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EDITORIAL

Evolving role of FDG-PET/CT in prognostic evaluation of resectable gastric cancer

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Abstract

Gastric cancer (GC) remains a leading cause of cancer death worldwide. Radical gastrectomy is the only potentially curative treatment, and perioperative adjuvant therapies may improve the prognosis after curative resection. Prognosis largely depends on the tumour stage and histology, but the host systemic inflammatory response (SIR) to GC may contribute as well, as has been determined for other malignancies. In GC patients, the potential utility of positron emission tomography/computed tomography (PET/CT) with the imaging radiopharmaceutical ^{18}F-fluorodeoxyglucose (FDG) is still debated, due to its lower sensitivity in diagnosing and staging GC compared to other imaging modalities. There is, however, growing evidence that FDG uptake in the primary tumour and regional lymph nodes may be efficient for predicting prognosis of resected patients and for monitoring tumour response to perioperative treatments, having prognostic value in that it can change therapeutic strategies. Moreover, FDG uptake in bone marrow seems to be significantly associated with SIR to GC and to represent an efficient prognostic factor after curative surgery. In conclusion, PET/CT technology is efficient in GC patients, since it is useful to integrate other imaging modalities in staging tumours and may have prognostic value that can change therapeutic strategies. With ongoing improvements, PET/CT imaging may gain further importance in the management of GC patients.

Key words: Gastric cancer; Prognosis; ^{18}F-fluorodeoxyglucose; Positron emission tomography-computed tomography; Bone marrow

Core tip: Gastric cancer (GC) is still a leading cause of cancer death worldwide. Prognosis depends on surgical curability, response to adjuvant therapies, tumour stage and histology, but also on the systemic inflammatory response to malignancy. While the diagnostic role of positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG) in GC is still debated, due to unsatisfactory sensitivity, there is growing evidence that FDG uptake, either at the tumour sites or in the bone marrow, may represent an efficient tool for predicting prognosis of resected patients and for monitoring tumour response to adjuvant treatments, and may have prognostic value in directing therapeutic strategies.

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INTRODUCTION

Gastric cancer (GC) remains a leading cause of cancer death worldwide, with poor prognosis despite significant advances in diagnosis and treatment. Survival rates are progressively increasing in western countries[1-3], and are highest in Japan, due to focused management of preventive and prognosis-related factors (*i.e.* infection and smoking, respectively)[2]. Prognostic factors related to GC are quite well established, such as local extension, lymph node involvement and presence of distant metastases, and can be adequately defined by the conventional imaging modalities, including endoscopic ultrasound (EUS), computed tomography (CT) and magnetic resonance imaging (MRI). However, some emerging prognostic factors related to the metabolism of tumour cells, such as the glucose avidity, or to the systemic inflammatory response (SIR) to the tumour can be better evaluated through the metabolic information that are provided by positron emission tomography (PET) integrated with CT, even though the role of PET/CT imaging in the evaluation of GC is still controversial.

CLASSIFICATION, THERAPEUTIC STRATEGIES AND PROGNOSIS

GC can be categorized according to anatomical location, as either true GC (non-cardia) or gastro-oesophageal-junction (cardia) cancer (GEJ)[1,2]. In general, GC are predominantly adenocarcinomas, classified according to the World Health Organization (WHO) classification into tubular, papillary, mucinous (MAC), poorly cohesive and rare variants[1-3]. The Lauren classification distinguishes GC according to intestinal type, diffuse type (including signet ring cell carcinoma (SRC)), mixed type and indeterminate type[1-3]. Classification of GC based on molecular subtyping has been proposed recently[1] and is promising for helping to improve the accuracy of prediction of individual prognosis and for providing individually-tailored therapies.

Radical surgical resection is the only potentially curative therapeutic option for resectable GC presently. Adequate surgery includes complete resection of the primary tumour and appropriate lymphadenectomy. Tumours of the lower two-thirds of the stomach can be selectively treated with distal subtotal gastrectomy; otherwise, total gastrectomy is recommended[2-4]. This approach has contributed in part to the amelioration of cure rates from 30% to over 50% in selected series over the past decade[1]. Early GC (EGC) is defined as limited to the mucosa or submucosa (T1 stage or lower), regardless of nodal status. Endoscopic resection is considered appropriate for small ($\leqslant$ 20 mm), non-ulcerated, superficial GC that are well differentiated and limited to the mucosa (T1a), because the incidence of regional lymph node metastases is very low[3]. If, however, the tumour has invaded the submucosa (T1b), radical gastrectomy with lymphadenectomy is required, since lymph node involvement is observed in up to 20% of cases[1,2].

Locally advanced GC (AGC; invading the muscularis propria and beyond (T2 stage or higher)) presents in most cases with metastases to lymph nodes, distant organs, or both. Patients without distant metastases are candidates for potentially radical surgery, either conventional or minimally invasive by laparoscopy[1-4]. Perioperative therapies for resectable GC include chemotherapy (CHT), radiotherapy and chemoradiotherapy, performed before and/or after surgery. Even though adjuvant and neoadjuvant therapies have been demonstrated to improve prognosis after potentially curative resection of locally AGC, the optimal strategy is still debated[1-3].

Despite substantial advances in the staging procedures, imaging techniques and treatment options, prognosis of GC remains poor, with postoperative 5-year survival rates of 25%-30% in western countries, because of the high incidence of advanced tumours[3]. Cardia GC and diffuse-type non-cardia GC have the worst prognosis. For resectable locally AGC, outcome depends on the surgical disease stage. Resection of EGC provides excellent 5-year survival rates, up to 90%. However, at the time of diagnosis GC is usually advanced, with reported involvement of the regional lymph nodes in 70% to 80% of cases. If the tumour invades the subserosa (T3 stage), 5-year survival decreases to less than 50%. Moreover, the presence of nodal involvement in T3 lesions further decreases 5-year overall survival to less than 30%[2].

Besides tumour-related factors, the survival of GC patients, as for other malignancies, is also dependent on the host's reaction to the cancer. SIR plays a critical role in carcinogenesis and tumour diffusion[5]. Several host SIR markers (SIRMs) have been identified as prognostic factors. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin and C-reactive protein (CRP) have been indicated, alone or in combination, as significant factors for predicting postoperative prognosis of GC patients[6,7].

ROLE OF PET/CT IN DIAGNOSIS AND PROGNOSTIC EVALUATION

Clinical evaluation of GC has greatly improved with the availability of EUS, CT, MRI, PET/CT and laparoscopic staging. PET/CT using ^{18}F-fluorodeoxyglucose (FDG) has proven useful for staging, detecting recurrence, evaluating treatment response and predicting prognosis[1-4,8,9]. However, the overall sensitivity of FDG-PET/CT for detecting GC is lower than for most other malignancies, so that its effective role in GC patients is still controversial[8,9]. FDG-PET may have different sensitivities for different histotypes, with better sensitivity for GEJ tumours, but significantly lower sensitivities for diffuse type adenocarcinoma, including SRC, or for MAC[8,9]. Since tumour size and depth of invasion are significant factors influencing FDG-PET detection of GC, sensitivity is low for EGC and far higher for AGC. Altogether, the role of PET/CT is limited in T staging due to its low spatial resolution[9]. For N staging in GC, the sensitivity and specificity of FDG-PET/CT range between 33.3%-64.6% and 85.7%-97.0%, respectively[8]. The low sensitivity in detecting lymph node metastases may be related to the histotype of the primary tumour, or even to the size of the metastatic lymph nodes; some small lymph nodes may be difficult to visualize because of the radioactive volume effect generated by the nearby primary cancer[8,9]. Nonetheless, FDG-PET/CT is considered to have higher specificity than CT and MRI in the N staging of GC, especially for the N2 and N3 groups[9]. FDG-PET/CT has lower sensitivity than CT for the diagnosis of peritoneal seeding, while being more efficient in the detection of solid organ metastases, including those involving the lung, liver, bone or adrenal gland, with near 100% sensitivity and specificity[8,9].

Despite these limitations, FDG-PET/CT is emerging as an effective tool for therapeutic and prognostic evaluation of AGC. Preoperative FDG uptake has been demonstrated as an independent, significant prognostic factor following curative gastrectomy[8,9]; although, the collective data are not in full agreement. Patients with lower preoperative FDG uptake in the GC have shown significantly lower incidence of recurrence and better recurrence-free survival after surgery[8,9]. Lower preoperative FDG uptake has been reported as a predictor of tumour curability at the time of surgery, since higher FDG uptake in the primary tumour and positive FDG uptake in local lymph nodes have been significantly associated with non-curative resection, suggesting that these patients should be candidates for neoadjuvant CHT[9].

Neoadjuvant treatments have been increasingly used for AGC to reduce tumour stage, plan the optimal surgical timing and strategies, and improve the overall prognosis[9]. About 30% to 60% of histologically partial or even total responders have been reported with different therapeutic regimens[8]. Since patients with clinical and pathological response to neoadjuvant therapies are considered to gain significant survival benefit, the prompt identification of responders seems to be essential. FDG uptake in PET/CT scans is actually considered an early and sensitive indicator of response to treatment[2,3,8,9], concordant with histopathological analysis for tumour response. Changes in FDG uptake soon after the initiation of treatment have been related to final outcome also. In some studies, metabolic responders have shown better prognosis than non-responders, while FDG non-avid tumours seem to have poor response rates to CHT and unfavourable prognosis, indicating that neoadjuvant therapies may be ineffective in metabolic non-responders and in patients with low FDG uptake at baseline PET imaging[8].

In neoplastic patients, FDG uptake in bone marrow (BM) on PET/CT has been shown to be significantly associated with SIRMs, suggesting that this imaging finding has a significant relationship with SIR to malignancy[7]. In non-small cell lung cancer patients with curative surgical resection, Lee *et al*[7] have recently shown that the FDG uptake in BM and the BM to liver uptake ratio (BLR) were significantly correlated with albumin and CRP levels, white blood cell count, NLR and PLR; moreover, the BLR was identified as an independent prognostic factor of recurrence-free survival. The authors concluded that the FDG uptake in BM for non-small cell lung cancer patients reflects the degree of SIR and can be used as a prognostic factor after curative surgery[7].

In a recent retrospective series of 309 GC patients undergoing curative surgical resection, Lee *et al*[10] demonstrated that the preoperative BM FDG uptake, and BLR especially, are correlated with SIRMs of GC. In addition, patients with AGC, recurrence and positive FDG uptake of primary cancer were shown to have higher BM FDG uptake than those with EGC, no recurrence and negative FDG uptake, respectively; thus, GC patients with advanced stage and aggressive features might have higher degrees of SIR. BLR was identified as an independent prognostic factor for predicting survival, along with T4 stage, lymph node metastasis and positive resection margin. The authors conclude that for GC, both tumour factors and SIR could play important roles in long-term prognosis of resectable patients, and that BM FDG uptake could

reflect the degree of SIR to cancer and provide information on prognosis after curative surgery.

CONCLUSION

In conclusion, PET/CT technology represents an efficient tool for use in GC patients, since it is useful to integrate other imaging modalities in staging tumours. Moreover, it can be effective in monitoring tumour response to treatments and may have prognostic value with the potential to change therapeutic strategies. Although some problems still persist, PET/CT imaging remains promising, and with ongoing improvements may gain further importance in the evaluation and treatment of GC patients.

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