The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer

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Abstract

Aim: In patients with colorectal cancer an accurate diagnostic work-up is mandatory in order to perform the most specific treatment. At this moment 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) is considered an accurate imaging technique in staging/restaging several malignancies. The aim of this paper is to review the scientific literature available about the role of FDG-PET in the management of patients with colorectal cancer.

Methods: An overview on Medline of scientific literature concerning FDG-PET and colorectal cancer was performed. The most relevant studies are reported. Advantages, limitations and new chances in using FDG-PET in these subsets of patients are summarized.

Results: FDG-PET is a useful tool in the evaluation of colorectal cancer. In comparison to conventional imaging technique, FDG-PET has an additional diagnostic value because it allows to metabolically characterize undetermined lesions suspected for recurrence of disease, to perform a complete pre-surgical staging and to identify occult metastatic disease. In clinical practice its use leads to a change in therapeutic choices in a high percentage of cases.

Conclusions: FDG-PET should be considered an essential diagnostic tool in the management of patients with colorectal cancer, especially in recurrent disease evaluation.

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Introduction

Colorectal cancer is the fourth most common neoplastic disease in the population after prostate, lung, and breast cancer and the second cause of death among tumors. At this moment screening programs allow an early diagnosis and, in localized disease, surgery is usually the treatment of first choice. On the other hand, in case of local extended disease, the use of neoadjuvant chemo-radiotherapy seems to lead to an improvement in patients’ prognosis.1,2 An adequate and complete pre-operative staging of disease is thus necessary to define the therapeutic plan. Because 40% of patients have disease recurrence after the primary treatment,3 the early detection of local or distant recurrence of disease is also mandatory in order to perform the most adequate therapy and to increase survival duration.

For these purposes many imaging modalities (contrast enhanced computed tomography (c.e. CT), ultrasound (US), magnetic resonance imaging (MRI), endoscopic procedures) are available and the introduction in clinical practice of whole body 18F-fluoro-deoxy-glucose-positron emission tomography (FDG-PET) scan has added a new “strategic” tool in this scenario. FDG-PET is included among molecular imaging techniques based on the representation by whole body images of radioactive tracers distribution in organs and tissues. At this moment 18F-fluoro-deoxy-glucose is
the most useful and used metabolic tracer in the oncological field; it accumulates in cells with high glycolytic activity, as tumoral cells, allowing to detect neoplastic lesions and to differentiate between the benign and malignant nature of lesions morphologically undetermined.

Several studies demonstrate that whole body FDG-PET scan is an accurate non-invasive technique in staging/restaging of several malignancies and its usefulness has also been proved in the management of patients with colorectal cancer. In particular, recent guidelines on the appropriate use of FDG-PET in oncology recognize an appropriate use of this technique in restaging patients with suspected recurrence of colorectal cancer with the elevation of serum tumor marker (CEA) and with a negative or inconclusive standard diagnostic work-up, and in pre-surgical evaluation of patients with recurrence of disease and potentially resectable metastatic lesions.

On the other hand the use of FDG-PET scan in the pre-operative staging of disease is considered potentially useful, but not sufficiently demonstrated.

Finally, in these patients the role of FDG-PET scan is promising in the follow up and in the evaluation of response to therapy.

**FDG-PET in recurrent colorectal cancer**

The usefulness and the additional diagnostic value of FDG-PET in this field was demonstrated in a meta-analysis performed in 2000 by Huebner et al. that showed that FDG-PET allows a change in clinical management in about 30% of patients with recurrent colorectal disease when added to standard imaging techniques in the diagnostic work-up.

This result is correlated, first of all, with the ability of this modality to detect early disease revealing metabolic changes in normal-size structures before morphological findings appear. Furthermore, FDG-PET scan allows the identification of neoplastic lesions missed at c.e. CT in patients with an altered abdominal anatomy after abdominal or hepatic surgical treatment. Then it can metabolically characterize suspected lesions in which c.e. CT is inconclusive.

On this basis in clinical practice its use is already consolidated to localize occult metastatic disease in patients with an increase in serum tumor marker (CEA) and without evidence of recurrence at conventional imaging techniques. In this subset of patients scientific data show that whole body FDG-PET scan identifies recurrence of disease in about 2 out of 3 cases, so its use in an early phase of the diagnostic work-up is recommended. Considering the high negative predictive value (around 95%) of this technique, in the presence of a negative PET scan in this subgroup of patients, the presence of detectable disease recurrence could be excluded even if a strict clinical follow up should be recommended.

Literature data demonstrate that another advantage of using PET scan in the restaging of patients with recurrent colorectal cancer is in the identification of additional unexpected metastatic sites (up-staging) when compared to c.e. CT alone. Flamen et al. evaluated FDG-PET and c.e. CT findings in 103 patients suspected of having recurrence of colorectal cancer. In this study FDG-PET showed higher sensitivity than c.e. CT in the abdominal cavity detecting metastatic lymphnodes negative at c.e. CT, especially when located in retroperitoneal and mesenteric sites and in detecting peritoneal disease. A statistically significant additional value of FDG-PET was also found in the evaluation of extra-abdominal regions, where it identified unexpected metastases, most of them located in the lung. In the evaluation of liver involvement discordant results are reported in literature. In the study of Flamen et al. no additional value of FDG-PET in terms of sensitivity was found in case of normal c.e. CT and/or MRI findings, but PET allowed to correctly classify anatomically
undefined liver lesions. Another study performed by Truant et al. also showed that the sensitivity of FDG-PET was equivalent to that of c.e. CT for the hepatic sites (79% vs 79%) for both, while it was highly superior for the extrahepatic abdominal sites (63% vs 25%). On the other hand a meta-analysis published in 2002 demonstrates that FDG-PET is superior to conventional diagnostic techniques (CT, ultrasonography and MRI) also in detection liver metastases presenting a sensitivity around 90% and that it can be considered “the most sensitive non-invasive imaging modality for the detection of hepatic metastases” from tumors of gastrointestinal tract especially from colorectal cancer.

In a wide group of patients (n = 115) presenting with recurrent colorectal cancer, Valk et al. reported that PET scan presents a global sensitivity of 93% and a global specificity of 98% in detecting metastatic sites, compared with 69% and 96%, respectively, for c.e. CT alone, confirming that in any case FDG-PET should be always performed in the follow up of these patients. In particular, in this study the most relevant finding is that PET scan identified unexpected metastases in 29% of patients presenting with only one site of recurrent disease at c.e. CT. Several studies evaluated the impact of FDG-PET or FDG-PET/CT on the treatment of patients presenting potentially curable liver metastases and underwent PET scan for a complete restaging of the disease.

Lai et al. demonstrated that PET scan identified unexpected metastases in 25% of patients referred to pre-surgical staging to evaluate liver metastases resectability. In this subset of patients PET scan allows to perform a complete pre-operative staging, assessing the absence or the presence of other neoplastic foci and to choose the most adequate treatment avoiding unnecessary surgery. For this reason FDG-PET should be performed in patients with evidence at standard imaging techniques of a single potentially resectable site of disease.

As reported before, FDG-PET has an important role in the metabolic characterization of indeterminate lesions on anatomical imaging. In particular the evaluation of presacral recurrences, which occur in a high percentage of patients, is a real clinical challenge. In fact, the conventional pelvic imaging evaluation (c.e. CT and transrectal ultrasound (TREUS)) finds difficulties in differentiating between postsurgical or radiotherapy residual fibrotic tissue from disease recurrence, which candidates the patient to further treatments. Flamen et al. showed that FDG-PET presents an additional diagnostic value in the 56% of cases when compared to c.e. CT alone and in 20% of cases when compared to c.e. CT joined to TREUS. Even-Sapir et al. demonstrated that PET/CT in patients with colorectal cancer underwent abdominoperitoneal or anterior resection has a sensitivity, a specificity, a positive predictive value, a negative predictive value and an accuracy of 98%, 96%, 90%, 97%, 93%, respectively, in distinguishing benign from malignant presacral abnormalities. We also evaluated the accuracy of PET/CT scan in this field which resulted around 96% in agreement with literature data (data not shown) (Fig. 2).

**FDG-PET in pre-surgical staging of primary colorectal cancer**

The role of FDG-PET in the pre-surgical staging of primary disease is still controversial and at this moment there are not evidences about its advantages on standard diagnostic work-up. In particular at this moment only few studies with a small number of patients are available. These studies...
reported a high sensitivity of this technique in detecting the primary tumor, also when in situ, ranging between 95–100%. The histopathological features of the tumor and the diameter of the lesion are strictly correlated with these data. Some false negative results are, in fact, reported in case of mucinous carcinoma and in the presence of small tumor foci in tubulovillous polyps or villous adenomas. Abdel-Nabi et al. reported also 4 PET false positive findings in 7 patients (positive predictive value: 90%) without colorectal cancer but, respectively, with inflammatory bowel disease or previous diagnostic polypectomy. In detecting liver metastases PET scan also shows a higher sensitivity (78–88%) than c.e. CT of abdomen/pelvis (38–67%) and sonography as well (25%) with high specificity levels (range: 96–100%).

On the other hand, in an other study FDG-PET doesn’t seem superior in terms of sensitivity and accuracy when compared to multidetector helical computed tomography for routine staging. In particular in this study FDG-PET shows a low sensitivity in the evaluation of lymph nodes involvement with value around 37% in comparison with c.e. CT sensitivity which results around 58%, but specificity levels remain high with value around 87%. Other studies confirmed in this field low sensitivity levels of PET scan with value around 30%. These results demonstrate that FDG-PET doesn’t give additional information to the standard diagnostic work-up (c.e. CT and colonoscopy) in detecting loco-regional lymph nodal metastases due to the risk of false negative findings in case of micrometastases or metastatic lymphnodes strictly near to the primary focus. The pathological uptake in lymphnodes, in fact, can be hidden by the high FDG uptake of the primary tumor lesion.

At this moment it can be assessed that the use of PET scan in staging primary colorectal cancer doesn’t apport a relevant change in clinical management when compared to standard diagnostic work-up.

New chances

Among promising uses of FDG-PET/CT there is the evaluation of disease response to chemo-radiotherapy in order to differentiate between responder from non-responder patients who would be candidates to different therapeutic strategies. This is performed by a semi quantitative evaluation of FDG tumor uptake through the measurement of the standardized uptake value (SUV). This parameter permits to evaluate tumor metabolic modifications that generally anticipate morphological changes. On this basis, as well as in Hodgkin disease, a new exiting use of FDG-PET is the early evaluation of disease response after 1–2 cycles of chemo-radiotherapy to perform a prognostic stratification of patients. Moreover, FDG-PET seems to have a role in the identification of planning target volume in radiotherapeutic treatment, however, in this field, further confirmations are needed.

FDG-PET limitations

Scientific data reported in the previous paragraphs demonstrates that FDG-PET is a useful tool, especially in restaging patients with suspected recurrent colorectal cancer, but some limitations have to be pointed out. FDG-PET can present false positive findings in abdominal recurrence evaluation in the presence of postsurgical inflammation and inflammatory disease (i.e. abscesses, colitis, rectal fistula). The physiological FDG uptakes in gastrointestinal and genitourinary tracts due to the excretion of tracer itself can mimic but also hide pathological sites.

On the other hand, the risk of false negative findings is high when in presence of miliary liver metastatic diffusion, due to physiological uptake of FDG in liver parenchyma and a low lesion/background ratio, or in diffuse peritoneal effusion, which can present low FDG uptake.

As well as anatomical site, the lesion diameter is another important conditioning factor of PET accuracy and it can be cause of false negative results, especially in lymph nodal or hepatic lesions with diameter inferior to 1 cm, being near to the technique spatial resolution. Finally, patient blood glucose levels, when high (>150 mg/dl), can deteriorate imaging quality and some metastatic lesions, especially when located in the liver can be missed. That justifies an accurate evaluation of blood glucose levels and at least 6 h fasting before scanning. The meta-analysis performed by Huebner et al. in 2000 evaluated the influence of false positive and false negative results on sensitivity and specificity of FDG-PET in patients with recurrence of disease. Final data showed that false positive had a major impact than false negatives results. In fact, the sensitivity of whole body PET scan resulted to be high (97%), with similar level both in the liver (91–96%) and in the pelvis (94%) involvement detection. On the other hand specificity values in the evaluation of recurrence were different for total body (76%), liver and pelvis (97–99%) due to the greater potential of false positive results in the whole body than in the isolated organ.

To date the introduction of combined PET/CT tomograph has added new advantages in the evaluation of many tumors and also of colorectal cancer. In fact it allows to correlate tissue abnormal metabolic changes detected at PET to anatomical structures defined at CT with an accurate localization and characterization of lesions. Cohade et al. showed how in-line PET/CT improves diagnostic accuracy of PET alone in restaging of recurrent colorectal cancer, especially in the evaluation of abdomino-pelvic extrahepatic disease, reducing false positive findings due to unspecified or inflammatory FDG uptakes. In this study the use of PET/CT instead of PET alone led to an improvement in diagnostic accuracy from 78 to 89%. A recent review also has evaluated the potential of PET/CT in this field comparing it with c.e. CT, MRI
and PET alone and suggesting that, when available, “FDG-PET/CT appears to be the diagnostic tool of choice in the early disease evaluation.” Furthermore, the use of low dose CT scan to correct PET emission images for attenuation (instead of transmission scan, obtained with external radioactive sources as in the past) allows to shorten the time necessary for the completion of the whole body acquisition, being at this moment around 25–30 min.

Conclusions

In conclusion, in clinical practice whole body FDG-PET scan has a key role especially in restaging patients treated for colorectal cancer presenting an additional value to standard diagnostic work-up and a high clinical impact. It should be considered an essential tool in this subset of patients to perform a better clinical management.

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