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*Published in:*
Journal of Surgical Oncology

*DOI:*
10.1002/jso.24761

*Publication date:*
2017

*Document Version*
Peer reviewed version

Link to publication in Discovery Research Portal

*Citation for published version (APA):*
Al-Najami, I., Drue, H. C., Steele, R., & Baatrup, G. (2017). Dual energy CT - a possible new method to assess regression of rectal cancers after neoadjuvant treatment. Journal of Surgical Oncology, 116(8), 984-988. https://doi.org/10.1002/jso.24761

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# Dual Energy CT - a possible new method to assess regression of rectal cancers after neoadjuvant treatment.

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Funding: The Danish Cancer Society, the Research Foundation of the Region of Southern Denmark, the Research Foundation of the University of Southern Denmark, and the Research Foundation of Odense University Hospital.

Key words: Pathological response, effective-Z, tumour regression.

This is the peer reviewed version of the following article: ' Dual energy CT - a possible new method to assess regression of rectal cancers after neoadjuvant treatment', *Journal of Surgical Oncology*, which has been published in final form at http://dx.doi.org/ 10.1002/jso.24761. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

List of abbreviations:

DECT : Dual Energy CT
TRUS : Trans Rectal UltraSound
DEI : Dual Energy Index
DER : Dual Energy Ratio
RCRG : Rectal Cancer Regression Grade
HU : Hounsfield Unit
CRT : Chemo Radio Therapy
nCRT: Neoadjuvant chemoradio therapy
pCR : pathologic Complete Response
cCR : complete Clinical Response
ypT : Post radiochemotherapy T stage
TME : Total Mesorectal Excision
TEMS: Transanal Endoscopic Micro Surgery
keV : kilo electron Volt
ROI : Region Of Interest

Running head: DECT measurements of tumour regression

Synopsis:

The assessment of rectal tumor regression grade is essential for offering a tailormade treatment to rectal cancer patients to avoid over-treatment or under-treatment. Thus far, no assessement tool has proven to be optimal, however, dual energy CT is a new imaging technique with promising potential.

**Abstract**

**Background and objectives**

**The** Measurement of tumour regression after neoadjuvant oncological treatment has gained increasing interest because it has a prognostic value and because it may influence the method of treatment in rectal cancer. The assessment of tumour regression remains difficult and inaccurate with existing methods. Dual Energy Computed Tomography (DECT) enables qualitative tissue differentiation by simultaneous scanning with different levels of energy.

We aimed to assess the feasibility of DECT in quantifying tumour response to neoadjuvant therapy in loco-advanced rectal cancer.

**Methods**

We enrolled eleven patients with histological and MRI verified loco-advanced rectal adenocarcinoma and followed up on them prospectively. All patients had one DECT scanning before neoadjuvant treatment and one twelve weeks after using the spectral imaging scan mode. DECT analysing tools were used to determine the average quantitative parameters; effective-Z, water- and iodine-concentration, Dual Energy Index (DEI) and Dual Energy Ratio (DER). These parameters were compared to the regression in the resection specimen as measured by the pathologist.

**Results**

Changes in the quantitative parameters differed significantly after treatment in comparison with pre-treatment, and the results were different in patients with different CRT response rates.

**Conclusion**

DECT might be helpful in the assessment of rectal cancer regression grade after neoadjuvant treatment.

## Introduction

Neoadjuvant chemo-radiotherapy (nCRT) given to patients with locally advanced rectal cancer improves local disease control after radical surgery and leads to variable degrees of tumour down staging[1]. Fifteen to twenty percent of the patients who undergo nCRT have a histo- pathological complete response (pCR) after 8 – 12 weeks in which no residual cancer is reported at histological examination of the resection specimen[2]. A pCR following nCRT is associated with excellent long-term survival with low rates of local recurrence and metastasis making it an independent predictor of prognosis [2].

Patients with comorbidity may benefit in terms of treatment-related morbidity and mortality from avoiding major rectal resections. Ongoing trials indicate that watchful waiting may become an option for patients with pCR and that some patients with partial response might be candidates for local excision instead of rectal excision or extirpation[3, 4] . Therefore it is of importance to be able to validate pCR with high accuracy after nCRT. Watchful waiting without surgery after pCR is still experimental but good long-term results have been reported [2]. Complete clinical response (cCR), often defined as no tumour identified at clinical examination post CRT, has been used to identify candidates for alternatives to major surgery. The most frequently used method for preoperative examination is digital rectal examination in combination with endoscopy, or high frequency endo-rectal ultrasound, and MRI. But there is no generally accepted standard for evaluating the response to nCRT, and previous studies show poor correlation between cCR and pCR. In a study from 2009,

transrectal ultrasound (TRUS) correctly classified the histological T stage in only 46% of tumours after neoadjuvant chemo-radiation [5]. A study from 2005 using MRI correctly classified 52 % of tumours, with various ypT-stages, with 38 % and 10.0 % over and under-staged respectively [6].

As demonstrated in earlier studies, simultaneous scanning with 2 x-ray beams with variable energy levels (DECT) allows for differentiation between benign and malignant tissue[7]. By scanning with varying energy levels, the patients can be exposed to a lower radiation dose using DECT compared to regular CT.
DECT allows for reduction in the image blurriness through an iterative reconstruction process which may enable dose reduction during scanning while maintaining diagnostic image quality. In clinical practice, the use of DECT may reduce CT patient dose depending on the clinical task, patient size and anatomical location of the region of interest, making its clinical implementation favorable.
Effective-z is the main outcome measure in DECT. The z value is a surrogate of the atomic mass and is therefore unique to different elements such as iodine or calcium, but it will vary in mixtures of material as in human tissue such as rectal tumors whereby the average atomic mass of a mixture represents the effective-z.
The objective of this feasibility study was to identify the best DECT unique quantitative parameters in the assessment of tumour regression, and to investigate whether DECT could be useful in the evaluation of tumour regression in patients with rectal cancer after neoadjuvant chemo-radiation.

## Materials and methods

### Patients

DECT images from 11 adult patients with biopsy and MRI verified rectal adenocarcinoma were prospectively included and analysed. All of them underwent neoadjuvant therapy according to national guidelines. All 11 patients were staged as T3 or T4 disease. Nine patients received radiation therapy consisting of 50 Gy in 25 fractions in combination with Capecitabine 825 mg/m2 bid. Two patients received radiation therapy but did not complete their chemotherapy. A DECT scan and a MRI scan was performed before and eight weeks after completing CRT (12 weeks after the initiation of nCRT). TME was made 2-4 weeks after the follow-up MRI and DECT scan.

### Dual Energy CT

All patients underwent 2 series of single source DECT scanning. The patients were given iodine based contrast agent (Omnipaque®, GE Healthcare®, 300mg/ml) and scanned with a DECT scanner (GE Discovery CT750 HD, GE Healthcare®, Milwaukee, WI). The Technical details have been described above.[7]

### Imaging analysis, quantitative parameters

The images were analysed with integrated imaging analytic tools for quantitative assessment of the iodine and water concentration, effective-z, dual energy index, and the dual energy ratio. (See figure 1).

A dedicated radiologist applied three circular regions of interest on each tumour on all DECT-scanning images. The three chosen ROIs were based on a macroscopic evaluation of the most representative images of the associated MRI scan.

**Histopathology**

A dedicated pathologist assessed the RCRG after resection and scored the tumour according to 5 RCRG levels[8]. RCRG 1: the tumour is either sterilised or contains only microscopic foci of adenocarcinoma. RCRG 2: marked fibrosis, but with macroscopic tumour still present. RCRG 3: little or no fibrosis in the presence of abundant macroscopic tumour which contains less than 50 % cancer cells. RCRG 4: little or no fibrosis in the presence of abundant macroscopic tumour which contains more than 50 % cancer cells. RCRG 5: no or little evidence of tumour shrinkage[8 9]. RCRG 1 was considered a complete response, RCRG 2+3 a partial response, and RCRG 4+5 as poor/ no response.

**Ethics**

This study has been conducted according to the principles established in the Helsinki declaration of October 2000. The study was approved by the Danish ethical committee of medical research with the registration number s-20130093. ClinicalTrials.gov ID: NCT02592304.

**Statistics**

The differences in the quantitative parameters within the different RCRG groups are given as means and standard deviations. An F-test is used to test the differences in means before and after chemo-radiation stratified to different RCRG groups, with a null hypothesis of equality. A P value of <0.05 was regarded as significant.

**Results**

*Diagnostic performance of the quantitative parameters*

Within the feasibility settings of this study, we aimed to determine the best quantitative unique DECT parameter for further assessment of the RCRG. As illustrated in Table 1 and figure 2, changes of the effective Z value was consistently correlated to the different RCRG groups. The change in the other parameters was similar to that of effective Z, but in a less consistent manner and with larger standard deviations (table 1). Only the effective Z value showed a high degree of correlation to the respective RCRG group with a correlation coefficient $r^2$= 0.96, making it the parameter of choice in this study.

Eleven patients were enrolled in the study. Extracted and calculated data from the Regions of interest were analysed and the change within each response group from before and after treatment is shown in table 1. The pathology results consisted of 2 complete responders, 6 partial responders and 3 non-responders.

*The effective Z pre- and post CRT compared to CRT response*

The mean effective Z of the pre-CRT DECT scans of all the enrolled patients was 8.82 (see table 1).

In relation to the complete responders the mean effective Z value was 8.31. Compared to the effective Z value pre-CRT there was a decrease of 7.0 % ($p < 0.05$). For the partial responders the mean effective Z value was 8.59 compared to the effective Z value obtained before treatment corresponding to a decrease of 3 % ($p < 0.05$). In the group of non-responders there was no significant change in the effective-z. The mean value was 8.83 compared to the pre-CRT effective Z value and we obtained a change of 0.3 % ($p > 0.05$). See figure 3+4 and table 1.

We demonstrated a 6 % decrease in the effective Z post CRT for complete responders (8.31) compared to non-responders (8.83).

**Discussion**

The aim of this feasibility study was to investigate whether DECT could measure and perhaps quantify the tumour regression grade in patients with loco-advanced rectal cancer by comparing DECT scanning before and after neoadjuvant treatment. We also compared the DECT unique effective Z post CRT in patients with different response to nCRT to assess the difference in the tumour regression grade.

The assessment of tumour regression is today based on a specific dedication to rectal cancer staging imaging. This imaging is often prone to the imaging modality dedication and the results of the staging are often operator dependent. One advantage of DECT is that it would be suitable for all centers and also less dedicated

MRI centers dealing with rectal cancer as the technique does not require investment in costly equipment but can be added to regular clinical CT scanners by software installation. It also has the potential of decreasing operator dependency by measuring objective quantitative parameters.

As shown in Table 1, all parameters in RCRG 1 had reduced values except for the water concentration parameter. As expected, the largest changes in the quantitative parameters were observed in the group with the highest regression grade. It is of interest that the changes were seen both in the measurements of the material composition being the effective-z and the iodine concentration, but also in the measurements based on the Hounsfield units and therefore being based on a difference in the materials attenuation. The fact that the technique enables differentiating materials in two different ways reduces the observer variability compared to MRI and TRUS. In addition to the objective information obtained from DECT images, it has the potential to improve image quality over conventional imaging techniques due to enhanced material separation.

By altering the energy levels of the image analysis it is not only possible to conduct the measured parameters, as was the focus of this study, but it is also possible to enhance certain types of materials of interest. This enhancement can be pointed out by using a color overlay based on material separation marking the area of interest that contains the material of interest, i.e. iodine figure 1 image E+F. 3D views are also obtainable to view the region of interest from different angles figure 1 image G+H.Even though the variability is reduced it does play a role in the determination of the ROIs in the DECT analysis. ROIs includes the supposed region of the highest

tumor attenuation and may be prone to sampling error whereby the lesion may not be completley included if the tumor shows irregular boarders.

Data from the quantitative parameters revealed a difference between complete and partial responders and effective-z, DER, DEI and iodine concentration which were all correlated to the pathological grading. We obtained smaller change the lower response rates were. In the non-responding tumours we saw almost no changes, and the most pronounced changes were demonstrated in the complete responding group.

Effective-Z has been useful in the determination of kidney stone composition[10] but until present, effective-z has not been used in tumour characterization outside our unit. In a study of malignant pelvic lymph nodes, we found a lower effective-z value in benign compared to malignant lymph nodes, corresponding to the pattern we saw in the tumours with the highest regression grade. The measurement of the effective-Z, DER and DEI could possibly support our earlier demonstrated benefits of DECT in benign/malignant differentiation and qualitative characterization of tumours[7].

When looking at figure 2 and table 1 we see a variation within each RCRG for DER, DEI and iodine measurements, and a wide range in the standard deviations suggesting a random distribution in each response group. Our study suggests that the effective-z could be used as an indicator to differentiate between a complete response and a no response in rectal cancer. However, the low number of subjects in this study does not allow for the exclusion of any of the other parameters in the quantification of tumour response to nCRT.

By observing a difference in the post CRT values of the effective Z value stratified in the different CRT response group we may be able to facilitate better allocation of patients to the most appropriate treatment. It might also facilitate more prompt surgical treatment to poor responders since they would not continue to experience tumour regression as would be the case with some of the partial responders[11].

Our results reveal a clear difference in the z-value between complete, partial and non-responders. However, the number of patients included in this study is too small to conclude that we can reproducibly differentiate between different degrees of partial response. A larger study is needed and it is in preparation.

**Conclusions**

This study is the first to evaluate the utility of DECT in measuring tumour response to nCRT in rectal cancer. Our preliminary data indicates that the effective-Z value might enable identifying and possibly quantifying pathological response.

DECTs clinical applicability must be preceded by a comparison to gold standard in the assessment of rectal tumor regression being MRI.

**References**

1. Perez RO, Habr-Gama A, Gama-Rodrigues J, Proscurshim I, Juliao GP, Lynn P, Ono CR, Campos FG, Silva e Sousa AH, Jr., Imperiale AR, Nahas SC, Buchpiguel CA. Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683). Cancer 2012;118:3501-11.

2. Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, van Dam RM, Jansen RL, Sosef M, Leijtens JW, Hulsewe KW, Buijsen J, Beets GL. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:4633-40.

3. Lambregts DM, Maas M, Bakers FC, Cappendijk VC, Lammering G, Beets GL, Beets-Tan RG. Long-term follow-up features on rectal MRI during a wait-and-see approach after a clinical complete response in patients with rectal cancer treated with chemoradiotherapy. Diseases of the colon and rectum 2011;54:1521-8.

4. Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, Lindebjerg J, Rafaelsen SR, Jakobsen A. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. The Lancet Oncology 2015;16:919-27.

5. Mezzi G, Arcidiacono PG, Carrara S, Perri F, Petrone MC, De Cobelli F, Gusmini S, Staudacher C, Del Maschio A, Testoni PA. Endoscopic ultrasound and magnetic resonance imaging for re-staging rectal cancer after radiotherapy. World J Gastroenterol 2009;15:5563-7.

6. Chen CC, Lee RC, Lin JK, Wang LW, Yang SH. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? Dis Colon Rectum 2005;48:722-8.

7. Al-Najami I, Beets-Tan RG, Madsen G, Baatrup G. Dual-Energy CT of Rectal Cancer Specimens: A CT-based Method for Mesorectal Lymph Node Characterization. Diseases of the colon and rectum 2016;59:640-7.

8. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680-6.

9. Martens MH, Subhani S, Heijnen LA, Lambregts DM, Buijsen J, Maas M, Riedl RG, Jeukens CR, Beets GL, Kluza E, Beets-Tan RG. Can perfusion MRI predict response to preoperative treatment in rectal cancer? Radiother Oncol 2015;114:218-23.

10. Kriegshauser JS, Silva AC, Paden RG, He M, Humphreys MR, Zell SI, Fu Y, Wu T. Ex Vivo Renal Stone Characterization with Single-Source Dual-Energy Computed Tomography: A Multiparametric Approach. Academic radiology 2016;23:969-76.

11. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P, Nadalin W, Perez RO. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Diseases of the colon and rectum 2013;56:1109-17.

**Text to tables and figures**

Table 1 describes the changes of the quantitative parameters stratified to the histopathological tumour regression grade. The percentages are the relative changes in the quantitative parameters from before to after CRT.

RCRG = Rectal Cancer Regression Grade, CRT= Chemo-Radiation Therapy, DER = Dual Energy Ratio, DEI = Dual Energy Index, Eff Z= Effective Z, cPR= complete Pathological response, pPR= partial Pathological Response, nPR= no Pathological Response.

Figure 1 DECT images and the corresponding analysis of the quantitative parameters. A. the implementation of the regions of interest (ROI) in the tumor for the assessment of the quantitative parameters, 3 ROIs was drawn in 3 different slices. B. Histogram of the measurement of the iodine concentrations in the ROIs, the three different colours represent 3 different ROIs in the same tumor. C. Histogram of the measurement of the effective Z value, the three different colours represent three different ROIs. D. Hounsfield unit curves, the slopes of the curves represent the DEI and DER. E. Represents a different visualization technique based on the enhancement of contrast media. F. Represents DECT image with a colour overlay to enhance the iodine concentration. G. Shows a DECT feature of 3D image reconstruction enhancing the tumor (red arrow) by enhancing vascularity. H. 3D image reconstruction, the tumor (red arrow) is enhanced by its iodine content.

Figure 2 the relative changes in percentages for all the quantitative parameters. Notice the pattern of the effective-Z showing a relative change corresponding to the anticipated change in the tumour regression. Note there were no patients with a RCRG 5.

Figure 3 the correlation of the effective-Z to the RCRG, with a mean fitted line indicating a linear increase of the effective-Z with increasing RCRG. The correlation coefficient is given as $R^2$= 0.98.

Figure 4 illustrates the increase in effective Z with the decreasing response to chemo radiation therapy, by comparing the effective Z before chemo radiation therapy (pre-CRT) to the three different rates of response.