“Perioperative radio/chemoradiotherapy for rectal cancer”
No disclosures to declare
**T-staging for rectal cancer**

**T1:** Invades submucosa (sm).

**T2:** Invades muscularis propria (mp).

**T3:** Through mp into subserosa or peri-rectal tissues.

**T4:** Invades other organs / structures and/or perforates visceral peritoneum.

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa but does not extend into circular muscle layer</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades but does not penetrate MP</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades subserosa through MP</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor extends &lt;1mm beyond MP</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor extends ≥1-5mm beyond MP</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumor extends &gt;5-15mm beyond MP</td>
</tr>
<tr>
<td>T3d</td>
<td>Tumor extends &gt;15mm beyond MP</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades:</td>
</tr>
<tr>
<td>T4a</td>
<td>Peritoneal reflection</td>
</tr>
<tr>
<td>T4b</td>
<td>Others organs</td>
</tr>
<tr>
<td>T1</td>
<td>5-10%</td>
</tr>
<tr>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>T2</td>
<td>15-20%</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 30%</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 50%</td>
</tr>
</tbody>
</table>
MRI high risk features

- Tumour within 1mm or beyond MR fascia
- T3 low lying tumour at/or below levators
- Tumour extending 5mm or more into peri-rectal fat (T3c)
- T4 tumours
- N2 tumours

Gina Brown
Treatment algorithm for localised rectal cancer

Figure 1. Treatment algorithm for localized rectal cancer. (Lateral LN: drainage of the a rectalis media (if present) or along the obturatorius or internal iliac vessels).
T-stage and Rectal Pre-op RT

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3 &gt;1mm*</th>
<th>T3 &lt;1mm*</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>-</td>
<td>-</td>
<td>- / S(\text{T3c/d})</td>
<td>L**</td>
<td>L**</td>
</tr>
<tr>
<td>Mid</td>
<td>-</td>
<td>-</td>
<td>S</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>- / S</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

S: Short; L: Long course of RT

** ESMO: “Intensive chemotherapy might be an option, which however has not yet systematically been proved”
SCRT

13 years follow-up
1168 patients
Surgery vs Surgery after pre-op RT (25Gy / 5 fractions)

<table>
<thead>
<tr>
<th></th>
<th>S + RT</th>
<th>S</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>9%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer specific survival</td>
<td>72%</td>
<td>62%</td>
<td>0.03</td>
</tr>
<tr>
<td>Overall survival</td>
<td>38%</td>
<td>30%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Benefits to all Dukes stages

(Folkesson et al, JCO 23, 24: 5644 - 5650)
The “Dutch” study (2001)

1861 patients
Operable rectal cancer
TME + RT (25 Gy in 5 fractions)

Local recurrence at 5 years

TME: 11.4%
TME + RT: 5.8% (p<0.001)

No survival benefit

(Kapiteijn et al, NEJM, 345 (9), 638-646, 2001)
### Recurrence and distance from anal verge

<table>
<thead>
<tr>
<th>Distance from Anal verge</th>
<th>TME (At 2 years)</th>
<th>RT/TME (At 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 15 cm</td>
<td>3.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>5 - 10 cm</td>
<td>10.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>&lt; 5 cm</td>
<td>10.0%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

(Kapiteijn et al., NEJM, 345 (9), 638-646, 2001)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Date</th>
<th>Local recurrence Surgery alone</th>
<th>Local recurrence Surgery + DXT</th>
<th>p value</th>
<th>Length of follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR02</td>
<td>1996</td>
<td>46%</td>
<td>36%</td>
<td>=0.04</td>
<td>5 years</td>
</tr>
<tr>
<td>CR03</td>
<td>1996</td>
<td>34%</td>
<td>21%</td>
<td>=0.001</td>
<td>5 years</td>
</tr>
<tr>
<td>North West</td>
<td>1994</td>
<td>36.5%</td>
<td>12.8%</td>
<td>=0.0001</td>
<td>8 years</td>
</tr>
<tr>
<td>Swedish</td>
<td>1997</td>
<td>27%</td>
<td>11%</td>
<td>&lt;0.001</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>26%</td>
<td>9%</td>
<td>&lt;0.001</td>
<td>13 years</td>
</tr>
<tr>
<td>Dutch</td>
<td>2001</td>
<td>8.2%</td>
<td>2.4%</td>
<td>&lt;0.01</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.4%</td>
<td>5.8%</td>
<td></td>
<td>5 years</td>
</tr>
</tbody>
</table>
Do we need to give RT?

Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.

David Sebag-Montefiore et al............

CRO7

Pre-op 25Gy in 5 fractions

V

Selected* post-op CRT (45Gy in 25#)

(* If tumour within 1mm of CRM)
CRO7

1350 pts

80 centre (UK, Canada, S.Africa, NZ)

Operable rectal cancer

674 / 676 in each arm
<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3yrs</td>
<td>5%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>5yrs</td>
<td>5%</td>
<td>17%</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

LR less in the pre-op group
LR less at all stages in pre-op group
DFS better in the pre-op group
Conclusions from CRO7

“.............short-course preoperative radiotherapy is an effective treatment for patients with operable rectal cancer.”
Short or Long course CRT for operable rectal cancer
Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery.

Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, Tamelis A, Pavalkis D.

AIM:
RCT: long-course chemoradiotherapy (chRT) v short-course radiotherapy (sRT) followed by delayed surgery.

METHOD:
83 patients
Resectable stage II and III rectal adenocarcinoma
Surgery was performed 6 weeks after preoperative treatment in both groups.

RESULTS:
• There were more patients with early pT stage [pT0 (complete pathological response) pT1] in the chRT group [21.8% vs 2.7% (P=0.03)] and more patients with pT3 disease in the sRT group [75.7% vs 52.2% (P=0.036)].

• The R0 resection rate was 91.3% in the chRT and 86.5% in the sRT group (P=0.734).

• Similar postoperative morbidity was observed in each group.

CONCLUSION:
Long-course preoperative chemoradiation resulted in greater statistically significant tumour downsizing and downstaging compared with short-term radiation, but there was no difference in the R0 resection rates.

A Polish randomised study* (n = 312) and an Australian randomised study** (n = 326) compared LCCRT and SCRT.

- Both trials showed a lower rate of early adverse effects using a short-course radiation regimen and no differences in long-term oncologic outcomes and late toxicity rates between groups.

- The small number of fractions makes short-course radiation less expensive and more convenient than chemoradiation therapy.

* Bujko BJS 2006; ** Ngan JCO 2012
The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group (TROG) Trial 01.04).

PATIENTS AND METHODS
Operable patients with T3N0-2M0 rectal cancer completed the European Organisation for Research and Treatment of Cancer quality of life questionnaire (QLQ-C30) and the colorectal cancer specific module (QLQ C38) at randomisation and 1, 2, 3, 6, 9 and 12 months later.

RESULTS
• Of 326 patients
• Baseline scores were comparable across the SC and LC groups.
• Patients reported low scores on sexual functioning and sexual enjoyment.
• Defaecation problems were the worst of the symptoms at baseline.
• Surgery had the most profoundly negative effect on HRQOL.
• The most severely affected domains were physical function and role function and the most severely affected symptoms were fatigue, pain, appetite, weight loss and male sexual problems.
• Most domains and symptoms returned to baseline levels by 12 months apart from body image, sexual enjoyment and male sexual problems.

CONCLUSION
There is no overall difference in HRQOL between SC and LC neoadjuvant treatment strategies, in the first 12 months, after surgery.
Short or Long course CRT for inoperable rectal cancer
Or....... we can reduce LR but can we improve survival?
Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomised phase III study.

cT3 or cT4 rectal cancers
5 × 5 Gy and FOLFOX4 x 3 (group A) v 50.4 Gy in 28 fractions (+ Ox/5FU/FA*) (group B) (*Bolus 5-FU 325 mg/m(2)/day and FA 20 mg/m(2)/day during the first and fifth week of irradiation along with five infusions of oxaliplatin 50 mg/m(2) once weekly).

RESULTS
• 541 patients.
• Acute toxicity was lower in group A than group B, P = 0.006.
• R0 resection rates and pCR rates in groups A and B were, respectively, 77% versus 71%, P = 0.07, and 16% versus 12%, P = 0.17.
• At 3 years, the rates of OS and DFS in groups A and B were, respectively, 73% versus 65%, P = 0.046, and 53% versus 52%, P = 0.85.
• Postoperative and late complications rates in group A and group B were, respectively, 29% versus 25%, P = 0.18, and 20% versus 22%, P = 0.54.

CONCLUSIONS
No differences were observed in local efficacy between 5 × 5 Gy with consolidation chemotherapy and long-course chemoradiation. Nevertheless, an improved overall survival and lower acute toxicity favours the 5 × 5 Gy schedule with consolidation chemotherapy.

Bujko K et al, Ann Oncol 27(5) 834-42, 2016
UK “Operable” trials (NCRN)  
..........can we improve survival?

COPPERNICUS (Simon Gollins)

62 pts
OxMdG x4 ....... 25 Gy/5# ....... op ....... OxMdG x8

BACCHUS (Rob Glynne-Jones)

30 + 30 pts
FOLFOX+Av x3 ..... PET ..... FOLFOX+Av x3 ..... Op
FOLFOXIRI+Av x3 ..... PET ..... FOLFOXIRI+Av x3 ..... Op
Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial.


DFS / OS improved

To close May/June 2016
Timing of surgery after SCRT?

ESMO: “2-3 days after END of SCRT”
Patients > 75 years

Dutch data van den Broek et al (EJC 2013)

TME trial - 600 pts (median age 67 years)

Patients > 75 years old operated 4-7 days post last # RT had a higher chance of dying compared to surgery 0-3 days post last # RT (4.7 v 2.1%).

Stockholm III (Petterson BJS 2010) also showed an increase in post-op complications for those treated 11-17days post starting RT.

Hartley et al, BJS 2002 – reduced risk of complications if overall treatment time < 10 days.

.........operate early after SCRT especially in elderly

..........................or? Delayed surgery
Short course and delayed surgery?
## SCRT and delayed op - 4 studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Patients</th>
<th>Operative Rate</th>
<th>Pathologic Complete Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden (Radu)</td>
<td>2008</td>
<td>46 pts</td>
<td>80%</td>
<td>11%</td>
</tr>
<tr>
<td>UK (Hatfield)</td>
<td>2009</td>
<td>43 pts</td>
<td>61%</td>
<td>RO: 85%</td>
</tr>
<tr>
<td>Sweden (Pettersson)</td>
<td>2012</td>
<td>112 pts</td>
<td>pCR 8%</td>
<td></td>
</tr>
<tr>
<td>Canada (Faria)</td>
<td>2014</td>
<td>52 pts</td>
<td>100%</td>
<td>RO: 100%</td>
</tr>
</tbody>
</table>
What about young patients?
Comparable survival for young rectal cancer patients, despite unfavourable morphology and more advanced-stage disease.

Orsini RG et al

Population-based data from the Netherlands Cancer Registry (NCR) were used (1989-2010). Younger patients (≤40 years) were compared with middle-aged patients (41-70 years)

FINDINGS:
37,056 patients were included (≤40 years n = 1,102).
Young patients were more likely to have stage III (33.8% v 27.8%) and stage IV (24.3% v 19.6%) disease (p < 0.001).
Young patients also presented more frequently with mucinous tumours (10.8% v 9.0%), signet cell carcinomas (2.6% v 0.6%) and poorly differentiated tumours (16.6% v 12.3%) (p = 0.001).
The treatment of stage I-III patients did not differ between the two groups, except regarding adjuvant chemotherapy, which was more often given to young patients (24.3% v 14.4%, p < 0.001).
Adjuvant chemotherapy was associated with improved survival in stage I-III patients (RER 0.76, 95% CI 0.70-0.83).
Young age was a prognostic factor for better survival in stage I-III patients (RER 0.82 CI 0.71-0.94).

Young patients present with more advanced disease and have more unfavourable tumour characteristics compared with middle-aged patients. Despite these characteristics, survival rates are equal, and young age is a prognostic factor for better survival (stage I-III).
Conventional European CRT

- 3 or 4 field CT planned volume (MLC)

Capecitabine 825mg/m² bd for 7/7 per week

Radiotherapy 45 GY in 25# *

(* to 5040Gy/28#
............and up to 54gy boost)
Chemoradiotherapy

- 4732 pts
- 77 phase II and III trials
- pCR 13.5%
- Adding 2nd drug to 5FU and total radiation dose were associated with higher pCR (small studies 20-30%)

Timing of surgery after LCRT?

ESMO: “4-8 weeks after END of LCRT”
Regression of Rectal Cancer with Radiotherapy with or without Concurrent Capecitabine and Optimising the Timing of Surgical Resection

A. S. Dhadda*, A. M. Zaitouny, E. M. Bessell

Aims: To determine tumour regression (volume-halving time) obtained after chemo/radiotherapy, and thereby the ideal interval between the start of treatment and surgery in order to obtain a high rate of complete response.

Materials and methods: In total, 106 patients with cT3,4 rectal cancer who received preoperative radiotherapy alone or concurrently with capecitabine chemotherapy at Nottingham City Hospital, UK were studied. The rectal tumour volume visible on the computed tomography planning scan was compared with the residual pathological volume and the tumour volume-halving time calculated. The radiotherapy response was graded according to the Mandard system.

Results: Fifty-three patients had radiotherapy alone, with 53 patients having concurrent chemoradiotherapy. The median tumour volume-halving time was found to be 14 days and not influenced by the addition of chemotherapy. The Mandard score, the interval from the start of treatment to surgery and the tumour volume-halving time were statistically associated with tumour regression. The median tumour volume in our series of 54 cm³ would require an interval of 20 weeks after the start of treatment to surgery to regress to 0.1 cm³ (10 volume-halving times; 140 days).

Conclusions: The initial tumour volume and median volume-halving time provide the best estimates for determining the optimum length of interval between the completion of preoperative chemo/radiotherapy and surgery. Probably need to wait longer than the standard 8 weeks..............maybe even even longer for larger tumours.
Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer.


All evaluable patients who underwent preoperative CRT for rectal cancer between 2009 and 2011 were selected from the Dutch Surgical Colorectal Audit. The interval between radiotherapy and surgery was calculated from the start of radiotherapy. The primary endpoint was pathological complete response (pCR).

1593 patients. The median interval between radiotherapy and surgery was 14 (range 6-85, interquartile range 12-16) weeks.

Outcome measures were calculated for intervals of less than 13 weeks (312 patients), 13-14 weeks (511 patients), 15-16 weeks (406 patients) and more than 16 weeks (364 patients). Age, tumour location and R0 resection rate were distributed equally between the four groups. Significant differences were found for clinical tumour category (cT4: 17·3, 18·4, 24·5 and 26·6 per cent respectively; P = 0·010) and clinical metastasis category (cM1: 4·4, 4·8, 8·9 and 14·9 per cent respectively; P < 0·001).

Resection 15-16 weeks after the start of CRT resulted in the highest pCR rate (18·0%; P = 0·013), with an independent association (hazard ratio 1·63, 95 per cent confidence interval 1·20 to 2·23).

CONCLUSION: Delaying surgery until the 15th or 16th week after the start of CRT (10-11 weeks from the end of CRT) seemed to result in the highest chance of a pCR.
IMRT for rectal cancer?
Patients with Inflammatory bowel disease (IBD)

EBRT should be used with caution

Grade 3 toxicity

Acute: 20% (Dutch Non-IBD data – 10.1%*)
Late: 15% (Late small bowel – 2-9%**)
Efficacy and safety of neoadjuvant intensity-modulated radiotherapy with concurrent capecitabine for locally advanced rectal cancer

Wang L, Li ZY, Li ZW, Li YH, Sun YS, Ji JF, Gu J, Cai Y (BEIJING, CHINA)

OBJECTIVE:
The objective of this study was to retrospectively review the efficacy, toxicity, and surgical complications following IMRT in patients who have rectal cancer.

PATIENTS:
This study included patients who underwent IMRT with gross tumor volume/clinical target volume of 50.6/41.8 Gy in 22 fractions with concurrent capecitabine.

RESULTS:
• 260 patients
• pCR 18.5%
• The grade 3 toxicity rate was 5.8% and there were no grade 4 toxicity and perioperative mortality
• The 30-day post-op and severe complication (≥grade 3) rates were 23.1% and 2.7%.
• The anastomotic leakage rate was 3.3% (5/152).

CONCLUSION:
IMRT-Cap regimen used to treat rectal cancer in this study has a high efficacy rate and a low toxicity rate.
CRT with Irinotecan
Irinotecan+5-fluorouracil with concomitant pre-operative radiotherapy in locally advanced non-resectable rectal cancer: a phase I/II study.


31 patients

MRI: 19/24 (79%) reduction in T-stage, 7pts cCR

OP: 28pts – 81% clear CRM

Ir: Irinotecan 60mg/m^2 wk1-4

5FU 200mg/m^2/day for 5 weeks

Radiotherapy 45 GY in 25# *
Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes.


Ir: Irinotecan 60mg/m² wk1-4

Capecitabine 650mg/m² bd for 7/7 per week

Radiotherapy 45 GY in 25# *

110 patients (MRI demonstration of tumour threatening (≤ 2 mm) or involving mesorectal fascia)

MRI: 72pts (67%) reduction in T-stage

OP: 107pts – 95 (89%) clear CRM (>2mm)

pCR: 22%
Capecitabine 650mg/m² bd for 5/7 per week

Radiotherapy 45 GY in 25# *

Ir: Irinotecan 60mg/m² wk1-4

Capecitabine 900mg/m² bd for 5/7 per week

Radiotherapy 45 GY in 25# *

Randomise

Tumour < 1mm from CRM
CRT with Irinotecan....?

...............under investigation
CRT with Oxaliplatin
CRT with Oxaliplatin

CAO/ARO/AIO-04 (1)
Ox5FU
1265pts, pCR 17 v 13% p=0.038
Increased toxicity with oxaliplatin arm

ACCORD 12/0405-Prodige 2 (2)
OxCap
598pts, pCR 19.2 v 13.9% NS
Increased toxicity with oxaliplatin arm

STAR-01 (3)
Ox5FU
747pts, pCR 16 v 16% NS
Increased toxicity with oxaliplatin arm

(NSABP) R-04 (4)
OxCap
1608pts
No sig diff in pCR
Increased toxicity with oxaliplatin arm

PETACC6 (5)
RCT Cap v OxCap with RT and adjuvant
1094pts
Reduced treatment compliance
(>90% dose: 91 v 63%)
Increased toxicity
(G3/4: 15.1 v 36.7%)
pCR 11.3 v 13.3% (p=0.31)

No

2: Gerard: JCO 28(10) 1638-44, 2010
4: O’Connell: JCO May 2014
5: Schmoll: ASCO 2013
CRT with VEGF inhibitors
<table>
<thead>
<tr>
<th>AVASTIN studies</th>
<th>Treatment</th>
<th>Number pts</th>
<th>pCR</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasparini 2012</td>
<td>RT + C + BVZ</td>
<td>43</td>
<td>14% (51% few cells)</td>
<td>CD34 Ki67 VEGFR-2</td>
</tr>
<tr>
<td>Volenik 2011</td>
<td>RT + C + BVZ</td>
<td>61</td>
<td>13%</td>
<td>62% developed peri-operative complications</td>
</tr>
<tr>
<td>Resch 2012</td>
<td>RT + C + BVZ</td>
<td>8</td>
<td>25%</td>
<td>Intestinal bleed Diarrhoea STOPPED</td>
</tr>
<tr>
<td>Crane 2010</td>
<td>RT + C + BVZ</td>
<td>25</td>
<td>32%</td>
<td>3 wound complications requiring surgical intervention</td>
</tr>
<tr>
<td>Spigel 2012</td>
<td>RT + 5FU + BVZ</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Willett 2009</td>
<td>RT + 5FU + BVZ</td>
<td>32</td>
<td>Regression in all pts (mean 5.0 – 2.4cm)</td>
<td>VEGF, IL6 sVEGFR1 PIGF, CECs (post-op complications)</td>
</tr>
<tr>
<td>Kennecke 2012</td>
<td>RT + C + BVZ + Ox</td>
<td>42</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

**Efficacious**

**Tolerance??**
Dual REctal Angiogenesis or MEK inhibition radioTHERAPY

Diagnostic biopsy

Capecitabine 825mg/m² bd for 7/7 per week

Radiotherapy 45 GY in 25#

AZD 2171 or AZD6244

DCE-MRI: √√ √

FLT-PET: √ √

Blood: √ √ √ √ √ √
9 out of 17 patients have had an ECPR* (1: exc – NET)

- cCR: 4
- pCR: 2 (TRG 1)
- Microfoci: 2 (TRG 2)
- cCR relapse: 1 (10 months after RT completed)

53% 41% cCR/pCR

ECPR: Excellent Clinical or Pathological Response
Operative versus non-operative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results.


METHODS:
265 patients with rectal adenocarcinoma considered resectable were treated by neoadjuvant chemoradiation (CRT; 5040cGY / 28# with 5FU/FA)
Patients with incomplete clinical response treated by surgery resulting in stage p0 were compared to patients with complete clinical response treated by nonoperative treatment.

RESULTS:
Overall and disease-free 10-year survival rates were 97.7% and 84%.
In 71 patients (26.8%) complete clinical response was observed following CRT (Observation group). Five-year OS and DFS rates were 88% and 83%, respectively, in Resection Group and 100% and 92% in Observation Group.

CONCLUSIONS

cCR rectal cancer disease is associated with excellent long-term results irrespective of treatment strategy. Surgical resection may not lead to improved outcome in this situation and may be associated with high rates of temporary or definitive stoma construction and unnecessary morbidity and mortality rates.
Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis.


METHODS
Preoperative chemoradiotherapy (45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy). Patients who had a clinical complete response were offered management with the watch-and-wait approach. We also included patients with a clinical complete response managed by watch and wait across three neighbouring UK regional cancer centres, whose details were obtained through a registry. For comparative analyses, we derived one-to-one paired cohorts of watch and wait versus surgical resection using propensity-score matching (including T stage, age, and performance status). The primary endpoint was non-regrowth disease-free survival from the date that chemoradiotherapy was started, and secondary endpoints were overall survival, and colostomy-free survival.

FINDINGS
• 259 patients
• 31 had a cCR (12%), managed by watch and wait.
• A further 98 patients were added to the watch-and-wait group via the registry.
• Of the 129 patients managed by watch and wait (median follow-up 33 months [IQR 19-43]), 44 (34%) had local regrowths (3-year actuarial rate 38% [95% CI 30-48]).
• 36 (88%) of 41 patients with non-metastatic local regrowths were salvaged.
• In the matched analyses no differences in 3-year non-regrowth DFS were noted between watch and wait and surgical resection (88% [95% CI 75-94] with watch and wait vs 78% [63-87] with surgical resection; time-varying p=0.043).
• Similarly, no difference in 3-year OS was noted (96% [88-98] vs 87% [77-93]; time-varying p=0.024).
• By contrast, patients managed by watch and wait had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% [95% CI 64-82] vs 47% [37-57]; hazard ratio 0.445 [95% CI 0.31-0.63; p<0.0001), with a 26% (95% CI 13-39) absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.

A substantial proportion of patients with rectal cancer managed by watch and wait avoided major surgery and averted permanent colostomy without loss of oncological safety at 3 years.
End-points for trials

Nature Reviews Clinical Oncology

The NCRI CTRad Academia-Pharma Joint Working Group Consensus Statement on Drug-Radiotherapy Combinations

Follow ESMO guide-lines for SCRT and LCRT !!

Adjuvant chemo for rectal cancer.................?
If operable disease and need RT........SCRT and not LCRT
Timing after SCRT........2-3 days (ASAP in elderly)
Timing after LCRT..........4-8 wks (? longer)
SCRT and delayed op........interesting

LCRT and fluoropyrimidine is standard
+ oxaliplatin.....no
+ irinotecan......under investigation
+ VEGFi..........under investigation........? No BVZ

Assessment of response.............path and MRI