Tailoring Therapy in Colorectal Cancer by PET/CT

Systematic Review

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Abstract

Positron emission tomography (PET) using \[^{18}\text{F}\]-fluoro-2’-deoxy-D-glucose (FDG) has an added value in the clinical management of patients with colorectal carcinoma (CRC). This includes restaging patients before surgical resection or local recurrence of liver metastases, assessment whether residual lesions are scar or recurrence and in pinpointing recurrence in case of unexplained increase in serum levels of carcinoembryonic antigen.

At present, there is an increasing interest in new roles for FDG-PET, especially for characterisation of lesions, for prognosis and response prediction and for early evaluation of treatment response to commenced therapy. FDG-PET may lead to better selection of patients for different therapeutic options or to early individual adjustment of current treatment.

This systematic review aims to provide an up-to-date overview of literature on the current and potential value of FDG-PET in CRC patients by addressing staging and recurrence detection, prognosis and response prediction and evaluation of preoperative (chemo)radiotherapy for primary rectal carcinoma, ablative treatment for unresectable liver metastases and chemotherapy for advanced CRC.

**Keywords:** Positron-Emission Tomography, Colorectal Neoplasms, Fluorodeoxyglucose F18, management, therapy, prognostic stratification, response evaluation
Introduction

Colorectal cancer (CRC) is the third most common malignancy and third leading cause of cancer-related deaths in the United States. Even though the annual age-adjusted incidence rates and death rates are slowly declining in the last two decades, it remains a large health problem worldwide.\(^1\) According to the National Cancer Institute\(^1,2\), the age-adjusted incidence rate in the United States (2001-2005) is 50.6 per 100,000 per year, with a cancer-related death rate of 18.8 per 100,000 per year and an overall 5-year survival rate of 64.4%. Approximately 5.3% of people will develop CRC during their lives and it is estimated that in 2008, 148,810 people were diagnosed with and 49,960 people died from CRC in the United States.

At time of diagnosis, approximately 40% of CRC is confined to the primary site, 36% has spread locoregionally and 19% of patients are suffering from metastasised disease (for 5% in this registration the stage was unknown).\(^1,2\) Progress has been made in improvement of patient prognosis with the introduction of hepatic resection for treatment of isolated liver metastasis and with the development of effective chemotherapeutic and targeted agents.\(^3,4\)

Positron emission combined with computed tomography (PET/CT) with \([^{18}\text{F}]\)-fluoro-2'-deoxy-D-glucose (FDG) has proven a useful diagnostic modality in different phases of CRC management. This comprehensive review discusses the current and potential future applications of FDG-PET in management decisions of patients with CRC. The literature is systematically reviewed on the (potential) role of FDG-PET in changing individual CRC patient management by addressing (i) the impact of FDG-PET on staging disease and detection of recurrence on individual management, (ii) the prediction of individual patient prognosis and therapy response, and (iii) the evaluation of treatment response.
Search strategy and selection criteria of literature

References for this review were identified by systematic searches in PubMed, EMBASE (OvidSP), MEDLINE (OvidSP) and the Cochrane Library up to December 31, 2008. The strategy of Mijnhout et al.\(^5\) was adapted for our research question. The construct of the query was: “(PET OR PET/CT) AND colorectal AND cancer”, using medical subject headings, synonyms and truncations for all three building blocks of the search question (table 1).

Only articles in English were included. A total of 1595 articles were retrieved and screened. Case-reports, small series (<15 patients), research by questionnaires, reviews, reports from meetings, abstracts of poster presentations, editorial comments or letters-to-the editor were excluded. Papers on disease (re)staging or recurrence detection which failed to describe the implications for clinical management or without verification of the results by histology or follow-up were excluded. Papers on treatment response without fixed outcome-parameters (e.g. histological or morphological response, patient survival) were excluded from further analysis. PET-tracers other than FDG were excluded. Results of the search strategy were supplemented by the references from included articles. In total 86 articles were considered suitable for further discussion in this review.

When considered appropriate, results have been pooled using fixed effects modelling, by weighting effect magnitudes (i.e. fraction management change) by their inverse variance. For calculation of the variance and confidence intervals of proportions the beta-distribution has been used since the commonly used asymptotic normal approximation only holds true for observed frequencies of five and larger.\(^6\) It should be noted, however, that the variation of results of individual papers is largely attributable to heterogeneity of the study populations.
1 Impact of FDG-PET on individual management in staging disease and detection of recurrence

Many articles address the impact of FDG-PET during initial staging of primary CRC or in detection of recurrence. Recurrence of CRC can be suspected due to several findings during routine clinical follow-up: abnormalities on morphological imaging and rise of the serum tumour-marker carcinoembryonic antigen (CEA). FDG-PET may have a pivotal role in patient management specifically in case of equivocal radiological studies, unexplained CEA rise or determination of resectability of local recurrence or colorectal liver metastases.

1.1 Influence of staging primary CRC by FDG-PET on individual management

In staging of primary rectal cancer, FDG-PET may influence on management in 12% to 27%. Heriot et al. showed in 46 patients with histology proven stage II-IV rectal cancer that the use of FDG-PET after routine staging by abdominal CT and pelvic MRI and/or transrectal endo-ultrasonography (TREUS) before neoadjuvant therapy changed previously proposed management in 17% of patients. Of these eight cases, surgery was cancelled in six cases due to identification of metastatic disease and in two the neoadjuvant radiotherapy field was altered to include common iliac lymphadenopathy as identified by PET. Gearhart et al. prospectively compared abdominal spiral CT and FDG-PET/CT after TREUS or pelvic MRI in 37 patients with previously untreated biopsy proven adenocarcinoma of the rectum and found discordant findings in 38%, leading to changes in the previously proposed treatment plan in 27%. Of these 10 cases, in five patients additional lymph node metastases were found not detected by CT alone leading to neoadjuvant treatment or extension of the radiotherapy field. In two cases, CT-positive lymph nodes proved negative on PET leading to cancellation of neoadjuvant treatment or radiotherapy. In three additional cases more extensive surgical resection was performed. Bassi et al. showed that additional staging by FDG-PET/CT in 25 T3,4 rectal cancer patients who were candidates for neoadjuvant chemoradiotherapy (CRT) prior to surgery led to
treatment changes in 16%. FDG-PET identified unknown nodal involvement and undiagnosed liver metastases. Another study in 83 patients performed by Davey et al.\textsuperscript{7} showed that staging FDG-PET/CT could lead to management changes in 12% of primary rectal cancer patients. Of these 10 cases, surgery was cancelled in six patients due to unexpected metastases, in three neoadjuvant CRT was considered necessary due to identification of pelvic nodal spread and in one patient neoadjuvant CRT was cancelled because iliac lymph node metastases on CT appeared to be false-positive.

In staging of primary CRC, FDG-PET may influence on management in 2%-27\textsuperscript{11}-27\textsuperscript{12}. Kantorova et al.\textsuperscript{13} found a change of treatment in 16% of 38 patients with histologically proven primary CRC which were prospectively staged by conventional imaging and FDG-PET (8% treatment modality change, 13% change in range of surgery). Park et al.\textsuperscript{12} studied 100 patients with primary CRC (45 colon and 55 rectum carcinoma: 3 stage I, 23 stage II, 25 stage III, 49 stage IV) planned for surgery with FDG-PET/CT who had increased CEA or showed equivocal signs of metastases on CT. In 27% of the patients, proposed treatment plan was modified: nine had treatment modality changes, 10 received more extensive surgery and in 8 unnecessary procedures could be avoided. The reason for a large proportion of patients in whom management changed might be that they only included patients with a relatively high likelihood of metastasised disease due to equivocal radiological findings or increased CEA levels. Veit-Haibach et al.\textsuperscript{14} performed FDG-PET/CT in 47 patients with suspicious lesions at colonoscopy (50 sites: 13 rectum and 37 colon cancer). They found that FDG-PET/CT compared to CT alone led to management changes in 9% of the patients. Another study, by Llamas-Elvira\textsuperscript{15}, showed that using FDG-PET/CT next to CT changed management in 12% of the 104 patients with histology proven CRC (56 rectum and 44 colon cancer) referred for surgery. In seven cases surgery was cancelled for extensive disease not detected by CT and in five the therapeutic approach was altered. In contrast, Furukawa et al.\textsuperscript{11} showed no impact of FDG-PET/CT over whole-body CT alone, as PET/CT only changed management in 1 of 44 patients (2%) with histologically proven primary CRC (38 rectum carcinoma). They attributed discordance with other authors to the less advanced disease stage in their patient series.
Pooling the data of the four studies on rectal carcinoma leads to a weighted mean change in management of 15.7% (95% confidence interval: 10.8%-21.7%), as shown in figure 1. For the studies with both colon and rectal carcinoma (CRC) the weighted mean change in management is 10.7% (95% confidence interval: 7.6%-14.5%). Apparently due to the limited influence of FDG-PET on management in these patients, the latest editions of the European Society for Medical Oncology (ESMO) guidelines for rectal cancer\textsuperscript{16} or CRC\textsuperscript{17} do not recommend to use this technique routinely for staging primary disease. They do however note that for staging in advanced CRC\textsuperscript{18}, FDG-PET can have a role.

1.2 Influence of FDG-PET in suspected recurrence on individual management

Many studies have been performed to investigate whether FDG-PET changes management in patients in whom recurrent CRC was expected based on equivocal lesions on conventional diagnostic follow-up, rising CEA levels with normal radiologic findings or during restaging before surgical treatment of local recurrence or metastases.

1.2.1 Equivocal radiologic findings suggestive for recurrence

After radiotherapy or surgery of the primary tumour, most patients develop a region of scar tissue in the surgical bed. These changes complicate the detection of local recurrence by ultrasound, CT or MRI. FDG-PET can distinguish metabolic active disease (tumour) from less active disease (scar tissue). An example is shown in figure 2.

Of the 35 patients with a history of resected primary CRC described by Beets et al.\textsuperscript{19}, eight cases were included for presacral masses with uncertain CT findings. FDG-PET correctly classified them as recurrence in 5 cases (62.5%) causing change in management in these patients. In the series of Simo et al.\textsuperscript{20}, patient management was altered in 14 of 31 patients (45%) with inconclusive imaging during follow-up after surgical resection of primary CRC. In all patients treatment changed from local therapy to systemic treatment for disseminated disease. Scott et al.\textsuperscript{21} described 93 patients with
residual structural after surgery for primary CRC suggestive of recurrence. Treatment changed in 66% of these patients.

One study\textsuperscript{22} examined the influence of FDG-PET during routine follow-up after a history of CRC when there was no sign of recurrence as physical examination, CT, MRI and CEA were all normal. FDG-PET changed individual management in only 2 of 31 cases (6%). The first was an omental metastasis and the second was a false positive PET causing unnecessary laparotomy. Therefore, follow-up of CRC by FDG-PET without any signs pointing to recurrence seems to be of limited value.

1.2.2 Unexplained rise in CEA

When serum CEA levels rise during postoperative surveillance in asymptomatic patients and history taking, physical examination and imaging do not lead to a distinct cause, treatment decisions are difficult to be made. With the aid of FDG-PET, localisation of the source of increased serum CEA levels may lead to a change in management in the majority of patients.

FDG-PET in patients with a history of CRC and CEA rise with normal (n=31) or equivocal (n=19) findings on conventional work-up (including abdominal CT and chest X-ray or CT) detected recurrent disease in 68% of patients in the study of Flamen \textit{et al.}\textsuperscript{23}, thereby changing management from observation to start of a new treatment (curative surgery for resectable disease or finding of non-resectable disease). Of the 56 lesions, 20% were local recurrences, 27% liver metastases, 9% lung metastases, 36% other abdominal lesions and 9% were non-pulmonary extra-abdominal lesions. In the subgroup of eight patients included in an earlier study by Flamen \textit{et al.}\textsuperscript{24} with a rising CEA level but negative findings on morphologic imaging, PET led to change in management in 3 (37.5%), due to detection of one local recurrence, one liver metastasis and one lymph node metastasis. Valk \textit{et al.}\textsuperscript{25} described 18 patients with a rise of CEA without abnormal findings on abdominal CT-scanning. Of these, 12 patients had detectable disease by FDG-PET (67%), which was subsequently histologically confirmed to be recurrent CRC. Simo \textit{et al.}\textsuperscript{20} described a subset of 58 patients with rise of CEA with
normal findings on conventional imaging. With FDG-PET, they found the cause in 34 patients (59%), resulting in change of management. Of these, 18 could be treated with curative surgery, whereas the remaining 16 were treated with systemic therapy. Even-Sapir et al.\textsuperscript{26} mentioned 16 cases with occult rising of CEA in which 13 (81%) tumour recurrences were detected. Of these patients nine were treated with chemotherapy and four with surgery. Only one patient had a negative PET despite an intraluminal recurrence at repeat colonoscopy. Shen et al.\textsuperscript{27} reported that PET had influence on individual management in 41 of 50 patients (82%) with suspicion of recurrent CRC based on asymptomatically elevated serum levels of CEA.

1.2.3 Restaging for resectable local recurrence

When local recurrence is confirmed, resectability of disease is assessed by restaging the patient. FDG-PET can be useful by detecting distant disease, which makes surgery futile.

In case of presumed resectable pelvic recurrence of rectal carcinoma, Faneyte et al.\textsuperscript{28} found management changes in 14\% of 32 cases due to discrepant PET findings after conventional imaging. These five cases caused cancellation of surgery for extensive disease in one, less extensive surgery in three and surgery instead of palliative therapy in one.

Flamen et al.\textsuperscript{24} described a subset of 23 patients with recurrent locoregional CRC which was presumed resectable based on clinical and radiological findings. In eight of these patients (35\%) management was altered due to unexpected findings of additional tumour sites in five and the exclusion of disease in three patients. Valk et al.\textsuperscript{25} described a subgroup of 78 patients with a history of CRC with local recurrence considered resectable based on conventional diagnostic workup. FDG-PET showed additional lesions in 23 patients (29\%) rendering these recurrences unresectable. In contrast, PET did not show any signs of recurrence in six patients, of whom two showed malignant local lesions during laparotomy. Kalff et al.\textsuperscript{29} asked the attending clinicians to assign a treatment plan to 102 consecutive patients with recurrent local CRC presumed being resectable based on conventional imaging. This treatment plan was then compared with that based on incremental
information supplied by FDG-PET. In 54 cases treatment plan was altered due to unexpected PET-findings and in 6 more cases referring oncologists would not commit to a management plan without access to PET-information (59%). Of all these cases, one false positive result was due to a pelvic abscess and in four the extent of metastatic disease was underestimated by PET.

1.2.4 Restaging for resectable liver metastases

FDG-PET can be used to restage disease in case of presumed resectable liver metastases to confirm resectability in these patients and to avoid futile liver surgery.

Wiering et al.\textsuperscript{30} performed a systematic review and a meta-analysis of 32 studies published up to 2003 concerning patients selected for surgical treatment for liver metastases. They found pooled sensitivity and specificity for FDG-PET to be 88.0% and 96.1% for hepatic lesions and 91.5% and 95.4% for extra-hepatic lesions. Pooling results of CT-scanning resulted in 82.7%, 84.1% (hepatic lesions), 60.9% and 91.1% (extra-hepatic lesions), respectively, underlining the higher sensitivity of FDG-PET for extra-hepatic lesions as compared to CT. Detection of extra-hepatic lesions may lead to management changes such as a different surgical approach or cancellation of surgery for extensive disease and starting of palliative chemo(radio)therapy. They noted that only 18 of 32 studies mentioned the change in patient management due to FDG-PET findings, the pooled value being 32% (range: 20-58%).

Our search query resulted in 25 papers\textsuperscript{19,20,24,31-52} in which FDG-PET was used in restaging patients prior to surgery for liver metastases (figure 3). Management changes were reported in 11%\textsuperscript{37} to 70%\textsuperscript{20}. The authors of the paper with lowest management change (11%)\textsuperscript{37} noted that in their population in only 5.5% of patients intra-abdominal unexpected extrahepatic metastases were present, a number which is exceptionally low. They attributed this to improvement of accuracy of conventional diagnostic imaging. The high percentage of management changes noted by Denecke et al.\textsuperscript{49} (52%) was possibly due to the fact that they included patients with recurrence after LASER induced thermotherapy of unresectable liver metastases. A high number of unexpected extrahepatic lesions was
found. In addition, when calculating management changes, 2 of 11 cases were included, in which false-positive FDG-PET results led to inadequate conclusions and unnecessary interventions. For Simo et al.,\textsuperscript{20} the high proportion of management changes (7 of 10 patients who were restaged before liver surgery) might be due to inclusion of 3 cases in which changes were limited to surgical planning (use of RFA or resection of additional lesions).

The pooled mean management change in these 1,060 patients is 22.3\% (95\% confidence interval: 19.8\%-24.9\%). An example of how FDG-PET can influence management in liver metastases is displayed in figure 4. The results of Scott et al.\textsuperscript{21} (management changes in 49\% of 98 patients) were not used for calculation of pooled management change, since they included both patients with potentially resectable hepatic and pulmonary CRC metastases. It was not possible to derive how many of these had liver lesions only.

The consequence of restaging these patients by FDG-PET prior to liver surgery is described in 2 cohorts of in total 203 patients who were selected for hepatic surgery.\textsuperscript{53} Patients staged by FDG-PET (group A, n=100) were compared to patients staged by CT alone (group B, n=103). Although futile laparotomy ratios were similar for both groups (19.4\% versus 28.0\%, p=0.186), significantly less extrahepatic disease was seen during surgery in the cohort of patients staged by FDG-PET (1.9\% versus 10\%, p=0.017). Most of these futile laparotomies were due to too extensive hepatic disease, but no difference between both cohorts were seen (17.4\% versus 17.0\%, p=1.000). Pawlik et al.\textsuperscript{54} on the other hand did show in a retrospective analysis of 461 patients surgically treated for liver metastases in the same period, that the rate of unnecessary laparotomies was significantly lower in patients restaged by FDG-PET compared to patients who did not have FDG-PET (5.6\% versus 12.4\%, p=0.009).

Fernandez et al.\textsuperscript{55} described improved overall survival in patient selected for surgery for liver metastases by FDG-PET. In their study, the outcome of 100 patients selected for resection of hepatic metastases by FDG-PET had better 5-year overall survival rates than in 19 reviewed similar studies (including 6,066 patients) not using functional imaging. Five year overall survival in this study was 58.6\% (95\% CI 45.6\%-71.6\%), which was higher than in the 19 other studies (30\%, ranging 12\%-41\%). Strasberg et al.\textsuperscript{36} noted that in their series of 35 patients restaged by PET before liver surgery, 3-
year overall survival was 77% and this proportion was higher than any of the 13 similar articles they reviewed that used conventional restaging (ranging 30%-58%). However, care must be taken to compare results with historic data, since the improvements in CT scans has led to stage migration and thus survival benefit. Wiering et al. found no differences in both overall survival (3-year: 57.1% versus 60.1%, p=0.678) and disease free survival (3-year: 29.9% versus 29.2%, p=0.656) between the group restaged by FDG-PET and the group without FDG-PET. They explain this discrepancy by stating that they used well-matched control group in contrast to the others who used a historical control group. The effect of FDG-PET on overall survival seemed lower than reported in these other studies. They concluded that tumour biology, resectability and chemotherapy response seem to be the major determinants of survival and that their results suggest that the intraoperative surgical approach to disease control and postoperative care in both groups were similar.

It should be noted that previous chemotherapy lowers sensitivity of FDG-PET when restaging patients before liver surgery for liver metastases. Akhurst et al. stated that sensitivity of FDG-PET in the detection of colorectal metastases during preoperative staging was decreased in patients pre-treated by neoadjuvant chemotherapy due to downregulation of hexokinase activity (lesion detection sensitivity: 63% versus 77%). No lesions larger than 1.2 cm were missed in the untreated group, but lesions up to 3.2 cm were missed after neoadjuvant chemotherapy. Interpretation of FDG-PET data should be done with caution in the context of concomitant chemotherapy. In this respect both the specific cytostatic agent(s) prescribed as the timing of PET scanning after neoadjuvant treatment are of relevance.

1.2.5 Overall effect on treatment decisions in suspected recurrence

The remaining papers dealt with heterogeneous populations of patients in whom during follow-up of CRC any recurrence or metastasis was suspected based on clinical findings, CEA increase or conventional diagnostic imaging (table 2). In these studies the detection ratio of local recurrence (sensitivity) by FDG-PET varied from 90% to 100%, which is higher compared to CT (71%-88%).
Specificity of PET and CT in these studies was similar (86%-92% for PET versus 85%-89% for CT). For hepatic metastases sensitivity and specificity for PET versus CT were 89%-100% versus 45%-100% and 91%-100% versus 60%-100%, respectively. For extra-hepatic metastases sensitivity and specificity were 94%-100% versus 64%-74% and 40%-100% versus 50%-96% for PET versus CT, respectively. Management changes in these 10 paper varied from 6%-30%. Huebner et al.66 performed a meta-analysis of 11 similar articles up to 1999 and found a pooled management change in 29% (95% confidence interval: 25-34%).

The consequence of PET-tailored management in follow-up of patients after curative resection of colonic or rectal cancer was investigated by Sobhani et al.67 They stratified and randomised 130 patients in a group with a standardised follow-up consisting of history taking, physical examination, biomarker assays and conventional imaging (ultrasound, thorax X-ray, abdominal CT) and a group in which this follow-up included a whole body FDG-PET after 9 and 15 months. They found the time to recurrence-detection was significantly shorter in the FDG-PET arm (12.1 versus 15.4 months, p=0.01) associated with more curative resections of recurrences (65% versus 9.5%, p<0.01).

The added value of fusing FDG-PET and CT was assessed by Fukunaga et al.68, who compared fused PET/CT with separate PET and CT in patients with suspected local recurrence after curative resection of rectal cancer. They reported improved accuracy of diagnosis of fused PET/CT over PET or CT alone of 93%, 79% (p=0.0138) and 88% (p=0.0156), respectively. Nakamoto et al.64 investigated 63 patients with suspected recurrent CRC but failed to show a significant improvement of diagnostic accuracy of FDG-PET/CT (CT alone: 78%, FDG-PET alone: 79%, FDG-PET and CT: 84% and fused FDG-PET/CT: 92%, p=0.13). Even-Sapir et al.26 showed in 62 patients with suspected recurrence or metastases after rectal cancer and preoperative staging for rectal cancer, that the specificity of fused PET/CT is higher than PET alone (89% versus 74%, p<0.05) with similar sensitivity (96% versus 88%).

It can be concluded that FDG-PET results in modification of individual patient management in situations where conventional diagnostic work-up shows equivocal findings in CRC patients (45%-
66%), in patients with unexplained rise in CEA (37.5%-82%), in preoperative restaging of resectable local recurrence (29%-59%) and assessment of patients before surgery for liver metastases (11%-70%). Interpretation of FDG-PET-images for detection of metastases should be carried out with caution during or soon after administration of chemotherapy, since the sensitivity for detection of metastases is lower than normal. Use of FDG-PET in patients with a history of CRC without clinical, biochemical or radiological signs of recurrence, appears of limited additional value.

The value of metabolic imaging next to morphologic imaging seems to have high sensitivity for local disease with similar specificity as CT. Especially in detection of extrahepatic metastases, the application of FDG-PET is superior to CT alone. In a population with suspected recurrence, management will change in about 6%-30% due to FDG-PET findings leading to earlier detection of recurrences and to more curative resections. Combined PET/CT is superior to PET alone in recurrence detection.

2 Prognostic stratification and response prediction by PET

2.1 Determination of prognosis by PET

The use of (semi)quantitative parameters for tracer uptake before start of treatment, such as the mean standardised uptake value (SUV$_{\text{mean}}$), maximum standardised uptake value (SUV$_{\text{max}}$) or parameters of FDG-metabolism in tumour lesions, can be related to overall patient outcome (prognosis). This might help in selecting the appropriate treatment for an individual patient (table 3).

Calvo et al. performed a study in primary rectal cancer treated by neoadjuvant CRT (45-50.4 Gy combined with 5FU/FA or tegafur) followed by surgical resection showed that the 3-year overall survival ratio in patients with a (arbitrarily chosen) SUV$_{\text{max}}$ of 6.0 or lower on baseline FDG-PET was significantly higher than for higher values for the SUV$_{\text{max}}$ (92% versus 60%, p=0.04), see table 3. The abovementioned paper of Scott et al. showed the prognostic potential of FDG-PET in a subgroup of 93 patients with residual structural lesions during follow-up of CRC after primary surgery. Significantly better 1-year progression free survival was found when no additional lesions were
detected by PET as compared to patients in whom PET showed additional lesions (60.5% versus 36.2%, p=0.04).

Most studies which used baseline PET to predict patient outcome used individuals with metastasised disease treated either with surgery or chemotherapy. Dimitrakopoulou-Strauss et al. published a paper on patients with metastatic CRC treated with second line FOLFOX (folinic acid / 5FU / oxaliplatin). They used FDG SUV$_{\text{mean}}$, fractal dimensions and pharmacokinetic rate constants combined in a discriminant analysis in 25 patients. SUV$_{\text{mean}}$ correctly classified 1-year overall survival in 67% and the pharmacokinetic parameters in 76%. Unfortunately, their discriminant functions with coefficients were not provided, which makes implementation of their model in different subsets of patients difficult. Our group used the FDG SUV$_{\text{mean}}$ in 152 patients with CRC metastases treated by resection or pyrimidine-based chemotherapy. The 76 patients with a SUV$_{\text{mean}}$ lower than 4.26 had a longer median overall survival than the rest of the patients (32 months versus 19 months, p=0.017). Riedl et al. performed a similar experiment in surgically treated liver metastases and found overall survival benefit in subgroups of patients with lowest SUV$_{\text{max}}$ for a range of cut-off values (table 3). Scott et al. showed prognostic ability of FDG-PET in another subgroup of 98 patients restaged before resection of presumable resectable hepatic and pulmonary metastases. In this group, significant better 1-year progression free survival was found when no additional lesions were detected by PET compared to patients in whom PET did show additional lesions (65.9% versus 39.2%, p=0.01).

2.2 Prediction of response by PET

The imaging of glucose uptake of CRC lesions before start of treatment might indicate which patients are more likely to respond to therapy. For patients that are less likely to respond to the opted treatment, a different therapeutic approach might be beneficial. For this purpose, baseline (semi)quantitative parameters of tracer uptake, such as the SUV$_{\text{mean}}$ are related to individual patient outcome (table 4).

For primary rectal cancer treated with 50 Gy of neoadjuvant radiotherapy prior to surgery, Oku et al. found a negative correlation between the shrinkage rate on CT and the baseline SUV$_{\text{mean}}$
measured by FDG-PET of the lesion (i.e. the larger the $SUV_{\text{mean}}$ prior to treatment the larger the treatment induced reduction in lesion size). However, this correlation was very weak and not significant (correlation coefficient: -0.162, $p=0.326$). They found that only follow-up $SUV_{\text{mean}}$ correlated with morphological changes and rationalised that a high SUV at follow-up indicated both a high $SUV_{\text{mean}}$ at baseline and a low reduction of uptake during treatment.

Dimitrakopoulou-Strauss et al.\textsuperscript{74} published a paper on patients with metastatic CRC treated with second line FOLFOX. They showed by discriminant analysis that the pretreatment $SUV_{\text{mean}}$ correctly identified nonresponders (96\% of 28 patients with progressive disease). The same limitations to implementation of their model apply as described in the previous paragraph.

Functional imaging of lesions before start of treatment can identify patients with poor prognosis or who are less likely to respond to treatment. These patients might benefit from treatment-modification, when alternatives exist. Using a baseline FDG-PET, it appears feasible to stratify patients with different prognosis and possible resistance to treatment in CRC. So far, no prospective randomised controlled trials have been published using baseline FDG-PET for determination of individual treatment strategy.

3 Treatment follow-up by PET-response evaluation

After localised or during systemic treatment, tracer uptake in lesions can be monitored. Uptake during follow-up can be compared to baseline uptake, can be used to assess the effect of therapy and might be used as (early) prediction of treatment response or be related to patient survival for prognostic purposes. Thereby it might contribute to early change in management, if alternative treatment options are available. Response evaluation is most often performed by morphologic imaging according to RECIST (response evaluation criteria in solid tumours)\textsuperscript{75,76}. In an era where new cytotoxic treatment is cytostatic rather than cytoreductive, metabolic changes may precede anatomical changes, PET-imaging might aid in early response evaluation.
3.1 Response evaluation of radiotherapy in rectal cancer

Engenhart et al.\textsuperscript{77} were the first to address the effect of irradiation on inoperable presacral recurrent rectal carcinoma in 21 patients. They noticed a small but significant decrease in FDG uptake during radiotherapy (2.3 to 1.6 uptake-units after 6 months, \(p=0.002\)). Oku et al.\textsuperscript{73} described a significant negative (\(r=-0.383\), \(p=0.0140\)) correlation between shrinkage rate on CT (fractional decrease in tumour axial diameter) and FDG SUV ratio (fraction remaining SUV of follow-up compared to baseline) after 50 Gy of radiotherapy to primary rectal cancer in 40 patients.

Two studies compare TNM tumour (T-)stage, relating baseline TREUS T-stage with follow-up histological T-stage. In 25 patients with local invasive primary rectal cancer treated with neoadjuvant CRT prior to surgery, Calvo et al.\textsuperscript{69} described a significant difference in SUV\textsubscript{max} reduction (\(\Delta\text{SUV}_{\text{max}}\)) between patients with reduction in T-stage compared to non-responders (-3.3 versus -1.9 SUV-units, \(p=0.03\)). Denecke et al.\textsuperscript{78} showed that a cut-off for \(\Delta\text{SUV}_{\text{max}}\) of -36% was able to separate responders from non-responders: 76% of FDG-PET responders demonstrated T-downstaging and 100% of FDG-PET non-responders did not show T-downstaging and (\(p=0.002\)) in 23 patients with advanced rectal carcinoma treated with neoadjuvant CRT in combination with hyperthermia. Results of PET were superior to CT or MRI in response prediction.

Many studies compared visual FDG-PET response\textsuperscript{79-81}, \(\Delta\text{SUV}_{\text{max}}\)\textsuperscript{79,82-89}, \(\Delta\text{SUV}_{\text{mean}}\)\textsuperscript{90,91}, SUV-ratio\textsuperscript{92} and \(\delta\text{TLG}\) (change in total lesion glycolysis: the product of metabolic volume and SUV) at different intervals after radiotherapy, varying from 12 days\textsuperscript{90} up to 7 weeks\textsuperscript{79,81} and all found a significant relation with semiquantitative histological response (table 5). Depending on response criteria, predictive values of FDG-PET response (NPV) ranged from 83%\textsuperscript{91} to 100%\textsuperscript{88} and predictive values of FDG-PET non-response (PPV) varied from 77%\textsuperscript{87} to 100%\textsuperscript{84,90}. The worst results were found by Engenhart et al.\textsuperscript{77} and Melton et al.\textsuperscript{88} who used rigorous criteria for definition of treatment response (complete SUV normalisation\textsuperscript{77} and \(\Delta\text{SUV}_{\text{max}} \geq -70\%\) determined by ROC analysis\textsuperscript{88}) and found a PPV of 20% and 58% respectively, which means 42%-80% of the patients without response on FDG-
PET, clinically did show local control\textsuperscript{77} or regression score during histopathological examination\textsuperscript{88}. Kristiansen \textit{et al.}\textsuperscript{81} on the other hand used a very strict criterion for pathological response (defined as no histological detectable residual carcinoma) and therefore 40\% false FDG-PET therapy responses were found (accuracy 53\%). This confirmed the data of Guillem \textit{et al.}\textsuperscript{93}, who found an accuracy of 60\% for PET to define the extent of pathological response. Rosenberg \textit{et al.}\textsuperscript{91} attributed their low predictive value of non-response FDG-PET (PPV: 64\%) to be due to influx of inflammatory cells.

The prognostic value of the metabolic response of rectal cancer to neoadjuvant CRT has been described in a few studies.\textsuperscript{80,85} Guillem \textit{et al.}\textsuperscript{85} dichotomised FDG-PET results in responders and non-responders in 15 patients with locally advanced primary rectal cancer treated by preoperative CRT. Responders were defined as those with only focal or diffuse FDG uptake with a maximum SUV\textsubscript{max} of 1.4 on the follow-up PET-scan. They showed higher median overall survival (>54 weeks versus 39 weeks, p=0.08) and higher median disease-free survival (>54 weeks versus 26 weeks, p=0.02) of responders compared to non-responders. The corresponding 5-year overall survival percentages were 91\% versus 70\% (p=0.024) and 5-year disease free survival percentages were 81\% versus 62\% (p=0.003). In another study in 34 patients treated with neoadjuvant CRT before curative surgery, visual PET response was categorised into complete remission, partial remission and stable or progressive disease before results of pathology were available. This PET-based response stratification showed 3-year overall survival percentages of 100\%, 79\% and 0\% respectively (p<0.0001) and 3-year disease free survival percentages of 100\%, 47\% and 0\% respectively (p<0.0001).\textsuperscript{80}

A drawback of post-radiotherapy FDG-PET is the radiation-induced inflammation.\textsuperscript{94} This causes influx and activation of macrophages, neutrophils, fibroblasts and granulation tissue, that can accumulate approximately 25\% of FDG uptake.\textsuperscript{95} On the other hand direct effect of radiation may induce tumour cell dormancy (“stunning”) which mimics glucose metabolic response.\textsuperscript{84} Siegel \textit{et al.}\textsuperscript{89} saw metabolic response (\(\Delta\text{SUV}_{\text{max}}=-39.3\%\)) after short course radiotherapy (25 Gy in 5 days) at day 9 but could not correlate these results to histopathology (negligible morphological response) which might partly be explained by the latter effect or due to the fact that surgery is performed immediately after radiotherapy in contrast to CRT where surgery is postponed 6 weeks.
FDG-PET allows prediction of pathological response in patients treated by neoadjuvant CRT. Moreover it seems able to predict overall and disease free survival after surgery with curative intent. However, the clinical consequences remain unclear. It does not seem possible to select patients who have no advantage of surgery after neoadjuvant treatment. It seems possible to demonstrate functional response after short-course radiotherapy\textsuperscript{89} but there are no data that shortening of neoadjuvant treatment prior to surgery (i.e. when no histopathological data is available) might benefit the subgroup of patients with early PET-response to CRT or that escalation of chemoradiation (e.g. increasing the radiation dose, adding regional hyperthermia, decision for intraoperative radiation) might benefit the subgroup of patients with no PET-response. Discrimination of responders to neoadjuvant chemoradiation from non-responders could also be used for preoperative selection for individualised surgery. This could include sphincter-saving surgery in deep-seated tumours, less aggressive treatment in limited disease or planning of intraoperative radiation therapy. However, no studies provide definitive evidence. Apart from selection for individualised surgery, FDG-PET-response might theoretically help to decide which patient benefits from adjuvant chemotherapy after surgery, but no studies concerning this have been published either, nor compared this to the use of histopathological data obtained during surgery.

3.2 Effect of local ablative therapy of liver metastases

Qualitative assessment of FDG-PET imaging after cryosurgical or radiofrequency ablation of unresectable liver metastases has advantages over conventional imaging such as CT, MRI and ultrasonography since latter techniques do not easily identify treatment failures at an early stage. This is due to hyperechogenicity and rim-like contrast enhancement caused by regional hyperperfusion, resembling residual tumour\textsuperscript{96}. The predictive value of a negative FDG-PET 3 weeks after local ablative therapy varied from 97\%\textsuperscript{97} to 100\%\textsuperscript{98} and of a positive PET from 80\%\textsuperscript{98} to 86\%\textsuperscript{97} in two studies treating 81 patients with 237 hepatic lesions. The lower positive predictive value is caused by false-positive results due to liver abscesses occurring after local ablative therapy (table 6).
Donckier et al.\textsuperscript{99} compared the predictive value of FDG-PET 1 week and 3 months after radiofrequency ablation of unresectable liver metastases. They found that an early negative PET (after 1 week) is less suitable for determining the disease free status as compared to a late negative PET (NPV: 54\% versus 75\%) whereas both early and late positive PET show 100\% (positive) predictive value for residual tumour or recurrence. Apparently the optimal timeframe to judge the effect of local ablative therapy is somewhere between 1 weeks and three months after surgery.

Denecke et al.\textsuperscript{49} used FDG-PET after LASER induced thermotherapy ablation (LITT) of unresectable liver metastases when tumour progression was suspected on MRI or obscure rising serum levels of CEA. Standardised visual interpretation of the images based on consensus of two blinded nuclear medicine physicians led to a negative predictive value of PET of 96\% and a positive predictive value of 97\%. Using the SUV\textsubscript{max} they found a negative predictive value of 96\% and a positive predictive value of 93\%. They concluded that FDG-PET is a promising tool for assessment of local control and whole-body restaging in patients with clinical suspicion of tumour progression after local ablative treatment for liver metastases. Timing of follow-up though was highly variable in this study, since FDG-PET was performed only when tumour progression was suspected and 11\% of follow-up scans were performed immediately (1-3 days post-LITT), 50\% at short term (within 6 months post-LITT) and 39\% after more than 6 months post-LITT.

FDG-PET seems a promising modality to select patients with incomplete tumour ablation or with early relapse after local ablative treatment for unresectable liver metastases. Assessment of local control by FDG-PET three weeks after local ablative treatment seems advisable.

3.3 Evaluation of response to chemotherapy

Depending on the drug and regimen, cytotoxic treatment has a clear influence on CRC adenocarcinoma cell lines. Oxaliplatin, 5FU and irinotecan cause decreased FDG uptake after 72 hours due to decrease in glucose transport, a decrease in hexokinase activity.\textsuperscript{100} This effect can be monitored by FDG-PET during systemic treatment of liver metastases.
Findlay et al. were the first to report the effect of 5FU with or without interferon-α chemotherapy on liver metastases larger than 3 centimetres in diameter with FDG-PET. They used morphological CT response as outcome measure and found that a reduction in tumour to normal liver (T:L) ratio of tissue activity concentrations of 15% or more has a sensitivity of 100% with a specificity of 75% to predict morphological response. They noted that patients with an increase in T:L 1-2 weeks subsequently had a reduction in T:L at 4-5 weeks, suggesting that this “flare” phenomenon is caused by infiltration of macrophages as response to tumour cell kill (i.e. early inflammatory reaction).

The two abovementioned papers by Dimitrakopoulous-Strauss et al. also evaluated treatment response by including follow-up FDG-PET in 28 and 25 patients treated with second line FOLFOX. The prognostic value of the metabolic response of liver metastases to chemotherapy is described in three papers. Dimitrakopoulous-Strauss et al. showed prognostic aspects of dynamic FDG-PET response in 25 patients treated with second line FOLFOX. Discriminant analysis based on SUV mean correctly classified overall survival in 69% of the patients and based on 2-compartment rate constants, vascular fraction and fractal dimensions correctly classified overall survival in 78% of the patients. As stated before they showed the accuracy of their model but by omitting the model coefficients, it is not transferable to other patient populations. In a different study by our group it was shown that the percentage decrease in SUV mean (ΔSUV mean) and glucose metabolic rate (MRglc, derived from 2-compartment kinetic analysis) are both able to distinguish subgroups with different median overall survival in 50 patients with stage IV CRC treated by various schedules of chemotherapy. Using a cut-off for ΔSUV mean of -20% distinguished subgroups with a median survival of 25 weeks from 15 weeks (p=0.009). Using a ΔMRglc cut-off of -65% distinguished subgroups with a median survival of 32 weeks from 18 weeks (p=0.021). These cut-offs were selected after analysis of a range of cut-off values. Small et al. show similar results using FDG-PET/CT to qualitatively monitor treatment of 54 patients with liver metastases by FOLFOX / FOLFIRI (folinic acid / 5FU / irinotecan) with or without bevacizumab. Univariate analysis showed the hazard ratio of PET/CT response (defined as absence or reduced uptake of FDG) during treatment was not significantly associated with overall survival (3.127, 95% confidence interval: 0.874-11.187), but was
significantly associated with disease-free survival (3.826, 95% confidence interval: 1.390-10.534). CT-response alone did predict overall survival (hazard ratio: 4.584, 95% confidence interval: 1.133-18.536) and progression free survival (hazard ratio: 2.925, 95% confidence interval: 1.078-7.937). Results of all abovementioned studies are displayed in table 7.

Thus, the degree of metabolic response during treatment appeared to correlate with both pathological response and survival. However, it is of concern that the test-retest reproducibility of the $\text{SUV}_{\text{mean}}$ using a semi-automatically delineation of the lesion (50% of maximum value) is limited. When comparing the $\text{SUV}_{\text{mean}}$ of 28 lung cancer patients determined on the same system setup on two consecutive days, Krak et al.\textsuperscript{104} found a standard deviation of the relative differences of both $\text{SUV}_{\text{mean}}$’s of 11%. In 26 cancer patients in whom a FDG-PET was repeated within 1-5 days, the standard deviation of the relative differences of both $\text{SUV}_{\text{mean}}$’s was 7%.\textsuperscript{105} These standard deviations are larger when using different setups (multicentre trials). This suggests that measured tumour responses of less than ~15%-20% (2 standard deviations) might be regarded as within the reproducibility limits of the method used and should thus be interpreted as no actual change in SUV.

Therapy decisions on PET-response seem feasible. However, before use in routine daily practice future randomised controlled trials are necessary to prove its value. Optimal cut-offs are not only dependent on patient, treatment setting and cytostatic agent, but are dependent on follow-up timing and reproducibility limits of this technique.\textsuperscript{106,107}

### Conclusions

FDG-PET has limited added value in staging primary CRC. It has a convincing role in detection of local recurrence when conventional imaging fails to distinguish scar tissue from recurrent or residual tumour and can influence management decisions in about 38%-82% of patients with unexplained rise in CEA. During pre-surgical restaging of local recurrence or metastases it may provide relevant information by detecting additional disease that renders laparotomy futile. The use of concomitant chemotherapy should be taken into account since it lowers sensitivity of PET.
Based on baseline FDG-PET, patients with recurrent or metastasised CRC treated by chemotherapy or surgical resection can be stratified in different subgroups based on prognosis or predicted therapy effect. This risk assessment might be used for individualised treatment assignment. The first studies that use this PET-based stratification for survival to select patients for different treatment schedules are currently being undertaken.

The relation between FDG-PET response to preoperative neoadjuvant (chemo)radiotherapy in rectal cancer, seems well-related to both histopathology and survival. The exact clinical significance of PET-based response evaluation for this group of patients remains to be investigated. Unfortunately, early response prediction of radiotherapy seems less feasible since the combined effects of stunning, proliferation and inflammation may cause incorrect FDG-PET findings. In assessment of local ablative treatment of liver metastases FDG-PET seems suitable. The high predictive ability of negative FDG-PET provides evidence that it can be used to assess radicality of tumour ablation. On the other hand, a positive FDG-PET might point to intensification of follow-up or even additional treatment. In case of chemotherapy response evaluation in metastasised CRC, there is a clear relation the results of FDG-PET early after start of treatment with pathological response and survival. This could improve patient management by reducing morbidity, efforts and costs of ineffective treatment in non-responders. Moreover in an era where new and expensive drugs have limited morphologic effect, it may provide an alternative to anatomy-based assessment of response. However, it appears impossible to give one single definition of metabolic response, since cut-off values depend on type of treatment, timing of evaluation and tumour type.
References


Figures

Figure 1

**Figure 1:** Forest plot of management changes with corresponding confidence intervals for staging of primary rectal (upper) and primary colorectal cancer (CRC) described in nine references. The size of the squares denotes the weight for calculation of the pooled average.
Figure 2: Example of a male patient with a pT₃N₀M₁ rectosigmoid carcinoma treated by rectosigmoid resection in combination with chemotherapy for synchronous liver metastases. During follow-up with FDG-PET a local recurrence in the pelvis near the rectal stump was detected by PET/CT that was equivocal on CT.
Figure 3: Forest plot of management changes with corresponding confidence intervals for preoperative restaging in colorectal liver metastases described in 25 references. The size of the squares denotes the weight for calculation of the pooled average.
Figure 4: Example of a male patient with a pT3N0M1 rectosigmoid carcinoma treated by rectosigmoid resection in combination with chemotherapy. After an initially good response, resection of liver metastasis was performed. During follow-up with ultrasound, CT and FDG-PET a recurrence in the liver was detected by PET/CT which was not detected by ultrasound or CT alone.
### Tables

**Table 1**

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*Table 1*: search strategy. MeSH: Medical Subject Heading, CT: X-ray computed tomography, PET: positron emission tomography, *truncation, †in EMBASE the corresponding subject heading is “Colorectal Cancer”
Table 2: Management changes and test characteristics in recurrent CRC by FDG-PET. CEA: carcinoembryonic antigen, CRC: colorectal carcinoma, CT: X-ray computed tomography, FDG: $[^{18}F]$-fluoro-2'-deoxy-D-glucose, N/A: not applicable, PET: positron emission tomography, Se: sensitivity, Sp: specificity. *including 1 patient in whom an incidental second tumour type was found, #test characteristics for extrahepatic metastases are based on detection of recurrent and metastatic CRC, †PET/CT compared to PET alone, §only locoregional lymph node metastases were included.

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Table 2: Management changes and test characteristics in recurrent CRC by FDG-PET. CEA: carcinoembryonic antigen, CRC: colorectal carcinoma, CT: X-ray computed tomography, FDG: $[^{18}F]$-fluoro-2'-deoxy-D-glucose, N/A: not applicable, PET: positron emission tomography, Se: sensitivity, Sp: specificity. *including 1 patient in whom an incidental second tumour type was found, #test characteristics for extrahepatic metastases are based on detection of recurrent and metastatic CRC, †PET/CT compared to PET alone, §only locoregional lymph node metastases were included.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>n</th>
<th>Inclusion</th>
<th>Therapy</th>
<th>PET-parameters</th>
<th>Outcome-parameter</th>
<th>Favourable criteria</th>
<th>Results</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvo⁵⁹</td>
<td>2004</td>
<td>25</td>
<td>cT2-4Nx primary rectal cancer</td>
<td>CRT (45-50.4Gy, 5FU/FA or tegafur) + resection</td>
<td>SUV$_{max}$</td>
<td>3-year overall survival</td>
<td>SUV$_{max}$ ≤ 6.0</td>
<td>92% vs 60%</td>
<td>0.04</td>
</tr>
<tr>
<td>Dimitrakopoulou-Strauss⁶⁰</td>
<td>2004</td>
<td>20</td>
<td>CRC metastases</td>
<td>2nd line FOLFOX</td>
<td>SUV$_{mean}$, k1-4, FD, Vb</td>
<td>1-year overall survival</td>
<td>SUV$_{mean}$ ≤ 4.26</td>
<td>CCR: 67% CCR: 76%</td>
<td>-</td>
</tr>
<tr>
<td>de Geus-Oei⁷¹</td>
<td>2006</td>
<td>152</td>
<td>CRC metastases</td>
<td>Resection or pyrimidine based chemotherapy</td>
<td>SUV$_{mean}$</td>
<td>Median overall survival</td>
<td>SUV$_{mean}$ ≤ 4.26</td>
<td>32mo vs 19mo</td>
<td>0.017</td>
</tr>
<tr>
<td>Riedl⁷²</td>
<td>2007</td>
<td>90</td>
<td>CRC liver metastases</td>
<td>Resection</td>
<td>SUV$_{max}$</td>
<td>Median overall survival</td>
<td>SUV$_{max}$ ≤ 5</td>
<td>&gt;72mo vs 48mo</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>SUV$_{max}$ ≤ 7</td>
<td>&gt;72mo vs 42mo</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SUV$_{max}$ ≤ 10</td>
<td>&gt;72mo vs 35mo</td>
<td>0.0095</td>
</tr>
<tr>
<td>Scott⁷³</td>
<td>2008</td>
<td>91</td>
<td>Suspected recurrence CRC based on CDW</td>
<td>Various sites detected</td>
<td>Additional sites detected</td>
<td>1-year progression free survival</td>
<td>No additional lesions detected</td>
<td>60.5% vs 36.2%</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96</td>
<td>Resectable liver or pulmonary metastases</td>
<td>Various sites detected</td>
<td>Additional sites detected</td>
<td>1-year progression free survival</td>
<td>No additional lesions detected</td>
<td>65.9% vs 39.2%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table 3:** Prognostic stratification by baseline FDG-PET. CCR: correct classification rate, CDW: conventional diagnostic workup, CRC: colorectal carcinoma, CRT: chemoradiotherapy, 5FU: 5-fluorouracil, FA: folinic acid, FD: fractal dimensions, FDG: [$^{18}$F]-fluoro-2'-deoxy-D-glucose, FOLFOX: 5FU/FA/oxaliplatin, k1-4: 2-compartment rate constants, PET: positron emission tomography, SUV: standardised uptake value, Vb: vascular fraction.
Table 4

<table>
<thead>
<tr>
<th>First Author</th>
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<th>Therapy</th>
<th>PET-parameters</th>
<th>Outcome-parameter</th>
<th>Favourable criteria</th>
<th>Results</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oku73</td>
<td>2002</td>
<td>40</td>
<td>cT2-4 and/or N1-3 primary rectal cancer</td>
<td>Radiotherapy (50Gy)</td>
<td>SUV&lt;sub&gt;mean&lt;/sub&gt;</td>
<td>CT shrinkage rate at 3-5 weeks</td>
<td></td>
<td>Correlation: -0.162</td>
<td>0.326</td>
</tr>
<tr>
<td>Dimitrakopoulou-Strauss&lt;sup&gt;·&lt;/sup&gt;</td>
<td>2003</td>
<td>28</td>
<td>CRC metastases</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line FOLFOX</td>
<td>SUV&lt;sub&gt;mean&lt;/sub&gt;</td>
<td>Clinical response (WHO-guidelines): PD, SD or PR</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>CCR: 96% (PD), 47% (SD) and 0% (PR)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 4:** Therapy response prediction by baseline FDG-PET. CCR: correct classification rate, CR: complete remission, CRC: colorectal carcinoma, CT: X-ray computed tomography, 5FU: 5-fluorouracil, FA: folinic acid, FDG: [<sup>18</sup>F]-fluoro-2'-deoxy-D-glucose, FOLFOX: 5FU/FA/oxaliplatin, PD: progressive disease, PET: positron emission tomography, PR: partial remission, SD: stable disease, SUV: standardised uptake value, WHO: World Health Organization.
<table>
<thead>
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<th>First Author</th>
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<th>Inclusion</th>
<th>Therapy</th>
<th>PET-parameter</th>
<th>Outcome-parameter</th>
<th>Response criteria</th>
<th>Results</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engenhart‡</td>
<td>1992</td>
<td>21</td>
<td>Unresectable recurrence</td>
<td>40Gy photons, 14Gy neutrons</td>
<td>SUVmax at 8-9wks</td>
<td>Local control</td>
<td>Complete response (SUVmax normalisation to background)</td>
<td>PPV: 3/15 (0.20) NPV: 4/15 (0.67)</td>
<td>-</td>
</tr>
<tr>
<td>Guillen‡</td>
<td>2000</td>
<td>15</td>
<td>cT1 or N1</td>
<td>Neoadjuvant CRT (50.4Gy, 5FU/FA)</td>
<td>VRS, ΔSUVmax</td>
<td>Histological response at 4-6wks</td>
<td>Any decrease</td>
<td>PPV: 15/15 (1.00) NPV: 0/15 (0.00)</td>
<td>-</td>
</tr>
<tr>
<td>Nakagawa‡</td>
<td>2002</td>
<td>40</td>
<td>cT2-4 or N1,1,3 Neoadjuvant radiotherapy (50Gy)</td>
<td>SUVmax-ratio at 3-5wks</td>
<td>CT shrinkage rate at 3-5wks</td>
<td>-</td>
<td>Correlation -0.383</td>
<td>0.0140</td>
<td></td>
</tr>
<tr>
<td>Kristiansen§</td>
<td>1981</td>
<td>119</td>
<td></td>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konski§</td>
<td>1983</td>
<td>53</td>
<td>cT3/4 or N1</td>
<td>cT3/4Nx or N1</td>
<td>Histological response at 8-10wks</td>
<td>Histological T-stage decrease</td>
<td>Responders: 3-3 Non-responders: -1.0</td>
<td>PPV: 6/11 (0.55) NPV: 13/14 (0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Melton§</td>
<td>1988</td>
<td>33</td>
<td>cT3/4 and/or N1</td>
<td>Neoadjuvant CRT (50.4Gy, 5FU/FA)</td>
<td>ΔSUVmax at 5wks</td>
<td>Histological down-staging</td>
<td>ASUV &gt; -52%</td>
<td>Mean OS: &gt;54wks vs ~72wks Mean DFS: &gt;54wks vs ~72wks Mean OS: &gt;54wks vs ~72wks Mean DFS: &gt;54wks vs ~72wks</td>
<td>0.08 0.02 0.03 0.01</td>
</tr>
<tr>
<td>Denecke‡</td>
<td>2004</td>
<td>23</td>
<td>cT3/4 or N1</td>
<td>Neoadjuvant CRT (50.4Gy, 5FU/FA)</td>
<td>ΔSTLG at 5wks</td>
<td>Histological response at 8-10wks</td>
<td>Histological complete response</td>
<td>PPV: 13/17 (0.76) NPV: 6/6 (1.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>Calvo¶</td>
<td>2005</td>
<td>25</td>
<td>cT3/4 or N1</td>
<td>Neoadjuvant CRT (50-55Gy, 5FU/FA or tegafur)</td>
<td>Absolute change in SUVmax at 4-5wks</td>
<td>Histological response at 6-8wks</td>
<td>Any T-stage decrease or &gt;65% volume reduction ASUV &gt; -36%</td>
<td>PPV: 13/17 (0.76) NPV: 6/6 (1.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>Capirci‡</td>
<td>2006</td>
<td>88</td>
<td>cT3, cT1b, and/or N1</td>
<td>Neoadjuvant CRT (50-56Gy, 5FU)</td>
<td>VRS, (SUVmax at 7wks)</td>
<td>VRS at 1 (focal/diffuse) or SUVmax &lt;1.4</td>
<td>5-yr DFS: 91% vs 70% 5-yr DFS: 81% vs 62%</td>
<td>0.024 0.003</td>
<td></td>
</tr>
<tr>
<td>Capirci†</td>
<td>2006</td>
<td>33</td>
<td>cT1a, and/or N1</td>
<td>Neoadjuvant CRT (45Gy, 5FU/FA + or - erlotinib)</td>
<td>ΔSUVmax at 12days</td>
<td>Histological response at 8wks</td>
<td>Histological response ≤ scattered residual cells ASUV &gt; -52%</td>
<td>ASUV &gt; -63% vs -22%</td>
<td>PPV: 13/13 (1.00) NPV: 18/20 (0.90)</td>
</tr>
<tr>
<td>Calvo¶</td>
<td>2005</td>
<td>20</td>
<td>cT3, and/or N1</td>
<td>Neoadjuvant CRT (45-55Gy ± fluoropyrimidine)</td>
<td>SUVmax at 3-4wks</td>
<td>Histological complete response</td>
<td>ASUVmax &lt; -57.7%</td>
<td>Mean OS: &gt;54wks vs ~72wks Mean DFS: &gt;54wks vs ~72wks Mean OS: &gt;54wks vs ~72wks Mean DFS: &gt;54wks vs ~72wks</td>
<td>0.08 0.02 0.03 0.01</td>
</tr>
<tr>
<td>Denecke‡</td>
<td>2006</td>
<td>34</td>
<td>cT3, N1, M1b</td>
<td>Neoadjuvant CRT (50Gy, 5FU/FA + oxaliplatin/carbo)</td>
<td>VRS at 3-4wks</td>
<td>Histological response at 6-8wks</td>
<td>Histological complete response</td>
<td>PPV: 9/9 (1.00) NPV: 18/20 (0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calvo¶</td>
<td>2007</td>
<td>45</td>
<td>cT3, cT1b, and/or N1</td>
<td>Neoadjuvant CRT (50-56Gy ± fluoropyrimidine)</td>
<td>ΔSUVmax at 4-5wks</td>
<td>Histological response at 8-11wks</td>
<td>Histological response ≤ scattered residual cells ASUV &gt; -66.2%</td>
<td>ASUVmax &gt; -75.9% vs -46.9%</td>
<td>0.0015</td>
</tr>
<tr>
<td>Konski§</td>
<td>2008</td>
<td>21</td>
<td>cT1a, and/or N1</td>
<td>Neoadjuvant CRT (50Gy±fluoropyrimidine)</td>
<td>ΔSUVmax at 6-10wks</td>
<td>Histological down-staging</td>
<td>ASUV &gt; -70%</td>
<td>ASUV &gt; -72% vs -44%</td>
<td>PPV: 7/12 (0.58) NPV: 9/9 (1.00)</td>
</tr>
<tr>
<td>Kristiansen§</td>
<td>2008</td>
<td>30</td>
<td>cT3, N1</td>
<td>Neoadjuvant CRT (60Gy, uracil, tegafur, FA)</td>
<td>ΔSUVmax at 3-4wks</td>
<td>Histological response</td>
<td>Complete histological response (T, N)</td>
<td>Responders: -67% Non-responders: -55%</td>
<td>0.08</td>
</tr>
<tr>
<td>Rosenzweig‡</td>
<td>2008</td>
<td>29</td>
<td>uT2, uN1</td>
<td>Neoadjuvant CRT (50Gy)</td>
<td>SUVmax-ratio at 2-3wks</td>
<td>Histological response at 3-11wks</td>
<td>Histological complete response (T, N)</td>
<td>PPV: 10/12 (0.83) NPV: 6/18 (0.33)</td>
<td>-</td>
</tr>
<tr>
<td>Nakagawa‡</td>
<td>2008</td>
<td>29</td>
<td>uT3-4, uN1, M1b</td>
<td>Neoadjuvant CRT (45Gy, 5FU)</td>
<td>ΔSUVmax at 14days and at 5wks</td>
<td>Histological response at 10wks</td>
<td>ASUV &gt; -35% Grade 1 histological response ASUV &lt; -57.7% Grade 1 histological response</td>
<td>PPV: 7/12 (0.58) NPV: 14/17 (0.82) PPV: 7/12 (0.64) NPV: 15/18 (0.83)</td>
<td>-</td>
</tr>
<tr>
<td>Siegel‡</td>
<td>2008</td>
<td>32</td>
<td>uT1N, or uT2N</td>
<td>Neoadjuvant short course CRT (25Gy, 5FU)</td>
<td>ΔSUVmax at 9days</td>
<td>Histological response at 2wks</td>
<td>Histological down-staging ≤ predominant fibrotic changes (TRG2)</td>
<td>ASUV &gt; -40%</td>
<td>No correlation</td>
</tr>
</tbody>
</table>
Table 5: Radiotherapy and multimodality (neoadjuvant) therapy response evaluation in locally advanced rectal cancer by FDG-PET, (C)RT: (chemo)radiotherapy, CT: X-ray computed tomography, DFS: disease free survival, FA: folinic acid, FDG: $[^{18}\text{F}]-\text{fluoro-2'-deoxy-D-glucose}$, FOLFOX: 5FU/FA/oxaliplatin, 5FU: 5-fluorouracil, MRI: magnetic resonance imaging, NPV: negative predictive value (fraction of responder on PET that are a clinical responder), OS: overall survival, PD: progressive disease, PET: positron emission tomography, PPV: positive predictive value (fraction of non-responder on PET that are clinical non-responders), PR: partial remission, RH: radiofrequency hyperthermia, SD: stable disease, SUV: standardised uptake value, TLG: total lesion glycolysis, TRG: tumour regression grade, T-stage: TNM-classification tumour stage, VRS: visual response score.

<table>
<thead>
<tr>
<th>Vliegen 82</th>
<th>2008</th>
<th>20</th>
<th>cT3/4</th>
<th>Neoadjuvant</th>
<th>CRT (50.4 Gy)</th>
<th>ASUV_{max} at 4-6wks</th>
<th>Histological response at 6-8wks</th>
<th>TRG ≤ 2</th>
<th>-83.6% vs -59.4%</th>
<th>0.025</th>
</tr>
</thead>
</table>

Table 5: Radiotherapy and multimodality (neoadjuvant) therapy response evaluation in locally advanced rectal cancer by FDG-PET, (C)RT: (chemo)radiotherapy, CT: X-ray computed tomography, DFS: disease free survival, FA: folinic acid, FDG: $[^{18}\text{F}]-\text{fluoro-2'-deoxy-D-glucose}$, FOLFOX: 5FU/FA/oxaliplatin, 5FU: 5-fluorouracil, MRI: magnetic resonance imaging, NPV: negative predictive value (fraction of responder on PET that are a clinical responder), OS: overall survival, PD: progressive disease, PET: positron emission tomography, PPV: positive predictive value (fraction of non-responder on PET that are clinical non-responders), PR: partial remission, RH: radiofrequency hyperthermia, SD: stable disease, SUV: standardised uptake value, TLG: total lesion glycolysis, TRG: tumour regression grade, T-stage: TNM-classification tumour stage, VRS: visual response score.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>n</th>
<th>Therapy</th>
<th>PET-parameters</th>
<th>Outcome-parameter</th>
<th>Response criteria</th>
<th>Results</th>
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<tbody>
<tr>
<td>Langenhoff98</td>
<td>2002</td>
<td>22</td>
<td>CSA or RFA</td>
<td>Visual interpretation within 3wks</td>
<td>Histopathology, follow-up &gt;9mo, CT</td>
<td>PET-negative</td>
<td>NPV: 17/17 (1.00) PPV: 4/5 (0.80)</td>
</tr>
<tr>
<td>Donckier99</td>
<td>2003</td>
<td>17</td>
<td>RFA</td>
<td>Visual interpretation at 1wk</td>
<td>Follow-up &gt;3mo by CT</td>
<td>PET-negative</td>
<td>NPV: 7/13 (0.54)  PPV: 4/4 (1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Visual interpretation at 3mo</td>
<td></td>
<td></td>
<td>NPV: 6/8 (0.75)  PPV: 8/8 (1.00)</td>
</tr>
<tr>
<td>Joosten97</td>
<td>2005</td>
<td>43</td>
<td>CSA or RFA</td>
<td>Visual interpretation within 3wks</td>
<td>Follow-up &gt;3mo by CT</td>
<td>PET-negative</td>
<td>NPV: 35/36 (0.97) PPV: 6/7 (0.86)</td>
</tr>
<tr>
<td>Denecke49</td>
<td>2007</td>
<td>21</td>
<td>LITT</td>
<td>Visual interpretation at suspected progression (MRI or CEA)</td>
<td>Histopathology, follow-up &gt;12mo by MRI</td>
<td>PET-negative</td>
<td>NPV: 24/25 (0.96) PPV: 28/29 (0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SUVmax at suspected progression (MRI or CEA)</td>
<td></td>
<td></td>
<td>NPV: 23/24 (0.96) PPV: 28/30 (0.93)</td>
</tr>
</tbody>
</table>

**Table 6:** Response evaluation for local ablative treatment for unresectable CRC liver metastases by FDG-PET. CEA: carcinoembryonic antigen, CRC: colorectal carcinoma, CSA: cryosurgical ablation, CT: X-ray computed tomography, FDG: $^{18}$F-fluoro-2’-deoxy-D-glucose, LITT: LASER induced thermotherapy, MRI: magnetic resonance imaging, NPV: negative predictive value (fraction of patients with response on PET having clinical response), PET: positron emission tomography, PPV: positive predictive value (fraction of patients with no response on PET having no clinical response), RFA: radiofrequency ablation, SUV: standardised uptake value.
<table>
<thead>
<tr>
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<th>Year</th>
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<th>Inclusion</th>
<th>Therapy</th>
<th>PET-parameters</th>
<th>Outcome-parameter</th>
<th>Response criteria</th>
<th>Results</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findlay101</td>
<td>1996</td>
<td>18</td>
<td>CRC liver metastases ≥3cm</td>
<td>5FU±IFα</td>
<td>ΔT:L at 4-5 weeks</td>
<td>CT response (WHO guidelines) at 12wks</td>
<td>CT response: CR or PR ΔT:L≥-15%</td>
<td>Sensitivity: 1.00 Specificity: 0.75</td>
<td>-</td>
</tr>
<tr>
<td>Dimitrakopoulou-Strauss74</td>
<td>2003</td>
<td>28</td>
<td>CRC metastases</td>
<td>2nd line FOLFOX</td>
<td>SUV_{mean}</td>
<td>Clinical response (WHO-guidelines)</td>
<td>Clinical response: PD, SD or PR</td>
<td>CCR: 92% (PD) 57% (SD) and 0% (PR)</td>
<td>-</td>
</tr>
<tr>
<td>Dimitrakopoulou-Strauss74</td>
<td>2004</td>
<td>20</td>
<td>CRC metastases</td>
<td>2nd line FOLFOX</td>
<td>SUV_{mean}, k1, k3, Vb at 3mo</td>
<td>1-year overall survival</td>
<td>SUV_{mean}, k1, k3, Vb, FD</td>
<td>CCR: 69% CCR: 78%</td>
<td>-</td>
</tr>
<tr>
<td>de Geus-Oei102</td>
<td>2008</td>
<td>50</td>
<td>CRC metastases</td>
<td>Various schedules</td>
<td>ΔSUV_{mean}, ΔMR_{glc} at 2mo</td>
<td>Median overall survival</td>
<td>ΔSUV_{mean} ≥ -20% ΔMR_{glc} ≥ -65%</td>
<td>25wks vs 15wks 32wks vs 18wks</td>
<td>0.009 0.021</td>
</tr>
<tr>
<td>Small103</td>
<td>2008</td>
<td>40</td>
<td>CRC liver metastases</td>
<td>Neoadjuvant FOLFOX / FOLFIRI ± bevacizumab</td>
<td>Visual PET-CT response</td>
<td>Overall survival Disease free survival</td>
<td>CR or PR</td>
<td>HR 3.127 HR 3.826</td>
<td>0.079 0.009</td>
</tr>
</tbody>
</table>
