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Detection of local residual tumor after laryngeal cancer treatment using FDG-PET

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Objective: Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is sometimes used as a means of follow-up after diagnosis and treatment of cancers of the head and neck region. The present study was undertaken to evaluate the ability of FDG-PET to detect local residual tumor after treatment of laryngeal cancer. ***Methods:*** Thirty-six patients with laryngeal cancer underwent FDG-PET before and after initial treatment. Of these patients, 20 received FDG-PET before treatment and 28 received it after treatment. The relationship between standardized uptake values (SUV) and the presence or absence of local residual tumor was investigated by setting the cut-off value of the SUV using the receiver operating characteristics (ROC) curve. ***Results:*** When the pre-treatment SUV threshold for laryngeal cancer was set at 7.20, the detection of local residual tumor after treatment using FDG-PET had a sensitivity of 77.78%, specificity of 81.82%, false positive rate of 18.18%, false negative rate of 22.22%, accuracy of 80% and a p value of 0.02. When the post-treatment SUV threshold for the larynx was set at 3.35, the test had a sensitivity of 93.75%, specificity of 91.67%, false positive rate of 8.33%, false negative rate of 6.25%, accuracy of 92.86% and a p value of 0.0001. ***Conclusions:*** FDG-PET was found to be useful for determining the presence of local residual tumor after treatment of laryngeal cancer.

Key words: laryngeal cancer, residual tumor, FDG-PET, SUV

INTRODUCTION

In the diagnosis of head and neck carcinoma, imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are widely used. CT and MRI provide detailed information about the anatomical extension of the disease and morphologic changes after treatment.[1,2] However, the changes in images obtained by these methods before and after treatment do not always reflect a decrease in tumor size.[3]

Positron emission tomography (PET) is a nuclear medical examination technique for the visualization of physiological and biochemical information in the body. In oncology, fluorine-18-fluorodeoxyglucose (FDG-PET) is widely used. Evaluation of glucose metabolism using FDG-PET plays a critical role in early tumor diagnosis, differential diagnosis between malignant and benign tumors, staging diagnosis, therapeutic strategy, evaluation of therapeutic outcomes and prediction of prognosis.[1,4–8]

The larynx is an important organ for speech. Radical surgery in the region of the larynx can result in severe damage to function, cosmetic appearance and quality of life (QOL). Recently, an organ-sparing approach including radiation therapy and chemotherapy has become important for laryngeal cancer. However, this therapy is associated with a high incidence of residual masses after therapy. It is important to differentiate between tumor recurrence and the presence of scar tissue. CT and MRI do not always provide an accurate picture of the disease due

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Table 1 Patient characteristics, SUV before therapy, local residual tumor after therapy

Patient no.	Age (yrs)	Sex	Histology	T	SUV	Local residual tumor
1	55	M	P/D	3	4.58	–
2	77	M	W/D	4	4.81	+
3	59	M	M/D	3	4.88	–
4	73	M	P/D	3	5.43	–
5	79	M	W/D	1	5.96	–
6	66	M	M/D	2	5.97	–
7	46	M	W/D	4	6.06	–
8	60	M	W/D	1	6.06	–
9	73	M	P/D	2	6.26	–
10	76	M	P/D	2	6.69	+
11	50	M	P/D	3	7.2	–
12	70	M	W/D	3	7.67	+
13	72	M	M/D	4	8.28	–
14	49	F	P/D	4	8.53	–
15	54	M	M/D	4	10.02	+
16	47	M	M/D	3	10.34	+
17	56	M	P/D	4	11.83	+
18	50	M	M/D	3	12.1	+
19	62	M	P/D	4	14.48	+
20	53	M	W/D	2	18.66	+

M: Male, F: Female, W/D: well differentiated squamous cell carcinoma, M/D: moderately differentiated squamous cell carcinoma, P/D: poorly differentiated squamous cell carcinoma, T: T stage, SUV: standardized uptake value

Table 2 Patient characteristics, SUV after therapy, local residual tumor after therapy

Patient no.	Age (yrs)	Sex	Histology	SUV	Local residual tumor
1	69	M	W/D	1.55	–
2	73	M	M/D	2.15	–
3	60	M	M/D	2.21	–
4	73	M	P/D	2.22	–
5	50	M	M/D	2.22	+
6	72	M	M/D	2.27	–
7	59	M	M/D	2.69	–
8	62	M	M/D	2.74	–
9	55	M	P/D	2.76	–
10	79	M	M/D	2.94	–
11	56	M	M/D	3.14	–
12	68	M	M/D	3.35	–
13	79	M	W/D	3.46	–
14	49	F	P/D	3.46	+
15	46	M	W/D	3.48	+
16	60	F	W/D	3.84	+
17	77	M	W/D	3.99	+
18	50	M	P/D	4.29	+
19	76	M	P/D	4.3	+
20	53	M	W/D	4.32	+
21	62	F	M/D	4.34	+
22	73	M	M/D	4.42	+
23	61	M	M/D	4.52	+
24	65	M	M/D	4.61	+
25	47	M	M/D	6.21	+
26	54	M	M/D	6.9	+
27	57	M	P/D	7.92	+
28	59	M	W/D	8.6	+

M: Male, F: Female, W/D: well differentiated squamous cell carcinoma, M/D: moderately differentiated squamous cell carcinoma, P/D: poorly differentiated squamous cell carcinoma, SUV: standardized uptake value

to the presence of radiation-induced diffuse soft tissue swelling and because both recurrent tumors and post-radiation fibrotic changes are associated with contrast enhancement.[4]

In this study, we evaluate local control of laryngeal cancer before and after therapy by quantitative assessment using FDG-PET.

MATERIALS AND METHODS

Patients

A retrospective study was conducted in 36 patients with laryngeal cancer who underwent FDG-PET between December 1994 and March 2004. In all cases, laryngeal cancer was classified as squamous cell carcinoma. FDG-PET was performed on 20 patients before treatment (Table 1) and on 28 patients after treatment (Table 2). Post-treatment FDG-PET was performed for a period of two years, beginning immediately after treatment. Of the 36 subjects, 33 were male and 3 were female, with ages ranging from 49 to 79 years (mean: 62). Eight patients were treated with radiotherapy alone, five patients received radiotherapy + chemotherapy, eighteen patients received radiotherapy + surgery and five patients received radiotherapy + chemotherapy + surgery.

PET imaging protocol

FDG was produced with the NKK-Oxford superconducting cyclotron and NKK synthesis system. A HEADTOME IV SET-1400W-10 (Shimadzu Corp., Japan), which has 4 detector rings providing 7 contiguous slices at 13 mm intervals, was employed for the PET studies. The effective spatial resolution was 14 mm at full width at half maximum (FWHM). Before emission scanning, transmission scans were performed with a $^{68}Ge/^{68}Ga$ ring source for attenuation correction. Images were obtained from 40 to 55 minutes after intravenous injection of 185–370 MBq FDG while fasting. Patients were kept at rest without speaking still the start of the scan after injection.[9]

Data analysis

For the quantitative evaluation of FDG uptake in the tumor, regions of interest (ROIs: round in shape and 8 mm in diameter) were placed on the area of highest FDG uptake within the laryngeal cancer or suspected lesions. The mean of the standardized uptake values (SUV = tissue concentration/activity injected per body weight) of the ROIs was determined.

Statistical analysis

The cut-off value of SUV for estimation of local residual tumor was determined by the ROC curve, and the sensitivity and specificity of FDG-PET were evaluated at this cut-off value. The relationship between SUV levels (below or above the cut-off value) and T classification, histology and local residual tumor was analyzed by Fisher's exact test. $p < 0.05$ was regarded as statistically significant.

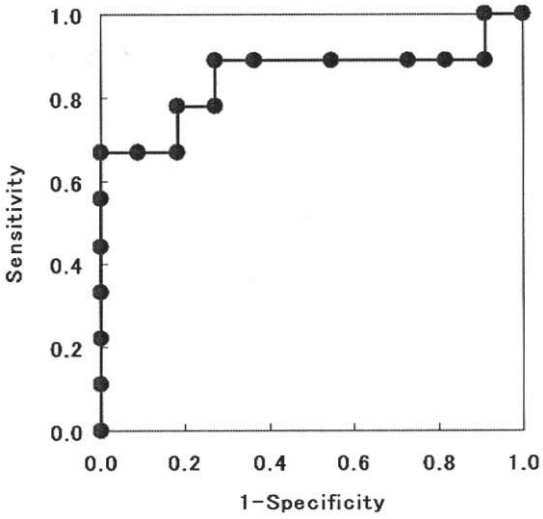

Fig. 1 Receiver operating characteristics (ROC) curve of the relationship between SUV before therapy and local residual tumor after therapy.

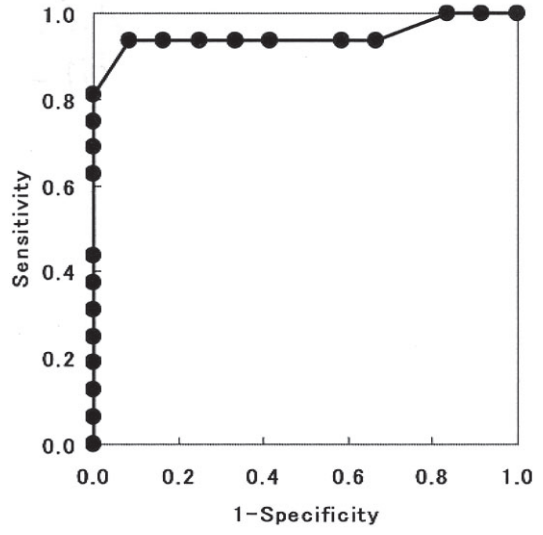

Fig. 2 Receiver operating characteristics (ROC) curve of the relationship between SUV after therapy and local residual tumor after therapy.

Clinical evaluation

Residual tumor was pathologically confirmed after surgical resection or biopsy in all patients suspected of having residual tumor on the basis of CT or MRI or PET or physical examination. All patients suspected of having no residual tumor were clinically followed up by physical and endoscopic examination for more than a year to establish the diagnosis.

Table 3 Relationship between SUV before therapy and local residual tumor after therapy

		Residual tumor		
		−	+	
SUV	Low	9	2	11
	High	2	7	9
		11	9	20

Table 4 Relationship between SUV after therapy and local residual tumor after therapy

		Residual tumor		
		−	+	
SUV	Low	11	1	12
	High	1	15	16
		12	16	28

RESULTS

Before treatment, FDG-PET was performed in 20 patients (Table 1). After treatment, local residual tumor was detected in 9 of these 20 patients. The relationship between SUV and local residual tumor was analyzed using the ROC curve (Fig. 1), and the cut-off value of SUV was set at 7.20. The patients were then divided by SUV into two groups: a low SUV group (SUV ≤ 7.20) and high SUV group (SUV > 7.20). The presence or absence of local residual tumor was compared between these two groups (Table 3). In terms of T classification and histology, there was no significant difference between the two groups. The detection of local residual tumor after treatment using FDG-PET had a sensitivity of 77.78%, specificity of 81.82%, false positive rate of 18.18%, false negative rate of 22.22%, accuracy of 80% and a p value of 0.02.

After treatment, FDG-PET was performed in 28 patients (Table 2). After treatment, local residual tumor was detected in 16 of these 28 patients. The relationship between SUV and local residual tumor was analyzed using the ROC curve (Fig. 2), and the cut-off value of SUV was set at 3.35. The patients were then divided by SUV into two groups: the low SUV group (SUV ≤ 3.35) and high SUV group (SUV > 3.35). The presence or absence of local residual tumor was compared between these two groups (Table 4), with the following results: sensitivity 93.75%, specificity 91.67%, false positive rate 8.33%, false negative rate 6.25%, accuracy 92.86% and p value of 0.0001. In terms of histology, there was no significant difference between the two groups.

DISCUSSION

Numerous reports have demonstrated the usefulness of FDG-PET in the diagnosis, staging and evaluation of responses to treatment of head and neck cancers. PET has been utilized for the purpose of distinguishing benign tumors from malignant tumors, assessing changes after treatment (edema, scarring, inflammation, fibrosis, etc.), and checking for the presence of residual tumor or recurrent tumors, all of which are difficult with conventional methods (CT, MRI or macroscopic inspection).

Regarding the findings from PET conducted before treatment of head and neck cancer, Schwartz et al. reported that when 54 patients with head and neck cancer (including 17 cases of laryngeal cancer) were analyzed, the overall survival rate and the recurrence-free survival rate were low in cases in which the pre-treatment SUV was 9 and over.[10] Halfpenny et al. reported that when 73 patients with head and neck cancer were analyzed, the prognosis was poor in cases where the pre-treatment SUV was over 10, irrespective of the stage or radius of the tumor.[11] Kitagawa et al. reported that when 20 cases of head and neck cancer were analyzed, the probability that the tumor would remain was high in cases in which the pre-treatment SUV was 7 and over.[12] In addition to these investigators, Allal et al., Minn et al. and Brun et al. also reported that a high pre-treatment SUV was associated with a poor prognosis.[13–15] In the present study, we focused only on laryngeal cancer as a specific head and neck region cancer. Similar to previous reports, the present study demonstrated that the probability that the tumor would remain locally was high in cases in which the pre-treatment SUV was over 7.20.

Regarding the evaluation of treatment responses, it has been reported that FDG-PET is better than conventional means such as CT, MRI and macroscopic inspection. Sakamoto et al. analyzed 22 cases of head and neck cancer (including 2 cases of laryngeal cancer) and reported that viable tumor remained in cases in which the post-treatment SUV was 3 and over.[3] To date there have not been any reported studies that specifically deal with the use of PET to determine the presence of residual tumor after treatment of laryngeal cancer. In the evaluation of PET in cases of head and neck cancers in general (including laryngeal cancer), PET was reported to have both high sensitivity and high specificity.[12,16–22] Terhaard et al. and Conessa et al., among others, reported that low FDG accumulation on PET indicates quite a low probability of the presence of residual tumor and thus in such cases there is no need for a biopsy.[15,18] They additionally reported that the probability of residual tumor is low if a biopsy is negative and FDG accumulation is low on follow-up PET even when the initial FDG accumulation is high. In our study, residual tumor was noted in all but one case in which SUV was over 3.35. This test had a sensitivity of 93.75% and a specificity of 91.67%, and the presence or

absence of residual tumor differed significantly depending on the SUV.

The larynx is an anatomically complex organ; it is indispensable for maintaining QOL (speech, etc.).[23] Responses to laryngeal cancer treatment should be assessed as early as possible, to determine the strategy for subsequent care and treatment. Because of changes such as inflammation after surgery or radiotherapy, it is difficult to examine for the presence of residual tumors using existing diagnostic imaging techniques (CT, MRI, etc.). FDG-PET has a high sensitivity and specificity when used as a means for checking for the presence of residual tumors. When the results of this test show low glucose metabolism, this suggests that the presence of residual tumors is unlikely. If PET is incorporated into the routine follow-up of patients with laryngeal cancer, their QOL may be improved. PET is thus recommended in the care of patients with laryngeal cancer.

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