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ORIGINAL ARTICLE

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Can hybrid FDG-PET/CT detect subclinical lymph node metastasis of esophageal cancer appropriately and contribute to radiation treatment planning? A comparison of image-based and pathological findings

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Abstract
Background. We aimed to determine the appropriateness of adding 18F-fluorodeoxyglucose (FDG)-positron-emission tomography (PET) to computed tomography (CT) and other pre-existing diagnostic imaging modalities for detecting subclinical lymph node metastasis of esophageal cancer, by comparing images from these modalities with the results of histopathological analysis.
Methods. Twenty patients who received radical surgery for squamous cell carcinoma of the esophagus were examined by PET-CT, and endoscopic ultrasound (EUS) examination before surgery. Based on these diagnostic modalities, the clinical target volume (CTV) was set as the gross tumor volume (GTV) plus a 1-cm margin. Histopathological diagnosis was performed in all patients immediately after resection.
Results. Fifty-three (3.0%) of 1764 nodes in the 20 patients were histopathologically positive for cancer cells. The CTV was not adequate to cover these histopathologically detected positive lymph nodes in 8 of 20 patients on CT, 5 of 20 on CT+EUS, 7 of 20 on PET-CT, and 5 of 20 on PET-CT+EUS.
Conclusion. The detection rate of subclinical lymph node metastasis did not improve with the use of PET-CT, for either the cervical and supraclavicular, mediastinal, or abdominal regions. It is not recommended to use FDG-PET or PET-CT alone as a diagnostic tool to determine CTV if pathologically involved lymphatic regions are to be included in the CTV in the treatment protocol. The accuracy of PET-CT must be further improved in order to better detect positive nodes and improve the definition of the CTV.

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Introduction

Many institutions are using large radiotherapy fields for elective nodal irradiation in chemoradiotherapy for esophageal cancer. However, it has been suggested that locoregional recurrence due to missed targets and treatment-related toxicities caused by large fields of radiation still occur in a substantial proportion of patients, and thus more accurate radiotherapy targeting is needed to improve locoregional control and reduce toxicity.[1] 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is frequently used to detect the primary tumor and metastasis to lymph nodes, and is reported to be useful to supplement computed tomography (CT) in the staging of esophageal cancer.[2–6] However, Yoon et al.[7] reported that this imaging modality had limited efficacy for presurgical diagnosis. In their study, Yoon et al. compared CT- and FDG-PET-based clinical diagnoses with the pathological diagnoses after surgery and reported that both FDG-PET and CT had low sensitivity for depicting nodal metastasis. Recently, Yuan et al.[8] reported that PET/CT was more effective than PET alone for assessing the involvement of locoregional lymph nodes in thoracic esophageal squamous cell carcinoma.

In a prospective trial of preoperative chemoradiotherapy for esophageal cancer, FDG-PET was shown to be useful in the staging and prediction of prognosis by detecting occult metastasis.[9] However, Vrieze et al.[10] showed that FGD-PET alone could not be used for treatment planning because the chance of a false-negative result on FGD-PET was not negligible, and thus the target volume should not be reduced based on a negative FDG-PET finding in a region with nodes that are suspect by other modalities. It has been shown that CT and FDG-PET image fusion has an impact on the planning of treatment and management of esophageal carcinoma, by altering the choice of gross tumor volume (GTV).[11] Similarly, Gondi et al.[12] suggested

that a hybrid FDG-PET/CT scanner had an impact on radiotherapy planning for esophageal cancer and non-small cell lung cancer.

In this study, we investigated the appropriateness of hybrid PET/CT for determining the clinical target volume (CTV) in patients with squamous cell carcinoma of the esophagus, by comparing the radiological diagnosis before surgery and the pathological diagnosis. We also compared the efficacy of hybrid PET/CT with that of CT alone, FDG-PET alone, and the combination of CT and endoscopic ultrasound (EUS) for CTV determination.

Patients, materials, and methods

Twenty patients (15 male and 5 female; median age, 61 years [range, 47–75 years]) with squamous cell carcinoma of the esophagus who consented to receive surgical esophagectomy were the subjects of this study. There were 3 stage I patients (staging according to International Union Against Cancer [UICC] *TNM classification of malignant tumors* 6th edition, 2002[13]), 8 stage II patients, and 9 stage III patients. Written informed consent was obtained from all patients.

All patients received a diagnostic workup consisting of CT, endoscopy and EUS, and FDG-PET within 2 weeks. A high-speed multidetector raw CT scan (ROBUSTO; Hitachi Medical, Tokyo, Japan) was used, with a slice thickness of 5 mm and an interval of 5 mm. An endoscopist performed the EUS (EU-M2000; Olympus Medical Systems, Tokyo, Japan) and provided a written report of the EUS results for all patients. F-18 FDG was purchased from Nihon Medi-Physics, (Tokyo, Japan). It was intravenously injected in patients who were instructed to fast for at least 4 h before PET imaging. Sixty minutes after the FDG injection, an attenuation-corrected whole-body image (three-dimensional [3D] mode) from the top of the skull to the proximal thighs was obtained at one bed position per 2.0 min using PET/CT (GEMINI-GXL; Philips, Amsterdam, the Netherlands).

Diagnostic specialists reviewed each image independently without reference to the other images. A radiologist examined each node and diagnosed it as positive if the maximum diameter was larger than 1.0 cm without calcification on transaxial CT. On PET-CT, each node was diagnosed as positive if the node showed increased FDG uptake relative to the surrounding tissue. The standardized uptake value (SUV) was used only for a reference. A cutoff SUV was not set. On EUS, an endosonographer diagnosed a node as positive if the visible lymph node showed a size of more than 5 mm and its shape was round or oval, with a mixed/hyperechoic internal texture.

A radiation oncologist determined the CTV by adding a 1.0-cm margin around the GTV, including local tumor and lymphatic involvement, based on either CT alone, CT with EUS, PET-CT alone, or PET-CT with EUS (Fig. 1). No other parameters were used, other than the GTV determined by each diagnostic image. The Japanese *Guidelines for clinical and pathologic studies on carcinoma of the esophagus*, *ninth edition*[14] was used to describe the locations of the lymphatic involvement (Table 1). Analysis of the results was performed by grouping these lymphatic locations into the cervical and supraclavicular (A), mediastinal (B), and abdominal (C) regions.

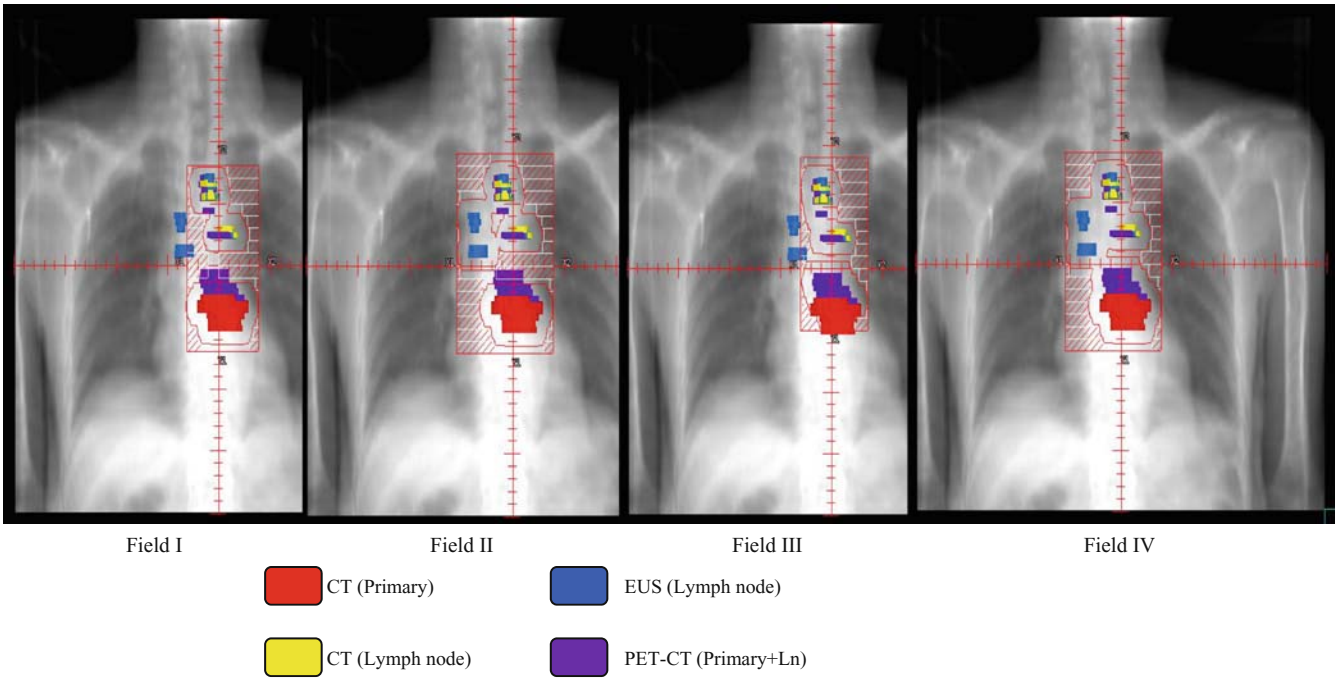

Fig. 1. An example of the change in the treatment field due to difference in clinical target volume (CTV) determined by various imaging modalities to cover the primary lesion and subclinical positive lymph node metastasis (case 4). The fields I, II, III, and IV correspond to the CTV determined by using computed tomography (*CT*), CT + endoscopic ultrasound (*EUS*), positron emission tomography (*PET*)-CT, and PET-CT + EUS. *Ln*, lymph node

Table 1. Numbering of lymph nodes according to the Japanese Guidelines for clinical and pathologic studies on carcinoma of the esophagus[14]

Group	Number	Description
(A) Cervical and supraclavicular region	101	Cervical paraesophageal lymph nodes
	102	Deep cervical lymph nodes
	104	Supraclavicular lymph nodes
(B) Mediastinal region	105	Upper thoracic paraesophageal lymph nodes
	106	Thoracic paratracheal lymph nodes
	107	Bifurcational lymph nodes
	108	Middle thoracic paraesophageal lymph nodes
	110	Lower thoracic paraesophageal lymph nodes
	111	Supradiaphragmatic lymph nodes
	112	Posterior mediastinal lymph nodes
(C) Abdominal region	1	Right cardiac lymph nodes
	2	Left cardiac lymph nodes
	3	Lesser curvature lymph nodes
	7	Left gastric artery lymph nodes
	9	Celiac artery lymph nodes
	19	Infradiaphragmatic lymph nodes

Table 2. Patient characteristics and findings

Patient no.	Age (years) /Sex	Primary	Stage	CT (LN >10 mm) LN no. according to ref 14	EUS LN no. according to ref 14	PET	Pathology findings No. of LNs detected	LN no. according to ref 14
1	50 M	Lt	3	–	101	Left cervical, upper mediastinum, lower esophagus	2/101	3
2	59 M	Mt	3	101, 104, 110, 3	101, 108		3/122	101, 108, 3
3	49 M	Mt	3	101, 106, 107	101	Rt. mediastinum, paratracheal	1/94	101
4	56 M	Mt	2	106	106	Upper mediastinum	1/82	106
5	62 F	Mt	2	–	–	Upper mediastinum	0/113	–
6	61 M	Mt	1	105, 106	–		0/63	–
7	62 M	Mt	3	–	108		0/103	–
8	71 M	Ut	2	–	–		0/60	–
9	55 M	Mt	2	101, 105, 106	105, 106		2/96	101, 106
10	65 M	Mt	3	101, 105, 106, 110	101, 7		1/94	9
11	66 M	Mt	1	106, 107	–		0/53	–
12	63 M	Lt	1	–	–		0/102	–
13	56 M	Lt, Ae	3	106, 9	7	Ln adherent to primary tumor	17/183	1, 2, 110
14	60 M	Lt	2	110	2, 110		8/32	2, 19, 110, 112
15	66 M	Mt	2	–	–		2/108	7
16	68 F	Ce	3	104	–	Upper mediastinum	2/46	101, 102, 104–
17	57 F	Lt, Ae	3	106	–		3/93	2, 7
18	75 M	Lt, Ae	2	–	–		7/50	1, 3, 7, 19, 110, 111
19	47 F	Lt	2	108	–		3/68	108
20	61 F	Lt	3	–	1		1/101	1

LN, lymph node; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; Ut, upper thoracic esophagus; Ae, abdominal esophagus; Rt., right; CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

Surgery was performed within 3 weeks after the end of the diagnostic workup, in principle. A pathological diagnostic report was made by a pathologist for each surgical specimen, regarding local extent and lymphatic spread. The positivity of metastasis to the lymph nodes was examined histopathologically.

We first calculated the diagnostic accuracy, sensitivity, and specificity of CT and PET-CT. Fisher's exact test was used to compare categorical data. Adequacy of the CTV to cover subclinical pathological positive lymph node metastasis was compared among the different diagnostic workups after pathological investigation. The portal size of each radiotherapy plan was also examined.

Results

The surgical specimens of the 20 patients contained 1764 lymph nodes. Of the 1764 nodes, 53 (3.0%) were histopathologically positive for cancer cells. The numbers and locations of the lymph nodes are shown in Table 2. The

Table 3. Number of patients requiring CTV enlargement to cover subclinical positive lymph node metastasis

	No. of patients	(A) Cervical + supraclavicular	(B) Mediastinal	(C) Abdominal
CT only	8	1	0	7
CT + EUS	5	1	0	4
PET-CT	9	2	1	6
PET-CT + EUS	5	1	0	4

accuracies of thin-slice CT and conventional PET-CT according to the location of the lymph nodes were 95% and 85% for the cervical and supraclavicular region (A), 95% and 60% for the mediastinal region (B), and 65% and 60% for the abdominal region (C).

The sensitivities were 100% and 50% (A), 86% and 14% (B), and 22% and 11% (C) for thin-slice CT and conventional PET-CT, respectively. The specificities were 94% and 94% (A), 69% and 85% (B), and 100% and 100% (C) for thin-slice CT and conventional PET-CT, respectively.

The number of patients with subclinical positive lymph node metastases that were not detected in the presurgical workup but were detected in the histopathological examination was determined for each of the combinations of imaging modalities. In the 20 patients, subclinical positive lymph node metastasis was not detected by CT alone (CT), in 8 patients, by CT and EUS (CT+EUS) in 5 patients, by PET-CT (PET-CT) in 7 patients or by PET-CT and EUS (PET-CT + EUS) in 5 patients.

To cover subclinical pathological positive lymph node metastasis, enlargement of the CTV was required for region (A) in one of eight patients with CT;, one of five with CT+EUS, two of nine with PET-CT, and one of five with PET-CT + EUS. For region (B), enlargement of the CTV was required in none of eight patients with CT, none of five with CT+EUS, one of nine with PET-CT, and none of five with PET-CT + EUS. For region (C), enlargement of the CTV was required in seven of eight patients with CT, four of five with CT+EUS, six of nine with PET-CT, and four of five with PET-CT + EUS (Table 3). There were no statistically significant differences among the regions with the different modalities, but the results suggested that enlargement of the CTV was required more frequently for region (C) than for regions (A) and (B).

Discussion

The accuracy, specificity, and sensitivity of FDG-PET for lymphatic metastasis of esophageal cancer in the present study were consistent with those of previously reported series.[15–18] Meltzer et al.[15] have reported that FDG-PET had 35%–41% sensitivity and 90% specificity, versus 63%–87% sensitivity and 14%–43% specificity for CT. Räsänen et al.[16] have shown that the sensitivity for local peritumoral lymph node metastasis was 37% for PET and 89% for EUS, and the specificity for local lymph node metastasis was 63% for PET, 66% for CT, and 75% for EUS. A systematic review showed that the pooled sensitivity and specificity for the detection of locoregional metastases were 51% (95% confidence interval [CI], 34%–69%) and 84% (95% CI, 76%–91%), respectively.[17] Katsoulis et al.[18] reported in a prospective study of the preoperative staging of thoracic esophageal and gastro-esophageal junction cancer that CT had 29% sensitivity and 67% specificity, whereas FDG-PET had 71% sensitivity and 67% specificity (P = 0.0412). In one of the largest series on squamous cell carcinoma (81 patients), Yoon et al.[7] showed that the sensitivity, specificity, and accuracy, respectively, of CT were 11%, 95%, and 83%, whereas these values for FDG-PET were 30%, 90%, and 82% (P values, <0.001, 0.009, and 0.382, respectively). Although there is some variation in the literature, the sensitivity of PET for the detection of lymph node metastasis should be considered insufficient, although the specificity may be better than that of a CT scan.

Yuan et al.[8] reported that PET/CT improved the sensitivity, accuracy, and negative predictive value of ^{18}F-FDG imaging in the assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. The sensitivity, specificity, and accuracy of PET/CT were 93.90% (77/82 nodal groups), 92.06% (290/315), and 92.44% (367/397), respectively, whereas these values for PET were 81.71% (67/82), 87.30% (275/315), and 86.15% (342/397), respectively (P = 0.032, 0.067, and 0.006, respectively). However, our results did not show that the detection rate of subclinical lymph node metastasis improved with the addition of PET-CT for the cervical and supraclavicular, mediastinal, or abdominal regions. The PET-CT used in the present study was a state-of-the-art machine, and thus the same results would be expected even if we would have used one of the other PET-CT machines available now.

Previous studies have reported that the use of FDG-PET resulted in a change of the CTV margin around the GTV compared with that determined by CT.[1,19] However, these same authors noted that determination of the CTV for the lymphatic region was a challenge even when using PET. Our results were consistent with their findings. The detection rate of subclinical lymph node metastasis did not improve with the addition of PET-CT for either cervical and supraclavicular nodes, mediastinal, or abdominal regions. In clinical practice, a larger CTV including larger lymphatic regions is often used to cover unpredictable widespread lymphatic metastasis in esophageal cancer treatment.[1] Radiological examinations such as CT, PET, EUS, and CT-PET are not yet sufficient for determination of the CTV for the lymphatic region. It is not conclusive whether we should treat all cervical, mediastinal, and abdominal

lymphatic regions for a majority of patients, and this is a subject better left for future investigations.

Enlargement of the CTV was required more frequently in the abdominal region (Table 3). EUS has the potential to visualize a small lymph node metastasis located around the esophageal and gastric wall, though EUS also has a limitation in its penetration depth of about 5 cm. PET-CT is expected to perform better than CT in the detection of lymph node metastasis. In our present study, the result with PET-CT was not sufficient for the detection of positive nodes. It may be that the amount of altered tissue glucose metabolism in subclinical lymph node metastases is not enough to be well visualized by extra-body PET detectors. FDG-PET/CT also has a limitation in detecting lymph node metastasis in deep abdominal lesions.

Our results suggest that PET-CT requires further improvement of its accuracy for the detection of positive nodes to improve accuracy in determining the CTV. Recently, a new PET with semiconductor detectors has been developed, and it is expected to have potential for the precise detection of small cancer metastases.[20] We need to continue to improve the various imaging modalities so that they can be used as reliable guides for radiotherapy.

In conclusion, it is not recommended to use FDG-PET or PET-CT alone to determine the CTV when all pathologically involved lymphatic regions are to be included in the CTV as a treatment strategy.

Conflict of interest statement

None of the authors have any financial disclosures.

References

1. Gao XS, Qiao X, Wu F, et al. (2007) Pathological analysis of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma. Int J Radiat Oncol Biol Phys 67:389–396
2. Block MI, Patterson GA, Sundaresan RS, et al. (1997) Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg 64:770–776
3. Luketich JD, Schauer PR, Meltzer CC, et al. (1997) Role of positron emission tomography in staging esophageal cancer. Ann Thorac Surg 64:765–769
4. Luketich JD, Friedman DM, Weigel TL, et al. (1999) Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. Ann Thorac Surg 68:1133–1136
5. Flanagan FL, Dehdashti F, Siegel BA, et al. (1997) Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol 168:417–424
6. Flamen P, Lerut A, Van Cutsem E, et al. (2000) Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 18: 3202–3210
7. Yoon YC, Lee KS, Shim YM, et al. (2003) Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection – prospective study. Radiology 227:764–770
8. Yuan S, Yu Y, Chao KS, et al. (2006) Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. J Nucl Med 47:1255–1259
9. Blackstock AW, Farmer MR, Lovato J, et al. (2006) A prospective evaluation of the impact of 18-F-fluoro-deoxy-D-glucose positron emission tomography staging on survival for patients with locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 64:455–460
10. Vrieze O, Haustermans K, De Wever W, et al. (2004) Is there a role for FDG-PET in radiotherapy planning in esophageal carcinoma ? Radiother Oncol 73:269–275
11. Moureau-Zabotto L, Touboul E, Lerouge D, et al. (2005) Impact of CT and ^{18}F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys 63:340–345
12. Gondi V, Bradley K, Mehta M, et al. (2007) Impact of hybrid fluorodeoxyglucose positron-emission tomography/computed tomography on radiotherapy planning in esophageal and non–small-cell lung cancer. Int J Radiat Oncol Biol Phys; 67:187–195
13. Sobin LH, Wittekind CH (2002) UICC: TNM classification of malignant tumors, 6th edn. Wiley-Liss, New York
14. The Japanese Society for Esophageal disease (2001) Guidelines for clinical and pathologic studies on carcinoma of the esophagus, ninth edn. Kanehara, Tokyo, pp 8–10
15. Meltzer CC, Luketich JD, Friedman D, et al. (2000) Whole-body FDG positron emission tomographic imaging for staging esophageal cancer: comparison with computed tomography. Clin Nucl Med 25:882–887
16. Räsänen JV, Sihvo EIT, M. Knuuti MJ, et al. (2003) Prospective analysis of accuracy of positron emission tomography, computed tomography, and endoscopic ultrasonography in staging of adenocarcinoma of the esophagus and the esophagogastric junction. Ann Surg Oncol 10:954–960
17. van Westreenen HL, Westerterp M, Bossuyt PMM, et al. (2004) Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 22:3805–3812
18. Katsoulis IE, Wong WL, Mattheou AK, et al. (2007) Fluorine-18 fluorodeoxyglucose positron emission tomography in the preoperative staging of thoracic oesophageal and gastro-oesophageal junction cancer: a prospective study. Int J Surg 5:399–403
19. Leong T, Everitt C, Yuen K, et al. (2006) A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 78:254–261
20. Shiga T, Morimoto Y, Kubo N, et al. (2009) A new PET scanner with semiconductor detectors enables better identification of intratumoral inhomogeneity. J Nucl Med 50:148–155