Up to 30% of the U.S. population suffers from symptomatic GERD
• 2 to 15% of those patients develop Barrett’s esophagus (BE)
• BE is associated with a 30-125 fold risk of cancer i.e. 0.5% to 2% per year risk
• 8 to 15% of patients with BE develop cancer
• 62% of esophageal adenocarcinoma is associated with BE

Altorki NK et al. Semin Surg Oncol 1997; 13:270-280

Barrett’s Esophagus

• Replacement (metaplasia) of normal esophageal squamous epithelium with columnar epithelium containing goblet cells (aka specialized intestinal metaplasia)

Adenocarcinoma on Barrett’s Esophagus

Modes of Spread

• Local invasion
• Nodal spread
• Metastatic spread
Diagnostic / Staging Studies

- CT scan
- Positron emission tomography (PET)
- Endoscopy and biopsy
- Endoscopic Ultrasound (EUS)
- VATS
- Laparoscopy

<table>
<thead>
<tr>
<th>Modality</th>
<th>T Accuracy (%)</th>
<th>N Accuracy (%)</th>
<th>M Accuracy (%)</th>
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<tbody>
<tr>
<td>CT</td>
<td>49–60</td>
<td>39-74</td>
<td>85-90</td>
</tr>
<tr>
<td>EUS</td>
<td>76-92</td>
<td>50-88</td>
<td>66-86</td>
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<tr>
<td>MRI</td>
<td>96</td>
<td>56-74</td>
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<tr>
<td>PET</td>
<td>48-76</td>
<td>71-91</td>
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<tr>
<td>VATS or Laparoscopy</td>
<td>90-94</td>
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</table>
EUS Layers

Management of GERD and Barrett’s Esophagus

EUS T2

Management of GERD

- Maximize medical management of GERD symptoms
  - PPI or H₂ Blockers
  - Weight and diet management
- Consideration of surgical antireflux procedure
- EGD should be performed on pts with:
  - Severe symptoms of GERD
  - Failure of relief with medical treatment
  - Family Hx of BE or esophageal CA
### Effect of Antireflux Surgery on Barrett’s Esophagus

- Excellent or good functional results: 90%
- Total Regression of BE: 19%
- Partial regression: 6%
- Total regression of low-grade dysplasia: 66%
- Possible cancer prevention role: progression to adenocarcinoma in only one per 72.5 patient years
- Surveillance endoscopy is still recommended after antireflux procedures for BE


### Management of BE and HGD

- Invasive adenocarcinoma is present in ~ 50%
- Esophagogastrectomy is the gold standard
- Alternatives:
  - Mucosal ablation:
    - PDT
    - RFA
    - ABC
    - Laser
    - EMR
  - EGD screening q 3 mos if pts refuse surgery and ablation

### Management of BE

If BE is identified, screening EGD with 4 quadrant biopsy should be performed:

- BE and no dysplasia: q 1-3 years
- BE and LGD: q 6 -12 mos
- BE and HGD: pathologic confirmation by 2nd pathologist

### Management of Esophageal Cancer
Curative Treatment Options

<table>
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<tr>
<th>Surgery</th>
<th>Post-operative chemotherapy</th>
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<tr>
<td>Pre-operative chemotherapy</td>
<td>Post-operative chemo-radiation</td>
</tr>
<tr>
<td>Pre-operative chemo-radiotherapy</td>
<td>Definitive chemo-radiotherapy</td>
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</table>

Transhiatal Esophagectomy

Esophagectomy

*Ivor Lewis Procedure*

“Let's a very simple procedure. We slice off the top of your head, scoop out your insides with a spoon, and carve out your eyes and mouth.”
Results of Open Esophagectomy

<table>
<thead>
<tr>
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<th>Michigan (n=195)</th>
<th>VA (n=177)</th>
<th>MSK (n=519)</th>
<th>Duke (n=379)</th>
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<tr>
<td>Mortality</td>
<td>4%</td>
<td>9.8%</td>
<td>4%</td>
<td>5.8%</td>
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<tr>
<td>Anastomotic Leak</td>
<td>13%</td>
<td>NR</td>
<td>21%</td>
<td>14%</td>
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<tr>
<td>Pneumonia</td>
<td>2%</td>
<td>21.4%</td>
<td>21%</td>
<td>16%</td>
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<tr>
<td>Vocal Cord Palsy</td>
<td>7%</td>
<td>NR</td>
<td>4%</td>
<td>NR</td>
</tr>
<tr>
<td>Gastric Tube Necrosis</td>
<td>0.83%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Chylothorax</td>
<td>1.7%</td>
<td>0.02%</td>
<td>NR</td>
<td>NR</td>
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</table>

Our Experience with Minimally Invasive Esophagectomy at OSU

- Single surgeon, single institution experience
- 36 month (6/04 to 6/07)
- 30 pts (29 male, 1 female)
- Indication for MIE: any patient with an indication for open esophagectomy and no prior major thoracotomy or laparotomy
- The mean age was 56
- Clinical stage was I in 10%, II in 50% and III in 30% (6 pts). 10% of patients had Barrett’s esophagus with HGD

Hospital Volume and Surgical Mortality in the United States

Esophagectomy mortality rates ranged from 8.1% at high-volume hospital to as high as 23% at low-volume hospitals

MIE Experience

- Surgical mortality rate (90 days) 10%:
  - mediastinitis and gastrobronchial fistula in 2 patients
  - aspiration pneumonia in 1 patient
  - All 3 in the first half of the study (18 mos)
- Morbidity rate 35%:
  - gastric staple line leak (1)
  - pneumonia (3)
  - Vocal cord paralysis (3)
  - contained radiologic leakage (5)
  - wound infection (1)
### MIE Experience

- All patients at follow-up are on a normal or soft diet
- Overall mean survival is 85.1% at a mean follow-up time of 11.6 months (5.2 to 38 months)
- Cause of late mortality (10%) was disease progression in all patients

### Palliative Treatment

- Stents
- Photodynamic Therapy
- Laser Therapy
- Radiation Therapy
  - ✓ External Beam Radiation
  - ✓ Intracavitary Radiation
- Surgery
  - ✓ Esophagectomy
  - ✓ Bypass
  - ✓ Endothoracic Endoesophageal Pull-Through
TE Fistula After Metal Stent Placement

Post Polyflex Stent Placement

Post Polyflex Stent Placement

Summary

- BE carries a 50-100-fold increased risk of esophageal adenocarcinoma
- Risk factors include male sex, smoking history, obesity, Caucasian ethnicity, age greater than 50, and a greater than 5 year history of reflux symptoms
- Fit patient with Barrett’s esophagus and high-grade dysplasia should undergo esophagectomy to prevent the risk of developing cancer
- For patients who are infirm, too old, or unwilling to undergo surgery, endoscopic ablative approaches may represent a reasonable alternative
Summary

• The role of surgery continues to be the primary treatment modality for invasive esophageal cancer
• MIE has many theoretical benefits, but the actual advantages over open esophagectomy are still currently under investigation
• In a disease where as many deaths occur as new cases are reported each year, we must strive to achieve better treatment options

Esophageal Cancer: Epidemiology

• 14,250 new cases
• 50% diagnosed as local/localized
• 13,300 deaths
• Adenocarcinoma histology >> 50%
• Esophageal cancer is the most rapidly growing cancer in the USA and is affecting middle aged Caucasian males mostly. Its incidence rate is 6 times, and its mortality 7 times what it was in the 1970s.

Multidisciplinary Approach to treating Esophageal (including Gastro-Esophageal) Cancers

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The Ohio State University – James Cancer Hospital

Introduction: The role of Preoperative Therapy

• Adenocarcinoma
  ✓ Preoperative chemotherapy (C) improves survival
  • 2 out of 3 recent phase III studies positive for OS
  • MAGIC trial: 13% improvement of 5yr OS
  • MRC OEO-2: 9% improvement of 2 yr OS

Introduction: The role of Preoperative Therapy

✓ Preoperative C+ Radiotherapy (CRT) with a ?
  • Achieves pCR in 10-30% of pts
  • 2 out of 5 recent phase III studies have shown a survival benefit to CRT


Non-operative Chemo-radiotherapy

U.S. RTOG Trial 85-01

Esophageal Ca
Squamous and Adeno

6400 cGy
Alone

5000 cGy + 5-FU/
Cis x 2
+5-FU / Cis x 2

Cooper JS, JAMA 281:1623-1627, 1999

Introduction: The role of Preoperative Therapy

• Squamous Cell Carcinoma
  ✓ Preoperative Chemotherapy with a ? (INT 113 and MRC OEO-2)
  ✓ CRT can cure patients (RTOG 85-01) without surgery
  ✓ Surgery following CRT with a ? (FFCD 9201)


Intergroup Esophageal Study RTOG 85
Survival by treatment ARM

Cooper JS, JAMA 281:1623-1627, 1999
Treatment schedule of preoperative chemoradiotherapy (arm A) and dose-escalated chemoradiotherapy without surgery (arm B)

- 187 pts, Squamous Ca
- 8 yrs to accrue

Kaplan-Meier plots showing (A) overall survival from the date of randomization among patients allocated to preoperative chemotherapy and surgery (arm A, n = 86) or chemoradiotherapy without surgery (arm B, n = 86) and (B) survival as randomized among patients treated according to their treatment arm excluding cross-over patients (arm A, n = 75; arm B, n = 81)

- Reduced local recurrence with surgery
- Non responders → Surgery: 35% 3 years survival after R0 resection
- Surgical salvage in non responders

Chemo RT → Surgery: Esophageal Cancer

- Path CR in 20-40%
- 5 year DFS 25-35%
- 5-FU + Cisplatin + RT:
  ✓ Severe GI toxicity
  ✓ Enteral feeding tube placement
- Phase III: small, inconclusive

Chemotherapy + Radiation (CRT) → Surgery (S): Phase III Trials Esophageal Cancer

- Bosset (1997), SqCC:
  ✓ 139 pts: S alone → mOS 18.6 mos, 5 yr OS 26%
  ✓ 143 pts: CRT → S → mOS 18.6 mos, 5 yr OS 26%
- Urba (2001): Adeno >> SqCC
  ✓ 50 pts: S alone → mOS 17.5 mos, 3 yr OS 15%
  ✓ 50 pts: CRT → S → mOS 17.5 mos, 3 yr OS 32% (p=0.07)
- Walsh (1997): AdenoCA
  ✓ 55 pts S alone → mOS 11 mos, 3 yr OS 6%
  ✓ 55 pts CRT → S → mOS 16 mos, 3 yr OS 32%

Bosset JF et al, NEJM 1997;337,161-167
Urba SG et al, JCO 2001; 19:305-313
Walsh TN et al, NEJM 1997;335, 462-467

Long-Term Results of RTOG Trial 8911 (USA Intergroup 113): A Random Assignment Trial Comparison of Chemotherapy Followed by Surgery Compared With Surgery Alone for Esophageal Cancer

CF x 3 → SURGERY

N = 443 SqCC and Adeno

Overall survival by type of resection

Overall survival by study arm for chemotherapy followed by surgery versus surgery only

Overall survival distribution curves on the basis of response to preoperative chemotherapy
The “MAGIC” Trial: Perioperative CT

N = 502

ECF x 3 → SURGERY → ECF x 3

R → SURGERY

- Time to recurrence improved: HR 0.7; \( P = 0.002 \)
- Trend in survival: 24 versus 19 months, \( P = 0.063 \)
- Increase in R0 resections: 79% versus 69%

Preoperative Chemotherapy

Boige et al., Abs 4510, ASCO 2007

The “MAGIC” Trial: Neo/Adjuvant Study


Survival

14% survival benefit with preoperative CF
13% improvement in R0 resection rate
No impact on tumor downstaging (EUS not used)
Major impact on systemic recurrence
56% (S) vs. 42% (CF + S)
No impact on local recurrence
Tolerable
(vs. MAGIC → EOS)

Boige et al., Abs 4510, ASCO 2007
Preoperative Chemotherapy

Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma

Thirion P., Michieles S., Le Maitre A., Tierney J.
The Meta-Analysis of Chemotherapy in Esophageal Cancer Collaborative Group

Meta Analyses: Preop Chemo

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial Number</th>
<th>Patient Number</th>
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<th>HR</th>
<th>P value</th>
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<tbody>
<tr>
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<td>9</td>
<td>2102</td>
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<td>0.0033</td>
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<tr>
<td>Madhanar</td>
<td>8</td>
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<td>Gevitski</td>
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<td>1724</td>
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<td>Adeno</td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
<td>0.014</td>
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<tr>
<td>Squam</td>
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<td></td>
<td></td>
<td>0.88</td>
<td>0.12</td>
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</tbody>
</table>

Trimodality therapy is superior to surgery alone in esophageal cancer: Results of CALGB 9781

Thirion et al., Abs 4512, ASCO 2007

Ilson, ASCO 2007

Thirion et al., Abs 4512, ASCO 2007

Preoperative Chemotherapy

- Individual Data from preoperative chemo trials including squamous (Sq) and adenocarcinoma (A) (~ 50:50)
- N= 2102 patients (9 trials)
- OS benefit in both Sq and A
  - A 20\(\rightarrow\) 27%
  - Sq 16\(\rightarrow\) 20%
- R0 improved by 5%
- No increase in operative MR
- Effect A >> Sq

M. Kranska, ASCO Gi 2008, Abs 40
Trimodality therapy is superior to surgery alone in esophageal cancer: Results of CALGB 9781

Preoperative Chemotherapy (C) vs. CRT

- Careful preoperative staging with EUS/Lap
- T3/T4 adenocarcinoma only
- Accrual goal not met
- No difference in R0 resection
  - C (69.5%) vs. CRT (71.7%)
- Improvement in pCR with CRT
  - C (2%) vs. CRT (16%)
- Increased postop mortality with CRT
  - C (3.8%) vs. CRT (10.2%)
- Strong trend favoring OS and FLTP* with CRT (nss)

Conclusions and Future Directions

- Adenocarcinoma of the Esophagus
  - Surgery is curative
  - Preoperative chemo improves survival
  - Preoperative CRT trends towards improved OS vs. C alone, but at the risk of increased toxicities (including mortality rate)
  - The role of RT needs to be better defined:
    - CRITICS: ECX → S → C +/- RT
    - Korean study → X + Cis → S → X + Cis +/- RT
Conclusions and Future Directions

- Squamous Cell Cancer of the Esophagus
  - Unsure about the role of preoperative C alone
  - CRT is potentially curative
    - Need to better define the role of post-CRT surgery (Local control)
  - Need to improve staging/selection of patients before therapy and before planned surgery
    - The role of PET scan as an early response predictor
New Agents For Combined Modality Treatment with Radiation Therapy

- Irinotecan
  - Combined with cisplatin
    - Ilson, Darling, Enzinger
- Taxanes
  - Combined with cisplatin or 5-FU
    - Adelstein, Blanke, Urba

New Agents For Combined Modality Treatment with Radiation Therapy

- Oxaliplatin
  - Combined with 5-FU
    - Khushalani, JCO, 2002
- Biological agents
  - Cetuximab
    - Irinotecan, cisplatin + cetuximab (DFCI)

Treatment Options for Advanced Cancers

Treatment: Metastatic Disease

- Preventing or treating luminal obstruction
  - No role for surgery
  - XRT of questionable value
  - Stent placement
  - Tube feeding
- Treatment of metastatic disease
  - Palliative chemotherapy
### Treatment: Metastatic Disease

<table>
<thead>
<tr>
<th></th>
<th>Webb ECF vs. FAMTX</th>
<th>Ajjani CF vs. DCF</th>
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<tbody>
<tr>
<td>Total Patients</td>
<td>274</td>
<td>463</td>
</tr>
<tr>
<td>Stratification</td>
<td>No</td>
<td>Yes(5)</td>
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<tr>
<td>Primary Endpoint</td>
<td>30% OS</td>
<td>TTP/OS</td>
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<tr>
<td>Metastatic Cancer</td>
<td>64%</td>
<td>97%</td>
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<tr>
<td>Esophageal (n)</td>
<td>51</td>
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<tr>
<td>GEJ</td>
<td>22%</td>
<td>33%</td>
</tr>
<tr>
<td>Response Rate</td>
<td>46%</td>
<td>23%</td>
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<td></td>
<td>21%</td>
<td>39%</td>
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**Ajjani JA, J Clin Oncol. 2007 Aug 1;25(22):3205-9.**

### Phase II Trials (146 pts)

<table>
<thead>
<tr>
<th>Author</th>
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<th>Cancer Type</th>
<th># pts</th>
<th>Major Response Rate</th>
<th>G3-4 Diarrhea</th>
<th>G4 ANC</th>
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<td>Ilson</td>
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<td>Esoph, GE jct</td>
<td>35</td>
<td>57%</td>
<td>11%</td>
<td>9%</td>
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<tr>
<td>Ajjani</td>
<td>weekly</td>
<td>GE jct gastric</td>
<td>38</td>
<td>58%</td>
<td>22%</td>
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<td>GE jct gastric</td>
<td>29 pretreated</td>
<td>31%</td>
<td>13%</td>
<td>9%</td>
<td>5mos</td>
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</table>

**Ajjani JA, J Clin Oncol. 2007 Aug 1;25(22):3205-9.**

### Biological Agents in UGI Cancers

- **EGFR Inhibitors**
  - Gefitinib
  - Esophagus: 12% RR (Ferry, ASCO 2004)
  - Esophagus: 12% RR (Van Grueningen, ASCO 2004)
- **Erlotinib**
  - Esophagus: 6% RR (Radovich, ASCO 2004)
  - SWOG 0127 (Dragovich, ASCO GI 2005)
  - GE junction: 9% RR
  - Distal stomach: 0% RR
### Biological Agents in UGI Cancers

- **EGFR Inhibitors**
  - Cetuximab: chimeric Mab active in CRC
    - DFCI
    - Operable esophagus
    - Cisplatin + irinotecan + cetuximab + radiation
  - SWOG S0415:
    - Esophagus only
    - 2nd line
    - Single agent