Prognostic Significance of Volume-based Metabolic Parameters by ^{18}F -FDG PET/CT in Gallbladder Carcinoma

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Abstract

Purpose We investigated the prognostic values of volume-based metabolic parameters by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/computed tomography (CT) in gallbladder carcinoma patients and compared them with other prognostic parameters.

Materials and Methods We enrolled 44 patients, who were initially diagnosed with gallbladder carcinoma and undergoing ^{18}F -FDG PET/CT. Various metabolic volume-based PET parameters of primary tumors, including maximum and average standardized uptake values (SUV_{max} , SUV_{avg}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), were measured in gallbladder carcinoma patients using mediastinal blood pool activity as a threshold SUV for determining the tumor boundaries. Overall survival analysis was performed using the Kaplan-Meier method with PET parameters and other clinical variables. For determining independent prognostic factors, Cox proportional hazards regression analysis was performed.

Results Of the 44 enrolled patients, cancer- or treatment-related death occurred in 30 (68.2 %). The mean clinical follow-up period was 22.2 ± 10.4 m (range, 0.6–35.9 m). Univariate analysis demonstrated that clinical or pathologic TNM stage ($P < 0.001$), treatment modality ($P < 0.001$), MTV (cutoff = 135 cm^3 , $P = 0.001$), and TLG (cutoff = 7,090, $P < 0.05$) were significant prognostic factors. In multivariate analysis, both clinical or pathologic TNM stage [hazard ratio (HR) = 2.019 (I vs II), 21.287 (I vs III), and 24.354 (I vs IV); $P = 0.001$] and TLG (HR = 2.930; $P < 0.05$) were independent prognostic factors for predicting overall survival.

Conclusions In gallbladder cancer, TLG of the primary tumor, a volume-based metabolic parameter, is a significant independent prognostic factor for overall survival in conjunction with the clinical or pathological TNM stage.

Keywords Gallbladder carcinoma · Prognosis · ^{18}F -FDG · PET/CT · Metabolic tumor volume · Total lesion glycolysis

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Introduction

Gallbladder carcinoma is the most common malignancy of the biliary tract and the fifth most common malignant neoplasm of the digestive tract [1]. Most studies report the 5-year survival rate for cancers of the gallbladder between 0 % and 10 % [2]. The poor prognosis is due to the anatomical position of the gallbladder and the delayed clinical presentation in most patients, primarily due to a lack of specific symptoms and low clinical suspicion. The only curative therapy for gallbladder carcinoma is surgical resection [3–5]. The goal of resection should always be total tumor extirpation with negative histologic margins. Definitive

surgical resection requires removal of the involved liver parenchyma and the regional lymph nodes.

The staging system for gallbladder carcinomas developed by Nevin and co-workers [6] had been widely used in the past but has been superseded by the TNM system put forth by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), based on the depth of tumor invasion, regional lymph nodes and distant metastases. However, accurate stratification for prediction of outcomes is still difficult based on anatomic stage only. A more accurate and reliable prognostic system incorporating additional features of the tumors such as biological and molecular information may be necessary to obtain a more accurate prediction of prognosis and to choose the most appropriate treatment modality and follow-up plan for gallbladder carcinoma.

^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) is an increasingly available noninvasive test for malignancy based on glucose metabolism. Recently, ^{18}F -FDG PET was demonstrated to have value for initial staging and for detecting recurrent disease in many kinds of tumors, including gallbladder carcinoma [7, 8]. ^{18}F -FDG PET is useful not only for diagnosing and staging, but also for evaluating the proliferative activity and malignancy grades of tumors reflecting prognosis. Maximum standardized uptake value (SUV_{max}) of the primary tumor, a semiquantitative parameter derived from ^{18}F -FDG PET, is known to be a significant prognostic factor for many types of tumors [9–11]. Despite being the most popular landmark in clinical situations, this parameter has only a single voxel value and cannot be used to indicate the metabolism of the whole tumor. Recent studies have reported that volumetric PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) using a threshold-based automatic volume of interest (VOI) were better prognostic predictors for survival in patients with malignant pleural mesothelioma, esophageal, tonsillar carcinoma and advanced head and neck squamous cell carcinomas [12–15]. Although the SUV of biliary carcinoma has been reported to be a useful prognostic predictor for overall survival [16], there are no published studies dealing with the correlation between volumetric PET parameters and prognosis in gallbladder carcinoma. In this study, we investigated the prognostic value of various volume-based metabolic parameters by ^{18}F -FDG PET/CT compared with other clinical parameters in gallbladder carcinoma.

Materials and Methods

Patients

The protocol of this retrospective study was reviewed and approved by the ethics committee of our institution.

In total, 44 patients (mean age, 65.3 ± 9.0 years; range, 40.2–80.6 years) who were initially diagnosed with gallbladder carcinoma and underwent ^{18}F -FDG PET/CT between Mar 2005 and Nov 2009 were enrolled. The patients were clinically staged according to The American Joint Commission on Cancer tumor-lymph node-metastasis (AJCC TNM 7th edition) system: six patients in stage I, 12 in stage II, three in III and 23 in IV. Most patients were diagnosed in the advanced stage with clinically evident disease and when curative surgical resection was not possible. Multiple computed tomography (CT) or magnetic resonance imaging (MRI) studies were performed to evaluate the extent of the disease. In all patients, the pathological tissues of the cholecystectomy specimen, liver specimen, omental seeding nodules, bile juice, and lymph nodes were collected to confirm gallbladder carcinoma. If ascites were present, a specimen was obtained for cytologic evaluation.

^{18}F -FDG PET/CT Imaging

All patients fasted for at least 6 h before PET/CT scans. Blood glucose level was measured and was required to be less than 200 mg/dl before ^{18}F -FDG injection. PET/CT scans were performed using two different dedicated PET/CT scanners (Discovery LS or Discovery STe, GE Healthcare, Milwaukee, WI, USA). Scans in 21 of the 44 patients were performed using the Discovery LS PET/CT scanner, and scans in 23 patients were performed using a Discovery STe PET/CT scanner. No intravenous or oral contrast materials were used. In the Discovery LS scanner, whole-body CT was performed by a continuous spiral technique using an eight-slice helical CT (140 KeV, 40–120 mAs adjusted to the patients' body weight, section width of 5 mm) 45 min after the injection of ~ 370 MBq ^{18}F -FDG. After the CT scans were complete, emission scans were obtained from thigh to head for 4 min per frame in two-dimensional (2D) mode. Attenuation-corrected PET images (voxel size = $4.3 \times 4.3 \times 3.9$ mm) were reconstructed using CT data by an ordered-subsets expectation maximization algorithm (28 subsets, two iterations). In the Discovery STe scanner, whole-body CT was performed by a continuous spiral technique using a 16-slice helical CT (140 KeV, 30–170 mAs with an AutoMA mode, section width of 3.75 mm) 60 min after the injection of ^{18}F -FDG (5.5 MBq/kg). After the CT scans were complete, emission scans were obtained from thigh to head for 2.5 min per frame in 3D mode. Attenuation-corrected PET images (voxel size = $3.9 \times 3.9 \times 3.3$ mm) were reconstructed using CT data and a 3D ordered-subsets expectation maximization algorithm (20 subsets, two iterations). Commercial software (Advantage Workstation version 4.4, GE Healthcare) was used to accurately co-register the separate CT and PET scan data.

Image Analysis

Image interpretation was based on the identification of regions with increased FDG uptake on the PET images and the anatomic delineation of all FDG-avid lesions on the co-registered PET/CT images. Semiquantitative and volumetric analyses of the primary tumors were performed using commercial software (Advantage Workstation version 4.4, GE Healthcare), which provides a convenient and automatic method to delineate the VOI of primary tumor using an isocontour threshold method based on SUV. In this study, mediastinal blood pool which was the reference organ for therapy response evaluation in lymphoma [17, 18] activity was used as a threshold for determining tumor boundary. A VOI consisting of 5×5 voxels was drawn at the aortic arch on a transverse PET image. The average SUV plus $2 \times$ SD (standard deviation) of that VOI was adopted as a threshold SUV for the tumor boundary determination in each patient. Using this threshold SUV, a VOI was placed over the primary tumor detected by PET on simultaneously displayed axial, coronal, and sagittal images (Fig. 1). Images of each gallbladder carcinoma were assessed semiquantitatively by measuring and calculating the SUV_{max} normalized to patient body weight. SUV_{max} was determined by the hottest pixel in the lesion. Volume-based PET parameters such as average SUV (SUV_{avg}) and MTV along with SUV_{max} were acquired

Fig. 1 Transverse (a), coronal (b), and sagittal (c) PET images of a 76-year-old male patient with gallbladder carcinoma showing an automatically generated volume of interest (VOI) of the primary tumor using an isocontour threshold method

using the automatically generated VOI of the primary tumor. Tumor volume was calculated by adding the axial delineations slice by slice to a total volume. TLG was calculated by multiplying SUV_{avg} and voxel number of the primary tumor.

Treatment and Clinical Follow-up

Treatment modalities were classified into three categories: 21 patients underwent surgery with adjuvant treatment, 13 underwent non-surgical treatment, and 10 received only supportive treatment. Surgical treatment included all operations with differing degrees of resection, including simple cholecystectomy, radical cholecystectomy involving subsegmental resection of segments IVb and V adjacent to the gallbladder bed, regional lymph node dissection, and common bile duct resection. Adjuvant chemotherapy with or without radiation therapy was administered according to an interdisciplinary decision of a clinical oncologist and a surgeon after surgery. If the patient's general condition was tolerable, adjuvant concurrent chemoradiation therapy was administered. Patients who were considered non-operable were referred to medical oncology for palliative chemotherapy or supportive treatment.

During the follow-up period, patients in early stages participated in clinical follow-up every 6 months with physical examination, chest radiography, tumor markers, and abdominal-pelvic CT imaging studies. In the advanced stage, they returned for clinical follow-up every 6 weeks. When we suspected patients had recurrence or progression based on clinical symptoms, imaging studies or tumor markers, histological confirmation or other relevant imaging studies such as ^{18}F -FDG PET/CT and CT were performed.

Statistical Analysis

Overall survival was measured from the date of diagnosis to date of death or final clinical follow-up. In this study, we defined an event for prognosis evaluation as cancer- or treatment-related death. Overall survival analysis was performed by the Kaplan-Meier method using PET parameters and other clinical variables including sex, age, clinical or pathologic TNM stage, or treatment modality. The log-rank test was used for univariate analysis of prognostic factors. Maximally selected log-rank statistics were used to determine the optimal cutoff showing the best discrimination of survival curves for continuous variables. For determining independent prognostic factors, Cox proportional hazards regression analysis was performed. An estimated hazard ratio (HR) with 95 % confidence interval (CI) was presented. Statistical analyses were performed using commercial software (SPSS Statistics 19, IBM, New York, USA). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. The mean clinical follow-up period was 22.2 ± 10.4 m (range, 0.6–35.9 m). Cancer- or treatment-related death occurred in 30 (68.2 %) of the 44 patients (26 men, 18 women). The final diagnosis and staging of each gallbladder carcinoma were based on the surgical findings in 21 patients and on the imaging findings and biopsy/cytology findings in the other 23.

The results of univariate analysis are shown in Table 1. The optimal cutoff values of age, SUV_{max} , SUV_{avg} , MTV, and TLG were 65.3 years, 10.1, 3.8, 135 cm^3 , and 7,090, respectively. According to the optimal cutoff of age (≥ 65.3 years), the patients were divided into two groups, with the number of patients in the older and younger age groups at 26 and 18, respectively. The numbers of patients in each subgroup divided by the cutoff values of SUV_{max} (≥ 10.1), SUV_{avg} (≥ 3.8), MTV ($\geq 135 \text{ cm}^3$), and TLG ($\geq 7,090$) were 21 and 23, 22 and 22, 7 and 37, 8 and 36, respectively. Univariate analysis demonstrated that clinical or pathological TNM stage ($P < 0.001$), treatment modality ($P < 0.001$), MTV ($P = 0.001$), and TLG ($P < 0.05$) were

significant prognostic factors (Fig. 2), indicating that advanced stage, non-surgical treatment or only supportive treatment, higher MTV, and higher TLG were associated with poor overall survival.

Multivariate analysis suggested that clinical or pathological TNM stage [HR=2.019 (I vs II), 21.287 (I vs III), and 24.354 (I vs IV); $P = 0.001$] and TLG (HR=2.930; $P < 0.05$) were independent prognostic factors for predicting overall survival (Table 2). Multivariate analysis showed that the only independent predictors of survival were clinical or pathological TNM stage and TLG; the other factors including treatment modality and MTV did not attain statistical significance.

Discussion

We investigated the prognostic values of volume-based metabolic parameters by ^{18}F -FDG PET/CT in gallbladder carcinoma compared with other clinical parameters. Many prognostic factors for gallbladder carcinoma have been reported, especially clinicopathologically. The clinical or pathologic staging, including tumor extension and nodal involvement, remains the best prognostic factor for gallbladder carcinoma [19–21]. This study demonstrated that TLG, a volumetric parameter of ^{18}F -FDG PET/CT, is an important independent prognostic factor for overall survival, along with clinical or pathological TNM stage; this parameter is a better predictor of overall survival than other PET parameters such as MTV or SUV.

The development of the PET scan offered a new diagnostic option through the visualization of tumor metabolic activity rather than the anatomic structures, thus PET/CT technology offers the advantage of improved anatomic localization. ^{18}F -FDG PET/CT has been useful as a staging tool in a variety of malignancies such as esophageal, lymphoma, lung, breast, colorectal, melanoma and head and neck cancers. The value of this test is not only in providing information about disease spread, but also in the evaluation of treatment response and prediction of long-term survival [22].

The progression of cancer stage means that the tumor has grown larger, has invaded deeper, and has metastasized to other organs. According to a study on breast cancer, ^{18}F -FDG uptake was influenced by the amount of metabolically active tumor cells, and the depth of invasion is associated with Glut-1 expression. Additionally, a positive correlation among increased incidence of lymph node, metastases and Glut-1 expression was seen in patients with gastrointestinal carcinoma [23–27]. When the cancer stage increases, SUV representing glucose uptake increases. However, in our study, neither the SUV_{max} nor the SUV_{avg} were statistically significant prognostic factors; this is in contrast to most previous results of clinical

Table 1 Patient characteristics and results of univariate analysis for predicting overall survival

Variable		No.	Mean OS ± SE (months)	<i>P</i> value
Age	≥65.3 years	26	18.0±3.3	0.277
	<65.3 years	18	12.0±2.4	
Sex	M	26	14.8±3.0	0.813
	F	18	15.4±2.9	
Stage	I	6	33.1±2.5	<0.001
	II	12	24.5±3.8	
	III	3	8.6±5.3	
	IV	23	6.0±1.1	
Treatment modality	Supportive treatment	10	3.5±1.2	<0.001
	Surgery + adjuvant treatment	21	25.6±2.8	
	Non-surgical treatment	13	7.0±1.5	
SUV _{max}	≥10.1	21	12.5±2.5	0.305
	<10.1	23	18.1±3.3	
SUV _{avg}	≥3.8	22	13.4±2.5	0.589
	<3.8	22	17.1±3.3	
MTV	≥135 cm ³	7	4.4±1.7	0.001
	<135 cm ³	37	17.4±2.4	
TLG	≥7,090	8	6.7±2.8	0.014
	<7,090	36	17.5±2.5	

SUV_{max} maximum standardized uptake value, SUV_{avg} average standardized uptake value, MTV metabolic tumor volume, TLG total lesion glycolysis, OS overall survival, SE standard error

Fig. 2 Kaplan-Meier curves for overall survival based on significant prognostic factors including stage (a), treatment modality (b), metabolic tumor volume (MTV) (c) and total lesion glycolysis (TLG) (d) in gallbladder carcinoma

studies on other malignancies [28–30]. Although SUV_{max} is a convenient quantitative measure, it has been argued that as it is a measurement of a single pixel with highest radiotracer concentration within the region of interest, it may not represent the heterogeneous character of the whole tumor. Moreover, SUV_{avg} may be partially explained by the partial-volume effect and the dependence of SUV on tumor size [31].

Although both MTV and TLG showed statistically significant values in univariate analysis, only TLG was a significant independent prognostic index in multivariate analysis. MTV represents only the amount of active metabolic tumor cells, but TLG, calculated by multiplying the tumor volume by the SUV_{avg} of the tumor, is a more effective independent prognostic parameter of overall survival. TLG may provide important information on risk stratification, which can be used to determine the follow-up and treatment plans. For example, in patients with advanced gallbladder carcinoma and high TLG, it may be justified to

perform detailed follow-up or recommend clinical trials using investigational therapy due to the poor prognosis.

Our present study has several limitations. First, it was designed retrospectively and performed with a relatively small number of patients. As such, our results may not be generalizable to all patients with gallbladder carcinoma. Second, we used two different kinds of scanners and acquisition protocols, which might have an effect on the measurement of PET parameters. Third, volumetric PET parameters were defined by the individual threshold SUV using mediastinal blood pool activity for determining the primary tumor boundary for simplicity of measurement and consistency with pathologic volume. Recently, the individual threshold SUV was used to evaluate the therapeutic response in patients with lymphoma; however, it is not universally applicable to all clinical settings. Therefore, we need to recognize that the optimal threshold can be used in various ways depending on the PET center, type of malignancy, and tumor characteristic. Finally, we evaluated the prognostic values of volumetric PET parameters for the primary tumor only because its measurement is simple and applicable to clinical practice compared with measurements of overall tumor burden including both the primary tumor and all metastatic lesions. In spite of these limitations, our study is valuable because it is the first to support the clinical value of volume-based PET parameters in gallbladder carcinoma. Additional larger and prospective studies using ^{18}F -FDG PET/CT using standardized protocols across different PET/CT scanners are required for the validation of our results.

In conclusion, in primary tumors, TLG, a volume-based PET parameter, is an important independent prognostic factor for overall survival along with clinical or pathological

Table 2 Multivariate analysis for overall survival using a Cox proportional hazard regression model

Variable	HR	95 % confidence interval	<i>P</i> value
Stage			
I	1.000	Reference	
II	2.019	0.216–18.863	0.538
III	21.287	1.960–231.158	0.012
IV	24.354	2.768–214.261	0.004
TLG (cutoff = 7,090)	2.930	1.250–6.865	0.013

HR hazard ratio, TLG total lesion glycolysis

TNM stage in patients with gallbladder carcinoma. Moreover, TLG is a better prognostic predictor than other PET parameters such as SUV_{max} , SUV_{avg} , or MTV. Therefore, TLG may be helpful for identifying patients with poor prognosis who require more aggressive treatment and closer follow-up.

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Conflict of interest statement The authors declare that there are no conflicts of interest.

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