Hounsfield units upon PET/CT are useful in evaluating metastatic regional lymph nodes in patients with oesophageal squamous cell carcinoma

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Objectives: This study evaluated the usefulness of measurements of X-ray attenuation (in Hounsfield units) obtained from unenhanced CT images for attenuation correction of the positron emission tomography (PET) data from PET/CT in the assessment of regional lymph node metastasis in oesophageal squamous cell carcinoma.

Methods: 17 patients with oesophageal squamous cell carcinoma underwent surgery after evaluation with PET/CT. After the excised lymph nodes were reviewed, we compared the histopathology and PET/CT findings, and analysed the lymph node metastasis. When 18-F fludeoxyglucose (FDG) uptake in the lymph nodes was focally prominent in comparison with background mediastinal activity (regardless of lymph node size), the lymph nodes were considered to be positive for malignancy by PET/CT. The mean Hounsfield units of mediastinal lymph nodes showing abnormally increased FDG uptake in PET/CT was retrospectively evaluated using images from the unenhanced CT component of PET/CT. Receiver operating characteristic (ROC) curve analysis was applied to determine the optimal cut-off value of mean Hounsfield units for detecting individual lymph node metastases.

Results: For depiction of malignant nodal groups in each lymph node group, the sensitivity, specificity and accuracy of PET/CT based on increased FDG uptake were 58.8%, 74.5% and 70.8%, respectively. For patients with nodal groups that were positive for uptake by PET/CT, the mean attenuation in lymph nodes as measured by CT was 48 ± 13 HU for malignant nodes and 75 ± 18 HU for benign nodes. This difference was statistically significant ($p < 0.001$). Using ROC curve analysis, we determined the cut-off as 71 HU. When we excluded lymph nodes with attenuation higher than 71 HU from the nodes determined as malignant by PET/CT, the specificity and accuracy for detecting metastatic lymph nodes improved to 90.9% and 83.3%, respectively.

Conclusions: When interpreting lymph node metastasis in oesophageal squamous cell carcinoma using PET/CT, the assumption that any lymph node with mean HU > 71 is benign can improve diagnostic accuracy.

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Oesophageal cancer is an uncommon neoplasm, but it is often highly aggressive and associated with a poor prognosis. Accurate staging is essential to the management of patients with oesophageal cancer. In particular, the staging of regional lymph nodes is an important independent prognostic factor [1]. CT is the most widely used imaging technique for staging oesophageal cancer, but the detection of metastatic disease within normally sized lymph nodes by CT remains a challenge. Positron emission tomography (PET) with 18-F fludeoxyglucose (FDG) has been reported to be useful for the initial staging of patients with oesophageal cancer [2, 3]. However,

the poor spatial resolution of PET limits the localisation of small metastatic lymph nodes. Integrated PET and CT (PET/CT) is currently being used widely in patients with various cancers [4, 5]. PET/CT combines anatomical and functional imaging and is superior to PET alone, especially in the assessment of locoregional lymph nodes in thoracic oesophageal squamous cell carcinoma [6].

However, we have experienced oesophageal cancer cases in which lymph nodes that were identified as having high FDG uptake upon PET/CT before surgery were proven benign upon pathological examination of the surgically excised tissue. In this study, we examined the usefulness of both measurements of X-ray attenuation in Hounsfield units taken from the unenhanced CT image component and FDG uptake in the PET/CT evaluation of lymph node metastasis in oesophageal cancer patients.

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Methods and materials

Patients

From June 2005 to April 2009, 92 patients with biopsy-proven oesophageal carcinoma underwent surgery at our hospital. Of these 92 patients, 19 patients underwent FDG-PET/CT for pre-operative tumour staging. The institutional review board approved this study protocol, and waived the requirement for informed consent for this retrospective study. Histological tumour types were squamous cell carcinoma in 17 of the 19 patients and adenocarcinoma in two. A previous study had concluded that standard uptake values (SUV) for PET show wide variations for different histological types [7]; thus, we excluded the two patients who had oesophageal adenocarcinoma. Accordingly, we analysed the data from 17 patients with squamous cell carcinoma of the oesophagus.

These patients, 16 males and 1 female, ranged in age from 52 to 75 years (mean age, 66.1 years). None of them had received pre-operative neoadjuvant chemotherapy or concurrent chemoradiation therapy before surgery. No patient with active inflammatory pulmonary disease or diabetes was included. The interval between the PET/CT scan and surgery ranged from 2 to 42 days (mean 13.5 days).

Surgery and pathology

All patients underwent transthoracic oesophagectomy with two-field (thoracoabdominal) lymph node

dissection. Following surgery, the surgeon dissected out all visible and palpable lymph nodes, taking into consideration the findings from the pre-operative PET/CT images. Each dissected node group was labelled according to the modified version of the lymph node mapping system for oesophageal cancer [8]. Surgical specimens were fixed, embedded, stained using a standard haematoxylin–eosin technique, and examined under a light microscope.

FDG-PET/CT

PET/CT scans were obtained using Allegro PET and 16-channel CT (Gemini Scanner; Philips, Bothell, WA). All patients fasted for at least 8 h before the PET/CT examination. While resting on a reclining chair, patients received 5.6 MBq kg⁻¹ (0.15 mCi kg⁻¹) of FDG intravenously. The imaging sequence was started 60 min after tracer injection. CT was performed at 120 kVp and 130 mAs with 5 mm slice collimation, and was followed by a PET emission scan. PET emission data were acquired at 3 min per frame in two-dimensional mode. Emission PET images were reconstructed with the CT data using iterative algorithms (ordered-subsets expectation maximisation, four iterations and eight subunits). Attenuation-corrected PET/CT images were reviewed at the workstation.

All PET/CT scans were retrospectively reviewed by one radiologist, who was not aware of the surgical outcomes. Regional lymph nodes were classified according

Table 1. Results of lymph node metastasis evaluated by PET/CT and histopathology findings in oesophageal squamous cell carcinoma

Patient	Sex/age (years)	Nodes identified as metastatic upon PET/CT	Malignant nodes upon histopathology
1	M/67	Left gastric node	Right upper paratracheal node, right lower paratracheal node, subcarinal node, left gastric node
2	M/59	None	None
3	M/70	Right jugular node, right tracheobronchial node	Right jugular node
4	M/62	Right upper paratracheal node, posterior mediastinal node, aortopulmonary node, subcarinal node	Posterior mediastinal node
5	M/71	Subcarinal node, left tracheobronchial node	None
6	M/70	None	None
7	M/66	Subcarinal node	Subcarinal node
8	M/74	Left gastric node	Left gastric node
9	M/60	Right upper paratracheal node	None
10	M/61	None	Left gastric node
11	M/75	Posterior mediastinal node, right lower paratracheal node, subcarinal node	Posterior mediastinal node, right lower paratracheal node, subcarinal node, left gastric node
12	M/73	Aortopulmonary node	Left gastric node
13	M/67	Right lower paratracheal node, left paratracheal node, right tracheobronchial node	None
14	M/70	None	None
15	M/70	None	None
16	F/52	Right lower paratracheal node, subcarinal node, lower paraoesophageal lymph node, left gastric node	Right upper paratracheal node, subcarinal node, left gastric node
17	M/57	Middle paraoesophageal lymph node	None

F, female; M, male; PET, positron emission tomography.

to the modified lymph node mapping system for oesophageal cancer [8]. FDG uptake within structurally identifiable nodes that was focally prominent compared with background mediastinal activity (regardless of lymph node size) was considered as positive for malignancy by PET/CT. We measured mean Hounsfield units values of the lymph nodes using images from the CT component of PET/CT.

Data analysis and statistics

The accuracy of correctly detecting lymph node involvement by PET/CT was determined using the histopathology results as reference standards. The sensitivity, specificity and accuracy of PET/CT were calculated using standard definitions [9]. Receiver operating characteristic (ROC) curve analysis was applied to determine the optimal cut-off value of mean Hounsfield units for detecting individual lymph node metastases. ROC curve analysis was performed with SPSS® version 12.0 [IBM Corporation (formerly SPSS Inc.), Armonk, NY]. To compare mean Hounsfield units values for benign and malignant lymph nodes (the latter as defined by

increased FDG uptake), we used the Student's *t*-test in SPSS. Differences were considered statistically significant when $p < 0.05$.

Results

The histopathological and PET/CT findings relating to lymph nodes excised from patients with oesophageal squamous cell carcinoma are summarised in Table 1.

Detection of malignant lymph nodes

A total of 72 lymph node groups (2 cervical, 43 mediastinal, 7 hilar and 20 abdominal) excised from the 17 patients were evaluated at pathology. At PET/CT, 24 nodal groups showed increased (positive) FDG uptake. Of these, 10 lymph node groups (1 cervical, 6 mediastinal and 3 abdominal) in 7 patients proved to be positive for malignancy (Figure 1). Of the 24 excised lymph node groups, 14 were found at pathology to contain no malignant tissue, despite having shown high uptake at PET/CT (Figure 2). Hence, the sensitivity, specificity

Figure 1. Oesophageal squamous cell carcinoma with a malignant lymph node in a 52-year-old female. Images obtained with (a) unenhanced CT, (b) fludeoxyglucose (FDG) positron emission tomography (PET) and (c) integrated PET/CT at the level of the right bronchus intermedius show increased FDG uptake in the subcarina (mean, 46 HU) (arrow). (d) Histological section of the subcarina shows a metastatic squamous cell carcinoma. (Haematoxylin–eosin stain; original magnification, $\times 40$.)

Figure 2. Oesophageal squamous cell carcinoma with calcified lymph node in a 71-year-old male. Images obtained with (a) unenhanced CT, (b) fludeoxyglucose (FDG) positron emission tomography (PET) and (c) integrated PET/CT at the level of the tracheal bifurcation show increased FDG uptake in the subcarinal lymph node (mean of 80 HU) (arrow). (d) Histological section of the subcarinal lymph node shows a wide area of collagenous fibrous tissue deposition surrounded by proliferating spindle-shaped fibroblasts and anthracotic pigments. (Haematoxylin–eosin stain; original magnification, $\times 40$.)

and accuracy of PET/CT for detection of malignant nodes were found to be 58.8, 74.5 and 70.8%, respectively.

Of the nodal groups that showed positive PET/CT uptake, the mean Hounsfield units of the malignant lymph nodes was measured upon CT as 48 ± 13 , whereas that of the benign lymph nodes was 75 ± 18 . The mean Hounsfield units difference between the malignant and benign lymph nodes groups was statistically significant ($p < 0.001$) (Table 2). The optimal cut-off value of mean Hounsfield units producing maximum sensitivity plus specificity for detecting individual lymph node metastases from the ROC analysis was 71 HU (Figure 3, Table 3).

When we considered the highly attenuated lymph node as benign, even if positive PET/CT was observed (using the mean cut-off value of 71 HU), the mean sensitivity, specificity and accuracy of our diagnosis of malignancy from the PET/CT scans were 58.8%, 90.9% and 83.3%, respectively (Table 4). Thus, when we excluded lymph nodes higher than 71 HU from the PET/CT diagnosis of metastases, the specificity and accuracy of our diagnoses were improved (Table 4).

Discussion

Metastasis to lymph nodes is a highly significant prognostic factor in oesophageal cancer [10]; furthermore, lymph node stage is an important independent prognostic indicator [11]. CT and PET have been described as not being accurate enough for evaluation of metastases to lymph nodes in oesophageal carcinoma. Variable ranges of sensitivity, specificity and accuracy have been reported for both modalities [11–13]. Because the detection of metastatic lymph nodes at CT is based primarily on the size of lymph nodes, CT has been non-sensitive for depicting metastatic spread to regional lymph nodes [14].

PET may also fail to enable detection of microscopic metastases in lymph nodes because of its limited resolution and scatter effects [11]. The recent use of PET/CT imaging with co-registration of anatomical and functional imaging data has improved the localisation of regions of increased FDG uptake and the accuracy of staging in patients with oesophageal cancer [15, 16]. Okada et al [16] found that the sensitivity, specificity and

Table 2. Mean Hounsfield units difference between malignant lymph nodes and benign lymph nodes

Characteristic	Malignant LN (n=10)	Benign LN (n=14)	p-value
LN sites (HU)	Right jugular node (64) Posterior mediastinal node (49) Posterior mediastinal node (50) Right lower paratracheal node (69) Subcarinal node (56) Subcarinal node (35) Subcarinal node (46) Left gastric node (35) Left gastric node (35) Left gastric node (36)	Right upper paratracheal node (73) Right upper paratracheal node (52) Right lower paratracheal node (65) Right lower paratracheal node (110) Left paratracheal node (86) Aortopulmonary node (76) Aortopulmonary node (83) Subcarinal node (55) Subcarinal node (80) Middle paraoesophageal lymph node (46) Lower paraoesophageal lymph node (76) Right tracheobronchial node (60) Right tracheobronchial node (93) Left tracheobronchial node (96)	
Mean (HU)	48 ± 13	75 ± 18	<0.001

LN, lymph node; PET, positron emission tomography.

Malignant LN, metastatic lymph node confirmed by histology with positive PET/CT uptake. Benign LN, not metastatic lymph node confirmed by histology, although positive PET/CT uptake.

accuracy of PET/CT for detecting metastatic regional lymph nodes were better than those of CT (60 *vs* 56%, 99.5 *vs* 97.3% and 94.8 *vs* 92.4%, respectively). In our study, however, PET/CT showed worse specificity and accuracy for detecting metastatic regional lymph nodes in patients with oesophageal cancer when compared with CT, despite a similar sensitivity. Similarly, Yoon et al [17] reported a relatively low specificity of PET (90%) *vs* CT (95%) for the depiction of nodal metastasis. These results may have been caused by reactive hyperplasia or by inflammation caused by granulomatous diseases, such as tuberculosis. Where such disease is present, lymph nodes show anthracotic pigmentation and macrophage infiltration with or without fibrotic micronodule formation in the medulla, and this macrophage infiltration might contribute to increased glucose uptake [18]. In particular, tuberculous lymphadenitis under treatment can accompany calcification in CT scans [19]. Takamochi et al [20] reported factors that were significantly associated with false-positive and false-negative CT

findings when diagnosing mediastinal node involvement in non-small cell lung cancer. For example, univariate analysis showed lymph node calcification to be a significant factor in false-positive scans ($p=0.01$). Therefore, PET/CT could improve the specificity of lymph node staging of calcified lymph nodes by reducing false positives, especially in populations where chronic granulomatous disease is endemic. Other aetiologies include infectious diseases such as histoplasmosis, tuberculosis, coccidioidomycosis and aspergillosis, and non-infectious causes such as silicosis and other benign inflammatory aetiologies [21].

No patient with active inflammatory pulmonary disease or occupational disease was included in this study. In this retrospective study, however, the clinical data available from hospital medical records did not

Figure 3. Receiver operating characteristic curve analysis for optimal cut-off value of mean Hounsfield units for detecting individual lymph node metastases. Area under curve is 0.896. We decided a cut-off producing maximum sensitivity plus specificity at a mean of 71=HU.

Table 3. Estimated relationship between the mean Hounsfield units and the corresponding operating point on receiver operating characteristic curve

Hounsfield units	Sensitivity	1-specificity
34.0000	0.000	0.000
35.5000	0.300	0.000
41.0000	0.400	0.000
47.5000	0.500	0.071
49.5000	0.600	0.071
51.0000	0.700	0.071
53.5000	0.700	0.143
55.5000	0.700	0.214
58.0000	0.800	0.214
62.0000	0.800	0.286
64.5000	0.900	0.286
67.0000	0.900	0.357
71.0000	1.000	0.357
74.5000	1.000	0.429
78.0000	1.000	0.571
81.5000	1.000	0.643
84.5000	1.000	0.714
89.5000	1.000	0.786
94.5000	1.000	0.857
103.0000	1.000	0.929
111.0000	1.000	1.000

Table 4. Comparison of the reliability of PET/CT scans in identifying regional lymph node metastasis from oesophageal cancer with and without the assumption that high-attenuating nodes are benign (mean cut-off at 71 HU)

Validity	All nodes with increased FDG uptake considered malignant	Only nodes with increased FDG uptake and attenuation ≤ 71 HU considered malignant
Sensitivity (%)	58.8	58.8
Specificity (%)	74.5	90.9
Accuracy (%)	70.8	83.3
PPV (%)	41.7	66.7
NPV (%)	85.4	87.7
FPR (%)	14.6	12.3

FDG, 18-F fludeoxyglucose; FPR, false-positive rate; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

allow us to determine tuberculous history accurately, although the presence of disease could be verified by checking the histology results for mediastinal lymph node findings. In this study, some of histology results for false-positive lymph nodes showed collagenous fibrous tissue and anthracotic pigmentations in the lymph nodes. We suggest that these results may have been caused by chronic inflammation due to granulomatous diseases, such as tuberculosis. Unfortunately, it was not possible to obtain mediastinal lymph node histology findings for all of the false-positives in this retrospective study because the pathologists were not alerted to look specifically for non-malignant diagnoses in the lymph nodes during the study period. As a consequence, the majority of lymph nodes were reported simply as "no malignancy", making it impossible to evaluate microscopic calcification or other aetiologies.

In this study, the mean Hounsfield units difference between the malignant and benign lymph nodes groups was statistically significant ($p < 0.001$). In order to maximise the accuracy of PET/CT, we generated ROC curves. These curves were used to identify the mean Hounsfield units at which the sensitivity and specificity, and consequently the accuracy, of CT in differentiating benign and malignant lymph nodes are maximised. This value was 71 HU. When lymph nodes that showed high CT attenuation (*i.e.* > 71 HU) were considered benign, despite high FDG uptake in corresponding PET/CT scans, specificity improved from 74.5 to 90.9%. Thus, considering calcified lymph nodes as benign can provide a means of enhancing the accuracy of lymph node staging in oesophageal cancer.

This study has some limitations. First, the population studied was relatively small and localised to one academic hospital system. As a result, this study may not be representative of the general population. Additional investigation with larger populations is necessary. Second, we excluded patients with advanced-stage oesophageal cancer, and included only patients who had undergone oesophagectomy with lymph node dissection. Accordingly, selection bias might have resulted in the underestimation of sensitivity and accuracy, and increased the false-positive rate. Third, only one radiologist interpreted the PET/CT images, which may have increased bias. Fourth, the optimal mean Hounsfield units cut-off value was calculated by maximising the sum of the sensitivity rate and the specificity rate for detecting individual lymph

node metastasis. A suitable cut-off value should be determined for each piece of equipment.

In conclusion, the interpretation of PET/CT scans of lymph nodes, particularly in areas with endemic chronic inflammatory diseases such as tuberculosis, should be performed cautiously. Furthermore, this study shows that when interpreting PET/CT, the assignment of highly attenuated lymph nodes with increased FDG uptake as benign can improve diagnostic accuracy for metastatic regional lymph nodes in patients with oesophageal cancer.

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