

The modern approach to managing locally advanced rectal cancer

The traditional approach to managing locally advanced rectal cancer has shifted to the concept of total mesorectal excision and the use of MRI for local staging and selecting patients for multimodal therapy. This case report highlights the key role of the pathologist, the benefits of preoperative concurrent chemoradiation and the importance of multidisciplinary discussion.

The last few years have seen some major changes in the management of rectal cancer. The old standards developed by the US National Institutes for Health in 1990 have now largely been left behind. The classical approach was to carry out surgical resection, followed by a pathology assessment of penetration of the tumour into the bowel wall, and the involvement of lymph nodes. This allowed us to estimate the stage and risk. Treatment was based on classical TNM factors, as recommended by the NIH consensus conference (Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990, 264:1444–1450). Surgery would be followed by postoperative concurrent chemoradiation, which had been shown to improve survival.

THE MODERN APPROACH

MRI staging

The first major change in the approach currently taken to rectal cancer is MRI staging before surgery. The mesorectum – the


European School of Oncology
e-grandround



The European School of Oncology now presents fortnightly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues with leading European experts in the field, from controversial areas and the latest scientific developments to challenging clinical cases. One of these will be selected for publication in each issue of *Cancer World*.

In this e-grandround, Andrés Cervantes, associate professor of medicine at the Hospital Clínico Universitario, Valencia, Spain, reviews a challenging case of locally advanced rectal cancer. His presentation was summarised by Sue Mayor.

The recorded version of this e-grandround, together with 25 minutes of discussion, is available at <http://tiny.cc/rectalcancer>

THE CASE

Presenting symptoms

A 55-year-old man presented with: constipation and rectal bleeding; false diarrhoea; increased urinary frequency; 20 kg weight loss in the last three months; performance status of 1.



Diagnostic tests

Physical examination detected no peripheral lymph nodes and no signs of ascitis or pleural effusion. A digital rectal exam detected a tumour at 10 cm from the anal edge with fixation of the surrounding tissues from 5 cm.

Rigid rectoscopy confirmed a fixed tumour at 10 cm from the anal verge completely obstructing the rectum.

Biopsy showed poorly differentiated invasive adenocarcinoma of the rectum.

Colonoscopy detected a tumour at 15 cm. The flexible colonoscope was not able to pass the rectal mass.

Endoscopic ultrasonography was not performed because it was not possible to go through the rectal mass.

Blood tests showed no anaemia or leucocytosis.

Biochemistry was within normal range, and there were no liver alterations. Carcinoembryonic antigen was 2.9 ng/ml.

Chest and abdominal CT scans showed no evidence of metastatic disease.

Barium enema showed the tumour starting 10 cm from anal verge. It was extensive, going up the colon for a considerable length.

fascia surrounding the rectum – can be visualised clearly by MRI (see p17).

The MRI scans show this patient has a bulky rectal tumour above the levators and located at 10 cm from the anal verge. There are several lymph nodes with suspected neoplastic involvement above the tumour. There is invasion of the presacral space and of the mesorectal fascia (circumferential resection margin) at the lateral left side. There was also suspected involvement of the right ureter and an extramural invasion of more than 10 mm, but no vascular invasion.

Multidisciplinary team discussion

The next step after MRI staging is multidisciplinary team (MDT) discussion. One of the main tasks for the MDT is to select patients for preoperative therapy. This includes systemic staging, which would usually include CT of the thorax and abdomen. However, the patient did not have metastatic disease. Local staging was performed using rectoscopy, endorectal ultrasound and digital rectal examination.

After local staging, MRI has a key role in defining:

- the circumferential resection margin (CRM) involvement – if it is T3-4 or is arising at, or below, the level of origin of the levator muscles. This is more or less the lower third of rectum and should be considered high risk
- extramural spread of more than 5 mm
- extramural vein invasion

- peritoneal involvement. If this is in the upper third of rectum, patients are at risk of the CRM being involved, and we would recommend preoperative treatment.

There are essentially three different groups of patients in terms of preoperative treatment strategies (see table below).

For group A, the risk is very low. This includes patients with T1, T2 or even T3 tumours, but less than 5 mm in diameter and no affected lymph nodes, or very small ones. For this group, we predict the CRM will be negative, so the patient can go to surgery. In contrast, for patients in group C, we predict that the CRM is going to be involved, so preoperative chemoradiation is indicated. In the middle group, it is safer for patients to have preoperative chemoradiation.

The impact of MDTs on surgery outcomes

The importance of MRI data being discussed with the MDT is illustrated by data published by Royal Marsden Hospital in the UK (Burton et al. *Br J Cancer* 2006, 94:391–397). From a total of 298 patients with rectal cancer, 76% of the 259 patients considered to be potentially curative were discussed in a MDT. Of these, 81 (41%) were considered to require preoperative therapy. Of those going to surgery alone, 97% had negative margins indicating that decision making was generally correct.

SELECTION OF PATIENTS FOR PREOPERATIVE THERAPY

Treatment group	MRI features	Treatment strategy
A	T1-2, T3 <5 mm, N0-1, Predicted CRM-	TME surgery
B	T3>5 mm, T4 N2 Predicted CRM-	Pre-op chemoradiation
C	Predicted CRM+	Pre-op chemoradiation

However, in the 62 patients not discussed by an MDT, where decisions were reached on an individual basis, 100% were sent on to surgery alone. A very high proportion – 26% – were found to have histological involvement of the margin, posing a high risk of local and systemic relapse.

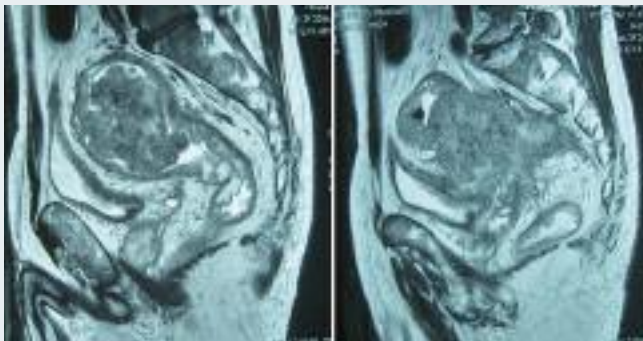
These data support a MDT discussion before taking decisions. Benefits include:

- improved coordination of care
- each case considered from the variety of perspectives provided by the MDT
- patients more likely to be offered a range of types of treatment at appropriate times
- a supportive environment where professionals can share their concerns
- feedback to the surgeons from histopathologists and other team members on the results of their work
- an optimal setting for clinical research.

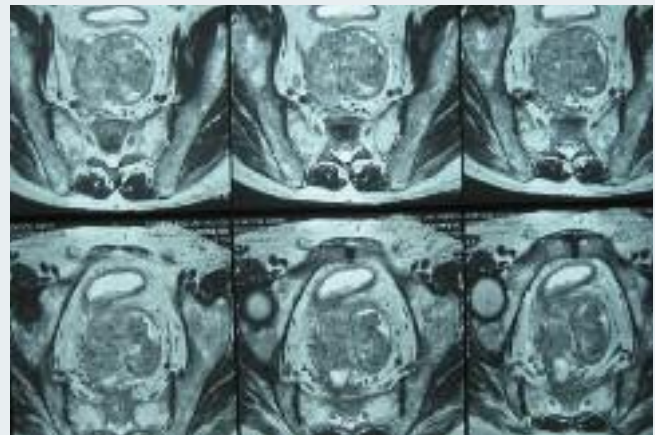
Preoperative chemoradiation

The MDT agreed that chemoradiation was indicated in the patient being considered in this e-grandround. The treatment plan was capecitabine (1,300 mg/m² per day from day 1 to the end of radiotherapy. Radiotherapy was 6 MeV photons at a dose of 45 Gy (180 cGy/day for

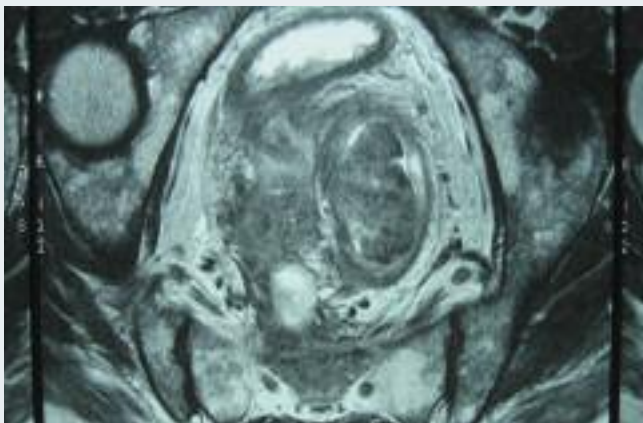
Magnetic resonance imaging



1. In this patient, MRI shows a very extensive tumour almost invading the sacrum, which is also pressing on the urinary bladder. This explains the urinary frequency that the patient was experiencing



2. The axial views depict the circumferential fascia as a straight line. The fact that the left part of this line is not well depicted indicates that the tumour is invading the pelvic wall



3. On the left side, the tumour can be seen completely invading the mesorectal fascia



4. The diagram drawn by the surgeon in the surgical report indicates that the tumour could not be resected because it was firmly adherent to structures in the pelvic wall

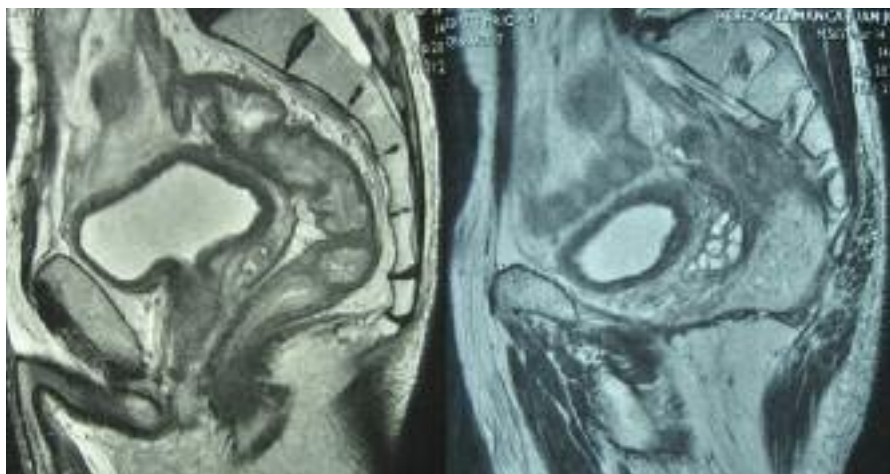
5 days/week), which took five weeks. Surgery was indicated 5–6 weeks after.

Side-effects included grade 1 diarrhoea and grade 1 cystitis with some urinary symptoms. There were no delays in dose due to toxicity, and radiotherapy was given as planned, over a five-week period.

TME surgical resection

MRI was performed before proceeding to total mesorectal excision (TME) surgical resection. This showed clear shrinkage of the tumour, with the bladder no longer being constricted by the tumour. However, despite this shrinkage, the tumour was still in contact with the presacral area towards the spine. The margin on the lateral right side was involved. We had to discuss the case very carefully with the surgeons, who, because of a lack of previous experience in operating on what had been considered a completely unresectable tumour, were reluctant to go ahead with surgery, but we considered that it was justified.

Surgery was performed six weeks after radiotherapy ended. A TME was performed with a sphincter-saving procedure (anterior resection); the levators were not involved. The patient also underwent a temporary ileostomy.



MRI assessment after chemoradiation. Shrinkage is clear, and the bladder is no longer pressed by the tumour. However, at the back, the tumour is still in contact with the presacral area

Pathology and risk assessment after surgery

The next step is a pathological assessment and estimation of risk. The classical pathology approach would be to assess bowel wall invasion, regional lymph node involvement and distant metastasis. The current pathological approach includes three further important assessments:

- the macroscopic integrity of the mesorectum
- the distance to CRM
- staging after preoperative chemoradiation.

The pathologist also audits the surgical skills applied, assessing the macroscopic of the excised mesorectum. Pathologists should

define planes of surgery as follows:

Mesorectal plane: intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; smooth CRM on slicing.

Intramesorectal plane: moderate bulk to mesorectum, but irregularity of the surface; moderate distal coning; muscularis propria not visible; moderate irregularity of the CRM.

Muscularis propria plane: little bulk to mesorectum with defects down onto muscularis propria and or very irregular CRM (Quirke et al, ASCO 2006).

Macroscopic assessment of the resected mesorectum showed an irregular area in the front section, in front of the sacrum, close to the presacral space. Ink staining showed that the mesorectal surface was smooth, with no mesorectum in the pelvic wall.

The pathology report showed that the rectosigmoidectomy specimen was 16 cm in length. The quality of the anterior mesorectum was complete, but the posterior mesorectum was partially complete.



Macroscopic assessment of the resected specimen

The tumour was located at 7 cm from one of the borders. The distal and circumferential margins were free, with the circumferential margin (macroscopically) at 7 mm from the tumour edge.

Microscopic assessment showed that there was extensive fibrosis. The tumour had completely regressed. There was some indication of postradiation angitis. None of the 23 lymph nodes examined were involved (ypT0 ypN0) – this was a good number to analyse as it is not easy to obtain a large number in surgical resection after radiation. Overall, the specimen indicated pathologically complete remission.

Postoperative chemotherapy

The patient should receive postoperative chemotherapy if this is indicated. Randomised trials over the last 28 years have shown major achievements in control of local relapse. In the early 1980s, 25%–30% of patients had local relapse, but recent trials with TME plus chemo-

therapy show this rate has fallen to 5%.

In contrast, the proportion of patients presenting with distal metastases has shown almost no change from the early 1980s to today.

There is currently no consensus on the use of adjuvant chemotherapy in patients with resected rectal cancer, but its use is widespread. Recent data from the UK QUASAR study (*Lancet* 2007, 370:2020–2029) for patients with an uncertain indication showed significant improvement in five-year survival with chemotherapy ($P=0.02$). In the subgroup of patients with rectal cancers, the benefit was marginal but almost significant ($P=0.06$).

Follow up

The patient had an intraoperative colonoscopy, which showed the absence of metachronic tumour or polyps. He was not given postoperative chemotherapy because he had a presacral abscess and slow recovery after surgery. The

ileostomy was reversed after six months. At two-year follow-up, his CEA was 1.9 ng/ml, which was within normal levels. Thoracic, abdominal and pelvic CT scans showed no evidence of metastatic disease and no local relapse.

Conclusions

In this patient, who presented with unresectable rectal cancer but no metastatic disease, multidisciplinary discussion was essential in optimising the treatment strategy, as for all rectal cancer cases. Successful multimodality treatment was given, with an R0 resection (complete resection with no microscopic residual tumour), and there was no relapse at two years. This case was the first I have had in which a patient underwent a colostomy in order to avoid obstruction during chemoradiation.

In conclusion, unresectable rectal cancer should be treated with concurrent chemoradiation using a multidisciplinary team approach.



Robert Glynn-Jones (RG-J), of the Mount Vernon Centre for Cancer Treatment, Northwood, UK, put questions to Andrés Cervantes (AC) about the case.



RG-J: You must have been delighted that you started off with a bulky tumour and got such a fantastic response. Is there more risk of an anastomotic leak with advanced tumours?

AC: Not with our surgical team. They always proceed to protective ileostomy and then close the ileostomy 4–6 months after treatment is complete to avoid leaks.

RG-J: In terms of the regression grades, a complete pathological response is very clear. How reproducible are the other regression grades?

AC: This requires some experience. We have gained experience discussing

all our cases and we try to reproduce the recommendation of Philip Quirke in having at least 20 slides of the specimen revised. If the pathologist is not careful, the probability of regression may be higher.

I think that sometimes it may be complicated to have the five grades, as proposed by Dvorak. However, good regression grades are related to better outcome – this is the best validity of the grading system.

RG-J: What about the standardisation of preoperative chemoradiation for all patients, even T1 and local excision? You would not usually give preoperative

chemoradiation for all patients?

AC: No. I do not like the approach of ignoring the patient in front of you and going straight to preoperative chemoradiation, because there are long-term toxicities, including sexual problems, urinary problems and problems with the sphincters after radiation. I prefer to select patients with MRI, because this reveals tumours that are involved or close to the margin, making it clear when we should give preoperative chemoradiation. ▶

Even if people do not feel that surgery is safe, I would consider preoperative chemoradiation, because with a mesorectal margin involved, it is difficult to put things back in the right way. I think people should think about it, but I would not consider preoperative therapy for all.

RG-J: *The original surgeon defunctioned the patient because of fear of obstruction. Right at beginning you could not introduce ultrasound because it was a very bulky tumour. Do you have a policy of when you defunction patients routinely?*

AC: In our series of 120 patients over the last seven years, we have defunctioned only two or three patients – those presenting with impending obstruction. It is important that the surgeon should not remove the tumour in these patients, which are locally advanced cases. Instead, a defunctioning colostomy should be performed. This takes one week – then you can start preoperative chemoradiation. However, this problem is very infrequent.

RG-J: *We saw the value of MRI in relation to the circumferential margin. What about lower down, below the levator? Does your MDT feel as confident in that?*

AC: In T3 and T4, we go directly to preoperative chemoradiation. However, the surgical team tries to confirm if the levators are involved with the tumour. If they are, and MRI is very clear on that, then a sphincter-preserving procedure may not be indicated.

RG-J: *You routinely operate 5–6 weeks after completion of chemoradiation. Do you restage patients with another CT to make sure they haven't developed disease outside the pelvis?*

AC: Yes, especially in trials, we always

do. When we give preoperative chemoradiation this adds 5–6 weeks, making 12 weeks in all. This is not a long time. But we do MRI just before surgery. Sometimes, we recommend restaging the liver or lung.

RG-J: *What about giving chemotherapy after surgery? This is an area where it can be difficult to make decisions. In a patient with a pathological complete response, are you going to give more chemotherapy?*

AC: Treating patients with locally advanced disease, there is no level 1 evidence, but I consider that adjuvant postoperative therapy may be beneficial. It is difficult to differentiate patients with colon cancers from those with rectal cancers. We have achieved major improvements in colon cancer. But if the control of systemic disease in patients with rectal cancer is not good, the situation is more difficult. In our programme, we favour postoperative chemotherapy for these patients. But the patient presented in our case study had mild chemotherapy – just capecitabine and radiation, and no oxaliplatin. It would be useful to have randomised controlled trials showing the effect of adding oxaliplatin.

RG-J: *What happens when patients don't respond to chemoradiation?*

AC: Assessment has to be done in the pathology report. If the pathology report after surgery indicates a bulky tumour, positive lymph nodes and vascular invasion, these are very negative signs indicating a high risk of relapse. There are several options. If the patient has had chemotherapy with 5-FU or an oral fluoropyrimidine, I would go ahead with oxaliplatin plus 5-FU. If the patient has had an R0 resection but is resistant to chemotherapy, they are probably OK and we would follow them up and give chemotherapy when

they relapse. I am not sure of the role of chemotherapy in patients who are resistant to chemoradiation.

RG-J: *In the UK, we give a short course of chemoradiation. Is there any role for short-course radiotherapy? We argue about this a lot, with concerns about morbidity for early tumours which MRI suggests are resectable.*

AC: The evidence is there, with three randomised controlled trials showing better local control. Before the use of MRI, I think it had a definite role. In patients who cannot tolerate chemoradiation, short-course radiation is a possibility. The problem is that it doesn't downsize tumours, so I am reluctant to give it for locally advanced tumours by MRI.

RG-J: *On another issue, how much do surgeons like having the quality of the mesorectum documented?*

AC: In our team, the surgical group is quite sensitive about this point. They have performed a lot of studies on this issue. Especially in the lower third, the results show they should check carefully. Reporting gives them feedback, improving the final result. It has been good to see the quality of surgery improving over the years. Now, we have 100% data on sphincters in pathology reports, which were almost absent five years ago. So we are sure the levators are in the specimen and analysed by the pathologist. These are points of quality. The way forward is for the surgical group to understand that feedback from pathology improves quality.

RG-J: *It's also a way of validating the MRI decision – you need the report on quality to validate this. If after surgery there is 20% involvement of the circumferential resection margin, you know that the decision was not well founded. Pathology helps us to move in the right direction.*