UPDATE IN RADIOLOGY

Prognostic factors and functional imaging in rectal cancer

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Abstract  The outcome of treatment for rectal cancer in recent years has been improved by diverse advances in the field of surgery and in neoadjuvant oncologic therapies. Heald’s introduction of the concept of the mesorectum as an anatomical unit (total mesorectal excision) in 1982 and the generalization of preoperative radiochemotherapy have improved the prognosis in a significant number of patients. Owing to these advances, it has become necessary for imaging studies to define a series of prognostic factors for tumors, both before and after neoadjuvant treatment, to make it possible to tailor treatment for individual patients with rectal tumors.

On the other hand, the advent of functional and molecular imaging techniques has provided a way to study a series of distinctive tumor characteristics in vivo, including the angiogenesis, metabolism, or cellularity of rectal tumors, and these techniques are making a growing contribution to the prognosis, staging, treatment planning, and evaluation of the response to therapy in patients with rectal cancer.

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Factores pronósticos e imagen funcional del cáncer de recto

Resumen  La evolución del tratamiento de cáncer de recto durante los últimos años ha estado condicionada por diversos avances en el campo de la cirugía y terapias oncológicas neoadyuvantes. La introducción por Heald en 1982 del concepto del mesorrecto como unidad anatómica (escisión mesorrectal total) y la generalización de la radioquimioterapia preoperatoria, han determinado una mejora del pronóstico en un número significativo de pacientes. Debido a estos avances, ha surgido la necesidad de que la imagen defina una serie de factores pronósticos del...
Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors. In one-third of the cases, CRC is diagnosed in the rectum, and rectal involvement has a worse prognosis due to a higher rate of local recurrence and a higher incidence of metastasis at diagnosis.\(^1\)

Although surgery is still the fundamental therapeutic tool, the management of rectal cancer patients has changed and is being delivered by a multidisciplinary team. These multidisciplinary teams tailor individualized treatment strategies according to patient and tumor features.\(^2,3\)

In this setting, imaging studies are no longer exclusively reliant on the TNM system to stage rectal cancer patients, but also on prognostic factors that were traditionally obtained through histopathological analysis. Significant prognostic factors are depth of the intramural/extramural invasion, distance from the tumor to the mesorectal margin, involvement of lymph nodes, vascularity and peritoneum, as well as involvement of the sphincter complex. The overall assessment of these factors determines both the need for neoadjuvant therapy and the type of surgical technique to be used.\(^4-7\)

Furthermore, as a result of a greater insight into tumor biology, we now know that neoplasms are very complex and variable pathologic models, where balance between certain processes, such as angiogenesis, tumor cellularity, metabolism, and oxygenation determines the behavior of these tumors. Many of these tumor features are currently assessed by functional or molecular imaging techniques,\(^8,9\) so that diagnostic imaging provides information that potentially helps both plan an individualized management of patients and predict tumor response to the treatment.

Basically, the ultimate goal of rectal cancer (RC) management would be to implement imaging techniques to obtain a set of morphologic and functional/molecular data related to the patient progress (survival, progression-free interval, etc.).\(^10\)

Prognostic factors in rectal cancer

In recent years, the role of presurgical assessment by rectal cancer imaging has changed significantly. This change is due to the implementation of total mesorectal excision (TME), to the good outcome after neoadjuvant therapy in selected patients, as well as to the interest in assessing response to such therapy. These events have shifted the focus of imaging techniques from the traditional TNM staging to the evaluation of the above mentioned prognostic factors. These factors enable individualized management of RC patients, characterization of tumor maps, planning of the appropriate surgical approach, and decision-making on the use of neoadjuvant therapy.\(^4,5,11\) Assessing all these elements and including them in the radiological report are crucial tasks for the radiologist. In this respect, the use of structured reports that systematically include these elements seems to enhance RC imaging evaluation by avoiding obviating key data to be considered for decision-making, by facilitating inter-department information exchange, and by fostering scientific research\(^12\) (on-line reporting form).

Topographic and morphologic tumor mapping

Crucial for accurate rectal neoplasm evaluation is the understanding of the mesorectal anatomy and its adequate imaging assessment, which is part of the information that must be provided to the surgeon or radiotherapeutic oncologist.\(^13,14\) Magnetic resonance (MR) imaging enables tumor mapping by determining the distance to the anal margin, endoluminal tumor extension, tumor morphology, and the involvement of the sphincter complex and the levator muscles (Fig. 1).\(^4,5,11\) All these aspects determine the type of potential surgical or radiotherapeutic approach, and could help set a standard of reference to audit the surgical outcomes. Moreover, some findings of tumor morphology (long or ulcerated tumors and wide involvement of the circumference of the rectal lumen) should alert the radiologist to the possible extramural tumor involvement, even if this is not conspicuous.\(^4\) Additionally, the diagnosis of mucinous tumor can be suggested in many cases because this type of tumor usually shows large hyperintense areas on T2-weighted sequences (Video 1). The degree of response of mucin-producing tumors to neoadjuvant therapy is normally lower.

Tumors located in the lower third of the rectum must be considered differently. These are a separate type of tumor because they are associated with a risk of involvement of the surgical circumferential resection margin (CRM) and because of their tendency to show higher recurrence rates. This is due to the fact that involvement of the lower third beyond the muscularis propria could lead to tumor infiltration into the margins in an ultralow TME or in a conventional abdominoperineal excision (APE).\(^15\) For this reason, these
Figure 1  (A and B) MRI tumor mapping of rectal cancer. Sagittal (A) and axial (B) TSE T2-weighted sequences featuring a cT4a rectal carcinoma. These images show MRI capacity to accurately yield important data, such as distance to anal verge (1 + 2 distance in A), tumor spread to rectal lumen (3), as well as involvement of the peritoneal reflection (white arrows).

neoplasms require neoadjuvant therapy in earlier stages (T2), and may require different surgical techniques such as extralevator/extrasphincteric APE, which resects the sphincter complex, levators, and en-bloc mesorectal excision (Fig. 2).

**Depth of mural/extramural tumor invasion and involvement of the surgical resection margin**

Current preoperative imaging techniques for local rectal cancer staging—i.e. endorectal ultrasonography, computerized tomography (CT), and MR—have proved generally of limited value in the accurate assessment of the 'T' stage (depth of mural infiltration and minimal extramural spread in the mesorectum). However, it is argued that the primary aim of imaging techniques for rectal cancer determination is not 'T' stage assessment, but to arrange groups of patients according to how they will be managed. In this regard, depth of extramural spread seems to predict the risk of local recurrence more accurately than the 'T' stage does. There is a body of research studies that advocate for this type of group management and provide evidence of the behavioral inhomogeneity of T3 tumors. Accordingly, T2 tumors with extensive involvement of the muscularis propria would have the same prognosis as T3 tumors with minimal (2 mm) extramural spread. Similarly, T3 tumors with extramural invasion <5 mm would have a much higher disease-free

Figure 2  Anatomy of the lower rectum and anal canal (left) and visualization of the excision plane with different surgical techniques in these locations (right). The images correspond to a patient with a lower rectum tumor invading the sphincter complex (white star). Red line: anterior total mesorectal excision plane. Yellow line: extra-levator abdominoperineal amputation plane. Fuchsia line: intersphincteric abdominoperineal amputation plane (adaptation from Shihab et al.15).
survival rate (85%) than those with extramural invasion >5 mm (53%). Apart from this, some authors hypothesize that preoperative neoadjuvant therapy would hardly be of any benefit to patients with tumors with extramural spread <5 mm.

The TME technique (a surgical technique in which the theoretical dissection plane is on the mesorectal fascia surrounding the mesenteric fat, together with the lymphatic system and rectal vessels as well as the rectum itself) shows how crucial the assessment of the preoperative state of the circumferential resection margin (CRM) is. A positive CRM is associated with high local and distant recurrence rates, since virtually all patients with CRM involvement (tumor cells within 1 mm of the CRM) after chemoradiotherapy present with tumor recurrence with a high risk of distant metastasis. Wibe et al. report local recurrence rates of 22% in patients with positive CRM and of 5% in patients with negative CRM after TME. For this reason, one of the main goals of assessment of adjuvant therapy planning for RC patients is to obtain a tumor-free CRM at surgery.

However, the mesorectal fascia should not be mistaken for the CRM (a margin that is defined postoperatively) although on MRI mesorectal fascia is taken as the theoretical reference margin. For this reason, a margin at risk at imaging can be interpreted as a histological tumor-free CRM (R0) or a CRM with microscopic (R1) or macroscopic (R2) invasion. Distance between the tumor and the mesorectal fascia would be the primary local prognostic factor in RC. It should not be forgotten, however, that this distance must be measured where the tumor has extended beyond the muscularis propria, which means that T1 and T2 tumors would be regarded as not having margins at risk (except for the anal canal).

Determination of the possible CRM involvement on MRI is variable. However, as a general rule, a CRM is considered to be involved when the primary tumor, a malignant lymph node, a venous or lymphatic invasion, and/or a tumor deposit are located at a distance ≤1 mm (Fig. 3). Because of its wide coverage and high spatial resolution, MRI has established itself as the modality of choice to predict tumor-free CRM (92% sensitivity).

Extramural vascular invasion

Although the term EVI (extramural vascular invasion) has been used to designate both vascular and lymphatic invasion in CRC, vascular invasion normally refers to venous invasion extending outside the muscularis propria. EVI is found in approximately 30% of cases, and is associated with poorer survival, with locally advanced tumors, with a high risk of metastatic disease, with high likelihood of tumor-positive mesorectal nodes, and with CRM positivity at surgery. MRI is the only imaging technique that provides appropriate EVI assessment (Fig. 4A, Video 2). Smith et al. provide a number of features suggestive of EVI, mainly vascular thickening in the vicinity of the tumor and heterogeneous intravascular signal intensity.

Involvement of the peritoneal surface and adjacent organs

MRI has good sensitivity for diagnosis of tumors invading organs or adjacent structures (T4a) or a peritoneal surface (T4b). Evaluation of RC by MRI must always involve assessment of the peritoneal reflection, which is a peritoneal surface that attaches in a V-shaped manner onto the anterior wall of the upper third of the rectum. Involvement of the peritoneal reflection suggests risk of peritoneal seeding (Fig. 4B and C; Video 3).

Nodal involvement

Nodal involvement is another independent negative prognostic factor for RC patients’ survival and local recurrence. Careful consideration of possible pathways of spread is required. In this regard, it should be taken into account that lower rectum tumors have a greater tendency to invade pelvic extramesorectal nodes, which are the only pathways for lymphatic spread in up to 6% of these tumors.

Nodal staging by imaging techniques is highly limited when relying on the criterion of size in the short axis. Brown et al. found that 55% of positive nodes are less than 5 mm in diameter and that 15% of nodes <5 mm are positive (mean size 3.8 mm). A number of research studies report on series that assess morphologic criteria (irrespective of nodal size) to determine the nonmalignant or malignant nature of lymph nodes. Brown et al. and Kim et al. suggest border contour and signal intensity as criteria for evaluation. Unfortunately,
the promising outcomes could not be reproduced in later studies. Recent studies suggest that diffusion-weighted MRI (DW-MRI) could help in nodal characterization prior to and following neoadjuvant therapy. New contrast media could also be an alternative option. The use of ultrasmall particles of iron oxide (USPIO) could be of value for characterization of nodal involvement by combining morphologic and functional criteria (USPIO uptake). Unfortunately, the use of particles of iron oxide has not been approved for clinical use, and its use requires training for suitable evaluation. Apart from this, vascular contrast media could help in determining the nature of lymph nodes. Beets-Tan et al. found that vascular contrast agents only enhance the vessels of normal tissues and normal nodes. However, this outcome must be taken with caution because of the low number of patients enrolled in this study.

### Imaging-based decision algorithms

Different studies provide data advocating for a change of priorities in RC imaging evaluation. On the one hand, surgery alone could be curative for T1 and T2 tumors as well as for some early-stage T3 tumors, with a low local recurrence rate with TME and tumor-free resection margins. For other tumors, in contrast, preoperative chemoradiation therapy has shown clear benefits, such as tumor size reduction, possibility of sphincter complex preservation at surgery, decrease of recurrence rate (10.1% of local recurrence with TME and 1% of local recurrence with TME plus radiotherapy), and most importantly, overall survival improvement.

Based on these data and taking into consideration the previously assessed factors, three main patient groups can be set up that require a different clinical management (Table 1):

1. Patients with a good prognosis that do not require neoadjuvant therapy (T1–T2 N0 tumors).
2. Patients with tumors that require a standard pattern of neoadjuvant therapy (mainly T3 tumors).
3. Patients with tumors that require a neoadjuvant therapy with intensified radiation therapy: T4 tumors or tumors threatening or invading the mesorectal fascia (Fig. 5A–C).

Differences between institutions arise when certain patients are classified:

1. Some authors include T3a and T3b tumors in the group with the best prognosis.
2. Brown et al. include T3a–b tumors with nodal involvement (N1) and no compromised CRM in the group that can only be treated with surgery, whereas the Dutch authors regard nodal involvement as a clear indication for neoadjuvant chemoradiotherapy (CRT).
3. EVI signs would mean risk of systemic involvement, requiring neoadjuvant therapy and adjuvant chemotherapy.

### Functional–molecular imaging in RC

Cancer has a number of distinctive features that determine its behavior such as self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of apoptosis, sustained angiogenesis, limitless replicative potential, and neighboring tissue invasion and metastasis. Anatomic evaluation and evaluation of the prognostic factors discussed enable the decision-making for patient treatment. However, evaluation of this type entails a limited tumor approach. Specific assessment of the distinctive tumor features in RC could allow a more individualized patient management; a more accurate definition of key elements of this management; to establish patient prognosis or the response to the different therapies. In this regard, some molecular and functional imaging techniques could complement current morphologic evaluation, which would enable the analysis of the following key tumor features (Table 2): angiogenesis (perfusion CT or dynamic MRI), cellularity (diffusion MRI), and cellular metabolism (PET). Apart from this, many of the specific tumor features have become the target of novel oncologic therapies for CRC treatment.
Table 1 Imaging-based therapeutic strategy in rectal cancer. Image findings define patient groups with different management.

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Image findings</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group with positive prognostic factors</td>
<td>T1, T2 (except for lower third), T3a and T3b N(−)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Free CRM</td>
<td>EVI(−)</td>
<td></td>
</tr>
<tr>
<td>Group with negative prognostic factors</td>
<td>T2 in lower third T3c and T3d N(+) EVI (+)</td>
<td>Chemoradiotherapy prior to surgery</td>
</tr>
<tr>
<td>Free CRM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group with mesorectal margin at risk</td>
<td>Invaded CRM or CRM at risk T4a and T4b</td>
<td>Chemoradiotherapy with dose titration prior to surgery</td>
</tr>
</tbody>
</table>

Note: EVI(+) adjuvant chemotherapy required.
EVI: extramural vascular invasion; CRM: circumferential resection margin; N: metastatic node involvement.

involving the development of new drugs inhibiting tumor growth factors, such as the vascular endothelial growth factor (VEGF), the epidermal growth factor receptor (EGFR), and vascular disrupters. This fact would further reinforce the significance of and need for imaging evaluation.

Angiogenesis: Perfusion CT and dynamic MR

Neo-angiogenesis development, a process regulated by certain mediators, such as VEGF, is key to tumor growth and metastasis. Until recently, research in angiogenesis focused on histologic aspects, involving assessment of parameters such as microvessel density. However, tumor vessels have a number of features different from those characterizing normal vessels, which could provide us with specific information about tumor vessels. These features are spatial heterogeneity and chaotic structure, high permeability, and multiple arterio-venous shunts. Compared with normal tissue, tumor tissue generally involves an increase in vascularization with a rapid enhancement peak, followed

Table 2 Functional–molecular imaging techniques in RC.

<table>
<thead>
<tr>
<th>Functional imaging technique</th>
<th>Biological properties on which the images are based</th>
<th>Quantitative parameters or biomarkers</th>
<th>Physiopathologic data featured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion-CT</td>
<td>Contrast medium uptake rate in tissues which is influenced by perfusion, vessel density, and vessel permeability</td>
<td>-Blood flow</td>
<td>-Vascular density</td>
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<tr>
<td></td>
<td></td>
<td>-Blood volume</td>
<td>-Vessel permeability</td>
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<td></td>
<td></td>
<td>-Mean transit time</td>
<td>-Perfusion pressure</td>
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<td></td>
<td></td>
<td>-Permeability surface</td>
<td>-Tumor grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Area under the gadolinium curve</td>
<td>-Vascular permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Transfer constants (k&lt;sub&gt;trans&lt;/sub&gt;, k&lt;sub&gt;ep&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Leakage space fraction (v&lt;sub&gt;L&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Plasma volume (v&lt;sub&gt;p&lt;/sub&gt;)</td>
<td>-Perfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Apparent diffusion coefficient (ADC)</td>
<td></td>
</tr>
<tr>
<td>Dynamic MRI</td>
<td>Contrast medium uptake in tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffusion MRI</td>
<td>Brownian motion of water</td>
<td>-Cell density, cell membrane integrity, extracellular space tortuosity, node formation, necrosis</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>Glucose metabolism</td>
<td>-Increased expression of GLUT-1 and hexokinase II activity</td>
<td></td>
</tr>
</tbody>
</table>

GLUT-1: type 1 glucose transporter; PET: positron emission tomography.
Figure 5  (A–C) Imaging-based radiotherapy planning. (A) Fusion of an axial TSE T2-weighted image and a false color map derived from a high-b-value (b = 800) diffusion image, acquired in the same plane. Fusion shows tumor implanted at the five o’clock position in contact with the mesorectal fascia (arrow). (B) Planning of imaging-based radiotherapy showing the increase in dose (60 Gy instead of 50, area in red) in the mesorectal margin at risk. (C) The postneoadjuvant fusion study shows partial tumor response with an increase in distance to the mesorectal margin, suggesting a possible free margin, which was confirmed at surgery (R0).

by early contrast washout. Additionally, the apparent role that angiogenesis plays in tumor growth has opened up an avenue towards the development of new drugs that inhibit tumor angiogenesis. Both angiogenesis and response to antiangiogenic or antivascular drugs have clear imaging applications.51 Technical advancement has promoted the development of new imaging techniques, such as perfusion CT and dynamic MRI, that enable the study of angiogenesis in RC tumors in a non-invasive manner.6,9,47,48,50,52 Apart from a mere qualitative assessment (morphology of uptake curves), both techniques provide quantitative evaluation of tumor angiogenesis based on mathematical analysis models, which yield information about a set of physiological parameters, such as blood flow, blood volume, mean fluid transit time, and transfer coefficient (ktrans).50,52 There are some differences between perfusion CT and dynamic MRI. CT studies assess the contrast medium attenuation of X-rays in the vascular and extravascular space over the course of the study, with a direct relation between contrast concentration and density (Fig. 6 and Video 4). Quantification by dynamic MRI is more challenging because there is no direct relation between MRI signal intensity and contrast concentration.57,48,52

In RC angiogenesis evaluation, correlation between functional imaging parameters and angiogenic markers (microvessel density, VEGF, and CD31 expression) varies between studies.53–55

Functional-imaging studies of RC have proved to be potentially useful for diagnosis, staging, and patient prognosis. Accordingly, perfusion CT has proved to be valid to differentiate CRC from normal bowel wall and from benign pathology (such as acute diverticulitis) by yielding clearly different values in different functional parameters.56

Moreover, perfusion-based studies could help in predicting patient prognosis since tumors with high perfusion values (blood flow or ktrans) seem to better respond to neoadjuvant chemoradiotherapy57,58—despite the low number of patients in these studies and their sometimes contradictory data.59 Perfusion CT could also play a role in detecting occult hepatic metastases, since the presence of micrometastasis is likely to alter hepatic perfusion patterns significantly.

Another interesting issue is the assessment of response to the treatment. Both perfusion CT and dynamic MRI show changes in their values as a response to chemoradiotherapy (Fig. 7 and Video 4).52,58,59 Both techniques seem to enable a prompt evaluation of tumor response to antiangiogenic and antivascular drugs, showing a decrease in tumor perfusion values in responders to such drugs.60

Cellularity: Diffusion-weighted MRI sequences

Diffusion-weighted MRI (DW-MRI) is an emergent technique for oncologic imaging. DW-MRI displays contrast images by tracking the differences in motion of water molecules in different media. DW-MRI provides biological information about different factors, such as cell density, the nucleus–cytoplasm relationship in cells, extracellular space tortuosity, the integrity of cell membranes, tissue organizational characteristics (e.g. gland formation in tissue), and tissue perfusion.61,62 The restriction grade of water
Figure 6  Perfusion-CT. Perfusion-CT involves sequential acquisition of images with high temporal resolution and a coverage that is dependent on the CT number of rows (4 cm in a scanner with 64 rows of detectors). Subsequently, in the workstation, a specific software programme generates intensity change curves of the lesion over time, and yields quantitative maps featuring different parameters (flow, blood volume, permeability, mean transit time) according to an analysis model, which varies depending on the manufacturer.

diffusion is inversely related to cell density and the integrity of cell membranes. Water molecule motion is more restricted in tissues with high cellularity and intact membranes (e.g. tumor tissue) than in areas with lower cellularity or abnormal membranes.

Another advantage of diffusion MRI is that it can be quantitatively analyzed based on calculation of the apparent diffusion coefficient (ADC) value. Tumors generally show low ADC values, whereas normal tissues and benign lesions usually show higher values. Validity of ADC for tumor characterization is reinforced by the fact that a number of important biological features, such as tumor proliferation index, tumor grade, and presence of necrosis or apoptosis, correlate with ADC.63

In RC, diffusion-weighted imaging has proved to be a useful technique for CRC detection,64 tumor volume delimitation (Fig. 8 and Video 5), and distant tumor staging, with detection and characterization of hepatic focal lesions. Diffusion-weighted imaging could also predict response to chemoradiotherapy with ADC values lower than pretreatment values in responsive primary tumors and metastases.65,66 This could be explained because tumors with high ADC values usually show necrosis, which is associated with poor response to the treatment.

Figure 7  (A–C). Perfusion-CT of RC hepatic metastasis and response to therapy. Acquisition images (A) and parametric map of blood volume with a 50% transparent color map (B). These images were acquired in a perfusion study of a hepatic metastatic lesion, which shows a marked peripheral neo-angiogenic component. (C) Ten days following administration of an antiangiogenic drug (anti-VEGF), the image shows a positive response of this lesion, which no longer shows the previously marked ring enhancement.
DW-MRI proves to be valuable for lymph node detection, and could be an alternative technique to assess their involvement.  

Assessment of response to treatment is, however, one of the main fields of application of DW-MRI. Expected changes vary depending on the treatment modality. Accordingly, response to a radio- and/or chemotherapy is associated with an early rise of ADC values, a rise that lasts longer with radiotherapy (due to persistent edema). In contrast, response to antiangiogenic drugs would lead to transient reductions of ADC values, which would be secondary to flow reduction, cellular edema, and reduced extracellular space\(^3\) (Table 3).

Metabolism: Positron emission tomography (PET)

PET enables to detect and quantify cellular processes in a non-invasive manner using radiotracers. In clinical practice, the main radiotracer is \([^{18}F]2\)-fluoro-2-deoxyglucose (FDG). Malignant tumors generally tend to have an increased cellular metabolism, together with an increased rate of glucose transport membrane proteins and an increased activity of hexokinase and phosphofructokinase, which prompt intracellular glycolysis. This results in an increased accumulation of FDG. Poor spatial resolution of PET can hinder tumor diagnosis with this technique. For this reason, modern PET/CT scanners have proved to be more useful, since they enable co-registration of not only functional–metabolic but also anatomical information. PET/CT shows advantages in diagnosis, staging, treatment planning, follow-up, detection of CRC recurrence and metastasis, and patient prognosis.\(^45,67,68\) PET/CT could also change RC management plan in a significant number of patients because these techniques enable the detection of unknown metastatic disease and the change of preoperative radiotherapy field according to the findings.\(^48,67,68\)

Nevertheless, the application of PET to RC treatment is not without limitations. Small tumors (<1 cm) or mucinous tumors usually have a low metabolic activity, and together with some necrotic tumors can prompt false-negatives. In contrast, inflammatory processes or bowel physiologic activity can prompt false-positives.\(^48,67,68\)

PET could enable to define biologically active tissue (Video 6), which is a big advantage when it comes to determining RC response to neoadjuvant therapy. However, several studies have reported contradictory data concerning the value of PET imaging when determining such response. Metastatic CRC treatment can currently rely on different therapeutic strategies with the incorporation of biological therapies, particularly those involving agents that block EGFR signaling, a well-known factor of tumor development. Few studies have been published that assess response to these drugs. However, the use of positron emission tomography FDG or fluorothymidine (a radiotracer that would help in the study of cellular proliferation) in the assessment of different tumor types could enable early evaluation of response to these drugs.\(^69\) This fact could facilitate the application of PET FDG to CRC treatment.

Other functional/molecular techniques

The development of different MRI sequences (BOLD and spectroscopic), new PET radiotracers, and other imaging...
techniques has significantly enhanced the analysis capacity using imaging techniques of different tumor processes and tumor environment. Some of these processes are hypoxia, cellular proliferation, apoptosis, and cellular metabolism. The clinical utility of all these techniques in RC is still to be defined, since most of them are not of common clinical use, and require complex implementation. Nevertheless, they could enable a more comprehensive and specific characterization of the biological features of rectal neoplasms.

**Multiparametric imaging: The forthcoming paradigm**

The possibility to obtain quantifiable parameters with different molecular and functional imaging techniques is a crucial advance in imaging evaluation in oncology. However, recent studies suggest that combining the information drawn from these different techniques would help in better understanding tumor biology. In this sense, current technological advances enable to obtain multiple data from one single imaging technique or by combining several modalities, which provide different data on the tumor. In the imaging study of RC, MRI alone would yield different parameters providing information about morphology and prognostic factors (high-resolution turbo-spin-echo (TSE) T2-weighted sequences), cellularity (diffusion), angiogenesis (perfusion), and tumor metabolism (spectroscopy) (Fig. 9A–C). The data reported by Goh et al. seem to reinforce the usefulness of combining different imaging techniques (PET and perfusion CT) in order to obtain assessment of a wide variety of parameters. The joint assessment of tumor perfusion and tumor metabolism analysis in RC would enable detection of tumors at risk of metastatic spread by identifying a mismatch between both factors (Fig. 10A–F). Similarly, Willet et al. reported a similar outcome in the response to bevacizumab administration alone in metastatic CRC after noting a significant decrease in angiogenesis and a poor decrease in tumor metabolism evaluated by PET.

Finally, one of the central aspects of the study of RC is response to neoadjuvant therapy. When determining the grade of tumor response, conventional imaging techniques seem to yield a limited evaluation, which poorly correlates with the pathologic findings. In this regard, functional/molecular imaging techniques, combining different parameters, could be a better alternative.
**Figure 10** (A–F) Multiparametric study of a cT3N2 RC based on the MRI findings. Fusion images of a TSE T2-weighted image and a false color map derived from a high-b-value diffusion image (A and D), PET image (B and E), and perfusion-CT parametric map of blood volume, acquired in pre- (A–C) and postchemoradiotherapy (D and E). These images show a partial tumor response with relative decrease of lesion volume, restricted diffusion, and diminished glucose metabolism (pre-therapy SUV = 20 and post-therapy SUV = 5), as well as poor blood volume change. The surgical sample confirmed a pT3N2 tumor with poor grade of histologic response (Dworak’s grade IV tumor regression).

**Table 3** Functional–molecular imaging techniques and tumor response to therapies in colorectal cancer. Biological effect of the different therapies and its evaluation with functional–molecular imaging techniques.

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Biological effect</th>
<th>Imaging techniques</th>
<th>Change of parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>Cell death, edema, inflammation and vascular disruption</td>
<td>Perfusion-CT</td>
<td>Tumor perfusion decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dynamic MRI</td>
<td>ADC increase</td>
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<tr>
<td></td>
<td></td>
<td>Diffusion MRI</td>
<td>SUV decrease</td>
</tr>
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<td></td>
<td></td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cell death</td>
<td>Perfusion-CT</td>
<td>Tumor perfusion decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dynamic MRI</td>
<td>General short-term ADC increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffusion MRI</td>
<td>SUV decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>Antiangiogenic drugs</td>
<td>Vascular normalization</td>
<td>Perfusion-CT</td>
<td>Marked tumor perfusion decrease</td>
</tr>
<tr>
<td>(anti-VEGF)</td>
<td></td>
<td>Dynamic MRI</td>
<td>Rapid but transient ADC decrease</td>
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<tr>
<td></td>
<td></td>
<td>Diffusion MRI</td>
<td>Poor SUV variation</td>
</tr>
<tr>
<td></td>
<td>Marked decrease in permeability</td>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>Anti-EGFR</td>
<td>Multiple effects, but inhibition of tumor proliferation</td>
<td>PET</td>
<td>SUV decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perfusion-CT</td>
<td>Poor tumor perfusion decrease in other tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dynamic MRI</td>
<td>Possible ADC increase (no clinical experience reported)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffusion MRI</td>
<td></td>
</tr>
</tbody>
</table>

ADC: apparent diffusion coefficient; EGFR: epidermal growth factor receptor; PET: positron emission tomography; SUV: standardized uptake value; VEGF: vascular endothelial growth factor.
Conclusion

Imaging techniques play a pivotal role in the strategies for management of RC patients. Of these techniques, MRI is currently the modality of choice because of its capacity to perform local staging, since it enables evaluation of anatomic aspects and prognostic factors that are key to choosing the appropriate surgical approach and determining the need for neoadjuvant treatment. Functional and molecular imaging techniques, able to detect physiologic and cellular processes, seem to open up the doors to a more individualized patient management and a more adequate evaluation of the novel oncologic therapies.

Authorship

Responsible for the integrity of the study: RGF, PCD and AGC.

Conception of the study: RGF and AGC.

Design: RGF and AGC.

Data acquisition: RGF, PCD, RGD, AVM and AGC.

Analysis and interpretation of data: RGF, PCD, RGD, AVM and AGC.

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Conflict of interest

The authors declare not having any conflict of interest.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rxeng.2012.05.004.

References