Intensity Modulated Radiation Therapy (IMRT) of gastric and pancreatic tumors

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Reggio Emilia, October 14-15, 2003
IMRT of gastric and pancreatic tumors

• 1. Radiotherapy of gastric tumors
• 2. Radiotherapy of pancreas tumors
• 3. The reasons of the an announced failure: why we need a technical improvement?
• 4. The 3D-CRT
• 5. IMRT: problems and possibles solutions
Survival of patients with gastric cancer

- 5-year survival rate

- Stage Ia: 90%

- Stage II: 29-37%

- Stage III: 11-18%

Hundhal 1997, Wanebo 1993
Radiation therapy has been used in the treatment of patients with gastric cancer in two clinical setting:
- definitive therapy for locally advanced, unresectable and recurrent tumors
- adjuvant therapy following surgery for high risk disease.
Definitive therapy for locally advanced, unresectable and recurrent tumors (I)

• For patients with locally advanced, unresectable or subtotally resected gastric adenocarcinoma, radiotherapeutic approaches, with or without chemotherapy, have been employed because these tumors appear localized, without clinical detectable metastases.

• Combined treatment (RT+CT) rarely results in long-term cure.
Randomized trial for Unresectable Gastric cancer: RT+-CT

- Mayo Clinic
- RT+CT vs RT
  - 48 pts
  - RT dose: 35-40 Gy
  - CT: 5FU
  - 5 y Surv: 12% (RT-CT) vs 0 (RT)
- GITSG
- RT+CT vs CT
  - 90 pts
  - RT dose: 50 Gy
  - CT: 5FU+Me-CCNU
  - Long-term surv.: 18% (RT-CT) vs 7% (CT) p<0.05
Definitive therapy for locally advanced, unresectable tumors (II)

- Although only a modest effect was seen on survival, importantly, these studies established the foundation of contemporary combined-modality therapy and have served to stimulate further clinical investigation.
  - on radiotherapy: set-up, Radiotherapy dose, Radiotherapy techniques
  - on medical oncology: drugs, dose
  - on association: timing
3. The reasons of the announced failure: why a technical improvement is needed?

• The important movements of CTV due to vicinity of hearth and lungs

• The concentration of organs at risk near the CTV (spinal cord, kidneys, liver and small bowell)
4. The 3D-CRT

- The site is a phantastic challenge for the 3D-CRT option.
- The procedure consists of:
  - CT scan
  - GTV & CTV design
  - OAR design (spinal cord, liver, small bowel, kidneys)
  - PTV expansion (margins: set-up + organ motion ????)
  - Simulation
  - Treatment
  - Quality Controls
Conformal therapy for pancreatic cancer: variation of organ position due to gastrointestinal distention – Implications for treatment planning. (I)

- 24 patients, 20 evaluable
- All underwent accelerated chemoradiation
- CT protocol (5-3 mm); three oral contrast --→ 3CT; normal exhalation
- Organ contour: pancreas (head, body, tail), kidneys, SMA.
- Contouring by two radiation oncologist

Radiology, 232: 681, 2002
Conformal therapy for pancreatic cancer: variation of organ position due to gastrointestinal distention – implications for treatment planning.

• On the basis of the assumption that target organ position on the CT scans are but one sample of a random distribution that occurs during treatment, pooled data of 60 CT scans were used to calculate the margins that should be added to the CTV to account for a variable gastrointestinal distention and a typical error (5 mm).

Radiology, 232: 681, 2002
Conformal therapy for pancreatic cancer: variation of organ position due to gastrointestinal distention implications for treatment planning (III)

<table>
<thead>
<tr>
<th>CTV expansion</th>
<th>R-L (mm)</th>
<th>A-P (mm)</th>
<th>C-C (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. tail</td>
<td>2.9</td>
<td>3.3</td>
<td>4.3</td>
</tr>
<tr>
<td>P. body</td>
<td>2.5</td>
<td>2.1</td>
<td>5.2</td>
</tr>
<tr>
<td>P. head</td>
<td>4.3</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>SMA</td>
<td>7.0</td>
<td>2.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

Radiology, 232: 681, 2002
Target identification

• In radical setting:
  - CT is the choice
  - PET can be useful for metastatic unknown spread (selection of patients) and for better identification of GTV T and N

• In postoperative setting CT-PET can be the only imaging for restaging ??
**Pitfalls in delineating GTV IMAGE FUSION by PET**  
**Treatment planning modification:**  
15%  
87 patients studied at IRCC Candiolo

<table>
<thead>
<tr>
<th>Tumor</th>
<th>N. Patients</th>
<th>M/F</th>
<th>Modif. Stage</th>
<th>Modif. Strategy</th>
<th>Modif. Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>26</td>
<td>21/5</td>
<td>10 (38%)</td>
<td>13 (50 %)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Hematological</td>
<td>24</td>
<td>13/11</td>
<td>8 (33 %)</td>
<td>9 (38 %)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15</td>
<td>8/7</td>
<td>2 (13 %)</td>
<td>4 (27 %)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>19</td>
<td>8/11</td>
<td>5 (35 %)</td>
<td>10 (50 %)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>1/2</td>
<td>1 (33%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>51/36</strong></td>
<td><strong>26 (30 %)</strong></td>
<td><strong>43 (50%)</strong></td>
<td><strong>13 (15%)</strong></td>
</tr>
</tbody>
</table>

Impact of PET in radiation therapy treatment planning

• 60 patients (23f, 37m)
• 26 unknow primary, 11 head and neck, 20 abdomen, 9 breast
• 18/60 (30%) \(\rightarrow\) alteration of treatment regimen: in 13 (22%) the target volume has to be modified

J. Schultze, ECCO 12, 2003
2D & 3D CUSHION POSITIONING

3D-CRT: isocenter identification
3D-CRT: Simulation

3D-CRT: Treatment position at Linac
Definitive RT of recurrent Gastric tumor with 3D-CRT

3D-CRT 3 fields MLC

Slice Max 102.0%
Max 102.0%
Min 94.5%
Mean 99.8%

3D view
3D-CRT with MLC

DVH for

PTV - ICRU point dose: 55.8 Gy
Rationale for implementation of IMRT in Radiotherapy of gastric cancer

- Radiotherapy dose escalation
- CTV better coverage at 95% ICRU dose
- OAR (kidneys, spinal cord, small bowel, ) sparing
IMRT: CT simulation

IMRT: Treatment position at Linac
5 fields
IMRT
Cumulative Dose Volume Histogram

3 cuore
4 renne sin
5 renne dx
7 ptv a 1.5 cm
8 fegato
9 midollo

PLAN 4 come 3, con setup

Gy
Dose (%)

% Volume

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

5c IMRT
DVH
61.2
Definitive RT of Gastric tumors:

3D-CRT vs IMRT

55.8 Gy vs 61.2 Gy
Gastric cancer
Intergroup 0116 GSAT randomized trial for high risk (T3-4, N+)

- After completely resected of gastric and gastro-oesophageal adenocarcinomas
  - observation vs RT/CT -

  - Significant improvement in DFS $p<0.0001$)
  - Significant improvement in OS $p=0.01$

McDonald J., Proc. ASCO 2000, 19, 1
& NEJM 345: 725, 2001
Gastric surgical and Radiotherapy consensus report: rationale and treatment implementation.

…..radiation oncologists must now clearly comprehend the principles governing the rationale supporting this therapy. The paper represents a consensus report reviewing data regarding radiotherapy and details for clinical application.…

SR Smalley, L. Gunderson, IJROBP 52: 283, 2002
2. Conventional RT of pancreatic tumors

- Curative RT of pancreatic tumors
- Postoperative RT of pancreatic tumors
- Preoperative RT of pancreatic tumors
3D-CRT of pancreatic tumors: first experience at IRCC (98-02)

• 21 patients with locally advanced/vessels infiltration
• All biopsy proven; all CT; 5 PET scan
• Protocol: CT (GEM 50-100 mg/m2 twice weekly
• +
• 3D-CRT (45–50.4 Gy) in 1.80 Gy/session

• Re-evaluation for surgery 45 days after radiotherapy

R. Fagiuolo et al, in press, 2003
3D-CRT of pancreatic tumors: first experience at IRCC (II)

Evaluable: 17/21

Results:  - PR: 3 (15%)  - SD: 14 (70%)
  - DFS: (m) 2, 3+, 5, 16, 24+
  - OS: (m) 7, 8+, 18, 23, 28+
  - Ca 19.9 reduction: 12/20 (60%)
  - Clinical benefit: 12/60 (60%)

5 patients underwent radical surgery (1 N+, all with free margins)

R. Faggiuolo et al, in press, 2003
Pancreas box
Open fields
Pancreas box
Open fields
BEV+DRR 0°
Pancreas
box open
DVH for
Dose: 50.4 Gy
Pancreas
3 fields
3D-CRT
Pancreas
3 fields
3DCRT
BEV + DRR 0°

Pancreas
3 fields
3DCRT
BEV + DRR 90°
Pancreas
3 fields
3DCRT
3D view
Pancreas:
curative RT
3 fields
3DCRT
DVH for
Dose: 61.2 Gy
5. IMRT: possible solutions

3D-CRT vs IMRT

- 1999-2001
- 10 randomly selected patients were planned simultaneously
- 3D-CRT and IMRT were compared using Volume at Risk Approach (VARA)
- For the evaluation of small bowel toxicity were employed DVH and NTCP

JC Landry, Emory Univ., Med Dos 27, 121, 2002
3D-CRT vs IMRT

- Aim of treatment:
  - 61.2 Gy to GTV
  - 45.0 Gy to CTV
  - Maintaining critical normal tissues to below specified tolerances

IMRT constraints:

PTV: (Priority 90%)
- Presc. D.: 50.4 Gy
- Min D: 45.0 Gy

GTV: (priority 90%)
- Presc. D.: 61.2 Gy
- Min. D.: 59.4 Gy

Small b.: (priority 80%)
- Max. D.: 45 Gy

JC Landry, Emory Univ, Med Dos 27, 121, 2002
### 3D-CRT vs IMRT

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>3D-CRT</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>% small bowell &gt; 50 Gy</td>
<td>19.2</td>
<td>31.4</td>
<td>0.04</td>
</tr>
<tr>
<td>% small bowell &gt;60 Gy</td>
<td>12-5</td>
<td>19.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Dose to 1/3 volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowell</td>
<td>30.0</td>
<td>38.5</td>
<td>0.006</td>
</tr>
<tr>
<td>% small bowell NTCP</td>
<td>9.3</td>
<td>24.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

JC Landry, Emory Univ, Med Dos 27, 121, 2002
Pancreas: curative RT
7c IMRT
66.6 Gy
Pancreas: curative RT
7c IMRT
DVH
66.6 Gy
Pancreas
7c IMRT
3D view
PANCREAS CANCER

3D-CRT vs IMRT

61.2 Gy vs 66.6 Gy
Investigation of the added value of High Energy Electrons in IMRT: four clinical cases (I).

• Theoretically inclusion of intensity and energy modulated HE electrons (15-50 Mev) offers additional possibilities to improve RT treatment of deep seated tumors.

• Material and methods: in a comparative treatment planning study, conventional treatment plans and various types of IMRT were constructed for four clinical cases (bladder, pancreas, chordoma and breast).

EW. Korevaar, IJROBP, 52: 236, 2002
Investigation of the added value of HE Electrons in IMRT: four clinical cases (II).

- Results: Large improvements in expected treatment outcome are found using IMRT plans compared to conventional plans, but differences in tumor control probability (TCP) and normal tissue complication probabilities (NTCP) values between IMRT plans with and without electrons are small. However the use of electrons improves the DVH for organs at risk, especially at lower dose levels (e.g. 0-40 Gy)

EW. Korevaar, IJROBP, 52: 236, 2002
Phase I study of concomitant gemcitabine and IMRT (I)

- Hypothesis: IMRT would protect normal tissues enough to allow the escalation of either gemcitabine or RT dose in unresectable pancreatic cancer
- Protocol: 30 Gy in 3 Gy/fr. and 350 mg/m2 of gemcitabine
- The plan was to alternate escalating the RT dose by 3 Gy and gemcitabine dose by 50 mg/m2.

CH. Crane, Int J Gastrointest Cancer 30: 123, 2001
Phase I study of concomitant gemcitabine and IMRT (II)

- Results: all 3 patients of the first cohort suffered dose limiting toxicity (DLT)
- A second cohort of patients received lower gemcitabine dose (250 mg/m2): all suffered DLT
- 4 patients required hospital admission, 1 died.
- Conclusions: Hypofractionated IMRT did not allow escalation of either RT or gemcitabine dose.

CH. Crane, Int J Gastrointest Cancer 30: 123, 2001
Conclusions

• IMRT can be useful for the treatment of gastric and pancreatic tumors if:
  - (re)staging by CT or better CT-PET
  - set-up uncertainties will decreased
  - organ motion are taken into account
  - dose escalation program is planned
  - the relationship between radio and chemotherapy is clearly defined in term of drug choice, timing and supportive care.