MANAGEMENT OF ESOPHAGEAL CANCER

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ESOPHAGEAL CANCER

Squamous
- Upper 1/3
- Associated with smoking, alcohol

Adenocarcinoma
- Lower
- Associated with Barrett’s Esophagus
- Increasing incidence
**Epidemiology of esophageal cancer in the United States, 2012**

<table>
<thead>
<tr>
<th></th>
<th>Squamous cell</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate, per 100,000 population</td>
<td>1.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>2.5:1</td>
<td>6.5:1</td>
</tr>
<tr>
<td>White-to-black ratio</td>
<td>1:4</td>
<td>4:1</td>
</tr>
<tr>
<td>Most common locations</td>
<td>Middle esophagus</td>
<td>Distal esophagus</td>
</tr>
<tr>
<td>Major risk factors</td>
<td>Smoking, alcohol</td>
<td>Barrett's esophagus</td>
</tr>
</tbody>
</table>

**Survival Rate After Surgery**

![Graph showing survival rate after surgery over years]
BARRETT’S ESOPHAGUS

Specialized intestinal metaplasia replaces the stratified squamous epithelium

Consequence of chronic GERD
- Gastro-esophageal reflux disease

Associated with adenocarcinoma esophagus

Screening recommended; no clear studies

Theory:
- Treatment of Helicobacter Pylori may increase incidence esophageal cancer

SURGICAL TREATMENT ESOPHAGEAL CANCER

Overall 5 year survival 15%

Surgical volume in hospital
- Comparing hospital less 2 cases a year vs.
  - 19 cases per year
  - 36% less mortality
DEFINITIVE CHEMOTHERAPY AND RADIATION THERAPY

Superior to radiation therapy alone
Never compared directly to surgery
Generally used in patients felt to be poor surgical candidates
Squamous cell patients with good response to chemo/radiation may not
• Benefit from additional surgery

RESEARCH IN ESOPHAGEAL CANCER

No good studies comparing surgery to chemotherapy and radiation therapy
Neoadjuvant therapy
• Some contradictory studies
SQUAMOUS CELL ESOPHAGUS

Two trials
Chemotherapy + radiation followed
- Surgery
- No surgery
  - For responding patients
No impact on survival

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg,
M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel,
G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta,
R.J.B. Blaise, O.R.C. Busch, F.J.W. ten Kate, G.J. Creemers, C.J.A. Punt,
J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken,
M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema,
A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus,
and A. van der Gaast, for the CROSS Group*
PRE-OPERATIVE THERAPY
MAINLY ADENOCARCINOMA

Radiation
- 41.4 Gy (23 fraction)

Chemotherapy
- Day 1,8,15,22,29
- Carboplatin AUC 2
- Paclitaxel 50 mg/m²

OVERALL SURVIVAL
49 MONTHS CHEMORADIOTherapy; 24 MONTH SURGERY ONLY
SIDE EFFECTS

<table>
<thead>
<tr>
<th>Event</th>
<th>Chemoradiotherapy and Surgery (N = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events of grade ≥3 during chemoradiotherapy — no. of patients (%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Esophageal perforation</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (1)</td>
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</table>

COMPLETE RESECTION (RO) NEGATIVE MARGINS

92% chemoradiotherapy
69 % surgery alone

> 90% completed full chemo-radiation rx
METASTATIC ESOPHAGEAL CANCER

Combination chemotherapy higher response single agent
Minimal improvement standard chemotherapy
- Median survival less one year

METASTATIC ESOPHAGEAL CANCER

Many drugs
- Cisplatinum
- 5FU
- Irinotecan
- Taxanes
- Trastuzumab (her-2 neu positive)
No clear benefit multiple agents same time
HER-2 NEU POSITIVE ADENOCARCINOMA

Approximately 20% of adenocarcinoma
Median survival 14 months
- 2.7 month advantage with Trastuzumab (anti her 2 neu)
- Not as dramatic an improvement as in Breast Cancer
Not approved in neo-adjuvant setting

IMMUNE THERAPY
METASTATIC GEJ ADENOCARCINOMA

FDA approved
  - Pembrolizumab
  - PD-L1 Positive Cancer
  - Progressed following
    - Two lines of chemotherapy

PEMBROLIZUMAB
GASTRO-ESOPHAGEAL ADENOCARCINOMA

PD-L1 positive
  - 13 % response rate
  - 1.4 % complete response rate
  - 26% of responses lasted at least one year

Response rate much lower than in
  - Melanoma, Non Small Lung Cancer, MSI High
IMMUNE CHECKPOINT INHIBITORS

Goyal G, Silberstein PT. Systemic Therapy in Metastatic Melanoma
Fed Pract. 2015 May;32(5(suppl 4)):57S-65S.

HARRY POTTER INVISIBILITY CLOAK

- Cancer makes an invisibility shield so that immune system can’t attack cancer
- These drugs break this shield
  - Allow immune system to attack cancer
PRESIDENT JIMMY CARTER

Metastatic Melanoma to
- Liver (resected)
- 4 lesions in brain (focused radiation)
On year of Anti-PD1

In Remission

IMMUNE THERAPY

Anti-CTLA 4
- Reduces T cell regulatory
- Increases immune response
- Side effects auto-immune diseases
- Approved for treatment of metastatic melanoma
- Used in combination with Anti PD-1

CTLA 4 agonists
- Approved for treatment of rheumatoid arthritis
ANTI PD-1, PDL-1, PDL-2

- Programmed cell death
- Reduces T reg; thus increases immune response
- Better response when combined with Anti-CTLA 4

Approved metastatic
- Non Small Cell Lung Cancer
- Melanoma
- Hodgkin’s Lymphoma
- Head neck, bladder, kidney, cervical, gastric,liver
- Merkel cell cancer
- Any cancer with MSI-high (mis-match repair abnormality); increased mutations.

TAIL CURVE
PROLONGED SURVIVAL METASTATIC MELANOMA.
LONG TERM SURVIVAL METASTATIC MELANOMA WITH ANTI-CTLA 4
SIDE EFFECTS
AUTO-IMMUNE

- Colitis
- Pneumonitis
- Dermatitis
- Thyroiditis
  - Less with Anti-PD1 than Anti CTLA-4
  - Anti PD1 much less side effects than
    - Standard chemotherapy

MICROSATELLITE INSTABILITY (MSI)

- Short, tandem repeated sequences
  - More Instable (MSI-High or MSI-H)- >30%
  - Marker of deficient mismatch repair
- 15% of colon cancers are MSI high
  - Lynch-3%, sporadic- 12%
MICROSATELLITE INSTABILITY

Clinical Benefit of Pembrolizumab Treatment

SUMMARY: ESOPHAGEAL CANCER NEOADJUVANT THERAPY

Squamous Cell
- No clear advantage to surgery in patients that responded to chemotherapy/radiation

Adenocarcinoma
- Survival advantage of
  - Chemo/Radiation/Surgery compared to
    - Chemo/Radiation
ESOPHAGEAL CANCER METASTATIC

Standard chemotherapy
- Survival less than one year

20% adenocarcinoma are Her-2 Neu
- Trastuzumab therapy modestly effective
  - Much more effective in breast cancer

Anti PD1 Therapy
- Approved
- 13% response rate
- More effective in other cancers.