IMRT for GI Malignancies

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Department of Radiation Oncology
Residency Program Director
Selective use of IMRT for GI malignancies

Advantages

- GEJ: Optimize lung/cardiac dose
- Rectal: Spare fixed bowel
- Pancreatic/Liver: Dose escalation near GI tract
  - Curative doses for nodes, pancreatic ca, HCC
- Anal: Spare genitalia
Advantages of IMRT
Gastric / GEJ

- Cardiac / lung sparing
- No advantage in GI toxicity
- Slight improvement in liver DVH
- Minority of patients (10%) important kidney sparing
  - Antral and body lesions
Contouring: Intact GEJ/stomach

- GTV EGD/CT/PET + 3 cm mucosal expansion=MTV + Gross Nodes=CTV1
- Elective nodes + 0.5cm rad, 1cm sup/inf= CTV2
  - Porta Hepatis
  - SMA
  - Celiac
  - Splenic Hilum
- CTV3=CTV1 + CTV2
- CTV3 + 1cm rad, 1.5 cm sup/inf=Final CTV
- Final CTV + 0.5 cm=PTV
Splenic: High risk for Upper 1/3

<table>
<thead>
<tr>
<th>Series (ref)</th>
<th>Upper 1/3/corpus</th>
<th>Lower 1/3/antral</th>
<th>Upper 1/3/corpus</th>
<th>Lower 1/3/antral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kodera et al. (47)</td>
<td>19/147 (13%)</td>
<td>0/12 (0%)</td>
<td>6/50 (12%)</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>Sunderland et al. (48)</td>
<td>21/50 (42%)</td>
<td>42/672 (6.3%)</td>
<td>3/416 (8.4%)</td>
<td>330/672 (49%)</td>
</tr>
<tr>
<td>Noguchi et al. (49)</td>
<td>58/416 (13.9%)</td>
<td>14/339 (4%)</td>
<td>8/150 (5%)</td>
<td>166/339 (49%)</td>
</tr>
<tr>
<td>Maruyama et al. (50)</td>
<td>18/150 (12%)</td>
<td>0/25 (0%)</td>
<td>2/21 (10%)</td>
<td>3/17 (18%)</td>
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<tr>
<td>Cuschieri et al. (20)**</td>
<td>12/48 (25%)</td>
<td>56/1048 (5%)</td>
<td>51/637 (8%)</td>
<td>504/1040 (48%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>128/511 (16%)</td>
<td>56/1048 (5%)</td>
<td>51/637 (8%)</td>
<td>504/1040 (48%)</td>
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* Includes splenic hilum and artery, corresponds to sites 10, 11 of the JRCGC classification.
† Includes nodes of most distal greater curve + inferior to pylorus, sites 6, 17, 18, 14, 13.
‡ Among those with T2–T4 primaries.
§ 0.7–1.7% of retropancreatic and mesenteric root.
|| Retropancreatic node evaluation only.
Table 3. Lymph node involvement by gastric subsite

<table>
<thead>
<tr>
<th>Series (ref)</th>
<th>Incidence lymph node metastasis (no. involved/no. patients)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Upper 1/3/cardia</td>
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GTV: EGD/CT/PET

Beam's Eye View DRR for "Beam_1"
GTV 3 cm mucosal expansion = MTV
Gross Node
Celiac
Porta Hepatis
Splenic Hilum
Final CTV
IMRT/IGRT/Gating for Liver primaries

Rationale = Dose escalation = curative treatment
Advances in HCC radiation addressing the challenges

- Understanding the risk of toxicity
- Identifying the tumor accurately
  - Contrast
  - Fiducials
  - TACE contrast
- Accounting for movement
  - Breath-hold
  - 4D CT
  - Respiratory gating
- Sophisticated treatment delivery
  - IMRT
  - IGRT
Defining the tumor: Contrast dynamics

Contrast intensity

Hepatic arterial  Hepatic parenchymal  Portal venous

Time (sec)

Aorta  Liver  HCC  Liver met
Fiducial Implantation

• 3 gold fiducial markers implanted in liver around tumor (1.2 mm diameter, 3 mm length)
Targeting the tumor: 4D-CT
RPM System Tracks Breathing Motion during CT

marker block with IR-reflecting dots
4D-CT with & without Contrast

1σ 95% # Data Pts

<table>
<thead>
<tr>
<th></th>
<th>1σ</th>
<th>±</th>
<th>95%</th>
<th>±</th>
<th># Data Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set-Up Error</td>
<td>±2.7 mm</td>
<td></td>
<td>±4.6 mm</td>
<td></td>
<td>120</td>
</tr>
<tr>
<td>Gating Precision</td>
<td>±1.1 mm</td>
<td></td>
<td>±2.2 mm</td>
<td></td>
<td>569</td>
</tr>
</tbody>
</table>

What we do - Liver IGRT

• What are we trying to avoid?
  – Bowel - duodenum and colon
  – Liver - lower volume / increased dose

• Implant fiducials for daily set up
  – If not possible, daily cone beam CT for set-up

• 4-D CT assessment of tumor motion + breath hold feasibility
  – <1cm- excursion or irregular breathing - ITV
  – >1cm- breath hold (ITV of ~5 trials to define gating window)

• Set up to fiducials / RPM for gating
Dose constraints

- **Liver**
  - V30 <50% for normal liver function
  - V30 <33% for Childs A or B
  - Mean dose 28Gy
- **Colon and duodenum**
  - < full thickness 55Gy
  - <5 cc can receive >60
- **Chest wall**
  - High dose may cause pain
  - Don’t limit dose, limit volume
Strategies – Locally advanced pancreatic cancer

• Start with systemic therapy
  – micro met dz at dx in 80+%  
  – Also select out worst biology

• Selective local treatment intensification
  – Clinical trials- novel biologic agents
  – Curative XRT doses (@ std fx) when possible
    • Respect GI tolerance (high end to small volumes undefined)
    • Or exceed it with good reason and appropriate informed consent
IMRT - Pancreatic Cancer

- IMRT useful for avoidance of GI tract
- Dose escalation beyond 50.4 Gy
- 70-75 Gy can be curative in selected patients
  - Pancreatic neck
Curable Subsets of Localized PaCa?
Recent Evidence

• MDACC Phase II trial (50.4Gy + cetuximab) POF
  – 30-40% with late local progression
  – ? Driving OS in a subset?

• JHU Rapid Autopsy series
  – 30% died with “locally destructive” pancreatic cancer phenotype
  – DPC4 mutations more common in LD tumors (p=0.007)
**Freedom from Local Tumor Progression**

1st Site LF (mo):
- 31.2,
- 25.0,
- 18.3,
- 16.7,
- 16.5,
- 16.1

*DM and LP endpoints coded independently and censored at the time of last imaging*

**Legend for the graph:**
- Survival Function
- Censored

**Graph Description:**
- DM dominant disease with good local disease control
- Local dominant disease with opportunity for further improvement in outcome by enhanced local treatment effect

**Timeline:**
- 16.0 mo
JHU Rapid Autopsy Series

Local only

limited metastatic

extensive metastatic

Iacobuzio-Donahue et al, JCO, 2009
Success of XRT Dose Escalation near the GI tract hinges on selection.

- **2000-2010 - Clinical selection**
  - Select out early DM phenotype
    - Chemo first, Ca 19-9>1000, poor PS

- **2010 and beyond - genotypic selection**
  - Identify ‘locally invasive’ phenotype
  - SMAD4 intact? (Iacobuzio-Donahue et al, JCO, 2009)
Selection and Tools
XRT dose escalation, LAD

• Favorable factors
  – Location, location, location (neck and proximal body)
  – Low initial Ca 19-9
  – Response to CTX
  – Good KPS
  – Small tumor
  – SMAD4?

• Control motion / escalate the dose / understand and respect tolerance of GI tract

• Tools
  – IMRT
  – Account for or control respiratory movement
    • 4-D CT, Gating, breath hold, fiducial based
The Pancreas:
Close to and surrounded by bowel
Pancreatic Protocol CT Fusion with Non Contrast Planning CT
Pancreatic Protocol CT Fusion with Non Contrast Planning CT
Pancreatic Protocol CT Fusion with Non Contrast Planning CT
Pancreatic Protocol CT Fusion with Non Contrast Planning CT
4-D Simulation technique

• Implant fiducials (stent will work if stable)
  • (implantable dosimeter?)
  • External fiducial (RPM)
• IV and oral contrast (gastrografin)
  – 45 Sec delay
  – We have abandoned diagnostic CT fusion for now
• 4D CT
  – If slight excursion, use ITV to account for motion (easiest technique)
  – If < 1cm from GI mucosa or large excursion
    • Breath hold technique
    • ITV-BH Take at least five series in breath hold
    • Set up to fiducials, monitor with RPM, CBCT q wk
A PHASE I RADIATION DOSE-ESCALATION STUDY OF IMRT WITH CONCURRENT FULL-DOSE, FIXED DOSE-RATE, GEMCITABINE IN PATIENTS WITH UNRESECTABLE PANCREATIC CANCER

Edgar Ben-Josef, MD
Associate Professor
Department of Radiation Oncology
University of Michigan
IMRT FOR PANCREAS CANCER
DOSE DISTRIBUTION
## Radiotherapy Dose

<table>
<thead>
<tr>
<th>Level</th>
<th>Total Dose</th>
<th>Dose per Fraction</th>
<th>BED*</th>
<th>Dose Equivalent (1.8 Gy/fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>45.0</td>
<td>1.8</td>
<td>53.1</td>
<td>45.0</td>
</tr>
<tr>
<td>Level 2**</td>
<td>50.0</td>
<td>2.0</td>
<td>60.0</td>
<td>50.4</td>
</tr>
<tr>
<td>Level 3</td>
<td>52.5</td>
<td>2.1</td>
<td>63.5</td>
<td>54.0</td>
</tr>
<tr>
<td>Level 4</td>
<td>55.0</td>
<td>2.2</td>
<td>67.1</td>
<td>57.0</td>
</tr>
<tr>
<td>Level 5</td>
<td>57.5</td>
<td>2.3</td>
<td>70.7</td>
<td>60.0</td>
</tr>
<tr>
<td>Level 6</td>
<td>60.0</td>
<td>2.4</td>
<td>74.4</td>
<td>63.0</td>
</tr>
</tbody>
</table>

* BED = Biological Effective Dose; $\alpha/\beta = 10$
** The initial dose level was Level 3
RESULTS

- Est median OS 23.1 mo
- 1 patient (4%) LP
- 2 R0 resections – pCR, mRD
### GI dose/volume mucosal tolerance

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum/ilium</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>50Gy</td>
<td>&lt;50%</td>
<td>100%</td>
<td>Single loop</td>
<td>100%</td>
</tr>
<tr>
<td>55Gy</td>
<td>?</td>
<td>&lt;50% circumference</td>
<td>&lt;5cc</td>
<td>100%</td>
</tr>
<tr>
<td>60Gy</td>
<td>&lt;5cc</td>
<td>&lt;5cc</td>
<td>0cc</td>
<td>&lt;50% circumference</td>
</tr>
<tr>
<td>70Gc</td>
<td>0cc</td>
<td>0cc</td>
<td>0cc</td>
<td>10cc</td>
</tr>
<tr>
<td>SBRT &gt;10Gy/fx</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
47 y/o WF neck lesion, s/p R2 distal pancreatectomy
Selective use of IMRT - Rectal Cancer

• IMRT not necessary to reduce toxicity
  – Exception, post-op cases with fixed bowel
• IMRT useful for:
  – Sparing genitalia / inguinal coverage <2cm from the AV
  – Definitive nodal treatment
# MDACC Pre-op Rectal Matched Pair Analysis

Capecitabine vs PVI 5-FU

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine</th>
<th>5-FU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3-4 toxicity</td>
<td>6%</td>
<td>6%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>22%</td>
<td>3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Diarrhea (≥ grade 1)</td>
<td>70%</td>
<td>83%</td>
<td>0.06</td>
</tr>
<tr>
<td>Diarrhea (≥ grade 2)</td>
<td>51%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>6%</td>
<td>19%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Das, IJROBP, 2006
Indications for Dose Adjustment
PVI 5-FU or Capecitabine

- ≥ Grade 2 GI toxicity or HFS
  - Optimize medical management

- After optimal medical management, interrupt for ≥ Grade 2 non-heme toxicity
  - Resume at 25% dose reduction

- Do not interrupt XRT
Dose volume considerations
Small bowel

• **V50.4 = 147cc**
  – 147cc (G0-G2) vs 503cc (G3) GI toxicity
  – Assessed from 2D plans, n=80
    • Minsky et al, JCO 1995

• **V15 = 127cc**
  – Pts with 127cc (G0-G2) vs 319 cc (G3) GI toxicity, n=40
    • Baglan, et al, IJROBP, 2002

• **V5-V30 trend to ≥ grade 2 diarrhea**
  – No statistically significant correlations, n=41
    • Tho et al IJROBP 2006

• **V15 <150cc, Grade ≥2 diarrhea, n=28 pts**
  • Gunnlaugsson et al Radiother & Oncol 2007
Threshold doses for G3 Diarrhea CXRT
Pre/post op CRT rectal ca, n=96

William Beaumont Hospital, Robertson, et al IJROBP, 2008
Sample DVH IMRT vs CRT (n=5)
Sparing of V35-V50 is at the expense of V15-V35

Urbano, IJROBP, 2006
RTOG 0822: A PHASE II Study of IMRT
Preop rectal cancer

• 45Gy/25 fx IMRT
• 5.4 Gy/3x boost CRT

Small bowel constraints
• No more than 180 cc above 35 Gy
• No more than 100 cc above 40 Gy
• No more than 65 cc above 45 Gy
• No small bowel volume should receive 50 Gy

– V5-30 unconstrained but will also be analyzed
  • If variable correlation with toxicity could provide important data

Micheal Garofalo, PI
Enhanced local control?

Dose painting nodes and margins
IMRT for improved local control

• Definitive treatment of unresectable nodes
  – Internal iliac nodes
  – Common iliac node
  – Paraaortic nodes

• Selective boost of close margin preoperatively

• Simultaneous in field boost
  – One wall of bowel < 5cc
    • 63Gy / 28 fx @ 2.25 Gy/fx to GTV
      – 50.4 to CTV

• Careful to avoid sciatic n. and ureters
  – IGRT
    • KV imaging, consider cone beam CT
Total Mesorectal Excision
Internal iliac nodes not resected
Case #1: Internal iliac node outside of the surgical field

Enlarged internal iliac node
Definitive IMRT 63 Gy/28 fx to internal iliac node
50.4 Gy 28 fx to mesorectal outside of the surgical field
Recurrent Sigmoid Colon ca
Recurrent/Persistent Unresectable Nodes
IMRT to Gross Node (63 Gy)
50.4 to PA nodes
T4 rectal cancer, sacral invasion
T4 rectal cancer
63Gy to radial margin, 50.4 Gy/28 fx to CTV
Caveats: IMRT for residual adenopathy

- Dose limited by GI mucosa
- *MINIMIZE VOLUME of BOWEL in HIGH DOSE*
  - Limit full thickness of segment of bowel to
    - 55 Gy
  - Focal areas limited to one wall of the bowel
    - 63 Gy (<5cc)
    - 70 Gy (0 cc)
Toxicities of Chemoradiation for anal cancer

- Moist desquamation
  - perianal
  - genitalia
- Diarrhea
- Dysuria in females
  - (from vulvar moist desquamation)
IMRT for Anal Cancer

Minimization of genitalia dose is the key
IMRT Can Enhance the Advantages of Neoadjuvant Chemoradiation

• Further reduce acute and late toxicity
  – Lower small bowel dose
    • V15 or V45?

• Change the operation
  – Increased resectability: T4 or recurrent tumors

• Enhanced local tumor control
  – Definitively treat what the surgeon will not remove
  – Nodes outside of the operative bed
Small bowel toxicity
Dose volume correlations

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      - 50.4 to CTV
  - No bowel within 1 cm of SIFB
    - 70Gy / 28 fx @ 2.5 Gy/fx to GTV
      - 50.4 to CTV
  - IGRT
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    - 70 Gy (0 cc)
IMRT for Anal Cancer

• Clear toxicity reduction
• The reason IMRT is better:
  • External genitalia sparing
    – Sexual function
    – Acute skin reactions
The Most commonly used technique for Anal Cancer is Actually a Vulvar Technique

- Narrow PA, wide AP, electron supplement
  - 45 to 55 Gy

- The vulva, scrotum, penis and small bowel are avoidance structures, not targets
Treatment Breaks are Bad

• **RTOG 92-08**: (5-FU/MMC 59.6 Gy/33 fx)

  Colostomy rate

  23% (N= 46) vs 11% (N=18)
  (2 wk break) (no planned break: 50% needed break)

• **AP/PA technique = worse skin reactions**

  Can J Sci Am, 1996,
pASTRO 97
MDACC Technique For Anal Cancer Since 1988

L5-S1

30.6 Gy

45 Gy

50.4-59 Gy

Optional block

24-25 Gy
MDACC POF: 5 Marginal Recurrences
Pre-sacral/ Iliac

N = 5/68 = 7%

N = 0/89 = 0%

1992-1999

Post- 1999
IMRT is Even Better

Spare small bowel + genitalia

Individualize nodal dose
Comparison of Genitalia Dose by Technique

• RTOG 98-11: AP/PA
  – 45Gy–60Gy

• MDACC AP/PA, then post 3-field
  – 100% 33Gy–35 Gy

• IMRT
  – 20 Gy; 25%>20Gy
Simulation

- Simulated in frog-leg position to reduce skin reaction
- Metallic marker placed at anal verge and urethra (females)
Vulvar Avoidance:
placing vaginal dilator during treatment
Stop at 5 mm from surface
Prescription to 95% PTV T1-T2

Single 25-fraction course

- Primary PTV: 200 cGy x 25 = 5000 cGy
- Iliac PTV: 180 cGy x 25 = 4500 cGy
- Inguinal PTV: 160 cGy x 25 = 4000 cGy

Courtesy Lisa Kachnic
Prescription to 95% PTV
T3-T4

Single 28-fraction course

- Primary PTV: 200 cGy x 28 = 5600 cGy
- Iliac PTV: 170 cGy x 28 = 4760 cGy
- Inguinal PTV: 150 cGy x 28 = 4200 cGy

Courtesy Lisa Kachnic
Beam Arrangement
7 angles, 10 fields
Isodoses, orthogonal planes

Courtesy Lisa Kachnic
Summary
Selective use of IMRT for GI malignancies

- GEJ: Optimize lung/cardiac dose
- Rectal: Spare fixed bowel
- Pancreatic/Liver: Dose escalation near GI tract
  - Curative doses for nodes, pancreatic ca, HCC
- Anal: Spare genitalia