The evolution of rectal cancer therapy

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Objectives

• Identify standard therapy: stage II/III rectal cancer
• Update recent adjuvant trials
• Discuss current and planned innovative rectal cancer studies
Where are we now?

• Low Locoregional relapse rates: 3-8%
  – 50-70% with LRR have Distant Relapse
• Poor DISTANT Disease Free Survival Rates
  - 5-Year DFS in modern trials: 56-74%
• Poor compliance with post-operative chemo
  - 60-70% in phase III studies
• DELAY of post-op systemic therapy
  - due to pre-op chemoXRT and surgery

Bosset NEJM 06, Sauer NEJM 04

Radiation Benefits & Issues

• 60% reduction in LRR
• Acute & Chronic Toxicity:
  5 Y Incontinence: XRT 62% vs. no XRT 38%
  5 Y Severe Incontinence: XRT 14% vs. no XRT 5%
  Sexual Dysfunction – men

Toxicities maintained at 14 years

• Lack of effect on distant disease – no DFS in modern studies OS

Glimelius Acta Oncologica 2003, Marijnen JCO 2005, ESMO 2014, Peeters JCO 05, Bosset NEJM 06, Gerard JCO 06
NSABP R04

3 Year Overall & L-R Recurrences

* No significant fluoropyrimidine by oxaliplatin interaction

Allegra GI ASCO 2014

5 YEAR OUTCOMES (%)

* No significant fluoropyrimidine by oxaliplatin interaction
Current Questions in Rectal Cancer

All 3 modalities needed for stage II/III disease?
- Surgery ✔?
- Radiation ?
- Chemotherapy ?

When is the best time to introduce therapy?
- Radiation – Pre-Op ✔
- Chemotherapy – Post-Op vs. Pre-Op?

Are we satisfied with patient outcomes?
- Short term (LR) ✔
- Long term (OS) X

Objectives

- Identify standard therapy: stage II/III rectal cancer
- Update: recent adjuvant trials
- Review recent phase II/III rectal trials
- Discuss innovative rectal studies
Adjuvant Chemotherapy in Rectal Ca

NCCN Database: 2005-10, N=1193
Stage II/III Rectal
Received Pre-Op ChemoXRT

Khrizman JCO 2013

2013: adjuvant rectal ca

- Cochrane: Adjuvant 5-FU/LV ↓ recurrence (HR 0.75) and death (HR 0.83)
- No evidence for adjuvant oxaliplatin. We give it anyways: 1. ypN+ and 2. cT4/N2
- Why oxali? Evidence from colon cancer: anatomically different but biologically similar.
- 3 RCTs adding oxaliplatin post-operatively.
Pre-OP Chemoradiation
Capecitabine 1650mg/m2 daily
d 1-33 w/o weekends
+/- Oxaliplatin 50mg/m2 weekly
d 1,8,15,22,29

Adjuvant Chemotherapy
Capecitabine 2000mg/m2 daily
d 1-14
+/- Oxaliplatin 130mg/2 d1
q d 22, for 6 cycles

Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33

TIME

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

Based on phase I/II trials:

RT 50.4 Gy + 5-FU/OX
Oxaliplatin: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap during 3rd week of RT

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)
study design

- Preoperative chemoradiotherapy with fluoropyrimidines
- Total mesorectal excision

ypStage II (ypT2-4N0)
ypStage III (ypT3, N1-2)

1:1 ratio

Stratified by
- ypStage: II vs III
- Participating centers

adjuvant FOLFOX

- Oxaliplatin 85 mg/m² on day 1
- Leucovorin 200 mg/m² on day 1
- 5-Fluorouracil 400 mg/m² bolus on day 1
- 2400 mg/m² IV for 48 hours
- Every 2 weeks, 8 cycles

adjuvant FL

- Leucovorin 20 mg/m²/day from days 1 to 5
- 5-Fluorouracil 300 mg/m²/day from days 1 to 5
- Every 4 weeks, 4 cycles

Discussion

3500 – 3501 – 3502

dfs plots

disease-free survival: PETACC-6

disease-free survival: AIO-04

disease-free survival: ADORE

presented by Carmen Allegra at 2014 ASCO Annual Meeting
How do We Explain the Different Outcomes?

- **AIO-04 & ADORE**
  - ADORE randomized AFTER surgery and excluded pCR and Stage 1
  - Arms reasonably balanced for drop-out, therapy completion & dose-intensity
- **PETACC-6**
  - Substantial imbalances between the arms in both drop-out & intended therapy rates & cape dose
  - 38% did not receive adjuvant CAPOX vs 23% who did not receive adjuvant single agent cape
  - Only 53% vs 68% of eligible pts received all intended adjuvant cycles in the CAPOX vs cape arms
  - 54% vs 36% received <90% of cape in the CAPOX vs cape arms
Conclusions

• Adjuvant FOLFOX improves 3-Y DFS
  * Await Overall Survival
• 4 months appears to be enough
• Rectal Cancer ≈ Colon Adjuvant
• Stage III should be treated, Stage II?

Subgroup Analysis of DFS: Pathological factors
Intention-to-treat

<table>
<thead>
<tr>
<th>Variable</th>
<th>5-FU Events/n</th>
<th>5-FU/OX Events/n</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT-category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0-1</td>
<td>13/122</td>
<td>21/153</td>
<td>1.36 (0.68, 2.72)</td>
</tr>
<tr>
<td>ypT2</td>
<td>41/183</td>
<td>29/160</td>
<td>0.77 (0.48, 1.24)</td>
</tr>
<tr>
<td>ypT3</td>
<td>120/278</td>
<td>92/260</td>
<td>0.78 (0.60, 1.03)</td>
</tr>
<tr>
<td>ypT4</td>
<td>17/26</td>
<td>9/17</td>
<td>0.76 (0.34, 1.70)</td>
</tr>
<tr>
<td>ypN-category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>94/423</td>
<td>75/416</td>
<td>0.78 (0.58, 1.06)</td>
</tr>
<tr>
<td>ypN1</td>
<td>53/131</td>
<td>45/133</td>
<td>0.82 (0.55, 1.22)</td>
</tr>
<tr>
<td>ypN2</td>
<td>44/60</td>
<td>30/42</td>
<td>1.09 (0.65, 1.81)</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>30/176</td>
<td>19/148</td>
<td>0.72 (0.40, 1.28)</td>
</tr>
<tr>
<td>Stage II</td>
<td>48/148</td>
<td>40/154</td>
<td>0.74 (0.49, 1.13)</td>
</tr>
<tr>
<td>Stage III</td>
<td>71/169</td>
<td>57/154</td>
<td>0.89 (0.63, 1.28)</td>
</tr>
<tr>
<td>ypT0ypN0</td>
<td>6/61</td>
<td>9/104</td>
<td>1.19 (0.43, 3.36)</td>
</tr>
<tr>
<td>Total</td>
<td>198/623</td>
<td>159/613</td>
<td>0.79 (0.64, 0.96)</td>
</tr>
</tbody>
</table>

5-FU/OX | 5-FU
better
Recent Rectal Cancer Trials

- Surgery
- Chemo
- XRT
Current Questions in Rectal Cancer
All 3 modalities needed for stage II/III disease?

- Surgery ✔?
- Radiation ?
- Chemotherapy ?

When is the best time to introduce therapy?

- Radiation – Pre-Op ✔
- Chemotherapy – Post-Op vs. Pre-Op?

Are we satisfied with patient outcomes?

- Short term (LR) ✔
- Long term (OS) X

Selective use of XRT

- Chemo reduces LRR vs XRT alone (HR 0.5)
- CO16 - Phase III, 1350 patients with operable rectal cancer.
- Standard Arm:
  - Pre-op XRT 25Gy/5 ➔ Surgery

- Experimental Arm:
  - Surgery
  ➔ Post-op chemoXRT 45Gy/25 ONLY if + CRM

Bossett NEJM 2006, Lancet 2009
RESULTS

• Results – inferior LRR with selective XRT post-op chemoXRT
  – 60% decrease (HR=0.4) in LRR with routine XRT
  – 3 year LR 6.2% versus 10.6%
  – 3 year DFS 77% versus 71%
  – No difference in OS

• Issues - patient selection & post-op therapy??
  – One-third of patients had low rectal cancer
  – 22% of pts with + CRM did NOT get post-op XRT
  – Post-Op chemo: Stage II 18%, Stage III 80%

MERCURY trial:
CAN WE USE MRI TO PREDICT + path CRM

- Missing pathology (n = 42)
- Complete data with surgery, MRI, and pathology (n = 477)

- Did not consent to follow-up (n = 61)

- Lost to follow-up (n = 12)
- Consented to follow-up (n = 386)
- Complete data: surgery, MRI, pathology, and follow-up (n = 374)

Taylor F G et al. JCO 2014
A. T2-weighted axial thin section magnetic resonance imaging scan
B. the corresponding histology section stained with hematoxylin and eosin.

Taylor F G et al. JCO 2014;32:34-43

Prognostic Value of mrCRM

Age 63 years
Pelvic XRT 42%
pathCRM + 9.6%

Sensitivity of mrCRM for pathCRM = 64%, PPV 94%
Specificity mrCRM for pathCRM = 91%, NPV 53%

Pathologic Stage

<table>
<thead>
<tr>
<th></th>
<th>mrCRM+</th>
<th>mrCRM-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Recurrence</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>30%</td>
<td>63%</td>
</tr>
</tbody>
</table>

*mrCRM strongest prognostic factor
**Canadian QuickSilver Study**

- Use MRI to exclude patients from pre-op radiation.
- Primary outcome: + pathCRM rate
- Aim to use MRI criteria to achieve a + pathCRM rate of ≤ 10%
- No primary evaluation distant outcomes

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**Canadian QuickSilver Study**

```
MRI predicted "good prognosis" tumour

Primary Surgery

pCRM-

pN-

No further treatment

pN+

Chemo x 6 months
(started within 8 weeks after surgery)

pCRM+

pN- or pN+

Post-operative CRT
```
QuickSilver MRI Criteria: risk stratification study

<table>
<thead>
<tr>
<th>Predicted CRM</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM &gt; 1 mm</td>
<td>CRM &lt; 1 mm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T-category* and Extramural depth of invasion (EMD)</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite T2, T2/early T3 or definite T3 with ≤ 5 mm EMD</td>
<td>Definite T3 with &gt; 5 mm EMD or T4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N-category</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0, N1, N2</td>
<td>N0, N1, N2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extramural vascular invasion (EMVI)</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent or equivocal</td>
<td>Present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour Height</th>
<th>Good Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any tumour 0-15 cm from anal verge with proximal extent at or below the sacral promontory and restorative resection is planned</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No evaluation of therapy

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PRE- Operative Chemotherapy

1. NCI-CTPM: Neo-adjuvant chemotherapy is the most promising development in rectal cancer
   - more effective than post-op chemo?
   - can it replace radiation in some?
Chemotherapy: Pre vs Post-operative

**STANDARD**
- Rectal Adenoca.
- MRI defined
- Advanced ≤12 cm: cT3 within 2mmMRF
- cT3 <6cm
- Any T4
- Any N+

**EXPERIMENTAL**
- CAPOX x4

C. Fernandez-Martoz JCO 2010

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### Pre vs Post-operative CAPOX

<table>
<thead>
<tr>
<th>TIME TO ADJUVANT CHEMO</th>
<th>post-Op</th>
<th>pre-Op</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ¾ tox with CRT</td>
<td>29%</td>
<td>23%</td>
<td>0.4</td>
</tr>
<tr>
<td>Grade ¾ tox with chemo</td>
<td>54%</td>
<td>19%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Chemo compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 ≤2</td>
<td>25%</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>3-4</td>
<td>14%</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>61%</td>
<td>98%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>Mean RDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>0.67</td>
<td>.91</td>
<td>.001</td>
</tr>
<tr>
<td>capecitabine</td>
<td>0.73</td>
<td>.94</td>
<td>.001</td>
</tr>
<tr>
<td>XRT</td>
<td>0.96</td>
<td>.94</td>
<td>.001</td>
</tr>
</tbody>
</table>
Can chemo replace radiation?  
**Neo-adjuvant FOLFOX-bev without radiation for locally advanced rectal ca**

- N=32 patients with Stage II/III (no T4, low) rectal ca
- All patients had ERUS and MRI
- Neo-adjuvant FOLFOX-Bev x 3 mo followed by surgery: Bev stopped at 2 mo
- 30 Completed chemo, 2 early surgery
- 100% had R0 Surgery, 1 pt received post-op XRT
- 4 Year Follow-up:
  - 0% LRR
  - 84% DFS

Schrag JCO 2014
PROSPECT

Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

- **Objective:**
  - To determine if selective use of chemoXRT is a reasonable alternative to routine preoperative chemoXRT for resectable rectal cancer that is amenable to sphincter sparing TME.
Protocol Concept Summary

- Objective:
  - To determine if selective use of chemoXRT is a reasonable alternative strategy to routine preoperative chemoXRT for resectable, non-low rectal cancer.

Background

- Neoadjuvant radiation associated with long term toxicity and results in overtreatment of some patients.
- Patients with rectal cancer succumb to metastatic disease and neoadjuvant radiation delays initiation of systemic therapy.
- Both systemic therapy and surgical technique have substantially improved in the last decade.
Study Schema

“Standard Arm”

RANDOMIZE 1:1

Response ≥20%

“Selective Arm”

Response <20%

Study Design and Update

• A phase II/III study:
  
  – Randomized phase II of 366 patients with early stopping rule if failure to complete R0 resections or if high rate of Local Recurrence

  – Phase III component to include 644 additional patients with the endpoint of Disease Free Survival.

  – 198/1000 Accrued

  – Canada : 12 – WE NEED TO DO BETTER

  – Passed First Safety Analysis
Inclusion Criteria

- Biopsy proven rectal adenocarcinoma at age 18+
- Tumor tissue located at 5-12 cm from the anal verge
- Candidate for sphincter sparing surgery according to TME experienced surgeon
- Baseline Clinical staging: T2N1, T3N0, T3N1
  - Physical exam by primary surgeon
  - Proctoscopy
  - MRI or ERUS (MRI preferred)
    - *MRI centrally reviewed, NOT in real time
  - CT scan of Chest/Abdomen/Pelvis

Criteria

EXCLUDE:
- Clinical T4 tumors
- Clinical N2 disease
  - Defined as 4 or more suspicious nodes >10mm in diameter
- EXCLUDE Low Tumors
- Tumor within 3mm of mesorectal fascia on MRI

Exclusion Experiences:
- Close CRM on MRI
- Clinical “N2” – 4 or more nodes >1 cm
Staging/Restaging Evaluation

• Baseline staging is identical in both arms

• Restaging is more intensive in selective arm
  – Evaluate whether rectal tumor is $\geq 20\%$ smaller

• Re-evaluation in selective arm:
  – Proctoscopy
  – Physical exam by primary surgeon
  – Contrast enhanced CT of Chest/Abdomen/Pelvis
  – MRI of Pelvis or ERUS (same test as done at baseline)

If response of primary tumor is:
  – $<20\%$, then 5FUCMT
  – $\geq 20\%$, then straight to TME

Criteria for Delivery of XRT in Selective Arm

• Preoperative ChemoXRT is administered if:
  – Evidence of clinical progression during pre-op FOLFOX
  – Restaging reveals rectal tumor response is $<20\%$
  – Unable to tolerate FOLFOXx6 at or above dose level-2
  – Patient withdraws consent
  – Central imaging review reveals pt was ineligible at baseline

• Postoperative ChemoXRT is recommended if:
  – TME pathology is T4
  – TME pathology is N2
  – TME pathology has any positive margin (R1 or R2 resection)
  – Surgeon’s self assessment is that TME was incomplete
  – Surgical/Path QA report indicates incomplete TME
Treatment Requirements

- Radiation
  - IMRT is allowed
  - Short course radiotherapy is not allowed

- Sensitizing Chemotherapy with Radiation
  - May give capecitabine or infusional 5FU

Post-Operative Chemotherapy

- Suggested, not mandated
- May include chemo without Oxaliplatin

  - Intervention Arm “selective use”:
    - If no ChemoXRT, then FOLFOX for 6 more cycles
    - If pre-op ChemoXRT, then FOLFOX for 2 more cycles

  - Standard Arm “control group”:
    - 8 cycles of post-op FOLFOX
Surgeon Credentialing in TME

**OPTION 1:** Credentialing before participants register requires:
- 3 op/path reports in last 3 years
- Photos from 1 TME specimen

**OPTION 2:** Credentialing after 1st participant registers:
- An uncredentialed surgeon may register 1 participant and then:
  - Submit credentialing materials within 8 weeks
  OR
  - Submit index participant’s TME photos/reports for review

• Surgeons credentialed for ACOSOG Z6051 will be considered credentialed for this trial. Email including approximate date must be sent to Regulatory@calgb.org

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**evolution of rectal cancer**

• Therapy for stage II/III rectal cancer needs to improve:
  - Consider BOTH local AND distant control
• Better staging → more tailored therapy
• Systemic therapy likely has a greater role:
  - Post-op, Pre-op instead of radiation?
• PROSPECT will help decide whether radiation can be avoided for some patients.