Original Article

Is early response by ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography a predictor of long-term outcome in patients with metastatic colorectal cancer?

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Background: Identify in advance responder patients to chemotherapy in metastatic colorectal cancer (CRC) would allow prompt interruption of ineffective therapies in non-responder patients. Hence, predictive markers are sought in numerous trials to detect responder patients, including tumor shrinkage measured by imaging methods. Usually, Response Evaluation Criteria in Solid Tumors (RECIST) is used to evaluate tumor response in metastatic CRC, but these criteria are questionable with use of biological agents associated to chemotherapy. Our aim was correlate early metabolic response by ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (^{18}FDG-PET-CT) with long-term outcome in metastatic CRC in first-line therapy.

Methods: We prospectively evaluated 36 patients with metastatic CRC in first-line treatment with 5-fluorouracil, leucovorin (folinic acid), oxaliplatin (FOLFOX) or 5-fluorouracil, leucovorin (folinic acid), irinotecan (FOLFIRI) associated with cetuximab or bevacizumab. ^{18}FDG-PET-CT was performed at baseline and after two cycles of chemotherapy. The early metabolic response [standardized uptake value (SUV)] was measured to identify responder and non-responder patients and correlated with overall survival (OS) and progression-free survival (PFS).

Results: Median age was 58.5 years (range, 41–74 years). PFS was 15.5 months for responder and 13.3 months for non-responder (P=0.42), OS was 55.7 months for responder and not reached for non-responder. There was no correlation between delta-SUV and clinical and pathological variables analyzed. In the subgroup of patients who did not undergo resection of metastasis (45%), PFS was higher for responders (15.3×6.8 months, P=0.02).

Conclusions: According to our findings, early response by ^{18}FDG-PET-CT was not a predictor of long-term outcome for patients with metastatic CRC treated in the first-line chemotherapy with a monoclonal antibody.

Keywords: Metabolic response; colorectal cancer (CRC); positron emission tomography

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Introduction

Colorectal cancer (CRC) is the third most common cancer in developed countries and is the second commonest cause of cancer deaths. CRC is highly treatable and often curable when localized to the bowel, however in metastatic or recurrent CRC the treatment is palliative (1).

The treatment of metastatic CRC is based on chemotherapy with fluoropyrimidine and oxaliplatin or irinotecan (2-5), associated with monoclonal antibodies: bevacizumab, cetuximab, panitumumab or the antiangiogenic agent aflibercept (6-11). Systemic treatment in metastatic CRC is not a curative approach, except when complete resection of metastases is feasible, leading to longer survival (12). Identifying responder patients to chemotherapy regimen is a critical goal in solid tumors, once this approach can save non-responders from long and toxic treatments, optimizing treatment selection.

The standard response assessment method in Medical Oncology is Response Evaluation Criteria in Solid Tumors (RECIST) (13,14), using tumor measurement by conventional imaging: computed tomography or magnetic resonance imaging (MRI). However, the accuracy of RECIST has been questioned with the use of biological agents, whereas they are more cytostatic than cytotoxic drugs, there can be tumor shrinkage without size changing due to post-therapy fibrosis (15). Furthermore, it can take long period to observe response in anatomic imaging, usually performed after eight weeks of treatment. The ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (^{18}FDG-PET-CT), as a technique to evaluate metastatic lesions in a metabolic scenario, appears attractive to assess early response. Currently ^{18}FDG-PET-CT has been used in metastatic CRC for staging before surgery, restaging and recurrence localization in patients with high serum carcinoembryonic antigen levels (CEA) and normal conventional imaging (16,17).

^{18}FDG-PET-CT is an imaging that quantifies the metabolic process in cancer cells; hence, it indirectly measures cellular proliferation and the effectiveness of the treatment (18,19).

^{18}FDG-PET-CT has established role in the early response evaluation in lymphoma, breast cancer, localized rectal cancer and operable metastatic CRC (20-25). PET-CT findings can induce treatment changes in metastatic CRC patients, but it lacks robust trials in the current context of new therapies with biological agents (26,27). de Geus-Oei *et al.* investigated response with FDG-PET-CT after two months of chemotherapy in metastatic colorectal patients. It was observed increasing in progression and death rates in the patients with worse metabolic response (28). They had previously demonstrated that in colorectal liver metastases a low FDG uptake prior the treatment predict a benefit survival (29).

Tam *et al.* had also observed that in liver colorectal metastases patients, a high standardized uptake value (SUV) prior therapy correlated to a shorter progression free survival (PFS), independently of other prognostic factors (30). However this analysis was retrospective and the PET-CT was not used for measure tumor response after chemotherapy.

Byström *et al.* studied PET-CT response after two cycles of chemotherapy without monoclonal antibody. There was no correlation between metabolic response and time to progression or overall survival (OS) (31).

Hendlisz *et al.* analyzed the impact of PET-CT after one cycle of chemotherapy [5-fluorouracil, leucovorin (folinic acid), irinotecan (FOLFIRI), 5-fluorouracil, leucovorin (folinic acid), oxaliplatin (FOLFOX) or capecitabine] in metastatic CRC and showed relation between metabolic response and OS. Nevertheless only 16% of these patients had used biological drugs associated to chemotherapy (32).

Recently, Lastoria *et al.* evaluated thirty-one patients with liver metastases from CRC, receiving pre-operative treatment with FOLFIRI and bevacizumab. They found association between metabolic responses based on FDG-PET-CT after one cycle and PFS and OS (33).

In sum, the previous trials had included heterogeneous chemotherapeutic regimens without biological agents in the majority of the patients and used different metabolic response criteria, except the latest study by Lastoria *et al.* However, their population is a select group with resectable liver metastases treated with a unique schema of chemotherapy (*Table 1*).

The aim of this present study was to evaluate the prognostic value of early response by FDG-PET-CT in metastatic CRC patients on first-line chemotherapy with monoclonal antibodies.

Methods

Patients

This study included patients with metastatic CRC, aged 18–75 years old, with Eastern Cooperative Group performance status of 0 or 1, scheduled to receive first-line treatment

Table 1 Comparison of PET-CT response trials in metastatic CRC

Trial	Trial Characteristics	N	Treatment regimen	PET schedule	Response criteria	Results
de Geus-Oei *et al.* [2008] (28)	Prospective	50	Irinotecan ± capecitabine; oxaliplatin + 5 FU or capecitabine; bevacizumab or cetuximab	Baseline and after 2 and 6 months	Decrease SUV >25%	Correlation between metabolic response and OS and PFS
Byström *et al.* [2009] (31)	Prospective	51	Irinotecan/5 FU/leucovorin	Baseline and after two cycles	Decrease SUV >25%	PET failed to reflect long-term outcome
Hendlisz *et al.* [2012] (32)	Prospective	41	FOLFIRI, FOLFOX or capecitabine	Baseline and after one cycle	Decrease SUV >15%	Correlation between metabolic response and OS
Lastoria *et al.* [2013] (33)	Prospective	31	FOLFIRI + bevacizumab	Baseline and after one cycle	Decrease SUV ≥50%	Correlation between metabolic response and OS and PFS

FOLFOX, 5-fluorouracil, leucovorin (folinic acid), oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin (folinic acid), irinotecan; CRC, colorectal cancer; SUV, standardized uptake value; OS, overall survival; PFS, progression-free survival; PET-CT, positron emission tomography-computed tomography.

with chemotherapy associated with a monoclonal antibody at AC Camargo Cancer Center, in the Medical Oncology Department, from March 2009 to October 2011.

The Institutional Review Board of AC Camargo Cancer Center approved the study and written informed consent was obtained from all patients.

All patients had histopathological diagnosis of colorectal adenocarcinoma, including the *KRAS* status analysis (codons 12 and 13) and at least one metastatic lesion on computed tomography or MRI.

Treatment

The Chemotherapy schema were based on physician's choice and administered intravenously every 14 days: FOLFIRI-irinotecan (180 mg/m^2 intravenous infusion on day 1), leucovorin (200 mg/m^2 intravenous infusion on day 1), 5-fluorouracil (400 mg/m^2 by intravenous bolus on day 1), and 5-fluorouracil (2,400 mg/m^2 46-h continuous infusion) or FOLFOX-oxaliplatin (85 mg/m^2 intravenous infusion on day 1), leucovorin (200 mg/m^2 intravenous infusion on day 1), 5-fluorouracil (400 mg/m^2 by intravenous bolus on day 1), and 5-fluorouracil (2,400 mg/m^2 46-h continuous infusion); bevacizumab was administered at 5 mg/kg by intravenous infusion over 90 min, at the first cycle, then, if tolerated, over 60 min or cetuximab was administered at 400 mg/m^2 as initial dose and 250 mg/m^2 weekly or every two weeks at 500 mg/m^2 as intravenous infusion over 120 min.

Imaging evaluation with CT or MRI was performed according to physician's judgment and analyzed by expert radiologists using RECIST criteria.

^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (^{18}FDG-PET-CT)

The patients underwent the first ^{18}FDG-PET-CT before starting the treatment in addition to conventional images (CT or MRI) of chest, abdomen and pelvis, besides routine laboratory tests. A second PET-CT was performed immediately before the third cycle of therapy, from twenty-five to thirty days after the beginning of treatment.

The images were obtained on a Gemini PET/CT (Philips Medical Systems) with whole-body PET scanner. The patients fasted for at least 6 hours prior PET imaging. Serum glucose level was measured and it had to be lower than 200 mg/dL for all patients. After that, the patients received an intravenous injection of 5.0 megabecquerels per kilogram (MBq/Kg) of ^{18}F-FDG, and the first images were acquired approximately 90 min after the radiotracer injection. The patients were laid in supine position during the study, and were comfortably positioned on the scanner table with both arms at their side.

The regions of interest (ROIs) were manually drawn on the slice with the highest radioactivity concentration. The lesions were analyzed using the maximum SUVmax method, which was defined as the maximum tissue concentration of

Table 2 Patients' characteristics

Characteristics	Number of patients	Percentage (%)
Median age	58.5 years (41–74 years)	
Sex		
Men	19	53
Women	17	47
Histology		
Adenocarcinoma	32	89
Mucinous adenocarcinoma	4	11
KRAS status (codons 12 and 13)		
Wild-type	22	61
Mutated	13	37
Unknown	1	2
Chemotherapy regimen		
FOLFIRI	23	64
FOLFOX	13	36
Monoclonal antibody		
Bevacizumab	21	59
Cetuximab	14	39
None	1	2
Metastases resection	19	55
Location of metastasis		
Liver	28	78
Lung	5	14
Lymph nodes	9	25
Peritoneum	2	5
Pelvis	2	5

FOLFOX, 5-fluorouracil, leucovorin (folinic acid), oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin (folinic acid), irinotecan.

FDG (fluor-deoxyglucose) in the ROI. The SUV max was calculated by the formula: tissue concentration (MBq/g)/injected dose (MBq)/body weight (g).

An experienced nuclear medicine physician interpreted the whole-body PET images, and was blinded for patient's history, clinical findings, and conventional imaging.

It was considered the difference the two ^{18}FDG-PET-CT for the early response assessment (delta Δ SUV). In patients with multiple metastases, it was chosen randomly three to five lesions with ^{18}FDG-PET-CT uptake. Patients with less than five lesions: all the lesions were evaluated. European Organization for Research and Treatment in Cancer (EORTC) criteria for PET-CT were used: partial response is when delta SUV drop more than 25%, disease progression is when delta SUV increases more than 25% or appearance of new metastatic lesions and stable disease when the SUV decrease be less than 25% or the increase be less than 25% (34).

A responder patient was defined as someone that had partial or complete response.

Statistical analysis

Demographic and clinical characteristics were summarized by medians and frequencies (*Table 2*). PFS was defined as the interval between diagnosis of metastasis and first documentation of progression or death. OS was calculated from diagnosis of metastasis to date of death due to any reason. Patients alive were censored at the last time point.

Differences in OS and PFS were estimated using the Kaplan-Meier Method and were compared between the groups by log-rank test. SPSS for Windows version 22.0 was used for data analysis (SPSS Inc., Chicago, IL, USA).

Pathological and clinical variables (age, sex, histologic subtypes, *KRAS* status, chemotherapy regimen, monoclonal antibody, resection of metastases and response by RECIST) were correlated with changes in SUV, as well as OS and PFS. Fisher's method was used to correlate response by ^{18}FDG-PET-CT and demographics parameters. The level of significance was set at 0.05.

Results

Patients' characteristics

Thirty-six patients with metastatic CRC were included in this prospective trial, with a median age of 58.5 years (range, 41–74 years). Demographic characteristics and treatment regimens are showed in *Table 2*. Five patients started monoclonal antibody only in the second cycle of chemotherapy, one patient started after the second cycle and another patient did not use monoclonal antibodies, the last two patients were excluded from analysis. Statistical analysis was performed with thirty-four patients that had used monoclonal antibody since the first or second cycle of chemotherapy. Complete metastases resection was controlled as covariate for the measurement of delta SUV cut-off value (35).

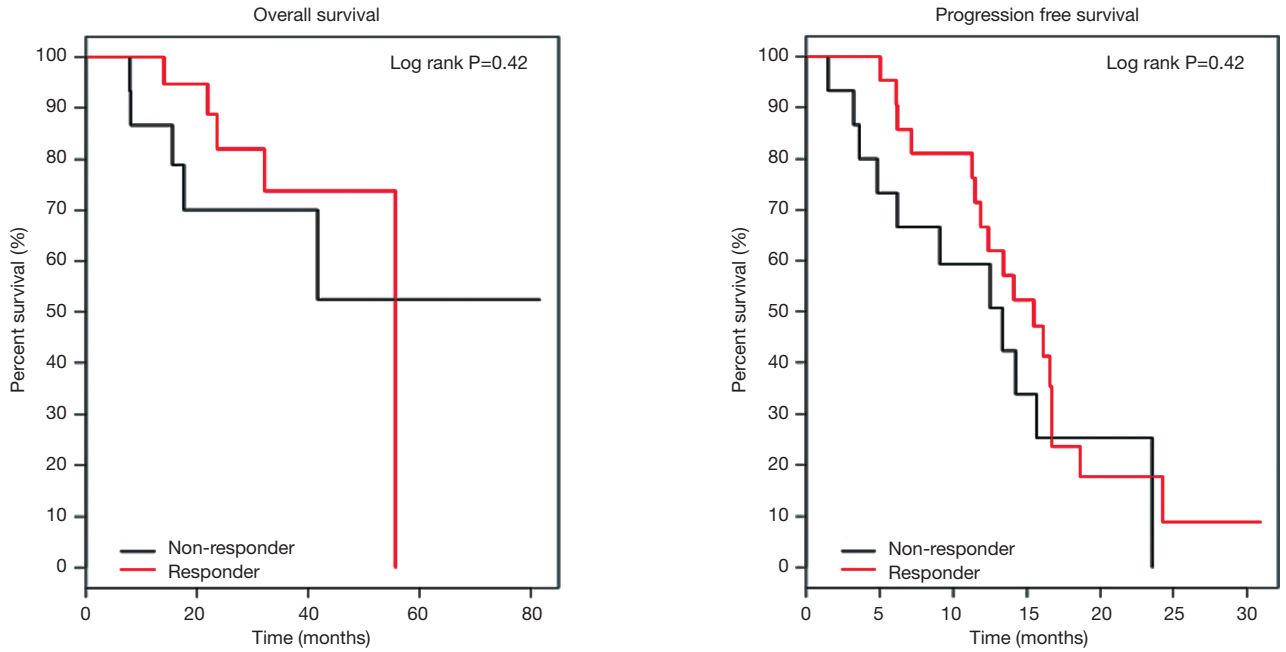

Figure 1 Kaplan-Meier curves according to PET-CT response by EORTC criteria (Δ SUV 25%): overall survival (OS) and progression-free survival (PFS). PET-CT, positron emission tomography-computed tomography; EORTC, European Organization for Research and Treatment in Cancer; SUV, standardized uptake value.

^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (^{18}FDG-PET-CT)

Based on EORTC criteria for ^{18}FDG-PET-CT response evaluation, there were 82% responder patients and 18% non-responder patients. With median follow-up of 24 months, there is no difference in PFS (15.5 *vs.* 13.3 months, P=0.42) neither OS (55.7 months and not reached for non-responders, P=0.42) between responders and non-responders (*Figure 1*).

None of the variables (*KRAS* status, histology subtype, early response by ^{18}FDG-PET-CT and chemotherapy regimen) was predictor of tumor progression in this series. Late response evaluation by conventional imaging (CT or MRI) was predictive of worse PFS (RR =8.12, P<0.01) and worse OS (RR =10.81, P<0.01) for non-responder patients, and metastases resection was a good prognostic factor.

Considering different thresholds for SUV response in the previous trials that evaluated metabolic response, for this population, it was identified a predictive SUV cut-off value by the method of Martingale-Residual (35). It was found a cut-off value of 55% for OS and 60% for PFS. Even thus, the curves of OS and PFS did not show difference between responder and non-responder patients.

As the majority of our patients (55%) were submitted to liver metastases resection, and this has a remarkable effect in prognosis, it was done an unplanned analysis of patient subgroup that had not had surgery. In fifteen patients, using the cut-off delta SUV <–60% for PFS, we had four responder patients and eleven non-responders (*Figure 2*). PFS for responder was 15.3 *vs.* 6.8 months for non-responders patients (P=0.02). OS was 21 months for responder and 15 months for non-responder patients (P=0.86).

Discussion

Apart from *KRAS* and *NRAS* mutation status, that selects potential responder patient to anti-epidermic growth factor receptor (EGFR) therapy, there are no more biomarkers available in daily practice for metastatic CRC. Therefore, early tumor shrinkage has been studied as a marker of response in metastatic CRC. It is a challenge selecting non-responder patients to change therapy prematurely, avoiding toxicity and excessive cost without negatively affecting PFS and OS (36). A questionable point is: which is the most suitable method to response evaluation with biological drugs? Antiangiogenic agents cause interstitial remodeling

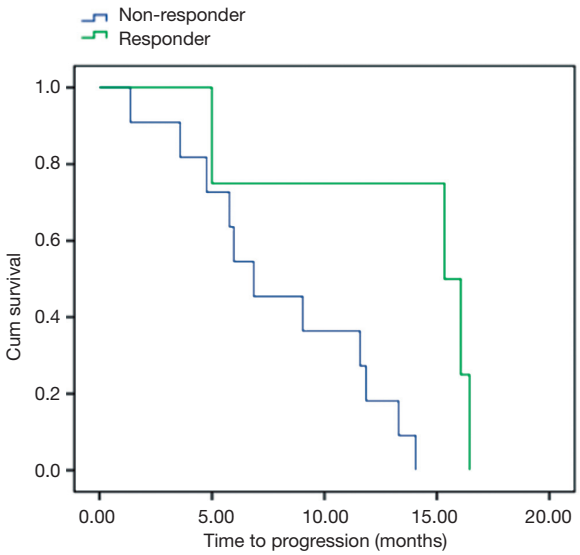

Figure 2 PFS curve of non-candidate patients for metastases resection considering SUV decrease of 60% (green line: responder; blue line: non-responder). SUV, standardized uptake value; PFS, progression-free survival.

and tumor activity decreasing without change in tumor diameters. ^{18}FDG-PET-CT, as a metabolic imaging, seems extremely attractive to predict effectiveness of treatment in metastatic CRC.

In Non-Hodgkin lymphoma, PET-CT is standard as response predict after one or two cycles of chemotherapy. In some protocols, patients that have negative PET after two cycles of chemotherapy can be treated with less intensive regimen (37).

In CRC, Piessevaux *et al.* reported the impact of tumor decreasing more than 20% in PFS and OS in patients with wild-type *KRAS* mCRC treated with cetuximab plus FOLFIRI or FOLFOX-4. Different from our study, this analysis was done with conventional imaging at eight weeks from beginning of treatment (38). Choi *et al.* showed in advanced CRC patients that absence of FDG uptake on follow-up PET scans was associated with markedly longer OS and time to progression in this population (39).

Early PET-CT response is still investigational in metastatic CRC. Questions to be answered are the standardization of PET-CT response criteria, time to perform PET-CT, number of lesions to be evaluated and how to interpret the response of different biological agents (antiangiogenic and anti-EGFR drugs).

We evaluated early metabolic response by ^{18}FDG-PET-CT as a predictor of long-term outcome in metastatic CRC patients treated in first line with chemotherapy plus monoclonal antibodies and we did not find positive correlation, following the negative results after two cycles of chemotherapy (without monoclonal antibodies) reported by Byström *et al.* (31). Some hypothesis can explain these findings: metabolic response after two cycles can be transient and right after the tumor develops resistance and long-term clinical results can not be predictable; besides that, SUV threshold and PET-CT timing are not standard through the prospective studies, and the majority of patients have partial response or stable disease with first line therapy, therefore PET-CT may not make difference in the first line response assessment. Other confounding factor is the heterogeneity of metabolic response within body tumor load. In a recent trial, in metastatic CRC patients treated with capecitabine and sorafenib, a PET-CT performed after the first cycle of therapy with at least one metabolically refractory lesion is associated with poor outcome (40).

An interesting result in the present study is the unplanned analysis of the patients had not submitted to metastases resection. In this group, early responder patients had longer PFS comparing to non-responder patients (15.3 *vs.* 6.8 months, P=0.02). For this analysis it was considered the Δ SUV of −60%, notwithstanding there were few patients in this trial. This threshold is higher than EORTC criteria and up to now the most appropriate cut-off values and standardization for PET-CT is under investigation. This point is pertinent and need to be confirmed by large prospective trials. Considering metastases resection a common practice in metastatic CRC, future studies should investigate the real value of PET-CT in non-operable patients and use PFS as primary endpoint, and the positive impact of PET-CT in this population need to be confirmed.

Conclusions

According to our findings, early metabolic response by ^{18}FDG-PET-CT is not a predictor of long-term outcome for patients with metastatic CRC treated in the first-line chemotherapy with a monoclonal antibody. Our results are, of course, limited by small sample size. For patients with no-resectable metastases, we found a better PFS for responders. However, we cannot draw conclusions for this subgroup, once this analysis was not planned.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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