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Colorectal cancer: Current imaging methods and future perspectives for the diagnosis, staging and therapeutic response evaluation

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Abstract

In the last 10 years the mortality rate of colorectal cancer (CRC) has decreased by more than 20% due to the rising developments in diagnostic techniques and optimization of surgical, neoadjuvant and palliative therapies. Diagnostic methods currently used in the evaluation of CRC are heterogeneous and can vary within the countries and the institutions. This article aims to discuss in depth currently applied imaging modalities such as virtual computed tomography colonoscopy, endorectal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis of CRC. Special focus is put on the potential of recent diagnostic developments as diffusion weighted imaging MRI, MRI biomarkers (dynamic enhanced MRI), positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG-PET) combined with computed tomography (PET/CT) and new hepatobiliary MRI contrast agents. The precise role, advantage and disadvantages of these modalities are evaluated

controversially in local staging, metastatic spread and treatment monitoring of CRC. Finally, the authors will touch upon the future perspectives in functional imaging evaluating the role of integrated FDG-PET/CT with perfusion CT, MRI spectroscopy of primary CRC and hepatic transit time analysis using contrast enhanced ultrasound and MRI in the detection of liver metastases. Validation of these newer imaging techniques may lead to significant improvements in the management of patients with colorectal cancer.

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Key words: Colorectal cancer; Imaging; Staging; Computed tomography; Magnetic resonance imaging; Diffusion weighted imaging; Contrast enhanced ultrasound

Core tip: This state-of-the-art review article covers current and future contribution of various imaging modalities in the diagnosis of colorectal cancer. Primary local staging, metastatic spread, restaging and posttreatment response evaluation are discussed in depth using emerging techniques such as virtual computed tomography (CT) colonoscopy, endorectal ultrasound and positron emission tomography/CT. The role and indications of more recently developed techniques as magnetic resonance imaging (MRI) with diffusion weighted images and hepatobiliary contrast materials are evaluated. The challenges and evolving role of functional imaging with MRI spectroscopy and hepatic transit time analysis using MRI and contrast enhanced ultrasound in the detection of liver metastases are also covered.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer death in the western world, with a high lifetime incidence of 6%. The prognosis of CRC is like other tumors staging dependent and the 5 years survival lies in the range of 40%-60%. Due to optimization of surgical techniques, introduction of neoadjuvant therapies and recent developments in diagnostic imaging modalities, the mortality rate has decreased significantly by 20% in the last years.

Utilization of different imaging modalities in diagnosing of CRC vary between countries and institutions. While computed tomography virtual colonoscopy (CTC) is a validated tool in the primary diagnosis of CRC in the United States^[1], this method is used with caution in many European countries due to radiation exposure and is thus not included as a screening modality in asymptomatic patients^[2]. The pros and cons of this rapidly evolving diagnostic modality compared to endoscopy are discussed controversially.

Imaging for surgical planning depicts the relationship of the tumor to surgical key landmarks and shows the presence of metastatic disease. Imaging features enable preoperative evaluation of prognostic features, which may guide patient selection for specific (*e.g.*, neoadjuvant) therapy^[3]. Recent developments in imaging technologies and validation of newer imaging techniques may lead to significant improvements in the management of patients with CRC. Diagnostic techniques such as diffusion weighted imaging (DWI), Fluorodeoxyglucose positron emission tomography (FDG-PET) and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) are increasingly used and have shown to be clinically useful in tumor characterization^[4-6]. Newly developed techniques such as perfusion computed tomography (CT) and MRI spectroscopy allowing insights in tumor biology have shown promising results, however they are not yet validated for clinical practice^[7,8].

This review discusses the current and future contribution of various imaging modalities to already established and recently developed techniques to improve the diagnosis for both-tumor detection and tumor characterization of CRC. In addition, the evolving role of newly developed methods for functional evaluation of otherwise “occult” hepatic metastases such as Doppler perfusion index (DPI)^[9] and hepatic transit time (HTT) analysis using contrast enhanced MRI^[10] will also be covered.

PRIMARY DIAGNOSIS OF COLORECTAL CANCER

Considering the high diagnostic performance, optical colonoscopy (OC) remains the gold-standard investigation in the early detection of CRC. Colonoscopy allows

biopsy samples to be taken for definitive diagnosis with a simultaneous opportunity for a therapeutic polypectomy, therefore improving a long-term prevention of CRC deaths^[11]. However, patients with tumor related stenosis, older patients and those with comorbidities are more likely to have an incomplete or difficult OC^[12,13].

VIRTUAL CT COLONOSCOPY

In recent years the role of CTC as a potential alternative to endoscopy has been widely studied^[14-16]. CTC image formation is based on the X-ray attenuation of low-density; high-intrinsic-contrast objects such as the air contained in the colonic lumen versus the large bowel walls, acting as an interface between intra luminal air and the extra luminal compartment. Low X-ray energy is sufficient to achieve diagnostic CTC images, resulting in a low radiation dose. If CTC is aimed at the sole examination of the colon (*e.g.*, for CRC screening purposes), the use of low radiation dose CT acquisition protocols is warranted. Conversely, regular dose CT protocols can be used if CTC is part of a CT examination in which all abdominal organs have to be investigated. This method is applied in patients with known CRC and incomplete OC, in whom CT plays a role for both complete assessment of the colonic lumen and for oncological staging (Figure 1). For adequate colonic distention to be achieved, air or carbon dioxide is usually delivered into the patients colon with a thin rectal catheter prior to CTC. Air has the advantage of no cost and the ease of administration, but is less tolerated as it is not absorbed by the colonic mucosa. Conversely, carbon dioxide is more comfortable as it is gradually absorbed by the colonic walls, although larger volumes must be supplied compared with air. In practical terms, administration of 1.0-1.5 liter of air or 3-4 liter of carbon dioxide is usually sufficient^[17]. The CT acquisition is usually performed twice: in supine and prone position (or vice versa). This is to optimize the distention of the various colonic segments depending on gravitational compression by the surrounding abdominal structures, as well as to distinguish polyps which may be fixed to the bowel walls from fluid and/or fecal residues. Colonic distention is also favored by parenteral administration of spasmolytic agents, such as glucagon or hyoscine-N-butyl bromide, which inhibit peristalsis and reduce the tone of the parietal musculature. By orally administering positive contrast material (barium or iodine), fecal and fluid tagging can be performed, helping to distinguish fecal/fluid residues from parietal polyps. Tagged residual fluid can then be electronically removed from CTC images by means of a dedicated software. 3D reconstructions enable accurate quantification of polyp volume, which can be helpful in a follow-up to assess growth of the polyps. Research is in progress on subtracting solid tagged stool in patients who do not undergo cathartic cleansing.

Pickhardt *et al*^[14] found CTC comparable to colonoscopy in detection of bigger colorectal polyps. Two meta-analysis studies showed a high sensitivity (100%) of CTC in the detection of colon cancer and 87.9% for adenomas less than 10 mm^[18,19]. Despite such promising data, there

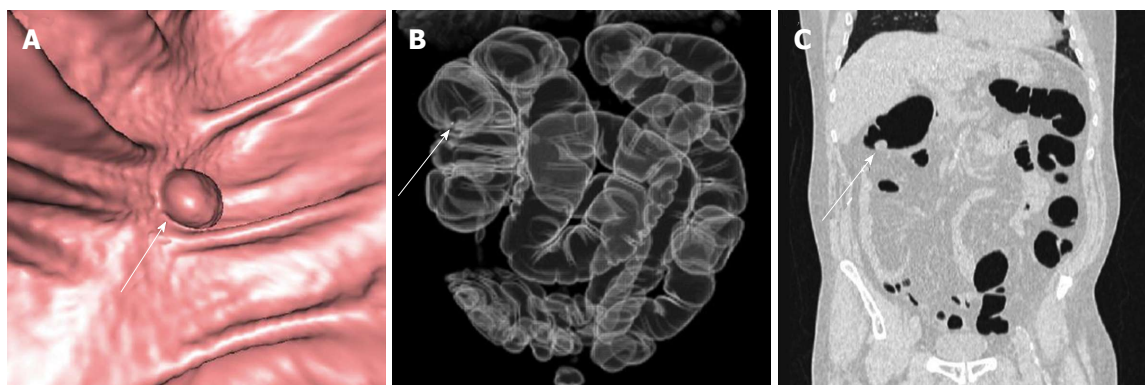


Figure 1 A 64-year-old male patient who underwent routine screening colonoscopy terminated due to severe discomfort. A: Virtual computed tomography (CT) colonoscopy detected a 1 cm polyp (arrow) in right colonic flexure, biopsy proved as adenocarcinoma; Fly-through with a 3D view of the polyp; B: The virtual X-ray reconstruction; C: Coronal reconstruction using the lung window shows the tumor clearly.

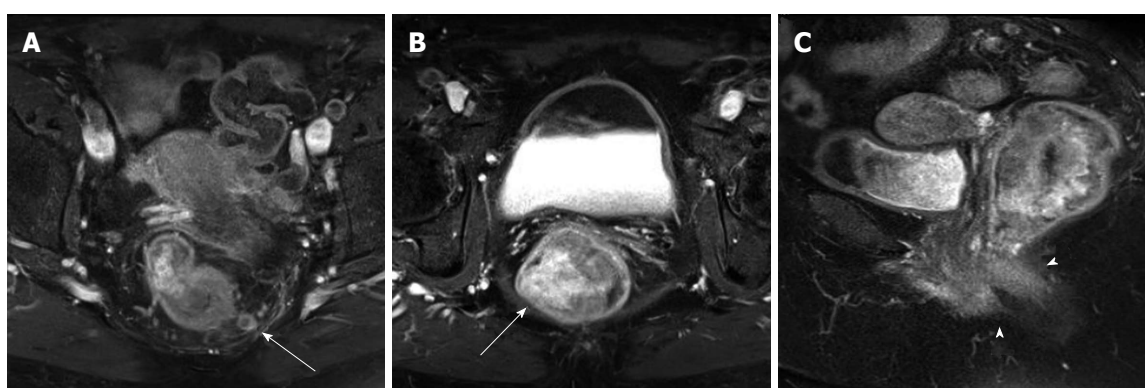


Figure 2 Abdominal magnetic resonance imaging for local staging of rectal adenocarcinoma in a 58-year-old female. A, B: Post-contrast fat-suppressed axial images show 7 cm long contrast enhancing neoplastic mass with lymph node metastases within the mesorectal fascia (arrow); C: Peripheral desmoplastic reaction (arrowheads) on T1 sagittal images.

is currently no transcontinental consensus on whether CTC should be used as a screening method in asymptomatic patients. Since 2008 CTC is recommended as a validated diagnostic tool by the American Cancer Society and is included among the screening tests of CRC^[1]. This recommendation was revalidated in a recent large patient sample (1610 patients) multicenter randomized trial by Atkin *et al*^[16], concluding that CTC is a similarly sensitive, less invasive alternative to colonoscopy. However, in many European countries the use of CTC as a screening method in asymptomatic populations is prohibited due to radiation related consequences and only advised in cases of incomplete preoperative colonoscopy^[2].

An alternative method to CTC could be MRI colonoscopy which is not radiation exposure related^[20]. However, currently there are insufficient study results available to recommend this method as a screening modality.

LOCAL STAGING OF CRC: MRI AND ENDORECTAL ULTRASOUND

The tumor node metastasis classification of the American Joint Committee on Cancer is the internationally accepted standard for the staging of CRC^[21]. The accurate diagno-

sis of local tumour extension, location, T stage, potential circumferential resection margins, mesorectal fascial involvement and extramural or venous invasion is essential for defining the treatment strategy. For this reason, MRI is the recommended modality for initial staging, due to its high accuracy for the definition of localization, determining the total extension and the relationship of the tumor to the peritoneal reflection^[22]. Furthermore, MRI is accurate in measuring the distance between the anorectal junction and the distal part of the tumor. It is also accurate for determining the length of the tumor. Although it has been the standard in the past, it is inappropriate to use the term circumferential resection margins (CRM) for initial clinical staging before surgery, since CRM can be defined only postoperatively by the surgical plane. The tumor growth on primary staging MRI should be best described in relation to an anatomical structure, like the mesorectal fascia^[23]. Most staging failures with MRI occur in the differentiation of T2 stage and borderline T3 stage with overstaging as the main cause of errors^[24]. Overstaging is often caused by desmoplastic reactions^[5] and it is difficult to distinguish on MRI between spiculation in the perirectal fat caused by fibrosis alone (stage pT2) and spiculation caused by fibrosis that contains tumor cells in stage pT3 (Figure 2).

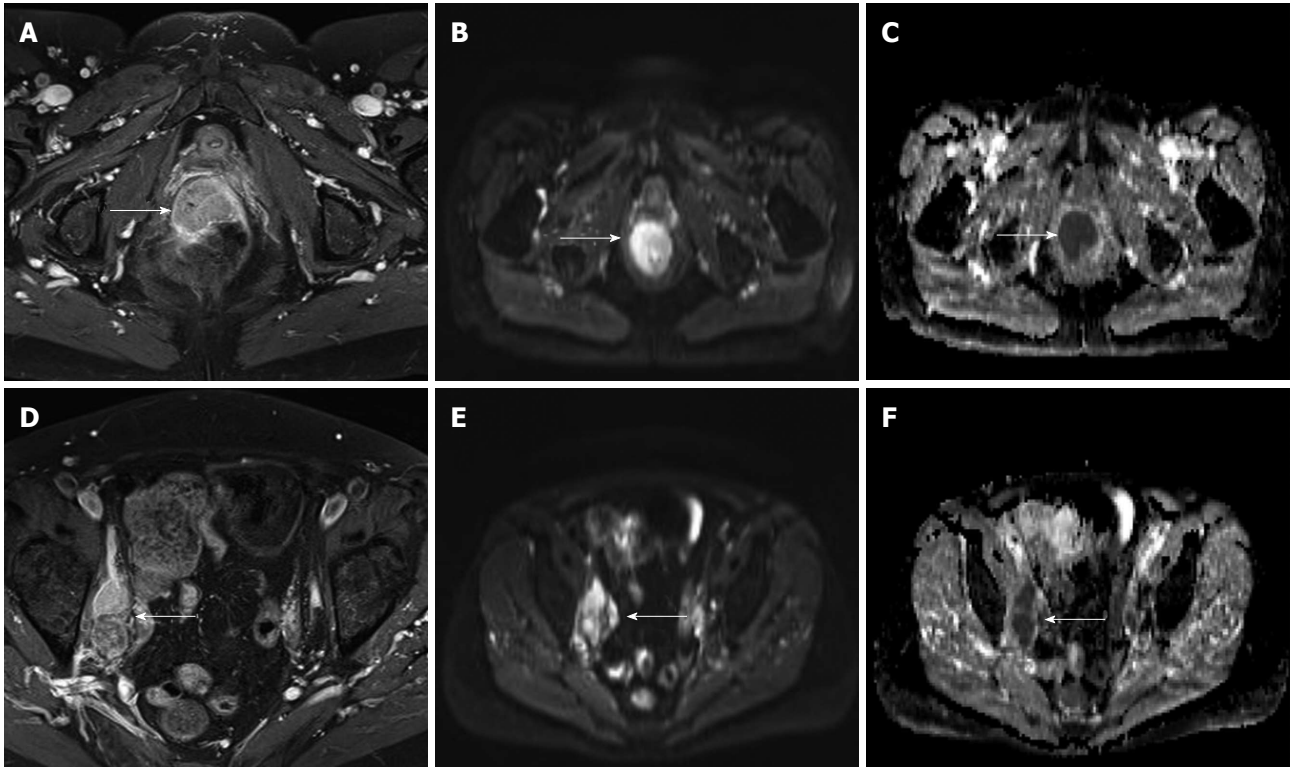


Figure 3 A 58-year-old female with biopsy-proven adenocarcinoma of the rectum. A: Post-contrast fat-suppressed axial T1 images show a contrast-enhancing mass (arrow), extending from rectum into the anal canal and invading the posterior aspect of the vagina; B, E: Both, the primary tumor and the lymph node metastases, show an hyperintense signal on diffusion weighted imaging; C, F: An reduced apparent diffusion coefficient reflecting the tight tumor cellularity; D: Enlarged, contrast-enhancing lymph nodes along the right iliac axis (arrow).

Although previous studies have not shown much advantage of dedicated phased-array coils^[25], our clinical experience is positive and at our institution we use phased-array coils as a standard in the primary diagnosis of colorectal cancer. The advantage of high spatial resolution with a large field of view is making phased-array MRI suitable for staging of both superficial and advanced rectal tumors. A standard phased-array MRI protocol for rectal cancer consists of T2-weighted turbo spin-echo (TSE) MR sequences with high spatial resolution. The strength of T2-weighted turbo spin-echo MRI of rectal cancer is that fat tissue remains high in signal intensity. In this way, the tumor contrasts well with the surrounding fat tissue, and even very thin hypointense structures such as the mesorectal fascia can always be identified independent of the body habitus of the patient, owing to the high contrast between the hypointense fascia and the hyperintense fat tissue in and outside the mesorectum^[5].

At our institution, phased-array MRI for primary rectal cancer staging is performed at 1.5 Tesla (Siemens Avanto and Espree, all Siemens Healthcare, Erlangen, Germany) and 3.0 Tesla (Siemens Prisma, Skyra and Verio). The protocol consists of a T2 SPACE 1.0 mm isovoxel sequence, a standard echo planar imaging sequence for diffusion (b-values: 0, 40, 400 and 800 s/mm²) including an apparent diffusion coefficient (ADC) map and a T1 TSE Dixon sequence with fat saturation (FS) and calculation of in-/opposed-/fat- and water maps before con-

trast administration (Figure 3). Post contrast sequences are just a standard transversal T1 TSE FS (SL 5 mm) and a T1 VIBE FS 1.2 mm isovoxel. The pre- and post contrast isovoxel sequences can be reconstructed in line with and perpendicular to the individual tumor.

Endorectal Ultrasound (ERUS) is now an established modality for evaluation of the integrity of the rectal wall layers. With accuracies for T staging varying between 69% and 97%, endorectal ultrasonography (US) is currently the most accurate imaging modality for the assessment of T1 tumors^[2]. ERUS and endorectal MRI have similar accuracy in the differentiation between superficial (T1 and T2) and T3 tumors^[26]. However, endorectal MRI is related to high costs, limited availability and is less patient friendly. Consequently, endorectal MRI is not recommended by the European Society for Medical Oncology Guidelines as a preferred imaging modality for clinical T stage in colorectal cancer^[22].

METASTATIC SPREADING OF CRC

In 25% of patients with colonic cancer and in 18% of patients with rectal cancer, metastases are present at the time of the first diagnosis. The most frequently used imaging modalities for the detection of CRC metastases are US, CT, MRI and PET/CT^[27]. Current National Comprehensive Cancer Network guidelines for initial staging of CRC suggest the use of chest/abdomen/pelvis CT or

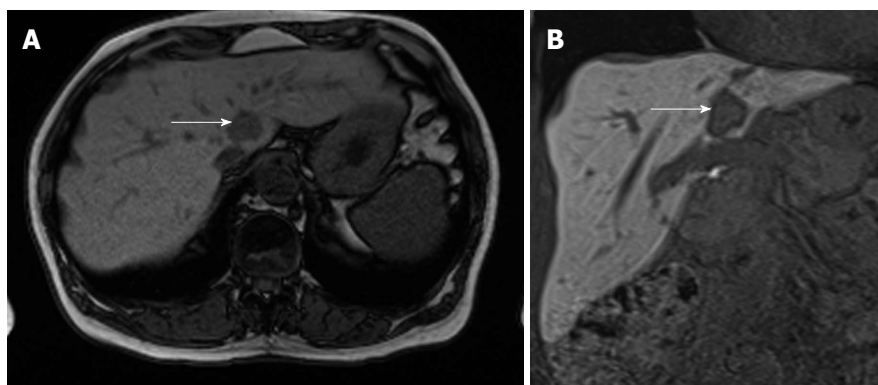


Figure 4 A 63-year-old female with colorectal cancer and suspected liver metastasis. A: Primovist images acquired 10 min *p.i.*, during the hepatobiliary phase using a T1 VIBE isovoxel sequence with coronal orientation; B: Due to the high resolution axial reconstructions are also done routinely. The lesion in segment I (arrow) is clearly demarcated as a contrast defect because of the missing hepatocytes in the metastasis while the other parts of the liver show a bright contrast enhancement.

MRI, while FDG-PET/CT is reserved for surveillance or problem solving.

N staging

ERUS, CT and MRI use the size as the main criterion in the assessment of nodal involvement, although the lymph node size is not an ideal indicator of metastasis and lacks sufficient accuracy for clinical decision-making^[28]. FDG-PET gives better insight in tumor biology, however, due to limited spatial resolution it does not allow for reliable detection of small lymph node metastases. FDG-PET/CT may provide additional information and could increase the accuracy of lymph node involvement significantly with a sensitivity and specificity of 51% and 85% for local lymph nodes and 62% and 92%, for distant lymph nodes^[29].

M staging

Correct detection of hepatic and pulmonary metastases can be challenging considering the possible difficulties in differentiation with benign lesions in these organs. CT has a better diagnostic performance (sensitivity 74%-84%, specificity 95%-96%) compared to US in detection of CRC liver metastases^[30]. A meta analysis of prospective studies comparing FDG-PET, MRI, and CT demonstrated a superior performance of MRI over the other two modalities on a lesion-by-lesion basis of the liver and in particular in evaluating lesions less than 1 cm in size (sensitivity 80%-88% and specificity 93%-97%)^[6].

Recently, DWI and hepatobiliary phase MRI with new hepatobiliary contrast agents have been integrated for the detection of liver metastases demonstrating improved sensitivity over routine MRI alone^[31]. The newest hepatobiliary contrast agent available is Gd-EOB Primovist® in Europe and Eovist® in United States and Canada (Bayer Healthcare, Leverkusen, Germany). Uptake of contrast within the hepatocytes results in peak parenchymal enhancement approximately 10-20 min *p.i.*, referred to as the hepatobiliary phase. As expected, lesions like metastases without containing hepatocytes are strongly hypointense compared to the surrounding enhanced parenchyma in this phase (Figure 4).

For the detection of pulmonary metastases imaging can be limited to chest X-ray. Although CT detects more

lesions compared to chest X-ray (CXR), a large number of these lesions (4%-42%) does not allow for a definitive diagnosis. Only one quarter of unspecified pulmonary lesions found on CT are demonstrated to be metastases, therefore the high sensitivity of CT cannot guarantee important benefit for the patients^[32]. This concept is supported by a recent study showing that preoperative staging chest CT is not beneficial for CRC patients without liver and lymph node metastasis on abdominal and pelvic CT who had a negative initial CXR finding^[33].

RESTAGING: THERAPEUTIC RESPONSE EVALUATION

General considerations

Patients after primary tumor resection and those treated with chemoradiation therapy (CRT) for locally advanced CRC require a regular post treatment evaluation. Within the first 5 years after curative therapy there is an increased chance for a locoregional relapse (3%-24%), occurrence of distant metastases (25%) and for developing metachronous secondary tumors (1.5%-10%). The introduction of preoperative adjuvant CRT has led to a reduction in local recurrency rates and has become standard of care for patients with locally advanced rectal cancer.

Several studies investigating the role of imaging for restaging after CRT suggest that neither MRI nor ERUS or FDG-PET are sufficiently accurate for identifying the true complete responders with positive predictive values ranging from 17%-50%^[34-36]. T2 weighted MRI has been standardly used for local restaging (Figure 5). Many recent reports have shown that DWI MRI may be useful for the response evaluation after CRT^[37,38]. DWI has shown to be feasible as an early marker of treatment response because cell death and vascular alterations typically occur before size changes. It also has been proved that DWI in addition to standard MRI significantly improves the performance of radiologists to select complete therapy responders compared to standard MRI only^[39,40]. In a recent systematic review and meta analysis study including 1556 patients from thirty-three studies MRI has shown to be useful for tumor-free CRM restaging, however nodal staging remained challenging^[41]. High b-value DWI is sensitive for detecting the location of lymph nodes, but

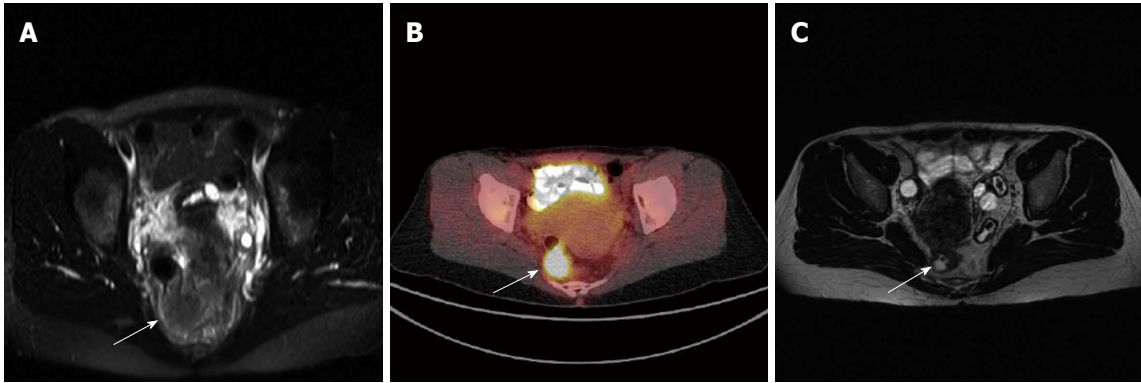


Figure 5 Initial rectal cancer staging of a 48 year old female. A: Occlusion of the rectum by solid tumor on magnetic resonance imaging (MRI) (arrow); B: Corresponding high Fluorodeoxyglucose metabolism in the Fluorodeoxyglucose positron emission tomography/computed tomography; C: Post treatment (chemoradiation therapy) magnetic resonance imaging shows a clear tumor size reduction (arrow) with a continuing lumen after chemoradiation therapy.

characterization of neoplastic nodes yields false-negative results and reactive hyperplastic nodes false-positive results.

It has been reported that transient decrease in the ADC may occur early in treatment related to cellular swelling, reduction in the blood flow or extravascular-extracellular space^[42]. However, early decreases in ADC values are not consistently seen and it has recently been reported that increases in ADC value with therapy response occur within 3-7 d in responding CRC patients treated with chemotherapy^[43]. Therefore the utilization of ADC values in the CRC evaluation needs further standardization and validation.

The role of FDG-PET in evaluating of recurrent colon cancer is controversial. Some of the previously published studies showed high specificity of this modality (up to 98%) based on evident FDG reduction after adjuvant CRT^[44]. Metabolic changes in response to treatment occur before any structurally detectable change (*e.g.*, tumor shrinkage). In the neoadjuvant setting, serial FDG-PET examinations may aid treatment planning to decide the appropriate length of neoadjuvant chemotherapy to maximize tumor response before surgical resection. In this setting, FDG-PET could lead to changes in therapies for those patients with tumors that show no metabolic change^[45]. On the contrary, other studies suggest that when radiation therapy is applied, FDG-PET cannot reliably identify pathologic complete response to CRT due to radiation related increased FDG uptake by rectal mucosa resulting in high false-positive data^[46,47]. For this reason, when using FDG-PET to monitor tumor response, it is not advocated within the first 4 wk after completion of CRT. FDG-PET/CT is a unique combination of the cross-sectional anatomic information provided by CT and the quantitative metabolic information provided by FDG-PET. In the past years, FDG-PET/CT has taken an important place in treatment response assessment^[48]. Limitations of FDG-PET/CT are that the technique is cost- and time-consuming (utilizing about 1.5 h per patient) and is not widely available.

Considering a very limited benefit of CRC follow-up in stage I tumors, described as only 1% increase in patient survival^[49], a regular follow-up in these patient group

is not indicated. In patients with advanced primary CRC (stage II and III), US is advised for the follow-up of liver metastases. US has a slightly lower sensitivity compared to CT in the detection of liver metastases, however the performed studies did not show a convincing advantage of CT over US in evaluation of asymptomatic patients^[50]. Therefore, abdominal US can be indicated as a cost-effective, widely available and relatively simple diagnostic modality in the follow-up of CRC liver metastases.

Up to 7% of all curatively treated patients with CRC develop distant pulmonary metastases which in 3.4%-30.0% are detected with chest X-Ray^[51]. Therefore CRX evaluation can be sufficient in follow-up of asymptomatic patients.

For anatomic objective response evaluation criteria based on assessment of the size of the tumor or metastases, Response Evaluation Criteria in Solid Tumors (RECIST) have been developed^[52]. RECIST uses unidimensional measurements of the sum of the longest lesion diameters of target lesions. At our institution we use a commercially available software for RECIST analysis (mint Lesion®, Mint Medical GmbH, Heidelberg, Germany), which will be discussed below.

Software based follow-up

Proper response assessment and reporting of metastatic lesions are crucial. A major pitfall in tumor response monitoring is the increasing incidence of mixed response to chemotherapy and subjective measurements of the lesions, *e.g.*, liver and lung metastases, also lesion measurements are time-consuming and can be investigator dependent. Computerized tools able to optimize the radiologist's workflow of the image reading process are spreading as the need for a systematic, standardized follow-up procedure grows. For example, the syngo® CT Oncology software (Siemens Healthcare, Erlangen, Germany) is able to perform automated measurement of neoplastic lesions helping to solve the long-standing issue of interobserver variability.

Another automated tool is mint Lesion® (Mint Medical GmbH, Heidelberg, Germany), developed at the German Cancer Research Center (Heidelberg, Germany)

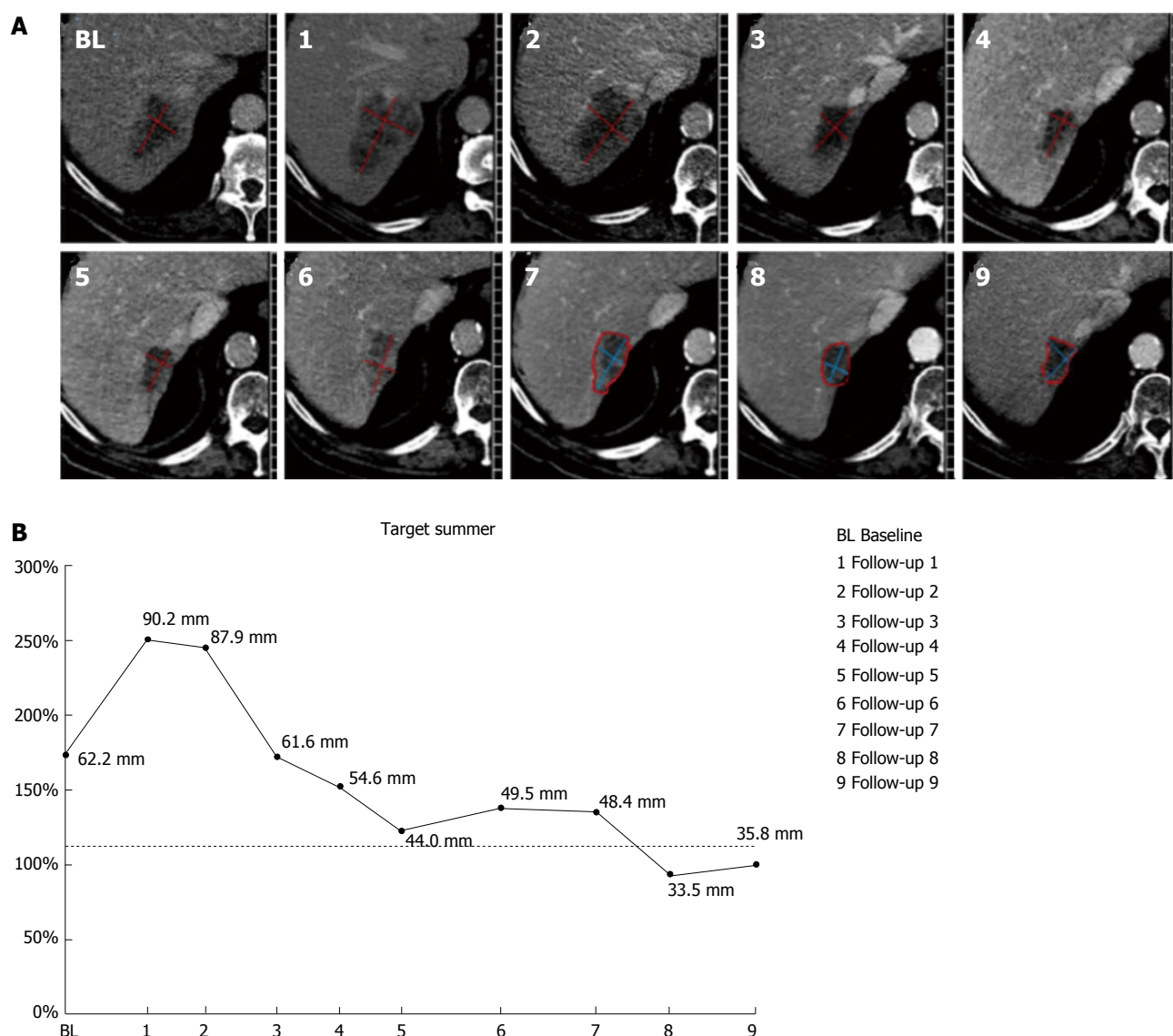


Figure 6 An automated software (mint Lesion®, Mint Medical GmbH, Heidelberg, Germany) used at our Institution for tumor treatment response evaluation. A: Computed tomography images show liver metastasis in a patient with colorectal cancer on nine follow-up examinations; B: Graphical evaluation depicts the measurement of the lesion standardized throughout the whole staging period consisting of baseline (BL) and nine follow up assessments (1-9). Tumor response is evaluated according to Response Evaluation Criteria in Solid Tumors.

which is currently routinely used at our institution for oncological assessment. Connected with our Picture Archiving Computer System (PACS) the mint Lesion software is able to continually synchronize and upgrade its worklist retrieving and matching precedent patients' related studies allowing a workflow optimization. It covers management of patient cohorts in terms of disease and treatment, assessment of lesions with respect to the overall patient treatment course, statistical response evaluation in line with response criteria, and consistent and comprehensive automated reporting.

In the initial baseline assessment target and non-target lesions are defined. In subsequent follow-up exams the software is able to correlate and match images of the previous studies allowing a faster recognition of previously described lesions; by showing exactly how quantitative measurements (*i.e.*, volumetry, density and intensity) were performed in previous studies, interobserver variability

is thus reduced. Apart from the reproducible measurements, assessment notes, treatment outcome statistics for patient cohorts and individual patients, mint Lesion® provides an automatically generated, consolidated visual and textual overview of a single treatment course (Figure 6). Graphical charts help to identify the dimensions of tumor load change with respect to baseline, nadir and previous exams. Therapy course overview is clearly depicted in the results and can be sent as digital imaging and communications in medicine to the PACS as well as actively included in the report. By such means, the standardization of the read workflow contributes to the assessment quality of longitudinal follow-up sequences providing comprehensible information for an interdisciplinary assessment of the therapy response by a tumor board.

Beyond resolution: Functional imaging

Functional imaging now has a growing role in colorec-

tal cancer assessment. Recent developments in imaging technologies and validation of these newer imaging techniques may lead to significant improvements in the management of patients with colorectal cancer.

To date, FDG-PET does not have an established role in primary diagnosis of colon cancer reflecting limited availability of resources and lack of convincing cost-benefit data^[53]. This technique has low sensitivity revealing mucinous adenocarcinomas in which metabolic activity is low. Partial volume averaging and necrotic lesions may cause false-negative results, and incidental physiologic bowel FDG uptake or inflammation will produce increased tracer uptake, giving rise to false-positive findings that can mimic a tumor. The controversial role of FDG-PET in the posttreatment setting has been already discussed above. Prediction of the nodal status by CRC remains problematic. A novel nanoparticle MRI lymphographic agent - ultrasmall superparamagnetic iron oxide particles showed an overall sensitivity and specificity of 88% and 96% in the detection of lymph node metastases of CRC^[54]. Regretfully these MRI contrast agents are not yet available for clinical practice.

Dynamic contrast-enhanced (DCE) CT and MRI have been described as potential prognostic biomarkers in CRC. The results of the studies evaluating DCE-CT as a biomarker for chemoradiation are controversial: while baseline low perfusion values were described to be associated with a poorer response in the study by Bellomi *et al.*^[55], another group reported the contrary^[56]. DCE-MRI data uses two compartments for contrast agent accumulation: blood plasma and extravascular-extracellular space. K^{trans} (volume transfer constant between the blood plasma and the extravascular-extracellular space, the washout rate, measured in minutes⁻¹) and K_{ep} (rate constant between the extravascular-extracellular space back to the blood plasma, the washout rate, measured in minutes⁻¹) determine the transport between these two compartments. Rectal tumors with higher K^{trans} values at presentation appear to respond better to CRT than those with lower values. After CRT, usually K^{trans} values are reduced, while persistent raised values indicate residual active disease^[57].

Experimental techniques in primary colorectal cancer diagnosis

In a study by Ng *et al.*^[58], CT texture features of primary colorectal cancer were studied in relation to 5-year overall survival rate. The authors studied the tumor heterogeneity using a range of parameters, including entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram. According to this study tumors demonstrating less heterogeneity at fine filter levels were associated with poorer survival, concluding that the addition of texture analysis to staging contrast-enhanced CT may improve prognostication in patients with primary colorectal cancer. Goh *et al.*^[8] assessed an interobserver agreement in a prospective study with integrated FDG-PET/CT and perfusion CT to evaluate the relationship between tumor glucose metabolism and vascularization.

FDG-PET/CT was used to localize the colorectal tumor, and CT coordinates were used to plan the subsequent perfusion. The study showed good intra- and interobserver agreement for the metabolic-flow differences, suggesting this approach as a robust parameter for clinical practice.

The role of MR Spectroscopy (MRS) has been of great interest in the recent years to improve the primary diagnosis of various cancer groups. In a small sample ex vivo prospective study on 24 subjects with colorectal cancer without neoadjuvant treatment, MRS was able to discriminate healthy from neoplastic tissue and to distinguish patients with different prognoses^[7].

Functional imaging in liver metastases of colorectal cancer

The liver is the first organ most likely to develop distant metastases from CRC. Knowledge of hepatic metastatic involvement during identification of the primary tumor is therefore crucial. The idea is not new and we can follow several attempts to get access to that information back to the nineteen-eighties. The approach is to detect the arterialization of the liver blood supply during the onset and development of liver metastases. In a normal healthy individual approximately two thirds of the blood supply of the liver arrives *via* the portal vein and one third *via* the hepatic artery. During the development of liver metastases, this relation changes: the above mentioned arterialization occurs, which means the arterial portion of the liver blood supply increases while the portal vein portion decreases^[59]. This has been shown first with technetium colloid scintigraphy to estimate the so called hepatic perfusion index (HPI) in overt liver metastases^[60-62]. Meanwhile it has been shown that the hemodynamic changes occur already at an early microscopic stage of metastasis formation^[63,64].

Leen *et al.*^[65] developed a Doppler ultrasound method to get a parameter similar to the HPI, the DPI, which gives the hepatic arterial blood flow relative to the portal venous flow. This ratio was raised in patients with liver metastases. The method demonstrated not only the possibility to detect overt liver metastases but also the arterialization due to occult metastases for the standard morphology based imaging methods. This study showed that patients with colorectal cancer, without liver metastases on first imaging and a raised DPI, had a much higher risk of developing liver metastases in the following five years than those with normal DPI. The DPI method thus seems to detect the presence of metastases which were occult to all other imaging modalities^[9]. Unfortunately, DPI measurements are strongly operator dependent and other groups could not reproduce Leen's results^[66,67]. HTT analysis of a microbubble ultrasound contrast agent has then been proposed as an alternative technique for detecting hepatic arterialization^[68]. It was initially used to show arterialization in patients with hepatic cirrhosis^[69,70]. Meanwhile several studies have shown that the method is able to detect hemodynamic changes in liver metastases but depends on the used contrast agent^[10,71-73] (Table 1).

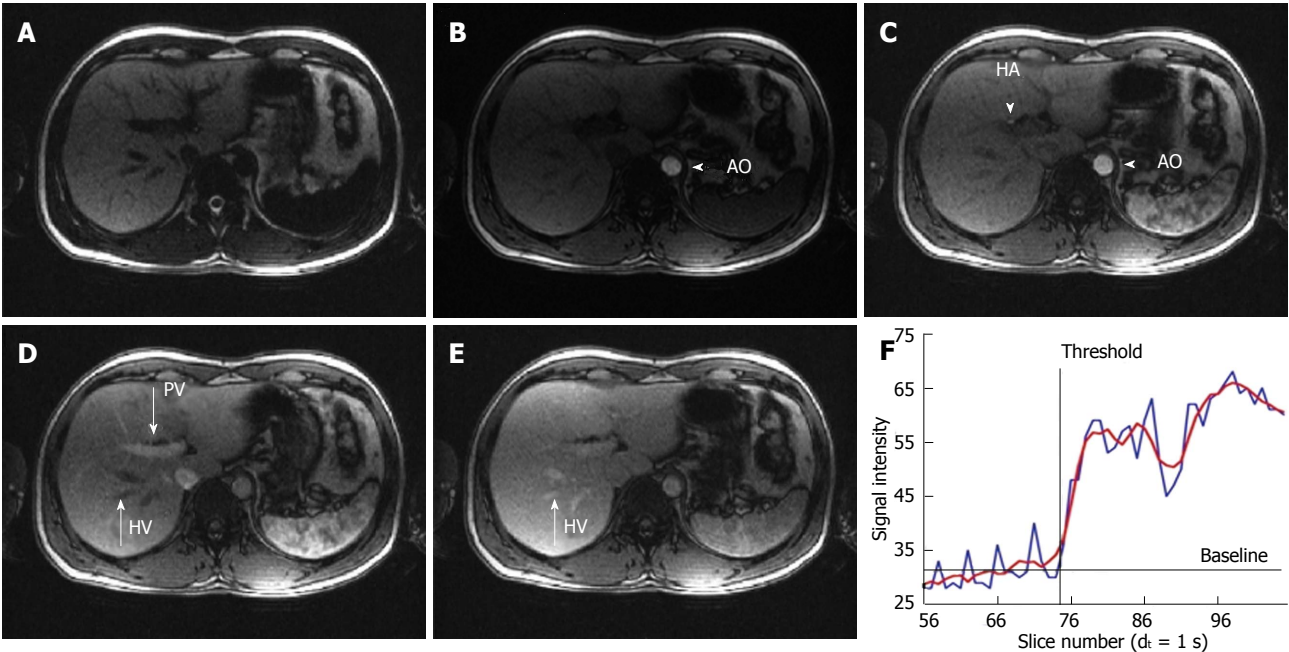


Figure 7 Magnetic resonance imaging images of the T1-weighted sequence for hepatic transit time analysis at different time points. A: Baseline image without contrast; B: Arterial phase with opacification of the aorta (AO); C: Arterial phase with opacification of the AO and the hepatic artery (HA); D: Portal venous phase with additional enhancement of the portal vein (PV); Note that the hepatic veins (HV) are still not enhanced; E: Venous phase with complete opacification of all vessels including the HV; F: Example of a typical time intensity curve acquired from a ROI placed at the position of the HA; The raw data in the graph (blue line) has a modulation due to patient breathing. Therefore the curve has to be fitted and smoothed (red line). The calculated baseline as well as threshold point, demonstrating the arrival time of the contrast agent is drawn.

Table 1 Summary of studies with measurement of hepatic transit times in subjects with and without the evidence of liver metastases

Study	Number of patients	Hepatic transit time (arterial to venous) (s)		contrast agent	modality
		Liver metastases	No liver metastases		
Bernatik <i>et al</i> ^[73]	28/36	6.7	15.4	Optison ¹	CEUS
Hohmann <i>et al</i> ^[10]	22/22	7.4	11.1	SonoVue ²	CEUS
Zhang <i>et al</i> ^[71]	5/3	6.2	11.3	SonoVue ²	CEUS
Haendl <i>et al</i> ^[72]	20/15	6.3	9.3	SonoVue ²	CEUS
Haendl <i>et al</i> ^[72]	12/14	9.9	14.8	Levovist ³	CEUS
Haendl <i>et al</i> ^[72]	20/15	6.3	9.2	Luminity ⁴	CEUS
Hohmann <i>et al</i> ^[78]	20/21	7.1	13.5	MultiHance ²	MRI

¹Amersham, Little Chalfont, United Kingdom; ²Bracco, Milano, Italy; ³Bayer, Berlin, Germany; ⁴Lantheus, N. Billerica, MA, United States. These are mainly studies using CEUS but also one study which used MRI. All other MRI studies used slightly different approaches and did not measure directly comparable values. CEUS: Contrast enhanced ultrasound; MRI: Magnetic resonance imaging.

There have also been other attempts to measure hepatic blood supply changes with CT and MRI. With CT this is usually a perfusion measurement with the calculation of different perfusion parameters such as hepatic artery and portal vein perfusion and the HPI^[74,75]. The major drawback of CT measurements is radiation exposure and, therefore, most of the studies are animal studies. Even though the results are promising, there are probably no realistic possibilities for CT perfusion measurements in humans.

With MRI the approaches are different which are

summarized under the term diffusion/perfusion measurements (Figure 7). Especially with focal or global perfusion methods, MRI seems to have great potential to detect hemodynamic changes due to focal liver lesions^[76]. While the first studies just measured perfusion parameters in one single plane^[77,78], this changed to measurements of the whole liver with 3D Datasets but with limited time resolution^[79,80]. It should currently be possible to increase this time resolution in further studies. All the previous mentioned methods required intravenous contrast material, which might have an influence on the results similar to the results on MRI as it was shown with CEUS. Therefore new methods without contrast material, like hemodynamic response imaging, which has proven to show therapy response in experimental settings, are very promising^[81].

Overall, for functional imaging in patients with colorectal cancer, MRI of the liver offers the widest variety of possibilities in the future. This might be essential for the detection of occult liver metastases at the time of first diagnosis of colorectal cancer and will then result in different therapeutic approaches due to the results of the measurement.

CONCLUSION

In recent years several attempts have been made to improve the diagnostic performance of imaging modalities for better characterization of CRC. To date, OC remains the most precise modality in the detection of primary CRC simultaneously allowing biopsy and therapeutic

polypectomy. Virtual CT colonoscopy is gaining importance as a potential alternative to OC, recently showing a similar diagnostic performance^[16]. However, radiation exposure and the lack of instantaneous therapeutic possibilities remain a primary concern. To date, there are insufficient study results to recommend MR Colonoscopy as a screening modality.

MRI and ERUS at present show the best results in the local staging of rectal carcinoma^[5,22,23]. MRI is the superior imaging modality for the evaluation of primary tumor location, extension and mesorectal fascia involvement. Overstaging remains problematic on MRI, related to difficulties in differentiating desmoplastic reaction caused by fibrosis alone (stage pT2) and by fibrosis that contains tumor cells (stage pT3). ERUS, with an accuracy of up to 97%, is currently the most accurate imaging modality in the assessment of T1 rectal tumor^[2]. For the detection of CRC distant metastases, US and CT are the most advocated modalities. Although FDG-PET/CT shows an increased accuracy in metastatic lymph node assessment, utilization of this modality is limited and cannot be applied broadly. Recent studies support the concept that in preoperative staging chest CT is not beneficial and imaging of the patients without hepatic and lymphatic metastases can be limited to CXR^[81].

Newer techniques in functional imaging may lead to significant improvements in the management of CRC. The hepatobiliary MRI contrast agent (Gd-EOB Primovist/Eovist®, Bayer Healthcare) is available to improve the detection of liver metastases and could be problem-solving in difficult cases. In treatment response monitoring, DWI is gaining a promising role as a reliable marker to improve MRI performance, however, characterization of metastatic lymph nodes remains challenging. Other MRI biomarkers in the treatment response evaluation such as Dynamic contrast enhanced MRI and perfusion CT might improve the insights in tumor biology to better characterize residual tumor. Experimental studies on MRI spectroscopy of primary CRC, MRI diffusion/perfusion and hepatic transit time analysis using MRI in the detection of metastatic liver disease are promising. However, further research in larger series is needed to be applicable in clinical practice.

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