Q J NUCL MED MOL IMAGING 2009;53:224-44

Tailoring therapy in colorectal cancer by PET-CT

D. VRIENS [1], L. F. DE GEUS-OEI [1], W. T. A. VAN DER GRAAF [2], W. J. G. OYEN [1]

[1]Department of Nuclear Medicine, Radboud University Nijmegen Medical Center Nijmegen, the Netherlands
[2]Department of Medical Oncology Nijmegen, the Netherlands

Positron emission tomography (PET) using [18F]-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 characterization 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.

KEY WORDS: Leukocytes - Radionuclide imaging - Radiolabelling.

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 metastasized 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 [18F]-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

Conflicts of interest.—The authors declare that none of them has a conflict of interest.

Corresponding author: D. Vriens, MD, Department of Nuclear Medicine (internal postal code 444), Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail: D.Vriens@nucmed.umcn.nl

CRC patient management by addressing 1) the impact of FDG-PET on staging disease and detection of recurrence on individual management, 2) the prediction of individual patient prognosis and therapy response, and 3) 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 I).

Only articles in English were included. A total of 1 595 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 (CIs) of proportions the β-distribution has been used since the commonly used asymptotic normal approximation only holds true for observed frequencies of ≥5.[6] It should be noted, however, that the variation of results of individual papers is largely attributable to heterogeneity of the study populations.

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 tumor-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.

TABLE I.—*Search strategy.*

PET OR PET/CT	Colorectal Cancer	
Positron emission tomography [MeSH]	Colorectal neoplasms [MeSH]**	Carcinom*
PET	Colorect*	Adenocarc*
PET/*	Colon	Cancer
PETscan*	Rectal*	Neoplas*
PET/CT*	Rectum*	Tumor
PET-CT*		Tumour
CT/PET*		Tumors
CT-PET*		Tumours
(Positron* AND emission* AND tomograph*)		

*Truncation; **In EMBASE the corresponding subject heading is "colorectal cancer". PET: positron emission tomography; CT: X-ray computed tomography; MeSH: Medical Subject Heading.

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% [7] to 27%.[8] Heriot *et al.*[9] 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 8 cases, surgery was cancelled in 6 cases due to identification of metastatic disease and in 2 the neoadjuvant radiotherapy field was altered to include common iliac lymphadenopathy as identified by PET. Gearhart *et al.*[8] 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 5 patients additional lymph node metastases were found not detected by CT alone

leading to neoadjuvant treatment or extension of the radiotherapy field. In 2 cases, CT-positive lymph nodes proved negative on PET leading to cancellation of neoadjuvant treatment or radiotherapy. In 3 additional cases more extensive surgical resection was performed. Bassi *et al.*[10] showed that additional staging by FDG-PET/CT in 25 T_{3-4} 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.*[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 6 patients due to unexpected metastases, in 3 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[11]-27%.[12] Kantorova *et al.*[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.*[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: 9 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 metastasized disease due to equivocal radiological findings or increased CEA levels. Veit-Haibach *et al.*[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 *et al.*,[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 48 colon cancer) referred for surgery. In seven cases surgery was cancelled for extensive disease not detected by CT and in 5 the therapeutic approach was altered. In contrast, Furukawa *et al.*[11] showed no impact of FDG-PET/CT over whole-body CT alone, as PET/CT only changed management in one 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.

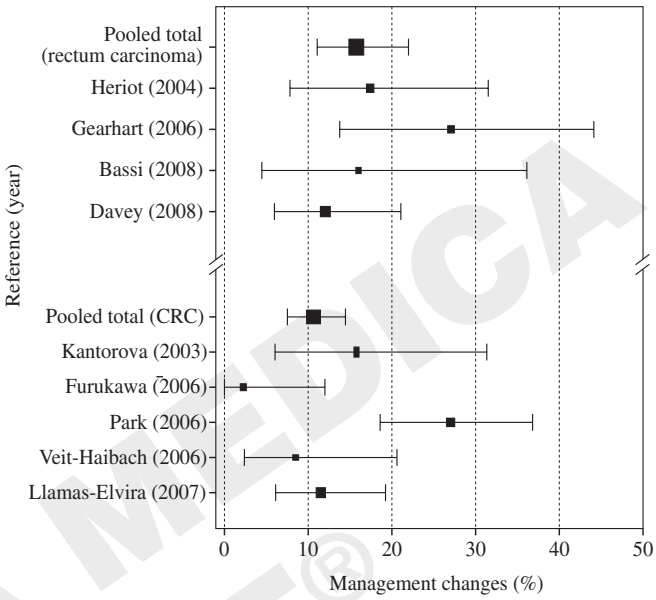

Figure 1.—Forest plot of management changes with corresponding confidence intervals for staging of primary rectal (upper) and primary colorectal cancer (CRC) described in 9 references. The size of the squares denotes the weight for calculation of the pooled average.

Pooling the data of the four studies on rectal carcinoma leads to a weighted mean change in management of 15.7% (95% CI: 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% CI: 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 [16] or CRC [17] do not recommend to use this technique routinely for staging primary disease. They do, however, note that for staging in advanced CRC,[18] FDG-PET can have a role.

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

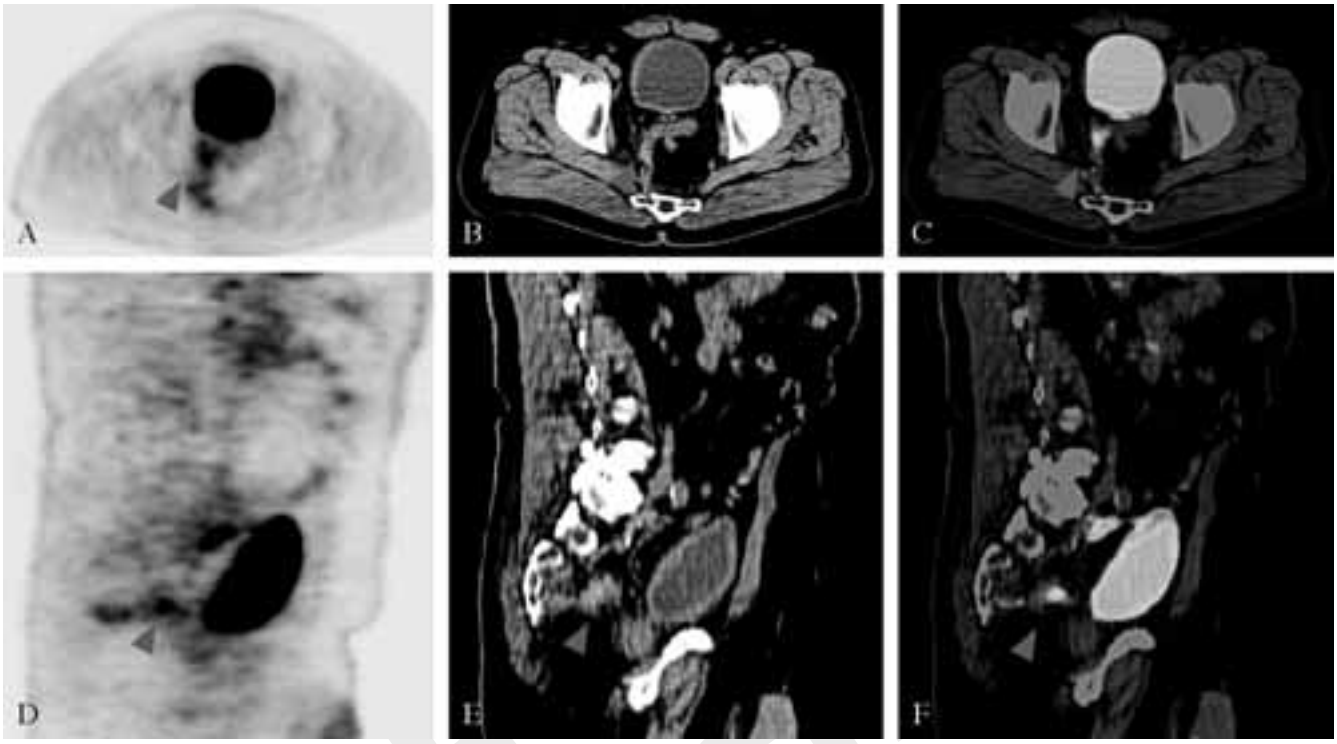

Figure 2.—Example of a male patient with a $pT_3N_0M_1$ rectosigmoid carcinoma treated by rectosigmoid resection in combination with chemotherapy for synchronous liver metastases. During follow-up with FDG-PET a local recurrence in the pelvis near the rectal stump (arrowhead) was detected by PET/CT that was equivocal on CT.

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.

Equivocal radiologic findings suggestive for recurrence.—After radiotherapy or surgery of the primary tumor, 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 (tumor) 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.*,[19] 8 cases were included for pre-sacral 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.*,[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.*[21] described 93 patients with residual structural after surgery for primary CRC suggestive of recurrence. Treatment changed in 66% of these patients.

One study [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.

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, localization 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 *et al.*,[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 8 patients included in an earlier study by Flamen *et al.*[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 *et al.*[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 *et al.*[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.*[26] mentioned 16 cases with occult rising of CEA in which 13 (81%) tumor recurrences were detected. Of these patients, 9 were treated with chemotherapy and 4 with surgery. Only 1 patient had a negative PET despite an intraluminal recurrence at repeat colonoscopy. Shen *et al.*[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.

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.*[28] found management changes in 14% of 32 cases due to discrepant PET findings after conventional imaging. These 5 cases caused cancellation of surgery for extensive disease in one, less extensive surgery in 3 and surgery instead of palliative therapy in one.

Flamen *et al.*[24] described a subset of 23 patients with recurrent locoregional CRC which was presumed resectable based on clinical and radiological findings. In 8 of these patients (35%) management was altered due to unexpected findings of additional tumor sites in 5 and the exclusion of disease in 3 patients. Valk *et al.*[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.*[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 4 the extent of metastatic disease was underestimated by PET.

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.*[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% 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

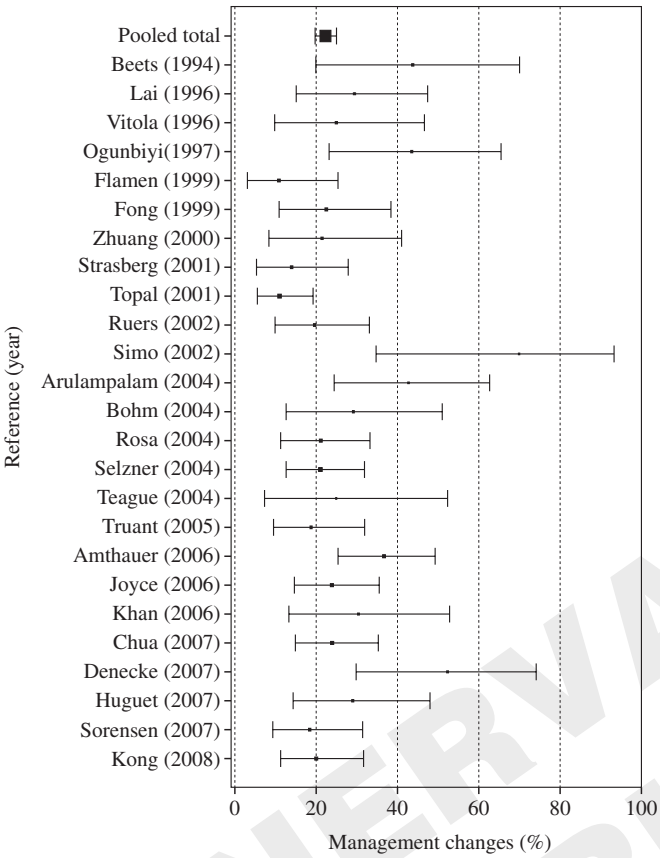

Figure 3.—Forest plot of management changes with corresponding confidence intervals for preoperative restaging in colorectal liver metastases described in 25 references. The size of the squares denotes the weight for calculation of the pooled average.

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 [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% [37] to 70%.[20] The authors of the paper with lowest management change (11%) [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.*[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.*[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 radiofrequency ablation [RFA] or resection of additional lesions).

The pooled mean management change in these 1 060 patients is 22.3% (95% CI: 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.*[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 two cohorts of in total 203 patients who were selected for hepatic surgery.[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% *vs* 28%; P=0.186), significantly less extrahepatic disease was seen during surgery in the cohort of patients staged by FDG-PET (1.9% *vs* 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% *vs* 17%; P=1). Pawlik *et al.*[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% *vs* 12.4%; P=0.009).

Fernandez *et al.*[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%; range: 12-41%). Strasberg *et al.*[36] noted that

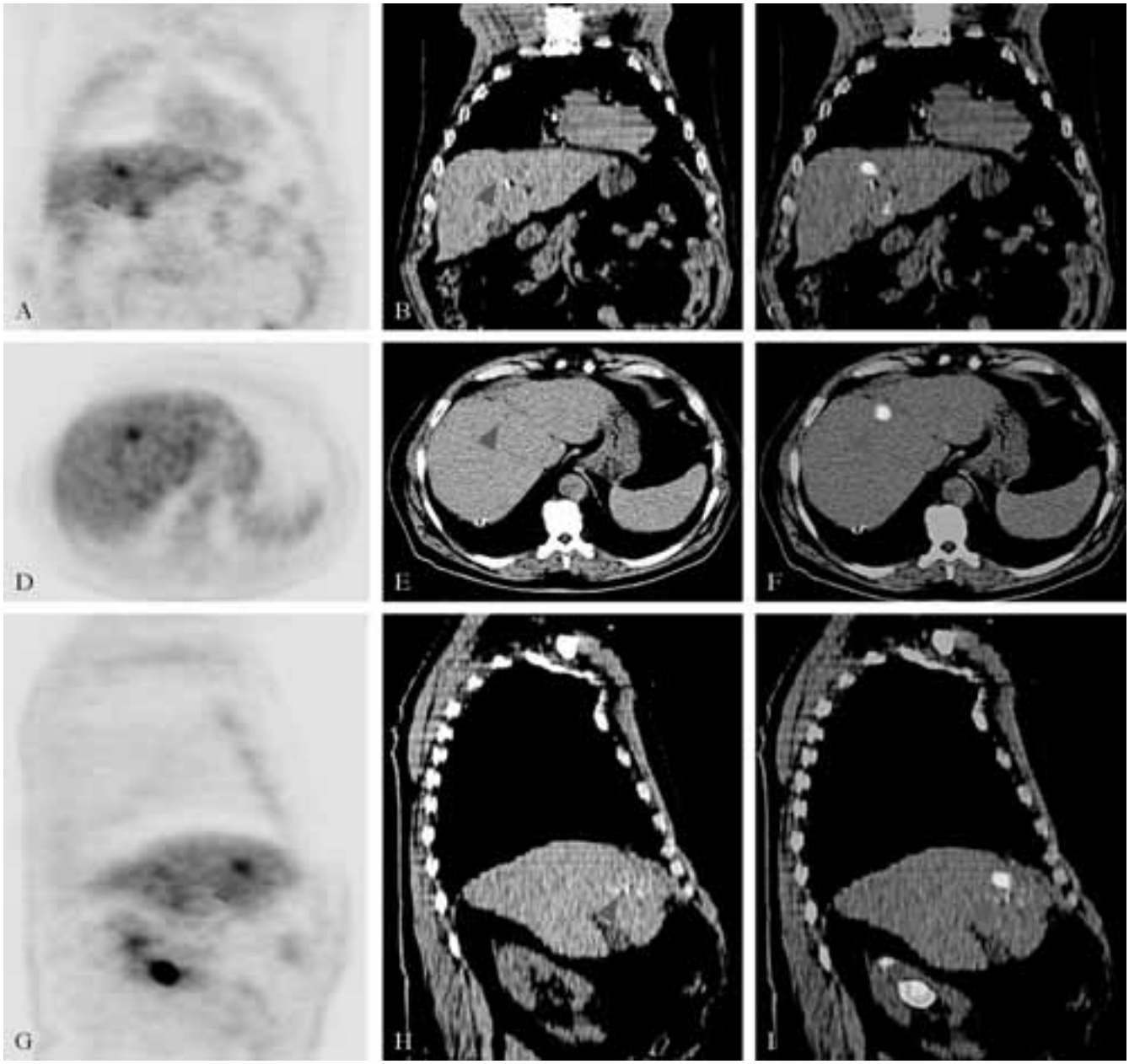

Figure 4.—Example of a male patient with a $pT_3N_3M_3$ rectosigmoid carcinoma treated by rectosigmoid resection in combination with chemotherapy. After an initially good response, resection of liver metastasis was performed. During follow-up with ultrasound, CT and FDG-PET a recurrence in the liver (arrowhead) was detected by PET/CT which was not detected by ultrasound or CT alone.

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 (range: 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.[56] Wiering *et al.*[53] found no differences in both overall survival (3-year: 57.1% *vs* 60.1%; P=0.678) and disease free survival (3-year: 29.9% *vs*

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 tumor 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.*[57] 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% *vs* 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.

Overall effect on treatment decisions in suspected recurrence.—The remaining papers [21, 26, 58-65] 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 II). 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 *vs* 85-89% for CT). For hepatic metastases sensitivity and specificity for PET *vs* CT were 89-100% *vs* 45-100% and 91-100% *vs* 60-100%, respectively. For extra-hepatic metastases sensitivity and specificity were 94-100% *vs* 64-74% and 40-100% *vs* 50-96% for PET *vs* CT, respectively. Management changes in these 10 papers varied from 6-30%. Huebner *et al.*[66] performed a meta-analysis of 11 similar articles up to 1 999 and found a pooled management change in 29% (95% CI: 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 randomized 130 patients in a group with a standardized 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 *vs* 15.4 months; P=0.01) associated with more curative resections of recurrences (65% *vs* 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% *vs* 74%; P<0.05) with similar sensitivity (96% *vs* 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 sus-

TABLE II.—*Management changes and test characteristics in recurrent CRC by FDG-PET.*

Author	Year	N.	Design	Inclusion
Delbeke *et al.*[58]	1997	52	Retrospective	Suspected recurrence in CRC follow-up
Ruhlmann *et al.*[59]	1997	59	Retrospective	Suspected primary, screening follow-up, suspected recurrence in CRC
Imdahl *et al.*[60]	2000	71	Prospective	Suspected recurrence or metastases in CRC follow-up
Whiteford *et al.*[61]	2000	105	Retrospective	Suspected recurrence or metastases
Arulampalam *et al.*[62]	2001	42	Prospective	Suspected or confirmed recurrence
Desai *et al.*[63]	2003	42	Prospective	Follow-up or preoperative staging with resectable disease on CT
Even-Sapir *et al.*[26]	2004	62	Retrospective	Suspected recurrence/metastases or preoperative staging in rectal cancer
Nakamoto *et al.*[64]	2007	63	Prospective	Suspected recurrence or screening follow-up PET/CT
Akiyoshi *et al.*[65]	2008	63	Prospective	Suspected metastases or pre-chemoradiotherapy staging

Author	Disease free/benign		Observation to start new new treatment	Cancel treatment for no disease	Cancel surgery for extensive disease	Cancel other treatmentfor extensive disease	Modifications to treatment plan	Inconclusive CDW treatment	Unecessary intervention	Total (%)
Delbeke *et al.*[58]	6/52	(histology or follow-up >12 months)	2	2	9		4			17 (33%)
Ruhlmann *et al.*[59]	14/59	(histology or suggested by CDW)	2		2			2		6 (10%)
Imdahl *et al.*[60]	20/71	(histology or suggested by CDW)	7		9					16 (23%)
Whiteford *et al.*[61]	22/105	(histology or follow-up >6 months)	4	8	14				4	30 (29%)
Arulampalam *et al.*[62]	12/42	(histology or follow-up)	9		3		2*		2	16 (38%)
Desai *et al.*[63]	0/42	(histology or follow-up)			17					17 (40%)
Even-Sapir *et al.*[26]	19/62	(histology or follow-up >6 months)	13	8		5		3		29 (47%)
Nakamoto *et al.*[64]	27/63	(histology or follow-up >6 months)	20	3			1	1		25 (40%)
Akiyoshi *et al.*[65]	0/63	(histology)			4		6			10 (16%)

Author	Test characteristics PET *versus* CT		
	Local recurrence	Hepatic metastases	Extra-hepatic metastases
Delbeke *et al.*[58]	N/A	Se: 0.91 *vs* 0.81 Sp: 0.91 *vs* 0.6	Se: 1 *vs* 0.74 Sp: 0.4 *vs* 0.5
Ruhlmann *et al.*[59]	N/A	N/A	N/A
Imdahl *et al.*[60]	Se: 0.92 *vs* 0.88 Sp: 0.87 *vs* 0.89	Se: 1 *vs* 0.87 Sp: 0.98 *vs* 0.91	Se: 0.94 *vs* 0.64 Sp: 1 *vs* 0.98
Whiteford *et al.*[61]	Se: 0.9 *vs* 0.71 Sp: 0.92 *vs* 0.85	Se: 0.89 *vs* 0.71 Sp: 0.98 *vs* 0.92	Se: 0.94 *vs* 0.67 Sp: 0.98 *vs* 0.96
Arulampalam *et al.*[62]	Se: 1 *vs* 0.75 Sp: 0.86 *vs* 1	Se: 1 *vs* 0.45 Sp: 1 *vs* 1	Se: 0.93 *vs* 0.73** Sp: 0.58 *vs* 0.75**
Desai *et al.*[63]	N/A	N/A	N/A
Even-Sapir *et al.*[26]	Se: 0.96 *vs* 0.88° Sp: 0.89 *vs* 0.74°	N/A	N/A
Nakamoto *et al.*[64]	Se: 0.89 *vs* 0.75 Sp: 0.96 *vs* 0.81		
Akiyoshi *et al.*[65]	N/A	Se: 0.92 *vs* 1 Sp: 1 *vs* 0.98	Se: 0.43 *vs* 0.89°° Sp: 0.95 *vs* 0.52°°

CRC: colorectal carcinoma; FDG: [^{18}F]-fluoro-2'-deoxy-D-glucose; PET: positron emission tomography; CDW: conventional diagnostic workup; CT: X-ray computed tomography; N/A: not applicable; Se: sensitivity, Sp: specificity. *Including one patient in whom an incidental second tumor 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 III.—*Prognostic stratification by baseline FDG-PET.*

Author	Year	N.	Inclusion	Therapy	PET-parameters	Outcome-parameter	Favourable criteria	Results	Sign.
Calvo *et al.*[69]	2004	25	cT2-4Nx primary rectal cancer	CRT (45-50.4Gy, 5FU/FA or tegafur) + resection	SUV_{max}	3-year overall survival	SUV_{max} ≥6	92% *vs* 60%	0.04
Dimitrakopoulou-Strauss *et al.*[70]	2004	20	CRC metastases	2nd line FOLFOX	SUV_{mean}, k1-4, FD, Vb	1-year overall survival	SUV_{mean}	CCR: 67%	—
de Geus-Oei *et al.*[71]	2006	152	CRC metastases	Resection or pyrimidine based chemotherapy	SUV_{mean}	Median overall survival	k1, k3, Vb & FD SUV_{mean} ≤4.26	CCR: 76% 32 months *vs* 19 months	0.017
Riedl *et al.*[72]	2007	90	CRC liver metastases	Resection	SUV_{max}	Median overall survival	SUV_{max}<5 SUV_{max}<7 SUV_{max}<10	>72 months *vs* 48 months >72 months *vs* 42 months >72 months *vs* 35 months	0.014 0.025 0.0095
Scott *et al.*[21]	2008	91	Suspected recurrence CRC based on CDW	Various	Additional sites detected	1-year progression free survival	No additional lesions detected	60.5% *vs* 36.2%	0.04
		96	Resectable liver or pulmonary metastases	Various				65.9% *vs* 39.2%	0.01

FDG: [18F]-fluoro-2'-deoxy-D-glucose; PET: positron emission tomography; CRT: chemoradiotherapy; 5FU: 5-fluorouracil; FA: folinic acid; SUV: standardized uptake value; CRC: colorectal carcinoma; FOLFOX: 5FU/FA/oxaliplatin; k1-4: 2-compartment rate constants; FD: fractal dimensions, Vb: vascular fraction; CCR: correct classification rate; CDW: conventional diagnostic workup.

pected 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.

Prognostic stratification and response prediction by PET

DETERMINATION OF PROGNOSIS BY PET

The use of (semi)quantitative parameters for tracer uptake before start of treatment, such as the mean standardized uptake value (SUV_{mean}), maximum standardized uptake value (SUV_{max}) or parameters of FDG-metabolism in tumor lesions, can be related to overall patient outcome (prognosis). This might help in selecting the appropriate treatment for an individual patient (Table III).

Calvo *et al.*[69] 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_{max} of 6 or lower on baseline FDG-PET was significantly higher than for higher values for the SUV_{max} (92% *vs* 60%; P=0.04) (Table III). The above-mentioned paper of Scott *et al.*[21] 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% *vs* 36.2%; P=0.04).

Most studies which used baseline PET to predict patient outcome used individuals with metastasized disease treated either with surgery or chemotherapy. Dimitrakopoulou-Strauss *et al.*[70] published a paper on patients with metastatic CRC treated with second line folinic acid/5FU/oxaliplatin (FOLFOX). They used FDG SUV_{mean}, fractal dimensions and pharmacoki-

TABLE IV.—*Therapy response prediction by baseline FDG-PET.*

First author	Year	N.	Inclusion	Therapy	PET-Parameters	Outcome-parameter	Favourable criteria	Results	Sign.
Oku *et al.*[73]	2002	40	cT_{2-4} and/or N_{1-3} primary rectal cancer	Radiotherapy (50 Gy)	SUV_{mean}	CT shrinkage rate at 3-5 weeks		Correlation: -0.162	0.326
Dimitrakopoulou-Strauss *et al.*[70]	2003	28	CRC metastases	2nd line FOLFOX	SUV_{mean}	Clinical response (WHO-guidelines): PD, SD or PR	SUV_{mean}	CCR: 96% (PD), 47% (SD) and 0% (PR)	—

FDG: [18F]-fluoro-2'-deoxy-D-glucose; PET: positron emission tomography; SUV: standardized uptake value; CT: X-ray computed tomography; CRC: colorectal carcinoma; FOLFOX: 5FU/FA/oxaliplatin; WHO: World Health Organization; PD: progressive disease; SD: stable disease; PR: partial remission; CCR: correct classification rate.

netic rate constants combined in a discriminant analysis in 25 patients. SUV_{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_{mean} in 152 patients with CRC metastases treated by resection or pyrimidine-based chemotherapy. The 76 patients with a SUV_{mean} lower than 4.26 had a longer median overall survival than the rest of the patients (32 months *vs* 19 months; P=0.017).[71] Riedl *et al.*[72] performed a similar experiment in surgically treated liver metastases and found overall survival benefit in subgroups of patients with lowest SUV_{max} for a range of cut-off values (Table III). Scott *et al.*[21] 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% *vs* 39.2%; P=0.01).

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_{mean} are related to individual patient outcome (Table IV).

For primary rectal cancer treated with 50 Gy of neoadjuvant radiotherapy prior to surgery, Oku *et al.*[73] found a negative correlation between the shrinkage rate on CT and the baseline SUV_{mean} measured by FDG-PET of the lesion (*i.e.* the larger the SUV_{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_{mean} correlated with morphological changes and rationalized that a high SUV at follow-up indicated both a high SUV_{mean} at baseline and a low reduction of uptake during treatment.

Dimitrakopoulou-Strauss *et al.*[74] published a paper on patients with metastatic CRC treated with second line FOLFOX. They showed by discriminant analysis that the pretreatment SUV_{mean} correctly identified non-responders (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 randomized controlled trials have been published using baseline FDG-PET for determination of individual treatment strategy.

Treatment follow-up by PET-response evaluation

After localised or during systemic treatment, tracer uptake in lesions can be monitored. Uptake during fol-

TABLE V.—*Radiotherapy and multimodality (neoadjuvant) therapy response evaluation in locally advanced rectal cancer by FDG-PET.*

First author	Year	N.	Inclusion	Therapy	PET-parameter
Engenhart *et al.*[77]	1992	21	Unresectable recurrence	40 Gy photons, 14 Gy neutrons	ΔSUV_{mean} at 8-9 weeks
Guillem *et al.*[93]	2000	15	cT_3 and/or N_1	Neoadjuvant CRT (50.4 Gy, 5FU/FA)	VRS, ΔSUV_{mean}, ΔTLG at 5 weeks
Oku *et al.*[73]	2002	40	cT_{2-4} and/or N_{1-3}	Neoadjuvant radiotherapy (50 Gy)	SUV_{mean}-ratio at 3-5 weeks
Amthauer *et al.*[84]	2004	20	$cT_{3/4}M_0$	Neoadjuvant CRT (45 Gy, 5FU/FA) + RH	ΔSUV_{max} at 2-4 weeks
Calvo *et al.*[69]	2004	25	cT_2-$4N_x$	Neoadjuvant CRT (45-50.4 Gy, 5FU/FA or tegafur)	Absolute change in SUV_{max} at 4-5 weeks
Guillem *et al.*[85]	2004	15	cT_3 and/or N_1	Neoadjuvant CRT (50.4 Gy, 5FU/FA)	ΔSUV_{max}, ΔTLG at 5 weeks
Denecke *et al.*[78]	2005	23	$cT_3/4M_0$	Neoadjuvant CRT (45 Gy, 5FU/FA) + RH	ΔSUV_{max} at 2-4 weeks
Konski *et al.*[86]	2005	20	$uT_{3/4}$ and/or N_1	Neoadjuvant CRT (45-55 Gy ± fluoropyrimidine)	ΔSUV_{max} at 3-4 weeks
Capirci *et al.*[79]	2006	88	$cT_{3/4}$ and/or N_{1-3} M_0	Neoadjuvant CRT (50-56 Gy, 5FU)	VRS, (SUV_{max}) at 7 weeks
Cascini *et al.*[90]	2006	33	$cT_{3/4}$ and/or N_1	Neoadjuvant CRT (45 Gy, FOLFOX + raltitrexed)	ΔSUV_{mean} at 12 days
Kalff *et al.*[80]	2006	34	$cT_{3/4}N_xM_0$	Neoadjuvant CRT (50.4 Gy, 5FU/FA ± oxaliplatin/carboplatin)	VRS at 3-4 weeks
Capirci *et al.*[87]	2007	45	$cT_{3/4}$	Neoadjuvant CRT (50-56 Gy ± fluoropyrimidine)	ΔSUV_{max} at 4-5 weeks
Melton *et al.*[88]	2007	21	$cT_{3/4}$ and/or N_1	Neoadjuvant CRT (50.4 Gy ± fluoropyrimidine or FOLFOX)	ΔSUV_{max} at 4-6 weeks
Konski *et al.*[83]	2008	53	$cT_{3/4}N_x$ or N_1	Neoadjuvant CRT (50.4-54 Gy, fluoropyrimidines, mitomycin-C)	ΔSUV_{max} at 3-4 weeks
Kristiansen *et al.*[81]	2008	30	$cT_{3/4}$	Neoadjuvant CRT (60 Gy, uracil, tegafur, FA)	Visual response at 7 weeks (PET/CT)
Nakagawa *et al.*[92]	2008	29	$uT_{3/4}$ or N_1	Neoadjuvant radiotherapy (50 Gy)	SUV_{mean}-ratio at 2-3 weeks
Rosenberg *et al.*[91]	2008	29	$uT_3N_xM_0$	Neoadjuvant CRT (45 Gy, 5FU)	ΔSUV_{mean} at 14 days and at 5 weeks
Siegel *et al.*[89]	2008	32	uT_2N+ or uT_3N_x	Neoadjuvant short course CRT (25 Gy, 5FU)	ΔSUV_{max} at 9 days
Vliegen *et al.*[82]	2008	20	$cT_{3/4}$	Neoadjuvant CRT (50.4 Gy, capecitabine)	ΔSUV_{max} at 4-6 weeks

(C)RT: (chemo)radiotherapy; CT: X-ray computed tomography; DFS: disease free survival; FA: folinic acid; FDG: [18F]-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: standardized uptake value; TLG: total lesion glycolysis; TRG: tumor regression grade; T-stage: TNM-classification tumor stage; VRS: visual response score.

Outcome-parameter	Response criteria	Results	Sigm.
Local control	Complete response (SUV_{mean} normalization to background)	PPV: 3/15 (0.2) NPV: 4/6 (0.67)	
Histological response at 4-6 weeks	Any decrease	PPV: 15/15 (1) NPV: 0/0 (n/a)	—
CT shrinkage rate at 3-5 weeks	—	Correlation -0.383	0.014
Histological response at 6-8 weeks	Histological CR/PR, ΔSUV_{max}>-36%	PPV: 6/6 (1.00) NPV: 13/14 (0.93)	<0.001
Histological response at 5-8 weeks	Histological T-stage decrease	Responders: -3.3 Non-responders: -1.9	0.03
Median OS and DFS	ΔSUV_{max}, ≥-62.5% ‰TLG ?-69.5%	Mean OS: >54 weeks *vs* ~39 weeks Mean DFS: >54 weeks *vs* ~26 weeks Mean OS: >54 weeks *vs* ~27 weeks Mean DFS: >54 weeks *vs* ~26 weeks	0.08 0.02 0.03 0.01
ΔT-stage at 6-8 weeks	Any T-stage decrease or >65% volume reduction ΔSUV_{max} <-36%	PPV: 13/17 (0.76) NPV: 6/6 (1.00)	0.002
Histological response at 6-8 weeks	Pathological complete response	ΔSUV_{max} -74.5% *vs* -52.1%	0.24
5-year OS and DFS	VRS ≤1 (focal/diffuse) or SUV_{max} <1.4	5-year OS: 91% *vs* 70% 5-year DFS: 81% *vs* 62%	0.024 0.003
Histological response at 8 weeks	Histological response ≤ scattered residual cells ΔSUV_{mean} ≥-52%	ΔSUV_{mean} -63% *vs* -22% PPV: 13/13 (1.00) NPV: 18/20 (0.9)	<0.0001
3-year OS and DFS	VRS: CR, PR or SD/PD	3-year OS: 100%, 79%, 0% 3-year DFS: 100%, 47%, 0%	<0.0001
Histological response at 8-10 weeks	Histological response ≤ scattered residual cells ΔSUV_{max} ≥-66.2%	ΔSUV_{max} -75.9% *vs* -46.9% PPV: 17/22 (0.77) NPV: 19/23 (0.89)	<0.0001 0.0015
Histological response at 8-10 weeks	Histological down-staging ΔSUV_{max} ≥-70%	ΔSUV_{max} -72% *vs* -44% PPV: 7/12 (0.58) NPV: 9/9 (1.00)	<0.001
Histological response	Histological complete response (T0N0)	Responders: -67% Non-responders: -55%	0.08
Histological response at 8 weeks	Complete histological response Negative PET on follow-up	PPV: 10/12 (0.83) NPV: 6/18 (0.13)	—
Histological response at 3-11 weeks	Grade 0-3 histological response	Significant correlation	0.047
Survival Histological response at 10 weeks	SUV_{mean}-ratio<1 ΔSUV_{mean} at 14 days ?-35% Grade 1 histological response ΔSUV_{mean} at 14 days ?-57.7%	Significantly longer PPV: 7/12 (0.58) NPV: 14/17 (0.82) PPV: 7/11 (0.64)	0.0121 —
Histological response at 2 weeks	Grade 1 histological response Histological down-staging ≤ predominant fibrotic changes (TRG2) ΔSUV_{max} ≥-40%	NPV: 15/18 (0.83) No correlation	—
Histological response at 6-8 weeks	TRG ≤2	-83% vs -59.4%	0.025

low-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 tumors).[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.

Response evaluation of radiotherapy in rectal cancer

Engenhart *et al.*[77] were the first to address the effect of irradiation on inoperable pre-sacral 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.*[73] described a significant negative (r=-0.383, P=0.014) correlation between shrinkage rate on CT (fractional decrease in tumor 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 tumor (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.*[69] described a significant difference in SUV_{max}-reduction (ΔSUV_{max}) between patients with reduction in T-stage compared to non-responders (-3.3 *vs* -1.9 SUV-units; P=0.03). Denecke *et al.*[78] showed that a cut-off for ΔSUV_{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,[79-81] $\Delta SUV_{max,}$ [79, 82-89] $\Delta SUV_{mean,}$ [90, 91] SUV-ratio [92] and γTLG (change in total lesion glycolysis: the product of metabolic volume and SUV) at different intervals after radiotherapy, varying from 12 days [90] up to 7 weeks [79, 81] and all found a significant relation with semi-quantitative histological response (Table V). Depending on response criteria, predictive values of FDG-PET response (NPV) ranged from 83% [91] to 100% [88] and predictive values of FDG-PET non-response (PPV) varied from 77% [87] to 100%.[84, 90] The worst results were found by Engenhart *et al.*[77] and Melton *et al.*[88] who used rigorous criteria for definition of treatment response (complete SUV normalisation [77] and ΔSUV_{max} ≥70% determined by ROC analysis [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 [77] or regression score during histopathological examination.[88] Kristiansen *et al.*[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 *et al.*,[93] who found an accuracy of 60% for PET to define the extent of pathological response. Rosenberg *et al.*[91] attributed their low PPV of 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.[80, 85] Guillem *et al.*[85] dichotomized 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_{max} of 1.4 on the follow-up PET-scan. They showed higher median overall survival (>54 weeks *vs* 39 weeks; P=0.08) and higher median disease-free survival (>54 weeks *vs* 26 weeks; P=0.02) of responders compared to non-responders. The corresponding 5-year overall survival percentages were 91% *vs* 70% (P=0.024) and 5-year disease free survival percentages were 81% *vs* 62% (P=0.003). In another study, in 34 patients treated with neoadjuvant CRT before curative surgery, visual PET response was categorized 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).[80]

A drawback of post-radiotherapy FDG-PET is the radiation-induced inflammation.[94] This causes influx and activation of macrophages, neutrophils, fibroblasts and granulation tissue, that can accumulate approximately 25% of FDG uptake.[95] On the other hand, direct effect of radiation may induce tumor cell dormancy ("stunning") which mimics glucose metabolic

TABLE VI.—*Response evaluation for local ablative treatment for unresectable CRC liver metastases by FDG-PET.*

First author	Year	N.	Therapy	PET-Parameters	Outcome-parameter	Response criteria	Results
Langenhoff *et al.*[98]	2002	22	CSA or RFA	Visual interpretation within 3 weeks	Histopathology, follow-up >9 months, CT	PET-negative	NPV:17/17 (1.00) PPV: 4/5 (0.80)
Donckier *et al.*[99]	2003	17	RFA	Visual interpretation at 1 week	Follow-up >3 months by CT	PET-negative	NPV: 7/13 (0.54) PPV: 4/4 (1.00)
				Visual interpretation at 3 months			NPV: 6/8 (0.75) PPV: 8/8 (1.00)
Joosten *et al.*[97]	2005	43	CSA or RFA	Visual interpretation within 3 weeks	Follow-up >3 months by CT	PET-negative	NPV: 35/36 (0.97) PPV: 6/7 (0.86)
Denecke *et al.*[49]	2007	21	LITT	Visual interpretation at suspected progression (MRI or CEA)	Histopathology, follow-up >12 months by MRI	PET-negative	NPV: 24/25 (0.96) PPV: 28/29 (0.97)
				SUV_{max} at suspected progression (MRI or CEA)		$SUV_{max} \leq 4.2$	NPV: 23/24 (0.96) PPV: 28/30 (0.93)

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: standardized uptake value.

response.[84] Siegel *et al*.[89] saw metabolic response (ΔSUV_{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,[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 individualized surgery. This could include sphincter-saving surgery in deep-seated tumors, less aggressive treatment in limited disease or planning of intraoperative radiation therapy. However, no studies provide definitive evidence. Apart from selection for individualized 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.

EFFECT OF LOCAL ABLATIVE THERAPY OF LIVER METASTASES

Qualitative assessment of FDG-PET imaging after cryosurgical or RFA 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.[96] The NPV of FDG-PET 3 weeks after local ablative therapy varied from 97% [97] to 100% [98] and of a positive PET from 80% [98] to 86% [97] in two studies treating 81 patients with 237 hepatic lesions. The lower PPV is caused by false-positive results due to liver abscesses occurring after local ablative therapy (Table VI).

Donckier *et al.*[99] compared the predictive value of FDG-PET 1 week and 3 months after RFA 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% *vs* 75%) whereas both early and late positive PET show 100% (P)PV for residual tumor or recurrence. Apparently the optimal timeframe to judge the effect of local ablative therapy is somewhere between 1 weeks and 3 months after surgery.

Denecke *et al.*[49] used FDG-PET after LASER induced thermotherapy ablation (LITT) of unresectable liver metastases when tumor progression was suspected on MRI or obscure rising serum levels of CEA. Standardized visual interpretation of the images based on consensus of two blinded nuclear medicine physicians led to a NPV of PET of 96% and a PPV of 97%. Using the SUV_{max} they found a NPV of 96% and a PPV 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 tumor 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 tumor 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 tumor ablation or with early relapse after local ablative treatment for unresectable liver metastases. Assessment of local control by FDG-PET 3 weeks after local ablative treatment seems advisable.

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 h due to decrease in glucose transport, a decrease in hexokinase activity.[100] This effect can be monitored by FDG-PET during systemic treatment of liver metastases.

Findlay *et al.*[101] were the first to report the effect of 5FU with or without interferon-α chemotherapy on liver metastases >3 cm in diameter with FDG-PET. They used morphological CT response as outcome measure and found that a reduction in tumor 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 tumor cell kill (*i.e.* early inflammatory reaction).

The two above-mentioned papers by Dimitrakopou-lou-Strauss *et al.*[70, 74] 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.[70, 102, 103] Dimitrakopoulou-Strauss *et al.*[70] 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 two-compartment rate constants, vascular fraction and fractal dimensions correctly classified overall survival in 78% of the patients.[70] 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 [102] it was shown that the percentage decrease in SUV_{mean} (ΔSUV_{mean}) and glucose metabolic rate (MR_{glc}, derived from two-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 ΔMR_{glc} 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.*[103] 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% CI: 0.874-11.187), but was significantly associated with disease-free survival (3.826; 95% CI: 1.39-10.534). CT-response alone did predict overall survival (hazard ratio: 4.584; 95% CI: 1.133-18.536) and progression free survival (hazard ratio:

TABLE VII.—*Chemotherapy response evaluation by FDG-PET for CRC metastases.*

First author	Year	N.	Inclusion	Therapy	PET-Parameters	Outcome-parameter	Favourable criteria	Results	Sign.
Findlay *et al.*[101]	1996	18	CRC liver metastases ≥3 cm	5FU±IF∝	ΔT:L at 4-5 weeks	CT response (WHO guidelines) at 12 weeks	CT response: CR or PR ΔT:L ≥-15%	Sensitivity: 1.00 Specificity: 0.75	—
Dimitrakopoulou-Strauss *et al.*[74]	2003	28	CRC metastases	2nd line FOLFOX	SUV_{mean}	Clinical response (WHO-guidelines)	Clinical response: PD, SD or PR	CCR: 92% (PD) 57% (SD) and 0% (PR)	—
Dimitrakopoulou-Strauss *et al.*[74]	2004	20	CRC metastases	2nd line FOLFOX	SUV_{mean}, k1-4, FD, Vb at 3 months	1-year overall survival	SUV_{mean} k1, k3, Vb, FD	CCR: 69%	—
de Geus-Oei *et al.*[102]	2008	50	CRC metastases	Various schedules	ΔSUV_{mean}, ΔMR_{glc} at 2 months	Median overall survival	ΔSUV_{mean} ≥-20% ΔMR_{glc} ≥-65%	CCR: 78% 25 weeks *vs* 15 weeks 32 weeks *vs* 18 weeks	0.009 0.021
Small *et al.*[103]	2008	40	CRC liver metastases	Neoadjuvant FOLFOX/FOLFIRI±bevacizumab	Visual PET-CT response	Overall survival Disease free survival	CR or PR	HR 3.127 HR 3.826	0.079 0.009

CCR: correct classification rate; CR: complete remission; CRC: colorectal carcinoma; CT: X-ray computed tomography; FA: folinic acid; FD: fractal dimensions; ^{18}F-FDG: [18F]-fluoro-2'-deoxy-D-glucose; FOLFIRI: 5FU/FA/irinotecan; FOLFOX: 5FU/FA/oxaliplatin; 5FU: 5-fluorouracil; IFα: interferon-∝; k1-4: 2-compartment rate constants; HR: hazard ratio; MR_{glc}: glucose metabolic rate; PET: positron emission tomography; PD: progressive disease; PR: partial remission; SD: stable disease; SUV: standardized uptake value; T:L: tumor to normal liver ratio; Vb: vascular fraction; WHO: World Health Organization.

2.925; 95% CI: 1.078-7.937). Results of all above-mentioned studies are displayed in Table VII.

Thus, the degree of metabolic response during treatment appeared to correlated with both pathological response and survival. However, it is of concern that the test-retest reproducibility of the SUV_{mean} using a semi-automatically delineation of the lesion (50% of maximum value) is limited. When comparing the SUV_{mean} of 28 lung cancer patients determined on the same system setup on two consecutive days, Krak *et al.*[104] found a standard deviation of the relative differences of both SUV_{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 SUV_{mean}'s was 7%.[105] These standard deviations are larger when using different setups (multicenter trials). This suggests that measured tumor responses of less than ~15-20% (two 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 randomized 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.[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 tumor 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 metastasized 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 individualized 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 tumor 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 metastasized 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 tumor type.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T *et al.* Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.
2. Ries L, Melbert D, Krapcho M, Stinchcomb D, Howlader N, Horner M, *et al.* SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site; 2008.
3. Punt CJ. New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 2004;15:1453-9.
4. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-9.
5. Mijnhout GS, Riphagen, II, Hoekstra OS. Update of the FDG PET search strategy. Nucl Med Commun 2004;25:1187-9.
6. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-72.
7. Davey K, Heriot AG, Mackay J, Drummond E, Hogg A, Ngan S *et al.* The impact of 18-fluorodeoxyglucose positron emission tomography-computed tomography on the staging and management of primary rectal cancer. Dis Colon Rectum 2008;51:997-1003.
8. Gearhart SL, Frassica D, Rosen R, Choti M, Schulick R, Wahl R. Improved staging with pretreatment positron emission tomography/computed tomography in low rectal cancer. Ann Surg Oncol 2006;13:397-404.
9. Heriot AG, Hicks RJ, Drummond EG, Keck J, Mackay J, Chen F *et al.* Does positron emission tomography change management in primary rectal cancer? A prospective assessment. Dis Colon Rectum 2004; 47:451-8.
10. Bassi MC, Turri L, Sacchetti G, Loi G, Cannillo B, La Mattina P *et al.* FDG-PET/CT imaging for staging and target volume delineation in preoperative conformal radiotherapy of rectal cancer. Int J Radiat Oncol Biol Phys 2008;70:1423-6.
11. Furukawa H, Ikuma H, Seki A, Yokoe K, Yuen S, Aramaki T *et al.* Positron emission tomography scanning is not superior to whole body multidetector helical computed tomography in the preoperative staging of colorectal cancer. Gut 2006;55:1007-11.
12. Park IJ, Kim HC, Yu CS, Ryu MH, Chang HM, Kim JH *et al.* Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. Eur J Surg Oncol 2006;32:941-7.
13. Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. J Nucl Med 2003;44:1784-8.
14. Veit-Haibach P, Kuehle CA, Beyer T, Stergar H, Kuehl H, Schmidt J *et al.* Diagnostic accuracy of colorectal cancer staging with whole-body PET/CT colonography. JAMA 2006;296:2590-600.
15. Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez-Sainz J, Gomez-Rio M, Bellon-Guardia M, Ramos-Font C *et al.* Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging 2007;34:859-67.
16. Glimelius B, Oliveira J. Rectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii31-2.
17. Van Cutsem EJ, Oliveira J. Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii29-30.
18. Van Cutsem EJ, Oliveira J. Advanced colorectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii33-4.
19. Beets G, Penninckx F, Schiepers C, Filez L, Mortelmans L, Kerremans R *et al.* Clinical value of whole-body positron emission tomography with [^{18}F]fluorodeoxyglucose in recurrent colorectal cancer. Br J Surg 1994;81:1666-70.
20. Simo M, Lomena F, Setoain J, Perez G, Castellucci P, Costansa JM *et al.* FDG-PET improves the management of patients with suspected recurrence of colorectal cancer. Nucl Med Commun 2002;23:975-82.
21. Scott AM, Gunawardana DH, Kelley B, Stuckey JG, Byrne AJ, Ramshaw JE *et al.* PET changes management and improves prognostic stratification in patients with recurrent colorectal cancer: results of a multicenter prospective study. J Nucl Med 2008;49:1451-7.
22. Selvaggi F, Cuocolo A, Sciaudone G, Maurea S, Giuliani A, Mainolfi C. FGD-PET in the follow-up of recurrent colorectal cancer. Colorectal Dis 2003;5:496-500.
23. Flamen P, Hoekstra OS, Homans F, Van Cutsem E, Maes A, Stroobants S *et al.* Unexplained rising carcinoembryonic antigen

(CEA) in the postoperative surveillance of colorectal cancer: the utility of positron emission tomography (PET). Eur J Cancer 2001; 37:862-9.
24. Flamen P, Stroobants S, Van Cutsem E, Dupont P, Bormans G, De Vadder N *et al*. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894-901.
25. Valk PE, Abella-Columna E, Haseman MK, Pounds TR, Tesar RD, Myers RW *et al*. Whole-body PET imaging with [18F]fluorodeoxyglucose in management of recurrent colorectal cancer. Arch Surg 1999;134:503-11; discussion 11-3.
26. Even-Sapir E, Parag Y, Lerman H, Gutman M, Levine C, Rabau M *et al*. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resection. Radiology 2004;232:815-22.
27. Shen YY, Liang JA, Chen YK, Tsai CY, Kao CH. Clinical impact of 18F-FDG-PET in the suspicion of recurrent colorectal cancer based on asymptomatically elevated serum level of carcinoembryonic antigen (CEA) in Taiwan. Hepatogastroenterology 2006;53:348-50.
28. Faneyte IF, Dresen RC, Edelbroek MA, Nieuwenhuijzen GA, Rutten HJ. Pre-operative staging with positron emission tomography in patients with pelvic recurrence of rectal cancer. Dig Surg 2008;25:202-7.
29. Kalff V, Hicks RJ, Ware RE, Hogg A, Binns D, McKenzie AF. The clinical impact of (18)F-FDG PET in patients with suspected or confirmed recurrence of colorectal cancer: a prospective study. J Nucl Med 2002;43:492-9.
30. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. Cancer 2005;104:2658-70.
31. Lai DT, Fulham M, Stephen MS, Chu KM, Solomon M, Thompson JF *et al*. The role of whole-body positron emission tomography with [18F]fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver. Arch Surg 1996;131:703-7.
32. Vitola JV, Delbeke D, Sandler MP, Campbell MG, Powers TA, Wright JK *et al*. Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. Am J Surg 1996;171:21-6.
33. Ogunbiyi OA, Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Birnbaum EH *et al*. Detection of recurrent and metastatic colorectal cancer: comparison of positron emission tomography and computed tomography. Ann Surg Oncol 1997;4:613-20.
34. Fong Y, Saldinger PF, Akhurst T, Macapinlac H, Yeung H, Finn RD *et al*. Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. Am J Surg 1999;178:282-7.
35. Zhuang H, Sinha P, Pourdehnad M, Duarte PS, Yamamoto AJ, Alavi A. The role of positron emission tomography with fluorine-18-deoxyglucose in identifying colorectal cancer metastases to liver. Nucl Med Commun 2000;21:793-8.
36. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. Ann Surg 2001;233:293-9.
37. Topal B, Flamen P, Aerts R, D'Hoore A, Filez L, Van Cutsem E *et al*. Clinical value of whole-body emission tomography in potentially curable colorectal liver metastases. Eur J Surg Oncol 2001;27:175-9.
38. Ruers TJ, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T *et al*. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388-95.
39. Arulampalam TH, Francis DL, Visvikis D, Taylor I, Ell PJ. FDG-PET for the pre-operative evaluation of colorectal liver metastases. Eur J Surg Oncol 2004;30:286-91.
40. Bohm B, Voth M, Geoghegan J, Hellfritzsch H, Petrovich A, Scheele J *et al*. Impact of positron emission tomography on strategy in liver resection for primary and secondary liver tumors. J Cancer Res Clin Oncol 2004;130:266-72.
41. Rosa F, Meimarakis G, Stahl A, Bumm R, Hahn K, Tatsch K *et al*. Colorectal cancer patients before resection of hepatic metastases. Impact of (18)F-FDG PET on detecting extrahepatic disease. Nuklearmedizin 2004;43:135-40.
42. Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann Surg 2004;240:1027-34; discussion 35-6.
43. Teague BD, Morrison CP, Court FG, Chin VT, Costello SP, Kirkwood ID *et al*. Role of FDG-PET in surgical management of patients with colorectal liver metastases. ANZ J Surg 2004;74:646-52.
44. Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. Br J Surg 2005;92:362-9.
45. Amthauer H, Denecke T, Hildebrandt B, Ruhl R, Miersch A, Nicolaou A *et al*. Evaluation of patients with liver metastases from colorectal cancer for locally ablative treatment with laser induced thermotherapy. Impact of PET with 18F-fluorodeoxyglucose on therapeutic decisions. Nuklearmedizin 2006;45:177-84.
46. Joyce DL, Wahl RL, Patel PV, Schulick RD, Gearhart SL, Choti MA. Preoperative positron emission tomography to evaluate potentially resectable hepatic colorectal metastases. Arch Surg 2006;141:1220-6; discussion 7.
47. Khan S, Tan YM, John A, Isaac J, Singhvi S, Guest P *et al*. An audit of fusion CT-PET in the management of colorectal liver metastases. Eur J Surg Oncol 2006;32:564-7.
48. Chua SC, Groves AM, Kayani I, Menezes L, Gacinovic S, Du Y *et al*. The impact of 18F-FDG PET/CT in patients with liver metastases. Eur J Nucl Med Mol Imaging 2007;34:1906-14.
49. Denecke T, Steffen I, Hildebrandt B, Ruhl R, Streitparth F, Lehmkuhl L *et al*. Assessment of local control after laser-induced thermotherapy of liver metastases from colorectal cancer: contribution of FDG-PET in patients with clinical suspicion of progressive disease. Acta Radiol 2007;48:821-30.
50. Huguet EL, Old S, Praseedom RK, Balan KK, Gibbs P, Jamieson NV. F18-FDG-PET evaluation of patients for resection of colorectal liver metastases. Hepatogastroenterology 2007;54:1667-71.
51. Kong G, Jackson C, Koh DM, Lewington V, Sharma B, Brown G *et al*. The use of 18F-FDG PET/CT in colorectal liver metastases--comparison with CT and liver MRI. Eur J Nucl Med Mol Imaging 2008;35:1323-9.
52. Sørensen M, Mortensen FV, Høyer M, Vilstrup H, Keiding S. FDG-PET improves management of patients with colorectal liver metastases allocated for local treatment: a consecutive prospective study. Scand J Surg 2007;96:209-13.
53. Wiering B, Krabbe PF, Dekker HM, Oyen WJ, Ruers TJ. The role of FDG-PET in the selection of patients with colorectal liver metastases. Ann Surg Oncol 2007;14:771-9.
54. Pawlik TM, Assumpcao L, Vossen JA, Buijs M, Gleisner AL, Schulick RD *et al*. Trends in nontherapeutic laparotomy rates in patients undergoing surgical therapy for hepatic colorectal metastases. Ann Surg Oncol 2009;16:371-8.
55. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240:438-47; discussion 47-50.
56. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604-8.
57. Akhurst T, Kates TJ, Mazumdar M, Yeung H, Riedel ER, Burt BM *et al*. Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol 2005;23:8713-6.
58. Delbeke D, Vitola JV, Sandier MP, Arildsen RC, Powers TA, Kelly Wright J *et al*. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med 1997;38:1196-201.

59. Ruhlmann J, Schomburg A, Bender H, Oehr P, Robertz-Vaupel GM, Vaupel H *et al*. Fluorodeoxyglucose whole-body positron emission tomography in colorectal cancer patients studied in routine daily practice. Dis Colon Rectum 1997;40:1195-204.
60. Imdahl A, Reinhardt MJ, Nitzsche EU, Mix M, Dingeldey A, Einert A *et al*. Impact of ^{18}F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. Langenbecks Arch Surg 2000;385:129-34.
61. Whiteford MH, Whiteford HM, Yee LF, Ogunbiyi OA, Dehdashti F, Siegel BA *et al*. Usefulness of FDG-PET scan in the assessment of suspected metastatic or recurrent adenocarcinoma of the colon and rectum. Dis Colon Rectum 2000;43:759-67; discussion 67-70.
62. Arulampalam T, Costa D, Visvikis D, Boulos P, Taylor I, Ell P. The impact of FDG-PET on the management algorithm for recurrent colorectal cancer. Eur J Nucl Med 2001;28:1758-65.
63. Desai DC, Zervos EE, Arnold MW, Burak WE, Jr., Mantil J, Martin EW, Jr. Positron emission tomography affects surgical management in recurrent colorectal cancer patients. Ann Surg Oncol 2003;10:59-64.
64. Nakamoto Y, Sakamoto S, Okada T, Senda M, Higashi T, Saga T *et al*. Clinical value of manual fusion of PET and CT images in patients with suspected recurrent colorectal cancer. AJR Am J Roentgenol 2007;188:257-67.
65. Akiyoshi T, Oya M, Fujimoto Y, Kuroyanagi H, Ueno M, Yamaguchi T *et al*. Comparison of preoperative whole-body positron emission tomography with MDCT in patients with primary colorectal cancer. Colorectal Dis 2008 [Epub ahead of print].
66. Huebner RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME *et al*. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000;41:1177-89.
67. Sobhani I, Tiret E, Lebtahi R, Aparicio T, Itti E, Montravers F *et al*. Early detection of recurrence by ^{18}FDG-PET in the follow-up of patients with colorectal cancer. Br J Cancer 2008;98:875-80.
68. Fukunaga H, Sekimoto M, Ikeda M, Higuchi I, Yasui M, Seshimo I *et al*. Fusion image of positron emission tomography and computed tomography for the diagnosis of local recurrence of rectal cancer. Ann Surg Oncol 2005;12:561-9.
69. Calvo FA, Domper M, Matute R, Martinez-Lazaro R, Arranz JA, Desco M *et al*. ^{18}F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. Int J Radiat Oncol Biol Phys 2004;58:528-35.
70. Dimitrakopoulou-Strauss A, Strauss LG, Burger C, Ruhl A, Irngartinger G, Stremmel W *et al*. Prognostic aspects of ^{18}F-FDG PET kinetics in patients with metastatic colorectal carcinoma receiving FOLFOX chemotherapy. J Nucl Med 2004;45:1480-7.
71. de Geus-Oei LF, Wiering B, Krabbe PF, Ruers TJ, Punt CJ, Oyen WJ. FDG-PET for prediction of survival of patients with metastatic colorectal carcinoma. Ann Oncol 2006;17:1650-5.
72. Riedl CC, Akhurst T, Larson S, Stanziale SF, Tuorto S, Bhargava A *et al*. ^{18}F-FDG PET scanning correlates with tissue markers of poor prognosis and predicts mortality for patients after liver resection for colorectal metastases. J Nucl Med 2007;48:771-5.
73. Oku S, Nakagawa K, Momose T, Kumakura Y, Abe A, Watanabe T *et al*. FDG-PET after radiotherapy is a good prognostic indicator of rectal cancer. Ann Nucl Med 2002;16:409-16.
74. Dimitrakopoulou-Strauss A, Strauss LG, and Rudi J. PET-FDG as predictor of therapy response in patients with colorectal carcinoma. Q J Nucl Med 2003;47:8-13.
75. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16.
76. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
77. Engenhart R, Kimmig BN, Strauss LG, Hover KH, Romahn J, Haberkorn U *et al*. Therapy monitoring of presacral recurrences after high-dose irradiation: value of PET, CT, CEA and pain score. Strahlenther Onkol 1992;168:203-12.
78. Denecke T, Rau B, Hoffmann KT, Hildebrandt B, Ruf J, Gutberlet M *et al*. Comparison of CT, MRI and FDG-PET in response prediction of patients with locally advanced rectal cancer after multimodal preoperative therapy: is there a benefit in using functional imaging? Eur Radiol 2005;15:1658-66.
79. Capirci C, Rubello D, Chierichetti F, Crepaldi G, Fanti S, Mandoliti G *et al*. Long-term prognostic value of ^{18}F-FDG PET in patients with locally advanced rectal cancer previously treated with neoadjuvant radiochemotherapy. AJR Am J Roentgenol 2006;187:W202-8.
80. Kalff V, Duong C, Drummond EG, Matthews JP, Hicks RJ. Findings on ^{18}F-FDG PET scans after neoadjuvant chemoradiation provides prognostic stratification in patients with locally advanced rectal carcinoma subsequently treated by radical surgery. J Nucl Med 2006;47:14-22.
81. Kristiansen C, Loft A, Berthelsen AK, Graff J, Lindebjerg J, Bisgaard C *et al*. PET/CT and histopathologic response to preoperative chemoradiation therapy in locally advanced rectal cancer. Dis Colon Rectum 2008;51:21-5.
82. Vliegen RF, Beets-Tan RG, Vanhauten B, Driessen A, Oellers M, Kessels AG *et al*. Can an FDG-PET/CT Predict Tumor Clearance of the Mesorectal Fascia after Preoperative Chemoradiation of Locally Advanced Rectal Cancer? Strahlenther Onkol 2008;184:457-64.
83. Konski A, Li T, Sigurdson E, Cohen SJ, Small W, Jr., Spies S, *et al*. Use of molecular imaging to predict clinical outcome in patients with rectal cancer after preoperative chemotherapy and radiation. Int J Radiat Oncol Biol Phys 2008 [Epub ahead of print].
84. Amthauer H, Denecke T, Rau B, Hildebrandt B, Hunerbein M, Ruf J *et al*. Response prediction by FDG-PET after neoadjuvant radiochemotherapy and combined regional hyperthermia of rectal cancer: correlation with endorectal ultrasound and histopathology. Eur J Nucl Med Mol Imaging 2004;31:811-9.
85. Guillem JG, Moore HG, Akhurst T, Klimstra DS, Ruo L, Mazumdar M *et al*. Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining longterm outcomes of rectal cancer. J Am Coll Surg 2004;199:1-7.
86. Konski A, Hoffman J, Sigurdson E, Haluszka O, Engstrom P, Cheng JD *et al*. Can molecular imaging predict response to preoperative chemoradiation in patients with rectal cancer? A Fox Chase Cancer Center prospective experience. Semin Oncol 2005;32:S63-7.
87. Capirci C, Rampin L, Erba PA, Galeotti F, Crepaldi G, Banti E, *et al*. Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemo-radiation therapy. Eur J Nucl Med Mol Imaging 2007;34:1583-93.
88. Melton GB, Lavely WC, Jacene HA, Schulick RD, Choti MA, Wahl RL *et al*. Efficacy of preoperative combined 18-fluorodeoxyglucose positron emission tomography and computed tomography for assessing primary rectal cancer response to neoadjuvant therapy. J Gastrointest Surg 2007;11:961-9; discussion 9.
89. Siegel R, Dresel S, Koswig S, Gebauer B, Hunerbein M, Schneider W *et al*. Response to preoperative short-course radiotherapy in locally advanced rectal cancer: value of f-fluorodeoxyglucose positron emission tomography. Onkologie 2008;31:166-72.
90. Cascini GL, Avallone A, Delrio P, Guida C, Tatangelo F, Marone P *et al*. ^{18}F-FDG PET is an early predictor of pathologic tumor response to preoperative radiochemotherapy in locally advanced rectal cancer. J Nucl Med 2006;47:1241-8.
91. Rosenberg R, Herrmann K, Gertler R, Kunzli B, Essler M, Lordick F *et al*. The predictive value of metabolic response to preoperative radiochemotherapy in locally advanced rectal cancer measured by PET/CT. Int J Colorectal Dis 2009;24:191-200.
92. Nakagawa K, Yamashita H, Nakamura N, Igaki H, Tago M, Hosoi Y *et al*. Preoperative radiation response evaluated by 18-fluorodeoxyglucose positron emission tomography predicts survival

in locally advanced rectal cancer. Dis Colon Rectum 2008;51:1055-60.
93. Guillem JG, Calle Jr JPL, Akhurst T, Tickoo S, Ruo L, Minsky BD *et al.* Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. Dis Colon Rectum 2000;43:18-24.
94. Haberkorn U, Strauss LG, Dimitrakopoulou A, Engenhart R, Oberdorfer F, Ostertag H *et al.* PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. J Nucl Med 1991;32:1485-90.
95. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose *in vivo*: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-80.
96. Antoch G, Vogt FM, Veit P, Freudenberg LS, Blechschmid N, Dirsch O *et al.* Assessment of liver tissue after radiofrequency ablation: findings with different imaging procedures. J Nucl Med 2005;46:520-5.
97. Joosten J, Jager G, Oyen W, Wobbes T, Ruers T. Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. Eur J Surg Oncol 2005;31:1152-9.
98. Langenhoff BS, Oyen WJ, Jager GJ, Strijk SP, Wobbes T, Corstens FH *et al.* Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumor recurrence after local ablative therapy for liver metastases: a prospective study. J Clin Oncol 2002;20:4453-8.
99. Donckier V, Van Laethem JL, Goldman S, Van Gansbeke D, Feron P, Ickx B *et al.* [F-18] fluorodeoxyglucose positron emission tomography as a tool for early recognition of incomplete tumor destruction after radiofrequency ablation for liver metastases. J Surg Oncol 2003;84:215-23.
100. Sharma RI, Smith TA. Colorectal tumor cells treated with 5-FU, oxaliplatin, irinotecan, and cetuximab exhibit changes in ^{18}F-FDG incorporation corresponding to hexokinase activity and glucose transport. J Nucl Med 2008;49:1386-94.
101. Findlay M, Young H, Cunningham D, Iveson A, Cronin B, Hickish T *et al.* Noninvasive monitoring of tumor metabolism using fluorodeoxyglucose and positron emission tomography in colorectal cancer liver metastases: correlation with tumor response to fluorouracil. J Clin Oncol 1996;14:700-8.
102. de Geus-Oei LF, van Laarhoven HW, Visser EP, Hermsen R, van Hoorn BA, Kamm YJ *et al.* Chemotherapy response evaluation with FDG-PET in patients with colorectal cancer. Ann Oncol 2008;19:348-52.
103. Small RM, Lubezky N, Shmueli E, Figer A, Aderka D, Nakache R, *et al.* Response to chemotherapy predicts survival following resection of hepatic colo-rectal metastases in patients treated with neoadjuvant therapy. J Surg Oncol 2009;99:93-8.
104. Krak NC, Boellaard R, Hoekstra OS, Twisk JW, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. Eur J Nucl Med Mol Imaging 2005;32:294-301.
105. Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by ^{18}F-FDG PET in malignant tumors. J Nucl Med 2008;49:1804-8.
106. Westerterp M, Pruim J, Oyen W, Hoekstra O, Paans A, Visser E *et al.* Quantification of FDG PET studies using standardised uptake values in multi-centre trials: effects of image reconstruction, resolution and ROI definition parameters. Eur J Nucl Med Mol Imaging 2007;34:392-404.
107. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT *et al.* The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging 2008;35:2320-33.