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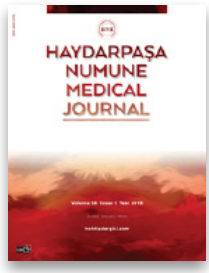

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ORIGINAL ARTICLE

Efficacy of Peroral CT Enterography with Lactulose Solution for Colorectal Cancer Staging

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Abstract

Introduction: In this study, we aimed to investigate the efficacy of computed tomographic enterography (CTE) with oral lactulose solution for preoperative staging of colorectal cancer.

Methods: Abdominal CTE examinations of 56 consecutive patients (37 men [66%] and 19 women [44%] with a mean age of 63.4 years and age range of 28–86 years) with colorectal carcinoma were retrospectively included in this study. The CTE images were independently evaluated by two radiologists. Disagreements were resolved by consensus. CTE findings were compared with pathologic results as the reference standard. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate of TNM staging were calculated.

Results: The overall accuracy of CTE for the T stage was 87.5% (49 of 56 patients). Overstaging and understaging occurred in two and five of 56 patients, respectively. The overall accuracy of the assessment of lymph node involvement CTE images was 76.8% (46 of 56 patients). Over and understaging occurred in five of 56 patients and eight of 56 patients, respectively.

Discussion and Conclusion: CTE with oral lactulose solution can be used as a useful technique for preoperative TNM staging of colorectal cancers.

Keywords: Colorectal cancer staging; CT enterography; Lactulose solution.

Colorectal cancer (CRC) is the third most common tumour in the United States and is the most common gastrointestinal cancer[1]. CRC is usually diagnosed with the detection of blood in the stool, intestinal obstruction, anaemia, or colonoscopy surveillance. For preoperative staging and initial evaluation of CRC, radiological methods such as computed tomography (CT), magnetic resonance imaging (MRI), and transrectal ultrasound (TRUS) are widely used[1].

The prognosis of the CRC patients is associated with the stage of the disease at the initial diagnosis. The most important factors affecting prognosis are the wall invasion depth, lymph nodes involvement and distant metastases[2].

CRC offers the best prognosis and limited surgical option for the patient before the malignancy invades or extends into the muscularis propria and involves lymph node[2]. Valid treatment methods are divided into local-primary tumour treatment and management of distant metastatic disease[1].

Imaging plays a critical role in the preoperative evaluation of CRC because it provides valuable information about pretreatment tumour staging and distant organ involvement; which is required for therapeutic planning.

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CT is superior compared to other imaging methods, such as MR and ultrasound with its higher availability, lower cost, and higher spatial resolution.[3] A very important technical need for CT examination of the bowel is the optimal distention of a clean lumen by the optimal separation of the intestinal walls; for both the small and large intestine. Collapsed bowel loops may resemble wall thickening and simulate pathological conditions, such as inflammatory bowel diseases, and also can hide even large lesions, such as tumours and polyps[4]. CT enterography (CTE) is a unique imaging technique that offers superior small bowel evaluation compared with routine abdominopelvic CT[5]. The CTE technique provides small bowel distension with a neutral agent or low-density oral contrast material and abdominopelvic CT examination following intravenous contrast medium administration[5].

Rapid advances in CT imaging technology have attracted attention to the potential role of CT in the diagnosis and staging of CRC[2]. However, the role of CT in CRC staging and the imaging technique to be applied remain controversial.

This study aims to investigate the efficiency of peroral CTE with oral lactulose solution in determining CRC staging.

Materials and Methods

Abdominal CT examinations of 56 consecutive patients (37 men [66%] and 19 women [44%] with a mean age of 63.4 years and age range of 28–86 years) with CRC were retrospectively included in this study. All patients underwent surgery within 45 days after CT examination and histopathological findings of resection material were accepted as the reference standard.

Exclusion criteria were a history of colorectal surgery or chemoradiation treatment for the colorectal disease, the possibility of bowel obstruction, age <18 years, general contraindications associated with iodinated contrast media and radiation.

CT Protocol

CT images were performed with a 6-detector-row MDCT scanner (Philips Brilliance 6, Philips Medical Systems, Amsterdam, The Netherlands), with 5 mm slice thickness axial images were provided according to the routine abdominopelvic CT protocol with the patient in the supine position. After the CT scan was completed, 2 mm thinner sections were also acquired to create sagittal, and coronal reformatted images for all patients. The CT images were performed from the diaphragm to the symphysis pubis.

Before the procedure, patients were recommended a liquid-rich diet for three days. All patients received oral purgative tablets contained sennoside A+B calcium (XM®; solution 250 mL, Yenişehir Lab, Ankara, Turkey) to ensure bowel clearance 12 h beforeCTE examination. All patients ingested a mixture composed of 1250 ml of water and 250 ml of lactulose (Osmolac, Biofarma, Istanbul, Turkey) orally before scanning, in about 1.5 h. The solution was drunk at a rate of 150–200 ml every 10 min. The last portion of fluid was ingested immediately before CT acquisition for optimal gastric distention. Intravenous contrast material (1.6 ml/kg, 3 ml/s rate and 65 s delay; iohexol (Omnipaque) 350 ml, GE Healthcare, Ireland) was used for all examinations.

Pathologic TNM Stage

Histopathologic findings of surgical resection material for the depth of tumor invasion and nodal involvement accepted as a reference standard. Liver and other distant metastases were evaluated by histopathologic examination or radiological follow-up. T and N staging were performed according to the international TNM classification, as follows: T1, tumour invading submucosal layer; T2 tumour invading muscularis propria or subserosa; T3 tumour invading serosa and pericolonic fat; and T4 tumour invading adjacent organs. For the node stage, N0 demonstrated no regional lymph node metastases; N1 indicated one to three pericolic lymph node metastases; and N2 indicated four or more pericolic lymph nodes metastases. M0 indicated no distant metastases and M1 indicated distant metastases.

Image Evaluation

Two radiologists NO (10-year abdominal radiology experience) and MAG (4-year general radiology experience) evaluated CTE images of all the patients on picture archiving and communication system (PACS) (Enlil, Eskisehir, Turkey). All images were independently evaluated by two radiologists for T stage on transverse CT images with multiplanar reformations. Disagreements were resolved using consensus. For lymph node evaluation only transverse images were used.

In the CT image analysis, for T stages, we used only three groups (T2, T3 and T4) instead of four T stages according to the TNM system. We combined T1 and T2 tumours to form a single group as T2. This classification was used because of the known limitations of CT to differentiate T1 and T2 lesions. T3 lesions were described as the tumour with round or nodular advancing margins. We did not consider the presence of spiculations around the peritumoral fat tissue

as a sign of invasion and grouped these lesions as T2 stage. T4 lesions were defined as tumours invading adjacent organs and structures.

For nodal staging, we accepted lymph nodes' maximum length larger than 10 mm on axial images as metastatic.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 20.0 statistical software (Armonk, NY: IBM Corp.). The continuous variables were expressed as the average±standard deviation. The accuracy of the CTE for TNM staging was calculated by comparing surgical and histopathological findings. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for T and N staging. Differences in accuracy for T and N staging were compared with literature findings.

Results

T Staging

According to the histopathologic examination, seven of 56 neoplasms were staged as T1 and T2, 45 of 56 as T3 and four of 56 as T4 (Figs. 1, 2). The overall accuracy of contrast-enhanced CTE for the T stage was 87.5% (49 of 56 patients) (Table 1). Overstaging and understaging occurred in two and five of 56 patients, respectively. Table 2 shows the sensitivity, specificity, positive and negative predictive values and accuracy rates for each stage of the tumour.

Five T3 pathological lesions were understaged as T1/T2 in CTE evaluation; however, none of these lesions showed pericolonic polypoid or nodular extension in the retrospective evaluation and pathological examination showed tumour spreading to the pericolic fat (Fig. 3). Two T3 pathological lesions were also overstaged as classified T4 radiologically. However, there was no fat tissue between the tumour and adjacent small intestine (Fig. 4).

N Staging

According to the histopathologic examination, 36 of 56 neoplasms were staged as N0, 15 of 56 as N1, and five of 56 as N2. The overall accuracy rate for lymph node involvement on contrast-enhanced CTE was 76.8% (46 of 56 patients). Over and understaging occurred in five of 56 patients and eight of 56 patients, respectively (Table 1). Table 3 shows the sensitivity, specificity, positive and negative predictive values and accuracy rates for each category of nodal staging.

Extracolonic Compartment Metastases

Contrast-enhanced CTE determined the presence of metastases in seven of 56 patients. All distant metastases were in the liver. The metastatic liver lesions were confirmed with the histopathological examination in four patients and with radiological findings and follow up in three patients.

Discussion

CT is widely used for CRC staging. CT has an important role in the preoperative evaluation of CRC and provides

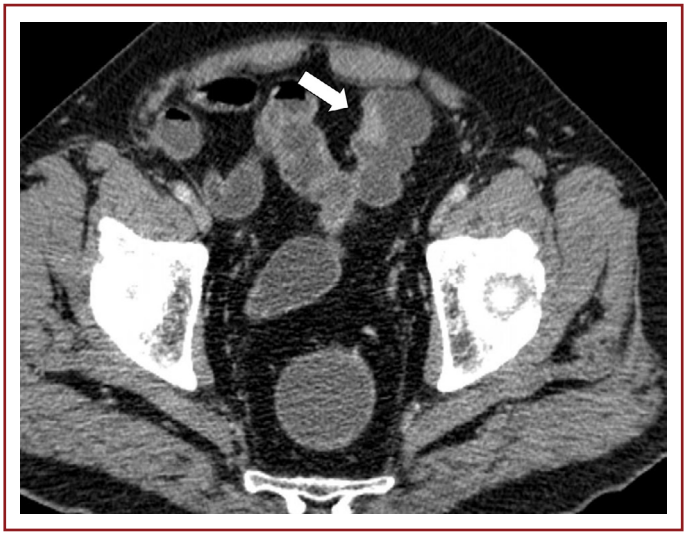

Figure 1. Transverse CTE image shows sigmoid colon adenocarcinoma (arrow). There is no tumor extending into the perirectal fat with a nodular margin. Lesion was evaluated as a stage T2 tumor, which pathologically confirmed.

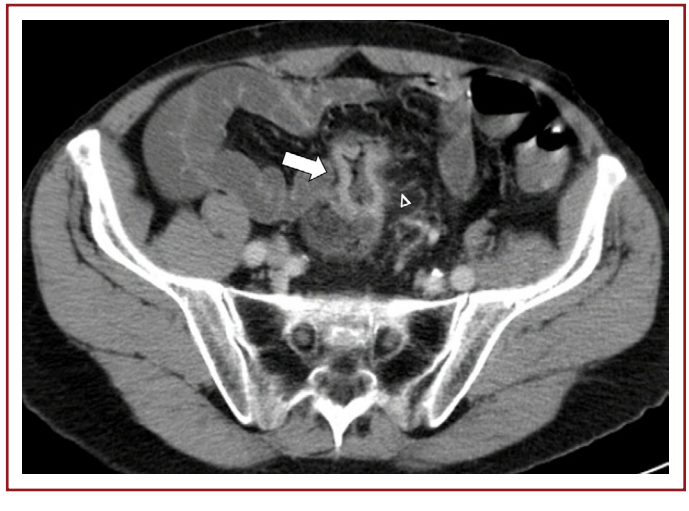

Figure 2. Transverse CTE image shows irregular sigmoid colon adenocarcinoma (arrow) with perirectal fat stranding and hyperattenuating spiculations (arrowhead). There is no tumor invading into the perirectal fat with a nodular margin. Lesion was assessed as a stage T2 tumor, which pathologically confirmed.

Table 1. Pathology and CT Enterography Staging of Tumor (T), and Node (N).

Pathology Stage	No. (%)	CT Enterography Stage					
		T1+T2	T3	T4	NO	N1	N2
T1+T2	7 (13)	7					
T3	45 (80)	5	38	2			
T4	4 (7)			4			
N0	36 (64)				31	4	1
N1	15 (27)				5	10	
N2	5 (9)				2	1	2
Total	56						

Table 2. Sensitivity, specificity, predictive values and accuracy for T staging

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
T1-T2	100	90.7	58.3	100	92
T3	84.4	100	100	72	88.9
T4	100	96.2	66.7	100	96.5

Table 3. Sensitivity, specificity, predictive values and accuracy for node staging

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
N0	86.1	65	81.6	72.2	78.5
N1	66.7	87.8	66.7	87.8	82.1
N2	40	98	66.7	94.3	92.9

unique information about local tumour stage and lymph node involvement, as well as about distant metastasis especially to the liver. The preoperative CT imaging of CRC appears to be the most beneficial method for evaluating distant metastases, regardless of the ability to estimate the T and N stage[1]. Furthermore, accurate assessment of distant metastases, such as liver, peritoneum, and retroperitoneum, is critical while curative surgical resection is still applicable. CRC patients with liver metastases can be treated with colorectal surgery combined with metastasectomy or intraoperative radiofrequency ablation for liver lesions[2].

Colon opacification and distention should be provided at the optimal level while evaluation of the large intestine with CT. For this purpose, many methods have been defined in the literature, and different methods are still applied[2-4,6-8]. Especially in cases with CRC, these methods are more important because they are closely related to the treatment process. For this purpose, various methods, such

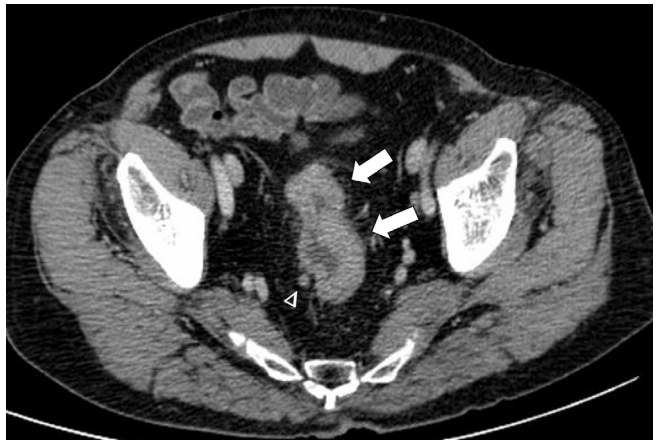

Figure 3. Transverse CTE image shows irregular sigmoid colon adenocarcinoma (arrows) with regional lymphadenopathy (arrowhead). There is no tumor invading into the perirectal fat with a nodular margin. Lesion was assessed as stage T2 tumor radiologically but lesion proved to be T3 pathologically.

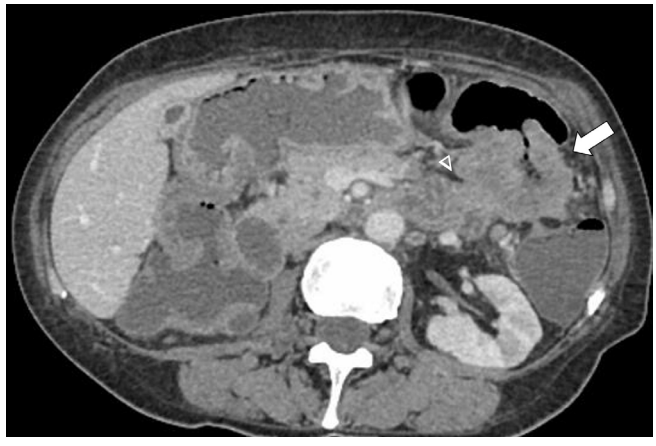

Figure 4. Transverse CTE image shows irregular splenic flexure adenocarcinoma (arrow) with extending into the perirectal fat with nodular margins and invading adjacent small bowel (arrowhead) wall was assessed as stage T4 tumor, which pathologically confirmed.

as oral or rectal positive contrast agents, rectal air or carbon dioxide applications, as well as oral or rectal neutral agents, were discussed in the literature[2,3,6,9-11].

CTE is widely used in the evaluation of the small intestine. For increasing contrast between the intestinal lumen and enhancing bowel wall, facilitating the evaluation of abnormal mucosal thickening and wall stratification-enhancement patterns, neutral or low-density oral contrast agents are essential for good quality CTE. Water-methyl cellulose solution, polyethylene glycol, water with mannitol and milk combination are some examples of neutral oral contrast agents with water-like CT attenuation. Water alone, although some authors advocate its use, often results in insufficient distention due to rapid absorption.[5] As a neutral contrast agent, lactulose is a synthetic disaccharide composed of galactose and lactose. The chemical structure of lactulose blocks intestinal absorption and expands the intestinal lumen[12]. Positive oral contrast agents containing iodine or barium are not routinely used in CTE because they may make it difficult to evaluate mucosal enhancement, intraluminal or intramural haemorrhage and assessment of subtle mural disease[5].

To our knowledge, no study has examined the staging of CRC by CTE with oral lactulose solution. The best results in evaluating the T stage were obtained from the studies performed using the multidetector CT colonography techniques; the accuracy rate was 80–95%[2,3,6]. In our study, we achieved similar results with these CT colonography studies. The overall accuracy of T stage with contrast-enhanced CTE was 87.5% (49 of 56 patients) in our study. However, the CT colonography technique requires serious bowel preparation and distension of the colon with gas to obtain ideal results[13]. Additionally, CT colonography has some other disadvantages, such as long viewing and interpretation times, and higher radiation dose and patient discomfort.

The main limitation of CT is that it cannot clearly distinguish the intestinal wall layers. As a result, high T3 and T4 lesions are evaluated more accurately than T2 or T3 lesions[14,15]. Fibrotic or peritumoral inflammatory changes are the causes of overstaging by CT. Differentiating tumours with a pericolonic polypoid or nodular extension, invading of the pericolic fat or adjacent organs are critical because these findings predict a worse prognosis than the patients with tumours restricted to the intestinal wall[3]. Overstaging, mainly due to desmoplastic peritumoral inflammation, as in other modalities, such as TRUS and MR, remains a challenge in CT[16]. All modalities, such as MR, TRUS and CT, are limited to distinguishing tumour from peritumoral edema and desmoplastic reaction, and none of these methods has 100% accuracy[17]. As described by Brown et al.[9] for MR imaging, the presence of tumour extending to peritumoral fat with a broad-based bulging configuration or advanced nodular margin, we evaluated as a T3 tumour. On the other hand, peritumoral spiculation within the fat that might be caused by fibrosis alone, we did not accept such tumours as stage T3 (Fig. 2)[2]. We correctly identified 38 of 45 (84%) T3 CRCs in our series, based on the CT criterion of broad-based bulging configuration or nodular advancing margins. Among these 45 cases, five were understaged and two were overstaged. In the five understaged cases, tumour erroneously staged as T2 at radiological evaluation was T3 at histopathologic examination, whereas the two overstaged cases were represented as neoplasms staged as T4 with small bowel invasion at CTE but were determined to be T3 at the histopathologic examination.

CT staging accuracy may be improved using multiplanar reformatted images that allow for true axial images through the colon. The accuracy of CT staging, especially the T and N stage, is significantly increases by evaluating true axial images in a plane perpendicular to the long axis of the tumour using multiplanar reconstructions[2,18]. Filippone et al.[2] showed an improvement in the accuracy of the T staging from 73 to 83%, and the nodal staging from 59 to 80%, using multiplanar reformatted images obtained from alongside axial images. We also used the multiplanar reformatted images and true axial images in a plane perpendicular to the long axis of the tumour for T staging to obtain more accurate results.

Based on imaging findings, nodal staging remains a challenge. On cross-sectional imaging for all methods, size is the primary criterion for predicting nodal metastasis. Although size is not an optimal guide for nodal evaluation, benign nodes may expand, and nodes below centimetres may be metastatic[17]. We considered the lymph nodes with the largest diameter of 10 mm in the axial plane as metastatic, and we reached a 76.8% accuracy rate. These results are consistent with some studies (e.g., those of Filippone et al. and Chung et al.[6] with an overall accuracy of 80% and 85%, respectively[2]. These authors used multiplanar reconstruction images, and we did not use them for nodal staging. Also, our study has better results than some others[3,19,20]. If we used MPR images for nodal staging, our accuracy rate would be higher. However, we have considered the axial diameter as a reference for nodal evaluation.

There are some limitations to the use of lactulose solution. First, there were some side effects, such as nausea and abdominal discomfort associated with the high volume of the lactulose solution digestion. These side effects generally reduce without treatment. The second disadvantage is the difficulty in diagnosis of intra- and extra-luminal fluid collections, such as cystic lesions, local ascites or abscesses. It is difficult to differentiate cystic lesions from enlarged bowel with lactulose solution. This negation can be overcome using dynamic evaluation and multiplanar reconstruction images[12]. One of the other important disadvantages is the failure to detect small lesions, such as polyps.

Our study had several limitations. First, a small number of patients were included in this study, especially in the T1+T2 and T4 stages, which made it impossible to adequately examine some of the findings. And the second limitation of the current study is its retrospective design.

Conclusion

Noninvasive CTE with lactulose solution as a neutral oral contrast agent is a simple, rapid and accurate method for evaluating CRC staging. This examination is a tubeless procedure (both rectal and oral) that increases patient comfort, requires less time to perform, costs less, decreases radiation exposure, and presents similar results to CT colonography methods. This method can also be used in daily practical applications at routine abdominal examinations as a neutral contrast agent instead of positive oral contrast material.

In daily practical applications, CTE can be applied in patients with the presence or suspicion of CRC for non-invasiveness, less radiation exposure, shorter evaluation period, higher patient comfort and similar TNM staging results.

Ethical Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.A.G., N.O.; Design: M.A.G., N.O., H.T.; Data Collection or Processing: M.A.G.; Analysis or Interpretation: N.O., H.T.; Literature Search: M.A.G., N.O.; Writing: M.A.G., N.O., H.T.

Conflict of Interest: None declared.

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