Role of Radiotherapy in Rectal cancers

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TATA MEMORIAL CENTRE

Tata Memorial Hospital (TMH)

Advanced Centre for Treatment, Research & Education in Cancer (ACTREC)

Centre for Cancer Epidemiology (CCE)
Role of local treatment for cancer

1: improved survival
2: local control
3: QOL (sphincter preservation)
# Post-Op ChemoRT vs Surgery

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>LF</th>
<th>DM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG 7175</td>
<td>Surgery Alone Chemo + RT</td>
<td>24%</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>1975-80</td>
<td>RT (40-48 Gy) Chemo (MeCCNU/5FU)</td>
<td>20%</td>
<td>30%</td>
<td>52%</td>
</tr>
<tr>
<td>202 pts</td>
<td></td>
<td>27%</td>
<td>27%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11%</td>
<td>26%</td>
<td>67%</td>
</tr>
<tr>
<td>NSABP R01</td>
<td>Surgery Alone RT (46-47 Gy)</td>
<td>25%</td>
<td>26%</td>
<td>43%</td>
</tr>
<tr>
<td>1977-86</td>
<td>Chemo (MOF)</td>
<td>22%</td>
<td>24%</td>
<td>53%</td>
</tr>
<tr>
<td>555 pts</td>
<td>RT (40-48 Gy)</td>
<td>26%</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>

(Males: 5-yr OS significant)

(5-yr DFS significant)
## Post-Op ChemoRT vs Single Modality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>LF</th>
<th>DM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP R02</td>
<td>Chemo (MOF or 5FU/LV) Chemo + RT (50.4 Gy)</td>
<td>13%</td>
<td>8%</td>
<td>NS (DFS &amp; OS)</td>
</tr>
<tr>
<td>1987-92</td>
<td></td>
<td></td>
<td>(p=.02)</td>
<td></td>
</tr>
<tr>
<td>694 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo NCCTG</td>
<td>RT (45-50 Gy) RT + Chemo (MeCCNU/Bolus 5FU)</td>
<td>25%</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>1980-1986</td>
<td></td>
<td></td>
<td>29%</td>
<td>53%</td>
</tr>
<tr>
<td>204 pts</td>
<td></td>
<td></td>
<td>(5-yr Act p=.025)</td>
<td></td>
</tr>
</tbody>
</table>
Rectal Cancers

“In contrast to colon cancer, there is a significant risk of local-regional failure as the only or first site of recurrence in patients with curative resected rectal cancer.”

– Stage I 5% to 10%
– Stage II 25% to 30%
– Stage III 50% or higher

“Combined post-op CT+ RT improves local control and survival in stage II and III patients and is recommended”

(NIH Consensus Conference on Adjuvant Therapy for Patients with Colon and Rectal Cancer, JAMA, Sept. 19, 1990)
Local-Regional Failure Characteristics

- Main prognostic determinant is Stage
- Local-Regional failure associated with significant morbidity
- Major mode of failure (+/- distant metastases)
- Most failures within 2-3 yrs and rare after 5 yrs (+/- distant metastases)
- Successful salvage is rare
Radiation therapy and Rectal cancers

Review by Swedish council of technology Assessment in Health care (SBU) Data-42
RCT’s, 3 Metaanalysis 131 scientific articles with 25,351 patients.

- Overall 5 yr survival has slowly improved compared to colon cancers. 70% vs 50%
- Mortality has decreased.
- Local failure rates at 5 years after TME have decreased from 28% to 10-15%.
Local recurrences in rectal cancer has in populations decreased from above 30% to about 8%

Improved surgery and radiotherapy
Developments in 1980’s

In Sweden: preoperative RT
5x5 Gy
local recurrence ↓
survival ↑

Heald: TME surgery
local recurrence ↓
Heterogeneity in rectal cancers

Rectal cancer represents a broad spectrum of Disease requiring tailored treatment regimens to maximize the outcome

M.Mohiuddin - IJROBP - 1993
The heterogeneity problem

- The Good
  stage I
- The Bad
  stage II-III
- The Ugly
  Unresectable
  Recurrent

Courtesy Dr V Valentini
Treatments- Early tumours

cT2 rectal cancers and cT1 with high risk factors are adequately treated with TME alone providing the nodes are negative (N0).
RT in treatment of early tumors

- pT1 with adverse pathologic factors
- pT2 without adverse factors
- Patients with co-morbidity or refuse surgery can be treated with local excision and postoperative radio(chemo)therapy
The bad tumors - Treatment of stage II - III tumors
Randomized trials after 2000

- Short ERT
  - Dutch Trial
  - MRC C07

- Long ERT
  - EORTC 22921
  - FFCD 9203
  - Polish Trial
  - TROG Trial
  - Scandinavian

Short RT+TME vs TME
Short RT+TME vs TME

Long RT vs Chemo RT
Long RT vs Chemo RT
Long RT vs Chemo RT

Winner
Short RT
Short RT
Issues

- Preop or postop?
- TME Alone or TME + RT?
- Short or long course?
- With or without chemotherapy
- +/- targeted drug?
- What target?
Pre-op RT

- To increase the probability of tumor control in the pelvis and to increase the frequency of sphincter preservation.

- To stop further dissemination of metastatic clonogens pending removal of the primary tumor.

CAO/ARO/AIO  Sauer et al., NEJM 2004
50.4 Gy + 5 FU preop vs 55.8 Gy + 5 FU postop

CAO/ARO/AIO-94

Preop. RCT:
• Local Control +
• Toxicity +
• Compliance +
• Sphincter +
• Risk: overtreatment (UICC I) -

No survival benefit

Sauer R et al., N Engl J Med 2004

Standard of care
<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Survival</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre – Post 5y %</td>
<td>Pre – Post 5y %</td>
</tr>
<tr>
<td>UPPSALA Trial</td>
<td>471</td>
<td>42 - 38</td>
<td>86 - 77</td>
</tr>
<tr>
<td>NSABP R03</td>
<td>254</td>
<td>75 - 66</td>
<td>89 - 89</td>
</tr>
<tr>
<td>CAO/ARO/AIO 94</td>
<td>823</td>
<td>74 - 76</td>
<td>94 - 85</td>
</tr>
<tr>
<td>Korean Trial</td>
<td>240</td>
<td>76 - 74</td>
<td>95 - 94</td>
</tr>
<tr>
<td>MRC C07</td>
<td>1350</td>
<td>70 - 68</td>
<td>96 - 89</td>
</tr>
</tbody>
</table>

* DFS p=0.011

Pahlman L et Al – Ann Surg - 1990
Sauer R et Al – NEJM – 2004
Roh MS et Al – JCO - 2009
Park J et Al – Cancer - 2011
## Pre- vs Post-operative RT

### Randomized studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pts</th>
<th>Sphincter Sav. Pre – Post %</th>
<th>Grade 3 Tox Pre – Post %</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPPSALA Trial</td>
<td>471</td>
<td>59 - 58 ns</td>
<td>20 - 41 0.03</td>
</tr>
<tr>
<td>NSABP R03</td>
<td>254</td>
<td>44 - 34 ns</td>
<td>52 - 49 ns</td>
</tr>
<tr>
<td>CAO/ARO/AIO 94</td>
<td>823</td>
<td>39 - 20 0.004</td>
<td>28 - 39 0.005</td>
</tr>
<tr>
<td>Korean Trial</td>
<td>240</td>
<td>68 - 42 0.008°</td>
<td>15 - 16 ns</td>
</tr>
<tr>
<td>MRC C07</td>
<td>1350</td>
<td>61 - 63 ns</td>
<td>na - na -</td>
</tr>
</tbody>
</table>

° 0-5 cm

na = not available

Pahlman L et Al – Ann Surg - 1990
Sauer R et Al – NEJM – 2004
Roh MS et Al – JCO - 2009
Park J et Al – Cancer - 2011
Randomized trials after 2000

- **Survival**: No significant survival improvement
- **Local control**: Significant improvement of Local Control
- **Toxicity**: Significant decrease of Acute toxicity
Consensus

All patients with cT3 rectal cancer who require additional therapy (chemoradiation or short course radiotherapy) should receive it preoperatively.
Issues

- Preop or postop? - Preop better
- TME Alone or TME + RT?
- Short or long course?
- With or without chemotherapy
- +/- targeted drug?
- What target?
**Treatment - Intermediate**

12 years Update of Dutch Trial

![Graph showing overall survival probability over years since surgery](chart.png)

Overall Survival

- **TME 48.8%**
- **RT + TME 47.6%**

**P = 0.891**

By the courtesy of C. Van de Velde
**Treatment - Intermediate**

12 years Update of Dutch Trial

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>RT + TME (295)</th>
<th>TME (298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal cancer</td>
<td>40.3%</td>
<td>51.0%</td>
</tr>
<tr>
<td>Other</td>
<td>59.7%</td>
<td>49.0%</td>
</tr>
</tbody>
</table>

P = 0.01

By the courtesy of C. Van de Velde
Quality of TME

- Commented by Pathologist

- Minimal 12-15 lymph nodes retrieval a must during grossing

- Reporting on CRM
Short or long course?
Preop RT - Short or long course?

RT alone
5 Gy x 5# (1 week Mon – Fri)

Surgery TME (Next week)

Chemoradiation 50Gy / 25# + Capecitabine

Response assessment after 6 weeks and surgery
Circumferential Resection Margins

Nagtegaal I et Al - JCO – 2008
Optimized RT
Circumferential Resection Margins

Preop Short RT

Preop Long RTCHEM

CRM + 13 % 4 %

P = 0.017

Bujko K et Al - Radioth Oncol – 2004
CT or MRI?

- MDCT has enabled thin sections and high quality reformats

- Yet MRI has shown superiority over MDCT for T staging and CRM status

- Current recommendation is MRI pelvis for local staging & MDCT chest and abdomen for distant workup.

- However in resource constrained environments, one can use MDCT with reformations.
Mesorectal fascia free (arrow) = CRM negative
Tumor reaches into perirectal fat, T3 CRM -
Rectal tumor(*) reaching MRF on left (white arrow) → T3 
CRM + 
Right internal iliac node (arrowhead) 
Small arrow – right perirectal node touching MRF
A. Pre-chemoradiotherapy & B. postchemoradiotherapy status.

Replacement of intermediate signal intensity in A by dark hypointensity is s/o fibrosis.
**Circumferential Resection Margins**

**CRM- vs CRM+**

Phased array MRI is highly accurate to predict CRM
Circumferential Resection Margins

Quirke P et Al - Lancet – 2009
Therefore: tailored treatment

“small” T3 short-term RT and TME

“large” T3 long-term CRT and TME

T4 long term CRT and TME
? With or without chemotherapy
RTCT rather than RT pre- or postoperatively

If prolonged course RT (45-50 Gy), we have good evidence that

RTCT is superior to RT alone

both pre- and postoperatively
RTCT rather than (the same) RT pre- or postoperatively?

- Old US postop trials (GITSG, NCCTG) + Cafiero
- Old negative preop trials (all inop T4)
- Three modern preop trials

Locally advanced (90% cT3, 10% op cT4):
- **EORTC 1011 pts** (Bosset et al NEJM 2006;355;1114-23)

- **FFCD 762 pts** (Gerard et al JCO 2006;24:4620-5)

Inoperable cT4:
- **Nordic LARCS 209 pts** (Braendengen et al JCO Aug 2008;)

Which Chemotherapy

- 5-FU explored in the randomised trials (oral likely equivalent)
- Capecitabine - convenient

- Now “everyone” use combinations (numerous publications)

All claim superiority, pCR considered an important endpoint (Glynne-Jones Red J 2006;66:319-20), all recognize more toxicity
More studies: for locally advanced tumors

<table>
<thead>
<tr>
<th></th>
<th>CRT</th>
<th>RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFCD 9203</td>
<td>8.1%</td>
<td>16.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>7.6-9.6%*</td>
<td>17.1%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Gerard, JCO 2006
Bosset, NEJM 2006
Issues

- Preop or postop? - Preop better
- TME Alone or TME + RT?
- Short or long course? - “small” T3 short-term RT+TME
  “large” T3+T4 long-term CRT and TME
- With or without chemotherapy – CTRT better
- +/- targeted drug?
- What target?
RTCT with targeted drug?

- Experimental evidence (but this can be found in at least one system for virtually everything)

Explored clinically (and as usual, "promising" activities in the phase I/II trials)

- At least one randomised phase II trial, EXPERT-C, accrual completed, n=164)

- Should not be used, but of course explored properly

All phase II trials!
• What target?
Why local failure in spite of TME or, what should be irradiated?

- Poor surgery due to incomplete TME?
- Remaining tumour cells in tissues not removed, e.g. in the lateral nodes?

Population-based study in Stockholm 1995-2004, 2495 pts, 2315 resections and TME, 155 recurrences (65(4%) RT+, 90(12%) RT-) Most recurrences anastomotic (high, non-RT pts), few from the lateral nodes

Location of the local failures (n=83)

Indicates that the target can be slightly modified, i.e. decreased

Syk et al IJROBP 2008
Br J of surgery 2009

The yellow box shows beam limits
## Rectal receiving NACTRT at TMH
### July 2006 Dec 2010  N=182

<table>
<thead>
<tr>
<th>Disease at presentation</th>
<th>Underwent surgical resection</th>
<th>Reasons for not undergoing surgical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable (n=108)</td>
<td>R0: 88 (81%) R1: 4 (3.7%)</td>
<td>6- Refused Surgery 5 – D.M 1- Died post CRT 4- Local progression</td>
</tr>
<tr>
<td>Unresectable (n=74)</td>
<td>R0: 33 (44.5%) R1: 6 (8%)</td>
<td>3- Refused Surgery 25- Locally unresectable post CRT 6 - D.M 1- Died post CRT</td>
</tr>
</tbody>
</table>

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**pCR rate - 21%**
Multivariate analysis for factors affecting DFS and OAS

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initially resectable vs. Unresectable</td>
<td>(p=0.001)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>pT stage</td>
<td>(p=0.16)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>pN stage</td>
<td>(p=0.002)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>pretreatment CEA levels more than 5ng/ml</td>
<td>(p=0.05)</td>
<td>(p=0.003)</td>
</tr>
<tr>
<td>signet ring cell carcinoma</td>
<td>(p=0.05)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>TRG ≤3</td>
<td>(p=0.33)</td>
<td>(p=0.04)</td>
</tr>
<tr>
<td>TRG &gt;3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: (p-values are provided for each factor's impact on DFS and OAS.)
IMRT plan for rectal cancer
5x5 Gy with delayed surgery as an alternative to radiochemotherapy

- Much simpler, but has it the same tumour down-staging and down-sizing effect?
- The simple answer is that we don’t know
- Many have successful anecdotal patients
- Retrospective study in Uppsala (Radu et al., Radiother Oncol. Aug 2008;87:343-9)
Local recurrence

Retreatment: Storm 97.03

Patients Selection

Pelvic Recurrence F0-3, M0,
Previous ERT (45-54 Gy)

Study Schema:

ERT 30+10 Gy
(120 cGy b.i.d.)

5FU 225 mg/m² PVI

Valentini V et Al - IJROBP – 2006
<table>
<thead>
<tr>
<th></th>
<th>59 pts %</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 surgery</td>
<td>36</td>
</tr>
<tr>
<td>pCR</td>
<td>8.5</td>
</tr>
<tr>
<td>Local Control (5y)</td>
<td>39</td>
</tr>
<tr>
<td>DFS (5y)</td>
<td>29</td>
</tr>
<tr>
<td>OS (5y)</td>
<td>39</td>
</tr>
<tr>
<td>Overall late toxicity</td>
<td>12</td>
</tr>
</tbody>
</table>

Median follow-up: 3 years
Wait & Watch only post CRT

Chemoradiation

Complete clinicoradiological response

No surgery only Wait & Watch policy ??

EMERGING CONCEPT – Only for research
173 patients

Stage II 63% Stage III 21% (tumor within 7 cm of anal verge)

RT 50.4 – 54 Gy + Inj 5FU
Assessment for surgery at 8 weeks

67 (39%) Complete response

Strict follow up
4- Local rec
3- Local excision
1- Brachytherapy
1- APR at 16 months

OAS 93% at 5 years

DFS 85% at 5 years
192 patients
CRT 50.4 Gy/ 28# + capecitabine.

Assessment of response 6- 8 weeks

Complete clinicoradiolocal response
21 patients

10 of 21 patients (48%) spared APR/colostomy

Cumulative probability of 2-year DFS - 89% (95% CI, 43% to 98%), and OS is 100%.
Compliance to NACTRT and surgery

- Proper counselling by the surgeon and the Radiation Oncologist

- If good response wait of >6 weeks

- More attempt for sphincter saving surgeries like LAR and ISR
TAKE HOME

- Preoperative RT preferred + TME
- Small tumors 5x5 Gy
- Large tumors: CRT

Reduced local recurrence
Some studies survival benefit!

Locally recurrent cancers can be treated with
reirradiation +/- Sx

Mutidisciplinary team