



[ Original Article ]

## Diagnostic and clinical usefulness of thin-slice CT/DWI in the diagnosis of esophageal cancer lymph node metastasis

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### Abstract

**Background:** We examined the complementary diagnostic results and clinical usefulness of Diffusion-weighted magnetic resonance imaging (DWI) in addition to the detection of esophageal cancer lymph node metastasis on thin-slice multidetector CT (thin-slice CT).

**Methods:** The subjects included 95 patients of preoperatively esophageal cancer who underwent radical resection. And the following two items were evaluated. (1) The diagnostic results for the lymph nodes were examined in a retrospective study using single thin-slice CT and a combination of DWI and thin-slice CT (thin-slice CT/DWI). (2) The relationship between lymph node metastasis and the survival rate was assessed according to the thin-slice CT/DWI diagnosis.

**Results:** (1) In the retrospective study based on the single thin-slice CT diagnosis, the sensitivity was 38%, the specificity was 80%, and the accuracy was 72%. On thin-slice CT/DWI, the sensitivity was 45%, the specificity was 99%, and the accuracy was 90%. (2) In a comparative study of the existence of positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis, the positive examples of lymph node metastasis were found to be significantly unfavorable.

**Conclusions:** Thin-slice CT/DWI is useful for evaluating the patient's condition and determining the prognosis.

**Key words:** esophageal cancer, lymph node diagnostics, MRI, diffusion-weighted imaging

## I . Introduction

Esophageal cancer is a disease that readily involves lymph node metastasis at the early stage, with lymph node metastasis observed in approximately 10-50% of cases of SM cancer[1].

Since neoadjuvant chemotherapy is recommended for cStage II/III esophageal cancer according to the results of JCOG9907, the pre-therapeutic diagnosis of lymph node metastasis has become more important [2]. Generally, CT, PET and EUS scans are often used to diagnose lymph node metastasis. Although PET scans have excellent specificity, their sensitivity is low due to poor spatial resolution[3]. While EUS displays excellent sensitivity and high specificity, there are restrictions as to which lymph nodes can be evaluated and this technique is not applicable in patients with stenosis[4].

The presence of small metastatic lymph nodes hinders the diagnosis of lymph node metastasis in cases of esophageal cancer. In addition, many of the lymph nodes around the trachea are often inflamed and swollen. Therefore, there are limits to obtaining the lymph node diagnosis based on diameter.

However, conventional modalities for acquiring a qualitative diagnosis, such as PET, have low spatial resolution and are not suitable for assessing small metastatic lymph nodes.

Diffusion-weighted imaging (DWI) of MRI provides functional images and has been applied clinically as a biomarker imaging technique in the domain of cancer treatment in recent years. The ADC value, a diffusion coefficient, correlates with the degree of histological success of CRT for esophageal cancer, and is reported to be useful for determining the therapeutic effects[5]. In addition, it has been demonstrated that the ADC value correlates with the VEGF level[6]. Additionally, compared to PET scans, which offer the same functional images, there is no radioactive exposure and the imaging time is shorter. Furthermore, the output limit based on the resolution is approximately 5 mm, which is superior to that of PET, which displays a resolution of approximately

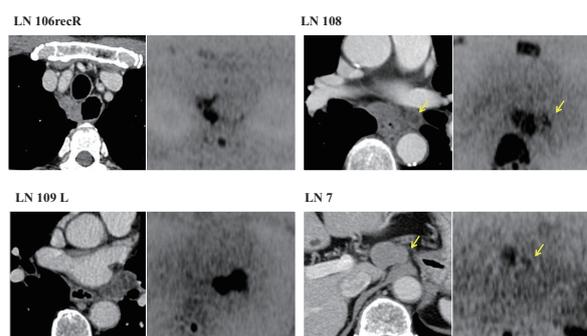


Fig. 1 histologically positive metastases cases with high signals on DWI as well as DWI images of positive lymph node metastases

10 mm. Figure 1 shows actual histologically positive metastases cases with high signals on DWI as well as DWI images of positive lymph node metastases (Fig. 1). In the present study, we examined the complementary diagnostic results and clinical usefulness of DWI in addition to the esophageal lymph node cancer diagnosis obtained using thin-slice CT.

## II . Material and methods

### Study items

#### (1) Retrospective study

- 1 . Metastatic lymph node diagnostic results obtained using single thin-slice CT
- 2 . Metastatic lymph node diagnostic results obtained in combination with DWI (hereinafter thin-slice CT/DWI)

#### (2) The relationship between positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis

- 1 . Comparative study of the existence of positive lymph node metastasis and the survival rate according to the single thin-slice CT diagnosis
- 2 . Comparative study of the existence of positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis
- 3 . In lymph node metastasis-negative group according to the thin-slice CT/DWI diagnosis. Comparative study of the existence of positive lymph node metastasis in the histologically and the survival rate

### Patient characteristics

A total of 95 patients with 99 lesions of preoperatively untreated esophageal cancer who underwent radical resection at our department in the period from August 2007 to August 201. The preoperatively untreated cases included patients who had not undergone preoperative chemotherapy due to having a preoperative diagnosis of Stage I disease or Stage II or III disease resulting from renal dysfunction, age, etc. The average patient age was 67 years, and 82 males and 13 females were included in this study. The background details of the subjects are shown in Table 1.

1. A total of 95 patients were subjects of the retrospective study conducted from August 2007 to October 2013
2. Sixty-five patients were the subjects of the survival rate study conducted from August 2007 to April 2012

### Operative procedure

In general, the operative procedure included right thoracalaparotomy subtotal esophagectomy, posterior longitudinal route gastric tube reconstruction and dissection of three lymph nodes in the neck, chest and abdominal region. Dissection of two lymph nodes (chest and abdominal region) was performed if the patient was diagnosed as being lymph node metastasis-negative based on the preoperative diagnosis of T1b or less lower esophageal cancer and abdominal esophageal cancer. The subjects included 64 patients treated with the dissection of three lymph nodes and 31 patients treated with the dissection of two lymph nodes.

### Diagnostic imaging

Thin-slice CT and MRI scans were obtained prior

to surgery. The imaging conditions were as follows: the imaging range of thin-slice CT extended from the neck to the pelvis, with an MRI diameter of 40~50 cm. Since the imaging range was limited, the presence of swollen lymph nodes was confirmed in advance using CT, such that the lesions fell into this range.

### Thin-slice MD CT imaging

The scanner was the Aquilion One (64 row, TOSHIBA) with the following settings: contrast material, 320 mg/ml, 2.5 ml/kg; delay time, 70 sec; parameter, 140 kVp; 200-250 mA; pitch, 1.3; thickness, 0.5 mm; configuration, 0.625 mm; WW/WL 300/60 HU.

### MRI imaging

The scanner was the Achieva 1.5T Nova Dual (Phillips) with the following settings: coil phased-array coil; sequence, T2WI fast spin echo; TR/TE, 3300/90 ms; 8-mm thick; DWI SENSE-STIR-EPI, b=0,1,000 sec/mm<sup>2</sup>; TR/TE, 10,000/75 ms; 4 mm, gap-1 mm.

### Thin-slice CT diagnosis

The range of lymph nodes for surgical dissection was determined using thin-slice CT, and a short diameter and the contrast effect were confirmed.

### Thin-slice CT/DWI diagnosis

The site was identified using thin-slice CT, and spots that appeared to be lymph nodes at the same site were confirmed on MRI T2WI. A high signal was confirmed on DWI performed at the same level, and the ADC value was measured using the ADC MAP (Fig. 2) for lymph nodes confirmed to have a high signal.

Table 1 95 patients with 99 lesions of preoperatively untreated esophageal cancer who underwent radical resection

Patient Demographics	Variables	Value
Part	Ce/Ut/Mt/Lt/Ae	3/8/40/36/12
Tumor diameter (Ave.)		40
T	pT1/pT2/pT3/pT4	67/11/17/4
N	pN1/pN2/pN3/pN4	57/13/20/2/3
Stage	0/ I / II / III / IV	8/40/25/14/8
Dissection range	2FD/3FD	31/64

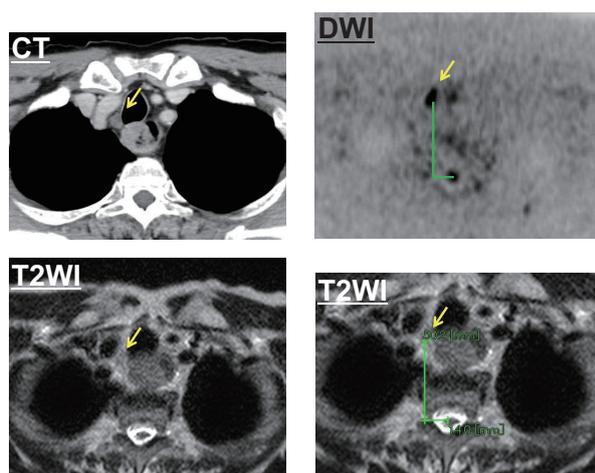


Fig. 2 The site was identified using thin-slice CT, and spots that appeared to be lymph nodes at the same site were confirmed on MRI T2WI. A high signal was confirmed on DWI performed at the same level, and the ADC value was measured using the ADC MAP

### Statistical methods

The Kaplan-Meier method was used for the retrospective study of the presence of metastatic lymph nodes on thin-slice CT and the survival rate based on the detection of metastatic lymph nodes on thin-slice CT/DWI, respectively. In addition, we examined the survival rate in the presence or absence of histological lymph node metastasis in the patients diagnosed as being metastasis-negative on thin-slice CT/DWI using the Kaplan-Meier method.

### Ethical statement

This study is approved by our ethics committee (3032).

Analysis was conducted in consideration of protection of personal information.

We have not obtained informed consent, because this study was retrospective mathematical analysis of medical images.

## III. Results

### (1) Retrospective study

The aforementioned 95 cases were studied, including 4,900 lymph node dissections, of which 128 lesions were found to be histologically metastatic lymph nodes.

A total of 630 lymph nodes (13%) were identifiable on the images, including 115 metastatic lymph nodes (2.3%).

#### 1. Metastatic lymph node diagnostic results obtained with single thin-slice CT

The number of metastatic lymph nodes diagnosed based on the contrast effect on single thin-slice CT is presented as the percentage. In the examination according to a short diameter, the maximum sensitivity + specificity was 6 mm; therefore, the cutoff value was set to 6 mm (Table 2). Based on these findings, the diagnostic criteria for metastasis on single thin-slice CT were a diameter greater than 6 mm or a center with low density surrounded by a contrast effect. We diagnosed as metastasis irrespective of size if there was such contrast effect. The sensitivity was 38%, the specificity was 80%, the positive predictive value was 30%, the negative predictive value was 85% and the correct diagnosis rate was 72% (Table 2).

#### 2. Metastatic lymph node diagnostic results obtained with thin-slice CT/DWI

We next evaluated the diagnostic performance of thin-slice CT/DWI for detecting lymph node metastasis.

First, in order to determine the cutoff value for ADC, a ROC analysis was performed using 64 lymph nodes with high signals confirmed on DWI. A total of 52 cases were found to be histologically metastasis-positive and

Table 2 Diagnosis for each minor axis in thin CT

Min Axis (mm)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Accu (%)
4	82	24	19	86	35
5	61	50	21	85	52
6	38	80	30	85	72
7	25	90	36	84	78

Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, Accu: Accuracy

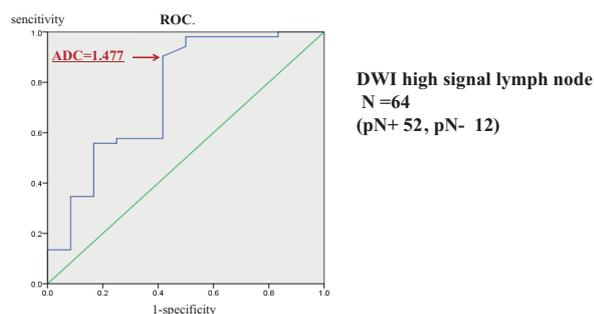


Fig. 3 a ROC analysis was performed using 64 lymph nodes with high signals confirmed on DWI

12 cases were found to be histologically metastasis-negative. The maximum sensitivity + specificity ADC value based on the ROC curve was 1.477 (Fig. 3).

Therefore, the cutoff value for ADC was set to 1.5, and the ADC value for the diagnostic criteria for metastasis on thin-slice CT/DWI was set to less than 1.5. In the retrospective study using these diagnostic criteria, the sensitivity was 45%, the specificity was 99%, the positive predictive value was 90%, the negative predictive value was 89% and the correct diagnosis rate was 90% (Table 3).

Table 3 Diagnosis of lymph node metastasis of esophageal cancer by thin-slice CT/DWI In the lymph nodes identified in the image

	Pathological N +	Pathological N -
<b>Thin-slice CT/DWI N +</b>	52	6
<b>Thin-slice CT/DWI N -</b>	63	509

	Thin-Slice CT/DWI (%)
<b>Sensitivity</b>	45
<b>Specificity</b>	99
<b>Positive Predictive Value</b>	90
<b>Negative Predictive Value</b>	89
<b>Accuracy</b>	90

Table 4 Diagnosis of lymph node metastasis of esophageal cancer by thin-slice CT/DWI In all lymph nodes dissected

	Pathological N +	Pathological N -
<b>Thin-slice CT/DWI N +</b>	52	6
<b>Thin-slice CT/DWI N -</b>	76	4766

	Thin-Slice CT/DWI(%)
<b>Sensitivity</b>	41
<b>Specificity</b>	99.8
<b>Positive Predictive Value</b>	90
<b>Negative Predictive Value</b>	98
<b>Accuracy</b>	98

In the study of 4900 lymph nodes dissected. The sensitivity was 41%, the specificity was 99.8%, the positive predictive value was 90%, the negative predictive value was 98, and the correct diagnosis rate was 98% (Table 4).

(2) Relationship between positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis

1. Comparative study of the existence of positive lymph node metastasis and the survival rate according to the single thin-slice CT diagnosis

In the comparative study of the existence of positive lymph node metastasis and the survival rate obtained using single thin-slice CT, there were no significant differences in the survival rate between the groups found to be positive and negative for lymph node metastasis on single thin-slice CT (Fig. 4a).

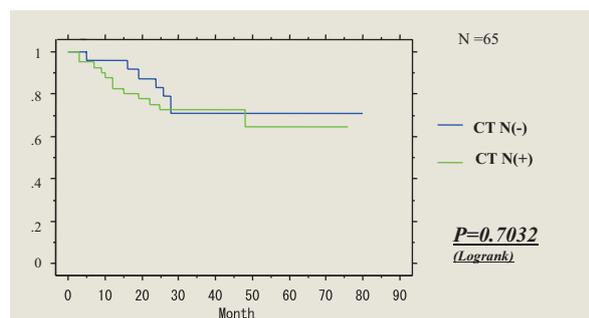
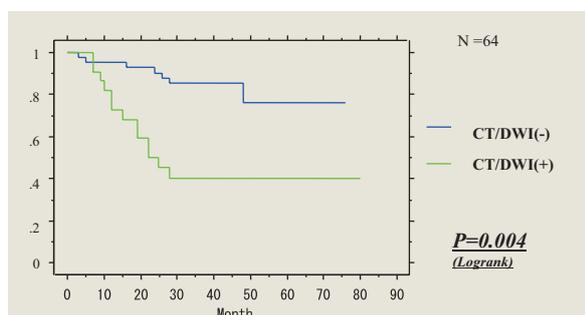
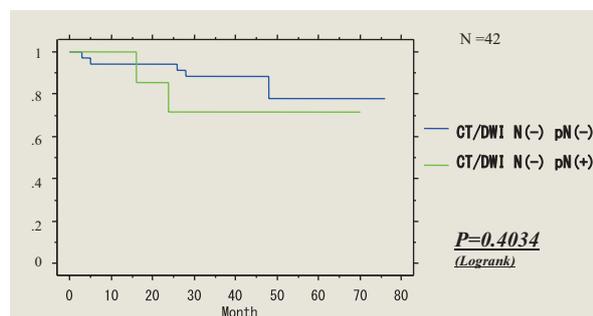
**(a) thin CT N(+) vs. N(-)****(b) thin CT/DWI N(+) vs. N(-)****(c) In thin CT/DWI N(-) Group pN(+) vs. pN(-)**

Fig. 4 Kaplan-Meier analysis

(a) In the comparative study of the existence of positive lymph node metastasis and the survival rate obtained using single thin-slice CT, (b) In the comparative study of the existence of positive lymph node metastasis and the survival rate obtained using thin-slice CT/DWI, (c) In lymph node metastasis-negative group according to the thin-slice CT/DWI diagnosis. Comparative study of the existence of positive lymph node metastasis in the histologically and the survival rate

## 2. Comparative study of the existence of positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis

In the comparative study of the existence of positive lymph node metastasis and the survival rate obtained using thin-slice CT/DWI, the positive examples of lymph node metastasis were found to be significantly unfavorable

compared with the negative examples (Fig. 4b).

## 3. In lymph node metastasis-negative group according to the thin-slice CT/DWI diagnosis. Comparative study of the existence of positive lymph node metastasis in the histologically and the survival rate

In lymph node metastasis-negative group according to the thin-slice CT/DWI diagnosis. Comparative study of the existence of positive lymph node metastasis in the histologically and the survival rate, there were no significant differences in the survival rate based on thin-slice CT/DWI (Fig. 4c).

In Histological lymph node metastasis on thin-slice CT/DWI in the negative cases, the three cases have not recurred for 40 months, 57 months, 70 months, One case survives for 16 months but another disease death, One case died of current illness in 24 month.

## IV. Discussion

### (1) Retrospective study

#### 1. Metastatic lymph node diagnostic results obtained with single thin-slice CT

For the single thin-slice CT diagnosis, the diameter was less than 6 mm; however, the rate of detection of lymph node metastasis based on the contrast effect was 0.5%. In other words, the thin-slice CT diagnoses contained a higher proportion of lesions diagnosed based on diameter than on the contrast effect.

The reason for the insufficient diagnostic performance of single thin-slice CT for detecting lymph node metastasis is that the number of lesions of histological lymph node metastasis exhibiting a large diameter was limited. Even non-metastatic lymph nodes often demonstrate swelling. Therefore, it is difficult to obtain a proper diagnosis taking only the diameter into consideration.

#### 2. Metastatic lymph node diagnostic results obtained with thin-slice CT/DWI

Improvements were observed in all factors of diagnostic performance on thin-slice CT/DWI;

however, the increase in the positive predictive value was particularly remarkable. The increased sensitivity made it possible to diagnose lymph nodes with a small diameter. Nevertheless, we suppose that the sensitivity remained 45% because many metastatic lymph nodes exhibit a low cancer rate. A total of 250 esophageal cancer metastatic lymph nodes were evaluated in our department among esophageal cancer surgery cases treated in the period from 2002 to 2011. Consequently, the rate of histological cancer (in which a pathologist estimated the proportion of cancer cells in the lymph nodes in 10% increments) was 18% for cancer cells accounting for less than 10% of the lymph nodes and 46% for cancer cells accounting for less than 50% of the lymph nodes, and many metastatic lymph nodes were confirmed to contain a low proportion of cancer cells histologically. Therefore, it is extremely difficult to diagnose lymph nodes comprising only a few cancer cells, even if modalities for obtaining a qualitative diagnosis are added. Taking this into consideration, we believe that a sensitivity of 45% is a reasonable result. Furthermore, the increase in the positive predictive value was due to the effects of obtaining an accurate diagnosis and improvements in diagnostic performance achieved by adding a qualitative DWI diagnosis of large non-metastatic lymph nodes. In addition, in the qualitative diagnosis using DWI, the diagnostic accuracy of lymph nodes with a large diameter was high. Hence, this method is useful for excluding the presence of metastasis.

## **(2) Relationship between positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis**

### **1. Comparative study of the existence of positive lymph node metastasis and the survival rate according to the single thin-slice CT diagnosis**

The results for positive lymph node metastasis on thin-slice CT showed no impact on the survival rate.

The thin-slice CT diagnosis is primarily obtained based on the diameter. In other words, a diagnosis obtained according to the diameter is considered to have little clinical significance.

### **2. Comparative study of the existence of positive lymph node metastasis and the survival rate according to the thin-slice CT/DWI diagnosis**

The results for positive lymph node metastasis diagnosed using thin-slice CT/DWI showed that this finding had an impact on the survival rate. Therefore, the detection of lymph node metastasis based on a qualitative DWI diagnosis is believed to have high clinical significance.

### **3. In lymph node metastasis-negative group according to the thin-slice CT/DWI diagnosis. Comparative study of the existence of positive lymph node metastasis in the histologically and the survival rate**

Considering the survival rates regarding single thin-slice CT and thin-slice CT/DWI described above, it is possible that a significant difference was observed in the survival rate because the diagnostic performance of thin-slice CT/DWI is greater. For this reason, the metastasis-negative group was examined using thin-slice CT/DWI. As a result, there were no significant differences in the survival rate with respect to the existence of histological lymph node metastasis on thin-slice CT/DWI in the negative group. In other words, our results suggest that the presence of histologically positive lymph node metastasis on thin-slice CT/DWI in lymph node-negative cases has little clinical significance. This is likely because DWI reflects the cell density; therefore, metastatic lymph nodes containing a low proportion of cancer cells and micro-metastases are less likely to be detected. However, such lymph nodes may be diagnosed if they have a certain diameter and high number of cancer cells. If metastatic lymph nodes with a low proportion of cancer cells and micro-metastases that cannot be identified on DWI are dissected via surgery, it is conceivable that there will be no effect on the survival rate.

We believe that, clinically, obtaining a diagnosis of lymph node metastasis on thin-slice CT/DWI is important, regardless of the existence of histologically positive metastasis.

### Conclusion

The thin-slice CT/DWI protocol examined in this study showed an improvement in the rate of diagnosis of lymph node metastasis. The detection of lymph node metastasis on thin-slice CT/DWI correlates with the survival rate and is useful for assessing the prognosis.

Thin-slice CT/DWI is a simple diagnostic method for obtaining a diagnosis of esophageal lymph node cancer and may also be useful for evaluating the prognosis.

### Authorship contribution

Tuguaki Kouno, Kiyohiko Shuto contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Conflict of interest

There are no financial or other relations that could lead to a conflict of interest

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