Journal of Cancer Research and Clinical Oncology (2019) 145:759–764
https://doi.org/10.1007/s00432-018-02832-9

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

FDG PET/CT to predict the curability of endoscopic resection for early gastric cancer

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Received: 15 November 2018 / Accepted: 21 December 2018 / Published online: 2 January 2019

Abstract

Purpose We evaluated the value of fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) as a complementary imaging modality to endoscopy to predict the curability of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC).

Methods The institutional review board approved this retrospective study with a waiver of informed consent. The records of patients who underwent FDG PET/CT for initial routine staging of gastric cancer from January 2012 to October 2017 were reviewed retrospectively. Among them, the patients who had EGC with well or moderately differentiated adenocarcinoma were included in this study. A total of 210 EGCs in 199 patients (mean age ± SD, 67 ± 10 years) were selected for this study. For the analysis of FDG PET/CT image, the radiotracer uptake by the primary tumor was compared with the background gastric uptake. Each case was classified as curable by ESD (no discrete radioactivity) and not curable by ESD (discrete radioactivity).

Results The detection rate of EGC by FDG PET/CT was 37.1% (78 discrete radioactivity in 210 EGCs). However, for the detection of EGC that is not curable by ESD, the sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve with 95% confidence intervals were 79% (67–87%), 91% (85–95%), 81% (71–88%), 89% (84–93%), and 0.85 (0.79–0.89), respectively.

Conclusion FDG PET/CT may be a useful complementary imaging modality to endoscopy to predict the curability of ESD for EGC.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Endoscopic resection · FDG PET/CT

Introduction

Because of cancer-screening programs and advancements in endoscopic technologies and skills, the detection of gastric cancer, particularly early gastric cancer (EGC), has increased (Pasechnikov et al. 2014). Good survival has been reported for localized EGC after curative resection (Strong et al. 2013). Recently, endoscopic submucosal dissection (ESD) has been widely accepted for treating EGC with an amenable size for en bloc resection and very low risk of lymph node metastasis (Tanaka et al. 2017). Because endoscopic treatment is a stomach-preserving method and may provide better quality of life compared with laparoscopic or open surgery, ESD is a preferable method if a similar prognosis is expected (Gotoda 2007).

To determine preoperatively whether EGC is curable by ESD, it is necessary to define tumor size, histopathological

This work described has not been published before and it is not under consideration for publication anywhere else. Its publication has been approved by all co-authors.

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type, depth of invasion, and whether ulceration is present. However, to date, these skills and knowledge are mainly dependent on the experience of the gastroenterological endoscopist, and the reliability of the preoperative diagnosis is not satisfactory (Ono et al. 2001).

Fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) is a well-known imaging method that is used to measure tumor glucose utility. The quantitative parameters measured by FDG PET/CT, such as the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), have been recommended for assessing tumor metabolism and aggressiveness (Chung et al. 2014; Lee et al. 2015, 2017). Poor survival was reported in patients with gastric cancer with a high FDG uptake (Chung et al. 2010; Coupe et al. 2014). In this study, we evaluated the value of FDG PET/CT as a complementary imaging modality to endoscopy to predict the curability of ESD for EGC.

Methods

Patients

This retrospective study was approved by our institutional review board with a waiver of the need to obtain informed consent. The medical records of consecutive patients with newly diagnosed gastric cancer who underwent FDG PET/CT as part of the routine tumor staging procedures at our center from January 2012 to October 2017 were reviewed. Primary gastric cancer was confirmed by endoscopic biopsy. Gastrectomy or ESD was performed in the indicated patients within 3 weeks of FDG PET/CT.

The pathological results obtained after surgery or ESD were evaluated to determine whether ESD was curative for gastric cancer. According to the clinical practice guidelines for endoscopic resection for EGC, the absolute indications of curative ESD include a lesion with a diameter ≤ 2 cm, pT1a (intramucosal cancer) predominantly differentiated carcinoma, no finding of ulceration, no finding of lymphatic and vascular infiltration, and negative surgical margins. Cases that fell under the expanded indications for curative ESD of lesions were those with (1) a diameter > 2 cm, pT1a predominantly differentiated carcinoma, and no ulceration; (2) a diameter < 3 cm, pT1a predominantly differentiated carcinoma, and ulceration; (3) a diameter < 2 cm, pT1a predominantly undifferentiated carcinoma, and no ulceration; or (4) a diameter < 3 cm, pT1b (cancer invasion < 500 μm from the muscularis mucosae) predominantly differentiated carcinoma; and no finding of lymphatic and vascular infiltration and the presence of negative surgical margins. To determine whether ulceration is present within the lesion, not only active ulcerations but also ulcers in the healing or scarring state are defined as ulceration according to the clinical guidelines (Lee et al. 2014; Ono et al. 2016).

The patients who had EGC that was pathologically proven after surgery or ESD with well or moderately differentiated adenocarcinoma were included in this study. The patients who had EGC with poorly differentiated adenocarcinoma and signet-ring cell carcinoma were not included in this study. Poorly differentiated adenocarcinoma and signet-ring cell carcinoma have been reported to show low FDG avidity, regardless of tumor size (Park et al. 2017). Thus, they are not appropriate for evaluation by FDG PET/CT to predict the curability of ESD for EGC. Finally, a total of 210 EGCs in 199 patients were selected for this study.

FDG PET/CT image acquisition

All patients fasted for at least 6 h prior to imaging. Blood glucose concentrations were checked before the PET/CT studies (< 120 mg/dl indicating patients without diabetes and < 200 mg/dl indicating the presence of diabetes). Individuals in the resting state were given intravenous injections of FDG (3.7 MBq/kg of body weight). Images were acquired 60 min later using a GEMINI TF 64 PET/CT scanner (Philips Medical Systems, Cleveland OH, USA). The axes of both the PET and CT systems were aligned mechanically. CT was performed from the skull base to the mid-thigh (without intravenous contrast) for the correction of attenuation and anatomical localization using a standardized protocol of 120 kV, 50 mA, a tube-rotation time of 0.5 s per rotation, a pitch of 0.83, and a section thickness of 4 mm. Immediately after CT, PET images were acquired for 1.5 min per frame using a conventional three-dimensional protocol (Lee et al. 2015).

FDG PET/CT image analysis

For this study, images were interpreted independently by two experienced nuclear medicine physicians who were unaware of the pathology results. However, any discrepancies were resolved by consensus. All images were reviewed on a workstation (Philips IntelliSpace Portal; Philips Healthcare). FDG PET/CT images were compared with endoscopic findings to localize the tumor. Therefore, retrospective interpretation of FDG PET/CT was performed. The same two nuclear medicine physicians read all the FDG PET/CT images.

According to the radiotracer uptake by the primary tumor compared with the background gastric uptake, each case was classified as curable by ESD (no discrete radioactivity) and not curable by ESD (discrete radioactivity). If hypermetabolic regional lymph node suggesting lymph node metastasis

was detected by FDG PET/CT, the case was classified as not curable by ESD regardless of the primary tumor uptake.

The SUVmax, MTV, and TLG values of the primary gastric tumor with discrete radioactivity were recorded to determine the tumor metabolic activity quantitatively. The volumetric region of interest was placed over the area of the primary tumor. The SUVmax was defined as the maximum concentration of FDG divided by the injected dose and normalized to the body weight of the patient. For tumors that had no discrete radioactivity, the SUVmax was recorded as zero. The metabolic tumor volume (MTV, in ml) was measured using an SUV-based automated contouring program. Initially, voxels with a threshold of 40% of the SUVmax in the volume of interest within the contouring margin were incorporated to define the tumor margin. If the tumor margin was not defined accurately, the percentage of the SUVmax threshold was adjusted accordingly. The TLG was calculated by multiplying the MTV by the corresponding average SUV determined in a selected contouring volume of interest (Lee et al. 2015).

Statistical analysis

Data were analyzed to determine test performance in the setting in which positive FDG PET/CT could be used to predict preoperatively the curability of ESD for EGC. The primary outcome was the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic (ROC) curve (AUC) of FDG PET/CT to detect EGC that is not curable by ESD. The sensitivity, specificity, PPV, NPV, and AUC of FDG PET/CT were estimated using the ROC curve. The 95% confidence intervals were obtained from the Wilson score interval for a binomial proportion. The size of tumors between the false-negative and false-positive cases was compared using a *t* test. MedCalc ver. 18.2.1 (MedCalc Software, Ostend, Belgium) and PASW statistics ver. 17.0 (SPSS, Chicago, IL, USA) were used for the analyses. A p value < 0.05 was considered significant.

Results

Patient characteristics

The clinical and pathological characteristics of 210 EGC lesions in 199 patients are summarized in Table 1. Synchronous EGCs were found in 11 out of the 199 patients. The review of the final pathological results revealed that 140 EGCs were curable by ESD and that 70 EGCs were not curable by ESD.

Table 1 Clinical and pathological characteristics of the study patients

	Value
Mean age (range)	67 ± 10 (39–92)
Male/female	150/49
Mean tumor size (cm)	2.3 ± 1.5 (0.2–13.5)
Tumor location in stomach	
Upper/middle/lower	29/50/131
Finding of ulceration −/+	113/97
Tumor differentiation	
Well/moderate	41/169
Depth of tumor invasion	
T1a (LP/MM)/T1b (SM1/SM2)	138 (42/96)/72 (18/54)
Tumor lymphatic infiltration −/+	192/18
Tumor vascular infiltration −/+	209/1
Tumor perineural infiltration −/+	209/1
Lymph node metastasis −/+	198/12

LP lamina propria, *MM* muscularis mucosae, *SM1* submucosa < 500 μm from the muscularis mucosae, *SM2* submucosa ≥ 500 μm from the muscularis mucosae

Imaging analysis

The detection rate for EGC by FDG PET/CT was 37.1%. Discrete radiotracer uptake by the primary tumor was found in 78 of the 210 EGCs (mean SUVmax = 4.9 ± 2.6, range 2.5–15.4; mean MTV = 1.4 ± 1.8, range 0.4–9.5; mean TLG = 7.5 ± 14.2, range 1.1–89.9).

The sensitivities, specificities, PPVs, NPVs, and AUCs of FDG PET/CT for detecting EGC that is not curable by ESD are shown in Table 2. A representative example of the performance of FDG PET/CT is shown in Fig. 1. The hypermetabolic regional lymph nodes were found by FDG PET/CT in 4 of the 210 EGCs. All the four EGCs showed a discrete radiotracer uptake by the primary tumor.

Among the 210 EGCs, 13 false-positive and 15 false-negative cases were found by FDG PET/CT. The mean size was 1.7 ± 0.6 (0.8–2.8) cm and 2.8 ± 1.3 (1.1–5.2) cm, respectively ($p = 0.01$). Ulceration was present in the false-positive and false-negative cases at a rate of 62% (8/13) and 53% (8/15), respectively.

Discussion

The present study found that FDG PET/CT showed good test performance in predicting the curability of ESD for EGC. To our knowledge, this is the first study to assess the value of FDG PET/CT in this clinical indication.

An appropriate treatment decision for patients with EGC is important for reducing complications and for improving quality of life. A diagnostic modality that complements

Table 2 Performance of FDG PET/CT in detecting EGC that is not curable by ESD

Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
79% (67–88) [55/70]	91% (85–95) [127/140]	81% (71–88) [55/68]	89% (84–93) [127/142]	0.85 (0.78–0.91)

PPV Positive predictive value, *NPV* negative predictive value, *AUC* area under the receiver operating characteristic curve, *CI* confidence interval

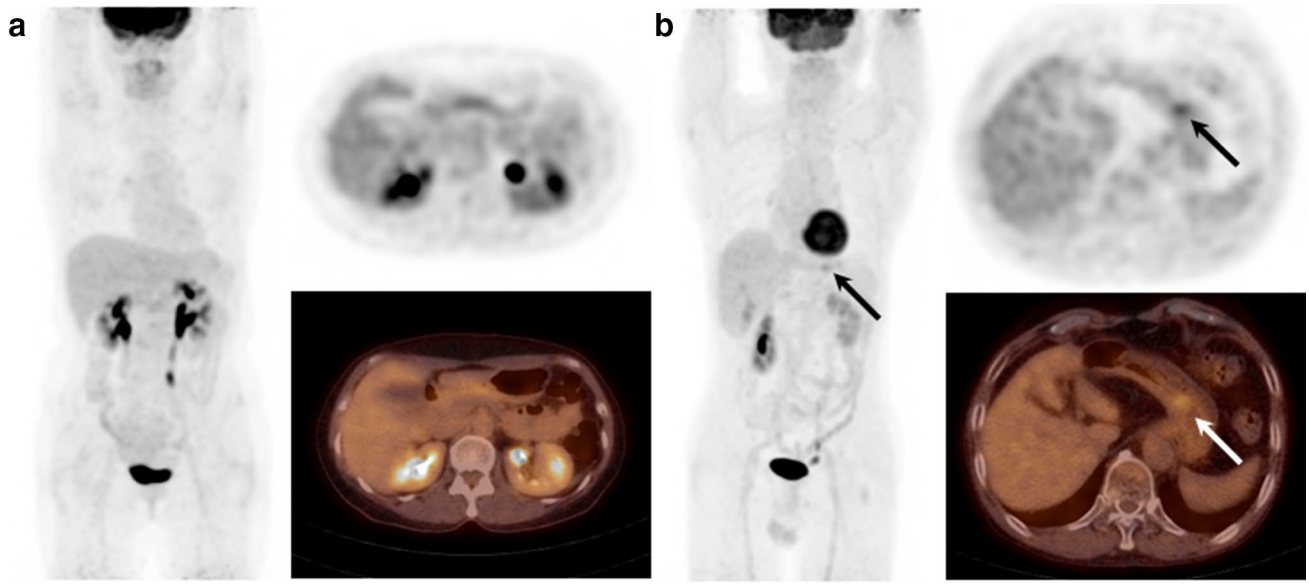

Fig. 1 **a** FDG PET/CT of a 57-year-old woman showing no discrete radioactivity on a tumor of the gastric antrum. The pathological result was a diameter of 2.8 cm, pT1a moderately differentiated adenocarcinoma with ulceration, and no lymphatic and vascular infiltration; i.e., this tumor fell under the expanded indication for ESD. **b** FDG PET/CT of a 69-year-old man showing discrete radioactivity on a tumor of the gastric body with a maximum standardized uptake value of 3.7, a metabolic tumor volume of 0.6, and total lesion glycolysis of 1.7. The pathological result was a diameter of 1.7 cm, pT1b (cancer invasion 3000 μm from the muscularis mucosae) moderately differentiated adenocarcinoma without ulceration, and no lymphatic and vascular infiltration; i.e., this tumor was not curable by ESD

endoscopy, to avoid additional surgery after ESD, has been required continuously. The selection of patients who need surgical resection rather than endoscopic resection is one of the major concerns in ESD. Absolute and expanded indications have been proposed to help decide preoperatively whether ESD should be the treatment for gastric cancer (Lee et al. 2014; Ono et al. 2016).

Evaluation of the depth of invasion in EGC is necessary to predict the curability of ESD. The pathological depth of invasion is defined as the deepest layer that has been invaded by the cancer. The invasive morphological change in EGC is often not reflected at the surface, and the mucosal structure remains, even when the cancer invades the submucosa; therefore, the reliable estimation of the depth of invasion based on surface appearance alone is difficult (Uedo et al. 2011). Endoscopic ultrasonography is a useful additional diagnostic modality to complement conventional endoscopy for the evaluation of tumor depth with high accuracy (Mouri et al. 2009). However, it is an operator-dependent approach and assesses advanced tumor stages (T3 and T4) better than it does less-advanced tumor stages (Cardoso et al. 2012). Furthermore, it cannot distinguish minute submucosal (SM1, <500 μm from the muscularis mucosae) cancers from deeper submucosal (SM2, ≥ 500 μm from the muscularis mucosae) cancers definitively, which results in the need for additional surgical resection after endoscopic resection (Abe et al. 2011).

Among the indications for ESD, differentiated carcinoma includes well or moderately differentiated tubular or papillary adenocarcinomas, while undifferentiated carcinoma includes poorly differentiated adenocarcinomas and signet-ring cell carcinomas (Ono et al. 2016). The histopathological type is determined through an endoscopic biopsy specimen that is collected using forceps before ESD. However, discrepancies in the pathological results between endoscopic biopsy and ESD may occur (Yao et al. 2000; Oishi et al. 2002a, b). This might be because the endoscopic biopsy sample is too small, or the targeted biopsy area could not be accessed because of the location of the lesion (Ryu et al. 2017a). To avoid these discrepancies, Ryu et al. have

suggested that age < 55 years, tumor size ≥ 10 mm, surface redness, and whitish discoloration are predictive factors of a diagnosis of undifferentiated EGC (Ryu et al. 2017b).

Precise measurement of the size of gastric cancer using endoscopy with visual assessment alone is also difficult. Endoscopists often underestimate the lesion size, because the areas of the image that are farther from the center appear to be smaller than they really are because of the spatial distortion caused by the lens of the endoscope (Margulies et al. 1994; Matsui et al. 2002). It has been reported that an image-processing technique for correcting distortion may improve the accuracy of such measurements (Vakil et al. 1994).

In this study, the size of the tumor was not related to the false-negative and false-positive findings. Even, the mean size of the false-negative cases was larger than the false-positive cases. This may suggest that tumor FDG uptake demonstrates tumor aggressiveness rather than just reflecting the size of the tumor.

Ulcerations within the tumor were found more often in false-positive cases than in false-negative cases in FDG PET/CT. FDG uptake indicates increased intracellular glucose metabolism; consequently, FDG is taken up not only by malignant cells but also by those that are involved in active inflammatory processes (Jamar et al. 2013). Thus, it is suggested that underlying ulceration should be considered carefully when predicting the curability of ESD for EGC using FDG PET/CT.

The most important limitation of this study was that the results were obtained by a retrospective review of a selected patient group. Only patients who had EGC with well or moderately differentiated adenocarcinoma were included in this study. Patients with poorly differentiated or signet-ring cell carcinoma were excluded. This patient selection bias may have increased the sensitivity of FDG PET/CT. However, in this study, 37% (78/210) of patients with EGC showed discrete radiotracer uptake by the primary tumor on FDG PET/CT images, which is in accordance with the known detection rate of EGC by FDG PET/CT (< 50%) (Shoda et al. 2007). Therefore, this study should be considered as a preliminary finding, and further prospective studies are needed to define the value of FDG PET/CT combined with endoscopy for patients with EGC.

In conclusion, after the detection of gastric cancer by endoscopy, FDG PET/CT exhibited a high sensitivity and specificity in determining the possibility of treating the lesion by ESD. This finding suggests that FDG PET/CT may be a useful complementary imaging modality to endoscopy for the prediction of the curability of ESD for EGC.

Compliance with ethical standards

Ethical statement This study was reviewed by the appropriate Ethics Committee and was, therefore, performed in accordance with the ethical standards laid down in the Declaration of Helsinki revised in Brazil 2013.

Informed consent This retrospective study was waived from the need to obtain informed consent by our Institutional Review Board (KUH1280106).

Conflict of interest Hyun Woo Chung, Jeong Hwan Kim, In-Kyung Sung, Sun-Young Lee, Hyung Seok Park, Chan Sup Shim, Ho Yoon Bang, Young So, and Eun Jeong Lee declare that they have no conflicts of interest.

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