

Review

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Imaging of colorectal cancer – the clue to individualized treatment

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Abstract: Colorectal cancer (CRC) is the most common gastrointestinal neoplasm and the second most common cause for cancer-related death in Europe. Imaging plays an important role both in the primary diagnosis, treatment evaluation, follow-up, and, to some extent, also in prevention. Like in the clinical setting, colon and rectal cancer have to be distinguished as two quite separate entities with different goals of imaging and, consequently, also different technical requirements. Over the past decade, there have been improvements in both more robust imaging techniques and new data and guidelines that help to use the optimal imaging modality for each scenario. For colon cancer, the continued research on computed tomography (CT) colonography (CTC) has led to high-level evidence that puts this technique on eye height to optical colonoscopy in terms of detection of cancer and polyps ≥ 10 mm. However, also for smaller polyps and thus for screening purposes, CTC seems to be an optimal tool. In rectal cancer, the technical requirements to perform state-of-the-art imaging have recently been defined. Evaluation of T-stage, mesorectal fascia infiltration and extramural vascular invasion are the most important prognostic factors that can be identified on MRI. With this information, risk stratification both for local and distal failure is possible, enabling the clinician to tailor the optimal therapeutic approach in non-metastatic rectal cancer. Imaging of metastatic CRC is also covered, although the complex ramifications of treatment options in the metastatic setting are beyond the scope of this article. In this review, the most important recent developments in the imaging of colon and rectal cancer will be highlighted. If used in

an interdisciplinary setting, this can lead to an individualized treatment concept for each patient.

Keywords: chemoradiotherapy; colorectal cancer; CT colonography; mesorectal fascia; MRI; PET/CT.

Introduction

Colorectal cancer (CRC) is a prevalent challenge in health-care with 447,000 new cases and 215,000 deaths in 2012 in Europe [1]. With changing treatment options for all kinds of cancer, it is now the second most common cancer for men and women in terms of mortality, only second to lung cancer [1]. The majority of patients suffer from colon cancer, whereas approximately a third of patients present with rectal cancer [2], although this number is quite variable throughout the literature. Five-year survival for CRC has improved over the last 30 years, ranging from around 50% in 1975 to 66% in 2012, for all stages [2, 3]. One part of this improvement is attributable to superior imaging techniques and early detection, leading to a more patient-oriented, tailored therapy compared to earlier times [4]. As anatomy, lymphatic and vascular drainage, and therapeutic options of colon cancer differ significantly from the ones of rectal cancer, the imaging techniques of these two entities will be covered separately. In rectal cancer, an exact locoregional staging is essential [5], whereas in colon cancer, other challenges like ruling out a second cancer proximal to a stenosing tumor play a more important role [6]. For both rectal and colon cancer, ruling out metastatic disease prior to a potentially curative surgical approach is mandatory. This review will give an overview of current imaging techniques and their applications in early to advanced stages of colon and rectal cancer, allowing the clinicians to offer a personalized approach for each patient.

General imaging/staging principles

In patients suspected of having colon or rectal cancer, a detailed physical examination, family history, and

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measurement of the carcinoembryonic antigen (CEA) level is recommended [5]. Usually, the first examination performed is optical colonoscopy (OC) with localization of the tumor and subsequent biopsy, and also to rule out other primary colonic tumors. In cases of incomplete colonoscopy, computed tomography (CT) colonography (CTC) can be performed to visualize tumors orally to a nonpassable stenosis. The sensitivity to detect colon cancer is similar for OC and CTC, ranging around 95% [7]. However, one of the advantages of OC is to subsequently biopsy a lesion, which leads to a primary recommendation for OC over CTC. CTC is considered as a viable second-line option in patients, where the lesion could not be reached by OC or who do have contraindications for OC [8, 9]. Barium enema is considered as the last method of choice, if neither OC nor CTC is available to locate the tumor [10]. CTC will be covered in more detail in a later paragraph.

Once the diagnosis of colon or rectal cancer is ascertained, staging should be performed using the latest version of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) classification [11]. As of January 2018, the reference standard will be the 8th edition, which is provided in an abbreviated form in Table 1. Changes from the 7th edition are minuscule for

CRC and affect mostly details relevant for histopathological staging [11]. The only change significant for pretherapeutic imaging is the introduction of the M1c stage in patients with peritoneal carcinomatosis.

Colon cancer

Specific imaging requirements for colon cancer

CT of the abdomen and thorax is the method of choice for staging in colon cancer [5]. It should be performed as a multiphase contrast-enhanced CT, ideally with an arterial phase covering the liver and a venous phase covering the chest and the abdomen [12]. It allows to identify the site of the tumor in most cases, bulky lymphadenopathy, ascites, profound carcinomatosis, and invasion into adjacent organs (Figure 1). Liver metastases >1 cm and lung metastases can also be identified with an accuracy of up to 95% [13] and benign lesions can be differentiated based on typical imaging appearances.

It must be taken into account that CT has only moderate reliability for T and N staging in colon cancer, with accuracies ranging around 67% and 69%. Apart from T4 tumors, the subclassification of T stage and nodal stage

Table 1: TNM staging of colon and rectal cancer.

T stage	
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades into pericolorectal tissues:
T3a	Invasion ≤ 1 mm
T3b	Invasion 1–5 mm
T3c	Invasion ≥ 6 –15 mm
T3d	Invasion ≥ 15 mm
T4a	Tumor penetrates the visceral peritoneum
T4b	Tumor invades into adjacent organs
N stage	
N0	No evidence of lymph node metastases
N1a	Metastasis in one regional lymph node
N1b	Metastases in 2–3 regional lymph nodes
N1c	Tumor deposits in the subserosa or pericolic/perirectal tissues (not to be differentiated by imaging)
N2a	Metastases in 4–6 regional lymph nodes
N2b	Metastases in 7 or more regional lymph nodes
M stage	
M0	No distant metastases
M1a	Metastases confined to one organ
M1b	Metastases in more than one organ
M1c	Metastases to the peritoneum with or without other organ involvement



Figure 1: Contrast-enhanced CT image with coronal reformation showing a T4 sigmoid cancer invading the urinary bladder (arrow). The intervening fat plane between the tumor and the bladder wall is obliterated, indicating the tumor infiltration.

does not change the surgical management and is, therefore, not required in the preoperative workup [14–16]. Even T4 colon cancers will usually not receive neoadjuvant treatment unless metastatic disease is present; however, it is of critical importance to report this finding to the treating surgeon, in order to enable optimal presurgical planning. In a recent retrospective study, the subgroup of T4b patients also seemed to have improved survival after neoadjuvant chemotherapy [17]. The concept to treat locally advanced, non-metastatic colon cancer with neoadjuvant chemotherapy is currently assessed in a large phase 3 trial with over 1000 patients, which has finished patient recruitment in late 2016 [18]. It has to be noted, though, that patients with early T1 tumors might be amenable for local excisional strategies (endoscopic mucosal resection, endoscopic submucosal dissection) [19]. These early stages cannot be identified with CT or magnetic resonance imaging (MRI) but require the use of endoscopic ultrasound (EUS), which will be covered in the section on rectal cancer.

Small liver metastases and small peritoneal deposits <5 mm also require additional techniques to optimally stage the patient, if clinically indicated [20]. An MRI of the liver with diffusion-weighted imaging and hepatocyte-specific contrast agent is mandatory for optimal assessment of liver metastases <1 cm. This will be covered in the chapter on metastatic CRC.

The 18-fluorodeoxy glucose (FDG) positron emission tomography (PET)/CT is currently not recommended in the primary staging of colon cancer due to lack of high-quality evidence of efficacy and cost effectiveness [21].

Screening for polyps and early colon cancer

As more than 90% of CRC arise from benign precursors through an adenoma/carcinoma sequence, early detection of adenomatous polyps poses a way to either prevent the development of CRC or to allow treatment of cancer in its early phase [22, 23]. Nevertheless, screening programs are not readily accepted by the population [24], or are not efficient enough, as is the case with fecal occult blood testing or barium enema [25, 26]. CTC is a well-validated technique to improve early detection of polyps and advanced adenomas [8, 27]. Sensitivities to detect advanced adenomas and cancer are comparable to OC [28]. As its performance is clearly superior to that of the barium enema, CTC is now recommended as the radiological method of choice for the detection of colorectal neoplasia [25]. Barium enema is no longer recommended for this indication. CTC is well tolerated by patients, safe,

and also cost effective [24, 29]. Being available as a diagnostic option to OC, CTC has the potential to increase the overall participation in CRC screening. It was recently included in the US Preventive Services Task Force screening guidelines for CRC [26]. However, in a joint statement of the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Society for Gastrointestinal Endoscopy, CTC is not recommended as a primary screening tool for CRC, although it can be used as an optional screening examination, on an individual basis [25]. Other techniques, like MR-colonography or plain abdominal CT, have inferior performance in the early detection of advanced adenomas or colon cancer and should, therefore, not be considered as the primary radiological technique in this situation [30].

Technique of CTC

As the sensitivity of standard abdominal CT to detect small intracolonic lesions is poor [31], optimal visualization in CTC requires both luminal distension and catharsis to enhance lesion detection [32]. The technical standards for CTC have been published in a consensus statement by the ESGAR in 2013 [33]. Similar to OC, bowel preparation on the day before the exam is performed, and patients will also receive a small amount of oral contrast media in order to increase lesion conspicuity and to differentiate small lesions from residual stool. A CT scan of the abdomen is performed without intravenous (IV) contrast in the prone and supine position, in order to allow for better visualization of polyps immersed in fluid or for clarification of mucosal folds, etc., which might be just an effect of positioning. Before the scan, luminal distension is provided by air or CO₂ that is applied endorectally. Two-dimensional (2D) and 3D reconstructions of the dataset are performed, allowing for standard interpretation of the abdominal CT scan as well as endoluminal “fly through” images, hence, the alias name virtual colonoscopy [32, 34] (Figure 2). As there is an intrinsically higher contrast between air and polypoid/cancerous lesions in the lumen of the colon, CTC can be performed with a lower radiation dose than a usual diagnostic CT scan. In addition, several dose-reduction algorithms, like iterative reconstruction, exist that will further decrease the radiation exposure, leading to scans in the low- to sub-millisievert – range [35, 36]. Dose reduction should not be pushed to the maximum possible, though, as the benefit of detecting colon cancer early outweighs the already low risk of radiation-induced carcinogenesis [37].

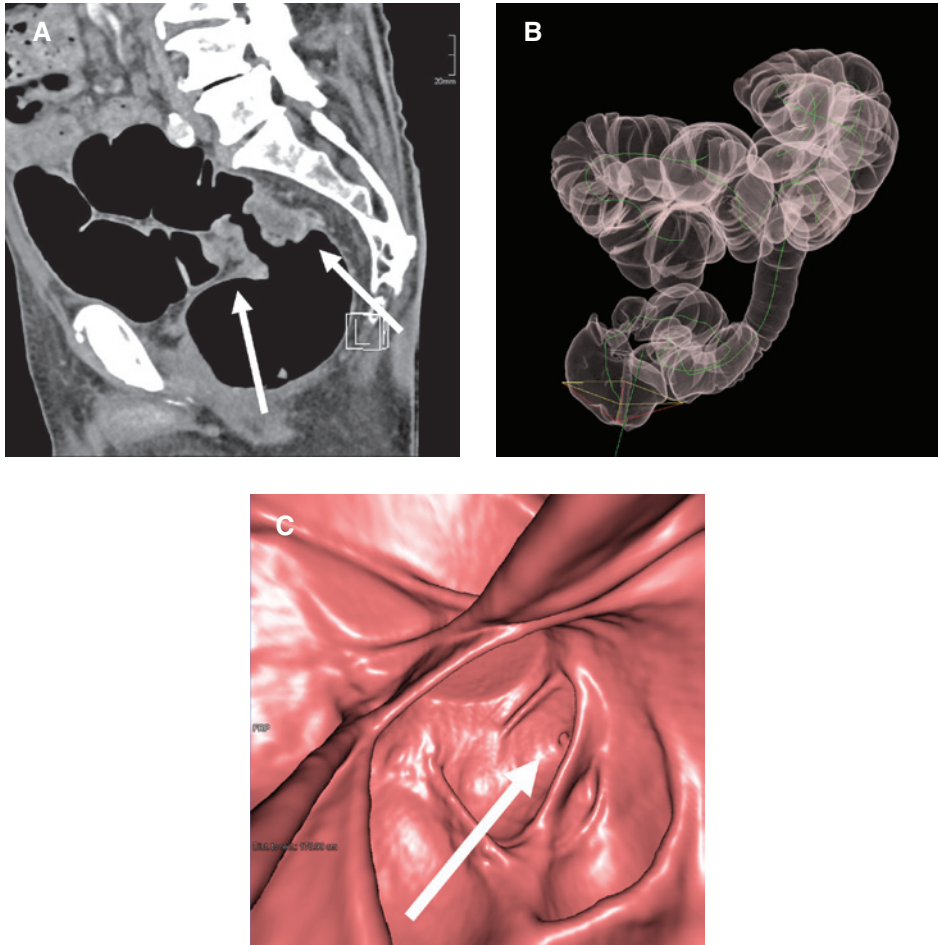


Figure 2: CT colonography after failed colonoscopy because of a stenosing rectosigmoidal cancer.

(A) Sagittal CT image showing the tumor with a circular stenotic thickening of the rectal wall. (B) Surface rendered colon map with virtual colonoscopic pathway (green line) indicating a complete visualization of the large bowel. (C) Endoluminal 3D image at the level of the cecum. The appendix orifice is indicated by the arrow. No additional tumors were detected.

Diagnostic performance and limitations of CTC

According to several trials in this field, the sensitivity to detect colon cancer is equally good for CTC [9] compared to OC [31] (96% and 95%, respectively). For the detection of adenomatous polyps ≥ 10 mm, the sensitivity is also considered to be equal (CTC vs. OC, up to 94% vs. 98%) [38]. Based on data from a recent meta-analysis, CTC also reaches comparable performance as OC in the detection of polyps/adenomas ≥ 6 mm in size (pooled analysis from seven trial CTC vs. OC, 73%–98% vs. 75%–93%). For lesions smaller than 6 mm, OC remains the superior technique in detection.

The performance of CTC can be affected by a number of pitfalls [39, 40]. As it was shown in some early CTC trials, suboptimal examination technique as well as interpretative errors by the radiologist can impair the performance

of CTC [41, 42]. This can, however, effectively be avoided by performing the examination in adherence to technical standards and by dedicated CTC reader training [33, 43, 44]. Last, the ability to endoscopically resect detected lesions and to obtain a tissue diagnosis is the reason why OC is still the method of choice for most clinicians.

Colonic visualization in patients with stenosing CRC

Preoperative visualization of the entire colon and rectum is needed in patients with CRC for identification of synchronous colorectal neoplasia. CT colonography is recommended as the method of choice in patients with incomplete colonoscopy or with contraindications to colonoscopy [25]. It is an effective and safe diagnostic option to complete colorectal visualization, if an obstructing CRC

prevents complete colonoscopic assessment. Performed in a preoperative setting after failed colonoscopy, in patients with obstructing CRC, CTC has shown to be highly accurate in assessing synchronous CRC and advanced neoplasia [negative predictive values (NPVs) of 100% and 97, respectively] [45]. CTC may further allow accurate segmental tumor location [46] and, if performed after IV application of contrast media, the assessment of extracolonic abdominal organs [25].

Rectal cancer

In rectal cancer, many of the principles described for colon cancer are also valid and should be followed in the primary workup of this condition. However, due to diverse treatment pathways that exist in rectal cancer, several locoregional risk factors have to be taken into account in order to correctly identify the risk for local or distant recurrence in patients suffering from rectal cancer [47]. The primary diagnosis of rectal cancer is often more straightforward, either using digital rectal examination or office-based proctoscopy without the need of an endoscopy suite. The modality of choice for locoregional staging in rectal cancer is MRI and EUS for specific cases [5]. In 2012 and 2016, an expert panel of the ESGAR published guidelines on how MRI in rectal cancer should be performed and reported. It also helps radiologists and clinicians to follow a standardized approach on how rectal cancer should be staged before treatment [48].

Similar to colon cancer, all patients should receive a full OC to rule out second colon cancers and a CT of the abdomen and thorax, in order to detect or rule out metastatic disease. Similarly, there is no indication for the routine use of FDG-PET/CT in the primary staging of rectal cancer [5].

Endoscopic ultrasound

Endorectal ultrasound is the most accurate method to perform T staging in early T1 and T2 tumors. The accuracy to correctly identify the invasion depth of rectal tumors is up to 97% in expert hands [49]; however, it drops considerably if used by less experienced operators [50]. In order to identify patients amenable for local excision, EUS is the sole method to identify early T1 (sm1-3) tumors, as MRI's local resolution is too low to allow this differentiation [48]. Also, the accuracy to differentiate between T1 and T2 tumors in MRI is not high enough. Therefore, the role of

MRI to stage very early tumors is limited. The limitations of the EUS, though, are high-seated lesions and stenosing tumors, which might impede complete visualization of these lesions. Also, the limited field of view might not allow complete visualization of the mesorectal fascia (MRF) and detection of pathological lymph nodes outside the mesorectum. Furthermore, it is a bit more invasive and not well tolerated by all patients [51].

MRI

According to the 2016 ESGAR guidelines for imaging rectal cancer, MRI should be performed in all patients with rectal cancer [48]. The method of choice is MRI with at least 1.5-Tesla field strength with an external phased-array coil. The use of an endorectal coil is no longer recommended. Because of the lack of robust evidence on this topic, there is no dedicated consensus whether spasmolytics or cleansing enema are needed prior to the examination [48]. Some centers, including ours, are performing these adjunct measures in order to optimize image quality. The MRI protocol should include high-resolution T2-weighted sequences performed in three planes. For optimal evaluation of T stage, and hence prognostic stratification, the slice thickness should be no more than 3 mm with a high resolution (“matrix”), leading to a voxel size of 1 mm³ or less. Diffusion-weighted sequences are increasingly performed. They are especially required in restaging of rectal cancer after chemoradiotherapy (CRT). In short, these sequences show more or less density of tissue, by visualizing the impairment of the Brownian movement after applying several magnetic gradients. The less freely protons can move in tissue, the higher the signal will be, especially in dense tumor tissues, i.e. primary rectal cancer or remnant tumor after CRT. There is no general consensus about the use of IV contrast agents; however, we perform it regularly for research purposes and sometimes to better depict tumor borders. However, this is not endorsed by the current guidelines [48].

Practical use of MRI

First, MRI can deliver anatomic information about the tumor location, the distance to the anal verge and sphincter complex, i.e. also puborectalis sling and levator muscles. For low-lying tumors, the radiologist should differentiate whether the internal sphincter, the intersphincteric fat plane, and/or the external sphincter is involved by the tumor, due to different surgical approaches possible in these situations [52]. Furthermore, the general

features of the tumor like whether it is bulky, flat, villous, etc., can be described. Moreover, the circular location (given on as, e.g. 1–3 o'clock in the axial orientation) can be provided, which might be helpful in the case of smaller tumors. For higher tumors in the upper third, the relation to the peritoneal reflection has to be taken into account as peritoneal spread might occur earlier than in lower rectal tumors. The surgical accessibility to the pelvis and tumor infiltration into adjacent organs can also be quickly identified. Tumor length measurements can give an estimation to the clinician about the tumor size; likewise, tumor volumetry or 3D measurements are also considered feasible [5, 48].

Next, the T stage is assessed, which can be done with an overall accuracy of around 70% [53]. It is one of the most important stratification criteria on how primary rectal cancer should be treated. Early tumors (T1/sm1), which can potentially be treated by local excisional therapies, need additional staging with endorectal ultrasound, as MRI cannot reach this degree of anatomical resolution or differentiate whether a tumor reaches the submucosa or not with sufficiently high accuracy. All tumors that are of higher T stage have a rapidly increasing risk of lymph node metastases and will potentially be treated with a total mesorectal excision (TME) without pretreatment [47]. In intermediate risk tumors (\leq T3b, very low-lying T2, questionable nodal positivity), short-term radiation followed by TME or TME alone are both endorsed by the current guidelines [47]. MRI is limited in the ability to discriminate between T3a and T2 tumors, mostly due to desmoplastic reaction in the mesorectal tissue adjacent to the tumor [53]. EUS has the same limitations as MRI;

however, prognostically, there is no significant difference between T3a and T2 tumors. Thus, at least in the European guidelines, treatment will not be different for these early T3 stages compared to that of T2 (TME with or without short-term RT) [47]. It has to be noted, though, that even in Europe, large geographical variations exist regarding the selection of neoadjuvant therapy in rectal cancer.

Tumors that reach more deeply into the mesorectum (T3c or higher, Figure 3A), and especially those which reach the mesorectal fascia (MRF, Figure 3B), will exhibit a higher risk for local treatment failure, independently of lymph node status. MRI is the gold standard to assess MRF endangerment or invasion; EUS is less accurate due to limited signal transmission and the difficulty in visualizing the entire MRF in many tumors [54, 55]. If the MRF is involved on MRI (distance of nearest tumor or lymph node \leq 1 mm), the likelihood of a possible circumferential resection margin after TME is high. Therefore, they should receive long-term chemoradiotherapy followed by TME after tumor board decision [47]. In expert hands, the capability of MRI to predict an endangered (\leq 1-mm distance to the tumor) or involved MRF is very good with a 92% concordance with pathology. A negative, i.e. clear MRF can be predicted with an NPV of 94% [55]. In general, the penetration depth into the mesorectum measured by MRI is considered equivalent to pathology and should, therefore, be mentioned in the MRI report [48]. CT has a role in assessing a negative MRF in patients that cannot receive MRI, but it is only reliable in mid- and upper third tumors [56]. FDG/PET CT did not show any additional benefit in the local staging of rectal cancer and should have no role in the routine setting [57].

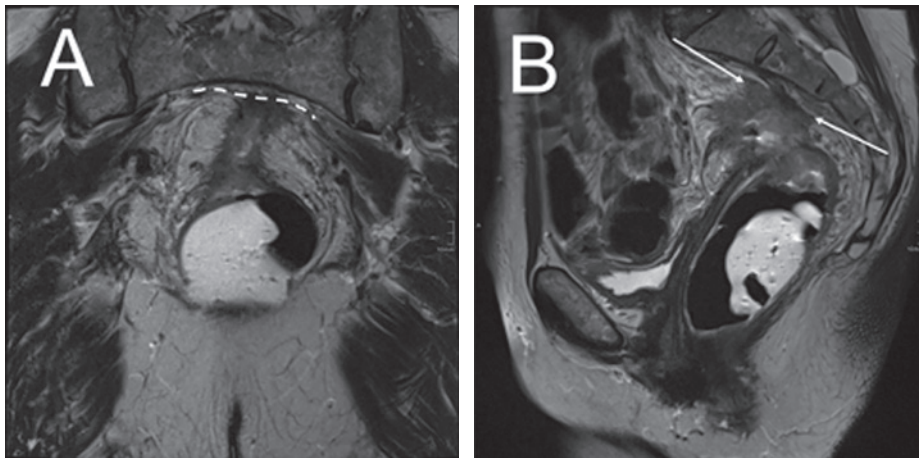


Figure 3: MRI in rectal cancer, T-stage and mesorectal fascia (MRF) assessment.

(A) Transverse T2-weighted MRI image showing a T4a tumor that invades far into the dorsal mesorectum, invades the MRF (dashed line) and extends into the presacral fat plane. (B) Sagittal T2-weighted MRI image showing invasion of the posterior MRF, as indicated by arrows. This patient is of high risk for local recurrence despite the favorable tumor location in the mid/upper third of the rectum.

Assessment of lymph node metastases

The general sensitivity and accuracy to correctly identify lymph node metastases with MRI is unfortunately quite low. Unlike other gastrointestinal malignancies, size criteria are unreliable (positive predictive value 62%) because up to 50% of metastatic lymph nodes are 5 mm or less in the short-axis diameter [49]. The additional assessment of shape, border, and signal heterogeneity can help in the assessment; however, it still remains far from being accurate. Twenty-five percent of lymph nodes are overstaged on MRI, which might trigger unnecessary preoperative treatment in these patients [48].

Therefore, risk assessment based on questionable lymph node metastases should be performed with caution, especially as $\leq T3b$ tumors have a favorable prognosis and local control rate, irrespective of nodal stage [58]. Special attention should also be paid to pelvic side wall lymph nodes or lymph nodes in the obturator fossa. These lymph nodes are outside the TME resection plane and also outside the standard radiation field, so the chance that they are left untreated remains high if not specifically addressed in the report. In a recent multicenter randomized trial from Japan, the importance of lateral lymph node dissection was highlighted. Patients with initially no lateral lymph node enlargement had a higher local recurrence rate (12.6% vs. 7.4%) if lateral nodes were not dissected, although 5-year overall survival and recurrence-free survival was not different [59]. It has to be noted though that although several studies from Asian centers demonstrated the safety and efficacy of this procedure [60], it is not widely accepted in

European and US centers, which might be due to demographic differences in the patient cohorts.

Extramural vascular invasion

An additional risk factor is the presence of extramural vascular invasion (EMVI). This feature is present when tumor signal is seen within a vessel that expands the vessel or leads to an irregular vascular contour (Figure 4). This observation can be made especially in patients that present with synchronous liver metastases (odds ratio, 5.7), but it has also been shown that these patients are of increased risk to develop distant metastases in the follow-up (odds ratio, 3.9) [61]. Hence, there is a discussion whether these patients might be candidates for upfront chemotherapy. However, this is still under debate. Also, the presence of EMVI can be determined with a graded scale, therefore, gauging the diagnostic confidence of this frequently underreported finding [62]. The presence or absence of EMVI should now be reported at the primary staging and at restaging, although it has been shown that MRI tends to overstage EMVI after CRT [5, 48, 63].

With these parameters, a pre-therapeutical risk stratification is possible, which is summarized in Figure 5. Of note, these recommendations were made by the European Society of Medical Oncology (ESMO). Several minor discrepancies exist between them and recommendations for risk-adapted treatment from other societies in this field. To cover all these differences is certainly beyond the scope of this manuscript.

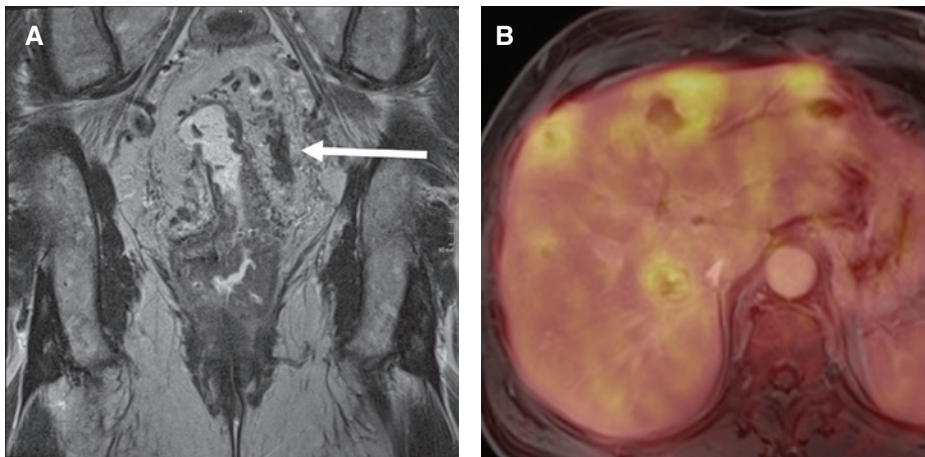


Figure 4: EMVI.

(A) Coronal T2-weighted MRI image showing longitudinal vascular expansion with intraluminal tumor signal (arrow). This sign is highly predictive of synchronous or metachronous liver metastases as shown in the transverse F18-FDG PET/MR image (fused T1-gradient echo sequence with fat suppression and PET) of the same patient (B).

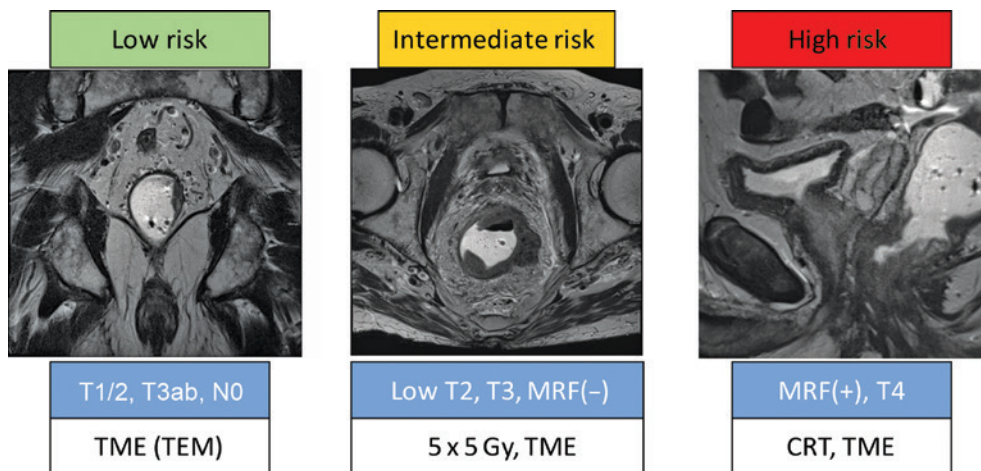


Figure 5: ESMO guidelines for the risk assessment in rectal cancer prior to treatment.

Response to neoadjuvant treatment

Another important and difficult application is restaging after neoadjuvant chemoradiotherapy in high-risk

patients. This is usually performed 6–8 weeks after the end of the treatment, allowing for the possibility of a prolonged effect of radiation [48]. Restaging with MRI should be performed at this stage and before a surgical procedure,

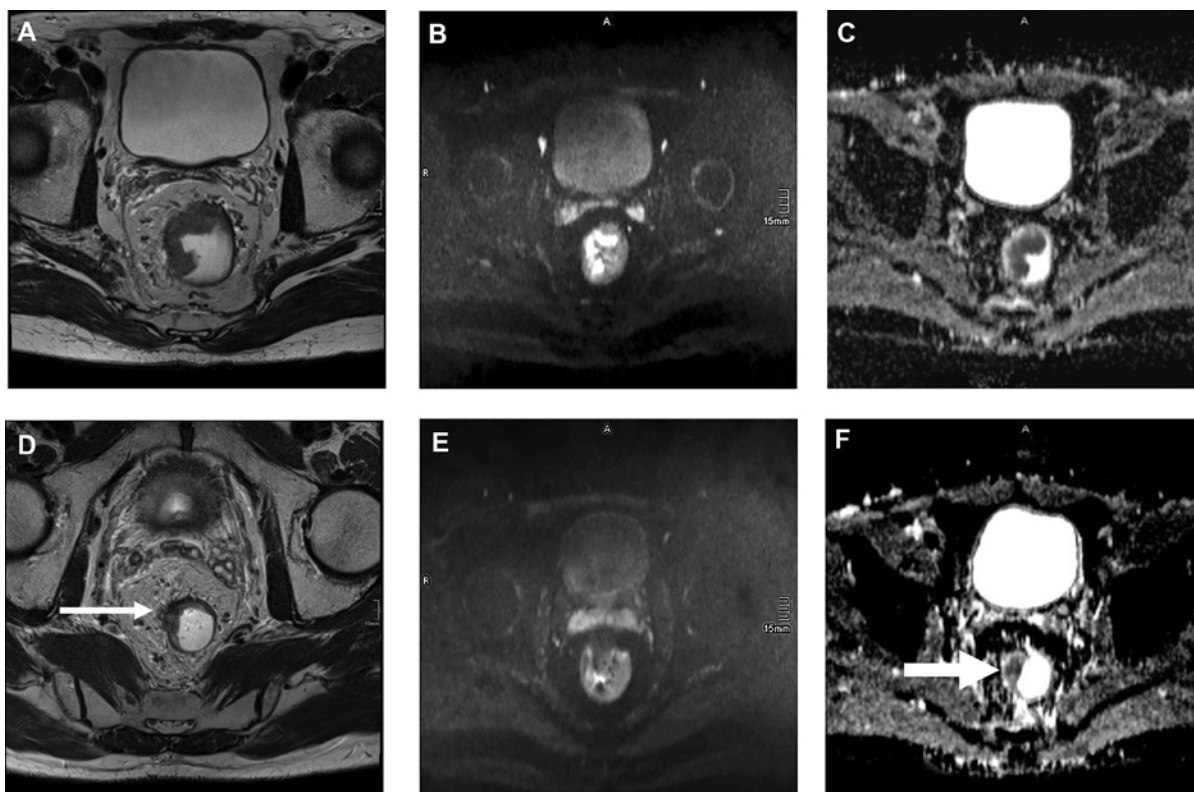


Figure 6: Restaging of rectal cancer after CRT with MRI.

(A) Transverse T2-weighted MR image showing a semi-circumferential tumor in the 7–1 o'clock position; (B + C): transverse diffusion-weighted image with a b-value of 800 s/mm^2 (B) and ADC map (C). There is a marked diffusion restriction, i.e. low apparent diffusion coefficient indicated by a dark signal within the rectal lesion; (D–F) similar sequences like (A–C); after long-course chemoradiotherapy, the tumor has decreased in size with questionable residual mesorectal infiltration; (E + F) no clearly increased signal on the b-800 image, but a focal area of dark signal (white arrow) on the ADC map indicates residual tumor, with a higher sensitivity than T2-weighted sequences.

as the surgical approach might be different in the case of a good response, and organ-sparing resections might be an option. Furthermore, the likelihood for complete pathological response (pCR) after CRT is around 25%, and these patients might be candidates for a watch-and-wait strategy, which is currently investigated in trials [64, 65]. The conventional T2-weighted sequences are insufficient to assess for residual tumors, which has been shown in a recent meta-analysis. Therefore other techniques, like diffusion-weighted imaging, have to be applied to improve the sensitivity from 50% to around 80% [66] (Figure 6).

Apart from an assessment with MRI, patients need a clinical and endoscopic reassessment, as only the combination of all the three parameters has the best accuracy to rule out residual tumor. The post-test probability of all the three modalities combined reaches 98%. However, in 15%, when a residual tumor is suspected, the finding is actually over-interpreted, and the tumor is already pCR. MRI also plays a role in the follow-up of patients who underwent organ-sparing local excision and who are watched with a

clinical pathological response [67]. Up to 25% of the recurrences appear below the mucosa or in the mesorectum and might be missed with endoscopic assessment only [64].

Workup of metastatic colorectal cancer

At primary staging, all patients with colon or rectal cancer should receive a CT of the abdomen and chest, although an X-ray of the chest to assess for metastases is generally considered feasible by the guidelines [5, 68]. In our practice, though, we do not rely on chest X-ray in the staging and restaging process due to the poor visualization of smaller lung metastases [69]. As resection of lung metastases is a valid element in the multimodal treatment concept of CRC lung metastases, we perform chest CT routinely for our patients. Although there is no evidence of improved survival in the follow-up after CRC resection [70], we do think that lung resection is generally underused, as we see several patients every week who might have been

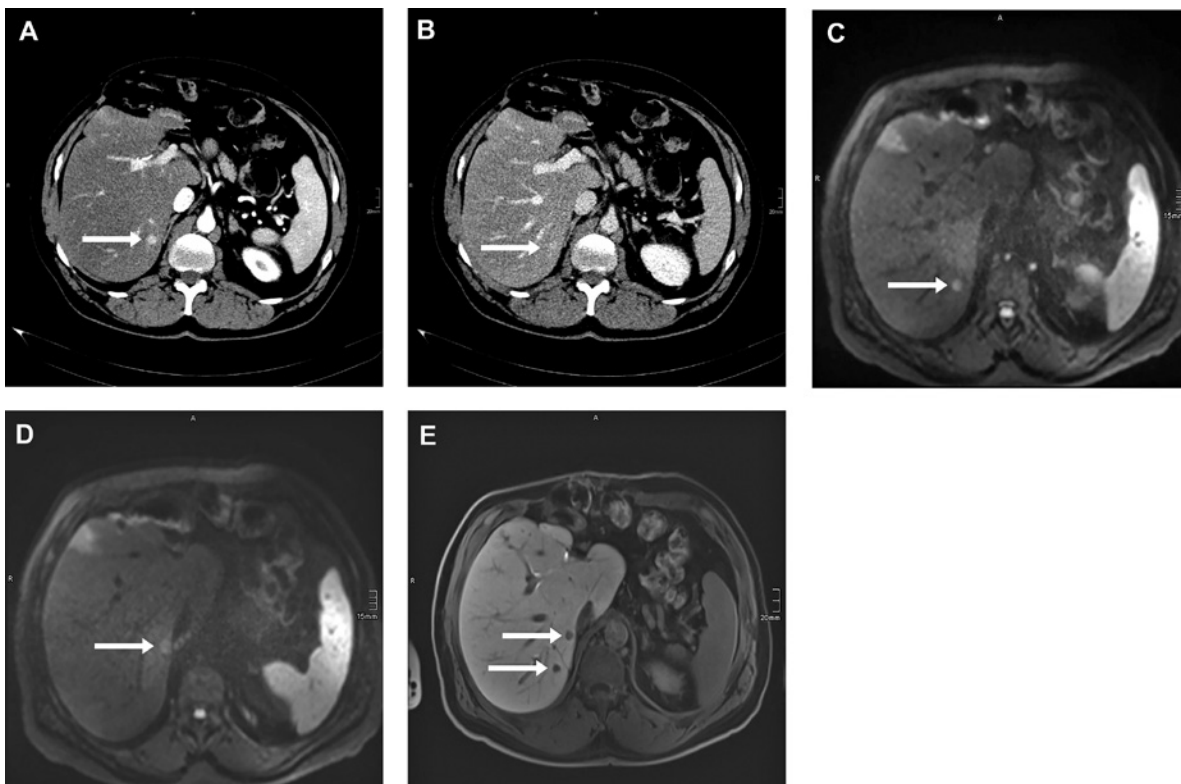


Figure 7: Multimodality staging of metastatic CRC: male patients with oligometastatic CRC scheduled for multiple atypical liver resections (not all hepatic lesions are shown on these images).

(A + B) Transverse CT image in the arterial (A) and portal-venous phase (B). A hypervascular lesion is seen in Segment VII, which is only faintly visible on the portal venous phase. In this region, no other metastases are visible. (C–E) MRI with DWI and hepatobiliary-phase imaging demonstrates an additional lesion (D), which changes the surgical management. (C + D) Axial DWI image with high b-value (600 s/mm²). An additional lesion more medial in Segment VII is visualized (D). (E) Transverse T1-gradient echo sequence with fat suppression 20-min post injection of gadoteric acid shows both lesions on the same image.

candidates for lung resection if presented to a thoracic surgeon at earlier times. These patients should regularly be re-evaluated in tumor boards, and this will only be possible in the case of optimal staging information. With modern scanners, radiation exposure becomes of less concern, and the reliability of the examination is greatly enhanced. For the detection of liver metastases ≥ 1 cm, contrast-enhanced CT is considered equal to liver MRI; however, the sensitivity drops considerably for smaller lesions, which might be important if a liver resection is considered [20]. Liver steatosis or steatohepatitis as a side effect of neoadjuvant chemotherapy, i.e. chemotherapy-associated steatohepatitis (CASH) leads to a decreased detection rate of liver metastases as well [71]. Therefore, in all patients that are potential candidates for liver resection, we endorse MRI with hepatocyte-specific contrast agents and diffusion-weighted imaging, as this has been shown to be the most accurate staging also for small liver metastases [72] (Figure 7). Of note, this procedure is only suitable to assess patients that might be amenable for liver resection. If there is extensive metastatic disease, frank peritoneal disease, bone metastases, or other reason why a curative resection cannot be performed, a CT scan is sufficient to follow for treatment response on palliative chemotherapy [5]. The use of PET/CT is still debated controversially in metastatic CRC. Although it has been shown in a recent randomized trial in patients with potentially resectable liver metastases that the change in management by PET/CT was minuscule with 8% [73], other meta-analyses suggest a higher number of extra-hepatic findings that were only picked up in PET/CT and changed management of patients [74]. Currently, there is no clear recommendation for the use of PET/CT in metastatic patients. At our center, we use it in difficult cases in which the presence of extrahepatic disease might distinguish between a potentially curative/resectable treatment approach.

Follow-up of colorectal cancer

There are limited data about the correct interval and frequency of imaging studies in the follow-up of colon and rectal cancer, similar to recommendations for clinical follow-up [6, 47, 56, 68]. There is some weak consensus to perform MRI in the follow-up after local excision of early rectal cancers; however, it is unclear, how frequent these examinations should be performed [5]. At our institution, we perform a tight follow-up in the first 2–3 years with 3–6 monthly CT of the chest and abdomen, as well as pelvic MRI if a higher risk for local recurrence is suspected. This interval increases to 6–12 monthly, up until

5 years. After 5 years, patients are further followed-up on an individual basis.

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Author Contributions

Dietmar Tamandl: conceptualization; methodology; software; supervision; validation; visualization; writing – original draft; writing – review and editing. Thomas Mang: conceptualization; methodology; supervision; writing – review and editing. Ahmed Ba-Ssalamah: conceptualization; methodology; supervision; validation; writing – review and editing.

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Supplemental Material: The article (<https://doi.org/10.1515/iss-2017-0049>) offers reviewer assessments as supplementary material.



Reviewer Assessment

Dietmar Tamandl*, Thomas Mang and Ahmed Ba-Ssalamah

Imaging of colorectal cancer – the clue to individualized treatment

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Reviewers' Comments to Original Submission

Reviewer 1: Michael Uder

Jan 14, 2018

Reviewer Recommendation Term: Accept with Minor Revision
Overall Reviewer Manuscript Rating: 85

Custom Review Questions	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	N/A
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	4
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

Title: OK

Abstract: Ok

Keywords: OK

Main document:

Page 3: “Colorectal cancer (CRC) is a prevalent problem with 447,000 new cases and 215,000 deaths in 2012 in Europe” ◊ Are there more up to date data?

“survival” instead of “Survival”

Page 4: “CT with an arterial phase covering the liver” ◊ can you provide evidence for this recommendation?

Page 7: “CTC can be performed using a lower radiation dose than a usual diagnostic CT scan” ◊ can you provide evidence for this recommendation?

“several dose reduction algorithms exist” ◊ please expand and provide more accurate information on this topic

Page 8: “a CT of the abdomen and thorax” instead of “a CT of the Liver/Abdomen and Chest”

Page 9: “there is no dedicated consensus whether spasmolytics or cleansing enema are needed prior to the examination” ◊ please provide references covering this topic

Tables/Figures:

Figure /legend 5:

Please provide information on the imaging modalities, sequence, etc.

Why are the metachronous liver metastases shown on an F18-FDG PET/CT image? Please provide a contrast enhanced CT (p.v. phase) or MR images showing the liver metastases.

Figure/legend 6:

“7 to 1 o'clock” instead of “7-to 1o'clock”

ADC: “Dark signal within rectal lumen” ◊ within tumor!

Please provide images showing high B-values

Figure/legend 7:

Please provide more information on the MRI sequences (B value, etc).

Why do you show F18-FDG PET/CT images for a liver lesion? Is this the accurate imaging modality? Is the “FDG-avid lesion” really in segment 7 and not in segment 8?

Please provide native and different phases following i.v. contrast agent administration (native, arterial, pv, late).

There are 2 liver lesions in the high B-value (please provide information on sequence, B-value, etc.). Were both lesions visible in the shown T2-sequence and in the delayed T1 sequence post contrast? Please provide images that show both lesions with arrows.

Please provide the CT which does not show the lesions.

Please include a Figure showing the different T-stages of rectal carcinoma (MRI, T2-weighted images) and include one CRM positive and one CRM negative carcinoma.

Reviewer 2: anonymous

Jan 30, 2018

Reviewer Recommendation Term:

Revise with Major Modification

Overall Reviewer Manuscript Rating:

20

Custom Review Questions**Response**

Is the subject area appropriate for you?

5 - High/Yes

Does the title clearly reflect the paper's content?

3

Does the abstract clearly reflect the paper's content?

4

Do the keywords clearly reflect the paper's content?

4

Does the introduction present the problem clearly?

4

Are the results/conclusions justified?

4

How comprehensive and up-to-date is the subject matter presented?

3

How adequate is the data presentation?

2

Are units and terminology used correctly?

5 - High/Yes

Is the number of cases adequate?

N/A

Are the experimental methods/clinical studies adequate?

N/A

Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	2
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	2
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

Abstract:

The technical requirement for MR imaging of rectal cancer have been identified more than a decade and not only since five years.

Key Words:

Nuclear medicine, PET/CT is not among the key words and should be among them considering the increased importance of this modality in colorectal cancer.

Introduction:

First line - prevalent problem should be rephrased with something more suitable. Prevalent disease in the population, prevalent challenge in healthcare or otherwise.

First paragraph - It is reported the change over the last 30 years although the change reported (should preferably also separate colon and rectal cancer) does only cover 20 years and are not recent figures. Evaluation of locoregional and metastatic disease extent is important both in rectal and colon cancer. I suggest rephrasing of the paragraph considering this.

Page 4- there are also other diagnostic advantages for colonoscopy vs CT-colonography than the possibility to obtain biopsies.

Colon cancer:

Page 5 - The importance of recognizing and reporting T4 tumours on preoperative CT, regardless of setting and technique should be emphasized since if the information is not transferred to the surgeon implies risk of inadequate laparotomy.

Regarding the current evidence for neoadjuvant treatment in colon cancer and the implications for imaging, this could be further elaborated beside the described ongoing multi center study.

The role of PET/CT as described by the meta analysis of Brush should also be further commented since 18F-FDG has a role in dedicated situations. This meta analysis is now also seven years old and some recent evidence should also be included. PET/MRI as well as whole body MRI should also be commented although there is not present recommendation for their routine use in colorectal cancer.

A large part of this chapter deals with CT-colonography, but in comparison, the role of other imaging modalities for imaging of colon cancer not only regarding detection, but also for staging should be described.

Rectal cancer:

The beginning of this chapter should mention the fact that the diagnosis of rectal cancer is often different due to the location of these tumours and their possibility to be diagnosed by rectal palpation and procto-rectoscopy. Regarding the ESGAR guidelines, it should be noted that it is not the organization itself rather fourteen abdominal radiologists and members of ESGAR that contributed to these guidelines. This chapter should consider the geographical variation in the use of neoadjuvant treatment (radiotherapy alone) or chemoradiation in Europe.

Page 12 - the description about the importance of lateral lymph node metastases is very brief and should include latest evidence in the field.

Page 13- the importance of timing of imaging from end of CRT is not described but should be commented.

Figures:

Figure 4 - The stratification of Low Intermediate and high risk cancer should be reconsidered since mrT3ab is frequently also regarded in the low risk group considering the results of the MERCURY follow up study.

General comments:

This is a review of the role of imaging in the management of colorectal cancer. The review is not completely proportional to the role of imaging in the field which should be reconsidered. Furthermore, regarding the implications for treatment, the review should consider difference in treatment allocation in different regions in Europe. The role of imaging in the metastatic setting, in particular evaluation of metastatic disease is not so much described.

Authors' Response to Reviewer Comments

Feb 09, 2018

Reviewer #1:

Title : OK

Abstract: Ok

Keywords: OK

Main document:

Page 3:

Q: "Colorectal cancer (CRC) is a prevalent problem with 447,000 new cases and 215,000 deaths in 2012 in Europe" Are there more up to date data?

A: Yes, there is for sure more detailed and recent data available, especially from single countries and the United states, which can provide yearly epidemiologic data for each cancer. The cited study is an excellent example of regional and European trends in the distribution of colorectal cancer. I would therefore ask to keep the study as it is a good example of how different regional cancer care is in Europe.

Q: "survival" instead of "Survival"

A: corrected

Q: Page 4: "CT with an arterial phase covering the liver" ◊ can you provide evidence for this recommendation?

A: A reference has been included (Fowler, J Am Coll Radiol 2017). We agree that this is usually not done to improve detection of CLM, but to improve characterization of other, possibly benign liver lesions. There are occasional hypervascular liver metastases of CRC, too, like it is now illustrated in the new Figure 7.

Q: Page 7: "CTC can be performed using a lower radiation dose than a usual diagnostic CT scan" ◊ can you provide evidence for this recommendation?

Q: "several dose reduction algorithms exist" ◊ please expand and provide more accurate information on this topic

A: Both these questions can be addressed simultaneously. We have added a new reference (Lubner Eur Radiol 2015) dealing with this topic. We think that going into more detail about iterative reconstruction and other dose reduction algorithms are not in the main interest of the surgically oriented reader. We feel that it is necessary to address the fact that radiation exposure is an issue compared to a technique with zero radiation, like optical colonoscopy. However, it is less of a concern with newer scanners and dose reduction techniques and that these developments somewhat outweigh this disadvantage. If the editor wants us to expand more on this topic we are more than happy to provide more data and background information.

Q: Page 8: "a CT of the abdomen and thorax" instead of "a CT of the Liver/Abdomen and Chest"

A: corrected

Q: Page 9: "there is no dedicated consensus whether spasmolytics or cleansing enema are needed prior to the examination" ◊ please provide references covering this topic

A: This has been amended. There is no clear data to favor either approach and there was less than 50% consensus on that topic. This was addressed in the text.

Tables/Figures:

Q: Figure /legend 5: Please provide information on the imaging modalities, sequence, etc.

Why are the metachronous liver metastases shown on an F18-FDG PET/CT image? Please provide a contrast enhanced CT (p.v. phase) or MR images showing the liver metastases.

A: Sequence information has now been included in the figure legend. Figure 5B shows a fused PET/MR image demonstrating liver metastases, which is highly associated with EMVI. In this patient, there was no further CE-CT performed since the diagnosis was certain based on these images.

Q: Figure/legend 6: "7 to 1 o'clock" instead of "7-to 1o'clock"

ADC: "Dark signal within rectal lumen" ◊ within tumor!

Please provide images showing high B-values

A: Amended; Figure 6 has also been updated with 2 new images showing high b-value DWI images.

Q: Figure/legend 7: Please provide more information on the MRI sequences (B value, etc).

Why do you show F18-FDG PET/CT images for a liver lesion? Is this the accurate imaging modality? Is the "FDG-avid lesion" really in segment 7 and not in segment 8?

Please provide native and different phases following i.v. contrast agent administration (native, arterial, pv, late).

There are 2 liver lesions in the high B-value (please provide information on sequence, B-value, etc.). Were both lesions visible in the shown T2-sequence and in the delayed T1 sequence post contrast? Please provide images that show both lesions with arrows.

Please provide the CT which does not show the lesions.

A: In order to avoid confusion, this image was completely exchanged with a different case. At our institution, native and late phase imaging is not performed for mCRC, hence only arterial and pv-phase images are available.

Q: Please include a Figure showing the different T-stages of rectal carcinoma (MRI, T2-weighted images) and include one CRM positive and one CRM negative carcinoma.

A: We are more than happy to do this, if requested by the editor. We already have 7 figures and a table which is the limit according to the instructions for authors. If more images are required to better present this to the reader, we can provide these.

Reviewer #2:

Abstract:

Q: The technical requirement for MR imaging of rectal cancer have been identified more than a decade and not only since five years.

A: This is correct, however we are not aware of a consensus statement made by a society dealing with this topic step-by-step, previous to the first ESGAR consensus guidelines in 2012. In the daily practice, this remains to be an issue, and we see many “pelvic MRIs” for rectal cancer that are performed incorrectly. If this would have been clear for decades, then it wouldn’t be an issue. This sentence was nevertheless amended.

Q: Nuclear medicine, PET/CT is not among the key words and should be among them considering the increased importance of this modality in colorectal cancer.

A: PET/CT is now included in the key words.

Q: First line - prevalent problem should be rephrased with something more suitable. Prevalent disease in the population, prevalent challenge in healthcare or otherwise.

A: This sentence was corrected.

Q: First paragraph - It is reported the change over the last 30 years although the change reported (should preferably also separate colon and rectal cancer) does only cover 20 years and are not recent figures.

A: This has been corrected and amended with newer data from the SEER database.

Q: Evaluation of locoregional and metastatic disease extent is important both in rectal and colon cancer. I suggest rephrasing of the paragraph considering this.

A: The paragraph was rephrased.

Q: Page 4- there are also other diagnostic advantages for colonoscopy vs CT-colonography than the possibility to obtain biopsies.

A: This has been rephrased.

Colon cancer:

Q: Page 5 - The importance of recognizing and reporting T4 tumours on preoperative CT, regardless of setting and technique should be emphasized since if the information is not transferred to the surgeon implies risk of inadequate laparotomy.

A: We agree 100%. This has now been addressed.

Q: Regarding the current evidence for neoadjuvant treatment in colon cancer and the implications for imaging, this could be further elaborated beside the described ongoing multi center study.

A: A new reference has been included and the text has been amended. Unfortunately, there is currently no robust evidence that justifies neoadjuvant chemotherapy in localized colon cancer.

Q: The role of PET/CT as described by the meta analysis of Brush should also be further commented since 18F-FDG has a role in dedicated situations. This meta analysis is now also seven years old and some recent evidence should also be included. PET/MRI as well as whole body MRI should also be commented although there is not present recommendation for their routine use in colorectal cancer.

A: The role of PET/CT in metastatic CRC is covered in a later chapter. Two high-impact studies are cited in that respective section (Moulton JAMA 2014 and Maffione EJNMMI 2015) and the value of this examination is addressed. Currently there is no role in the primary staging of CRC using PET/CT if there is no evidence of metastatic disease. We are using PET/MRI in a research setting in patients with rectal cancer, however, at this point we are not aware of robust evidence that whole body MRI has a role in the workup of localized or metastatic CRC. There is one study with 12 patients (Paspulati, Abdom Imag 2015) dealing with the accuracy of PET/MRI, but so far we felt that this is too little evidence to mention it in this review of standard imaging techniques of CRC.

Q: A large part of this chapter deals with CT-colonography, but in comparison, the role of other imaging modalities for imaging of colon cancer not only regarding detection, but also for staging should be described.

A: This was now corrected. For polyp/adenoma detection, CTC is the most accurate method, however, MR-colonography is now covered too.

Rectal cancer:

Q: The beginning of this chapter should mention the fact that the diagnosis of rectal cancer is often different due to the location of these tumours and their possibility to be diagnosed by rectal palpation and procto-rectoscopy.

A: This has been addressed.

Q: Regarding the ESGAR guidelines, it should be noted that it is not the organization itself rather fourteen abdominal radiologists and members of ESGAR that contributed to these guidelines.

A: This has been addressed.

Q: This chapter should consider the geographical variation in the use of neoadjuvant treatment (radiotherapy alone) or chemoradiation in Europe.

A: This has now been discussed.

Q: Page 12 - the description about the importance of lateral lymph node metastases is very brief and should include latest evidence in the field.

A: thank you for making us aware of new literature in this field. The most recent studies including results from the JCOG0212 trial show an increase in local recurrence if lateral dissection was not performed. This was inserted.

Q: Page 13- the importance of timing of imaging from end of CRT is not described but should be commented.

A: This was already mentioned under the paragraph “response to neoadjuvant treatment” and therefore not altered.

Figures

Q: Figure 4 - The stratification of Low Intermediate and high risk cancer should be reconsidered since mrT3ab is frequently also regarded in the low risk group considering the results of the MERCURY follow up study.

A: Fig 4 has been amended. In the text, it is mentioned that different societies endorse assessment of individual risk differently and that it would be beyond the scope of this review to consider all those individual recommendations.

General comments

Q: This is a review of the role of imaging in the management of colorectal cancer. The review is not completely proportional to the role of imaging in the field which should be reconsidered. Furthermore, regarding the implications for treatment, the review should consider difference in treatment allocation in different regions in Europe. The role of imaging in the metastatic setting, in particular evaluation of metastatic disease is not so much described.

A: The authors are not quite sure, how to interpret this question. Is the review too extensive or too brief? Please advise. The comment about different treatment allocations in Europe has been addressed. The paragraph on mCRC was expanded.

Reviewers' Comments to Revision

Reviewer 2: anonymous

Feb 13, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	50
Custom Review Questions	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	3

Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	3
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	No: Almost ready for publication

Comments to Authors:

The details addressed in the previous review of the paper have been adequately addressed

Page 17, it can be questioned to endorse Gadovate only since there are other liver specific contrast agents on the market despite the preferences of the authors. For this reason it is preferred to write

MRI with liver specific (or hepatocyte specific) contrast agents.

In figure 5 and 7 the term VIBE should be replaced with the generic pulse sequence name and also

Use the full generic name for Gd EOB

In figure 6 MRI-image should be changed to MR image

Authors' Response to Reviewer Comments

Feb 19, 2018

Dear Sir,

I am happy to resubmit the corrected version of "Imaging of colorectal cancer - the clue to individualized treatment" to your Journal. I have made improvements to the manuscript according to the reviewers' comments, which are provided below. You will find a step-by-step Q/A-type workup of all the issues covered.

I am more than happy to answer all questions that might still occur.

Best regards,

Reviewer #2:

The details addressed in the previous review of the paper have been adequately addressed

Q: Page 17, it can be questioned to endorse Gadovate only since there are other liver specific contrast agents on the market despite the preferences of the authors. For this reason it is preferred to write

MRI with liver specific (or hepatocyte specific) contrast agents.

A: corrected

Q: In figure 5 and 7 the term VIBE should be replaced with the generic pulse sequence name and also use the full generic name for Gd EOB

A: corrected

Q: In figure 6 MRI-image should be changed to MR image

A: corrected