

New Updates in Diagnostic Imaging and Treatment of Rectal Cancer

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Ginevra Danti¹, Diletta Santini¹, Francesca Treballi¹, Matilde Anichini¹, Caterina Giannessi¹,
Claudia Lucia Piccolo², Margherita Trinci³, Vittorio Miele^{1,4}

¹Department of Radiology, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy

²Department of Radiology, Fondazione Policlinico Universitario Campus Bio-Medico, 00128 Rome, Italy

³Department of Radiology, Colline Dell'Albegna, Azienda USL Toscana Sud-Est, 58015 Arezzo, Italy

⁴Department of Experimental and Clinical Biomedical Sciences “Mario Serio”, University of Florence, 50121, Florence, Italy

Colorectal cancer (CRC) is the third most common tumour in men and the second most common in women. It ranks as the third leading cause of new cancer cases and cancer-related deaths in both sexes. Due to differences in embryonic origin, rectal cancer (RC) is considered a distinct entity from colon cancer in terms of staging and treatment. Mortality rates in more developed countries are decreasing, largely due to increased screening and advances in the staging and treatment of rectal cancer. Current screening methods include faecal occult blood testing (FOBT) and rectosigmoidoscopy. For staging, the most commonly used imaging modalities are abdominopelvic magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS) for locoregional evaluation, and computed tomography (CT), MRI, or positron emission tomography (PET) for detecting distant metastases. Traditionally, the standard treatment for rectal cancer has been total mesorectal excision. However, more recently, it has been observed that patients with non-advanced stages of the disease may benefit from neoadjuvant radiochemotherapy, which can allow for less invasive surgery at a later stage. In recent years, radiomic studies have emerged to identify predictive features of tumour progression, with the goal of personalising treatment according to each patient's characteristics.

Keywords: rectal cancer; MRI; prognosis; treatment; radiomics

Introduction

Colorectal cancer (CRC) is the third most common cause of new malignancies, the third most prevalent tumour in men, and the second most frequent cancer in women. In the United States, CRC is the third leading cause of cancer-related death in both sexes. Overall, incidence is higher in more developed countries; however, according to a recent review by Horvat *N et al.* [1], mortality rates in these countries are lower compared to less developed regions, largely due to the expansion of screening programmes and advances in staging techniques.

The colon and rectum have distinct embryonic origins: the colon arises from the midgut, while the rectum arises from the hindgut. Their functions differ, the receptor gradients along these tracts vary, and tumours originating in the colon and rectum exhibit unique histological characteristics.

Wei EK *et al.* [2] suggest that differences in pH levels between the colon and rectum may influence how each responds to environmental factors. The progression from

normal rectal epithelium to dysplasia and eventually to invasive carcinoma typically occurs over a period of 10–15 years, during which genetic, somatic, and/or germline mutations accumulate.

Accurate diagnosis begins with clinical suspicion and a thorough medical history, followed by a physical examination that includes digital rectal examination. Diagnostic confirmation is achieved through endoscopic examination, which also helps determine the distance between the tumour and the anal verge (less than 15 cm) [3].

The first objective of this manuscript is to highlight the importance of magnetic resonance imaging (MRI) in the diagnosis, locoregional staging and treatment of rectal cancer. MRI is essential not only for initial tumour staging but also for evaluating the tumour's relationship with surrounding tissues, which significantly influences surgical and chemoradiotherapy planning.

The second objective is to describe the effectiveness of neoadjuvant therapy and its impact on surgical timing, as well as the role of chemoradiotherapy (CRT) in reducing the risk of local recurrence.

Finally, the third objective is to explore the potential of radiomics in extracting tumour characteristics and personalised treatment, emphasising the vital role of modern imaging in improving rectal cancer management.

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Correspondence to: Ginevra Danti, Department of Radiology, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy (e-mail: ginevra.danti@gmail.com).

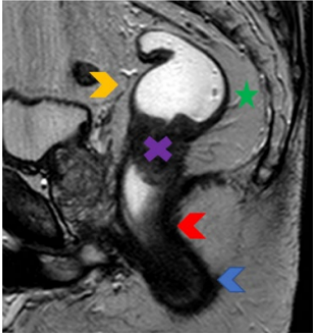
T2- weighted MRI	Anatomical landmark	Definition	Clinical relevance
	★ Retrorectal space	Virtual space between the posterior aspect of the MRF and presacral fascia	Posterior plane of the dissection in TME
	➡ Peritoneal reflection		
	✕ Tumor		
	➡ Anorectal ring	Muscular structure at the anorectal junction, on the top of the puborectalis muscle	Distance from the inferior edge of the tumor to the anal verge defines the tumor location as low, mid-, or high rectum
	➡ Anal verge	Lower edge of the anal canal	Inferior edge of the tumor in relation to the anal verge indicates high, mid-, or low rectal cancer

Fig. 1. Sagittal illustration and MRI image showing the retrorectal space, anorectal ring and anal verge. TME, total mesorectal excision; MRI, magnetic resonance imaging. The images are from AOU Careggi University Hospital and informed consent from the patient has been obtained.

Anatomy and Histology

The rectum is the final segment of the large bowel. It begins at the rectus-sigmoid junction, located at the level of the third sacral vertebra or the sacral promontory, and ends at the anorectal ring. The rectum measures approximately 12–15 cm in length; its lower portion is widened and referred to as the rectal ampulla.

The peritoneum is reflected at the level of the rectum, dividing it into intra- and extra-peritoneal portions. The rectovesical recess is lined by peritoneum extending from the rectum to the posterior wall of the bladder. Posteriorly, the rectum is separated from the pelvic nerves and the presacral vein by the presacral fascia.

Anterior to the rectum lies the fascia of Denonvilliers (also known as the rectoprostatic fascia), which separates the rectum from the prostate and seminal vesicles in men, and from the vagina in women (Fig. 1).

In recent years, surgical treatment of rectal cancer has increasingly aimed to preserve the anal sphincters. For this reason, it is crucial to determine the distance between the rectal tumour and the anal sphincters. The anal sphincter complex consists of internal and external sphincters, which are separated by an intersphincteric plane. The internal sphincter is the terminal part of the internal smooth muscle layer of the rectum, while the external sphincter is a continuation of the puborectal muscle and originates from the lower attachment of the elevator muscles of the anus (Fig. 2) [4].

The majority of rectal cancers are adenocarcinomas (90%), while less common types include adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma and gastrointestinal stromal tumours [5,6].

Rectal cancer adenocarcinomas can be further subclassified into cribriform, medullary, micropapillary, serrated, mucinous and ring cell types. Based on the proportion of glands, adenocarcinomas are graded as well-differentiated (more than 95%), moderately differentiated (more than 50%) or poorly differentiated (less than 49%). Additionally, they are grouped into two broader categories with prognostic significance: low grade (well to moderately differentiated) and high grade (poorly differentiated). A pathological diagnosis of mucinous or ring cell carcinoma is made when more than 50% of the stained cells exhibit these characteristics [7,8].

According to Lotfollahzadeh S *et al.* [3], the differential clinicopathological diagnosis includes neuroendocrine tumours [9–12], hamartomas, mesenchymal tumours, and lymphomas. MRI cannot reliably distinguish between anal and rectal tumours, as both rectal and anal adenocarcinomas typically present with intermediate signal intensity on T2-weighted imaging and show restricted diffusion. Therefore, as Congedo A *et al.* [13] emphasise, biopsy is essential for definitive diagnosis.

Epidemiology and Clinical Presentation

In the United States, approximately 135,439 new cases of CRC are diagnosed annually, with rectal cancer accounting for about 30% (39,910) of these cases. However, many cases of rectal cancer are still misclassified as colon cancer, making it difficult to obtain accurate mortality data specific to rectal cancer. Approximately 18% of rectal cancer cases occur in individuals under the age of 50, often presenting at a more advanced stage and with a poorer prognosis. Since 2004, the overall prevalence of CRC has been decreasing by 3% per year, except among screened young adults, where it

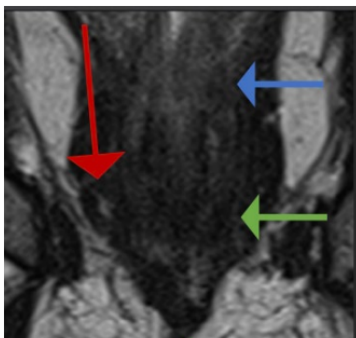
T2- weighted MRI	Anatomical landmark	Definition	Clinical relevance
	→ Internal sphincter	Continuation of the circular muscular layer of the rectum (smooth muscle)	Helps determine the stage of low rectal cancer, a higher risk of the involvement of the CRM (narrow mesorectum); involvement indicates worse outcomes; provides relevant information for determining whether to perform a sphincter-sparing surgery
	→ External sphincter	Mainly the continuation of the levator ani with puborectalis sling (skeletal muscle)	
	→ Intersphincteric groove	Plane between the external and internal sphincter	

Fig. 2. Coronal illustration and MRI image showing the internal sphincter, external sphincter complex and intersphincteric space. CRM, circumferential resection margin. The image is from AOU Careggi University Hospital and informed consent from the patient has been obtained.

has been increasing by 2% annually. In this group, the rise is largely attributed to cancers of the left colon and rectum, which have increased by 3.9% per year.

Incidence rates are generally higher in developed countries, particularly among individuals with lower socioeconomic status. This association is stronger for rectal cancer and weaker for right colon cancers. The trend is believed to be linked to limited access to healthcare and a higher prevalence of risk-related behaviours among lower socioeconomic populations [3].

According to Hadhr AF *et al.* [14], numerous reviews and studies have investigated the risk factors for colon and rectal cancers. However, only a few have attempted to distinguish between the environmental and genetic factors contributing to these cancers. Some studies suggest that a family history of CRC has a stronger influence on the risk of colon cancer than on rectal cancer [2]. Additionally, the prevalence of *K-RAS* and *p53* gene mutations in rectal cancer differs from that observed in colon cancer.

Recent reviews indicate that the gut microbiota plays a role in the development of rectal cancer [15–17]. Specifically, the gut microbiota has been shown to influence inflammatory processes and the anti-cancer immune response, particularly in patients with chronic inflammatory bowel disease [18].

Age and gender are significant risk factors for both colon and rectal cancers. A notable increase in colon cancer risk has been associated with greater height. Fazeli MS and Keramati MR [4] report that a history of radiotherapy for prostate cancer is an additional risk factor for rectal cancer. Environmental factors, such as diet and physical activity, may also affect risk. The link between cigarette smoking and rectal cancer is weaker than that for colon cancer [2].

Fortunately, a large number of early-stage cases are diagnosed through current screening programmes worldwide. Signs and symptoms of rectal cancer, which typically appear in more advanced cases, include changes in bowel

habits such as diarrhoea, constipation, or more frequent bowel movements; dark brown or bright red blood in the stool; narrow stools; a sensation of incomplete bowel emptying; abdominal pain; unexplained weight loss; and fatigue [4,19].

Screening

CRC mainly originates from adenomatous polyps, benign tumours caused by the proliferation of intestinal mucosal cells, which can take 7–15 years to transform into malignant forms. It is during this time window that screening allows for the early identification and removal of polyps before they acquire dangerous characteristics. The aim of colon and rectal cancer screening is to detect adenocarcinomas at an early stage and to resect adenomatous polyps. To achieve this, adequate coverage of the target population is essential, as stated by Shaukat *et al.* [20].

Polyps can be detected because they tend to bleed and protrude from the mucosa, making them visible on the surface. For this reason, the screening tests currently in use are faecal occult blood testing (FOBT) and rectosigmoidoscopy. The Ministry of Health recommends FOBT every two years for people aged between 50 and 69. In Italy, colonoscopy is only recommended if the FOBT test is positive. Regarding virtual colonoscopy, there is currently no evidence that it is superior to the tests used in screening programmes [21].

Histological examination of tissue is therefore necessary to confirm the diagnosis, which is followed by accurate staging. Genetic susceptibility is one of the most significant risk factors for developing colon and rectal cancers, which explains the importance of family history, particularly multiple affected first-degree relatives or early-onset CRC. In such cases, screening with colonoscopy is recommended even for the average-risk population.

Although screening rates decreased during the COVID-19 pandemic, Sutton TS *et al.* [22] report that patients with rectal cancer do not appear to present with higher acuity.

Staging

After the detection of rectal cancer, it is necessary to determine the local and distant extent of the tumour to guide the subsequent treatment strategy.

The American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 2018 Tumour, Lymph Node, Metastasis (TNM) staging system is the preferred system for staging CRC. It is based on three key factors:

The extent (size) of the tumour (T):

- Mucosa: the inner lining.
- Submucosa: the intermediate fibrous tissue beneath the aforementioned muscular layer.
- Muscularis propria: the thick muscle layer.
- Mesorectum: the fatty tissue surrounding the rectum, containing lymph nodes and lymph vessels.
- Mesorectal fascia (MRF): the thin layer surrounding the mesorectum.
- Spread to nearby lymph nodes (N).
- Spread (metastasis) to distant sites (M) (Table 1, Fig. 3) [23,24].

Abdominopelvic MRI and transrectal ultrasound (TRUS) are used for locoregional assessment. Distant metastases can be identified by computed tomography (CT), MRI, or positron emission tomography (PET), except for mucinous colorectal liver metastases, for which fluorodeoxyglucose (FDG)-PET has a significant false-negative rate [25]. For staging the primary tumour, it is important to perform rectal MRI to assess tumour location and morphology, T category, anal sphincter involvement, circumferential resection margin (CRM) status, pelvic lateral wall invasion, extramural venous invasion (EMVI), and N category. The location of the tumour should be described in the craniocaudal direction (lower, middle, or upper rectum) and in the circumferential plane (clock-face position), as well as its longitudinal length, distance to the anterior peritoneal reflection, and distance from the lower border of the tumour to the anal verge and the anorectal junction. Tumours are classified as low (0–5 cm from the anal verge), middle (5.1–10 cm from the anal verge), or high (10.1–15 cm from the anal verge). The morphological pattern of the tumour (polypoid, ulcerating, circumferential, or semi-circumferential), and particularly its presentation (non-mucinous or mucinous) must also be reported. Precise staging is essential to determine the need for neoadjuvant CRT or more invasive surgery.

The CRM refers to the surface of the non-peritonealised portion of the rectum that is removed during surgery. Its status is considered potentially positive if the measured distance is less than 1 mm or between 1 and 2 mm. It is important to remember that the rectum is not completely surrounded by the MRF. Therefore, CRM status is not applicable when the tumour is located in a peritonealised area of the rectal wall. A positive CRM is the main predictor of local relapse and poor prognosis.

EMVI, which has moderate sensitivity and high specificity, is an important prognostic factor and a predictor of

metastatic disease, as shown in other cancers studied using dual-energy CT [26–30]. EMVI is defined as the extramural extension of the tumour within the mesorectal vessels, characterised by wall abnormalities, focal enhancement, and/or the presence of tumour signal inside the vessel. Many metastatic lymph nodes in rectal cancer are smaller than 5 mm, but size alone is not a reliable indicator. However, several studies have shown that lymph nodes larger than 8 mm in the short axis are highly specific for metastatic involvement. According to Maggialelli N *et al.* [31], the assessment of malignant lymph nodes should consider size and morphological features, including irregular borders, heterogeneous signal intensity, and round shape.

Regional lymph nodes involved in rectal cancer include the mesorectal, superior rectal, middle rectal, inferior rectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, sacral promontory, and internal iliac nodes. Lymph nodes involved outside this group are classified as distant metastases (M1) [1]. Biller LH and Schrag D [32] report that 20% of patients with newly diagnosed CRC have metastatic disease at the time of diagnosis.

Prognostic Factors

The outcome of patients with rectal cancer is influenced by various factors, such as the tumour's adherence to or invasion of adjacent organs [33]. The disease spreads via the lymph nodes, many of which may be positive for distant metastases. Bowel perforation or obstruction is a serious complication for the patient. Positive surgical margins, lymphovascular and perineural invasion, and poorly differentiated histology are other high-risk pathological features [34,35]. The CRM, the depth of tumour invasion through the intestinal wall measured in millimetres, is an important factor in tumour staging. Finally, as reported by Keller DS *et al.* [36] and Wang Q *et al.* [37], the presence of microsatellite instability (MSI) is another important prognostic factor [38]. More recently, several new approaches have shaped therapeutic models, including changes in the timing, sequence, and duration of therapies, along with potential de-escalation of therapeutic agents, as described by Deschner BW *et al.* [39].

Diagnostic Imaging of Rectal Cancer

When rectal cancer is suspected, the initial clinical evaluation typically includes several key steps: physical assessment, history taking, digital rectal examination, colonoscopy, biopsy, carcinoembryonic antigen (CEA) testing, immunohistochemistry, and DNA mismatch repair or MSI testing, as outlined by the National Cancer Institute (NCI) [21].

Imaging evaluation involves several approaches. Sigmoidoscopy and colonoscopy are common tools for diagnosing and screening rectal cancer, although endoscopy is ultimately required for tissue biopsy. Double contrast barium enema (DCBE) is another diagnostic tool, but is no longer widely used. Other imaging techniques, such as MRI and

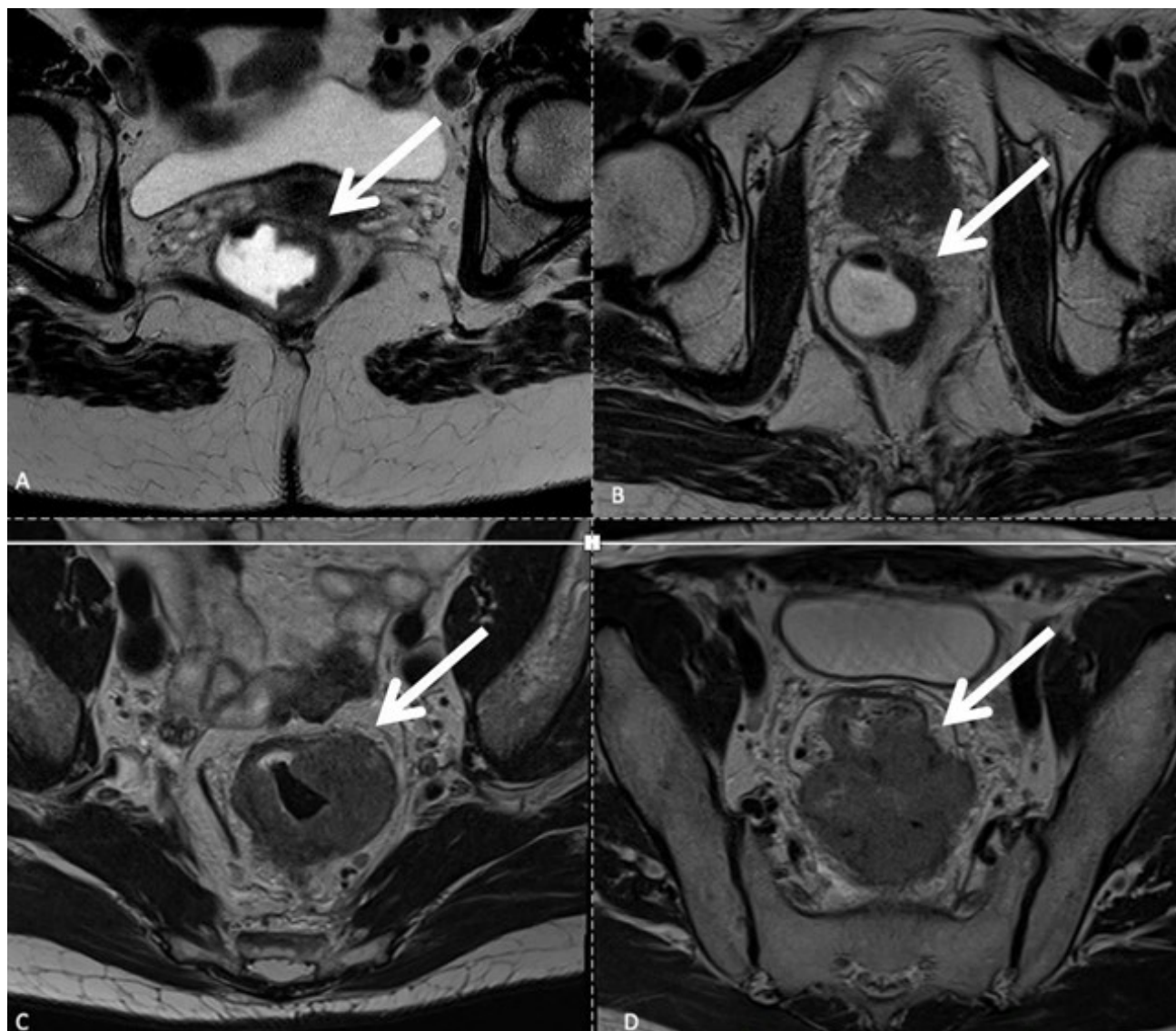


Fig. 3. Staging. (A) T2 staging: the tumour extends from the mucosa (T1) to the muscularis propria (T2) (white arrow). (B) T3a-b staging: the tumour extends beyond the muscularis propria by 1–5 mm (white arrow). (C) Tc-d staging: the tumour extends beyond the muscularis propria by more than 15 mm (white arrow). (D) T4 staging: the tumour extends into the peritoneal cavity (white arrow). The images are from AOU Careggi University Hospital and informed consent from the patient has been obtained.

endoscopic ultrasound (either transrectal or transvaginal), are used to stage the tumour. TRUS is particularly useful for differentiating between localised cancers involving only the mucosa and submucosa and those extending into the muscularis propria or perirectal fat.

MRI is a highly precise imaging modality for staging rectal cancer and plays an important role not only in the early stages of the tumour but also in assessing response to treatment and detecting local recurrence. CT scans can identify both local and distant metastases in rectal cancer patients and evaluate tumour-related complications such as obstruction, perforation or fistula formation. Although PET is not routinely recommended for preoperative staging of rectal cancer, it may be useful in locating sites of relapse in patients with elevated serum CEA levels [4].

Endoscopy

TRUS has been shown to be an effective method for local stage classification, especially in early-stage rectal cancer. It has a sensitivity and specificity of 88% and 98%, respectively, for T1 stage tumours, and 81% and 96% for T2 stage tumours. Compared to MRI, TRUS demonstrates higher specificity (86% vs. 69%) with comparable sensitivity in evaluating muscularis propria invasion (T1 vs. T2 tumours). Therefore, it is currently recommended for distinguishing between T1 and T2 primary tumours, as noted by Patel UB *et al.* [40].

However, TRUS has limitations, particularly in nodal staging, due to its limited field of view, which may reduce its effectiveness in assessing more distant lymph nodes. Nevertheless, studies have shown that TRUS and MRI have comparable accuracy for regional nodal staging [41]. Ad-

Table 1. TNM classification of rectal cancer.

T	Category
Tx	Primary tumour cannot be assessed
T0	No evidence of a primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1	Submucosa
T2	Muscularis propria
T3	Subserosa and perirectal tissue
	a <1 mm b 1–5 mm c 5–15 mm d >15 mm
T4	a: Tumour penetrates to the surface of the visceral peritoneum b: Tumour invades or is adherent to other organs or structures
N	Category
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	a: 1 lymph node b: 2–3 lymph nodes c: Tumour deposit(s) in the subserosa, mesentery or non-peritonealised perirectal tissues
N2	a: 4–6 lymph nodes b: 7 or more regional lymph nodes
M	Category
M0	No distant metastasis
M1	Distant metastasis
	a: Metastasis confined to one organ or site (e.g. liver, lung, nonregional lymph nodes) b: Metastasis in more than one organ and/or site or in the peritoneum

TNM, Tumour, Lymph Node, Metastasis.

ditionally, as highlighted by Kalisz *et al.* [42], TRUS has limited utility for local staging after neoadjuvant treatment, since ultrasound struggles to differentiate between residual tumour and fibrosis [43].

CT and PET

CT has shown variable accuracy in staging primary rectal tumours and in evaluating the CRM [44]. However, some improvements have been made due to technological advances, such as the introduction of contrast-enhanced multidetector computed tomography (MDCT), dual-energy CT (DECT) [45–47], virtual monoenergetic imaging (VMI) [48], and the use of multiplanar reformatted images.

The primary role of CT in rectal cancer is M staging, which involves assessing metastatic spread. Common sites of metastasis include the liver, lungs, nervous system, bones, and peritoneal areas. Additionally, CT is useful for evaluating nodal metastases, although identification is pri-

marily based on size criteria, with 6 mm considered the ideal cut-off for the short-axis measurement when assessing mesorectal and lateral pelvic lymph nodes.

Granata V *et al.* [49] emphasise the importance of structured CT reports, which are essential during the staging phase to enhance communication between radiologists, multidisciplinary team members, and patients.

Recent studies, including those by Borgheresi A *et al.* [50] and Scialpi M *et al.* [51], have demonstrated that integrating PET into staging, especially for M staging rather than nodal staging, holds promise as a prognostic tool. This integration could help stratify patients into more precise clinical categories for precision medicine and appropriate treatments. Nevertheless, PET is not currently recommended for initial local staging [42].

Computed tomographic colonography (CTC) is another accurate and widely accepted non-invasive imaging modality for the colon [52].

MRI

As the treatment of rectal cancer evolves and becomes more precise, high-resolution imaging techniques enable the identification of key tumour features, facilitating the development of more appropriate management strategies.

Since the initial recommendation to include MRI in the assessment of rectal cancer, this technique has increasingly influenced treatment strategies over the past decade by providing valuable predictive and prognostic information. MRI is now an integral and essential part of the standard diagnostic pathway for patients [33,53].

MRI is critical for primary tumour staging, as it enables the assessment of the relationship between the mass and surrounding structures. It also allows for the analysis of related characteristics that might influence the surgical procedure or chemoradiation treatment for the patient [54].

The primary cancer stage is mainly determined using high-resolution T2 MRI images and diffusion-weighted imaging (DWI) maps [55–57]. T1 and T2 tumours are confined to the rectum and are evaluated by comparing the tumour to the outer layer of the surrounding hypointense muscularis propria. However, MRI has limitations in distinguishing between T1 and T2 tumours: T1 tumours are limited to the relatively hyperintense submucosal layer, whereas T2 tumours extend beyond the submucosa without crossing the muscularis propria. It is not always easy to differentiate between these stages on MRI due to the similar signal intensity of the tumour and the muscularis propria.

For early-stage cases, TRUS is recommended, as it has been shown to offer improved specificity with comparable sensitivity [53].

If the lesion extends beyond the muscularis propria and infiltrates the mesorectal adipose tissue, it is classified as T3. These lesions can be further subdivided based on the depth of extramural infiltration into the mesorectal adipose tissue: T3a (<1 mm infiltration), T3b (1–5 mm infiltration), T3c (5–15 mm infiltration), and T3d (>15 mm infiltration). T3a tumours have a more favourable outcome, comparable to that of T2 tumours [58].

Invasion of adjacent tissues is indicated by the loss of the characteristic fat layer that normally separates the tumour from surrounding structures, or by direct replacement, evidenced by tumour signal intensity within a nearby structure. MRI is also used for post-treatment evaluation, by comparing tumour volume on images acquired before and after chemoradiation treatment, using T2-weighted, high spatial resolution, axial oblique MRI images [59–61].

In addition, MRI plays a crucial role in surgical planning, particularly when the tumour is located in the lower rectum, where the relationship between the tumour and the anal canal is important for selecting the optimal surgical procedure. MRI is also essential in cases of locally advanced or recurrent tumours that invade nearby pelvic organs and may require more complex procedures, such as pelvic exenteration.

With the advent of organ-preserving approaches—including local transanal excision and the ‘watch and wait’ strategy—MRI facilitates patient selection for these therapies, ongoing follow-up, and the detection of tumour regrowth [53].

However, it should be noted that these techniques have several limitations [62]. Firstly, conventional MRI methods for lymph node staging have modest predictive accuracy for detecting lymph node metastases when size alone is used to determine disease involvement, due to significant dimensional overlap between benign and malignant lymph nodes [53,62]. Morphological criteria defined by high-resolution MRI improve the precision of lymph node stage classification. Indeed, research has shown that size by itself has low accuracy, but incorporating morphological features based on shape, margin, and signal intensity characteristics enhances precision [53,62].

Secondly, distinguishing the possible presence of residual tumour from post-treatment changes based solely on T2-weighted MRI sequences can be challenging. In these cases, DWI sequences provide significant assistance [63], as highlighted by Fusco R *et al.* [64]. Similar to the pre-treatment phase, tumour assessment and re-staging after chemoradiation are based on TNM and AJCC criteria. MRI combined with volumetric analysis has been shown to be highly accurate in distinguishing T0–T2 tumours from those with T3 disease [65].

According to Petrillo A *et al.* [66], Dynamic contrast-enhancement (DCE)-MRI is a promising option for distinguishing responders from non-responders after neoadjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC).

For rectal cancer, MRI-based structured reporting should be adopted to standardise staging and post-treatment restaging as much as possible, thereby facilitating patient management by oncologists and surgeons [67], as noted by Fusco R *et al.* [68]. Additionally, Rossi A *et al.* [69] highlight another advantage of using MRI in staging these pathologies: whole-body MRI (WB-MRI) examinations are generally well tolerated by adult patients with various malignancies and bone diseases, including lung and CRC.

Treatment

The management of rectal cancer has seen significant advances over the past four decades with the introduction of a standardised surgical technique for tumour removal: total mesorectal excision (TME). An increased understanding of the surgical oncology of rectal cancer, combined with the addition of adjuvant and neoadjuvant treatments alongside surgery, has led to a substantial decrease in local recurrence and improvements in overall survival [70]. This progress has encouraged a multidisciplinary approach to disease management. Appropriate patient selection for different surgical options and the use of a multimodal strategy can greatly influence recurrence rates and prognosis [71]. In managing rectal cancer in elderly patients, it is vital to

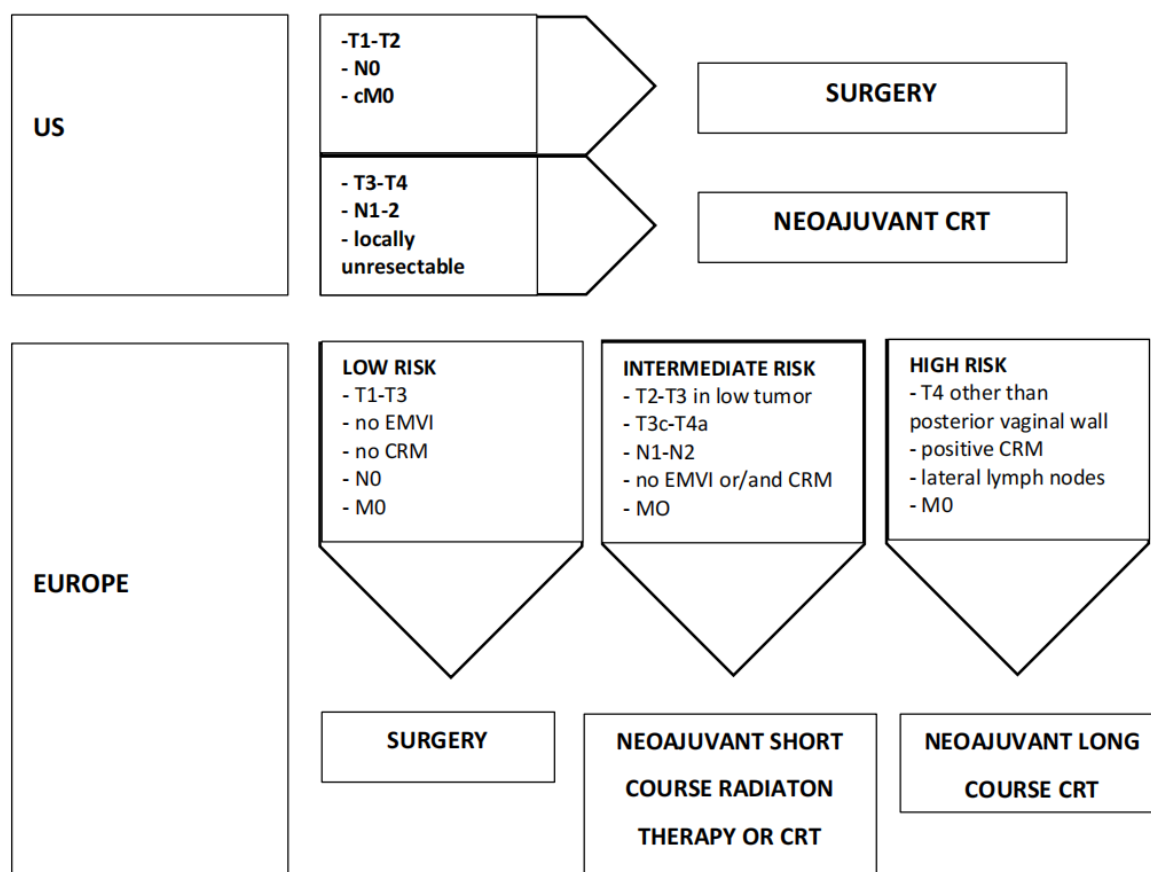


Fig. 4. Schematic flowchart summarising the current management concepts of rectal cancer in the United States and Europe. CRT, chemoradiotherapy.

tailor therapeutic strategies according to life expectancy and individual tolerance, as emphasised by Huang *et al.* [72]. Principles of rectal cancer management in the United States and Europe are outlined in Fig. 4. Endoscopic resection (ER) is limited to selected low-risk patients with early-stage disease (cT1N0M0) who have undergone complete excision of a rectal polyp. Surgical resection (RC) is indicated for lesions that do not infiltrate the muscularis propria and are lymph node negative (cT2N0M0). For locally advanced but potentially curable rectal cancer (cT3-4N0-2M0), neoadjuvant combination chemoradiotherapy (CRT) is recommended. Adjuvant therapy is strongly advised for T3 tumours and/or those with lymph node positivity. Surgery combined with perioperative chemotherapy remains a viable curative option for patients with oligo-metastatic colorectal lung and liver cancer. For patients ineligible for surgery, with locally advanced unresectable disease, or with a high metastatic burden, palliative systemic chemotherapy is proposed to improve quality of life, and prolong survival, as reported by Lotfollahzadeh S *et al.* [3].

Radiotherapy and Chemotherapy

Neoadjuvant Therapy

There is strong evidence supporting the use of neoadjuvant therapy in stage II (T3 or T4 with negative lymph nodes)

and stage III (with positive lymph nodes) rectal cancer, although the optimal treatment approach has not yet been fully defined. The ideal timing for surgery after neoadjuvant therapy varies according to guidelines: the National Comprehensive Cancer Network (NCCN) recommends 5–12 weeks, while the European Society For Medical Oncology (ESMO) suggests 4–12 weeks.

Clinical trials have shown that CRT administered within these time windows does not increase the risk of surgical complications. Compared to postoperative CRT, preoperative CRT has been shown to reduce local recurrence rates (6% vs. 13%) and toxicity (27% vs. 40%), but it does not affect the rate of distant metastases (29%) or 10-year overall survival (59%). The European Organisation for Research and Treatment of Cancer (EORTC) trial 22921 highlighted the benefit of adding chemotherapy to preoperative radiotherapy, followed by either three cycles of adjuvant chemotherapy or observation alone, as confirmed by Vendrely V *et al.* [73].

Chemoradiotherapy (CRT) consists of delivering 45 Gy to the posterior pelvis, divided into 25 fractions of 1.8 Gy over five weeks. The combination of fluorouracil and leucovorin (FU/LV) is considered the current standard chemotherapy regimen, although capecitabine has emerged as a viable alternative (Fig. 5) [3].

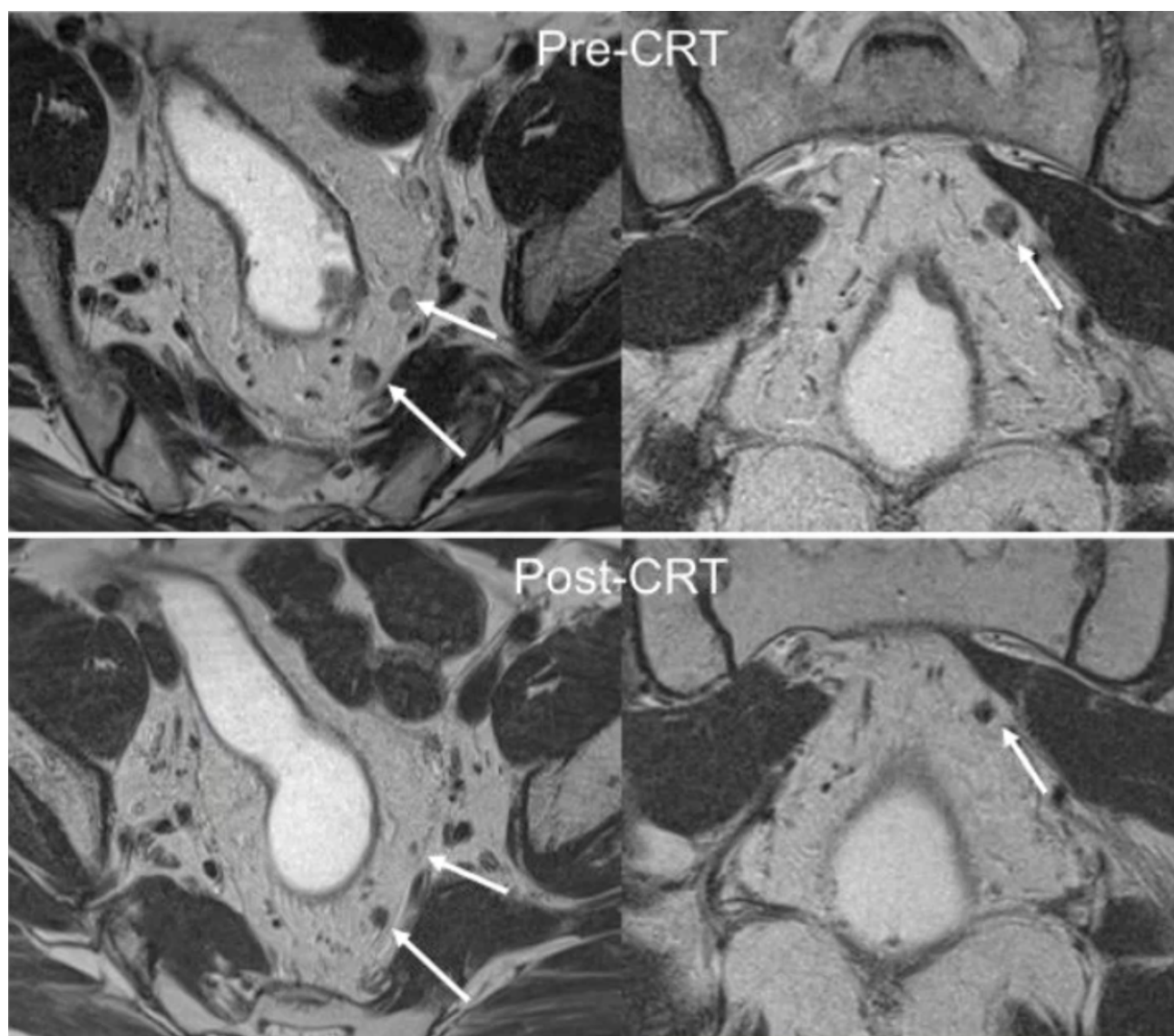


Fig. 5. Assessment of response after therapy. Above: initial MRI of rectal cancer before CRT; Under: Follow-up MRI after treatment. The white arrows indicate the lymph nodes before and after treatment. The images are from AOU Careggi University Hospital and informed consent from the patient has been obtained.

According to Mantello G *et al.* [74], when assessing a patient with relapsed rectal cancer, re-irradiation (Re-RT) should be considered as part of a multidisciplinary discussion, as it may increase the chances of surgical resection and improve prognosis. The choice of neoadjuvant strategy is a key step in managing patients with LARC, as highlighted by Borelli B *et al.* [75].

Additionally, approximately 90% of patients with rectal cancer survive three years after receiving neoadjuvant CRT followed by surgery [75]. Recent clinical trials in LARC have shown that combinations of chemotherapy and PD-1/PD-L1-targeted immunotherapy can be safely administered prior to surgery with curative intent. Indeed, integrating PD-1-targeted immune checkpoint blockade offers the possibility of activating antitumour immunity, which increases the likelihood of complete tumour eradication and reduces the risk of metastasis [76].

Adjuvant Therapy

For stage II (T3–T4) and stage III disease (with positive lymph nodes), adjuvant therapy is strongly recommended. Five-year cancer survival rates with surgery alone may range from 30% to 60%. Both American Society of Clinical Oncology (ASCO) and NCCN guidelines recommend that all patients with stage II and III rectal carcinoma be offered adjuvant therapy, regardless of the surgical resection results. In contrast, ESMO recommends reserving adjuvant therapy for patients with high-risk factors for recurrence, such as positive margins, perforation, involvement of nearby organs, incomplete TME, tumour implants, and extracapsular nodules.

According to NCCN guidelines, postoperative chemotherapy—using FOLFOX regimens as described by Bimonte S *et al.* [77], or CAPOX, given sequentially

before and/or after combination chemoradiotherapy (with fluoropyrimidine as a radiosensitizer), is recommended within 4–6 weeks after recovery from surgery. The total duration should not exceed 6 months, or 4 months if CRT was performed prior to surgery.

ASCO guidelines emphasise that chemotherapy dosage should be calculated based on the patient's weight. Furthermore, as highlighted by Boldrini L *et al.* [78], the application of radiomics and artificial intelligence (AI) in image-guided radiotherapy (IGRT) protocols has a significant impact on all phases of radiotherapy.

Surgery

The surgical management of rectal cancer varies according to patient- and tumour-related factors, with the primary goal of maximising survival and preserving function while minimising the risk of recurrence. A thorough clinical assessment of the tumour by the colorectal surgeon, through physical examination, is crucial in developing the treatment plan. This assessment includes analysis of tumour location, tumour mobility, distance from the sphincter, and pelvic floor status [32].

Two main surgical approaches are central to the debate: radical surgery, which involves removal of the rectum and surrounding mesentery, and conservative organ-sparing techniques, which focus on local excision of the lesion or, in some cases, complete deferral of surgery, as described by De Muzio F *et al.* [79].

ER

ER aims for the complete removal of the tumour by local excision. This procedure is offered to patients who are willing to undergo rigorous surveillance, accept the possibility of surgical resection if the disease progresses to T2, and/or are considered unfit for conventional surgery [80].

ER of rectal cancer (RCA ER) is recommended for patients with stage T0–T1 tumours that are smaller than 3 cm, mobile, have adequate resection margins as assessed by TRUS, show no distant metastases, and do not present any of the previously described high-risk factors [3].

According to Li W *et al.* [81], transanal endoscopic microsurgery is a promising alternative for managing early-stage rectal cancer, as it preserves the anorectal sphincter structures and thus has minimal or no impact on the patient's quality of life, particularly regarding continence.

Surgical Resection

The main goal of surgical excision for advanced rectal cancer (RCA) is to completely remove the tumour and eliminate lymphovascular invasion with negative margins: a minimum of 5 cm proximal margin, 2 cm distal margin, and 1 mm radial margin. A secondary objective is to restore intestinal transit, either through a one-stage primary anastomosis or a two-stage temporary diversion.

Although open transabdominal surgery remains the preferred technique, laparoscopic methods are recommended

for select patients. The choice of surgical procedure depends on whether the sphincter can be spared via low anterior resection (LAR) or if an abdominoperineal resection (APR) is required, based on preoperative staging and the feasibility of achieving adequate distal margins with LAR [82].

Regardless of the approach, all APR and LAR procedures should include TME to ensure safe margins and lymphadenectomy, as described by Rega D *et al.* [83]. LAR remains the reference standard and is favoured when negative margins under 1 cm are achievable, particularly in cases of poorly localised RCA, salvage surgery, and poor anorectal function [3].

However, radical resection carries a significant risk of post-operative complications and can substantially reduce quality of life [84,85], including LARS syndrome (LARS)—a range of bowel dysfunctions occurring after low or ultra-low anastomosis, as described by Zhang R *et al.* [86].

TME is the transabdominal surgical gold standard for managing rectal cancer. Its use significantly improves clinical outcomes and quality of life. TME involves complete removal of the mesorectum following the MRF plane.

LAR is the primary transabdominal procedure for tumours of the middle or upper rectum and is performed with TME plus partial or total resection of the sigmoid colon. For tumours in the lower rectum beyond the anorectal junction, ultra-LAR offers a sphincter-sparing option, creating a coloanal anastomosis approximately 1 cm below the tumour's lower edge.

Standard APR with TME is reserved for tumours invading the anal canal or sphincter, tumours less than 1 cm from the anal verge, or cases where sphincter preservation would result in incontinence. This procedure involves removal of the sphincter complex and the creation of a permanent colostomy.

Intersphincteric abdominoperineal surgery is a sphincter-sparing procedure for patients whose intersphincteric plane is not involved by cancer. Resection is carried out within the intersphincteric plane, preserving the external sphincter. Extralevator APR is reserved for tumours invading the intersphincteric plane, external sphincter, and/or levator muscles of the anus. This procedure involves a more extensive sphincter complex removal, avoiding the 'hourglass' shape typical of conventional APR and producing a cylindrical surgical specimen. Its primary goal is to reduce the risk of bowel perforation and tumour contamination during surgery, as well as to prevent positive radial surgical margins (CRM), as described by Horvat N *et al.* [1].

Robotic surgery is an emerging technology that can overcome the technical limitations of traditional laparoscopic approaches, enhancing the precision and effectiveness of radical surgery [87].

Systemic Therapy

Over half of patients with CRC present with metastases, predominantly in the liver (80%–90%). The prognosis for

patients with advanced, metastatic, unresectable CRC remains poor, with a mean overall survival (mOS) of only 5–6 months, even with the best supportive care. An exception is a subgroup of patients with hepatic or pulmonary oligo-metastases, who may be eligible for treatment with perioperative chemotherapy.

The goals of systemic treatment for unresectable metastatic CRC are to control symptoms, improve quality of life, and prolong survival. The current variety of nine different classes of antineoplastic drugs and over a dozen treatment options for metastatic CRC (mCRC) has resulted in a wide range of treatment combinations and sequences, with no definitive guidelines. The ideal therapy balances the highest overall response rate (ORR), the greatest impact on metastases to enable surgical conversion, and/or prolonged progression-free survival (PFS) and overall survival (OS), as reported by Hsu *et al.* [88], while maintaining a manageable toxicity profile.

Treatment decisions are strongly influenced by predictive biomarkers such as *RAS* and *BRAF* mutation status and MMR/MSI status, as well as the primary tumour and metastasis sites, patient condition (including performance status and comorbidities), and clinical objectives (palliation or surgery). First-line therapy typically involves a regimen based on folinic acid (also called leucovorin), fluorouracil, and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CAPOX), or folinic acid, fluorouracil, and irinotecan (FOLFIRI), combined with an anti-*EGFR* agent (cetuximab or panitumumab) for wild-type *RAS/BRAF* tumours located in the left colon, or an anti-*VEGF* agent (bevacizumab) for *RAS/BRAF*-mutant or right colon tumours.

According to reports by Lotfollahzadeh S *et al.* [3] and Avallone A *et al.* [89], in cases of disease progression or intolerable toxicities, treatment is changed to an alternative second-line therapy, either by continuing the previous anti-*VEGF* agent or introducing a new biological agent, regardless of tumour site.

Radiomic Features

Radiomics is a novel technique capable of extracting multiple features from medical imaging, showing significant promise for disease detection, patient classification [90], predicting local treatment response [91–93], estimating disease-free survival [94–96], as reported by Xue K *et al.* [97], and identifying features otherwise invisible to the human eye [98,99]. The growing importance of radiomics in oncology, particularly for optimising diagnosis, staging, tumour classification and improving personalised treatment, is now widely recognised [100–103].

Additionally, radiomics is emerging as a promising tool for characterising liver metastases in rectal cancer [104,105], evaluating lymph nodes [106–111], and aiding preoperative diagnosis of T2 and T3 rectal cancer by analysing radiomic features of mesorectal fat MRI. It is also useful in predicting extranodal extension, as suggested by Li H *et al.* [112] and Wang C *et al.* [113].

Given the limitations of current imaging modalities and the understanding that radiological images provide far greater detail than can be perceived by the human eye, there is growing focus on radiomics. This technology has been widely used for non-invasive quantitative analysis of various neoplasms to assess tumour aggressiveness [114–116], treatment resistance, and histopathological, genomic, and proteomic characteristics of lesions [93,117,118]. According to Chiloire G *et al.* [119] and Marinkovic M *et al.* [120], the radiomic signature could also support the personalisation of therapies for patients with the same clinical stage of rectal cancer.

Radiomic analysis is based on the automated extraction of various quantitative features from imaging data, providing valuable support for clinical decision-making, as highlighted by Chen J *et al.* [121]. Previous studies have investigated the role of radiomics in MRI to differentiate malignant tumours from benign tissues, provide insight into cancer aggressiveness, and predict response to CRT [121–124]. In particular, Santini *et al.* [124] and Zhao R *et al.* [125] proposed an MRI-based radiomic model capable of predicting treatment response in patients with LARC.

Another study by Jayaprakasam *et al.* [126] evaluated radiomic features of mesorectal adipose tissue predictive of good or poor response in patients with rectal cancer undergoing neoadjuvant therapy. These features could discriminate early disease with strong surgical potential from disease likely to regress with medical therapy, potentially reducing the need for surgery in some patients or facilitating earlier management decisions at presentation. The use of radiomics in combination with FDG-PET imaging has also shown promise in predicting the efficacy of CRT [126].

Today, accumulating evidence shows that not all clinical risk characteristics are equivalent, and the decision to treat rectal cancer with adjuvant chemotherapy requires evaluation by a multidisciplinary team [53,127]. In this context, radiomics could provide an important additional tool in the clinical workup of rectal cancer. Recent studies have focused on preoperative differentiation between low- and high-grade rectal cancer and the prediction of lymph node metastasis.

However, radiomics still faces some limitations that challenge its routine clinical use [53]. In particular, the lack of standardisation and validation, poor reproducibility, and the absence of multicentre prospective studies remain major obstacles that must be overcome to implement radiomics in clinical practice [127,128].

Conclusions

MRI plays a fundamental role in the care of patients with rectal cancer by enabling accurate local staging and identifying risk factors for local and distant relapse. This information helps guide treatment decisions and improve patient prognosis. Additionally, the effectiveness of neoadjuvant chemoradiation enhances the success of subsequent surgical treatment by reducing disease recurrence. Significant

research efforts in radiomics are ongoing, which may help select the most appropriate patients for specific treatments through improved risk stratification.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, GD and VM; methodology, GD, DS; investigation, GD; resources, GD, MT; data curation, GD, FT; conception and design: MT and CG; analysis and interpretation data: MA and CP; writing—original draft preparation, GD, FT, CG; writing—review and editing, GD, MA, MT; visualization, CP; supervision, VM; project administration, VM, FT. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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