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ORIGINAL ARTICLE

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Differentiation between malignant and benign rectal tumors by dual-energy computed tomography - a feasibility study

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ABSTRACT

Introduction: To assess the performance of Dual Energy Computed Tomography (DECT) in the differentiation between benign and malignant tumors in the rectum.

Material and methods: We enrolled 8 subjects with rectal tumors suspected to be an early rectal cancer during colonoscopy. All subjects underwent Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Endorectal Ultrasound (ERUS) for staging. Furthermore, all subjects underwent fast switching of tube voltage between 80 and 140 kVp DECT of the pelvis. The 8 subjects had histopathological verified benign adenomas after transanal endoscopic microsurgery resection (TEM). The 8 subjects were matched with 8 consecutively selected subjects with histopathologically verified malignant rectal tumors. The DECT images were analyzed to assess the difference between malignant and benign rectal tumors. All DECT images were reviewed by experienced radiologists. In each DECT scanning, we applied three regions of interest (ROIs) for the acquisition of the DECT unique quantitative parameters. The mean atomic mass (effective Z value), iodine concentration, dual energy ratio (DER) and dual-energy index (DEI) was determined in both groups.

Results: The comparison of the 2 groups showed a significant difference in effective Z and a nonsignificant difference regarding iodine concentration, DER, and DEI in the two groups.

Conclusion: Dual-energy CT demonstrated a difference in the mean atomic mass in benign colorectal tumors in comparison to malignant colorectal tumors.

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Introduction

The use of imaging modalities in colorectal cancer has evolved during the last 20 years, and the range of modalities has broadened [1]. Several modalities such as Magnetic Resonance Imaging (MRI), Endoscopic Rectal Ultra-Sound (ERUS) and Positron Emission Tomography–Computed Tomography (PET CT) are used, to distinguish between benign and malignant tumors but they still all have limitations and low accuracy in the differentiation between advanced benign and early malignant tumors [2].

Despite the use of several imaging modalities, we still need a more accurate imaging modality to differentiate between advanced rectal adenomas and rectal carcinomas. The correct diagnosis is crucial for further treatment. Patients with benign lesions should be offered an organ-sparing treatment by a mucosectomy either by transanal endoscopic microsurgery (TEM), endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [3,4]. Patients with malignant lesions should be offered a more in-depth surgery with a full wall thickness local resection, or a segmental bowel resection [5]. This treatment is associated with higher rates of morbidity, and a careful selection is therefore important.

MRI is the standard method for preoperative staging of rectal cancer, but it is limited to accuracy rates of 65%–86%. Especially in distinguishing between adenomas and early adenocarcinomas. [6,7,8] Furthermore, it is highly dependent on the radiologist's dedication and experience [9].

The ERUS modality is suitable for assessing the extent of tumor invasion into the rectal wall, but its accuracy in evaluating the depth of invasion varies with the tumor stage [10], and several studies have shown that ERUS does not adequately discriminate adenomas from adenocarcinomas [11,12].

The PET CT modality allows the visualization of colorectal cancer using the metabolic changes in tumors [13,14], but metabolic changes are also seen in benign tumors making the differentiation difficult. The utility of PET-CT scanning for initial staging of rectal cancer remains unclear, and it may be particularly useful for demonstration of metastatic spread [15].

Computed Tomography is not a standard investigation to identify the colorectal tumors because of its lack in ability to determine tumor extension in the intestinal wall, but is typically used to rule out distant metastases, as it can assess the entire abdomen, pelvis, and thorax [16]. However, studies have demonstrated the ability of CT to visualize the

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colorectal tumors restricted to advanced tumors [14]. The Dual Energy Computed Tomography (DECT) is a new CT technology that can provide more objective quantitative measurements in addition to regular CT images. By simultaneous scanning with 2 different energy levels, DECT provides quantitative information about tissue composition, such as the mean atomic mass (mean effective z value) of the scanned tissue and measurement of concentrations of certain materials of interest (e.g., iodine, calcium, and water) [17,18]. These objective measurements can aid in the differentiation between different materials, such as malignant or benign rectal tumors. DECT is used to improve the differentiation between malignant and benign tissue in different organs such as the thymus [19], pancreas [20], stomach [21], lungs [22], thyroid [23] and head and neck [24]. Furthermore, DECT has shown good results in the differentiation of metastatic and benign lymph nodes from different cancers [25,26].

The objective of this study is to assess the feasibility of DECT to distinguish between early rectal carcinomas and advanced rectal adenomas in patients with equivocal cases of rectal tumors.

Material and methods

Included subjects

Eight subjects were referred to a dedicated out clinic because the initial endoscopy indicated advanced adenoma or early cancer in the rectum.

The subjects were referred to tumor staging by MRI, ERUS, and CT according to Danish national guidelines [27]. In addition, all subjects underwent a DECT of the pelvis.

Subjects with putatively benign tumors underwent transanal endoscopic microsurgery (TEM), while subjects with malignant rectal tumors underwent total mesorectal excision (TME).

The benign or malignant histopathological confirmation was obtained from the resected specimens. None of the 8 subjects with putatively benign tumors turned out to have malignant tumors after TEM. For comparative reasons, we included 8 consecutively subjects with an early malignant rectal tumor, defined as a T1 or T2. The 8 patients with histo-pathologically verified adenocarcinoma of the rectum, were selected consecutively as early tumors according to their preoperative imaging assessment.

DECT scan

The subjects were scanned with a DECT scanner (GE Discovery CT750 HD, GE Healthcare). Subjects were placed in a supine position and were injected with an iodine-based contrast (Omnipaque®, GE Healthcare®, 300 mg/ml) at a flow rate of 3 ml/s. An amount of 1 mg/kg was injected intravenously before the scan. The spectral imaging scan mode was used, which involve fast switching of tube voltage between 80 and 140 kVp from view to view.

We used the spectral imaging acquisition protocol for the abdomen: 600 mAs; helical scan with pitch, 0.984:1000; rotation time, 10 seconds; collimation thickness, 0.625×64.000 mm; reconstruction field of view, 30 cm. Typically, the average computed tomography dose index volume was 32.01 mGy.

The DECT scan provided us with 101 sets of monochromatic images with ranges from 40 to 140 KeV, based on the attenuation from scanned individuals. These images were processed to obtain the DECT unique quantitative parameters. We analyzed these parameters in the 8 benign rectal tumors in comparison to tumors from 8 subjects with malignant rectal tumors.

Image analysis and quantitative parameters

The DECT image analysis was performed offline on AW 4.4 Advantage Workstations (GE Healthcare, Waukesha, WI, USA). The malignancy status of the cases was blinded to the radiologist. The overall preoperative assessment of the patients was not affected by the DECT scans. Image analysis was done after the surgical treatment.

Each tumor was identified on the monochromatic DECT images macroscopically by a dedicated reader. Three circular ROIs were applied on the DECT images in 3 different sections in each tumor. The sections were chosen as discretion of the radiologist based on the macroscopically most representative areas of evident tumor tissue. ROI's were drawn as large as possible to cover as large an area of the tumor as possible.

All the derived data from the ROI's were exported in excel form for further analysis. All ROI's were treated as individual measurements.

By using the data acquired from the ROIs, we were able to assess the effective Z value, and iodine content in the tumor and we could calculate the dual energy ratio (DER) and dual-energy index (DEI) for each tumor (Figure 1). DER and DEI are a surrogate measure of the slope of the HU curves. DER and DEI give an estimate of the slopes of the HU curves at different energy levels. [28,29,30].

Statistics

Summary statistics for the Quantitative parameters: effective Z-value and Iodine concentration, DEI and DER were expressed as means and 95% confidence intervals. The Wilcoxon signed rank test was used in the statistical comparison of the two groups. We used the Wilcoxon test, as the data did not follow a normal distribution, as tested by quantile-quantile-plots.

Ethics

This study was planned according to the principles settled in the Helsinki Declaration, from 2013. The study was approved by the Danish ethical committee in medical research, with the registration number: s-20130093, and is registered at ClinicalTrials.gov with the ID-number: NCT02592304. All the subjects included received oral and written information, and all gave written consent.

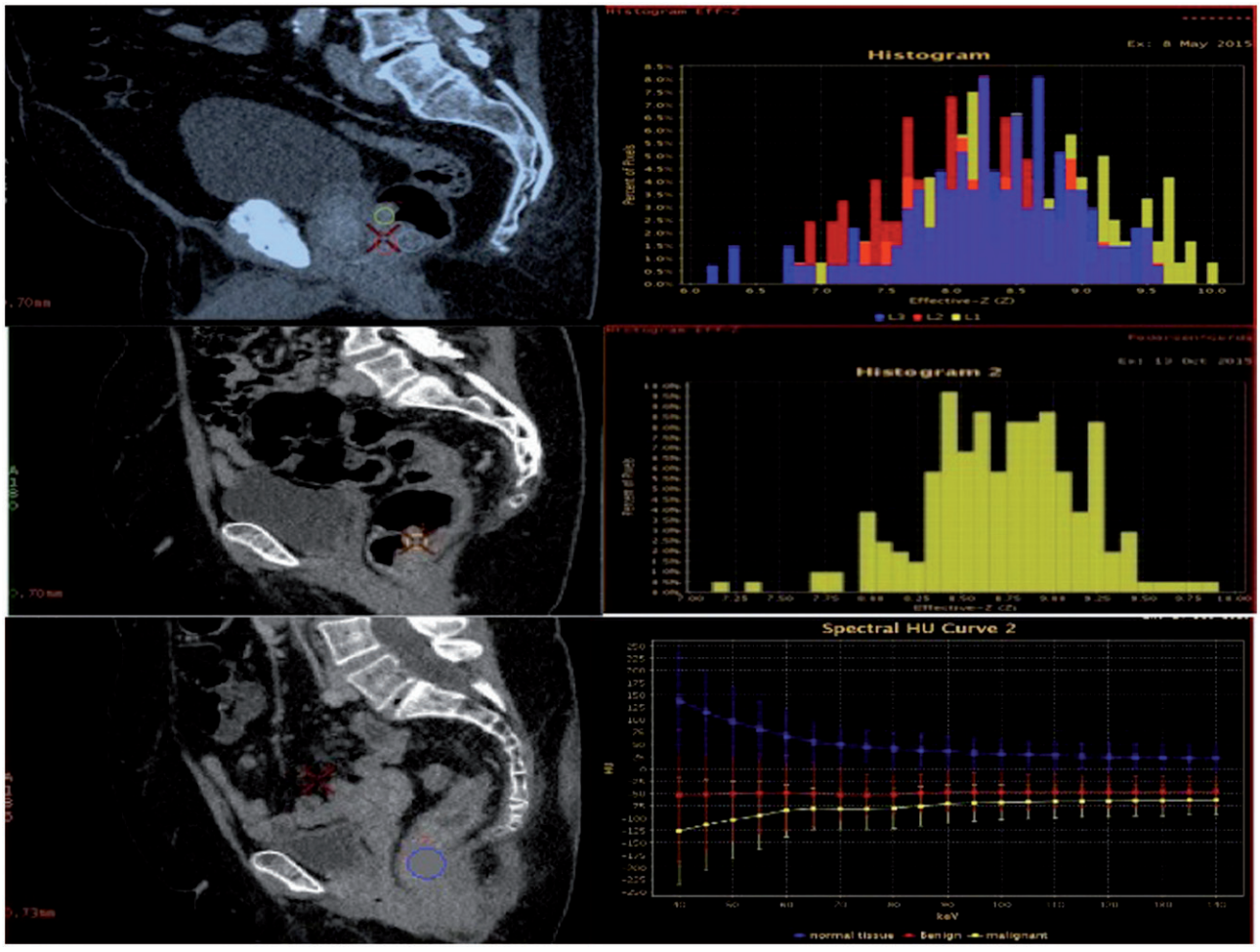

Figure 1. DECT scan demonstrating histogram of effective-z values obtained from monochromatic images at 70 KeV. The top left image is from a malignant tumor with its corresponding effective-z histogram. Middle left is from a benign tumor with its corresponding effective-z histogram. Bottom left is from normal bowel tissue, bottom right shows line graphs for malignant, benign and normal tissue illustrating the difference in HU values at different energy levels in monochromatic images. Circular Roi's are drawn as large as possible to cover as much of the tumor as possible.

Results

Demographics

Sixteen subjects were enrolled 9 male and 7 female, mean age was 68.8 years.

There were 4 tubulovillous adenomas, 3 tubulous and 1 serrated adenoma, in the benign group. Six had a low-grade dysplasia and 2 had high-grade dysplasia.

In the malignant, there were 2 T1 cancers and 6 T2 cancers all well differentiated.

The baseline characteristics of the included subjects are listed in Table 1.

Quantitative parameters

The effective Z values showed a significant difference between benign and malignant 8.48 mg/mm^3 (8.23–8.72) vs. 8.93 mg/mm^3 (8.82–9.23); $p = .03$.

Neither the iodine concentration in the benign and malignant group 17.53 100 μg/cm^3 (12.69–22.37) vs.18.07 100 μg/cm^3 (12.03–24.12), the DER values 0.85 (0.64–1.06) vs. 0.95 (0.75–1.15) or the DEI values 0.09 (−0.02–0.20) vs. 0.04 (0.03–0.05) were significantly different; $p > .05$ (Figure 2).

Discussion

The objective of this study was to assess the feasibility of DECT in the differentiation between malignant and benign tumors of the rectum.

DECT is a new technology that has been used in several studies assessing malignant tissue in different organs, but this is the first investigation of its feasibility in differentiating benign and malignant rectal tumors, and the first study to quantitatively describe rectal tumors by DECT.

We observed a significant difference in the effective z-value in benign tissues compared to malignant tissue. Although a previous study of colonic neoplasia showed no difference in attenuation of malignant and benign neoplasia using CT [31], our study contrastingly proposed differences in parameters relying on attenuation differences. These differences could be due to advances in the scanning technique and performance. More important differences could be due to random variation in the results of the referenced study as well as ours due to small numbers of enrolled subjects.

Our results are in accordance with results described by Ming li et al [23] who demonstrated higher effective z-values in malignant tissue in the thyroid. We compared four

Table 1. Distribution of the mean age and sex of the included subjects. The distribution of the grade of dysplasia and types of adenomas for the benign group, and the T-stages and grade of differentiation for the malignant group.

Characteristics	All subjects	Benign	Malignant
Sex			
Male	9	5	4
Female	7	3	4
Age			
Mean (years)	68.8 (57–87)	70.1 (58–87)	67.5 (57–82)
Type of adenoma			
Tubulovillous		4	
Tubular		3	
Serrate		1	
Grade of dysplasia			
Low grade		6	
High grade		2	
Tumor stage			
T1			2
T2			6
Grade of differentiation			
Low			–
Medium			4
High			1
Not given			3

different quantitative parameters, and the effective z-value was the only parameter which showed a significant difference. The difference between the benign and malignant tumors can be explained by difference in structure and strain between these tissues because malignant tumors have increased density due to necrosis, inflammation, and calcification.

Furthermore, the difference in iodine uptake would result in a difference in effective z value as a consequence of increased density with increased iodine uptake in the tumor. That could contribute to the higher z value in malignant tumors.

As expected the iodine concentrations in the benign tumors were lower than in the malignant tumors. Although the difference did not reach statistical significance, this can be explained by a high level of angiogenesis, increased blood and contrast supply in the malignant tumors. This finding is interesting because DECT's ability to measure the concentration of iodine may potentially facilitate differentiation between benign and malignant tumors. Furthermore, many tumor-specific contrast agents are under evaluation [32,33] and DECTs ability to measure concentrations of materials may gain a role in detecting these contrast agents in tumors which may improve the tumor imaging diagnostics.

Our study has several limitations. First of all, the low number of subjects in each group does not allow us to conclude any statistical difference except for the z-value measurements. Studies have demonstrated good results regarding DECTs abilities to distinguish benign from malignant tissue in different organs, but these studies had a larger sample than ours [34–36].

Second, the application of the ROIs was made manually to cover the largest possible area of the tumor. Application of ROIs could be reader dependent and data obtained by ROIs depends on the section where they were applied in the tumor. Tumors could have irregular borders and differences in composition at different sections, especially if they were too close to intraluminal gas, and this may give a variation in our data obtained from the ROI's.

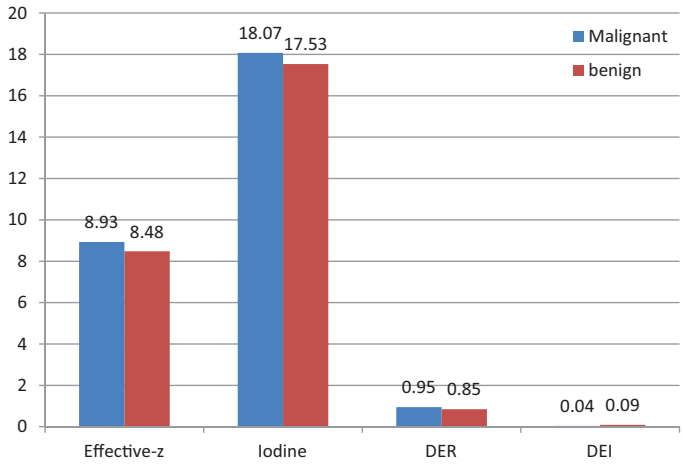

Figure 2. Box graph illustrating the differences in means for all the measured DECT specific quantitative parameters.

Finally, the subjects in this study present a selected population, because they all were suspected of rectal cancer after their colonoscopies. As a result of this, all of the included benign tumors were advanced, and not representative for simple benign rectal adenomas. The decision of focusing on advanced adenomas was made to increase clinical applicability because simple polyps will not be subjected to further diagnostics before excision.

Despite the limitations, there are strengths in the DECT as an imaging modality, such as its ability to produce quantitative parameters compared to other imaging modalities. These parameters could be a supplement to the usual MRI, ERUS, or PET. In addition, DECT allows the assessment of distant metastasis and rectal tumor staging in the same CT session and potentially could supersede the MRI of the pelvis.

In the clinical setting, MRI is used as the gold standard of rectal tumor staging. By combining the image analysis of DECT with MRI the diagnostic accuracy may be improved compared to MRI alone. In this study, we demonstrated that DECT is feasible and may complement with objective values describing material density. The effective z value seems to be especially promising. However, cut off values for the quantitative parameters for benign vs. malignant tumors remains unknown, and future larger studies are needed to investigate clinically applicable cut off values.

Conclusion

This study is the first to evaluate if DECT can be used in the differentiation between benign and malignant rectal tumors.

The study indicates a possible role for the effective z-value measurements in the differentiation between advanced benign adenomas and early rectal cancers. However, this is a feasibility study with a small sample size, and larger sample studies are needed.

Disclosure statement

No potential conflict of interest was reported by the authors.

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