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Unexplained rising carcinoembryonic antigen (CEA) in the postoperative surveillance of colorectal cancer: the utility of positron emission tomography (PET)

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Abstract

The aim of the study was to evaluate the use of positron emission tomography with [^{18}F]-fluorodeoxyglucose (FDG-PET) in patients with unexplained rising carcinoembryonic antigen (CEA) in the postoperative surveillance of colorectal cancer. 50 consecutive patients with elevated CEA levels and a completely normal ($n=31$) or equivocal ($n=19$) conventional diagnostic work-up (CDW) were retrospectively selected. All PET images were reviewed with full knowledge of the CDW. The gold standard consisted of histology, or clinical follow-up of more than 1 year. Recurrent disease was established in 56 lesions in 43 patients. On a patient-based analysis, the sensitivity of FDG-PET was 34/43 (79%), and the positive predictive value 34/38 (89%). In 14/50 patients (28%), the FDG-PET findings led to a surgical resection with curative intent. On a lesion-based analysis, FDG-PET detected 42/56 lesions (sensitivity: 75%), the positive predictive value was 79% (42/53). These results demonstrate that FDG-PET can have a clear impact on patient management in patients with an unexplained elevation in CEA levels.

Keywords: Positron emission tomography (PET); Colorectal cancer; Carcinoembryonic antigen

1. Introduction

Elevation of circulating carcinoembryonic antigen (CEA) levels is a very sensitive sign of recurrence, widely used in the postoperative surveillance of colorectal cancer [1,2]. Serum levels of CEA may increase before the development of cancer-related symptoms with a median lead time of 4.5 to 8 months [3]. Multivariate analysis has indicated that CEA monitoring is the most cost-effective indicator for recurrent disease [4]. The routine use of CEA in asymptomatic patients is justified by the potential of a curative treatment in early stages of recurrence. Indeed, several reports indicated that resection of a solitary liver or lung metastasis results in a 5-year survival of approximately 25–30% [5–7]. Moreover, if surgery is not indicated, early chemotherapy in asymptomatic metastatic colon cancer can increase symptom-free survival and quality of life [8]. Therefore, the colorectal cancer surveillance guidelines issued by the American Society of Clinical Oncology (ASCO) recommend that, if resection of solitary metastases is clinically indicated, postoperative CEA testing should be performed every 2–3 months in patients with stage II or III disease for at least 2 years after diagnosis [9]. Conventional diagnostic work-up (CDW), including computed tomography (CT) and endoscopy, does not always lead to the localisation of the recurrence sites. This often results in a delay of a potentially curative treatment, and, to considerable psychological distress to the patient. An increased serum CEA level leads to a suspicion of recurrent disease, however, the therapeutic decision-making is hampered by its limited specificity with a false-positivity rate of approximately 10–30%. However, CEA-directed second-look laparotomies were reported to have resectability rates of only 44–58% due

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to the unforeseen presence of extended disease [10]. Therefore, in this particular patient subset, a non-invasive technique is needed with a superior sensitivity than the existing imaging techniques, first, for confirmation of recurrent disease, and, secondly, for selecting those patients eligible for a potentially curative resection of the recurrent lesion.

Positron emission tomography using [^{18}F]-fluorodeoxyglucose (FDG-PET) as the radiotracer is a novel imaging technique allowing a highly sensitive whole-body search for malignant foci detected by their increased glucose metabolism compared with benign tissues. Several studies are now available that indicate its added value for diagnosis and preoperative staging of recurrent colorectal cancer [11–18]. This led to the reimbursement of the use of PET in this indication in several countries, including the USA. However, only limited published data, often obtained in small patient samples, are presently available on the utility of this technique for the detection of occult recurrent disease in patients with rising CEA levels [11,12,19].

The hypothesis of this study was that the high sensitivity of FDG-PET for detecting metastatic deposits, together with its ability to screen the whole-body in one examination session should result in a high detection rate of occult cancer foci and in a significant impact on therapeutic management.

2. Patients and methods

2.1. Patients

A retrospective study was conducted in the PET centres of two tertiary care university hospitals. The PET-databases of both centres were searched for all patients who underwent whole-body FDG-PET for the detection of occult recurrent colorectal cancer between July 1996 and July 1999. Inclusion criteria were: patients previously treated for colorectal cancer with an elevated CEA level ($\geqslant$5 ng/ml) who had undergone CDW including abdominal CT, with a normal or equivocal result. Of the 58 cases, we had to exclude 8 patients in whom no adequate follow-up data could be obtained, thus 50 patients met the study criteria: 39 (78%) from the University Hospitals of Leuven and 11 (22%) from the Academic Hospital of the Vrije Universiteit of Amsterdam. Follow-up data of outpatients were obtained through a questionnaire sent to the referring physician.

Patient characteristics are shown in Table 1. The mean time elapsed between the primary surgery and the date of PET was 1108 days (median: 825 days; range: 123–3738 days). The mean CEA level at the date of the PET was 28.3 ng/ml (median: 16.5 ng/ml; range: 5–180 ng/ml).

2.2. Conventional diagnostic work-up

18 patients (36%) underwent CDW at one of the University Hospitals, whereas 32 patients (64%) underwent their CDW side of the hospital and were referred specifically for PET.

All patients underwent a CT of the abdomen (n=50). Additional CDW consisted of colonoscopy (n=19; 38%), chest CT (n=15 (30%), chest X-ray (n=35 (70%)), abdominal ultrasound (n=16; 32%), and bone scan (n=8 (16%)). The results of the CDW were copied from the clinical patients records. The interval between the CDW and FDG-PET was less than 1 month in 41 patients (82%), between 1 and 3 months in 4 (8%) and more than 3 months in 5 patients (n=10%).

2.3. FDG-PET imaging

The PET imaging was performed with a CTI-Siemens 931 or HR+ scanner (Knoxville, TN) with an axial field of view of 10.1 and 15 cm, respectively, and a spatial resolution of 8 and 6 mm, respectively. All patient fasted for at least 6 h preceding the tracer administration. 60 min after the intravenous (i.v.) injection of 6.5 Mbq/kg [^{18}F]-FDG (to a maximum of 555 Mbq) a whole-body emission scan was performed. The raw imaging data were reconstructed in a 128×128 matrix with the use of an iterative reconstruction algorithm.

For this study, all PET images were reviewed by two nuclear medicine physicians who had a broad experience in clinical PET (4500 and 1500 PET reports, respectively) and were familiar with normal variants, artifacts and the pitfalls in the interpretation of PET studies. At the time of the image review, these observers were fully aware of the history of the patients, and of

Table 1
Characteristics of the included patients and their resected primary colorectal carcinomas

Patients	
Number	50
Male/female	32 (64%)/18 (36%)
Age mean (S.D.)	60 years (10 years)
Age range	31–78 years
Primary CRC	n (%)
Histological type	
Adenocarcinoma	50 (100)
Localisation	
Colon	28 (56)
Rectum	22 (44)
Stage of primary CRC	
Stage I	3 (6)
Stage II	13 (26)
Stage III	17 (34)
Stage IV	9 (18)
Unknown	8 (16)
Previous surgery for recurrence	12 (24)

S.D., standard deviation; CRC, colorectal carcinoma.

the results of the CDW as provided by the referring physicians. Retrospective correlation of PET with CT or other CDW images was not performed. The observers were blinded to the clinical data obtained after the PET scan.

In cases of diagnostic discordances between the observers, a consensus diagnosis was generated. The PET lesions were classified as indeterminate or suspect for recurrence. Suspect lesions were defined as distinct and intense lesions of which the aspect, location and intensity of the [^{18}F]-FDG-accumulation allowed an assessment of a high probability of an underlying malignancy. Indeterminate lesions were defined as lesions which the observers considered as having an intermediary probability for an underlying malignancy. The reviewers thought that, based on the PET images alone, a definite opinion about the nature of these PET lesions was impossible.

2.4. Data analysis

The lesions found by CDW and FDG-PET were compared with a 'gold standard' which consisted of histology, or of clinical and radiological follow-up. A negative follow-up of 12 months was needed for a definite negative diagnosis.

For the lesion-based analysis, only the lesions for which a definite gold standard was available were included in the analysis of the diagnostic accuracy of FDG-PET. Sensitivity and positive predictive value of FDG-PET were calculated using standard definitions. For these calculations, PET lesions that were scored as indeterminate were classified as positive.

The patient-based analysis was performed in all patients based on the clinical PET report. If more than one lesion was present in the same patient with discordant diagnostic PET classifications, the following rules were used. A patient with at least one true-positive PET finding was considered true-positive, and a patient with a false-negative and a false-positive lesion was classified as a false-negative. Differences of the CEA levels between groups were tested using the Student's *t*-test.

3. Results

The gold standard established the diagnosis of recurrent disease in 56 lesions in 43 patients (disease prevalence: 86%). Table 2 lists the location of these lesions coupled to the results of the CDW, and to the relative frequency of the used modalities for establishing the true-lesion status. The median (range) interval between the date of PET and the confirmation of the true-lesion status of the 27 lesions with histological confirmation was 45 days (range: 8–917 days), and for the 29 lesions with a confirmation through clinical follow-up was 70 days (range: 1–603 days).

According to the gold standard, 7 patients were considered disease-free. In 5, CEA levels returned to normal and clinical follow-up of more than 1 year did not suggest recurrent disease. In 2 other patients, however, CEA levels continued to rise slowly, without any sign of disease. One of them is still considered disease-free 2 years after the PET date; the other patient died three years after the date of PET from a disseminated recurrence. Intense follow-up of this patient, including frequent CT scanning, first indicated enlarged retroperitoneal lymph nodes 2.5 years after the PET date.

3.1. Lesion-based analysis

FDG-PET detected 42 of the 56 lesions (sensitivity: 75%). Nine of the 42 PET lesions (21%) were scored as indeterminate by the PET reviewers.

Forty-two true-positive PET lesions were found in 34 patients. Nineteen (45%) of these lesions were confirmed by histology, whereas in 23 (55%) lesions clinical follow-up established the true-lesion status. The mean CEA level in these patients at PET was 29 ng/ml (median: 17 ng/ml, range: 5–180 ng/ml). In these patients, CDW had been classified as equivocal in 7, and completely normal in 27 patients. 10 of the 34 (29%) patients had undergone their CDW in a tertiary referral university hospital. The time-frame between CDW and PET in these true-positive patients was less than 1 month in 28/34 patients, between 1 and 3 months in

Table 2
Distribution of the recurrences and the methods used to define the true lesion status (gold standard)

	No. of recurrences *n* (%)	CDW results		True lesions status defined by:	
		Normal	Equivocal	Histology	Follow-up
Local	11 (20)	7	4	5	6
Liver	15 (27)	13	2	8	7
Lungs	5 (9)	5	0	2	3
Abdominal[a]	20 (36)	16	4	10	10
Extra-abdominal[b]	5 (9)	3	2	2	3
Total	56 (100)	44 (79%)	12 (21%)	27 (48%)	29 (52%)

[a] Excluding the liver and local area.
[b] Excluding lungs.

4/34, and more than 3 months in 2/34 patients (6%). The lesions were located at the postsurgical site ($n=8$), in the liver ($n=10$), lungs and mediastinum ($n=3$), extra-hepatic abdomen ($n=17$), and extra-abdominal excluding the lungs ($n=4$).

Seven of the 42 true-positive PET lesions were located outside the field-of-view of the CT. These lesions were located in the supraclavicular region ($n=2$), in the lungs and/or mediastinum ($n=3$), in the brain ($n=1$) and in the bone ($n=1$). Three of the 10 liver lesions were located at the postsurgical section plane in patients that had already undergone a partial hepatectomy (Fig. 1). In 4 patients, hepatic lesions had been reported on CT, but were incorrectly classified as benign (CT diagnoses: 2 haemangioma, 1 hepatorenal polykystosis, 1 cirrhosis). In 3 other patients, CT, repeated on the basis of the PET results, confirmed the PET findings.

The 14 false-negative PET lesions were found in 9 patients and located at the postsurgical site ($n=5$), liver ($n=3$), extrahepatic abdomen ($n=5$), and extra-abdominally ($n=1$). The mean CEA level in these patients was 43 ng/ml (median: 19 ng/ml; range: 6–150 ng/ml), and was not significantly different from the CEA levels in the whole patient population. The mean time elapsed between PET date and confirmation of the true-lesion status of these lesions was 158 days (median: 47 days; range: 8–365 days). In 3 false-negative patients the missed lesions ($n=4$) were located in the post-surgical area. The final diagnosis of recurrent disease was made after an extended asymptomatic follow-up period of 246, 334 and 365 days. Their CEA levels at the time of the PET were 10, 20 and 15 ng/ml, respectively. In 5 other patients, five tumour sites were located in the liver ($n=2$), peritoneal space, lungs and in an inguinal lymph node. They were all smaller than 1 cm in diameter. The CEA levels in these patients were, 40, 7, 150, 15 and 6 ng/ml, respectively. In 2 other patients, three false-negative lesions had been falsely considered as physiological tracer distribution: an intensely hypermetabolic tumoral nodule in continuity with the roof of the bladder, incorrectly considered as a bladder diverticle; a modest and heterogeneous tracer uptake at the gastrohepatic ligament, falsely considered as physiological uptake in the stomach; and a third patient had a small and discrete lesion in the abdominal wall in the scar of the laparotomy, which was not considered suspect. The final two false-negative lesions were found in the only 2 patients who were scanned during or shortly after (1 month) adjuvant chemoradiotherapy. These patients developed recurrences at short notice, located at the postsurgical and retroperitoneal area.

The positive predictive value of FDG-PET on a lesion-basis was 42/53 (79%). False-positive PET lesions were found in 11 cases in 10 patients. Ten of the 11 lesions were reported as indeterminate PET findings during the blinded PET review. These lesions were located in the local presacral postsurgical area ($n=4$), the hepatic margin ($n=2$), the splenic angle of the colon ($n=1$), the lung hilus ($n=1$), and in glands (one parotid, one thyroid). Only one of the false-positive PET lesions was reported as definitely suspect. It was situated in the perianal region in a patient with a history of rectal carcinoma, and was intense and nodular. Endoscopic ultrasound and colonoscopy were performed and did not show any signs of malignancy. In the same patient, PET showed a suspect lesion in the liver, confirmed by magnetic resonance imaging (MRI), and a peritoneal lesion. The patient was considered as inoperable and chemotherapy was started.

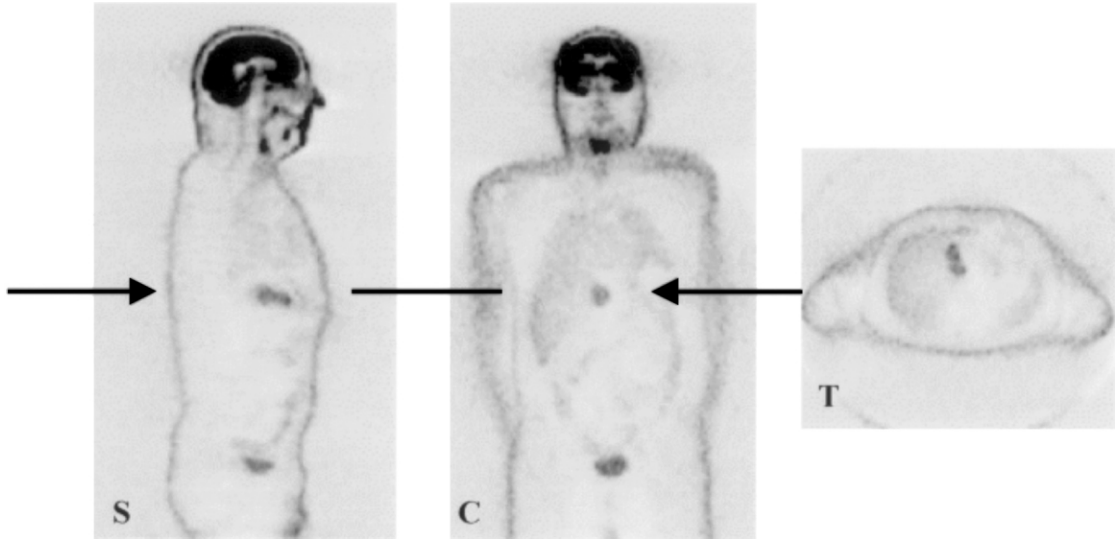

Fig. 1. Sagital (S), coronal (C) and transverse (T) slices of whole-body [^{18}F]-fluorodeoxyglucose (FDG-PET) centered on a liver metastasis found in a patient with rising carcinoembryonic antigen (CEA) levels without CT abnormalities. The lesions were located at the resection margin of a previously performed partial hepatectomy.

3.2. FDG-PET for equivocal CDW findings

Twenty-two lesions in 19 patients were considered as equivocal by CDW. The prevalence of recurrent disease in this patient subset was 16/19 (84%). The lesions were located in the postsurgical, local area ($n=7$), liver ($n=5$), extrahepatic abdominal ($n=6$), lung ($n=1$), bone ($n=2$), and supraclavicular lymph nodes ($n=1$). The gold standard established the diagnosis of malignancy in 12/22 (55%) lesions based on histology ($n=7$) or follow-up ($n=5$). Recurrent disease was excluded in 6/22 (27%). In 5/22 (23%) equivocal CDW lesions, a true-lesion status was not established due to the absence of a gold standard. The accuracy of FDG-PET in this subset of lesions was 11/17 (65%), with a sensitivity and specificity of 7/11 (64%) and 4/6 (67%), respectively. The positive and negative predictive value of FDG-PET was 7/9 (78%) and 4/8 (50%). On a patient-based analysis, the sensitivity of FDG-PET was 13/16 (81%) and the positive predictive value 13/15 (87%).

3.3. Indeterminate FDG-PET findings

Twenty-four FDG-PET lesions in 21 patients were reported as indeterminate by the blinded reviewers. These lesions were located in the thorax ($n=6$), extrahepatic abdomen ($n=9$), postsurgical site ($n=7$), parotid gland ($n=1$), and in the thyroid ($n=1$). The reasons for classifying them as indeterminate were possible inflammatory uptake, physiological uptake in the intestines, and uptake in benign adenomas (thyroid, parotid gland).

In 5/24 (21%) indeterminate FDG-PET lesions a true-lesion status was not available due to the lack of a gold standard. A true-lesion status was thus obtained in 19/24 (79%) lesions. The gold standard established the diagnosis of malignancy in 9/19 (47%) lesions based on histological ($n=4$) or follow-up ($n=5$) evidence.

3.4. Impact of FDG-PET on patient management

The sensitivity of FDG-PET for diagnosing recurrent disease in a patient was 34/43 (79%). In the patient subset with equivocal CDW findings, the sensitivity of FDG-PET was 13/16 (81%). Table 3 shows the results of the patient-based analysis and the diagnostic impact of the positive PET findings. In the clinical reports, positive PET findings were reported in 38 patients: a solitary PET lesion in 23 patients, and multiple PET lesions in 15. Subsequent dedicated diagnostic procedures induced by the PET findings led to a resection with curative intent in 14 patients. These resected lesions were located in the liver ($n=5$), at the postsurgical site ($n=7$), in the abdominal cavity ($n=1$), and in the thyroid ($n=1$, medullary thyroid carcinoma). In 20 patients, a positive PET finding led to the diagnosis of irresectable recurrent disease. In all these patients chemotherapy was initiated. The positive predictive value of FDG-PET for the presence of recurrent disease on a patient-basis was 34/38 (89%). 4 patients were incorrectly considered as having recurrent disease based on the PET findings. In all of them the false-positivity was based on a solitary PET lesion which was classified as indeterminate in the retrospective blinded analysis. These lesions were located in the postsurgical area ($n=2$), in the periphery of the liver ($n=1$) and in the hilus of the lung ($n=1$).

Table 3
Patient based-analysis: PET impact on patient management

- PET positive ($n=38$)
  - Solitary PET lesion ($n=23$)
    - ⇒True-positive PET ($n=19$)
      - • Curative surgery for resectable disease ($n=11$)
        - ○ Liver ($n=3$)
        - ○ Local ($n=6$)
        - ○ Non-local abdomen ($n=1$)
        - ○ Thyroid ($n=1$)
      - • Non-resectable disease ($n=8$)
    - ⇒False-positive PET ($n=4$)
      - • Disease-free
  - Multiple PET lesions ($n=15$)
    - • Curative surgery for resectable disease (n = 3)
      - ○ Liver ($n=2$)
      - ○ Local ($n=1$)
    - • Non-resectable disease (n = 12)
- PET negative ($n=12$)
  - ⇒True-negative ($n=3$)
  - ⇒False-negative ($n=9$)

4. Discussion

The results of this study demonstrate that in the majority of patients with unexplained increased CEA levels, after having undergone a battery of conventional imaging modalities, whole-body FDG-PET provides decisive diagnostic clues guiding further diagnostic and therapeutic interventions. In our group consisting of such 50 patients, having a prevalence of disease of 86%, whole-body FDG-PET detected tumour relapse in 34/43 (79%) patients. From a clinical point of view, these findings led to a surgical intervention with a curative intent in 28% of the patients. In 40%, PET indicated the presence of irresectable disease, leading to a treatment with chemotherapy. In a similar study with 22 included patients with CEA elevation and negative CT scans (disease prevalence: 68%), Flanagan and colleagues reported a 100% sensitivity of FDG-PET [19]. In 4/22 (18%) of these patients, a definitive curative surgical intervention was performed based on the PET result. Valk and coworkers studied a group of 32 patients (disease prevalence: 63%) who underwent PET for

investigation of serum CEA elevation. Only 18, however, had undergone a (negative) CT before PET, while 14 of them did not [12]. The overall sensitivity of PET was 90%. In the CT-negative subset of patients, the PET sensitivity was 67%, which is in line with our results. Seven (22%) of the 32 included patients were resected for cure based on the PET findings.

False-negative PET findings in our study were found in 9/43 (21%) of the patients. This compares relatively unfavourably to 0 and 10% false-negative PET findings in the studies of Flanagan and colleagues and Valk and coworkers, respectively [12,19]. However, several reasons may account for this: intergroup differences in the extent of disease, the high quality of the conventional work-up in our study, the time-frame between CDW and the date of the FDG-PET, and the length of follow-up defined as the criterion for true- or false-negativity. The underlying causes for false-negativity in this study are 3-fold and represent the known limitations of PET in this regard which have been described for other types of tumours. Firstly, limitations of the spatial resolution of the PET device results in a progressively decreasing sensitivity for lesions smaller than approximately 10 mm diameter. Secondly, chemotherapy and radiotherapy in responding lesions can reduce the intensity of the signal below the detection levels for these lesions although they still contain residual viable and proliferating tumour cells [24,25]. Thirdly, tumour recurrences can be located at certain sites known by the reviewer to be sites where aspecific physiological or inflammatory FDG accumulation can occur such as postoperative scar tissue, epigastric areas and paravesical areas.

False-positive FDG-PET findings remain a major problem in the diagnosis of cancer patients [21].These findings can lead to incorrect FDG-PET-directed management changes, induce unnecessary further patient distress, expose the patient to iatrogenic morbidity of unnecessary confirmatory examinations, and also result in a waste of health care resources. This negative impact of false-positives has in our department led to the use of more cautious interpretations on the likelihood of malignancy for a particular lesion. Therefore, in this study, the PET lesions were classified as definitely suspect or indeterminate according to the estimated high versus intermediary probability for malignancy. Thus, 24 of the 63 (38%) PET lesions were scored as indeterminate because, based on the FDG-PET images alone, the readers could not classify the lesions as definitely suspect. The results of this study validated this diagnostic attitude by showing that 47% of these indeterminate lesions were malignant, while 53% were benign lesions as established by the gold standard. Notably, 10 out of the 11 false-positive PET diagnoses were reported as indeterminate, thereby potentially reducing the negative impact on patient management. The proportion of indeterminate PET results is primarily determined by the reviewers' experience and associated knowledge about the causes and frequency of false-positive PET lesions. The most frequent location of indeterminate lesions in the present study were in the abdomen (67%) where it is well known that physiological or inflammatory bowel or urinary tract uptake can mimic neoplastic foci. The other lesions were located in the lungs and/or mediastinum (25%) where underlying focal inflammation can induce false-positivity, and in parotid or thyroid gland (8%) where false-positive uptake in adenomas are frequently found [20]. The most important way to reduce the rate of reporting indeterminate lesions is performing a close correlation between the metabolic data obtained in the PET images and the structural data obtained by morphological methods, such as CT and MRI [21]. The basis for such 'correlative' interpretation is 2-fold. First, the paucity of anatomical landmarks in the PET images renders accurate lesion localisation difficult and, secondly, aspecific FDG accumulation can sometimes mimic tumoral deposits and result in false-positivity (or false-negativity).

Therefore, all suspect or indeterminate PET lesions have to be correlated with the clinical diagnostic methods (CDM) before final inclusion of the PET result into the decision-making process. Unlike in the study by Flanaghan and colleagues [19] this was not performed in the current study which explains at least partially the relatively high level of indeterminate PET reports. Frequently, however, a structural correlate for these abdominal PET lesions cannot be found, requiring further dedicated diagnostic techniques or an intensified follow-up [21]. The advent of new imaging technology combining PET and CT imaging in one session using one gantry may reduce the problem of unresolved indeterminate PET lesions [22]. A major issue of this study is the way such indeterminate PET lesions were handled in the lesion-based analysis and how this influenced the results. In this study, the authors chose to classify these lesions as positive, because they believe that in this specific setting such PET findings must induce a diagnostic momentum in order to timely identify resectable relapses. Nine of the 42 (21%) true-positive PET lesions and 10 of the 11 (91%) false-positive PET lesions had been reported as indeterminate. Classifying indeterminate PET lesions as negative would have resulted, on a lesion-based analysis, in a sensitivity of 59% (versus 75%) and a positive predictive value of 98% (versus 79%).

This study clearly demonstrates a higher sensitivity of FDG-PET for tumour detection compared with CDW. From recently published series, it can be inferred that the frequency of meeting a patient with an increased CEA level in whom CDW (including CT of the abdomen) does not allow disease localisation is very low, ranging from 3 to 8% [11,23]. This might indicate that

in most patients the difference in sensitivity between CDW and FDG-PET is not clinically relevant because the tumour load and disease extent is already far beyond the sensitivity of CDW at the time of detection. If, however, the systematic use of CEA will increase in asymptomatic patients, or newer, more sensitive, tumour markers appear, the superior sensitivity of FDG-PET will certainly result in a more prominent role in the diagnostic and therapeutic management because tumour load will more frequently fall below the sensitivity threshold of the CDW.

In a patient subgroup with increased CEA levels, performing FDG-PET as the first-line examination will probably not reduce the total cost for imaging studies. Because of high disease prevalence, more than 80% in our study group, the majority of FDG-PET imaging will be reported suspect or indeterminate requiring further confirmation by guided conventional imaging. Thus the cost-effectiveness of FDG-PET will predominantly be dependent on the lead time and the subsequent benefit in survival and/or quality of life. The exact length of the lead time provided by inclusion of FDG-PET in the diagnostic work-up of these patients cannot be inferred from this study due to its inherent unblinded and retrospective nature, with the PET result having an important influence on the choice and analysis of the confirmatory examinations. As the lead time brought by FDG-PET could result in a survival and/or quality of life benefit, it certainly represents a major element in the assessment of the cost-effectiveness of new PET-based diagnostic algorithms. Therefore, a definite conclusion in this regard can not yet be drawn. Large multicentric studies with a prospective and blinded study design in which FDG-PET is performed in parallel to CDM are now needed to finally confirm the lead time and cost-effectiveness of FDG-PET in the post-operative follow-up of colorectal cancer.

In conclusion, the results of this study can be summarised as follows: (1) FDG-PET allowed a highly accurate diagnosis in patients with clinically occult recurrent colorectal cancer in daily clinical practice; (2) FDG-PET findings can lead to potentially curative or survival-prolonging therapeutic actions; (3) the use of a category of so-called indeterminate PET lesions with an intermediate probability of malignancy is essential to avoid the negative impact of false-positive diagnosis on patient care and costs.

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