Complete Clinical Response Following Neoadjuvant Chemoradiation

Operate or Observe?

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Disclosures

• I have no disclosures
Standard of Care in locally advanced rectal cancer

• Multimodality therapy

• Preoperative chemoradiotherapy or radiotherapy followed by en bloc resection of the tumour bearing rectum and mesorectum with negative margins

• Restoration of continence if possible

• Oncologic outcomes equal to or surpass colon cancer
Patients with an apparent complete clinical response to neoadjuvant therapy should be offered a definitive resection. Grade of Recommendation: Strong recommendation based upon moderate quality evidence, 1B.
Multimodality therapy - Risks

• Quality of life issues:
  • pain, non healing, permanent colostomy
  • Bowel, bladder and sexual dysfunction

• Interest in applying radiation and chemotherapy selectively
  • Patient selection
  • Maximize benefit and minimize toxicity

• Selective surgery?
Rationale for selective surgery

• Success of Neoadjuvant Chemoradiation

• 10-20% of patients achieve pCR

• pCR associated with better outcomes
  • 5 yr disease free survival and overall survival

Meng et al Biosci Trends 2014, Park et al JCO 2012
### Rationale for selective surgery - Complete pathologic response

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Disease stage</th>
<th>Preoperative chemotherapy</th>
<th>Preoperative RT, Gy</th>
<th>Interval to surgery, weeks</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr-Gama</td>
<td>265</td>
<td>T2-T4</td>
<td>Concomitant fluorouracil and folinic acid</td>
<td>50-4</td>
<td>8 to assessment</td>
<td>27% (observation group); 7%</td>
</tr>
<tr>
<td>EXPERT</td>
<td>77</td>
<td>Low T3; CRM threatened; tumour ≤5 mm into mesorectum; T4; T1-T4 N2</td>
<td>Induction: oxaliplatin and capcitabine; Concomitant: capcitabine</td>
<td>50-4-54</td>
<td>6</td>
<td>24%</td>
</tr>
<tr>
<td>RTOG 0012</td>
<td>106</td>
<td>Distal T3 or T4</td>
<td>CVI fluorouracil; or CVI fluorouracil and irinotecan</td>
<td>55-2-60; or 50-4-54</td>
<td>7</td>
<td>26% both groups</td>
</tr>
<tr>
<td>EORTC 22921</td>
<td>1011</td>
<td>T3 or T4</td>
<td>Fluorouracil and folinic acid</td>
<td>45</td>
<td>5-4</td>
<td>53% (radiation-alone group) vs 13% (CRT groups)</td>
</tr>
<tr>
<td>FFC0 9203</td>
<td>733</td>
<td>T3 or T4</td>
<td>Fluorouracil and folinic acid</td>
<td>45</td>
<td>3-10</td>
<td>3.7% (radiation-alone group) vs 11.7% (CRT group)</td>
</tr>
<tr>
<td>CORE</td>
<td>85</td>
<td>Low T3; CRM threatened; T4; T1-T4 N2</td>
<td>Oxaliplatin and capcitabine</td>
<td>45</td>
<td>6-8</td>
<td>13%</td>
</tr>
<tr>
<td>CALGB 89901</td>
<td>32</td>
<td>T3 or T4</td>
<td>Oxaliplatin and fluorouracil</td>
<td>50-4</td>
<td>4-6</td>
<td>25%*</td>
</tr>
</tbody>
</table>

*25% pCR in 22 patients on phase II oxaliplatin dose. RT=radiotherapy. CRM=circumferential resection margin. RTOG=Radiation Therapy Oncology Group. CVI=continuous venous infusion; EORTC=European Organisation for Research and Treatment of Cancer. FFCO=Fédération Francophone de Cancérologie Digestive. CORE=capecitabine, oxaliplatin, radiotherapy, and excision. CALGB=Cancer and Leukemia Group B.

**Table 1: Selected trials of preoperative CRT for rectal cancer**

O’Neill et al. Lancet Oncol 2007; 8:625-33
A 52 y.o. male T3N0M0 lesion 1 cm above the dentate line lying on top of the upper sphincter at the anorectal junction

• Neoadjuvant chemoRT

• On re-examination at 8 weeks:
  • no palpable lesion, no visible lesion on rigid sig, no visible lesion on flex sig, biopsies negative; MRI scar no visible tumour
Watch and wait strategy

• Nakagawa et al 2002

• Habr Gama 2004
  • Clinical response cCR surrogate marker for cPR
  • Intensive follow up regimen

• Critique
  • Follow up for 12 DF months prior to entry into the trial
  • Patients who failed in the first 12 months were excluded from analysis
  • Biases the results in favour of the observation group
# Watch and Wait - Selected Studies

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of patients observed</th>
<th>Number of patients operated</th>
<th>Median follow-up (months)</th>
<th>cCR</th>
<th>Local regrowth</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass 2011 [36]</td>
<td>21</td>
<td>20</td>
<td>15 (observed)</td>
<td>100%</td>
<td>1 patient</td>
<td>2-year OS 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35 (operated)</td>
<td></td>
<td></td>
<td>2-year DFS 89%</td>
</tr>
<tr>
<td>Dalton 2012 [31]</td>
<td>12</td>
<td>37</td>
<td>25.5 (mean)</td>
<td>24%</td>
<td>50%</td>
<td>Disease free at follow-up</td>
</tr>
<tr>
<td>Habr-Gama 2014 [17]</td>
<td>93</td>
<td>90</td>
<td>60</td>
<td>49%</td>
<td>31%</td>
<td>5-year OS 91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-year LRFS 69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-year DFS 68%</td>
</tr>
<tr>
<td>Smith 2015 [34]</td>
<td>73</td>
<td>72</td>
<td></td>
<td>26%</td>
<td></td>
<td>4-year OS 91% (obs) vs. 95% (surg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-year DSS 91% (obs) vs. 96% (surg)</td>
</tr>
<tr>
<td>Smith 2015 [35]</td>
<td>18</td>
<td>30</td>
<td>68.4 (mean)</td>
<td>1 patient</td>
<td></td>
<td>Alive with pelvic disease at 54 months</td>
</tr>
</tbody>
</table>
Issues

• Can we predict pCR prior to pathologic evaluation?

• What is the risk for locoregional failure (regrowth)?

• What is the chance of successful salvage surgery?

• What is the long term survival following salvage?

*Keep in mind these patients have a high rate of cure*
Can we predict pCR prior to pathologic evaluation?

• cCR surrogate for pCR
• Following nCRT
  • cCR 20-30%
  • pCR 10-20%

• Clinical assessment of response is unreliable
  • Clinical examination (DRE, Endoscopy)
  • Sensitivity of 25% specificity of 60-90% for excluding residual disease
  • False positive rate for pCR based on clinical assessment was 27%¹
  • Addition of full thickness biopsy?
    • poor healing, pain, scarring, affect on function, planes on MRI

¹Smith et al DCR 2014
Strict definition of cCR

• Complete clinical response
  • Absence of induration in the rectal wall
  • Whitening of the mucosal surface
  • Telangiectasia

• Incomplete response
  • Residual deep ulceration
  • Superficial ulcers or irregularities (even if confined to the mucosa)
  • Palpable nodule/induration on DRE

Habr Gama, 2014
Cross sectional imaging

- PET scan - not reliable

- High resolution MRI
  - Comparison of pre and post treatment MRI
  - MRI tumour regression grade
  - Grade 1 or 2 observation
    - TRIGGER trial

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**TABLE 30-3. MRI tumor regression grade (mrTRG)**

<table>
<thead>
<tr>
<th>mrTRG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tumor bed with low signal intensity signaling fibrosis with no residual intermediate tumor signal</td>
</tr>
<tr>
<td>2</td>
<td>Tumor bed with predominance of fibrosis with minimal residual intermediate tumor signal</td>
</tr>
<tr>
<td>3</td>
<td>Substantial intermediate intensity tumor signal present, but does not predominate over low intensity fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>5</td>
<td>No change from baseline</td>
</tr>
</tbody>
</table>

Mercury study group, Patel Am J Roentgenol. 2012
A. Complete response
B. Equivocal response
C. Residual tumour
D. Smooth scar
E. Small ulcer
F. Residual tumour


coefficient
T2W- MRI hypointense residual wall thickening  White scare with stenosis distortion  DWI absence of diffusion restriction indicating CR

What is the risk for locoregional failure (regrowth)?

• Updated report by Habr-Gama
  • True risk for local regional failure is approximately 30%
  • Most tumour growth is in the first 12 months

• Undetected viable tumour
  • Risk of nodal metastases in patient with pCR is between 5-9%
  • Tumour growth deep to the mucosa delayed recognition
  • Radiation fibrosis may interfere with evaluation

• Follow up strategy - intense
  • DRE/ endoluminal examination every 3 months
  • Biopsy of suspicious lesions
  • Repeat MRI imaging 3-6 months for the first two years
  • CEA
What is the chance I can perform successful salvage surgery?

Systematic review Heriot et al DCR 2017

• Rates of salvage surgery
  • 5 retrospective and 4 prospective observational studies
  • Evaluation
    • DRE
    • Endoscopy with biopsy
    • Cross sectional imaging (MRI)
  • 370 patients watch and wait
  • 69.2% complete clinical response cCR
  • 105 patients 28.4% had tumour regrowth (about 1/3)
  • 74% were clinical T3/4 tumours
Salvage surgery

Heriot et al DCR 2017
• Salvage surgery possible in 83.3%
• No difference in overall survival and disease free survival
• BUT median follow up only 3 years

• Limitations
  • Retrospective studies
  • Small sample size
  • Heterogeneity in assessment of cCR
  • Short median follow up
  • Bias of treating physicians
What is the long term survival following treatment failure?

• Unknown

• Short term follow up seems to be acceptable

• Short term < 5 year follow up may not be enough as 25% of the recurrences in the German AIO study were observed after 5 years
Outcome of residual locoregional disease

- Habr-Gama Int J Radia Oncol Biol Phys 2014
- 90 patients
  - Regrowth in 31% at 60 months
  - 4/28 had unsalvagable locoregional disease
  - 5/28 developed metastatic disease
A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Dossa F\(^1\), Chesney TR\(^2\), Acuna SA\(^3\), Baxter NN\(^4\). Lancet Gastroenterol Hepatol 2017;7:501-13

- 23 studies; 867 patients; Median follow up 12-68 months
- 2 year regrowth  15.7\% (95\% CI 11.8-20.1)
- Salvage therapy in  95.4\% (95\% CI 89.6-99.3)

<table>
<thead>
<tr>
<th>Comparing watch and wait (cCR) with Radical resection (cPR)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non regrowth recurrence</td>
<td>NS</td>
<td>RR (1.46, 95%; CI 0.7-3.05)</td>
</tr>
<tr>
<td>Cancer specific mortality</td>
<td>NS</td>
<td>RR (0.87, 95%; CI 0.38-1.99)</td>
</tr>
<tr>
<td>OS</td>
<td>NS</td>
<td>HR (0.73, 95%; CI 0.35-1.51)</td>
</tr>
<tr>
<td>DFS Resection better</td>
<td>Sig</td>
<td>HR (0.47, 95% CI 0.28-0.78)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Comparing watch and wait (cCR) with Radical resection (cCR)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Non regrowth recurrence</td>
<td>NS</td>
<td>RR (0.58, 95% CI 0.18-1.90)</td>
</tr>
<tr>
<td>Cancer specific mortality</td>
<td>NS</td>
<td>RR (0.58, 95% CI 0.06-5.84)</td>
</tr>
<tr>
<td>DFS</td>
<td>NS</td>
<td>HR (0.56, 95% CI 0.20-1.60)</td>
</tr>
<tr>
<td>OS</td>
<td>NS</td>
<td>HR ( 3.91, 95% CI 0.57-26.72)</td>
</tr>
</tbody>
</table>

More prospective studies are needed to confirm long term safety
UNRESOLVED QUESTIONS

• What is the long term oncologic efficacy?

• What is the optimal surveillance protocol?

• Does leaving viable cells increase the patients risk of distant metastases?

• Are future sphincter sparing procedures compromised?
Summary Watch and wait

• Proof in principle but ...
• Data is limited
  • Small, not prospective, heterogenous, relatively short follow up

• Identifying the appropriate patient with pCR is difficult
• Follow up regimens not standardized
• Most patients who recur can undergo salvage surgery
• Long term efficacy unknown
  • Regrowth rate 15-30%; 18% metastatic disease
Should we operate?

Yes

• Watch and wait is not standard of care – yet
• Should it be mentioned as an option outside of standard of care?

• It should be within a trial or a registry
• Canadian trial
If you are considering watch and wait ...

Consider the following:

• High chance of cure following standard of care in the setting of cPR
• Must be full disclosure to the patient regarding the risks of recurrence, the chances of salvage for cure and the potential for distant disease
• Should be decided in a multidisciplinary setting
• Requires patient cooperation with a rigid follow up protocol
• Requires radiologist with experience in evaluating tumour regression on MRI
• Commitment on the part of the surgeon
Future Directions

• Predicting pCR
  • Tumour markers – genetic footprints predicting response
  • Improved imaging MRI combined clinical surveillance

• Improved chemoradiation

• Consolidative chemotherapy
What do I do?

• Highly selective
• At 8-10 weeks clinical assessment DRE Proctoscopy, MRI
• Discussion at MDC consolidation chemotherapy

• Clinical assessment (DRE proctoscopy)
  • First two years, every 3 months
  • Third, four fifth year every 6 months

• Radiology
  • First year CT, MRI every three months
  • Second year CT MRI every 6 months
  • Third fourth and fifth year every 12 months