Clinical complete response should be treated by surgery

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Debate: Surgery or Watchful Waiting
When a Complete Response is Achieved in Rectal Cancer?

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• I have no disclosures
TME: the real picture
TME optimizes local control

- Mortality: 2-4%
- Morbidity: 30-40%
- Temporary stoma: 80-100%
- Permanent stoma: 30-50%
- Urogenital dysfunction: 80%
- LARS: 50-60%
- Impaired QoL: 100%

BUT.....

Watch and wait: It is not standard of care!

- Changing the paradigm
  - Surgery is the ‘cornerstone’ in cure for rectal cancer

- Non-curable local situation is unacceptable

ypT0-1
5Y cancer-related survival: 98%
5Y disease-free survival: 91%

Wolthuis et al, Ann Surg Oncol 2011
What is low rectal cancer?
Follow-up should be done by the same surgeon
Only for low rectal cancer? DRE depends on surgeon’s experience.
pCR has best prognosis but, how to get there.....?
Actual problems - questions

- Accuracy restaging modalities

- Role of biopsy – local excision
  - Residual mucosal abnormalities vs. Early regrowth

- Interval
  - When to assess
  - What to do during the interval
  - Impact on outcome

- Follow-up
  - When, how and by whom
What is a complete clinical response?

- Whitening of the mucosa
- Association of teleangiectasia
- Subtle loss of pliability/light stiffness
- Tumor cannot be felt or seen
Heterogeneity in definition of cCR

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Definition of clinical complete response stipulated by each study</th>
</tr>
</thead>
</table>
| Menzies et al 2016 | 1. DRE: digital rectal examination  
- Absence of masses or nodules  
- Absence of endoscopically visible rectal lesions  
2. Radiological examination  
- Normal contrast enema and CT scan   |
2. TRUS assessment  
- No evidence of hypoechoic or hyperechoic lesions with irregular borders  
- Absence of thickening or erosion of the bony wall   |
| Appelt et al 2015 | 1. Endoscopic examination  
- Small, white, flat lesion in the rectal wall  
- Superficial erosion or ulceration without palpable tumor  
- If persistent, biopsy at the edge to ensure no evidence of disease   |
- Absence of residual ulceration, mass, or mucosal irregularity  
- Absence of endoscopic evidence of neovascularization  
2. Radiological assessment  
- MRI: absence of residual low-signal-intensity area  
- Diffusion-weighted MRI: absence of restricted diffusion   |
| Smith et al 2012 | 1. DRE  
- No palpable tumor  
2. Endoscopic examination  
- No visible pathology other than a flat scar (selective biopsy)  
- EUS and biopsy of scar tissue   |
| Dalton et al 2012 | 1. ERUS and biopsy of scar tissue  
- Residual mucosal ulcer is considered tumor even if biopsy is benign  
2. MRI assessment  
- Absence of evidence of residual tumor  
- PI Rafter that any residual disease before cCR is considered   |
| Waterston et al 2011 | 1. DRE  
- No palpable tumor when initially palpable before NACRT  
2. Endoscopic examination  
- No residual tumor  
- Small residual erythematous ulcer or scar  
- Negative biopsies from the scar, ulcer, or former tumor location   |
| Nakagawa et al 2021 | 1. Complete regression of lesion and negative biopsy   |

cCR = clinical complete response; DRE = digital rectal examination; ERUS = endoscopic retrograde ultrasound; MRI = magnetic resonance imaging; NACRT = neoadjuvant chemoradiotherapy; TRUS = transrectal ultrasound
Change of opinion
What to do with cCR?

52 years old, fit and well, 4 cm from anal verge cT3N0

- Resection and restore bowel continuity +/- temporary stoma: 67/132 (2007), 41/122 (2013), p = 0.0004

São Julião, Colorectal disease 2014
How sure are you?
We are getting close, but.....

- Selection of patients to undergo neoadjuvant therapy
  - Improve local control rate
  - Margin-negative resection
  - Sfincter-saving surgery
  - Induce complete response
- Selection of type of neoadjuvant (chemo)radiotherapy
- Selection of restaging modalities and interval assessment
- No reliable test to predict pathological complete response
Are we good at predicting response?

Value of adding dynamic contrast-enhanced MRI visual assessment to conventional MRI and clinical assessment in the diagnosis of complete tumour response to chemoradiotherapy for rectal cancer

Marc J. Gollub, O. Ivan Bralic, S. Felder, A. Kreuzwieser, M. Gornet, J. Garcia Aguilar, P. Philip, J. Joshua Smith

![Graphs and data from the study](image)

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>T2wMRI+DWP</th>
<th>T2wMRI+DWI+DCE</th>
<th>Clinical + T2wMRI+DWI+DCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65</td>
<td>62</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>55.0 (31.5–76.9)</td>
<td>42.1 (20.3–66.5)</td>
<td>52.6 (28.9–75.6)</td>
<td>42.1 (20.3–66.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td>86.7 (73.2–94.9)</td>
<td>76.7 (61.4–88.2)</td>
<td>75.6 (60.5–87.1)</td>
<td>92.6 (84.9–99.5)</td>
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<tr>
<td>PPV</td>
<td>64.7 (38.3–85.8)</td>
<td>44.4 (21.5–69.2)</td>
<td>47.6 (25.7–70.2)</td>
<td>80.0 (44.4–97.5)</td>
</tr>
<tr>
<td>NPV</td>
<td>81.3 (67.4–91.1)</td>
<td>75.0 (59.7–86.8)</td>
<td>79.1 (64.0–90.0)</td>
<td>79.6 (66.5–89.4)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.69 (0.54–0.84)</td>
<td>0.66 (0.51–0.81)</td>
<td>0.68 (0.54–0.83)</td>
<td>0.72 (0.57–0.87)</td>
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PPV: positive-predictive value, NPV: negative-predictive value, AUC: area under the ROC curve, ROC: receiver operating characteristic

*a Univariate analysis results; cut-off for calculation of diagnostic parameters was set between confidence levels 1 and 2 for clinical assessment and between levels 2 and 3 for MRI assessments

*b Multivariate analysis results; cut-off for calculation of diagnostic parameters was set at the maximum value of Youden's J statistic, sensitivity + specificity = 1 = 0.38
Good diagnostic performance?
Retrospective data
Expert MRI readers!

Accuracies
- A: 100%
- B: 74%
- C: 86%
- D: 92%

FIGURE 2: Four morphological patterns were defined, which were each subdivided into diffusion-weighted imaging (DWI)-positive and DWI-negative subpatterns. Pattern A includes cases with either a complete normalization of the DWI signal (ipsilaterally) or a complete residual tumour mass after chemoradiotherapy (CRT). Patterns B, C, and D are defined on the basis of the signal intensity of the residual tumour mass after CRT, which shows either a focal high signal intensity, a focal high signal intensity with a high signal intensity rim, a focal high signal intensity with a high signal intensity rim and a high signal intensity rim, or a complete or focal high signal intensity, respectively. The patterns are illustrated in the figure. The patterns are: (A) complete response, (B) residual tumour mass, (C) focal high signal intensity, and (D) residual tumour mass with a high signal intensity rim.
Combine all modalities and more...

Prospective data

- Sensitivity 75%
- Specificity 94%
- PPV 80%
cCR ≠ pCR!

\[ \text{cCR @ 12 weeks, TME} \rightarrow \text{ycT1N0} \]

\[ \text{ycT2N0 @ 12 weeks, TME} \rightarrow \text{ycT0N0} \]
Limitations of a watch and wait approach

- No exact correlation between cCR and pCR
  - Local regrowth (recurrence): 16-28%
  - Fibrosis vs residual tumor cells

- Salvage surgery = feasible and safe
  - Higher APR rate
  - Higher local recurrence rate (3% vs 0% p=0.04)

- No prospective evidence (no wider clinical applicability)
  - No standardization in patient selection, neoadjuvant therapy regimen, diagnostic technique for response assessment, definition of local recurrence, and follow-up
The problem = local re-growth!

Do we harm our patients?

- Local regrowth rate = 22%
- 96% within 3y f.u.
- Salvage surgery 88%, and 93% R0 resection
- 3Y OS: 94%
cCR+W&W (113) vs TME+pCR (136)

- 22 local regrowths (19%)
- Worse survival
- 5Y DFS: 75% W&W vs 92% pCR
How about salvage of local re-growth?

- Local recurrence: 31% (early and late)
- >50% within 12 months after initial cCR
- Salvage possible >90%
- Disease control: 94%

Could all of these patients have been saved by upfront TME?
Review: 215 TME vs 98 W&W

Wait and see approach for rectal cancer with a clinically complete response after neoadjuvant concurrent chemoradiotherapy

Hyun Jung Kim,1,2 Jin Ho Song3,4 Hyung Sik Ahn1,2 Bong-Hui Choi5,6 Hojin Jeong7,4 Hoon Sik Choi7 Yun Hee Lee3,4 Ki Mun Kang3,4 Bae Kwun-Jeong3,4

A: Recurrence

B: DFS, C: OS
Regrowth rate 15.7%

- W&W with cCR vs Surgery with pCR
- Better DFS after surgery
Overall salvage of local re-growth

- Systematic review (2017)
- 9 studies
- Salvage possible in 84%

- Conclusion:
  majority can be salvaged, but **insufficient evidence** on oncological safety
Does ypN+ matter?

- National Cancer Database
- CRT for LARC 2005-2014: n = 12271
- 30% residual nodal disease
- Associated with survival

<table>
<thead>
<tr>
<th>ypT0-is</th>
<th>ypN1</th>
<th>ypN2</th>
<th>ypN+</th>
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<tr>
<td></td>
<td>6%</td>
<td>0.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>ypT1</td>
<td>12%</td>
<td>2%</td>
<td>14%</td>
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</table>
Good responders with N+ do worse

- Recurrence-free survival

![Graph showing recurrence-free survival by different tumor sizes and lymph node statuses](image.png)

- T0-2N0
- T0-2N+
- T3-4N0
- T3-4N+
Adjuvant chemotherapy?

- pCR patients do not benefit from adjuvant chemo
- Patients with residual disease benefit from adjuvant chemo!
Conclusion

• TME remains gold standard to cure patients

• Assessment of cCR is unreliable at present

• When in doubt, it has to come out

• Patient selection for w&w approach is key

• Local regrowth has worse outcome
Surgery vs W&W?
Complementary friends!