Clinical, radiological and pathological prognostic factors for local relapse, distant metastases and long-term survival in patients with locally advanced rectal cancer treated with neoadjuvant long-course oral fluoropyrimidine- and oxaliplatin-based chemoradiotherapy and total mesorectal excision:

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TESIS DOCTORAL

Clinical, radiological and pathological prognostic factors for local relapse, distant metastases and long-term survival in patients with locally advanced rectal cancer treated with neoadjuvant long-course oral fluoropyrimidine- and oxaliplatin-based chemoradiotherapy and total mesorectal excision:

Can we move towards a more personalised approach?

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Background: Neoadjuvant radiotherapy previous to radical surgery, both as short-course radiotherapy (SCRT) and as long-course radiotherapy combined with 5-FU-based chemotherapy (LCRCT), is routinely used in the management of locally advanced rectal cancer, with consistent benefits in the reduction of the local relapse risk. Unfortunately, survival benefits have been elusive to demonstrate with this approach, especially in the setting of radical surgery in the form of total mesorectal excision (TME). Concerns about over-treating early-stage patients and of the possible long-term side effects have also cast more doubts in a blanket approach of treating all patients with neoadjuvant radiotherapy, especially with LCRT.

Material and methods: Retrospective review of a prospective base of patients with cT3-T4 and/or N+ rectal cancer treated at our Institution between 1999 and 2014 with LCRCT and oral fluoropyrimidines and (in 65% of patients) oxaliplatin, followed by TME and adjuvant 5-FU-based chemotherapy. We report clinical, radiological and pathological prognostic factors for local relapse, distant metastases and long-term survival endpoints (disease-free survival (DFS) and overall survival (OS))

Results: 203 patients were analysed. The risk of early progression was small and most proceeded to surgery; a TME was done in 89.7%. The downstaging rate was 70.4% and the pathological complete response rate was 14.9%. No benefit was seen with the addition of oxaliplatin to LCRCT.

Local relapse rate was 8.3%. Risk factors for local relapse and distant metastases were, to a varying degree for each situation, an unsuccessful TME, the unsatisfactory quality of the mesorectum, an R2 resection, involvement of the circumferential (CRM) and distal margins, no downstaging, poorly differentiated tumours, moderate or minimal regression, perineural invasion, pathological lymph node invasion and heavy lymph node burden. Classical pathological data such as ypT and ypN stage were better prognostic factors than tumour regression grading. In the multivariate analysis, CRM and perineural invasion retained their prognostic value.

Compliance to adjuvant chemotherapy was poor, especially in elderly patients; less than half of patients received the full intended dose.

5- and 10-year DFS and OS were 71.4% and 54.9% and 75.4% and 62.4%, respectively. Elderly patients had an overall worse survival compared to younger patients; this was linked to higher unexpected toxicity and a lower compliance with LCRCT and adjuvant chemotherapy. Mucinous tumours showed a very poor response to LCRCT. Significant factors in the multivariate analysis for OS and DFS were older age, CRM involvement, an unsuccessful TME and a heavy lymph node burden.

Conclusions: The prognosis of patients with locally advanced rectal cancer is determined by two competing factors: the risk of local relapse and the risk of distant metastases. The identification of patients with an extremely low risk of local relapse where radiotherapy would presumably offer little benefit is based on the premise of an exquisite imaging staging with MRI, supplemented with EUS, and a surgical team specialized in the TME procedure. A free CRM and a successful TME procedure are the most important factors; lower rectal tumours and a heavy lymph node burden are also important. In patients with invasion of the mesorectal fascia in the MRI, LCRCT should be used in order to lower the risk of a positive CRM. The role of adjuvant chemotherapy remains surprisingly undefined, although the compliance rates are poor in all published trials. Neoadjuvant chemotherapy is a possible option, especially in patients with a higher risk of distant metastases. On the other hand, other, better tolerated, options such as SCRT should be used in elderly or frail patients.

Fundamentos: La radioterapia (RT) neoadyuvante previa a la cirugía, ya sea la radioterapia de duración corta (RTDC) como la radioterapia de duración larga combinada con quimioterapia (QT) basada en 5-FU (QRTLD), es usada de forma rutinaria en el manejo del cáncer de recto localmente avanzado, con beneficios consistentes en el riesgo de recidiva local. Desafortunadamente, no se han podido demostrar mejorías en la supervivencia, especialmente en los casos tratados con cirugía radical en forma de una escisión mesorectal total (EMT). El riesgo de sobretratar a algunos pacientes y los posibles efectos secundarios a largo plazo han provocado a su vez dudas sobre el manejo con RT neoadyuvante, especialmente con QRTLD, en todos los pacientes con cáncer de recto localmente avanzado independientemente de su riesgo basal de recidiva local.

Material y métodos: Revisión retrospectiva de una base prospectiva de pacientes con cáncer de recto cT3-T4 y/o cN+, tratados entre 1999 y 2014 con QRTLD basada en fluoropirimidinas orales y (en un 65%) oxaliplatino, seguido de EMT y QT adyuvante basada en 5-FU. Evaluamos factores pronóstico clínicos, radiológicos y patológicos para un mayor riesgo de recidiva local y de metástasis a distancia y una menor supervivencia libre de progresión (SLP) y supervivencia global (SG).

Resultados: 203 pacientes fueron analizados. El riesgo de progresión precoz fue bajo y la mayor parte de pacientes procedieron a cirugía; hubo una EMT satisfactoria en el 89.7%. La tasa de infraestadiaje fue del 70.4% y el porcentaje de respuestas completas patológicas fue del 14.9%. No hubo ningún beneficio con la adición de oxaliplatino a la QRTLD. La tasa de recidivas locales fue del 8.3%. Los factores de riesgo para la recidiva local y para las metástasis a distancia fueron, con un valor variable para las dos situaciones, una EMT no exitosa, la calidad insuficiente del mesorecto, una resección R2, afectación del margen circunferencial radial (MCR) y del margen distal, no infraestadiaje, tumores pobremente diferenciados, regresión tumoral moderada o mínima, invasión perineural, afectación patológica linfática y una gran carga tumoral linfática. Los factores pronóstico clásicos como el estadio ypT ó ypN tuvieron mayor importancia que la regresión tumoral patológica. En el análisis multivariante, la afectación del MCR y la invasión perineural mantuvieron la significación. La cumplimentación de la QT adyuvante fue pobre, especialmente en los pacientes ancianos; menos de la mitad recibieron la dosis completa prevista.

La SLP y SG a 5 y 10 años fue del 71.4% y 54.9% y del 75.4% y 62.4%, respectivamente. Los pacientes ancianos tuvieron una peor SLP y SG; ello estaba ligado a un aumento de las toxicidades graves no previsibles y una menor cumplimentación de la QRTLD y de la QT adyuvante. Los tumores mucinosos mostraron una respuesta muy pobre a la QRTLD. Factores significativos en el análisis multivariante para SLP y SG fueron una mayor edad, afectación del MRC, una EMT no exitosa y una gran carga tumoral linfática.

Conclusiones: El pronóstico de los pacientes con un cancer de recto está determinado por dos factores competitivos: el riesgo de recidiva local y el de las metástasis a distancia. La identificación de los pacientes con un riesgo muy bajo de recidiva local, en donde el beneficio de la RT sea escaso depende de una exquisita estadificación con RMN y de un equipo quirúrgico especializado en la EMT. Un MRC libre y una EMT exitosa son los factores más importantes; los tumores rectales bajos y la carga linfática son también importantes. La QRTLD debería ser usada en los pacientes con una fascia mesorectal afecta clínica. El papel de la QT adyuvante es controvertido, aunque la cumplimentación es pobre. La QT neoadyuvante es una opción atractiva, especialmente en los pacientes con un mayor riesgo de metástasis a distancia. Por el contrario, otras opciones menos agresivas y mejor toleradas, como la RTCD, deberían ser usadas en pacientes ancianos o frágiles.

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1. Background

Surgery remains the mainstay of curative treatment in the management of localised rectal cancer. However, chemotherapy and radiotherapy are frequently used alongside surgery in the management of resectable rectal cancer patients, due to the high local and systemic relapse seen in patients treated with only surgery. Unfortunately, the best way to integrate all of these treatment approaches is highly controversial. Short-course preoperative radiotherapy (5 Gy in 5 fractions, SCRT) is an easy and economic option and has improved local control rates in several phase III trials [1–5]. In one trial it improved overall survival (OS) [3]. Despite this, it has not gained widespread acceptance in our medium.

Most efforts have focused on the use of preoperative combined therapy with chemotherapy and conventionally fractionated long-course radiotherapy (LCRCT), usually with bolus or infusional 5-fluorouracil (5-FU) (LCRCT). The possible advantages of long-course preoperative treatment include lower toxicity, increased resectability and an increased rate of conservative surgery of the anal sphincter [6, 7]. A German trial that compared preoperative combined 5-FU-based therapy with standard 5-FU-based postoperative chemoradiotherapy in 823 patients with T3-4 or N-positive disease showed a higher local control rate and less toxicity with the neoadjuvant approach, although there was no disease-free survival (DFS) or overall survival (OS) benefit [6]. A smaller American trial of 267 patients randomised to one of those approaches showed a DFS but no OS benefit with the preoperative treatment. Strikingly, there was no local control benefit and grade 4 or higher toxicity was increased with neoadjuvant treatment [7].

Novel regimens with new agents or targeted therapies have been tested in several phase I–II trials, with promising results in improving pathological complete response (pCR) rates compared to historical comparisons, although recent phase III trials have been more disappointing. In this sense, oral fluoropyrimidines, because of their ease of administration, constitute an attractive alternative to 5-FU. UFT is one of the oral formulations of the fluoropyrimidines that combines uracil and tegafur in a fixed molar ration of 4:1. Tegafur is a prodrug that is converted to FU by the mitochondrial system of the liver. Uracil competitively inhibits dihydropyrimidine dehydrogenase, the principal enzyme responsible for the catabolism of 5-FU. Pharmacokinetic studies have demonstrated that UFT administered orally reaches plasma concentrations of 5-FU similar to when 5-FU is administered in continuous infusion [8]. Encouraging results were found with the use of UFT alongside preoperative RT in a Spanish trial of 94 patients; toxicity was mild and the pCR was 9% [9].

Capecitabine is a fluoropyrimidine carbamate that is absorbed intact through the intestinal wall and then converted to 5-FU in three sequential enzymatic reactions. The third enzyme, thymidine phosphorylase, is present at consistently higher levels in tumour compared to normal tissue, thereby providing the basis for enhanced selectivity for tumour cells and better tolerability. A phase II trial of concomitant capecitabine and radiotherapy demonstrated a pCR rate of 12%, a rate similar to that expected with infusional 5-FU [10]. Results of a phase III trial that compared capecitabine with infusional 5-FU-based chemoradiotherapy in 161 patients with resectable rectal cancer demonstrated a higher downstaging rate, although there was no survival benefit [11].

Oxaliplatin, a platinum analogue, has become an important component of treatment for advanced colorectal cancer; in addition, oxaliplatin plus 5-FU and leucovorin (LV) outperforms 5-FU/LV in the adjuvant treatment of stage III colon cancer and has been adopted as a standard regimen [12]. Oxaliplatin is usually given in

combination with 5-FU. The use of oral fluoropyrimidines and oxaliplatin is especially attractive due to the activity of the combination and the ease of administration for patients. A number of uncontrolled studies with oxaliplatin-based combined therapy (with 5-FU or oral fluoropyrimidines) in the last decade suggested at least a short-term benefit with higher rates of pCR and downstaging [13-16]. However, a possible benefit in the long-term survival rates with the use of oxaliplatin in the context of randomised trials has not been reported until recently.

In this context, we report our long-term experience with the combined use of oral fluoropyrimidines alongside oxaliplatin in a prospective fashion in the management of resectable rectal cancer treated at our institution. Our aim is to report clinical, radiological and pathological prognostic factors for local relapse, distant metastases and long-term survival endpoints (disease-free survival (DFS) and overall survival (OS)) in a fairly homogeneous population of patients treated with fluoropyrimide-based long-course neoadjuvant chemoradiotherapy.

Secondary endpoints include oncological (compliance with treatment, toxicity rates, differences with the use or not of oxaliplatin), surgical (rate of successful total mesorectal excision (TME), sphincter-preserving surgery, frequency of R1-R2 resections, early and late surgical complications) and pathological (quality of mesorectum, lymph node yield, tumour regression grade, rates of pathological complete response, downstaging rates) variables.

2. Material and methods

A retrospective study on a prospectively maintained database was performed on patients undergoing neoadjuvant radiochemotherapy for locally advanced rectal cancer at the University Hospital La Fe of Valencia, Spain between March 1999 and March 2014.

Patients needed to have been diagnosed with an adenocarcinoma of the rectum that was histologically proven and localised by rigid rectoscopy evaluation to the proximal, mid or distal third (between 1 and 15 cm from the pectineal line). Endorectal ultrasound (EUS) and/or magnetic resonance imaging (MRI) had to show cT3 or cT4 or any cT with positive N. Clinical and pathological staging was done according to the American Joint Committee on Cancer, TNM classification of Colon and Rectal Carcinomas, 7th edition (TABLE 1) [17]. All patients had an Eastern Cooperative Oncology Group performance status (PS) less than 2, adequate renal and hepatic function, and adequate bone marrow reserve (white blood cell count > 4000/mm3, haemoglobin >10 g/dl and platelet count >150,000/mm3). For each patient, we calculated the neutrophil-lymphocyte ratio (RNL) on the 7 days previous to the start of neoadjuvant therapy and on the 7 days previous to the surgical procedure. Patients with distant metastases were excluded. Staging evaluation included a complete colonoscopy, a thoracic-abdomen-pelvis computed tomography (CT) scan, a serum carcinoembryonic antigen (CEA) level and a serum carbohydrate antigen 19-9 (CA 19.9) level. All patients were discussed at our weekly multidisciplinary colon cancer committee.

2.1. Primary tumour staging

Primary tumour staging could be performed with an EUS and/or an MRI. cT and CN stage was collected in all patients; where it was performed, invasion of the levator muscle and the internal sphincter was also analyzed. EUS was the preferred staging method until 2004, when MRI was introduced in our Hospital and it became our standard imaging method of choice, although EUS is still routinely used in low rectal cancers. Specific MRI features such as mesorectal fascia invasion, extramural venous invasion, depth of invasion in T3 tumours as described by the MERCURY group ("a" (< 1 mm outside the wall), "b" (1–5 mm), "c" (5–15 mm), and "d" (> 15 mm)) and lateral pelvic lymph nodes were also analysed.

2.2. Chemotherapy administration

Preoperative treatment was administered on an outpatient basis and scheduled for 5 weeks. The initial 107 patients received UFT at a dose of 400 mg/m2 in three fractions per day between meals during the days of RT administration (Monday to Friday, with the weekend as a rest period). Because the packets of UFT contained 100 mg of tegafur, the administered dose was rounded up when the fraction was >50 mg. From November 2007, due to the removal of UFT from the Spanish market, capecitabine was given alongside RT at a dose of 825 mg/m2 every 12 h during the days of RT administration (Monday to Friday, with the weekend as a rest period).

Oxaliplatin was given as a 2-h intravenous infusion at a dose of 85 mg/m2 every two weeks during RT in all but the first 32 patients from October 2001 and until August 2011 (131 patients in total), moment when we decided to remove oxaliplatin from the regimen, when the initial results of several phase III trials showed that oxaliplatin was not effective in this setting [18-21]. Thus, from that moment onwards and till the present time, patients were treated with capecitabine monotherapy alongside radiotherapy (56 patients have been treated in this manner)

American Joint Committee on Cancer. TNM classification of Colon and Rectal Carcinomas, 7th edition [17]	
The same classification is used for both clinical and pathological staging	
Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ:* intraepithelial or invasion of lamina propia
T1	Tumour invades submucosa
T2	Tumour invades muscularis propia
T3	Tumour invades through the muscularis propia into pericolorectal tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastases
N1	Metastases in 1-3 regional nodes
- **N1a**	Metastases in 1 regional lymph node
- **N1b**	Metastases in 2-3 regional lymph nodes
- **N1c**	Tumour deposits in the subserosal, mesentery or nonperitonealized pericolorectal tissues with no regional nodal metastases
-	
N2	Metastases in 4 or more regional lymph nodes
- **N2a**	Metastases in 4-6 regional lymph nodes
- **N2b**	Metastases in seven or more regional lymph nodes
Distant metastases (M)	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1a	Metastases confined to one organ or site
M1b	Metastases in more than one organ or site or peritoneal metastases

Stage¶	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

¶ cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0M0

TABLE 1: The American Joint Committee on Cancer TNM classification of Colon and Rectal Carcinomas, 7th edition used for the clinical and pathological staging of all cases [17]

2.3 Radiotherapy administration

A pelvic plane CT in the treatment position for virtual simulation was performed on all patients. CT images were obtained using a 5 mm slice thickness at 1 cm separation (5 mm slices through the tumour), from L5-S1 to 1.5 cm distal to the anus. The planning target volume (PTV) was defined as clinical target volume (CTV)1+ 1 cm margin: (1) diagnostic imaging (CT) was used to define gross target volume (GTV); (2) CTV1, including the GTV+2 cm in all directions, perirectal, internal iliac and presacral nodes up to the promontory; for T4 (vesicle involvement, prostate, vagina or uterus), external iliac nodes were also included. The inguinal areas were irradiated in those patients who had invasion of the anal canal. Treatment was delivered through three to four fields via the axial beam technique, shaped with multi-leaf collimator and high-energy photons of 10 MV (this being possible using photons of 6 MV in the PA).

The total dose administered was 45 Gy with conventional fractions of 1.8 Gy/day five times per week in the first 94 patients. In the following 109 patients, the total dose was increased to 50.4 Gy with a prespecified tumour area boost of 5.4 Gy, after the initial results of the phase III ACCORD-12/0405-Prodige-2 and other trials [21]. which showed better local control with the higher dose. The prescribed dose was specified at the International Commission on Radiation Units and Measurements point (intersection of the central axes of the 3–4 beams) and isodose distribution to the PTV (95–105%).

Toxicity of the combination treatment was evaluated weekly in each patient. A complete blood count was obtained; toxicity scoring was performed using the Common Terminology Criteria for Adverse Events, Version 4.0. No restaging procedure was done routinely after the end of chemo-radiotherapy, except if there was a suspicion of progressive disease or other unexpected findings.

2.4. Surgery

Patients were scheduled for surgery between the sixth and eighth week following the conclusion of the combination therapy and were treated with TME. Relevant surgical end-points were collected. Of these, the definition of the resection status took into account both the clinical intraoperative judgment and the pathologic results [22-24]. With regards to the first factor, the surgeon was to report at the end of operation if this was considered curative and if the TME was deemed successful, based on the absence of gross residual distant metastases or loco-regional tumour, otherwise the resection was considered non-curative (R2). With regards to the second factor, R1 was defined in potentially curative cases as microscopic tumour at or less than 1mm from the cut surgical margin, and R0 where microscopic tumour was greater than 1mm away from the cut surgical margin.

3.5. Pathological analysis

The analysis of the quality of the mesorectum was performed according to previously defined criteria as satisfactory, partially satisfactory and unsatisfactory [25-27]. The criteria are shown in TABLE 2. Pathological staging was done according to the American Joint Committee on Cancer, TNM classification of Colon and Rectal Carcinomas, 7th edition [17]. Analysis of the response to preoperative treatment was defined clinically as well as pathologically. Downstaging was considered when pathologic T (pT) or N (pN) was less than ultrasound or MRI-defined T (cT) or N (cN). No response was considered when pT and cT were similar. Disease

progression was when pT was more than cT, when pN was more than cN or when metastases were observed during surgery. We also analysed the different rates of downstaging according to the imaging criteria used (MRI or EUS) in case both were performed in the same case.

As stated previously, R1 was defined in potentially curative cases as microscopic tumor at or less than 1mm from the cut surgical margin; we differentiated between the circumferential margin invasion (CRM) and the distal margin invasion accordingly [23-24].

Due to the heterogeneity of the tumour regression grades scores used in these 15 years of follow-up [17, 28-32] (at our institution, the Dworak, Mandard, Rich and Wheeler scores were most frequently used), we decided to unify these scores in common groups: tumour with complete response, tumours with nearly-complete response, tumours with moderate regression and tumour with minimal or no regression. The equivalencies are shown in TABLE 3 [33]. If a tumour had differing scores, we chose the score with a worse prognosis and allocated the patient accordingly. A pCR was considered when no malignant cells were observed, when the sample contained nonviable cells or only large acellular pools of mucin. Surprisingly no mention is made of the lymph node status in these classifications; however, we also collected the data of patients with ypT0 N-positive disease. Nonviable cells were those that showed pyknosis, karyorrhexis, karyolysis, cytolysis, or extreme distortion and hyperchromasia of the nucleus. Other pathological signs of interest collected include the presence of perineural invasion, lymphatic or vascular embolization and infrequent types of rectal adenocarcinoma (mucinous and signe-cell carcinomas). RAS analysis was not done routinely except in cases where it was necessary for the beginning of advanced-disease treatment.

Grading of specimen
Satisfactory: Mesorectal plane (good plane of surgery achieved) - Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing
Partially satisfactory: Intramesorectal plane (moderate plane of surgery achieved) - Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin
Unsatisfactory: Muscularis propria plane (poor plane of surgery achieved) - Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both

TABLE 2: Grading of the quality of the mesorectum in the surgical specimen [25-27]

	Dworak [28]	Mandard [29]	AJCC [17]	Wheeler [30]	Rich [31]	Ryan [32]
Complete regression	No tumour cells (TRG 4)	No residual cancer cells (TRG 1)	No viable cancer cells (TRG 0)	Sterilization or only microscopic focii remaining with marked fibrosis (TRG 1)	Sterilization or only microscopic focii remaining with marked fibrosis (TRG 3 and 4)	No viable cancer cells, or single cells or small groups of cells (TRG 1)
Near complete regression	Very few tumour cells (TRG 3)	Rare residual cancer cells (TRG 2)	Single or small groups of cells (TRG 1: moderate response)			
Moderate regression	Dominantly fibrotic changes with few tumour cells or groups (TRG 2)	Predominant fibrosis with increased number of residual cells (TRG 3)	Residual cancer outgrown by fibrosis (TRG 2: minimal response)	Marked fibrosis but macroscopic disease present (TRG 2)	Isolated microscopic focii of tumor (less than 3) although the fibrosis predominates (TRG 2)	Residual cancer outgrown by fibrosis (TRG 2)
Minimal regression	Dominantly tumour mass with obvious fibrosis (TRG 1)	Residual cancer outgrowing fibrosis (TRG 4)	Minimal or no tumour cells killed (TRG 3: poor response)	Little or no fibrosis, with abundant macroscopic disease (TRG 3)	Abundant residual tumour with little or no fibrosis (TRG 1)	Significant fibrosis outgrown by cancer or no fibrosis with extensive residual cancer (TRG 3)
No regression	No regression (TRG 0)	No regressive change (TRG 0)				

TABLE 3: Equivalencies between the different tumour regression grade (TRG) scores used in clinical practice [33]

2.6. Adjuvant chemotherapy

Following surgery, patients treated with UFT and UFT-oxaliplatin received four cycles of FU (425 mg/m2) and LV (20 mg/m2) on days 1–5. This scheme was repeated every 28 days. Patients treated with capecitabine-oxaliplatin or capecitabine monotherapy received four cycles of adjuvant capecitabine (1000 mg/m2 every 12 h for 14 days) and oxaliplatin (130 mg/m2) every 21 days. There was not fixed date for the beginning of treatment, although treatment was usually begun on the fourth to sixth week after surgery. No adjuvant chemotherapy was started twelve weeks after the surgical procedure.

2.7. Follow-up

Following the conclusion of treatment, patients had outpatient clinic appointments every 3 months for the first 2 years, at which time chest X-ray, abdominal ultrasound, CT scans of the thorax, abdomen and pelvis, and a blood analysis, including CEA, were performed. Between the third and fifth years, the appointments were every 6 months. A complete physical examination was conducted at each clinical visit, as was CEA measurement. CT scans were done in an alternating fashion with chest X-rays and abdominal ultrasound. Follow-up colonoscopies were done at the end of adjuvant chemotherapy (if the colonoscopy at diagnosis was not complete), one year after diagnosis, five years after diagnosis and every five years from then on. These intervals were shorter if any abnormalities appeared, such as advanced polyps.

2.8. Aims of the study

Our aim is to report clinical, radiological and pathological prognostic factors for local relapse, distant metastases and long-term survival endpoints (DFS and OS) in patients treated with neoadjuvant chemoradiotherapy for locally advanced rectal cancer. We also analysed if our study population would fit the Valentini nomogram [34] and the Dhadda score [35], two prognostic scores in patients with locally advanced rectal cancer, both with differing elements included. The Valentini nomogram (FIGURE 1) defines three categories of patients (low-risk, intermediate-risk and high-risk patient) treated with neoadjuvant (chemo)radiotherapy and radical surgery for local relapse, systemic relapse and death at five years and includes items such as pT, pN, cT, type of surgery (abdominoperineal resection versus low anterior resection), age, sex, radiotherapy dose and use of concomitant and adjuvant chemotherapy.

On the other hand, the Dhadda score defines four groups of patients (excellent, good, moderate and poor prognosis) treated also with neoadjuvant (chemo)radiotherapy and radical surgery for local relapse, DFS and OS and includes four items: pN, perineural invasion, invasion of the circumferential margin and the tumour regression grade. A score for each factor was calculated: TRG 1 = 0, TRG 2 =1, TRG 3-5 = 2; 0 nodes positive = 0, 1-3 nodes positive = 2, 4 or more nodes positive = 4; perineural invasion absent = 0, perineural invasion present = 4; CRM clear = 0, CRM involved = 4). A final score was thereafter calculated for each individual patient with a higher value indicative of a worse prognosis. This allowed a value between 0 and 14, with four groups defined: excellent prognosis group (score 0), good prognosis group (score 1-3), moderate prognosis group (score 4-8), poor prognosis group (score 9-14).

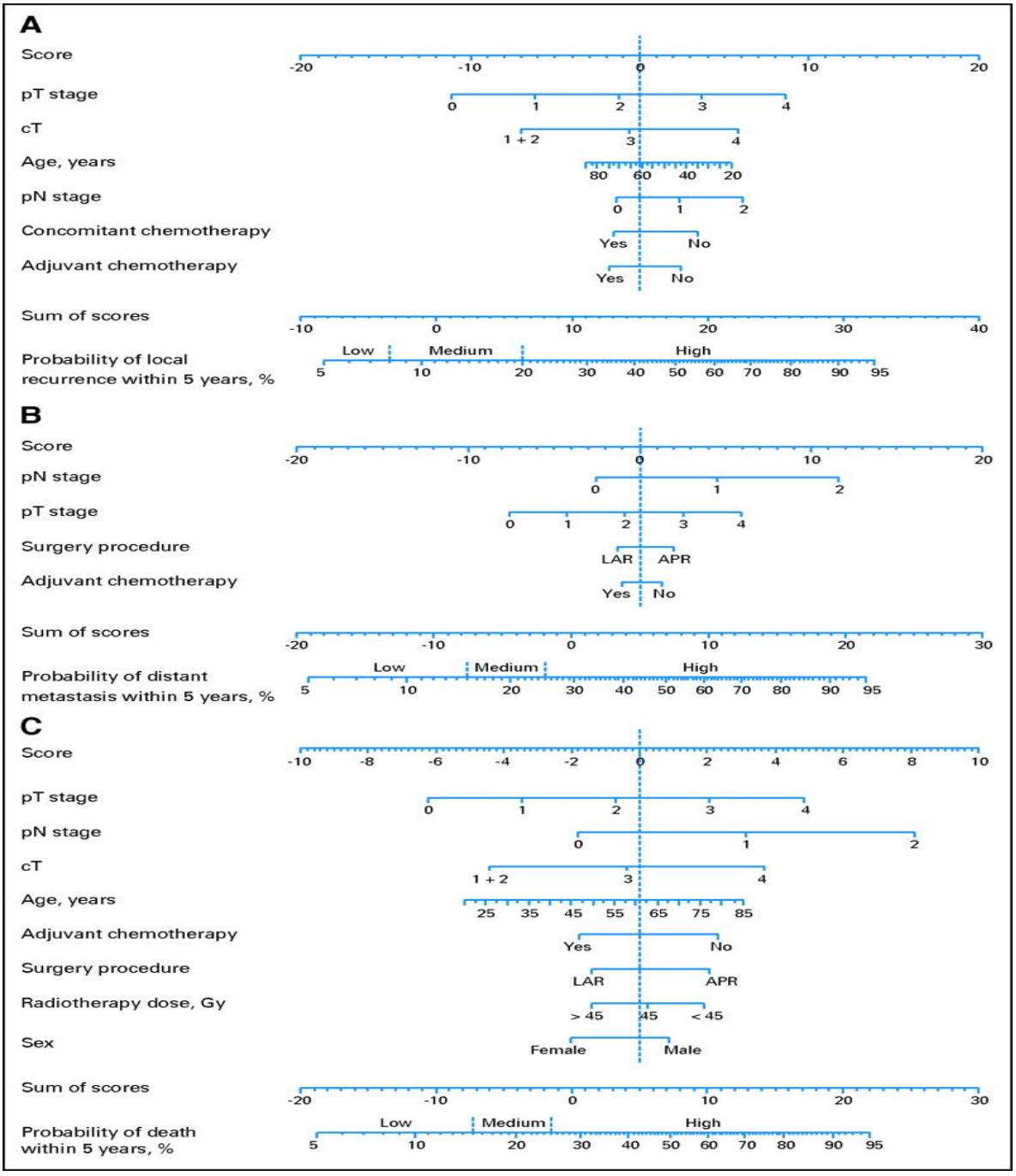


FIGURE 1: The Valentini nomogram defines three categories of patients (low-risk, intermediate-risk and high-risk patient) treated with neoadjuvant (chemo)radiotherapy and radical surgery for local relapse, systemic relapse and death at five years [34]. Reprinted with the permission of the Journal of Clinical Oncology

2.9. Statistical analysis

Local relapse was defined as the presence of any anastomotic, pelvic, or perineal tumor documented by proctoscopic, radiologic, or histopathologic examination. Distant relapse was defined as evidence of recurrent disease in any other location. Calculation of local relapse rates included patients who developed local relapse only and patients who developed both local and distant recurrence. DFS was defined as the time from diagnosis to the date of cancer relapse or death by any cause. OS was defined as the time from diagnosis to the date of death by any cause. Cancer-specific survival (CSS) was defined as the time from diagnosis to the date of relapse or death by cancer-related deaths; patients with other causes of death were not included in the analysis.

Univariate analysis was performed using 2-tailed chi-square test or Fisher's exact test for categorical variables and Mann–Whitney test for numerical variables. Multivariate analyses were performed using a Cox proportional hazards regression model. Time to local and overall relapses (cumulative risk at certain time) were estimated using the Kaplan–Meier method and comparison was done using log rank test. Univariate analysis of DFS and OS were calculated using the Kaplan-Meier procedure-limit method and reported as median survival and estimated 5-year survival. Multivariate analysis was performed using the Cox proportional hazards regression method. For each variant, hazard ratio was calculated including 95% confidence intervals.

All tests were 2-tailed and statistical significance was set at $p < 0.05$. The Statistical Package for the Social Sciences (SPSS version 23; Chicago, Ill, USA) was used for data management and statistical analyses. The analysis was performed on July 2016.

3. Results

3.1. Baseline characteristics

A total of 203 patients were included in a prospective fashion in this treatment regimen between March 1999 and March 2014. Four sequential cohorts of patients according to the oral fluoropyrimidine given and to the use of oxaliplatin or not were identified. Clinical and tumour-related characteristics of all patients and for each of these cohorts are shown in TABLES 4, 5 and 6, respectively. Baseline characteristics were similar for the four subgroups, except for a non-statistically increase of stage III patients and patients with a higher CEA level (p 0.056 and p 0.088, respectively) in the third cohort, compared to the earlier groups.

The most frequent clinical stage was cT3N1 (69 patients, 34.0%), followed by cT3N2 (35 patients, 17.2%), cT4N1 (20 patients, 9.8%) and cT4N2 (14 patients, 6.9%). Clinical lymph node involvement was seen in 159 patients (78.4%). More than a half of patients (55.2%) were staged with MRI; specific radiological characteristics of the 124 MRI procedures done are shown in TABLE 7. Of note, in a half of patients staged with MRI there were findings suggestive of involvement of the circumferential radial margin and in 12 patients (9.2%) there were positive lateral pelvic lymph nodes (9.7%). In 20 patients, the Involvement of the cirumferential margin was described in the endoscopic ultrasound

Clinical characteristic	Number (%)
Median age, years (range)	63 (33-84)
- **70 yrs. or older**	43 (21.2)
- **75 yrs or older**	15 (7.4)
Sex	
- **Male**	137 (67.5)
- **Female**	66 (32.5)
Tumour location in rigid colonoscopy	
- **Upper third**	12 (5.9)
- **Middle third**	99 (48.8)
- **Lower third**	92 (45.3)
Media distance from anal margin to distal tumour border, cm (range)	5.70 (0-15)
Anterior rectal wall involvement in rigid colonoscopy	
- **Yes**	89 (44.1)
- **No**	66 (34.2)
- **Whole circumference**	44 (21.8)
Median baseline Hb level, g/dl (range) ¶	13.4 (7.9-18)
- **Baseline Hb less than 10 g/dl¶¶**	11 (5.6)
Median baseline CEA level, ng/ml (range)	3.1 (0.2-1850.1)
- **CEA level above the upper limit of normality of 5 ng/ml**	59 (31.1)
Median baseline CA 19.9 level, UI/ml (range)	6.75 (0-1118.7)
- **CA 19.9 level above the upper limit of normality of 30 UI/ml**	24 (14)
Median baseline leucocyte count, /mm3 (range)	7300 (2660-21260)
- **Median baseline neutrophil count, /mm3 (range)**	4200 (1103-14260)
- **Median baseline lymphocyte count, /mm3 (range)**	2030 (367-4590)
Median baseline neutrophil-lymphocite index (NRI)	2.06 (0.30-10.33)
- **10th percentile**	1.18
- **75th percentile**	2.68
- **90th percentile**	4.23
Median baseline platelets count, /mm3 (range)	253.000 (310-2380000)

CA 19.9: carbohydrate antigen 19-9; CEA: carcino-embryonic antigen; cm: centimetres; Hb: hemoglobin; pts: patients; yrs: years. ¶All patients had their baseline blood analyses performed seven days before the beginning of neoadjuvant therapy. ¶¶ At our Institution, the normal values for these parameters are: CEA less than 5 ng/ml, CA 19.9 less than 30 UI/ml; hemoglobin: 14-16 g/dl; leucocyte counts: 4000-12000/mm3; neutrophil counts: 2500-9000/mm3; lymphocyte counts: 1000-4000/mm3; platelets 150000-400000/mm3

TABLE 4: Clinical and laboratory parameters at diagnosis of the whole group of 203 patients

Radiological characteristics	Number (%)
Baseline imaging test	
- **Endoscopic ultrasound**	78 (38.4)
- **Magnetic resonance imaging (MRI)**	74 (36.5)
- **Both techniques**	51 (25.1)
Differences between endoscopic ultrasound and MRI	
- **No differences in stage**	6 (3)
- **Higher stage with MRI**	30 (14.8)
- **Higher stage with endoscopic ultrasound**	15 (7.4)
Maximum stage performed by	
- **Endoscopic ultrasound**	93 (45.8)
- **Magnetic resonance imaging**	110 (55.2)
Maximum clinical T stage	
- **cT0**	1 (0.5)
- **cT1**	0 (0.0)
- **cT2**	15 (7.4)
- **cT3**	136 (67.0)
- **cT4**	40 (19.7)
- **cTx**	1 (0.5)
Maximum clinical N stage	
- **cN0**	38 (18.7)
- **cN1**	108 (49.7)
- **cN2**	56 (27.6)
- **cNX**	8 (3.9)
T3 subdivision, if performed	72 (35.5)
- **cT3a/cT3b/cT3c/cT3d (%)**	14.3 /4.9/2.5 /13.8
T4 subdivision, if performed	42 (20.7)
- **cT4a/cT4b (%)**	4.4/16.3
N1 and N2 subdivision if performed	135 (67.5)
- **cN1a/cN1b/cN2a/cN2b (%)**	16.3/25.1/8.9/17.3
Disease stage	
- **Stage II**	38 (18.7)
- **Stage III**	159 (78.4)
- **Not assessed**	6 (3.0)

TABLE 5: Tumour-related characteristics at diagnosis of the whole group of 203 patients.

Patient and tumour characteristics	Overall cohort n 203 (%)	UFT n 32 (%)	UFT-oxaliplatin n 75, (%)	Capecitabine-oxaliplatin n 56, (%)	Capecitabine n 38, (%)
Period	03.99-03.14	03.99-09.01	10.01-09.07	10.07-08.11	09.11-03.14
Median age, years (range)	63 years (33-84)	63 years (44-76)	63 years (33-76)	62 years (42-78)	64 yrs (46-84)
70 years or older	43 (21.2)	5 (15.6)	14 (18.2)	11 (19.6)	13 (34.2)
Male sex	137 (67.5)	20 (62.5)	52 (67.5)	37 (66.1)	28 (73.7)
Median CEA at diagnosis, ng/ml (range)	3.1 (0.2-1850.1)	1.8 (0.7-17.6)	2.7 (0-1850.1)	4.2 (0.8-84.3)	2.9 (1-326.9)
CEA level above ULN	59 (31.1)	6 (18.8)	21 (27.3)	23 (41.4)	9 (25.7)
Lower third tumours	92 (45.3)	17 (53.1)	41 (53.2)	29 (54.7)	22 (57.9)
Grade 3-4 tumours	13 (6.4)	-----	6 (7.8)	3 (5.4)	4 (10.5)
Clinical stage **- Stage II** **- Stage III** **- Not assessed**	 38 (18.7) 159 (78.4) 6 (3.0)	 7 (21.9) 23 (71.9) 2 (6.2)	 20 (26.0) 56 (70.2) 3 (3.8)	 4 (7.1) 51 (91.1) 1 (1.8)	 7 (18.4) 31 (81.6) ------
Baseline imaging test **- EUS** **- MRI** **- Both**	 78 (38.4) 74 (36.5) 51 (25.1)	 32 (100) --- ---	 66 (85.7) 30 (39.0) 20 (26.0)	 11 (19.6) 55 (98.2) 9 (16.1)	 22 (57.9) 38 (100) 22 (57.9)

CEA: carcino-embryonic antigen; EUS: endoscopic ultra-sound; MRI: magnetic resonance imaging; ULN: upper level of normality

TABLE 6: Comparison table for the whole group of patients and for the four sequential cohorts of patients

Radiological characteristics	Number (%)
Primary tumour location	
- **Lower third**	48 (39.0)
- **Middle third**	66 (53.7)
- **Upper third**	10 (7.3)
Median distance to the anal margin, cm (range)	6.0 (0-13)
cT3 subdivisions	
- **cT3a**	22 (17.9)
- **cT3b**	9 (7.3)
- **cT3c**	5 (4.1)
- **cT3d**	23 (18.7)
cT4 subdivisions	
- **cT4a**	7 (5.7)
- **cT4b**	25 (20.3)
cN1 or cN2 subdivisions	
- **cN1a**	19 (15.4)
- **cN1b**	30 (24.4)
- **cN2a**	17 (13.8)
- **cN2b**	33 (26.8)
Involvement of the cirumferential radial margin¶	
- **Yes**	72 (50.0)
- **No**	72 (50.0)
Extramural venous invasion (EMVI)	
- **Yes**	29 (23.4)
- **No**	95 (76.6)
Internal sphincter involvement	
- **Yes**	34 (26.8)
- **No**	99 (73.2)
Levator involvement	
- **Yes**	19 (15.4)
- **No**	28 (22.8)
- **Not assessed**	76 (61.8)
Positive lateral pelvic lymph nodes	
- **Yes**	12 (9.7)
- **No**	112 (9.3)

¶ In 20 patients, the Involvement of the cirumferential margin was described in the endoscopic ultrasound

TABLE 7: Specific radiological characteristics of the 124 baseline MRI procedures performed

3.2. Neoadjuvant chemoradiotherapy

Compliance rates, dose intensity, duration of treatment and other treatment-related factors are shown in TABLE 8. 133 patients (65.5%) received radiosensitizing oxaliplatin alongside the oral flouropyrimidines and radiotherapy. The total intended dose of radiotherapy was given on 192 patients (94.6%), while 173 patients (85.4%) were able to receive the full intended dose of chemotherapy.

The overall and grade 3–4 toxicity rates to the neoadjuvant protocol are shown in TABLE 9. A 24.1% percentage rate of grade 3–4 toxicity was seen in 49 patients, mainly chemotherapy-linked gastrointestinal toxicity (diarrhoea and emesis). Radiotherapy-associated toxic deaths (cystitis, proctitis and radiodermitis) was present in 142 patients (69.9%), although only 7 patients (3.5%) had grade 3-4 toxicity.

6 patients (3.0%) had serious cardiovascular complications: 2 episodes of pulmonary thromboembolic disease, 1 episode of stroke and 1 episode of ischemic colitis. Four patients (2.0%) did not finish the combined neoadjuvant treatment as surgery had to be performed due to two episodes of acute intestinal obstruction, one episode of intestinal perforation and a case of ischemic colitis; unfortunately, the two latter patients died, for a treatment-related death rate of 1.0%. TABLE 10 shows factors linked with an increased grade 3-4 toxicity and an increase in unexpected serious complications (cardiovascular and surgical complications): patients that were 70-years old or older, surgery performed in the last cohort period and an interval between RT and surgery longer than 8 weeks were associated with a statistically significant increase of unexpected serious complications.

Characteristics	Frequencies
Total dose of radiotherapy	
- **Less than 45 Gy**	8 (3.9)
- **Between 45 Gy and 50.4 Gy**	86 (42.4)
- **50.4 Gy**	107 (48.3)
- **Higher than 50.4 Gy**	2 (1)
Tumour radiotherapy boost	107 (52.7)
Median duration of radiotherapy, days (range)	37 (1-82)
Total expected dose of radiotherapy given	192 (94.6)
Type of concomitant chemotherapy	
- **UFT**	32 (15.8)
- **UFT-oxaliplatin**	77 (37.9)
- **Capecitabine-oxaliplatin**	56 (27.6)
- **Capecitabine**	38 (18.7)
Radiosensitizing oxaliplatin	
- **Yes**	133 (65.5)
- **No**	70 (34.5)
Median number of radiosensitizing oxaliplatin cycles, range	3 (1-6)
Total dose of chemotherapy given	
- **100% of intended dose**	173 (85.4)
- **75% of intended dose**	16 (7.7)
- **Less than 75%**	14 (6.9)

TABLE 8: Compliance rates, dose intensity, duration of treatment and other treatment-related factors of the neoadjuvant regimen of chemoradiotherapy.

Type of toxicity	All grade toxicity, number (%)	Grade 3-4 toxicity, number (%)
Diarrhoea	68 (33.5)	20 (9.9%)
Nausea & Vomiting	35 (17.2)	7 (3.4%)
Stomatitis	8 (3.9)	-----
Leucocyte	22 (10.8)	6 (3)
Neutropenia	17 (8.4)	3 (1.5)
Anemia	17 (8.4)	3 (1.5)
Thrombocytopenia	15 (7.4)	1 (0.5)
Palmo-plantar erytrodisesthesia	5 (2.5)	-----
Cystitis	51 (25.1)	-----
Proctitis	48 (23.6)	3 (1.5)
Radiodermitis	42 (20.7)	4 (2)
Fatigue	33 (16.3)	1 (0.5)
Anorexia	14 (6.9)	----
Peripheral neurotoxicity	24 (11.8)	3 (1.5)
Central neurotoxicity	----	2 (1.0)
Infusion-related reactions	----	5 (2.5)
Cardiovascular complications - **Stroke** - **Thromembolic venous disease** - **Ischæmic colitis**	 ---- ---- ----	 1 (0.5) 4 (2) 1 (0.5)
Surgical complications - **Intestinal perforation** - **Intestinal subocclusion**	 ---- ----	 1 (0.5) 2 (1.0)
Overall patients with grade 3-4 toxicity	----	49 (24.1)
Number of patients with Hospital admissions		12 (5.9)
Urgent surgical procedures		4 (2)
Treatment-related deaths after combined therapy		2 (1)

TABLE 9: Overall and grade 3–4 toxicity rates with combined chemoradiotherapy and other treatment-related endpoints.

Characteristic	Overall g3-4 toxicity			Cardiovascular and surgical complications		
	Grade 3-4 toxicity	Toxicity in comparator arm	p-value	Cardiovascular and surgical complications	Toxicity in comparator arm	p-value
70 years or older	34.9%	21.3%	0.064*	9.3%	2.5%	0.042*
Lower third of rectum	78%	73.6%	0.473	1.8%	6.6%	0.089
cT3-4	77.7%	56.3%	0.058	3.8%	6.3%	0.493
Interval between RT and surgery higher than 8 weeks	36.2%	21.1%	0.087	10.6%	2.1%	0.026*
Surgery between 2010 and 2014	33.3%	21.5%	0.123	13%	1.2%	< 0.001*

* Statistically significant

TABLE 10: Clinical, tumour- and treatment-related factors associated with an increased rate of serious toxicity

3.3. Surgery

202 patients (99.5%) proceeded to surgery. The main surgical endpoints are shown in TABLE 11. 4 patients (2.0%) were deemed unresectable at the moment of surgery. Almost half of the remaining patients (99 patients, 48.8%) required an abdominoperineal resection. A total mesorectal excision was technically feasible in 182 patients (89.7%) and an R0 resection was described by the surgeon in 188 patients (92.6%); in the remaining patients, there were doubts about the completeness of the surgery in 10 patients (4.9%) and there was macroscopical residual disease in five patients (2.5%). A provisional diversion loop ileostomy was performed in 59 patients of the 100 patients with a lower anterior resection (59.0%). Early surgical complications were seen in 74 patients (36.5%), although only in 18 patients (8.9%) a surgical reintervention was needed. 7 patients (3.5%) died in the first 30 days after surgery.

In order to evaluate the surgical trends in the 15 years of the study, we performed an analysis of these surgical endpoints in three approximate time periods of five years; the results are shown in TABLE 12. Compared to earlier periods, the rate of abdominoperineal resections has decreased, while the laparoscopic approach and the routine use of diversion loop ileostomies has increased.

Surgical feature	Number, (%)
Type of surgery	
- **Abdominoperineal resection**	99 (48.8)
- **Low anterior resection**	100 (49.3)
- **Unresectable tumour**	4 (2.0)
Laparoscopic approach	65 (32.2)
Total mesorectal excision	
- **Yes**	182 (89.7)
- **No**	21 (10.2)
Type of resection	
- **R0 resection**	188 (92.6)
- **R1 resection**	10 (4.9)
- **R2 resection**	5 (2.5)
Median time from end of radiotherapy to surgery, days (range)	48 (2-176)
- **Interval less than six weeks**	61 (30.0)
- **Interval between six and eight weeks**	95 (46.8)
- **Interval longer than eight weeks**	47 (23.2)
Definitive colostomy	114 (56.7)
Routine diversion loop ileostomy	
- **Yes**	59 (29.4)
- **No**	28 (13.9)
Early surgical complications	74 (36.5)
- **Managed with medical therapy**	56 (27.6)
- **Needed surgery**	18 (8.9)
Type of serious surgical complications:	
- **Abscess-sepsis**	7 (3.5)
- **Fistula formation**	4 (2.0)
- **Anastomotic leak**	4 (2.0)
- **Intestinal occlusion**	3 (1.5)
- **Acute hemorrhage**	1 (0.5)
Mortality in the first 30 days after surgery	7 (3.5)

TABLE 11: 203 patients proceeded to surgical resection. Here displayed are the main features of the surgical procedure.

	1999-2004 (n 83)	2004-2009 (n 63)	2010-2014 (n 53)	*p*-value
Rate of abdominoperineal resections	49.5%	30.3%	20.2%	0.049*
Laparoscopic approach	16.7%	50.0%	33.3%	< 0.001*
Total mesorectal excision	42.3%	30.8%	26.9%	0.676
Satisfactory mesorectum	83.1%	66.6%	73.6%	0.069
Provisional diversion loop ileostomy	8.5%	43.5%	47.2%	< 0.001*
Mortality in the first 30 days after surgery	2.4%	0%	3.8%	0.333
Need of early surgical reintervention	15.7%	12.7%	7.5%	0.379

* Statistically significant

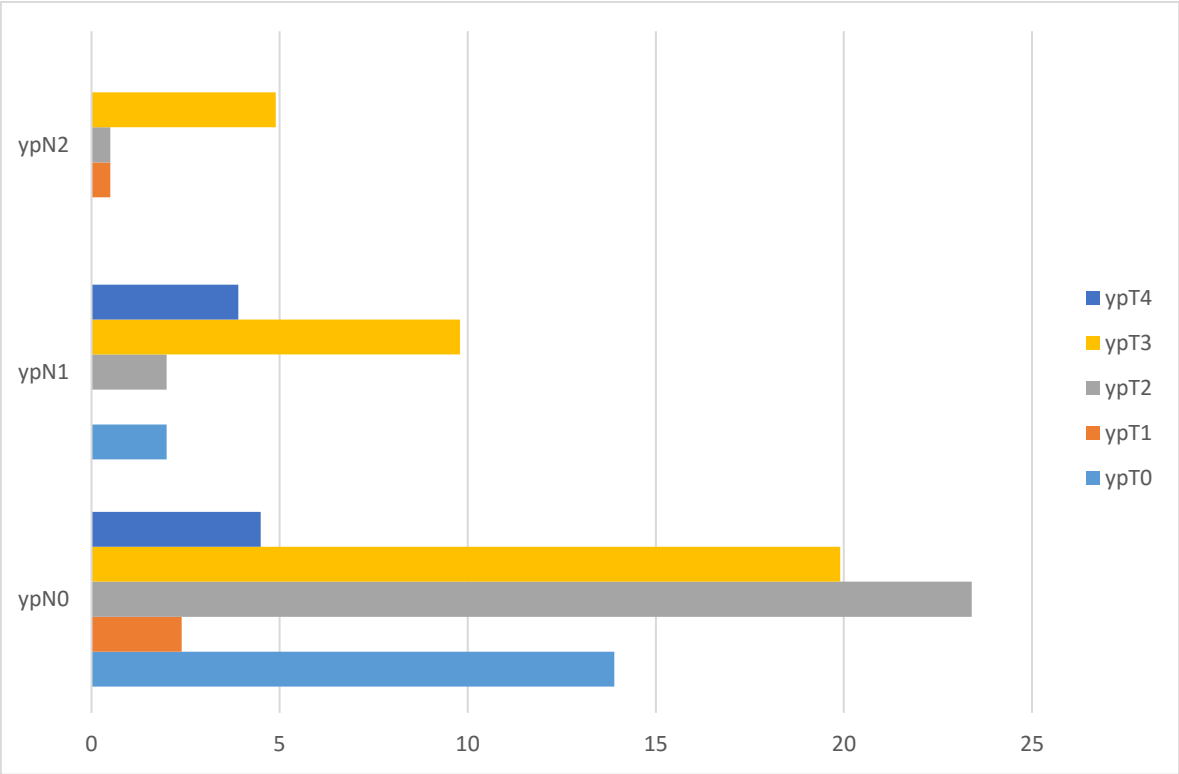
TABLE 12: Time trends in different surgical endpoints of interest in the management of rectal cancer

3.4. Pathology

The main endpoints of the pathological analysis of the surgical specimen are shown in TABLE 13. The quality of the mesorectum was deemed satisfactory in 150 patients (73.9%), although involvement of the circumferential radial margin was only seen in 43 patients (21.6%). 26 patients (14.5%) had poorly or undifferentiated tumours. The most frequent ypT stage was ypT3 in 74 patients (36.6%), followed by ypT2 in 57 patients (28.7%); there were 30 cases (14.9%) with ypT0 (pathological complete response). There was no lymph node involvement in 149 patients (74.9%). FIGURE 2 is a graphic representation of these ypT and ypN substages.

Pathologic features	Number, (%)
Quality of mesorectum	
- **Satisfactory**	150 (73.9)
- **Partially satisfactory**	9 (4.4)
- **Unsatisfactory**	43 (21.7)
Mucinous tumours	21 (10.3)
Tumour grade	
- **Residual tumour-not assessed**	73 (40.3)
- **Well-differentiated, grade 1**	48 (26.8)
- **Moderately differentiated, grade 2**	54 (30.2)
- **Poorly or undifferentiated, grade 3-4**	26 (14.5)
Pathologic T stage	
- **ypT0**	30 (14.9)
- **ypT1**	21 (10.4)
- **ypT2**	58 (28.7)
- **ypT3**	74 (36.6)
- **ypT4**	19 (9.4)
Pathologic N stage	
- **ypN0**	149 (74.9)
- **ypN1**	35 (17.6)
- **ypN2**	15 (7.5)
Median number of lymph nodes harvested, range	8 (0-34)
Median number of infiltrated lymph nodes, range	0 (0-13)
Pathologic N stage subdivisions	
- **ypN1a**	18 (8.9)
- **ypN1b**	19 (9.4)
- **ypN2a**	10 (4.9)
- **ypN2b**	3 (1.5)
Distal margin less than 1 cm from the surgical margin	
- **Yes**	41 (20.9)
- **No**	155 (79.1)
Involvement of the circumferential resection margin	
- **Yes**	43 (21.3)
- **No**	159 (78.7)

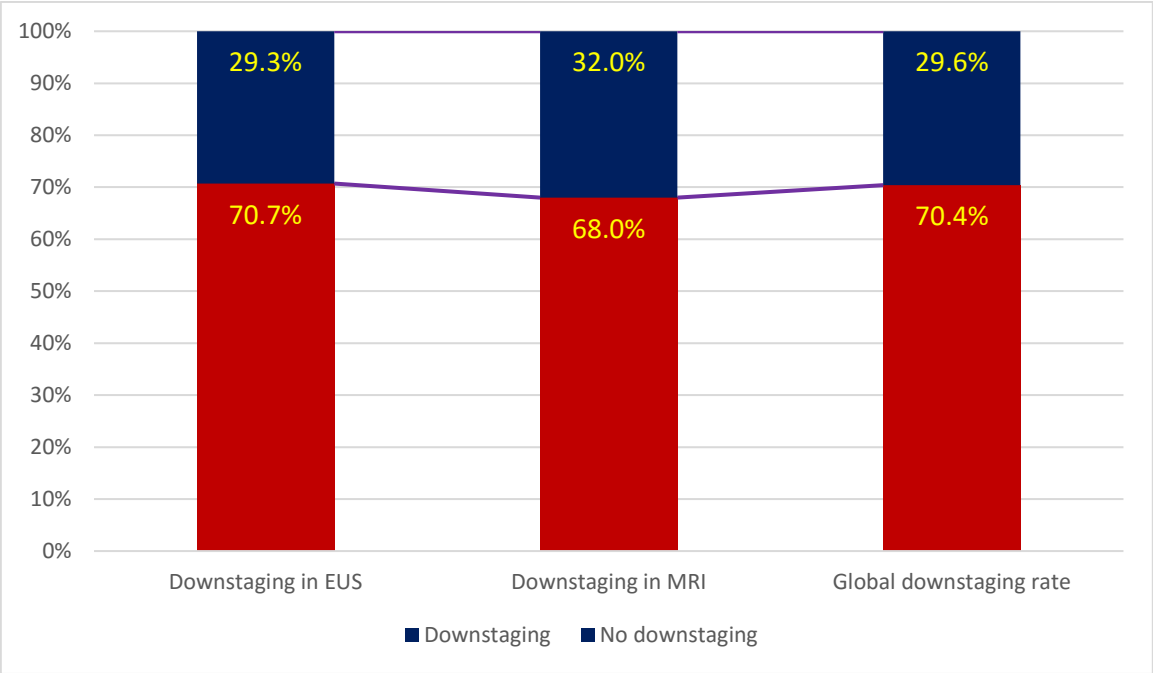
TABLE 13: Pathological analysis of the surgical specimen.



	ypN0 (n 149), %	ypN1 (n 35), %	ypN2 (n 15), %
ypT0 (n 30), %	13.9	2.0	0.0
ypT1 (n 21), %	2.4	0.0	0.5
ypT2 (n 58), %	23.4	2.0	0.5
ypT3 (n 74), %	19.9	9.8	4.9
ypT4 (n 19), %	4.5	3.9	0.0

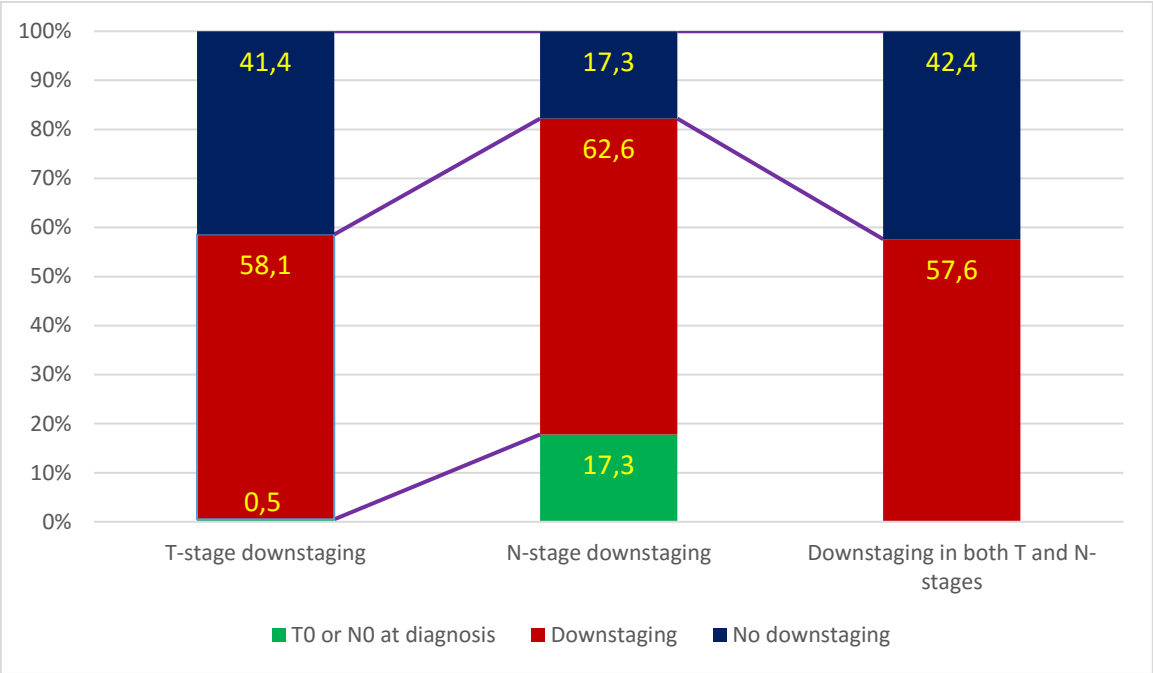
FIGURE 2: Graphic representation of the different ypT and ypN stages in the surgical specimen; note there was no lymph node involvement in 74.9% of patients

There was a 70.4% rate (143 patients) of downstaging compared to the clinical stage; the rate was broadly similar for patients staged either with EUS and MRI (70.7% vs 68.0; FIGURE 3). This downstaging was driven by the rate of lymph node sterilization, rather than T downstaging, as seen in FIGURE 4. The absolute numbers of patients, with their associated clinical and pathological staging, both in the overall group of patients and in those patients staged either by EUS or MRI, are shown in FIGURE 5, 6 AND 7, respectively.



Imaging test	Downstaging, %	No downstaging, %
Downstaging in EUS	99 (70.7)	41 (29.3)
Downstaging in MRI	84 (68.0)	40 (32.0)
Overall downstaging rate	143 (70.4)	60 (29.6)

FIGURE 3: Overall and MRI- or EUS- specific downstaging rate when comparing the clinical stage and the pathological stage after neoadjuvant therapy



Downstaging	T stage, %	N stage, %	Both T and N stages, %
Clinical T0 or N0 at diagnosis	1 (0.5)	35 (17.3)	----
Downstaging	119 (58.1)	127 (62.6)	117 (57.6)
No downstaging	84 (41.4)	41 (20.2)	86 (42.4)

FIGURE 4: Downstaging rate in both the ypT and the ypN stages, and for both at the same time. This downstaging is driven by the rate of lymph node sterilization, rather than ypT downstaging

	ypT 0N0	ypT 1N0	ypT 2N0	ypT 3N0	ypT 4N0	ypT 0N1	ypT 1N1	ypT 2N1	ypT 3N1	ypT 4N1	ypT 1N2	ypT 2N2	ypT 3N2	ypT 4N2
cT0 N0														
cT1 N0														
cT2 N0		1	1	2										
cT3 N0	5	4	9	3									2	
cT4 N0	1	1	3	4		2			1					
cT1 N1														
cT2 N1	1							2						
cT3 N1	9	8	13	15	3	1			15			1	4	
cT4 N1		3	5	2	3	1			1	4				1
cT1 N2														
cT2 N2		1	2	2								1		
cT3 N2	10	1	9	8	1			1	2				3	
cT4 N2			4	3	2			1	2	2				
Tx N1	1													
T2 Nx	1													
T3 Nx		2												
T4 Nx				1						1				
Tx NX			1											

Red cells: downstaging; yellow cells: similar clinical and pathological staging with no downstaging; blue cells: pathological staging was higher than clinical staging with no downstaging; white cells: it was not possible to assess downstaging

FIGURE 5: Graphic representation of the 201 patients, with their respectives cTN and ypTN stages.

	ypT 0N0	ypT 1N0	ypT 2N0	ypT 3N0	ypT 4N0	ypT 0N1	ypT 1N1	ypT 2N1	ypT 3N1	ypT 4N1	ypT 1N2	ypT 2N2	ypT 3N2	ypT 4N2
cT0 N0														
cT1 N0														
cT2 N0		1		1										
cT3 N0	1	3	9	2		1							1	
cT4 N0		1	1	1										
cT1 N1														
cT2 N1	1					1								
cT3 N1	5	5	9	6	3			1	7			1	3	
cT4 N1		2	2	2										
cT1 N2														
cT2 N2				1										
cT3 N2				1										
cT4 N2									1					
Tx N1	1													
T2 Nx	1													
T3 Nx		2												
T4 Nx				1							1		1	
Tx NX			1											

Red cells: downstaging; yellow cells: similar clinical and pathological staging with no downstaging; blue cells: pathological staging was higher than clinical staging with no downstaging; white cells: it was not possible to assess downstaging

FIGURE 6: Graphic representation of the 93 patients staged with endoscopic ultrasound, with their respectives cTN and ypTN stages.

	ypT 0N0	ypT 1N0	ypT 2N0	ypT 3N0	ypT 4N0	ypT 0N1	ypT 1N1	ypT 2N1	ypT 3N1	ypT 4N1	ypT 1N2	ypT 2N2	ypT 3N2	ypT 4N2
cT0 N0														
cT1 N0														
cT2 N0			1	1										
cT3 N0	4	1		1		1							1	
cT4 N0	1		2	3					1					
cT1 N1														
cT2 N1			3					2						
cT3 N1	4	3	4	9				1	8				1	
cT4 N1		1	3		3	1			1	4				1
cT1 N2														
cT2 N2		1	2	1								1		
cT3 N2	10	1	9	7	1			1	2				3	
cT4 N2			4	3	2			1	1	2				
Tx N1														
T2 Nx														
T3 Nx														
T4 Nx														
Tx NX														

Red cells: downstaging; yellow cells: similar clinical and pathological staging with no downstaging; blue cells: pathological staging was higher than clinical staging with no downstaging; white cells: it was not possible to assess downstaging

FIGURE 7: Graphic representation of the 108 patients staged with magnetic resonance imaging, with their respectives cTN and ypTN stages.

Other relevant pathological endpoints are shown in TABLE 14. There were four patients (2%) with ypT0 disease but with lymph node involvement. Vascular, lymphatic and perineural invasion was found in 8.5%, 16.6% and 9.6% of patients, respectively. A complete or nearly-complete TRG was seen in 99 patients (50.0%), while there was minimal or no regression in 50 patients (25.3%). Other signs of regression, such as acellular mucinous lakes and dystrophic calcifications were found in 6.9% and 2.5% of patients, respectively.

Pathologic features	Number, (%)
Pathological complete response (ypT0, irrespective of N)	30 (14.9)
- **ypT0 with lymph node involvement**	4 (2.0)
Small vessel (lymphatic or vascular) or perineural involvement	51 (25.5)
Vascular embolization	
- **Yes**	17 (8.5)
- **No**	182 (91.5)
Lymphatic embolization	
- **Yes**	33 (16.6)
- **No**	166 (83.4)
Perineural invasion	
- **Yes**	19 (9.6)
- **No**	180 (90.4)
Mucinous changes suggestive of tumour regression	14 (6.9)
Dystrophic calcifications suggestive of tumour regression	5 (2.5)
Tumour regression grade	
- **Complete response**	27 (13.6)
- **Near-complete response**	72 (36.4)
- **Moderate regression**	49 (24.7)
- **Minimal regression**	50 (25.3)

TABLE 14: Pathological analysis of the surgical specimen.

3.5. Adjuvant chemotherapy

Adjuvant chemotherapy administration was possible in 165 patients (81.3%); the details of the adjuvant chemotherapy regimen are shown in TABLE 15. The most frequent reasons for no administration were patient-related factors, such as advanced age, comorbidities and poor or long recovery from the surgical procedure (25 patients, 12.8%). The median time from surgery to adjuvant chemotherapy was 5 weeks, although a quarter of patients did not begin adjuvant treatment until 7 weeks after surgery. Only 93 patients (45.9%) received the full intended adjuvant dose of chemotherapy; most patients needed a dose reduction or an early stop to treatment due to toxicity or poor tolerance. There were 25 (15.6%) treatment-related hospital admissions compared to 12 admissions (5.9%) in the neoadjuvant part of the regimen. However, no treatment-related deaths were observed.

Characteristics	Number (%)
Adjuvant chemotherapy	
- **Yes**	165 (81.3)
- **No**	38 (18.7)
Type of adjuvant chemotherapy	
- **Bolus 5-FU (*Mayo* regimen)**	96 (47.3)
- **Capecitabine-oxaliplatin**	68 (33.5)
- **Capecitabine**	1 (0.5)
Reason for no adjuvant chemotherapy	
- **Age, surgical complications and/or or comorbidity**	25 (12.8)
- **Early disease progression**	8 (3.9)
- **Early death**	4 (2)
Median time from surgery to adjuvant chemotherapy, days (range)	35 (10-131)
- **75th percentile**	45
- **90th percentile**	55
Total dose of adjuvant chemotherapy	
- **100% of intended dose**	93 (45.9)
- **75% of intended dose**	56 (27.6)
- **Less than 75%**	16 (7.9)
Median duration of adjuvant chemotherapy, weeks (range)	12.0 (3.0-134.7)
- **75% percentile**	13.0
- **90% percentile**	14.8
Treatment-related hospital admissions	25 (15.2)
Treatment-related deaths	0 (0.0)

TABLE 15: Characteristics of the adjuvant chemotherapy regimen given

3.6. Other secondary endpoints

Other secondary long-term endpoints are shown in TABLE 16. Late surgery-related complications were observed in 16 patients (7.9%). The median time to ileostomy reconstruction was nine months, although in a quarter of patients it was more than one year after the initial surgery. In a third of patients with a routine provisional loop ileostomy, it was not corrected, due to age, comorbidity and/or poor anal function, early progression and/or death or surgical complications. There were 28 cases (13.8%) of metachronous malignant tumours in the follow-up of these patients; of these, 4 cases (2%) were early stage colon cancers treated with local therapies; no adjuvant treatment was necessary. 3 (1.5%) genetic syndromes were diagnosed in the follow-up of these patients: one patient with a mutation of the *BRCA1* gene*,* one patient with a mutation of the *DOG1* gene and one patient with an attenuated familiar colonic polyposis and a mutation of the *APC* gene.

Secondary long-term endpoints	Number (%)
Routine diversion loop ileostomy	59 (29.4)
- **Ileostomy reconstruction**	39 (19.5)
Median time to ileostomy reconstruction, months (range)	9.0 (1.0-133.0)
- 75th percentile	12.6
- 90th percentile	20.4
No ileostomy reconstruction	20 (9.9)
- Age, comorbidity and/or poor anal function	7 (3.5)
- Early progression and/or death	12 (5.9)
- Surgical complications	1 (0.5)
Late surgery-related complications	16 (7.9)
- **Intestinal occlusions**	7 (3.4)
- **Incisional ventral hernia**	3 (1.5)
- **Colostomy prolapse**	3 (1.5)
- **Chronic fistulæ and/or other infectious complications**	3 (1.5)
Second malignancies	28 (13.8)
- **Breast cancer**	5 (2.5)
- **Lung cancer**	4 (2.0)
- **Large bowel cancer**	4 (2.0)
- **Bladder cancer**	3 (1.5)
- **Head & Neck cancer**	3 (1.5)
- **Prostate cancer**	2 (1.0)
- **Biliary tract cancer**	2 (1.0)
- **Endometrial cancer**	1 (0.5)
- **Kidney**	1 (0.5)
- **Neuroendocrine tumour**	1 (0.5)
- **Sarcoma**	1 (0.5)
- **Meningioma**	1 (0.5)
Type of colon cancer	
- **In situ adenocarcinoma**	2 (1)
- **Stage II carcinoma**	2 (1)
Deaths related to second malignancy	14 (6.9)

TABLE 15: Other secondary long-term endpoints of interest

3.7. Local relapse and distant metastases

61 patients (30%) relapsed (TABLE 16). As the first site a recurrence, a local relapse was seen in 17 patients (8.3%), although in 10 patients (4.9%), there was a local and systemic relapse at the same time. Distant metastases were seen in 54 patients (26.6%). The most common site of distant relapse was in the lungs (19 patients, 9.4%) followed by the liver (14 patients, 6.9%) and both in the liver and the lungs (9 patients, 4.4%). *K-RAS* analysis was performed in 28 patients (13.8%); of these patients, 19 (9.4%) had wild-type disease while 9 patients (4.4%) had *K-RAS* mutations.

The median time to relapse was 20 months and in 50 patients (88.3%), the relapses took place in the first five years of follow-up; FIGURE 8 and 9 are graphic representations of these findings. There were no differences in the median time to relapse between patients with a local recurrence and those with distant metastases (FIGURE 10). In 23 patients (11.4%) there was a potentially resectable relapse, of which, only 2 patients (1%) had a local relapse.

Characteristics	Number (%)
Disease relapse	
- **Yes**	61 (30.0)
- **No**	142 (70.0)
Site of first relapse	
- **Locoregional**	7 (3.4)
- **Distant metastases**	44 (21.7)
- **Both sites**	10 (4.9)
Site of distant metastases	
- **Lung**	19 (9.4)
- **Liver**	14 (6.9)
- **Peritoneum**	6 (3.0)
- **Lymph nodes**	1 (0.5)
- **More than one metastatic location**	14 (6.9)
○ **Liver and lung**	9 (4.4)
Median time to first relapse, months (range)	20.8 (2.8-128.7)
- **25th percentile**	10.0
- **75th percentile**	40.5
- **90th percentile**	64.6
Median time to locoregional relapse, months (range)	14.7 (3.0-128.7)
Median time to distant relapse, months (range)	14.7 (3.0-128.1)
Potentially resectable relapse	23 (11.4)
- **Locoregional relapse**	2 (1.0)
- **Systemic relapse**	21 (10.4)
Types of rescue surgery for relapse	
- **Hepatic surgery**	11 (5.5)
- **Lung surgery**	7 (3.4)
- **Peritoneal surgery**	0 (0.0)
- **Abdominoperineal surgery**	2 (1.0)
Median disease-free survival in patients who relapsed, months (range)	41.3 (32.7-50.0)
- **Surgical rescue**	113.4 (21.6-205.1)
○ **5-year DFS**	61.5%
- **No surgical rescue**	39.6 (33.9-45.3)
○ **5-year DFS**	28.9%

TABLE 16: Distinguishing features of patients who suffered a local or distant relapse

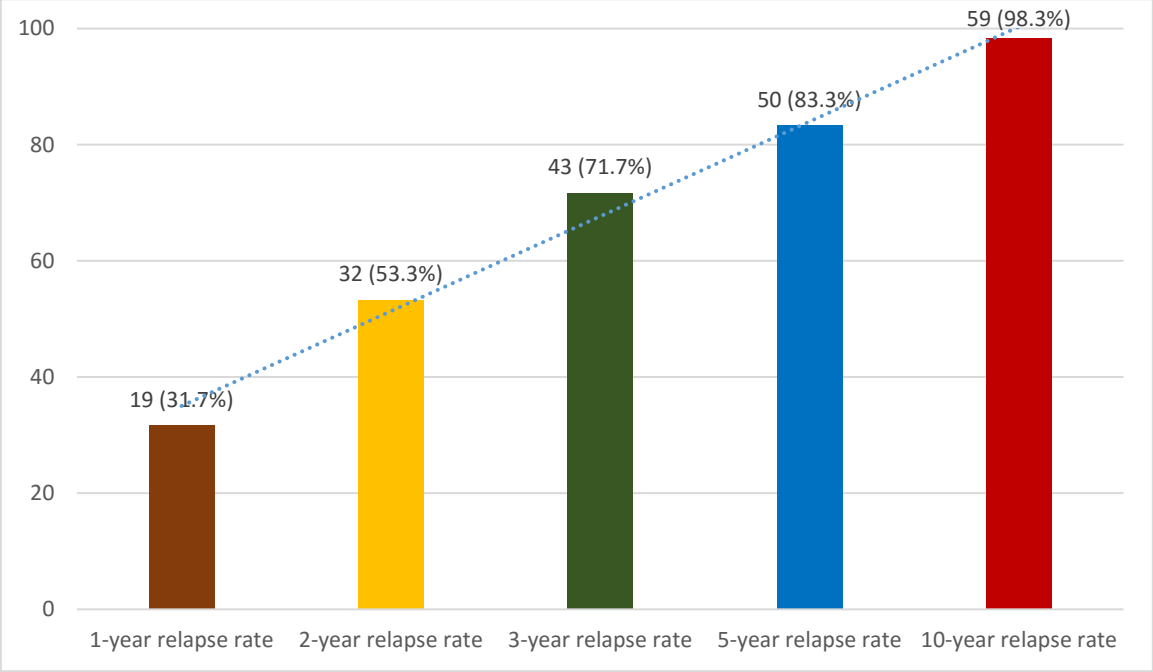


FIGURE 8: Overall relapse rates in the first ten years of follow-up

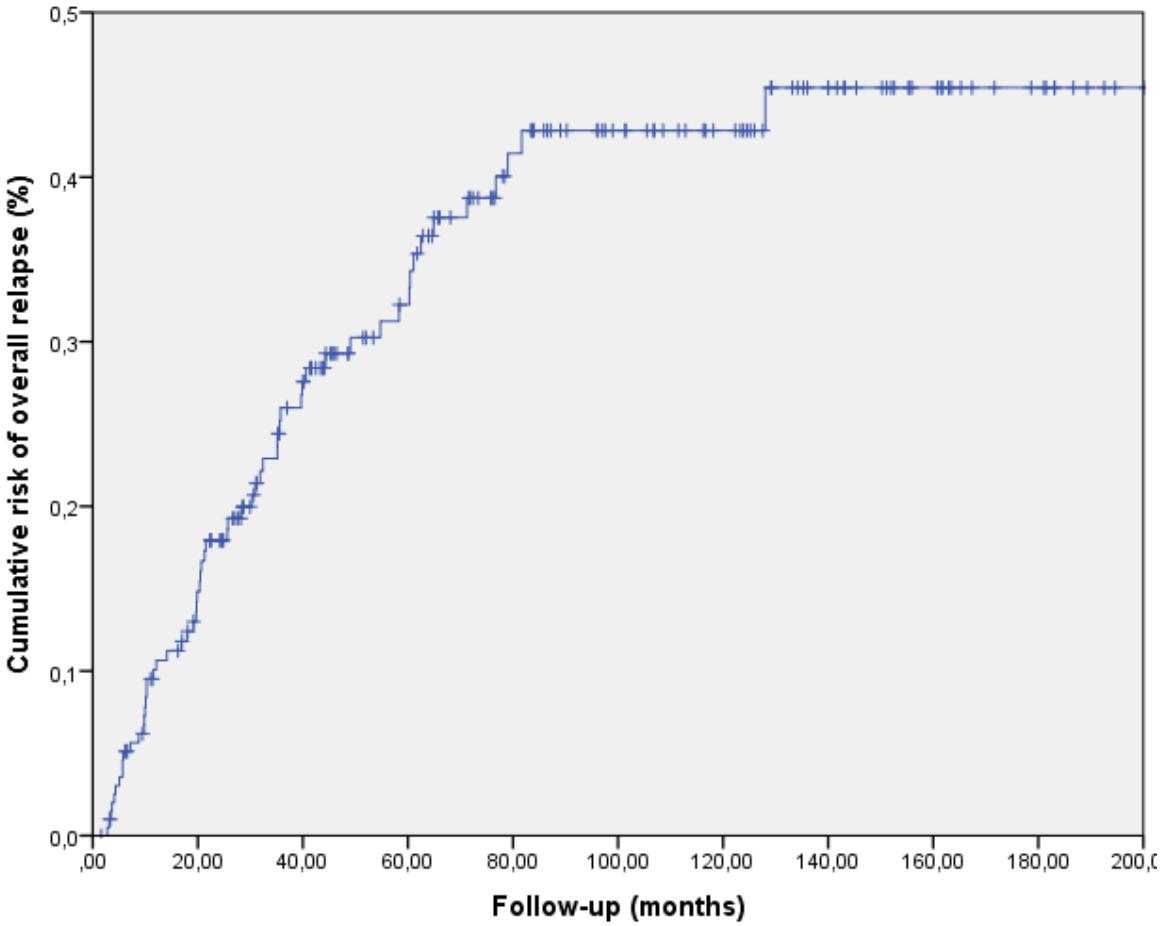
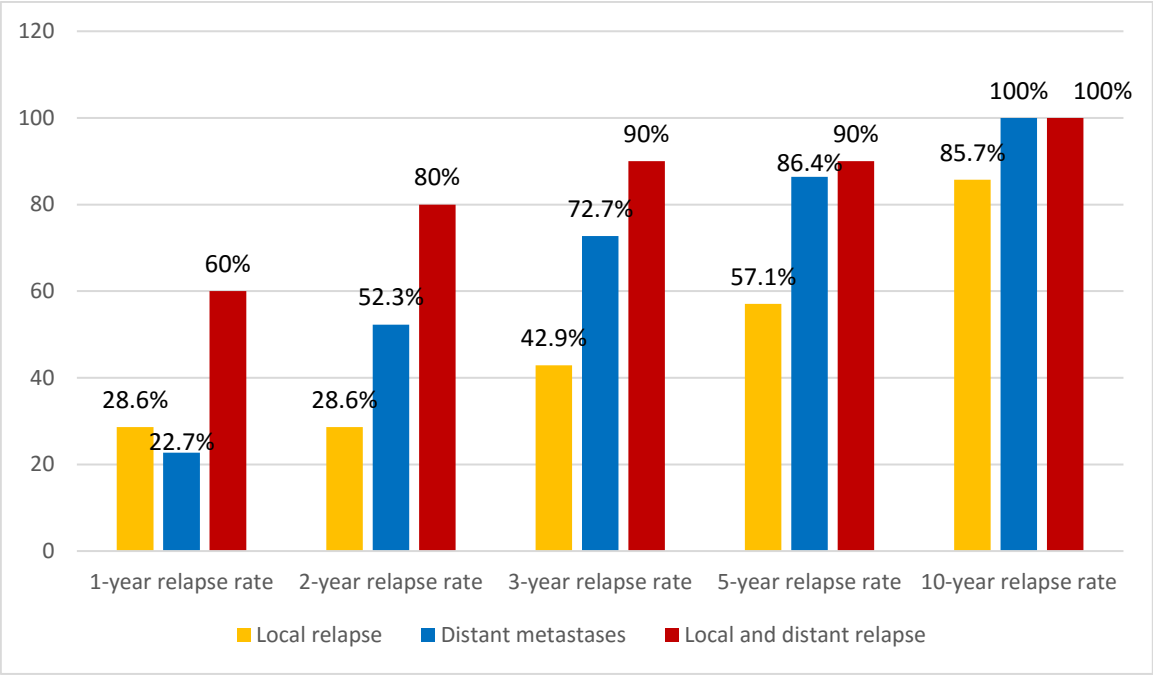


FIGURE 9: Cumulative risk of overall relapse curve. Note that almost 90% of all relapses took place in the first five years of treatment.



Relapse rate	Local relapse, (%)	Distant metastases, (%)	Both local and distant relapse, (%)
1-year relapse rate	2 (28.6)	10 (22.7)	6 (60)
2-year relapse rate	2 (28.6)	23 (52.3)	8 (80)
3-year relapse rate	3 (42.9)	32 (72.7)	9 (90)
5-year relapse rate	5 (57.1)	38 (86.4)	9 (90)
10-year relapse rate	6 (85.7)	54 (98.3)	10 (100)

FIGURE 10: Relapse rates according to recurrence site in the first ten years of follow-up

3.7.1. Risk factors for local relapse and pathological stage III disease

We performed an analysis of baseline clinical and radiological factors that could increase the local relapse and the presence of pathological lymph nodes in the surgical specimen, as they are the factors most closely linked to the prescription of adjuvant chemotherapy. The results are shown in TABLE 17 and 18.

A higher cT stage, poorly and undifferentiated tumours, a hemoglobin level less than 10 g/dl and patients 70 years or older had an increased risk of a local relapse. We did not see an association however with lymph node positive disease (cN), a clinical higher lymph node burden, involvement of the mesorectal fascia, lower rectal tumours and an elevated NRL ratio.

On the other hand, there was an increase in the risk pathological lymph nodes with clinical mesorectal fascia involvement, extramural venous invasion, elevated values of CEA and CA 19.9, positive lymph node disease and lower rectal tumours. There was no significant link with age, an elevated NRL ratio and age. Curiously, those patients with lateral pelvic lymph node disease had a lower risk of pathological lymph nodes.

Baseline characteristics	Local relapse, %	*p*-value
Male vs female	8.8 vs 9.4	0.544
70 years or older vs younger	10.8 vs 2.4	0.073*
CEA higher or lower than ULN	12.3 vs 7.7	0.229
CA 19.9 higher or lower than ULN	16.7 vs 8.8	0.199
Hemoglobin higher or lower than 10 g/dl	8.1 vs 27.3	0.067*
NLR higher or lower than median	9 vs 9.2	0.964
Rectal lower third vs other thirds	6.4 vs 12.1	0.163
Anterior wall involvement vs no involvement	8.4 vs 10.3	0.658
Grade 12 vs grade 34	7.5 vs 30.8	0.020*
cT012 vs cT34	0.0 vs 9.8	0.280
cT0123ab vs cT3cd4	5.6 vs 13.4	0.050*
Mesorectal fascia involvement vs no involvement	11.3 vs 10	0.807
Extramural venous invasion vs no invasion	17.2 vs 7.0	0.107
Sphincter invasion vs no invasion	12.7 vs 7.2	0.225
Puborectal muscle invasion vs no invasion	17.6 vs 9.1	0.194
Lymph node involvement vs no invasion	10.3 vs 2.6	0.115
cN1b2 vs cN01a	7.7 vs 10.4	0.501
Lateral pelvic lymph node involvement vs no invasion	9.1 vs 9.1	0.731

* Statistically significant

TABLE 17: Baseline clinical and radiological factors associated with an increased local risk of relapse

Baseline characteristics	Pathological lymph node invasion, %	*p*-value
Male vs female	21.6 vs 28.6	0.287
70 years or older vs younger	24.4 vs 23.7	0.928
CEA higher or lower than ULN	30.4 vs 19.5	0.080
CA 19.9 higher or lower than ULN	39.1 vs 20.7	0.050*
Hemoglobin higher or lower than 10 g/dl	23.8 vs 11.1	0.379
NLR higher or lower than median	22.9 vs 24.2	0.827
Rectal lower third vs other thirds	29.2 vs 17.6	0.040*
Anterior wall involvement vs no involvement	19.8 vs 29.0	0.409
Grade 12 vs grade 34	23.2 vs 24.7	0.313
cT012 vs cT34	13.3 vs 24.7	0.258
cT0123ab vs cT3cd4	21.5 vs 27.5	0.342
Mesorectal fascia involvement vs no involvement	34.8 vs 20.3	0.050*
Extramural venous invasion vs no invasion	39.3 vs 20	0.040*
Sphincter invasion vs no invasion	24.1 vs 25.0	0.527
Puborectal muscle invasion vs no invasion	34.0 vs 18.2	0.113
Lymph node involvement vs no invasion	27.9 vs 10.5	0.026*
cN1b2 vs cN01a	25.2 vs 22.3	0.633
Lateral pelvic lymph node involvement vs no invasion	0.0 vs 27.8	0.035*

* Statistically significant

TABLE 18: Baseline clinical and radiological factors associated with an increased risk of pathological lymph node invasion

3.7.2. Relationship between neoadjuvant therapy and local relapse and pathological endpoints of response

Due to the relationship between the use of neoadjuvant (chemo)radiotherapy and the decreased risk of local relapse and an increased downstaging rate, we performed an analysis of these factors. The results are shown in TABLES 19 and 20.

There was a numerically but not statistically significant increase of local relapse with increasing durations of the radiotherapy regimen. However, we did not see any difference with the use of radiosensitizing oxaliplatin, with the total dose of radiotherapy or with the use of a radiotherapy boost. There were also no differences according to the interval between the end of radiotherapy and the surgical procedure.

With regards to pathological regression endpoints, there was no improvement with the use of oxaliplatin, the use of a radiotherapy boost and the duration of the radiotherapy regimen. However, we did see an increased rate of downstaging and complete or nearly complete tumour regression with higher doses of radiotherapy and an increased rate of pathological complete response with longer intervals between the end of radiotherapy and the surgical procedure.

	Local relapse, %	*p*-value
Oxaliplatin		
- **Yes**	10.0	0.501
- **No**	7.3	
Radiotherapy dose		
- **< 45 Gy**	14.3	0.687
- **45-50 Gy**	7.1	
- **≥ 50.4 Gy**	10.1	
Interval between end of radiotherapy and surgery		
- **< 6 weeks**	10.3	0.914
- **6-8 weeks**	8.4	
- **> 8 weeks**	8.5	
Radiotherapy duration		
- **< 38 days**	5.4	0.076**
- **≥ 38 days**	12.5	
Radiotherapy boost		
- **Yes**	10.3%	0.497
- **No**	7.5%	

* Statistically significant

TABLE 19: Relationship between neoadjuvant treatment-related factors and the risk of local relapse

	Downstaging	*p*-value	Pathologic complete response	*p*-value	Complete or nearly complete tumour regression	*p*-value
Oxaliplatin						
- **Yes**	69.2%	0.585	12.0%	0.648	51.5%	0.546
- **No**	72.9%		14.3%		47.1%	
Radiotherapy dose						
- **< 45 Gy**	12.5%		0%		12.5%	
- **45-50 Gy**	68.6%	0.01*	10.5%	0.308	48.8%	0.030*
- **≥ 50.4 Gy**	76.1%		15.6%		53.7%	
Interval between end of radiotherapy and surgery						
- **< 6 weeks**	65.6%		3.3%		45.9%	
- **6-8 weeks**	70.5%	0.461	16.8%	0.029*	52.7%	0.942
- **> 8 weeks**	76.6%		17%		50.0%	
Radiotherapy duration						
- **< 38 days**	71.0%	0.641	12.7%	0.970	50.9%	0.915
- **≥ 38 days**	68.8%		12.9%		48.9%	
Radiotherapy boost						
- **Yes**	75.7%	0.083	15%	0.334	53.8%	0.084
- **No**	64.6%		10.4%		45.7%	

* Statistically significant

TABLE 20: Relationship between neoadjuvant treatment-related factors and pathological regression endpoints

3.7.3. Pathological features and risk of local relapse and distant metastases.

Pathological features in the surgical specimen and an increased risk of local relapse and distant metastases are shown in TABLES 21 and 22, respectively. Factors linked to both endpoints were an unsuccessful TME, the unsatisfactory quality of the mesorectum, an R2 resection, involvement of the circumferential and distal margins, no downstaging, poorly differentiated tumours, moderate or minimal regression, perineural invasion, pathological lymph node invasion and heavy lymph node burden. In the multivariate analysis, CRM invasion and perineural invasion retained their prognostic significance for both endpoints.

A pathological complete response was associated with a decreased risk of local relapse, but with no difference in distant metastases. Vascular invasion was linked with an increased risk of distant metastases, but not with local relapses. There was a borderline statistically significant link of abdominoperineal resection with a higher local relapse rate and of mucinous tumours with increased distant metastases.

Baseline characteristics	Local relapse, %	*p*-value
Abdomino-perineal excision vs lower anterior resection	11.3 vs 4	0.055**
Laparoscopy vs no	10.6 vs 8.2	0.376
Total mesorectal excision vs no Mesorectal excision	6.6 vs 31.6	0.003*
Quality of mesorectum satisfactory vs no	5.4 vs 19.6	0.004*
R0 vs R12 resection	7 vs 38.5	0.003*
Mucinous tumour vs no	14.3 vs 8.4	0.288
Distal margin < 1 cm vs ≥ 1 cm	25.6 vs 3.9	< 0.001*
Circumferential margin invasion vs no invasion	25.0 vs 4.4	< 0.001*
Grade 12 vs grade 34	4.6 vs 16.0	0.052*
Vascular embolization vs no	12.5 vs 7.2	0.349
Lymphatic embolization vs no	6.3 vs 7.9	0.547
Perineural invasion vs no	21.1 vs 6.2	0.043*
Downstaging vs no downstaging	4.9 vs 19.3	0.001*
Pathological complete response vs no	0 vs 10.3	0.072
ypT0 vs ypT12 vs ypT34	0.0 vs 3.8 vs 15.4	0.005*
Tumour regression grade - **Complete or nearly completed regression** - **Moderate regression** - **Minimal regression**	 2 10.4 10.8	0.003*
ypN0 vs ypN12	6 vs 14.9	0.056
ypN01 vs ypN2	7.7 vs 6.7	0.679

* Statistically significant

TABLE 21: Pathological features in the surgical specimen associated with an increased risk of local relapse

Pathological characteristics	Distant metastases, %	*p*-value
Abdomino-perineal excision vs lower anterior resection	29.3 vs 23.0	0.122
Laparoscopy vs no	24.2 vs 27.7	0.753
Total mesorectal excision vs no mesorectal excision	24.2 vs 47.6	0.012*
Quality of mesorectum satisfactory vs no	22.0 vs 39.6	0.004*
R01 vs R2 resection	24.7 vs 100.0	0.001*
Mucinous tumour vs no	47.6 vs 24.2	0.057
Distal margin < 1 cm vs ≥ 1 cm	34.1 vs 24.5	0.001*
Circumferential margin invasion vs no invasion	44.2 vs 21.4	< 0.001*
Grade 12 vs grade 34	22.7 vs 46.2	0.035*
Vascular embolization vs no	45.1 vs 19.5	0.001*
Lymphatic embolization vs no	38.2 vs 23.5	0.200
Perineural invasion vs no	65.0 vs 21.2	< 0.001*
Downstaging vs no downstaging	20.3 vs 41.7	0.004*
Pathological complete response vs no	15.4 vs 28.2	0.187
ypT0 vs ypT12 vs ypT34	20.0 vs 10.1 vs 41.9	< 0.001*
Tumour regression grade - **Complete or nearly completed regression** - **Moderate regression** - **Minimal regression**	 12.1 34.7 44.0	< 0.001*
ypN0 vs ypN12	20.7 vs 44.7	0.005*
ypN01 vs ypN2	23.4 vs 60.0	0.007*

* Statistically significant

TABLE 22: Pathological features in the surgical specimen associated with an increased risk of distant metastases

3.8. Special groups of patients: Elderly patients and patients with mucinous tumours.

Long-term outcomes for elderly patients (defined as 70-year patients or older) were poorer than for younger patients. We performed an analysis of possible factors that could explain these findings; the most significant results are shown in TABLE 23. Although no differences where seen with respects to classical pathological findings, we found that elderly patients had a poorer compliance to overall treatment, with more than half of patients receiving a radiotherapy dose less than 45 Gy, with a borderline statistically significant increase of grade 3-4 toxicity and of unexpected cardiovascular and surgical events, compared to their younger counterparts. The rate of abdominoperineal resections was higher in elderly patients while the poor compliance to the neoadjuvant treatment was linked to a lower rate of complete or near complete tumour regressions. The compliance of adjuvant treatment was particularly poor, with less than a quarter of elderly patients receiving the full intended dose, compared to more than half of younger patients.

Mucinous tumours, defined as tumours with more than 50% of a mucoid component were found in 21 patients (10.3%). These tumours were linked to higher overall rates of poor response to neoadjuvant chemo-radiotherapy and other poor-prognosis pathological endpoints compared to non-mucinous tumours, as shown in TABLE 24.

Characteristics	Patients younger than 70 years (n 160)	Patients aged 70 or more (n 43)	*p*-value
Clinical node-positive disease	80.6%	62.8%	0.030*
Grade 3-4 toxicity	21.3%	34.9%	0.064
Cardiovascular or surgical grade 3-4 toxicity	2.5%	9.3%	0.064
Abdominoperineal resection	44.4%	65.1%	0.047*
Pathologic complete response	15.0%	4.7%	0.071
Complete or near-complete response	52.3%	41.9%	0.038*
Radiotherapy dose < 45 Gy	37.5%	62.5%	0.014*
Adjuvant chemotherapy given	85.0%	62.8%	0.001
Full-dose adjuvant chemotherapy	51.2%	23.2%	< 0.001

* Statistically significant

TABLE 23: Differences between patients 70-years or older and younger patients

Characteristics	Mucinous tumours (n 21)	Non-mucinous tumours (n 179)	*p*-value
Total mesorectal excision	76.2%	91.2%	0.049*
Satisfactory mesorectum	52.4%	76.4%	0.021*
R0 resection	85.7%	93.4%	0.088
ypT3-4	71.4%	43.1%	0.014*
T-stage downstaging	23.8%	62.1%	0.003*
ypN1-2	47.6%	21.7%	0.012*
Overall downstaging	33.3%	74.7%	< 0.001*
Pathologic complete response	0.0%	14.3%	0.048*
Circumferential margin involvement	38.1%	19.3%	0.050*
Vascular embolization	23.8%	6.7%	0.021*

* Statistically significant

TABLE 24: Patients with mucinous tumours had higher overall rates of poor response to neoadjuvant chemo-radiotherapy and other poor-prognosis pathological endpoints compared with non-mucinous tumours

3.9. Survival analysis

With a median follow-up of 124.9 months (range 14.4-212.3), median DFS and median CSS were 139.8 months (106.0-173.6) and 198.1 months (133.8-262.4), respectively; median OS has not been reached yet. Estimated 5-year DFS, CSS and OS are 71.4%, 75.8% and 75.6%, respectively (FIGURES 11, 12 and 13 and TABLE 25). At the moment of the present analysis, 114 (55.7%) of patients are alive and free of disease, 11 (5.4%) are alive but with active disease, 8 (3.9%) are alive and free of disease after resection of the disease relapse, 44 (21.7%) have died secondary to cancer-related causes, 7 (3.4%) have had treatment-related deaths and 20 (9.9%) have died for non-related causes.

The median DFS and OS times of the 61 patients that relapsed according to the location of the relapse are shown in TABLE 26. Of note, 5-year DFS was significantly improved in those patients who were candidates for surgical rescue of the relapse versus those where it was not (61.5% vs 28.9%); These differences were statistically significant ($p < 0.001$).

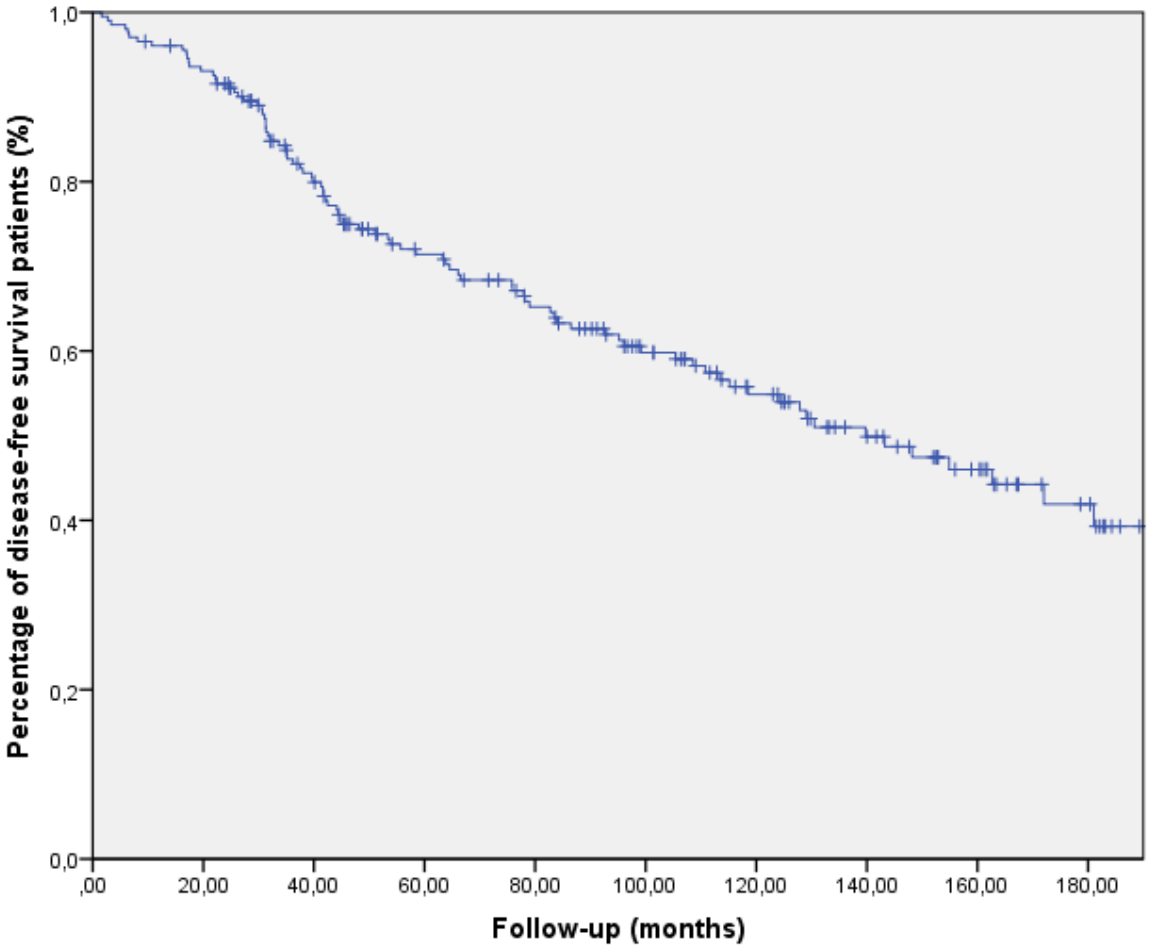


FIGURE 11: Disease-free survival curve of the whole cohort of patients

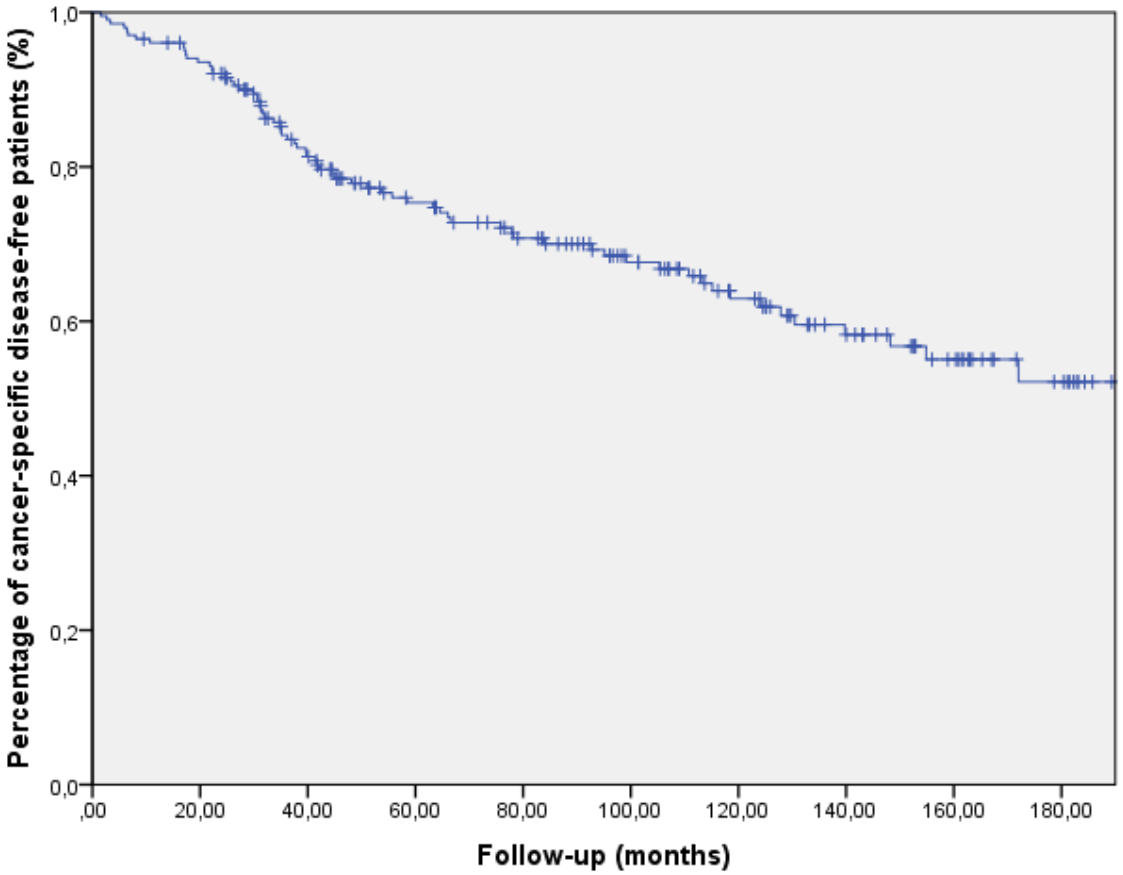


FIGURE 12: Cancer-specific survival curve of the whole cohort of patients

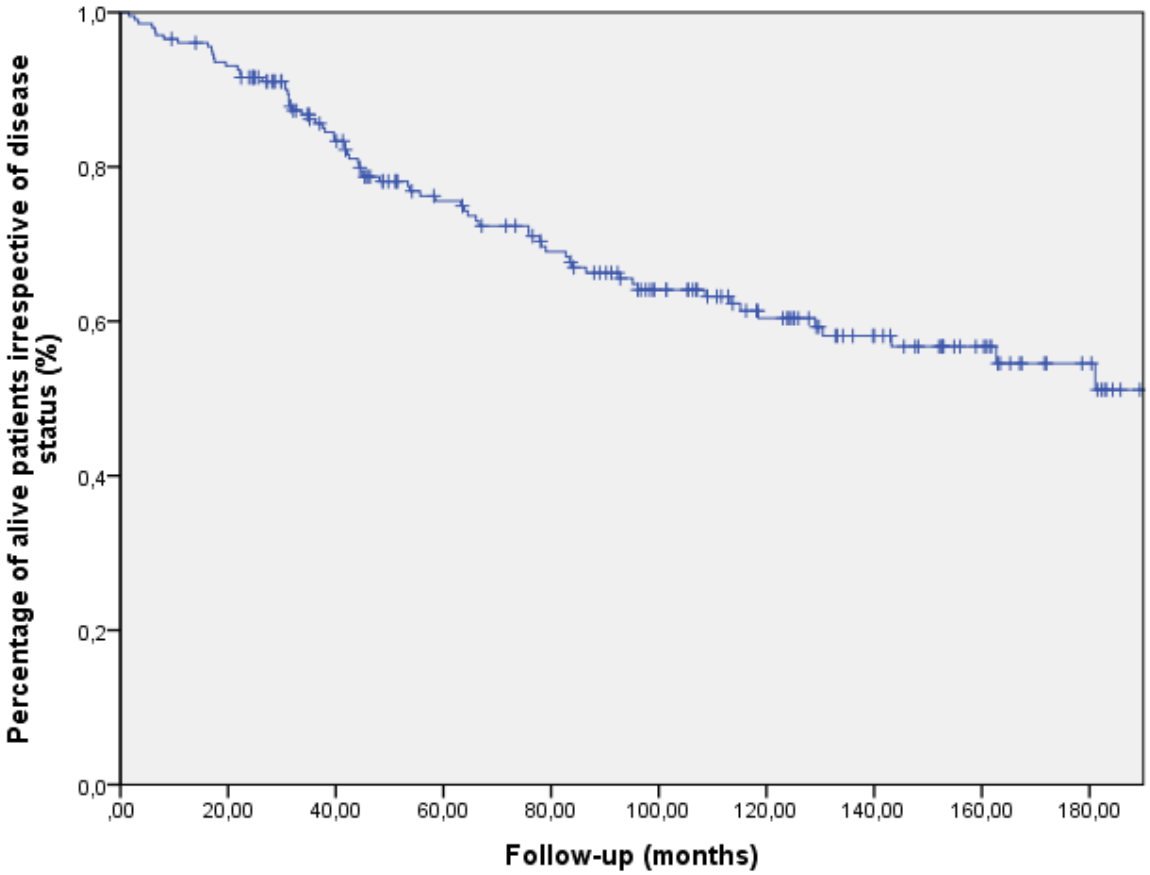


FIGURE 13: Overall survival curve of the whole cohort of patients

	Disease-free survival, months (95 CI)	Cancer-specific survival, months (95 CI)	Median overall survival, months (95 CI))
	139.8 (106.0-173.5)	198.1 (133.8-262.4)	Not reached
Survival rate			
- **1-year**	96.1%	98.3%	96.1%
- **3-year**	82.6%	85.7%	86.2%
- **5-year**	71.4%	75.8%	75.6%
- **10-year**	54.9%	60.4%	62.4%

TABLE 25: Disease-free, cancer-specific and overall median survival times and survival rates of the whole cohort of patients.

	Number, %	Median disease-free survival, months (range)	Median overall survival, months (range)
No relapse	142 (70)	Not reached	Not reached
Locoregional relapse	7 (3.4)	78.0 (8.8-147.1)	115.2 (9.1-221.3)
Distant metastases	44 (21.7)	44.8 (31.3-58.2)	55.7 (32.9-78.5)
Both local and distant relapse	10 (4.9)	31.6 (25.7-37.6)	37.5 (29.8-45.3)

TABLE 26: Median disease-free and overall survival times according to the appearance of a relapse or not and the location of the relapse

3.9.1. Univariate analysis for prognostic factors for DFS and OS

Possible clinical, neoadjuvant treatment-related, surgical and pathological factors were included in the univariate analysis, both for DFS and OS; the results are summarized in TABLES 27, 28, 29 and 30.

Significant baseline clinical factors included older age (FIGURE 14), elevated values of CEA and CA 19.9, poorly differentiated tumours in the diagnostic biopsy, radiological sphincter involvement and a clinical heavy lymph node burden (defined as more than one lymph node involvement, cN1b-2ab). There was no relationship with tumour location, anterior wall involvement, clinical cT3-4 stage or cN stage, independently of the number of nodes. No link was seen between the baseline NLR and improved survival at any level (quartiles, median, 10^{th} or 90^{th} percentiles or > 5).

With regards to treatment-related factors, both neoadjuvant and surgical, only a successful TME improved DSF and OS (FIGURE 15), while a shorter interval between the end of radiotherapy and surgery improved DFS; results were poorer if the interval was longer than eight weeks. Curiously, a low presurgical RNL was associated with poor survival outcomes, both in DFS and OS.

Pathological endpoints which improved DFS and OS included a satisfactory mesorectum, no lymph node invasion, a lower lymph node burden (FIGURE 16), overall, T-stage and N-stage downstaging, circumferential margin involvement (FIGURE 17), no vascular and perineural invasion, no complete or nearly-complete tumour regression (FIGURE 18) and a non-mucinous histology. On the other hand, prognosis was especially poor in patients with ypN2 disease (TABLE 31 and FIGURE 19). Improvement only in DFS were seen with lower T stages, well differentiated tumours and a pathologic complete or or nearly-complete response (ypT01). Lymphatic embolization and an involved distal margin were not significant factors.

Clinical and radiological characteristics	5-year disease-free survival (%)	*p*-value	5-year overall survival (%)	*p*-value
Sex				
- **Male**	69	0.461	75	0.930
- **Female**	76		77	
Age				
- **< 70 yrs**	74	0.09*	78	0.013*
- **≥ 70 yrs**	62		66	
Baseline CEA level				
- **CEA < ULN**	77	0.011*	80	0.045*
- **CEA ≥ ULN**	59		67	
Baseline CA 19.9 level				
- **CA 19.9 < ULN**	75	0.001*	77	0.008*
- **CA 19.9 ≥ ULN**	41		55	
Baseline Hb level				
- **Hb < 10 g/dl**	62	0.053	72	0.139
- **Hb ≥ 10 g/dl**	71		75	
Baseline NRL level				
- **NRL < median 2.08**	69	0.405	73	0.357
- **NRL ≥ median 2.08**	73		78	
Tumour grade at diagnosis				
- **Grade 0-2**	72	0.011*	76	0.575
- **Grade 3-4**	53		59	
Tumour location				
- **Lower rectum**	72	0.068*	73	0.517
- **Mid- or proximal rectum**	70		77	
Sphncter involvement				
- **Yes**	70	0.031*	75	0.328
- **No**	72		78	
Anterior wall involvement				
- **Yes**	71	0.468	76	0.756
- **No**	72		76	
Clinical T stage				
- **cT0-2**	68	0.422	77	0.263
- **cT3-4**	60		60	
Clinical N stage				
- **cN0**	72	0.750	77	0.945
- **cN1-2**	71		75	
Lymph node burden				
- **cN0-1a**	78	0.037*	82	0.021*
- **cN1b-2ab**	65		69	

* Statistically significant

TABLE 27: Univariate analysis of baseline clinical and radiological prognostic factors for worse disease-free survival and overall survival

Treatment-related factors	5-year disease-free survival (%)	*p*-value	5-year overall survival (%)	*p*-value
Presurgical NRL level				
- **NRL < 10th percentile**	42	0.033*	42	0.009*
- **NRL ≥ 10th percentile**	74		79	
Neoadjuvant chemoradiotherapy variables				
Radiosensitizing oxaliplatin				
- **Yes**	73	0.997	77	0.767
- **No**	67		75	
Radiotherapy boost				
- **Yes**	66	0.309	74	0.907
- **No**	77		77	
Radiotherapy dose				
- **< 45 Gy**	63	0.126	63	0.187
- **45-50.4 Gy**	78		78	
- **≥ 50.4 Gy**	66		75	
Interval between end of radiotherapy and surgery				
- **< 6 weeks**	83	0.042*	83	0.245
- **6-8 weeks**	69		73	
- **> 8 weeks**	59		69	
Radiotherapy duration				
- **< 38 days**	74	0.388	78	0.997
- **≥ 38 days**	71		73	
Surgical variables				
Type of surgery				
- **Abdominoperineal excision**	69	0.120	75	0.150
- **Lower anterior resection**	76		79	
Laparoscopy				
- **Yes**	72	0.780	80	0.313
- **No**	76		74	
Total mesorectal excision successful				
- **Yes**	75	< 0.001*	80	< 0.001*
- **No**	42		42	

* Statistically significant

TABLE 28: Univariate analysis of neoadjuvant treatment-related and surgical prognostic factors for worse disease-free survival and overall survival

Pathological factors	5-year disease-free survival (%)	*p*-value	5-year overall survival (%)	*p*-value
Quality of the mesorectum				
- **Satisfactory**	78	< 0.001*	83	< 0.001*
- **Moderately satisfactory**	52		61	
- **Unsatisfactory**	53		55	
Pathological staging variables				
Pathological T stage				
- **ypT0-2**	79	0.004*	79	0.169
- **ypT3-4**	63		72	
Pathological N stage				
- **No lymph nodes involved**	75	0.019*	80	0.034*
- **Lymph nodes involved**	61		65	
Lymph node burden				
- **ypN0-1**	75	< 0.001*	79	< 0.001*
- **ypN2**	46		52	
T-stage downstaging				
- **Yes**	78	0.007*	82	0.020*
- **No**	63		67	
N-stage downstaging				
- **Yes**	77	0.015*	81	0.011*
- **No**	60		64	
Overall stage downstaging				
- **Yes**	78	0.009*	78	0.023*
- **No**	56		56	
Pathological complete response				
- **Yes**	86	0.032*	86	0.093
- **No**	69		74	
Complete or almost complete pathological response				
- **ypT0-1**	81	0.022*	81	0.208
- **ypT2-4**	69		74	

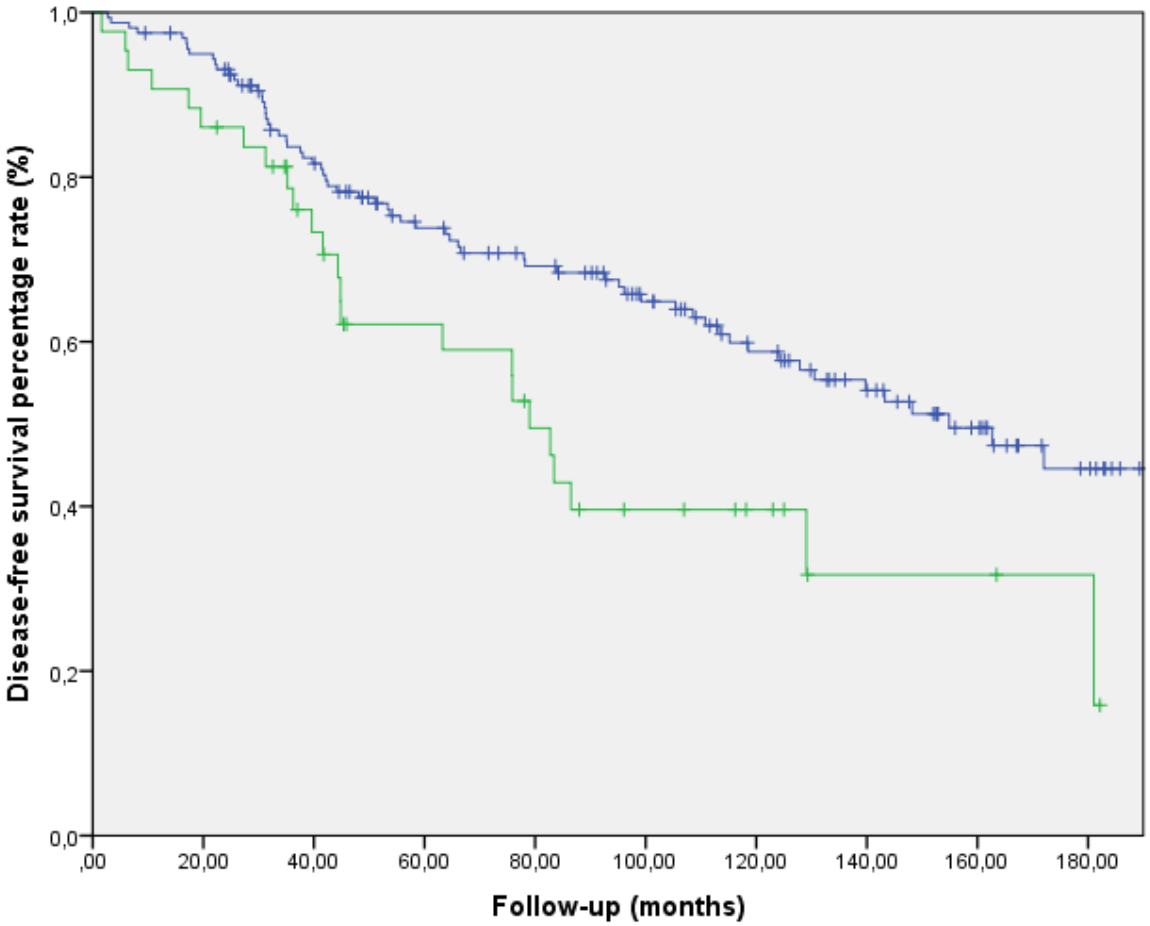
* Statistically significant

TABLE 29: Univariate analysis of pathological prognostic factors for worse disease-free survival and overall survival

Pathological factors	5-year disease-free survival (%)	*p*-value	5-year overall survival (%)	*p*-value
Other pathological endpoints				
Circumferential margin invasion				
- **Yes**	53	< 0.001*	59	< 0.001*
- **No**	77		81	
Distance from anal margin				
- **< 10 mm**	62	0.061	69	0.239
- **≥ 10 mm**	74		78	
Pathological tumour grade				
- **Grade 0-2**	75	0.011*	80	0.069
- **Grade 3-4**	53		59	
Vascular embolization				
- **Yes**	47	0.020*	61	0.024*
- **No**	75		78	
Lymphatic embolization				
- **Yes**	60	0.153	77	0.978
- **No**	75		77	
Perineural invasion				
- **Yes**	39	< 0.001*	52	< 0.001*
- **No**	77		80	
Tumour regression grade				
- **Complete or nearly completed regression**	80	0.005*	81	0.043*
- **Moderate regression**	71		80	
- **Minimal regression**	53		63	
Mucinous tumours				
- **Yes**	45	0.029*	48	0.023*
- **No**	74		78	

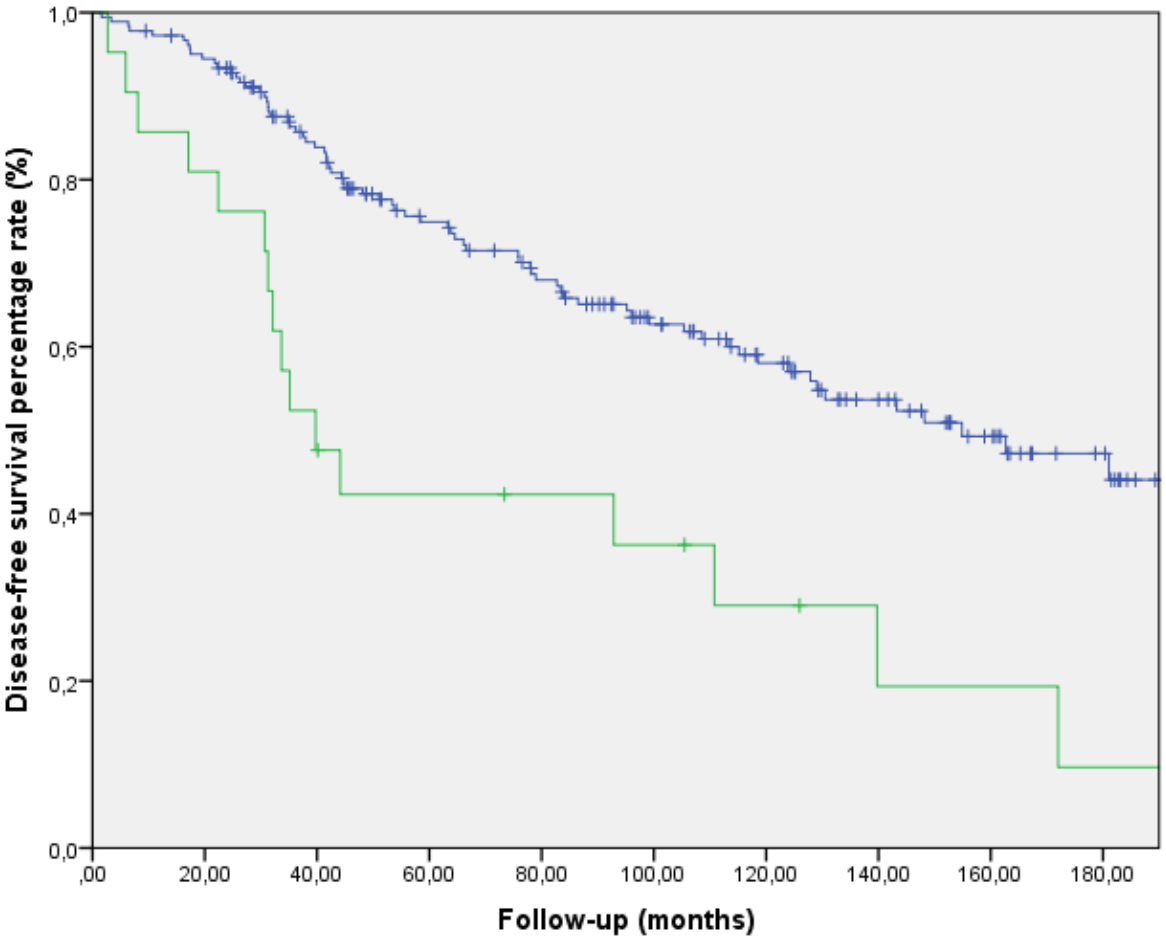
* Statistically significant

TABLE 30: Univariate analysis of pathological prognostic factors for worse disease-free survival and overall survival



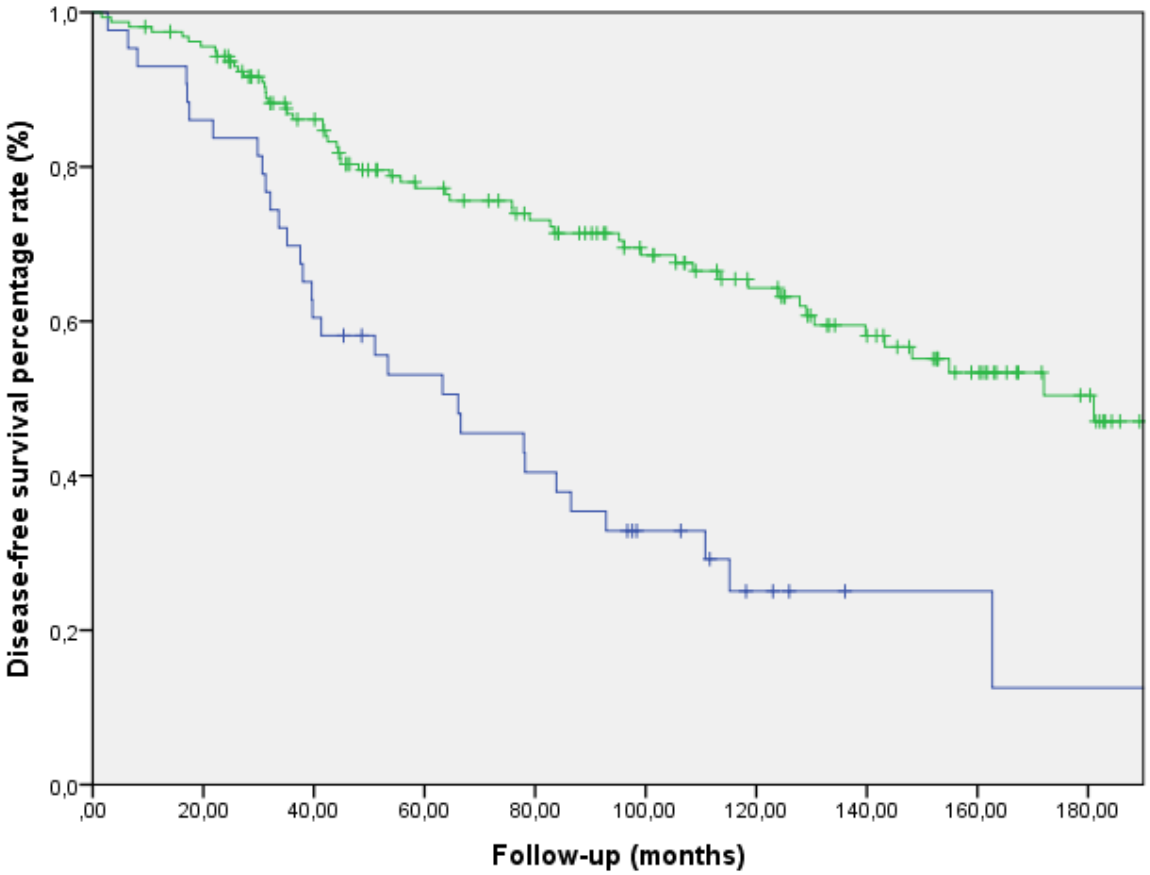
	Median disease-free survival, months (95% confidence interval)	p-value
< 70 years	154.9 (117.6-192.1)	0.001
≥ 70 years	79.0 (69.4-88.6)	

FIGURE 9: Median disease-free survival curves according to the age at diagnosis



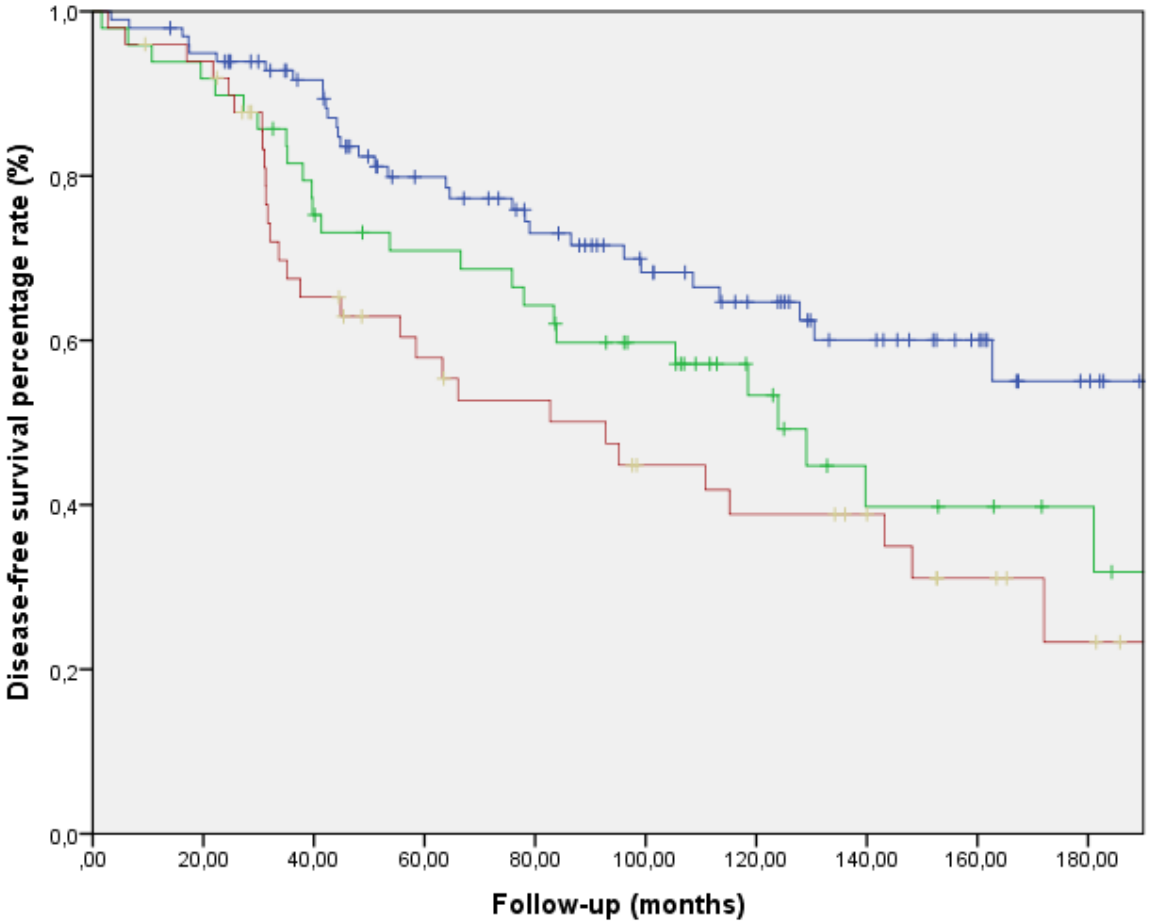
	Median disease-free survival, months (95% confidence interval)	*p*-value
Total mesorectal excision	154.7 (113.4-196.3)	< 0.001
Not feasible total mesorectal excision	39.7 (24.6-54.9)	

FIGURE 10: Median disease-free survival curves according to a successful total mesorectal excision



	Median disease-free survival, months (95% confidence interval)	*p*-value
Circumferential margin invasion	66.1 (33.8-98.3)	< 0.001
No circumferential margin invasion	181.1 (162.1-200.1)	

FIGURE 11: Median disease-free survival curves according to the status of the circumferential margin

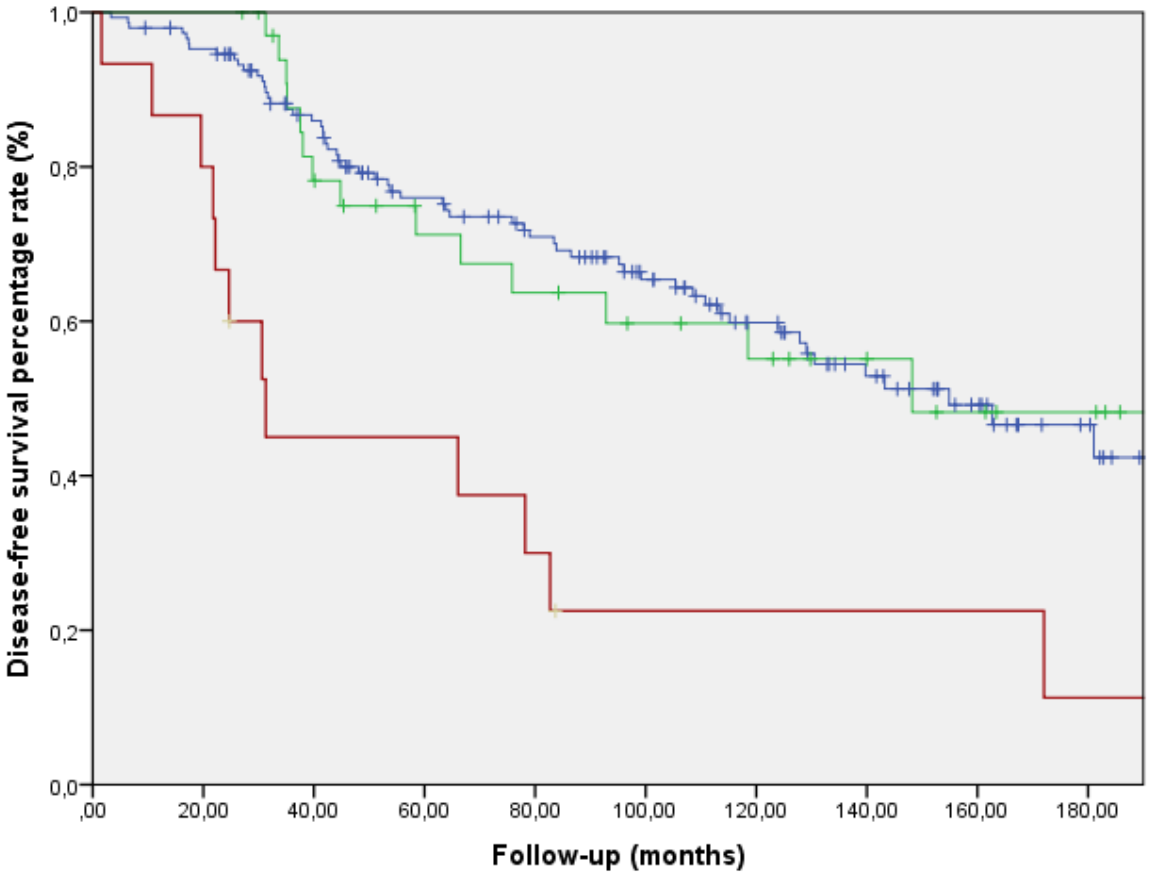


	Median disease-free survival, months (95% confidence interval)	*p*-value
Complete or near-complete regression	Not reached	0.005
Moderate regression	124.0 (93.3-154.6)	
Minimal regression	92.8 (47.1-138.6)	

FIGURE 12: Median disease-free survival curves according to the tumour regression grade

	Median disease-free survival, months (95% confidence interval)	*p*-value
ypN1a	Not reached	< 0.001
ypN1b	148.2 (73.0-223.4)	
ypN2a	24.6 (13.0-36.3)	
ypN2b	31.3 (16.0-46.5)	

TABLE 30: Median disease-free survival times according to the pathological lymph node burden



	Median disease-free survival, months (95% confidence interval)	*p*-value
ypN0	154.9 (114.9-194.9)	< 0.001
ypN1	148.2 (118.4-178.0)	
ypN2	31.3 (19.8-42.8)	

FIGURE 13: Median disease-free survival curves according to the pathological lymph node stage

3.9.2. Multivariate analysis for prognostic factors for DFS and OS

Significant factors in the univariate analysis were included in the multivariate analysis, both for DFS and OS. Results are shown in TABLES 32 and 33. In our model, age 70 years or older, circumferential margin invasion, an unsuccessful TME procedure and a pathological heavy lymph node burden remained statistically significant factors for worse survival outcomes.

Variables introduced into the model	B	Standard error	Wald statistic	Degrees of freedom	p-value	Hazard ratio	95% confidence interval for hazard ratio	
							Lower limit	Upper limit
Elevated CEA	,270	,341	,630	1	,427	1,310	,672	2,554
70 years or older	,762	,337	5,104	1	,024	2,142	1,106	4,149
Elevated CA 19.9	,486	,508	,916	1	,339	1,626	,601	4,402
Baseline Hb < 10 g/dl	,462	,715	,418	1	,518	1,587	,391	6,443
High-grade tumours	,201	,735	,075	1	,785	1,222	,289	5,166
Quality of mesorectum insatisfactory	,242	,339	,512	1	,474	1,274	,656	2,475
Mucinous tumours	,624	,782	,638	1	,425	1,867	,403	8,647
T stage downstaging	,453	,397	1,304	1	,253	1,574	,723	3,426
Pathologic ypT3-4 stage	-,171	,430	,158	1	,691	,843	,363	1,957
Circumferential margin invasion	,684	,356	3,695	1	,055	1,982	,987	3,982
Vascular embolization	-,156	,612	,065	1	,799	,856	,258	2,837
Perineural invasion	,403	,439	,843	1	,358	1,496	,633	3,538
Pathological complete response	,632	,633	,996	1	,318	1,881	,544	6,504
Minimal tumour regression	,459	,453	1,025	1	,311	1,582	,651	3,846
Mesorectal excision not successful	1,189	,543	4,791	1	,029	3,283	1,132	9,516
High lymph node burden (ypN2)	1,110	,541	4,206	1	,040	3,035	1,050	8,771
Global downstaging	,727	,446	2,659	1	,103	2,070	,863	4,961

TABLE 32: Multivariate analysis of prognostic factors for a worse disease-free survival. The dark blue cells represent the factors statistically significant in the analysis.

Variables introduced into the model	B	Standard error	Wald statistic	Degrees of freedom	p-value	Hazard ratio	95% confidence interval for hazard ratio	
							Lowe limit	Upper limit
Elevated CEA	,319	,372	,735	1	,391	1,376	,663	2,855
70 years or older	1,068	,364	8,588	1	,003	2,910	1,424	5,943
Elevated CA 19.9	,146	,599	,060	1	,807	1,158	,358	3,748
Baseline Hb < 10 g/dl	,274	,828	,110	1	,740	1,316	,260	6,669
High-grade tumours	,455	,819	,308	1	,579	1,576	,316	7,854
Quality of mesorectum insatisfactory	,453	,367	1,521	1	,218	1,573	,766	3,230
Mucinous tumours	,944	,837	1,271	1	,260	2,570	,498	13,256
T stage downstaging	,519	,429	1,462	1	,227	1,680	,724	3,898
Pathologic ypT3-4 stage	,320	,479	,446	1	,504	1,377	,539	3,521
Circumferential margin invasion	,929	,394	5,568	1	,018	2,531	1,170	5,474
Vascular embolization	-,027	,736	,001	1	,971	,974	,230	4,122
Perineural invasion	,355	,525	,456	1	,499	1,426	,509	3,992
Pathological complete response	,563	,639	,775	1	,379	1,755	,501	6,145
Minimal tumour regression	,337	,535	,396	1	,529	1,400	,490	3,997
Mesorectal excision successful	1,289	,614	4,413	1	,036	3,631	1,090	12,092
High lymph node burden (ypN2)	1,279	,574	4,959	1	,026	3,594	1,166	11,079
Global downstaging	,576	,516	1,250	1	,264	1,780	,648	4,888

TABLE 33: Multivariate analysis of prognostic factors for a worse overall survival. The dark blue cells represent the factors statistically significant in the analysis.

3.9.3. Adjuvant chemotherapy and the risk of local relapse and distant metastases.

We did not perform a survival analysis according to the type of adjuvant chemotherapy given as we did not consider it a baseline prognostic factor and the survival analysis would be subject to many selection biases. However, we performed an exploratory analysis of the relationship between the administration and the dose intensity of adjuvant chemotherapy and the risk of developing a local relapse and distant metastases. We excluded those patients that did not receive adjuvant chemotherapy due to early progression and/or death. The results are shown in TABLE 34. There were no differences in the risk of local relapse with the use of adjuvant chemotherapy. However, there was a detrimental effect on the appearance of distant metastases with a lower administration of adjuvant chemotherapy or no adjuvant chemotherapy compared to full-dose systemic therapy (16.3% vs 31.4%, p 0.050)

	No relapse, number (%)	Local relapse, number (%)	Distant metastases, number (%)	*p*- value
Dose intensity of adjuvant chemotherapy				
- **100% dose**	74 (80.4)	3 (3.3)	15 (16.3)	0.159
- **< 100% dose**	47 (64.4)	3 (4.1)	23 (31.5)	
- **No chemotherapy**	11 (69.2)	0 (0.0)	8 (30.8)	
Dose intensity of adjuvant chemotherapy				
- **100% dose**	74 (80.4)	3 (3.3)	15 (16.3)	0.050*
- **< 100% dose or no adjuvant CT**	65 (65.7)	3 (3.0)	31 (31.3)	

* Statistically significant

TABLE 34: Exploratory analysis of the relationship between the administration and the dose intensity of adjuvant chemotherapy and the risk of developing a local relapse and distant metastases

4.9.4. Validation of the study group with the Valentini nomogram and the Dhadda score

Finally, we analysed if our study population would fit the Valentini nomogram [34] and the Dhadda score [35]. We categorized our patients in one of the three Valentini prognostic subgroups; the results are shown in TABLE 35 and in FIGURES 14 and 15. The use of nomogram predicted fairly accurately a fairly large group of patients with a high risk of distant relapse (61.8%) and worse OS (52.5%): in contrast, only 16% of our patients had a high risk of local relapse with the use of the nomogram.

Risk category for local relapse¶	Number (%)	Local relapse rate (%)	*p*-value
Low risk (< 10% risk of local relapse)	80 (40.2)	0 (0)	0.003*
Moderate risk (10-30% of local relapse)	83 (42.8)	11 (13.4)	
High risk (> 30% risk of local relapse)	31 (16)	4 (13.3)	

¶ Risk defined by cT, pT, pN, use of concomitant chemotherapy alongside radiotherapy and use of adjuvant chemotherapy

Risk category for systemic relapse¶	Number (%)	Systemic relapse rate (%)	*p*-value
Low risk (< 10% risk of systemic relapse)	32 (16.1)	4 (2.5)	0.004*
Moderate risk (10-30% of systemic relapse)	44 (22.1)	5 (11.4)	
High risk (> 30% risk of systemic relapse)	123 (61.8)	43 (35.4)	

¶ Risk defined by pT, pN, type of surgery (abdominoperineal resection versus low anterior resection) and use of adjuvant chemotherapy

Risk category for death at 5 years¶	Number (%)	5-year disease-free survival (%)	*p*-value	5-year overall survival (%)	*p*-value
Low risk (< 10% risk of death at 5 years)	48 (24.2)	85.0	0.001*	87.6	0.009*
Moderate risk (10-30% of death at 5 years)	46 (23.2)	77.2		79.7	
High risk (> 30% risk death at 5 years)	104 (52.5)	66.2		73.0	

¶ Risk defined by pT, pN, cT, type of surgery (abdominoperineal resection versus low anterior resection), age, sex, radiotherapy dose and use of adjuvant chemotherapy

TABLE 35. Allocation of the patients in our series in the different risk categories proposed by Valentini *et al* for local relapse, systemic relapse and death at 5 years.

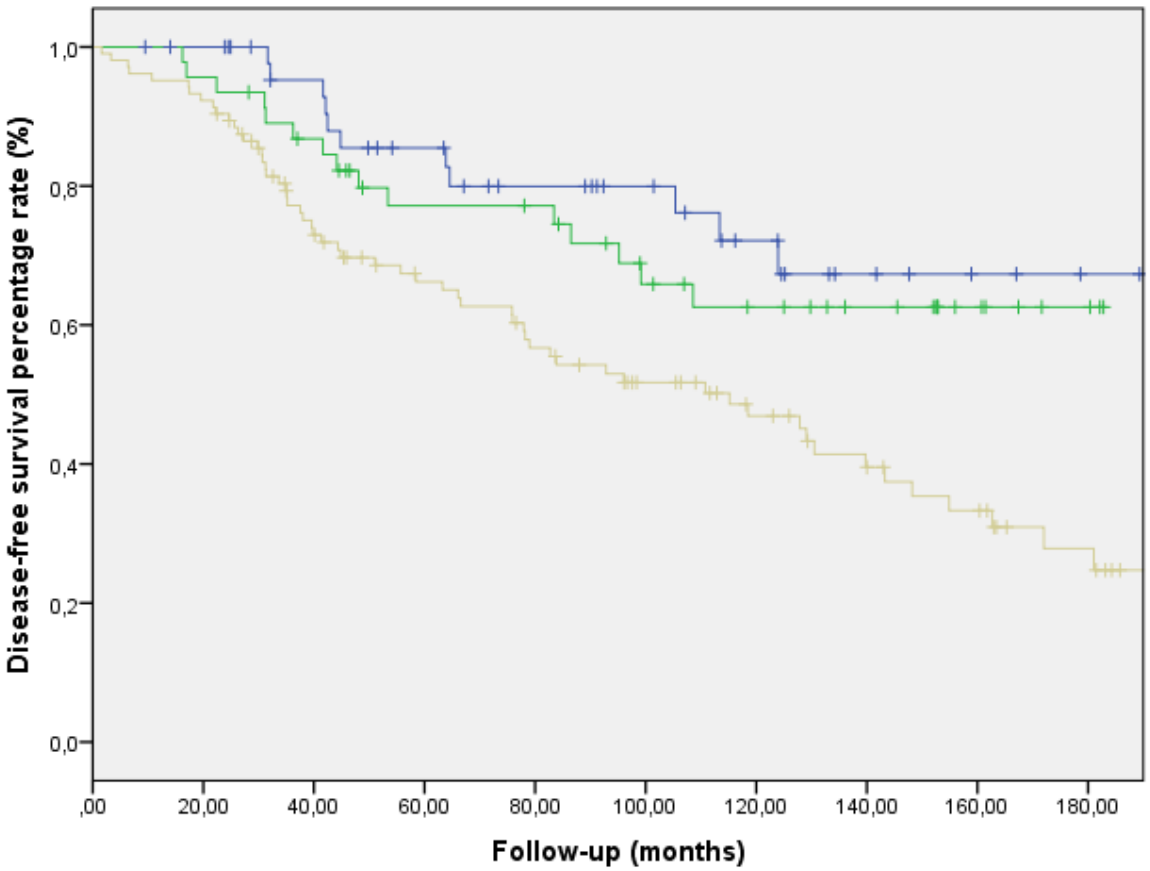
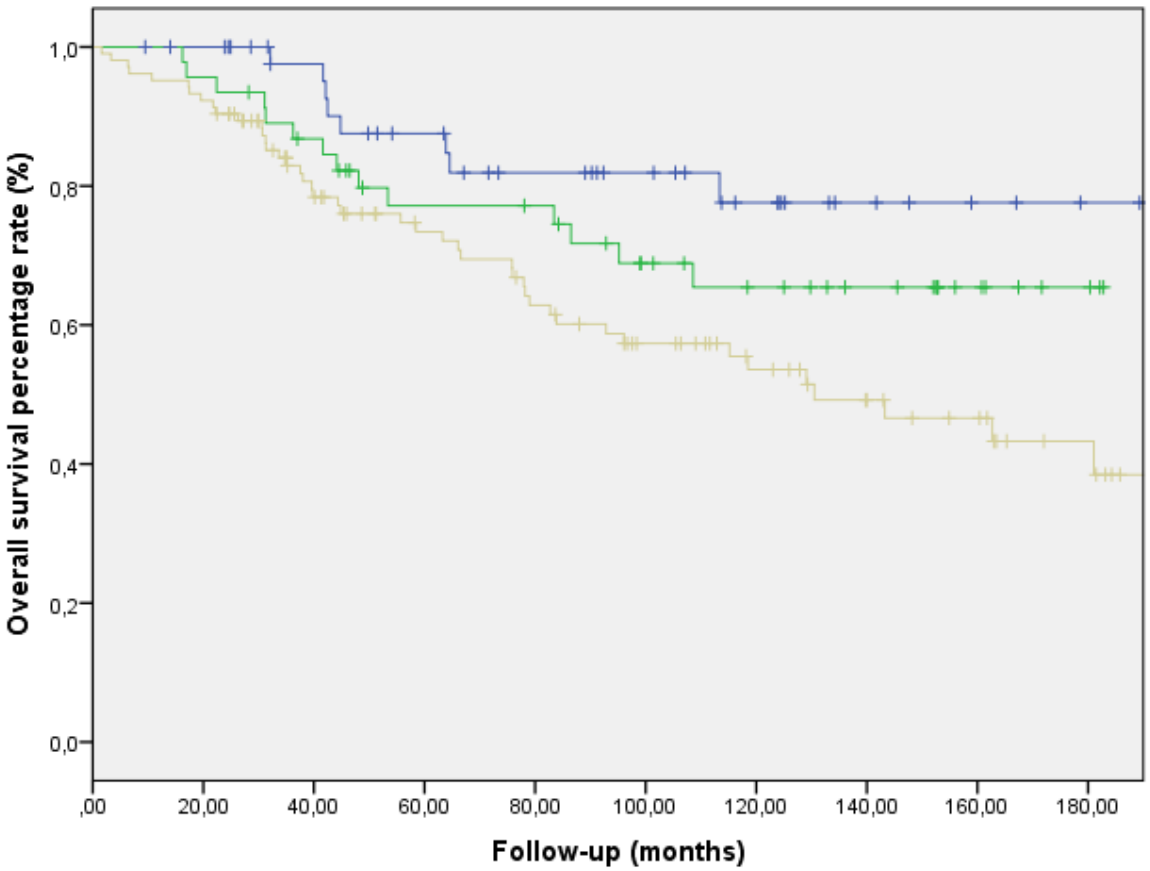


FIGURE 16: Disease-free survival curves for patients allocated to the three risk categories proposed by Valentini *et al* [34].



Risk category for death at 5 years	Median disease-free survival	Median overall survival
Low risk	Not reached	Not reached
Moderate risk	Not reached	Not reached
High risk	115.2 months	130.5 months

FIGURE 17: Disease-free and overall survival curves for patients allocated to the three risk categories proposed by Valentini *et al* [34]

We also categorized our patients in one of the four Dhadda prognostic subgroups; the results are shown in TABLE 38 and in FIGURES 16 and 17. With this classification, most patients belonged to the excellent (42.6%) and good (26.2%) prognosis groups; there were no differences in DFS and OS between these two groups in our population, although there was a slightly higher risk of local relapse (5.9% vs 0%) in the good prognosis group. 23.6% and 7.7% of patients belonged to the moderate and poor prognosis groups and there were clear differences in the DFS and OS between these two stages and with the other two stages; however, the risk of local relapse was curiously higher in the moderate risk group than in the poor risk group.

Risk category for death at 5 years¶	Number (%)	Local relapse, %	Median DFS, months	5-year DFS, %	Median OS, months	5-year OS, %
Excellent prognosis	83 (42.6)	0 (0.0)	Not reached	81.0	Not reached	81.0
Good prognosis	51 (26.2)	3 (5.9)	181.1	82.0	Not reached	89.0
Moderate prognosis	46 (23.6)	10 (22.7)	86.5	59.2	118.5	66.5
Poor prognosis	15 (7.7)	2 (14.3)	41.1	46.7	63.3	53.3
***p*-value**		< 0.001	< 0.001		< 0.001	

¶ Prognosis defined by pN, perineural invasion, invasion of the circumferential margin and the tumour regression grade

TABLE 38. Allocation of the patients in our series in the different risk categories proposed by Dhadda *et al* for disease-free survival (DFS) and overall survival (OS)

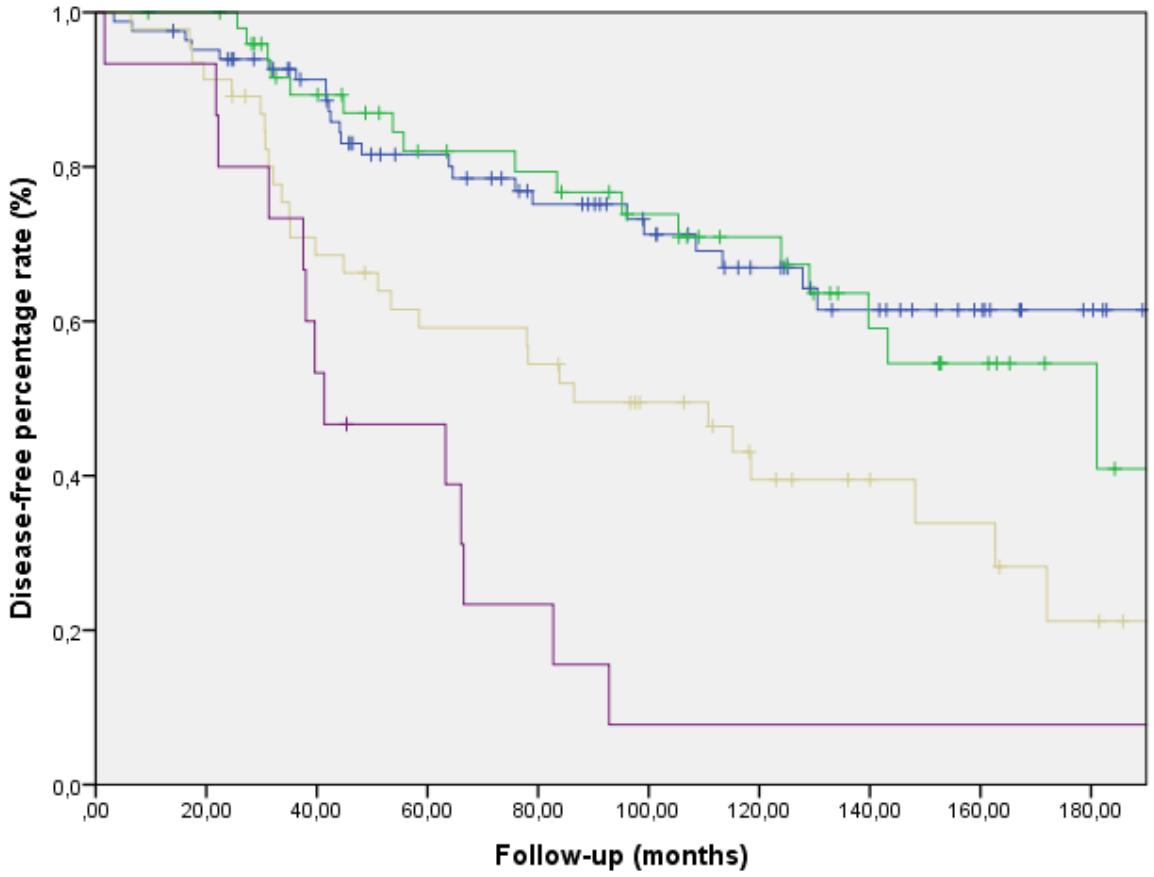


FIGURE 18: Disease-free survival curves for patients allocated to the four risk categories proposed by Dhadda *et al* [35]

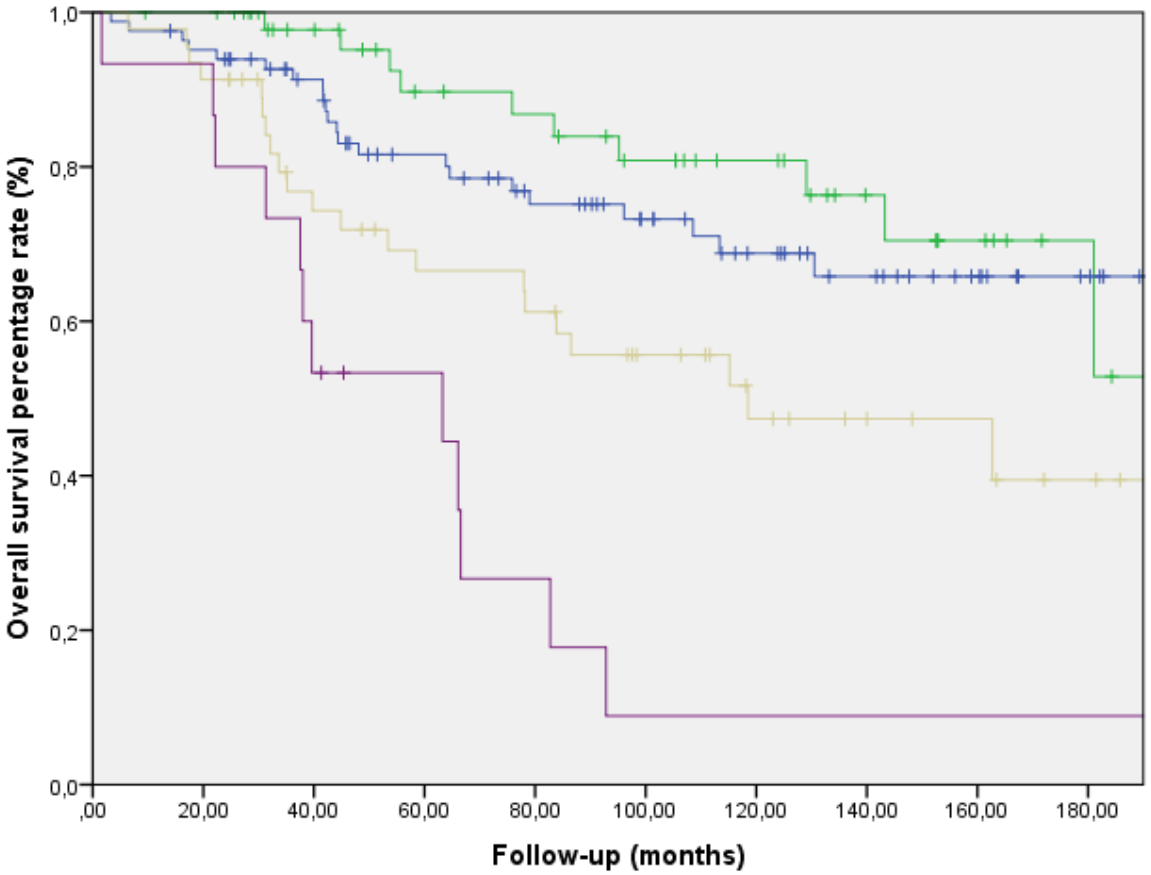


FIGURE 19: Overall survival curves for patients allocated to the four risk categories proposed by Dhadda [35]

4. Discussion

4.1. Introduction

The treatment of locally advanced rectal cancer has been one of the success stories in Oncology of the last decades. From where we were in the 1980s, when up to 50% of the patients suffering from a locally advanced tumour developed a pelvic recurrence, the decrease in this event to less than 10% with the incorporation of radiotherapy and without any contribution from new drugs, except of 5-FU, is a landmark observation in the management of this malignancy. Several factors are behind these improvements: the widespread introduction of TME as the standard surgical approach, the improvement in the clinical staging of these patients with EUS and, especially, with high-quality MRI, the integration of (neo)adjuvant radiotherapy and chemotherapy in localized disease, a better pathological diagnosis with the recognition of the fundamental prognostic role of the CRM and, lastly but not less important, the management of these patients in the setting of multidisciplinary units, where the most appropriate approach can be decided between the different disciplines [36].

However, despite these benefits, several shortcomings are now evident in the management of our patients. With the marked improvement in the risk of pelvic recurrences, distant metastases are now the main cause of death in around 30% of patients; unfortunately, in the vast majority of randomized trials of chemotherapy and/or radiotherapy, no overall survival benefits have been observed, despite the marked improvement in local control rate. The integration of adjuvant chemotherapy, in the same manner as in colon cancer, has been difficult and compliance rates have been poor; moreover, the benefit is much less clear than in colon cancer, especially after LCRCT and surgery. Although clinical staging has improved enormously, there is still an important group of patients that are over- or understaged, especially in the identification of pathological lymph nodes, probably the most important prognostic factor alongside the invasion of the CRM. Finally, and perhaps more under-recognised, are the risks of late toxicity. Recognised long-term side-effects of pelvic radiotherapy for rectal cancer include faecal incontinence, sexual and urinary dysfunction, and sterility [37-39]. There are also suggestions of an increase in the risk of second malignancies [40-41]. These risks can be accumulative; quality-of-life data from some trials have demonstrated a significant impairment in sexual function attributable to surgery and a further detriment due to radiotherapy and a similar pattern for faecal incontinence [37].

In this sense, the long-term results of our study of patients with locally advanced rectal cancer are broadly similar to other studies of LCRCT followed by surgery and we think that they can be considered moderately successful: there was a local relapse rate of less than 10%, with a downstaging rate of 70% and a pCR rate of 14.8%. 30% of patients relapsed, the vast majority in the form of distant metastases and the 10-year OS rate was 62.4%, with most relapses taking place in the first five years of follow-up. However, there were several concerning factors: older patients fared poorly compared to their younger counterparts; despite the use of LCRC and specialized surgery, the quality of the mesorectum was unsatisfactory in around a quarter of patients and 21% had a positive CRM; finally, the compliance in the use of adjuvant chemotherapy was rather poor, with less than half of patients receiving the full intended dose and around a quarter of patients not receiving any type of adjuvant treatment. We followed a blanket approach of treating all patients with cT3-4 and/or lymph node positive disease with LCRCT and adjuvant chemotherapy, irrespective of response, as our standard treatment, as is usually done in the United States and in many countries of Europe. However, as we will see, the risk factors of local relapse and distant metastases are different although overlapping. In this sense, how can we improve our results? Can we offer a more personalized approach taking into account these differing risks of local and metastatic relapse, as is recommended by ESMO and NICE? Can we better select

patients for adjuvant chemotherapy or for neoadjuvant radiotherapy with clinical, radiological and/or pathological data? How can we optimize the use of radiotherapy and chemotherapy? What can we do in elderly and/or frail patients? These were some of the aims of our study.

4.2. Treatment of locally advanced rectal cancer. Where are we now?

4.2.1. What is the basis for the use of LCRCT?

Historically, in the pre-TME era, postoperative 5-FU-based chemoradiotherapy showed improved survival over surgery alone among patients with stage II-III rectal cancer [42-43]. Logically, the next step forward was to translate this benefit into the neoadjuvant setting. Perceived advantages of this approach included a higher likelihood of achieving a resection with negative margins, a higher rate of sphincter preservation, a reduction in toxicity, particularly enteritis, and higher compliance, given that the ability to deliver treatment is not dependent on recovery from surgery. However, there were also reasons to be cautious, as clinical staging was less accurate than pathologic staging, there was concern that tumour progression during neoadjuvant therapy would result in losing the window of opportunity for curative resection, and there was the possibility of increased postoperative complications such as impaired wound healing or anastomotic leaks when operating on radiated tissue.

With this in mind, several studies investigated pre- and postoperative CRT in patients with locally advanced rectal cancer, with the aim of determining the best sequence of CRT administration with surgery [44-47]. Despite these efforts, the optimal sequence did not become clear until results from the German Rectal Cancer Study Group trial became available in 2004 (TABLE 39) [45]

	Number of patients	RT dose	Treatment arms	pCR	Sphincter sparing	5-year local relapse	5-year overall survival	Grade 3-4 acute toxicity
CAO/ARO/AIO-94 [44-45]	823	50.4 Gy +/- 5.4 Gy boost	CT-RT with CI 5FU during RT, pre vs postoperative	8% vs NA	39% vs 19%*	6% vs 13%*	76% vs 74%	27% vs 40%*
NSBAP R-03 [59]	267	50.4 Gy + 5.4 Gy boost	CT-RT with bolus 5-FU during RT, pre vs postoperative	15% vs NA	NS	10.7% vs 10.7%	74.5% *v* 65.6% (5-year DFS 64.7% *v* 53.4*)	52% vs 49%
FFCD-9203 [49]	733	45 Gy	RT vs CT-RT with bolus 5-FU, both preoperative	11.4% vs 3.6%*	57.7% vs 58.3%	8.1% vs 16.5%*	67.4% vs 67.9%	14.6% vs 2.7%*
EORTC 22921 [47-48]	1011	45 Gy	RT vs CT-RT with bolus 5-FU, both preoperative	13.7 vs 5.3%*	52.8% vs 50.5%	8.7% vs 17.1%	65.8% vs 64.8%	13.9% vs 7.4%

* Statistically significant
NA: not assessable; pCR: pathological complete response
TABLE 39: Randomized trials which compared neoadjuvant versus adjuvant LCRT in patients with locally advanced rectal cancer

The German Rectal Cancer Study Group trial was initiated in February 1995, and enrollment was extended through September 2002 [44]. The study enrolled 823 patients with clinical stage T3 or T4 or node-positive disease. Patients were then randomly assigned to receive either preoperative or postoperative LCRCT. The preoperative treatment consisted of 50.40 Gy concurrently with infusional 5-FU. The primary endpoint was OS. All patients underwent surgery 6 weeks after the completion of LCRCT. One month after this surgery, 4 additional cycles of adjuvant 5-FU were administered. LCRCT was identical in the postoperative treatment group, except for the delivery of a boost of 54 Gy in the latter group.

Results from a 46-month median follow-up analysis showed that preoperative treatment was associated with a significantly lower cumulative incidence of local relapse than postoperative CRT. However, there were no significant differences in 5-year DFS and OS. Following preoperative CRT, there was a significant shift toward earlier TNM staging, which was suggestive of a significant downstaging effect. 8% of the patients in the preoperative CRT group had a pCR, and only 25% had positive lymph nodes (compared with 40% in the postoperative group). Of note, in patients with tumours that had been predicted preoperatively by a surgeon to require an APR, the rate of sphincter-preserving surgery was more than twice as high after preoperative CRT compared with postoperative CRT (39% vs 19%). However, postoperative treatment was associated with a significant increase in the rate of short- (27% vs 40%) and long-term toxic effects (14% vs 24%). A recent update of the trial with an 11-year follow-up confirmed these conclusions, with a significant, albeit smaller, benefit in the risk of local relapse but no difference in DFS and OS [45]. This trial established the superiority of preoperative over postoperative LCRCT.

However, two concerning facts were also evident: 18% of patients in the postoperative treatment group with no CRT prior to surgery who were determined preoperatively to have T3 or T4 disease or lymph node metastasis were found to actually have T1 or T2 or node-negative tumors on pathologic examination of the resected specimen. This important observation clearly highlights the limitations of preoperative staging, especially at the time the study was performed. Also, compliance with the postoperative arm was worse than in the preoperative arm, with 92% of patients in the preoperative arm receiving a full dose of RT, compared with only 54% in the postoperative arm and 89% compared with 50% receiving a full dose of chemotherapy; both of these findings were statistically significant and may have justified the local control benefit observed.

Another important earlier randomized trial tried to answer two relevant questions: the benefit of preoperative versus postoperative radiotherapy and the benefits of concomitant chemotherapy alongside radiotherapy. With this in mind, The European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Group initiated the EORTC 22921 trial in 1993, which randomized more than 1,000 patients with T3-T4 resectable rectal cancer, using a 2 × 2 factorial design, to one of the following four treatment regimens (along with surgery): 1) preoperative radiotherapy (the control arm), 2) preoperative LCRCT, 3) preoperative radiotherapy and postoperative chemotherapy, or 4) preoperative CRT and postoperative chemotherapy. Preoperative and postoperative chemotherapy regimens involved bolus 5-FU plus leucovorin. In addition to effects on local tumor control, the ability of the four treatment approaches to improve OS and progression-free survival (PFS) was analyzed. [47]

Combined chemoradiotherapy resulted in downstaging of tumors and increased local control rates. Local failure rates were significantly lower in all three groups that received chemotherapy, compared with the control arm (preoperative RT alone), regardless of whether chemotherapy was given prior to or following surgery. Patients undergoing preoperative CRT had a significantly higher rate of pathologic complete response (pCR; 14% vs 5%). However, the addition of chemotherapy, either concurrently with preoperative RT or

postoperatively again was not associated with any improvement in PFS or OS. Updated long-term results of this study were published in 2014. The reported cumulative incidence of local relapse at 10 years was 22.4% in patients who received RT alone, compared with 11% to 15% in the three groups that received chemotherapy [49-50] Ten-year DFS and OS was similar in patients who received preoperative CRT vs RT alone. One important finding was that adjuvant 5-FU–based chemotherapy after preoperative RT (with or without chemotherapy) still did not affect DFS or OS [48].

Other studies, such as the Fédération Francophone de Cancérologie Digestive (FFCD) trial 9203 [53] yielded similar results and showed that the addition of 5-FU to RT significantly increased the pCR and local disease control rate, with no benefit in DFS or OS.

In a Cochrane analysis that included the EORTC, the FFCD and four other trials which compared SCRT and LCRCT [52-56] the addition of chemotherapy to preoperative RT for the treatment of locally advanced rectal cancer was associated with a lower risk of local relapse that was statistically significant [57]. With all these results, the addition of chemotherapy to conventional fractionation RT became a standard approach in the treatment of locally advanced rectal cancer, likely because of the reduction in local recurrence and improvement in pCR rates observed with CRT.

On the other hand, in addition to these trials, two other prospective randomized trials with the same aim were initiated in the United States by the Radiation Therapy Oncology Group (RTOG; trial 94-01) and the National Surgical Adjuvant Breast and Bowel Project (NSABP; protocol R-03). Unfortunately, both studies were closed prematurely due to poor accrual. However, the NSABP Group published their results with the 257 patients accrued [58]. Surprisingly, there was a significant benefit in DFS with the preoperative approach, with no benefit in the local relapse rate; there was surprisingly a higher acute grade 3-4 toxicity with the preoperative arm. These findings are difficult to harmonize with the European trials. The unusual chemotherapy regimen, alongside the high RT dose and the non- standard use of TME, alongside the early closure of the trial, may justify some of these findings, although the explanation remains elusive [59].

With the establishment of 5-FU based LCRT, following the development of orally active fluoropyrimidines (ie, capecitabine or UFT), the natural question was whether these drugs could replace infusional 5-FU in this setting. Two clinical trials studied the effect of using capecitabine in place of infusional 5-FU, combined with RT, on pCR, sphincter-sparing surgery, and surgical downstaging. Unfortunately, there are no phase III trials with UFT and it was removed from the Spanish market on 2007.

The first trial [61] was a neoadjuvant, open-label, multicenter, noninferiority, randomized phase III study that explored the substitution of capecitabine for infusional 5-FU [60]. A total of 401 patients with locally advanced rectal cancer were enrolled and randomly assigned to either the oral or intravenous fluoropyrimidine group. There were no differences in 5-year OS and and 3-year DFS was higher in the capecitabine group in both the adjuvant and neoadjuvant cohorts. The local recurrence rate was similarly low for capecitabine and intravenous 5-FU (6% vs 7%), but fewer patients developed distant metastases in the capecitabine group.

The second phase III trial, which was conducted by the NSABP [61] employed a 2 × 2 factorial noninferiority design to compare four regimens administered concomitantly with RT (45 Gy in 25 fractions over 5 weeks, followed by a boost). The aim of this study was to determine the optimal neoadjuvant chemotherapy regimen for stage II/III rectal cancer, including the best sequence of administration of preoperative CRT. The trial

evaluated the substitution of capecitabine for IV 5-FU, as well as the intensification of chemotherapy via the addition of oxaliplatin.

Between September 2004 and August 2010, a total of 1.608 patients with clinical stage II or III rectal cancer were enrolled in the trial. There were no significant differences between the capecitabine and infusional 5-FU regimens (regardless of oxaliplatin treatment) for the rates of pCR (21% vs 18% for the capecitabine and infusional 5-FU regimens, respectively), sphincter-sparing surgery, or surgical downstaging. Patients who received capecitabine had rates of locoregional control (the primary endpoint) comparable to those in patients who received IV 5-FU (regardless of oxaliplatin treatment). OS rates were also similar.

Both of these trials supported the equivalence of capecitabine and intravenous 5-FU during RT for neoadjuvant therapy; however, different toxicity profiles were evident (patients who received capecitabine had significantly more hand-foot syndrome, fatigue, and proctitis, but less neutropenia), which may be important in elderly and/or frail patients. There was no benefit with the addition of oxaliplatin, as we will see in the following sections.

As we have mentioned, LCRCT is a standard treatment approach in the United States and in many countries of Europe. It has shown to decrease the risk of local relapse and it allows tumour downstaging in patients where the CRM is involved or where a non-curative resection would be performed if surgery was performed upfront. TABLE 40 shows some of the advantages and disadvantages with the use of LCRCT.

Advantages	**Disadvantages**
Early partial treatment of micrometastases	Less than systemic doses of chemotherapy
Can prevent repopulation during radiotherapy	Delays full systemic adjuvant chemotherapy 18-26 weeks
Tumour will have intact blood supply	Worse compliance to chemotherapy treatment
Potential for organ sparing if downstaged	Expensive
Potential for curative resection if downstaging	Only partially compensates for a positive circumferential resection margin
Potential for brachytherapy boost	
Potential for avoiding radical surgery?	
Avoids surgery for resistant/progressive tumours	
Response can define prognostic groups	
Trials show improved local control	

TABLE 40: Advantages and disdvantages of LCRCT in the management of patients with locally advanced rectal cancer

4.2.2. Short-course radiotherapy

SCPRT represents a flexible schedule of a short accelerated and hypofractionated intensive RT, administering 25 Gy in five fractions over 5 days and it has become the favoured radiotherapy regimen in the United Kingdom and in other northern European countries in those cases of resectable cancers where staging imaging suggests that a conventional TME would enable a curative resection without margin involvement and where tumour shrinkage is not required.

The basis of the use of SCRT is based on several randomized trials published in the last decades (TABLE 10). Three trials prior to the introduction of TME [62-64] compared SCPRT followed by immediate surgery with surgery alone. All of these trials showed a significant reduction in local relapse. Afterwards, the Swedish Rectal Cancer Trial [65] compared SCPRT and immediate surgery with initial surgery followed by postoperative split-course RT for patients with stage II and III disease (at that time, Dukes B and C histology). Local relapse was also reduced from 27 % to 11 % and, more surprisingly, 5-year OS increased from 48 % with surgery alone, to 58 % after SCPRT and surgery, respectively; these differences remained significant after 13 years of follow up [66]. Probably the OS improvement in this trial was linked to the use of non-standadized, non-TME surgery.

Trial	Number	Radiotherapy dose	Treatment arms	Local relapse	Distant metastases	Long-term overall survival
Swedish Rectal Cancer trial [65-66]	1168 (preTME)	25 Gy in 5 fractions	Surgery vs preoperative SCRT	26% vs 9%*	34% vs 34%	30% vs 38%* (13-years F/U)
Dutch TME study [68]	1861	25 Gy in 5 fractions	TME surgery vs preoperative SCRT	11% vs 5%*	28% vs 25%	49% vs 48% (11.6-years F/U)
MRC CR07 [69]	1350	45 Gy in 25 fractions 25 Gy in 5 fractions	Selective postoperative CT-RT vs preoperative SCRT	11.5% vs 4.7%*	21% vs 19%	67.9% vs 70.3% (5-year OS)
Pach *et al* [70]	154	25 Gy in 5 fractions	Surgery performed 1 week or 4-5 weeks after SCRT	1.5% vs 7%	12.3% vs 2.8*	63% vs 73% (5-year OS; 60 vs 90% if downstaging was seen*)

* Statistically significant

TABLE 41: Randomized trials which compared SCRT and surgery versus surgery alone in patients with locally advanced rectal cancer.

In this sense, subsequent trials were designed to test whether SCPRT still reduced local relapse if TME was performed. By then, it was recognised that the risk of pelvic recurrence, after a potentially curative resection, was mainly explained by microscopic tumour cells within 1 mm of the CRM [67].

The Dutch trial [68] and the Medical Research Council CR07 trial [69] compared routine SCPRT and immediate surgery against initial surgery with a policy of selective postoperative treatment restricted to patients with involvement of the CRM (the Dutch trial used radiotherapy alone and the MRC CR07 trial used concurrent 5FU-based LCRCT). Both trials showed a sustained reduction in LR in the SCPRT group, although there was no survival benefit and the risk of distant metastases prevailed. In the MRC 07 trial, all patients benefited from the use of SCRT, even those deemed of low risk. However, in both trials, independently of radiotherapy administration, a positive CRM was associated with local recurrence and decreased survival. As such, while the results of this trial support the use of radiotherapy in locally advanced patients, the data underscore the importance of obtaining a negative CRM with high quality surgery. Unfortunately, radiotherapy is not able to compensate fully for a positive CRM; however, the same can be said of LCRCT.

Unfortunately, there were several shortcomings in the trial that have made it somewhat different to interpret these results. For example, the number of patients who were intended to, and actually received postoperative radiotherapy in the Dutch trial, is not known. In the CR07 trial there were no details on compliance in the 53 patients who received selective postoperative LCRCT, while only 19% received radiotherapy alone and 9 % did not receive any type of radiotherapy.

At the same time, compared to the CAO/AOC/AIO 94 German trial [49], it was not clear whether the majority of recurrences occurred in the treated or non-treated patients. Adjuvant chemotherapy was not used in the Dutch trial, whereas most patients with stage III received 5FU chemotherapy in the CR07 trial. In the CR07 trial, doses of RT mandated were low (45 Gy) compared with standard postoperative CRT trials (such as 55.4 Gy in the German Trial).

Finally, accrual for the MRC 07 trial began in 1998, and surgical quality control was not emphasized at the start of the trial. As such, it is difficult to know the extent to which variation in the quality of surgical resection may have played a role in the higher local recurrence rate in the selective therapy arm. As we have said previously, the overall survival improvement in the Uppsala trial was probably linked to the use of non-TME surgery. However, the CR07 trial did show that the plane of surgical resection, which may be considered a surrogate of surgical quality, was highly correlated with outcome [70]. For patients treated within the proper plane whose radial margins were clear, there was a very low rate of local treatment failure of 6%, even among patients with node positive disease found on pathologic evaluation, an important finding, as we will see; patients with low burden lymph node disease may not need necessarily neoadjuvant radiotherapy, as the risk of local relapse will probably be low in case high quality surgery is performed.

There are several advantages to the use of SCRT (TABLE 42). Compliance is high because toxicity, mainly digestive and genitourinary, is usually only experienced after treatment is completed. The short overall treatment time, with immediate surgery (ideally within 7 days), leaves an insufficient interval for radiation-induced fibrosis to appear and avoids the accelerated repopulation that may occur in the latter part of LCRCT. It is also a cheap alternative. Decisions on the requirement for postoperative adjuvant chemotherapy can be made without modification of the pathological stage or effacement of the nodes. Adjuvant chemotherapy with systemically active regimens, such as FOLFOX, can be started with minimal delay, within a few weeks of diagnosis. However, an important criticism is the difficult in integrating systemic chemotherapy in the

neoadjuvant setting alongside SCRT. Although this is probably true in the original reports of SCRT, there are several reported small trials, which have shown that neoadjuvant, concomitant and even sequential chemotherapy can be administered to patients treated with SCRT [71-74].

Advantages	Disadvantages
Excellent compliance	No downstaging if immediate surgery
Tumour will have intact blood supply	No potential for organ sparing if downstaged
Allows chemotherapy within 10 days of radiotherapy	Does not increase the chance of a curative resection
Trials show improved local control	Only partially compensates for a positive circumferential resection margin
Cheap	

TABLE 42: Advantages and disdvantages of SCRT in the management of patients with locally advanced rectal cancer

Many clinicians are mindful of the potential risk of higher acute and late toxicity from the large individual 5 Gy fractions within the SCPRT regimen (according to the linear quadratic formula, this schedule is equivalent to 21 x 2 Gy fractions in terms of acute and late effects) [75-77]. This view was originally raised by the reports from the Stockholm I and II trials that showed a significant increase in postoperative mortality and venous thromboembolism, pelvic and femoral neck fractures, small bowel obstruction and postoperative fistulæ [62-63], although the two-field large treatment volumes used at that moment were probably responsible.

The Dutch TME study did show more perineal complications following SCPRT and abdominoperineal excision. In the postoperative period, many patients who had SCPRT became neutropenic, which probably increased the risk of postoperative complications and death [78]. In particular, elderly patients aged over 75 years who were operated on 4 to 7 days after RT had a higher chance of dying due to non-cancer-related causes during the TME-trial compared with an interval of up to 3 days. [79]

Compared to LCRCT, where few publications have reported late complications after preoperative CRT, late-onset toxicity is well documented with SCRT. Effects on sexual function [80] urinary incontinence [81] bowel function [82] and faecal incontinence [83] have been reported. SCPRT impacts on continence-related QoL compared with patients treated with surgery alone [84]. These complications may depend on the size of the radiation field, shielding, the overall treatment time, the fraction size and the total dose [85]. More worryingly, the Dutch study after 11- years follow-up did report a higher risk of second malignancy from SCPRT [66]

4.2.3. Can we select which patients will benefit either from SCRT or LCRCT?

Both neoadjuvant approaches, SCRT and LCRCT, have shown consistent benefits in the risk of local relapse in locally advanced rectal cancer, although the vast majority of trials have not shown an improvement in distant metastases or in survival times. As we have seen, both of these approaches have advantages and disadvantages (TABLE 40 and 42). Unfortunately, indirect comparisons between the different phase III trials

are neither feasible or correct, as the entry criteria for the LCRCT and SCRT trials were usually different. However, we can make some comparisons, as shown in TABLE 44. The main difference probably is the downstaging potential of LCRCT and SCRT.

	Short-course radiotherapy	Long-course radiochemotherapy
Total radiation dose	25 Gy in 5 fractions	45-50.4 Gy in 25-28 fractions
Fraction size	5 Gy	1.8 Gy
Radiaton duration	1 week	5-5.5 weeks
Biologically effective dose	66.7 Gy	72-84 Gy
Recommended time to surgery	3-7 days	6-12 weeks
Downstaging	Not unless surgery is delayed 10-12 weeks from start of radiotherapy	Yes, approximately 50%
Concomitant chemotherapy	No	Yes
Acute toxicity	Difficult to assess due to early surgery	10-25% grade 3-4
Late toxicity	< 10%	Less studied; < 10%?

TABLE 44: Differences between short-course radiotherapy and long-course (chemo)radiotherapy

Luckily, in the last decade, three phase trials have been reported that compared face-to-face both of these treatments; they are shown in TABLE 45.

	Polish Trial [54-55]	Australian Trans-Tasman TROG 04.01 [56]	Bujko K et al, 2016 [87]
Number	316	326	515
Clinical stage	cT3-T4	cT3N any (56% N0)	Fixed cT3 or cT4
Short-course RT arm	25 Gy in 5 fractions	25 Gy in 5 fractions	25 Gy in 5 fractions followed by 3 cycles of FOLFOX
Long-course CT-RT arm	50.4 Gy + bolus 5-FU	50.4 Gy + CI 5-FU	50.4 Gy + bolus 5-FU +/- oxaliplatin
Adjuvant CT	Not required	Bolus 5-FU (4-6 cycles)	Not stated
Results	LC CT-RT vs SCPRT	LC CT-RT vs SCPRT	LC CT-RT vs SCPRT
- **pCR**	16 vs 1%*	15% vs 1%*	12% vs 16%
- **Sphincter-saving procedures**	58 vs 61%	69% vs 63%	----
- **Positive circumferential resection margin**	4 vs 13%*	4% vs 5%	R0: 71% vs 77%*
- **Compliance**	69% vs 98%	85% vs 100%	---
Local relapse	14.2% vs 9%	4.4% vs 7.5%**	21% vs 22%
Distant metastases	34.6% vs 31.4%	30% vs 27%	27% vs 30%
Overall survival	66.2% vs 67.2%	70% vs 74%	73% vs 65%*

* Statistically significant

** A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short-course radiation and there were no failures with long-course chemoradiation

TABLE 45: Reported randomized trials comparing short-course radiotherapy and long-course chemoradiotherapy in the management of locally advanced rectal cancers.

The Polish Colorectal Group study was the first reported trial [54-55]. It randomized 316 patients with T3/4 disease to either SCRT or LCRCT before TME resection and optional adjuvant chemotherapy. The trial aimed to evaluate the hypothesis that the downstaging effects of preoperative LCRCT with a 4 to 6-week delay to surgery would increase the rate of sphincter-preserving resection compared with SCPRT and immediate surgery. However, no difference was observed for the primary endpoint of sphincter-sparing interventions. There were no significant differences in the 5-year rate of local relapse and in DFS or OS. LCRCT was associated with an increased rate of acute toxicity compared to SCRT (18.2% vs. 3.2%), with 2 reported deaths during and immediately after concurrent treatment; however, no difference in late toxicity was noted. As could be expected, LCRCT improved both pCR rates and negative CRM rates; however, this did not translate into a significant difference in distant metastases or improved DFS or OS.

The TROG 01.04 trial randomized 323 patients with only T3 disease to SCRT or LCRCT before TME resection [56]. Adjuvant chemotherapy was prespecified with bolus 5-FU and folinic acid. Compliance was high (more than 80%) and similar in both arms. Three-year LR rates were 7.5% for SCRT and 4.4% for CRT, corresponding to a nonsignificant 3.1% difference and a failure to meet the trial's primary end point; however, a subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short-course radiation while there were no failures with long-course chemoradiation. As in the Polish trial, a

higher rate of pCR was achieved with LCRCT, but no difference in DFS or OS was noted and the rate of late toxicity was similar.

What can we make of these two trials? Both of them were underpowered to detect modest but clinically significant differences in long-term outcomes and neither trial provides sufficient evidence to definitively compare efficacy between SCPRT and LCRCT. Both approaches seem broadly similar. However, LCRCT does have some advantages in those patients where a downstaging is needed, especially if the mesorectal fascia is threatened, and in lower tumours, where the risk of local relapse is higher. On the other hand, SCRT seems to be more effective in mid-rectal tumours. Acute toxicity is higher with LCRCT (although it is usually manageable), with the exception of acute neurogenic pain, which is observed in <1–2 % of patients receiving SCPRT, is usually reversible and dependent on the radiotherapy fields used [88-89]. With a more limited field size, this side effect has not been observed in more recent trials, such as in the CR07 trial, and have not been reported after LCRCT.

The third trial recently reported is another study of The Polish Colorectal Group study [87]. The trial included 515 patients with fixed cT3 or cT4 rectal cancer. Patients were randomly assigned to SCRCT and three cycles of FOLFOX4 after one-week rest, or to standard LCRCT, with bolus 5-FU, leucovorin and oxaliplatin; of note, after data showed there was no advantage of adding oxaliplatin to LCRCT in 2012, the study protocol was amended and oxaliplatin could be omitted at the discretion of the participating study site.

No significant difference was found between patients assigned both arms in respect to the primary endpoint, the rate of radical resection. There were also no differences in the pCR rates, nor in DFS and incidence of local and/or distant relapse. However, surprisingly, although the follow-up is short, the 3-year OS rate was significantly higher for patients assigned to the SCRCT and combined chemotherapy arm. Similar downstaging results were recently reported with the interim results of the Stockholm III trial comparing SCRT and SCRT with surgery delayed 4–8 weeks; the trial demonstrated higher rates of primary tumor downstaging and pathologic complete response (11.8% vs 1.7%) in the delayed surgery arm [90]. A caveat of the Polish trial however, is the use of oxaliplatin alongside LCRCT, which we know now is ineffective and more toxic and can reduce the dose-intensity of LCRCT and worsen outcomes.

All these preliminary results seem to show that the differences between LCRCT and SCRT seem to be blurring. Perhaps the combination of SCRT and induction chemotherapy can be a better tolerated option, especially in more frail and/or elderly patients that is similarly effective than standard LCRCT. The use of SCRCT with a delay to surgery in these locally advanced tumours when the patient is not fit for LCRCT has been reported previously with encouraging results [91-93].

4.2.4. Applicability of these results in the TME-era

In most if not all recent phase III SCRT and LCRCT trials, reductions in local relapse have not led to improvements in survival. Possible reasons include a variable interpretation of available radiologic imaging by different radiologists, varying indications for treatment, different preoperative chemo-radiotherapy regimens, and poor compliance of postoperative adjuvant chemotherapy. TABLE 46 is a representation of these differing features between the pivotal trials and highlights the great variability in the trial design.

	Time period	Age limits and median age	Standard staging MRI	Standard staging EUS	Total mesorectal excision	Quality of mesorectal excision	Median number of nodes resected
Long course chemoradiotherapy							
CAO/ARO/AIO-94 [44-45]	1995-2002	< 75 yrs 62 (30-75)	No	Yes	Yes	Not analysed	Collected but not stated
NSABP R03 [59]	1993-1999	None 56% > 60 yrs	No	Not stated	No	No data	Not stated
EORTC 22921 [53]	1993-2003	None 63 (22-79)	No	No	38%	No data	7 after CT-RT
FFCD 9203 [49]	1993-2003	< 75 yrs 63 (22-81)	No	No	No data	No data	Not stated
Polish trial [54-55]	1999-2002	< 75 yrs 60 (30-75)	No	No	Unknown	Unknown	8 after CT-RT
TROG 01.04 [56]	1993-2003	None 63 (23-80)	If EUS not possible	Yes	Unknown	Unknown	Not stated
Short course radiotherapy							
Swedish Rectal Cancer trial [65-66]	1987-1990	< 80 yrs	No	No	No	No	Not stated
Dutch TME study [68]	1996-1999	None 65 (23-92)	No	No	Yes	50%	7
MRC CR07 [69]	1998-2005	None 65 (36-87)	No	No	Recommended	52%	11
Polish trial [54-55]	1999-2002	< 75 yrs 60 (30-75)	No	No	Unknown	Unknown	9 after SCRT
TROG 01.04 [56]	1993-2003	None 63 (23-80)	If EUS not possible	Yes	Unknown	Unknown	Not stated

TABLE 46: Several defining characteristics of the pivotal phase III trials of SCRT and LCRCT in the management of patients with locally advanced rectal cancer

Regional biases are also noted, with Northern European and Scandinavian countries preferring SCRT, and the United States and most Southern European countries preferring LCRCT, for not entirely clear reasons [94]. In most centres, however, given the significant morbidity associated with local relapse and where high-risk factors such as CRM involvement, extramural spread, higher nodal stage, and low tumor position exist, LCRCT remains the preferred strategy in these cases.

However, we are seeing a gradual change of the philosophy in the management of these patients, coupled with the increased knowledge that obtaining a negative CRM is widely considered the most important factor in the treatment of rectal cancer patients [95-96] and that those treated at institutions that perform well in terms of the surgical margin have better outcomes [97].

In effect, as the quality of preoperative imaging and staging modalities have improved, the CRM is in many cases now considered a potentially modifiable factor. If neoadjuvant SCRT and LCRCT were considered until a few years an indispensable part of the multimodality treatment in locally advanced cases, many centres consider now these approaches as important adjuncts that can aid the surgeon in obtaining the desired endpoints of clear resection margins and sphincter preservation with a low risk for local treatment failure when combined with an optimal surgical technique [98]. Norwegian population data suggested low rates of local recurrence for patients with pathological findings of a clear CRM >3 mm and pN0 [95]. The MRC 07 showed that optimal quality-controlled surgery in terms of TME in the trial setting can be associated with local recurrence rates of less than 10% whether patients receive radiotherapy or not [47].

There are also several prospective series [99-103] which show a local failure rate of less than 10% (TABLE 47), with an adequate selection of patients and with the aid of high-quality MRI, in tumours treated directly with surgery and with a low baseline risk of local relapse (unthreatened CRM, low lymph node burden, middle or superior rectal cancers). NICE, EORTC and ESMO support this personalized approach to localised rectal cancer, that is based on the performance of high-quality MRI imaging [97-98, 100] (TABLE 48).

However, critics, especially in the United States, have pointed out that this treatment approach guided by MRI-risk categorization is based on results of prospective observational studies conducted in institutions with significant expertise in rectal cancer and has not been tested in prospective randomized trials. They may not be adequate for smaller centres with less experience or with smaller economic resources; in this sense, the NCCN guidelines still recommend a blanket approach of neo-adjuvant LCRCT in most, if not all, patients with cT3-T4 and/or N+ positive disease [104, 105].

Despite these discrepancies, it is becoming evident, as we will see further on, that there are several endpoints in the management of locally advanced rectal cancers, that will require an adequate selection of patients and of the different therapeutic modalities (surgery, radiotherapy, neoadjuvant and adjuvant chemotherapy or even watchful waiting) in order to improve our patients' outcomes [106]. In patients with a high risk of distant metastases, our endpoint will be to improve the long-term survival outcomes; in patients with a high risk of local relapse, we will try to obtain a downstaging in order to lower the risk, particularly in order to free the CRM; and more recently, in patients with low-lying tumours, where an abdominoperineal excision would be necessary, we might try organ-sparing approaches with intensive neoadjuvant regimens and even non-surgical approaches. Of course, in any given patient, we might have more than one objective to fulfill.

Author	Site	n	Staging procedure	Patient selection	Treatment	Local relapse rate	Survival endpoints
Engelen et al [99]	Multicentric Netherlands	228	MRI	- Low risk (CRM > 2 mm and N0 status) - Intermediate (the rest) - High risk (close/involved CRM, N2 status or distal tumours)	- Low risk: Surgery (49) - Intermediate: SCRT + surgery (86) - High risk: LCRCT + surgery (93)	3-year LR of 2.2%	3-year DFS: 80% 3-year OS: 84.5%
MERCURY [100]	Multicentric United Kingdom	122	MRI	- Good prognosis: MRI-predicted T2/T3a/T3b, regardless of N	No preoperative RT in good-prognosis patients (122 of 374)	3.3%	5-year DFS: 64.7% 5-year OS: 68.2%
Mathis *et al* [101]	One centre United States	655	Variable (1990-2006)	Retrospective review of stage I-III patients treated with surgery only	Abdominoperineal excision (246) and lower anterior resection (409)	5-year LR of 4.3%	5-year DFS: 90%
Frasson et al [102]	One centre Spain	152	EUS (49.3%), MRI (51.7%)	cT2N+, cT3N0, or cT3N+	No preoperative therapy	5-year LR of 9.5% (5.4% if free clinical CRM)	5-year DFS: 65.4% 5-year CSS: 77.8%
Marinello *et al* [103]	One centre Spain	178	Variable (1992-2010)	Retrospective review of upper third rectal cancers compared to other locations	Partial mesorectal excision in 147 with no preoperative therapy in 94.4%	5-year LR of 4.9%	5-year DFS: 82.0 % 5-year CSS: 91.6 %

CSS: Cancer-specific survival; DFS: disease-free survival; OS: overall survival

TABLE 47: Selected surgical series where patients with a low baseline risk of local relapse were treated with upfront surgery with encouraging results with respect to pelvic recurrences and survival endpoints

	Extramural spread	Nodal stage	Circumferential resection margin	Tumour location	Extramural venous invasion
Low risk	≤ 5 mm	N0	Not at risk	High	Absent
Moderate risk	> 5 mm	N1-2	Not at risk	Low or high	Present
High risk	> 5 mm	N2	At risk	Low	Present

TABLE 48: MRI-staging criteria defined by the MERCURY group in order to define patients with a low risk of local relapse and who could be treated with upfront surgery

We used a blanket-approach of treating all our locally advanced rectal cancer patients, defined as cT3-T4 and/or N+ disease with LCRCT followed by TME-surgery and adjuvant chemotherapy, regardless of the pathological tumour response. However, all the previous data have shown us that the future lies in a more personalised approach, especially in the setting of better clinical imaging and improvement in surgical techniques. Taking all these factors into account, from a practical point of view, we will centre on several questions in the management of our patients and we will try to determine which were the prognostic and predictive factors that may help us in that goal of a more personalised approach in the future and a more rational sequencing of the different therapeutic modalities in locally advanced rectal cancer

4.3. How can we improve the results of long-course chemoradiotherapy?

4.3.1. Can we maximize the efficacy of radiotherapy?

Our protocol required the use of LCRCT followed by surgery in the 5-8 weeks after the end of the radiotherapy, as is standard with most of these regimens reported. Compliance to the radiotherapy regimen was excellent, with almost 95% of patients receiving the full intended dose and almost a half of patients proceeding to surgery in the sixth to eight-week after the end of radiotherapy. Serious acute radiotherapy-related toxicity was low, with only 3.4% of patients suffering from grade 3-4 toxicity. In this sense, modern and better-tolerated radiotherapy techniques, with more precise radiation fields, and better supportive care have improved the results with this technique (FIGURE 20 shows the radiotherapy planification imaging of one of our patients)

Unfortunately, as in most other centres, most of the radiotherapy treatment parameters were determined in an empiric manner. For example, why 6 to 8 weeks? Do we really know what is the ideal interval between radiotherapy and surgery in order to obtain the maximal downstaging benefit? Is there a radiotherapy dose-response lineal relationship, like in other tumours, such as in head and neck cancer? Can we maximize radiotherapy in order to obtain more pCR and subsequently to increase the possibility of organ-sparing surgical approaches or even watch- and- wait approaches? Most of these questions have not been answered in a satisfactory manner.

Regarding the first question, the optimal interval between (chemo)radiotherapy and surgery has long been a subject of investigation. The Lyon R90-01 trial established the current reference standard of 6 to 8 weeks between neoadjuvant LCRCT and surgical resection nearly 2 decades ago after demonstrating superior outcomes compared to a 2-week interlude [108]. The primary endpoint of the study was the rate of sphincter-preserving resection. Although increased rates of objective response (71.7% versus 53.1) and major pathological tumour regression (26% versus 13%) were observed in the delayed-surgery group, these did not translate into a statistically significantly higher rate of sphincter-preserving surgery in the intention-to-treat population. Similarly, a numerically higher but not statistically significant difference in favour of the delayed-surgery group (41% versus 23%) was found in the low rectal cancer patient population.

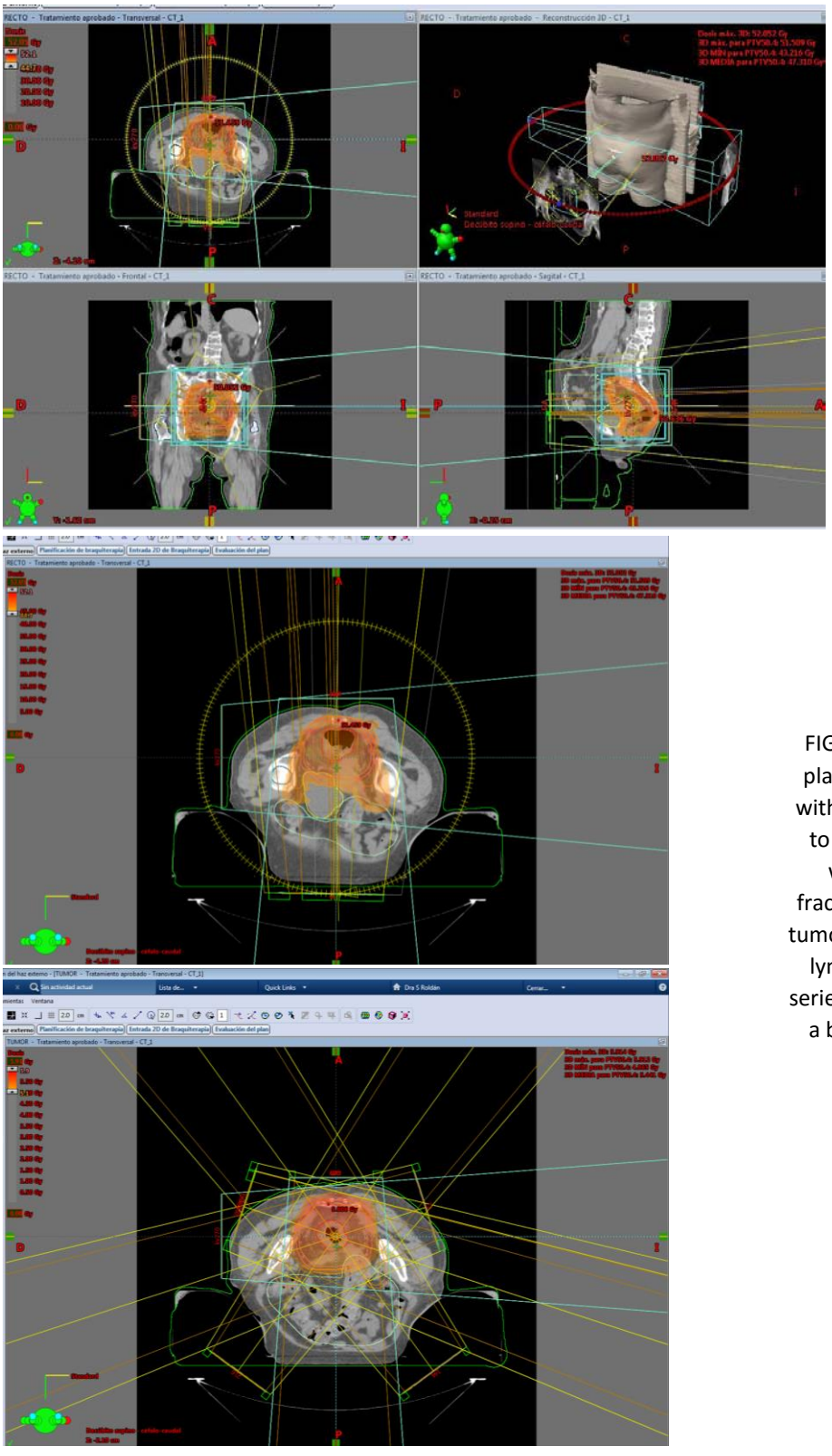


FIGURE 30 (Case 175): Radiotherapy planification in a 70-year old woman with a cT4bN1b mid-rectal cancer due to uterus invasion. She was treated with a first series of 45 Gy in 25 fractions, with a CTV that covered the tumour with margins and the perirectal lymph nodes, followed by a second series of 5.4 Gy in 3 fractions in form of a boost in the tumour with margins

However, other more recent publications suggest an even longer time frame may lead to still better tumour regression and downstaging with no increase in surgical morbidity and long-term oncologic and functional outcomes [109]. A meta-analysis of 13 mostly retrospective studies also evaluated the association between LCRCT and time to surgery in 3584 patients and found that pCR rates improved where the interval was 6 to 8 weeks or more [110]; however, this did not translate into a DFS or OS advantage. Other smaller retrospective reviews have advocated a longer time frame of 10 to 14 weeks as a result of higher pCR rates and tumor volume reduction; although follow-up was too short to report long-term survival data [111-112]. In effect, in one of these studies [111], the rate of pCR gradually increased with time and reached the peak after 15-16 weeks from the start of standard LCRCT. In the multivariate analysis, the time interval between chemoradiotherapy and surgery was an independent predictive factor for pCR.

Finally, outcomes were reported from a retrospective review of data on 6805 patients captured by the American National Cancer Data Base [113] A significant association between an increasing LCRCT-to-surgery interval and improved pCR existed up to 75 days although it disappeared thereafter. Surprisingly, beyond a 60-day interval, there was an increment in the rate of positive surgical margins and, more importantly, a significant decrease of 25% in OS. However, these worrying data must be taken with caution, as, probably, those patients where surgery was delayed where poor-prognosis patients, where there was a longer recovery time from LCRCT due to higher toxicity or other causes. The retrospective nature of the analysis is also a problem for definitive conclusions to be obtained.

As we have seen previously, there is also data with SCRT that a longer interval between SCRT and surgery may allow downstaging and a higher pCR. Pre-planned interim analyses of the Stockholm III trial have demonstrated that postponing surgery until 4-8 weeks after SCRT does not increase the risk of post-operative complications and is associated with significantly higher rates of pCR (11.8% versus 1.7%) and tumour regression (grade 2-4 according to Dworak, 43% versus 20.1%) and a lower tumour stage compared to immediate surgery [90]. The recent phase III Polish trial of LCRCT vs SCRT with a delayed interval to surgery showed similar results [87].

Despite these encouraging results, possible benefits deriving from a delayed surgery are to be carefully weighed against potential disadvantages including an increased risk of tumour regrowth/metastases, of peri-operative complications and of a delayed start of post-operative systemic chemotherapy. In this sense, Increasing the interval between neoadjuvant CRT and surgery warrants further investigation in a randomized controlled trial. The NCT01037049 trial is aiming to recruit 218 patients to neoadjuvant CRT and TME surgery after either 6 or 12 weeks, with a planned primary end point of T-stage downstaging on MRI.

Regarding the question of dose intensity, there is little data for a dose-response relationship in locally advanced rectal cancer, particularly for larger T4 or fixed tumours. Traditional preoperative doses in the randomised trials are, conventionally, 45 to 50.4 Gy using 1.8 Gy per fraction. However, the most effective total dose and schedule are not known. Meta-analyses of preoperative radiotherapy for rectal cancer suggest that there is an advantage to treating to a biological equivalent dose (BED) of at least 30 Gy [114]. Three different doses were investigated in a Canadian sequential phase II trial [55]. Sequential schedules of radiation combined with 5-FU dose-escalated from 40 Gy in 20 fractions to 46 Gy in 23 fractions, and finally to 50 Gy in 25 fractions [115]. Local control was significantly better for doses of 46 Gy and above, but there was no difference between 46 Gy and 50 Gy. There was a trend to higher pathological complete response rates with increasing the radiation dose of 13%, 21% and 31% for 40 Gy, 46 Gy and 50 Gy, respectively. The trial concluded that there was no advantage in routinely increasing total dose to or above 46 Gy. In contrast, the

conclusion of another randomised trial comparing both oxaliplatin and 50 Gy with capecitabine and 45 Gy, is that 50 Gy is a new standard [116]; in fact, we adopted that dose from that moment.

A pooled analysis did suggest that higher rates of pCR were associated with higher total doses of radiation [117]. In practice, however, few prospective phase I-II studies have used total doses > 50 Gy, the exception being the EXPERT trial, which boosted to 54 Gy [118]. Results of this study appeared impressive with respects to pCR, with a 29% rate but we do not know the relative contributions of the induction chemotherapy and the concurrent chemoradiotherapy schedule or the high dose of pelvic radiotherapy. For instance, in the same group's subsequent study, in the arm with an identical chemotherapy schedule but with a lower radiotherapy dose of 50.4 Gy, the pathological complete response fell to 15% [119].

In this sense, higher doses are likely to result in better tumour responses but this will necessarily entail greater acute and late toxicity. Waiting for the highest degree of radiotherapy-induced tumour regression may optimise the selection of patients who are candidates for a local excision or a "watch and wait approach" following the achievement of a complete or near clinical complete tumour [120]. This assumption is supported by the data reported by several groups (especially in Brazil) which suggest that a delayed but strict assessment of clinical response, could identify the true responders (while excluding those with suboptimal response or early tumour re-growth/progression) and lead to an improved outcome for patients who are managed nonoperatively [121].

Our data are consistent with all these findings (TABLE 19 and 20); there was an increased rate of downstaging and complete or nearly complete tumour regression with higher doses of radiotherapy and an increased rate of pathological complete response with longer intervals between the end of radiotherapy and the surgical procedure. Increased duration of radiotherapy (due to delays or other causes) was detrimental, with a numerically (although statistically not significant) increase in the risk of local relapse. This is most likely due to the increased risk of malignant repopulation at the end of long-course radiotherapy regimens [75-77]. Although there was an increased downstaging rate with longer intervals, this did not translate into a survival benefit. On the contrary, longer intervals were associated worse DFS. This apparent discrepancy can be explained in the same manner as the American registry study. In our protocol, surgery was specified to be 6 to 8 weeks after the end of radiotherapy; those patients in where the interval was longer, there was a cause for the delay, usually toxicity or other serious complications, that imply a poorer prognosis and which would obscure any benefit with an increased downstaging rate.

Practical conclusions of radiotherapy:

1. International guidelines recommend that patients who are candidate for neoadjuvant treatment should undergo surgery from 6 to 8 weeks (ESMO) or 5 to 12 weeks (NCCN) after completion of long-course chemoradiotherapy or within 7-10 days of completion of short-course radiotherapy.
2. However, there is compelling data that an even longer time frame may lead to still better tumor regression and downstaging, both in LCRCT and in SCRT. Our data are consistent with these data. With this in mind, we can tailor the treatment in individual cases. For example, SCRT followed by a longer interval in order to increase downstaging can be useful in elderly or frail patients, where a LCRCT would be necessary but not feasible. However, we must wait the results of prospective randomized trials in order to adopt a widespread approach of increasing the interval between RT and surgery.
3. There is an imperfect relationship between higher radiotherapy dose and an increased pCR. These differences are probably not significant with doses higher than 45 Gy, before radical surgery, but will probably be useful in patients where a non-operative management is planned. Again, prospective randomized trials are needed in this sense.

4.3.2. What is the role of intensification of neoadjuvant chemotherapy alongside long-course radiotherapy?

Our results with the addition of radiosensitizing oxaliplatin alongside oral fluoropyrimidines were extremely disappointing. There was no benefit in the rates of local relapse, distant metastases, downstaging or pCR. There was also no benefit in DFS and OS. This lack of benefit is similar to the observed in the different phase III trials published in the last few years in patients with easily resectable tumours (TABLE 40), which compared standard fluropyrimide-LCRCT to the same regimen with oxaliplatin.

	Number	RT dose	Treatment arms	pCR	Sphincter sparing	5-year local relapse	5-year disease-free survival	5-year overall survival	Grade 3-4 acute toxicity
NSBAP-R04 [122]	1608	50.4 Gy in 28 fractions	Capecitabine or 5-FU +/- oxaliplatin	19.1 %vs 20.9%	63.6 vs 60.4%	4.7% vs 3.1%	64.2 vs 69.2%	79% vs 81.3%	6.6% vs 15.4%* (0.9% toxic deaths)
CAO/ARO/AIO-04¶ [123-124]	1265	50.4 Gy in 28 fractions	Bolus 5-FU +/- oxaliplatin	13% vs 17%*	76% vs 75%	23% vs 12%	71.2% vs. 75.9* (3-year DFS)	88% vs 88%	8% vs 12%* (2 vs 4 toxic deaths)
PETACC-6¶ [127]	1081	45 Gy in 25 fractions	Capecitabine +/- oxaliplatin	11.3 % vs 13.3%	NR	7.6% vs 4.3%	74.5% vs 73.9 (3-year DFS	89.5% vs 87.4%	15.1% vs 36.7%*
STAR-01 [126]	747	50.4 Gy in 28 fractions	5-FU +/- oxaliplatin	16% vs 16%	78% vs 79%	Not reported	Not reported	Not reported	4% vs 15%*
ACCORD 12 [116, 125]	598	45-50 Gy in 25 fractions	Capecitabine +/- oxaliplatin	13.9% vs 19.2%	74.6% vs 75.4%	6.1% vs 4.4% (3-year rate)	69,7% vs 72.7% (3-year DFS)	87.6% vs 88.3% (3-year OS)	3.2% vs 12.6%*
FOWARC¶	495	46-50.4 Gy in 23-25 fractions	Infusional 5-FU vs mFOLFOX and RT vs mFOLFOX with no RT	14.0% vs 27.5% vs 6.6%*	84.4% vs 87.2 vs 89.5%	NR	NR	NR	12.9% vs 19% vs 5.7%*

* Statistically significant

¶ Oxaliplatin was evaluated in these trials as part of both neoadjuvant and adjuvant treatment alongside fluoropyrimide chemotherapy

TABLE 49: Reported randomized trials that evaluated the use of oxaliplatin alongside standard 5-FU-based long-course radiotherapy in patients with locally advanced rectal cancers

The main conclusion of five of these trials is that oxaliplatin increased grade 3 to 4 toxicity in all trials with little benefit in any endpoint. Curiously, we did not see such an increase with the addition of oxaliplatin in our series. Only the German CAO/ARO/AIO-04 trial had a significantly higher rate of pathological complete response [123-124] and an improvement of three-year DFS; there were no survival benefits in any of the other trials. There were hints of a higher activity in some cases, as some schedules did appear to reduce the positive

CRM rate [123-124, 127]. Due to the short follow-up period, there are no data yet on late toxicity, especially persistent neurotoxicity.

The benefit in DFS in the German Trial, although statistically significant, is difficult to quantify, as the standard LCRCT regimen included substandard doses of infusional bolus 5-FU. Adjuvant oxaliplatin-based chemotherapy was also used in the oxaliplatin arm and we do not know which part of the treatment is responsible of the benefit. As in all the other trials, serious toxicity was more frequent with the use of oxaliplatin and there were 4 treatment-related deaths compared to 2 in the standard arm.

The short-term outcomes of 4 of these trials (NSABP R-04, CAO/ARO/AIO-04, STAR-01, and ACCORD 12/0405) have been collated and examined in a recent meta-analysis [129]. An overall improvement in pCR rates and decreased perioperative metastases were reported with the addition of oxaliplatin. However, this was associated with increased grade 3-4 toxicity and a lower rate of planned radiotherapy completion, although there was no difference in chemotherapy completion rates.

Why did oxaliplatin fail? The theoretical basis for its use is evident. Oxaliplatin in combination with fluoropyrimidine therapy improves outcomes for colon cancer in the adjuvant setting and in metastatic colorectal cancer [12], and it has known radiosensitizing properties. There were also promising phase II data which were the initial basis of the use of oxaliplatin in a majority of our patients [13-16].

The most logical explanation is the increased toxicity rate, which had a deleterious effect on the compliance of the proven beneficial treatment, namely 5-FU- based LCRCT. Systemically active doses of chemotherapy are difficult to deliver concurrently with chemoradiotherapy schedules because of overlapping toxicities. The (small) benefits in increased pCR rates and free CRM margin in some of the trials were not able to compensate this poor radiotherapy compliance.

A second important factor is that all these randomised trials in rectal cancer selected patients with easily resectable tumours. The majority of these patients were probably node negative. Based on the results of the QUASAR and MOSAIC studies [130-131], stage II patients are unlikely to show a large benefit in terms of DFS even from 5-FU chemotherapy – and minimal benefit from the addition of oxaliplatin. This lack of benefit of oxaliplatin is probably more pronounced in elderly patients [132]. The poorer tolerance to capecitabine to infusional 5-FU in elderly patients is also well known and may justify this higher toxicity, when combined with oxaliplatin.

However, there are also some positive trials. In more advanced unresectable tumours, oxaliplatin has shown to improve DFS and OS alongside standard LCRCT in a randomized phase III trial and is used frequently [133]. Also, initial results from the FOWARC study have been recently reported [128] that show that compared with single-agent 5-FU, mFOLFOX6 concurrent with radiotherapy preoperatively results in a higher rate of pCR (14.0% v 27.5%), a higher good response rate, good compliance, and acceptable toxicity for Asian patients with stage II-III rectal cancer. The results also show that a comparable rate of downstaging can be achieved with perioperative mFOLFOX6 alone compared with traditional 5-FU-based LCRCT. These preliminary results suggest that a strategy of combining full-dose chemotherapy with radiation over chemosensitizing radiation may be a new option for neoadjuvant treatment. Finally, a recent meta-analysis that included seven randomized trials showed an improvement in the distant metastasis rate, in the rate of pCR and a marginal improvement in DFS, albeit at the expense of a higher toxicity rate [134].

Despite these positive studies, there is little evidence to support the use of concomitant oxaliplatin in resectable rectal cancer patients. Oxaliplatin has activity in locally advanced rectal cance, but its administration concomitant to LCRT is probably not the best way to administer the drug. In this sense, the drive to potentiate LCRCT with a second cytotoxic drug, which caused so much interest in the last two decades appears to have waned as we have realized that this may cause additional toxicities and possibly enhance surgical morbidity [135].

4.3.3. Is there a role of induction or consolidation chemotherapy alongside neoadjuvant chemoradiotherapy?

As we will analyze posteriorly, we observed poor compliance rates of adjuvant chemotherapy in our group of patients, especially in the elderly. Induction or consolidation chemotherapy before surgery has several theoretical advantages. It treats occult micrometastases several months earlier and increases treatment compliance, potentially enhancing the efficacy of chemotherapy in preventing distant metastases and ultimately improving survival. Other benefits include increased response of the primary tumor, early identification of nonresponders, and earlier removal of the loop ileostomy.

Unfortunately, several phase 2 trials have administered 2 to 4 cycles of induction capecitabine-oxaliplatin or FOLFOX before LCRCT (TABLE 50), with mixed results in most cases [118, 136-141]. The addition of induction chemotherapy showed a modest increase in the downstaging rate, but with no benefit in pCR or long-term outcomes in most cases. Grade 3-4 toxicity was increased with the addition of induction chemotherapy. Worryingly, in some trials there was an increase in serious cardiovascular events, especially in the elderly.

Study	n	Entry criteria	Induction chemotherapy	RT dose (Gy)	DS	pCR	LR	5-year DSF and OS	G3-4 toxicity¶¶	Toxic deaths
Schou et al [137]	84	Poor-risk MRI features	XELOX	54	69% (T)	23%	2%	63% and 67%	18%	4/84
EXPERT [118]	105	Poor-risk MRI features	XELOX	54	35%	20%	6%	64% and 75%	34%	4/105
Marechal et al [138]	57	T2-T4 N+ by MRI	FOLFOX (28) vs no CT (20)	45	61% vs 72%	25% vs 28%	NR	NR	36% vs 7%*	1/28
GEMCAD [136, 139-141]	108	Poor-risk MRI features	XELOX (56) vs no CT (52)	50.4¶	43% vs 58% (T)	14% vs 13%	5% vs 2%	62% and 75% vs 75% and 78%	54% vs 19%*	3/56
Calvo et al [142]	335	T3-T4 and/or N+	FOLFOX (28) vs no CT (20) (no randomized)	45-50.4	63% vs 54% (T)*	NR	7% vs 9%	10-year DFS: 72% vs 68% Global 10-year OS: 75%	NR	NR
Targeted therapies										
AVACROSS [148]	47	High-risk MRI features	XELOX + bevacizumab	50.4¶¶¶	NR	36%	NR	NR	33% (18% needed surgery)	1/47
Dipetrillo et al [149]	26 (stopped early)	EUS-staged stage II-III	FOLFOX-bevacizumab	50.4¶¶¶¶	N$	20%	1/26	Not stated	76% (36% wound complications)	0/26
EXPERT 2 [57]	165 (90 *KRAS* wild-type)	Poor-risk MRI features	XELOX +/- cetuximab (44 vs 46)	50.4 +/- cetuxi-mab	51% vs 71% *	11% vs 7%	2% vs 4%	HR of DFS: 0.65 HR of OS: 0.27*	81% vs 83%	2/46

TABLE 50: Prospective studies that evaluate the role of induction chemotherapy before LCRCT, with or without targeted therapies, in patients with locally advanced rectal cancer

* Statistically significant

¶ Combined chemoradiotherapy with capecitabine and oxaliplatin
¶¶ Cardiovascular events in 2, 9, 0, 2, NR, NR, 1 and NR, respectively
¶¶¶ Capecitabine and bevacizumab alongside radiotherapy
¶¶¶¶ Capecitabine, oxaliplatin and bevacizumab alongside radiotherapy

Perhaps of these trials, the most interesting is the Spanish Grupo Cancer de Recto [136, 139-141]. This large prospective trial recruited 108 patients with MRI-defined poor risk disease 47 and compared four cycles of neoadjuvant or adjuvant capecitabine-oxaliplatin with TME-surgery. Serious toxicity was significantly increased in the adjuvant arm, as could be expected, and a higher relative dose intensity for both capecitabine and oxaliplatin was achieved with preoperative treatment (91% vs. 61% and 94% vs. 73% respectively). However, 3 deaths were reported in each cohort, including 2 related to cardiovascular or thromboembolic events. There was no benefit in pCR, local relapse, distant metastases or 5-year DFS and OS. Despite this, although the study was underpowered to detect long-term benefits, the neoadjuvant approach showed better tolerability and compliance and equivalent efficacy parameters.

The chemotherapy backbone can also be of interest. We know in advanced colon cancer that is similar in efficacy to FOLFOX, although in most trials, the tolerance of FOLFOX, with its infusional 5-FU, is better [143]. A recent study investigated the safety and efficacy of FOLFOX before LCRCT, demonstrating excellent treatment compliance and no evidence of serious adverse effects requiring treatment delay. All patients undergoing TME had an R0 resection, and nearly half had a tumor response greater than 90%, including 30% who had a pCR [144].

Another option is to give chemotherapy after LCRCT. A possible advantage of this approach is that, as we know, extending neoadjuvant chemotherapy requires a delay to surgery after chemoradiation, and we know this delay is significantly associated with a better response and a higher proportion of patients achieving a pathological complete response [145]. There is less evidence of this strategy, however. The TIMING trial, which completed accrual in 2012, did show that delivering two, four, or six cycles of FOLFOX after CRT in patients with locally advanced tumours increased the pCR rates up to 25%, 30%, and 38%, respectively, compared with CRT alone (18%), without any associated increase in adverse events or surgical complications [146]. Eighty percent of patients received consolidation CT without interruption. [147]. Despite these interesting results, we have concerns with this approach, as, in our anecdiotal evidence, tolerance to chemotherapy after LCRCT, even before surgery, tends to be poorer, not only in rectal cancer but in othe tumours such as pancreatic or esophageal cancer.

The addition of targeted antiangiogenic therapies, such as bevacizumab, have yielded disappointing results, with an increase in surgical complications in the two largest studies reported [148-149]. These results are not altogether surprising, as there is no activity of bevacizumab in the adjuvant treatment of colon cancer [150] and there are no great increases in the response rate with the addition of bevacizumab to standard chemotherapy in advanced colon cancer [151]. Curiously, in both trials, bevacizumab was used with capecitabine as induction chemotherapy and also alongside LCRCT, which probably explains the high rate of surgical complications.

More promising are the results of anti-EGFR agents, such as cetuximab, alongside induction chemotherapy in patients with *KRAS* wild-type tumours [119, 152-153], reported in trials such as the EXPERT-C trial [119], which showed an increase of the downstaging rate in the experimental arm, with an improvement in overall survival, although the follow-up was short. Unfortunately, the grade 3-4 toxicity rate was high in both arms of induction CT. These benefits have been proven to be higher in patients with all-*RAS* native tumours [154-155]

Practical aspects of chemotherapy intensification:

1. Although theoretically promising, the addition of concomitant oxaliplatin alongside standard LCRCT is not beneficial. The integration of systemic CT alongside 5-FU-based CRT is difficult, due to the existence of synergistic toxicities which worsen the compliance rate and the chance of completing successfully the treatment plan
2. Results with induction chemotherapy (before LCRCT) or consolidation chemotherapy (after LCRCT) are somewhat more promising and are included in some guidelines. Compliance is better compared to adjuvant chemotherapy. However, patients should be selected accordingly, as toxicity is higher, especially in elderly and/or frail patients, and there is an increased risk of serious cardiovascular events.
3. Despite the lack of data from large prospective studies, some guidelines recommend neoadjuvant chemotherapy alongside standard LCRCT is included as a treatment option.
4. We have concerns with the consolidation approach, as, in our anecdotal evidence, tolerance to chemotherapy after LCRCT, even before surgery, tends to be poorer, not only in rectal cancer but in othe tumours such as pancreatic or esophageal cancer.
5. There is no benefit with the addition of antiangiogenic targeted therapies, with an increased risk of surgical complications. There are hints of better activity of the combination of induction CT with antiEGFR targeted therapies, although, again, serious toxicities are worrying.

4.4. Is there any role of adjuvant chemotherapy after long-course chemoradiotherapy and surgery?

In our series, adjuvant chemotherapy was given to all patients, if feasible, regardless of the pathological response observed; this was possible in more than 80% of patients. However, as in most other published trials, the tolerance to the adjuvant regimen was poor with less than half of these patients receiving the full intended dose and there were almost three-times more hospital admissions related to toxicity than with neoadjuvant treatment. This was especially evident in elderly patients, where almost a quarter of patients did not receive any kind of treatment after surgery. The median time from the surgery to the beginning of adjuvant treatment was 5 weeks, but a quarter of patients did not begin treatment until seven weeks after. There did not seem to be a benefit in local relapse rates with the use of adjuvant therapy, but there was an improvement in the rate of distant metastasis with the administration of full-dose adjuvant therapy. On the other hand, patients with ypN-positive disease that were not treated with adjuvant treatment, fared very poorly.

We know that with neoadjuvant (chemo)radiotherapy and modern surgical techniques, such as TME, the risk of local relapse is low and the risk of distant metastases predominates. In the CAO/ARO/AIO-94 study nearly 30% of the patients treated with neoadjuvant therapy developed distant metastatic disease by 10 years, findings similar to our series [6]. In this sense, locally advanced rectal cancer would seem to be a prime candidate for true multimodality therapy, in where patients would benefit from systemic chemotherapy at full doses, beyond what is delivered as a radiosensitizer concurrently with radiation therapy. There is also the proven role of adjuvant chemotherapy in colon cancer, which showed first the superiority of adjuvant 5-FU and leucovorin relative to surgery alone, and subsequently the value of adding oxaliplatin to 5-FU [12, 156].

In reality, for patients treated without preoperative (chemo)radiotherapy or TME-surgery (which results in high numbers of locoregional recurrences) adjuvant chemotherapy does seem to be effective. A systematic review and meta-analysis of of 21 randomized controlled trials showed that adjuvant chemotherapy did improve DFS and OS in this group of patients [157]; however, this review included only two studies in which patients had had preoperative (chemo)radiotherapy [47, 131]. The QUASAR [131, 158] study showed a borderline-significant improvement in OS for patients with rectal cancer; however, only 21% of patients with rectal cancer or both colon and rectal cancer received preoperative radiotherapy. Furthermore, results of a Japanese trial also showed improved overall survival and disease-free survival in patients with stage III rectal cancer who were randomly assigned to adjuvant chemotherapy after standardised mesorectal excision [158] However, none of the patients in this trial received preoperative (chemo)radiotherapy and standardised mesorectal excision included selective lateral lymphadenectomy.

The current recommendations for use of adjuvant chemotherapy in patients treated with LCRCT and TME is based in part on these data and extrapolation from colon cancer data, and these patients are usually treated with 5-FU or capecitabine +/- oxaliplatin-based adjuvant chemotherapyCT [12, 156] However, as was seen in our study, despite these recommendations, up to 27% of eligible patients with locally advanced rectal cancer never start adjuvant chemotherapy and less than 50% [48] receive the full prescribed treatment without interruptions or delays [48, 123], resulting from postoperative complications, slow recovery, interference with closure of their temporary ileostomy [160] or simply refusal of treatment.

Do we have data on the effectiveness of adjuvant chemotherapy in patients treated specifically with LCRCT and TME-surgery? Yes, we do but, unfortunately, the results are not very promising. These trials that have addressed the use of chemotherapy specifically in rectal (as opposed to colon) adenocarcinoma patients have not shown a clear benefit for its use (TABLE 51). Two of the trials were closed prematurely due to poor accrual and one of them has only been reported in abstract form.

	n	Clinical criteria	Treatment arms	TME	Adjuvant CT	Compliance with adjuvant CT	Distant metastases	5-year disease-free survival	5-year overall survival
Randomized phase III trial after neoadjuvant (chemo)-radiotherapy									
EORTC 22921 [48, 161]	1101	cT3-T4	2x2 factorial design; preop RT +/- CT; Postop CT vs no	50%	5-FU	27% no cycles; 43% full dose CT	34.1% vs 33.4%	58% vs 52% (10-year: 47 vs 47.3%)	67.2% vs 63.2% (10-year: 51.8% vs 48.4%)
I-CNR-RT [163]	653	cT3-4 N0-2 Preop CT-RT (5-FU)	Adjuvant 5-FU vs no	No	5-FU	28% no cycles; ≥ 3 cycles in 58%	21% vs 19.6%	62.8% vs 66.3%	66.9% vs 66.1%
PROCTER-SCRIPT [165]	437¶	Pathologic stage II-III after preop CT-RT (5-FU)	Adjuvant CT vs no	Yes	Capecitabine (65%), 5-FU (35%)	4.6% no cycles; 73.4% full dose CT	38.5% vs 34.7%	55.4% vs 62.7%	79.2% vs 80.4%
CHRONICLE [162]	113¶	No pCR after after preop CT-RT	Capecitabine -oxaliplatin vs no	Yes	Capecitabine -oxaliplatin	48.1% full dose CT	27.2% vs 22.2%	71.3% vs 77.9%	87.8% vs 88.8%
Meta-analysis									
Breugom *et al* [166]	1196	Individual patient data Pathologic stage II-III after preop CT-RT		Not clear	No benefit with adjuvant CT with respect to distant metastases (HR 0.94), disease-free survival (HR 0.91) or overall survival (HR 0.97) Benefit in DFS in tumours 10-15 cm from the anal verge (HR 0.56, p 0.005)				

* Statistically significant

¶ Trials closed early due to poor accrual

TABLE 51:Phase III trials and meta-analysis that have evaluated the use of adjuvant chemotherapy (CT) after LCRCT and TME-surgery

Of all these trials, the EORTC trial has the longest follow-up. This trial that randomized 1011 patients found no 10-year DFS or OS survival benefit for adjuvant bolus 5-FU/leucovorin following neoadjuvant radiotherapy or chemoradiotherapy in T3 or T4 disease, including node-positive patients [48-161]. With a long-term follow-up of more than ten years, there was no difference in 10-year OS (51.8% vs 48.4%), 10-year DFS (51.8% vs 47% vs 43.7%) or in the cumulative incidence of distant metastases. Of the 506 patients who received adjuvant

chemotherapy, 57% did not receive the intended 4 cycles as scheduled, and 27% could not start adjuvant treatment at all [48, 161].

The CHRONICLE study randomly assigned patients receiving neoadjuvant chemoradiotherapy to 6 months of postoperative chemotherapy (six cycles of capecitabine-oxaliplatin) versus observation [162]. Patients were required to have received at least 45 Gy with concurrent fluoropyrimidine-based chemotherapy. Only 113 patients were accrued. Surprisingly, despite the observation group having more node-positive patients, there was no trend toward improved outcomes with adjuvant chemotherapy, even though we know patients with pathological stage III disease fare very poorly. However, these results are difficult to interpret because of the small numbers of patients randomized.

In the larger study I-CNR-RT trial [163], 655 patients with cT3 or T4 disease were randomly assigned to six cycles of bolus 5-FU versus observation; the clinical design was very similar to the EORTC study and the chemotherapy was given in a similarly reduced-dose bolus fashion postoperatively. Despite this, compliance was poor and there were no differences in survival. The cumulative incidence of local relapse was 7.4% versus 8.7% and there there were no differences in distant metastases (24.3% for postoperative chemotherapy versus 23.9% for no postoperative chemotherapy).

Finally, investigators from the Dutch Colorectal Cancer Group performed a randomized in 470 patients treated initially with radiation or chemoradiotherapy followed by TME [164]. Again, despite a high incidence of pathological stage III disease (81.9% of patients in the postoperative chemotherapy arm and 85.5% in the observation) there was no difference in DFS and OS at a median of 5 years of follow-up. Again, this study was similarly small and underpowered to detect a small survival benefit.

A meta-analysis of these trials [165], showed, that with a median follow-up of 7 years, the cumulative incidence of distant recurrences at 5 years was 36·5% in patients in the observation group and 35·5% for patients who received adjuvant chemotherapy (hazard ratio 0·94, 95% CI 0·78–1·14; p=0·523) . OS did not differ significantly between groups. Adjuvant chemotherapy did not provide a benefit for any endpoint in any of the ypN subgroups. With regards to oxaliplatin, the investigators limited their analysis to trials that had an observation group without adjuvant chemotherapy, and no randomised trials testing oxaliplatin were eligible.

All these trials concluded that the benefit of adjuvant chemotherapy noted for patients with colon cancer seems to be lost for patients with rectal cancer neoadjuvant (chemo)radiotherapy. The reasons for this discrepancy are difficult to explain. Lack of activity might be due to the fact that after neoadjuvant treatment and the surgically complex TME, which often has prolonged recovery period, there is a chemotherapy-free period of approximately 20 weeks until adjuvant systemic treatment can be administered, many times at a reduced dose [48, 123]. In all trials, compliance rates were suboptimal.

Secondly, the absolute benefit of postoperative chemotherapy on OS may be less in the modern era after preoperative radiation as a result of stage migration and other mitigating factors. It is also true that in colon cancer, the benefit of adjuvant chemotherapy is largely restricted to patients with node-positive disease, and we still do not know how to identify those stage II patients that will benefit from adjuvant CT; the same can probably apply to rectal cancer, where, of course, the weak point in the clinical staging is the identification of N+ positive disease; most clinicians in these cases, even despite an excellent response after LCRCT, as we will see, are afraid to omit postoperative chemotherapy “in case the nodes were originally positive.”. On the other hand, there is the concern that some of the patients with pathologic node negative disease actually had nodal

disease that responded to therapy. These patients are at increased risk for systemic disease recurrence given the nodal status. In addition, these patients have treatment sensitive disease and might be more likely to benefit from additional chemotherapy. [166]

Other authors suggest that this difference in response to adjuvant chemotherapy between rectal and colon cancer could be the result of biological and genetic differences between the two diseases [165]. The finding in the recent meta-analysis that adjuvant chemotherapy improved DFSl and distant recurrences (although still not OS) in those tumours 10–15 cm from the anal verge lends some support to the idea of a possible difference between cancer of rectum and of the colon. An analysis of individual patient data pooled from five randomised trials showed that adjuvant chemotherapy significantly contributed to local control, had no effect on distant recurrences, and had a small effect on overall survival [34]. The assumption that (chemo)radiotherapy could mask the effect of chemotherapy on local spread of the primary tumour is intriguing, but no clinical trial has directly addressed this issue. Some ongoing trials with a chemotherapy-only preoperative group could offer some insight on the effect of chemotherapy on local control, but they will not definitively answer this question. Of note, we did not show any benefit in local relapse rates with the use of adjuvant chemotherapy. However, although this is an intriguing hypothesis, it is not entirely convincing, as there is little data in different molecular studies to suggest that rectal cancers behave differently to colon cancers, especially to distal colon cancers [167]

4.4.1. Can we select which patients would benefit most from adjuvant chemotherapy?

To add more controversy to the role of adjuvant chemotherapy, the need for adjuvant treatment in patients with a complete or near-complete response after CRT has been questioned [168-169]. Recent work from a multi-institutional retrospective analysis of 3133 patients shows that the benefit of adjuvant therapy differs between LARC subgroups. For example, patients with ypT1-2 or ypT3-4 tumors benefitted the most from adjuvant therapy compared with patients who had ypT0N0 tumours [170].

There are centres that now adapt adjuvant chemotherapy according to the pathological response after LCRCT. A recent phase 2 randomized study in 321 patients with postoperative pathologic stage II or stage III rectal cancer following preoperative fluoropyrimidine-based LCRCT found that adjuvant 5-FU and oxaliplatin improved 3-year DFS (71.6%) compared to 5-FU (62.9%) [171]. This trial restricted the use of adjuvant chemotherapy to patients with LARC who had ypT3-4N0 or ypTanyN1-2 tumors afterneoadjuvant treatment. Patients were randomly assigned to adjuvant chemotherapy with either four cycles of 5-FU or eight cycles of FOLFOX. The administration of FOLFOX after surgery was associated with prolonged DFS in stage III patients but not in stage II patients. A main strength of this study is that 96% of the patients completed the intended 4 cycles of adjuvant chemotherapy, which may justify this benefit, alongside the selection of patients with stage II or III residual disease. A risk-adapted approach proposed by a Spanish Group showed interesting DFS benefits [172], in the intention-to-treat analysis, when patients were selected according to their pathological response. In effect, 5-year DFS for patients in the good-prognosis group (downstaging to ypT0-2 N0, who received only 5-FU adjuvant chemotherapy) and for patients in the poor- prognosis group (pT3-4 or N positive disease, who received oxaliplatin-based combination chemotherapy) were 79.4% and 66.3%, respectively.

However, other studies suggest that these patients who have a higher downstaging with LCRCT are those that benefit most from adjuvant chemotherapy. These were the original findings of the EORTC trial, where patients downstaged to ypT02 benefitted from adjuvant CT, whereas none was seen in ypT34 patients [48].

Interestingly, the benefit of adjuvant chemotherapy in patients with ypT0-2 seen in the first analysis has disappeared with a longer follow-up [161].

What can we conclude of all these trials? Patients with poor downstaging should probably be offered some type of adjuvant chemotherapy, for only the lack of better options, especially in patients with node-positive disease. Involved regional lymph nodes at histopathology after radical surgery for T3-4 cancers confer a high risk of locoregional recurrence and distant metastases; however, compliance can be a problem. In patients not treated with neoadjuvant radiotherapy, we do not support the use of postoperative (chemo)radiotherapy if the surgical specimen shows involved margins or other factors of local relapse. In the Trans-Tasman Radiation Oncology Group (TROG) trial, positive resection margins, histopathogically involved lymph nodes following radiotherapy in the resected specimen, and baseline carcinoembryonic antigen level were independently associated with LR [56]. In the MRC 07 trial, significant risk factors included anterior quadrant tumor involvement, extramural vascular invasion, and N stage (N2 > N1) [173]. However, not only we know that postoperative RCT is poorly tolerated but also that these factors also increase the risk of distant metastases and worse survival; in our study, CRM invasion was one of the significant factors in the multivariate analysis for a worse DFS and OS.

More difficult is to decide what to do with patients with a good downstaging and especially those with a pCR. Selecting patients with fluoropyrimidine-sensitive disease is an attractive option, but the data suggest that the absolute benefit is relatively small. It is certainly likely that there is a subset of patients with good prognostic markers (such as cT3N0 disease, tumors high in the rectum, tumors with pCR) that do not gain much additional benefit from adjuvant chemotherapy. However, currently we do not have enough information on how to identify these patients. Patients with a pCR from neoadjuvant chemotherapy have better outcomes in terms of DFS and OS than patients who do not [6, 170, 174]. Is that enough basis for not giving adjuvant chemotherapy.?. Probably not, but we can take solace in that, in this group of patients, the benefit of adjuvant chemotherapy is probably relatively small [175].

In terms of specific molecular biomarkers, microsatellite instability testing might be of value if considering single-agent 5-FU therapy, although MSI-high tumours are rate in the rectum [167-168]. Unfortunately, in most circumstances, more advanced gene expression assays are not likely to be beneficial in determining the need for adjuvant chemotherapy in this setting.

The potential, unproven, benefits of adjuvant chemotherapy should be balanced with its potential short-term and long-term negative effects. Such effects include deterioration in quality of life; increased mortality associated with postoperative chemotherapy, probably higher among elderly patients; increased grade 3 and higher toxic effects caused by the combination of fluorouracil and oxaliplatin; the need to postpone diverting stoma; and direct and indirect health-care costs. Other, long-term adverse events include permanent deterioration in quality of life and neuropathy in patients who take oxaliplatin.

Unfortunately, we are not going to have high-quality randomized trials evaluating adjuvant CT after (chemo)radiotherapy in the future. Instead, we should turn to exploration of large research archives, cancer centre networks, and population registries. This approach will be more affordable and should be used to address the ongoing uncertainties of prescribing adjuvant chemotherapy after preoperative (chemo)radiotherapy for rectal cancer.

In a case-by-case basis, when deciding which patients to consider for adjuvant chemotherapy with ypT3-T4N0 rectal cancer the decision needs to be made on an individual basis discussing the risks and benefits for each patient. Patient comorbidities and performance status following neoadjuvant chemoradiation and their operation are also important. In general, the likely benefit for adjuvant chemotherapy remains quite small in this specific setting, although there is a minority of patients that might derive significant benefit. In our study, both the Valentini nomograms and the Dhadda score defined poor-prognosis patients, with a high risk of local relapse and distant metastases. The use of these nomograms may aid us in the selection of patients' candidates for adjuvant chemotherapy, although, again, as they are scores based in pathological criteria, they can only be used after surgery.

Another possible approach to resolve this conundrum is the use of neoadjuvant chemotherapy; the objective in this case is not to increase downstaging, as the induction trials we mentioned previously, but to decrease the risk of distant metastases [175]. We know from all clinical trials that adjuvant chemotherapy is poorly tolerated after neoadjuvant radiotherapy and surgery for rectal cancer, with 25% of patients not receiving anything. With this in mind, several authors have proposed the use of systemic treatment before, rather than after, surgery. Randomised trials with neoadjuvant systemic therapy are in progress; they usually do not include radiotherapy or, if they do, only SCRT (RAPIDO, PROSPECT, COPERNICUS). In the meantime, four small phase 2 studies have addressed this novel concept of neoadjuvant chemotherapy without LCRCT with encouraging results (TABLE 52).

Study	n	Entry criteria	Chemotherapy	S	Downs-taging	pCR	LR	Survival endpoints	G3-4 toxicity	Toxic deaths
High-risk patients										
Ishi *et al* [177]	26	cT3-4, cN0-2	5-FU and irinotecan	26	T: 46% N: 50%	4%	12%	5-year DFS: 74% 5-year OS: 84%	4%	0/26
NSOG 03 [178]	32	cT3-4, cN+, CRM +, EMVI	XELOX-bevacizumab	30	T: 60% N 83.3%	13%	NR	NR	25%	1/32
Schrag *et al* [179]	32	cT3	FOLFOX-bevacizumab	32	T: 69.0% N: NR	4.3%	0%	4-year DFS: 84% 4-year OS: 92%	NR	1/32
Hasegawa *et al* [180]	23	cT4, cN +	XELOX-bevacizumab	23	T: 69.6% N: 78.9%	25%	4%	3-year DFS: 71% 3-year OS: 88%	28%	1/23
Standard-risk patients										
GEMCAD 0801 [181]	44	cT3	XELOX-bevacizumab	44	T: 48% N: 56%	20%	2%	NR	39%	3/44

* Statistically significant.

TABLE 51: Selected trials of neoadjuvant chemotherapy with no preoperative radiotherapy in patients with locally advanced rectal cancer. Most patients proceeded to surgery (S)

Practical aspects of adjuvant chemotherapy.

1. We offered adjuvant chemotherapy to all patients after surgery, regardless the response rate. However, as in most other published trials, the tolerance to the adjuvant regimen was poor with less than half of these patients receiving the full intended dose; this was especially evident in elderly patients.
2. We observed a small but significant decrease in the rate of distant metastases with adjuvant CT; no benefit in local control was obtained.
3. There is controversial evidence on the use of adjuvant CT after LCRCT and TME-surgery; most trials have not shown any survival benefit. However, compliance to treatment was uniformly poor, which may explain this lack of benefit. Unfortunately, we are not going to have randomized trials which will answer this question
4. Patients with poor downstaging, high lymph node burden or other poor prognostic factors (high grade, minimal regression perineural or vascular invasion, involved CRM, mucinous tumours) should probably be offered adjuvant chemotherapy if feasible, if only for a lack of better options. The use of nomograms and scores, such as the Valentini momogram or the Dhadda score, were helpful in our case in selecting patients with poor prognosis.
5. If there is a benefit, it is probable small in patients with downstaging and especially in those who have pCR; the doubts over the effectiveness of adjuvant chemotherapy should be transmitted to patients and a shared-decision should be taken over its use.
6. We did not use neoadjuvant chemotherapy regimens, alone or alongside LCRCT or SCRT, as there are only phase II evidence for its activity, but results are promising.
7. Improvements in clinical staging, with a better identification of pathological lymph nodes, are needed to identify those patients with a higher risk of systemic relapse, who will benefit from more intensive oxaliplatin-containing (neo)adjuvant regimens, probably in the neoadjuvant setting.

4.5. How can we improve clinical staging in order to define which patients have a higher risk of local relapse and distant metastases?

4.5.1. Primary tumour staging

The importance of local staging in rectal cancer is dependent on the multimodality approach policy that is used. In patients with locally advanced tumours treated with a blanket approach of neoadjuvant LCRCT, as was our case, staging procedures are less important, although we know that there is an inherent higher risk of over- and under-treating patients. In centres where a more progressive and selective policy is adopted, relation of the tumour margin to the CRM is imperative for decision making, as involvement of the CRM supercedes all other prognostic indicators for the use of neoadjuvant chemoradiation. In both cases, however, the challenge for an imaging study is not just to be able to use it to determine resectability, but also to be able to use it to predict the likelihood of local relapse and distant metastases—and thereby define the optimal neoadjuvant strategy, and determine whether the tumor will respond to standard fluoropyrimidine-based CRT.

As we used in all patients neoadjuvant LCRCT, the utility of clinical factors that increase the risk of local relapse are probably not very useful. We observed a higher risk of local relapse in older patients, anaemic patients (where we know that radiotherapy is less effective), poorly differentiated tumours and bulky tumours. Curiously, involvement of the mesorectal fascia was not a significant factor, probably due to the fact that almost 40% of patients were staged with EUS, which does not identify well CRM invasion in most cases, and that LCRCT compensates somehow for an involved CRM. What is perhaps most interesting is that there was no relationship between local relapse and lymph node involvement. The poor sensitivity of cN staging, as we will see later, is probably a factor. However, it is also true that with better surgical rechniques, a successful TME procedure would probably remove all pathological lymph nodes and that would not necessarily indicate a higher risk of local relapse.

Both EUS and MRI are commonly recommended for rectal cancer staging, although most guidelines now agree that MRI has become a required standard for evaluating locally advanced disease, particularly in those patients with potential CRM involvement. This is despite the fact that in the the published meta-analysis, EUS does not perform any differently to either CT or MRI. However, these analyses limited assessment to T and N staging only and did not take into account the important prognostic variables that should also be assessed by imaging, such as depth of extramural spread in millimetres, relationship of tumour to the mesorectal fascia and extramural vascular invasion [182]. EUS has other disadvantages, such as its inability to stage high, bulky and obstructing tumours [183]. The limited views of the whole mesorectum and pelvis with EUS does not allow us to exclude tumour deposits, pathological lymph nodes, discontinuous vascular invasion and mesorectal fascia involvement by tumour, which will inevitably lead to understaging [184]. In effect, that is what we saw in our study, as in most patients staged by both imaging modalities, EUS understaged in comparison to MRI, especially in cN disease, upper rectal cancers and stenotic tumours (FIGURES 32 and 33)

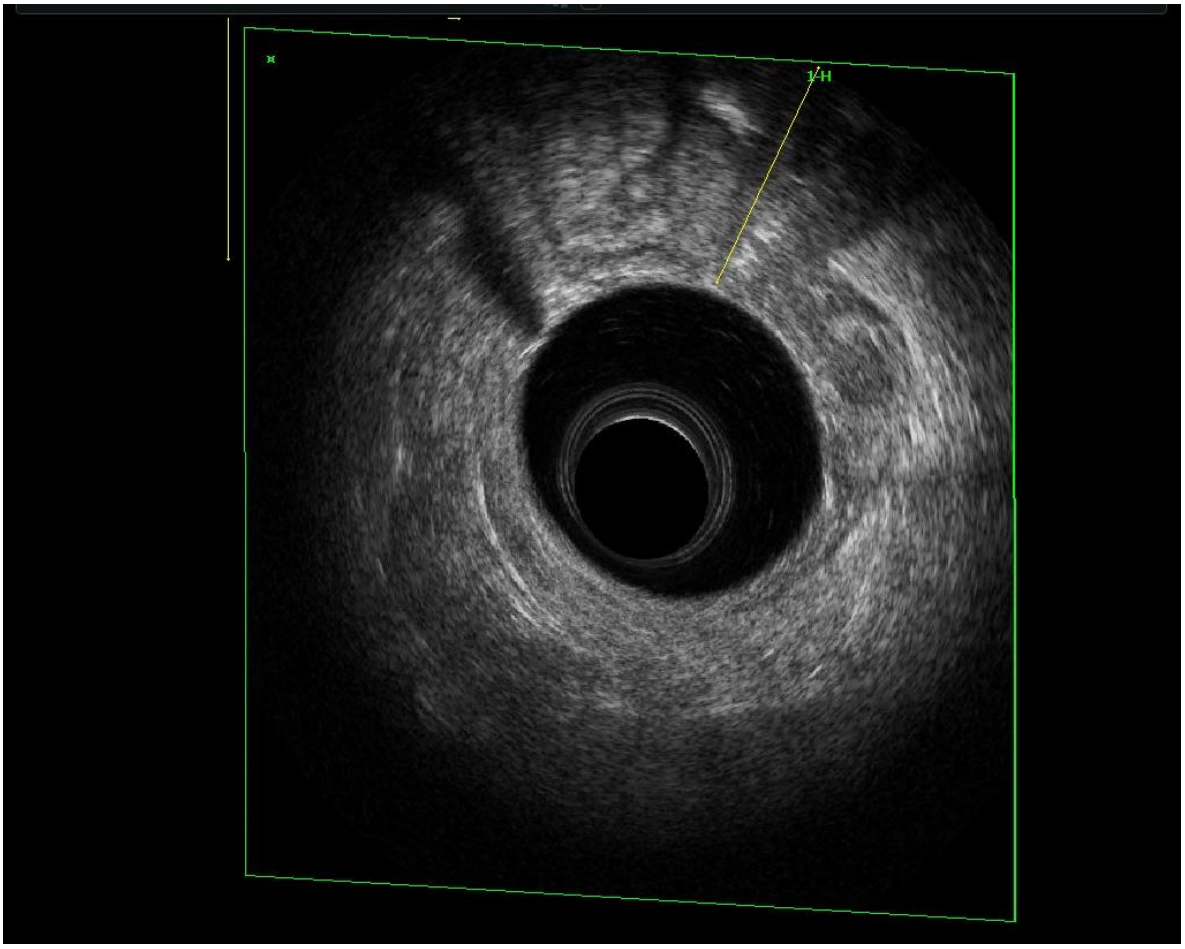


FIGURE 31: (Case 202) Endoscopical ultrasound (EUS) in a 65-year old patient which showed a mid-rectal hypoecogenic lesion that affected the perirectal fat, with one pathological lymph node and classified as an uT3N1a tumour. However, the test was unsatisfactory due to the stenotic nature of the lesion, a common shortcoming of EUS. The MRI performed showed a cT3bN2b with a threatened mesorectal fascia

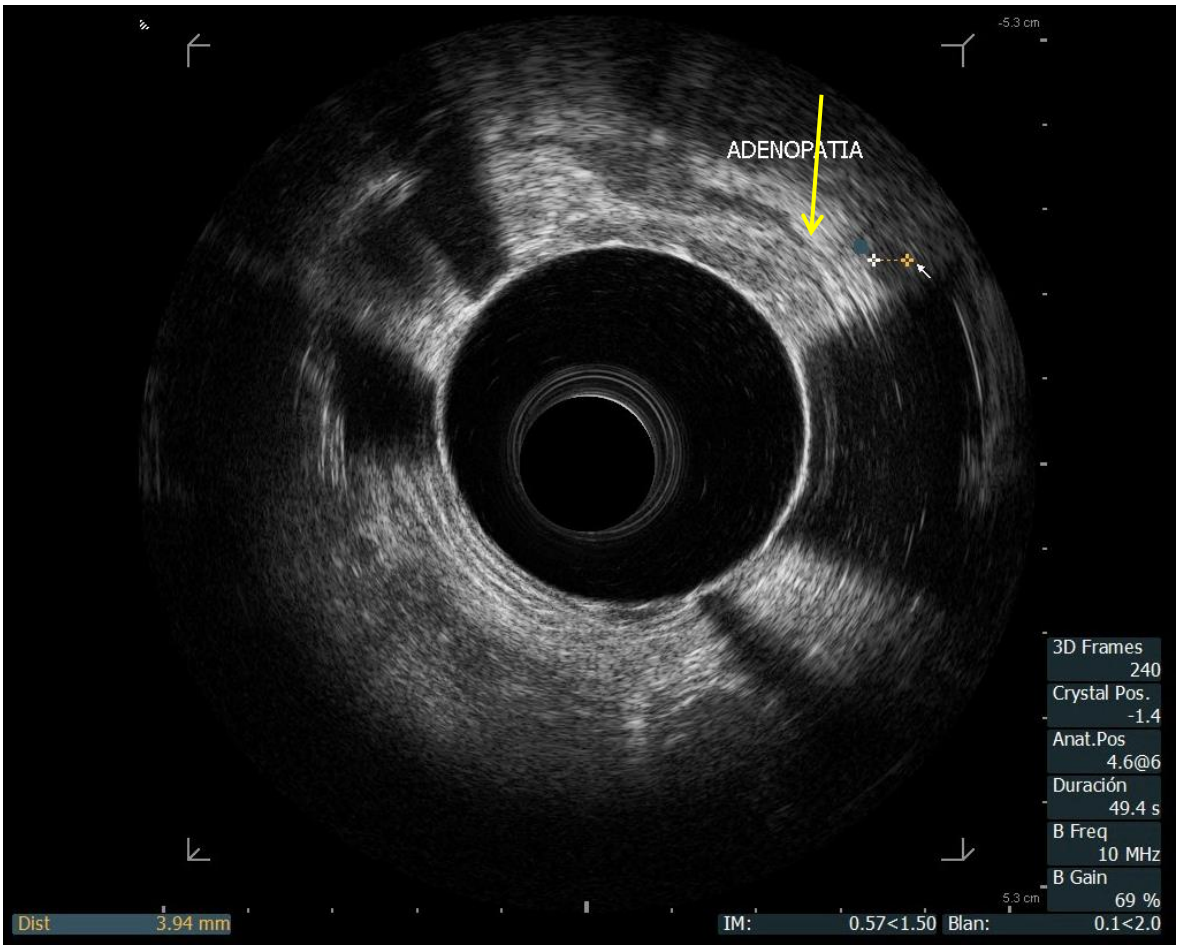


FIGURE 32: (Case 202) Endoscopical ultrasound (EUS) in the same 65-year old patient which showed a mid-rectal hypoecogenic lesion that affected the perirectal fat, with one pathological lymph node (yellow arrow) and classified as an uT3N1a tumour. However, the test was unsatisfactory due to the stenotic nature of the lesion, a common shortcoming of EUS. The MRI performed showed a cT3bN2b with a threatened mesorectal fascia

MRI, on the other hand, provides excellent soft-tissue contrast at high spatial resolution. The ability to visualize the tumor and surrounding structures in coronal, axial, and sagittal planes means that MRI is currently the optimal method for staging rectal cancer and evaluating the potential CRM. As we have seen, the MERCURY group has proposed a risk classification (TABLE 48) that allows us to stratify tumours depending on the presence of several high-risk features that are not limited to T and N stage (CRM and EMVI status (FIGURES 33 and 34), depth of extramural invasion (FIGURE 35), presence of discontinuous extramural vascular spread/deposits, presence of mucin (FIGURE 36) and grade of tumour regression to preoperative treatment). These have all been proven to influence disease-free and overall survival rates in prospective multicentre studies [185-187]. In recurrent rectal cancer, MRI allows the delineation of tumour extent within the pelvic compartments, can assess the pattern and mode of local recurrence and predict resectability of the disease.

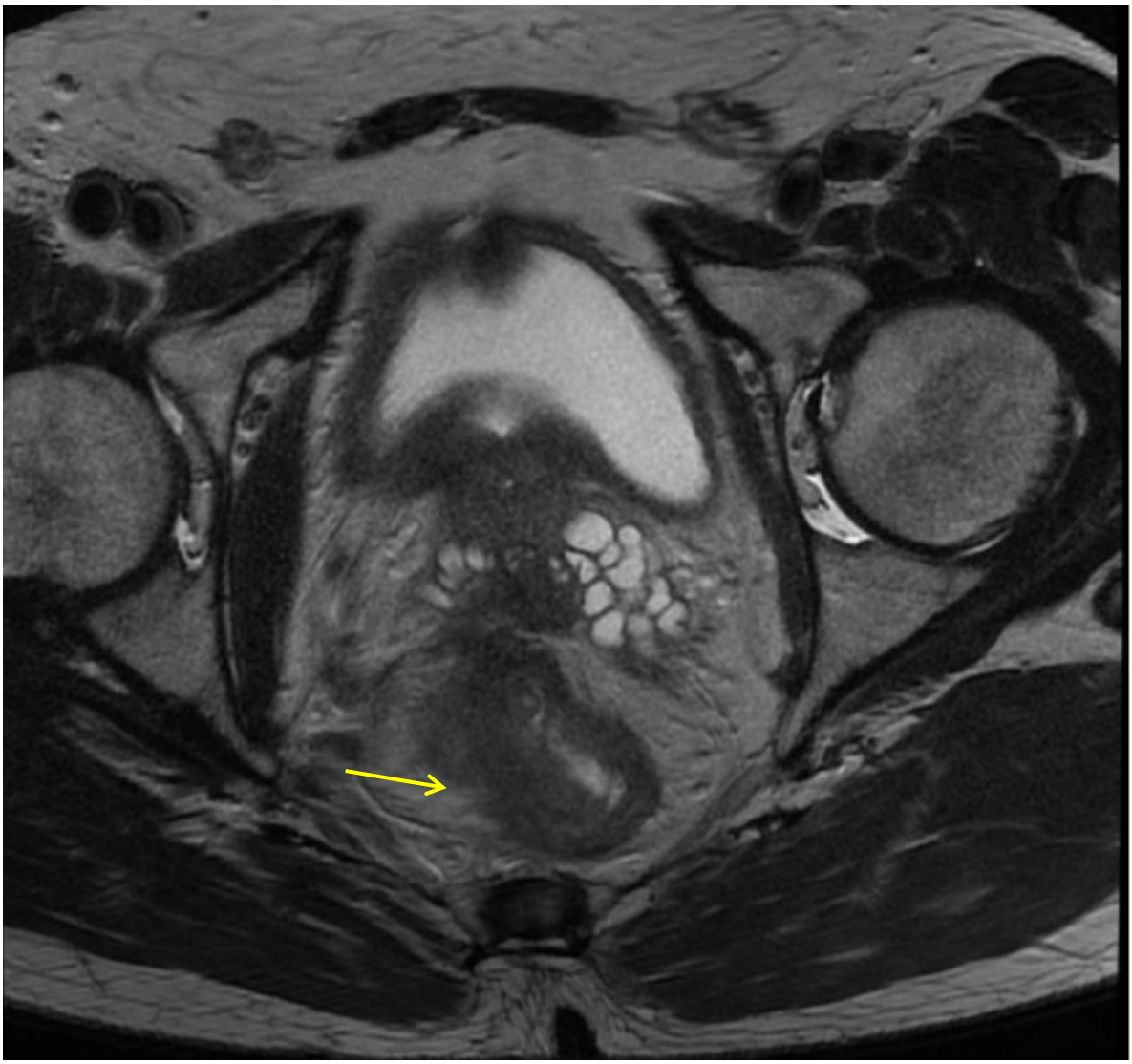


FIGURE 33a: (Case 182) Coronal MRI images of a cT4bN1b rectal cancer in a 56-year old male patient, six centimetres from the distal margin, and with extensive infiltration of the mesorectal fascia (shown by the yellow arrows) and invasion of the prostate and the seminal vesicles.

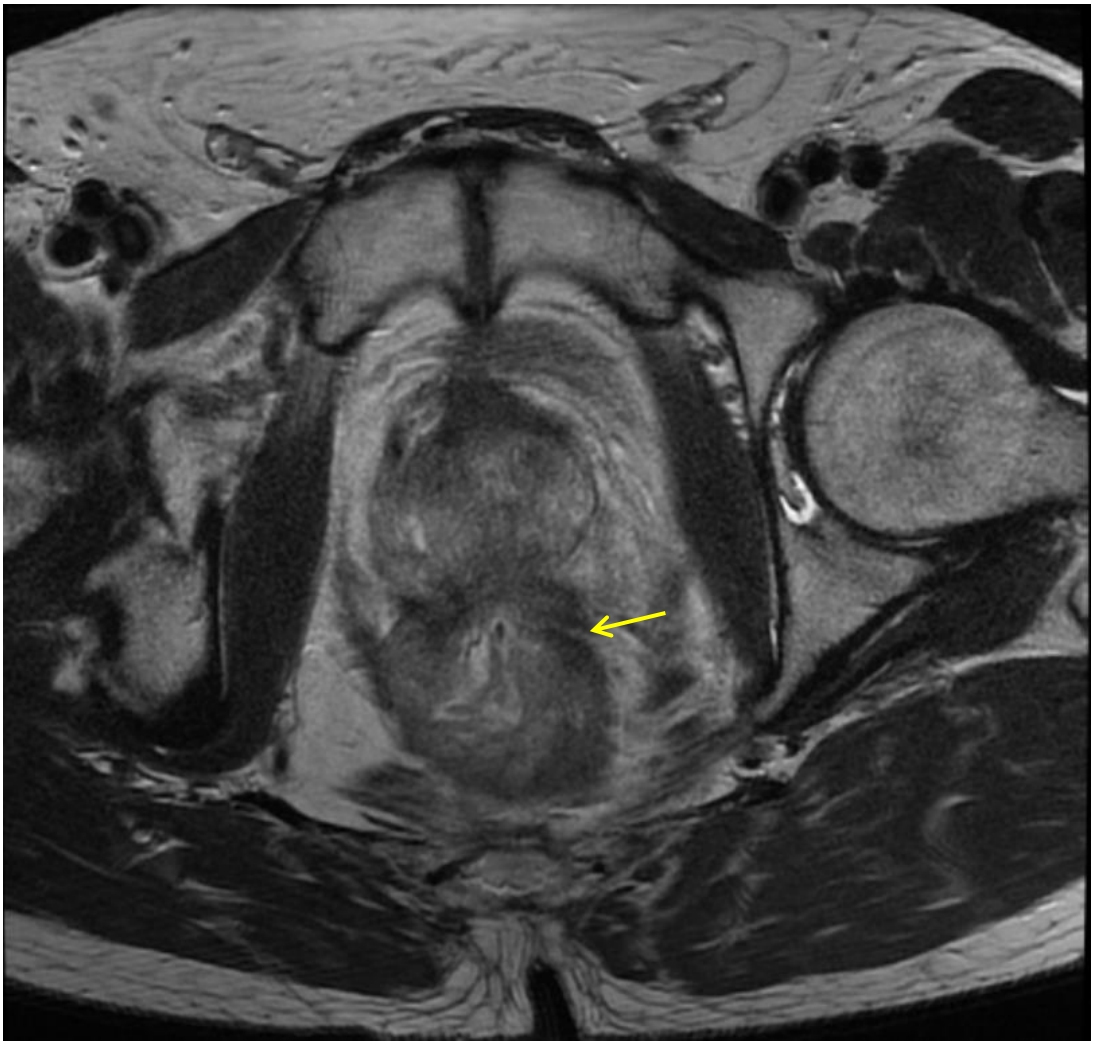


FIGURE 33b: (Case 182). Coronal MRI images of a cT4bN1b rectal cancer in a 56-year old male patient, six centimetres from the distal margin, and with extensive infiltration of the mesorectal fascia and invasion of the prostate and the seminal vesicles (shown by the yellow arrows)

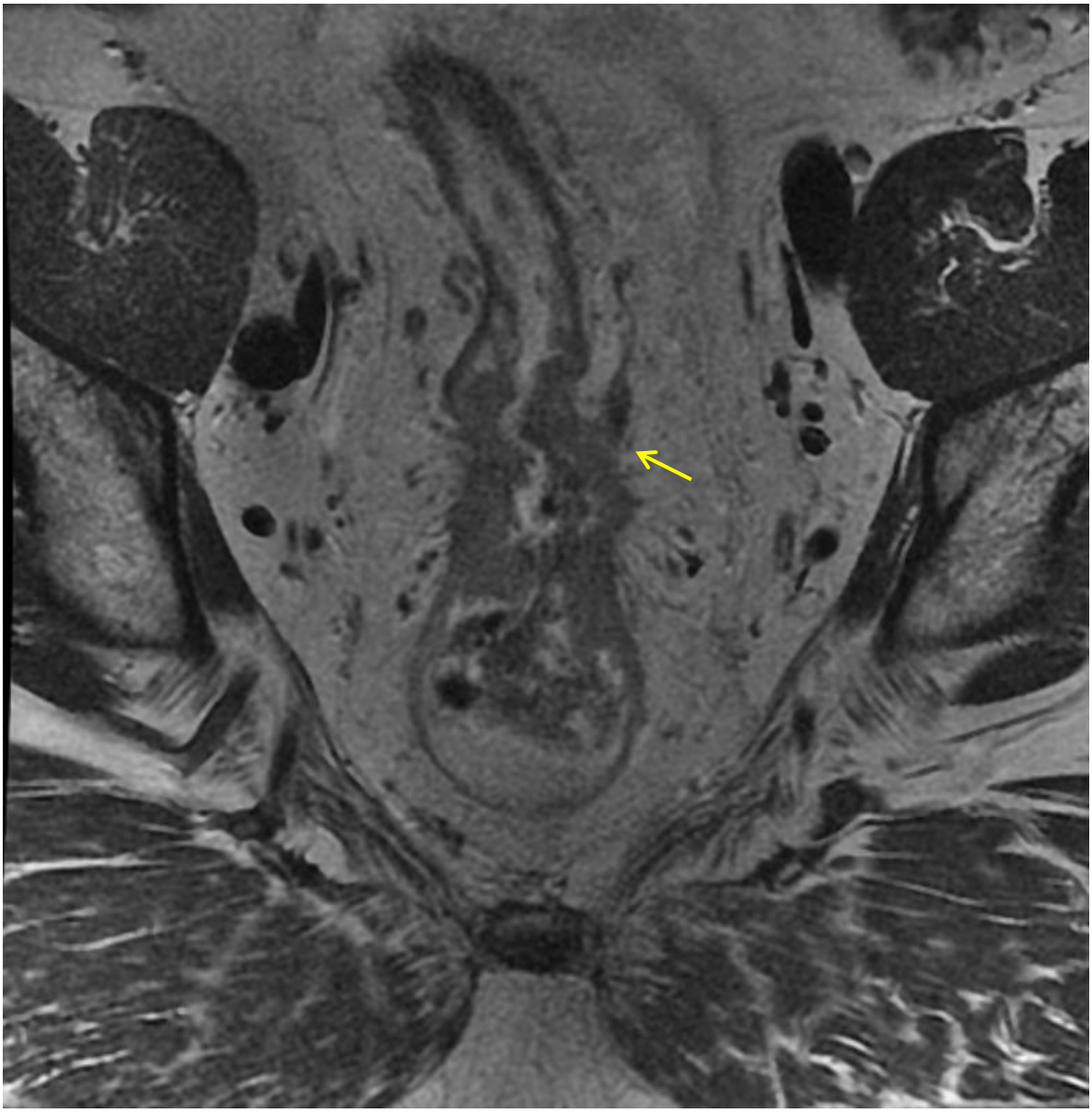


FIGURE 34a: (Case 201) Coronal MRI images of a 56-year old male patient with a locally advanced mid- to upper rectal cancer staged cT4aN1b, with extramural venous invasion (yellow arrow)

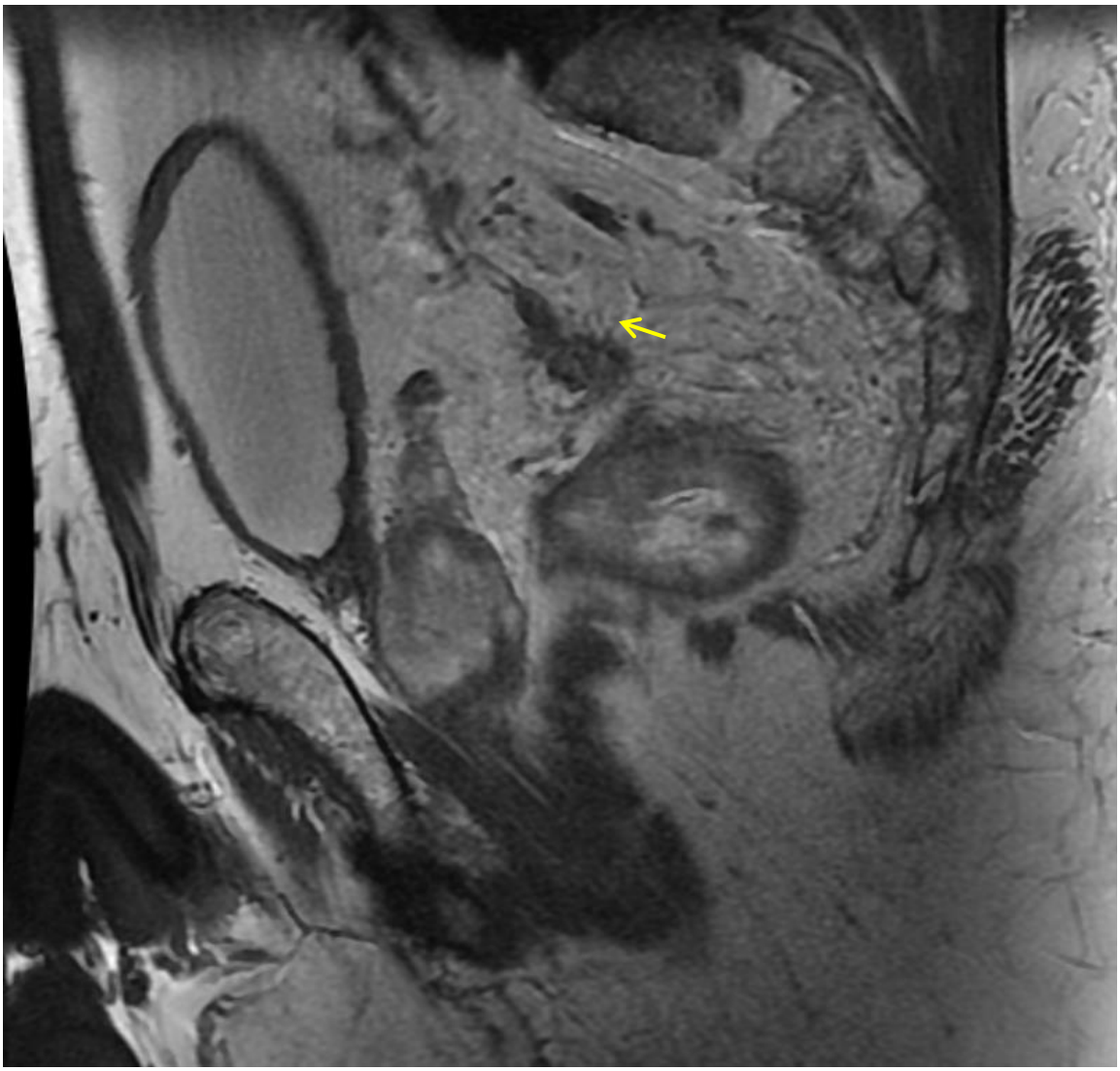


FIGURE 34b: (Case 201) Coronal and sagittal MRI images of a 56-year old male patient with a locally advanced mid- to upper rectal cancer staged cT4aN1b, with extramural venous invasion (yellow arrow)

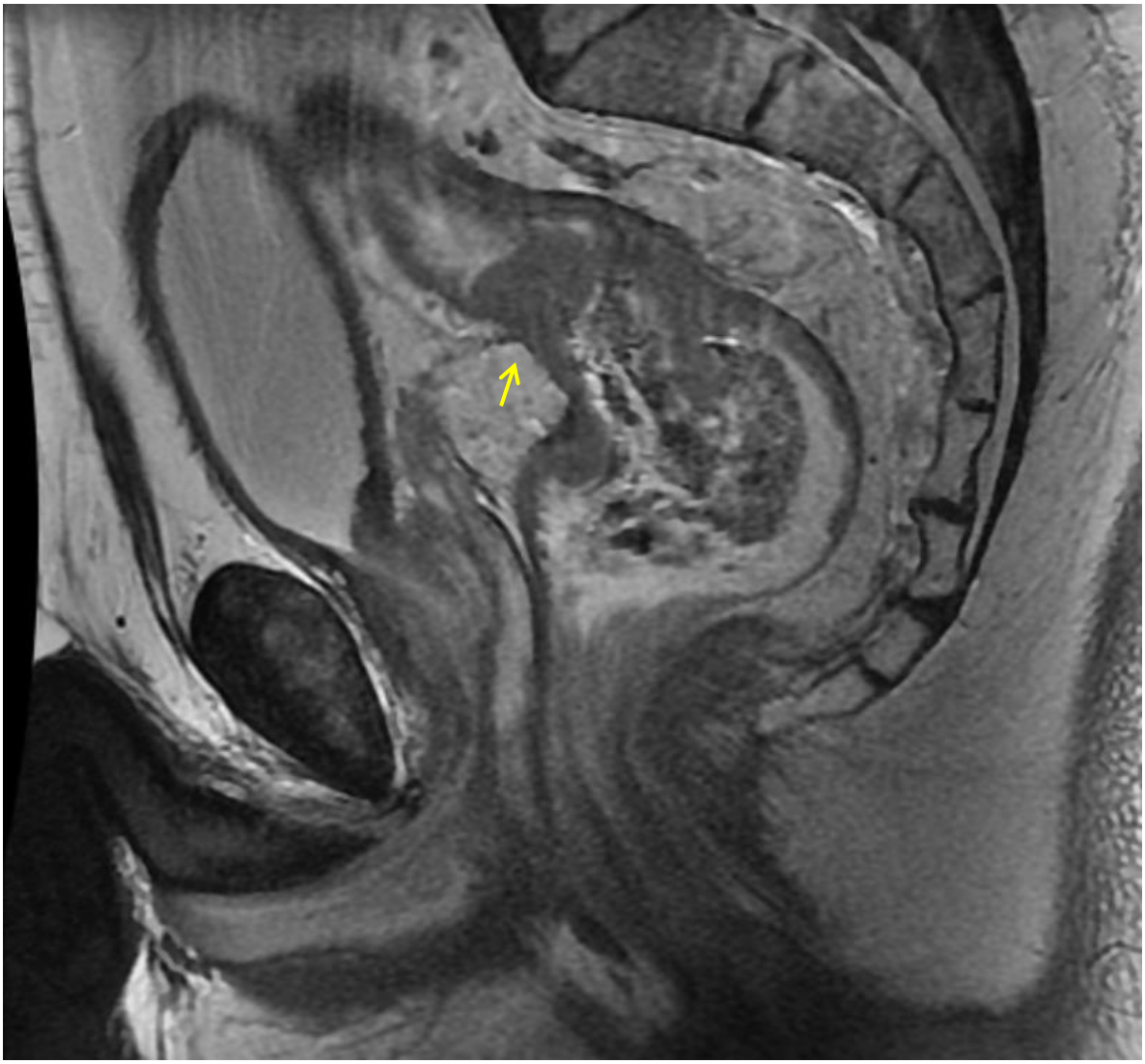


FIGURE 35: (Case 201) Sagittal MRI images of the same 56-year old male patient with a locally advanced staged cT4aN1b, secondary to infiltration of the peritoneal reflexion (yellow arrow)

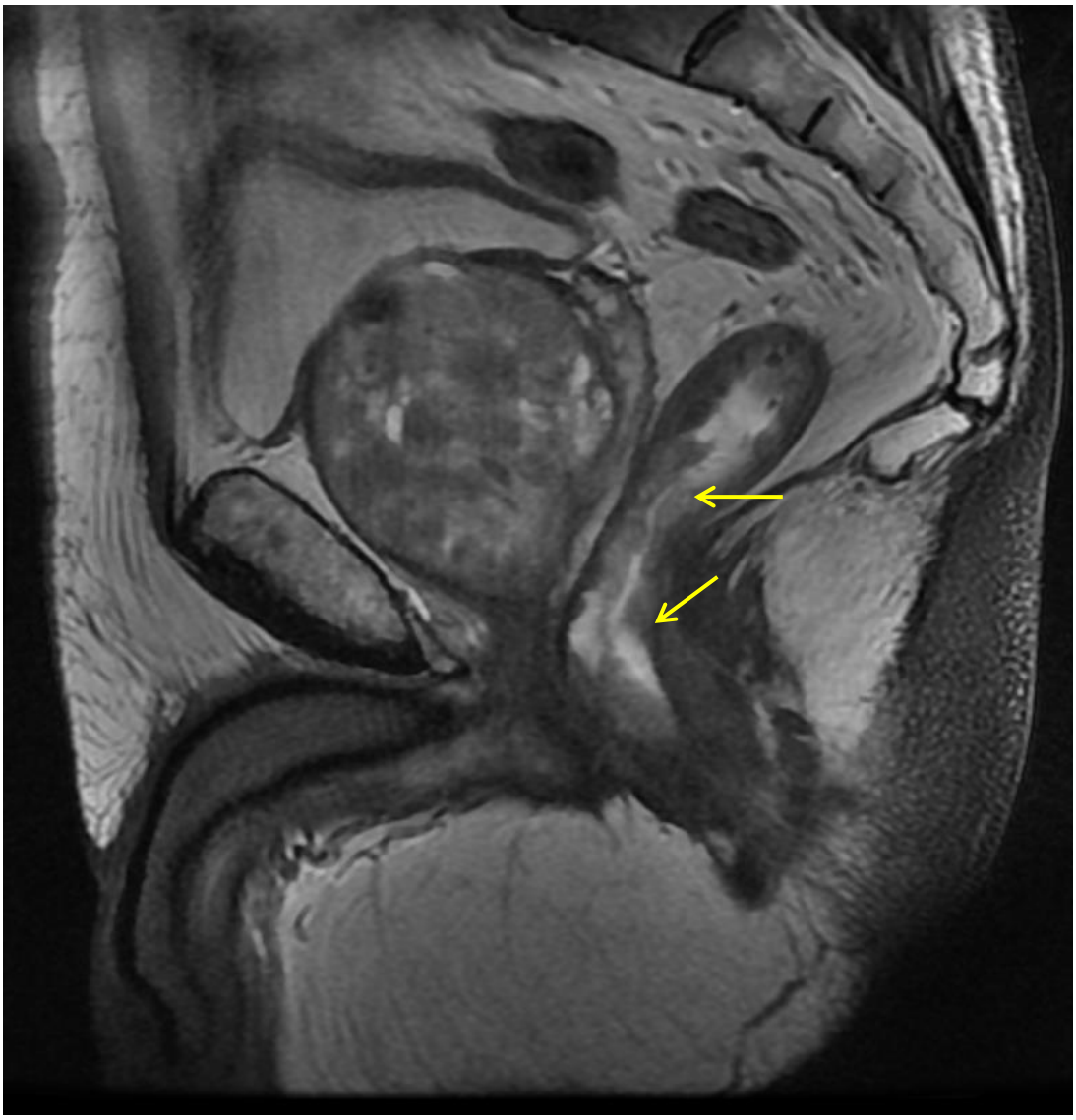


FIGURE 36: (Case 191). Sagittal MRI images of a locally advanced mucinous lower rectal cancer staged as cT2N2a in a 65-year old male patient (primary tumour shown by the yellow arrows)

MRI can also give us more important information. The risks of local failure are much higher for cancers below the peritoneal reflection, and for those in the lower rectum below or involving the levators (FIGURE 37). Low rectal cancers that are anteriorly located and fixed are more difficult to resect and have a higher risk of local relapse [188-189]. The depth of tumour penetration in those patients staged as cT3 with MRI has also prognostic importance. As we have mentioned, the MERCURY Study Group used preoperative MRI to extend the clinical subclassification of T3 into four groups: “a” (< 1 mm outside the wall), “b” (1–5 mm), “c” (5–15 mm), and “d” (> 15 mm). An exploratory subset analysis of T3 tumors demonstrated local relapse rates for SCPRT vs selective postoperative LCCRT of 2.7% vs 5.8% in T3a (≤ 1 mm) tumors; 2.9% vs 9.6% in T3b (> 1–5 mm) tumors; and 9.6% vs 21.9% in T3c (> 5–15 mm) tumors. [173]. Other groups have also shown that T3c and T3d rectal cancers have markedly worse progression-free and cancer-specific survival compared with T3a and T3b cancers [190]

As we have seen, in those centres where a risk-adapted approach is used, relation of the tumour margin to the CRM is imperative for decision making. In a landmark study, rigorous histopathologic analysis revealed 27% of all rectal cancers demonstrated an occult positive CRM (< 1 mm) after potentially curative surgery [191]. MRI can accurately predict CRM status and direct risk-stratified management strategies so as to select patients appropriate for preoperative CRT. MRI prediction of CRM as compared with histopathology suggested the use of a wider threshold with MRI (2 mm) than with pathology [56]; however, the MERCURY group based their analysis on an MRI cutoff of < 1 mm [100] and a prospective study also showed that a 1-mm cutoff on MRI predicts clear margins in 96.7% of cases [192]. Finally, In the MRC CR07 trial, the rate of finding a positive CRM fell from 21% in 1998 to a low of 10% in 2005 [70] secondary to an improvement in the quality of the mesorectal plane of excision (predominantly in patients undergoing anterior resection). The preoperative results of MRI were compared with the histopathologic findings in the resected specimens, and showed an accuracy for preoperative MRI of 90.9% [193]

These are impressive results and have been adopted by NICE, EORTC and ESMO for a more personalized approach to localised rectal cancer, that is based on the performance of high-quality MRI imaging [97-98, 100]. However, we must also point out that this treatment approach guided by MRI-risk categorization is based on results of prospective observational studies conducted in institutions with significant expertise in rectal cancer and has not been tested in prospective randomized trials. They may not be adequate for smaller centres with less experience or with smaller economic resources.

There are also other problems with MRI imaging. A current limitation is the significant learning curve associated with image evaluation; there is also the uncertainty regarding nodal involvement. The widespread use of preoperative LCRCT (leading in most cases to nodal downstaging) offers limited opportunities to the radiologist to audit performances in pretreatment MRI assessments. Another caveat is the evaluation of levator involvement in low rectal cancer (FIGURE 37) and the diagnosis of nodal involvement, which remain difficult even with newer MRI sequences, such as diffusion-weighted imaging. Finally, there is no clear evidence currently that MRI can discriminate between tumor grades; there are no specific texture features on standard images, and no clear relationship with diffusion-weighted MRI in the small studies published to date.

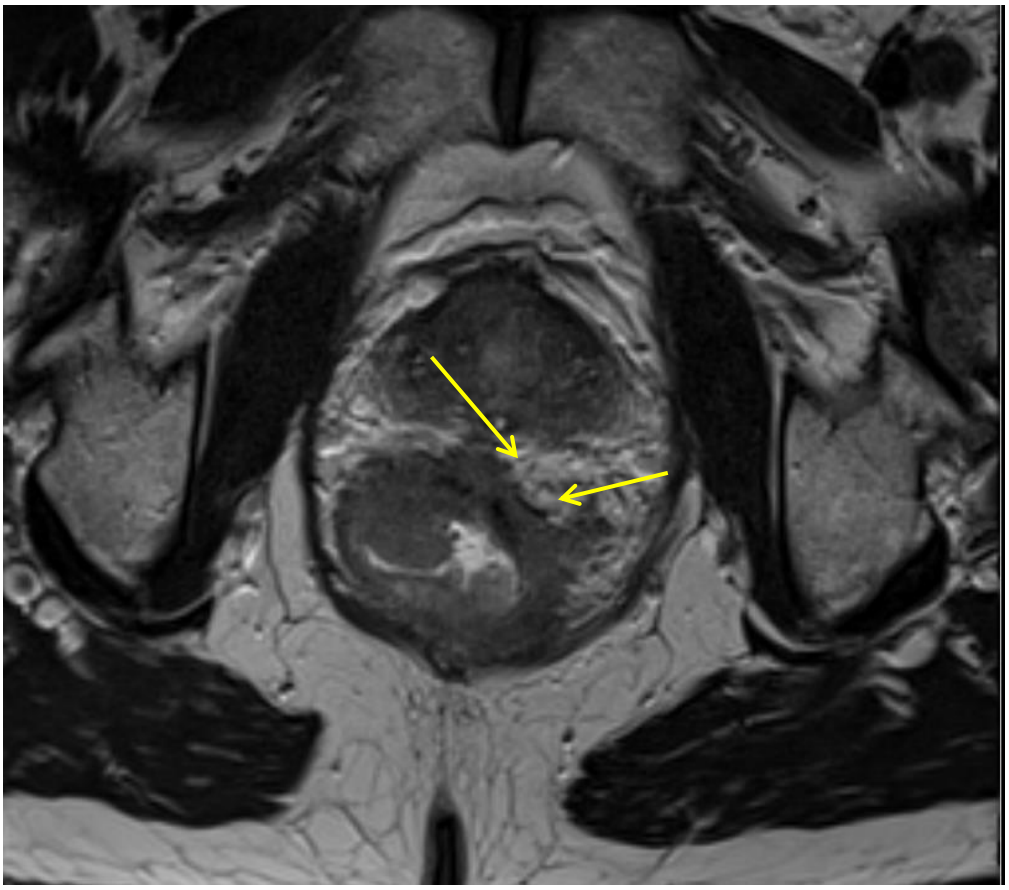


FIGURE 37a: (Case 143) Coronal and sagittal MRI images of a 62-year old male patient with a locally advanced lower rectal cancer staged cT3N1b with circumferential margin invasion (infiltration shown by the yellow arrow) and invasion of the intersphincter space.

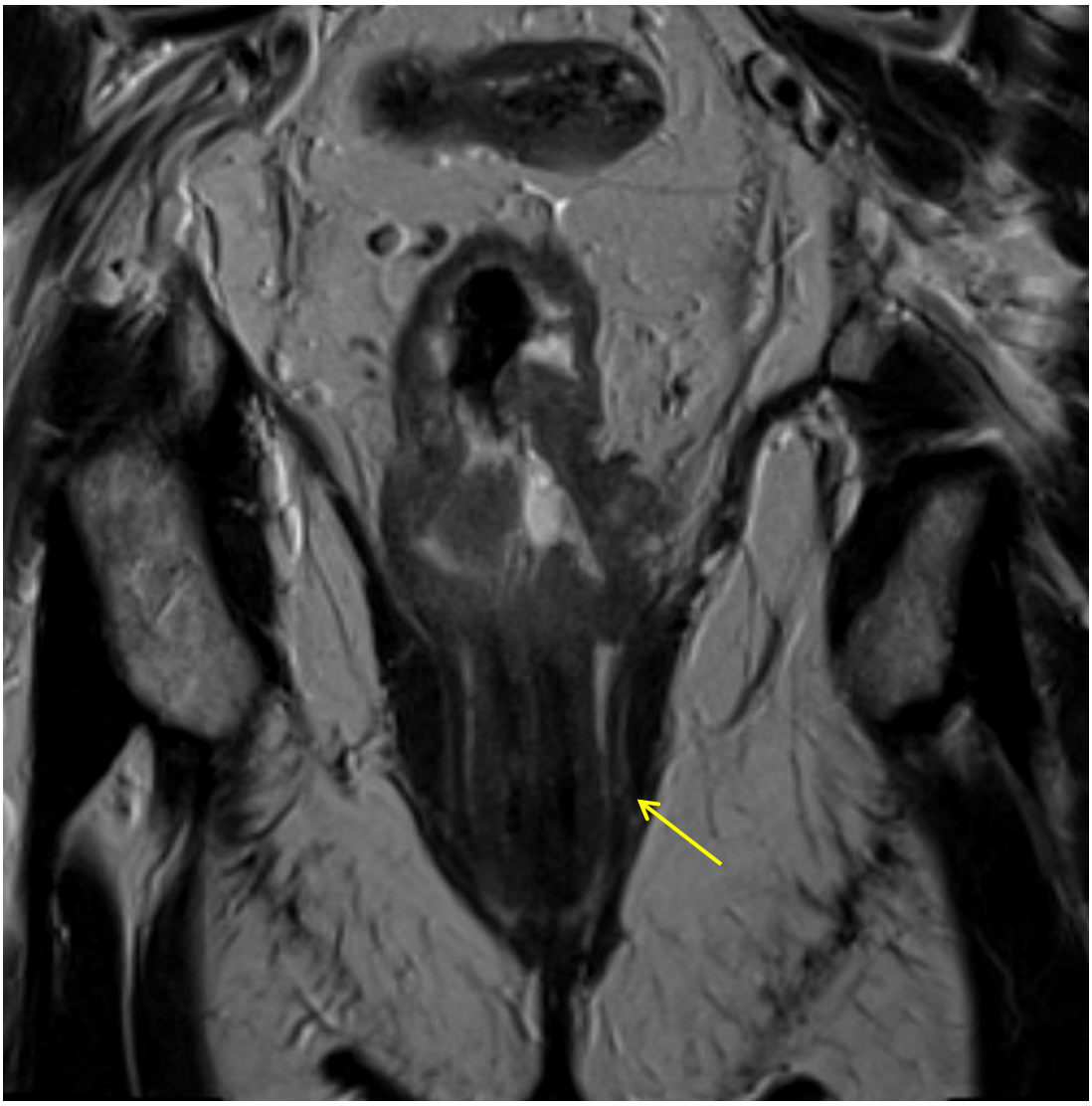


FIGURE 37b: (Case 143) Coronal and sagittal MRI images of a 62-year old male patient with a locally advanced lower rectal cancer staged cT3N1b with circumferential margin invasion (infiltration shown by the yellow arrow) and invasion of the intersphincter space.

4.5.2. Lymph node staging

Pathological stage III disease is the most important prognostic factor in localized rectal cancer and patients with a heavy lymph node burden fare very poorly. This is especially important now that surgical improvements and better identification of risk factors for local relapse, such as the circumferential margin invasion, have decreased the risk of pelvic recurrence and the risk of distant metastases predominates. We also know that neoadjuvant (chemo)radiotherapy does not improve survival and that adjuvant chemotherapy compliance is poor and difficult to administer after LCRCT.

The logical step, as we have discussed previously, is to identify those patients with a high risk of distant metastases, which would include most patients with lymph node disease, and offer them neoadjuvant chemotherapy alone or alongside LCRCT and SCRT. In our series, where the majority of patients were staged by MRI, baseline factors that predicted an increased risk of pathological lymph nodes included positive clinical lymph node disease (as would be expected) and other poor prognostic factors, such as mesorectal fascia invasion, extramural venous invasion, lower rectal tumours and elevated CEA and CA 19.9 levels. On the other hand, nodal staging is of questionable importance as a predictor for local recurrence in patients receiving radical surgery for primary tumours; however, it still should be assessed if local excision is considered.

Unfortunately, the clinical lymph node staging remains the Achilles heel in the baseline staging of patients with locally advanced rectal cancer, even with the use of high-quality MRI. In effect, although the preoperative MRI has proven to predict both T category and circumferential resection margin with good accuracy, the accuracy for predicting lymph node metastasis has been poor [182, 194-195], with moderate sensitivity (60-84%) and specificity (59–81%). One limitation in detecting positive lymph nodes by MRI is that a great number of detected nodes turn out to be normal or benign reactive nodes. In a node-to-node study of lymph nodes in rectal cancer, only 76 out of 521 nodes (14.6%) were confirmed malignant nodes by histology [196]. Currently, identifying malignant nodes mainly relies on the size of nodes (FIGURES 38 and 39). That is a useful, but imperfect strategy, as studies have confirmed that the proportion of positive nodes increases with larger nodal size [197-199]. However, there is no widely accepted consensus on the size criterion of enlarged lymph nodes, and substantial overlap exists between benign and malignant nodes. Although very small lymph nodes can be observed by high resolution MRI, the diagnosis of metastasis from detected lymph nodes is challenging, and the interobserver agreement in diagnosis of lymph nodes metastases varies among radiologists, especially for sub-centimeter lymph nodes [200-201].

Others have found that besides nodal size, lymph nodes with spiculated or indistinct border and mottled heterogeneous appearance were useful to predict positive nodes [198-199]. Despite this, in one study, even when the criteria of positive lymph nodes were strict (heterogeneous texture, irregular margin, and nodal size > 10 mm), the total accuracy was only 63%, with a sensitivity of 85% and specificity of 41% [202]. Most of these studies only had a small number of patients and multivariate analyses were rarely used to assess the relationship between these parameters and the nodal size. In other cases, the border, shape or intrinsic signal is difficult and inaccurate for very small nodes (less than 3–5 mm) in MRI. To make things more difficult, some low-signal-intensity rim in small lymph nodes is difficult to distinguish between normal lymph node capsule and tumor with necrosis, and tumor without necrosis in lymph node will present similar intensity with normal lymph nodes.

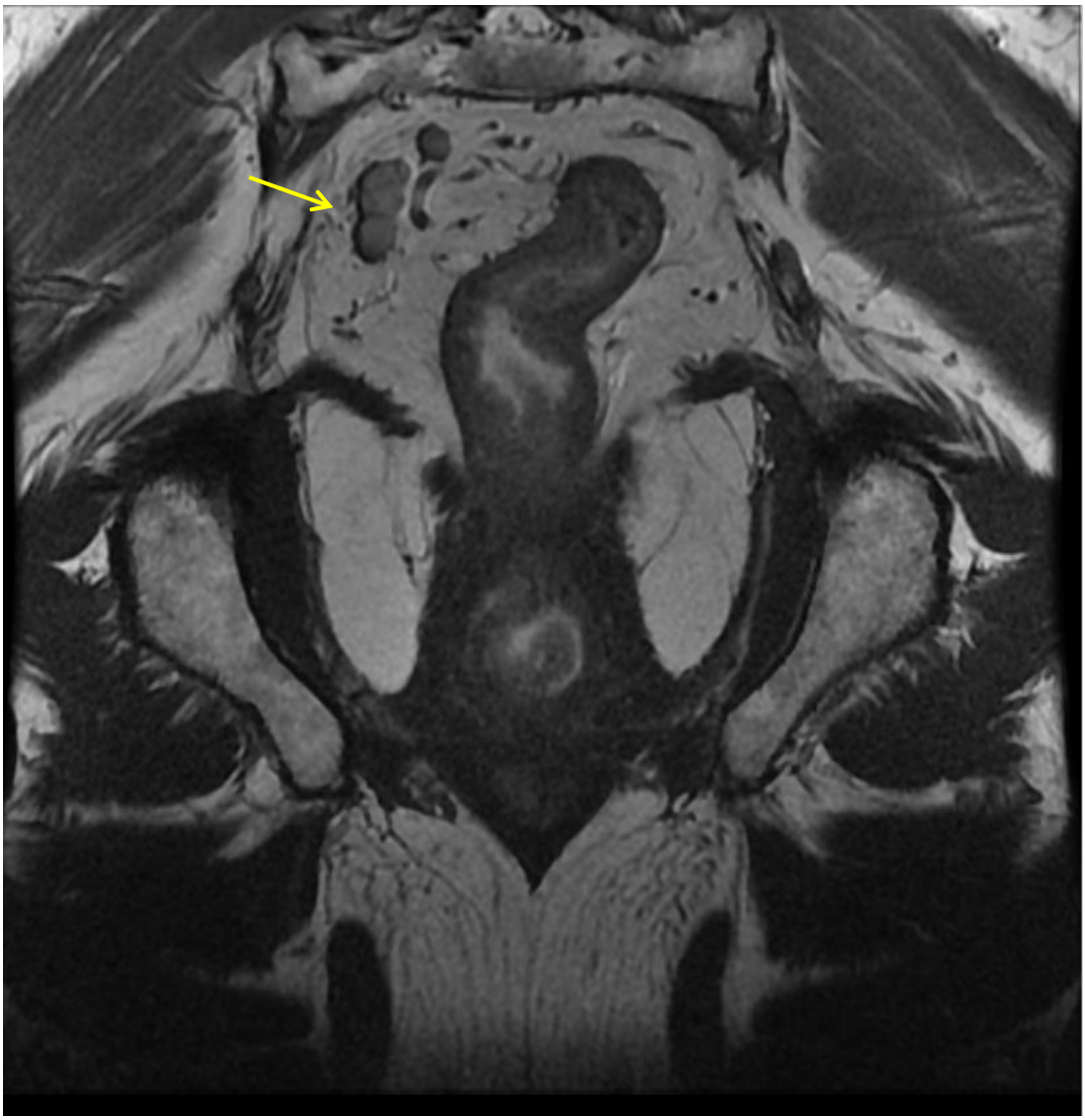


FIGURE 38: (Case 191) Coronal MRI images of a locally advanced mucinous lower rectal cancer staged as cT2N2a in a 65-year old male patient (pathological mucinous lymph nodes shown by the yellow arrows)

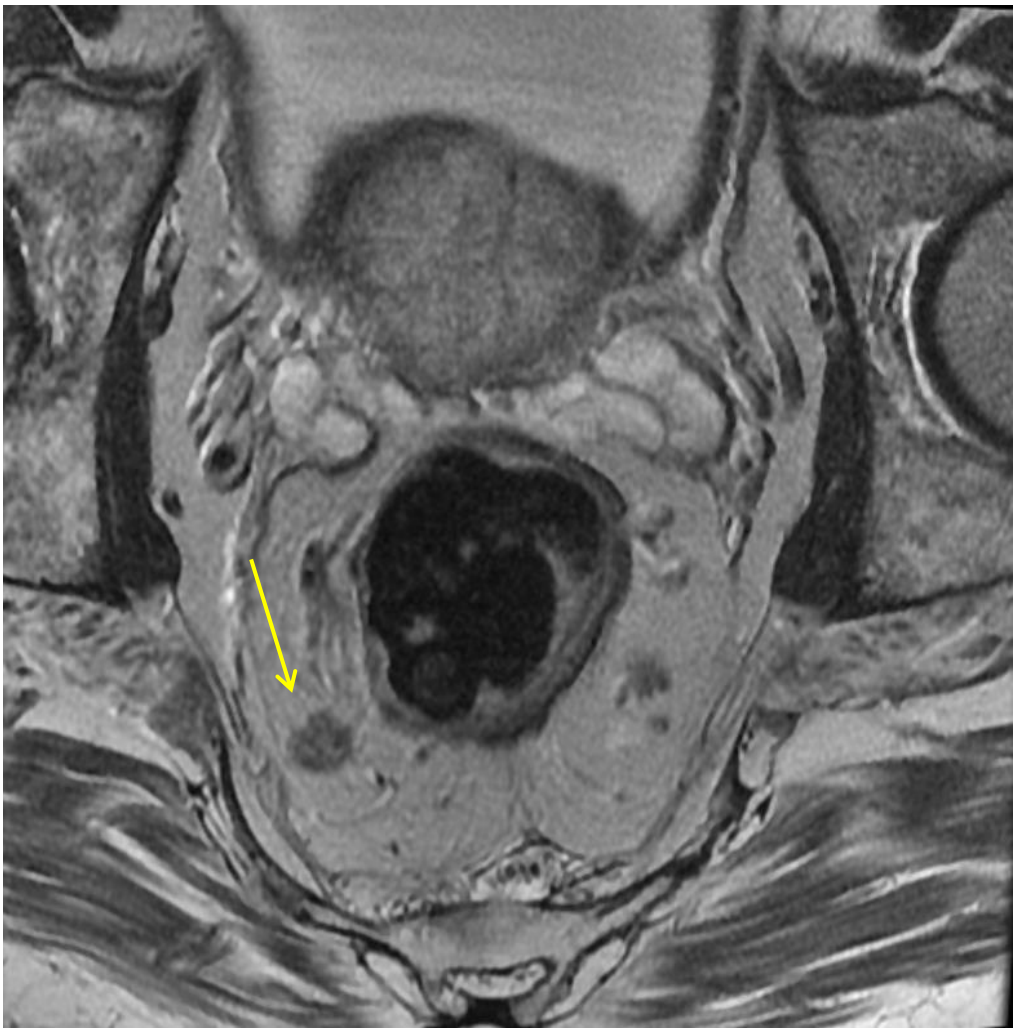


FIGURE 39: (Case 192) Coronal MRI images of a 58-year old male patient with a locally advanced lower rectal cancer staged cT3dN1b (yellow arrow points to the pathological mesorectal lymph nodes); a pathological complete response was obtained after neoadjuvant chemoradiotherapy

4.5.3. Why do we not restage patients after neoadjuvant therapy?

We found CRM invasion, a heavy lymph node burden and an unsuccessful TME as pathological risk factors of a worse survival. In this sense, accurate assessment of tumour response could be useful in order to stratify patients into low- and high-risk groups after neoadjuvant treatment, but before surgical resection and pathologic evaluation, intensified strategies could be planned.

However, as recommended by most organizations, we did not perform post-neoadjuvant therapy imaging routinely, except in patients where progression is suspected. There are several reasons for this. Unfortunately, tumour downstaging is usually overestimated by conventional MRI evaluation. EUS does not fare much better. Around 50% of patients have tumours that are relatively resistant to CRT and that change little. Larger T3/T4 tumors tend to respond by fragmentation and can be difficult to assess after CRT, whereas smaller T2/T3a tumors tend to shrink back to the endoluminal point of origin. Individual lymph node size also is a poor predictor of nodal metastases following CRT [199] although there is a high negative predictive value if previously imaged involved nodes return to normal.

Lastly, theoretically, a good clinical response could offer the opportunity to change the original plan for surgery, and to perform a less mutilating resection if an adjacent organ was originally involved or facilitate sphincter-sparing surgery in distal tumours. On the real world, however, there is very little evidence to support the view that preoperative CRT increases the chance of a sphincter-preserving resection [203]. In the majority of patients with a mid and upper rectal cancer, an anterior resection is feasible without tumour shrinkage. Very low tumours less than 4 cm from the anal verge usually require an abdomino-perineal excision. Therefore, it is only in a very small group of patients whose distal tumour extent is 4–6 cm from the anal verge where preoperative CRT may play a role in achieving a sphincter-preserving procedure

There are some studies in this regard. The MERCURY group assessed a modified Mandard grading system of tumour response and proved it to be a reliable tool for assessing tumour response in rectal cancer with MRI [204]. This grading scale is based on qualitative assessment of intermediate signal vs low signal (the latter considered as fibrosis and the former as residual disease) within the treated tumour. MR TRG 1–2 can be described as low signal intensity scar or low density fibrosis with no evident macroscopic intermediate signal intensity within it, mrTRG3 dominant fibrosis outgrowing the tumour mass and mrTRG 4–5 predominantly intermediate signal intensity with minimal or no signs of fibrosis. MERCURY experience showed that patients with complete and near complete response (mrTRG 1–3) have better prognosis, disease-free and overall survival compared to poor responders [205]. Although interesting findings, what should we do these findings? As we will see later, fibrosis after neoadjuvant treatment is not a uniform phenomenon and is not always synonymous of response. Pathological stage is probably a more important prognostic factor than TRG. Lymph node invasion remains difficult to identify, even more so after neoadjuvant radiotherapy.

In this sense, prospective trials should be done in order to assess of tumour response in order in order to stratify patients into low- and high-risk groups after neoadjuvant treatment, but before surgical resection and pathologic evaluation, intensified strategies could be planned

.

Practical aspects of radiological staging:

1. The use of a blanket-approach of treating all locally advanced rectal cancers with LCRCT, as we used, lowers somewhat the importance of a precise primary tumour staging, although we know there is an inherent higher risk of over- and under-treating patients. The importance of baseline prognostic factors for local relapse and distant metastases for selecting patients for risk-adapted approaches also diminishes with this approach.
2. Broadly speaking. MRI and EUS show a similar sensitivity and specificity with respect to cT staging; EUS is particulary useful for the staging of early tumours, such as T1-T2. However, a limited view field, poor assessment of the CRM and the difficulty in staging stenotic tumours are disadvantages with EUS, with a tendency to understage tumours. In our series, when both tests were performed, EUS understaged in comparison to MRI, especially in cN disease, upper rectal cancers and stenotic tumours.
3. MRI is especially preferred in locally advanced rectal cancer by its assessment of cT and invasion of the mesorectal fascia and other prognostic factors, such as EMVI, lateral lymph pelvic nodes or tumour deposits. Any risk-adapted approach should include a high-quality MRI, as the mesorectal rectal status is the most important factor in determining the need of downstaging and of neoadjuvant (chemo)radiotherapy.
4. Clinical N staging remains a problem, as MRI, and even more so EUS, has poor sensitivity and specificity for this indication. Lymph node size is a poor distinguishing factor. Other features such as irregular borders and a heterogeneous signal can help, although results are still far from satisfactory.
5. Despite the difficulties in cN staging, the presence of cN positive disease, mesorectal fascia invasion, extramural venous invasion, lower rectal tumours and elevated CEA and CA 19.9 levels predicted a higher risk of distant metastases. These are poor-prognosis patients and they would be prime candidates to any neoadjuvant full-dose chemotherapy approach
6. We found that there was an increased risk of local relapse in poorly differentiated tumours and bulky tumours; perhaps more importantly, as in other studies, we did not find a higher risk with cN positive disease, especially in N1 tumours. This may reflect the difficulties in staging lymph node disease with all imaging modalities but also that a successful TME will probably remove satisfactorily all pathological nodes.
7. We did not use restaging procedures after neoadjuvant therapy. Their use, although attractive, is misleading in many cases, as MRI tends to over-estimate downstaging and there is no evidence that surgeons will change their intended original approach with these results. EUS fares even worse. Radiological TRG, such as those proposed by the MERCURY group, suffer from the same problems as histological TRG; they could probably be useful in patients complete or near-complete regression, but not in patients with lesser degrees of regression.

4.6. Why did our older patients not benefit from our multimodality approach?

On our series, age was the most important clinical factor in predicting worse OS and DFS after neoadjuvant LCRCT (TABLE 13). Patients older than 70 years fared poorly in almost all aspects of the multimodality treatment. We found that elderly patients had a poorer compliance to overall treatment, with more than half of patients receiving a radiotherapy dose less than 45 Gy, with a borderline statistically significant increase of grade 3-4 toxicity and of unexpected cardiovascular and surgical events, compared to their younger counterparts. The rate of abdominoperineal resections was higher in elderly patients while the poor compliance to the neoadjuvant treatment was linked to a lower rate of complete or near complete tumour regressions and a higher risk of local relapse. The compliance of adjuvant treatment was particularly poor, with less than a quarter of elderly patients receiving the full intended dose, compared to more than half of younger patients. Despite these results, there was no evidence of differences in classical pathological risk factors. More strikingly, there were even hints of less aggressiveness in these older patients' tumours, with less cN-positive staging. How can we explain these differing conclusions? The most plausible explanation is that LCRCT is probably not the best approach in elderly and/or frail patients, and less aggressive multimodality treatments should be considered.

Other studies support this view. Recent analyses of the Dutch total mesorectal excision (TME) study and two large population-based registries in the Netherlands showed that, unlike younger patients, patients more than 75 years of age did not experience gains in overall survival after the introduction of preoperative radiotherapy and TME surgery [207]. In addition, analyses from the ACCENT database and MOSAIC trial failed to show a benefit to adjuvant combination chemotherapy in elderly patients [130, 208]. This lack of benefit seen in elderly patients compared with younger patients may partly be due to high rates of treatment deviation. This poorer tolerance is essentially due to non-hematological side effects of various origins reflecting the heterogeneity among older patients in terms of physiology and frailty. Our study, like others, provides useful insight into how older patients tolerate therapy, especially considering that 30% of 40% of rectal cancer cases occur in patients 75 years and older.

There are also population-based studies that indicate a high rate of deviation from a full course of combined modality therapy [209-210]. A Surveillance, Epidemiology, and End Results (SEER)–Medicare study of patients more than 65 years of age who were receiving postoperative therapy for rectal cancer showed that whereas 97% of Stage III rectal cancer patients completed radiation therapy, only 68.2% completed chemotherapy [209]. Among stage II cancer patients, 91.5% completed radiation therapy but only 49.8% completed chemotherapy. Unfortunately, population-based studies are not able to identify why doctors choose to discontinue adjuvant treatment for elderly patients, or why elderly patients decline further treatment. In this study, the most commonly cited reason for early discontinuation of adjuvant chemotherapy was the patient's performance status. In effect, that was the main reason for giving no adjuvant chemotherapy in our patients. Another poorly recognized factor is that even low-grade toxicities can lead to treatment discontinuation in elderly patients, with a lower threshold than in younger patients [211].

The two previously mentioned SEER–Medicare studies [209-210] showed that patients who completed adjuvant chemoradiotherapy had improved cancer-specific survival compared with those who do not, supporting the efforts of oncologists to enable patients to complete a full course of therapy. Yet such studies are limited because of selection bias and other potential confounders of the relationship between age and treatment completion, such as comorbidity. A Canadian study also showed that elderly patients with stage III colon cancer frequently received either no adjuvant chemotherapy or only capecitabine monotherapy

because of advanced age and comorbidities., although the effect of adjuvant chemotherapy on survival was similar across age groups, with comparable side effects and rates of treatment modifications [212]. However, in another Dutch registry study, the combination of capecitabine and oxaliplatin was associated with significantly more grade 3-4 toxicities than capecitabine monotherapy, which had a pronounced impact on the cumulative dosage received and completion of all planned cycles [213]

Does that mean that elderly patients should not be offered multimodality treatment?. Probably not. Most experts agree that chronological age itself is not sufficient grounds for withholding cancer treatment [214], as it is not possible to judge whether a patient is fit for radical rectal cancer treatment merely by looking at their date of birth. Unfortunately, however, multiple studies have demonstrated that treatment decisions in elderly cancer with colorectal cancer patients are still largely based on age [215-218]. Tailoring of care is needed, and for this reason, some form of geriatric evaluation is increasingly being incorporated in oncologic care [219-220]. A geriatric evaluation can help identify previously unrecognized health issues that have been demonstrated to be associated with prognosis and treatment-related complications and can provide guidance in balancing the risks and benefits of treatment. [219]. Such studies should not only incorporate a geriatric evaluation but also those outcome measures most relevant to older patients in their treatment decisions, such as care dependence and quality of life.

TABLE 49 shows the few trials that have evaluated specifically the role of LCRCT or SCRT in elderly patients with locally advanced rectal cancer; most used some kind of geriatric or comorbidity grading of patients. Although there is wide variability between all these studies and the numbers are relatively small, all the trials seem to agree with our findings. Compliance with the multimodality treatment was poor. Patients with comorbidities or poor performance status fared worse, as could be expected, secondary to higher acute toxicities. There were no clear evidences that, if the treatment was given accordingly to plan, the efficacy results were worse than those in younger patients. Surgical complications were not higher, but were more serious and took longer to resolve than in younger patients. Of all these studies, the study of the ACCORD12 phase III trial is probable the most interesting, as it showed, that in the context of a well-defined phase III trial, elderly patients (defined as patients older than 70 years), although there were no differences in efficacy endpoints, there was a higher grade 3-4 toxicity and a statistically significant decrease in the number of surgical resections.

Author	Setting and time period	Age	Geriatric scale used	Comparison	LR	G3-4 toxicity	Toxic deaths	Survival endpoints
Maas *et al* [221]	Netherlands Public registry 2002-2004	≥ 75 yrs	Severe comorbidity patients	Only surgery (296) vs SCRT-surgery (342)	2% vs 6%*	42% vs 58% * (postoperative) 10% vs 16%* (infections)	Increased early deaths in "severe comorbidity" patients	Worse OS if postop complications
Cai *et al* [222]	China Single centre	≥ 70 yrs	Charlson comorbidity index	(Chemo)-LCRT and surgery (126)	NS	Not influenced by Charlson or comorbidities	NS	3-year OS of 48.1% (26.4% if ≥4 Charlson*)
Margalit et al [223]	United States Single centre 2002-2007	≥ 75 yrs	Mild, moderate, severe comorbiditie s	Pre or postop LCRTCT and surgery (36)	NS	39% did not finish treatment 17% completed treatment without deviation Worse compliance if severe comorbidities		NS
De Felice *et al* [224]	Italy Single centre	≥ 70 yrs	Adult comorbidity evaluation-27 score	LCRTC and surgery (20)	NS	15% (diarrhoea) Comorbidity index was related to higher severe acute toxicity		NS
Tougeron *et al* [225]	France Two centres	≥ 70 yrs	None	LCRTC and surgery (125)	NS	15% Postoperative morbidity of 16%	2/125	2-year OS of 84%
François *et al* [21, 226]	Not preplanned study of the ACCORD12 phase III trial	≥ 70 yrs	None	LCRTC and surgery in ≥ 70 (142) and < 70 (442)	NS	25.6% vs 15.8* Less stoma closure: 33.2% vs 22.8%* Less surgical resection: 95.8% vs. 99.0%*		NS No differences in pCR or R0 resection rate

* Statistically significant
LR: local relapse; NS: Not significant

TABLE 52: Selected trials that have evaluated specifically the role of LCRCT or SCR in elderly patients with locally advanced rectal cancer

With all these results in mind, although older patients should benefit from some kind of multimodality therapy, perhaps standard LCRCT may not be the most appropriate approach and SCRT would be preferable. In the Dutch TME-study, patients aged 75 years and older showed a better response in the study arm when compared to younger patients with SCRT. Younger patients have a significantly lower local recurrence rate of 5.2% after preoperative radiotherapy versus 11% for patients without preoperative radiotherapy. However, overall survival at 5 years, distant metastases free survival and cancer-free survival were not improved. In the elderly, however, apart from the local recurrence rate, DFS and cancer-specific survival were improved. All this suggests that the biological behavior of rectal cancer in the elderly in response to radiotherapy is better than in younger patients [227]. No significant differences with respect to postoperative morbidity and mortality were found between neoadjuvant RT and surgery only. Therefore, neoadjuvant RT and surgery may be the optimal treatment strategy in elderly patients, especially in patients medically fit for the operation. In effect, this was the main conclusion of the ACCORD12 trial in elderly patients. [226]. In very frail patients, new radiotherapy approaches, such as image-guided radiotherapy (IMRT), may be used to lower acute toxicity and to improve their tolerance to radiation and allow them to have curative resection despite the associated comorbidity. Also, in cases where downstaging is needed, we know that there are promising results with SCRT and a longer interval to allow downstaging in patients not fit for LCRCT [71-74]. The recent results of the Stockholm III and the Polish Trial show that this can be a feasible approach [87, 90]

Practical aspects of age as a prognostic factor:

1. Our elderly patients fared poorly in almost all aspects of the multimodality treatment. This was especially evident in an increased risk of serious unexpected (usually cardiovascular or surgical) complications, and a lower compliance to neoadjuvant radiotherapy and, especially, to adjuvant chemotherapy.
2. Disease-free and overall survival were worse in the elderly, even though we did not find any signs of higher aggressiveness in these tumours, compared to their younger counterparts. There is also no evidence to suggest that older patients have poor responses to (chemo)radiotherapy. In particular, there seems to be a greater radiosensitivity in these patients.
3. Other secondary endponts, such as stoma closure or the rate of sphincter-conserving surgery, were also worse for the older patients.
4. Chronological age, however, should not be the only determining factor un the decision of the type of multimodality treatment offered. Evaluation of comobirbidites, especially cardiovascular, and more formal geriatric assessments would be helpful in this regard.
5. LCRCT perhaps is not the best option for older patients, especially in frail or with other comorbidities. All these results warrant the development of specific therapeutic strategies more optimal for patients above 70–75 years, including fit patients over 80 years. SCRT followed by delayed surgery to decrease toxicities and permit tumor downsizing is a promising approach. Developing less toxic treatments should allow a higher percentage of patients to undergo surgery.

4.7. Can TME-surgery be improved? The problem of low rectal tumous and of lateral pelvic lymph nodes

The analysis of our surgical series shows, in a long period of 15 years, an improvement in the surgical expertise and evidence of a learning curve; the rate of abdominoperineal resections decreased from almost half of patients in the first period between 1999 and 2004 to just 20% in the period of 2010-2014; the laparoscopic approach increased significantly and the rates of unsuccessful TME also decreased. 30-days mortality after surgery was consistently low. A total mesorectal excision was technically feasible in almost 90% of patients, while an R0 resection was described by the surgeon in more than 90% of patients. These results were obtained, we must remember, in a poor prognosis-group of patients, with invasion of the mesorectal fascia in 50% of the 144 patients where it was evaluable (unfortunately, that was not possible in the initial group of patients staged only by EUS). In the pathological analysis, there was a 70% downstaging rate, although there was still involvement of the circumferential resection margin in 21% of patients.

We also observed a progressive increase in the use of provisional diversion loop ileostomies after LCRCT as it became clearer the higher risk of anastomotic leakages, especially in ultra-low anastomosis, where there are reports of an incidence ranging from 10% to 28%. A recent trial and meta-analysis and systematic review of the literature in 2008 both found that a diverting stoma is associated with fewer clinical leaks and recommended a diverting stoma in all low rectal anastomoses [228-229] Similar findings were reported from pooled data from major multicentre European trials. These results, in general, seem satisfactory and in line with other series [230].

However, as we have mentioned, this blanket-approach of treating all patients with neoadjuvant LCRCT probably under- and overtreats a group of patients. We also know that neoadjuvant (chemo)radiotherapy lowers the local relapse rate but does not improve survival and, more importantly, limits the possibility of giving the full-intended dose of adjuvant chemotherapy and can have long-term side effects. On the other hand, we also know from the MRC07 trial of SCRT, that all patients, even those with low risk tumours, benefit from radiotherapy. We also know that these possible long-term side effects will probably diminish with the continuous improvements in radiotherapy techniques (smaller fields, use of IMRT, better delimitation of the tumour with MRI etc). Finally, as we have seen, despite the difficulties in staging, the risk factors of local relapse and distant metastases are overlapping but not entirely the same.

How can we balance the proven benefits of radiotherapy in the risk of local relapse with the most certain overtreatment if we treat all patients with neoadjuvant (chemo)radiotherapy?

In centres with surgical expertise in rectal cancer surgery and where high-quality MRI can be performed, in a multidisciplinary setting, we can probably select patients with a very low risk of local relapse, who could be treated with surgery, with or without SCRT. Mid rectal tumours with little penetration into the meso-rectal fat (the MERCURY group defined a 5 mm cut-off point, while others have defined a 4 mm cut-off point) and, perhaps, more importantly, with no or minimal clinical lymph node disease (N1a or N1b) and with a clear MRF, are probably the best candidates for this approach, which we have adopted in the last few years.

However, the main problem, in our opinion, are the low rectal tumours. Even when TME principles are applied, for low tumours, the local relapse rates are higher for tumors treated with an abdominoperineal excision compared with a sphincter-saving procedure, such a lower anterior resection [4]. Originally, this different risk

was attributed to the difficulties in staging and in possible differences in tumour biology and patterns of spread: for example, low rectal cancers 3-4 centimetres from the margin are at a higher risk of positive CRM involvement, especially those located anteriorly [231]. It is also more difficult to predict levator involvement even with high-quality MRI and there is a 15% risk of lateral pelvic lymph nodes. However, apart from these well known factors, there is evidence from pathology audits that inadequate surgery may also play a role [232-233].

A locally advanced rectal cancer located in the vicinity of the anorectal ring likely involves the levator muscle or external anal sphincter. Extending the dissection along the mesorectal fascia to the level of the anorectal ring separates the rectal wall from the levators and risks exposing the tumour closer to the CRM [233]. Pathologic studies of abdomino-perineal resection specimens have found a smaller volume of tissue around the muscularis propria of the rectum and a higher rate of positive CRMs compared with specimens from low anterior resections [234]. The Dutch TME-trial found higher positive CRMs and more perforations in specimens from patients with low rectal cancer [232]. In their study, patients undergoing an abdominoperineal excision had a higher risk of a positive CRM, independent of tumor height as well as higher local relapse rates.

In order to improve these results, some authors have proposed a more radical abdominoperineal excision, in which the dissection along the mesorectal fascia ends at the upper level of the levators, and the levator muscles are left in their natural position, attached to the distal rectum. This procedure has been called cylindrical or extralevator abdominoperineal excision (ELAPE), distinguishing it from the standard abdominoperineal excision (SAPE) in which the levators are not removed with the specimen [233, 235]. The results of a single institution randomized trial [236] and a recent meta-analysis of several case series indicate that ELAPE is associated with lower rates of intraoperative perforation, lower rates of positive CRM and local relapse, and similar complication rates compared with SAPE [237]. On the other hand, other population-based tumor registry analyses have not demonstrated the benefit of ELAPE compared with SAPE [237-238].

Introduction of ELAPE principles has raised awareness about the importance of adequate preoperative imaging for surgical planning in patients with locally advanced rectal tumours who would require an abdominoperineal excision. In the future, we might see a more selective approach in patients with low rectal tumours, especially if an abdominoperineal excision is not required, but at the moment, due to the surgical difficulties and the higher risk of local relapse, these patients are probably best served with some type of neoadjuvant therapy at the moment; in our centre and in most others, the majority of these patients are still treated with standard LCRCT and TME-surgery.

We observed in our series a 9.7% rate of lateral pelvic lymph nodes (in those patients staged with MRI, FIGURE 40). There is controversy as to the management and relevance of these lateral pelvic side-wall nodes. In Japan the presence of these lymph nodes mandates their surgical resection via lateral pelvic lymphadenectomy, a more aggressive surgical approach that carries an increase in morbidity and long-term quality of life complications [239]. In a retrospective review of 237 patients with T3-4 low rectal cancer who underwent R0 resection, including lateral pelvic lymphadenectomy, the incidence of lateral nodal involvement increased with decreasing tumour height, with an incidence of 45% in those tumours less than two centimetres away from the margin. Other factors predicting an increased risk of involved lateral nodes were involved mesorectal nodes, female patients, advanced T stage, poor tumour differentiation, lymphovascular invasion and low rectal cancer [240]. However, in Europe, these patients are still usually treated with LCRCT and TME-surgery. There is evidence that this approach may be as effective as nodal removal, with less morbidity. Of note, in our

series, none of the patients with involved lateral pelvic lymph nodes at diagnosis had ypN disease in the surgical specimen, casting more doubts in the significance of these clinically staged lymph nodes.

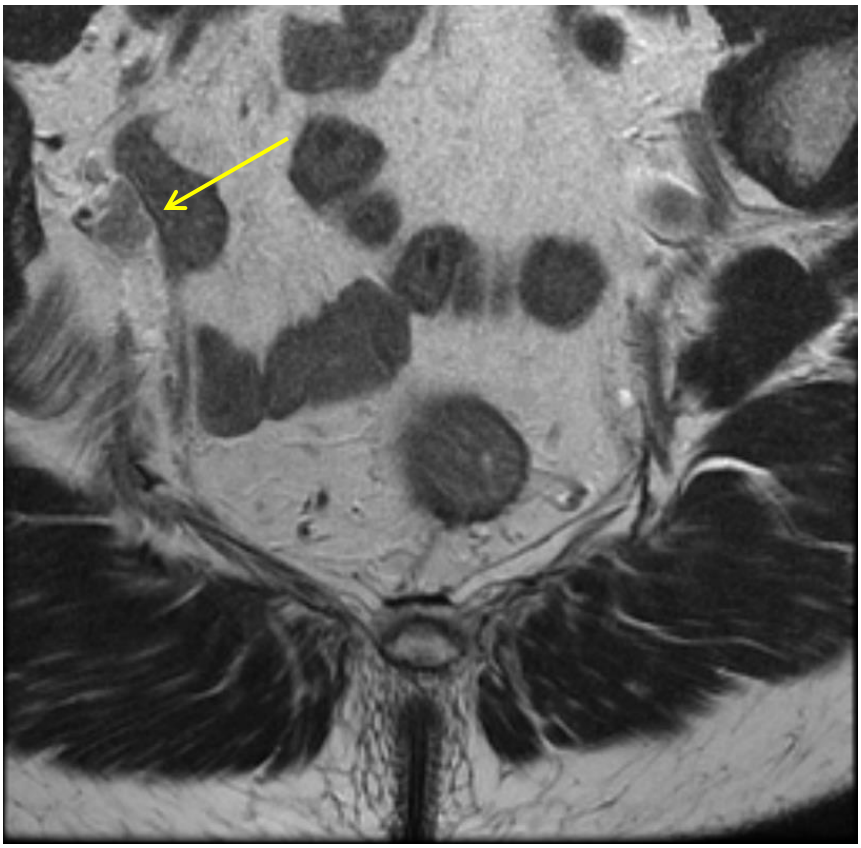


FIGURE 40a: (Case 170) Coronal MRI images of a 52-year old male patient with a locally advanced lower rectal cancer staged cT3dN2b with positive lateral pelvic lymph nodes (yellow arrow points to these pathological lymph nodes); a nearly-complete pathological response was obtained after neoadjuvant chemoradiotherapy

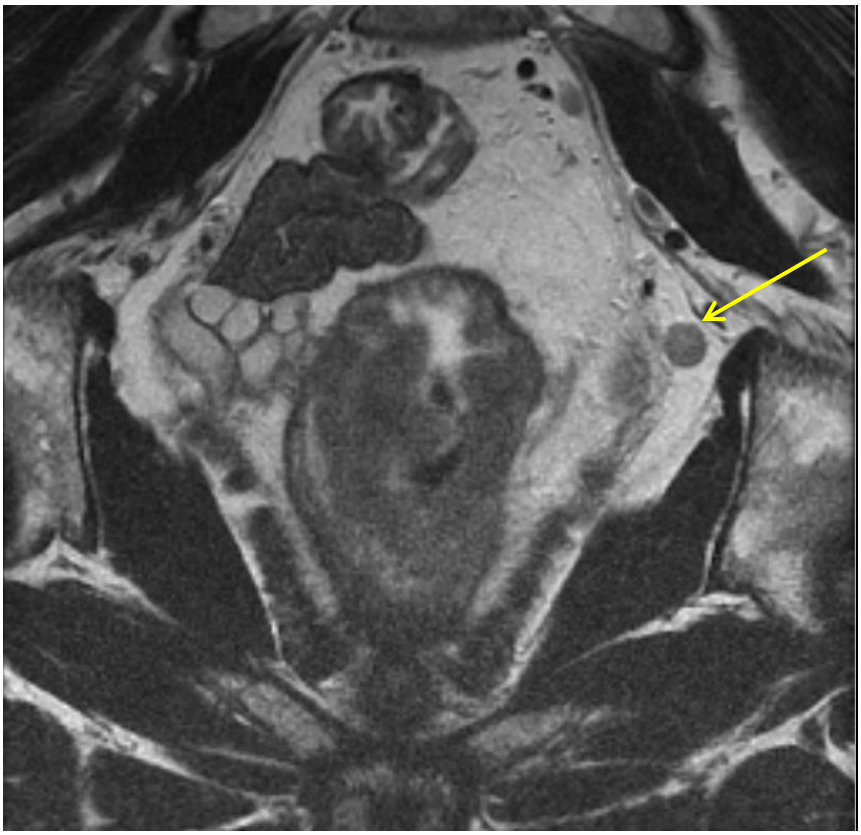


FIGURE 40b: (Case 170) Coronal MRI images of a 52-year old male patient with a locally advanced lower rectal cancer staged cT3dN2b with positive lateral pelvic lymph nodes (yellow arrow points to these pathological lymph nodes); a nearly-complete pathological response was obtained after neoadjuvant chemoradiotherapy

Practical aspects of surgery as part of the multimodality approach

1. A blanket-approach of neoadjuvant (chemo)radiotherapy to all patients with locally advanced rectal lowers the local relapse rate but does not improve survival and, more importantly, limits the possibility of giving the full-intended dose of adjuvant chemotherapy and can have long-term side effects. On the other hand, all patients, even those with low risk tumours, benefit from radiotherapy and we can expect all long-term side effects will probably diminish with the continuous improvements in radiotherapy techniques.
2. Mid rectal tumours with little penetration into the meso-rectal fat and with no or minimal clinical lymph node disease (N1a or N1b) and with a clear MRF, are probably the best candidates for a surgery-first approach.
3. Low rectal tumours, especially if treated with abdominoperineal resection, have a higher risk of local relapse. Risk factors include anterior rectal location, levator involvement and the difficulty in obtaining a successful TME. These patients are probably best served with some type of neoadjuvant therapy for the moment. Improvements in surgical techniques such as extra-levator abdominoperineal resection should also help us move forward.
4. The significance of lateral pelvic lymph nodes in MRI is unclear. Although a lateral pelvic lymphadenectomy could be performed, as is done in the East, these patients do as well with LCRCT and TME-surgery, with less morbidity and long-term complications.

4.8. Pathological prognostic factors after LCRCT. Can we move forward from the TNM clasification?

The 1999 consensus statement of the College of American Pathologists indicated that pathologic TNM stage, extramural venous invasion, and preoperative CEA level were the most important prognostic factors in colorectal cancer [242]. These remain the most widely used factors in making treatment decisions. Important recent additions that pertain to rectal carcinomas are the quality of the mesorectal excision procedure and the status of the CRM. Other important factors include tumour grade, perineural invasion, lymphatic embolization, other types of carcinoma histologies (such as mucinous tumours), Finally, we must also take into account other factors secondary to the use of neoadjuvant treatment, namely downstaging, tumour regression grade (TRG) and the rate of pCR.

In line with this statement, in our series, pathological factors that predicted a worse DFS and OS included most of these factors, such as an unsatisfactory mesorectum, lymph node invasion, a higher lymph node burden, no overall, T-stage or N-stage downstaging, circumferential margin involvement, vascular or perineural invasion, minimal or moderate regression and a non-mucinous histology. Improvement in only DFS were seen with lower T stages, well differentiated tumours and a pathologic complete or or nearly-complete response (ypT01). Lymphatic embolization and an involved distal margin were not significant factors. On the multivariate analysis, however, of these factors, only a positive CRM, a heavy pathological lymph burden and perineural invasion retained their significance (alongside older age as a clinical factors).

4.8.1 The circumferential resection margin remains the most important prognostic factor

Even after neoadjuvant treatment, the CRM status trumps all other prognostic factors (FIGURE 41 and 42). As we have seen repeatedly, awareness of the importance of this factor has altered both the management of this disease and the pathologic assessment of rectal cancer resection specimens. In 1986, Quirke first described the importance of lateral spread and the role of involvement of the radial margin in predicting recurrence of rectal cancer [27]. After slicing 52 unopened rectal resection specimens serially and analyzing whole-mount sections, positive lateral resection margins were found in 14 (27%), and recurrent tumors developed in 12 of these 14 patients [27]. As we know, these results were confirmed in larger studies in which positive radial margins predicted not only local recurrence but survival [26]. These studies were the basis of the introduction of TME. Not only that, we have also been able to recognize that the effectiveness of TME is not simply the result of prevention of positive margins but of the removal of unrecognized tumor deposits that are often located deep within the perirectal adipose tissue [243]. Results from the Dutch TME trial showed that even when the radial margin is negative, the distance (in millimeters) from the deepest point of tumor penetration to the margin is predictive of local and distant recurrence [244] Based on these data, it is recommended that pathologists provide an exact measurement of the distance of the tumor to the deep margin in pathology reports.

We also know from the Dutch-TME study, where approximately 55% of TMEs were complete, 20% were nearly complete, and 25% were considered incomplete, that, in cases in which the CRM was negative, the TME status was predictive of tumor recurrence [4]. The MRC-07 trial did also show that the quality of the mesorectum was a prognostic factor independent of the CRM status [5,70]. However, others have not replicated these findings, and a poor-quality mesorectum or an unsatisfactory TME is probably not as important in the long-term if the CRM is free [105, 245].

The importance of the distal margin is much less important. Studies of resected specimens have shown that so long as the distal margin itself is uninvolved then the risk of recurrence is not increased, provided that adequate circumferential clearance has been achieved. It is very uncommon for rectal cancer to spread more than 1 cm below the distal palpable margin of the tumour [246]. An exception is when the tumour is poorly differentiated, when distances up to 4.5 cm have occasionally been reported [247]. As a matter of fact, poorly differentiated tumours in our series were associated with a higher risk of local relapse.

4.8.2. Pathological residual lymph node disease implies a highly aggressive phenotype

The seventh edition of the *AJCC Cancer Staging Manual* states that it is important to obtain at least 10 to 14 lymph nodes in colon and rectal cancer resection specimens that have not been subject to neoadjuvant therapy [17]. There is also evidence that patients who have more lymph nodes harvested do better than those with fewer nodes, likely because lymph nodes block tumor cell spread [248]. The ratio of involved nodes to the total number of nodes has also emerged as a potential prognostic factor, possibly more accurate than the total number of involved nodes [249-250].

However, after LCRCT, most studies have shown that fewer total lymph nodes are recovered and that only a fraction of specimens contain adequate lymph nodes after neoadjuvant CRT for rectal cancer [251-256] Nonetheless, studies have come to conflicting conclusions as to whether increased lymph node retrieval is associated with outcome after neoadjuvant LCRCT [252-259]. A recent study of of 4790 patients with stage I-III rectal cancer diagnosed from 2000 to 2007 who underwent trimodality therapy failed to demonstrate that reduced lymph node retrieval is associated with worse outcome in node negative rectal cancer [260]. What is perhaps more important from that study was the dreadful prognosis of patients with persistent lymph node disease after neoadjuvant LCRCT, especially if there is a heavy lymph node burden (ypN2). In effect, that was one of our main findings and is consistent with multiple other studies (FIGURE 42). Persistent lymph node metastases after neoadjuvant 5-FU-LCRCT reflects a more aggressive phenotype of malignant cells that have spread to the regional lymphatics and are resistant toward neoadjuvant chemoradiotherapy [261-263]. There are also studies that show that an even worse prognosis is seen in patients with a high ratio of involved nodes to the total number of nodes harvested [264]. Future studies should investigate intensification of therapy or novel strategies in this subset of patients with a particularly poor prognosis

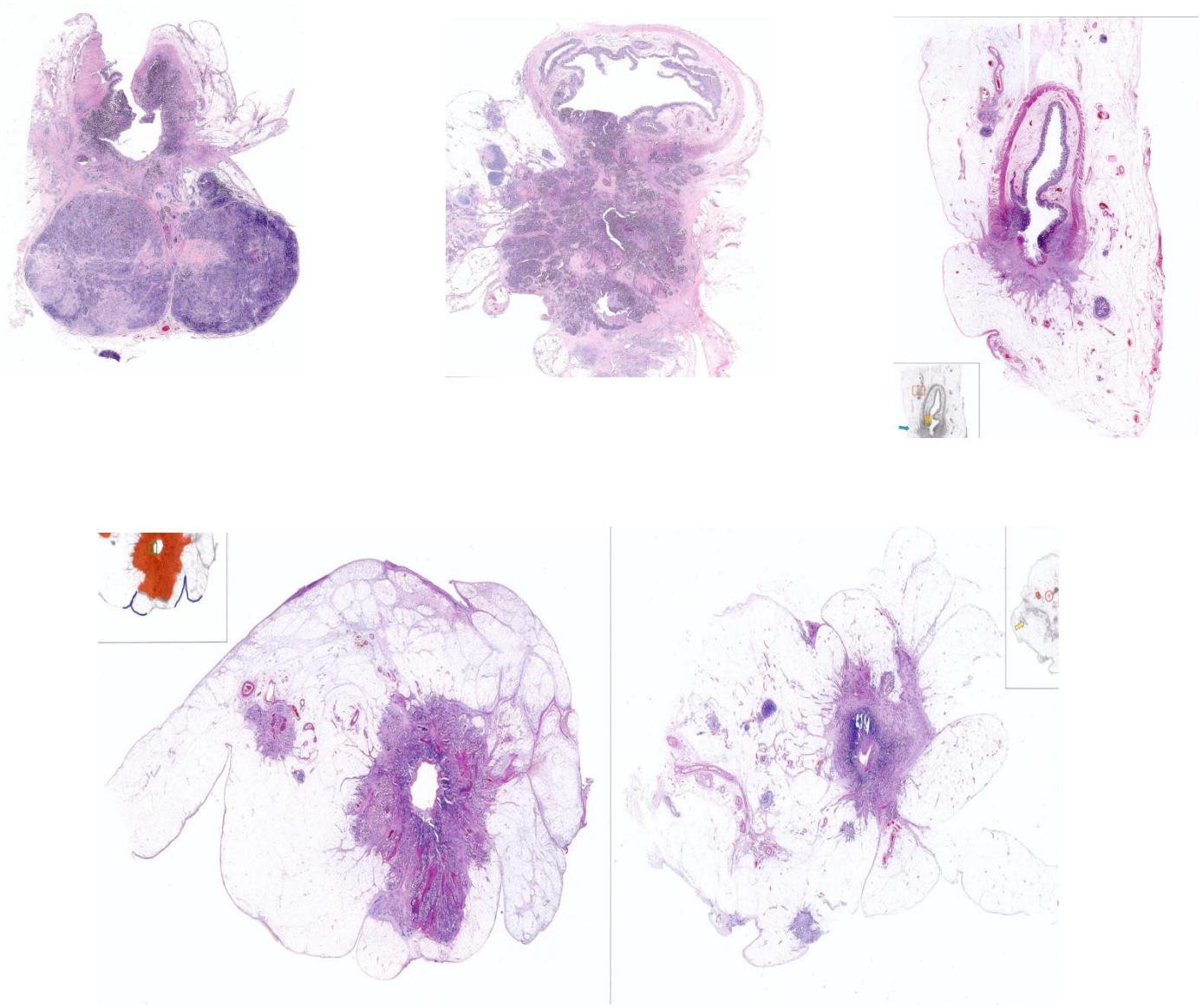


FIGURE 41: The invasion of the circumferential margin is an important predictor of local relapse, distant metastases and worse disease-free and overall survival. Several surgical specimens with this feature can be seen in this figure

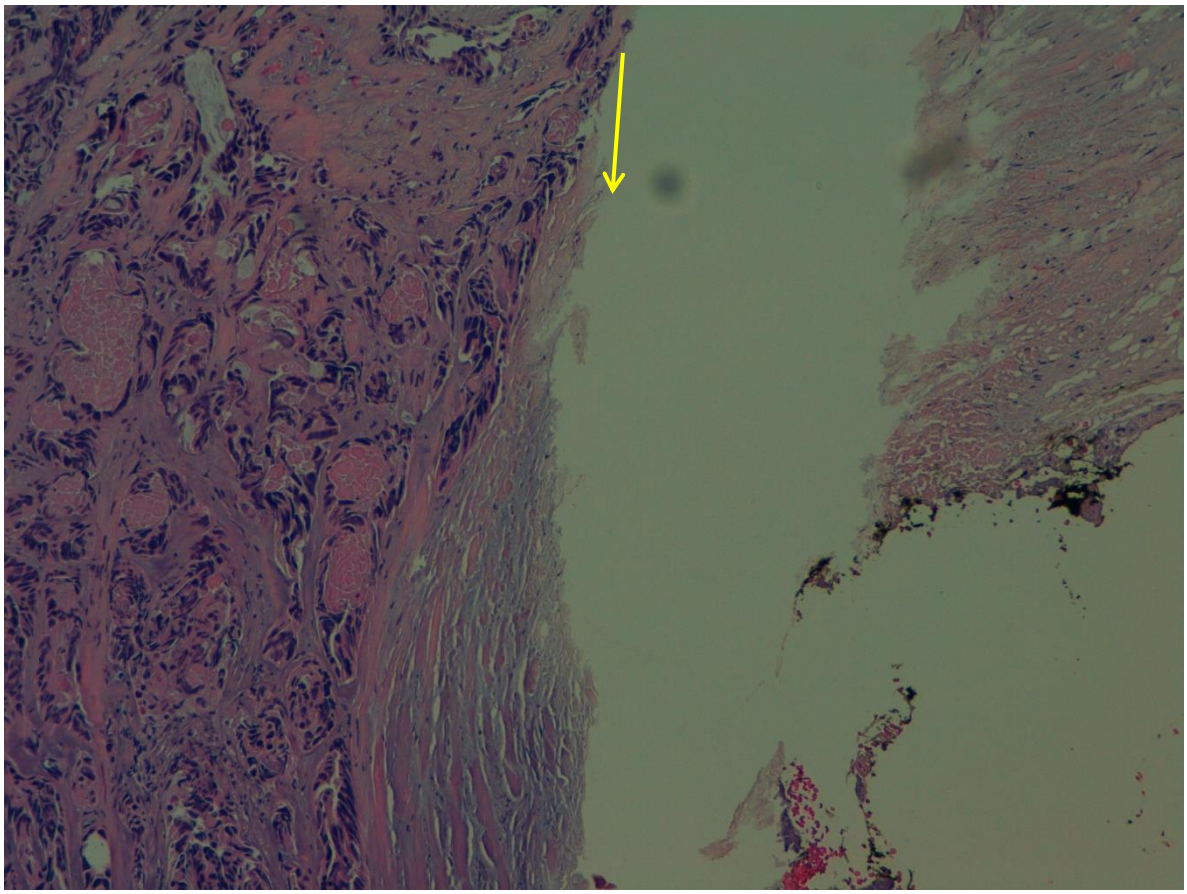


FIGURE 42 (Case 182): Minimal regression and no downstaging was seen in this 62-year old male patient with a locally advanced lower rectal cancer with invasion of the mesorectal fascia. Unfortunately, there was circumferential margin invasion in the surgical specimen (infiltration shown by the yellow arrow) and invasion of the intersphincter space. The final pathological diagnosis was ypT3bN1G2, Mandard grade 3, Wheeler grade 2.

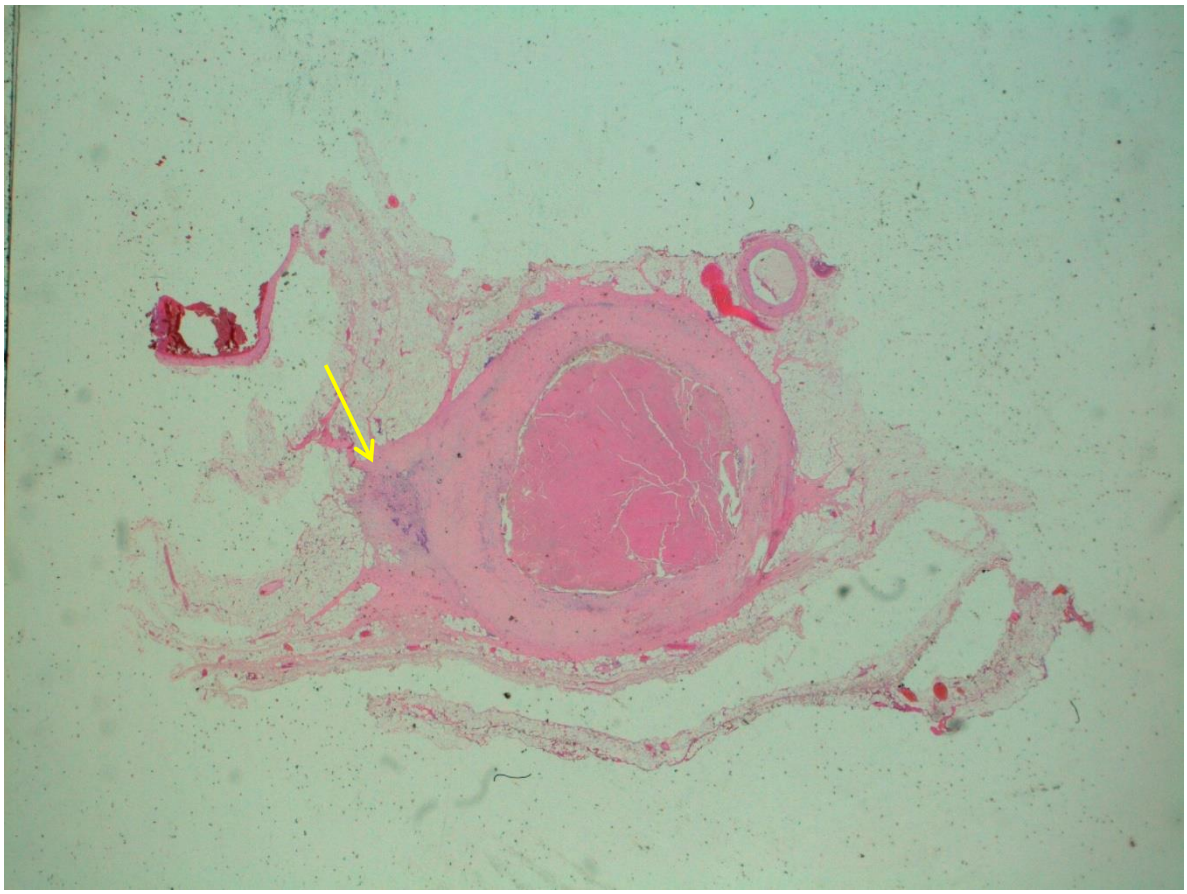


FIGURE 43 (Case 168): Three pathological lymph nodes, all with capsular rupture (yellow arrow), were found in this 51-year old male patient with a ypT3N1b after neoadjuvant treatment for a cT3Nx upper rectal tumour; the lymph nodes were not seen in the baseline MRI

4.8.3. Perineural invasion is an under-recognised but major pathological prognostic factor

Perineural invasion, defined as tumor invasion of nerve structures and spread along nerve sheaths [265] (FIGURE 44), is generally poorly reported in most series, which is unfortunate, as it is becoming clear that it is a pathological prognostic factor of major importance in colorectal cancer [35, 266-270], as in other malignancies, such as head and neck and prostate cancers.

In our series it is present in 9.6% of patients, in keeping with other series [35, 266] and was a positive factor in the multivariate analysis for local relapse, distant metastases, DFS and OS. It was also associated with a poor tumour differentiation and a higher pathological stage. Studies in other malignancies have led to similar conclusions. This prognostic value is present not only in patients treated surgically from the start but also in patients treated with neoadjuvant therapy, as our and other studies show (TABLE 53). The main drawback, unfortunately, is that perineural invasion cannot be identified with imaging tests, even with high-quality MRI.

Mechanisms of perineural invasion remain poorly understood. The significant association between perineural invasion and angioinvasion has previously been shown in rectal cancer [265] and in our case, due to the strong prognostic role of perineural invasion, vascular embolization was not significant in the multivariate analysis (FIGURE 45). The most common metastatic sites of colorectal cancer are the liver, the lung and the retroperitoneum, all richly innervated by autonomic nerve fibers. The sympathetic fibers innervating the liver share a preganglionic origin with the sympathetic nerves that innervate the colon and rectum. A study involving analysis of serial nerve sections from three pancreas cancer specimens revealed that cancer cells could be followed within the nerves from the body of the tumor, along the superior mesenteric artery to the celiac ganglia, without invasion of the surrounding tissues [265]. Metastatic colorectal cancer cells exhibit neurotropism, and on reaching, by either hematogenous or lymphatic spread, the nerve-rich retroperitoneum and/or liver, they might be able to establish a paracrine interaction with these nerve fibers that would facilitate metastatic growth.

Author	Number of patients, time period	PNI+ patients, (%)	Median DFS (PNI+ vs PNI-), months	Median OS (PNI+ vs PNI-)	Multivariate significance of PNI
Chablani *et al* [268]	110 2004-2011	14 (16%)	13.5 vs 39.8*	NR	Yes (HR 5.72)
Cienfuegos *et al* [269]	324 1992-2007	In patients with PNI or lymphovascular invasion, the prognostic role of TRG disapperared			Yes
Huang *et al* [270]	88 2007-2011	24 (27.3%)	5-year DFS: 50.7% vs 61.1%*	5-year OS: 37.4% vs 80.1%*	Yes
Dhadda *et al* [35]	158 2001-2008	28 (18%)	Not reported specifically but statistically significant		Yes (HR 2.97)

* Statistically significant

TABLE 53: Selected series that have shown a prognostic role of perineural invasion (PNI) in patients with rectal cancer treated with neoadjuvant (chemo)radiotherapy and surgery

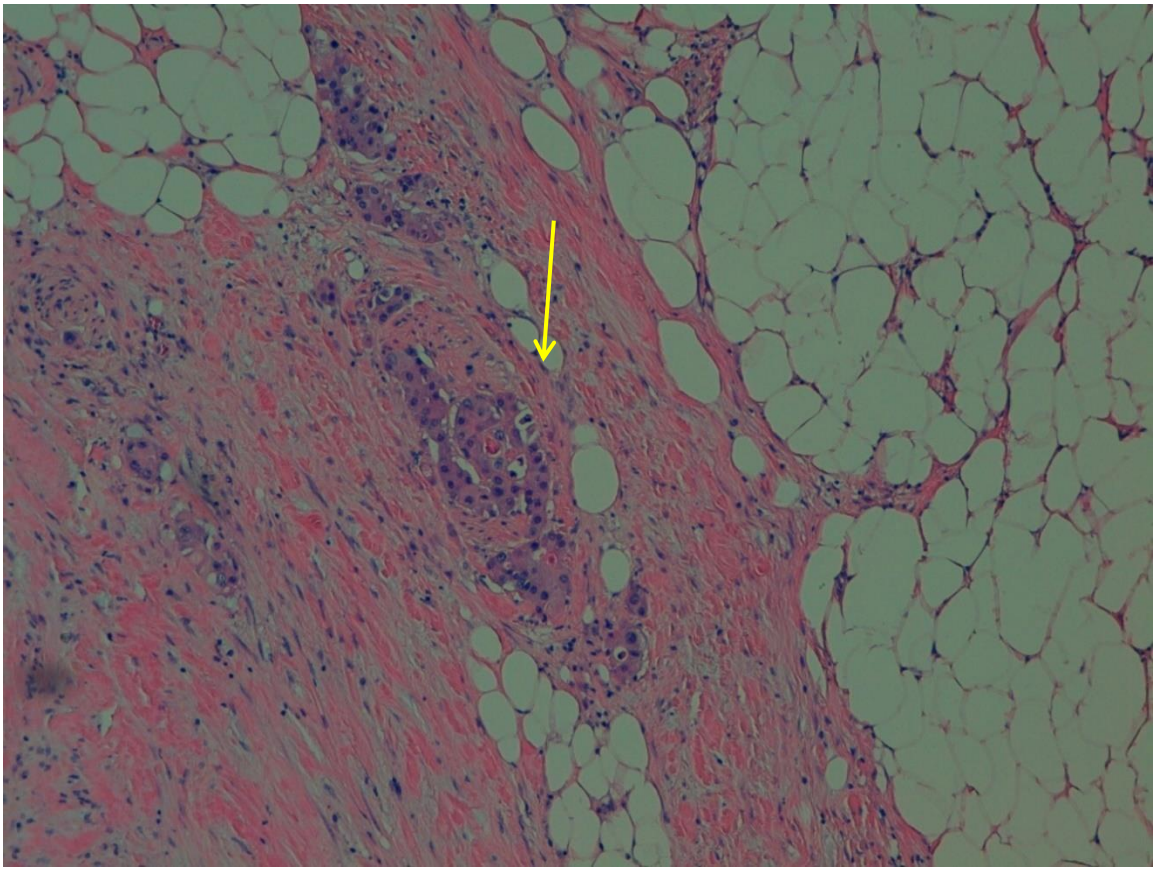


FIGURE 44 (Case 201): Perineural invasion (yellow arrows) can be seen in the surgical specimen after neoadjuvant chemoradiotherapy in this 56-year old male patient with a locally advanced rectal cancer ; the final pathological staging was ypT3dN2aG3

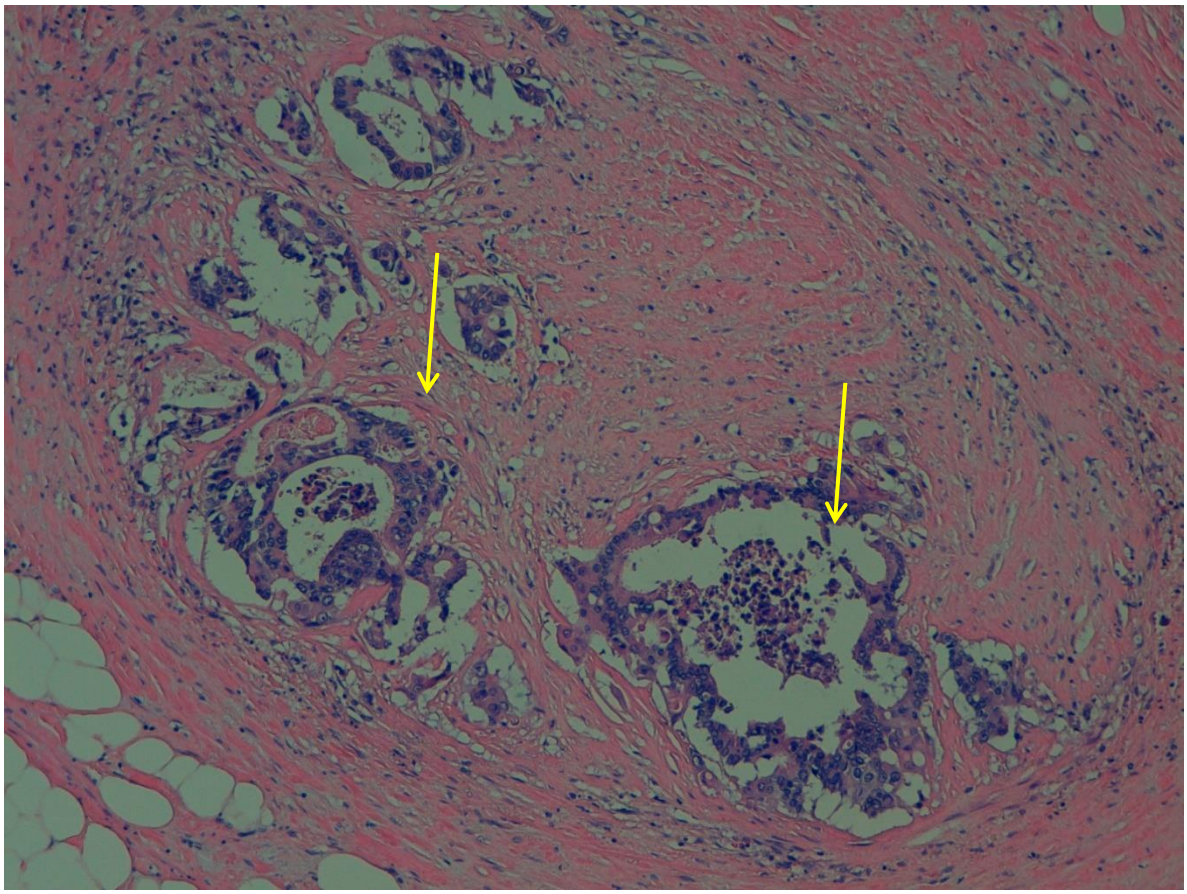


FIGURE 45 (Case 201): Vascular embolization (yellow arrows) can be seen in the surgical specimen after neoadjuvant chemoradiotherapy in the same patient of FIGURE 44; perineural invasion is frequently associated with vascular embolization

4.8.4. *Downstaging and tumour regression grade were weaker prognostic factors than we expected.*

We did not find TRG a strong prognostic factor. Although there was an improvement in local relapse, distant metastases and survival endpoints, these were modest and basically centered in those patients with complete or nearly-complete pathological responses. However, the prognostic role in cases with moderate and minimal regression were more difficult to ascertain. As we explained, due to the heterogeneity of the TRG scores used in our centre [26-31] (at our institution, the Dworak, Mandard, Rich and Wheeler scores were most frequently used), we decided to unify these scores in common groups; this was probably easier in patients with very good regressions, but subject to more errors in patients with lesser grades of regression.

Why is there such controversy with the role of TRG? TRG as a measurement of response to neoadjuvant (chemo)radiotherapy was first proposed by Mandard in 1994 for use in the assessment of pathological specimens of squamous cell carcinoma of the oesophagus following neoadjuvant chemoradiotherapy [29]. From then onwards, several TRG scales have been proposed, with different pathological criteria, although most categorize three- or four-tiered groups: patients with complete or nearly complete regression, moderate regression and minimal or no regression. The most used TRG used in rectal cancer have been shown in TABLE 3. This is unfortunate, as it has made difficult to perform cross-trial comparisons. There is also an imperfect relationship between TRG and downstaging: a tumour may have regressed little but may have been downstaged from T3 to T2, whereas a tumour showing a good response with only microscopic foci of tumour cells in the subserosa may still be staged as T3 (FIGURE 46).

Additional histological features such as mucin pools (FIGURE 47), necrosis, foamy macrophages, haemosiderin and dystrophic calcifications (FIGURE 48) may also indicate regression (or not), but they are not included in most TRG. Most TRG scores (such as the frequently used Mandard and Dworak scores) tend to assess the predominance of fibrosis over tumour cells as a major criteria of a good response (FIGURES 49, 50 and 51); however, fibrosis can be seen without previous chemoradiation and is not specific for regression, as it can be also secondary to usual tumour desmoplasia or to a response of normal tissue to chemoradiation. The true origin of fibrosis can be difficult to ascertain; some authors have suggested that the amount of tumour present is the most important factor, irrespective of the amount of fibrosis [271]. Other problems with currently used TRG scores is that they do not provide a clear indication of whether a grade is reached on the ‘worst’ section (containing the most tumour) or an average of the grades of regression observed in all slides.

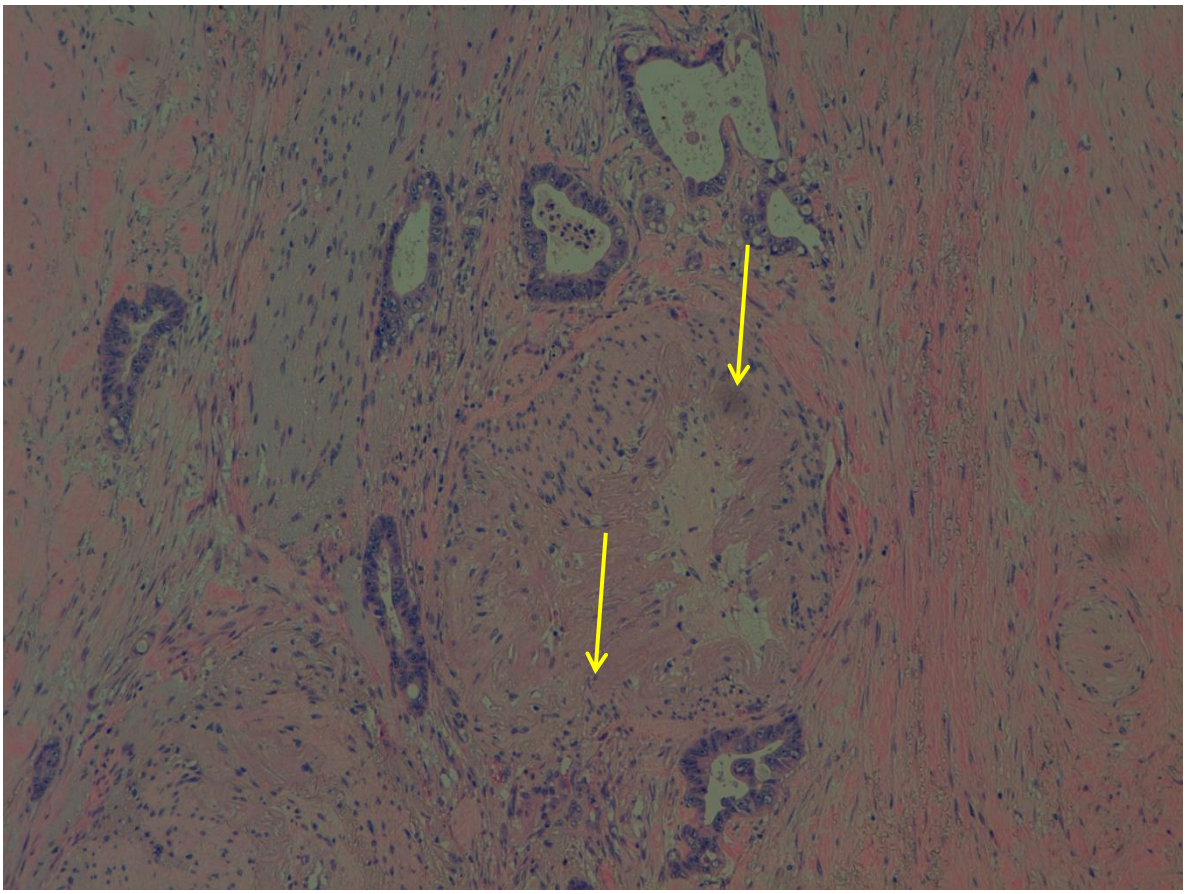


FIGURE 46: (Case 182) Although the tumour regression grade was nearly-complete (Dworak grade 3) after neoadjuvant therapy in this patient with a cT4bN1b rectal cancer, there was invasion of the seminal vesicles (yellow arrows) and the final pathological diagnosis was of a ypT4bN0 tumour. This highlights the discrepancies that can be seen between the TNM downstaging and the different tumour regression grades

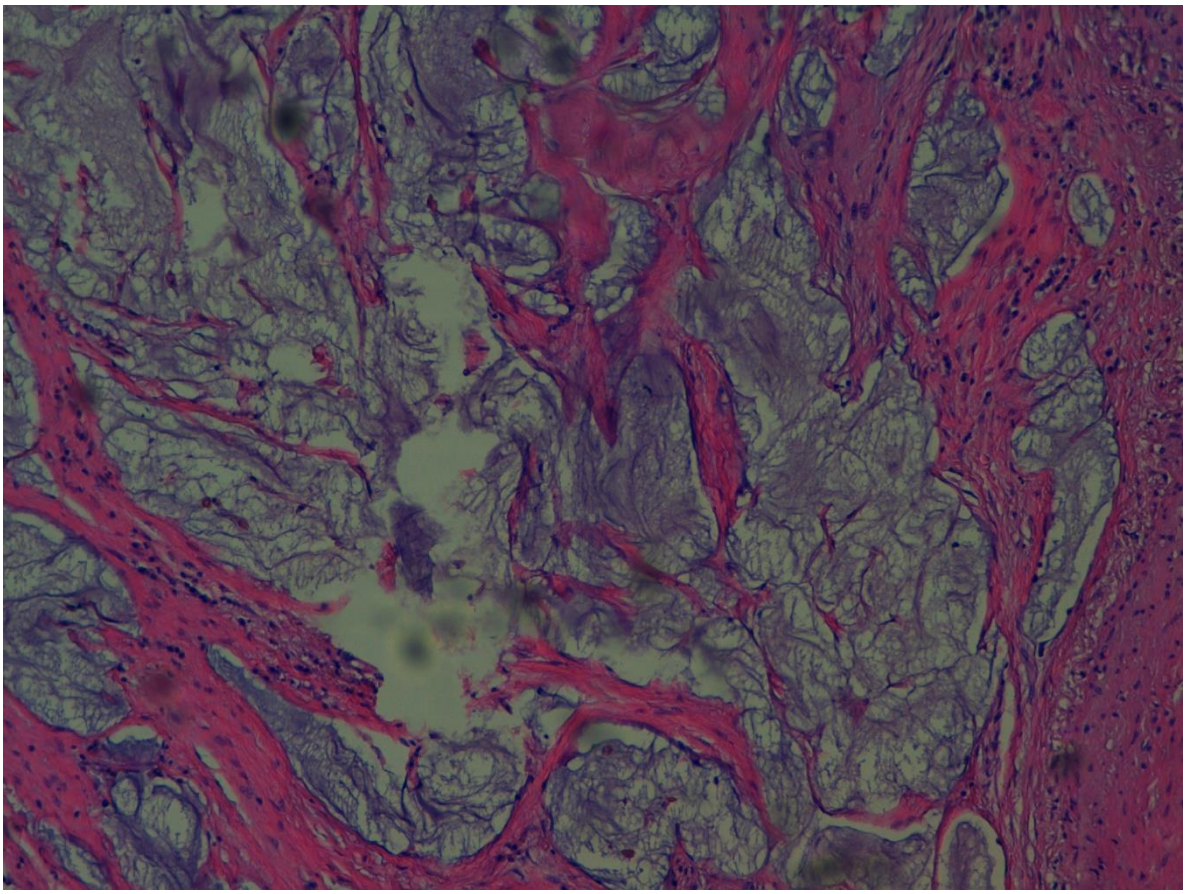


FIGURE 47: (Case 158) Only acellular mucin lakes with no viable malignant cells were seen in this 58-year old woman with a mid-rectal non-mucinous cancer staged initially as cT3aN2a. These treatment-related mucinous changes should be differentiated from mucinous tumours, that are poorly responsive to radiochemotherapy

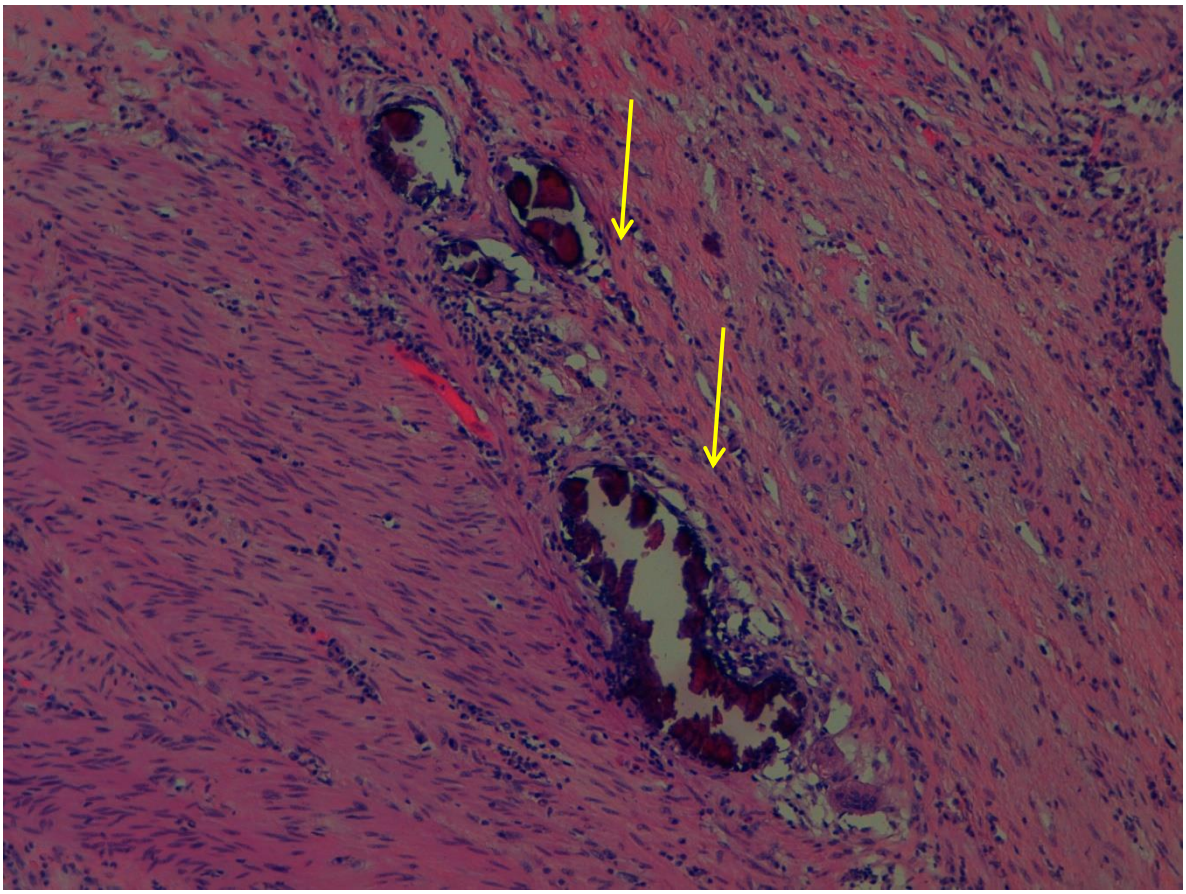


FIGURE 48 (Case 101): The presence of dystrophic calcifications is seen occasionally as a sign of tumour regression, as can be seen in this image (yellow arrows)

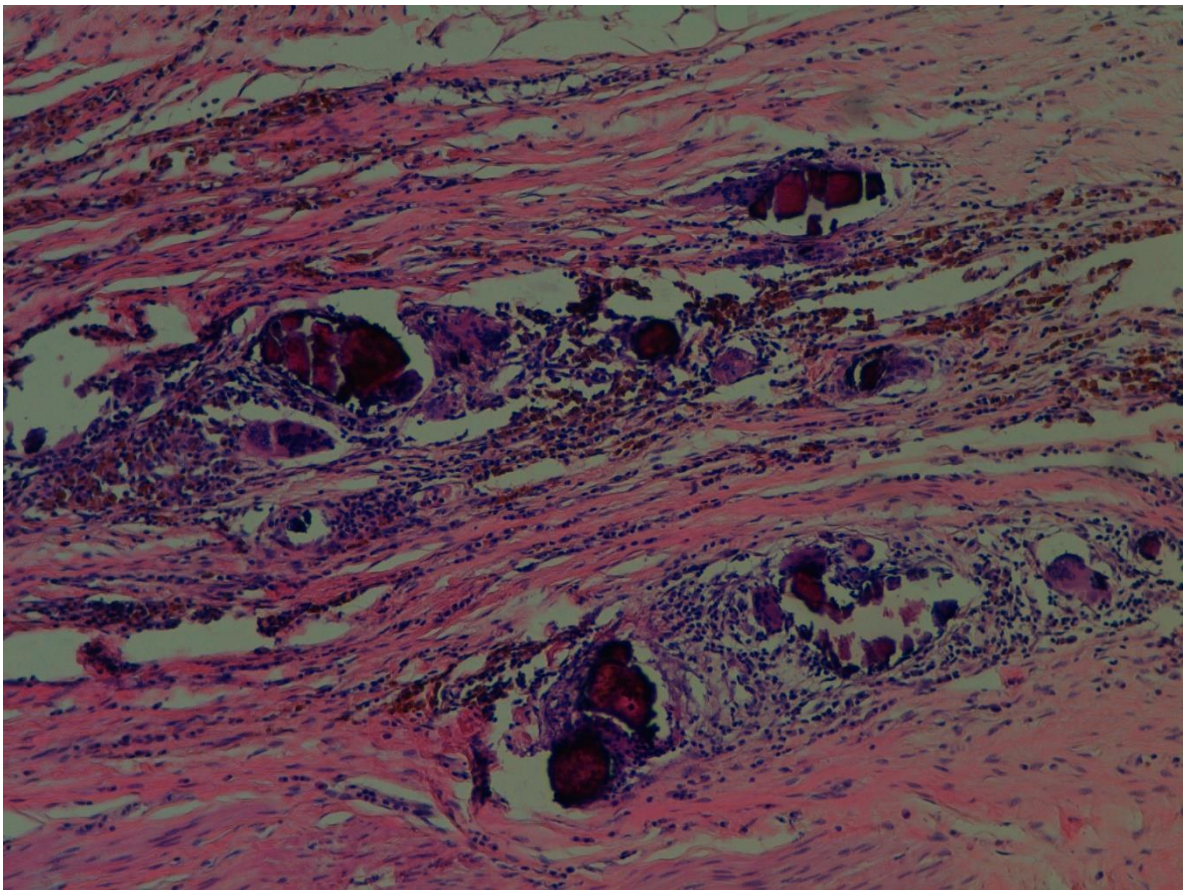


FIGURE 49 (Case 101): Most of the tumour is occupied by fibrosis with little malignant cells deposits; the tumour was staged as ypT2N0

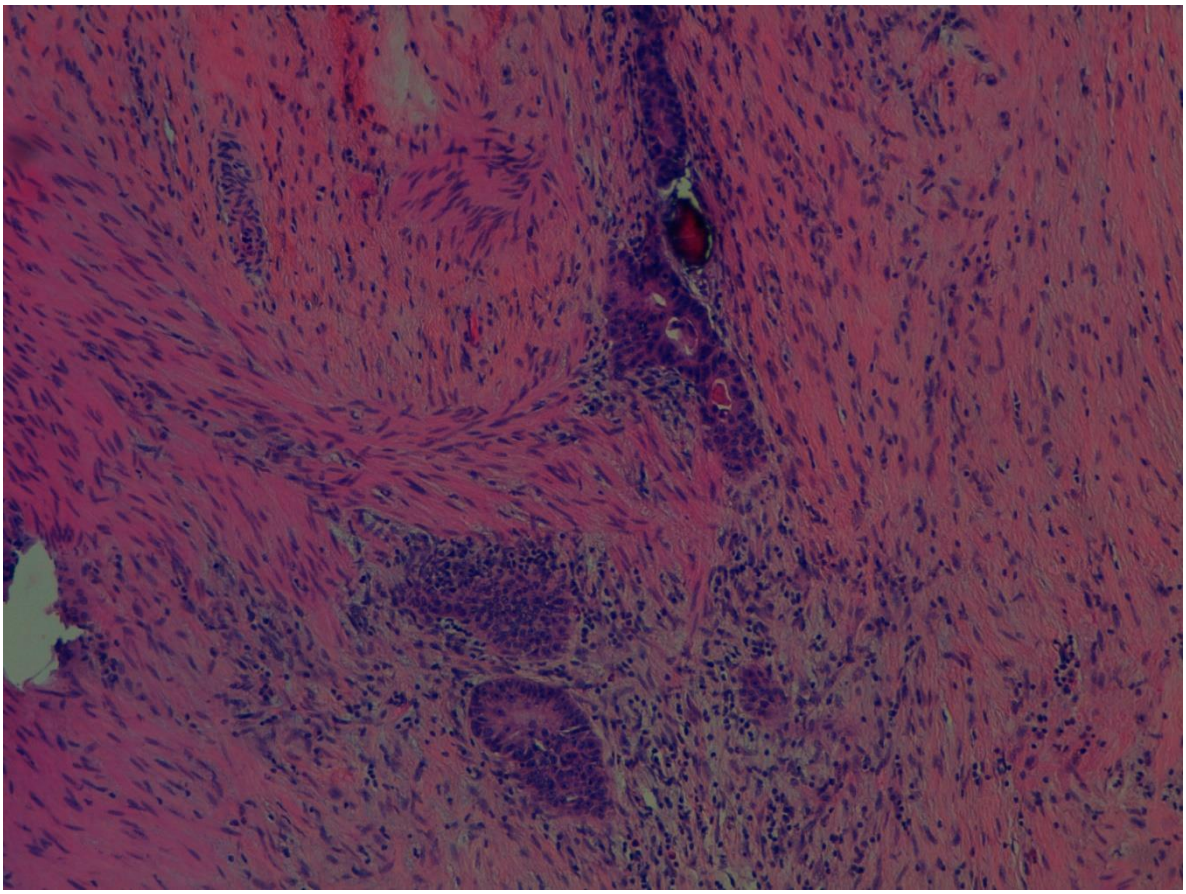


FIGURE 50 (Case 101): A nearly-complete pathological response was seen in this 58-year old male patient with a locally advanced middle rectal cancer staged initially as cT4bN0 and with circumferential margin invasion. Sterilization or only microscopic focii remaining with marked fibrosis can be seen, and it was classified as Wheeler grade 1 and Rich grade 3

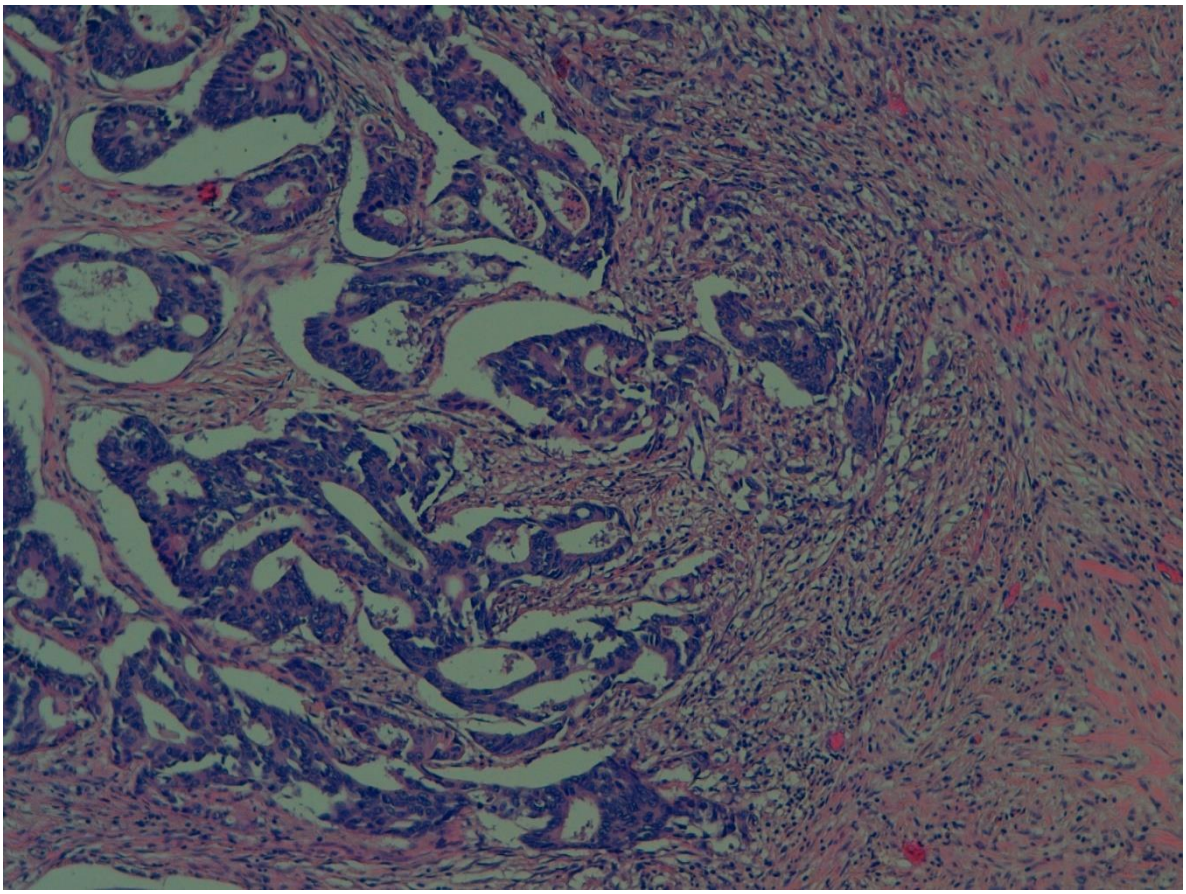


FIGURE 51 (Case 201): Minimal tumour regression (Dworak grade 1) after neoadjuvant chemoradiotherapy in this 56-year old male patient with a locally advanced mid- to upper rectal cancer staged cT4aN1b; the final pathological staging was ypT3dN2aG3

We know that a pCR is a good prognostic factor (FIGURES 52 and 53). In the previously mentioned meta-analysis of 3105 patients who received neoadjuvant chemoradiotherapy followed by surgery, 484 patients had a pCR [170]. The group with pCR had more clinically and radiologically staged T1 or T2 tumours than those without pCR. At 5 years, those with pCR had improved DFS (83.3% vs 65.6%), a lower risk of local relapse (2.8% vs 9.7%), better chance of being free from distant metastasis (88.8% vs 74.9%) and an increased OS (87.6% vs 76.4%, $p<0.0001$). The benefit of pCR was confirmed on multivariate analysis. These results are also supported by the MERCURY study investigators, who reported that a ypT0 resection following neoadjuvant chemoradiotherapy was associated with increased DFS and OS, as well as decreased rates of local recurrence [101]

As we have seen, in these patients with pCR the benefit of adjuvant chemotherapy is probably small and the risk-benefit ratio should be discussed with the patient. However, this is an inference from these trials and many clinicians would still offer adjuvant chemotherapy even if the patient had a pCR, especially if there were worrying baseline risk factors, such as cN+ disease, high CEA levels or poorly differentiated tumours or in younger patients.

On the other hand, despite a large number of studies examining this question of the prognostic role of lesser degrees of regression, only two have shown them to be prognostic factors on a multivariate analysis [272-273]. In one of these studies, partial tumour regression was only found to predict progression in lymph node negative rectal cancers [272]. Due to the lack of standardisation of the way the specimen is analysed, the various reporting schemes utilised and the lack of inter-observer reproducibility for those patients with an incomplete response to therapy, a definitive conclusion to the debate about the significance of lesser grades of regression is not likely to be resolved at present. [274]. Unfortunately, in this sense, the development of TRG for the assessment of response to preoperative chemoradiotherapy in rectal cancer is hampered by the current lack of a universally accepted grading system. There is a clear need for international agreement both on a standardised method of specimen analysis and a reliable and reproducible way to score the presence of residual tumour. One such approach has been proposed recently [275].

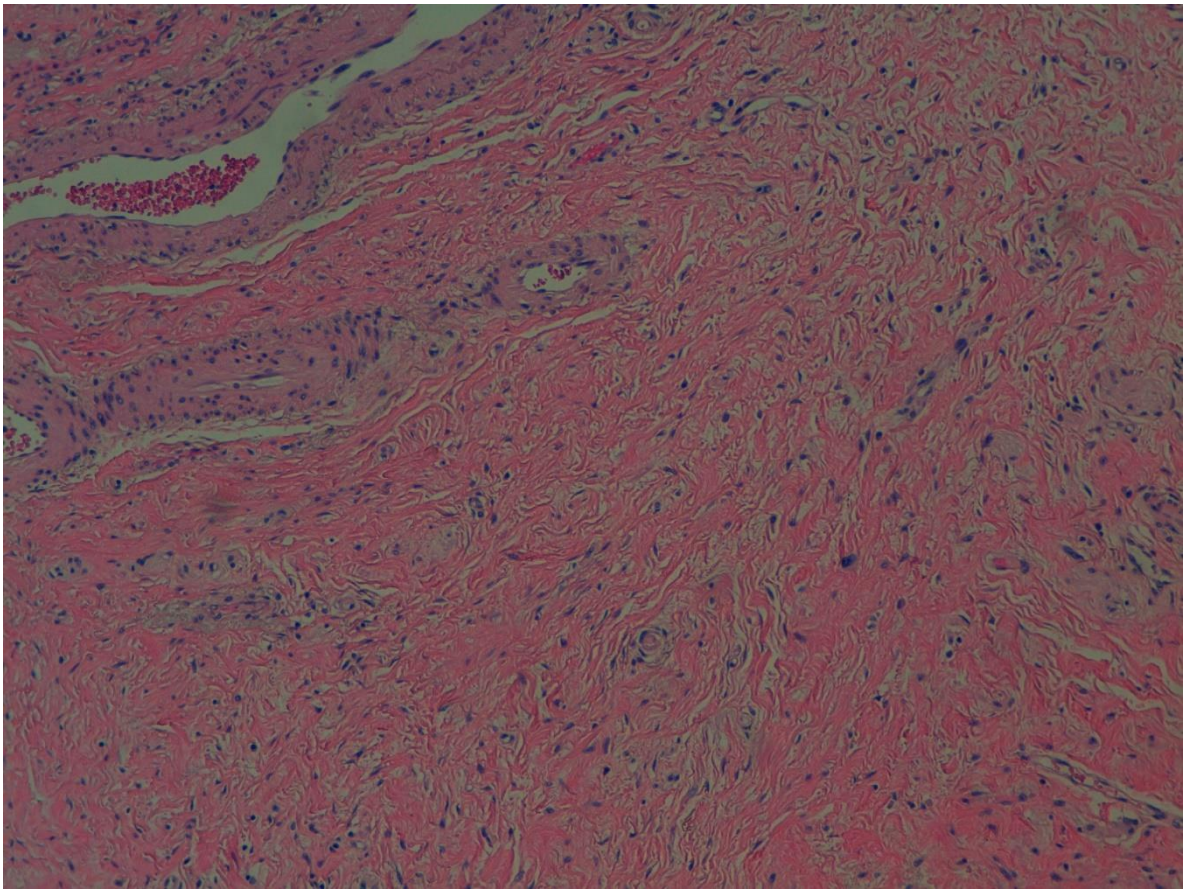


FIGURE 52 (Case 192): A pathological complete response was obtained after neoadjuvant chemoradiotherapy in this 58-year old male patient with a locally advanced lower rectal cancer originally staged cT3dN1b. No malignant cells can be seen and there is widespread fibrosis.

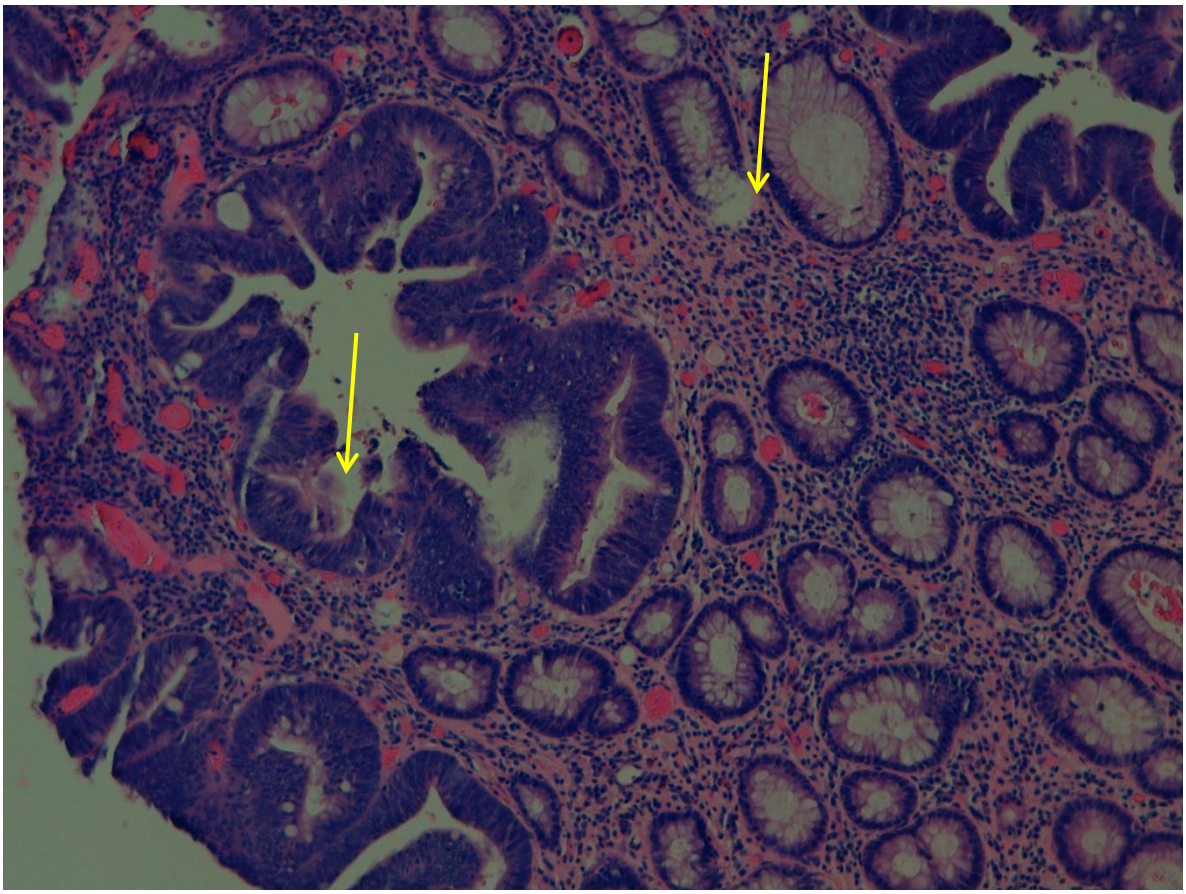


FIGURE 53: (Case 170) A nearly-complete pathological response was seen in this 52-year old male patient with a locally advanced lower rectal cancer originally staged cT3dN2b. However, at a higher magnification, some residual tumour cells can be seen in the base of the glands (yellow arrows), although there is no invasive component; the final pathological stage was ypTisN0

The use of downstaging as a prognostic factor, although more straightforward than TRG, also has its shortcomings. There are not uniformly standardized criteria to define downstaging and its effectiveness depends basically in the sensitivity and specificity of the clinical staging. In our study, the downstaging rate was basically driven by cN downstaging, more than cT staging. In effect, in our series, 81.3% of patients were stages as cN+ disease, while in the pathological analysis 74.9% of patients were ypN negative. Although there was undoubtedly a lymph node sterilization in an important number of patients, due to the poor sensitivity of MRI, and especially EUS, in N-staging, there will probably have been false-positive cases. Differences between ypT1 and ypT2 are probably not very significantly. However, as we have mentioned before, the persistence of ypT34, and especially, ypN12 disease, are very poor prognostic factors, as they imply an aggressive phenotype with a high risk of distant metastases. These were the findings of our study, where patients with a heavy lymph node burden after LCRCT had worse DFS and OS in the multivariate analysis, independently from the CRM status or perineural invasion.

4.8.5. We need new ways to grade tumours, especially after neoadjuvant therapy.

The importance of histologic grading as a prognostic factor is supported by the consistent finding of independent statistical significance in studies with multivariate analyses [240]. Unfortunately, well-differentiated tumors make up only a small fraction of tumors in most series, and the difference in outcome between well-differentiated versus moderately differentiated tumors is not as clear as the difference between either well- or moderately differentiated tumors and poorly differentiated tumors. Most authorities now recommend that the traditional three-grade system be collapsed into a two-tiered grading system where low-grade tumors encompass both well- and moderately differentiated tumors, and high-grade tumors represent poorly differentiated tumors. Although not evaluated in our trial, the presence of poorly differentiated clusters of malignant cells is a very promising approach that may surpass the classical histological grading and can be performed easily in the initial diagnostic biopsy and in the surgical specimen [276].

Practical conclusions of the pathological analysis of the surgical specimen

1. Most of the classical factors described as poor prognostic features in rectal cancer were significant in our analysis. These included an unsatisfactory mesorectum, lymph node invasion, a higher lymph node burden, no overall, T-stage or N-stage downstaging, circumferential margin involvement, vascular or perineural invasion, minimal or moderate regression and a non-mucinous histology.
2. Circumferential margin involvement, perineural invasion and ypN2 disease (alongside old age) were the only remaining independent prognostic factors for worse survival in the multivariate analysis.
3. CRM invasion portends a poor prognosis, even despite the use of LCRCT. Distal margin involvement, on the other hand, is a much less important factor if the CRM is uninvolved, except in poorly differentiated tumours, where the risk of local relapse remains high due to the infiltrative dissemination of these undifferentiated tumours.
4. Perineural invasion is a consistent prognostic factor in most studies for worse local relapse, distant metastases, DFS and OS. Unfortunately, it is not evaluated routinely in many centres. It is also not visible in imaging tests, included high-quality MRI, which limits its usefulness in the clinical staging.
5. Patients with complete or nearly-complete pathological response fared very well and many physicians opt not to offer adjuvant chemotherapy, due to the small expected benefit. However, many other clinicians would still offer adjuvant chemotherapy, especially if there were worrying baseline risk factors, such as cN+ disease, high CEA levels or poorly differentiated tumours or in younger patients.
6. The prognostic role of lesser grades of regression remains unconvincing, especially compared to other pathological risk factors. Variability in the different TRG scores is problematic and the current lack of a universally accepted grading system remains a problem.
7. There are not uniformly standardized criteria to define downstaging and its effectiveness depends basically in the sensitivity and specificity of the clinical imaging performed. Clinical lymph node staging remains unsatisfactory and N-downstaging is probably not very reliable. However, the persistence of ypT34, and especially, ypN12 disease, portend a poor prognosis and high risk of distant metastases.

4.9. What is the prognostic role of mucinous tumours?

10.3% of our patients had mucinous tumours, defined as tumours with more than 50% of a mucoid component. These tumours were linked to higher overall rates of poor response to LCRCT and other poor-prognosis pathological endpoints compared to non-mucinous tumours (TABLE 24). They were also linked in the univariate analysis to worse DFS and OS; however, this was lost in the multivariate analysis. These data are similar to other studies published in the literature [277-279]

They should be differentiated from *adenocarcinoma with mucinous features* or *adenocarcinoma with mucinous differentiation, terms which* are often used to describe tumors that have a significant mucinous component (>10% but <50%). Most mucinous adenocarcinomas have free-floating strips of neoplastic epithelium or individual tumor cells in the mucin (FIGURES 54 and 55). A variable number of signet ring cells also may be seen. If more than 50% of the tumor is composed of signet ring cells, the tumor is best classified as signet ring cell carcinoma, even if more than 50% of the tumour is composed of extracellular mucin; these tumours represent 1% of all colon carcinomas, are aggressive and usually present in advanced stages. Curiously we did not find any cases of signet ring cell carcinoma in our series. This is an important distinction, as most studies that have evaluated the prognostic role of mucinous tumours have included patients both with mucinous and signet ring cell tumours, making it difficult to evaluate the real prognostic role of these mucinous tumours. Another problem, as we have mentioned previously, is that, as the Dutch TME study results showed, there are two distinct classes of mucinous carcinoma: those that are pre-existing and mucinous carcinomas that are induced by preoperative radiotherapy (FIGURE 47), with a better prognosis for those that are induced. Acellular mucin pools, these are not considered to represent residual tumor, although some studies have suggested that the presence of acellular mucin pools is associated with earlier local recurrence [280-281]

Another problem is the difficulty in identifying the mucinous or signet ring cell subtype before starting treatment. As the diagnosis is based on the limited material available from colonoscopy, a satisfactory diagnosis of both of these carcinoma histologies is usually difficult to establish. One method to establish this would be to identify the mucinous component using MRI and grouping these tumors as mucinous neoplasms, which may be superior in identifying mucinous tumors to biopsy (FIGURE 56) [282]

The margins of the tumor are often dissecting and infiltrative, which probably contributes to the overall poor prognosis in some patients with these tumors, which we observed in our study, where there were statistically worse rates of a successful TME and of a satisfactory quality of the meso-rectum.

Mucinous tumors represent a greater proportion of right colon tumors, are more common in females, and are less frequent in the distal colon and rectum. A large national database analysis from the MD Anderson Cancer Center reported that among rectal adenocarcinoma cases, the incidence of mucinous tumours was 7.08% and that of signet ring cell carcinomas was 0.7% [283] Another single-institution series from China reported an incidence of 5% and 1.6% of cases, respectively, among rectal cancer cases [284]

They are more common in young individuals and in patients with Lynch syndrome, and they are more likely to be at an advanced stage at presentation. The type of genetic alterations in these tumors suggests that the molecular pathogenesis is different from that of usual adenocarcinomas (TABLE 54). Defects in DNA MMR and MSI-H are more common in mucinous adenocarcinomas although a mucinous phenotype shows a low degree of sensitivity as a marker for this genotype [285] MSI-H mucinous tumors are found more often in younger

individuals and are more likely to be exophytic and to have an expanding growth pattern, compared with non–MSI-H mucinous cancers. Expression of HATH1, a transcription factor that activates MUC2 expression in intestinal epithelium, is maintained in both mucinous and signet ring cell carcinomas but is repressed in nonmucinous cancers, which indicates a possible biologic basis for mucinous neoplasms [286]. Compared with usual adenocarcinomas, mucinous tumors are more likely to develop peritoneal implants and to invade adjacent viscera and less likely to be cured by surgical resection. They are also more likely to show lymph node involvement beyond the pericolonic region. [287-288]

Many studies have reported that the mucinous subtype is less responsive to chemoradiotherapy than the classic subtype [289-291]; that was one of our main findings of our study. Some authors have even proposed to avoid LCRCT in mucinous tumours [292]. However, this is controversial, as the clinical identification of these tumours remains difficult and the risk of R1 resection and CRM involvement is high with these tumours. Postoperative LCRCT is poorly tolerated. On the other hand, if we identify these patients before surgery, they may be better candidates for more intensive neoadjuvant chemotherapy regimens or novel radiotherapy regimens, which would increase the downstaging rate. Some authors have proposed more aggressive approaches such as a prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) might help in preventing peritoneal recurrence, a predominant location of recurrence in the aggressive variants [293].

The association between mucinous subtype and survival is controversial. Although many studies have shown that these tumors are associated with a relatively poor prognosis, others have not. A recent meta-analysis showed that mucinous carcinomas did not manifest at a higher stage than usual adenocarcinomas, but there was a 2% to 8% increased hazard of death [295] The relative contribution of signet ring cell carcinomas may explain these discrepancies, with the latter phenotype being more aggressive. However, the most important factor in determining survival in mucinous tumours is the MSI-status. In particular, it is now recognized that cancers with MMR deficiency have characteristic molecular genetic alterations and are associated with a significantly better overall survival. Paradoxically, mucinous, signet ring cell, and undifferentiated cancers are more prevalent in cases that show MMR deficiency [296]

	Chromosomal instability	Microstatellite instability	CpG island methylator phenotype	Other phenotypes
Histology	Adenocarcinoma	Mucinous adenocarcinoma	Sessile serrated adenocarcinoma	Traditional serrated adenocarcinoma
KRAS mutation	Yes	Occasionally	No	No
BRAF mutation	Occasionally	Yes	Yes	Occasionally
MLH1 methylation	No	Yes	Yes	No
MGMT methylation	No	No	No	Yes
Anatomical site	No preference	Proximal colon	Proximal colon	Distal colorectum
Anatomical site	No preference	Proximal colon	Proximal colon	Distal colorectum

TABLE 54: The molecular pathogenesis of some mucinous adenocarcinomas may differ with respects to conventional adenocarcinoma

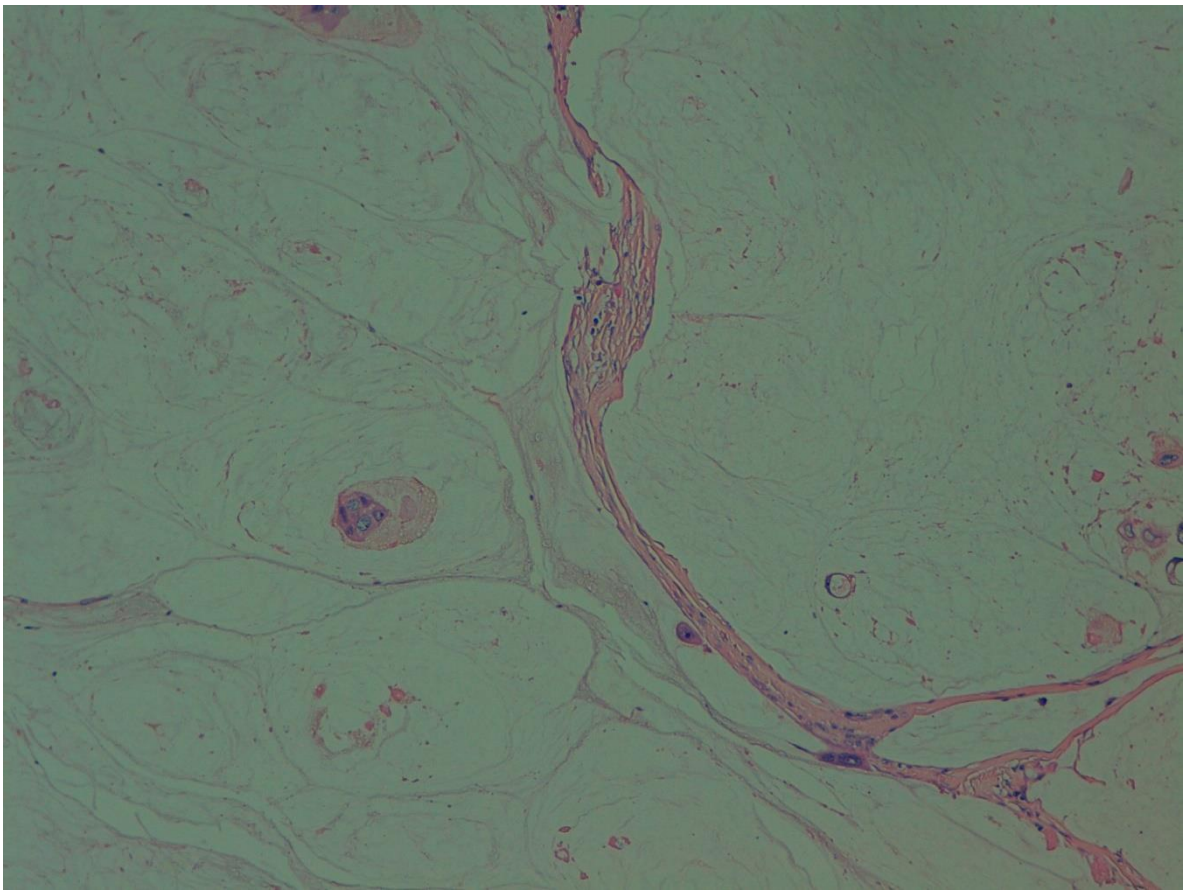


FIGURE 54: (Case 191) Minimal regression and no downstaging was seen in this 65-year old male patient with a locally advanced mucinous lower rectal cancer staged as cT2N2a; the final pathological stage was ypT2N2aG3

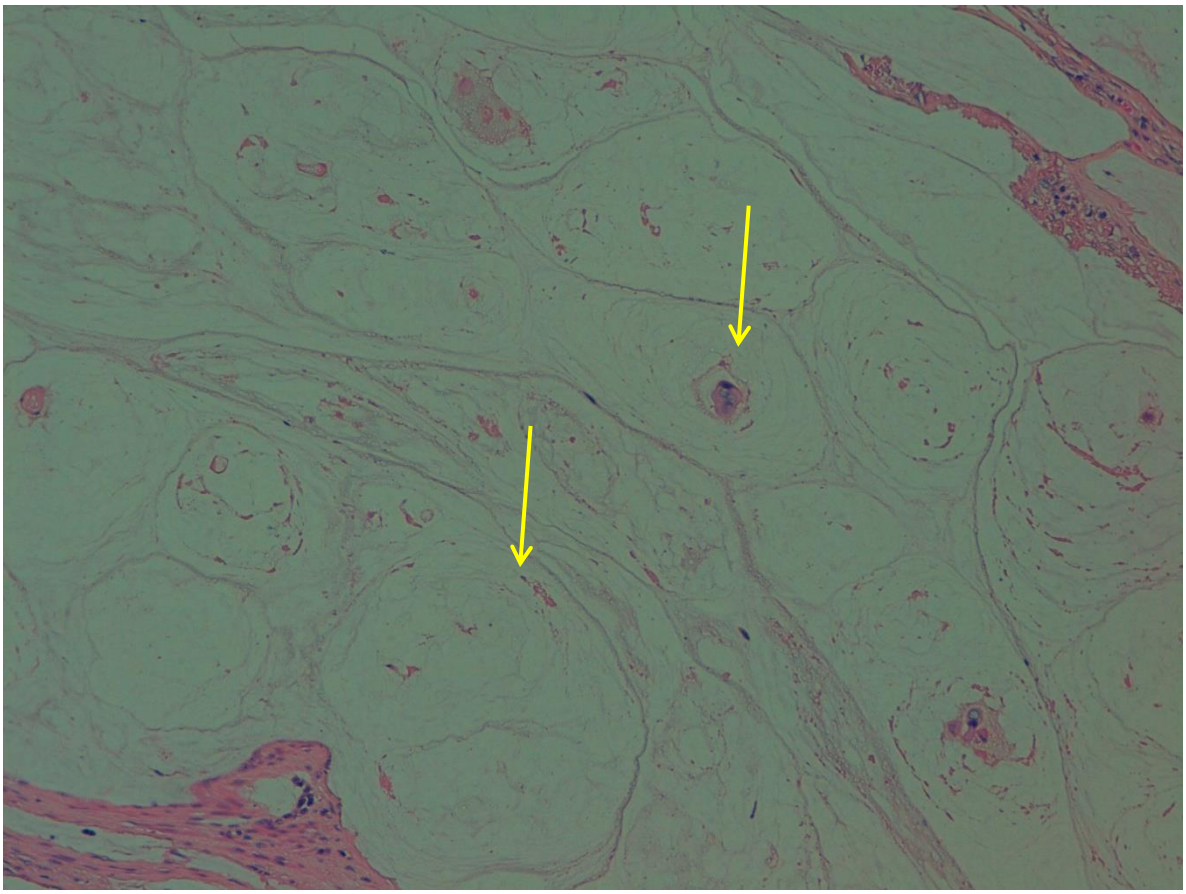


FIGURE 55 (Case 191): In the same patient as in FIGURE 54, we can see that most of the tumour is occupied by mucinous lakes (yellow arrows); malignant cells can be seen intertwined in the lakes.

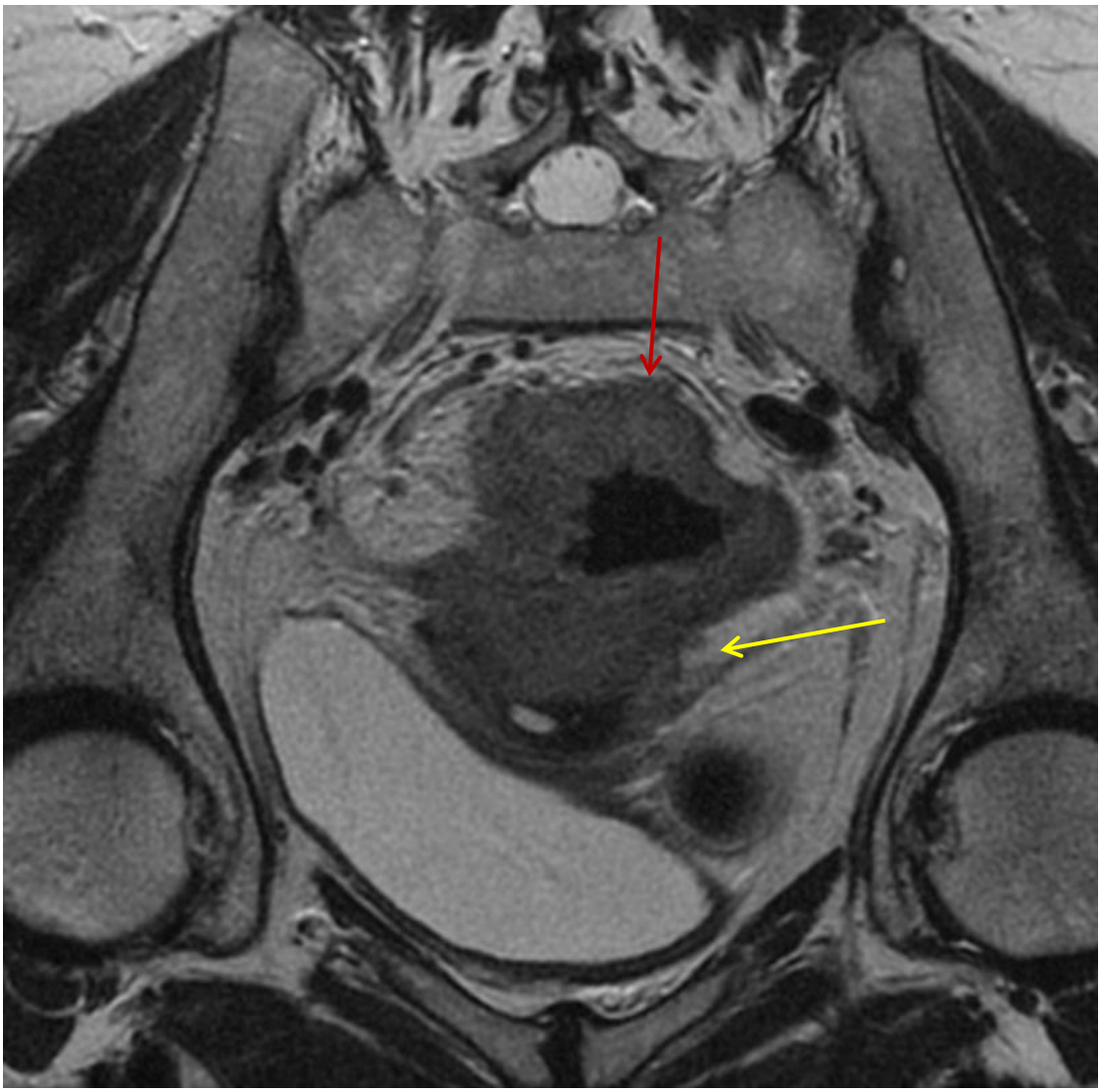


FIGURE 56 (Case 139) Coronal MRI images of a 59-year old female patient with a locally advanced voluminous mucinous upper rectal cancer (shown by red arrows) staged cT4N1b with invasion of the uterus and collapse of the endometrial lumen (infiltration shown by the yellow arrows)

Practical aspects in the management of mucinous tumours:

1. We observed a 10% rate of mucinous tumours in our study, a rate similar to other studies in the Western World. These tumours were linked to higher overall rates of poor response to LCRCT and other poor-prognosis pathological endpoints compared to non-mucinous tumours.
2. The correct characterization of the prognostic role of mucinous tumours is hampered by the difficulty in obtaining a definitive diagnosis in the initial biopsy, its association with signet cell cancer cells (which have a poorer prognosis) and the presence of mucin-induced changes after radiotherapy, that have a much better prognosis than non-induced mucinous tumours.
3. MRI may help in the clinical identification of mucinous tumours.
4. Most studies do show that there is a usually poor response to neoadjuvant therapy in mucinous tumours. However, worse survival outcomes are difficult to prove and results are contradictory; the relative contribution of signet cell cancer cells in some studies may explain these discrepancies.
5. The MSI status is probably more important; MSI-low or MSS mucinous tumours are aggresive compared with MSI-high tumours. Unfortunately, we do not perform it routinely.
6. Mucinous tumours, especially those MSS or MSI-low if identified, would be optimal candidates for more intensive neoadjuvant chemotherapy regimens or novel radiotherapy regimens, which would increase the downstaging rate and the possibility of a radical resection

5. Recapitulation of conclusions

The long-term results of our study of patients with locally advanced rectal cancer are broadly similar to other studies of LCRCT followed by surgery and we think that they can be considered moderately successful: there was a local relapse rate of less than 10%, with a downstaging rate of 70% and a pCR rate of 14.8%. 30% of patients relapsed, the vast majority in the form of distant metastases and the 10-year OS rate was 62.4%, with most relapses taking place in the first five years of follow-up. However, there were several concerning factors: older patients fared poorly compared to their younger counterparts; despite the use of LCRC and specialized surgery, the quality of the mesorectum was unsatisfactory in around a quarter of patients and 21% had a positive CRM; finally, the compliance in the use of adjuvant chemotherapy was rather poor, with less than half of patients receiving the full intended dose and around a quarter of patients not receiving any type of adjuvant treatment. We followed a blanket approach of treating all patients with cT3-4 and/or lymph node positive disease with LCRCT and adjuvant chemotherapy, irrespective of response, as our standard treatment, as is usually done in the United States and in many countries of Europe.

We analyzed the different aspects in the diagnosis and management of our series in a stepwise manner, which we summarize in the following sections:

5.1. Radiotherapy:

1. International guidelines recommend that patients who are candidate for neoadjuvant treatment should undergo surgery from 6 to 8 weeks (ESMO) or 5 to 12 weeks (NCCN) after completion of long-course chemoradiotherapy or within 7-10 days of completion of short-course radiotherapy.
2. However, there is compelling data that an even longer time frame may lead to still better tumor regression and downstaging, both in LCRCT and in SCRT. Our data are consistent with these data. With this in mind, we can tailor the treatment in individual cases. For example, SCRT followed by a longer interval in order to increase downstaging can be useful in elderly or frail patients, where a LCRCT would be necessary but not feasible. However, we must wait the results of prospective randomized trials in order to adopt a widespread approach of increasing the interval between RT and surgery.
3. There is an imperfect relationship between higher radiotherapy dose and an increased pCR. These differences are probably not significant with doses higher than 45 Gy, before radical surgery, but will probably be useful in patients where a non-operative management is planned. Again, prospective randomized trials are needed in this sense.

5.2. Neoadjuvant chemotherapy intensification

1. Although theoretically promising, the addition of concomitant oxaliplatin alongside standard LCRCT is not beneficial. The integration of systemic CT alongside 5-FU-based CRT is difficult, due to the existence of synergistic toxicities which worsen the compliance rate and the chance of completing successfully the treatment plan
2. Results with induction chemotherapy (before LCRCT) or consolidation chemotherapy (after LCRCT) are somewhat more promising and are included in some guidelines. Compliance is better compared to adjuvant chemotherapy. However, patients should be selected accordingly, as toxicity is higher, especially in elderly and/or frail patients, and there is an increased risk of serious cardiovascular events.
3. Despite the lack of data from large prospective studies, some guidelines recommend neoadjuvant chemotherapy alongside standard LCRCT is included as a treatment option.
4. We have concerns with the consolidation approach, as, in our anecdotal evidence, tolerance to chemotherapy after LCRCT, even before surgery, tends to be poorer, not only in rectal cancer but in othe tumours such as pancreatic or esophageal cancer.
5. There is no benefit with the addition of antiangiogenic targeted therapies, with an increased risk of surgical complications. There are hints of better activity of the combination of induction CT with antiEGFR targeted therapies, although, again, serious toxicities are worrying.

5.3. Role of adjuvant chemotherapy

1. We offered adjuvant chemotherapy to all patients after surgery, regardless the response rate. However, as in most other published trials, the tolerance to the adjuvant regimen was poor with less than half of these patients receiving the full intended dose; this was especially evident in elderly patients.
2. We observed a small but significant decrease in the rate of distant metastases with adjuvant CT; no benefit in local control was obtained.
3. There is little high-quality evidence on the use of adjuvant CT after LCRCT and TME-surgery; most trials have not shown any survival benefit. However, compliance to treatment was uniformly poor, which may explain this lack of benefit. Unfortunately, we are not going to have randomized trials which will answer this question
4. Patients with poor downstaging, high lymph node burden or other poor prognostic factors (high grade, minimal regression perineural or vascular invasion, involved CRM, mucinous tumours) should probably be offered adjuvant chemotherapy if feasible, if only for a lack of better options. The use of nomograms and scores, such as the Valentini momogram or the Dhadda score, were helpful in our case in selecting patients with poor prognosis.
5. If there is a benefit, it is probable small in patients with downstaging and especially in those who have pCR; the doubts over the effectiveness of adjuvant chemotherapy should be transmitted to patients and a shared-decision should be taken over its use.
6. We did not use neoadjuvant chemotherapy regimens, alone or alongside LCRCT or SCRT, as there are only phase II evidence for its activity, but results are promising.
7. Improvements in clinical staging, with a better identification of pathological lymph nodes, are needed to identify those patients with a higher risk of systemic relapse, who will benefit from more intensive oxaliplatin-containing (neo)adjuvant regimens, probably in the neoadjuvant setting.

5.4. Radiological staging

1. The use of a blanket-approach of treating all locally advanced rectal cancers with LCRCT, as we used, lowers somewhat the importance of a precise primary tumour staging, although we know there is an inherent higher risk of over- and under-treating patients. The importance of baseline prognostic factors for local relapse and distant metastases for selecting patients for risk-adapted approaches also diminishes with this approach.
2. Broadly speaking. MRI and EUS show a similar sensitivity and specificity with respect to cT staging; EUS is particulary useful for the staging of early tumours, such as T1-T2. However, a limited view field, poor assessment of the CRM and the difficulty in staging stenotic tumours are disadvantages with EUS, with a tendency to understage tumours. In our series, when both tests were performed, EUS understaged in comparison to MRI, especially in cN disease, upper rectal cancers and stenotic tumours.
3. MRI is especially preferred in locally advanced rectal cancer by its assessment of cT and invasion of the mesorectal fascia and other prognostic factors, such as EMVI, lateral lymph pelvic nodes or tumour deposits. Any risk-adapted approach should include a high-quality MRI, as the mesorectal rectal status is the most important factor in determining the need of downstaging and of neoadjuvant (chemo)radiotherapy.
4. Clinical N staging remains a problem, as MRI, and even more so EUS, has poor sensitivity and specificity for this indication. Lymph node size is a poor distinguishing factor. Other features such as irregular borders and a heterogeneous signal can help, although results are still far from satisfactory.
5. Despite the difficulties in cN staging, the presence of cN positive disease, mesorectal fascia invasion, extramural venous invasion, lower rectal tumours and elevated CEA and CA 19.9 levels predicted a higher risk of distant metastases. These are poor-prognosis patients and they would be prime candidates to any neoadjuvant full-dose chemotherapy approach
6. We found that there was an increased risk of local relapse in poorly differentiated tumours and bulky tumours; perhaps more importantly, as in other studies, we did not find a higher risk with cN positive disease, especially in N1 tumours. This may reflect the difficulties in staging lymph node disease with all imaging modalities but also that a successful TME will probably remove satisfactorily all pathological nodes.
7. We did not use restaging procedures after neoadjuvant therapy. Their use, although attractive, is misleading in many cases, as MRI tends to over-estimate downstaging and there is no evidence that surgeons will change their intended original approach with these results. EUS fares even worse. Radiological TRG, such as those proposed by the MERCURY group, suffer from the same problems as histological TRG; they could probably be useful in patients complete or near-complete regression, but not in patients with lesser degrees of regression.

5.5. Role of surgery in the multidisciplinary approach

1. A blanket-approach of neoadjuvant (chemo)radiotherapy to all patients with locally advanced rectal lowers the local relapse rate but does not improve survival and, more importantly, limits the possibility of giving the full-intended dose of adjuvant chemotherapy and can have long-term side effects. On the other hand, all patients, even those with low risk tumours, benefit from radiotherapy and we can expect all long-term side effects will probably diminish with the continuous improvements in radiotherapy techniques.
2. Mid rectal tumours with little penetration into the meso-rectal fat and with no or minimal clinical lymph node disease (N1a or N1b) and with a clear MRF, are probably the best candidates for a surgery-first approach.
3. Low rectal tumours, especially if treated with abdominoperineal resection, have a higher risk of local relapse. Risk factors include anterior rectal location, levator involvement and the difficulty in obtaining a successful TME. These patients are probably best served with some type of neoadjuvant therapy for the moment. Improvements in surgical techniques such as extra-levator abdominoperineal resection should also help us move forward.
4. The significance of lateral pelvic lymph nodes in MRI is unclear. Although a lateral pelvic lymphadenectomy could be performed, as is done in the East, these patients do as well with LCRCT and TME-surgery, with less morbidity and long-term complications.

5.6. Management of older patients

1. Our elderly patients fared poorly in almost all aspects of the multimodality treatment. This was especially evident in an increased risk of serious unexpected (usually cardiovascular or surgical) complications, and a lower compliance to neoadjuvant radiotherapy and, especially, to adjuvant chemotherapy.
2. Disease-free and overall survival were worse in the elderly, even though we did not find any signs of higher aggressiveness in these tumours, compared to their younger counterparts. There is also no evidence to suggest that older patients have poor responses to (chemo)radiotherapy. In particular, there seems to be a greater radiosensitivity in these patients.
3. Other secondary endponts, such as stoma closure or the rate of sphincter-conserving surgery, were also worse for the older patients.
4. Chronological age, however, should not be the only determining factor un the decision of the type of multimodality treatment offered. Evaluation of comobirbidites, especially cardiovascular, and more formal geriatric assessments would be helpful in this regard.
5. LCRCT perhaps is not the best option for older patients, especially in frail or with other comorbidities. All these results warrant the development of specific therapeutic strategies more optimal for patients above 70–75 years, including fit patients over 80 years. SCRT followed by delayed surgery to decrease toxicities and permit tumor downsizing is a promising approach. Developing less toxic treatments should allow a higher percentage of patients to undergo surgery.

5.7. Pathological prognostic factors

1. Most of the classical factors described as poor prognostic features in rectal cancer were significant in our analysis. These included an unsatisfactory mesorectum, lymph node invasion, a higher lymph node burden, no overall, T-stage or N-stage downstaging, circumferential margin involvement, vascular or perineural invasion, minimal or moderate regression and a non-mucinous histology.
2. Circumferential margin involvement, perineural invasion and ypN2 disease (alongside old age) were the only remaining independent prognostic factors for worse survival in the multivariate analysis.
3. CRM invasion portends a poor prognosis, even despite the use of LCRCT. Distal margin involvement, on the other hand, is a much less important factor if the CRM is uninvolved, except in poorly differentiated tumours, where the risk of local relapse remains high due to the infiltrative dissemination of these undifferentiated tumours.
4. Perineural invasion is a consistent prognostic factor in most studies for worse local relapse, distant metastases, DFS and OS. Unfortunately, it is not evaluated routinely in many centres. It is also not visible in imaging tests, included high-quality MRI, which limits its usefulness in the clinical staging.
5. Patients with complete or nearly-complete pathological response fared very well and many physicians opt not to offer adjuvant chemotherapy, due to the small expected benefit. However, many other clinicians would still offer adjuvant chemotherapy, especially if there were worrying baseline risk factors, such as cN+ disease, high CEA levels or poorly differentiated tumours or in younger patients.
6. The prognostic role of lesser grades of regression remains unconvincing, especially compared to other pathological risk factors. Variability in the different TRG scores is problematic and the current lack of a universally accepted grading system remains a problem.
7. There are not uniformly standardized criteria to define downstaging and its effectiveness depends basically in the sensitivity and specificity of the clinical imaging performed. Clinical lymph node staging remains unsatisfactory and N-downstaging is probably not very reliable. However, the persistence of ypT34, and especially, ypN12 disease, portend a poor prognosis and high risk of distant metastases.

5.8. Management of mucinous tumours

1. We observed a 10% rate of mucinous tumours in our study, a rate similar to other studies in the Western World. These tumours were linked to higher overall rates of poor response to LCRCT and other poor-prognosis pathological endpoints compared to non-mucinous tumours.
2. The correct characterization of the prognostic role of mucinous tumours is hampered by the difficulty in obtaining a definitive diagnosis in the initial biopsy, its association with signet cell cancer cells (which have a poorer prognosis) and the presence of mucin-induced changes after radiotherapy, that have a much better prognosis than non-induced mucinous tumours.
3. MRI may help in the clinical identification of mucinous tumours.
4. Most studies do show that there is a usually poor response to neoadjuvant therapy in mucinous tumours. However, worse survival outcomes are difficult to prove and results are contradictory; the relative contribution of signet cell cancer cells in some studies may explain these discrepancies.
5. The MSI status is probably more important; MSI-low or MSS mucinous tumours are aggresive compared with MSI-high tumours. Unfortunately, we do not perform it routinely.

6. Mucinous tumours, especially those MSS or MSI-low if identified, would be optimal candidates for more intensive neoadjuvant chemotherapy regimens or novel radiotherapy regimens, which would increase the downstaging rate and the possibility of a radical resection

6. What is the future in the management of locally advanced rectal cancer?

The prognosis of patients with locally advanced rectal cancer is determined by two competing factors: the risk of local relapse and the risk of distant metastases. The identification of patients with an extremely low risk of local relapse where radiotherapy would presumably offer little benefit is based on the premise of an exquisite imaging staging with MRI, supplemented with EUS, and a surgical team specialized in the TME procedure. With the current imaging tests, we can define fairly reasonably those patients with a high risk of local relapse, who will benefit from neoadjuvant radiotherapy and we can probably avoid radiotherapy in those patients with a low risk of relapse. There are also promising data with the combination of SCRT and chemotherapy, with promising results with regards to downstaging and pCR rates; in this sense, the differences between LCRCT and SCRT are blurring and we will probably be able to tailor these multimodality treatments according to the characteristics of the patient (age, comorbidities) and of the tumour.

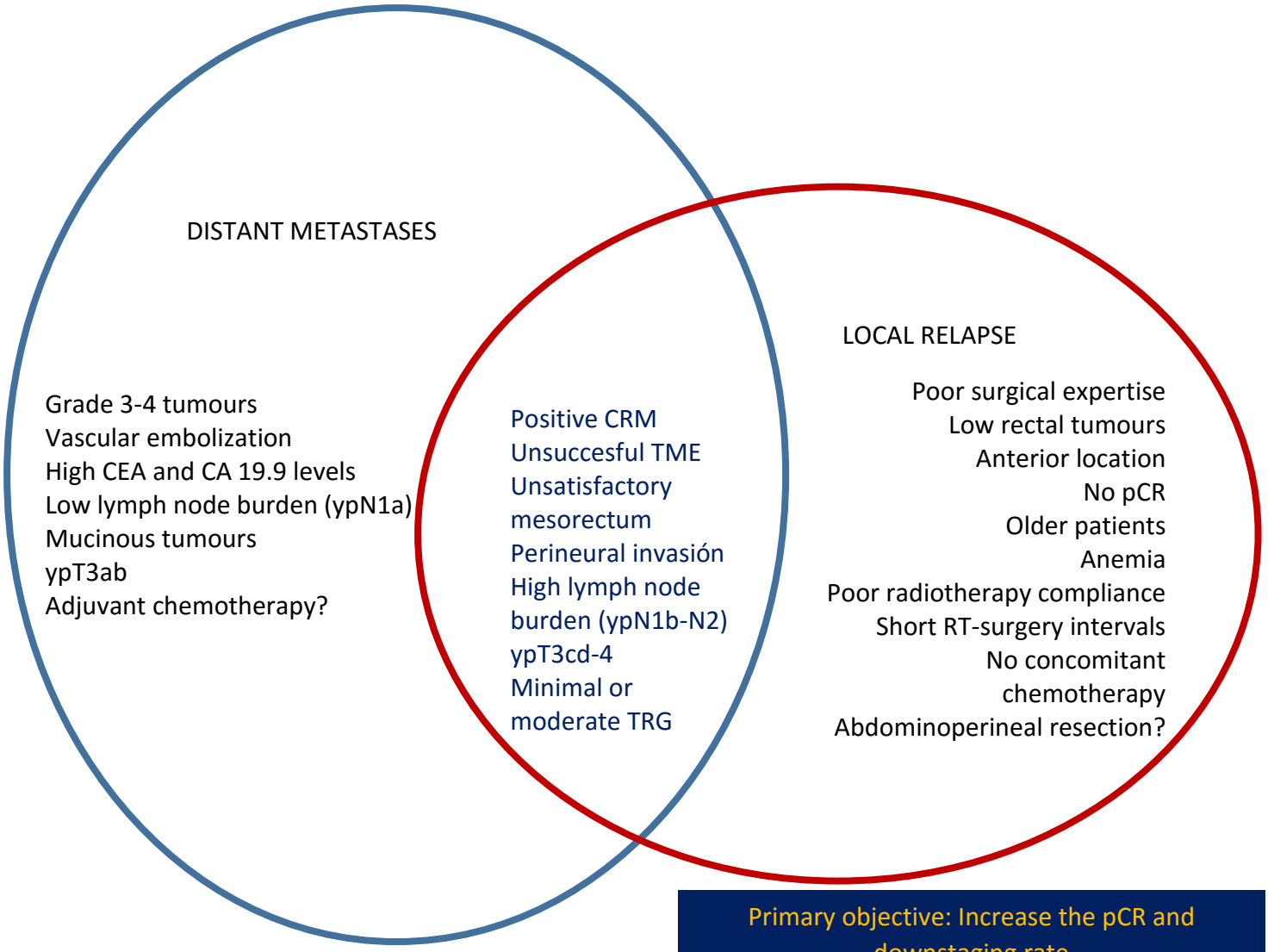
In this sense, the future management of rectal cancer patients will depend on what is the objective we are trying to achieve: in patients with a high risk of distant metastases, we know that induction chemotherapy is a suboptimal approach and these patients will benefit from a better integration of systemic chemotherapy in the neoadjuvant setting. In those patients with a high risk of local relapse, the role of radiotherapy will remain essential and we will try to maximize its use, be it with improved radiotherapy technique (IMRT, better-defined fields), higher doses, longer intervals between radiotherapy and surgery, better integration of concomitant and neoadjuvant chemotherapy and novel radiotherapy approaches, like the use of brachytherapy boosts. This essential role of neoadjuvant (chemo)radiotherapy will play also a role in organ-sparing approaches or even non-surgical management of patients with complete clinical responses. Although in its infancy, compared to other tumours, such as lymphomas, breast or lung cancer, newer insights into the molecular subtypes of colorectal cancer may help us tailor the systemic approaches in each individual patient (TABLE 55) [297].

All these improvements need the input of the multidisciplinary team, where improvements in radiological staging, in the pathological diagnosis and in the introduction of better surgical techniques will benefit our patients and allow us a more personalised approach to the management of our patients. We offer finally a graphical representation of what we think the future management of locally advanced rectal cancer will be.

Molecular subtype	Frequency	Molecular characteristics
CMS1 Immune activated	14%	Microsatellite-instability, immune pathway activation, righ-side tumours, older age, females, hypermutation, *BRAF* mutations, intermediate survival
CMS2 Canonical	41%	High chromosomal instability, strong WNT/MYC pathway activation, left-side tumours, *TP53* mutant, *EGFR* amplification or overexpression, better survival
CMS3 Metabolic	8%	Low chromosomal instability, moderate WNT/MYC pathway activation, *KRAS* and *PIK3CA* mutant, IGFBP2 overexpression, intermediate survival
CMS4 Mesenchymal	20%	Heterogeneity in chromosomal or microsatellite instability, mesenchymal/TGF-beta activation, younger age, NOTCH3/VEGFR2 overexpression, worse survival

TABLE 55: Four consensus molecular subtypes (CSM) in colorectal cancer which will probably be the basis for future clinical stratification and subtype-based targeted interventions [297]

Surgery in centres with experience, new surgical tecniques (ELAPE, interesphincteric surgery)
Improvements in baseline staging: High-quality MRI, identification of pathological lymph nodes, restaging MRI after neoadjuvant therapy, definition of the role of PET
Improvement in pathological diagnosis: recognition of perineural and vascular invasion, improvement in the harvest of lymph nodes, quality of the mesorectal study, standardized TRG, new prognostic factors (poorly differentiated clusters, immune infilitrates)



Primary objective: Improve DFS and OS

How: Better integration of chemotherapy at full doses

Potential approaches:
Induction chemotherapy before LCRCT
Consolidation chemotherapy after LCRCT or SCRT
Neoadjuvant chemotherapy with no RT
New agents: antiEGFR in *RAS*-native tumours

Primary objective: Increase the pCR and downstaging rate

How: Improve the effectiveness of neoadjuvant (chemo)radiotherapy

Potential approaches:
Improve radiotherapy compliance (IMRT, better-defined fields)
Longer intervals between LCRCT and surgery
6-8 week- interval between SCRT and surgery
Higher radiotherapy doses
Brachytherapy boost

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