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Local staging of sigmoid colon cancer using MRI

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Abstract

Background: An accurate radiological staging of colon cancer is crucial to select patients who may benefit from neoadjuvant chemotherapy.

Purpose: To evaluate the diagnostic accuracy of preoperative magnetic resonance imaging (MRI) in identifying locally advanced sigmoid colon cancer, poor prognostic factors, and the inter-observer variation of the tumor apparent diffusion coefficient (ADC) values of diffusion-weighted imaging (DWI).

Material and Methods: Using 1.5 T MRI with high resolution T2-weighted (T2W) imaging, DWI, and no contrast enhancement, 35 patients with sigmoid colon cancer were assessed. T-stage, N-stage, extramural vascular invasion (EMVI), and ADC values of the tumors were assessed and blindly compared by two observers using postoperative histopathological examination as the gold standard. Early tumors were defined as T1 to T3ab, and advanced tumors as T3cd or T4.

Results: The accuracy of the two radiologists in staging early versus advanced tumors, N-stage, and identification of EMVI was 94%/89%, 60%/66%, and 77%/60% with an inter-observer agreement of $\kappa = 0.86$ (95% confidence interval [CI] = 0.67–1.00), $\kappa = 0.64$ (95% CI = 0.39–0.90), and $\kappa = 0.52$ (95% CI = 0.23–0.80). All the measured mean ADC values were below 1.0×10^{-3} mm^2/s with an intra-class correlation coefficient in T3cd–T4 tumors of 0.85.

Conclusion: Preoperative MRI can identify locally advanced sigmoid colon cancer and has potential as the imaging of choice to select patients for neoadjuvant chemotherapy. Initial experience with ADC measurement was achieved with an excellent inter-observer agreement in advanced tumors.

Keywords
Colonic neoplasms, radiology, diffusion-weighted imaging (DWI), magnetic resonance imaging (MRI)

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Introduction

Colorectal cancer is associated with significant morbidity and mortality and is one of the most common types of cancer in the developed countries (1). With an increasing age of the population, colorectal cancer will also in the years to come represent a considerable burden to the individual patient and to the healthcare system. The only curative treatment is radical resection, but even if this is performed, locally advanced colon cancer has a poor prognosis. Progress in treatment is therefore of utmost importance and surgery combined with other treatment modalities may improve the outcome. Preoperative (neoadjuvant) chemotherapy is effective in a number of advanced gastrointestinal cancers, including rectal cancer, and has shown promising results in the first trials on locally advanced colon cancer (2–4). Preoperative imaging is essential in identifying patients with locally advanced colon cancer at high risk of relapse and therefore candidates for

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neoadjuvant therapy. Contrast-enhanced multi-detector computed tomography (MDCT) is currently the standard modality for preoperative local staging of colon cancer and has shown a reasonable accuracy in discriminating between locally and non-locally advanced colon cancer (5,6). In rectal cancer, magnetic resonance imaging (MRI) is well established for preoperative local staging (7) and recent studies have suggested that MRI may also have an advantage over CT in precise local staging of colon cancer (8,9). Functional MRI sequences such as diffusion-weighted imaging (DWI) are increasingly applied to provide additional quantitative characterization of the tumors before, during, and after chemotherapy expressed by the tumor's apparent diffusion coefficient (ADC) values (10). The reproducibility of ADC values among observers is therefore important to evaluate.

The aims of this study were, first, to evaluate the diagnostic accuracy of preoperative MRI in identifying locally advanced sigmoid colon cancer and poor prognostic factors and, second, to gain an initial experience with measuring of tumor ADC values on DWI by determining the inter-observer variability.

Material and Methods

The study was approved by the Danish Data Protection Agency. During the years 2010–2015, 331 patients underwent elective operation for a carcinoma in the sigmoid colon at the Department of Surgery, Vejle Hospital. By retrospectively reviewing our Radiology Information System (RIS)-Picture Archiving and Communications System (PACS) we identified 41 out of the 331 patients as having a preoperative MRI of the lower abdomen/pelvis performed. In six of these patients, however, DW sequences had not been performed. A total of 35 patients with a complete preoperative MRI were thus included in the study, none of which were treated with neoadjuvant therapy.

The MRI scans were carried out using an Ingenia 1.5 T MRI unit release 4.1.3.3 with a 32-channel Philips dStream Torso coil over the pelvis (Philips Medical Systems, Best, The Netherlands). After localizer scans, fast T2-weighted (T2W) spin-echo sequences were obtained. The scan included 3-mm axial slices at a 90° angle to the tumor, and the axial scans were prepared by the MRI radiographer assisted by a radiologist to ensure perpendicular images. No contrast enhancement was used. DWI was performed perpendicular to the tumor using an echo planar imaging (EPI) factor of 61. Five different b values (strength and timing of the gradients to generate DWI) were used applying diffusion-sensitive gradients; $b = 0$, $b = 200$, $b = 400$, $b = 600$, and $b = 800\,s/mm^2$. The first series was a set of image sequences formed by echo-planar spin-echo T2W imaging ($b = 0$). The next series formed gradients at the x, y, and z directions and formed isotropic images obtained by calculating diffusion vector projections of the three directions. ADC maps of the isotropic images were created automatically by the Philips Ingenia software. Patients were scanned in the supine position. Bowel cleansing was not performed and no oral or rectal contrast media was administered.

All images were evaluated using an Easyviz Impax PACS (Picture Archive Communication System) workstation (Medical Insight, Valby, Denmark) with a monitor (1600 × 1200 pixels), Megapixels Diagnostic Display System, Coronis (Barco, Kortijk, Belgium). ADC maps in grayscale were automatically generated by the Philips system using a mono-exponential decay model.

The MRI scans were retrospectively assessed by two independent observers, i.e. observer 1 was a senior resident in radiology and observer 2 was an experienced gastrointestinal radiologist. Additionally, the observers were blinded to one another, results of other imaging, the pathology reports, and clinical data apart from the endoscopic findings of tumor location. The observers recorded the tumor size, T-stage, extent of extramural tumor invasion (ETI), presence of metastatic lymph nodes, presence of extramural vascular invasion (EMVI), and ADC value of the tumors.

Size was reported as the largest tumor diameter in one of the perpendicular planes. T-stage assessed by MRI was evaluated according to the TNM system. ETI was defined as maximal tumor outgrowth from the intestinal wall in millimeters. T4 tumors and T3 tumors with more than 5 mm ETI (T3cd–T4) were classified as locally advanced and T1, T2, and T3 tumors with ETI 5 mm or less were classified as early (i.e. non-locally advanced). Regional lymph nodes, regardless of metastatic status, were detected using both T2W and DWI sequences. After detection, the lymph nodes with size (short axis) alone ≥10 mm or with size (short axis) >5 mm combined with an irregular border and/or inhomogeneous signal intensity on T2 images were defined as metastatic. EMVI was considered present if the tumor invaded a pericolic vessel. ADC values were reported as the mean ADC acquired by manually drawing of a precise region of interest (ROI) on the ADC map delineating the most restrictive part of the solid tumor on a single slice, avoiding intraluminal air. Surgery was performed within a median of 12 days (range = 1–23 days) after the MRI. The resected specimens were transferred to the Department of Pathology and fixed for two days in neutral, buffered formalin. After fixation, all tumors were sliced transversally. The tumor size and deepest penetration from the outer edge of tunica muscularis were measured on the slices and confirmed microscopically.

The resected specimens were classified according to the pTNM system (11) by an experienced gastrointestinal pathologist. The peritoneal surface was considered involved (pT4) if viable cancer was detected outside the peritoneal lining or infiltrating adjacent organs. The pathologist was blinded to the MRI findings.

A complete postoperative histopathological examination was regarded as the end-point.

Statistical analysis

All patients had an evaluable MRI and histopathology report for statistical analysis. Data were entered into the Number Cruncher Statistical System software (NCSS), (Kaysville, UT, USA). Descriptive statistics were applied. Sensitivity, specificity, and accuracy with 95% confidence intervals (CI) were calculated. A P value < 0.05 was considered to indicate a statistically significant difference. Comparison of proportions was performed using the X^2 test or, when appropriate, Fisher's exact test. Unweighted Cohen's Kappa coefficients (κ) for categorical outcomes were calculated for inter-observer comparison and categorized as poor, fair, moderate, good, and very good agreement according to Kappa (κ) values < 0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00, respectively. Inter-observer variability in relation to tumor ADC measurements was analyzed by calculating the intra-class correlation coefficient (ICC) (0.00–0.20 = poor, 0.21–0.40 = fair, 0.41–0.59 = moderate, 0.60–0.74 = good, and 0.75–1.00 = excellent).

Results

The study population included 35 patients with histopathology verified sigmoid colon cancer. The mean age was 70 years (range = 47–83 years). Twenty-one patients (60%) were male. All patients had one tumor in the sigmoid colon with a mean size of 3.6 cm (range = 1.7–7.0 cm) measured at the final pathological examination. The final histopathological findings revealed ten patients (29%) with metastatic lymph nodes and nine (26%) with EMVI.

The correlation between observer staging of the tumors by MRI as early or advanced and histopathological classification is shown in Table 1. The overall accuracy of the two observers in identifying locally advanced colon cancer was 94% and 89% using histology as the gold standard. The sensitivity of both observers was 89% (95% CI = 51–99). The specificity was 96% (95% CI = 78–100) for observer 1 and 88% (95% CI = 69–97) for observer 2. The inter-observer agreement in staging the tumors as early or advanced was very good with a Cohen kappa value of $\kappa = 0.86$ (95% CI = 0.67–1.00). The correlation between the identification of lymph node involvement assessed by MRI for each observer and histopathology is shown in Table 2. The overall accuracy of the two observers compared with histology in identifying nodal involvement was 60% and 66%. The sensitivity of both observers was 90% (95% CI = 54–99). The specificity of observer 1 was 48% (95% CI = 28–68) and 56% (95% CI = 35–75) for observer 2. The inter-observer agreement as to identification of nodal involvement was good with a Cohen kappa value of $\kappa = 0.64$ (95% CI = 0.39–0.90).

The correlation between histopathology and extramural vascular invasion found on MRI by each observer is shown in Table 3. The overall accuracy of the two observers in identifying EMVI based on tumor invasion

Table 1. Summary statistics of identifying locally advanced tumors by MRI.

	MRI			
	Observer 1		Observer 2	
	T1–T3ab*	T3cd–T4†	T1–T3ab*	T3cd–T4†
Pathology				
T1–T3ab	25	1	23	3
T3cd–T4	1	8	1	8

*Non-locally advanced tumors: T1, T2, or T3 tumor with an extramural tumor invasion <5 mm.
†Locally advanced tumors: T3 with extramural tumor invasion ≥5 mm or T4 tumor.
Observer 1: accuracy = 94%, sensitivity = 89% (51–99%), specificity = 96% (78–100%), positive predictive value (PPV) = 89% (51–99%), negative predictive value (NPV) 96% (78–100%).
Observer 2: accuracy = 89%, sensitivity = 89% (51–99%), specificity = 88% (69–97%), PPV = 89% (51–99%), NPV = 88% (69–97%).
Inter-observer agreement: Kappa = 0.86 (0.67–1.00).

Table 2. Summary statistics of lymph node involvement by MRI.

	MRI			
	Observer 1		Observer 2	
	N0*	N+†	N0*	N+†
Pathology				
N0	12	13	14	11
N+	1	9	1	9

*No lymph nodes >10 mm or >5 mm with an irregular border/inhomogeneous signal intensity.
†N1 or greater.
Observer 1: accuracy = 60%, sensitivity = 90% (54–99%), specificity = 48% (28–68%).
Observer 2: accuracy = 66%, sensitivity = 90% (54–95%), specificity = 56% (35–75%).
Inter-observer agreement: Kappa = 0.64 (0.39–0.90).

Table 3. Summary statistics of extramural vascular invasion by MRI for both observers.

	MRI			
	Observer 1		Observer 2	
	EMVI−*	EMVI+†	EMVI−*	EMVI+†
Pathology				
EMVI−	21	5	16	10
EMVI+	3	6	4	5

*No vascular invasion.
†Tumor invasion of pericolic vessel.
Observer 1: accuracy = 77%, sensitivity = 67% (31–91%), specificity = 81% (60–93%).
Observer 2: accuracy = 60%, sensitivity = 56% (23–85%), specificity = 62% (41–79%).
Inter-observer agreement: Kappa = 0.52 (0.23–0.80).

in a pericolic vessel was 77% and 60% compared with histological examination. The sensitivity and specificity for observer 1 was 67% (95% CI = 31–91) and 81% (95% CI = 60–93), respectively, and for observer 2 it was 56% (95% CI = 23–85) and 62% (95% CI = 41–79), respectively. The inter-observer agreement in EMVI identification was moderate with a Cohen kappa value of $\kappa = 0.52$ (95% CI = 0.23–0.80).

ADC measurement could be performed in all patients and the mean ADC in all tumors showed values below 1.0×10^{-3} mm^2/s. The ICC between the two observers using single slice ROIs on the DWI MRI for both early and advanced tumors was moderate to good (ICC = 0.60), whereas the ICC for advanced tumors only was excellent (ICC = 0.85). A subgroup analysis showed no significant difference of the measured mean ADC values ($\times 10^{-3}$ mm^2/s) in the pathology-based categories of local tumor: T1–T3ab (n = 26) versus T3cd–T4 (n = 9), 0.74 (95% CI = 0.68–0.79) versus 0.70 (95% CI = 0.61–0.80); node status: node-negative (n = 25) versus node-positive (n = 10), 0.72 (95% CI = 0.60–0.77) versus 0.75 (95% CI = 0.65–0.84); and EMVI status: EMVI-negative (n = 26) versus EMVI-positive (n = 9), 0.72 (95% CI = 0.67–0.78) versus 0.74 (95% CI = 0.65–0.84) in observer 1 or observer 2; 0.63 (95% CI = 0.55–0.70) versus 0.67 (95% CI = 0.54–0.80), 0.63 (95% CI = 0.55–0.70) versus 0.67 (95% CI = 0.52–0.81), and 0.64 (95% CI = 0.56–0.72) versus 0.63 (95% CI = 0.52–0.74) respectively.

Discussion

An accurate radiological staging of colon cancer is crucial to select patients with locally advanced tumors at high risk of relapse who may benefit from preoperative chemotherapy (12).

This study aimed to determine the diagnostic accuracy of preoperative MRI in identifying locally advanced sigmoid colon cancer and poor prognostic factors with postoperative histopathologic findings as the gold standard. Also, we wanted to evaluate the inter-observer agreement of the ADC values of the tumors on DWI.

The results showed that MRI is able to detect locally advanced sigmoid colon cancer defined as T3cd–T4 tumors. The accuracy of MRI in relation to the two observers in identifying locally advanced sigmoid colon cancer was very good at 94% and 89%, respectively, with a very good inter-observer agreement of $\kappa = 0.86$ (range = 0.67–1.00). This is in accordance with a previous study of 28 patients reporting an accuracy of MRI for two observers at 90% and 93%, respectively, with an inter-observer agreement of $\kappa = 0.79$ (range = 0.56–1.00) (8). Other studies have shown an accuracy of MRI in detecting locally advanced tumors at 75% for both observers with an inter-observer agreement of $\kappa = 0.41$ (range = 0.17–0.64) (55 patients) (9) and 75% and 71% for the two observers, respectively (55 patients), with an inter-observer agreement of $\kappa = 0.55$ (12). The performance of CT in identifying locally advanced colon cancer has been investigated in several studies. A recent meta-analysis showed a pooled sensitivity and specificity of 77% and 70%, respectively, for CT in discriminating between T1–T3ab and T3cd–T4 tumors (a total of 281 patients) (5).

MRI may be superior CT in differentiating between early and locally advanced tumors based on the literature. MRI may be better than CT at discriminating malignant tissue from the muscularis propria and defining the extent of tumor infiltration. The inability of CT to differentiate between desmoplastic and neoplastic pericolic fat infiltration is a well-known problem in colorectal staging by CT (5). On the other hand, we only included sigmoid tumors in this study. Staging of tumors in other sites of the colon may be more difficult due to peristalsis, breathing artifacts or dislocation of the bowel during scanning (13). Shrinkage could be a drawback using pathology as the endpoint. The pathologic evaluation of ETI measured after fixation in formalin may not correlate precisely with ETI estimated on MRI. Destruction of the muscularis propria by the advancing cancer may introduce some subjectivity to the histological measurement. Shrinkage of the specimen in formalin may also be a minor source of uncertainty.

The overall accuracy of MRI for the two observers in identifying metastatic lymph nodes was 60% and 66% with a good inter-observer agreement of 0.64 (95% CI = 0.39–0.90). Other studies have shown an accuracy of MRI in detecting metastatic lymph nodes in the range of 57–73% (8,9,13) and 53% with CT (6).

The diagnosis of nodal involvement by imaging remains a problem in patients with colon cancer since the lymph node diameter is not a reliable indicator of nodal metastasis in this disease (14). False-positive results are caused by benign lymph nodes enlarged due to inflammation. Conversely, false-negative results are caused by microscopic metastases in lymph nodes with a normal diameter. Different cutoffs of lymph node diameter have been used in order to find a balance between the sensitivity and specificity in detecting nodal involvement as illustrated in a CT study where the long-axis diameter cutoff was lowered to 5 mm resulting in increasing sensitivity (81%) but decreasing specificity (26%) (6). DWI may help detection of lymph nodes. The differentiation between benign and malignant lymph nodes using DWI has, however, not proved to be reliable for rectal cancer, so this differentiation was not attempted in this study (15). We instead evaluated the lymph nodes according to size, heterogenicity in signal and shape because these criteria may improve the detection of nodal involvement. However, small lymph nodes are difficult to evaluate (16). Efforts to enhance the accuracy of MRI in metastatic lymph node detection using ultra small superparamagnetic iron oxide particles have shown promising results with a 65% sensitivity and 93% specificity (17), but the contrast agent is not yet approved and larger studies are required to elucidate the effect of this drug.

The overall accuracy of MRI for the two observers in the identification of EMVI was 77% and 60% with a moderate inter-observer agreement of 0.52 (95% CI = 0.23–0.80). Other studies have shown an accuracy of MRI in identifying EMVI in the range of 69–76% (8,9,12) and 53% by CT (6).

EMVI is a poor prognostic factor in colon cancer and increases with increasing ETI (18). As with lymph nodes imaging has problems detecting microscopic metastasis and misdiagnosing macroscopic inflammatory chances. Correct detection of EMVI by MRI can be missed at the histological examination (19).

All the measured mean ADC values on MRI were below 1.0×10^{-3} mm^2/s. The inter-observer reproducibility of ADC values was excellent (ICC = 0.85) in locally advanced tumors and moderate to good (ICC = 0.60) overall in early and locally advanced tumors. This is in accordance with a study measuring ADC values on single slice and solid sample ROIs in rectal cancer, where the ICCs are in the range of 0.42–0.65 (20). The inter-observer agreement of ADC measurements in our study might have been better using whole-volume ROIs, which seem easier reproducible than single slice ROI measurements (20). The high level of reproducibility of ADC values found in the locally advanced tumor is important, since these values to a higher extent are being used to predict pathologic response to neoadjuvant radio chemotherapy of rectal cancer (10). An increase in ADC is predictive of response to radio chemotherapy in rectal cancer (21) and future studies are needed to evaluate whether this is also the case in colon cancer.

To date, very few studies have assessed the reproducibility of measured ADC in extra-cranial body organs. Some investigators use volumetric rather than single ROI-based tumor assessment and some have demonstrated high variability in the measured ADC. Others have found less variability in the measured ADC (22). The majority of investigators found standardized acquisition protocols to improve reproducibility and the measured ADC to be dependent on the specific anatomy and size of the ROI (22). We used a precise delineated single slice ROI-based tumor assessment which is less time-consuming than the whole-volume ROI method and therefor may be more transmissible to clinical practice. However, the quantification of the tumors diffusion is depending on the image protocol and experience of the readers (23). Further validation of ADC reproducibility is warranted and one should still be careful using ADC values to differentiate between normal and cancerous tissues or even between tumor grades. However, for the assessment of response to neoadjuvant treatment ADC measures is a promising tool.

Other limitations of this study include the retrospective evaluation, a small sample size, and possible selection bias since not all sigmoid colon cancer patients had an MRI. Our limited number of patients made it impossible to perform a subgroup analysis of peritoneal carcinomatosis. We did not use spasmolytic agents to reduce motion artifacts, the use of which might have improved our results. We compared our staging results with the results from published data on CT staging. It would have been more valuable with a direct comparison on the same material. However, a larger prospective study comparing MRI and CT in staging of tumors in the whole extent of the colon is under preparation.

An accurate radiological staging of colon cancer is crucial to select the patients who may benefit from neoadjuvant chemotherapy. MRI may have an advantage over CT in identifying patients with locally advanced colon cancer due to better soft tissue discrimination. Although remaining a challenge MRI seems more accurate than CT in predicting poor prognostic factors such as lymph node metastases and EMVI. The detection of liver metastases is more accurate with MRI than CT (24) and favors MRI in the preoperative assessment of colon cancer, but further studies are warranted.

In conclusion, preoperative MRI was found to reliably identify locally advanced sigmoid colon cancer

defined as T3cd–T4 tumors and has potential as the imaging of choice when selecting patients for neoadjuvant chemotherapy. Initial experience with primary tumor ADC measurement has been achieved with an excellent inter-observer agreement in advanced tumors.

Declaration of conflicting interests

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