Curr Colorectal Cancer Rep (2015) 11:352–359
DOI 10.1007/s11888-015-0291-4

How Should a Multi-disciplinary Team (MDT) Approach the Issue of Non-Operative Management in Rectal Cancer?

Rob Glynne-Jones[1] · Angela Wheeler[1] · Kyle Dunlea[1] · Colin Elton[1] · Gary Atkin[1] · Luis Soares[1] · Elaine Burns[1] · Sheida Vessal[1] · Lauren Carp[1] · Margaret Lynch[1] · Matthew Train[1] · On behalf of the Barnet Colorectal Multidisciplinary Team

Published online: 16 September 2015

Abstract A sustained clinical complete response (CCR) after preoperative chemoradiation (CRT) is observed in 10–20 % of patients with locally advanced rectal cancer (LARC). A selective non-operative management with close surveillance is increasingly being advocated for patients achieving a CCR—on the assumption that outcomes compare favourably with patients subjected to radical surgery (usually requiring a permanent stoma). The aim of this present opinion piece was to capture individual views of an MDT and elicit common themes regarding the question "How should a multidisciplinary team (MDT) approach the issue of non-operative management in rectal cancer?" A vignette of a real patient was discussed, and all members explained their own perspective in the context of the vignette. Several common themes emerged. Long-term prospective observational studies and randomized studies with more uniform inclusion criteria are required to evaluate the risk-benefit of the standard surgical approach compared against a non-operative approach.

Keywords Rectal cancer · Chemoradiation · Neoadjuvant · Preoperative · Complete clinical response · Colostomy · Stoma · Non-operative treatment · Avoidance of surgery · Deferral of surgery · "Watch and wait" · "Wait and see" · Omission of surgery · Observation · Organ sparing

This article is part of the Topical Collection on *Localized Colorectal Cancer*

✉ Rob Glynne-Jones
rob.glynnejones@nhs.net

[1] Barnet and Chase Farm Hospital, London, UK

Introduction

Colorectal cancer is the third most common cancer in the UK with approximately 40,000 new cases registered each year. Rectal cancer comprises about one third. Based on randomized trials, many patients with locally advanced rectal cancer (LARC) receive preoperative chemoradiation (CRT) prior to radical surgery to reduce the risk of local recurrence [1–4]. CRT can lead to significant tumour regression (downsizing) and a lower stage (downstaging) both in primary tumour and perirectal lymph nodes [1–5]. Approximately 10–20 % achieve a complete pathological response [1, 3, 4]. However, the addition of preoperative short-course preoperative radiotherapy (SCPRT) and CRT increases surgical complications including a 2–8 % postoperative death rate, which is higher in older adults. SCPRT and CRT also adversely impact on urinary and sexual functions [5, 6].

A permanent colostomy is required in 10–20 % of cases, particularly if the cancer is low, which can be associated with significant morbidity [7], permanent alteration in body image and high psychological morbidity. Even if sphincter preservation is feasible, marked deterioration in bowel function (the so called "low anterior resection syndrome" or LARS) is also recognized to be a frequent and chronic pain [8]. These symptoms may be worsened by the addition of SCPRT/CRT [9, 10]. Hence, if the patient undergoes mutilating surgery with a permanent colostomy after CRT and cancer cells cannot be identified in the histopathological specimen, radical surgery and its attendant risks could be construed as an unnecessary overtreatment.

In Brazil, CRT is recommended for the majority of patients with rectal cancers below 7 cm from the anal verge. Habr-Gama has capitalized on this management and developed a selective non-operative "watch and wait protocol" by defining a

novel early endpoint "sustained clinical complete response" (SCCR) [11]. This strategy has been documented in a series of reports [12–22, 23•, 24]. Patients are meticulously reassessed 8–10 weeks after completion of CRT and prior to undertaking surgery. Patients who have no apparent tumour on clinical and radiologic criteria are designated as CCR, and the patient does not proceed to radical surgery. A meticulous and rigorous follow-up programme with digital rectal examination (DRE) and endoscopic and radiological surveillance is undertaken for 1 year. Patients still clinically in remission at 12 months from CRT completion are considered to have an SCCR. Results have been progressively clearer and defined more prospectively [25].The definition of CCR has been adapted to include the absence of residual rectal wall irregularity on DRE and proctoscopy [19, 26] and magnetic resonance imaging (MRI) changes, such as the presence of residual low-signal-intensity areas with absence of restriction to diffusion at MRI, and an absence of residual FDG/PET uptake within the rectal wall [27].

Views regarding the feasibility and appropriateness of this selective non-operative approach are highly polarized. Previous surveys of surgeons showed the majority (69 %) will never consider non-operative management in patients fit for curative surgery [28], although it seems likely from discussions in the literature that this view is changing [29–31].

In the UK, multi-disciplinary teams (MDTs) have a pivotal role in optimizing care for patients with colorectal cancer. Currently, attention is also focussed on the patient as an individual in terms of psychosocial needs, quality of life, rights and empowerment in the face of cancer. Clinicians are increasingly embracing shared decision-making, which is impractical if the patient lacks sufficient information to exercise choice. There is little current data regarding the individual specialist views within colorectal MDTs on a non-operative approach and their assessments of risk-benefit.

The aim of this discussion was to examine the views of all members of an MDT with regard to the efficacy and safety of a non-operative approach after CRT in LARC. We sought to elicit common themes regarding the question "How should a multi-disciplinary team (MDT) approach the issue of non-operative management in rectal cancer?" We also reviewed the medical literature, with emphasis on the oncological outcomes (local recurrence, disease-free survival (DFS) and overall survival (OS), functional outcomes, potential for salvage surgery, morbidity, quality of life and patient preferences).

Methods

Patient Vignette

A 53-year-old male company director presented with rectal bleeding, mucous discharge and pain on defecation. He has a good appetite and has not lost weight. He has no comorbidity factors, takes no regular medication, plays football regularly, but smokes approximately 10–15 cigarettes a day. On digital rectal examination, there is a hard mass extending from 2 cm from the anal verge corkscrewing around the anal canal and extending 5 cm up into the rectum and involving approximately half the circumference of the anal canal anteriorly to about 7 cm from the anal verge. A biopsy confirms moderately differentiated adenocarcinoma. Computerized axial tomography (CAT) scan does not identify any liver, lung or peritoneal disease, and there are no enlarged lymph nodes in the abdomen or pelvis. An MRI scan confirms a bulky 6-cm cancer cT3a but compromising the levator muscles on the left and identifying five abnormal mesorectal lymph nodes suspicious of involvement and an enlarged left obturator node (cT2/T3aN2). The MDT decision is that the patient should be offered neoadjuvant CRT and proceed to abdominoperineal resection if restaging/ reimaging following CRT is favourable. The patient is counselled and initially agrees to this plan of management. By the time the patient starts the chemoradiation, he has developed persistent sacral/buttock pain which requires analgesia and finds it uncomfortable to sit down. Neoadjuvant CRT to a dose of 45 Gy in 25 daily fractions over 5 weeks is administered with concurrent capecitabine 850 mg/m^2 per oral twice daily. A repeat MRI 6 weeks after the completion of CRT suggests a CCR has been achieved. The patient feels well and is back to playing football. DRE reveals no evidence of any residual tumour. The MDT reviews the post-treatment scans and makes a recommendation for surgery, but the nurse navigator and the surgeon are aware that the patient is keen to avoid surgery.

Individual members of the colorectal MDT for Barnet Hospital, which meets weekly and is responsible for the care of approximately 120 new patients each year (i.e. all patients with colorectal cancer referred to the hospital), provided their views on the above vignette of a real patient that had been discussed and treated 3 years ago. We presented the details as a new patient. The MDT meeting lasts approximately 2.5 to 3 h. All members are required formally to sign in their attendance, and peer review requirements dictate an 80 % attendance throughout the year, so all are accustomed to working closely together.

We provided a vignette. Hence, all members of the MDT were asked individually to provide 50–100 words explaining their own perspective on being faced with such a patient. We then selected the common themes and summarized and discussed them further.

We also searched Medline and Embase for the MeSH and free terms: rectal; cancer; carcinoma; tumor; or neoplasm; and chemotherapy; and neoadjuvant or preoperative chemoradiation; complete clinical response; colostomy; stoma; non-operative treatment; avoidance of surgery; deferral of surgery; "watch and wait"; "wait and see"; omission of surgery; observation; organ sparing. No date or language restrictions were applied. No randomized trials comparing non-operative

management with radical surgery in operable rectal cancer were identified.

The Concerns Expressed

The Clinical Oncologist

I have not given the optimal radiotherapy dose to destroy the cancer. If a non-operative approach had been the MDT decision from the outset, I would have used different field sizes and higher doses and boosted the primary tumour with brachytherapy. Can I really expect only 45 Gy to control the cancer long-term? How long will we have to keep him under follow-up?—probably at least 10 years?

The patient has already made up his mind. If he has not made up his mind, then what can I say are the risks of this approach and how likely is it to be a permanent solution—bearing in mind this was a very advanced cancer initially? Also if the cancer regrows, will we still be in a position to salvage with radical surgery in terms of a curative resection? Finally, if the patient originally was clinically staged as node positive, i.e. stage III, should I now offer "adjuvant" chemotherapy? If so, should this be a 4- or 6-month duration?

The Colorectal Surgeon 1

This is a 55-year-old patient who is fit. The aim should be to offer him the best chance of disease-free survival. The adage "that we should base our surgery on the pre-treatment MRI" pre-dates modern management of rectal cancer. I feel although the pre-treatment MRI is important, the post-treatment MRI should perhaps be more valuable in guiding the surgeon. If this man truly has a normal-feeling rectum on digital examination and a normal MRI, he would be a candidate for a "watch and wait" policy. However, this does not feel right for such a young patient who had such a locally aggressive tumour. The safest option would be a radical surgery which would mean the best chance of local control, but clearly would involve an abdominoperineal excision of his rectum and anus with a permanent colostomy, with all the associated morbidity permanent change in body image and small risk of mortality. Adopting a "watch and wait" policy does not mean that surgery is completely avoided. It should mean a meticulous follow-up with MRI, CT, rectal and endoscopic examination, along with good patient compliance to this regime. It ultimately is up to the patient to decide, based on all the available evidence and his personal wishes, and I would support him, even if he decided to adopt the "watch and wait" policy.

The Colorectal Surgeon 2

The dilemma for the colorectal surgeon lies between proceeding routinely to radical surgery which may entail a permanent stoma, prolonged healing and a small risk of death. If the subsequent histology demonstrates a pCR when the histology is presented to the MDT, the implication in the MDT is that an unnecessary and mutilating operation has been performed. Active surveillance for further potential ongoing regression and tumour downstaging to complete clinical response avoids surgical management. This delay produces a risk in the longer term if recurrence is observed that allows a tumour to become unresectable. If surveillance is to be the chosen option, then follow-up must be meticulous and long-term over 5–10 years and involve regular clinical visits and imaging. So as a surgeon, am I showing myself sufficiently open-minded and motivated to consider all possible options and what is in the best interest of the patient?

The Surgeon in Training (Registrar)

My main concerns around watchful waiting for rectal cancer following good clinical response to neoadjuvant chemoradiotherapy are the paucity of literature. The sensitivity and specificity of the definition of a clinical response is variable. The evidence base for such an approach relies heavily on small retrospective studies. Clinical trials will shed light on these factors. In the meantime, the decision to operate or not operate must be made by patients themselves after counselling as to what is known and unknown in this area.

The Radiologist 1

The problem for the radiologist is the degree of confidence in the MRI regarding post-treatment change versus residual disease. Tumour recurrence is easier to detect as the tumour regrows over serial imaging, but the worry is of systemic failure and metastatic disease, so serial body CT is also required as part of the monitoring and is perhaps best done in a trial setting. Tumour fibrosis is the commonest response to chemoradiotherapy and manifests itself as spiculated low T2 signal on MRI, with a reduction in tumour volume. However, there is always a worry of persistent viable tumour cells, for example, in residual mucin pools, which are invisible to MRI.

The Radiologist 2

My concern is the limitations of the imaging, which includes CT, MRI, endoanal ultrasound and PET in attempting to distinguish viable tumour from chemoradiation changes. A multimodality approach does minimize weaknesses and maximize the sensitivity, but which modalities should we use? How often and for how long should we reimage our patient?

Chemoradiation changes involve the tumour and adjacent tissue including tumour necrosis, oedema, ulceration, fibrosis, calcification, muscle wall changes and inflammatory infiltrates. These changes can lead to under or over measuring

local tumour load. The MRI changes in T2 signal as well as diffusion characteristics are useful; however, the initial stage of cT3N1 gives a potential for metastatic spread as well as the local recurrence. Vigilant global scanning with CT is paramount. Using combination serial imaging, clinical examination, DRE, and following the CEA trend coupled with regular discussion at our MDT, we may develop our confidence over time in our findings. However, reassurance from research from a large volume of patients as well as our own patient database would help us achieve this earlier.

The Colorectal Clinical Nurse Specialist/Nurse Navigator

The challenge for the colorectal clinical nurse specialist (CNS) is to present the risks and benefits of the treatment options to enable informed decision-making to take place. How do we ensure that patients have a good enough understanding of the possible implications when they come with differing levels of knowledge and preconceptions? In view of the lack of RCT evidence for non-operative management versus surgery, how can we make information given to the patient at consultations consistent? There is a risk that patients can come away from a consultation with uncertainty and a loss of trust. Also, in a fragmented medical system, how can we *ensure* that the scrupulous surveillance required for a "watch and wait" policy is adhered to, and the patient does not miss investigations or become "lost to follow-up"?

View of the Patient

When I was first diagnosed, there was initial shock; however, this was tempered by being told that this would not kill me. I then pestered my surgeon to tell me the treatment, which consisted of radiotherapy, chemotherapy and surgery which included a non-reversible stoma. I answered that I would undertake the treatment with the exception of the surgery. I was then told that there was no option, as in this country, this was the treatment, and that there was only one surgeon worldwide who treated this condition without surgery and she was in Brazil.

I told my surgeon that I did not see this as a problem and that he could send me to Brazil, as I was determined *not* to undergo the surgery. Subsequently, I met two oncologists, who both gave me hope that this condition could be treated without surgery.

At 53 years old, I still felt young. I still played football, and still do today, 5 years later. I enjoy family holidays with my wife and am generally active. It took me 53 years to form my body and personality, and I knew that if I had gone ahead with the surgery, whilst I would have lived, it would have been a life that I could not have accepted.

Summary of Views

Certain themes are regularly expressed. There are concerns from all disciplines about the reproducibility and safety of this approach. How can we be sure that there is no tumour?; how often should we be imaging the patient, and for how long?; and what to tell the patient? There was a general dissatisfaction that there are no randomized trials to aid us in the decision-making. The question of the role of further adjuvant chemotherapy and the inaccuracy of clinical staging was also highlighted by the oncologist.

Discussion

Safety

Any additional benefit of radical surgery with TME or APER in patients with a CCR to CRT is unproven, because the cancer is likely to have been completely extirpated already, i.e. in the case of a subsequent pathological finding of a pCR, and the combination of SCPRT/ CRT and surgery is associated with inferior function and quality of life (QOL). Some enthusiasts have extended the Brazilian non-operative strategy to "watch and wait" for cancers in the mid and upper rectum even if the original tumour extended to the circumferential resection margin (CRM). Our MDT has concerns regarding broadening the approach beyond the Brazilian criteria where salvage is usually achieved [25] to more advanced patients because local regrowth in these patients may not be endoluminal and recurrence at the mesorectal fascia could compromise a curative salvage resection.

Several themes keep surfacing across the disciplines. The uncertainty involved in not removing the cancer appears pivotal. It is a surgical tenet that a cancer should be removed radically in its entirety as soon as possible after diagnosis in order to achieve the best outcomes. It took a long time and several randomized studies to persuade surgeons that any delay to surgery could be acceptable with the use of neoadjuvant CRT or SCPRT. However, a non-operative strategy raises the concern that the cancer may still be present (albeit at a microscopic level) and the delay may allow regrowth to become unresectable, raising the spectre of uncontrolled disease within the pelvis, or to metastasize to distant organs.

The CNS has concerns on how to be open and honest with the patient when the evidence is so anecdotal, and there are no randomized studies to say we are sure about this.

The oncologist has the concern that if the cancer has not been eradicated, then the regrowth may be more resistant to cytotoxic agents and no further radiotherapy will be available because it has already been employed. Metastasis may be more likely if irradiated, but still, viable tumour remains after irradiation [32, 33].

If the original decision had been to avoid surgery, higher doses of radiotherapy or brachytherapy would have been used. There is good evidence that brachytherapy can achieve high rates of CCR [34••], achieving good sphincter function in the majority, but bleeding from the rectal mucosa is a recognized late toxicity.

All disciplines have worries that the confirmation of a CCR is an imperfect science because the radiologist cannot distinguish between active microscopic residual cancer and mucin- or CRT-induced fibrosis. Without resorting to full pathological examination of the whole mesorectum, nodal status is uncertain. Transrectal ultrasound and CT have poor reliability. Some authors suggest that using both standard T2-weighted MRI and diffusion-weighted MRI can enhance the sensitivity for identifying a CCR, with a specificity of >90 % [27]. Others suggest MRI restaging can lead to either over-staging or under-staging [35]. It is also sometimes difficult to distinguish between tumour and radiation-induced ulceration or proctitis. Small residual extramural tumours may be obscured by persistent fibrosis, or small pelvic nodes initially not imaged may remain involved [36]. Also, a decrease in the standard uptake values (SUVmax) on PET/CT of >67 % between baseline and 6-week SUVmax or 76 % between baseline and 12-week SUVmax may help to [22] discriminate between responders and poor responders and allow a longer wait to be undertaken safely.

The change in carcinoembryonic antigen levels may be helpful to confirm a CCR [37], but even a biopsy after the completion of chemoradiation may not give sufficient information. Any irregularity on DRE of the mucosal surface or tissues beneath could herald persistent disease, and biopsy can only confirm disease recurrence, but not the absence of tumour in the pelvis. Biopsies at 6–12 weeks following CRT are potentially misleading because although a positive biopsy in the area of the rolled edges of the original has some use in deciding management, non-viable cancer cells may appear morphologically intact [38]; it is difficult to define the best site to biopsy, and in contrast, an absence of cells does not necessarily infer a pCR [39, 40]. Biopsy is therefore likely to provide both false positives and false negatives [41].

Non-operative management of LARC patients with a ycCR following CRT may be feasible with strict selection criteria and frequent follow-up and may be more relevant for older adults [42] and for patients with severe comorbidity, particularly if a permanent colostomy is envisaged.

There are prospective trials of deferral of surgery in good responders [43], but there are no randomized prospective studies. The most recent Brazilian series showed favourable outcomes, which are supported by a small Dutch, English and American study [11, 25, 26, 44, 45•]. In the Dutch series [26] only 1/21 patients experienced an endoluminal local recurrence at 22 months. All studies were heterogeneous in staging, inclusion criteria, study design and rigour of follow-up post-CRT, which might explain the different outcomes. Our MDT recognized that CCR is inconsistently defined, with only partial concordance with pCR. There was anxiety that patients who are observed but subsequently fail to sustain a CCR may fare worse than those immediately resected. However, overall other studies outside Brazil and the Netherlands have documented less encouraging results for unselected patients (unfit for or refusing surgery) using lower doses of radiotherapy, in more advanced cases and employing less rigorous follow-up [45•, 46–51] (see Table 1).

Histopathological pCR and CCR appear to be slightly different clinical entities with different prognostic factors and possibility of management. If small early tumours are irradiated, there is a high rate of pCR [52•, 53, 54] and a high rate of CCR (about 40 %) and high rate of concordance between pCR and CCR (about 70 %). In the ACOSOG Z6041 trial, a CCR was concordant with a ypCR in 31 of 36 patients (86 %) [54]. For larger more advanced tumours, there is a more moderate rate of achieving a pCR (about 15 %), with a much lower rate of CCR (about 5 %) and a low rate of concordance between pCR and CCR (in about 70–80 % of patients with pCR, clinically persistent (fibrous) tumour is present).

Most local regrowth occurs within 12 months and can be salvaged successfully, but prospective trials are needed to confirm these findings. Cancers arising in the mid rectum above 7 cm from the anal verge (which are not treated with a selective non-operative approach by Habr-Gama and Perez) are more difficult to keep under surveillance if beyond the reach of the finger, and endoluminal failure, although often the first event, is more difficult to detect.

Additional Chemotherapy

More recent series from Brazil have extended the initial delivery of 5-fluorouracil and folinic acid following the chemoradiation component and claimed higher rates of CCR [25]. The series from the Netherlands added FOLFOX in the majority of

Table 1 Published reports of a non-operative strategy in rectal cancer after finding CCR or near CCR

	No	CCR	Failing
Rossi 1998	16	38 %	5/6=83 %
Lim 2007	48	56 %	18/48=38 %
Hughes 2008	32	12 %	6/10=60 %
Seshadri 2011	23	?	10/23=43 %
Dalton 2011	12	24 %	6/12=50 %
Yu 2011	22	?	9/22=41 %
Maas 2011	192	21 %	1/21=5 %
Smith 2012	?	32 %	6/32=19 %
Yeo 2013	577	5 %	2/5=40 % 176 pts

? not stated

cases after CCR was achieved even in clinically staged II patients [26]. Finally recent data from the Memorial Sloan Kettering suggests that additional courses of FOLFOX after chemoradiation and before total mesorectal excision have the potential to increase pCR and hence theoretically could broaden the options for patients in terms of less invasive treatment strategies [55••]. Yet in the postoperative adjuvant setting, chemotherapy has only improved local control and made no impact on DFS or OS [56].

Our current inability to distinguish and discriminate when a tumour has been completely destroyed, and the lack of overlap between a CCR and a PCR, has caused concern for some clinicians. Equally, patients who continue to show residual abnormalities following CRT, such as ulceration or an indurated mass, often demonstrate a pCR despite these unfavourable appearances. This finding has persuaded some authors that it is safe to delay surgery for even longer in an attempt to capture all who will eventually express a pCR. They argue that we should routinely defer surgery if a good response is observed allowing an opportunity for further/complete resolution of tumour to occur. This philosophy lies behind the ongoing deferral of surgery trial (NCT01047969) sponsored by the Royal Marsden [43].

Conclusion

In the MDT, anxieties remain regarding the reproducibility of published results and the long-term oncological outcomes. The rationale of a "wait and see policy" relies mainly on retrospective observations, with prospective studies small and more recent, with shorter follow-up. Surgical resection is still regarded by most surgeons as the mainstay of curative therapy. Omission of such surgery in selected patients clearly limits many common adverse effects. However, the available studies suggest there is likely to be a 25–30 % risk of eventual local tumour regrowth, which is almost invariably endoluminal if patients are rigorously followed up. Proof of principle for safety has been demonstrated in small low rectal cancers, where clinical assessment is easy. But, the approach should not be extrapolated uncritically to more advanced cancers beyond DRE, where the CRM is predicted threatened and initial nodal involvement is common. Regrowth could compromise cure. Long-term prospective observational studies and randomized studies with more uniform inclusion criteria are required to evaluate the risk-benefit.

It must be emphasized that non-operative management requires frequent endoscopic and radiographic surveillance with long-term follow-up. Optimal shared decision-making requires all members of the team to be well informed. Surgeons, oncologists, nurse navigators and patients need to know the risks and to quantify the gains in function and QOL against the potential risk of compromising cure. Surgeons also need to be both open-minded and motivated to consider all possible options.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
2. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-T4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24:4620–5.
3. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemoradiotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355:1114–23.
4. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Alegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R03. J Clin Oncol. 2009;27:5124–30.
5. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, for the Polish Colorectal Study Group. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23.
6. Bruheim K, Guren MG, Dahl AA, et al. Sexual function in males after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2010;76(4):1012–7.
7. Camilleri-Brennan J, Steele RJ. Objective assessment of morbidity and quality of life after surgery for low rectal cancer. Color Dis. 2002;4:61–6.
8. Feddern ML, Jensen TS, Laurberg S. Chronic pain in the pelvic area or lower extremities after rectal cancer treatment and its impact on quality of life. A population-based, cross-sectional study. Pain. 2015.
9. Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. Color Dis. 2013;15(9):1130–9.
10. Chen TY, Wiltink LM, Nout RA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. Clin Colorectal Cancer. 2014. doi:10.1016/j.clcc.2014.12.007.
11. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg. 2006;10(10):1319–28.

12. Habr-Gama A, de Souza PM, Ribeiro U, Nadalin W, Sousa GR, Jr AH, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum. 1998;41:1087–96.
13. Habr-Gama A, de Souza PM, Ribeiro U. Multimodality therapy in low rectal cancer: long-term outcome of complete responders. Dis Colon Rectum. 2001;44:A18.
14. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro Jr U, Silva e Sousa Jr AH, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240:711–71.
15. Habr-Gama A, Perez RO, Nadalin W, Nahas SC, Ribeiro Jr U, Silva E, et al. Long-term results of preoperative chemoradiation for distal rectal cancer: correlation between final stage and survival. J Gastrointest Surg. 2005;9:90–101.
16. Habr-Gama A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Color Dis. 2006;8 suppl 3:21–4.
17. Habr-Gama A, Perez RO, Sabbaga J, et al. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum. 2009;52(12):1927–34.
18. Habr Gama A, Perez R, Proscurshim I, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation for distal rectal cancer. Surg Oncol Clin N Am. 2010;19:829–45.
19. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum. 2010;53(12):1692–8.
20. Habr-Gama A, Perez RO, São Julião GP, Proscurshim I, Nahas SC, Gama-Rodrigues J. Factors affecting management decisions in rectal cancer in clinical practice: results from a national survey. Tech Coloproctol. 2011;15(1):45–51.
21. Habr-Gama A, Perez RO, São Julião GP, Proscurshim I, Gama-Rodrigues J. Nonoperative approaches to rectal cancer: a critical evaluation. Semin Radiat Oncol. 2011;21(3):234–9.
22. Perez RO, Habr-Gama A, São Julião GP, et al. Predicting complete response to neoadjuvant CRT for distal rectal cancer using sequential PET/CT imaging. Tech Coloproctol. 2014;18(8):699–708.
23.• Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88(4):822–8. **This report suggests that patients are not disadvantaged by a 'watch and wait' approach even if they fail as salvage is the norm, and few have uncontrolled disease in the pelvis**.
24. Habr-Gama A, São Julião GP, Perez RO. Nonoperative management of rectal cancer: identifying the ideal patients. Hematol Oncol Clin N Am. 2015;29(1):135–51.
25. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109–17.
26. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633–40.
27. Lambregts DM, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol. 2011;18:2224–31.
28. Wynn GR, Bhasin N, Macklin CP, George ML. Complete clinical response to neoadjuvant chemoradiotherapy in patients with rectal cancer: opinions of British and Irish specialists. Color Dis. 2010;12(4):327–33.
29. Rouanet P. Complete response for rectal carcinoma after neoadjuvant therapy: to operate or not to operate? Surgeon's view. Bull Cancer. 2011;98(1):25–9.
30. Chang GJ. 'Watch-and-wait' for rectal cancer: what's the way forward? Oncology (Williston Park). 2014;28(7):617–8.
31. Manceau G, Panis Y. Is there a place for organ preservation in infiltrating rectal cancer? Minerva Chir. 2015;70(4):283–96.
32. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH, Pathology Review Committee; Cooperative Clinical Investigators. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol. 2002;26(3):350–7.
33. Gosens MJ, Klaassen RA, Tan-Go I, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. Clin Cancer Res. 2007;13(22 Pt 1):6617–23.
34.•• Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015. doi:10.1016/S1470-2045(15)00120-5. **A very important study which suggests that boosting the dose to the primary tumour with brachytherapy can facilitate a 'watch and wait' strategy**.
35. Huh JW, Kim HC, Lee SJ, et al. Diagnostic accuracy and prognostic impact of restaging by magnetic resonance imaging after preoperative chemoradiotherapy in patients with rectal cancer. Radiother Oncol. 2014;113(1):24–8.
36. Perez RO, Pereira DD, Proscurshim I, Gama-Rodrigues J, Rawet V, São Julião GP, et al. Lymph node size in rectal cancer following neoadjuvant chemoradiation—can we rely on radiologic nodal staging after chemoradiation? Dis Colon Rectum. 2009;52(7):1278–84.
37. Perez RO, Sao Juliao GP, Habr Gama A, Kiss D, Proscurshim I, Campos FG, et al. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemotherapy for distal rectal cancer. Dis Colon Rectum. 2009;52(6):1137–43.
38. Suit HD, Gallagher HS. Intact tumor cells in irradiated tissue. Arch Pathol. 1964;78:648–51.
39. Smith FM, Chang KH, Sheahan K, et al. The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy. Br J Surg. 2012;99(7):993–1001.
40. Smith FM, Wiland H, Mace A, et al. Depth and lateral spread of microscopic residual rectal cancer after neoadjuvant chemoradiation: implications for treatment decisions. Color Dis. 2014;16(8):610–5.
41. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. Assessment of a novel, full-thickness incisional biopsy model to restage rectal tumours after neoadjuvant chemoradiotherapy: results of an ex vivo pilot study. Tech Coloproctol. 2015;19(3):159–64.
42. Smith FM, Rao C, Oliva Perez R, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum. 2015;58(2):159–71.
43. Yu SK, Brown G, Heald RJ, Chua S, Cook G, Barbachano Y, et al. Deferral of rectal surgery following a continued response to preoperative chemoradiotherapy (Watch and Wait) study: a phase II multicenter study in the United Kingdom. J Clin Oncol. 2011;29(suppl 4; abstr 489).
44. Dalton R, Velineni R, Osborne M, et al. A single centre experience of chemo-radiotherapy for rectal cancer: is there potential for non-operative management? Color Dis. 2012;14(5):567–71.
45.• Smith JJ, Chow OS, Eaton A, et al. Organ preservation in patients with rectal cancer with clinical complete response after neoadjuvant therapy. 2015 ASCO Gastrointestinal Cancers Symposium.

Abstract 509. **This is an important study which confirms the feasibility of a watch and wait strategy in a unit outside Brazil**.

46. Rossi B, Nakagawa W, Novaes P, Filho WD, Lopes A. Radiation and chemotherapy instead of surgery for low infiltrative rectal adenocarcinoma: a prospective trial. Ann Surg Oncol. 1998;5(2):113–8.
47. Lim L, Chao M, Shapiro J, Millar JL, Kipp D, Rezo A, et al. Long term outcomes of patients with localized rectal cancer treated with chemoradiation or radiotherapy alone because of medical inoperability or patient refusal. Dis Colon Rectum. 2007;50(12):2032–9.
48. Hughes R, Harrison M, Glynne-Jones R. Could a wait and see policy be justified in T3/4 rectal cancers after chemo-radiotherapy? Acta Oncol. 2010;49(3):378–81.
49. Seshadri R. Clinical complete response following neoadjuvant chemoradiation for rectal cancers: can surgery be avoided? Ann Oncol 2011; 22 (suppl 5) v133 (abstract P-0410).
50. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg. 2012;256:965–72.
51. Yeo SG, Kim DY, Oh JH. Long-term survival without surgery following a complete response to preoperative chemoradiotherapy for rectal cancer: a case series. Oncol Lett. 2013;6(6):1573–6.
52.• Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer. Lancet Oncol. 2010;11(9):835–44. **This pooled analysis shows the highly favourable outcomes when a pCR is achieved after chemoradiotherapy, and suggests a pCR is much easier to attain for early stage cancers**.
53. Gérard JP, Chamorey E, Gourgou-Bourgade S, Benezery K, de Laroche G, Mahé MA, et al. Clinical complete response (cCR) after neoadjuvant chemoradiotherapy and conservative treatment in rectal cancer. Findings from the ACCORD 12/PRODIGE 2 randomized trial. Radiother Oncol. 2015;115(2):246–52.
54. Garcia-Aguilar J, Shi Q, Thomas Jr CR, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol. 2012;19(2):384–91.
55.•• Garcia-Aguilar J, Chow OS, Smith DD, et al. Timing of Rectal Cancer Response to Chemoradiation Consortium. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015. doi:10.1016/S1470-2045(15)00004-2. **This study suggests additional chemotherapy following chemoradiation may enhance the chance of achieving a pathological complete response at surgery and hence broaden the options for patients in terms of a non-operative strategy**.
56. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(2):200–7. doi:10.1016/S1470-2045(14)71199-4.