



## Prognostic significance of venous invasion and maximum standardized uptake value of $^{18}\text{F}$ -FDG PET/CT in surgically resected T1N0 esophageal squamous cell carcinoma

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### Abstract

**Background:** The purpose of this study was to analyze the risk factors of recurrence in patients with early stage esophageal squamous cell carcinoma (ESCC).

**Methods:** We retrospectively analyzed the medical records of 190 patients with confirmed T1N0M0 ESCC after curative esophagectomy. The following potential prognostic factors for recurrence were investigated: age, sex, pathologic T category, tumor location, differentiation grade, tumor size, venous invasion, angiolymphatic invasion, perineural invasion and the maximum standardized uptake value (SUVmax) of the primary tumor.

**Results:** There were 174 male and 16 female patients with a median age of 66.0 years (range, 42.0–79.0 years). The pathologic status of the surgically resected ESCCs was T1a in 93 patients (48.9%) and T1b in 97 patients (51.1%). The median number of dissected lymph nodes was 35 (range, 10 to 86), and all lymph nodes were negative for tumors. The multivariate analysis showed presence of venous invasion [HR (hazard ratio), 11.433;  $P < 0.001$ ] and SUVmax  $\geq 3.2$  (HR, 2.830;  $P = 0.011$ ) as independent risk factors for recurrence. The 5-year recurrence-free survival (RFS) was 25.0% for patients with venous invasion and 78.9% for those without ( $P < 0.001$ ). The 5-year RFS was 67.1% for patients with an SUVmax  $\geq 3.2$  and 81.5% for those with an SUVmax  $< 3.2$  ( $P = 0.003$ ).

**Conclusions:** Venous invasion and high SUVmax could be important prognostic factors coupled with the TNM staging system, in patients with early stage ESCC.

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**Keywords:** Esophageal neoplasms; Esophagectomy; Positron-emission tomography; Recurrence

### Introduction

Lymph node metastasis is considered one of the most important prognostic factors in localized esophageal cancer.<sup>1</sup> The long-term survival of patients with esophageal cancer remains poor, with a 5-year survival rate of only

22.8% for patients with nodal disease and 41.3% for those without.<sup>2</sup> Although, multimodal therapy has been developed for localized esophageal cancer, surgical resection is the best curative option that can ensure long-term survival for patients with early stage esophageal squamous cell carcinoma (ESCC).<sup>3–5</sup> However, recurrence after curative esophagectomy will eventually develop in approximately 20% of these patients, which is the major cause of death.<sup>6</sup>

Currently, along with lymph node metastasis, histopathological parameters such as the depth of invasion, cancer

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location, histologic grade, and the presence of distant metastasis are the main prognostic determinants proposed by the 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system.<sup>7</sup> In addition, various clinicopathologic parameters other than the TNM stage, such as tumor size, venous invasion, angiolymphatic invasion, perineural invasion, and the maximum standardized uptake value (SUVmax) of the primary tumor, have also been reported to be associated with the prognosis, supporting the notion that there is a great deal of heterogeneity in the prognosis of patients with ESCC.

Thus, identifying the patients within the subgroup who are at high risk for tumor recurrence may help to predict long-term prognosis and to identify those who may benefit from perioperative treatment and effective surveillance. In this study, we aimed to identify the clinicopathologic factors other than the TNM system that predicts postoperative recurrence after curative resection for early stage ESCC.

## Materials and methods

This study was approved by the Institutional Review of Board at the National Cancer Center (protocol number: NCC 2014-2012), and the requirement for patient consent was waived due to the retrospective nature of this study.

The medical records of 786 consecutive patients with esophageal cancer who underwent surgical resection in our hospital, between August 2001 and May 2015 were reviewed. Demographic characteristics, operative details, pathologic findings, adjuvant treatment, and follow-up data for survival and recurrence were obtained through medical records, telephone interviews and the database of the National Health Insurance Service. Patients were included in this study if they had (1) histologically proven ESCC with complete transthoracic esophagectomy and lymph node dissection and (2) pathologic-staging T1N0M0 disease according to the 7th edition of the AJCC TNM staging system.<sup>7</sup> Patients who received adjuvant chemotherapy were excluded ( $n = 2$ ). We identified 190 patients with pT1N0M0 ESCC who met these criteria and were enrolled in the study. Each patient underwent esophagogastroduodenoscopy with biopsy, endoscopic ultrasonography, chest and abdominal computed tomography (CT), bronchoscopy, and 18F-fluorodeoxyglucose positron emitted tomography (FDG-PET)/CT to determine preoperative staging.

## Surgical approach

All patients underwent transthoracic esophagectomy with conventional two- or three-field lymphadenectomy without neoadjuvant treatment. The Ivor-Lewis procedure or the three-hole (modified McKeown) operation, based on the tumor location, was the standard procedure for esophagectomy at our hospital. The colon was used as an alternative

conduit when the stomach was unavailable. The surgical approach included an abdominal lymphadenectomy and an extended en bloc mediastinal lymphadenectomy in all patients. For patients with upper esophageal carcinoma, cervical lymphadenectomy was routinely performed.<sup>8</sup>

## FDG-PET/CT protocol

FDG-PET/CT was performed using a dedicated PET/CT scanner (Discovery LS; GE Healthcare or Biograph LSO; Siemens Medical Systems). Patients with blood glucose levels lower than 6.67 mmol/l (120 mg/dl) were injected intravenously with 7.4 MBq/kg of FDG after fasting for at least 8 h, and then PET/CT scan was performed 60 min after injection. Low-dose non-contrast CT images of 2 to 4 mm sections for attenuation correction and localization of lesions identified by PET were obtained from the skull to the mid-thigh of each patient using a standard protocol. The SUV of a lesion was obtained by manual placement of regions of interest around the lesion, and the most prominent SUV visible in the scanned body (SUVmax) within a region of interest was used to minimize partial-volume effects.

## Histopathologic reviews

The histologic slides were reviewed by dedicated pathologist (L.G.K) according to the 7th edition of the AJCC TNM staging system.<sup>7</sup> The pathologic features recorded included the histologic type of the tumor, the depth of invasion, nodal status, the histologic grade of the tumor, tumor size, the presence of venous invasion, angiolymphatic invasion, and perineural invasion. Venous invasion was defined as the presence of tumor cell in the sizable veins with thick walls containing smooth muscle.<sup>9</sup> (Fig. 1). Angiolymphatic invasion was defined as the presence of tumor cell in the thin walled vessels containing little or no muscle, without

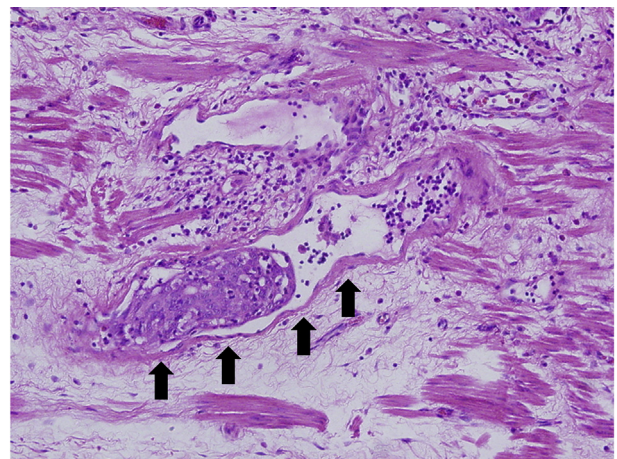


Figure 1. Invading tumors in the submucosal veins with thick or thinned smooth muscle layer (HE, X200). Arrows indicate smooth muscle layer of variable thickness.

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