Radiation Therapy Update for Esophagogastric Cancers

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SWOG, San Francisco
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Disclosures

- Advisory Board: DOR Biopharma
- ABR Trustee

Discussion Points

- Radiation Oncology Primer
- Specialized Radiation Techniques
- Adjuvant “Radiochemotherapy” for Esophagus & Gastric Cancers
- Management of GE Junction Tumors
- Role of Conformal Radiation
What Is Radiation?

- High energy photons in the electromagnetic spectrum
- Low energy X-rays are used for diagnostic radiology (~100-400 keV), high energy X-rays (4-18 MeV, more penetrating) are used for treatment of benign or malignant tumors
- Dose deposited in tissue is measured in Gray (Gy)
  1 Gy = 100 rads

Radiation Path in Tissue

Radiation Effects on Cells

- **Photons (X-rays)** cause ionizing events in cells
- **Lethal event**: DNA double strand breaks (multiply damaged sites)

RT Effect on Tumor & Normal Tissue

- Radiation damages DNA indiscriminately.
- How can we use RT if it damages tumor and normal tissue?
  - Physics: Focus dose on tumor while sparing surrounding normal tissues
  - Biology: Take advantage of differences in the response of tumor versus normal tissue to radiation
Fractionation

- Morbidity is caused by imperfect normal tissue repair, and depends on
  - total radiation dose
  - radiation dose per fraction
  - volume treated
- We fractionate (give small daily doses) in order to let the normal tissue repair before giving another dose, (typically 1.8-2.0 Gy/fraction per day, M-F)
- Most curative treatments take 5-8 weeks

Why Does Radiation Technique Matter?

- Morbidity is caused from radiation to normal tissues
- Therefore, the less normal tissue irradiated, the fewer the side effects
- CONFORMAL tumor treatment is critical for normal tissue sparing and for maximizing the radiation dose to the tumor

What Is the Process?

First, a simulation (radiation planning session)

2D Simulation

- Requires less time and patients can start treatment faster
  - Plain X-rays taken with patient in the treatment position from the Beam’s eye view
  - Tumor dose and dose to nearby tissues (ie. heart, lung and spinal cord) are not known with exact precision
  - Blocks are drawn on the films to block radiation from non-target tissues
Radiation Planning: From 2D to 3D

2-Dimensional Planning
- Requires less time and patients can start treatment faster.
- Plain X-rays taken with patient in the treatment position from the Beam’s eye view.
- Tumor dose and dose to nearby tissues (i.e., heart, lung and spinal cord) are not known with exact precision.
- Blocks are drawn on the films to block radiation from non-target tissues.

3-D Planning (Simulation)
- Patient placed in the treatment position and CT scanned.

3-D CT Based Planning
- Tumor and normal structures are drawn on each 2-5 mm CT slice by the rad onc physician.

3-D CT Based Planning
- A plan is generated based on dose constraints to normal tissues and the prescription dose to the tumor & reviewed by the rad onc doc & physicist.
Specialized Radiation Delivery Techniques

Specialized Radiation Therapy Techniques

1. From 3D to 4D Treatment Planning
2. Intensity-Modulated Radiation Therapy (IMRT)
3. Image-Guided Radiation Therapy (IGRT)
4. Stereotactic Radiation (SRS, SRT)
Specialized Radiation Therapy Techniques

1. From 3D to 4D Treatment Planning
2. Intensity-Modulated Radiation Therapy (IMRT)
3. Image-Guided Radiation Therapy (IGRT)
4. Stereotactic Radiation (SRS, SRT)

What Is IMRT?

- IMRT stands for *Intensity Modulated Radiation Therapy*
- Uses 3-D or 4-D CT based planning
- Blocks move in and out of the beam to modulate the dose through a given portal
- Multiple beams are used (5-9 beams)
- It takes about 3x as long to treat a patient because the beam is blocked much of the time
Multileaf Collimator in LINAC

Increasing Conformality with IMRT
- Rt. parotid salivary gland is protected
- Cord is spared

Specialized Radiation Therapy Techniques

1. From 3D to 4D Treatment Planning
2. Intensity-Modulated Radiation Therapy (IMRT)
3. Image-Guided Radiation Therapy (IGRT)
4. Stereotactic Radiation (SRS, SRT)

Varian Trilogy® with “Star Field”
Image-Guided Radiation Therapy (IGRT)

Varian On-Board Imaging® (OBI)
Daily X-ray films (kV and CT) for precise set-up

Combined with patient custom immobilization (vac-loc) for on-the-millimeter precision.

Cone Beam Match Anal Cancer

Cone Beam Match Gastric Cancer

Specialized Radiation Therapy Techniques

1. From 3D to 4D Treatment Planning
2. Intensity-Modulated Radiation Therapy (IMRT)
3. Image-Guided Radiation Therapy (IGRT)
4. Stereotactic Radiation (SRS, SRT)
<table>
<thead>
<tr>
<th>Stereotactic Radiosurgery (SRS)</th>
<th>Invasive Immobilization with Gamma Knife or LINAC SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ Stereotactic radiosurgery (SRS) is high dose radiation focused on a small volume (&lt; 4 cm)</td>
<td>◦ SRS Frame (pins pierce skin and affix to skull to ensure no slippage)</td>
</tr>
<tr>
<td>◦ Doses are usually 10-20 Gy in one fraction (fractionated radiation uses ~ 2 Gy/day)</td>
<td>◦ Joint procedure of Rad Onc and Neurosurgery</td>
</tr>
<tr>
<td>◦ Can be intracranial or extracranial</td>
<td>◦ Body Fix (“seal a meal”)</td>
</tr>
<tr>
<td>◦ Invasive head frame--set up accuracy &lt;1 mm needed for accelerator-based cranial SRS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CyberKnife® Frameless Radiosurgery</th>
<th>Stereotactic Radiosurgery (SRS): Brain Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ An image guided robotic stereotactic irradiation technique</td>
<td>◦ Lesion is encompassed by several arcs using a linear accelerator (4-6 MV photons); dose based on size of lesion</td>
</tr>
<tr>
<td>◦ Does not require invasive immobilization</td>
<td></td>
</tr>
<tr>
<td>◦ Continually checks and compensates for any movement you make during treatments, ensuring accuracy</td>
<td></td>
</tr>
<tr>
<td>◦ Decreased treatment margins to allow for reduced radiation exposure to surrounding critical organs</td>
<td></td>
</tr>
<tr>
<td>◦ Maneuverability significantly more versatile than conventional LINAC</td>
<td></td>
</tr>
</tbody>
</table>
Gastric cardia adenocarcinoma
1975 - 1988: 12 → 22 cases per million, stabilized since

Esophageal adenocarcinoma
1975 - 2001: 4 → 23 cases per million, ~6-fold increase

Disease Specific Survival by Stage:
Esophageal cancer

Similar outcomes after surgery alone for gastric cancer.
Adjuvant Therapy for Esophagogastric Cancer

- Esophageal Cancer
  - Preoperative chemoradiation

- Gastric Cancer
  - Postoperative chemoradiation
  - Perioperative chemotherapy

- Management of GE junction cancers?

Rationale for Preoperative Radiation/Chemoradiation Therapy for Esophageal Cancer

- Margin (+) rate after surgery alone for locally advanced tumors is between 20-30%.
- Positive margins are associated with poor outcomes.
- Chemoradiation produces downstaging that may influence margin positive resection rate.

Select Trials of Neoadjuvant Chemoradiation

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Chemo</th>
<th>RT Dose</th>
<th>pCR</th>
<th>OS-3yr Surg</th>
<th>OS-3yr CRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh</td>
<td>113</td>
<td>Cis/5FU</td>
<td>40 Gy</td>
<td>25%</td>
<td>6%</td>
<td>32%</td>
<td>0.01</td>
</tr>
<tr>
<td>Bosset</td>
<td>297</td>
<td>Cis</td>
<td>37 Gy</td>
<td>26%</td>
<td>34%</td>
<td>36%</td>
<td>0.78</td>
</tr>
<tr>
<td>Urba</td>
<td>100</td>
<td>Cis/5FU/Vinblastine</td>
<td>45 Gy</td>
<td>28%</td>
<td>16%</td>
<td>30%</td>
<td>0.15</td>
</tr>
<tr>
<td>Burmeister</td>
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<td>30%</td>
<td>33%</td>
<td>0.57</td>
</tr>
<tr>
<td>Tepper</td>
<td>56</td>
<td>Cis/5FU</td>
<td>50.4 Gy</td>
<td>40%</td>
<td>16%</td>
<td>39%</td>
<td>0.002</td>
</tr>
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Select Randomized Trials of Neoadjuvant Chemoradiation

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<td>39%</td>
<td>0.002</td>
</tr>
<tr>
<td>Van Der Gaast CROSS</td>
<td>350</td>
<td>Carbo/taxel</td>
<td>41.4 Gy</td>
<td>32%</td>
<td>48%</td>
<td>59%</td>
<td>+ (p-value not given)</td>
</tr>
</tbody>
</table>
Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study of surgery vs. CRT

CROSS study group

ASCO 2010

Chemoradiotherapy regimen:
- Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
- Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)

Primary endpoint: median overall survival (16 vs. 22 mo.) and QoL

175 pts per arm (stratify on histology)

Overall Survival

Toxicity of CRT

- Major toxicities (grade 3-5 NCI-CTC 3.0)
  - Hematologic: n=12 (6.8%)
    - Grade 3: n=12
    - Grade 4: n=0
    - Grade 5: n=0
  - Non-hematologic: n=28 (16%)
    - Grade 3: n=26
    - Grade 4: n=1
    - Grade 5: n=1
Resection Rate and Resection Margins

Resection rate of all randomized patients:

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162/188 (86%)</td>
<td>157/175 (90%)</td>
</tr>
</tbody>
</table>

Resection margins:

<table>
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<tr>
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<th>CRT + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>110 (67%)</td>
<td>145 (92.3%)</td>
</tr>
<tr>
<td>R1</td>
<td>52 (33%)</td>
<td>12 (7.6%)</td>
</tr>
</tbody>
</table>

p<0.002

R0 = no tumor within 1 mm of the resection margins

Pathology after CRT

pCR rate 32% in resected tumors

Tumor Regression Grade

- TGR1: No vital cells (pCR)
- TGR2: <10% vital cells
- TGR3: 10-50% vital cells
- TGR4: >50% vital cells

Morbidity and Mortality (Postoperative)

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary complications</td>
<td>66%</td>
<td>69%</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7 (3.8%)</td>
<td>6 (3.4%)</td>
</tr>
</tbody>
</table>

HR’s (95% CI) for death according to baseline variables

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>N0</th>
<th>N1</th>
<th>Male</th>
<th>Female</th>
<th>AC</th>
<th>SCC</th>
<th>WHO 0</th>
<th>WHO 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.67 (0.49 – 0.91)</td>
<td>0.49 (0.27 – 0.90)</td>
<td>0.72 (0.50 – 1.04)</td>
<td>0.62 (0.44 – 0.87)</td>
<td>0.92 (0.45 – 1.89)</td>
<td>0.82 (0.58 – 1.16)</td>
<td>0.34 (0.17 – 0.68)</td>
<td>0.67 (0.49 – 0.94)</td>
<td>0.67 (0.32 – 1.41)</td>
</tr>
<tr>
<td>WHO 1</td>
<td>0.0</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall
**Comments**

- Neoadjuvant CRT with weekly administrations of carboplatin and paclitaxel and concurrent RT followed by surgery improves survival compared to surgery alone, independent of histology.
- No increase in postoperative complications or postoperative mortality with preoperative CRT.
- Largest randomized trial performed for neoadjuvant therapy.
- Outstanding control arm.
- Low pulmonary toxicity reflective of RT dose/field design.
  - Is 41.4 Gy enough?
- Patients are representative of who we now see.
- This will likely become the definitive study of neoadjuvant chemoradiation therapy.

**Rationale for Adjuvant Therapy for Gastric Cancer**

- Most patients present with advanced disease.
- Survival is poor with surgery alone.
- High rate of both metastatic and loco-regional recurrence.

**Gastric Cancer: Patterns of relapse after surgery**

- Rationale: LRR occurs in 40-60% after surgery alone

556 subjects:
- Adenocarcinoma of stomach or GEJ (20%)
- Stage Ib-IVM0
- Gastrectomy
- R0 resection required
- D2 node dissection recommended (54% were D0)

**INT 0116: Postoperative ChemoRT**

- Observation (N=275)
- Postop Chemo RT (N=281)

  - Chemo IVB: 5-FU (425mg/m2/d) + LV (20 mg/m2/d)
  - RT: 45 Gy/1.8 Gy fx/25

INT 0116: Radiation Details

45 Gy in 25 fractions of 1.8Gy/fx to:
- Primary tumor bed
- Regional lymphatics including the perigastric, splenic,* pancreaticoduodenal,* porta hepatis, celiac, local para-aortic
  - Lower paraesophageal nodes were included for GE junction primaries
- Distal deafferented duodenum/stomach remnant and proximal anastomosis plus 2 cm margin

INT 0116 Outcomes
Median followup = 60 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No</th>
<th>DFS-3y (%)</th>
<th>P</th>
<th>OS-3y (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>275</td>
<td>31</td>
<td>--</td>
<td>41</td>
<td>--</td>
</tr>
<tr>
<td>Postop ChemoRT</td>
<td>281</td>
<td>48</td>
<td>&lt;0.001</td>
<td>50</td>
<td>0.005</td>
</tr>
</tbody>
</table>

INT 0116 Patterns of Failure

**Sites of Relapse**

- In CRT group:
  - 64% completed treatment as planned
  - 17% stopped due to toxicity

Postoperative Chemoradiation after D2 Dissection

- Samsung Medical Center
  - Observational Study
    - 544 treated with post-op chemo/RT
    - 446 observed
    - Adjuvant therapy group higher risk
    - 98% had > 15 nodes assessed, 87% had > 25 nodes assessed

*Because patients could have relapses at multiple sites, the total number of relapses is greater than the number of patients in each group who had relapses.*
MAGIC Trial: Perioperative Chemotherapy

- RCT conducted by UK MRC from 1994-2002.
- Rationale: ECF ~50% RR. Downstage, relieve symptoms, and eliminate micromets.

503 subjects:
- Resectable adenocarcinoma of stomach (74%), GEJ (11%), or lower 1/3 esophagus (15%).
- Stage II-IVM0

Surgery alone (N=253):
- Total or partial gastrectomy
- LND at discretion of surgeon

Perioperative Chemotherapy (N=250):
- ECF x 3: Epirubicin (50mg/m2) d1+
  Cisplatin (60mg/m2) d1+
  CI 5-FU (200mg/m2/d) d1-21.
- Surgery 3-6 weeks after cycle 3
- ECF x 3 started 6-12 w postop

MAGIC Trial Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No</th>
<th>PFS-5y (%)</th>
<th>P</th>
<th>OS-5y (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>253</td>
<td>18</td>
<td>--</td>
<td>23</td>
<td>--</td>
</tr>
<tr>
<td>Perioperative chemotherapy</td>
<td>250</td>
<td>38</td>
<td>&lt;0.001</td>
<td>36</td>
<td>0.009</td>
</tr>
</tbody>
</table>

MAGIC Trial: Path Findings

- Median maximum diameter of tumor
  - Resected group: 5 cm
  - Perioperative group: 3 cm (P<0.001)
- T1 or T2 tumors
  - Resected group: 36.8%
  - Perioperative group: 51.7% (P=0.002)
- N0 or N1 status (vs. N2 or N3)
  - Resected group: 70.5%
  - Perioperative group: 84.4% (P=0.01)
MAGIC Trial: Patterns of Recurrence

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Surgery group (%)</th>
<th>Perioperative chemo Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>20.6</td>
<td>14.4</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>36.8</td>
<td>24.4</td>
</tr>
</tbody>
</table>

- Treatment tolerance in experimental arm:
  - 86% of those assigned (and 90% who started) preop chemo, finished it.
  - 97% of those proceeded to surgery
  - 66% of those started postop chemo (18% did not start because of progressive disease or death)
  - 76% of those completed postop chemo.
- OVERALL: 42% completed perioperative chemo regimen.

Overall Conclusions: Treatment of Resectable Gastric Cancer

- Both regimens improve OS & DFS over surgery alone.
  No direct comparison.

<table>
<thead>
<tr>
<th></th>
<th>INT 0116</th>
<th>MAGIC</th>
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<tbody>
<tr>
<td>CRT</td>
<td>S</td>
<td>S Peri-CT</td>
</tr>
<tr>
<td>LF%</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>DM%</td>
<td>18</td>
<td>33</td>
</tr>
</tbody>
</table>

- Summary:
  - INT 0116: Postoperative CRT
    - May improve cure rate by locoregional control
    - 90% get at least 3 cycles of chemo and surgery
  - MAGIC: Perioperative chemotherapy
    - May improve cure rate by substantial improvement in DM rate
    - 64% complete regimen: unclear where they drop out

Which Approach?

- Generally favor perioperative chemotherapy because:
  - Many patients will not receive postoperative therapy.
  - Rates of curative resection are HIGHER with preoperative chemotherapy.
  - Role of radiation therapy after perioperative therapy is still unknown and under investigation.

CRITICS Trial (Ongoing Trial)

CRITICS Trial:
  - Randomize
  - Cape + Cisplatin + 45 Gy RT
  - ECF x 3

N = 788
**Multidisciplinary Treatment of GE Junction Cancers—What Is the Best Approach?**

“GE junction”—reflects unclear separation of distal esophageal and proximal gastric cancer

Convergence of therapies for **advanced** gastric and esophageal cancers since mid 1990s.

What about for **localized** disease?

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**All 3 Approaches Are Acceptable in the Treatment of Resectable GE Junction Cancers**

- Neoadjuvant chemoradiation
- Adjuvant chemoradiation
- Perioperative chemotherapy

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**Conformal Radiation for Esophagogastric Cancers:**

No Level 1 Evidence to Support Routine Use of IMRT

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**Dosimetric Studies of IMRT in Esophageal Cancer**

- Several dosimetric studies have been published comparing 3D CRT vs. IMRT:
  - Nutting 2000, 2001
  - Wu 2004
  - Zhao 2004
  - Chandra 2005

- These studies show the ability of IMRT to reduce dose to normal tissue while coverage of target remains the same.
Conformal Radiation Delivery

**IMRT**

**3D**

IMRT & Low Doses to Lung

Lung Dose and Postoperative Complications

IMRT Spares More Heart Dose

IMRT Spares More Kidney & Liver

3-D ...... IMRT~~

Clinical Studies of IMRT in Gastric Cancer

- Retrospective Stanford comparison of 3D vs. IMRT (Minn, Cancer 2010):
  - 57 pts
  - similar outcomes
  - dosimetric sparing in kidneys leads to physiologic sparing (median serum creatinine increase in 3D, not IMRT)

6 Field IMRT GEJx Plan
Conclusions in Adjuvant Therapy for Esophagogastric Cancers

- Level 1 evidence supports chemoradiation followed by surgery as the standard of care for esophageal cancer.
- Level 1 evidence supports both perioperative chemotherapy and postoperative chemoradiation as two standards for gastric cancer. These two approaches have not been directly compared for gastric cancer.
- For GE junction cancers, treatment is individualized.
- No evidence to support routine use of IMRT.

Future Directions

- Role of trastuzumab in HER2 overexpressing esophagogastric cancer:
  - RTOG 1010
- Other molecular targeted therapies:
  - PARP inhibitors
  - EGFR inhibitors (RTOG 0436, ACOSOG Z4051, REAL 3)
  - VEGF inhibitors (MAGIC 2)
- Role of radiation therapy (CRITICS)
- Role of IMRT (TBD)

Thanks for Your Attention!
For Further Information, Visit our Website at:

https://bmc.org/radonc