Impact of third-line treatment with irinotecan plus cetuximab on non-tumor standardized uptake values in patients with metastatic colorectal cancer

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Abstract. The correct interpretation of metabolic response in cancer cells to therapy requires knowledge of how tumor-free tissue responds to the same treatment. The aim of this study was to evaluate standardized uptake values (SUVs) in tumor-free regions of patients with metastatic colorectal cancer prior to and following therapy, via the use of 18-fluoride fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography/computed tomography (PET/CT). On baseline 18F-FDG PET/CT scans (n=51), volumes of interest (VOI) were obtained from tumor-free tissue (aortic arch, liver and spleen) and SUVs normalized to total body mass were registered. The procedure was repeated for a follow-up scan two weeks following a single administration of the third-line treatment with irinotecan plus cetuximab. The mean differences in SUV prior to and following therapy were non-significant (P>0.05) in all the registered tumor-free regions. Correlation coefficients indicated a significant result between the variables (0.74-0.84; P<0.001). This study suggests that the early assessment of metabolic response may be made following the administration of third-line therapy with irinotecan plus cetuximab in patients with metastatic colorectal cancer refractory to second-line treatment with irinotecan.

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Introduction

With an estimated incidence of 333,330 cases in the European Union (2008) and reports of high mortality rates, colorectal cancer (CRC) is one of the most common causes of cancer-related mortality in the US and Europe (1). Metastatic disease is present in approximately 25% of patients at the time of diagnosis, with 50% of patients likely to develop metastases. The majority of these patients are unlikely to be available for surgical resection with a primary curative intention.

Therapy for advanced cancer, either on an individual basis or via clinical trials, may often be toxic to the patient and also costly and response rates are considered to be relatively low. The timely discontinuation of treatment is therefore crucial. The decision to continue, alter or terminate a specific treatment regimen is often based upon morphological imaging. The RECIST criteria (2,3) have, until the introduction of positron emission tomography (PET), been used as a 'gold standard' for response evaluation. Imaging of glucose metabolism in cancer cells with quantitative PET applying the glucose analog 18-fluoride fluoro-2-deoxy-D-glucose (18F-FDG), has emerged as a powerful tool (4-6), with numerous studies reporting a positive correlation between the tumor 18F-FDG uptake immediately following or during treatment and the clinical outcome. Changes in tumor metabolism may be observed prior to changes in tumor size, providing information that may be used for early individual risk assessment or as an early surrogate endpoint in a clinical trial.

The metabolic response on an 18F-FDG PET scan may be determined using qualitative and quantitative approaches. The most common method for quantifying FDG uptake is via the application of standardized uptake values (SUVs), which may be normalized to body mass, lean body mass or body surface area. Being relatively easy to access, SUVs have gained popularity in the clinic. Standardized protocols, including patient preparation, scanning procedure, image reconstruction and image analysis, are essential when patients are studied over a period of time or are participating in multicenter studies (7-10).

As changes in plasma glucose levels and/or differences in FDG plasma clearance among scans may interfere with the interpretation of SUV results (11,12), factors affecting these parameters should also be standardized. The European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) and the European Association of Nuclear Medicine have all made consensus recommendations with regard to SUV and the issues mentioned above (9,13,14). Although these recommendations are followed, studies assessing metabolic response to therapy also have to address the following consideration: SUVs in reproducible, tumor-free regions of interest (ROI) should be significantly consistent throughout therapy, therefore a significant change in tumor SUV would be indicative of a therapeutic metabolic response.

By using 18F-FDG PET/CT, the aim of this study was to evaluate SUVs in non-tumor volumes of interest (VOI) in patients with metastatic CRC refractory to second-line treatment with irinotecan just prior to and 2 weeks following a single administration of third-line therapy with irinotecan plus cetuximab.

Materials and methods

Selection and description of participants. The study occurred at a specialist cancer treatment center. Only patients with metastatic CRC participated in the study. The inclusion and exclusion criteria are listed in Fig. 1. A total of 51 patients (mean body weight, 74±18 kg; range, 47-132 kg; follow-up, 74±17 kg, range, 47-130 kg) underwent a baseline 18F-FDG PET/CT scan prior to a single administration of irinotecan (180 mg/m^2) plus cetuximab (500 mg/m^2). A follow-up scan was performed at two weeks following treatment. The procedure followed was according to a protocol approved by the Regional Ethics Committee of Copenhagen County and with the Helsinki declaration (2008). Oral and written informed consent from the patients were obtained prior to any patient participating in the study.

Methods. A dose of 4 MBq/kg (maximum 400 MBq) of 18F-FDG was injected intravenously (i.v.) following a minimum 6-h fast in patients with blood glucose levels <120 mg/dl. PET/CT data were acquired at 60 min post-injection (p.i.) on a GE Healthcare Discovery™ (Buckinghamshire, UK) VCT PET/CT scanner (15). A helical diagnostic CT scan was acquired with oral (E-Z-Cat® 0.9 l solution) and i.v. contrast (Ultravist® 370 mg I/ml) using a standard CT protocol with a scan field of view of 70 cm. Data were reconstructed with a standard filter into transaxial slices with a field of view of 50 cm, matrix size of 512x512 (pixel size 0.98 mm) and a slice thickness of 3.75 mm. The CT scan was followed immediately by a PET scan performed using a standard whole-body acquisition protocol with 6-7 bed positions, a slice overlap of 7 and an acquisition time of 2.5 min per bed position. The scan field of view was 70 cm. The attenuation correction was based on the CT scan. The PET data were reconstructed into transaxial slices with a matrix size of 128x128 (pixel size 5.47 mm) and a slice thickness of 3.75 mm using iterative 3D-OSEM (2 iterations, 28 subsets). Corrections for attenuation, randoms, dead time and normalization were carried out inside the iterative loop. Analyses of CT, PET and fused PET/CT data were performed using a GE Healthcare Volume Viewer® on a GE Healthcare Advantage Workstation® version 4.4. Approximately 10 cm^3 VOI was drawn in the aortic arch, in tumor-free liver and in the spleen and SUVs (maximum and mean) normalized to total body mass were registered for all regions. Baseline and follow-up data were obtained using the same PET/CT scanner. To avoid possible inter-observer bias, the same physician analyzed all scans (16,17).

Inclusion criteria:

- Age ≥18 years
- Histologically proven, irinotecan-resistant, metastatic colorectal cancer
- Former treatment with oxaliplatin
- Performance status (WHO) <3
- Life expectancy >3 months
- Normal hematological values (neutrophil granulocytes, thrombocytes, bilirubin and ASAT/ALAT)
- Oral/written informed consent

Exclusion criteria:

- Age <18 years
- Former or concurrent malignancy
- Pregnant and/or lactating women
- Patients not able to follow treatment and evaluation schemes
- Ongoing infection and/or concurrent serious medical illness
- Known hypersensitivity to any of the components in the treatment scheme
- Abnormal hematological values
- Lack of oral/written informed consent

Figure 1. Criteria for inclusion and exclusion.

Statistical analysis. Calculations of sample size and power were performed using the Altman nomogram (18). The minimal relevant difference (MIREDIF) in SUV was set to be equal to the standard deviation, yielding a standardized difference of 1.0. The power of the study was determined to be 0.94. Any other statistical analyses were performed using MedCalc 11.1.1® (Mariakerke, Belgium) and SPSS Statistics 17.0® (Chicago, IL, USA). The SUV results were compared with Gaussian distributions by applying the D'Agostino-Pearson omnibus test (19,20). The SUV measurements passed the test for normality ($P>0.05$). Paired samples t-test was used to compare two sets of results to assess whether there was any difference between the means. Correlation coefficients were calculated to measure the strength of correlation between variables. $P<0.05$ was considered to indicate a statistically significant result.

Results

The results of this study showed significantly consistent SUVs (SUV_{max} and SUV_{mean}) in the aortic arch, liver and spleen

Table I. Baseline SUVs prior to treatment.

Region (10 cm^3 VOI)	Mean ± SD	CI (95%)	Normal distribution (P-value)
Aortic arch SUV_{max}	1.66±0.37	1.55-1.76	0.66
Aortic arch SUV_{mean}	1.18±0.26	1.10-1.25	0.66
Liver SUV_{max}	2.13±0.50	1.99-2.27	0.16
Liver SUV_{mean}	1.58±0.34	1.49-1.68	0.62
Spleen SUV_{max}	1.83±0.48	1.70-1.97	0.07
Spleen SUV_{mean}	1.35±0.36	1.25-1.45	0.33

N=51. P<0.05 was considered to indicate a statistically significant result. Data were tested for normal distribution using the D'Agostino-Pearson omnibus test. SUV, standardized uptake value; SD, standard deviation; CI, confidence interval; VOI, volume of interest.

Table II. SUVs following treatment.

Region (10 cm^3 VOI)	Mean ± SD	CI (95%)
Aortic arch SUV_{max}	1.70±0.48	1.57-1.83
Aortic arch SUV_{mean}	1.20±0.34	1.10-1.29
Liver SUV_{max}	2.12±0.55	1.96-2.27
Liver SUV_{mean}	1.59±0.41	1.47-1.71
Spleen SUV_{max}	1.89±0.54	1.74-2.04
Spleen SUV_{mean}	1.35±0.39	1.24-1.46

N=51. SUV, standardized uptake value; SD, standard deviation; CI, confidence interval; VOI, volume of interest.

tumor-free regions prior to and 2 weeks following a single administration of third-line treatment with irinotecan plus cetuximab in patients with irinotecan refractory metastatic CRC (Tables I and II).

The mean differences were non-significant (P>0.05; Table III) in the aortic arch, liver and spleen regions of interest and SUV_{max} and SUV_{mean}. The correlation coefficients were significant (P<0.001; Table III), ranging from 0.74 to 0.84.

Discussion

Semi-quantitative analysis of glucose metabolism in tumors with 18F-FDG PET in the prediction of clinical outcome is gaining popularity (4-6), due to the evidence that changes in tumor metabolism may be observed prior to changes in tumor size. Knowledge of how tumor-free tissue responds to the same treatment regimen is required for the correct interpretation of metabolic response in cancer cells to therapy. Thus, a significant change in tumor SUV would be indicative of a therapeutic metabolic response if SUVs in reproducible, non-tumor ROI are consistent throughout therapy. Response rates to therapy for metastatic colorectal cancer are markedly low and a swift individual assessment for different treatment regimens is crucial.

Assuming all consensus recommendations with regard to data acquisition and patient preparation are fulfilled (9,13,14), this study demonstrates significantly consistent SUVs (both SUV_{max} and SUV_{mean}) in three different tumor-free regions (aortic arch, liver and spleen) prior to and 2 weeks following a single administration of third-line treatment with irinotecan plus cetuximab in patients with irinotecan refractory metastatic CRC. This study provides the fundamental data needed for studies focusing on the early assessment of therapeutic response in these patients with this specific treatment regimen.

Table III. Comparison of SUV prior to and following treatment (paired samples t-test and test of correlation).

Region (10 cm^3 VOI)	Mean difference ± SD	CI (95%)	P-value	Correlation	P-value
Aortic arch SUV_{max}	-0.045±0.32	-0.135-0.045	0.32	0.74	<0.001[a]
Aortic arch SUV_{mean}	-0.022±0.23	-0.086-0.042	0.50	0.74	<0.001[a]
Liver SUV_{max}	0.010±0.30	-0.074-0.094	0.82	0.84	<0.001[a]
Liver SUV_{mean}	-0.006±0.26	-0.080-0.068	0.87	0.77	<0.001[a]
Spleen SUV_{max}	0.053±0.33	-0.145-0.039	0.25	0.80	<0.001[a]
Spleen SUV_{mean}	-0.004±0.24	-0.072-0.064	0.91	0.80	<0.001[a]

N=51. [a]P<0.05 was considered to indicate a statistically significant result. SUV, standardized uptake value; SD, standard deviation; CI, confidence interval; VOI, volume of interest.

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