Evaluation of early metabolic responses in rectal cancer during combined radiochemotherapy or radiotherapy alone: Sequential FDG-PET-CT findings

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Metabolic imaging

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ABSTRACT

Background and purpose: The purpose of this study was to prospectively investigate metabolic changes of rectal tumors after 1 week of treatment of either radiochemotherapy (28 × 1.8 Gy + Capecitabine) (RCT) or hypofractionated radiotherapy (5 × 5 Gy) alone (RT).

Materials and methods: Fourty-six rectal cancer patients, 25 RCT- and 21 RT-patients, were included in this study. Sequential FDG-PET-CT scans were performed for each of the included patients both prior to treatment and after the first week of treatment. Consecutively, the metabolic treatment response of the tumor was evaluated.

Results: For the patients referred for pre-operative RCT, significant reductions of SUV_{mean} ($p < 0.001$) and SUV_{max} ($p < 0.001$) within the tumor were found already after the first week of treatment (8 Gy biological equivalent dose (BED). In contrast, 1 week of treatment with RT alone did not result in significant changes in the metabolic activity of the tumor ($p = 0.767$, $p = 0.434$), despite the higher applied RT dose of 38.7 Gy BED.

Conclusions: Radiochemotherapy of rectal cancer leads to significant early changes in the metabolic activity of the tumor, which was not the case early after hypofractionated radiotherapy alone, despite the higher radiotherapy dose given. Thus, the chemotherapeutic agent Capecitabine might be responsible for the early metabolic treatment responses during radiochemotherapy in rectal cancer.

During the last years, sequential ^{18}F-fluorodeoxyglucose positron-emission-tomography (FDG PET) imaging has been increasingly studied to monitor the metabolic response of the tumor to multimodality treatment of rectal cancer [1–12]. For rectal cancer, pre-operative short-course radiotherapy (RT) was shown to result in improved local control, whereas pre-operative treatment with radiochemotherapy (RCT) was found to result in a significant downsizing and downstaging of the tumor, increasing the rate of complete surgical resection [2–4,9,12]. In 15–30% of the patients being pre-operatively treated with RCT, even complete tumor regression was observed 6–8 weeks after finishing the pre-operative treatment [3,4,12,13]. Over the years, many studies have been published reporting metabolic treatment response determinations of rectal carcinomas using dual time PET-imaging both before and after therapy, presenting a significant reduction of FDG uptake due to pre-operative treatment with neo-adjuvant RCT [1,3–7,10,12,14,15]. However, in contrast to response evaluations based on PET-imaging before and after treatment, monitoring the tumor response early during pre-operative treatment enables response-guided modifications of the treatment protocol on the basis of early changes of FDG uptake, possibly strengthened by additional clinical or biological factors. A significant reduction of the FDG uptake within rectal carcinomas was observed already after 2 weeks of pre-operative RCT, with the reduction of the FDG uptake being a good predictor of pathological treatment response [2,8,11]. However, not much is known about the possible cause of early changes in the metabolic activity of rectal tumors undergoing pre-operative RCT. Therefore, in order to better understand the early metabolic changes within the tumor during RCT, we thought it might be helpful to compare the metabolic response early during RCT with the metabolic response occurring after treatment with RT alone. This could lead to a better understanding of the biological basis for early changes and could help to improve the percentage of early responding tumors, thereby also possibly improving the prognosis of patients with rectal cancer. To our knowledge, very few direct comparative studies have been performed so far [9]. Thus, a prospective study was initiated to compare early metabolic treatment response in rectal cancer undergoing either concomitant RCT or RT alone.

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Materials and methods

Patient characteristics

Fourty-six patients diagnosed with rectal cancer were included in this study, from which the clinical TN staging was obtained from a pre-treatment MR-scan according to the TNM classification of malignant tumors (Edition 6) (Table 1). The included patients were treated according to the national and regional guidelines. According to these guidelines, patients with a T2N0-1 or a mid- or high-rectal T3N0-1 tumor with a predicted CRM on MR > 2 mm were pre-operatively treated with short-course hypofractionated RT (5 fractions of 5 Gy on consecutive working days). Patients with N2 disease, with low seated T3 tumors and patients with a tumor close to or invading the mesorectal fascia (CRM < 2 mm) were treated with neo-adjuvant RCT (28 fractions of 1.8 Gy daily; Capecitabine 825 mg/m^2 BID). Twenty-five of the included patients were pre-operatively treated with RCT, whereas 21 patients were pre-operatively treated with RT alone. For the patients treated with hypofractionated short-course RT, a TME was planned within 3 days after the last RT fraction, whereas for the patients pre-operatively treated with RCT, the TME was planned approximately 3 months after the first RT fraction. The Medical Ethics Committee according to the Dutch law approved the trial. All patients gave written informed consent before entering the study.

PET-CT imaging and processing

Sequential FDG-PET-CT scans, both static and dynamic, were performed for each of the included patients at two different time points. The patients treated with RCT were imaged prior to RCT and 1 week after the onset of RCT (10.8 Gy, which corresponds to a biological effective dose (BED) of 8.0 Gy) (Fig. 1A) [16]. Patients treated with RT were imaged prior to the start of RT and at the day of the fifth RT fraction (total dose of 25 Gy, corresponding to a BED of 38.7 Gy) (Fig. 1B) [16]. All PET-CT scans were performed as earlier described [17]. Prior to each FDG injection, the patients blood glucose level (BGL) was measured using an automatic device (LifeScan One Touch Ultra, LifeScan Inc., Milpitas, USA).

All acquired PET-data were normalized for the BGL using the following equation:

$$SUV_{normalized} = SUV \cdot \frac{[Glu]}{100},$$

with [Glu] the measured BGL [mg/dl] [18,19].

Also, all dynamic PET-data were corrected for tumor motion during dynamic imaging, using the Image-Fusion-toolbox of the PMOD software package (PMOD Technologies Ltd., Zurich, Switzerland).

PET analysis

For each PET-CT scan, both static and dynamic, a tumor contour was generated using automated standardized-uptake-value (SUV) thresholding with the threshold depending on the tumor-to-background signal ratio with the gluteus muscle selected as a relevant background [20,21]. From the static PET-data, SUV_{mean} and SUV_{max} within the tumor were calculated using dedicated software (TrueD VC50, Siemens MI, Erlangen, Germany). For the dynamic PET-CT scans, a tumor contour was obtained from the last time frame of the dynamic PET-scan using PMOD (version 2.9, PMOD Technologies Ltd., Zurich, Switzerland). From the mean and maximum time-activity-curves (TACs) within the tumor, the FDG uptake rates (ΔSUV/min.) were calculated over the last 8 time frames of the dynamic PET-data. Subsequently, changes in the metabolic activity of the tumor, SUVs and FDG uptake rates, were quantified by calculation of the response indices (RIs), representing the percentage reduction relative to the pre-treatment measured value.

Table 1
Overview of the clinical TNM staging of the patients, the maximum standardized-uptake-values (SUV_{max}) at both PET-CT imaging time points as well as the response indices (RIs) for the patients included in this study and referred to treatment with respectively radiochemotherapy (RCT) or short-course hypofractionated radiotherapy (RT).

RCT	cTNM	SUV_{max} [−] Pre	SUV_{max} [−] 1 week	RI SUV_{max} [%]	RT	cTNM	SUV_{max} [−] Pre	SUV_{max} [−] 1 week	RI SUV_{max} [%]
1	T4N2M0	14.4	10.6	26.4	1	T3N1M1	18.9	19.3	−2.1
2	T3N2M0	12.5	9.8	21.6	2	T3N1M0	12.6	10.2	19.0
3	T3N1M0	20.3	10.9	46.3	3	T2N0M0	11.8	9.3	21.2
4	T2N1M0	17.7	9.0	49.2	4	T3N1M0	13.0	13.9	−6.9
5	T3N2M0	20.8	12.0	42.3	5	T2N0M0	12.2	14.3	−17.2
6	T3N2M0	13.2	14.1	−6.8	6	T2N0M0	13.4	11.3	15.7
7	T3N2M0	27.6	27.4	0.7	7	T2N1M0	8.7	9.0	−3.4
8	T3N1M0	28.1	16.9	39.9	8	T3N1M0	22.8	16.8	26.3
9	T3N2M0	14.3	12.3	14.0	9	T3N1M0	24.2	27.5	−13.6
10	T3N1M0	16.0	10.6	33.8	10	T3N1M0	17.6	15.5	11.9
11	T3N1M0	14.2	9.0	36.6	11	T2N0M0	9.4	10.3	−9.6
12	T3N1M0	26.0	22.7	12.7	12	T3N1M0	12.4	12.2	1.6
13	T3N2M0	15.2	14.1	7.2	13	T2N0M0	12.9	14.5	−12.4
14	T3N0M0	7.4	9.0	−21.8	14	T3N1M0	22.9	16.7	27.1
15	T3N2M0	26.2	19.9	24.0	15	T3N1M0	12.5	11.0	12.0
16	T4N1M0	10.2	10.1	1.0	16	T3N0M0	14.2	15.2	−7.0
17	T3N1M0	13.4	12.9	3.7	17	T3N0M0	16.9	14.6	13.6
18	T3N2M0	17.3	12.5	27.7	18	T3N1M0	13.5	14.5	−7.4
19	T3N1M0	19.0	18.9	0.5	19	T3N0M0	29.3	26.1	10.9
20	T3N2M0	11.1	10.0	9.9	20	T3N1M0	15.7	18.8	−19.7
21	T3N0M0	11.5	12.7	−10.4	21	T3N0M0	5.7	6.9	−21.1
22	T4N1M0	15.3	7.6	50.3					
23	T3N1M0	7.0	8.0	−14.3					
24	T3N0M0	15.8	12.3	22.2					
25	T3N1M0	15.4	11.8	23.4					
Mean		16.4	13.0	17.6			15.3	14.7	1.8
SD		5.8	4.8	20.5			5.7	5.2	15.4
Min.		7.0	7.6	−21.8			5.7	6.9	−21.1
Max.		28.1	27.4	50.3			29.3	27.5	27.1

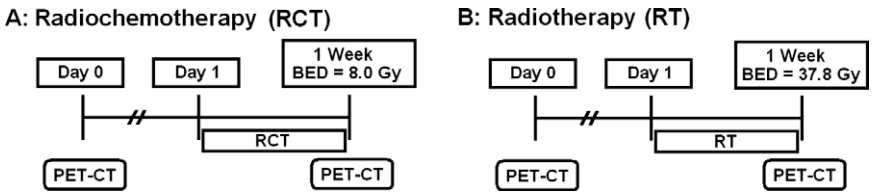

Fig. 1. PET-CT study scheme for the assessment of the early metabolic treatment response during treatment of rectal cancer. (A) Study scheme for the patients treated with pre-operative radiochemotherapy (RCT). (B) Scheme for the patients treated with only pre-operative short-course hypofractionated radiotherapy (RT).

Statistical analysis

Statistical analyses were performed using SPSS (version 15.0; SPSS Inc., Chicago, IL, USA). All quantitative values were expressed as mean ± standard deviation (SD) and range (min. to max.). Comparisons of related measurements were performed using a Wilcoxon-signed rank test, whereas a Mann–Whitney *U* test was used in case of independent samples.

Results

Metabolic treatment response during RCT

A significant decrease of the metabolic activity within the tumor was observed already early during pre-operative RCT (Fig. 2A). SUV_{mean} and SUV_{max} decreased from respectively 8.5 ± 2.8 (range: 4.0–15.1) and 16.4 ± 5.8 (range: 7.0–28.1) measured prior to the onset of RCT to 6.9 ± 2.2 (range: 4.3–12.7) ($p < 0.001$) and 13.0 ± 4.8 (range: 7.6–27.4) ($p < 0.001$) after the first week of RCT (Table 1). Comparable time-trends were found for the mean and maximum FDG uptake rates within the tumor, with RIs of respectively 21.0 ± 31.3% (range: −40.6% to 65.2%) ($p = 0.003$) and 11.4 ± 41.5% (range: −73.1% to 60.7%) ($p = 0.062$) after the first week of RCT (Fig. 2A).

Metabolic treatment response during RT

In contrast to RCT, for the patients pre-operatively treated with RT, no significant reduction of the tumors metabolic activity (SUV_{mean} and SUV_{max}) was observed early during therapy (Fig. 2B). Average values of respectively 8.3 ± 2.9 (range: 3.4–15.1) and 15.3 ± 5.7 (range: 5.7–29.3) were found for the pre-treatment PET-CT scan and 8.2 ± 2.7 (range: 4.4–14.3) ($p = 0.767$) and 14.7 ± 5.2 (range: 6.9–27.5) ($p = 0.434$) for the follow-up PET-data (Table 1). For the mean and maximum FDG uptake rate of the tumor, RIs of respectively −9.9 ± 30.5% (range: −52.6% to 44.9%) ($p = 0.334$) and −6.7 ± 22.4% (range: −41.2% to 33.0%) ($p = 0.293$) were found (Fig. 2B).

RCT versus RT

When comparing the metabolic treatment response of the two different treatment schemes after 1 week of treatment, a significant higher metabolic response was found for the patients treated with RCT when compared to pre-operative treatment with RT alone (Fig. 3 and Table 1). The average reduction of SUV_{mean} of 16.4 ± 18.2% (range: −20.9% to 47.6%) after the first week of RCT was found to be statistically significantly higher when compared to the average reduction of only 0.1 ± 14.7% (range: −29.4% to 23.5%) for the patients treated with RT alone ($p = 0.004$) (Fig. 3).

Also, the percent reduction of SUV_{max} of 17.6 ± 20.5% (range: −21.8% to 50.3%) after 1 week of RCT was found to be statistically significant higher than the average reduction of SUV_{max} of 1.8 ± 15.4% (range: −21.1% to 27.1%) after 1 week of RT alone ($p = 0.009$) (Fig. 3 and Table 1).

Discussion

In the present report we provide first evidence that the significant reduction of the metabolic activity of the tumor, as seen early during pre-operative RCT might be induced by the chemotherapeutic agent Capecitabine, since no such changes in the metabolic activity of the tumor could be determined after 1 week of treatment with RT alone, despite the much higher applied BED. When looking at only the dose levels of RT, a higher metabolic treatment response was expected for the patients treated with hypofractionated RT at the time of the follow-up PET-CT scan as these patients

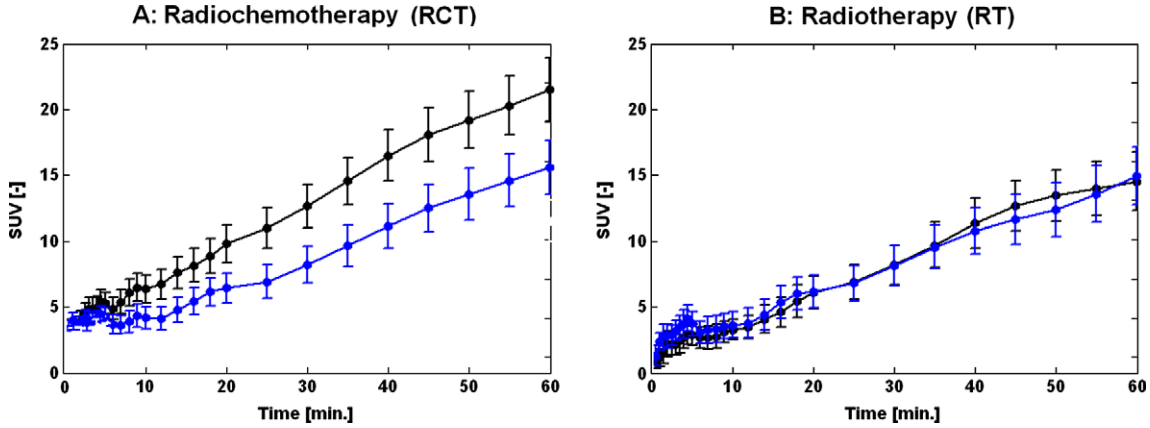

Fig. 2. Mean time-activity-curves (TACs) of the tumor, indicating the amount and rate of FDG uptake over time. (A) Mean TACs at the two imaging time points for the patients treated with radiochemotherapy, respectively pre-treatment (black) and 1 week (blue) after the onset of treatment, indicating a significant reduction of the metabolic activity of the tumor already during the first 2 weeks of treatment. (B) Mean TACs at both time points for the patients treated with short-course radiotherapy, respectively pre-treatment (black) and after 1 week of treatment (blue), presenting a stable FDG uptake within the tumor during treatment with RT.

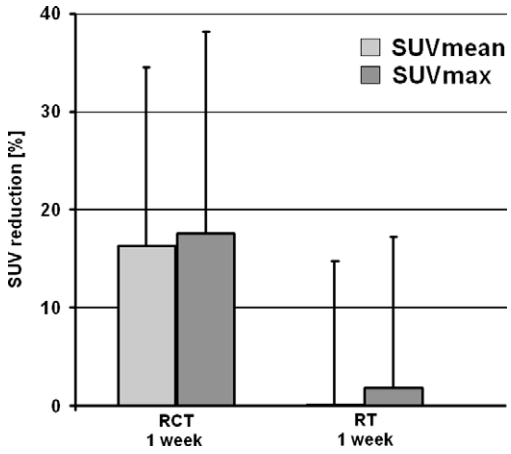

Fig. 3. Average reductions of both SUV_{mean} and SUV_{max} within the tumor after 1 week of treatment for the patients treated with respectively radiochemotherapy (RCT) and short-course hypofractionated radiotherapy (RT).

received a higher BED when compared to the patients treated with RCT. However, this study presents with opposite findings. These findings imply that the addition of the chemotherapeutic agent Capecitabine to RT-treatment can induce the early metabolic decrease in the FDG uptake, which is more and more used as a predictor of the pathological treatment response.

A comparative study, investigating the metabolic activity of the tumor early during chemotherapy alone was unfortunately not feasible, because initial chemotherapy alone is not standard care in our region. However, earlier clinical studies have already indicated important and even prognostic significant differences in FDG uptake as early as one to three weeks after the first cycle of chemotherapy in various cancer types [22–26]. For chemotherapy with 5-FU, a comparable chemotherapeutic drug to Capecitabine, a consistent decrease in FDG uptake by 50% was already present as early as 3 days after the start of the chemotherapy [27]. In contrast, chemotherapeutic agents like doxorubicin or paclitaxel increased FDG uptake [27]. The early reduction in FDG uptake under 5-FU treatment might be related to a decreased activity of either the glucose transporter Glut-1 or the phosphorylation enzyme hexokinase [27]. Also for rectal cancer patients, a significant reduction of FDG uptake was observed when applying chemotherapy alone without additional RT [28–30]. Sharma and Smith presented data demonstrating a significant reduction of the hexokinase activity in colorectal tumor cells after treatment with chemotherapy [31]. Hexokinase is an enzyme known to phosphorylate six-carbon sugars, including FDG, making it unable to move or be transported out of the cell [31]. A reduction of the hexokinase concentration leads to a decreased amount of FDG trapped within the cells resulting in decreased SUVs [31]. The degree of chemotherapy-induced changes in metabolic activity of colorectal tumors were shown to be highly predictive for patient outcome [30].

Such FDG uptake measurements provide a valuable surrogate for the intratumoral biodistribution of the drug within solid tumors and thereby also for the intratumoral effectiveness. A homogeneous intratumoral biodistribution of the drug Capecitabine is an important prerequisite for its effectiveness as a radiosensitizing cancer cell agent during RT [32].

In contrast to chemotherapeutic agents, RT alone on cancer cells does not lead to early changes in its glucose transport or cellular hexokinase activity [32]. Instead, RT induces changes on the cellular cell cycle, the DNA repair and apoptosis, all of which do probably not lead to early changes in the FDG uptake of cancer cells, as seen in our study [32]. Thus, the metabolic changes in PET images after the first week of RCT in rectal cancer might be more seen as activity changes in the cells ability to incorporate glucose under the influence of the chemotherapeutic drug rather than as RT-induced cytotoxicity.

This is the first study presenting significant different reaction patterns of rectal tumors to pre-operative treatment with either radiochemotherapy or radiotherapy alone already early during treatment. Knowledge about early reaction patterns within malignancies during pre-operative treatment is important for further evaluation of PET-based response predictions which are the first elements of individualized treatment schemes in the near future.

One published study presented with contradicting results as they found a significant reduction in the FDG uptake after a short-course hypofractionated RT [9]. One of the differences between the study of Siegel et al. and our study was the later time point of 2 days of the follow-up PET-CT scan [9]. However, the average difference of only 2 days is very unlikely to explain such a dramatic reduction of more than 35% for the SUV_{max}. Instead, another explanation for the discrepancy of the results might be the reproducibility of SUV determination [12,18,20,33–36]. The patients BGL at the time of PET-imaging and the time-interval between FDG injection and the start of PET-imaging are known to influence the SUVs resulting from PET analysis [12,18,33–36]. The study of Siegel et al. did not perform a normalization of the sequential PET-data for the patient's BGL at the time of the PET-imaging [9]. A lack of BGL-normalization however could in cases of large intra-patient BGL fluctuations lead to misinterpretations of the SUV time-trends [12,33–36]. Also, Siegel et al. performed only static PET-acquisition approximately 60 min after intravenous injection of FDG. The major drawback of static PET-imaging however is the time dependency of SUV determination because of continuous FDG uptake within the tumor for several hours after FDG injection [12,33]. The use of an identical time-interval between FDG injection and the start of PET-imaging is essential when performing sequential FDG-PET-CT-scans for metabolic response evaluations [12]. To overcome this time dependency, we additionally performed dynamic PET-imaging in the majority of the study patients. By looking at the average FDG uptake rate within the tumor, before reaching a plateau, instead of only at a SUV at a single time point, the time dependency of SUV determination no longer influences the time-trends of FDG uptake during therapy. Another important confounder in the use of PET-imaging is a peritumoral inflammatory reaction, as inflammatory cells are known to avidly consume FDG [11,37]. An increased FDG uptake by inflammatory cells in the direct neighborhood of the tumor can lead to an underestimation of the SUV decrease within the tumor [8,11]. To ensure a reliable comparison of the metabolic treatment response of the two treatment schemes without bias due to inflammatory reactions, only patients without a visually observable peritumoral inflammatory reaction were included in this study.

As described, the patients included in this study were treated according to the national guidelines with either short-course hypofractionated radiotherapy or radiochemotherapy, based on their clinical TNM stage and predicted CRM determined from MR-imaging. So, the included patients were not enrolled in a randomized two-arm trial. However, this was not expected to result in a bias of the results of this study. The patients diagnosed with locally advanced rectal cancer presented with higher tumor volumes compared to the patients diagnosed with non-locally advanced rectal cancer. Larger tumors are more likely to have hypoxic regions, being less sensitive to radiotherapy treatment. So, a possible bias would have more likely resulted in a higher metabolic treatment response in the smaller non-locally advanced rectal tumors treated with a high BED when compared to the larger locally advanced rectal tumors treated with a relatively low BED, which is the opposite of our findings.

In conclusion, already after the first week of radiochemotherapy, the metabolic activity of the tumor was found to decrease sig-

nificantly, which was not detectable early after treatment with radiotherapy alone, suggesting the chemotherapeutic agent Capecitabine as the primary initiator of the observed reduction of the tumors metabolic activity.

Conflict of interest statement

We are not aware of any actual or potential conflicts of interest.

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