2015 ASTRO Refresher Course: The Management of Gastrointestinal Cancers

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Disclosure

- I have no conflicts of interest to disclose.
Acknowledgements

• Joseph Herman, MD
• Lisa Kachnic, MD
• Laura Dawson, MD
Objectives

• Summarize modern clinical trials establishing the standard of care for GI malignancies

• Review standard treatment planning practices for GI sites

• Discuss advances in radiotherapy techniques and approaches for GI malignancies
Selected GI Sites

• Esophageal and Gastroesophageal Junction Cancer
• Gastric Cancer
• Pancreas Cancer
• Liver Tumors: Metastases and HCC
• Rectal Cancer
• Anal Cancer
Esophageal and Gastroesophageal Junction Cancer
Rising Incidence in GE Junction Cancers

- GE junction adenocarcinoma as a separate entity is rising in incidence
  - 2.5-fold increase from 1973-1992 (SEER Registry)

Graph: Incidence of adenocarcinoma of the esophagus, GEJ, and stomach
1973-2008, United States

Buas et al. Sem Rad Onc, 2013
GE Junction Anatomy: Siewert’s Classification
Role of Radiotherapy in Esophageal and GE Junction Cancers

• Definitive Therapy
  – Appropriate radiotherapy dose
  – Role of salvage surgery

• Pre-operative Therapy
  – Benefits and risk of trimodality therapy

• Palliation
## Role of Definitive Chemoradiation

### RTOG 85-01

- **121 Stage I-III Esophageal ca**
  - EBRT (50 Gy)
    - 5-FU + Cis
  - EBRT (64Gy)

<table>
<thead>
<tr>
<th></th>
<th>CMT</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>14.1 mos</td>
<td>9.3 mos</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td>Persistence of dz</td>
<td>25%</td>
<td>37%</td>
</tr>
<tr>
<td>Grade 4 tox</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Local failure</td>
<td>45%</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Herskovic, NEJM 1992; Al Sarraf, JCO 1997; Cooper, JAMA 1999*
Dose Escalation: INT 0123

- Trial stopped early - increased toxicity in high dose arm
- 11 treatment deaths in high-dose arm (7 at/before 50.4 Gy) v. 2 in standard arm

Minsky, JCO 2002
Dose Escalation: INT 0123

No difference in:

• Median survival (13.0 v. 18.1 mos)
• 2 yr survival (31% v 40%)
• Locoregional failure/persistence (56% v 52%)
• Criticisms:
  – Prolonged treatment times
  – Large treatment fields
  – Older techniques

For pts receiving assigned RT dose

Minsky, JCO 2002
Role of Surgery after Chemoradiation

• Only way to reliably assess pCR
  – EUS, CT, PET still not able to distinguish between post-RT fibrosis + inflammation versus residual tumor

• Treatment-related mortality 2-10%

• Does upfront surgery improve survival?

• Is the strategy of selective surgical salvage a viable option?
Chemoradiation ± Surgery

GOCSG

• 172 locally advanced esophageal SCC pts
• FLEP X 3 → EP + 40 Gy → surgery
• FLEP X 3 → EP + > 66Gy

CMT alone arm: altered fractionation boost or HDR brachytherapy

Stahl, JCO 2005
## Chemoradiation ± Surgery

### GOCSG

<table>
<thead>
<tr>
<th></th>
<th>Pre-op + S</th>
<th>CRT alone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year OS</td>
<td>31.3%</td>
<td>24.4%</td>
<td>NS</td>
</tr>
<tr>
<td>2-year Local PFS</td>
<td>64.3%</td>
<td>40.7%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Median survival</td>
<td>16.4 mos</td>
<td>14.9 mos</td>
<td>NS</td>
</tr>
<tr>
<td>Tx-related mortality</td>
<td>12.8%</td>
<td>3.5%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

**Stahl, JCO 2005**

![Graphs showing survival outcomes](image-url)
Chemoradiation ± Surgery

FFCD 9102

- 445 pts with locally advanced esophageal adenocarcinoma or SCC (~85%)
- All received induction 5-FU/Cisplatin + 46Gy or 30Gy split course → re-evaluated
- 259 pts ≥ PR randomized
  - Surgery
  - 5-FU/Cis + 20Gy or 15Gy split course

Bedenne, JCO 2007
Chemoradiation ± Surgery

FFCD 9102

- No difference in OS
- Higher treatment-related mortality
- More palliative procedures (stent placements) on CRT arm

<table>
<thead>
<tr>
<th></th>
<th>Pre-op + S</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>17.7 mos</td>
<td>19.3 mos</td>
</tr>
<tr>
<td>2 yr OS</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>Death w/in 3 mo</td>
<td>9%*</td>
<td>1%*</td>
</tr>
</tbody>
</table>

Bedenne, JCO 2007
Salvage Surgery after Chemoradiation

RTOG 0246

- Phase II study of Taxol-based chemo/RT + selective surgical salvage
- 43 resectable esophageal adeno/SCC patients

Swisher, IJROBP, 2012
Salvage Surgery after Chemoradiation

RTOG 0246

- 18 pts (44%) underwent resection
  - 17/18 had residual tumor
- 23 pts (56%) did not undergo surgery
  - 14 had cCR
  - 3 had DM
  - 1 medically inoperable
  - 5 died
- Median follow-up 16 mos
- 4 treatment-related deaths
  - 10% - higher than expected

1 year OS = 71%
Did not meet $H_0 \geq 77.5\%$
Rationale for Pre-operative Chemoradiation

- Surgery – mainstay of therapy for operable pts
  - Surgery alone for early stage disease
  - Curative resections (R0) achieved in 60% for locally advanced tumors**
  - 5-year OS approximately 20%**

- Pre-operative therapy for locally advanced esophageal cancer
  - Initially conflicting results in Phase III studies

**Kelsen, NEJM 1998; Burmeister, Lancet Oncol, 2005
## Results of Pre-operative Chemoradiation v. Surgery Alone Trials

<table>
<thead>
<tr>
<th></th>
<th>Walsh</th>
<th>Bosset</th>
<th>Urba</th>
<th>Burmeister</th>
</tr>
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<tbody>
<tr>
<td>Published</td>
<td>1996</td>
<td>1997</td>
<td>2001</td>
<td>2002</td>
</tr>
<tr>
<td>$n$</td>
<td>113</td>
<td>297</td>
<td>100</td>
<td>128</td>
</tr>
<tr>
<td>Histology</td>
<td>Adeno</td>
<td>SCC</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>RT</td>
<td>40Gy/15</td>
<td>18.5Gy/5</td>
<td>45Gy (bid)</td>
<td>35Gy/15</td>
</tr>
<tr>
<td>Chemo</td>
<td>5-FU/cis</td>
<td>Cis</td>
<td>5-FU/cis/vin</td>
<td>5-FU/cis</td>
</tr>
<tr>
<td>pCR rate</td>
<td>25%</td>
<td>26%</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>MS-surg</td>
<td>11 mos</td>
<td>19 mos</td>
<td>18 mos</td>
<td>19 mos</td>
</tr>
<tr>
<td>MS-CRT</td>
<td>16 mos</td>
<td>19 mos</td>
<td>17 mos</td>
<td>22 mos</td>
</tr>
<tr>
<td>3-year OS</td>
<td>6% v. 32%</td>
<td>37% v. 39%</td>
<td>16% v. 30%</td>
<td>~38% v. 35%</td>
</tr>
</tbody>
</table>
Role of Neoadjuvant Therapy

CALGB 9781

- 5-FU/CDDP x 2 + 50.4Gy → surgery v. surgery
- Accrual goal: 500 pts, entered: 56 pts
- Median follow-up: 6yrs

<table>
<thead>
<tr>
<th>#</th>
<th>Arm</th>
<th>MS</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Pre-op</td>
<td>4.5 yr</td>
<td>39%</td>
</tr>
<tr>
<td>26</td>
<td>Surgery</td>
<td>1.8 yr</td>
<td>16% ( p=0.02 ) ( p=0.005 )</td>
</tr>
</tbody>
</table>

- No surgical deaths on pre-op arm, 2 on surgery alone arm

Role of Neoadjuvant Therapy

CROSS Trial

- 363 esophageal and GEJ cancer patients (75% adeno) randomized to:
  - Pre-op Carboplatin/Taxol + 4140cGy → Surgery
  - Surgery alone
- 5-year OS: 47% v. 34%
- MS: 49 mos v. 24 mos
- HR 0.66, p = 0.003

Role of Neoadjuvant Therapy

CROSS Trial

• 18/37 (49%) of SCC had pCR (v. 23% in adenoca group)

# Role of Neoadjuvant Therapy

## CROSS Trial

<table>
<thead>
<tr>
<th></th>
<th>Pre-op CRT</th>
<th>S Alone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR</td>
<td>14%</td>
<td>34%</td>
<td>&gt;.001</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>4%</td>
<td>14%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hematogenous spread</td>
<td>29%</td>
<td>35%</td>
<td>.025</td>
</tr>
</tbody>
</table>

*Oppedijk, J Clin Oncol, 2014*
Role of Neoadjuvant Therapy

POET Trial

- Locally advanced GE junction cancers
- Randomized to:
  - Arm A: induction chemotherapy (15 weeks) followed by surgery
  - Arm B: chemotherapy (12 weeks) followed by chemoradiotherapy (3 weeks) followed by surgery
- Chemotherapy
  - Induction: cisplatin, fluorouracil, leucovorin (PLF)
  - Chemoradiation: cisplatin, etoposide, 30Gy

Role of Neoadjuvant Therapy

POET Trial

- Closed early due to poor accrual, only 126 of 354 patients
- Improved pCR rate in Arm B:
  - 15.6% v. 2.0%
- Improved N0 rate
  - 64.4% v. 37.7%
- 3-year OS
  - 47% v. 28% (p=.07)

## Role of Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>MS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9781 (N=56)</td>
<td>Pre-op CRT</td>
<td>4.5 yr</td>
<td>5y 39%</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>1.8 yr</td>
<td>5y16%</td>
</tr>
<tr>
<td>CROSS (N=363)</td>
<td>Pre-op CRT</td>
<td>4.1 yr</td>
<td>3y 59%</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>2.2 yr</td>
<td>3y 48%</td>
</tr>
<tr>
<td>POET (N=126)</td>
<td>Pre-op CRT</td>
<td>2.8 yr</td>
<td>3y 47%</td>
</tr>
<tr>
<td></td>
<td>Pre-op CT</td>
<td>1.8 yr</td>
<td>3y 28%</td>
</tr>
</tbody>
</table>

*p* = 0.07

*Tepper, J Clin Oncol; 2008
Consensus

- Neoadjuvant chemoradiation improves outcomes in some patients
  - Increases pathologic response rates
  - Reduces local recurrence rates
  - Improves survival

- Optimal neoadjuvant regimen has not been established
Future Directions: Targeted Therapy

• VEGF
  – Phase II bevacizumab trials not promising

• Her-2
  – Similar rate of overexpression as breast cancer
  – Trastuzumab has OS benefit in metastatic disease (ToGA trial)
  – RTOG 1010: preop chemoRT ± trastuzumab

• EGFR
  – EGFR overexpressed in up to 55% of esophageal cancers
  – SCOPE1: negative
  – RTOG 0436: negative
  – ECOG trial closed early due to excessive toxicity with cetuximab
Definitive Chemoradiation + Targeted Agents

**SCOPE1**

- Phase 2 PRT
- Stopped before Phase 3
- Median OS **worse** in CRT + cetuximab arm

<table>
<thead>
<tr>
<th>258 Esophageal adeno/SCC pts</th>
<th>50 Gy Cape + Cis</th>
<th>50 Gy + Cetux Cape + Cis</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Median OS</th>
<th>25.4 mo</th>
<th>22.1 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 non-heme toxicity</td>
<td>63%</td>
<td>79%</td>
</tr>
</tbody>
</table>

*Crosby, Lancet Oncol, 2013*
Definitive Chemoradiation + Targeted Agents

**RTOG 0436**

- **Histology:**
  1. Adenocarcinoma
  2. Squamous

- **Cancer lesion size:**
  1. < 5 cm
  2. ≥ 5 cm

- **Celiac nodes:**
  1. Present
  2. Absent

**Arm 1:**
Radiation therapy + paclitaxel + cisplatin + cetuximab

**Arm 2:**
Radiation therapy + paclitaxel + cisplatin

- Addition of Cetuximab to weekly Cisplatin/Paclitaxel + RT
  - No improvement in overall survival or clinical CR, regardless of histology
Definitive Chemoradiation + Targeted Agents

RTOG 0436

Overall Survival

2-Year Rates:
- Adenocarcinoma: 43.5%
- Squamous Cell: 41.8%

Stratified log-rank p-value = 0.72

Overall Survival by Histology

Stratified log-rank p-value = 0.72

HR = 0.92 (0.71, 1.20)

HR = 1.09 (0.81, 1.44)
Definitive Chemoradiation + Targeted Agents

Overall Survival by Clinical Disease Status

Adenocarcinoma Patients

Squamous Cell Patients

HR = 1.59 (1.11, 2.26)

HR = 3.67 (2.22, 6.07)
ECOG 2205: Phase II Study to Measure Response Rate and Toxicity of Neoadjuvant CRT with Oxaliplatin and Infusional 5-FU plus Cetuximab in Patients with Operable Adenocarcinoma of the Esophagus

- 45Gy + oxaliplatin, 5-FU PVI, weekly cetuximab
- 18/22 enrolled went to surgery
- pCR in 7 (32% of all pts)
- 4 post-op deaths (22%) due to ARDS!!
- 7/22 deaths total (32% mortality rate)
- Study closed due to unacceptable toxicity
Directed Therapy

• How can we predict the good responders or poor responders upfront?

• How can we predict which tumors will respond to which therapy?

• Risk stratification
PET Imaging in Esophageal Cancer

• Staging

• Prognostic/Predictive Marker
  – Baseline SUV
  – Post-treatment SUV
  – Reduction in SUV
MUNICON-1 trial

Response definition: Decrease of the $\text{SUV}_{\text{mean}} \frac{\text{PET}_{d14}}{\text{PET}_{\text{baseline}}} > 35\%$


Lordick, Lancet Oncol 2007
Comparison with Historic Cohort

Ott et al. *J Clin Oncol* 2006;24:4692-8
CTx for 12 weeks in all patients

Survival (median)
Responders: not reached
Non-Responders: 18 months

MUNICON-1 study; 2007
CTx stopped after 2wks in Non-Responders

Survival (median)
Responders: not reached
Non-Responders: 26 months
MUNICON II Trial

AEG type I-II → CTx → PET d0

 PET d14

- Non-Responder → Resection
- Responder → CTx: 3 months → Resection

CTX: 5-FU/Leuvorin/Cisplatin +/- Paclitaxel
R-CTx: 2 x 1.6 Gy/day: total dose 32 Gy + Cisplatin

Response definition: Decrease of the SUV\textsubscript{mean} \(\frac{PET\text{d14}}{PET\text{baseline}}\) > 35%

MUNICON II Results

- Median follow-up of 38 mos

<table>
<thead>
<tr>
<th></th>
<th>R0 Resection</th>
<th>Complete path response (&lt;10% residual)</th>
<th>Median EFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET Responders N=33</td>
<td>82%</td>
<td>12% (36%)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>PET Non-Responders N=23</td>
<td>70%</td>
<td>4% (26%)</td>
<td>15.4 mo</td>
<td>18.3 mo</td>
</tr>
</tbody>
</table>

- 0% major histologic remissions in non-responders in MUNICON I

Zum Buschenfelde, J Nuc Med, 2011
CALGB 80803: Randomized Phase II Trial

Randomize

T3/4 or N1 Esophageal Adenoca PET Scan pre-treatment

Induction Chemo: modified FOLFOX6 days 1,15, 29

PET Scan day 36-42

PET-responders: ≥ 35% SUV decrease: continue initial chemo + concurrent RT (5040cGy in 180cGy fx)

Surgical resection 6 weeks post-RT

Induction Chemo: Carboplatin/Paclitaxel days 1,8,22,29

PET- nonresponders: < 35% SUV decrease: cross-over to alternative chemo + concurrent RT (5040cGy in 180cGy fx)
Palliation

TROG 03.01/NCIC CTG ES2

• PRT of palliation of dysphagia and quality of life in patients treated with RT or CRT for advanced esophageal cancer

• 220 patients randomized to:
  – RT [35 Gy in 15 fx or 30 Gy in 10 fx]
  – CRT with Cisplatin and 5FU

• No sig difference in dysphagia improvement or QOL analysis

• Increased toxicity in patients receiving CRT

• Median survival was 210 days for CRT, 203 days for RT

• Some patients (n=21) still alive at 2 years post treatment
Treatment Planning Considerations

• 50.4 Gy to tumor
  • Standard 3DCRT fields:
    • 5 cm superiorly and inferiorly, 2 cm radially
  • IMRT (with motion management for GE junction tumors):
    • CTV: 4 cm sup/inf, 1cm radial;
    • PTV: 0.5cm expansion
    • KV imaging to be considered for distal lesions along with planning 4D-CT

• Dose-limiting structures
  • Spinal cord max 45 Gy
  • Lung*: V20 < 20-30%, V10 < 40%, V5 < 60%
  • Heart: V40 < 30% (V30 < 30%, mean dose <25 Gy for IMRT)
  • Liver: mean < 25 Gy, V30 < 30%
  • Kidney: combined mean < 18 Gy (V18 <33% for IMRT)

• non-operable vs operable setting
Thoracic Nodal Stations

IASLC Lymph Node Map

GE Junction Tumors

Abdominal Nodal Stations

Added stations 15-20
- 15: Posterior crural
- 16: Paracardial
- 17: Left gastric
- 18: Common hepatic
- 19: Splenic
- 20: Celiac

Kim TJ, Radiographics, 2009
AJCC Staging Manual 2010
Lymph Node Drainage Patterns

Leers J, J Thorac Cardiovasc Surg, 2009
Esophageal Cancer Contouring Atlas

PET for Treatment Planning

- Accurate delineation of tumor volume essential to adequately treat esophageal tumors

- Conformal radiotherapy techniques (IMRT, protons)

- CT imaging suboptimal for identifying extent of primary tumor and for regional nodes
PET for Treatment Planning
PET for Treatment Planning

- 9 studies evaluating impact of PET/CT on target volume definitions
  - PET data found to both increase and reduce GTV compared to CT alone
  - Inclusion of lymph nodes not visible on conventional imaging
- Threshold setting is problem for PET
- 4 studies looked at pathologic correlation
  - Best correlation using SUV of 2.5 as threshold

Muijs CT, Radiother Oncol, 2010
IMRT for Esophageal and GE Junction Cancers
IMRT Reduces Cardiac Dose

Kole, T. et al., Int J Rad Oncol, 2012
Cardiac Sparing

- IMRT resulted in significant reduction ($p < 0.05$) compared with 3DCRT in:
  - mean heart dose (23 vs. 28 Gy)
  - V30 to heart (24.8% vs. 61.0%)
  - mean RCA dose (24 Gy vs. 36 Gy)

Kole T, Int J Rad Onc Biol Phys, 2012
# IMRT: The MDACC Experience

<table>
<thead>
<tr>
<th>Weight Loss (% Body Weight)</th>
<th>3DCRT (N=302)</th>
<th>IMRT (N=254)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10%</td>
<td>76.8%</td>
<td>84.4%</td>
<td>p=0.040</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>23.2%</td>
<td>15.6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feeding Tube Placement</th>
<th>3DCRT (N=302)</th>
<th>IMRT (N=254)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>66.8%</td>
<td>67.8%</td>
<td>p=0.962</td>
</tr>
<tr>
<td>Before RT</td>
<td>25.1%</td>
<td>23.9%</td>
<td></td>
</tr>
<tr>
<td>During/After RT</td>
<td>7.5%</td>
<td>8.3%</td>
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<table>
<thead>
<tr>
<th>Esophagitis (Grade)</th>
<th>3DCRT (N=302)</th>
<th>IMRT (N=254)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13.6%</td>
<td>18.6%</td>
<td>p=0.230</td>
</tr>
<tr>
<td>1</td>
<td>18.9%</td>
<td>20.9%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57.2%</td>
<td>49.8%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10.1%</td>
<td>10.3%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
<td>0.03%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02%</td>
<td>0%</td>
<td></td>
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<table>
<thead>
<tr>
<th>Nausea (Grade)</th>
<th>3DCRT (N=302)</th>
<th>IMRT (N=254)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45.5%</td>
<td>41.5%</td>
<td>p=0.086</td>
</tr>
<tr>
<td>1</td>
<td>10.6%</td>
<td>16.9%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35.4%</td>
<td>34.9%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8.6%</td>
<td>6.6%</td>
<td></td>
</tr>
</tbody>
</table>

Trimodality vs CRT alone pts evenly distributed [~50:50] Lin et. al., IJROBP 2012
## Overall Survival

*Overall Survival*

![Survival Graph](image)

### Overall Survival Results

<table>
<thead>
<tr>
<th></th>
<th>Median Follow-up</th>
<th>Median Survival</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>34.8 months</td>
<td>36 months</td>
<td>42.4%</td>
</tr>
<tr>
<td>3-D</td>
<td>81.2 months</td>
<td>24 months</td>
<td>31.3%</td>
</tr>
</tbody>
</table>

*Lin et. al., IJROBP 2012*
Gastric Cancer
Role of Radiotherapy in Gastric Cancer

- **Post-op**
  - Stage III
  - Positive margins
  - T2N0 with unfavorable features (LVS and/or < D2 lymph node dissection)

- **Pre-op**
  - Borderline resectable at presentation
  - GE junction

- Unresectable
Post-op Chemoradiation

SWOG-INT 0116

Pts with Gastric Cancer

<table>
<thead>
<tr>
<th>Adjuvant CMT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival 36 months</td>
<td>27 months</td>
</tr>
<tr>
<td>3 yr DFS 49%</td>
<td>32%</td>
</tr>
<tr>
<td>3 yr OS 50%</td>
<td>41%</td>
</tr>
</tbody>
</table>

MacDonald, NEJM 2001
Post-op Chemoradiation
SWOG-INT 0116 10-year update

- Adjuvant CRT cohort benefit:
  - **Overall Survival** - HR = 1.32 (95% CI, 1.10 to 1.60; p=0.0046)
  - **Relapse-Free Survival** - HR = 1.51 (95% CI, 1.25 to 1.83; p<0.001)

- Second malignancies 21 pts (vs. 8 in the control group), however this was not statistically significant, p=0.21

Smalley JCO 2012
Post-op Chemoradiation
SWOG-INT 0116 10-year update

(A) Overall survival
(B) Relapse-free survival

(A) Overall survival: Median survival time:
- FU + leucovorin + RT: 35 months
- Observation: 27 months

(B) Relapse-free survival: Median survival time:
- FU + leucovorin + RT: 27 months
- Observation: 19 months
Post-op Chemoradiation v. Chemo

ARTIST Trial

Ib-IVa
D2
Gastric
458 pts
(2004-2008)

XP x 6

XP x 2 → CRT → XP x 2

XP: Capecitabine 1000 mg/m2 bid, CDDP 60 mg/m2

CRT: 45 Gy in 25 fractions + capecitabine 825 mg/m2 bid

Primary endpoint: DFS

Lee et. al., JCO 2012
Post-op Chemoradiation v. Chemo

ARTIST Trial

Subgroups who benefited from CRT:

- Node-positive disease
- Higher lymph node ratio
- Intestinal type GC

Lee J, J Clin Oncol. 2012
Park S, J Clin Oncol, 2014
## Pre-operative Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-op chemo</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intergroup 0113</strong></td>
<td>Median survival: 14.9 mos</td>
<td>16.1 mos</td>
</tr>
<tr>
<td></td>
<td>2 yr OS: 35%</td>
<td>37% (NS)</td>
</tr>
<tr>
<td><strong>MRC OEO2 Trial</strong></td>
<td>Median survival: 16.8 mos</td>
<td>13.3 mos</td>
</tr>
<tr>
<td></td>
<td>5 yr OS: 23%</td>
<td>17% (S)</td>
</tr>
</tbody>
</table>

Kelsen NEJM 1998; Allum, GI ASCO 2008
Peri-operative Chemotherapy

MAGIC trial

- Resectable gastric or GE junction tumors
- Randomization: surgery alone vs. ECF x 3 cycles before and after surgery
- 5-year overall survival: 36 v 23%
- However, no increase in pathologic response rate

Cunningham, NEJM 2006
On-going Studies

- **ARTIST-II**: Chemoradiotherapy versus two chemotherapy regimens (S1 versus S1 and oxaliplatin), based on Adjuvant Chemotherapy Trial of TS-1, and the CLASSIC trial in lymph node + gastric cancer after D2 lymph node dissection

- **TOPGEAR trial**: Perioperative chemotherapy (three cycles of ECF pre- and post-surgery) versus preoperative chemoradiotherapy (two cycles of ECF followed by 45 Gy with 5-FU) and postoperative chemotherapy (three cycles of ECF)

- **CRITICS (Chemoradiotherapy After Induction Chemotherapy of Cancer in the Stomach) trial**: Perioperative treatment with ECX alone versus ECX followed by adjuvant chemoradiotherapy with cisplatin and capecitabine
Treatment Planning Considerations

- 45Gy adjuvant; 50.4-54Gy microscopic/gross disease
- APPA or 4-field; IMRT if constrained by heart/kidney
  - Simulate and Rx with “empty” stomach
  - Daily KV; CBCT and 4D-CT use to be considered if unresectable/preoperative, proximal, concern with kidney constraints and/or considering boost > 45 Gy

- Dose-limiting structures
  - Spinal cord max 45 Gy
  - Lung: V20 < 30%, V10 < 40%, V5 < 60%
  - Heart: V40 < 30%, V25 < 50%
  - Liver: mean < 25 Gy, V30 < 60%
  - Kidney: combined mean < 18 Gy
  - Small bowel: V45 < 150 cc, V30 < 300 cc
Treatment Planning Principles

- Target: residual stomach and resected tumor bed, stump, anastomoses, defined based on pre-operative imaging and placement of surgical clips

- Nodes: lesser and greater curvature; celiac axis including pancreaticoduodenal; suprapancreatic, splenic, and porta hepatis; paraesophageal/lower mediastinum for proximal lesions

Gastric LN Contouring Atlas; Wo et al.; PRO 2012
Abdominal Lymph Nodes

Lymph Node Stations

Matzinger O, Radiother Oncol, 2009
Gastric LN Contouring Atlas; Wo et. al.; PRO 2012
Pancreas Cancer
Pancreas Anatomy

Goals of RT in Pancreatic Cancer

- Locally Advanced
  - Address local disease burden
  - Minimize locally obstructive symptoms and address pain
  - Convert to resectability
- Borderline Resectable
  - Convert to resectability
- Resectable
  - Address micrometastatic disease
  - Prevent local recurrence
Locally Advanced Pancreatic Cancer

- 2 outdated randomized studies established chemoradiation as standard of care for LAPC

**GITSG-9273**
- 194 pts with LAPC
  - 60 Gy
  - 40 Gy + 5-FU
  - 60 Gy + 5-FU  
  MS 20 wks  36 wks  40 wks
  Moertel CG *et al*, Cancer, 1981

**GITSG-9283**
- 43 pts with LAPC
  - 54 Gy + 5-FU then SMF x 2 yrs
  - SMF x 2 yrs (streptozocin, MMC, 5-FU)
  42 wks  32 wks
Locally Advanced Pancreatic Cancer

FFCD-SFRO Study

119 LAPC pts

60Gy + cisplatin/5-FU then Gem

MS 8.6 mos 65%

Grade 3-4 toxicity

Gem 13 mos 40%

• Significantly more toxicity on CHRT arm

• Only 42% of CHRT pts received at least 75% of planned therapy v. 73% in Gem arm

Chauffert B. et al, Ann Oncol 2008
Locally Advanced Pancreatic Cancer

ECOG E4201

- 74 LAPC pts
  - Gem x 7 cycles
  - 50.4 Gy + Gem then Gem x 5

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MS</th>
<th>9.2 mo</th>
<th>11.0 mo</th>
<th>p = 0.044</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem x 7 cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.4 Gy + Gem then Gem x 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Closed due to poor accrual
- More Grade 3-4 toxicity on Arm B

Locally Advanced Pancreatic Cancer

• Induction Chemotherapy followed by Chemoradiation?

• Retrospective evaluation of outcomes from prospective studies
  – MS: 15 v. 11 mo
  – 1 yr OS: 65% v. 47%

SCALOP Trial: Gemcitabine vs. capecitabine-based CRT for LAPC

- Histologically proven LAPC (tumor diameter ≤ 7 cm)
- After 12 weeks of induction CTX* (gemcitabine + capecitabine)
  - Patients w/stable/responding disease**, ➔ subsequent CTX cycle* ➔ randomized (1:1) to Gem (300 mg/m²) or Cap (840 mg/BID) in combination with radiation (50.4 Gy in 28 fractions)
- Primary endpoint- 9-month progression-free survival

Mukherjee et al. Lancet Onc 2013
SCALOP Trial

74 randomly allocated

36 allocated to capecitabine group

38 allocated to gemcitabine group

P=0.01

Mukherjee et al. Lancet Onc 2013
## SCALOP Trial

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS- 9 months</strong></td>
<td>62.9%</td>
<td>51.4%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>12.0 months</td>
<td>10.4 months</td>
</tr>
<tr>
<td><strong>Median OS (p =0.01)</strong></td>
<td>15.2 months</td>
<td>13.4 months</td>
</tr>
<tr>
<td><strong>1 year OS</strong></td>
<td>79.2%</td>
<td>64.2%</td>
</tr>
<tr>
<td><strong>Grade 3/4 hematological toxicities (p =0.08)</strong></td>
<td>None</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Non- hematological toxicities</strong></td>
<td>12%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Mukherjee et al. Lancet Onc 2013
Locally Advanced Pancreatic Cancer

LAP07 Trial

**R1**

A: Gem 4 months
B: Gem + erlotinib 4 months

Non Progressive Tumor

**R2**

1. Chemotherapy (no RT)
   - A1 Gemcitabine 2 months, then stop until progression
   - B1 Gemcitabine + Erlotinib (100mg/d) 2 months, then erlotinib maintenance (150 mg/d) until progression

2. Chemoradiotherapy (CRT)*
   - A2 CRT then stop until progression
   - B2 CRT then erlotinib maintenance (150 mg/d) until progression

*54 Gy + Capecitabine

Hammel P. et al, PASCO, 2013
LAP07 Results

• First Randomization: Gem v. Gem + Erlotinib
  – MS: 13.6 mos v. 11.8 mos

Hammel P. et al, PASCO, 2013
LAP07 Results

• Second Randomization: CT v. CRT
  – MS: 16.5 v. 15.3 months
  – $H_0$: CRT increases MS from 9 to 12 months

Hammel P. et al, PASCO, 2013
LAP07 Results

Progression-free survival

Site of first progression

<table>
<thead>
<tr>
<th></th>
<th>CT (n= 125)</th>
<th>CRT (n= 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>58 (46%)</td>
<td>35 (32%)</td>
</tr>
<tr>
<td>M+</td>
<td>55 (44%)</td>
<td>67 (60%)</td>
</tr>
<tr>
<td>unknown</td>
<td>12 (10%)</td>
<td>9 (8%)</td>
</tr>
</tbody>
</table>

Huguet F. et al, PASCO 2014
Why was LAP07 a negative trial?

• Inadequate radiosensitization?
  – Gem v. 5-FU based concurrent chemo?
  – Poor drug delivery?

• Is pancreas cancer an intrinsically radioresistant tumor
  – Tumor hypoxia
  – Tumor microenvironment, desmoplasia

• Is systemic disease not well controlled with gem alone so impact of local control less important?
SBRT for Pancreatic Cancer

• Advantages of SBRT over conventionally fractionated radiotherapy
  – 1-2 weeks vs 6 weeks of therapy
  – Greater dose conformality
    • Fewer acute complications
  – No delay in administration of systemic chemotherapy
### SBRT: Trials for Pancreas Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prior EBRT</th>
<th>Regimen</th>
<th>Median OS Months</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koong, Phase I</td>
<td>15</td>
<td>2</td>
<td>15-25Gy /1 fx</td>
<td>11</td>
<td>33% G1-2 acute/NR</td>
</tr>
<tr>
<td>Koong, Phase II</td>
<td>16</td>
<td>16</td>
<td>45Gy/25 fx + 25Gy/1 fx</td>
<td>8.3</td>
<td>12% G3 acute/G2 late ulcers</td>
</tr>
<tr>
<td>Schellenburg,</td>
<td>16</td>
<td>0</td>
<td>25 Gy/1 fx</td>
<td>11.4</td>
<td>6% acute G3/ 13% late G3</td>
</tr>
<tr>
<td>Hoyer,</td>
<td>0</td>
<td>0</td>
<td>45 Gy/3 fx</td>
<td>5.7</td>
<td>18% severe GI toxicity</td>
</tr>
<tr>
<td>Mahadevan, 2010</td>
<td>36</td>
<td>0</td>
<td>24-36 Gy/3 fx</td>
<td>20.0</td>
<td>5% G3</td>
</tr>
<tr>
<td>Polistina, 2010</td>
<td>23</td>
<td>0</td>
<td>30 Gy/3 fx</td>
<td>10.6</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Tozzi, 2013</td>
<td>30</td>
<td>0</td>
<td>45 Gy/6 fx</td>
<td>11.0</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Gurka, 2013</td>
<td>11</td>
<td>0</td>
<td>25 Gy/5 fx</td>
<td>12.2</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Herman, 2013</td>
<td>49</td>
<td>0</td>
<td>33 Gy/5 fx</td>
<td>13.9</td>
<td>8% late G3</td>
</tr>
</tbody>
</table>
Phase II Study of Gemcitabine + SBRT

Locally Advanced Pancreatic CA → Gemcitabine → 25 Gy → Gemcitabine

- 16 patients received 1-3 weeks of gemcitabine prior to SBRT
- Median follow-up: 9.1 months
- Median OS: 11.4 months, 2 year OS: 12.5%
- Median TTP: 9 months
  - 3 patients had LR by PET/CT
  - 14/16 had DM as first site of progression

<table>
<thead>
<tr>
<th>Grade</th>
<th>Complication</th>
<th>Prior Surgery</th>
<th>Therapy</th>
<th>Weeks post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Gastritis and pain</td>
<td>CDJ-GJ</td>
<td>None</td>
<td>&lt;6 wks</td>
</tr>
<tr>
<td>2</td>
<td>Gastritis and pain</td>
<td>Aborted Whipple</td>
<td>Medical</td>
<td>&lt;6 wks</td>
</tr>
<tr>
<td>3</td>
<td>Ulcer, gastritis, pain</td>
<td>CDJ-GJ</td>
<td>Medical and J-tube</td>
<td>6 wks</td>
</tr>
</tbody>
</table>

*CDJ – Choledocojejunostomy

*GJ - Gastrojejunostomy

# Late Complications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Complication</th>
<th>Weeks After SBRT</th>
<th>Previous surgery</th>
<th>Tx received</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Duodenal-Jejunal ulcer</td>
<td>29</td>
<td>CDJ-GJ</td>
<td>Medical management</td>
</tr>
<tr>
<td>2</td>
<td>Duodenal ulcer</td>
<td>22</td>
<td>CDJ-GJ</td>
<td>Medical management</td>
</tr>
<tr>
<td>2</td>
<td>Duodenal ulcer</td>
<td>26</td>
<td>CDJ-GJJ</td>
<td>Medical management</td>
</tr>
<tr>
<td>2</td>
<td>Gastric-Duodenal ulcer</td>
<td>32</td>
<td>None</td>
<td>Medical management</td>
</tr>
<tr>
<td>2</td>
<td>Duodenal ulcer</td>
<td>20</td>
<td>None</td>
<td>Medical management</td>
</tr>
<tr>
<td>3</td>
<td>Duodenal stricture requiring stent</td>
<td>46</td>
<td>None</td>
<td>Duodenal Stent</td>
</tr>
<tr>
<td>4</td>
<td>Duodenal ulcer &amp; perforation requiring surgery</td>
<td>34</td>
<td>CDJ-GJ</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Duodenal Doses

- Median time to duodenal toxicity: 6.2 mos
- 6- and 12-mo actuarial rates of toxicity: 11% and 29%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>Incidence of Grade 2–4 duodenal toxicity (%)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V5</td>
<td>&lt;25 cm³</td>
<td>28</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>≥25 cm³</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>V10</td>
<td>&lt;16 cm³</td>
<td>15</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>≥16 cm³</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>V15</td>
<td>&lt;9.1 cm³</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥9.1 cm³</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>V20</td>
<td>&lt;3.3 cm³</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥3.3 cm³</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>V25</td>
<td>&lt;0.21 cm³</td>
<td>12</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>≥0.21 cm³</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

* V5 refers to the volume of duodenum receiving 5 Gy.
† Cutoff refers to the median value.
‡ Actuarial incidence at 12 months.

Murphy J, et al., IJROBP, 2012
Danish SBRT Experience

• Phase II trial of SBRT (15 Gy x3) for locally advanced pancreatic cancer
• 22 patients treated to tumor (GTV) and surrounding edema (CTV) + 5mm radial margin, 10 mm cranio-caudal margin (PTV)
• Electa or Varian planning and delivery systems

Hoyer M, et al., Radiother Oncol, 2005
Danish SBRT Experience

- Median survival was 5.7 months
- 1 year OS 5%
- 79% progressed to ≥ Grade 2 toxicity within 14 days of SBRT

Hoyer M, et al., Radiother Oncol, 2005
Induction Gemcitabine → SBRT

- 47 patients histo/cytologically confirmed locally advanced pancreas cancer
- 2 cycles of gemcitabine 1000 mg/sqm q 3/4 weeks
- 2 patients did not tolerate/refused chemotherapy
- Restaging CT angiogram, CA19-9
  - 39 patients non-metastatic locally advanced pancreas cancer
  - 8 patients metastatic disease
  - Cycle 3 of gemcitabine, fiducial placement and treatment planning
  - 3 fraction SBRT (8-12 Gy × 3) between 3rd and 4th gemcitabine cycles
  - Continue gemcitabine until minimum of 6 cycles, tolerance or progression

Mahadevan, Int J Rad Oncol Biol Phys, 2011
Induction Gemcitabine → SBRT

- 8 of 47 patients (17%) had metastatic disease after 2 cycles of gemcitabine
- 39 patients received SBRT
- Median follow-up for survivors was 21 months
- Median OS was 20 months
- Median PFS was 15 months
- Local control rate was 85%
- Late Grade 3 toxicities (GI bleeding and obstruction) in 9% (3/39) of patients

Mahadevan, Int J Rad Oncol Biol Phys, 2011
Prospective SBRT Trial

Phase II Multi-Institutional Study of Stereotactic Body Radiation Therapy for Unresectable Pancreatic Cancer

(Herman, Chang, Goodman, Koong PI’s)

(GEM, up to 1 Cycle allowed)*

1 week break

SBRT 6.6 Gy x 5 Mon-Fri

1 week break

GEM Chemotherapy (3 wks on, 1 wk off) Until toxicity or progression

Primary endpoint: Late GI Toxicity > 4 months

Secondary: Tumor Progression Free Survival, pre-tx biopsy, PET/CT QOL, biomarkers.

49 patients with LAPC were analyzed
# SBRT Dose Constraints

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTV</strong></td>
<td>V33Gy=95.0%</td>
</tr>
<tr>
<td><strong>Proximal Duodenum</strong></td>
<td>V15Gy&lt;9.0 cc</td>
</tr>
<tr>
<td></td>
<td>V20Gy&lt;3.0 cc</td>
</tr>
<tr>
<td></td>
<td>V33Gy&lt;1.0 cc</td>
</tr>
<tr>
<td><strong>Proximal Stomach</strong></td>
<td>V15Gy&lt;9.0 cc</td>
</tr>
<tr>
<td></td>
<td>V20Gy&lt;3.0 cc</td>
</tr>
<tr>
<td></td>
<td>V33Gy&lt;1.0 cc</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>V12Gy&lt;50%</td>
</tr>
<tr>
<td></td>
<td>V33Gy&lt;1.0 cc</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>V12Gy&lt;50%</td>
</tr>
<tr>
<td><strong>Kidney combined</strong></td>
<td>V12Gy&lt;75%</td>
</tr>
<tr>
<td><strong>Cord</strong></td>
<td>V8Gy&lt;1.0 cc</td>
</tr>
</tbody>
</table>
Overall Survival

Median: 13.9 mos

Herman et al. Cancer, 2014
SBRT Toxicity and QOL

• **Toxicity**
  - Acute GI
    • Grade 1-2: 10%
    • Grade ≥3: 0%
  - Late GI
    • Grade ≥3: 8%
    - GI bleed (2)

• **Quality of Life (EORTC)**
  - Mean global QOL
    • scores unchanged pre/post SBRT
  - Pancreas specific QOL
    • Improved (p<0.05)
      - pancreatic pain
      - body image

_Herman et al. Cancer, 2014_
## Borderline Resectable

Resection Determined by Vessel Involvement

<table>
<thead>
<tr>
<th></th>
<th>AHPBA/SSAT/SSO\textsuperscript{1,2}</th>
<th>MD Anderson\textsuperscript{5,8}</th>
<th>NCCN 2012\textsuperscript{17,c}</th>
<th>Intergroup trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV-PV</td>
<td>Abutment\textsuperscript{a}, encasement\textsuperscript{b}, or occlusion</td>
<td>Occlusion</td>
<td>Abutment with impingement or narrowing</td>
<td>Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall, and/or reconstructable\textsuperscript{d} occlusion</td>
</tr>
<tr>
<td>SMA</td>
<td>Abutment</td>
<td>Abutment</td>
<td>Abutment</td>
<td>Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall</td>
</tr>
<tr>
<td>CHA</td>
<td>Abutment or short-segment encasement</td>
<td>Abutment or short-segment encasement</td>
<td>Abutment or short-segment encasement</td>
<td>Reconstructable\textsuperscript{d}, short-segment interface between tumor and vessel of any degree</td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>No abutment or encasement</td>
<td>Abutment</td>
<td>No abutment or encasement</td>
<td>Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall</td>
</tr>
</tbody>
</table>

Katz et al. ASO 2013
160 (7%) of 2,454 PCA were borderline resectable

125 (78%) completed CXRT and restaging, 66 (41%) underwent PD

- 62 of these (94%) underwent a margin-negative resection, and only 30% node positive

Median OS was 40 mo for the 66 patients who completed all therapy and 13 mo for the 94 patients who did not undergo pancreatectomy (p < 0.001)
**RECIST of 122 patients restaged following neoadjuvant therapy**

<table>
<thead>
<tr>
<th>RECIST</th>
<th>Example</th>
<th>N (%)</th>
<th>Resected n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable Disease</strong></td>
<td>![Example Image] +6%</td>
<td>84 (69)</td>
<td>70 (83)</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>![Example Image] -38%</td>
<td>15 (12)</td>
<td>15 (100)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong> (Local)</td>
<td>![Example Image] +22%</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

21 (17%) progressive disease due to metastases, 0 resected

*Katz, Cancer 2012*
Alliance A021101
Treatment Schema

- Pre-enrollment phase with centralized radiographic review of staging
- Centralized review of restaging studies and use of objective response metrics
- Standardized indications for operation
- Protocol-mandated operative procedures / vascular resection
- Analysis and reporting of survival rates
Resectable Pancreatic Cancer

MSKCC Database Jan 1983 – Jan 2006

n = 985

Courtesy of Peter Allen, MD
Resectable Pancreatic Cancer

• Even after R0 resection, 50-75% rate LR

• Deficient historical studies of RT for adjuvant therapy
  • Low RT doses with planned treatment breaks
  • Ineffective radiosensitization

• Delivering adequate RT dose limited by normal tissue tolerances of neighboring abdominal structures

## Adjuvant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient No.</th>
<th>Treatment Regimen</th>
<th>Median Survival (mos)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985)</td>
<td>21</td>
<td>40 Gy split course + 5-FU, then 5-FU x 2 yr</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Observation</td>
<td>10.9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>40 Gy split course + 5-FU, then 5-FU x 2 yr</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>EORTC (1999)</td>
<td>60</td>
<td>40 Gy split course + 5-FU</td>
<td>17.1</td>
<td>37 (2 yr)</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>Observation</td>
<td>12.6</td>
<td>23 (2 yr)</td>
</tr>
<tr>
<td>ESPAC-1 (2004)</td>
<td>73</td>
<td>40 Gy split course + 5-FU</td>
<td>13.9</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>40 Gy split course + 5-FU, then 5-FU x 6 cycles</td>
<td>19.9</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>5-FU and folinic acid monthly for 6 mo</td>
<td>21.6</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>Observation</td>
<td>16.9</td>
<td>11</td>
</tr>
</tbody>
</table>
RTOG 97-04

Postoperative patients

N = 442

5-FU cont. infusion x 3 weeks

Gemcitabine weekly x 3 weeks

XRT (5040 cGy) plus concurrent C.I. 5-FU

5-FU C.I. (4 weeks on, 2 weeks off) x 2 cycles

Gemcitabine (3 weeks on, 1 week off) x 3 cycles
RTOG 97-04

• No difference in OS for all pts, trend toward in improvement for Gem arm in pancreatic head tumors
  – 5 yr OS: 22% v. 18%
  – MS: 20.5 v. 17.1 mo
• First site of relapse:
  – local recurrence in 28%
  – distant relapse in 73%

Adjuvant Chemotherapy

CONKO trial

- Randomized to surgery alone v. surgery + adjuvant gemcitabine (6 cycles)
- 368 patients with gross complete (R0 or R1) resection of pancreatic cancer
- Limited to patients with CA-19-9 < 2.5 x nl
- Grade 3+ toxicity was rare
- Significant improvement in:
  - Median DFS: 13.4 v. 6.9 mo
  - MS: 22.8 mos v. 20.2 mos, p=0.005
  - 5 yr OS: 21% v. 9%

Oettle H. et al, JAMA, 2007
Oettle H. et al. PASCO, 2008, ab 4504
RTOG 0848 Schema

**FIRST RANDOMIZATION**

### STRATIFY

**Nodal Status:**
1: involved
2: uninvolved

**CA19-9 result:**
1: \( \leq 90 \)
2: \( > 90 - 180 \)

**Surgical margins:**
1: positive (R1)
2: negative (R0)

**RANDOMIZE**

- Arm 1:
  - Gemcitabine x cycles
- Arm 2:
  - Gemcitabine + erlotinib x 5 cycles

Evaluate to Confirm No Progression

---

If no progression, then:

**SECOND RANDOMIZATION**

For Non-Progressing Patients

### STRATIFY

**First Randomization Treatment**

**Arm:**
1. Arm 1 gemcitabine vs.
2. Arm 2 gemcitabine + erlotinib

### RANDOMIZE

- Arm 3:
  - 1 cycle of chemotherapy
- Arm 4:
  - 1 cycle of chemotherapy followed by XRT with either capecitabine or 5-FU
Neoadjuvant Therapy

- MDACC Phase II trial of gemcitabine-based pre-operative therapy
  - 86 pts with resectable pancreatic cancer
  - Weekly gemcitabine x 7 plus RT (30 Gy in 10 fractions over 2 weeks), 6 wks then surgery
  - At re-staging, 13 (15%) had POD
  - 64 (74%) underwent a successful PD
- MS: 22.7 mos, 5-year OS = 27%
  - MS: 34 mos v. 7 mos for pts who underwent PD v. no resection
  - 5-year OS: 36% and 0%

Neoadjuvant Therapy

- Meta-analysis of 111 studies
- Neoadjuvant CT in 96%, RT in 93%

Treatment Planning Considerations

• 50.4-56 Gy adjuvant/gross disease IMRT preferred over 3-D based on published experience
  • Simulate and Rx with “empty” stomach, IV + PO contrast
  • Daily KV; 4-D CT and CBCT for unresectable/borderline resectable or localizable positive margin

• Dose-limiting structures:
  • Spinal cord max 45 Gy
  • Liver: mean < 25 Gy, V30 < 60%
  • Kidney: combined mean < 18
  • Small bowel/Stomach: V45 < 150 cc, V30 < 300 cc; V50< 10%, V45 < 15%, V20 < 50% and max < 56 Gy for each
Radiotherapy Quality Assurance

- RT fields prospectively reviewed in RTOG 97-04
  - 48% of treatment plans did not meet protocol requirements.
- Based on “per protocol” versus “not per protocol” radiation delivery
  - Grade 3/4 toxicity did not vary significantly on the 5-FU arm but did show a trend of less toxicity for patients on the gemcitabine arm
- Survival was significantly increased for patients treated per protocol (p=0.019)

Abrams R. et al. IJROBP, 2012
Radiotherapy QA on RTOG 0848

• Prospective radiation quality control is required
• Central review will be performed prior to treatment delivery
• CT-based planning is required
• Either 3D conformal (3DCRT) or intensity-modulated radiotherapy (IMRT) planning
ROI's

Structures:
- PV
- PI
- AORTA
- SMA
- CA
- Tumor Bed
Coronal/Sagittal Views
Liver Tumors:
Colorectal Liver Metastases
Primary Liver Tumors
# Radiation Induced Liver Disease

- Whole liver irradiation associated with risk of radiation-induced liver disease (RILD)

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Pathologic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fatigue</td>
<td>- Hyperemia acutely</td>
</tr>
<tr>
<td>- Elevated liver enzymes (Alk phos)</td>
<td>- Veno-occlusive disease</td>
</tr>
<tr>
<td>- Tender anicteric hepatomegaly</td>
<td>- Central venous congestion, sparing large veins</td>
</tr>
<tr>
<td>- Ascites</td>
<td>- Atrophy of adjacent hepatocytes</td>
</tr>
</tbody>
</table>
Unresectable Liver Metastases

- 150,000 cases of colorectal cancer diagnosed annually
- 50% of CRC patients will develop liver metastasis
- Surgery is gold standard for CRC liver metastases
  - 5-year survival approximately 50%
- Only 15% of CRC liver metastases are resectable
- Chemotherapy
  - 12-24 months median survival
  - Historical 5-year survival <5%
- Alternative liver-directed therapies: RFA, HAI, SBRT
Single Fraction SBRT Outcomes

Median Follow-up = 14 mos

Median Survival: 22.4 months

Overall Survival

Cumulative Incidence of LF

1 year LF = 23%

Goodman KA, et al., IJROBP, 2010
Hypofractionated SBRT

- Phase I/II Study
  - Dose escalation: 36 – 60 Gy in 3 fractions
- 47 patients with 56 lesions (1-3 lesions)
  - 13 pts received <60Gy, 36 received 60Gy
  - Median lesion volume: 15 cc
  - Respiratory gating
  - At least 700 cc had to receive < 15Gy
- Median follow-up: 16 mos
- 2 yr LC: 92% (100% for lesions ≤3cm)
- Grade 3+ toxicity: <2%

Rusthoven K, et. al., J Clin Oncol, 2009
Hypofractionated SBRT

- Phase I study of individualized 6 fraction SBRT for liver metastases in 68 pts
- Median SBRT dose: 41.8 Gy (27.7 to 60 Gy)
- Median tumor vol: 75 cc
- 1-year LC: 71%
- Minimal Toxicity
  - 2 grade 3 LFT changes
  - 6 acute grade 3 toxicities
  - No RILD

Lee M, et. al., J Clin Oncol, 2009
**Hypofractionated SBRT**

- Phase I/II Study UT Southwestern
  - 28 patients/136 tumors – 27 patients evaluable
  - Dose escalation to 60 Gy (5 fractions)
  - No Grade 3+ treatment-related toxicities

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Response rate (n=9)</th>
<th>2 yr LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>30%</td>
<td>56%</td>
</tr>
<tr>
<td>50</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>60</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Hypofractionated SBRT

- 61 patients with 76 liver metastases treated on Phase II trial of SBRT
- Objective: In-field local control, assess toxicity
- 75 Gy in 3 fractions to CTV
  - PTV covered by 67% - 50Gy in 3 fractions
  - Dose reduction of up to 30% in 14 patients
- No RILD, 1 Grade 3 chest wall pain
- 1 yr median f/u, 1 yr LC – 94%, 1 yr OS – 84%

Scorsetti M, Int J Rad Oncol Biol Phys, 2013
MSKCC Experience

• 46 patients, 50 tumors (10 primary, 40 metastases) treated with SBRT from 3/04-3/11

Local Failure

Overall Survival

2 yr Cumulative Incidence of Local Failure = 25%

Median Survival – 15.4 mos

Katsoulakis, Am J Clin Oncol, 2013
Predictors of Local Control

- 3 Late Grade 3-4 GI toxicities, all in 24Gy single fraction and central lesions

Katsoulakis E, Am J Clin Oncol, 2013
<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>Local control (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren/'98</td>
<td>20</td>
<td>2-4x10-20Gy</td>
<td>Mean 9.6</td>
<td>95</td>
<td>Mean 17.8m</td>
</tr>
<tr>
<td>Herfarth/'01</td>
<td>102</td>
<td>1x20-26Gy</td>
<td>Mean 14.9</td>
<td>66, 60</td>
<td>76, 55</td>
</tr>
<tr>
<td>Fuss/'04</td>
<td>17</td>
<td>6x6Gy or 3x12Gy</td>
<td>6.5</td>
<td>94, NRC</td>
<td>80, NRC</td>
</tr>
<tr>
<td>Wulf/'01</td>
<td>51</td>
<td>3x12-12.5Gy or 1x26Gy or 3x10Gy or 4x7Gy</td>
<td>15</td>
<td>100, 82 (high)</td>
<td>72, 34</td>
</tr>
<tr>
<td>MéndezRomero/'06</td>
<td>34</td>
<td>3x10-12.5Gy</td>
<td>12.9</td>
<td>100, 86</td>
<td>85, 62</td>
</tr>
<tr>
<td>Hoyer/'06</td>
<td>141</td>
<td>3x10 Gy</td>
<td>52</td>
<td>NRP, 86</td>
<td>67, 38</td>
</tr>
<tr>
<td>Katz/'07</td>
<td>182</td>
<td>17.5 – 56 Gy in 2-10 fx</td>
<td></td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Rusthoven/'09</td>
<td>47</td>
<td>3 x 12-20Gy Dose escalation</td>
<td>16</td>
<td>95, 92</td>
<td>Median 17.6m</td>
</tr>
<tr>
<td>Lee/'09</td>
<td>68</td>
<td>Individualized dose 27.7-60Gy/ 6 fx</td>
<td>10.8</td>
<td>71, NRP</td>
<td>47% @18mo</td>
</tr>
<tr>
<td>Goodman/'10</td>
<td>19</td>
<td>18-30Gy single fx</td>
<td>17.3</td>
<td>77, NRP</td>
<td>62, 49</td>
</tr>
<tr>
<td>Rule/'11</td>
<td>136</td>
<td>5 x 6-10Gy Dose escalation</td>
<td>20</td>
<td>56/56</td>
<td>56 @ 2yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100/89</td>
<td>67 @ 2yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100/100</td>
<td>50 @ 2yr</td>
</tr>
</tbody>
</table>
Unresectable Hepatocellular Carcinoma

• Until recently, minimal role for RT
  – Perceived radioresistance of HCC
  – Underlying liver dysfunction increased risk of liver toxicity

• CT-based planning allowed more targeted RT

• Studies of 3DCRT in Asia and Univ. of Michigan demonstrated feasibility of dose escalated RT

• 1-year local control ranged from 50-80%
SBRT for Primary Liver Tumors

- 102 patients with locally advanced HCC enrolled on 2 prospective studies of SBRT
  - Childs A liver function
  - Tumor vascular thrombosis in 55%
- Prescribed a variable dose (24 – 54 Gy) over 6 fractions
- Median gross tumor volume was 117.0 cc (1.3 to 1,913.4 cc)
- Median follow-up was 31.4 months

Bujold A, et. al., J Clin Oncol, 2013
SBRT for Primary Liver Tumors

- 1 year LC was 87%
- Median OS was 17 mos
- Grade 3+ toxicity in 30%
- Possible Grade 5 in 7 patients (2 with TVT PD)
- Dose >30 Gy improves LC rates
- Even in this high-risk HCC population, SBRT associated with good LC

_Bujold A, et. al., J Clin Oncol, 2013_
Phase I-II Trial of SBRT in Patients with HCC, Child-Pugh Class A and B

- Interim analysis of variables affecting toxicity and outcome

<table>
<thead>
<tr>
<th></th>
<th>CPC A</th>
<th>CPC B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dose/# Fractions</td>
<td>4800cGy/3</td>
<td>4000cGy/5</td>
</tr>
<tr>
<td>2 yr LC</td>
<td>87%</td>
<td>85%</td>
</tr>
<tr>
<td>2 yr PFS</td>
<td>55%</td>
<td>28%</td>
</tr>
<tr>
<td>2 yr OS</td>
<td>81%</td>
<td>28%</td>
</tr>
<tr>
<td>Grade 3-4 Liver Toxicity</td>
<td>14%</td>
<td>33%</td>
</tr>
</tbody>
</table>

- Mean Tumor Volume = 33 cc
- For CPC B pts, volume effect on Grade III/IV liver toxicity
- SBRT for CPC A patients is feasible and safe
- SBRT for CPC B patients is still associated with significant toxicity in uncompensated liver and while SBRT results in LC, the overall outcome of this disease may not be addressed by local therapy

Lasley FD, ASTRO 2012
# SBRT Trials for HCC

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>Local control (%) 1, 2 years</th>
<th>Survival (%) 1, 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendez-Romero/’06</td>
<td>5 CPC A, 2 CPC B, 1 w/o cirrhosis, 11 lesions</td>
<td>5 Gy x 5 or 10-12.5 Gy x 3</td>
<td>12.9</td>
<td>75% at 22 mo</td>
<td>75%, 40%</td>
</tr>
<tr>
<td>Tse/’08</td>
<td>21 CPC A</td>
<td>36 Gy (24-54 Gy) in 6 fx</td>
<td>17.6</td>
<td>65% @ 1yr</td>
<td>48% @ 1yr</td>
</tr>
<tr>
<td>Cardenes/’10</td>
<td>6 CPC A, 11 CPC B</td>
<td>12-16 Gy x 3, 8 Gy x 3</td>
<td>24</td>
<td>100%</td>
<td>75%, 60%</td>
</tr>
<tr>
<td>Lasley/’12</td>
<td>36 CPC A/ 21 CPC B</td>
<td>48Gy in 3 or 40Gy in 5 fx</td>
<td></td>
<td>87%/85% @ 2yr</td>
<td>81%/35% @ 2 yrs</td>
</tr>
<tr>
<td>Dawson/’13</td>
<td>102 CPC A</td>
<td>24Gy - 54Gy in 6</td>
<td>31</td>
<td>87% @ 1yr</td>
<td>Median Survival = 17 mo</td>
</tr>
</tbody>
</table>
## SBRT for Unresectable Intrahepatic and Hilar Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>1 Year Local control (%)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse/’08</td>
<td>10 IHCC</td>
<td>32.5 in 6 fx</td>
<td>17.6</td>
<td>65%</td>
<td>15 mo</td>
</tr>
<tr>
<td>Kopek/’10</td>
<td>27 (26 hilar CC, 1 IHCC)</td>
<td>45 Gy in 3 fx</td>
<td>60 mo</td>
<td>84%</td>
<td>10.4 mo</td>
</tr>
<tr>
<td>Goodman/’10</td>
<td>5 IHCC</td>
<td>18-30Gy in 1 fx</td>
<td>17</td>
<td>77%</td>
<td>29 mo</td>
</tr>
<tr>
<td>Barney/ ’12</td>
<td>10 pts, 12 lesions</td>
<td>55 Gy in 3-5 fx</td>
<td>14</td>
<td>100%</td>
<td>14 mo</td>
</tr>
<tr>
<td>Mahadevan/’12</td>
<td>20 pts/25 lesion</td>
<td>30 Gy in 3 fx</td>
<td>93%</td>
<td>17 mo</td>
<td></td>
</tr>
</tbody>
</table>
RTOG1112: RANDOMIZED PHASE III STUDY OF SORAFENIB VERSUS STEREOTACTIC BODY RADIATION THERAPY FOLLOWED BY SORAFENIB IN HEPATOCELLULAR CARCINOMA

Sample size: 368
Primary endpoint: median survival 10.5 to 14.5 mo

<table>
<thead>
<tr>
<th>Registration</th>
<th>Randomize</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td>Daily sorafenib</td>
<td>SBRT alone (27.5 Gy – 50 Gy in 5 fractions)</td>
<td>Followed by Sorafenib alone daily</td>
</tr>
<tr>
<td>Hepatitis B vs. C vs. other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North American site vs. Non-North American site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment Planning Considerations

• Limited visualization of the target
• Organ deformation with respiration
• Changes in GI organ luminal filling
  – Critical structures (stomach) may change in shape and position between planning and treatment
• Interfraction target displacement with respect to bony anatomy
CT v. MRI

• The CT and MRI volumes agreed best for patients with metastatic disease (concordance volumes between 77% and 86%)

• CT tended to overestimate the GTV for primary liver cancer, as compared with MRI

Voroney, JP, et. al., Int J Rad Oncol Bio Phys, 2006
CT phase: Liver Metastases & IHCC

- Portal venous phase

Colorectal Liver Metastases

Intrahepatic Cholangiocarcinoma
CT phase: HCC

- Late arterial and portal venous phases
Fiducial Markers

visicoil
Fiducial Markers

EUS-guided placement
Fiducial Markers: Daily Set-Up
Simulation

- Supine, arms up immobilized in alpha cradle
- IV and PO contrast
- NPO 4 hours prior to simulation
  - Empty stomach for simulation and for daily treatment
- For respiratory gating patients
  - Scan during end-exhalation breath hold
  - 2.5 mm slice thickness
  - 4DCT with voice coaching
- For compression belt patients
  - Fluoro to determine pressure needed
  - PET/CT with compression applied
Motion Management Techniques

**Respiratory Gating**
- Cyclical delivery of RT
- Patient compliance with breathing instructions
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Poor quality CBCT
- Standard fractionation RT

**Abdominal Compression**
- Continuous delivery of RT
- Patient tolerance of the compression belt
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Less motion artifact in CBCT
- SBRT
Abdominal Compression

• Abdominal belt with inflatable bladder
• Inflation: 15-40 mmHg
Abdominal Compression

• 44 patients treated with SBRT between 2004-2012 using abdominal compression belt
  – Liver (30), adrenal glands (6), pancreas (3) and lymph nodes (30)
• 2-3 radiopaque fiducial markers or clips
• Craniocaudal (CC) motion measured fluoroscopically with and without pneumatic pressure
• Objective: reduce CC motion ≤ 5 mm peak to peak

Lovelock M, et. al., TCRT, 2014
“It keeps me from looking at my phone every two seconds.”
Rectal Cancer
Risk of CRC

- General population: 5%
- Personal history of colorectal neoplasia: 15%–20%
- Inflammatory bowel disease: 15%–40%
- HNPCC mutation: 70%–80%
- FAP: >95%
Causes of CRC

Sporadic (65%–85%)

Familial (10%–30%)

Familial adenomatous polyposis (FAP) (<1%)

Hereditary nonpolyposis colorectal cancer (HNPCC) (3-4%)

Other rare CRC syndromes (<0.1%):

- Attenuated Familial adenomatous polyposis (AFAP)
- MUTYH-associated polyposis (MAP)
Lynch Syndrome

- Results from germline mutations in DNA mismatch repair (MMR) genes
  - *MLH1* and *MSH2* (most common), *MSH6*, *PMS1*, and *PMS2*

- Testing
  1) IHC for MMR protein expression
  2) PCR analysis for microsatellite instability (MSI), resulting from MMR deficiency
    - Changes in length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units
    - 15% of sporadic colorectal cancer have MSI resulting from the hypermethylation of the MLH1 gene promoter
Amsterdam Criteria: “3-2-1”

Lynch Syndrome Clinical Diagnostic Criteria

• **Three** or more relatives, one a 1st degree relative of the other 2

• **Two** or more successive generations

• **One** or more family member diagnosed at less than 50 years of age
Revised Bethesda Guidelines

- Presence of synchronous or metachronous CRC or other Lynch-associated tumors, regardless of age
- CRC with high microsatellite instability (MSI) histology diagnosed in a patient < 60 yrs
Screening

• General population
  – Colonoscopy Q5-10 years, starting age 50
  – If benign polyp, then q1yr until no polyps found

• Family history/HNPCC
  – Annual FOB & endoscopic surveillance at age 35

• US National Polyp Study
• Minnesota Colon Cancer Control Study
- Above dentate line to below the peritoneal reflection
- Adenocarcinoma
Lymph Node Drainage

- Upper and middle third:
  - Superior rectal (hemorrhoidal) artery (SRA) to IMA

- Distal third: Dual drainage
  - SRA to IMA
  - Middle & inferior hemorrhoidal vessels to IVC via Internal iliacs

- Extension to anus
  - Inguinal nodes
Patient Evaluation

- H & P, DRE (fixed - mobile - ulcerated – exophytic; distance from verge; anal tone; adjacent organ involvement)
- CT chest, abdomen, pelvis
- Full colonoscopy (synchronous disease in 5%)
- TRUS & rectal MRI for local staging, 80-90% accuracy for T stage; less accurate for N stage
- CBC (Hct), BUN/Cr, LFTs, CEA
Surgical Options

- LAR - low anterior resection (including very low anterior resection with coloanal anastomosis)
  - sphincter preservation
- APR - abdomino-perineal resection
  - colostomy
- LE - local excision
  - sphincter preservation for low-lying tumors
Historical Surgical Results

• Rationale for neoadjuvant/adjuvant therapy based on patterns of failure after potentially curative surgery
  – T1-2N0M0        →        LF <10%
  – T3N0M0, T1N1M0  →        LF 15-35%
  – T3-4N1-2M0      →        LF 45-65%

• Local failure debilitating, with limited ability to salvage
Role of Adjuvant Radiotherapy

- 22 Randomized Trials
  - Postoperative: 2157 patients in 8 trials
  - Preoperative: 6350 patients in 14 trials
- Local Recurrence
  - 37% decrease in postoperative trials
  - 46% decrease in preoperative trials
- Survival – No Significant Improvement

Colorectal Cancer Collaborative Group.
1990 NCI Consensus Statement

“Combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II/III rectal cancer patients and is recommended.”
Preoperative Radiotherapy Alone

• 20 + Randomized Trials:
  – Majority Short Course Hypofractionated RT
  – All Decrease LR
  – Swedish Rectal Cancer Trial Showed Survival Advantage
  – Problem = Ano-rectal Morbidity & Late Effects
Swedish Rectal Cancer Trial

1168 Resectable Rectal Cancers

25 Gy in 5 Fxs Surgery 1 Wk Later (RT→S)

Surgery (S)

# Swedish Trial Outcomes 13 Years

<table>
<thead>
<tr>
<th></th>
<th>RT→ S</th>
<th>S Only</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>9%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>38%</td>
<td>30%</td>
<td>0.008</td>
</tr>
<tr>
<td>CSS</td>
<td>72%</td>
<td>62%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

N.B. Only trial to show survival advantage with RT alone.

Total Mesorectal Excision

- Sharp Dissection of the Entire Mesorectum and Rectal Tumor En Bloc, Cutting Along Avascular Fascial Planes
- Smooth Contour = Fascial Plane
Dutch CKVO 95-04 TME Trial

1805 Operable Rectal Cancers

- 25 Gy in 5 Fxs TME 1 Wk Later (RT → S)
- Total Mesorectal Excision Surgery (TME)

# Dutch CKVO 95-04 Outcomes 10 Years

<table>
<thead>
<tr>
<th></th>
<th>RT→ S</th>
<th>S Only</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>5.1%</td>
<td>11.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>47.6%</td>
<td>48.8%</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>24.9%</td>
<td>28.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Dutch CVKO 95-04 Study

In unplanned subgroup analysis:

Preop RT yields OS advantage at 10 years (50% vs. 40%) in Stage III patients with negative circumferential margins

van Gijn, Lancet Oncol, 2011
Dutch Study: Important Caveats

- Over-Tx: 31% Stage I pts
- Short Interval to Surgery
  - Lyon R90-01 Trial (2 wk vs. 6-8 wk)
- No Chemotherapy
- Late Effects
Swedish Trial: Late Effects

- Increase in Perineal Infections\(^1\)
  - 20% vs. 10%, \(P < 0.001\)

- Increase in Hospital Admissions for First 6 Months\(^2\)

- Increase in SBO & Impaired Bowel Function\(^3\)\(^-\)\(^5\)
  - 14 yr incidence of SBO: 13.9% vs. 5.5%

Goals of Pre-op RT in TME Era

1. Minimize risk of local failure
   - Reduce rate of CRM +
   - Address lateral pelvic sidewall nodes
2. Downstage tumors to allow for sphincter preservation
   - Optimal timing and schedules of RT
3. Identify patients with favorable tumor biologies
   - pCR associated with better outcomes
German Rectal Cancer Study

- Statistically significant increase in sphincter preservation among patients receiving preoperative chemoradiotherapy

Locally Advanced Rectal Cancer

- Preoperative 5FU +5040cGy pelvic RT
- Surgery: TME

- Postoperative 5FU +5580 cGy pelvic RT
- Surgery: TME

Graph showing cumulative incidence of local recurrence with Preoperative and Postoperative chemoradiotherapy.

<table>
<thead>
<tr>
<th>Months</th>
<th>Preoperative chemo-radiotherapy</th>
<th>Postoperative chemo-radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>20</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>30</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>40</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>50</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>60</td>
<td>13%</td>
<td>6%</td>
</tr>
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</table>

No. at Risk

<table>
<thead>
<tr>
<th>Preoperative chemoradiotherapy</th>
<th>397</th>
<th>368</th>
<th>312</th>
<th>250</th>
<th>190</th>
<th>133</th>
<th>97</th>
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</thead>
<tbody>
<tr>
<td>Postoperative chemoradiotherapy</td>
<td>384</td>
<td>351</td>
<td>299</td>
<td>240</td>
<td>184</td>
<td>135</td>
<td>85</td>
</tr>
</tbody>
</table>
Prognostic Factors: Tumor Regression

Tumor Regression Grade 4 (pCR)
  • No local recurrence, 86% 5-year DFS

Tumor Regression Grade 2-3
  • 4% local recurrence, 75% 5-year DFS

Tumor Regression Grade 0-1
  • 6% local recurrence, 63% 5-year DFS

Rodel, J Clin Oncol;2005
Role of Chemotherapy

- 2 studies compared pre-op RT v. pre-op RT/5-FU

### EORTC 22921

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT-CT</th>
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<tbody>
<tr>
<td>pCR</td>
<td>5.3%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Mean # involved LN</td>
<td>1.52</td>
<td>0.86</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>64.8%</td>
<td>65.8%</td>
</tr>
</tbody>
</table>

### FFCD 9203

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT-CT</th>
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<tbody>
<tr>
<td>pCR</td>
<td>3.7%</td>
<td>11.7%</td>
</tr>
<tr>
<td>pN1-2</td>
<td>21%</td>
<td>19%</td>
</tr>
<tr>
<td>R1 CRM</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Sphincter Preserv</td>
<td>52%</td>
<td>53%</td>
</tr>
<tr>
<td>5 yr LF</td>
<td>16.5%</td>
<td>8%</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td>56%</td>
<td>59%</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>66%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Bosset, NEJM;2006; Gerard, JCO, 2006
2014 Standard of Care for Locally Advanced Rectal Cancer

NCCN Guidelines Version 1.2015
Rectal Cancer

**PRIMARY TREATMENT**

- Chemo/RT
  - Capecitabine/RT or infusional 5-FU/RT or (category 1 and preferred for both)
  - Bolus 5-FU/leucovorin/RT
- Transabdominal resection
  - Resection contraindicated

**ADJUVANT TREATMENT**

(6 MO PERIOPERATIVE TREATMENT PREFERRED)

- FOLFOX (preferred) or CapeOx (preferred) or FLOX or 5-FU/leucovorin or capecitabine
- Active chemotherapy regimen for advanced disease (See REC-E)

**Surveillance** (See REC-8)

- Therapeutic advances over the last 2 decades
  - Improvements in surgical technique
  - Introduction of more effective chemotherapeutic agents
  - Advances in radiotherapy planning and delivery
How are we doing?

• 331 patients uT3/4 and/or N1/2 rectal cancer at MSKCC from 1998 to 2004
• Received standard preoperative chemoradiation followed by TME
• Median follow-up of 46 months
• 22% developed recurrences
• 7 (2%) local only
• 63 (19%) distant only
• 2 (1%) both local and distant recurrence
• Actuarial 5-year DFS = 74%

Quah, Cancer;2008
Neoadjuvant Chemoradiation: Overview of Emerging Options

- Incorporating new chemotherapy agents
  - Phase III data evaluating role of Oxaliplatin with concurrent 5-FU based chemoradiation
- Incorporating novel RT techniques
  - Intensity modulated radiotherapy
- Tailoring therapies for rectal cancer
  - Selective use of radiotherapy
  - Total neoadjuvant therapy
  - Non-operative management
Pre-op CRT in Oxaliplatin Era

• What is the role of Oxaliplatin in pre-operative CRT for Stage II-III Rectal Cancer?

• Oxaliplatin combined with 5-FU + RT in multiple phase II studies demonstrated promising pCR rates

• 4 prospective randomized trials evaluated addition of oxaliplatin to 5-FU-based pre-op CRT

### Randomized Trials of Oxaliplatin

<table>
<thead>
<tr>
<th></th>
<th>STAR-01</th>
<th>ACCORD-12</th>
<th>NSABP-R04</th>
<th>CAO/ARO-04</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N° Pts</strong></td>
<td>720</td>
<td>596</td>
<td>1,608</td>
<td>1,265</td>
</tr>
<tr>
<td><strong>Cum Dose Oxaliplatin</strong></td>
<td>360 mg/m²</td>
<td>250 mg/m²</td>
<td>250 mg/m²</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td><strong>Dose RT (Gy)</strong></td>
<td>50.4</td>
<td>45-50</td>
<td>50.4-55.8</td>
<td>50.4</td>
</tr>
<tr>
<td><strong>GI Tox G3-4</strong></td>
<td>7 v. 24%</td>
<td>11 v. 25%</td>
<td>7 v. 15%</td>
<td>8 v. 12%</td>
</tr>
<tr>
<td><strong>ypCR</strong></td>
<td>16%</td>
<td>13 v. 19%</td>
<td>19 v. 21%</td>
<td>13 v. 17%*</td>
</tr>
<tr>
<td><strong>Sph Sav S</strong></td>
<td>78%</td>
<td>75%</td>
<td>62%</td>
<td>88%</td>
</tr>
</tbody>
</table>

# Clinical Outcomes

<table>
<thead>
<tr>
<th>ACCORD Trial</th>
<th>Cap45</th>
<th>Capox50</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>6 %</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>DFS</td>
<td>69 %</td>
<td>74 %</td>
<td>NS</td>
</tr>
<tr>
<td>OS</td>
<td>88 %</td>
<td>88 %</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAO/ARO/AIO-04</th>
<th>5-FU</th>
<th>FOLFOX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>71%</td>
<td>76 %</td>
<td>.03</td>
</tr>
</tbody>
</table>

Gerard, Proc ASTRO, 2011; Rodel Proc ASCO 2014
Neoadjuvant Chemoradiation: Overview of Emerging Options

• Incorporating new chemotherapy agents
  – Phase III data evaluating role of Oxaliplatin with concurrent 5-FU based chemoradiation

• Incorporating novel RT techniques
  – Intensity modulated radiotherapy

• Tailoring therapies for rectal cancer
  – Selective use of radiotherapy
  – Total neoadjuvant therapy
  – Non-operative management
Advances in RT Techniques

- Multiple dosimetric studies have compared conventional fields (bony anatomy) and IMRT planning.
- Target coverage and bowel volume irradiated better for all plans compared to conventional.

*Urbano M, IJROBP, 2006; Callister M, Proc ASTRO, 2006; Guerrero Urbano MT, IJROBP 2006; Arbea L, Radiat Oncol, 2010; Tho LM, IJROBP. 2006*
Primary endpoint: Comparison of Grade 2+ GI toxicity to RTOG 0247 (non-IMRT)
RTOG 0822

- 68 analyzable patients
  - 90% T3, 55% N+
- 51% Grade 2+ GI toxicity compared to 58% on RTOG 0247 (NS)
- Criticism: Increased toxicity associated with concurrent oxaliplatin
- Central review of RT contours and plans
  - Contouring based on RTOG anorectal atlas
  - Only 5 (7%) had unacceptable volumes

Garafalo M, ASTRO 2011
IMRT v. Conventional Pelvic RT

- 92 rectal cancer pts treated from 2004-2009
- 61 – CRT, 31 – IMRT
- 45/50.4 Gy for CRT
- 45/50 Gy for IMRT using an integrated boost

Samuelian JM, IJROBP, 2012
<table>
<thead>
<tr>
<th></th>
<th>IMRT (%)</th>
<th>CRT (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2+ GI toxicity</td>
<td>48</td>
<td>62</td>
<td>.006</td>
</tr>
<tr>
<td>Grade 2+ Diarrhea</td>
<td>23</td>
<td>30</td>
<td>.62</td>
</tr>
<tr>
<td>Grade 2+ enteritis</td>
<td>10</td>
<td>38</td>
<td>.10</td>
</tr>
<tr>
<td>pCR</td>
<td>19</td>
<td>28</td>
<td>NS</td>
</tr>
</tbody>
</table>

Samuelian JM, IJROBP, 2012
Neoadjuvant Chemoradiation: Overview of Emerging Options

• Incorporating new chemotherapy agents
  – Phase III data evaluating role of Oxaliplatin with concurrent 5-FU based chemoradiation

• Incorporating novel RT techniques
  – Intensity modulated radiotherapy

• Tailoring therapies for rectal cancer
  – Selective use of radiotherapy
  – Total neoadjuvant therapy
  – Non-operative management
Selective Use of Radiotherapy

Can radiotherapy be avoided in a subset of patients with negative margins after TME?
MRC CR07

1350 pts with operable Rectal Cancer

Preoperative RT 25Gy/5 fx

Surgery: TME

Selective post-op 5FU + 45Gy pelvic RT

12% CRM +

<table>
<thead>
<tr>
<th></th>
<th>Pre-op RT</th>
<th>Selective post-op CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yr LR</td>
<td>4.4%</td>
<td>10.6% p&lt;0.0001</td>
</tr>
<tr>
<td>3 yr DFS</td>
<td>77.5%</td>
<td>71.5% p=0.013</td>
</tr>
<tr>
<td>3 yr OS</td>
<td>80.3%</td>
<td>78.6% p=0.40</td>
</tr>
</tbody>
</table>

Sebag-Montefiore, Lancet; 2009
CR-07 PR Bowel Dysfunction

- No Difference in Defecation Dysfunction
  - 25% at baseline and in f/u for both arms

- Incontinence Increased Over Baseline
  - Doubling of dysfunction with preop RT (25 to 50%)

Selective Use of Radiotherapy

Can radiotherapy be avoided in a subset of patients after a good clinical response to neoadjuvant chemotherapy?
• 32 patients enrolled
  – 17/32 (53%) were female, Clinical stages T2-3, N0-2
  – 2 patients withdrawn after cycle 1-2 (MI and cardiac rhythm disturbance attributed to infusional 5FU)
  – 30 completed induction therapy and surgery without RT
  – Median age of 30 patients: 51 years (26 – 81 years)
MSKCC Pilot Results

• Of 32 patients accrued to pilot study
  – 32/32 had R0 resections
  – 8/32 (25%) had a pCR
  – 1/32 post-op death
  – 0/32 have had LR
  – 3/32 have had distant recurrence (pulmonary mets)
    • 1 patient has died

Schrag D, J Clin Oncol, 2014
**PROSPECT Trial Schema**

**“Standard Arm”**
- **Randomize 1:1**
- **FOLFOX x 6**
- **5FUCMT**
- **TME**
- **FOLFOX x 8**

**“Selective Arm”**
- **Response <20%**
- **FOLFOX x 6**
- **5FUCMT**
- **TME**
- **FOLFOX x 2**

- **Response ≥20%**
- **TME**
- **FOLFOX x 6**
- **FOLFOX x 2**
Key Inclusion Criteria

• Tumor tissue located at 5-12 cm from anal verge

• Baseline Clinical staging: T2N1, T3N0, T3N1
  – MRI or ERUS (MRI preferred)

• Candidate for sphincter sparing surgery
  – Physical exam by primary surgeon

• Surgeon is TME credentialed
Total Neoadjuvant Therapy

• Distant recurrence rates now exceed local recurrence rates
• Move systemic therapy upfront to address micrometastatic disease earlier
• Particularly in high-risk patients
  – node positive disease
  – bulky primary tumors
• Two phase II studies have evaluated induction chemotherapy followed by CRT
MRI to Risk Stratify Rectal Cancer

- Determine extent of extramural tumor
- Identify risk of CRM positivity

1- Mercury Study group, Radiology, 2007
2- Mercury Study group, British Medical Journal, 2006
Induction Chemotherapy

• 105 patients with poor-risk rectal cancer defined by MRI:
  – tumor within 1mm or beyond mesorectal fascia
  – T3 low-lying tumor at or below the levators
  – Tumor extending ≥ 5 mm into perirectal fat
  – T4 or N2

• CAPOX x 12 wks → 54Gy + Cape → TME → CAPOX x 12 wks

• 97 underwent surgery, 20% pCR rate

• 3-year PFS and OS: 68% and 83%

• 3-year RFS after complete resection was 74%

Chua, Lancet Oncol; 2010
Induction Chemotherapy

• 108 pts with poor-risk rectal cancer based on MRI:
  – tumors extending to within 2mm or beyond mesorectal fascia
  – ≤ 6 cm from anal verge
  – cT3 or resectable cT4, any cT3N+

Path CR  |  13.5 %  |  14.3%
Dose intensity
Cape     |  0.67    |  0.91
Oxali    |  0.73    |  0.94

Fernandez-Martos, J Clin Oncol;2010
Induction Chemotherapy

• Median follow-up of 70 months

<table>
<thead>
<tr>
<th></th>
<th>Post-op CAPOX x 4</th>
<th>Pre-op CAPOX x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path CR</td>
<td>13.5 %</td>
<td>14.3%</td>
</tr>
<tr>
<td>% Received CAPOX x 4</td>
<td>57%</td>
<td>94%</td>
</tr>
<tr>
<td>5 year DFS</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td>5 year Cum Incidence LR</td>
<td>1.9%</td>
<td>5.3%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>78%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Fernandez-Martos, Proc GI Symposium, 2014
Induction Chemotherapy at MSKCC

• Retrospectively reviewed the records of all patients with clinical stage II/III rectal cancer (T3/4, N1-2) based on endorectal ultrasound or MRI treated with ICT followed by CRT and TME

• Of ~300 patients treated with pre-operative CMT at MSKCC between 2007 and 2012, 61 received some or all of their planned FOLFOX as initial therapy
Results

• 61 patients received a median of 7 cycles ICT
• Median RT dose = 50Gy
• 4 patients achieved an excellent response to chemotherapy alone, declined radiation, and proceeded directly to TME
• 49 patients who underwent TME
  – Median 6.5 cycles of ICT
  – 100% R0 resections
  – pCR in 13 (27%)
  – >90% treatment effect in 23 (47%)

Cercek A, JNCCN, 2014
Results

• 12 did not undergo TME
  – 9 had clinical response managed non-operatively
  – 1 refused recommended surgery despite incomplete tumor regression,
  – 1 was deferred due to comorbidities
  – 1 developed distant metastatic disease

• A total of 22 patients had either
  – Pathologic complete response (n=13)
  – Complete clinical response (9)
    • leading to non-operative management
    • 2 local recurrences, salvaged and both NED
    • 7 remain NED without local recurrence
Non-operative Therapy

Can surgery be avoided in the setting of complete clinical response to preoperative treatment?
Paradigm shift?

Anal Cancer

Definitive surgery (before 1970’s)

↓

Preoperative chemoradiation (1970’s)

↓

Definitive chemoradiation (Present)

Distal rectal cancer

Definitive surgery (before 1990’s)

↓

Preoperative chemoradiation (Present)

↓

Definitive chemoradiation

Definitive chemoradiation?
Non-operative Therapy: Brazilian Data

- 265 pts treated with pre-operative CRT
  - 71 pts (27%) had a cCR
  - 194 pts (73%) incomplete response → surgery
    - 22 pts had a pCR

<table>
<thead>
<tr>
<th></th>
<th>Clinical complete response: 71 pts</th>
<th>Pathologic complete response: 22 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean followup:</td>
<td>57 months</td>
<td>48 months</td>
</tr>
<tr>
<td>Local recurrence:</td>
<td>2.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Pelvic recurrence:</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Distant metastasis:</td>
<td>4.2%</td>
<td>14%</td>
</tr>
<tr>
<td>5-year OS:</td>
<td>100%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Habr-Gama, Ann Surg 2004
## Non-operative Therapy: Brazilian Data

2006 Update: 361 patients, 99 with clinical CR (27%)

<table>
<thead>
<tr>
<th>Mean followup:</th>
<th>60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence:</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>4 surgical salvage</td>
</tr>
<tr>
<td></td>
<td>1 brachytherapy salvage</td>
</tr>
<tr>
<td></td>
<td>No subsequent recurrence</td>
</tr>
<tr>
<td></td>
<td>Mean interval to recurrence: 52 months</td>
</tr>
<tr>
<td>Pelvic recurrence:</td>
<td>0%</td>
</tr>
<tr>
<td>Distant metastasis:</td>
<td>8%</td>
</tr>
<tr>
<td>5-year OS:</td>
<td>93%</td>
</tr>
</tbody>
</table>
MSKCC Experience

• Retrospective review of stage I-III rectal cancer pts treated at MSKCC between Jan 2006 and Aug 2010

265 Rectal Resection & TME

32 cCR and NOM vs. 57 (22%) pCR

208 (78%) no pCR

• NOM pts compared to resected pts found to have pCR

## Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>cCR &amp; NOM</th>
<th>pCR &amp; RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Median follow up (range)</td>
<td>28m (9-70m)</td>
<td>42 (1-70m)</td>
<td></td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>70</td>
<td>60</td>
<td>0.009*</td>
</tr>
<tr>
<td>Co-morbidity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (47%)</td>
<td>16 (28%)</td>
<td>0.07†</td>
</tr>
<tr>
<td>No</td>
<td>17 (53%)</td>
<td>41 (72%)</td>
<td></td>
</tr>
<tr>
<td>Distance from the anal verge (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6cm (0.5-12)</td>
<td>22 (69%)</td>
<td>39 (78%)</td>
<td>0.3†</td>
</tr>
<tr>
<td>7cm (2-12)</td>
<td>10 (31%)</td>
<td>11 (22%)</td>
<td></td>
</tr>
<tr>
<td>cT stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 (56%)</td>
<td>31 (61%)</td>
<td>0.7†</td>
</tr>
<tr>
<td>2</td>
<td>14 (44%)</td>
<td>20 (39%)</td>
<td></td>
</tr>
<tr>
<td>cN stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18 (56%)</td>
<td>31 (61%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>14 (44%)</td>
<td>20 (39%)</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment AJCC Stage: III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>18 (56%)</td>
<td>31 (61%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>II</td>
<td>6 (19%)</td>
<td>18 (35%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (25%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

†Chi-squared test
*T-test
Results

- 6 NOM patients had LR (median 11 mos post CRT (range 7-14mos), no LR in pCR group
- 3 distant recurrences in each group
- 26 of 32 NOM pts (81%) achieved durable cCR and successfully avoided rectal resection with median follow up of 28 mo
Non-operative Therapy: Dutch Data

- Prospective cohort study of “watch and wait” approach
- 192 patients with LARC treated with CRT from 2004-2010
- Response assessed 6-8wks post-CRT
  - MRI, Endoscopy
- Clinical CR: no residual tumor or fibrosis only on MRI/small residual ulcer or scar on endoscopy; no palpable tumor on DRE
- 21 (11%) patients fulfilled these criteria

Maas M, Clin Oncol, 2011
Non-operative Therapy: Dutch Data

Pre-CRT

Post-CRT
Counterarguments to Non-operative Management

- Clinical response is not always predictive of pathologic response

- Primary tumor response is not always predictive of lymph node response
  - 7% of pathologic CR in primary tumor have pathologically positive mesorectal nodes in MSKCC series (Stipa Ann Surg Oncol 2004)
ACOSOG Z6041: Phase II Local Excision and Neoadjuvant CRT for T2 Rectal Cancer

Patients with Stage I Rectal Cancer (uT2uNO) by ERUS staging

- tumor ≤4 cm
- ≤40% of rectal circumference
- mobile

Primary Endpoint: 3 yr DFS
ACOSOG Z6041: Preliminary Outcomes

• Chemoradiation
  – 54Gy to primary, 45 Gy to nodes
  – Capecitabine (825 mg/m\(^2\) days 1–14 and 22–35) and oxaliplatin (50 mg/m\(^2\) weeks 1, 2, 4, and 5)
  – Capecitabine reduce to 725 mg/m\(^2\) twice a day, 5 days a week, for 5 weeks
  – RT reduced to 50.4 Gy

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 77) (%)</th>
<th>Original dose (n = 52) (%)</th>
<th>Revised dose (n = 25) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margins</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Clinical CR</td>
<td>43 (56)</td>
<td>30 (58)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Path CR</td>
<td>34 (44)</td>
<td>25 (48)</td>
<td>9 (36)</td>
</tr>
</tbody>
</table>

Garcia-Aguilar J, Ann Surg Oncol. 2011
CT Simulation

- Prone
- Belly Board / Bowel Compression if Prone
- Aquaplast / Vac-loc Bag (or equivalent)
- Full Bladder
- Contrast: IV and Oral (if not having obstructive sx)
- Anal marker
- ≤ 5mm Slice Thickness
- Use Multiple Fields
- Consider IMRT for Select Cases (nodal burden, small bowel issues, post-operative therapy, anal canal involvement)
Treatment Planning Considerations

- **GTV**: Primary tumor + involved nodes
  - As defined on physical exam, ERUS, MRI, CT, and/or PET
  - Include tumor + entire rectal circumference at that level

- **CTV**: Elective nodal regions
  - Standard: Peri-rectal, internal iliac, and superior hemorrhoidal (CTVA)
  - For T4 tumors extending anteriorly: include external iliac (CTVA + B)
  - For tumors invading anal canal: include inguinal and external iliac (CTVA+B+C)

Anal Cancer
Rising Incidence of Anal SCC
Risk Factors

• Human Papilloma Virus (HPV)
  – HPV types 16, 18
  – E6 viral oncoprotein inactivates p53 gene product
  – E7 viral oncoprotein binds to Rb gene product

• Immunosuppression
  – HIV

• Anal fistula/benign anal lesion

• Smoking
Anatomy

3 regions
A. Lower rectum
B. Anal canal
C. Perianal skin (anal margin)
Phase II Dose escalation

• ECOG 4292
  – Concurrent 5-FU/cisplatin + 59.6Gy pelvic + perineal RT given over split course w/2 wk rest
  – 68% CR, 79% Grade 3+ toxicity rate
Induction Chemo

- CALGB Phase II (Meropol, JCO 2008)
  - Induction chemo for advanced anal canal ca (T3-4, N+)
  - Induction 5-FU/cisplatin → concurrent 5-FU/MMC + 45Gy wks 1 + 5 (+/- 9 Gy boost)
  - 80% CR
  - 4 yr colostomy free survival = 50%, 4 yr OS = 68%
RTOG 98-11

(T2-4 Nx M0)

R

P

MMC 10 mg/m²

5-FU 1g/m²

RT: 45 Gy

T3/4; N+,
T2 with RD

Boost 10-14 Gy

P

F

5-FU 1g/m²

Cisplatin 75 mg/m²

5-FU 1g/m²

RT: 45 Gy

T3/4; N+,
T2 with RD

Boost 10-14 Gy
### RTOG 98-11

<table>
<thead>
<tr>
<th>5-Year Rates</th>
<th>PF – RT+PF n=320 (%)</th>
<th>RT+MMC/F n=324 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free Survival</td>
<td>54</td>
<td>60</td>
<td>0.17</td>
</tr>
<tr>
<td>Local Relapse</td>
<td>33</td>
<td>25</td>
<td>0.07</td>
</tr>
<tr>
<td>Colostomy</td>
<td>19</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>19</td>
<td>15</td>
<td>0.14</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>70</td>
<td>75</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Ajani JA et al., JAMA 2008;299:1941-1921
### U.S. GI Intergroup RTOG 9811

#### Relapse by TN Category

<table>
<thead>
<tr>
<th>TN Category</th>
<th>No. Pts</th>
<th>Local-Regional</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TF(#) 5yr(%)</td>
<td>TF(#) 5yr(%)</td>
</tr>
<tr>
<td>T2N0</td>
<td>302</td>
<td>50 19</td>
<td>31 12</td>
</tr>
<tr>
<td>T3N0</td>
<td>115</td>
<td>25 22</td>
<td>12 14</td>
</tr>
<tr>
<td>T4N0</td>
<td>31</td>
<td>13 50</td>
<td>5 21</td>
</tr>
<tr>
<td>T2N1-3</td>
<td>95</td>
<td>37 40</td>
<td>22 31</td>
</tr>
<tr>
<td>T3N1-3</td>
<td>47</td>
<td>27 58</td>
<td>12 32</td>
</tr>
<tr>
<td>T4N1-3</td>
<td>25</td>
<td>14 64</td>
<td>4 17</td>
</tr>
</tbody>
</table>

*Gunderson, Int J Rad Oncol Bio Phys, 2013*
RT: 50.4 Gy

ACT II (T1-4 Nx M0)

- Cisplatin 60 mg/m²
- MMC 12 mg/m²
- 5-FU 1g/m²
- RT: 50.4 Gy

No Maintenance

P
F
P
F
## ACT II

<table>
<thead>
<tr>
<th></th>
<th>RT+PF n=469 (%)</th>
<th>RT+MMC/F n=471 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>95</td>
<td>94</td>
<td>0.53</td>
</tr>
<tr>
<td>G 3/4 Hem.-AE</td>
<td>13</td>
<td>25</td>
<td>0.001</td>
</tr>
<tr>
<td>G 3/4 Non-Hem.-AE</td>
<td>65</td>
<td>61</td>
<td>0.22</td>
</tr>
<tr>
<td>CRT + CT N=448</td>
<td>CRT alone n=446</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence-free Survival</td>
<td>HR 0.89, 95% CI 0.68-1.18</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>HR 0.79, 95% CI 0.56-1.12</td>
<td>0.19</td>
<td></td>
</tr>
</tbody>
</table>
ACCORD 03 (T2>4cm-4 Nx M0)

- **Cisplatin 80 mg/m²**
- **5-FU 800/m²**
- **RT: 45 Gy**

**RT Boost**
- 15 Gy
- 20-25 Gy
## ACCORD 03 (n=307)

<table>
<thead>
<tr>
<th></th>
<th>PF- RT/PF low dose</th>
<th>PF- RT/PF high dose</th>
<th>RT/PF low dose</th>
<th>RT/PF high dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong></td>
<td>78%</td>
<td>86%</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Colostomy-free Survival at 3 years</strong></td>
<td>83%</td>
<td>85%</td>
<td>86%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Conroy et al. J Clin Oncol 2009; abstr 4033
SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL: PATTERNS AND PREDICTORS OF FAILURE AND IMPLICATIONS FOR INTENSITY-MODULATED RADIATION TREATMENT PLANNING

JEAN L. WRIGHT, M.D.,* SUJATA M. PATIL, PH.D., † LARISSA K. F. TEMPLE, M.D., ‡ BRUCE D. MINSKY, M.D., § LEONARD B. SALTZ, M.D., || AND KARYN A. GOODMAN, M.D. ¶

*Department of Radiation Oncology, University of Miami, Miami, FL; †Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY; ‡Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; §Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, IL; ||Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; and ¶Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

180 patients

45 locoregional persistence or failure

28 local-only

7 local and regional

10 regional only
Posterior-anterior field

Lateral field
RTOG 0529
Dose-Painted IMRT in Anal Cancer

Mitomycin-C 10 mg/m² IV bolus on days 1 & 29
IMRT
5-FU 1000 mg/m²/day by CI on days 1-4 & 29-32
with DP IMRT*

Primary endpoint – reduction in combined grade 2+ GI and GU acute toxicity compared to 9811
Planned secondary endpoints - heme, GI and GU acute toxicity reduction

T2 and above HIV pts eligible

Kachnic et al, IJROBP 2012
## RTOG 0529: Dose-Painted IMRT vs. RTOG 9811

<table>
<thead>
<tr>
<th></th>
<th>0529 (n=52)</th>
<th>9811-MMC-arm (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Morbidity</strong>#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Grade 3 GI/GU AE</td>
<td>22*</td>
<td>36*</td>
</tr>
<tr>
<td>≥ Grade 3 skin AE</td>
<td>20*</td>
<td>47*</td>
</tr>
<tr>
<td><strong>Endpoint</strong>&amp;</td>
<td>2y-%</td>
<td>2y-%</td>
</tr>
<tr>
<td>Local-Regional Failure</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Colostomy Failure</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Disease-Free Survival</td>
<td>77</td>
<td>71</td>
</tr>
<tr>
<td>Colostomy-Free Survival</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Kachnic L, Int J Rad Oncol Bio, 2013
## Chemoradiation with Capecitabine

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Treatment</th>
<th>CR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynne-Jones 2008</td>
<td>31</td>
<td>RT: 50.4 Gy Capecitabine 825 mg/m² bid M-F weekly Mitomycin C 12 mg/m²</td>
<td>77%</td>
<td>Compliance with CT 68%, RT 81%</td>
</tr>
<tr>
<td>Eng C ASCO 2009</td>
<td>20</td>
<td>RT: 45-59 Gy Capecitabine 825 mg/m² bid M-F weekly Oxaliplatin 50 mg/m² weekly</td>
<td>90%</td>
<td>Omission of CT in week 3 and 6 due to toxicity</td>
</tr>
</tbody>
</table>
MSKCC Approach

Capecitabine 825 mg/m² BID M-F

Mitomycin 10 mg/m²

RT: 45/50 Gy IMRT

Boost 6 Gy
### MSKCC Retrospective Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>5-FU + MMC N=64</th>
<th>Cape + MMC N=44</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ Neutropenia</td>
<td>32 (50%)</td>
<td>4 (9%)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Grade 3+ Leucopenia</td>
<td>33 (52%)</td>
<td>11 (25%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Grade 3+ Thrombocytopenia</td>
<td>10 (16%)</td>
<td>2 (5%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Grade 3+ Anemia</td>
<td>5 (8%)</td>
<td>1 (2%)</td>
<td>0.397</td>
</tr>
<tr>
<td>Treatment break</td>
<td>26 (41%)</td>
<td>7 (16%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Median treatment duration (days)</td>
<td>40</td>
<td>37</td>
<td>0.002</td>
</tr>
</tbody>
</table>
NCCN Guidelines

NCCN Guidelines Version 1.2015
Anal Carcinoma

CLINICAL PRESENTATION

Anal canal cancer

WORKUP

Biopsy: squamous cell carcinoma

• Digital rectal examination (DRE)
• Inguinal lymph node evaluation
  › Biopsy or FNA if suspicious nodes
• Chest/abdominal/pelvic CT or MRI
  › Consider PET scan for T2-4, N0 or Any T, N+
• Anoscopy
• Consider HIV testing + CD4 level if indicated
• Gynecologic exam for women, including screening for cervical cancer

CLINICAL STAGE

T1-2, N0

Mitomycin/5-FU + RT or
Mitomycin/Capecitabine + RT

T3-T4, N0 or Any T, N+

Metastatic disease

Cisplatin-based chemotherapy ± RT

PRIMARY TREATMENT

Mitomycin/5-FU + RT or
Mitomycin/Capecitabine + RT
Treatment Planning Considerations

• Similar to Rectal Cancer
• CTVA, B, C
IMRT plan for Anal Cancer
Contouring and Constraints for IMRT

- **Gross Disease**
- **Nodal Areas at Risk:**
  - Inguinal
  - Internal & external iliac
  - Mesorectal (peri-rectal and presacral)
  - Rectum and associated mesentary are target, not avoidance structures

**Table 1** Dose-painted intensity modulated radiation therapy dose constraints for normal tissues

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose (Gy) at &lt;5%</th>
<th>Dose (Gy) at &lt;35%</th>
<th>Dose (Gy) at &lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>volume</td>
<td>volume</td>
<td>volume</td>
</tr>
<tr>
<td>Small bowel*†</td>
<td>45 (&lt;20 cc)</td>
<td>35 (&lt;150 cc)</td>
<td>30 (&lt;200 cc)</td>
</tr>
<tr>
<td>Femoral heads*</td>
<td>44</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>External genitalia</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Bladder</td>
<td>50</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Large bowel†</td>
<td>45 (&lt;20 cc)</td>
<td>35 (&lt;150 cc)</td>
<td>30 (&lt;200 cc)</td>
</tr>
</tbody>
</table>

Organs are listed in order of decreasing priority.
* Assigned criteria for major and minor violations; major violations were considered as part of the feasibility secondary endpoint.
† Dose constraints based on absolute volume instead of % volume.
Key Points to Take Home

• Esophageal Cancer
  – CROSS Trial has clearly demonstrated benefit of neoadjuvant chemoradiation
  – PET response is prognostic for outcome and may help to direct therapy

• Gastric Cancer
  – ARTIST trial demonstrated a benefit for adjuvant chemoradiation in Node +, Intestinal type histologies
  – Ongoing studies to evaluate other sequences and regimens of neoadjuvant/adjuvant therapy
Key Points to Take Home

• Pancreas Cancer
  – For locally advanced/marginally resectable disease
    • LAP07 trial demonstrated a reduction in local progression with Gem + CRT v. Gem alone, but no survival difference
    • SBRT is an evolving option for LAPC, 6.6Gy x 5 - safe
    • Pre-operative chemoradiation is being evaluated in MR
  – Resectable disease
    • Ongoing controversy over adjuvant chemoradiation, results of RTOG 0848 will help to address this question

• Liver SBRT
  – In patients Childs A liver function or better, SBRT is a safe effective option
    • Fiducials, motion management, CBCT allow for accurate, focal delivery of high doses of SBRT
Key Points to Take Home

• Rectal Cancer
  – Pre-operative chemoradiation remains standard of care for locally advanced rectal cancer to improve local control
  – Emerging options to individualize therapy are being evaluated
    • Omitting RT
    • Non-operative management
    • Induction chemotherapy

• Anal Cancer
  – IMRT using CTV A, B, C – standard
  – Capecitabine (per NSABP R04 dosing) can replace 96hr 5-FU infusion, MMC 10mg/m² weeks 1 + 5, still standard
Thanks for Your Attention!

goodmank@mskcc.org