Neoadjuvant Treatment in Rectal Ca

Dr Yeh Chen Lee
Colorectal Ca

- 3rd most common Ca in Australia
  - 1 in 12 would develop CRC by age 85
  - Incidence projected to increase w aging population

- 2nd leading cause of Cancer death after Lung Ca

- 40% of Colorectal Ca occurs in the Rectum

- National Bowel Screening Program (2006)
  - Limited one-off test for age 50, 55, and 65
### Stage information for Rectal Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Dukes</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>B1</td>
</tr>
<tr>
<td>II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B2</td>
</tr>
<tr>
<td>III</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B2</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B3</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1–T2</td>
<td>N1/N1c</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
</tr>
<tr>
<td>T1</td>
<td>N2a</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T3–T4a</td>
<td>N1/N1c</td>
<td>M0</td>
<td>C</td>
<td>C2</td>
</tr>
<tr>
<td>T2–T3</td>
<td>N2a</td>
<td>M0</td>
<td>C</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td>T1–T2</td>
<td>N2b</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
<td>C</td>
<td>C2</td>
</tr>
<tr>
<td>T3–T4a</td>
<td>N2b</td>
<td>M0</td>
<td>C</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N1–N2</td>
<td>M0</td>
<td>C</td>
<td>C3</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Timeline progression

- Surgical technique: TME
- Imaging technique
  - Stage migration
  - Better evaluation of localized disease
- Movement to pre-op Therapy
Stage 1 (T1-2 No):
- surgery alone

Stage 2-3 (T3-4 or Node positive):
- pre-op chemorad tx– surgery – 4-6 mths postop chemo

Preop Imaging w MRI essential
S2& S3 Rectal Cancer

* Neoadjuvant Chemoradtx
* Surgery : TME
* Adjuvant chemo

Issues:

• Benefit of Radtx in addition to TME?
• Chemoradtx before / after surgery?
• Radtx vs Chemoradtx?
• What Type of Chemotherapy?
Benefit of Radtx

Dutch Colorectal Cancer Group

* 1861 Pt w rectal Ca, Ramdomized to :
  * 25 Gy in 5# + TME
  * TME alone

2% vs 8%
local recurrence at 3 yrs

Figure 2. Rates of Local Recurrence in the Population of 1748 Eligible Patients Who Underwent Macroscopically Complete Local Resection, According to Treatment Group.
At two years, the rate of local recurrence was 2.4 percent in the group assigned to radiotherapy and surgery and 8.2 percent in the group assigned to surgery alone (P<0.001).

TABLE 4. RESULTS OF UNIVARIATE LOG-RANK ANALYSES OF TWO-YEAR RATES OF LOCAL RECURRENCE AMONG THE 1748 ELIGIBLE PATIENTS WITH A MACROSCOPICALLY COMPLETE LOCAL RESECTION, ACCORDING TO SELECTED PROGNOSTIC VARIABLES. *

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RADIOThERAPY plus SURGERY</th>
<th>SURGERY ALONE</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO. OF PATIENTS AT RISK</td>
<td>LOCAL RECURRENCE AT 2 YR</td>
<td>NO. OF PATIENTS AT RISK</td>
</tr>
<tr>
<td>Overall</td>
<td>873</td>
<td>2.4%</td>
<td>875</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>555</td>
<td>2.5%</td>
<td>557</td>
</tr>
<tr>
<td>Female</td>
<td>318</td>
<td>2.2%</td>
<td>318</td>
</tr>
<tr>
<td>Distance of tumor from anal verge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1–15 cm</td>
<td>262</td>
<td>1.3%</td>
<td>271</td>
</tr>
<tr>
<td>5.1–10 cm</td>
<td>372</td>
<td>1.0%</td>
<td>350</td>
</tr>
<tr>
<td>≤5 cm</td>
<td>237</td>
<td>5.8%</td>
<td>253</td>
</tr>
<tr>
<td>Type of resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low anterior</td>
<td>577</td>
<td>1.2%</td>
<td>603</td>
</tr>
<tr>
<td>Abdominoperineal</td>
<td>248</td>
<td>4.9%</td>
<td>232</td>
</tr>
<tr>
<td>Hartmann†</td>
<td>47</td>
<td>3.2%</td>
<td>39</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>265</td>
<td>0.5%</td>
<td>244</td>
</tr>
<tr>
<td>II</td>
<td>251</td>
<td>1.0%</td>
<td>241</td>
</tr>
<tr>
<td>III</td>
<td>298</td>
<td>4.3%</td>
<td>324</td>
</tr>
<tr>
<td>IV (distant metastases but complete local resection)</td>
<td>47</td>
<td>10.1%</td>
<td>48</td>
</tr>
</tbody>
</table>

*Patients with missing data were excluded from the analysis of local recurrence. Twenty-eight patients without a tumor (TNM stage 0) were excluded from the multivariate analysis because they were not at risk for local recurrence. In a Cox proportional-hazards analysis of age (as a continuous variable), the hazard ratio for local recurrence at two years was 0.99 (95 percent confidence interval, 0.95 to 1.04; P=0.77) in the group of 873 patients assigned to radiotherapy and surgery and 1.01 (95 percent confidence interval, 0.99 to 1.04; P=0.21) in the group of 875 patients assigned to surgery alone. TNM denotes tumor–node–metastasis.

†A Hartmann resection is a low anterior resection without the construction of an anastomosis.
Pt w Stage 2 and 3 Rectal Ca would receive significant benefit from pre-op Radiotherapy

However

In patients with S2 disease with high rectal Ca?
Chemoradiation: Pre-op vs Post-op

* German Rectal Trial

823 patients with T3 or T4 rectal cancer
Ultrasonography T3/4 or N+ < 16 cm anal verge
Age < 75

Preoperative 5-FU/radiotherapy
Surgery + Postoperative 5-FU

50.4 Gy in 28#
5FU 1g/m2 daily for 5 days, W1 & W5

Surgery

Postoperative 5-FU/radiotherapy + 5-FU

Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, andCompleteness of Resection, According to Actual Treatment Given."

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy (N=415)</th>
<th>Postoperative Chemoradiotherapy (N=384)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological finding (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>40</td>
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</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
GRT - results

Figure 2. Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis. Follow-up data were available for 781 patients.

GRT -results

**Table 4.** Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy (N=415)</th>
<th>Postoperative Chemoradiotherapy (N=384)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection deemed necessary — no. (%)</td>
<td>116 (28)</td>
<td>78 (20)</td>
<td></td>
</tr>
<tr>
<td>Sphincter-preserving surgery performed — no./total no. (%)</td>
<td>45/116 (39)</td>
<td>15/78 (19)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Table 5.** Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.*

<table>
<thead>
<tr>
<th>Type of Toxic Effect</th>
<th>Preoperative Chemoradiotherapy (N=399)</th>
<th>Postoperative Chemoradiotherapy (N=237)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of patients</td>
<td>% of patients</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Hematologic effects</td>
<td>6</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>Dermatologic effects</td>
<td>11</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>27</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal effects†</td>
<td>9</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td>Strictures at anastomotic site</td>
<td>4</td>
<td>12</td>
<td>0.003</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>2</td>
<td>4</td>
<td>0.21</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>14</td>
<td>24</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*All patients who received any preoperative or postoperative radiotherapy according to protocol were included in this analysis. Some patients had more than one toxic effect.

†The gastrointestinal effects were chronic diarrhea and small-bowel obstruction. The incidence of small-bowel obstruction requiring reoperation was 2 percent in the preoperative-treatment group and 1 percent in the postoperative-treatment group (P=0.70).
### German Rectal Trial - conclusions

<table>
<thead>
<tr>
<th></th>
<th>PRE-op Chemoradtx</th>
<th>POST-op Chemoradtx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr Local recurrence</td>
<td>6%</td>
<td>13%</td>
<td>0.006</td>
</tr>
<tr>
<td>5-yr Overall survival</td>
<td>76%</td>
<td>74%</td>
<td>0.8</td>
</tr>
<tr>
<td>Sphincter-preservation surgery</td>
<td>39%</td>
<td>19%</td>
<td>0.004</td>
</tr>
<tr>
<td>Toxicity profile - acute</td>
<td>27%</td>
<td>40%</td>
<td>0.001</td>
</tr>
<tr>
<td>Toxicity profile – long-term</td>
<td>14%</td>
<td>24%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years


See accompanying editorial on page 1901; listen to the podcast by Dr Hong at www.jco.org/podcasts

Sauer et al. JCO 2012
Fig 3. Cumulative incidence of local recurrences after macroscopically complete local tumor resection in the intention-to-treat population (A) and according to treatment received (B). CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.
Neoadjuvant Chemoradiation is the preferred option
MORE Questions

In Neoadjuvant setting

What about

* Radtx alone vs Chemoradtx?
EORTC 22921

1011 Patients underwent randomization

- 252 Assigned to preoperative radiotherapy
- 253 Assigned to preoperative chemoradiotherapy
- 253 Assigned to preoperative radiotherapy and postoperative chemotherapy
- 253 Assigned to preoperative chemoradiotherapy and postoperative chemotherapy

- Resectable T3-T4 Tumour
- Pre-op radtx 45 Gy
- Pre-op 5-FU bolus on wk1 & wk5
- Primary End Point = OS

EORTC - results

Figure 2. Overall Survival According to Preoperative Radiotherapy or Preoperative Chemoradiotherapy (Panel A) and Overall Survival According to Postoperative Treatment or No Postoperative Treatment (Panel B).

EORTC - results

**Figure 4. Cumulative Incidence of Local Recurrence as a First Event.**

The cumulative incidence of local recurrence as a first event at 5 years was 17.1% in the preoperative-radiotherapy group, 8.7% in the preoperative-chemoradiotherapy group, 9.6% in the group receiving preoperative radiotherapy and postoperative chemotherapy, and 7.6% in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy.

EORTC 22921 and FFCD 92-03

Screen for eligibility

Randomly assigned

Preoperative RT
-> Surgery

Preoperative RT-CT
-> Surgery

Preoperative RT
-> Surgery
-> Post-operative CT

Preoperative RT-CT
-> Surgery
-> Post-operative CT

Gerard et al. JCO 2006
Gerard et al. JCO 2006

**Preop-radiotherapy alone had higher local recurrence rate, however not affecting the overall survival.**

**Addition of Chemotherapy confers significant benefit in local control**

**criticism**
* only 36% receive TME,
* Bolus 5FU
Now that we established that neoadjuvant chemoradtx is necessary and beneficial,

What About

The use of Capecitabine?
The addition of Oxaliplatin?
NSABP-R-04:
P3 Randomized Study in US
1608 pt w Clinical S2/3 Rectal Ca ,
undergoing pre-op Radtx (45Gy + boost) +
1) Continuous infusion 5-FU
2) Continuous infusion 5-FU+ oxaliplatin
3) Capecitabine (825mg/m2 BD 5 days/wk)
4) Capecitabine + Oxaliplatin (50mg/m2/wk x 5)

Primary End point: pCR, SSS, surgical downstaging

Roh et al. ASCO, 2011
Interim Results

- NO Sig Difference btw 5FU vs CAPE regimen
- No Sig Difference btw regimens with or without OX
- Increase G3/4 toxicity w Ox

Roh et al. ASCO, 2011
Capecitabine / infusional 5 FU-2

Hofheinz et al

* Non-inferiority P3 study of 401 pt w S2,S3 Rectal Ca, all pt receive pre-op radtx +
  * 2 arm (CAPE vs 5 FU)
  * 2 Strata (Neoadjuvant vs adjuvant)

* Primary End point : OS
* 2nd End points : DFS and safety

Hofheinz et al. ASCO, 2011
**CAPE not inferior to 5FU regimen in 5 yrOS**

**Significant difference in 3 yr DFS, favouring CAPE**

**Neoadjuvant better tolerated + improve nodal downstaging**

Hofheinz et al. ASCO, 2011
capecitabine = CVI 5FU in preop CRT

The addition of oxaliplatin DID NOT improve preliminary outcomes but added significant toxicities

Mature data to follow

Roh et al. ASCO, 2011
Hofheinz et al. ASCO, 2011
* Surgery: TME is SOC

* In Neoadjuvant setting:
  * Pre-op > Post-op Chemoradiation therapy
  * CAPE = 5FU regimen
  * Addition of Oxaliplatin increase toxicity
Thank you
Additional Slides
Adjuvant Chemotherapy

Derived From:

**MOSAIC study**
- P3 study in Europe
- 2246 pt w S2, S3 Colon Ca
- FL +/- Oxaliplatin for 6 mth
- De Gramont Regimen
- 1’ end point was DFS

**NSABP C-07**
- P3 study in US
- 2407 Pt w S2, S3 Colon Ca
- FL +/- Oxaliplatin for 6 mth
- Roswell-Park Regimen
- 1’ end point was DFS

Kuebler et al. JCO 2007
* Significant DFS at 3 yrs (77.8% vs. 72.9%; P = .01) in favour of FOLFOX4
* No significant difference in OS


* Significant DFS at 4 yrs (73.2% vs. 67%; P = <.004) in favour of FLOX
* No significant difference in OS

Kuebler et al. JCO 2007
Current Gold-standard adjuvant chemotherapy schedule is extrapolated from Colon Ca Trial

Oxaliplatin-based Chemotherapy
MOSAIC vs NSABP-C07

MOSAIC – De Gramont Regimen
* FOLFOX 4: 2 hr 200 mg/m2 leucovorin, bolus 5FU 400mg/m2 then 22hr 600mg/m2 5 FU on 2 consecutive days every 14 days for 12 cycle
* +/- 2 hr oxaliplatin 85mg/m2

NSABP-C-07 – Roswell Park Regimen
* FLOX : 2 hr leucovorin 500mg/m2, bolus 5FU 500mg/m2 D1,8,15,22,29, 36 then 2 wk rest period
* +/- 2 hr oxaliplatin 85mg/m2 on D1, 15,29 of 8 wk cycle
Figure 22: Cancers of the colon, rectum and anus (ICD-10 C18–C21), Australia, males

Figure 21: Cancers of the colon, rectum and anus (ICD-10 C18–C21), Australia, females