Is Neoadjuvant Radiotherapy always Necessary for locally advanced Mid-High Rectal Cancers?

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Rectal Cancer

- Historically, high both local recurrence and requirement for a permanent stoma
- Now, within specialized rectal cancer teams, recurrence < 10%. With CXRT
- The desire to avoid local recurrence and a permanent stoma drove the initial swing for preoperative RT

Kennedy ED et al, Cancer 2011;117:2853–62
Short-course XRT?

- 25 cGy in 5 fractions
- Northern Europe approach
- No concurrent chemo(5FU) radio-sensitizer
- Surgery within a 1-2 weeks
- No down-staging (not for T4 or concern re CRM)

Swedish Rectal Cancer Study

- Rectal Ca
- Preop RT (25 cGy in 5 fractions)
  - LR 11%, 5yr OS 58%
- Immediate surgery
  - LR 27%, 5yr OS 48%

NEJM 1997
**Dutch Colorectal Group (NEJM 2001)**

- Preop RT + TME (25 cGy in 5 fractions)
  - LR 5.6%
- TME alone
  - LR 10.9%

Kapiteijn NEJM 2001

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**MRC CR-07 (NCIC CO-16)**

**Trial Design**

- Clinically operable adenocarcinoma of the rectum ≤15 cm from anal verge, no metastases

**Randomize**

**PRE**
- Pre operative RT 25Gy/5F
- Surgery
- Pathology

**POST**
- Surgery
- Pathology
- CRM -ve
- No RT
- CRM +ve
- Post-op CRT 45Gy/25F + concurrent 5FU

**N=1,350**

Adjuvant chemotherapy given as per local policy (90%)

Lancet 2009; 373: 821–28

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LR by treatment (ITT)

- **PRE**
  - N: 674
  - Events: 23
  - 3yr LR: 5%
  - 5yr LR: 5%

- **POST**
  - N: 676
  - Events: 61
  - 3yr LR: 11%
  - 5yr LR: 17%

HR(95%CI) = 2.47 (1.61, 3.79) \( p < 0.0001 \)

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Randomized Phase III Trials of Preoperative Radiotherapy vs Surgery Alone as initial therapy for Resectable Rectal Cancer

<table>
<thead>
<tr>
<th>Control</th>
<th>Preoperative Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Local Relapse Rate at 5 y</td>
</tr>
<tr>
<td>SWEDISH (1997)</td>
<td>585</td>
</tr>
<tr>
<td>DUTCH (2001)</td>
<td>924</td>
</tr>
<tr>
<td>MRC CR07 (2006)</td>
<td>676</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2185</td>
</tr>
</tbody>
</table>

Preoperative radiation reduces significantly local relapses even in the resected patients.
Preoperative Chemoradiotherapy

- North American/Southern Europe approach
- For patients with locally advanced disease
  - T3/T4 or N+
- More protracted RT course 5-6 weeks (45-50.4 cGy)
- Concurrent 5FU based chemotherapy
- Followed by Surgery 6 - 11 weeks later

421 receive preoperative and 402 receive postoperative CXRT
- The overall 5 year survival rates were 76% and 74% (P=0.80)
- The 5 year incidence of local relapse 6% for preoperative and 12% in the postoperative group (P=0.006)
- Grade 3 or 4 acute toxicity occurred in 27% of the patients in the preoperative-treatment group, as compared with 40% of the patients in the postoperative-treatment group (P=0.001)
Cumulative Incidence of Local Relapses
Intent-to-treat Analysis (Med. F/up: 40 mos)

Overall Survival
Intent-to-Treat Analysis (Med. Follow-up: 40 mts)
German Rectal Study Conclusions

- Preop CXRT significantly improves local control
- Preop CXRT improves sphincter preservation in low-lying tumors
- Preop CXRT reduced acute and chronic toxicity
- Preop CRT should be the standard treatment in cT3/4 or cN+ rectal cancer

????

- 10% getting benefit
- What about the 90% who are radiated without benefit? any harm?
**RT Late effects**

- **Bregendahl S et al Colorectal Dis. 2015 Jan**
  - 516 patient
  - 6 years follow up
  - Voiding difficulties (OR = 1.63, 95% CI 1.09-2.44)
  - Reduced vaginal dimensions (OR = 4.77, 95% CI 1.97-11.55)
  - Dyspareunia (OR = 2.76, 95% CI 1.12-6.79)
  - Lack of desire (OR = 2.22, 95% CI 1.09-4.53)
  - Reduced sexual activity (OR = 0.55, 95% CI 0.30-0.98).

**RT Late effects**

- Sexual dysfunction (**Marijnen et al 2005**)
  - 990 patients without recurrence
  - RT had a negative effect on sexual functioning in males (P .004) and females (P .001)
  - Irradiated males had more ejaculation disorders (P .002) and erectile functioning deteriorated over time (P .001)

- **Second malignancy (13.7% vs. 9.4) in Dutch trial** (**van gijn et al 2011**)

- Unexplained late cardiac effects
- Higher % of SBO
Fecal incontinence

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Therapy strategy</th>
<th>Follow-up (yrs; median)</th>
<th>Fecal incontinence (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeters 2005</td>
<td>177 vs. 185</td>
<td>5x5 Gy versus TME</td>
<td>5.1</td>
<td>62 vs. 38*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pollack 2006</td>
<td>21 vs. 43</td>
<td>5x5 Gy versus conventional surgery</td>
<td>14</td>
<td>57 vs. 26</td>
<td>0.013</td>
</tr>
<tr>
<td>Braendengen 2006</td>
<td>18 vs. 19</td>
<td>Preop. RTX versus RCTX</td>
<td>4-12</td>
<td>58 vs. 38*</td>
<td>0.013</td>
</tr>
<tr>
<td>Coco 2007</td>
<td>100</td>
<td>50.4 Gy</td>
<td>12</td>
<td>46 vs. 14</td>
<td>0.013</td>
</tr>
<tr>
<td>Urso † 2006</td>
<td>12</td>
<td>Pre- and postoperative</td>
<td>19 mths</td>
<td>75</td>
<td>0.01</td>
</tr>
<tr>
<td>Bruehm † 2010</td>
<td>69 vs. 240</td>
<td>Pre- and postoperative versus TME</td>
<td>4.8</td>
<td>71 vs. 58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Karoline Horisberger, Pablo Palma. www.intechopen.com

You will get rid of your cancer but you won’t be able to urinate, defecate or have sex!! Is that ok with you?
Surgeon & Patient Priorities

- The desire to avoid local recurrence and a permanent stoma overrode concerns regarding long-term bowel, urinary and sexual function. **Surgeon view**

Surgeon vs. patient desires

- These priorities are not currently shared by patients. Patients may be keen to avoid a permanent stoma, but value good functional outcomes, and are prepared to trade off and accept a higher risk of local recurrence to achieve that!

Why Question Use of Neoadjuvant XRT?

- Current standard of care for all Stage II-III rectal cancer is tri-modality therapy—has been so since 1990
- Only ± 10% get real benefit from nXRT
- Neoadjuvant XRT may be overtreatment in some cases (due to inaccurate pre treatment staging)
- Pelvic radiation causes short and long-term morbidity
- Landmark TME trials showed that XRT marginally improves LR rates, but not survival
Original research

Is it safe to omit neoadjuvant chemo-radiation in mucinous rectal carcinoma?

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HIGHLIGHTS

• We are studying the oncologic outcome of patients having mucinous rectal carcinoma with or without Neoadjuvant chemoradiation.
• Partial tumor regression occurred in limited percentage of patients.
• A considerable percentage of patients developed tumor progression during chemoradiation and became unresectable.
• No difference between groups in the disease free survival and overall survival after total mesectrectal excision.

102 patients of mucinous rectal carcinoma

• 61 receive preoperative CXRT
• 29 had partial response, 26 no response and 6 disease progression
• No difference in the overall five-year survival rates, 69% and 67% (P=0.39)
• The five-year incidence of local relapse 21% for preoperative and 23% in the postoperative group (P=0.29)
Conclusions

- In most MRC, tumor regression is not significant after nCXRT and there is considerable possibility of tumor progression during nCXRT.
- So, nCXRT should be used with close follow-up in MRC for early detection of possible tumor progression.
- If the patient can’t tolerate nCXRT, it is possibly safe to do surgery followed by pCXRT.

New concepts after MDT

- Rectal cancer should no longer be considered a single monolithic disease entity, with a simple unifying management strategy.
- Outcome depends on:
  - Tumor location, CRM status, whether it is exophytic (polypoid or sessile) or ulcerated, mobile or fixed as well as its (TNM) staging.
  - Histopathological parameters are also important as mucinous/signet ring tumors.
  - Lack of data about factors affecting response to XRT.
How to solve problems of RT complications and the wide spectrum of response?

Theoretical solutions

- Neoadjuvant chemotherapy alone
- Tailored protocols
- Study predictors for good response to RT
- Change size of radiation field and/or dose
**Neoadjuvant Chemotherapy Pilot Study**

- Phase II pilot at MSKCC administered 6 cycles of induction FOLFOX+Bev to patients with clinical T2N1, T3N0, T3N1 RC who were candidates for LAR
- XRT planned if no response or any positive margin
- 30 participants, none required preoperative XRT
- With more than 4 years median follow up:
  - 1 post-op death, 2 cancer deaths
  - **No local recurrences**
  - 4 recurrences, all with metastases to lung

JCO Jan 2014

**Challenging routine CXRT PROSPECT**

N1048-CALGB81001-ACOSOGZ6052

An NCI Cooperative Group Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

University of Alexandria
PROSPECT: N1048

Objective:
- To determine if selective use of neoadjuvant XRT is a safe alternative strategy to routine use of XRT for management of locally advanced rectal cancer that is amenable to sphincter sparing TME.

PROSPECT: Study Design

- A phase II/III NCI Cooperative Group study:
  - Randomized phase II of 366 patients with early stopping rule if failure to complete R0 resections or if an unacceptably high rate of Local recurrences.
  - Phase III will include 644 additional patients if stopping criteria are not met.
Study Endpoints

Primary Outcomes:
- Randomized Phase II Component
  - R0 Resection Rate
  - Time to local recurrence (TLR)
- Phase III Component:
  - Time to local recurrence (TLR)
  - Disease free survival (DFS)

Secondary Outcomes:
- Pathologic complete response rate (Pcr)
- Overall survival (OS) ■ Quality of life (QOL)
- Rates of receiving 5FUCMT

PROSPECT: Study Schema

"Standard Arm"

Randomize 1:1
- FOLFOX x 6
- Response ≥20%
- Chemo per primary MD

"Selective Arm"

- 5FUCMT*
- TME
- Response <20%
- 5FUCMT = infusional or oral 5FU + radiation therapy

*5FUCMT = infusional or oral 5FU + radiation therapy
Radiation in the Intervention Arm is Used Selectively

- **Preoperative 5FUCMT is to be administered if:**
  - Evidence of clinical progression during pre-op FOLFOX
  - Restaging reveals rectal tumor response is an estimated <20%
  - Unable to tolerate FOLFOXx6 at or above dose level-2
  - Patient withdraws consent

- **Postoperative 5FUCMT is recommended if:**
  - TME pathology is T4
  - 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

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Preliminary Conclusions

- Neoadjuvant chemotherapy strategies are an *investigational* approach for patients with resectable rectal CA amenable to sphincter sparing TME
- XRT is a mainstay of Rx for a curable cancer 5-12 cm from the anal verge: *selective* approach appropriate on a trial
- Patients with threatened margins are inappropriate candidates for selective use of XRT
- Induction FOLFOX for pts
  - who can’t have XRT due to prior therapy
  - with stage IV disease amenable to R0 resection
  - With suspected metastatic disease
41 patients. The completion rate of the preoperative XELOX was 90.3%.

- 4 Major complications occurred in 6/40 patients (15.0%)
- Pathological complete response (pCR) rate was 12.2%.
- Good tumor regression was exhibited in 31.7%.
- N down-staging (cN1 to ypN0) and T down-staging were detected in 56.7% and 52.5%, respectively.
- Clinical T4 tumor was a predictor of poor pathological response (p < 0.001).

**Conclusions:** We could show the favorable pCR rate after preoperative XELOX alone.

- T and N down-staging rate was likely to be insufficient.
- When tumor regression is essential for curative resection, the use of preoperative CRT is likely to be recommended.
On going Trials

<table>
<thead>
<tr>
<th>STUDY (Reference)</th>
<th>Pre-operative Treatment</th>
<th>Entry criteria</th>
<th>Status</th>
<th>RT/ORT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III trials</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GEMCAD (Gomez-Manzano et al.) 2010</td>
<td>Capsule-based radiation + bevacizumab 7 cycles then cap + rad + CRT</td>
<td>MRI defined entry</td>
<td>Recruiting</td>
<td>CRT according to response</td>
<td>Primary endpoint Response rate at 12 months</td>
</tr>
<tr>
<td>RAPID III (Tal et al. 2016-02-2017) 888 patients</td>
<td>SCRT 5 Gy/3 daily followed by Oxaliplatin + bevacizumab 6 cycles + CRT</td>
<td>MRI defined entry</td>
<td>Open to entry</td>
<td>CRT 50.4 Gy/35 fractions with bevacizumab</td>
<td>Primary endpoint 3 year DFS</td>
</tr>
<tr>
<td>Peritoneal Study ESPRO 1019 NCT00031351 340 patients</td>
<td>SCRT (5 x 5 Gy) followed by FU/5FU (3 cycles) + oxaliplatin CRT + chemotherapy</td>
<td>Yet to open</td>
<td>CRT 50.4 Gy/35 fractions with bevacizumab</td>
<td>CRT or CRT only for progression of disease</td>
<td>Primary endpoint 5 year DDFS</td>
</tr>
</tbody>
</table>

Randomized Phase II trials

| BACCHUS NCRI Randomized phase II 60 patients | FOX/FR5FU for 8 weeks then randomized to oxaliplatin + SCRT or CRT | MRI defined entry | Open to entry | CRT or CRT only for progression of disease | Primary endpoint 5 year DFS |
| GRECCAR 4 404 patients | FOX/FR5FU for 8 weeks then randomized to oxaliplatin + SCRT or CRT | MRI defined entry | Open to entry | CRT or CRT only for progression of disease | Primary endpoint 5 year DFS |
| French phase II NCT000533949 91 patients | FOX/FR5FU for 6 cycles then CRT with bevacizumab or placebo | Not MRI | Ongoing | CRT not meaningful | Primary endpoint DFS |
| Chinese Randomized phase II NCT00113121 60 patients | FOX/FR5FU for 4 cycles then CRT with oxaliplatin | Not MRI | Ongoing | CRT not meaningful | Primary endpoint DFS |
| SWOG study NCT00058436 Up to 65 patients | Multiple regions | T4 tumor necrosis | Ongoing | CRT with cap + rad + CRT | Primary endpoint DFS |

130 patients with locally advanced mid and low rectal cancer

- Long-course nCXRT followed by radical surgical resection were included in the study
- Paraffin-embedded sections obtained in diagnostic biopsies were assessed by immunohistochemical staining for molecular markers and classified using a semi-quantitative method
- Results were related with T-downstaging and tumor regression grade using Mandard scoring system on surgical specimens
Predictors for response to nCXRT

- Predictive markers of response in univariate analysis:
  - Expression of B-cell lymphoma 2 (anti-apoptotic protein)
  - B-catenin
  - VEGF
  - Apoptotic protease activating factor 1 \((P = 0.03)\)
  - Tumor differentiation grade \((P < 0.001)\)
- Multivariate analysis
  - Tumor differentiation grade
  - Bcl-2 expression

Still a lot to go....proteomics!!! Genetic!!

What else?

- Expanding options for more effective & individualized combinations of chemotherapy and biological treatments which may improve radiotherapy effectiveness
- Potentially more effective systemic chemotherapy may avoid the need for radiotherapy all together and this is currently under investigation in many trials
- Predictors for good response to RT are being studied
Challenges

- Which patient do not need to receive preoperative RT?
- Is neoadjuvant chemotherapy an alternative?
- How do we select the most appropriate treatment between chemotherapy, CXRT?
- What is the optimal chemotherapy regime alone or to combine with RT?
- What is the optimal RT dose?
- What are the optimal radiotherapy fields?
- Should we use standard or tailored protocols?

Thank you