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Combined FDG-PET/Contrast-Enhanced CT in the Diagnosis of Recurrent Colorectal Cancer: A Prospective Monocentric Study

Research Article

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Abstract

Contrast-enhanced CT scan and 18FDG-PET are used in the staging and surveillance of colorectal cancer (CRC). We here evaluate the feasibility of combined FDG-PET/contrast-enhanced CT in one diagnostic session in the diagnostic of recurrent colorectal cancer.45 patients underwent planned 159 procedures. 109 (68%) were performed as a combined modality in a single session and 50 were planned as two separate procedures at different times. Fourteen patients experienced recurrence during the study period. Sensitivity of 18FDG-PET scan and contrast-enhanced CT scan in detecting a recurrent disease was 84.4% and 86.6 % respectively with a specificity of 96% and 97% respectively. FDG-PET and contrast-enhanced CT findings were concordant in 79% of cases. The overall sensitivity and specificity in detecting CRC recurrence were 80% and 99% respectively in the combined procedure and 89% and 98% respectively in the two-time procedure. The positive predictive value of the procedure (combined or two-time procedure) for detection of recurrent CRC was 100% with, however a shorter delay for decision with the combined [7.7vs 12.2 days] ($p<0.05$).

The combined procedure is feasible in almost 2/3 of cases. When compared to the two-time procedure, it is performant in detecting recurrent CRC with shorter delay to therapy.

Keywords

PET; CT; 18FDG; Colon; Cancer

Introduction

Mortality rates from colorectal cancer (CRC) have declined significantly in the last years [1]. This improvement is attributed, at least in part, to recent development in diagnostic imaging modalities. Contrast-enhanced computed tomography (CT) is recognized as an effective tool for diagnosis, staging and monitoring of CRC [2]. In the last years, fluorodeoxyglucose positron emission tomography (FDG-PET) has been increasingly used for assessment of early recurrence and therapy response monitoring. Indeed, our group has reported the first study on the early detection of CRC by using FDG-PET as a

survey tool [3]. More recently, metabolic response shown by FDG-PET has been suggested to be a more useful exam as compared to contrast-enhanced CT for detecting early recurrences in various diseases [4]. However, in a recent open-label multicentre trial, adding routine 6-monthly 18FDG-PET increased costs without decreasing treatment failure rates in patients in remission of CRC (stage II perforated, stage III, or stage IV) [5]. Furthermore, in a recent update of a Cochrane Review, there were no effects on overall survival of intensifying the follow-up programs of patients after curative surgery for colorectal cancer [6]. We suggest that the combination of imaging information from multiple modalities in a single procedure may offer a promising tool for prompt clinical diagnosis and therapeutic applications. Combined FDG-PET/contrast-enhanced CT in one diagnostic session has been shown as an innovative and cost-effective imaging tool in the monitoring strategy of aggressive lymphoma [7] while studies in CRC are still lacking. The aim of our study was to assess the performance and the technical feasibility of this combined procedure in detecting early recurrences compared with FDG-PET and contrast-enhanced CT performed as separate acquisitions at different times.

Patients and Methods

From 2008 to 2014, in the area of CRETEIL, 45 patients with high-risk CRC recurrence treated and followed up in a 3-yr period in two public hospitals (i.e. the University Hospital Henri Mondor and Intercommunal de Créteil-CHIC) were enrolled in the study (Table 1). They were all assigned to have a combined procedure and were prospectively evaluated currently for feasibility, performances and results. The study protocol was approved by the institutional ethics committee (Comite de Protection des Personnes, protocol n PP 13–043)(CPP 07-035; revised Jan. 2008 and April 2012; National Ministry Register 2007-AO1138-45) and patients provided written informed consent before study inclusion. High risk recurrence during a 3-year follow-up was defined as stage II CRC with tumor perforation, stage III CRC or stage IV CRC with complete resection of all synchronous and metachronousmetastases with or without neo adjuvant therapy. All patients were routinely assessed prospectively at regular 3-monthly intervals up to 36 months after curative surgery, or until death. All patients had to be scheduled for either a single combined or a two-time procedure FDG-PET/contrast-enhanced CT every 6 months during the follow-up period. When conditions of the combined procedure were not met (mostly for logistical reasons), patients underwent FDG-PET then a contrast-enhanced CT as separate acquisitions at different times (different days) with results analyzed independently. Body contrast-enhanced CT systematically included CT acquisition covering the cervical region to the pelvic groin, which was initiated 70 s after the injection of 1.5 cc/kg of contrast agent. Post-processing reconstructions were performed on native data in the transverse plane to yield at least 2.5-mm-thick sections for image analysis. All acquisitions were performed using multi-slice CT scanner. Body 18FDG-PET/CT was performed on fasting patients (≥6 h), controlled by glycaemia <2 g/L, 60 min after IV injection of 4–5 MBq/kg 18FDG. Examinations consisted of a low-dose CT followed by an emission scan in 9–11 steps from cervical to pelvic regions; they were reconstructed without and with attenuation correction by using iterative algorithms for SUV computation.

Table 1: Main characteristics of patients enrolled

Patients' characteristics	Number of patients N=45 (%)
Gender	- Men: 20 (44.4) - Women: 25 (55.6)
Disease stage at inclusion	- II: 6 (13.3) - III: 22 (48.9) - IV: 17 (37.8)
Tumor localization	- Colon: 33 (73.3) - Rectum: 12 (26.7)
neoadjuvant therapy	- Yes: 18 (40) - No: 27 (60)
adjuvant therapy	- Yes: 36 (80) - No: 9 (20)

When contrast-enhanced CT and 18FDG-PET were performed in a single process (where contrast-enhanced CT scan was performed immediately after completion of PET acquisition, planned with the same scout view), 18FDG was infused first and CT contrast agent was injected after the scanning of 18FDG-PET was completed. All readers had access to the patient's clinical history. A senior nuclear medicine specialist and a senior radiologist reviewed 18FDG-PET and CECT images, respectively, and classified the recurrence status as yes, no or doubtful. In the evaluation of 18FDG-PET, a lesion was considered positive whenever it showed a non-physiological increase of FDG uptake.

The primary outcome was the detection of a recurrent disease or death. All images were reviewed during the MDT meetings to confirm the recurrence or the remission and consequently to decide of the upcoming treatment strategy. Thus, the performance of the different imaging

modalities in the detection of a recurrent disease (true positive) and the confirmation of a remission (true negative) were referred to the MDT decision. Recurrent diseases were validated either by histopathology or by clinical-radiological assessment in multidisciplinary team (MDT) meetings. We performed a comparative analysis of procedures performed as initially planned – i.e. combined FDG-PET/contrast enhanced CT during the same session versus the two examinations performed separately. The feasibility rate of the combined procedure was determined and the mean delay to a formal diagnosis of relapse was calculated in the two groups.

Results

All the 45 patients enrolled underwent 159 procedures in the study period, including109as a combined 18FDG-PET/contrast-enhanced CT and50procedures consisting of two separate exams (18FDG-PET and contrast-enhanced CT as separate acquisitions at different times). Thus, the feasibility of the combined procedure in routine was 68%. The combined procedure was missed because of missing appointments or lack of recent renal function tests.

Table 2: Performance of 18 FDG-PET and IV CT scan in detecting CRC recurrence

18FDG-PET (n=159)		Contrast-enhanced CT (n=159)	
Positive lesions 38/159	Confirmed recurrence 27/38	Positive lesions 32/159	Confirmed recurrence 26/32
Negative PET 121/159	Confirmed recurrence 5/121	Negative CT 127/159	Confirmed recurrence 4/127

Table 3 : Performance of separated and combined FDG-PET/ IV CT scan in detecting CRC recurrence

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

IV CT: contrast-enhanced CT

Procedure		
FDG-PET/ IV CT one acquisition (n=109)		FDG-PET/ IV CT separate acquisitions (n=50)
Performance in the diagnosis of recurrent CRC (%)		
Se	80	89
Sp	99	98
PPV	100	100
NPV	99	97

According to the MDT's decision, the sensitivity of 18FDG-PET scan and contrast-enhanced CT scan in detecting a recurrent disease was 84.4% and 86.6 % respectively with a specificity of 96% and 97% respectively (Table 2). The overall concordance rate between18FDG-PET and contrast-enhanced CT findings was 79% (126/159 procedures). A total of 88concordant findings were identified in the combined modality group (n=109, 80%) and 38 in the two-time procedure group (n=50, 76%). False positive 18FDG-PET results (n= 11) were mainly due to increased 18FDG uptake in the bowel whereas false positive contrast-enhanced CT results (n=6) were related to non-specific post-operative peritoneal adhesions (n=3, 50%), two false-positive lung lesion and one hepatic lesion. We observed 5/121 (4.13%) false negative results with 18FDG-PET and 4/127 (3.14%) with contrast-enhanced CT. All false negative findings were finally detected after combining the two exams. According to the MDT criteria, fourteen patients (31%) had recurrent disease at the end of the study period**.** The overall sensitivity and specificity of the imaging in detecting CRC recurrence was 80% and 99% respectively in the combined procedure and 89% and 98% respectively in the two-time procedure. When 18FDG-PET and contrast-enhanced CT scans were both positive, recurrent disease was always confirmed (positive predictive value of 100%).The median delay between the first imaging study and the multidisciplinary staff decision was 7.7 days [range 1-16 days] with the combined procedure and 12.2 days [range 2-22 days] with the two-time procedure ($p<0.05$).

Discussion

Here we evaluate the feasibility and the performance of a combined 18FDG-PET/contrast-enhanced CT procedure for both metabolic and morphological assessment of CRC recurrence in a series of 45 patients with high risk of recurrence. This procedure appears feasible in more than 50% of cases in the course of routine care. There was no discrepancy in all 14 patients with documented recurrence. Hence, combining IV injection to PET/CT with the implemented technical protocol does not impede the individual performance of each modality.

Despite the efficiency of both 18FDG-PETand contrast-enhanced CT in detecting CRC metastases, 3%–15% of recurrences may be missed by each of these procedures when performed alone and the respective sensitivity and specificity of both techniques is not significantly different.

Interestingly however, false negative findings on either technique appear to be detected on the other one. In addition, contrast-enhanced CT may be limited by kidney failure impeding the IV injection of contrast media, and 18FDG-PET may be limited in detecting liver metastasis because of low SUV due to chemotherapy or mucous component of the primary tumor [8]. These biases cannot always be avoided in the routine practice, although in the current study all patients had normal renal function tests and have ended their chemotherapy before entering the follow up period. The value of combining 18FDG-PET to contrast enhanced CT in the routine surveillance of CRC remains controversial. In a recent open-label multicentre trial, we showed that monitoring CRC recurrence with18FDG-PET added every 6 months increased costs without decreasing treatment failure rates in patients in remission of CRC [5]. Thus, we suggested that 18FDG-PET should be limited to selected patients such as those of stage IV CRC who should undergo curative surgery or those with rise of blood tumor marker. Since the fused anatomical images from CT and functional images from PET have been shown relevant for better detection of distant metastases and/or recurrence after curative surgery [9], we currently suggest a single hybrid imaging including two exams as a valuable alternative. The benefits of the combination of 18FDG-PET and contrast-enhanced CT over contrast-enhanced CT alone and unenhanced 18FDG-PET have been well established for the monitoring of abdominal and pelvic malignant diseases [10] and lymphoma [11]. A retrospective study performed in 53 patients showed that contrast-enhanced 18FDG-PET/CT was superior to non-enhanced 18FDG-PET/CT for exact definition of regional nodal status in rectal cancer [12] when another study conducted on 100 patients with various malignant diseases showed that contrast-enhanced CT provides additional value for patient therapy management as compared to low-dose non-contrast CT in 18FDG-PET/CT protocols [13].

In our study, abnormal images as detected by both metabolic and anatomical imaging were always associated with recurrent disease. That is to notice that misdiagnosis or delay in making medical decision observed with 18FDG-PET and contrast-enhanced CT performed as two separate exams was mostly related to false positive 18FDG-PET results(n=7) and to additional exams implied by doubtful contrast-enhanced CT images. We acknowledge that the major limitation of our study is the absence of abdominal MRI, which is now considered the preeminent imaging modality for the characterization, and detection of liver metastases. However, surveillance is rarely performed for liver metastasis alone and MRI is limited in the evaluation of extra hepatic disease, particularly the lungs, hence the current preference for CT over MRI. In conclusion, although both modalities provide similar Se and Sp figures for the detection of tumor recurrence in treated CRC patients, 18FDG-PET/contrast-enhanced CT as a combined exam can provide morphologic and functional data in a single session reducing additional diagnostic imaging exams. The availability of combined contrast-enhanced CT images and 18FDG-PET images improves diagnosis of colorectal cancer recurrence. The combined procedure often leads to prompt therapy decision with probably lower costs compared to the two-time procedure. Patient's clinical pathway should certainly be reviewed to increase the feasibility of this protocol in order to identify individuals most likely to benefit from this imaging approach.

Statements

Statement of ethics

All patients were informed that anonymised data from their medical files could be used for medical research purposes and that they were free to refuse such use of the data in accordance with French legislation.

Disclosure statement

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Author Contributions

Iradj Sobhani and Alain Luciani contributed to design and conduct the study.

Sebastien Mule Emmanuel Itti, Isabelle Baumgaertner, Hugo Rotkopf, Julie Assaraf, Charlotte Gagniere and Aurelien Amiot contributed to interpret the findings and to write the manuscript.

Jenny Tannoury took the lead in writing the manuscript.

All authors contributed to analyse the data and critically revised the manuscript for important intellectual content.

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