Role of FDG-PET/TC in follow-up of patients treated with resective gastric surgery for tumour

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INTRODUCTION: *Gastric cancer has a poor prognosis and a high rate of recurrences after surgery. The optimal method for assessing early recurrences is not defined: conventional imaging (ultrasonography, CT, and MRI) have difficulty in detecting them, because they don't give information regarding metabolic features or tumor response to chemotherapy. Actually 18F-fluorodeoxyglucose positron emission (18FDG-PET) has several indications for the primary staging and the follow-up of colon-rectal, lung, breast, neck cancers and lymphoma, but its clinical role in gastric cancer is not assessed. Our study analyzes the role of 18FDG-PET integrated with CT scan in the detection of gastric cancer recurrence.*
MATERIALS AND METHODS: *We retrospectively reviewed 50 patients which underwent follow-up 18FDG-PET/CT from 2006 to 2009 after radical surgery for gastric adenocarcinoma. Each study was repeated every 6 months for the first two years after surgery and every 12 months for the subsequent three years.*
RESULTS: *18FDG-PET/CT was positive for suspected neoplastic disease in 29 (58%) and negative in 21 (42%) patients, with 3 false positive and 3 false negative results. 18FDG-PET/CT showed highly effectiveness in early detection of recurrences, as observed in 17 patients that were totally asymptomatic, allowing the initiation of multimodal treatment resulting in an important increasing of survival.*
CONCLUSIONS: *18FDG-PET-CT has a very good sensitivity (89.7%) and specificity (85.7%) in detecting local and distant recurrences during post-operative follow-up. Positive 18FDG-PET/CT findings may lead to an early change in the management of these patients, directing them towards rescue surgery or chemotherapy, thereby improving their overall survival.*

KEY WORDS: 18F-fluorodeoxyglucose, Follow-up Gastric cancer, Positron emission tomography, Computed tomography, Recurrence.

Introduction

Gastric cancer is the fourth most common cancer and the second cause of cancer-related death worldwide. It has a poor prognosis with a 5-years overall survival below 30% and often it is diagnosed in an advanced stage [1]. Though radical surgery is to date the only therapeutic option, up to 70% of patients undergoing R0 surgery develop recurrence within 5 years [2]. Adjuvant treatments such as chemotherapy or radiotherapy provide a slightly improved survival rate. Peri-operative chemotherapy may increase the possibility of complete surgical resection, improving disease-free and overall survival (5-year overall survival of 36% vs 23% with surgery alone) as shown in the MAGIC Trial [3].
Early detection of recurrences may also improve survival, allowing for expeditious chemotherapic or radiotherapic treatment, and sometimes additional surgery.

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ABBREVIATIONS: ^{18}FDG: ^{18}F-fluorodeoxyglucose; PET: positron emission tomography; SUV: standardized up-take value; CT: computed tomography; MR: magnetic resonance imaging; FLT: 3-deoxi-3-^{18}F-fluorothymidine.

^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET) has been reported to have a low sensitivity in the primary detection of gastric cancer but even better results in evaluating clinical responders to neoadjuvant therapy and in detecting lymphatic or haematogenous metastases [4,5].

Pre-operative staging and post-operative follow-up are based on conventional imaging, such as ultrasonography, contrast Computed Tomography (CT) and magnetic resonance imaging (MRI), and only a few studies are available regarding the use of ^{18}FDG-PET follow-up of patients after gastric surgery for malignancy [6-10].

Our aim is to analyze the value of ^{18}FDG-PET combined with chest-abdomen-pelvis CT (^{18}FDG-PET/CT) in the follow-up of patients receiving surgical resection for gastric adenocarcinoma.

Materials and Methods

From 2006 to 2009, 50 patients underwent surgery for gastric adenocarcinoma at our Institution. After surgery, follow up included clinical examination, serum markers dosage (CA 19.9, CEA, alphafetoprotein, CA 125), upper endoscopy and ^{18}FDG-PET/CT. Each study was repeated every six months for the first two years after surgery and every 12 months for the subsequent three years.

Their mean age at gastric surgery was 68.4 years. Thirty-two patients were staged by ^{18}FDG-PET/CT at the time of diagnosis, while 18 patients received only contrast CT in the preoperative setting. Of the 50 patients, 9 had stage IA disease (18%), 8 stage IB (16%), 8 stage II (16%) 9 stage IIIA (18%), 2 stage IIIB (4%) and 14 stage IV (28%) at the time of surgery. We performed 19 subtotal gastrectomies (38%), 28 total gastrectomies (56%) and 3 gastric stump resections (6%); D1 lymphectomy was performed in 11 (18%) patients and D2 lymphectomies in 39 (78%). Twenty-three patients had intestinal histological patterns according to Lauren classification, 22 were diffuse, 1 hepatoid and 4 mixed. Twenty-one patients underwent adjuvant chemotherapy and 8 were treated with peri-operative chemotherapy according to the MAGIC Trial.

Patients undergoing ^{18}FDG-PET/CT were asked to comply with a hypoglycemic diet the day before the study and to fast for at least 6 hours before the examination; ^{18}FDG was then administered based on patient's weight (4.5 MBq/Kg) and basal glycemia (<150 mg/dl). Data acquisition was performed 60 minutes after the injection by an integrated Positron Emission Tomography and CT scan system (Discovery ST, GE Healthcare, Chalfont St. Giles, United Kingdom; General Electric Company, Fairfield, CT, USA). CT scan was performed after the PET with 5-millimeters-thick sections, at 350-380 mA and 140 Kw, from the neck to the perineum.

^{18}FDG-PET was considered positive for neoplastic disease when abnormal non-physiologic metabolic activity was shown. Quantification of metabolic activity was obtained using the Standardized Up-take Value (SUV) normalized to body weight. Mean +/- standard deviation of maximum-pixel SUV (SUV max) of the lesions were calculated. Diffuse mild metabolic activity in the intestinal tract was considered normal physiologic up-take. CT imaging showed pathological findings and gave anatomy-based diagnosis of the areas of increased metabolism, identifying their nature.

Results

Among the 50 patients analyzed, ^{18}FDG-PET/CT was positive for suspected neoplastic disease in 29 (58%) and negative in 21 (42%). ^{18}FDG-PET/CT diagnosed 25 recurrences of malignancy (8 hepatic, 6 local, 5 lymphatic, 3 peritoneal, 1 pulmonary and 1 cutaneous). One patient had metabolic activity localized in the right colon, and endoscopy revealed a polyp in the caecum that proved to be severe dysplasia on biopsy.

We observed 3 false positive and 3 false negative results. Two patients with positive ^{18}FDG-PET/CT had metabolic activity localized in the colon. In one patient endoscopy revealed left colonic diverticulosis while no pathology was observed in the other patient. In one patient ^{18}FDG-PET/CT was suspicious for pulmonary recurrence but high resolution chest CT-scan showed no pathological findings. In two patients presenting with initial peritoneal carcinomatosis and one with brain metastases, ^{18}FDG-PET did not show metabolic activity; in these patients diagnosis of recurrence was done by clinical examinations, serum marker levels and brain CT-scan.

In our series the sensitivity of ^{18}FDG-PET/CT for detecting neoplastic disease is 89.7% and specificity is 85.7%. Positive and negative predictive values are 89.7% and 85.7% respectively.

Elevated neoplastic markers (CA19.9, CEA or both) occurred in 16 patients (14 of those had ^{18}FDG-PET/CT positive for recurrences), whereas normal levels were observed in 34 patients (11 had ^{18}FDG-PET/CT positive for recurrences). In our experience sensitivity of neoplastic markers (CA19.9, CEA or both) in detecting gastric adenocarcinoma recurrence is 56% and specificity is 88%.

Seventeen patients with positive ^{18}FDG-PET/CT fin-

dings were totally asymptomatic at the diagnosis of recurrences. Four patients with liver metastases underwent hepatic resections, one patient affected by peritoneal carcinomatosis underwent surgery because of intestinal occlusion and two patients had cutaneous metastasis excised: histopathology confirmed gastric adenocarcinoma recurrences. All of them underwent rescue chemotherapy with a median overall survival of 25 months. Cytological examination of paracentesis liquid revealed neoplastic cells in 3 patients. In the remainder 15 patients recurrences were diagnosed by imaging and clinical and laboratory examinations. In total, 18 patients underwent chemotherapy after the diagnosis of recurrence, the remainder were limited to supportive care due to their co-morbidities and clinical conditions.

Mean follow-up was 25.9 months (median 24 months) and neoplastic recurrences occurred at 11.2 months (median 6 months). Overall survival of patients for which developed recurrences was 19.8 months from surgery; death occurred on average 8.7 months after the diagnosis of relapse.

Discussion

Gastric cancer is a neoplasm with a poor prognosis and radical surgery is the only therapeutic option to date. Only about 20% of patients have local disease (T1-2 N0 M0) at the diagnosis, whereas 65% have locally advanced (T1-2 N+ or T3-4 N0/+ M0) disease and 15% metastatic disease. Moreover the 50-70% of patients that undergo R0 surgery develop recurrences within 5 years. Five-year overall survival in patients after gastric surgery for adenocarcinoma is 60-70% when lymph nodes are not involved and decreases to 5-35% in locally advanced neoplasms, with a median survival of 24 months [1,2]. Adjuvant treatments such as chemotherapy or radiotherapy provide little benefit in improving overall survival. Peri-operative chemotherapy may increase the possibility of complete surgical resection, improving progression-free and overall survival (5-years overall survival of 36% compared with 23% of patients treated by surgery alone) as shown in the MAGIC Trial, but others studies are needed to confirm the true benefit of peri-operative chemotherapy [3].

There is no optimal method for assessing early recurrences during post-operative follow-up. Conventional imaging (ultrasonography, CT-scan and MR imaging) have difficulty detecting early recurrences, such as lymphatic involvement, and in re-staging gastric cancer after surgery [11-14]. Conventional imaging technologies assess anatomical or morphologic tumor features, but don't give information regarding metabolic tumor features or response to chemotherapy; whereas molecular imaging technology does.

Actually, ^{18}FDG-PET has a variety of indications for primary staging and detecting recurrence disease of colorectal, lung, breast, head and neck cancers and lymphoma, there are only few reports concerning its role in gastric cancer [6-10, 15-19]. Preliminary data has demonstrated a variable sensitivity rating from 58 to 94% and a specificity ranges from 78 to 100% in detecting primary gastric cancer [20-23]. In the identification of lymph nodes metastases, low sensitivity has been described from 17.6 to 46.4% in contrast to a high specificity ranging between 91 and 100% [20-24]. In the early detection of recurrence ^{18}FDG-PET seems to have a sensitivity and negative predictive value of respectively 70 and 60% [25]. Yoshioka et al. found a sensitivity and specificity of 85% and 74% for the detection of liver metastases, and 67% and 88% for lung recurrences [18]. ^{18}FDG-PET has a poor sensitivity (from 0 to 50%) and a relatively high specificity (from 63 to 99%) in detecting peritoneal carcinomatosis [18, 20, 24].

So gastric cancer staging and detecting recurrence may be improved by fusion of ^{18}FDG-PET and CT imaging. ^{18}FDG-PET/CT augments the detection accuracy by locating PET hot spots on anatomical landmarks, increasing sensitivity and specificity. Moreover CT spatial resolution allows a precise detection of smaller findings, such as lymph nodes or liver lesions. Sun et al. reported a ^{18}FDG-PET/TC accuracy of 82.6% in diagnose gastric cancer recurrence, with a positive predictive value and a negative predictive value of 85.7% and 77.7% respectively [9]. Nakamoto et al., in their multicenter experience, described a sensitivity rating from 50 to 81% and a specificity ranging between 79 and 85% of ^{18}FDG-PET/TC detecting gastric cancer recurrence [26].

Our results confirmed that ^{18}FDG-PET integrated with CT scan reaches good results in diagnosing gastric cancer recurrence, with a sensibility of 89.7%, a specificity of 85.7%, and with positive and negative predictive values of 89.7% and 85.7% respectively. CT-scan provides additional anatomical and morphologic information beyond the ^{18}FDG-PET, allowing a clearer identification and localization of pathological findings. Additionally, all our ^{18}FDG-PET/CT images were analysed by the same physician specialist both in radiology and in nuclear medicine.

In our series, neoplastic markers serum values (CA 19.9, CEA or both) showed a sensibility of 56% and specificity is 88%: so their elevation must be considered an alarm bell, but is not enough to diagnose or exclude a gastric adenocarcinoma recurrence, and imaging investigation is mandatory. In fact, 32% (11/34) of patients that presented negative neoplastic markers, had recurrences diagnosed by ^{18}FDG-PET/CT.

In our experience ^{18}FDG-PET/CT is highly effective in early detection of recurrences, as observed in 17 patients that were totally asymptomatic, allowing the initiation of multimodal treatment such as surgery followed by chemotherapy, chemotherapy alone, or radio-chemoradiation. Four patients, with resectable liver metastases, were treated integrating surgery and chemotherapy and

they showed exceptional survivals of 36, 34, 18 and 12 months (all eventually died of peritoneal carcinomatosis). Another patient with a skin recurrence on the back (showed only by ^{18}FDG-PET/CT and excised) underwent chemotherapy and survived 30 months after first surgery. Early detection of recurrences may allow an early treatment and may improve overall survival in select cases.

^{18}FDG-PET/CT may be helpful not only in detecting early tumor relapses, but can also reveal other unknown neoplasms, (benign, malignant, or inflammatory) and again allow earlier treatment options.

Limitations of our experience include that it is a retrospective study and that in 15 patients the positive ^{18}FDG-PET/CT uptake was not confirmed pathologically (they didn't undergo any biopsy or resective surgery) so the diagnosis of recurrence was based on imaging, clinical evaluation and blood tests (12 of them had elevated neoplastic markers and a ^{18}FDG-PET/CT suspected for lymph nodal or peritoneal recurrences).

Specificity may be limited by some pathological features of gastric adenocarcinoma. In fact many reports indicated a clear difference in sensitivity of ^{18}FDG-PET between intestinal and diffuse subtype, with a consistently low rate of ^{18}FDG-uptake by non-intestinal subtype and signet ring cells carcinoma [22,23,27,28]. We can support this observation with our limited experience. A patient affected by a signet ring cells gastric carcinoma that at the diagnosis showed hypermetabolic ^{18}FDG-uptake localized only in the gastric wall; during the operation we noted multiple liver synchronous metastases previously unknown. Three gastric tumors didn't show pre-operative metabolic activity: they were two diffuse and one mixed adenocarcinomas.

FLT-PET seems to be a potential superior imaging modality for staging gastric cancer. FLT (3-deoxi-3-^{18}F-fluorothymidine) is a pyrimidine analogue that has proven to be a stable PET tracer that accumulates in proliferating and malignant tissues [29]. Hermann et al. showed, in a pilot study, that FLT-PET had a sensitivity of 100% for primary tumour detection (60% of tumours were non-intestinal subtype), compared to a sensitivity of ^{18}FDG-PET of 69% [30]. However further studies are needed to evaluate the value of FLT-PET in gastric cancer.

Conclusions

Our results reveal that ^{18}FDG-PET/CT has a very good sensitivity (89.7%) and specificity (85.7%) in detecting local and distant recurrences during post-operative follow-up of patients undergoing gastric surgery for adenocarcinoma.

Moreover, positive ^{18}FDG-PET/CT scan findings may lead to an early change in the management of these patients, directing them towards rescue surgery or chemotherapy, thereby improving their overall survival.

Conflict of interest statement

The authors declare that they have no financial and personal conflict of interest.

Riassunto

BACKGROUND: Il cancro gastrico presenta una prognosi alquanto infausta ed il tasso di recidiva dopo chirurgia gastrica curativa è elevato. Ancora non ben definito risulta l' iter per la diagnosi di recidiva dopo chirurgia. Attualmente la ^{18}FDG-PET/TC ha indicazione sia per la stadiazione primaria pre-chirurgica che per la diagnosi di recidiva di neoplasie quali in cancro del colon, del polmone, della mammella e le neoplasie linfoproliferative. Il ruolo di questa tecnica d' imaging per il cancro gastrico non è ancora noto. Il nostro studio ha lo scopo di definire il ruolo della ^{18}FDG-PET/TC nella diagnosi della recidive da neoplasia gastrica.

MATERIALI E METODI: Presso il nostro istituto abbiamo retrospettivamente analizzato 50 pazienti sottoposti a ^{18}FDG-PET/TC dal 2006 al 2009 dopo essere stati sottoposti a chirurgia gastrica per adenocarcinoma gastrico. La ^{18}FDG-PET/TC viene eseguita ogni sei mesi per i primi due anni ed ogni anno per i successivi 3 anni.

RESULTATI: La ^{18}FDG-PET/TC è risultata essere positiva in 29 pazienti (58%) e negativa IN 21 (42%), 3 pazienti sono risultati falsi positivi e 3 pazienti falsi negativi.

La ^{18}FDG-PET/TC ha mostrato una elevata accuratezza diagnostica, come osservato in 17 pazienti clinicamente asintomatici, in modo da poter attuare una strategia terapeutica multimodale ed incrementando la sopravvivenza.

CONCLUSIONI: La ^{18}FDG-PET/TC ha una elevata sensibilità (89,7%) e specificità (85,7%) nella diagnosi di recidive locali o sistemiche durante il follow-up di pazienti sottoposti a chirurgia gastrica recettiva per neoplasia. Inoltre la ^{18}FDG-PET/TC, alcune volte permettendo una diagnosi precoce della recidiva, permette di mettere in atto un trattamento multimodale, chitutgico e medico, e quindi di migliorare la sopravvivenza.

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