CHRISTIE COLORECTAL CANCER MDT

FOLLOW-UP GUIDELINES

Following clinical complete response

Circulated to Christie Colorectal MDT on 2nd May 2018
For wider circulation to Colorectal Pathway Board 15th May 2018
Finalised 2nd July 2018

Preface

These guidelines are distinct from the follow-up guidelines for patients with non-metastatic colorectal cancer following curative resection. They are primarily for use within the framework of the Christie Colorectal and Pelvic Cancer Multidisciplinary Meeting (MDT), and can be adapted by the Greater Manchester Pathway Board.

These guidelines are new (rather than an update). There has previously been a Patient Information Sheet (PIS) dated 12th December 2015. This PIS has been updated with the development of these guidelines and attached as Appendix A.

These guidelines include a section on the OnCoRe research database and how patients can be recruited to this database.

These guidelines have been developed in parallel with the 2017 ACPGBI guidelines (1) and through discussions within the IWWD (International Watch and Wait Database) network (2).

These guidelines should be considered 'dynamic' as there will be further refinements as we continuously audit.

Definition of clinical complete response

After chemoradiotherapy for rectal cancer, clinical complete response is identified in 10% to 15% of patients (using regimens commonly used in the UK) (3).

- Internationally accepted criteria for the definition of clinical complete response have been described by Hama-Gabr (4) – namely, absence of residual ulceration, stenosis, or mass within the rectum during digital rectal examination and endoscopic examination.

These criteria include the absence of mesorectal lymph nodes and suspected sub-mucosal tumour regrowth (uncommon).

Patient group

- These guidelines apply to patients with rectal cancer (up to 15 cm from the anorectal junction) who have undergone pre-operative (sometime referred to as neoadjuvant) chemoradiotherapy (sometimes referred to as long-course chemoradiotherapy) and found to have a clinical complete response, as defined above, typically 8 or more weeks after completion of chemoradiotherapy.
- Clinical complete response occasionally occurs after short course radiotherapy, typically where there is a wait of greater than six weeks to re-assessment. These occurrences are relatively uncommon. The present guidelines do not apply to this setting.
- Rarely, clinical complete response occurs after neoadjuvant chemotherapy alone. This is setting is broadly ‘untested’. The present guidelines do not apply to this setting.

‘Watch and wait’ strategy

In the above setting of a clinical complete response after chemoradiotherapy in rectal cancer, patients may be offered a non-surgical approach through ‘watch and wait’. The literature uses other terms such as ‘watchful wait’ and ‘watch and see’. The preferred term in these guidelines is ‘watch and wait’. The strategy of ‘watch and wait’ offers a patient an opportunity to avoid major resection surgery and stoma formation.

Indications for intensive ‘watch and wait’

There is no internationally accepted ‘watch and wait’ follow-up program. Here, we recommend an intensive ‘watch and wait’ program for the following reasons:

- Follow-up may be beneficial through the early detection of treatable tumour regrowth (defined next section). There is now a reasonable amount of evidence that local tumour regrowth in this setting is generally amenable to salvage resection with good outcomes.
- Other indications for follow-up may include: audit of other oncological outcomes; the detection and treatment of adverse-effects from chemoradiotherapy without surgery, and for the appraisal of patient-reported outcomes (PROs).

For the purpose of this document, the main emphasis will be on the early detection and treatment of local (tumour) regrowth.

Local growth

- The use of the term local regrowth was encouraged by the 2014 Champalimaud conference (5). It is generally believed that local regrowth is amenable to salvage resection, with low proportion of margin positivity, and good oncological outcomes.
- This terminology distinguishes local tumour regrowth from local recurrence after conventional rectal cancer resection where salvage surgery is very challenging, associated with a high proportion of margin positivity, with high morbidity, and poor outcome.

A stratified approach to 'watch & wait '

- Currently, there is a wide range of local regrowth rates across many studies ranging (at 2 years) from 3% to 33% (6). It is generally felt that this reflects differences in patient and tumour characteristics across centres.
- There is no evidence suggesting clinically meaningful differences in rates of local regrowth within centres due to age, stage, nodal status or radiotherapy regimen used. Thus, a stratified approach to 'watch and wait' is currently not recommended.

Role of magnetic resonance (MR) imaging

- MR imaging is commonly used as part of the re-assessment of a rectal cancer for surgery after long-course chemoradiotherapy at 8 to 12 weeks. The use and reporting of tumour regression grade (TRG: 1 to 5) at this re-assessment is encouraged.
- The scoring of TRG1 or TRG2 may alert the MDT to the presence of a clinical complete response, and the need to re-assess through endoscopic and digital

examination. The MR scan finding itself is not considered criteria in the definition of clinical complete response.

- The use of MR imaging supplements the criteria defining clinical complete response by excluding the presence of mesorectal lymph nodes or suspected sub-mucosal tumour regrowth (uncommon).

Role of endoscopy and biopsy

- Endoscopic or intra-luminal examination of the rectal mucosa is the key assessment tool for defining the presence of a clinical complete response.
- This assessment should include digital examination.
- Similarly, endoscopic or intra-luminal examination of the rectal mucosa, with digital examination, is the key assessment tool for monitoring for a sustained complete response.
- For the majority of patients, endoscopic and digital examination can be undertaken in the endoscopic suite, typically with a flexible sigmoidoscopy.
- Biopsy is required for abnormal mucosal findings.
- Blind biopsy of normal or scarred mucosa is discouraged. Repeated blind biopsies have been associated with chronic pain and radio-necrotic ulcers.
- Colonoscopic surveillance is the same as that for follow-up after rectal cancer surgery – namely a year 1 ‘clean’ colonoscopy (which can double-up as the endoscopic examination of the rectal mucosa) and an ‘exit’ year 5 colonoscopy.

‘Near complete’ response/ initial local excision/ contact radiotherapy

- The term ‘near complete’ response is found in the literature but is incompletely defined, and not covered by these guidelines.
- Some studies describe the use of local excision as ‘belt and braces’ for clinical complete response. There are reports that this is associated with increased morbidity and is not included in these guidelines.
- Some studies describe the use of contact radiotherapy (of which Papillon is an example) for ‘near complete’ response (7). This indication is for highly selected cases and is not included in these guidelines

Role of adjuvant chemotherapy

- Some studies describe the use of adjuvant chemotherapy as ‘belt and braces’ in the setting of clinical complete response. This is not routine clinical practice across studies in this field and is generally not recommended.

Functional outcomes

- There are a small number of studies that have evaluated functional outcome in patients on a 'watch and wait' programs. This is an area of ongoing research.
- One notable observation in these early studies indicates that many patients suffer with symptoms that constitute the Low Anterior Syndrome (LARS), even though there has been no surgery (8, 9).

Follow-up schedule

- A patient information sheet may be offered to patients considering chemoradiotherapy prior to surgery for rectal cancer, and to all patients who have completed chemoradiotherapy and found to have a clinical complete response.
- The follow-up schedule is shown in **Table 1**. The proposed schedule is similar to the protocol used by the Beets group (originally in Maastricht; now Amsterdam) (8) and more intensive than the Sao Paulo protocol (10, 11) - see Appendix B.
- The key principles are: regular MR scans in the first 3 years; and endoscopy and digital examination in the first 5 years.
- Attendance to clinics between these examinations depends on local pathways. Alternative patient contact and communication might be through telephone follow-up clinics or letters.
- This schedule differs from that for follow-up after rectal cancer surgery up to year 5. Thereafter, follow-up is the same as that for follow-up after rectal cancer surgery.
- CT (Thorax, abdomen, pelvis) scanning is the same as that for follow-up after rectal cancer surgery throughout.

Multidisciplinary team

- At the Christie NHS Foundation Trust, patients with clinical complete response are managed through the Colorectal and Pelvic Cancer MDT.
- In some regions of the country, there are stand-alone Rectal Cancer Clinical Complete Response MDTs. The need for such a stand-alone MDT should be monitored.

Table 1 'Watch and wait' (W&W) follow-up schedule: clinical complete response after chemoradiotherapy in rectal cancer

	Baseline W&W	Year 1				Years 2 to 5 (in months)							
		3 mo	6 mo	9 mo	12 mo	18	24	30	36	42	48	54	60
Path review	Generally not required												
Digital exam	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Pelvic MR	✓	✓	✓	✓	✓	✓	✓	✓	✓				
PET-CT	Optional												
CT (TAP)	✓		✓		✓		✓		✓		✓		✓
Flexible sigmoidoscopy	✓	✓	✓	✓		✓	✓	✓	✓		✓		
Colonoscopy					✓								✓
Recruitment to OnCoRe	Encouraged												

TAP: thorax-abdomino-pelvic

Prospective audit and research (OnCoRe)

- In 2010, a network of approximately 16 centres in the North West of England and North Wales, established a regional audit program evaluating the management of patients with rectal cancer and clinical complete response following chemoradiotherapy managed by watch and wait. From an initial audit of enumerating cases, a more detailed audit registry was established and funded through the BDRF (Bowel Disease Research Foundation), and became known as the OnCoRe (Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer) registry.
- At over 120 cases by 2015, this became one of the largest collections of these patients worldwide, and was published as a matched cohort analysis in Lancet Oncology in late 2015. This study had three key findings: (i) the majority of local regrowths occur in the first 3 years, and the rate of regrowth is approximately a third; (ii) matched by age, performance status and cT stage, survival outcomes were not inferior to those managed by standard care, namely surgical resection after chemoradiotherapy; and (iii) the watch and wait strategy is associated with avoidance of permanent colostomy in those destined for a stoma in approximately a quarter.
- In 2017, the OnCoRe registry was converted, under ethics approval, to the OnCoRe Research Database. The 'mechanics' entry into this database are near identical to those for the registry with two key differences: (i) patients are now consented and (ii) recruitment is mandated within 90 days from the decision of watch and wait.
- As a CRN portfolio badged study (CPMS ID 37613), recruitment will be facilitated through NCRN Trust research nurses and will be returnable as trial activity.
- As a research database, there are several additional benefits including:
  (i) Data can now be scrutinised as research questions – for example, with advanced statistical tool for causal inference.
  (ii) Data can be shared with other centres within formalised consortia, such as the IWWD and the InterCoRe projects.
  (iii) Data can serve as a source to link with biological tissue questions – for example, response prediction using MCRC biobank captured tissue analyses linked with high-quality clinically-relevant outcomes.
  (iv) Data can serve as a source to 'piggy-back' functional outcome studies – for example, cross-sectional evaluation of bowel, urinary and sexual function.

(v) Data can serve as a source to 'piggy-back' quality of life and life impact studies.

July 2018

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And ratified by the core relevant members of the Colorectal and Pelvic Cancer MDT group: Mr Malcolm Wilson, Professor Sarah T O'Dwyer, Mr Chelliah.Selvasekar, Mr Omer Aziz (Colorectal Surgery); Dr Mark Saunders (Clinical Oncologist); Dr Rohit Kochhar (Radiology); Dr Bipasha Chakrabarty (Pathology); Rebecca Halstead (Cancer Nurse Specialist).

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Appendix A

Information for Patients

Rectal Cancer – Clinical Complete Response after Chemo-Radiotherapy

Appendix B

Follow-up schedules in patients with a clinical complete response

Surveillance strategies Number of assessments/ year		A&J Gama	AvL/MUMC	OncoRe
Year 1	DRE	6-8 weeks	4x	4x
	Endoscopy	6-8 weeks	4x	4x
	MRI	2x	3x	4x
	Serum CEA	6-8 weeks	4x	Min. 2x
	CT-chest / abdomen			2x*
Year 2	DRE	4x	4x	2x
	Endoscopy	4x	2x	2x
	MRI	2x	2x	2x
	Serum CEA	4x	4x	Min. 2x
	CT-chest / abdomen			2x*
Year 3	DRE	2x	2x	2x
	Endoscopy	2x	2x	2x
	MRI	2x	2x	2x
	Serum CEA	2x	2x	Min. 2x
	CT-chest / abdomen			1x*
Year 4-5	DRE	2x	2x	
	Endoscopy	2x	2x	2x
	MRI	1x	2x	
	Serum CEA	2x	2x	
	CT-chest / abdomen			2x*

*The CT imaging is thorax, abdomen and pelvis. The regimen is the same as that used following surgical resection for rectal cancer