Current Colorectal Cancer Reports (2019) 15:170–174
https://doi.org/10.1007/s11888-019-00444-0

DIAGNOSTIC AND INTERVENTIONAL RADIOLOGY INNOVATIONS IN COLORECTAL CANCER (S GOURTSOYIANNI, SECTION EDITOR)

Colon Cancer Staging: When Does High Resolution MRI Have a Role?

Luís Curvo-Semedo [1,2]

Published online: 26 November 2019

Abstract

Purpose of Review Contrarily to what happens with rectal cancer, the role of magnetic resonance imaging (MRI) in the assessment of colon cancer has been limited. However, we may witness a 'paradigm shift' in the future. Classically, colon cancer has been assessed by computed tomography (CT) which is considered the workhorse for evaluating this neoplasm as it provides insights not only about local and regional disease as well as about distant metastases. However, as the accuracy of CT is somewhat limited, recent reports about the use of MRI in colon cancers have been published. In this review we will assess the potential role of MRI in the setting of colon cancer, with particular emphasis on primary staging.

Recent Findings Overall, MRI seems to offer the potential to distinguish between locally advanced and not locally advanced colon cancers. High resolution MRI may have an advantage in comparison to other techniques – namely CT – related to its high soft tissue discrimination. MRI can, in most studies, identify prognostic factors such as T-stage and extramural venous invasion. However, nodal characterization by MRI has some drawbacks that have a negative impact on the accuracy of the technique.

Summary Current evidence about the role of MRI in colon cancer staging is still limited. Although the works published so far offer promising results, the role of this imaging modality is largely dependent on the possible implementation of neoadjuvant chemotherapy for locally advanced colon cancers. In this setting, MRI may be very helpful in selecting patients who can benefit from that therapy. Further research on the field, including large multi-institutional studies, is warranted.

Keywords Colon cancer · Magnetic resonance imaging · Staging · Neoadjuvant chemotherapy · Surgery · Computed tomography

Introduction

Even though the only available curative treatment for colon cancer is radical surgery, recently there has been a growing debate about the potential benefit of pre-operative, neoadjuvant chemotherapy (nChT) for patients with locally advanced cancers at increased risk of recurrence, upon recognition of adverse prognostic factors, some of which can be determined by imaging. Pre-treatment imaging may become therefore of pivotal importance in this setting. The first works about nChT in colon cancer have showed very promising results, with some good pathological responses, but a larger body of evidence is still needed in order to establish a definite role for this therapeutic option [1–3].

In particular, great expectations are put upon the FOXTROT trial, which was designed to evaluate the potential benefits of nChT for patients with locally advanced colon cancer [1]. If that will be the case, neoadjuvant treatment in patients with colon cancer could become standard of care, as in patients with rectal cancer. Therefore, pre-operative imaging will become an invaluable tool to select patients for nChT [4••].

On the other hand, as a great proportion of colon tumors are now being surgically removed by laparoscopic techniques, it is important to recognize the subgroup of patients for whom laparoscopy might not be suitable, either because the tumor is bulky or locally advanced [5].

In summary, imaging may be needed in order to select: 1) early cancers that do not require neoadjuvant treatment and may proceed directly to surgical excision; 2) locally advanced cancers that may need nChT before surgery or that may

This article is part of the Topical Collection on *Diagnostic and Interventional Radiology Innovations in Colorectal Cancer*

✉ Luís Curvo-Semedo
curvosemedo@gmail.com

[1] University Clinic of Radiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[2] Clinical Academic Centre of Coimbra, Coimbra, Portugal

require an open approach/radical surgery because of involvement of adjacent organs; and 3) metastatic cancers for which curative surgery is not primarily indicated [6••]. Traditionally, this selection has been performed by computed tomography (CT), but this imaging method is far from being perfect [7•]. Therefore, in the last few years, some works have focused on the role of magnetic resonance imaging (MRI) in the evaluation of colon cancer [4••, 6••, 8, 9••, 10••].

Technical Notes

In general, the colon poses a greater challenge for MRI in comparison to the rectum due to anatomical considerations, peritoneal coverage, motility, and tortuosity [8]. No standardized MR protocols exist at present, but nevertheless some general rules apply. Examinations should be performed on 1.5 T or 3 T magnets using phased array coils. Preparation previous to image acquisition includes fasting for at least 3–4 h, but no bowel cleansing is warranted. Intra-muscular or intra-venous spasmolytic agents such as hyoscine butylbromide or glucagon may be helpful in order to minimize bowel movements and image artifacts. Oral administration of contrast agents to fill the small bowel is probably optional.

High-resolution T2-weighted images, parallel and perpendicular to the long axis of the tumor, are thought to provide the most useful information. Axial diffusion-weighted images (DWI) with at least one b value above 500 s/mm^2 may be helpful, particularly for localizing small tumors. T1-weighted images, preferably with fat-suppression, before and after intra-venous administration of a gadolinium chelate, could also be included in the protocol. It is also important to assure that the whole abdominal cavity is scanned so that metastatic disease can be detected.

T Staging

For T staging, the primary endpoint should be the assessment of advanced cancers. Of major importance is the selection of poor prognosis neoplasms (T3 tumors with >5 mm of extramural invasion – T3 cd – and T4 tumors) as this was proven to possess a greater prognostic significance than the differentiation between T2 and T3 tumors [11], being also the current entry criteria for the FOXTROT trial [1].

T3 tumors are defined as limited to the subserosa or pericolic fat, identified at MRI by a broad-based bulge or nodular projection of intermediate tumor signal intensity beyond the outer muscle coat. The extension of that projection allows differentiation between T3ab (≤5 mm) and T3 cd (> 5 mm) (Fig. 1). T4 tumors show extension of the intermediate tumor signal intensity into adjacent organs or through the peritoneal surface [6••].

In 2013, Rollven et al. reported an accuracy by two observers of 90% (reader 1) and 93% (reader 2) in distinguishing locally advanced colon cancers from non-locally advanced tumors with MRI. In this study of 28 patients, understaging of tumors was the main cause of error, either because of failure to demonstrate invasion beyond the muscular layer of the colon (due to microscopic invasion of peri-colic fat) or to identify serosal involvement [8].

More recently, Hunter et al. assessed the accuracy of MRI for the identification of T3 cd/T4 disease in 53 patients, with values of 75% (reader 1) and 79% (reader 2), with moderate agreement between readers. The authors suggested that their results could be attributed to less than optimal image quality, since when only the good quality MRI examinations were considered (60%), the accuracy of MRI was higher (81% for reader 1 and 77% for reader 2). As an additional note, this study reported an accuracy for the identification of T3+ disease of 75% (reader 1) and 57% (reader 2) and a stage-for-stage T-stage accuracy of 55% (reader 1) and 40% (reader 2) with moderate interobserver agreement [6••].

Nerad et al. studied 55 patients, reaching a sensitivity and specificity for MRI in detecting T3 cd/T4 tumors of 40% and 88% (reader 1) and 60% and 75% (reader 2), with a moderate interobserver agreement. The area under the curve (AUC) for detecting serosal involvement was 0.88 (reader 1) and 0.72 (reader 2), with a good agreement between readers. Of additional interest, the AUC for differentiating between T1 to T2 and T3 to T4 tumors was 0.88 (reader 1) and 0.85 (reader 2) and for this reading the agreement was good [4••].

Dam et al. evaluated 35 patients with sigmoid cancers only, by means of pelvic MRI, reaching an accuracy in identifying locally advanced cancers of 94% (reader 1) and 89% (reader 2) using histology as the gold standard [10••].

Park et al., in a work published in 2018, enrolled 38 patients with colon cancer. The authors reported AUCs of 0.872 (reader 1) and 0.908 (reader 2) for pT3 cd/T4 diagnoses, with very good interreader agreement. This same study interestingly demonstrated that using DWI or gadolinium-enhanced T1-weighted images combined with T2-weighted images did not significantly improve the accuracy for the diagnosis of T3 cd/T4 disease when compared with T2-weighted images alone [9••].

Based on the available reports from the literature, it seems reasonable to affirm that the detection of T3 cd/T4 tumors remains somewhat problematic with MRI. The low sensitivity reported by some authors [4••, 6••] indicates that the lesions tend to be understaged presumably due to microscopic invasion of the peri-colic fat, which is impossible to depict with the currently available imaging techniques. Overstaging, mainly due to desmoplastic reaction surrounding the neoplasms, is also an important source of false results. The apparent discrepancy between these and other studies which have yielded higher sensitivity values [8, 9••, 10••] may be explained by

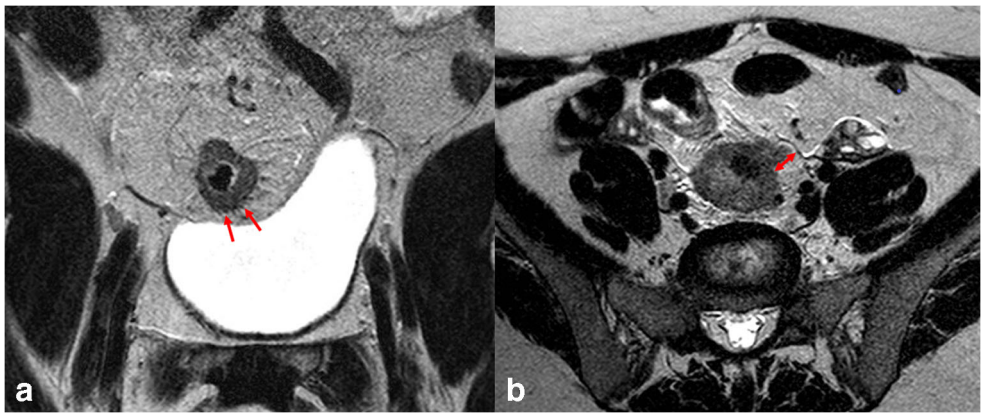

Fig. 1 T2-weighted images of sigmoid cancers in two different patients. In a), arrows indicate minimal projection of intermediate tumor signal intensity beyond the outer muscle coat (measured as 1.8 mm), corresponding to T3ab (≤5 mm) disease. In b), the extension of that projection (double arrow) is more extensive (8.2 mm) and nodular, indicating T3 cd (> 5 mm) disease

several factors, including differences in patient selection, technical protocol and image interpretation.

Therefore, it looks obvious that further larger, multi-institutional studies as well as further technological development of methods with higher spatial resolution and fewer artifacts, are still necessary to definitely assess the real role and value of MRI of the colon as the imaging modality to better select patients for nChT if this treatment becomes standard for colon cancer.

N Staging

For positive nodal involvement, the criteria used varied among studies, and included a short axis diameter of ≥8 mm and/or a cluster of 3 or more lymph nodes with a short axis diameter of >5 mm [4••]. For other authors these thresholds were both 10 mm [9••]. In other studies lymph nodes with irregular borders or mixed internal heterogeneous signal intensity were considered to indicate the presence of metastasis on MRI [6••, 9••].

Overall, results for nodal staging by MRI are relatively poor. Rollven et al. reported moderate accuracies for N staging for both readers (72% and 69%) with low inter-observer agreement [8].

In the study by Hunter et al., the accuracy for the identification of N+ disease was 62% for reader 1 and 63% for reader 2, with fair agreement between readers [6••].

Nerad et al. reached a sensitivity and specificity for detecting nodal involvement of 47% and 86% (reader 1) and 68% and 64% (reader 2), with moderate interobserver agreement [4••].

In the study by Dam et al., the overall accuracy of the two observers compared with histology in identifying nodal involvement was 60% and 66%, and the agreement between readers was good [10••].

Park et al. reported accuracies for nodal involvement ranging from 75% to 78%, approximately [9••].

It is known that lymph node diameter is not accurate for assessing nodal metastasis in colon cancer [12]. False negative results are thus related to microscopic metastatic deposits in normal-sized nodes, whereas false-positives are caused by benign lymph nodes that are enlarged because of inflammatory or reactive changes. As nodal staging is truly an "Achille's heel" of imaging, additional research is warranted, in order to improve the detection of nodal metastases in patients with colon cancer. If the results coming from nodal characterization studies in patients with rectal cancer could be extrapolated to patients with colon cancer, then the use of contrast media can be of help, whereas DWI is probably not useful for the characterization of lymph nodes [13–15].

Extramural Venous Invasion

Extramural venous invasion (EMVI) can be recognized on MRI as direct invasion of the tumor growing into or along a vascular structure, an irregular expansion of peritumoral veins and/or irregular margins of the vessel wall near the tumor site [16, 17].

Hunter et al. reported an accuracy for the identification of EMVI+ disease of 75% for both readers in the study, with fair agreement only [6••].

In the study of Nerad et al., the AUC for detecting EMVI was 0.77 for both readers, thanks to a high sensitivity (88%–100%) but with a moderate specificity (62%–70%) and inter-observer agreement between both readers [4••].

Dam et al. disclosed an overall accuracy of the two observers in identifying EMVI based on tumor invasion in a pericolic vessel of 77% and 60% compared with histological examination [10••].

The study by Park et al. showed an accuracy of approximately 75% in the assessment of EMVI [9••].

These results may have their explanation in the fact that, similarly to what happens with lymph nodes, imaging has some problems in detecting microscopic metastasis and misdiagnosing inflammatory changes.

Comparison with CT

Distant and local staging of colon cancer is currently performed mainly with CT, which serves to assess resectability and as a roadmap to surgery, apart from detecting distant metastases. This is largely due to the fact that there is not a definite role for nChT in colon cancer, and therefore imaging is not crucial for selecting patients for pre-operative treatments. However, this may be changing in the (near) future as the benefits of neoadjuvant chemotherapy for patients with locally advanced colon cancer are currently under investigation [1]. If imaging will become a pivotal tool for the selection of patients for nChT, then imaging modalities that need to be as accurate as possible are required. Nevertheless, a recent meta-analysis demonstrated that it remains a challenge for CT to detect tumor invasion beyond the bowel wall of 5 mm or more (T1–T3ab vs T3 cd–T4) and nodal involvement; pooled sensitivities were 77% and 71%, respectively, whereas pooled specificities were 70% and 67%, respectively [7•]. These numbers have raised a growing interest towards the use of MRI for the assessment of patients with colon cancer, as an alternative to CT.

Analyzing some of the works that have compared MRI and CT, the study by Rollven et al. showed that, for differentiating locally advanced colon cancer from non-locally advanced, MRI had a significantly higher accuracy than CT. Inter-observer agreement was also in favor of MRI ($\kappa = 0.79$) in comparison to CT ($\kappa = 0.64$) [8]. The work of Hunter et al., on the contrary, showed no significant difference between the accuracy of CT and MRI for either reader, as it was moderate on both imaging modalities for the identification of T3 or greater disease [6••]. Park et al. stated that the diagnostic performance of MRI was better than that of MDCT in predicting histopathologic T3 cd/T4 cancers, but with a significant difference between the two modalities observed in only one of the two readers [9••].

For nodal staging, Rollven et al. disclosed comparable moderate accuracies for N-staging using both MRI (accuracies of 72% and 69%) and CT (accuraciy of 72% for both readers) and higher sensitivity with MR than with CT, but lower specificity. Inter-observer agreement overall was quite low for N-staging with MRI ($\kappa = 0.10$) but better with CT ($\kappa = 0.66$), this being explained by overstaging of different patients with MRI by the two observers [8]. In the study by Hunter et al., the difference in accuracy between CT and MRI in assessing N+ disease was non-significant for both readers [6••]. For Park et al., MRI and MDCT showed an accuracy of approximately 82% and 74%, respectively, in the assessment of node metastasis. This was attributed to the superior intrinsic soft-tissue contrast of MRI [9••].

Regarding detection of EMVI, Rollven et al. showed a higher inter-observer agreement for MRI ($\kappa = 0.75$) than for CT ($\kappa = 0.22$) [8]. In the study by Hunter et al., the difference in accuracy between CT and MRI for assessing EMVI+ disease was non-significant for reader 1, whereas reader 2 was significantly more accurate assessing EMVI using MRI (75%) than CT (54%; $p = 0.029$) [6••]. Park et al. demonstrated that MRI and MDCT revealed approximately 75% and 63% accuracies for demonstrating EMVI, respectively, a difference that was also statistically significant [9••].

Overall, there seems to be a trend towards the ability to distinguish between locally advanced colon cancer defined as tumor stage T3 cd-T4 from non-locally advanced cancers by either high resolution MRI or CT, even if CT is performed with general staging imaging protocol. However, high resolution MRI may possess an advantage over CT, which is related to its high soft tissue discrimination that allows identification of certain prognostic factors, such as T-stage and extramural venous invasion. Nodal staging remains considerably imperfect to assess by both imaging modalities. Moreover, MRI does not involve ionizing radiation exposure nor injection of iodinated contrast media and furthermore imaging of the colon can be combined with the imaging of the liver. Since MRI is the optimal modality in the detection of liver metastasis with a significantly higher sensitivity than that of CT [18], it may be used as a 'one-stop-shop' to evaluate the whole abdomen.

Other Applications and Future Trends

Some authors have evaluated MRI as an imaging biomarker in colon cancer. In one recently published paper, Nerad et al. specifically addressed the role of the apparent diffusion coefficient (ADC) as a potential imaging biomarker to assess aggressiveness of colon cancer, by predicting metastasis, both nodal and in distant organs, based on the ADC-value of the primary tumor [19•]. The authors enrolled 30 patients and showed that advanced tumors (as defined by the presence of lymph node metastasis and/or distant metastasis) had significantly lower mean ADC values than early tumors, having reached an AUC of 0.83 and a sensitivity and specificity of 81% and 86% respectively. The whole tumor mean ADC value had a 100% sensitivity and specificity in predicting lymph node metastasis. Consequently, tumor ADC values showed potential in identifying patients eventually eligible for neoadjuvant treatments, therefore using not only qualitative, but also quantitative biomarkers as an adjunct to better select patients.

Conclusions

The available literature suggests that MRI has the potential to become a valuable tool in preoperative staging of colon cancer, mainly by identifying locally advanced tumors and additional risk factors, such as serosal involvement and EMVI.

Nodal staging still needs improvement as characterization of lymph nodes by MRI is unreliable.

Combined with its high sensitivity in detecting liver metastatic disease, MRI can become a valuable abdominal staging modality for patients with colon cancer.

Moreover, if there is a paradigm shift in the diagnostic and therapeutic work-up of colon cancer with introduction of nChT for T3 cd-T4 disease, MRI may contribute to select patients who will benefit from that therapeutic approach.

Ultimately, as the available research on this subject is still limited, more works are needed to better define the role of MRI in colon cancer staging.

Compliance with Ethics Guidelines

Conflict of Interest Luís Curvo-Semedo declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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