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

PRACTICE PARAMETERS

Practice Parameters for the Management of Rectal Cancer (Revised)

J. R. T. Monson, M.D. • M. R. Weiser, M.D. • W. D. Buie, M.D. • G. J. Chang, M.D.
J. F. Rafferty, M.D.; Prepared by the Standards Practice Task Force of the American Society of Colon and Rectal Surgeons

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.

DCR 2013; 56(5): 535-550

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

Trial	n	Disease stage	Preoperative chemotherapy	Preoperative RT, Gy	Interval to surgery, weeks	pCR
Habr-Gama[1]	265	T2–T4	Concomitant fluorouracil and folinic acid	50·4	8 to assessment	27% (observation group); 7% (surgical group)
EXPERT[22]	77	Low T3; CRM threatened; tumour ≥5 mm into mesorectum; T4; T1–T4 N2	Induction: oxaliplatin and capecitabine; Concomitant: capecitabine	50·4–54	6	24%
RTOG 0012[23]	106	Distal T3 or T4	CVI fluorouracil; or CVI fluorouracil and irinotecan	55·2–60; or 50·4–54	7	26% both groups
EORTC 22921[24]	1011	T3 or T4	Fluorouracil and folinic acid	45	5·4	5·3% (radiotherapy-alone group) *vs* 13·7% (CRT groups)
FFCD 9203[25]	733	T3 or T4	Fluorouracil and folinic acid	45	3–10	3·7% (radiotherapy-alone group) *vs* 11·7% (CRT group)
CORE[26]	85	Low T3; CRM threatened; T4; T1–T4 N2	Oxaliplatin and capecitabine	45	6–8	13%
CALGB 89901[27]	32	T3 or T4	Oxaliplatin and fluorouracil	50·4	4–6	25%*

*25% pCR in 32 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. FFCD= Fédération Francophone de Cancérologie Digestive. CORE=capecitabine, oxaliplatin, radiotherapy, and excision. CALGB=Cancer and Leukemia Group B.

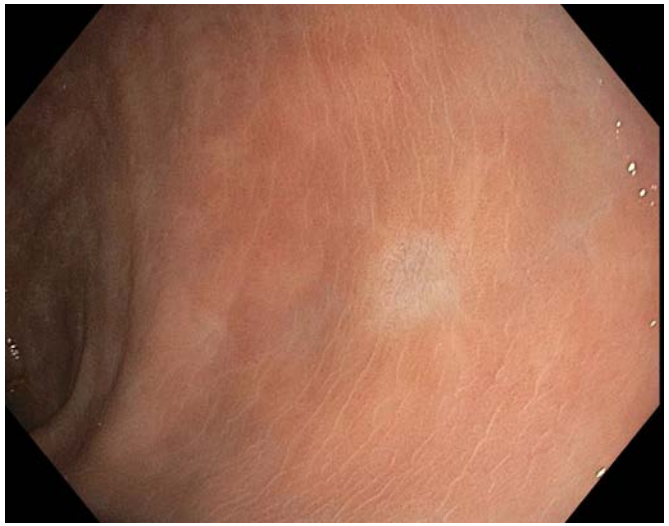
Table 1: **Selected trials of preoperative CRT for rectal cancer**

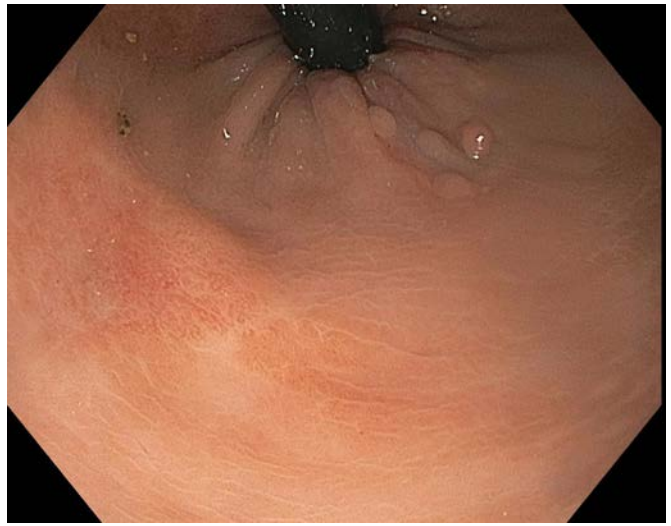
O'Neill et al. Lancet Oncol 2007; 8:625-33

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 30-2. Comparison of selected modern studies

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

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

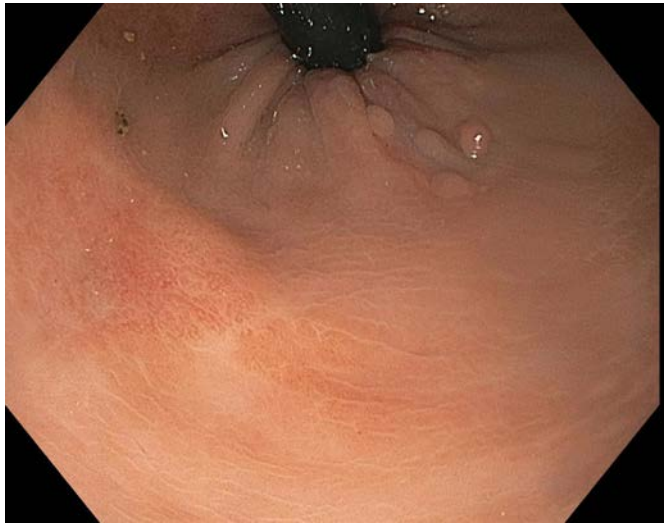
Can we predict pCR prior to pathologic evaluation?

- 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

[1]Smith 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

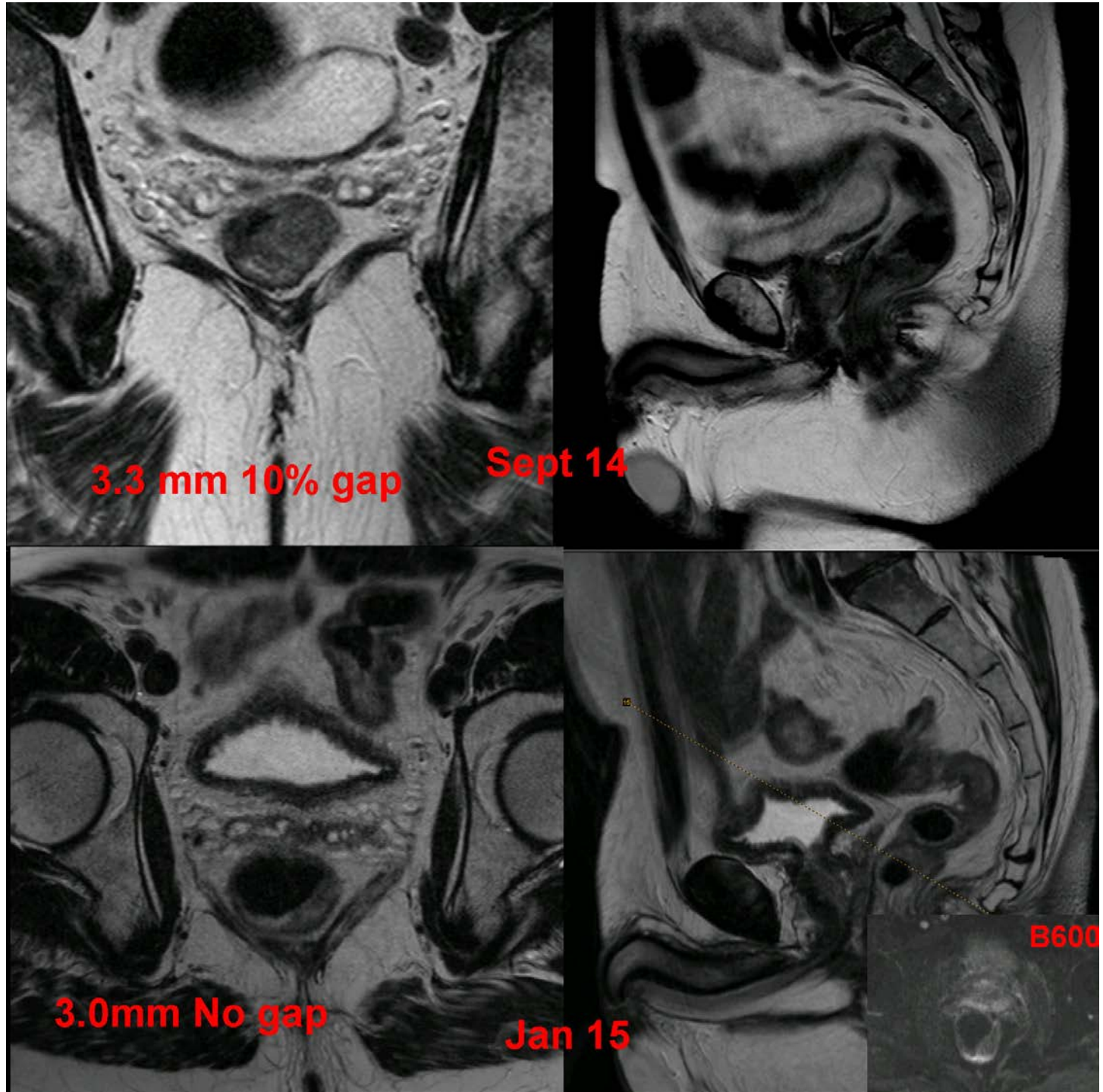
- PET scan - not reliable

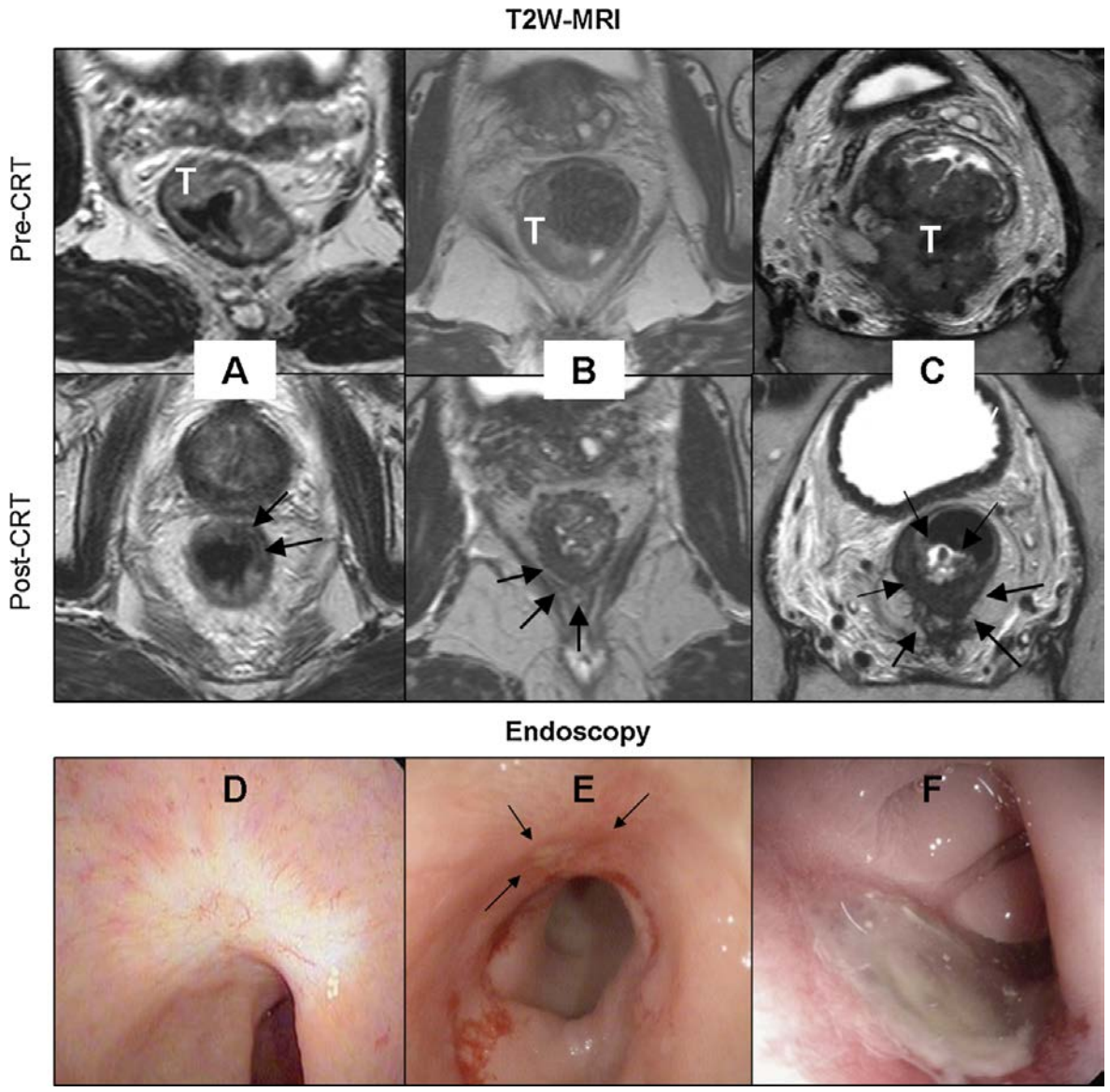
- High resolution MRI
  - Comparison of pre and post treatment MRI
  - MRI tumour regression grade
  - Grade 1 or 2 observation
    - TRIGGER trial

Mercury study group, Patel Am J Roentgenol. 2012

TABLE 30-3. MRI tumor regression grade (mrTRG) [54]

mrTRG	Description
1	Tumor bed with low signal intensity signaling fibrosis with no residual intermediate tumor signal
2	Tumor bed with predominance of fibrosis with minimal residual intermediate tumor signal
3	Substantial intermediate intensity tumor signal present, but does not predominate over low intensity fibrosis
4	Minimal fibrosis
5	No change from baseline


3.3 mm 10% gap
Sept 14
3.0mm No gap
Jan 15
B600

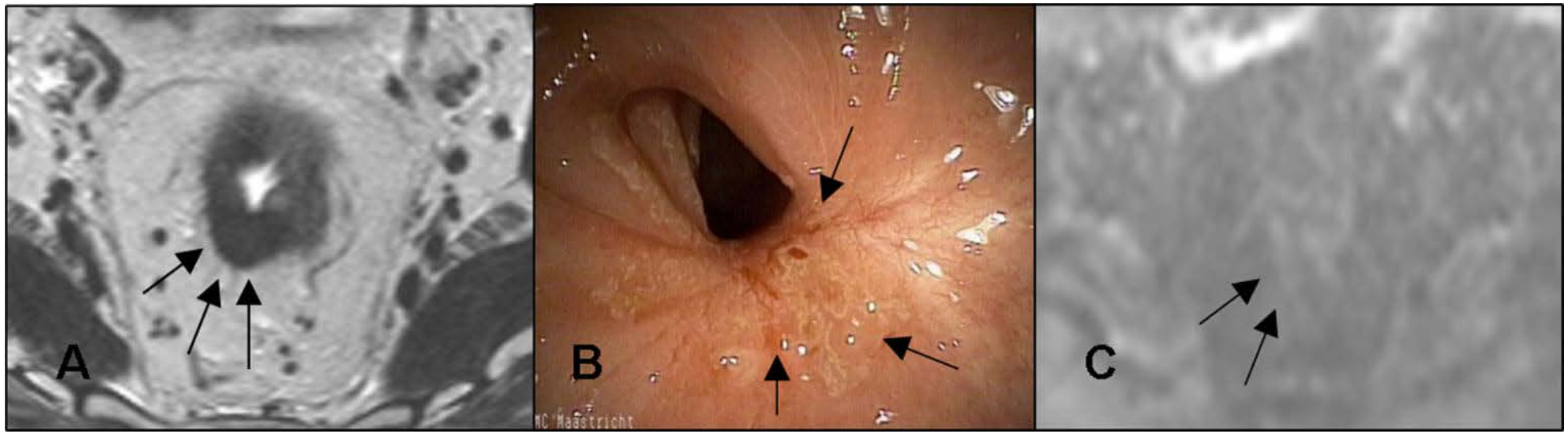


A. Complete response
B. Equivocal response
C. Residual tumour
D. Smooth scar
E. Small ulcer
F. Residual tumour

Mass et al. Ann Surg Oncol (2015)22:3878-3880

ation, *ADC* apparent diffusion coefficient

Mass et al. Ann Surg Oncol (2015)22:3878-3880



T2W- MRI hypointense residual wall thickening

White scare with stenosis distortion

DWI absence of diffusion restriction indicating CR

Mass et al. Ann Surg Oncol (2015)22:3878-3880

Mass et al. Ann Surg Oncol (2015)22:3878-3880

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 he 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 locoregonial 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 Gastoenterol 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)
- Comparing watch and wait (cCR) with Radical resection (cPR)
  - Non regrowth recurrence NS RR (1.46, 95%; CI 0.7-3.05)
  - Cancer specific mortality NS RR (0.87, 95%; CI 0.38-1.99)
  - OS NS HR (0.73, 95%; CI 0.35-1.51)
  - DFS Resection better Sig HR (0.47, 95% CI 0.28-0.78)
- Comparing watch and wait (cCR) with Radical resection (cCR)
  - Non regrowth recurrence NS RR (0.58, 95% CI 0.18-1.90)
  - Cancer specific mortality NS RR (0.58, 95% CI 0.06-5.84)
  - DFS NS HR (0.56, 95% CI 0.20-1.60)
  - OS NS HR (3.91, 95% CI 0.57-26.72)

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

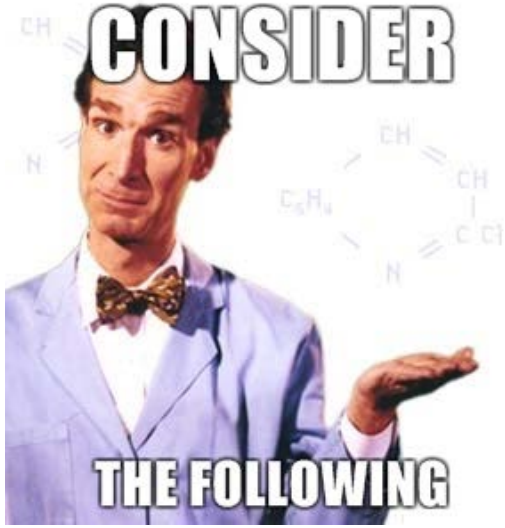
Should we operate?

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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