FDG-PET for prediction of survival of patients with metastatic colorectal carcinoma

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Background: The current study focuses on the prognostic value of pretreatment metabolic activity in metastases as measured with [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET), as an indicator of survival in colorectal cancer.

Patients and methods: In a prospective series of 152 patients with metastatic colorectal cancer, of whom 67 were treated with resection of metastases and 85 with chemotherapy, standardized uptake values (SUV) as measured with FDG-PET, were calculated prior to treatment. Survival probabilities were estimated by Cox proportional regression analysis. For Kaplan–Meier analysis SUV was stratified by the median value. Survival differences were assessed using the log-rank test.

Results: SUV in metastases was a significant predictor for overall survival (hazard ratio 1.17, 95% confidence interval 1.06–1.30, P = 0.002), independent of the subsequent treatment. According to the median value of the patient population a low (SUV <4.26) and high uptake group (SUV >4.26) was defined. The median survival and the 2- and 3-year survival rates were 32 months, 59% and 45%, respectively, in the low-uptake group and 19 months, 37% and 28%, respectively, in the high-uptake group (P = 0.017).

Conclusion: A significant survival benefit was observed in patients with low FDG uptake in metastases of colorectal cancer.

Key words: FDG-PET, metastatic colorectal cancer, prognostic value, SUV

Introduction

In Europe and in the United States, each year more than 150,000 people develop metastases from colorectal carcinoma [1]. The prognosis has improved substantially with the introduction of hepatic resection for treatment of isolated liver involvement and of effective chemotherapeutic agents. Over the past 10 years, median survival times for patients with advanced colorectal carcinoma have almost doubled, ranging from 20 months for patients with less favorable prognostic factors up to 50 months in patients with the most favorable prognostic factors [2–4]. Several chemotherapeutic agents can be combined, such as fluoropyrimidines, irinotecan and oxaliplatin, chemotherapy can be given alone or in combination with molecular-targeted agents such as cetuximab or bevacizumab, and one can vary in duration and sequence of therapy [4]. Furthermore, in the past two decades remarkable progress was made regarding the surgical techniques and postoperative management of major hepatic surgery [5, 6]. Consequently, the indications for hepatectomy have been extended. As individualized treatment strategies become more relevant, there is a need for identification of novel biologic pretreatment factors that potentially predict outcome, to ensure that patients benefit from hepatic surgery, novel anticancer therapies and intensive treatment combinations. These pretreatment factors may be of particular value in stratifying patients for clinical trials. Therefore, there is growing interest in metabolic imaging of cancers.

Many malignancies, including colorectal carcinoma, have increased glucose metabolism. They accumulate the positron-emitting glucose analog [¹⁸F]fluorodeoxyglucose (FDG) and can thus be visualized using positron emission tomography (PET). Previous studies clearly indicated that FDG-PET is of value in the diagnostic work-up of patients with colorectal liver metastases and that FDG-PET as a complementary staging method improves the therapeutic management, especially by detecting unsuspected extraphepic disease [7–9]. A recent study reported on therapy response monitoring with FDG-PET and the biologic basis of the change of tumor FDG uptake in patients treated with neo-adjuvant chemotherapy [1]. Several investigators have speculated that the amount of FDG uptake correlated with biologic factors such as Ki-67, proliferating cell...
nuclear antigen, Glut-1 and hexokinase [1], and that FDG uptake resembles the biological behavior of the tumor and might be associated with intrinsic biologic characteristics, like hypoxia [10], low apoptosis rate [11], cell viability [12], proliferative activity [13] and p53 overexpression [14]. These characteristics are all potentially adverse factors in patients treated with radiotherapy or chemotherapy, while some of them may also impact negatively in patients treated surgically.

The advantage of FDG-PET is that it is a non-invasive, in vivo method that cannot only visualize, but can also quantify FDG uptake to distinguish metabolically active from less active tumor. This quantitative analysis of FDG uptake can be done before any treatment has been performed. In the current study, the predictive value of quantitative pretreatment FDG uptake for patient prognosis in metastatic colorectal carcinoma was investigated. If the amount of FDG uptake in metastases of colorectal carcinoma is of prognostic significance, this diagnostic modality could be an important adjunct to traditional staging and could improve appropriate selection of high-risk candidates for aggressive therapies and treatment combinations and could be useful as an early indicator of tumor chemo-sensitivity, which could help to refine therapeutic strategies.

patients and methods

patients
From 2000 to 2005, a prospective series of 152 patients with histologically proven metastatic colorectal cancer (64 female, 88 male patients; mean age 61.6 years, range 33–86 years) underwent FDG-PET in the diagnostic work-up before a decision was made between surgical resection of metastases or treatment with chemotherapy. Exclusion criteria were poorly regulated diabetes mellitus and pregnancy. Follow-up closed on 1 December 2005.

FDG-PET
A dedicated PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA) was used for data acquisition. Prior to FDG injection, patients fasted for at least 6 h. One hour after intravenous injection of 200–220 MBq FDG (Mallinckrodt Medical, Petten, The Netherlands), emission and transmission images were acquired. The images were corrected for attenuation and reconstructed using the ordered-subsets expectation maximization (OSEM) algorithm.

FDG-PET analysis
All patients underwent FDG-PET within 6 weeks prior to treatment. Two experienced nuclear medicine physicians primarily interpreted FDG-PET images for staging on the basis of a visual inspection. For this study, all studies were reanalyzed to acquire semiquantitative data. For that purpose volumes of interest were drawn around all metastases using an automatic 50% isocontour (ECAT software tool), which enclosed pixels with 50% or more of the maximum radioactivity within the volume of interest. Standardized uptake values (SUV) were calculated using the concentration of FDG in the volume of interest as measured by PET, divided by the injected dose and multiplied by body weight as a normalization factor. A volume weighted mean value of each PET scan was derived from all lesions to give one average SUV (SUV<sub>avg</sub>, hereafter SUV) for each PET scan. Survival data served as a reference for the FDG-PET data.

treatment
Surgical decision-making, as well as the decision for chemotherapy, was made by a multi-disciplinary team including surgeons, medical oncologists, radiation oncologists, pathologists, radiologists and nuclear medicine physicians for all patients. Resection of metastases was considered the treatment of choice in case CT and FDG-PET indicated resectable liver metastases and/or less than three resectable lung metastases in the absence of other extraperitoneal disease. Hepatic causes for irresectability included involvement of major blood vessels or extensive bilobar liver disease, which would either preclude negative resection margins or would result in inadequate hepatic reserve. After curative surgery, patients were considered to be free of disease. Curative liver resection was defined as any procedure (resection, radiofrequency ablation or the combination of both) that rendered the patient free of all hepatic disease. Patients not eligible for surgery were treated with 5-fluorouracil (5-FU) based chemotherapy in combination with leucovorin (LV), capcitabine, irinotecan or combination therapy (capcitabine with irinotecan or 5-FU with oxaliplatin and LV) as first-line treatment. Irinotecan or capcitabine in combination with oxaliplatin was given as second-line treatment.

clinical follow-up
Overall survival was defined as the time interval from date of FDG-PET until death related to malignancy or date of last follow-up. In the surgically treated patient group, disease-free survival was also estimated. Disease-free survival was defined as the time interval between FDG-PET and the first recurrence of the disease (local-regional or distant recurrence). Follow-up was performed according to a stringent protocol for 3 years. Apart from clinical examinations, routine laboratory tests and carcinoembryonic antigen (CEA) measurement, patients underwent a CT scan of the abdomen every 3 months and a CT scan of the chest every 6 months and, in cases of inconclusive findings on CT, an additional FDG-PET scan, an ultrasound and/or MR scan was performed. For the surgically treated group the variables that form the prognostic scoring system according to Fong et al. [15] (node-positive primary, disease-free interval from primary to metastases, number of liver metastases, diameter of the largest liver lesion, and the preoperative CEA level) were also recorded prospectively. These five variables were dichotomized into a low- and a high-risk category. A patient variable was assigned to the high-risk category if the disease-free interval was 12 months or more after resection of the primary tumor, if the number of liver lesions was more than one, if the largest liver lesion was more than 5 cm, if the primary tumor was node-positive and if the preoperative CEA level exceeded 200 ng/ml. The clinical risk score according to Fong et al. assigns each of the five criteria one point if it is part of the high-risk category, resulting in a score of zero to five.

statistical analysis
The predictive value of SUV for overall and disease-free survival was determined. The main end point was overall survival. Overall and disease-free survival probabilities were estimated by the univariate Cox regression analysis and the estimated hazard ratio and 95% confidence interval (CI) were reported. SUV, disease-free interval from the primary to discovery of the liver metastases (months), number of liver metastases, diameter of the largest liver lesion (cm) and the preoperative CEA level (ng/ml) were analyzed as continuous variables. Invasiveness of the primary tumor (pT), nodal status of the primary (pN) and the histologic grade of the primary were analyzed as categorical variables. The overall survival curve with respect to SUV was generated using Kaplan–Meier estimates. SUVs were stratified by the median value to avoid data-driven significance for the cut-off level. Significance of the differences between the low and high SUV group was assessed using the log-rank test. Spearman’s rho correlations were used to determine associations between the SUV and the degree of tumor cell.
differentiation of the liver metastases and the SUV and the Fong’s score. Statistical analyses were performed using the SPSS 12.0.1 package. Statistical tests were based on a two-sided significance level and the level of significance was set at 0.05.

results

patients

The median follow-up was 17 months (range 2–61 months) for surviving patients. At the closeout date 71 of the 152 patients had died. No patients were lost to follow-up. Assessment of preoperative CT and FDG-PET revealed that most patients had metastatic involvement of the liver (n = 149). Lung metastases were found in 14 patients. The histological tumor type was adenocarcinoma in 134 patients, mucinous adenocarcinoma in three patients, adenocarcinoma with some mucinous components in 13 patients, adeno-acanthoma in one patient and adenocarcinoma with neuroendocrine morphology in one patient. In 67 patients, liver surgery with curative intent was performed, using resection (n = 42), radiofrequency ablation (n = 9) or resection combined with radiofrequency ablation (n = 16). Four out of these 67 patients received chemotherapy postoperatively. In 85 patients, metastases were not resectable. In first-line treatment these patients received capectabine, irinotecan or combinations of capectabine and irinotecan or 5-FU (with or without oxaliplatin) and LV (n = 72). In second-line treatment patients received irinotecan or capectabine in combination with oxaliplatin (n = 13).

survival

In the surgically treated patients disease-free survival was estimated using the Fong-criteria as an independent variable (Table 1). During follow-up 35 out of the 67 surgically treated patients presented with recurrent disease and 32 remained disease-free. The aggregated Fong-criteria proved to be a predictor for disease-free survival (hazard ratio 1.75, 95% CI 1.24–2.47, P = 0.002) as shown in Table 1. The individual variables that are assessed in the prognostic scoring system of Fong were not predictive for recurrence or survival (Table 1). There was no association between SUV and Fong’s score (r = −0.006, P = 0.96) or between SUV and the degree of tumor cell differentiation of the liver metastases (r = 0.04, P = 0.66). Median overall survival in the whole group was 15.5 months (range 1–61 months). Median overall survival in the surgery group was 22 months (range 2–61 months), which was significantly longer than the median survival in the chemotherapy group (12 months, range 1–54 months, P < 0.001).

FDG uptake

For the whole study population, the mean and median of the SUV were 4.33 and 4.26, respectively (range 0.5–12.14). In the group of patients who underwent curative liver surgery (n = 67), the mean and median of the SUV were 3.65 and 3.60 (range 0.80–9.60). In the chemotherapy group (n = 85), the mean and median of the SUV were 4.86 and 4.66 (range 0.50–12.14), being significantly higher than in the surgery group (P < 0.03). The mean SUV in the group of patients, who remained free of disease after hepatic resection, was not significantly different from the mean SUV in the group of patients with recurrent disease after hepatic resection (3.47 ± 1.69, n = 35 versus 3.84 ± 1.96, n = 32, respectively).

prediction of survival by FDG-PET

Although median SUV proved to be higher in the group of patients treated with chemotherapy compared with patients treated by surgery, the SUV of individual patients proved to be highly variable and largely overlapping in both groups. Therefore, SUV of metastatic lesions was evaluated for the whole group. SUV of the metastases proved to be an independent and significant predictor for overall survival (hazard ratio 1.17, 95% CI 1.06–1.30, P = 0.002), irrespective of the subsequent choice of therapy (i.e. surgery or chemotherapy). A one-unit increase in SUV corresponded to a 17% increase in the risk of death. To generate Kaplan–Meier survival curves, SUV values were dichotomized at 4.26, being the median value of the study cohort. The Kaplan–Meier survival analysis further confirmed the value of SUV to predict survival, as the difference in survival was highly significant (P = 0.017, log-rank test, Figure 1). The 2-year survival rates according to Kaplan–Meier were 59% in the low-upgrade group (SUV <4.26) and 37% in the high-upgrade group (SUV >4.26); the 3-year survival rates were 45% in the low-upgrade group and 28% in the high-upgrade group. Median survival in the low-upgrade group was 32 months.

Table 1. Results of univariate Cox proportional regression analysis for predicting overall survival and disease-free survival in the surgically treated group (n = 67)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall survival</th>
<th></th>
<th>Disease-free survival</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>P value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>pT</td>
<td>1.34</td>
<td>0.47–3.78</td>
<td>0.59</td>
<td>1.87</td>
</tr>
<tr>
<td>pN (dichotomized N0 versus N1–3)a</td>
<td>0.93</td>
<td>0.47–1.84</td>
<td>0.82</td>
<td>1.01</td>
</tr>
<tr>
<td>CEA preoperative (ng/ml)a</td>
<td>1.11</td>
<td>0.81–1.52</td>
<td>0.51</td>
<td>1.13</td>
</tr>
<tr>
<td>Disease-free interval (month)a</td>
<td>0.99</td>
<td>0.94–1.04</td>
<td>0.62</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of liver metastasesa</td>
<td>0.97</td>
<td>0.78–1.20</td>
<td>0.76</td>
<td>1.03</td>
</tr>
<tr>
<td>Largest liver lesion (mm)a</td>
<td>1.25</td>
<td>0.54–2.90</td>
<td>0.60</td>
<td>0.88</td>
</tr>
<tr>
<td>Histologic grade of primary tumor</td>
<td>0.85</td>
<td>0.52–1.36</td>
<td>0.49</td>
<td>1.12</td>
</tr>
<tr>
<td>Fong criteria</td>
<td>1.34</td>
<td>0.80–2.22</td>
<td>0.27</td>
<td>1.75</td>
</tr>
</tbody>
</table>

aVariables that are assessed in the prognostic scoring system according to Fong et al.
have a much poorer outcome than patients with resectable avid (i.e. the most aggressive) lesion. 

observed when analyzing all metastases or only the most FDG uptake group. Comparable survival rates and hazard ratio were survival of 32 months, compared with 19 months in the high-uptake group (mean age 62.0 years, 31 females, 45 males) with the high-uptake group (mean age 61.2 years, 33 females, 43 males). The hazard ratio did not change significantly when analyzing the SUV of just one lesion per PET-scan, i.e. the SUV of the most FDG avid lesion of the patient (hazard ratio 1.19, 95% CI 1.08–1.31, P <0.0001). Also the median survival and the 2- and 3-year survival rates were comparable, being 32 months, 59% and 45%, respectively, for the low-uptake group (SUV <4.53) and 19 months, 36% and 28%, respectively for the high-uptake group (SUV >4.53).

discussion

Compared with the tumors of patients with colorectal liver metastases who were taken to surgery, the tumors of patients who underwent chemotherapy were on average metabolically somewhat more active, which may reflect enhanced tumor aggressiveness. However, uptake of FDG in tumors proved to be highly variable within the two treatment groups with considerable overlap between the groups. However, when analyzing SUV for the whole group, the metabolic activity of the metastatic colorectal carcinoma as depicted by FDG uptake, proved to be a significant independent predictor for overall survival, regardless of whether patients subsequently underwent curative surgery or chemotherapy. A one-unit increase in SUV corresponded to a significant increase in the risk of death with 17%. When dichotomizing SUV values at the median value of the patient population, there was a highly significant difference in survival, as patients in the low-uptake group had a median survival of 32 months, compared with 19 months in the high-uptake group. Comparable survival rates and hazard ratio were observed when analyzing all metastases or only the most FDG avid (i.e. the most aggressive) lesion.

It is well established that patients with unresectable disease have a much poorer outcome than patients with resectable disease. The 5-year survival for hepatic metastasectomy now approaches 30%–40%, with a median survival up to 50 months in patients with the most favorable prognostic factors. Unresectable patients who are treated with current state-of-the-art multidrug systemic therapy have a median survival of 18–20 months [3]. However, many of the patients treated with systemic therapy have more advanced disease than patients who are selected for liver metastasectomy, which may contribute to the difference in survival observed between these groups [4]. Nevertheless, the present study suggests that metabolic activity of the metastases is also an important factor, since SUV proved to be an independent predictive factor for survival, no matter if the patient had resectable or irresectable, more widespread disease. Thus, our data indicate that intense glucose metabolism in metastases of colorectal cancer is a negative marker of prognosis.

To the best of our knowledge, there are no studies addressing the predictive value of FDG uptake for survival in metastatic colorectal carcinoma. However, our results are in line with the results of previous reports on the prognostic information of FDG uptake in patients with primary tumors such as non-small-cell lung cancer (NSCLC) [16–22], head and neck squamous cell carcinoma (HNSCC) [23–29], breast cancer [14, 30, 31], glioma [32], esophageal carcinoma [33, 34], pancreatic cancer [35–38] and hepatocellular carcinoma [39].

As early as 1985, Patronas et al. [32] already reported a significant correlation between FDG uptake and survival in patients with gliomas. Several studies in patients with NSCLC treated with complete resection reported that SUV and pathologic tumor size, provided excellent independent prognostic information [16, 17, 19]. The combination of SUV and pathologic tumor size identified a subgroup of patients at highest risk of death as a result of recurrent disease after resection. Other studies in NSCLC found that staging of tumor-node-metastasis and SUV were independent prognostic variables [20–22]. However, the SUV for the primary tumor was the strongest prognostic factor, whereas the prognostic ability of the SUV for the regional lymph nodes remained uncertain. There was an indication that primary tumors showing high SUVs have the potential to be resistant to therapy and to metastasize [22]. Jeong et al. found that the SUV of squamous cell carcinoma was higher than that of adenocarcinomas [20].

Previous clinical series in HNSCC [23–29] also suggested that highly elevated primary tumor FDG uptake predicted worse prognosis. It was shown that patients with an advanced clinical stage [26] or tumors of lesser differentiation [25, 26] display higher FDG uptake and that higher baseline SUV predicted inferior response to radiotherapy, local disease control, and survival [27, 29].

In pancreatic cancer SUVs were also introduced as a new metabolic predictor of prognosis [35–38]. Most previous studies in this tumor type demonstrated that tumor-associated histologic characteristics are important in defining prognosis. However, most of them were available only after a resection procedure has been performed [36]. In another series of pancreatic cancer, the SUV was not able to predict survival in a subgroup of patients with resectable tumors [35]. In the subgroup with unresectable tumors, however, SUV proved to be an independent prognostic indicator for overall survival.
In breast tumors FDG uptake was also a significant predictor of prognosis [30] and some investigators [14, 31] examined the possible association between FDG uptake and several histopathological and immunohistochemical factors. The results of the present study also support the hypothesis that FDG uptake reflects biological aggressiveness [23].

conclusions

Pretreatment FDG uptake in metastatic colorectal cancer predicts outcome, irrespective of the subsequent treatment modality, as patients with FDG avid disease show reduced overall survival. FDG-PET could become an important adjunct modality, as patients with FDG avid disease show reduced predicts outcome, irrespective of the subsequent treatment survival after lung cancer resection. J Clin Oncol 2004; 22: 3255–3260.


