Future Prospects with Total Neo-Adjuvant Treatment in Rectal Cancer
The Optimal Sequencing
The Radiation Oncologist Point of View

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Standard chemoradiation: room for improvement

- Standard chemoradiation
  - RT 45 - 50Gy
  - 5-FU/capecitabine
  - Interval to surgery

Outcome = heterogeneous

- 15 – 20% pCR rate → favorable oncological outcome
- Organ preservation?

70% 5Y overall survival

Problem = distant metastasis despite adjuvant chemotherapy
Standard chemoradiation: room for improvement

- 15 – 20% pCR rate → favorable oncological outcome → Organ preservation

Increase in tumor response? → More patients eligible for organ preserving strategies?

70% 5Y overall survival

- Problem = distant metastasis despite adjuvant chemotherapy

Early administration of systemic therapy → Better oncological outcome?
Total Neoadjuvant Treatment

= combination of preoperative (chemo)radiotherapy with preoperative chemotherapy rather than adjuvant chemotherapy

Optimal treatment sequence?
Chemo first vs. radiotherapy first

Two-fold aim

1. Compliance to therapy
2. Disease outcome (Organ preservation & DFS)
Total Neoadjuvant Treatment

**Chemo first**

- **Spanish GCR-3 trial (n = 108)**
  - 4x CAPOX + CRT (CAPOX)
  - CRT (CAPOX) + adj. 4x CAPOX

- **EXPERT trial (n = 105)**
  - 4x CAPOX + CRT (cape) + adj. cape

- **EXPERT-C trial (n = 165)**
  - 4x CAPOX+cet + CRT (cape+cet) + adj 4x CAPOX+cet
  - 4X CAPOX +CRT (cape) + adj. 4x CAPOX

**RT first**

- **Garcia-Aguilar (n = 259)**
  - CRT (5FU) + adj. 8x mFOLFOX6
  - CRT (5FU) + 2x mFOLFOX 6 + adj. 6x mFOLFOX6
  - CRT (5FU) + 4x mFOLFOX 6 + adj. 4x mFOLFOX6
  - CRT (5FU) + 6x mFOLFOX 6 + adj. 2x mFOLFOX6

- **Polish II Trial (n = 515)**
  - SCRT + 3x FOLFOX4
  - CRT (5FU/OX)
Chemotherapy first

**Pro**
- Early introduction of treatment for micrometastases
- Increased compliance to chemotherapy
  - Spanish GCR-3 trial¹: 94%
  - EXPERT trial²: 87%
  - EXPERT-C trial³: 94%

**Con**
- Potential decrease in compliance to subsequent CRT
- Potential induction of accelerated repopulation thereby hampering CRT efficacy⁴

² Chua et al. Lancet Oncol 2010
³ Dewdney et al. JCO 2012
⁴ Glynne-Jones et al. Br J Cancer 2006
Radiotherapy first

**Pro**
- No induction of accelerated repopulation by induction chemotherapy
- Increased compliance to chemoradiotherapy
- Still early introduction of systemic treatment for micrometastases

**Con**
- Potential decrease in compliance to subsequent chemotherapy in interval
  - Garcia-Aguilar\(^1\): 77% - 81% - 82%
  - Polish II trial\(^2\): 72%

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\(^1\) Garcia-Aguilar et al. *Lancet Oncol* 2015


Adapted from Ludmir et al. *Cancer* 2017
What about disease outcome?
### Survival

<table>
<thead>
<tr>
<th>Chemo first</th>
<th>RT first</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5Y OS</strong></td>
<td><strong>5Y OS</strong></td>
</tr>
<tr>
<td>Spanish GCR-3 trial: 74%</td>
<td>Garcia-Aguilar: NR</td>
</tr>
<tr>
<td>vs 77% (standard arm)</td>
<td>Polish trial: 73%</td>
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<tr>
<td><strong>5Y DFS</strong></td>
<td><strong>5Y DFS</strong></td>
</tr>
<tr>
<td>Spanish GCR-3 trial: 64%</td>
<td>Garcia-Aguilar: NR</td>
</tr>
<tr>
<td>vs 62% (standard arm)</td>
<td>Polish II trial: 53%</td>
</tr>
<tr>
<td>EXPERT trial: 62%</td>
<td>vs 52% (standard arm)</td>
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</tbody>
</table>

- **No head-to-head comparison**
- Studies mostly focusing on pathological outcome ➔ No conclusion on which strategy is preferable
<table>
<thead>
<tr>
<th>Pathologic Complete Response</th>
<th>Chemo first</th>
<th>RT first</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish GCR-3 trial</td>
<td>- 14% vs 13% (standard arm)</td>
<td>- 20% (no standard arm)</td>
</tr>
<tr>
<td></td>
<td>- Expert C trial (KRAS wt only)</td>
<td>- Garcia-Aguilar</td>
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<tr>
<td></td>
<td>- 7%</td>
<td>- 3x FOLFOX4: 16% vs 12% (standard arm)</td>
</tr>
<tr>
<td></td>
<td>+ cetuximab: 11%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no standard arm</td>
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</tbody>
</table>

Variation in pCR rate: Heterogeneity in patient cohorts, Heterogeneity in treatment, Timing interval to surgery, Lack of randomisation

➔ Difficult to draw conclusion
Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12

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Phase II pick-the-winner design

Hypothesis = increased pCR rate of 25% after TNT compared with standard 15%
Patients recruited and randomly assigned
(N = 311)

Allocated to TNT group A
(sequence chemotherapy/CRT/S ; n = 158)
- Excluded (n = 2)
  - Consent withdrawal (n = 1)
  - Protocol entry violation (n = 1)
- Eligible for TNT group A (n = 156)
  - Started induction chemotherapy (n = 156)
  - Started CRT (n = 151)
  - Did not receive CRT (n = 5)
- Patients who did not receive surgery (n = 13)
  - Refused because of cCR (n = 6)
  - Refused because of other reason (n = 4)
  - Had progressive disease (n = 2)
  - Died before surgery (n = 1)
  - Had missing data for surgery (n = 1)
- Had surgery (n = 142)
  - Included in intention-to-treat analysis (n = 156)
  - Included in safety analysis of chemotherapy (n = 156)
  - Included in safety analysis of CRT (n = 151)
  - Included for surgical morbidity (n = 142)

Allocated to TNT group B
(sequence CRT/chemotherapy/S; n = 153)
- Excluded (n = 3)
  - Consent withdrawal (n = 2)
  - Protocol entry violation (n = 1)
- Eligible for TNT group B (n = 150)
  - Started CRT (n = 149)
  - Did not receive CRT (n = 1)
  - Started consolidation chemotherapy (n = 140)
  - Did not receive consolidation chemotherapy (n = 10)
- Patients who did not have surgery (n = 6)
  - Refused because of cCR (n = 4)
  - Refused because of other reason (n = 1)
  - Died before surgery (n = 1)
  - Had missing data for surgery (n = 2)
- Had surgery (n = 142)
  - Included in intention-to-treat analysis (n = 150)
  - Included in safety analysis of CRT (n = 149)
  - Included in safety analysis of chemotherapy (n = 140)
  - Included for surgical morbidity (n = 142)
<table>
<thead>
<tr>
<th></th>
<th>Chemo first (n = 156)</th>
<th>RT first (n = 150)</th>
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</thead>
<tbody>
<tr>
<td>CRT-related gr. 3-4 toxicity</td>
<td>37%</td>
<td>27%</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-dose RT: 91%</td>
<td>concomitant 5-FU: 78%</td>
<td>concomitant oxaliplatin: 93%</td>
</tr>
<tr>
<td></td>
<td>concomitant oxaliplatin: 76%</td>
<td>consolidation chemo: 85%</td>
</tr>
<tr>
<td></td>
<td>induction chemo: 92%</td>
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</tbody>
</table>
Main Findings

Lower toxicity and higher CRT-compliance if RT first
- Concurrent 5FU/Oxali might contribute to increased toxicity to CRT and reduced compliance (especially after induction chemo)

Higher compliance to induction chemo if chemo first compared to consolidation chemo if RT first
- However, interval if RT first = 90d vs 45d if chemo first
- Translation of higher pCR rate into better oncological outcome?
  - No data yet
- Worse compliance to consolidation could impact DFS
The winner has been identified!

... has he?

Different TNT regimen for different therapeutic goal or patient group?
→ RT first if local tumor regression is desirable
→ Chemo first if high risk of micrometastatic disease

Long-term oncological outcome is needed!
The winner has been identified!

... has he?

Different TNT regimen for different therapeutic goal or patient group?

→ Need for better molecular risk stratification
→ Validation of high-risk imaging features
→ Liquid biomarkers (circulating tumor DNA/tumor cells, ...)

Reducing the risk of overtreatment in low risk disease!

Hong et al. JAMA Oncology 2018
Ongoing trials

MSKCC (NCT02008656)
- FOLFOX/CAPOX + CRT vs CRT + FOLFOX/CAPOX
- Organ preservation is possible
- Primary endpoint = DFS

CAO/ARO/AIO-18 Phase III
- CRT (5FU/Oxali) + FOLFOX
- Primary endpoint = DFS

NRG-GI002 (NCT02921256)
- FOLFOX + CRT vs FOLFOX + CRT/veliparib + CRT/pembro + CRT/? (additional arm?)
- Primary endpoint = NAR score (Valentini et al.)

PROSPECT (NCT01515787)
- CRT + TME vs FOLFOX → response >20%
- TME → response < 20%
- CRT + TME
- Primary endpoints: R0 resection, DFS

... and other trials
ACO/ARO/AIO-18.1 Randomized Phase III Trial

A

- RT: 28 x 1.8 Gy (50.4 Gy)
- 5-FU\(^1\): 225 mg/m\(^2\), civ, d1-38 of RT

B

- RT: 28 x 1.8 Gy (50.4 Gy)
- 5-FU: 250 mg/m\(^2\), civ d1-14, d22-35 of RT
- Oxaliplatin 50 mg/m\(^2\), d1, 8, 21, 29 of RT

\(^1\) 5-FU can be replaced with capecitabine: 825 mg/m\(^2\) bid, po, d1-38 of RT

- 6-8 weeks
- 2 1/2 weeks

Surgery\(^*\)

- d80-94
- Optional adjuvant chemotherapy\(^2\) as described in trial protocol

Surgery\(^*\)

- 5 weeks

\(^*\) Optional Watch\&Wait management in case of clinical complete response
Thank you!