

## Clinical significance of SUVmax on preoperative 18F-fluorodeoxyglucose positron emission tomography in patients who underwent R0-esophagectomy for esophageal cancer

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### ABSTRACT

The standardized uptake value (SUV) is a marker of tumor glucose metabolism, detected using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and may reflect tumor aggressiveness. The purpose of this study was to evaluate the clinical significance of maximum SUV (SUVmax) of primary esophageal cancer (EC) lesions. A total of 86 patients with EC who underwent pre-treatment FDG-PET and R0-resection were included in our study. The mean patient age was 65 years, and 87% were men. Histologically, cancers included squamous cell carcinomas, adenocarcinomas, and other tumors in 72, 3, and 11 patients, respectively. Preoperative chemotherapy with or without radiotherapy was performed in 4 and 37 patients, respectively. Measured patient outcomes included the correlation between the SUVmax of the primary EC lesion and clinicopathological factors in patients who did not undergo preoperative treatment (n = 45), and the investigation of relapse-free survival (RFS) according to SUVmax and the relationship between SUVmax and recurrence sites in all patients (n=86). The mean SUVmax was  $8.9 \pm 4.6$ , and SUVmax values significantly correlated with tumor invasion depth and stage. The 5-year RFS for the enrolled patients was 57%, and the RFS of patients with SUVmax < 7.0 was better than that of patients with SUVmax  $\geq 7.0$ , with a marginal difference (p = 0.0892). Lymph node recurrences were significantly more common in patients with SUVmax  $\geq 7.0$ , compared to patients with SUVmax < 7.0. Therefore, the SUVmax value of the primary EC lesion before preoperative treatment may be predictive of RFS and lymph node recurrence.

Keywords: esophageal cancer, PET, prognostic factors

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### INTRODUCTION

The incidence of esophageal cancer (EC) has been increasing. In 2012, approximately 455,800 people were newly diagnosed with EC, and EC caused approximately 400,200 deaths worldwide.<sup>1)</sup>

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Curative resection is a standard treatment for non-metastatic EC, and accurate prognostication facilitates the identification of patients who are at high risk of recurrence and may benefit from adjuvant therapies and surveillance planning. The most important prognostic indicator of EC is stage; however, additional prognostic value might be obtained from other modalities.

<sup>18</sup>F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG-PET) is an imaging modality that evaluates cellular glucose metabolism and provides functional information pertaining to malignant pathological changes.<sup>2,3)</sup> Many studies have investigated the use of a standardized uptake value (SUV) of a primary lesion as a prognostic indicator for patients with EC; however, the results are conflicting.<sup>4-16)</sup> The aim of this study was to clarify the clinical significance of maximum SUV (SUVmax) in patients who underwent R0-esophagectomy for EC.

## MATERIALS AND METHODS

### *Patients and Methods*

A total of 86 patients with EC who underwent a pre-treatment FDG-PET/CT scan, followed by R0-esophagectomy, between April 2006 and December 2014 were enrolled in this study. The patients' mean age was 65 (range: 45–81), and 75 patients were men. There were 72 patients with squamous cell carcinoma, 3 with adenocarcinoma, and 11 with other histological types (adenosquamous carcinoma, basaloid squamous carcinoma, carcinosarcoma, endocrine cell carcinoma, adenoid cystic carcinoma, spindle cell carcinoma, and pCR due to preoperative therapy in 3, 3, 1, 1, 1, 1, and 1 case(s), respectively). The tumor was located in the upper, middle, and lower esophagus in 19, 40, and 27 patients, respectively. A total of 41 patients underwent preoperative treatment, i.e., 37 patients underwent chemotherapy (the most common treatment regimen: CDDP/5-FU), and 4 patients underwent chemoradiotherapy (CDDP/5-FU and 50–60 Gy). Preoperative chemotherapy was commonly performed for patients with clinical stage II or III EC,<sup>17)</sup> and was also performed for patients with cT4 EC. A total of 30 patients received post-operative adjuvant therapy, 28 received chemotherapy (CDDP/5-FU), 1 received radiation therapy, and 1 underwent chemoradiotherapy.

FDG-PET was performed before preoperative treatment or surgery. The Discovery ST Elite system or the Discovery PET/CT 600 Motion system (GE Healthcare, Buckinghamshire England, UK) were used to obtain separate images of CT and PET scan images, which were accurately combined later, using a computer. The scanners had an axial field of view of 50.0 cm and a spatial resolution of 3.3 mm. The whole-body CT scan covered the area from the supraorbital foramen to the femoral region. The imaging test was initiated 40–45 minutes after an intravenous injection of <sup>18</sup>F-fluorodeoxyglucose tracer. Blood glucose levels were within the normal range in all patients. An OSEM reconstruction was used,<sup>18)</sup> and SUVmax was defined as the maximum value of SUV in the entire area of a primary EC.

We classified the pathological factors according to the 2010 UICC classification.<sup>19)</sup> The relationship between SUVmax and pathological tumor invasion depth (T), lymph node metastases (N), and stage were investigated in patients who did not undergo preoperative treatment (n = 45). The patients' medical records were investigated, in order to identify evidence of recurrence. Follow-up data were collected for all survivors, through July 2016. The relationship between SUVmax and relapse-free survival (RFS) was evaluated in all study patients (n=86). In addition, the relationship between SUVmax and sites of recurrence was evaluated. This study was performed retrospectively; therefore, the ethics committee of our hospital did not consider patient consent necessary.

*Statistical analysis*

Categorical variables were compared using the  $\chi^2$  test or Fisher's exact test. Continuous variables are presented as the mean ( $\pm$  SD) and were compared with Student's t test, Mann-Whitney U test, or Kruskal-Wallis test, as appropriate. Survival curves were estimated using the Kaplan-Meier method. The log rank test was employed to determine the differences in survival between the groups. A multivariate analysis was performed for the factors with p values  $< 0.10$  in the univariate analysis. The Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs). RFS was calculated based on the time from the date when preoperative treatment (preoperative chemotherapy or chemoradiotherapy) began or from the date of surgery, for patients who did not undergo preoperative treatment, until the date when recurrence was first identified. Statistical analysis was performed using the JMP software program (version 10.0 for Windows, SAS Institute Inc., Cary, NC, USA), at a significance level of  $p < 0.05$ .

## RESULTS

The patient demographics are presented in Table 1. The mean SUVmax of primary EC was  $8.9 \pm 4.6$  (2.2–22.5), and the SUVmax values significantly correlated with pathological depth of tumor invasion and stage in the 45 patients who did not undergo preoperative therapy (Table 2).

**Table 1** Patient demographics

|  | Total<br>(n=86)          | Patients without<br>preoperative<br>therapy<br>(n=45) | Patients with<br>preoperative<br>therapy<br>(n=41) | P      |
|--|--------------------------|---|--|--------|
| Age<br>(mean $\pm$ SD, range (years))                      | 65.2 $\pm$ 7.0 (45–81)   | 65.8 $\pm$ 8.2 (45–81)                                | 64.6 $\pm$ 5.0 (53–76)                             | 0.4352 |
| Sex (M:F)  | 75:11                    | 39:6  | 36:5   | 0.8746 |
| Histology<br>(SCC <sup>a</sup> : AC <sup>b</sup> : others) | 73:3:10                  | 36:3:6  | 37:0:4   | 0.1984 |
| Location<br>(upper : middle : lower)                       | 19:40:27                 | 11:21:13  | 8:19:14  | 0.8083 |
| Tumor diameter<br>(mean $\pm$ SD, range (mm))              | 44 $\pm$ 25 (0–108)      | 52 $\pm$ 26 (14–108)                                  | 36 $\pm$ 20 (0–90)                                 | 0.0033 |
| Depth of tumor invasion<br>(T1a:T1b:T2:T3:T4a)             | 12:212:19:29:5           | 4:14:7:17:3   | 8:7:12:12:2  | 0.2090 |
| Lymph node metastasis<br>(N0:N1:N2:N3)                     | 31:27:18:10              | 18:13:7:7   | 13:14:11:3   | 0.3686 |
| Stage (I:II:III)   | 25:18:43                 | 14:12:20  | 12:6:23  | 0.3623 |
| SUVmax <sup>c</sup><br>(mean $\pm$ SD, range)              | 8.9 $\pm$ 4.6 (2.2–22.5) | 8.3 $\pm$ 4.6 (2.2–18.5)                              | 9.6 $\pm$ 4.5 (3.3–22.5)                           | 0.1712 |

a) SCC: squamous cell carcinoma, b) AC: adenocarcinoma, c) SUVmax: maximum standardized uptake value

**Table 2** Relationship between SUVmax and clinicopathological factors in 45 patients treated without preoperative therapy

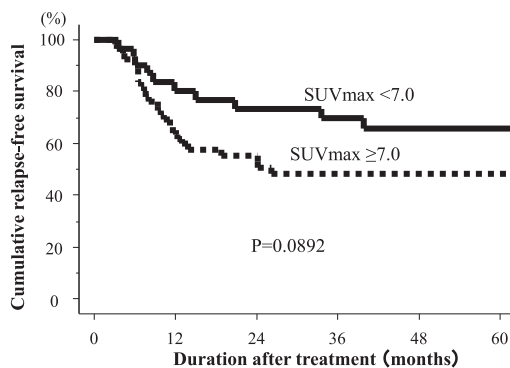
|                             | n  | SUVmax   | p       |
|-----------------------------|----|----------|---------|
| Age                         |    |          |         |
| <65                         | 20 | 8.6±4.6  | 0.6681  |
| ≥65                         | 25 | 8.0±4.7  |         |
| Sex (M : F)                 |    |          |         |
| M                           | 39 | 8.1±4.7  | 0.6266  |
| F                           | 6  | 9.1±4.2  |         |
| Location                    |    |          |         |
| Upper                       | 11 | 6.1±3.6  | 0.3019  |
| Middle                      | 21 | 9.2±5.0  |         |
| Lower                       | 13 | 8.6±4.4  |         |
| Tumor diameter (mm)         |    |          |         |
| <40                         | 18 | 6.9±4.9  | 0.1226  |
| ≥40                         | 27 | 9.1±4.3  |         |
| Depth of tumor invasion (T) |    |          |         |
| pT1a                        | 4  | 4.4±1.4  | <0.0001 |
| pT1b                        | 14 | 5.2±3.6  |         |
| pT2                         | 7  | 6.2±3.2  |         |
| pT3                         | 17 | 11.4±3.5 |         |
| pT4a                        | 3  | 14.1±2.7 |         |
| Lymph node metastasis (N)   |    |          |         |
| pN0                         | 18 | 7.6±5.7  | 0.3683  |
| pN1                         | 13 | 7.8±4.0  |         |
| pN2                         | 7  | 10.1±4.7 |         |
| pN3                         | 7  | 9.1±2.0  |         |
| Stage                       |    |          |         |
| I                           | 13 | 4.9±3.7  | 0.0014  |
| II                          | 12 | 8.4±5.5  |         |
| III                         | 20 | 10.3±3.4 |         |

Bold values indicate statistical significance ( $p < 0.05$ ).

The median follow-up period of the patients in this study was 34.8 months (interquartile range: 7.5–62.1 months), and the 5-year RFS was 57%. When the differences in RFS were examined by bisecting the SUVmax within an interval, between 3.0 and 14.0, the largest difference in RFS between the two groups was observed at a SUVmax of 7.0. The RFS for patients with SUVmax  $\geq 7.0$  was lower than that of patients with SUVmax  $< 7.0$ , and the 5-year RFS was 48% and 66% in patients with SUVmax values  $\geq 7.0$  and  $< 7.0$ , respectively ( $p = 0.0892$ , Fig. 1). Although similar results were observed in a subgroup analysis of the 45 patients who did not undergo preoperative treatment ( $p = 0.0698$ ), there was little difference for the 41 patients who received preoperative treatment ( $p = 0.7633$ ) (Fig. 2(a), (b)).

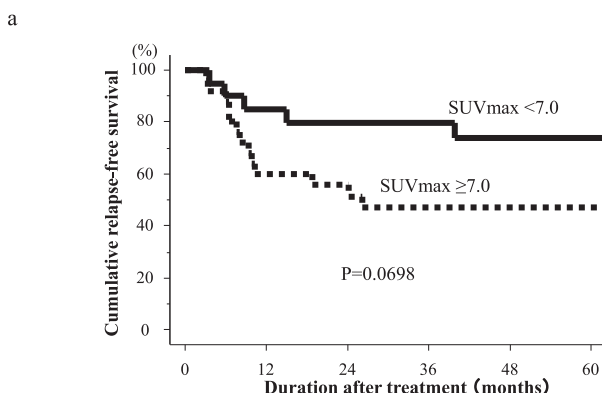
The univariate analysis of the relapse-free survival, based on clinicopathological factors and SUVmax, showed that tumor diameter, depth of invasion, lymph node metastasis, stage, and

Significance of esophageal cancer SUV



| Number at risk |    |  |    |    |
|----------------|----|--|----|----|
| SUVmax <7.0    | 31 |  | 18 | 13 |
| SUVmax ≥7.0    | 55 |  | 17 | 14 |

**Fig. 1** Kaplan-Meier survival curves for relapse-free survival of patients who underwent R0 resection for esophageal cancer based on the maximum value of SUV (SUVmax) in the primary tumor

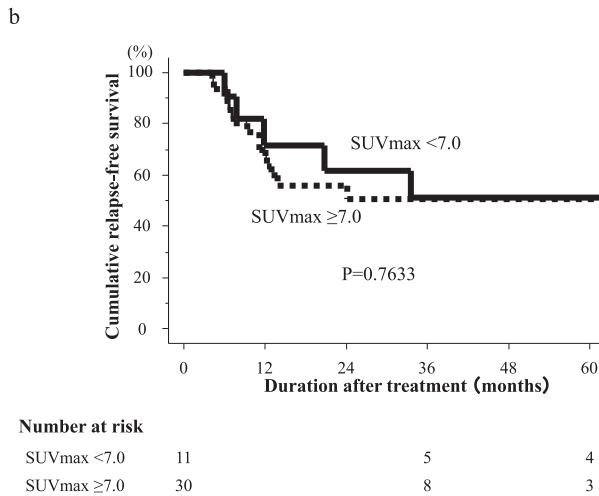


| Number at risk |    |  |    |   |
|----------------|----|--|----|---|
| SUVmax <7.0    | 20 |  | 13 | 9 |
| SUVmax ≥7.0    | 25 |  | 9  | 8 |

**Fig. 2(a)** Kaplan-Meier survival curves for relapse-free survival of patients who underwent R0 resection for esophageal cancer without preoperative therapy

histology significantly correlated with RFS. The subsequent multivariate analysis showed that stage and histology were significantly associated with RFS (Table 3). A subgroup analysis for patients with or without preoperative therapy showed similar results (data not shown).

Disease recurrence was detected in 37 patients during the observation period. The sites of recurrence were the lymph nodes, organs (lungs, liver, or bones), or peritoneum in 26, 20, and 3 patients, respectively. Patients with a SUVmax ≥ 7.0 had a significantly higher risk of lymph node recurrence than patients with a SUVmax < 7.0 (relative risk = 2.37; p = 0.0325, Table 4).



**Fig. 2(b)** Kaplan-Meier survival curves for relapse-free survival of patients who underwent R0 resection for esophageal cancer with preoperative chemo- or chemoradiotherapy

**Table 3** Relapse-free survival (RFS) according to the clinicopathological factors

|                         |                 | Univariate analysis |                   | Multivariate analysis |                         |        |
|-------------------------|-----------------|---------------------|-------------------|-----------------------|-------------------------|--------|
|                         |                 | 5-y RFS (%)         | p                 | Hazard ratio          | 95% confidence interval | p      |
| Age                     |                 |                     |                   |                       |                         |        |
|                         | <65 (n=41)      | 52.2                | 0.5444            |                       |                         |        |
|                         | ≥65 (n=45)      | 55.0                |                   |                       |                         |        |
| Sex (M : F)             |                 |                     |                   |                       |                         |        |
|                         | M (n=75)        | 53.2                | 0.6297            |                       |                         |        |
|                         | F (n=11)        | 62.3                |                   |                       |                         |        |
| Location                |                 |                     |                   |                       |                         |        |
|                         | upper (n=19)    | 50.4                | 0.3597            |                       |                         |        |
|                         | middle (n=40)   | 49.0                |                   |                       |                         |        |
|                         | lower (n=27)    | 72.9                |                   |                       |                         |        |
| Tumor diameter (mm)     |                 |                     |                   |                       |                         |        |
|                         | <40 (n=42)      | 67.4                | <b>0.0158</b>     | 1                     | 0.61–2.79               | 0.5126 |
|                         | ≥40 (n=44)      | 42.2                |                   |                       |                         |        |
| Depth of tumor invasion |                 |                     |                   |                       |                         |        |
|                         | pT1 (n=33)      | 77.5                | <b>0.0009</b>     |                       |                         |        |
|                         | pT2,3,4a (n=53) | 39.6                |                   |                       |                         |        |
| Lymph node metastasis   |                 |                     |                   |                       |                         |        |
|                         | pN0 (n=31)      | 78.2                | <b>&lt;0.0001</b> |                       |                         |        |
|                         | pN1 (n=27)      | 62.0                |                   |                       |                         |        |
|                         | pN2 (n=18)      | 16.2                |                   |                       |                         |        |
|                         | pN3 (n=10)      | 30.0                |                   |                       |                         |        |

## Significance of esophageal cancer SUV

|                      |        |      |                   |      |            |               |
|----------------------|--------|------|-------------------|------|------------|---------------|
| Stage                |        |      |                   |      |            |               |
| I                    | (n=25) | 86.7 |                   | 1    |            |               |
| II                   | (n=18) | 63.3 | <b>&lt;0.0001</b> | 3.44 | 0.88–16.74 | 0.0763        |
| III                  | (n=43) | 33.0 |                   | 8.91 | 2.70–40.94 | <b>0.0001</b> |
| Histology            |        |      |                   |      |            |               |
| SCC <sup>a)</sup>    | (n=72) | 57.7 |                   | 1    |            |               |
| AC <sup>b)</sup>     | (n=3)  | 0.0  | <b>0.0023</b>     | 6.10 | 1.38–19.35 | <b>0.0211</b> |
| others               | (n=11) | 46.7 |                   | 2.03 | 0.67–5.10  | 0.1916        |
| Preoperative therapy |        |      |                   |      |            |               |
| no                   | (n=45) | 58.5 |                   |      |            |               |
| yes                  | (n=41) | 49.7 | 0.5129            |      |            |               |
| SUVmax <sup>c)</sup> |        |      |                   |      |            |               |
| <7.0                 | (n=31) | 65.8 |                   | 1    |            |               |
| ≥7.0                 | (n=55) | 48.4 | 0.0892            | 0.86 | 0.37–2.16  | 0.7399        |

Bold values indicate statistical significance (p<0.05).

a) SCC: squamous cell carcinoma, b) AC: adenocarcinoma, c) SUVmax: maximum standardized uptake value

**Table 4** Relationship between SUVmax<sup>a)</sup> and recurrence sites

| SUVmax <sup>a)</sup> | Lymph node |     |               | Organ |     |        | Peritoneum |     |        |
|----------------------|------------|-----|---------------|-------|-----|--------|------------|-----|--------|
|                      | (-)        | (+) | p             | (-)   | (+) | p      | (-)        | (+) | p      |
| <7.0                 | 26         | 5   | <b>0.0325</b> | 24    | 7   | 0.9114 | 29         | 2   |        |
| ≥7.0                 | 34         | 21  |               | 42    | 13  |        | 54         | 1   | 0.2609 |

Bold values indicate statistical significance (p<0.05)

a) SUVmax: maximum standardized uptake value

## DISCUSSION

This study evaluated the prognostic significance of SUVmax in patients who underwent R0-esophagectomy for EC and revealed that patients with a SUVmax ≥ 7.0 tended to have a lower RFS and a significantly higher risk of lymph node recurrence than patients with a SUVmax < 7.0.

Compared to normal cells, cancer cells are characterized by active glycolytic pathways and increased expression of plasma membrane glucose transporter proteins, which facilitate glucose uptake. The uptake of the radiolabeled glucose analog FDG by cells throughout the body is similar to the uptake of glucose. FDG accumulates in cells, without being further metabolized, after phosphorylation. Thus, the accumulation of FDG is observed in tissues with an active glucose metabolism, such as cancer cells, and the visualization of this accumulation is used for detecting pathological changes. The FDG accumulation rates in tissues is quantified as SUVs.

Previous reports have associated high SUVs in the primary tumor with greater depths of tumor invasion and higher incidences of lymph node metastases.<sup>5,8,9,12)</sup> In our study, patients with deeper tumor invasion and higher tumors stages had higher SUVmax values. In addition, the RFS in patients with a SUVmax ≥ 7.0 tended to be lower than that in patients with a SUVmax < 7.0. However, the relationship between SUVmax and RFS in patients with preoperative treatment was weak, which may be due to down-staging during preoperative treatment. These findings are consistent with those of a previous study by Swisher *et al.*<sup>7)</sup>

Several studies have reported that high SUVs are associated with poor RFS or overall survival (OS) of patients with EC;<sup>4-12)</sup> however, some studies have also shown no correlation between SUV and RFS or OS.<sup>13-16)</sup> The divergence of these results may be due to the different assessment methods that are used for SUV. Since SUVmax represents the value of 1 voxel and does not reflect the glucose metabolism of the entire tumor, SUVmax can be high even in situations when only some of the tissue has high glucose metabolism. On the other hand, metabolic tumor volume (MTV) is an indicator that reflects the size of the tissue that has a high rate of glucose metabolism. Total lesion glycolysis (TLG), which is the product of the mean SUV and MTV, reflects glucose metabolism of the entire tumor.<sup>16)</sup>

Our study showed that the risk of lymph node recurrence in patients with a SUVmax  $\geq 7.0$  was significantly higher than that in patients with a SUVmax  $< 7.0$ , although there were no significant associations between SUVmax and lymph node metastases in patients who did not receive preoperative treatment. Therefore, a high SUV may indicate the presence of lymphatic spread, which cannot be controlled by surgery.

We acknowledge that our study has several limitations. First, this was a retrospective study, which was conducted at a single institution, and the number of patients was limited, which inhibits generalization of our results and the robustness of our conclusions. It will be necessary to conduct a multi-institutional SUV assessment study that includes a large number of patients to confirm our results. Second, the present study included patients with several kinds of EC histology, and SUVmax of the primary tumor may be related to the tumor histology. Third, few patients underwent a preoperative PET scan after preoperative chemotherapy/ chemoradiotherapy, due to the high cost of FDG-PET. Therefore, we were unable to examine the relationship between SUVmax changes before and after preoperative treatment, or the relationship between post-neoadjuvant therapy preoperative SUVmax and RFS. Previous reports have indicated that patients who experience decreased SUVs after preoperative treatment have favorable prognoses.<sup>20-22)</sup>

In conclusion, the SUVmax of EC that is obtained from FDG-PET, before esophagectomy, may serve as an indicator of RFS and lymph node recurrence. The results of our study have important clinical relevance, with respect to preoperative treatment and postoperative follow-up planning.

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