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Comparison of barium swallow, CT and thallium-201 SPECT in evaluating responses of patients with esophageal squamous cell carcinoma to preoperative chemoradiotherapy

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The aims of this study were to compare the results of thallium-201 (Tl-201) SPECT, barium swallow and CT in the assessment of the effect of preoperative chemoradiotherapy. This study consisted of 28 patients with advanced esophageal squamous cell carcinoma (AESCC) who underwent the three imaging modalities before and after preoperative chemoradiotherapy. The results were quantified using the bidimensional method for barium swallow and contrast-enhanced CT and the tumor-to-lung ratio for SPECT. The percent decrease in these quantitative values after therapy was defined as %Dba, %Dct and %Dtl respectively. The histological effect of the chemoradiotherapy was determined from the resected surgical specimen of the esophagus: grade 0, 100% viable tumor cells; grade 1a, 99–67%; grade 1b, 66–34%; grade 2, 33–1%; grade 3, no viable cells. A statistically significant difference of %Dtl between the subgroups of each grade was evident ($p = 0.0433$), whereas no significant differences were evident for %Dba ($p = 0.1778$) or %Dct ($p = 0.7377$). However, the overlap of %Dtl between these groups was marked. Although thallium-201 SPECT cannot be used to evaluate the therapeutic effect with acceptable accuracy, SPECT may be of additional value to barium swallow and CT in assessing the response of AESCC to preoperative chemoradiotherapy.

Key words: SPECT, thallium-201, esophageal carcinoma, preoperative chemoradiotherapy, therapeutic effect

INTRODUCTION

PATIENTS with esophageal carcinoma usually have a very poor prognosis since they develop symptoms at a late stage and therefore present for treatment when the tumor is advanced. Before the use of neoadjuvant chemotherapy, surgery and/or radiation therapy was the only method of treating patients with esophageal carcinoma despite its poor outcome and survival rate. Recently, a series of reports on a randomized controlled trial by the Radiation Therapy Oncology Group (RTOG) demonstrated a significant benefit of chemoradiotherapy.[1–3] In addition, patients who exhibit a response to preoperative chemoradiotherapy have improved survival rates compared with non-responders.[4,5]

Radiological techniques such as barium swallow, computed tomography (CT), endoscopic ultrasound and magnetic resonance imaging have been used to detect, stage and manage esophageal carcinoma. However, these modalities may be of limited value in assessing the response to chemoradiotherapy in patients with esophageal carcinoma because radiologists cannot always differentiate

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fibrosis or edema from residual tumor using purely morphological information. Indeed, some authors have reported that barium swallow and CT are less useful diagnostic tools for this assessment.[6–8]

In contrast to structural imaging, nuclear imaging can detect a variety of malignancies on the basis of their function, metabolism or activity. For example, gallium-67 (Ga-67) scintigraphy is highly predictive of clinical response and prognosis in patients with malignant lymphoma[9,10] and may be used to evaluate the therapeutic response in such patients. We recently applied Ga-67 single-photon emission computed tomography (SPECT) to esophageal carcinoma.[11] Although we verified that Ga-67 SPECT detects esophageal cancer with considerable sensitivity, our preliminary results failed to demonstrate its applicability to predicting the response of esophageal cancer to treatment.

Thallium-201 (Tl-201) is a tumor-seeking radiopharmaceutical that is used to evaluate the viability of brain tumors or osteosarcoma.[12,13] In 1996, Tl-201 SPECT was first applied to one patient with esophageal carcinoma[14] and a more recent study detected 13 of 15 esophageal carcinomas using Tl-201 SPECT.[15] Here, we focused on chemoradiotherapeutic evaluation of the tumor rather than on the detection of advanced esophageal squamous cell carcinoma. This study was conducted at the same time as our previous study,[11] although registration of the pre- and post-chemoradiotherapy SPECT images was needed to reliably quantify tumor uptake especially when uptake was visually faint or absent. The commercially available software, Automatic Registration Tool (Toshiba Corporation, Tokyo), has recently been installed in our nuclear medicine workstation.

This study compares the results of Tl-201 SPECT, barium swallow and CT in assessing the effects of preoperative chemoradiotherapy in patients with advanced esophageal squamous cell carcinoma. We also examined whether Tl-201 SPECT can serve as a useful adjunct to barium swallow and CT in the management of these patients.

MATERIALS AND METHODS

Between January 1997 and July 2001, 28 patients with squamous cell carcinoma of the esophagus were studied with Tl-201 SPECT, barium examination and CT both before and after preoperative chemoradiotherapy and before surgery. In addition, all patients were studied with Ga-67 SPECT as in our previous study.[11] Thallium-201 SPECT was performed more than 3 days before Ga-67 SPECT to avoid photon contamination between the studies. None of the 26 male and 2 female patients (mean age, 61 years; range, 50–74 y) had received prior treatment for esophageal carcinoma. Tumors were located in the middle third of the thoracic esophagus in 15 patients, in the lower third in 9, in the upper third in 3, and in the cervical esophagus in 1.

Preoperative chemoradiotherapy was started in all patients within 3 weeks after completing pre-chemoradiotherapeutic radiological assessments. The overall therapy consisted of concurrent chemotherapy and radiotherapy. Cisplatin at a dose of 70 mg/m^2 body surface area (BSA) (n = 18) or nedaplatin at a dose of 80 mg/m^2 BSA (n = 10) was rapidly infused i.v. on day 1. All patients also received intravenous 5-fluorouracil at a dose of 700 mg/m^2 BSA on days 1–5 (120 hours). External radiotherapy was delivered to the anterior and posterior fields at the following dosage: 2 Gy per fraction (per day), 5 fractions per week, up to a total dose of 30 Gy (n = 16), and 1.3 Gy per fraction, 2 fractions per day, 10 fractions per week, up to a total dose of 39 Gy (n = 12). The interval between preoperative chemoradiotherapy and surgery was about 4–5 weeks.[11]

Thallium-201 SPECT was performed using a triple-headed rotating gamma camera Toshiba GCA-9300A (Toshiba Corporation, Tokyo) equipped with low-energy, high-resolution parallel-beam collimators. The energy peak and window level were set at 71 keV ± 20%. SPECT scans were started 120–150 min after an intravenous injection of 185 MBq of Tl-201 chloride. All patients were scanned in the supine position with their arms raised. Image data were obtained for 20 min in 360° rotation with 60 projections 6° apart, which resulted in a total count of 3.3–5.4 × 10^6 per SPECT acquisition. The matrix size for data acquisition and image reconstruction was 3.2 mm (128 × 128). Data were processed using the medical image processor, Toshiba GMS-9300A/UI (Toshiba Corporation, Tokyo). Transaxial slices of 3.2 mm thickness were processed using a Butterworth filter (order, 8; cut-off frequency, 0.13 cycles/pixel) and reconstructed by back-projection through a ramp filter. Full width at half maximum (FWHM) was about 13 mm in air at a distance of 11 cm. Scatter and attenuation were not corrected.

Pre-chemoradiotherapy SPECT and corresponding CT images were visually correlated. When a lesion was visually positive, a region of interest (ROI) was established to quantify tumor uptake. A tumor ROI was manually drawn over the area of tumor uptake on the transaxial slice of the lesion that exhibited the highest uptake. A large elliptical background ROI (380–450 pixels) was placed on a transaxial slice in the right middle lung field because background and tumor ROIs could not be established in the same slice from patients with cervical or lower thoracic esophageal cancer.

Post-chemoradiotherapy SPECT images were automatically re-sliced using the commercially available software, Automatic Registration Tool (Toshiba Corporation, Tokyo) to correspond to pre-chemoradiotherapy SPECT images. Ardekani et al. have described the theory of the registration.[16] The location of physiological uptake such as the heart, liver, muscle or thyroid was compared on pre- and post-chemoradiotherapy SPECT images to

determine precise image registration. Post-chemoradiotherapy tumor and lung ROIs were automatically placed on the re-sliced post-chemoradiotherapy SPECT images at the same location as the corresponding pre-chemoradiotherapy ROIs.

The quantitative tumor-to-lung ratio (TLR) was calculated by dividing the average counts per pixel in the tumor ROI by those of the lung. Based on pre-chemoradiotherapy TLR (TLRpre) and post-chemoradiotherapy TLR (TLRpost), the percent decrease in TLR (%Dtl) was defined as follows:

$$\%\mathrm{Dtl} = \frac{\mathrm{TLRpre} - \mathrm{TLRpost}}{\mathrm{TLRpre}} \times 100. \qquad \text{Eq. 1}$$

Over 10 radiographs were obtained per study of single or double contrast barium studies. In each patient, radiographs taken at the same position were compared before and after chemoradiotherapy. Tumor volume was quantified using the bidimensional measurement method described by Agha et al.[17] This method is outlined in the 'Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus' issued by the Japanese Society for Esophageal Disease.[18] Tumor volume was determined by multiplying the maximal measured longitudinal length and perpendicular depth of the tumor.

All patients underwent contrast enhanced spiral CT from the neck to the upper abdomen using a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee) with 10-mm collimation and a pitch of 1. Contiguous transaxial CT images with a thickness of 10-mm were obtained at a peak voltage of 120 kV and a tube current of 200 mA at 1 s per slice. The maximal longitudinal length was determined based on the number of contiguous transaxial CT slices in which the esophageal wall thickness was >5 mm, and depth was measured based upon the transaxial slice in which the esophageal wall was thickest. The value of tumor length multiplied by depth was used for quantitative analysis.

All patients underwent esophagectomy after the completion of the post-chemoradiotherapeutic radiological assessments. A single pathologist examined all of the resected esophageal specimens and assessed the viability of tumor cells following chemoradiotherapy in a blinded fashion. Tissue sections (2–3 μm thick) from a series of 5-mm paraffin-embedded esophageal segments that covered the entire tumor and the surrounding tissue were stained with H&E and evaluated by microscopy.

The effects of chemoradiotherapy were assessed according to the 'Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus' issued by the Japanese Society for Esophageal Disease[18] as follows: grade 0, 100% of tumor cells viable; grade 1a, 67–99% viable; grade 1b, 34–66% viable; grade 2, 1–33% viable and grade 3, apparently absent viable cells. Patients from whom esophageal specimens exhibited a grade 0, 1a or 1b response were considered to be non-responders, whereas those with grade 2 or 3 responses were considered to be responders.

One radiologist who was blinded to the histological data, quantified the barium or CT images. The percent decrease (%Dq) was calculated using the formula:

$$\%\mathrm{Dq} = \frac{\mathrm{Qpre} - \mathrm{Qpost}}{\mathrm{Qpre}} \times 100, \qquad \text{Eq. 2}$$

Table 1 Correlation of the SPECT results of visual analysis with histological response grade

Histological response grade	No. of thallium studies	
	Thallium positive	Thallium negative
3	1	2
2	10	1
1b	5	0
1a	9	0

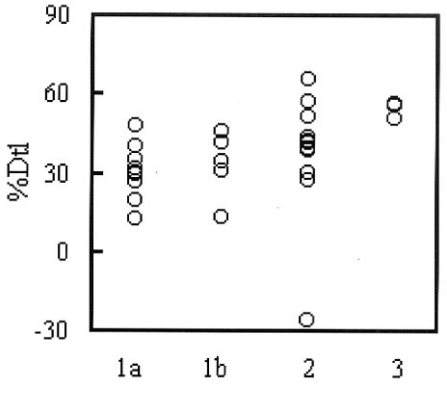


Fig. 1 Comparison between percent decreases in tumor-to-lung ratios in Tl-201 SPECT (%Dtl) and histological response grade.

Table 2 Correlation of the SPECT results of quantitative analysis with histological response grade

Histological response grade	No. of thallium studies			
	%Dtl > 50	50 > %Dtl > 35	35 > %Dtl > 20	20 > %Dtl
3	3	0	0	0
2	3	5	2	1
1b	0	2	2	1
1a	0	3	4	2

%Dtl was defined as [(TLRpre − TLRpost)/TLRpre] × 100

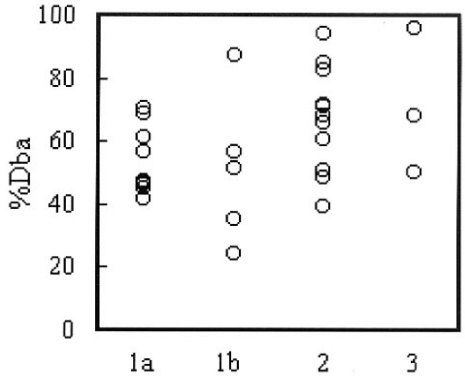


Fig. 2 Comparison between percent decreases in multiplication products of tumor length and perpendicular depth in barium swallow and histological response grade.

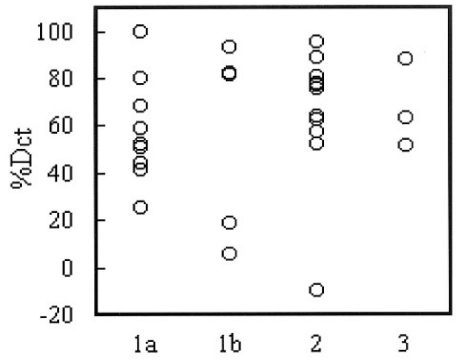


Fig. 3 Comparison between percent decreases in multiplication products of tumor length and perpendicular depth in CT and histological response grade.

in which Qpre = quantitative value on pre-chemoradiotherapy images and Qpost = quantitative value on post-chemoradiotherapy images. The recorded percent decreases from the barium examination (%Dba), CT (%Dct) or %Dtl were compared with the grade of the histological response.

The Kruskal-Wallis test compared the values of %Dba, %Dct or %Dtl with the grade of histological response. An unpaired t-test compared %Dba, %Dct or %Dtl in responders with the corresponding indices in non-responders. A p value below 0.05 was considered statistically significant.

RESULTS

The responses of the 28 cancers varied. Nine patients had a grade 1a response, whereas the grades of 5, 11 and 3 patients were 1b, 2 and 3, respectively. All 28 tumors were detected by pre-chemoradiotherapy SPECT, showing that the sensitivity was 100%. Thus, a TLRpre value could be calculated for all patients.

The results of visual analysis for tumor uptake on post-chemoradiotherapy SPECT were shown in Table 1. Table 2 shows the SPECT results of quantitative analysis from the 28 patients. The %Dtl tended to be higher in patients with higher response grades (Fig. 1). The Kruskal-Wallis test revealed a statistically significant difference in %Dtl among the histological response grades ($p = 0.0433$). Among all 28 patients, the %Dtl was not significantly higher in responders than in non-responders (41.1 ± 22.0 vs. 31.6 ± 10.9, $p = 0.1577$). However, the %Dtl of one patient was quite different from that of the others (Fig. 1) because clinical and endoscopic evidence revealed esophagitis after chemoradiotherapy. Thus, post-chemoradiotherapy SPECT depicted an area of intense accumulation in the lesion with the TLRpost being higher than the TLRpre. %Dba and %Dct in the patient were 39.1 and −10.0, respectively. Moreover, the area of increased accumulation evident in the esophagus was greater than the area of the lesion evident on the barium swallow image and pre-chemoradiotherapy SPECT. Analysis of the data after excluding this patient indicated that the %Dtl was significantly higher in responders than in non-responders (46.2 ± 11.2 vs. 31.6 ± 10.9, $p = 0.0021$).

Figures 2 and 3 show that histological response grades did not correlate with either %Dba ($p = 0.1778$) or %Dct ($p = 0.7377$). The %Dba was more useful in differentiating between responders and non-responders among all 28 patients ($p = 0.0229$) than either %Dtl ($p = 0.1577$) or %Dct ($p = 0.4079$). Even after excluding the above-mentioned patient who developed severe esophagitis, despite the significant difference in the %Dba between responders and non-responders ($p = 0.0086$), %Dba did not significantly correlate with the histological response grade ($p = 0.0851$).

DISCUSSION

Preoperative chemotherapy and/or radiotherapy of primary esophageal carcinoma are applied in many institutions since they have a beneficial effect upon prognosis.[19] In particular, the survival of responders to neoadjuvant therapy is better than that of non-responders, suggesting that an accurate prediction of the response to chemoradiotherapy before surgery could significantly impact clinical management. To our knowledge, few reports have compared imaging modalities to assess the effects of chemoradiotherapy on esophageal carcinoma. Our study demonstrated that Tl-201 SPECT was superior to barium swallow and CT in predicting the microscopic viable cell fraction in patients who had undergone preoperative chemoradiotherapy.

The effects of cancer treatment are commonly evaluated by barium swallow and CT on the assumption that structural changes will reflect the therapeutic response. In 1991, Samuelsson et al.[20] reported that barium swallow can assess the effect of preoperative chemoradiotherapy on esophageal cancer. In that study, barium examination was a reliable tool for evaluating whether cancer in the

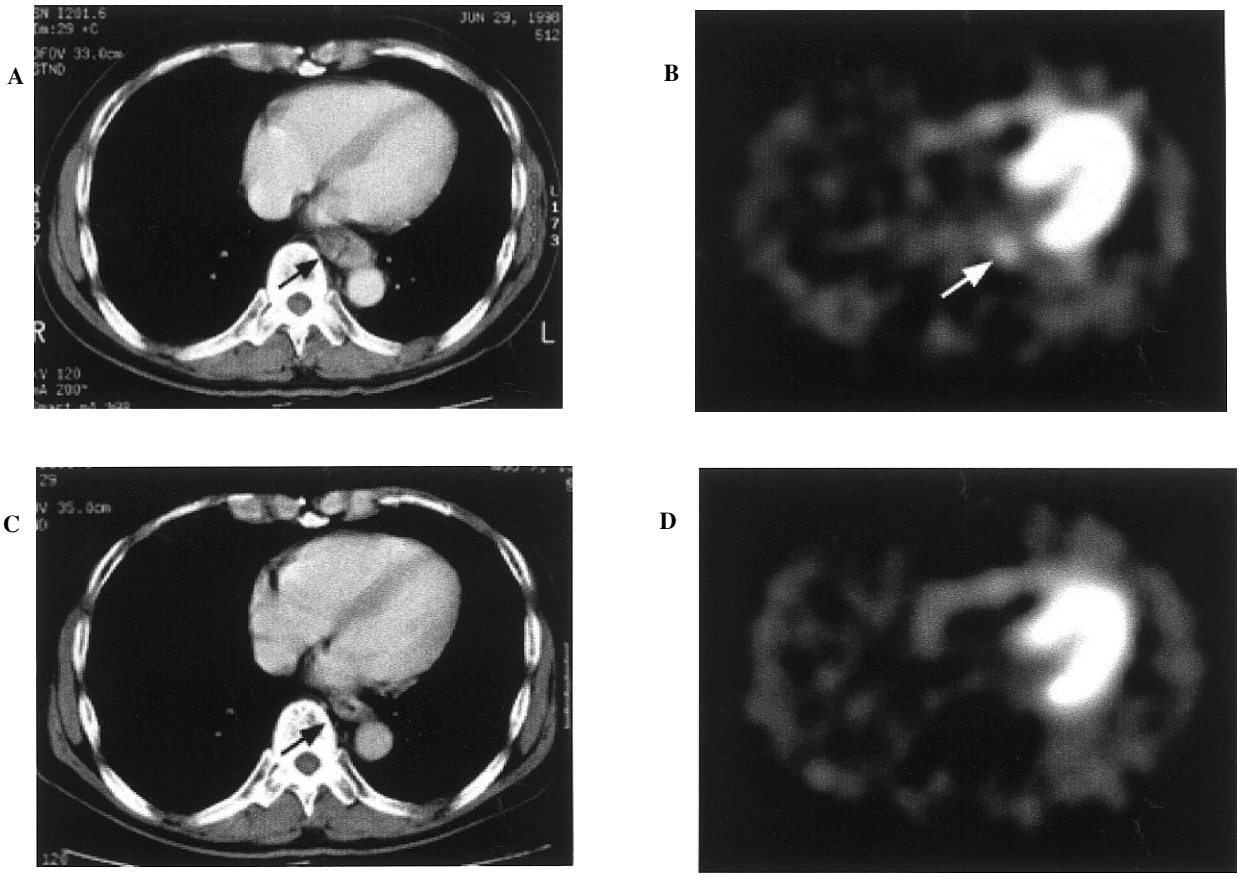
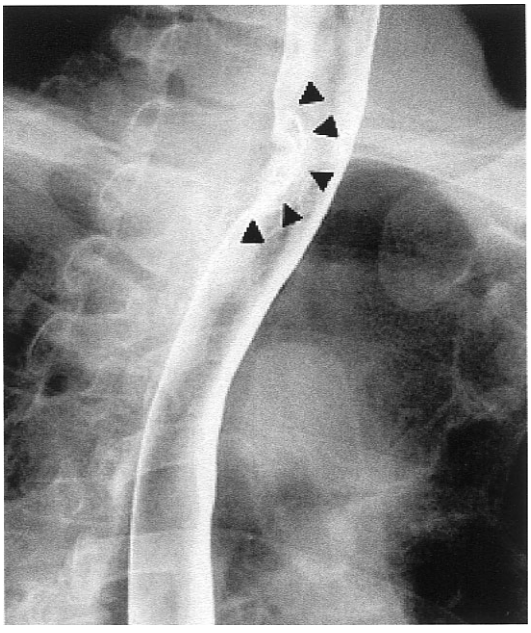


Fig. 4 A 61-year-old man with poorly differentiated squamous cell carcinoma in the lower thoracic esophagus who had a pathologically complete response after chemoradiotherapy. A, Pre-chemoradiotherapy CT demonstrated a thickened esophageal wall, representing advanced esophageal carcinoma. B, Pre-chemoradiotherapy thallium-201 SPECT showed an area of increased accumulation near an area of physiological uptake by the heart, corresponding to the esophageal carcinoma identified on the CT images. C, Post-chemoradiotherapy CT demonstrated that the thickened wall revealed by contrast enhancement persisted despite a decrease in wall thickness. D, Post-chemoradiotherapy SPECT images did not reveal any focal accumulation in the esophagus.

esophagus was absent, microscopic or macroscopic. However, the present study categorized the histological response by the proportion of viable cells. We demonstrated that barium swallow could discriminate between responders (residual viable cells of 0–33%) and non-responders (34–100%) (Fig. 2), but then, this trend was also evident according to Tl-201 SPECT (Fig. 1). Therefore, Tl-201 SPECT could be a useful adjunct to barium swallow in differentiating responders from non-responders.

In our study, it was difficult to demonstrate that CT can predict therapeutic responses. The disadvantage of CT evaluation in our study was that scanning proceeded with 10 mm collimation and 10 mm image reconstruction that could have rendered measurements of tumor volume inaccurate. However, fibrous tissue or edema located around the tumor can also affect measurements of residual tumors and this may be one explanation for the poor prediction of the pathologic tumor response.[6,7] Furthermore, although Liang et al.[21] reported a new technique for measuring the volume of esophageal cancer, and Griffith et al.[22] applied it to assessing responses to chemotherapy, CT could not predict tumor responses. Although the new technique was quite accurate in measuring tumor volume in the former report, the latter found that the percent decrease in measured volume did not correlate with histological assessment of the therapeutic effect. Although contrast enhancement might be one of the clues to tumor viability, this finding may not always suggest residual tumor. Figures 4 and 5 illustrate representative cases in which it was difficult to evaluate the therapeutic effect with CT alone.

Thallium-201 is a potassium analog that has long been used for myocardial perfusion imaging. Although the mechanism of Tl-201 uptake in tumor cells is not fully understood, it is partially dependent on cellular metabolism and Na^+-K^+ ATPase activity.[23] Thallium-201 uptake is therefore believed to partially reflect the number of viable tumor cells. Thallium-201 scintigraphy has been



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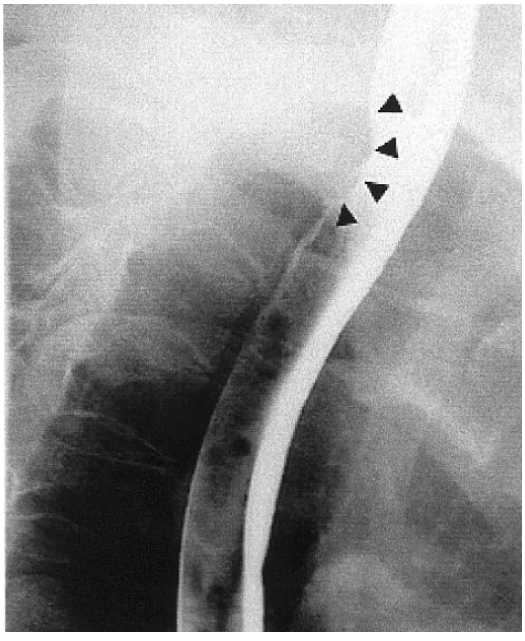

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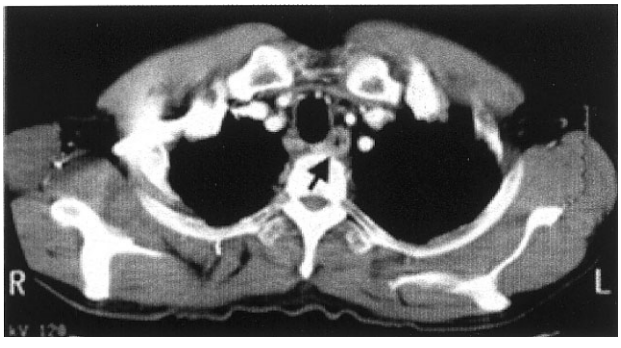

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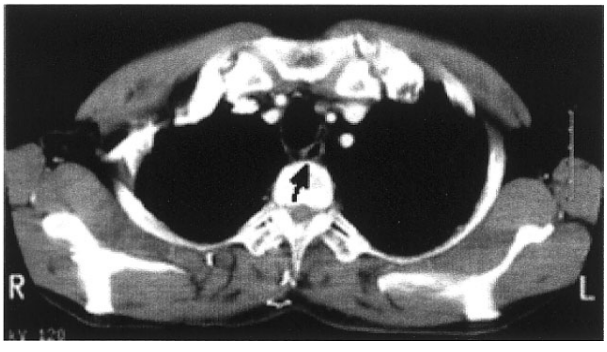

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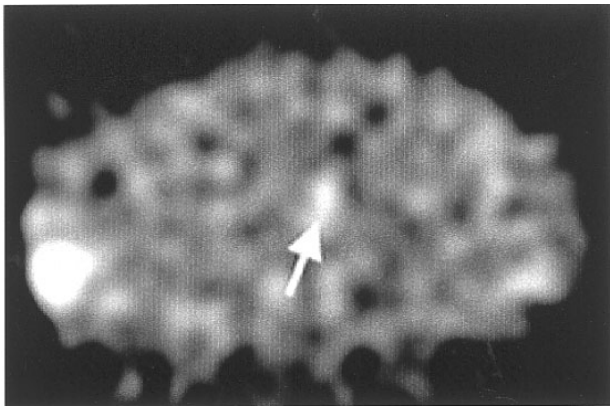

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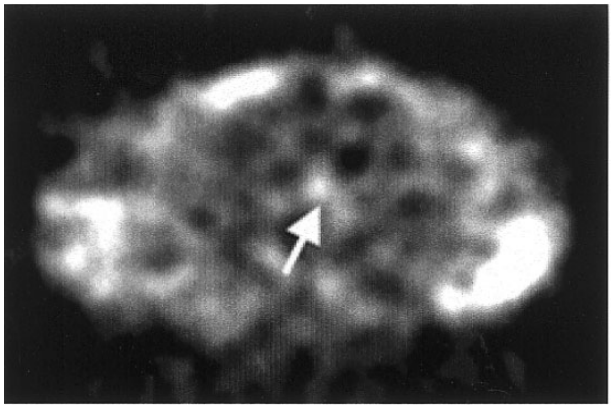

F

Fig. 5 A 55-year-old man with advanced esophageal cancer who had a pathologically poor response (grade 1a) after chemoradiotherapy. A, Pre-chemoradiotherapy barium swallow showed an advanced cancer in the upper third of the esophagus. B, Pre-chemoradiotherapy CT demonstrated a thickened esophageal wall. C, Pre-chemoradiotherapy SPECT showed abnormal uptake in the esophageal cancer. D, Post-chemoradiotherapy barium swallow showed an approximately 50% decrease in tumor volume. E, Post-chemoradiotherapy CT showed that contrast enhancement in a part of esophageal wall was suspected. However, whether residual tumor viability would be present was uncertain because there was no detectable wall thickening at the tumor site. F, Post-chemoradiotherapy SPECT revealed residual uptake at the tumor site.

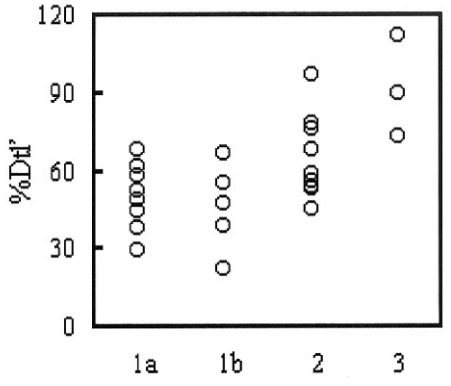

Fig. 6 Comparison between percent decreases in %Dtl′ values and histological response grade. One patient who developed severe esophagitis was excluded in this graph chart.

proven clinically effective in localizing viable tumor tissue in brain tumors and osteosarcoma.[24] In particular, Tl-201 scintigraphy can accurately predict the effect of neoadjuvant chemotherapy in patients with osteosarcoma since the correlation between the percentage of tumor necrosis and the percentage change in the quantitative value of Tl-201 uptake closely correlate.[13,25,26] F-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is a promising tool for evaluating responses to preoperative chemotherapy.[27] In that study, the percent decrease in quantitative values of tumor uptake, as used in the present study, was a useful indicator that facilitated the discrimination of responders from non-responders. The sensitivity and specificity of detecting a response were 100% and 55% respectively in a study of 24 patients with esophageal squamous cell carcinoma by Brucher et al.[28] Weber et al.[29] reported that FDG PET provided a sensitivity of 93% and specificity of 95% for predicting the responses of 40 patients with adenocarcinoma of the esophagogastric junction. In our study, with the borderline of %Dtl separating responders from non-responders set at 35%, the sensitivity and specificity are 79% and 64% respectively. Although Tl-201 SPECT seems less accurate than FDG PET, if PET is unavailable, Tl-201 SPECT may be an effective tool to predict the response in patients with esophageal squamous cell carcinoma. These reports and our report suggested that functional information obtained with nuclear imaging would provide thoracic surgeons with more useful information regarding the therapeutic effect gained before surgery. Again, in the representative cases Tl-201 SPECT was helpful in assessing the therapeutic response.

Published opinions differ concerning the histological assessment of therapeutic effects upon esophageal cancer. In 1994, Mandard et al. proposed a regression grading system that classifies histological responses into five categories according to the relative amounts of residual tumor and fibrosis.[30] This system is widely used and is considered to be a significant predictor of disease-free survival. However, we used the proportion of viable tumor cells because it is recommended by the 'Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus' issued by the Japanese Society for Esophageal Disease. In addition, Dunne et al. recently reported that their regression grading had no significant effect on survival[31] and noted that no reliable predictors of response to treatment currently exist. In this respect, our histological assessment may not correlate with patient prognosis. However, we believe that %Dtl can be reliably compared with the proportion of viable tumor cells, and that Tl-201 SPECT will be a useful adjunct to barium swallow and CT.

The main limitation of this study is that it is retrospective and that only 3 patients had a pathologically complete response (grade 3). Therefore, to provide an accurate indication of the diagnostic performance of Tl-201 SPECT is difficult. In particular, the true negative rate (or negative predictive value) for the assessment of tumor viability was unclear. This is important because a complete pathological response is highly predictive of increased long-term survival.[32] Further studies in larger numbers of patients are needed to clarify the usefulness of Tl-201 SPECT in predicting the therapeutic response in patients with esophageal carcinoma.

Other limitations were that Tl-201 chloride has two inherent shortcomings: physiological uptake around the esophagus (e.g. heart or thyroid) and possible increased uptake by the inflamed esophagus. The former produces artifacts and scatter that can influence the quantitative uptake value. Among 28 patients with positive pre-chemoradiotherapy SPECT results, tumor uptake was easy to visually identify. When uptake in the lesion was faint, CT was very helpful. Therefore, setting the pre-chemoradiotherapy tumor ROI was a simple matter. However, as shown in Figure 4, the ROI probably includes not only tumor activity but also scatter or noise that can result in calculation error and which might be responsible for some overlap of %Dtl between responders and non-responders (Fig. 1). Given that additional counts originating from scatter or noise are equal to counts in the lung, the tumor uptake ratio could be re-defined as (TLR − 1). As a result, the percent decrease in tumor uptake could be re-defined as follows:

$$\%Dtl' = \frac{(TLRpre - 1) - (TLRpost - 1)}{TLRpre - 1} \times 100. \quad \text{Eq. 3}$$

Figure 6 compares %Dtl′ and histological response grade. The %Dtl′ between responders and non-responders slightly overlapped. However, since the influence of photon scattering on tumor uptake is significant near the heart or thyroid, %Dtl′ still cannot be used to evaluate the therapeutic effect. In this regard, a new reconstruction method that reduces scatter and noise, such as transmission dependent convolution subtraction,[33] might be an essential first step before the clinical application of Tl-201

SPECT to chemoradiotherapeutic evaluation. As mentioned above, the most important point of the present paper is that the degree of tumor uptake calculated from SPECT images could partially reflect the viability of esophageal cancer cells.

The uptake of Tl-201 chloride is increased in the inflamed esophagus of patients with radiation-induced esophagitis or gastroesophageal reflux disease (GERD).[34] As mentioned above, one patient had clinical and endoscopic esophagitis after chemoradiotherapy. In such cases, Tl-201 SPECT cannot accurately evaluate the therapeutic response. However, increased uptake over a length of the esophagus that is wider than the tumor area might indicate inflammatory esophagitis.[35]

We could not perform automatic registration between SPECT and CT images because our network system is available only within the nuclear medicine laboratories. In other words, CT data could not be transferred to the nuclear medicine network in Digital Imaging Communications in Medicine (DICOM) format. Picture archiving and communication systems (PACS) that provide radiological images and clinical reports as an electronic medical record, are under development at our hospital, and should soon resolve this issue.

CONCLUSIONS

Thallium-201 SPECT cannot be used for evaluation the response of advanced esophageal carcinoma to preoperative chemoradiotherapy with acceptable accuracy. However, Tl-201 SPECT may have the potential to serve as an adjunct to barium swallow and CT in patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy.

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