

Improved Selection of Patients for Hepatic Surgery of Colorectal Liver Metastases with ^{18}F -FDG PET: A Randomized Study

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With the increasing possibilities for surgical treatment of colorectal liver metastases, careful selection of patients who may benefit from surgical treatment becomes critical. The addition of PET to ^{18}F -FDG may significantly improve conventional staging by CT. Up to now, definitive evidence that the addition of ^{18}F -FDG PET to conventional staging leads to superior clinical results and improved clinical management in these patients has been lacking. In this randomized controlled trial in patients with colorectal liver metastases, we investigated whether the addition of ^{18}F -FDG PET is beneficial and reduces the number of futile laparotomies. **Methods:** A total of 150 patients with colorectal liver metastases selected for surgical treatment by imaging with CT were randomly assigned to CT only ($n = 75$) or CT plus ^{18}F -FDG PET ($n = 75$). Patients were followed up for at least 3 y. The primary outcome measure was futile laparotomy, defined as any laparotomy that did not result in complete tumor treatment, that revealed benign disease, or that did not result in a disease-free survival period longer than 6 mo. **Results:** Patient and tumor characteristics were similar for both groups. The number of futile laparotomies was 34 (45%) in the control arm without ^{18}F -FDG PET and 21 (28%) in the experimental arm with ^{18}F -FDG PET; the relative risk reduction was 38% (95% confidence interval, 4%–60%, $P = 0.042$). **Conclusion:** The number of futile laparotomies was reduced from 45% to 28%; thus, the addition of ^{18}F -FDG PET to the work-up for surgical resection of colorectal liver metastases prevents unnecessary surgery in 1 of 6 patients.

Key Words: colorectal cancer; ^{18}F -FDG-PET; liver metastases; staging; surgery

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Liver metastases are an important issue in the treatment of colorectal cancer. After apparently curative resection of the primary tumor, the liver is often the first site of metastatic disease and may be the only site of spread in as many as 30% of the patients (1,2). Hepatic resection is the only potentially curative treatment in a subset of patients with colorectal liver metastases. Eligibility for hepatic surgery depends on the possibility that all metastases are resected and adequate liver reserve is maintained. There should be no extrahepatic disease, with the possible exception of few resectable lung metastases (3).

To assess whether these strict criteria are met, conventional staging comprising contrast-enhanced CT or MRI of the liver, with additional abdominal and chest CT to exclude extrahepatic disease, is used. Despite current diagnostic work-up, up to 40% of patients prove to have unresectable liver metastases at the time of surgery (4–7). Moreover, within 1 y after potentially curative resection up to 50% of patients show metastatic disease elsewhere, suggesting unrecognized tumor foci at the time of hepatic resection despite extensive radiologic imaging (8–11). Therefore, more accurate staging of patients with colorectal liver metastases is needed to restrict surgical treatment to those who will potentially benefit from the surgery.

Recently, PET with ^{18}F -FDG has been introduced as an additional staging modality in patients with colorectal liver metastases. ^{18}F -FDG PET, as a functional imaging modality, may be of value in the characterization of liver lesions or in the detection of extrahepatic disease. Descriptive studies on the use of ^{18}F -FDG PET have shown an average sensitivity in detecting hepatic metastases of approximately 75% (12,13). Moreover, ^{18}F -FDG PET improved detection

of extrahepatic disease and changed the treatment plan in 25%–30% of the patients (14–17).

These studies were generally aimed at the assessment of accuracy. Such studies are subject to bias and may lead to an overestimation of the added value of ^{18}F -FDG PET. Consequently, without randomized data it remains unclear whether the introduction of ^{18}F -FDG PET to the work-up of patients with potentially resectable liver metastases may indeed prevent unnecessary surgery, being surgery that does not result in complete tumor clearance. A randomized study that compares the standard of care with the new diagnostic strategy is required to comply with the ever-increasing need for evidence-based practice. In the present prospective randomized trial, we investigated the value of the addition of ^{18}F -FDG PET to conventional CT-based diagnostic imaging in patients considered eligible for hepatic surgery of colorectal liver metastases. Outcome measures were the number of futile laparotomies, disease-free survival (DFS), and overall survival (OS).

MATERIALS AND METHODS

Study Design, Eligibility, and Randomization

Patients were enrolled in a phase III randomized, multicenter trial between May 2002 and February 2006. Eligible patients were required to have a history of histologically documented colorectal cancer treated by R0 surgical resection (tumor-free resection margins); 1–4 suspected potentially resectable colorectal liver metastases, without evidence of extrahepatic metastatic disease (with the exception of a maximum of 2 resectable lung metastases) on contrast-enhanced CT of the abdomen, pelvis, and chest; no signs of recurrent or second colorectal carcinoma on barium enema or colonoscopy; and World Health Organization performance status 0–2. In addition, patients were required to be aged 18–75 y. Exclusion criteria included previous malignancies other than in situ carcinoma of the cervix or nonmelanoma skin cancer, unless there had been a disease-free interval of at least 10 y; signs of liver dysfunction (bilirubin, alkaline phosphatase > 3 times the upper limit of normal); active infection; and poorly regulated diabetes mellitus. Four surgical departments experienced in liver surgery and 3 centers for nuclear medicine experienced in ^{18}F -FDG PET participated in this trial. The study was approved by the institutional review boards of all participating centers, and all patients provided written informed consent. The study was registered in the NIH database (NCT00119899; ClinicalTrials.gov).

After standard work-up by CT, all patients were evaluated for eligibility by a multidisciplinary oncology team, including a surgeon and a radiologist specializing in hepatobiliary oncology. Resectable disease was defined as the possibility to obtain negative resection margins with sufficient future liver remnant, after meticulous assessment of CT chest and abdomen scans by the multidisciplinary team. When considered eligible for potentially curative hepatic resection, patients were randomly assigned to the conventional arm (control arm), using no further imaging beyond CT, or to the experimental arm, using additional ^{18}F -FDG PET.

Randomization was performed at the central trial office (by central telephone at the Radboud University Nijmegen Medical Centre) and was based on permuted blocks of 4, with stratification according to center. When randomized to the conventional arm,

patients were scheduled for hepatic surgery without any further diagnostic procedures. When randomized to the experimental arm, additional whole-body ^{18}F -FDG PET was performed, generally within 2 wk (range, 1–5 wk), and results of both CT and ^{18}F -FDG PET scans were again reported at a multidisciplinary oncology meeting. All available data were jointly assessed to review clinical information and diagnostic imaging on a case-by-case basis. In case of discordance between CT and ^{18}F -FDG PET, it was at the referring surgeon's discretion to refrain from surgical resection, opt for additional imaging (e.g., another CT or MRI scan) or additional diagnostic procedures (e.g., ultrasound-guided biopsy), or still attempt surgical resection of the liver metastases.

Imaging

CT. During the study period, all CT examinations of the abdomen (including pelvis) and chest were performed with multi-detector CT scanners. The scan parameters were 120 kV and 150–200 mAs. All patients received about 1 L of diluted ionic oral contrast (Telebrix Gastro; Guerbet) 1 h before the CT examination. Subsequent to a non-contrast-enhanced CT scan of the liver, an intravenous contrast agent containing 35–45 g of iodine (Omnipaque 350 [GE Healthcare] or Xenetix 300 [Guerbet]) was injected using a CT injector (injection rate, 4 mL/s), followed by scans of the liver in 3 distinct enhancement phases (arterial, portal, and late venous phases). The chest and whole abdomen were scanned in combination with the portal phase. The timing of the venous phase was 70 s. Contiguous reconstructed sections were obtained. Reconstructed section thickness was 3–5 mm using a lung and soft-tissue reconstruction kernel. All CT data were stored on optical disks and were evaluated by 2 radiologists with special experience in hepatic imaging.

^{18}F -FDG PET. Patients were referred to 1 of the 3 participating PET centers. Patients fasted for at least 6 h and were hydrated with sugar-free liquids. Patients received a dose of approximately 4 MBq of ^{18}F -FDG per kilogram of body weight. Scans were acquired 60–90 min after ^{18}F -FDG injection on either the ECAT Exact or the ECAT Exact HR+ PET scanners (Siemens CTI) and processed according to the protocols of the respective center. All scans were visually analyzed by experienced nuclear medicine physicians. Standardized uptake values were not calculated. At the time of the study, integrated PET/CT scanners were not available in the participating centers.

Surgical Procedures and Follow-Up

^{18}F -FDG PET was performed within 1–2 wk after randomization, and laparotomy was generally performed within 4 wk after randomization (range, 1–7 wk). At laparotomy, the abdominal cavity was carefully examined for extrahepatic disease. In the case of any suggestion of extrahepatic disease, biopsies were taken for frozen sections. When the biopsy results were positive, further surgical treatment was at the surgeon's discretion, as long as complete tumor clearance could be obtained. Otherwise, further surgical treatment was abandoned by protocol.

Intraoperative ultrasound was performed in all cases to detect and localize all metastatic liver lesions. In case intraoperative examination showed more than 4 lesions, surgical treatment was still performed when possible. Surgery was aimed at obtaining tumor-negative resection margins, when possible, with a safety margin of more than 1 cm. The type of liver resection (anatomic, wedge, or combination) was at the surgeon's discretion, as was the decision made during surgery to use radiofrequency ablation ($n = 8$ in the

control arm, $n = 6$ in the experimental arm). After hepatic surgery, patients did not receive any standard (adjuvant) chemotherapy. Chemotherapy was started only in the case of unresectable disease or tumor recurrence that was not amenable for surgical reintervention. During the study period, systemic chemotherapy consisted of 5-fluorouracil, leucovorin, and oxaliplatin in the first line and irinotecan in the second line. Bevacizumab was added to the standard chemotherapy regimen in 2005.

All patients were followed prospectively at regular predetermined intervals. After hepatic resection, standard follow-up implemented during the first 9 mo consisted of checking once every 3 mo the serum carcinoembryonic antigen (CEA) levels and undergoing abdominal and chest contrast-enhanced CT. Thereafter, patients with normal CEA levels before hepatic resection continued this imaging regimen for the next 3 y, whereas patients with elevated CEA levels before hepatic resection were followed up by having CEA levels checked (once every 3 mo) and undergoing once every 3 mo an abdominal ultrasound and a chest radiograph for the next 3 y. In the case of inconclusive findings, additional imaging (e.g., MRI or ^{18}F -FDG PET) or diagnostic procedures (e.g., biopsy) were used to determine a recurrence of disease.

Statistical Analysis

The primary outcome measure of the study was the number of futile laparotomies. Futile laparotomy was defined as any laparotomy that did not result in complete tumor clearance either intrahepatically or extrahepatically or that revealed benign disease at laparotomy or histopathologic examination. Although arbitrary, laparotomy and surgical treatment were also considered futile when disease recurrence occurred within 6 mo after surgery. The time frame of 6 mo was chosen because of the apparent lead time of ^{18}F -FDG PET, as compared with CT (18).

At the time of study design, the data in the literature suggested that 60% of the patients who undergo laparotomy for colorectal liver metastases would have curative hepatic resection by intention (4,6,7). The study was designed to detect a 15% reduction in the number of futile laparotomies. To detect such a difference, 75 patients were needed in each study arm.

For testing differences in clinical outcome measures, P values of 0.05 or less were considered to be statistically significant. DFS and OS were assessed from the day of randomization. Data on patients who were alive or free of recurrence were censored at the time of last follow-up. The rate of recurrence was calculated on the basis of all eligible patients undergoing laparotomy.

DFS and OS analyses were performed using the Kaplan–Meier method. All statistical analyses were performed with SPSS statistical software (version 15.0; SPSS Inc.). For the membership of groups, the Fisher exact test was used, and t tests were used for the quantitative measures. Group differences for survival were analyzed with the log-rank test.

RESULTS

Characteristics of Patients

A total of 150 eligible patients were randomly assigned to 1 of the 2 diagnostic strategies. All 150 patients were evaluable and met the inclusion criteria for considering hepatic resection of colorectal liver metastases. No patients were lost to follow-up. Patient and tumor characteristics were similar between the 2 strategy groups (Table 1). None of these patients received preoperative chemotherapy. For

TABLE 1. Demographic Data

Variable	Control arm (CT; $n = 75$)	Experimental arm (CT plus PET; $n = 75$)	P
Mean age (y)	62.9	62.6	0.94
Age range (y)	37.9–79.9	32.8–78.1	
Sex (female:male)	19:56	27:48	0.21
Primary tumor			0.87
pN0	34	32	
pN ≥ 1	41	43	
DFS			0.40
<12 mo	29	35	
≥ 12 mo	46	40	
Number of hepatic tumors*			1.0
1	41	42	
>1	34	33	
Size of greatest hepatic tumor*			0.84
<50 mm	60	58	
>50 mm	15	17	
CEA preoperatively			1.0
<200 ng/mL	75	75	
≥ 200 ng/mL	—	—	
Fong criteria			0.76
0	9	7	
1	17	24	
2	29	24	
3	19	19	
4	1	1	
5	—	—	

*As preoperatively predicted on CT, at time of randomization. No statistically significant differences were found between groups.

further comparison, both strategy groups were analyzed according to the prognostic scoring system for hepatic resection of colorectal liver metastases according to Fong et al. (19). The distribution of the various prognostic scores was identical in both groups.

Futile Laparotomies

Additional ^{18}F -FDG PET findings resulted in cancellation of planned resection of the suspected liver metastases in 5 patients. Follow-up of these patients showed that ^{18}F -FDG PET correctly predicted benign disease in 2 patients and unresectable extrahepatic disease in 3. So, in total 75 patients in the conventional arm without ^{18}F -FDG PET and 70 patients in the experimental arm with ^{18}F -FDG PET underwent laparotomy (Table 2). At laparotomy, 17 (23%) patients in the conventional arm and 7 (9%) patients in the experimental arm showed either significant additional metastatic disease (not detected at CT or ^{18}F -FDG PET) precluding any further curative surgical treatment or benign disease, both of which led to futile laparotomy ($P = 0.043$). In both groups, 1 additional patient underwent futile resection because of benign disease shown at definite histopathologic examination.

TABLE 2. Outcome Measures

Variable	Control arm (no PET; <i>n</i> = 75)	Experimental arm (PET; <i>n</i> = 75)
No laparotomy	0	5 (7)
Confirmed benign disease	—	2
Confirmed extrahepatic disease	—	3
Laparotomy	75 (100)	70 (93)
Futile laparotomy	34 (45)	21 (28)
Extrahepatic disease at laparotomy*	6	2
Too-extensive liver disease at laparotomy*	8	3
Benign disease at laparotomy	3	2
Benign disease after resection	1	1
Disease recurrence < 6 mo	16	13

*Not resectable or too extensive to perform potentially curative resection.

Data are numbers of patients, with percentages in parentheses.

In addition, follow-up showed disease recurrence within 6 mo after surgical treatment in 16 and 13 patients in the conventional and experimental groups, respectively. As a result, a significantly greater proportion of patients underwent futile laparotomy in the control arm without ^{18}F -FDG PET (45%) than in the experimental arm with ^{18}F -FDG PET (28%) ($P = 0.042$). The relative risk reduction was 38% (95% confidence interval, 4%–60%). The absolute difference of 17% means that 6 patients need to undergo ^{18}F -FDG PET to avoid 1 futile laparotomy. Futile laparotomy was not related to other prognostic factors as measured by the Fong score ($P = 0.539$).

Survival

All patients were followed up for at least 3 y after randomization. For all patients randomized, 3-y OS and DFS in the experimental group were 61.3% and 35.5%, respectively (Figs. 1 and 2). In the control group, 3-y OS and DFS were 65.8% and 29.8%, respectively. Thus, both OS and DFS were not significantly different between the experimental and control groups ($P = 0.378$ and $P = 0.194$, respectively).

^{18}F -FDG PET Findings

In 7 patients, ^{18}F -FDG PET detected additional extrahepatic disease initially missed on the CT scan (lung or mediastinal metastases in 5 patients and extensive abdominal lymph node metastases in 2 patients). A reassessment of the CT scan confirmed extrahepatic disease in 1 patient with multiple mediastinal and pulmonary metastases and in both patients with abdominal extrahepatic (i.e., nodal) disease. In these 3 patients, futile laparotomy was avoided. In the other 4 patients, chest lesions predicted on ^{18}F -FDG PET did not result in any change of strategy, and hepatic

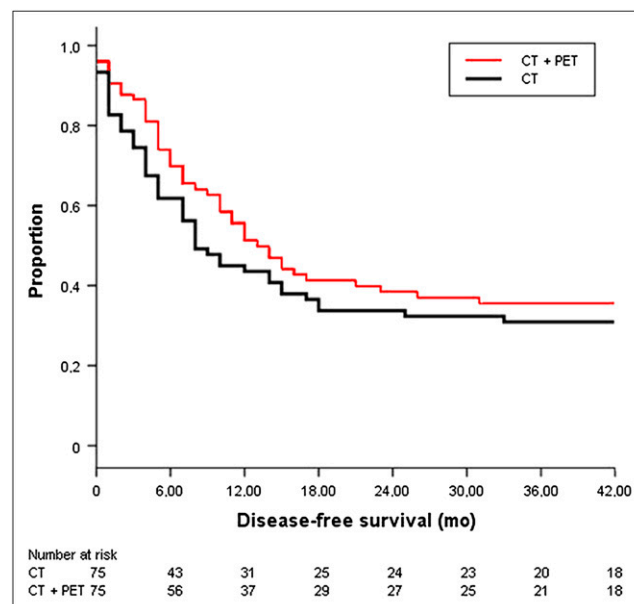


FIGURE 1. Kaplan-Meier analysis for DFS. Numbers at risk mentioned at corresponding months.

resection was performed. In all 4 patients, mediastinal or lung metastases were confirmed by chest CT within 6 mo after hepatic resection.

In 5 patients, ^{18}F -FDG PET did not show uptake in focal liver lesions, indicating benign liver disease. Laparotomy was cancelled in 2 patients, in whom additional follow-up in the first year of randomization confirmed benign lesions. The multidisciplinary team disregarded the ^{18}F -FDG PET result in 3 cases after assessment of all available data. At the

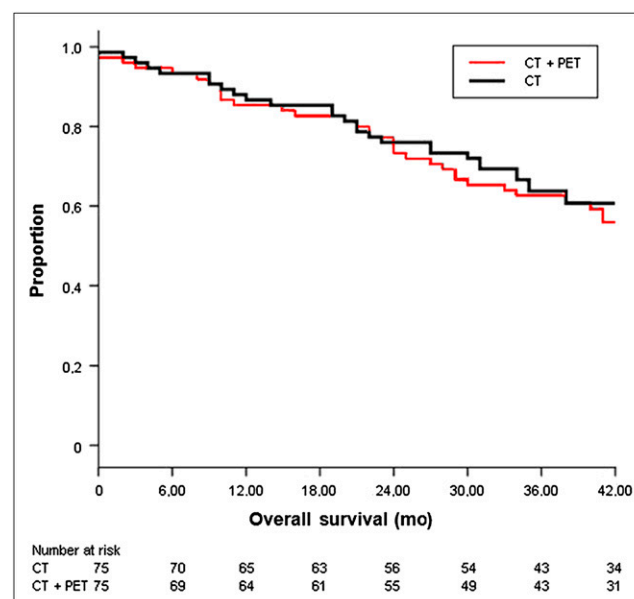


FIGURE 2. Kaplan-Meier analysis for OS. Numbers at risk mentioned at corresponding months.

subsequent laparotomy, all 3 lesions proved to be benign. In 2 of these patients, laparotomy showed hemangioma or multiple cysts that did not require any surgical intervention. One patient underwent resection of a deep-seated lesion not recognized as a benign fibrotic lesion at laparotomy.

In 18 patients, ^{18}F -FDG PET showed additional liver findings discordant with CT. In 15 patients, additional liver lesions were observed (1 in 11 patients, 2 in 3 patients, and 6 in 1 patient). In all these 15 patients, the clinical team decided that hepatic resection was still possible and ^{18}F -FDG PET did not influence the treatment decision for hepatic surgery. Indeed, all patients eventually underwent potentially curative resection. In the other 3 patients, however, ^{18}F -FDG PET predicted extensive central liver involvement judged resectable on CT but most likely unresectable on ^{18}F -FDG PET, because of the larger metastases than anticipated after CT. In all 3 patients, resection was judged impossible at laparotomy, and further surgical treatment was cancelled. Thus, ^{18}F -FDG PET predicted futile laparotomy in at least 15 patients. However, the clinical team disregarded the ^{18}F -FDG PET results in 10 of these cases and proceeded to laparotomy.

DISCUSSION

Futile laparotomy is a significant issue in patients taken to surgery for potentially resectable colorectal liver metastases. In the present randomized study, we showed that the addition of whole-body ^{18}F -FDG PET to a full CT-based conventional work-up of patients with potentially resectable liver metastases from colorectal cancer actually reduced the number of futile laparotomies by 38%. Furthermore, this study also shows that disregard of the ^{18}F -FDG PET findings by the multidisciplinary team was responsible for 10 additional futile laparotomies in the ^{18}F -FDG PET group. Thus, a retrospective scenario analysis indicated that if the correct clinical decision was made by accepting ^{18}F -FDG PET findings, the number of futile laparotomies would have been reduced even further, by more than 65%.

For DFS and OS, no differences between the experimental and conventional groups were found in the first 3 y of follow-up. So, although fewer laparotomies were performed in the experimental group than in the conventional group, this was not at the expense of a decrease in DFS or OS. The present study was performed before adjuvant chemotherapy was considered standard after hepatic resection. It is highly unlikely, however, that adjuvant chemotherapy would have selectively affected survival in one of the study arms.

The results observed in our study could differ from the addition of ^{18}F -FDG PET to conventional staging in an actual clinical setting, because all CT scans were more extensively reviewed by an expert panel than is standard routine before the patient was assessed for randomization. This means that in daily practice the value of additional ^{18}F -FDG PET may even be higher than that observed in the

present study. Moreover, the most favorable category of patients with liver metastases included those patients with a maximum of 4 liver lesions. However, an increasing trend to consider also patients with more significant liver involvement for surgical resection of the liver metastases exists. It is well feasible that the clinical effect of the addition of ^{18}F -FDG PET in patients with more extensive liver disease may even be higher.

The results of the current study confirm the results of previous retrospective and nonrandomized studies, which were recently summarized in 2 metaanalyses (12,16). Bipat et al. showed that ^{18}F -FDG PET had a significantly higher sensitivity on a per-patient basis for detection of liver metastases than did the other modalities (12). However, on a per-lesion basis, sensitivity of CT, MRI, and ^{18}F -FDG PET was similar. In earlier studies, we concluded that the combined sensitivity and specificity of ^{18}F -FDG PET has added value in the diagnostic work-up of patients with colorectal liver metastases in preoperative staging, especially for excluding or detecting extrahepatic disease (16). Sahani et al. also reported that ^{18}F -FDG PET, compared with MRI (which itself proved more useful in detecting smaller liver metastases), provided additional information about extrahepatic disease (20).

In the present series, 14 patients (18.7%) in the control arm underwent futile laparotomy because of too-extensive liver disease at laparotomy or detection of extrahepatic disease. This number of patients is similar to that given in the most recent series in the literature. In a European Organisation for Research and Treatment of Cancer study investigating the role of adjuvant perioperative chemotherapy, 16.4% of the randomized patients in the control arm did not undergo planned hepatic resection (21).

The current study was performed using stand-alone PET scanners, because integrated PET/CT scanners were not available at the time of the study. Comparison with CT was done by side-by-side viewing. At present, integrated PET/CT is considered the state of the art for oncologic staging. For clinical implementation of the results of the present study, this means that most probably the number of clinically significant ^{18}F -FDG PET findings that are disregarded by multidisciplinary teams will decrease, because integrated ^{18}F -FDG PET/CT provides immediate and a direct correlation of functional changes depicted by ^{18}F -FDG PET with anatomic abnormalities shown on CT (22). Thus, the actual reduction of futile laparotomies will be larger than 38%, especially because of the reduction of disregarded ^{18}F -FDG PET findings. The present study does not imply that ^{18}F -FDG PET/CT can and should replace diagnostic CT, because in the study all patients were preselected for ^{18}F -FDG PET by diagnostic contrast-enhanced CT of the chest and abdomen, thereby excluding patients with more than 4 liver metastases, technically unresectable liver metastases, and extrahepatic metastatic disease already apparent on CT.

In addition to the recent introduction of PET/CT, MRI of the liver is now considered part of the standard of care in

colorectal cancer with hepatic involvement. In a study of 65 patients with colorectal liver metastases, Kong et al. observed similarly excellent performance for PET/CT and manganese-enhanced MRI of the liver on a per-patient basis and a small, but nonsignificant benefit of MRI on a per-lesion basis (23). In a small series of 24 patients with colorectal liver metastases, PET/CT and unenhanced MRI of the liver were equivalent on a per-patient basis; MRI, however, detected more smaller liver lesions than did PET/CT, which at least in part may be due to previous or even ongoing chemotherapy (24). Nevertheless, MRI of the liver may decrease another major source of futile surgery besides extrahepatic disease (i.e., underestimation of the degree of liver involvement). The recent concept of hybrid PET/MRI scanners may further enhance the power of multimodality imaging for this indication.

CONCLUSION

The introduction of ^{18}F -FDG PET in the preoperative work-up of patients with colorectal liver metastases that are considered resectable on CT significantly reduces the number of futile laparotomies due to unexpected unresectable disease. When considering surgical intervention for liver metastases, one should not disregard suspected extrahepatic disease on ^{18}F -FDG PET and PET-negative liver lesions. Therefore, ^{18}F -FDG PET should be implemented in the diagnostic algorithm before laparotomy for resection of colorectal liver metastases is performed.

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