What is the role of postoperative adjuvant chemotherapy?

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Possible Role of Chemotherapy in Rectal Cancer

In addition to perioperative radiotherapy:
- enhance efficacy
- improves local control → resection and sphincter preservation

Adjuvant systemic therapy - after perioperative (chemo)radiation
- eradicates micrometastasis
- reduces rate of distant relapse

Before perioperative chemoradiation
- reduces local tumor size and eradicates micrometastases

PreOP Trials: Patterns of Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Local Failure vs.</th>
<th>Distant Mets. vs.</th>
<th>OS (5y) vs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFCO</td>
<td>AT vs. RCT</td>
<td></td>
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<tr>
<td>EORTC</td>
<td>AT vs. RCT</td>
<td></td>
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<tr>
<td>AUC/CAO/ARO</td>
<td>Pre vs. post</td>
<td></td>
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<tr>
<td>Dutch trial</td>
<td>5x5 vs. 5x2</td>
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</tbody>
</table>

Despite significant reduction of local relapse, no influence on distant mets. and survival observed

Overall Survival Data with 5-FU: Colon vs. Rectal Cancer

Colon Ca. St. II
Colon Ca. St. III
Rectal-Ca. St. III

QUASAR Trial

Recurrence free survival
- 29% (p=0.04): stage III rectal cancer pts.

EORTC Trial: Contribution of Chemotherapy

Contribution of Chemotherapy
**EORTC Trial:** Contribution of Adjuvant Chemotherapy

Bosset et al., NEJM 2006

**Progression free survival @ 5 yrs.** **Overall survival @ 5 yrs.**

Which Patients Benefit From Adjuvant 5-FU/FA?

Downsized T category - yes?

EORTC trial, Collette et al., J Clin Oncol 2007

...only T downsized after RT – and not after chemo-RT?

What could be other selection criteria?

**Molecular profile?**
- But yet differences for stage II and III colon cancer
- Conflicting data about predictive value of MSI and LOH18q
  - Sargent et al., ASCO 2008, Tejpar et al., ASCO 2009
  - 18 gene set from QUASAR, for stage II rectal cancer?
  - Kerr et al., ASCO 2009

**Patient characteristics?**
- No oxaliplatin for pts. > 70y?
  - McCleary et al., ASCO 2009
2 Conclusions, so far:
Although we do not have level 1A evidence, it is obvious that systemic treatment contributes to cure
...but 5-FU/FA is not the solution

How to improve treatment?
More impact from intensive preop chemorad or from adjuvant treatment?
How to optimize adjuvant treatment?

EORTC Study:
What has more impact on patients’ prognosis?

Preoperative Chemoradiation: Add Oxaliplatin to SFU or Cape?

<table>
<thead>
<tr>
<th></th>
<th>PRODIGE 2 N=563</th>
<th>STAR N=732</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cape 45 Gy</td>
<td>Cape 50 Gy</td>
</tr>
<tr>
<td>ypCR</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>CRM +ve</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>M1 at resection</td>
<td>4%</td>
<td>3%</td>
</tr>
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</table>

Gérard et al., ASCO 2009; Aschele et al., ASCO 2009; WCGIC 2009;
**Preoperative Chemoradiation: Add Oxaliplatin to 5FU or Cape?**

<table>
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<tr>
<th>Procedure 2</th>
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<tr>
<td>N=563</td>
<td>N=722</td>
</tr>
<tr>
<td>Cape 45 Gy</td>
<td>Cape-50 Gy</td>
</tr>
<tr>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>CRM +ve</td>
<td>CRM +ve</td>
</tr>
<tr>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>MT at resection</td>
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</tr>
<tr>
<td>0.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Cumulative Oxaliplatin</td>
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</tr>
<tr>
<td>250</td>
<td>360</td>
</tr>
<tr>
<td>Adjuvant continuation?</td>
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</tr>
<tr>
<td>According to site</td>
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*Gerard et al., ASCO 2009; Aschele et al., ASCO 2009; WCGIC 2009;* 

**ChemotheraPYOr No chemotherapy In CLEar margins after neoadjuvantchemoradiationin locally advanced rectal cancer (CHRONICLIE).**

Closed because of poor accrual

- With 800 patients and p<0.05:
  - Primary endpoint: 3-yr DFS-85% power to detect a 10% increase at 40% - 50%
  - Secondary endpoints: overall survival, toxicity

**NSABP US-Intergroup Trial - Rectal Cancer**

Locally Advanced Rectal Cancer Stage II or III

- 5-FU RTx
- 5-FU OXaliplatin RTx
- Capecitabine RTx
- Oxaliplatin 6 courses based chemotherapy

- 2 x 2 factorial study

N = 1800 NSABP R-04

**Postoperative Chemotherapy: 5FU/FA vs. FOLFIRI**

Closed because of bevacizumab

Disease-free survival

*Pedrian et al., ASCO 2009*

**Treatment Arms in PETACC-6 Trial**

Intending DFS improvement of 7% @ 3y

**Adjuvant Treatment Characteristics**

<table>
<thead>
<tr>
<th>Pre OP CRT</th>
<th>Patients starting adjuvant CT</th>
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<tr>
<td>FFCD 3295</td>
<td>5FU/RT or RT 70%</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>5FU/RT or RT 77%</td>
</tr>
<tr>
<td>ARO/AIO/CAO</td>
<td>5FU/RT pre/post 80%</td>
</tr>
</tbody>
</table>

*Brasselet et al., JCO 2006; Gerard et al., NBr 2006; Bauer et al., NBr 2006; Gerard et al., ASCO 2009; Sebag-Montiflor et al., ASCO 2009; Naker, Arnold et al., JCO 2007*
Adjuvant Treatment Characteristics

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<td>ARMO/AIO/CAO</td>
<td>FU-RT pre / post 85%</td>
</tr>
<tr>
<td>PRODIGE-2*</td>
<td>FU-RT 42%*</td>
</tr>
<tr>
<td></td>
<td>Cape-Ch-R 30%*</td>
</tr>
</tbody>
</table>

*recommendation for CT

Bosset et al., JCO 2006; Gerard et al., NEJM 2006; Sauer et al., NEJM 2004; Gerard et al., ASCO 2009; Sebag-Montifiore et al., ASCO 2009; Rödel, Arnold et al., JCO 2007

Inverse Course of Treatment, Starting with Chemotherapy?

Spanish randomized phase II trial

<table>
<thead>
<tr>
<th>Arm A: N=43</th>
<th>Arm B: N=54</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Any 3-4 tox @ CRT</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Any 3-4 tox @ CT</td>
<td>51%</td>
<td>17%</td>
</tr>
<tr>
<td>ypCRT</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>pCR/PR</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.74</td>
<td>0.96</td>
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Fernandez-Mentes et al., ASCO 2009

While waiting for phase III’s:
What should be regarded as a standard?

5-FU / (FA)
- Standard in post-OP-CRT era
- Positive trials: EORTC (trend), QUASAR (subgroup)
- Capecitabine? (colon transfer, AIO rand. phase 2 Hofheinz, ASCO 2009)

Capecitabine / Oxaliplatin?
- Large phase II dataset in rectal cancer (CORE, German Trial)
- Targeted drug combinations? (yet?)

5-FU / Oxaliplatin?
- Standard in colon cancer stage III (high risk) → colon transfer?
**Neoadjuvant XELOX followed by Chemoradiation in MRI defined Poor-Risk Rectal Cancer**

- **Oxaliplatin**
- **Capcitabine**

- Poor Risk:
  - ≥ 5mm into perirectal fat
  - ≤ 1mm to mesorectal fascia
  - T3 at or below levators
  - T1-4N2

- CR+PR: 88%
- CR+PR: 97%
- pCR: 24%

**Rectal Cancer different from Colon Cancer?**

- **specific anatomical location:**
  - yes, but only a risk for local relapse, not for survival
- **metastatic behavior different:**
  - no data demonstrating real difference
- **different sensitivity to chemotherapy:**
  - rectal vs colon primary tumor: no sign. difference
- **different biology/gene signature:**
  - probably, but not related to clinical behavior, chemosensitivity etc.

**Chemorad: Substitute FU by Capecitabine?**

- **Capcitabine**
  - 3%
  - 52% (2.4-4.3%)

  - T downsizing Trend (p=0.17)

- **Pre-OP strata**
  - N Downstaging Improved (P=0.03)

**Chemorad: Add Oxaliplatin to FU or Cape?**

- **STAR; N=732**
  - ypCR 12% → 25%
  - 3yDFS: 75% → 82%

- **PRODIGE-2; N=563**
  - ypCR: 11% → 20%

**Phase II Trials with Pre- and postoperative CapeOX**

- **AIO: N=110; CORE N=85**
  - AIO: 66%
  - CORE: 55%

*Rödel, Arnold et al. J Clin Oncol 2007; **Sebag-Montefiore et al., ASCO GI 2009*