# Clinical parameters associated with pathologic complete response after neoadjuvant chemoradiotherapy followed by surgery in locally advanced thoracic esophageal squamous cell carcinoma

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# ABSTRACT

## Clinical parameters associated with pathologic complete response after neoadjuvant chemoradiotherapy followed by surgery in locally advanced thoracic esophageal squamous cell carcinoma

***Purpose:*** Neoadjuvant chemoradiotherapy (nCRT) followed by surgery has emerged as a standard treatment strategy for locally advanced esophageal cancer. Pathologic complete response (pCR) after nCRT is associated with improved survival outcomes; however, the factors predicting pCR remain elusive. In this study, we investigated the correlation between pCR and clinical outcomes and identified clinicopathological predictors of pCR in patients with locally advanced esophageal squamous cell carcinoma (ESCC) who underwent nCRT followed by surgery.

***Materials and Methods:*** We assessed 103 patients with ESCC who underwent nCRT and subsequent surgical resection between January 2011 and March 2024. Patients with tumors located in the cervical esophagus or with distant metastases were excluded. To assess the therapeutic effect of nCRT, gross and metabolic changes in the primary tumor and metastatic lymph nodes were evaluated in pre-CRT and post-CRT, but preoperative, images. Overall, 74 patients underwent pre- and post-CRT positron-emission tomography/computed tomography and were included in the metabolic change analysis. Factors associated with pCR were assessed using logistic regression analysis.

***Results:*** After nCRT and subsequent surgical resection, pCR was achieved in 31 patients (30.1%). Age (odds ratio [OR] 1.083, 95% confidence interval [CI] 1.016–1.155), clinical T stage (OR 0.303, 95%CI 0.104–0.879), clinical N stage according to the Japan Esophageal Society (JES) 11$^{th}$ edition (OR 0.260, 95%CI 0.094–0.719), and percent change in tumor volume (OR 1.024, 95%CI 1.001–1.047) were associated with the likelihood of pCR. However, achieving pCR was not associated with overall or recurrence-free survival in this study. In the metabolic analysis group, clinical N stage according to the JES 11$^{th}$ edition (OR 0.251, 95%CI 0.082–0.766) and preoperative metabolic tumor volume (OR 0.892, 95%CI 0.800–0.994) were identified as independent factors associated with pCR.

***Conclusion:*** Age, clinical T stage, tumor volume reduction, and clinical N stage based on the JES 11th edition criteria were associated with achievement of pCR. A lower preoperative metabolic tumor burden also increased the likelihood of achieving pCR. However, further studies are required

to elucidate these prognostic factors.

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Key words: chemoradiotherapy, esophageal cancer, pathologic complete response, positron-emission tomography/computed tomography

# I. INTRODUCTION

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide [1]. Surgery has long been the primary treatment option for patients with resectable esophageal cancer; however, the efficacy of surgery alone remains unsatisfactory. Furthermore, because most patients are diagnosed when the disease has advanced or has reached an unresectable stage, the use of combined treatment strategies to improve treatment outcomes has been studied [2].

Approximately 10 years ago, the multicenter randomized controlled CROSS trial compared neoadjuvant chemoradiotherapy (nCRT) followed by surgery with surgery alone for esophageal cancer. The study showed an improvement in overall survival (OS) when nCRT was followed by esophagectomy as compared to esophagectomy alone; this outcome remained consistent in long-term follow-up data, with a 10-year OS rate of 38% versus 25% with esophagectomy alone [3-5]. Therefore, many guidelines recommend nCRT followed by surgery as the standard treatment for resectable localized advanced esophageal cancer [6, 7].

The rate of pathologic complete response (pCR), defined as the absence of cancer cells in both the primary tumor and lymph nodes (LNs) in patients with esophageal cancer who undergo nCRT, is approximately 25% [8, 9]. In the CROSS trial, pCR was achieved in 49% of patients with squamous cell carcinoma (SCC) and in 23% of patients with adenocarcinoma [3-5]. Additionally, patients who attained pCR demonstrated improved survival as compared to those with a lower treatment response [8, 9]. However, even though several studies have attempted to predict which patients will achieve a pCR, a definitive predictive clinicopathological feature remains elusive.

Hence, this study aimed to verify the association between pCR and clinical outcomes and sought to identify the clinicopathological predictors of pCR among patients with locally advanced thoracic esophageal SCC (ESCC) who were treated with nCRT followed by surgery.

# II. MATERIALS AND METHODS

## 2.1. Patient population

We retrospectively reviewed 188 patients with ESCC who underwent nCRT between January 2011 and March 2024. Only patients who completed CRT followed by surgical resection were included in the study. Patients with tumors located in the cervical esophagus or with distant metastases were excluded. We included patients with supraclavicular LN (SCL) metastasis, classified as distant LNs according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8$^{th}$ edition classification, as well as those with non-regional

LN metastasis that could be treated within the same radiation field as the primary lesion and regional LNs. A total of 103 eligible patients were identified. Clinical staging was assessed based on two guidelines: the AJCC/UICC 8th edition and the Japan Esophageal Society (JES) 11th edition [10, 11]. This study was approved by the institutional review board of Severance Hospital (4–2024–0961).

## 2.2. Treatment

All patients underwent intensity-modulated radiation therapy (RT). Most patients received concurrent chemotherapy with either 5-fluorouracil/cisplatin (38/103, 36.9%) or paclitaxel/carboplatin (43/103, 41.7%), with a total radiation dose of 44–44.1 Gy delivered in 20–21 fractions. The radiation target volumes were defined as follows: gross tumor volume (GTV), encompassing the primary tumor and regional LNs identified via positron emission tomography (PET)/computed tomography (CT); clinical target volume (CTV), including the GTV plus a margin of at least 4 cm longitudinally and 1 cm radially; and planning target volume (PTV), which added a 0.3-cm margin to both the GTV and CTV (defined as PTV1 and PTV2, respectively). A dose of 44–44.1 Gy was prescribed for PTV1, whereas PTV2 received 37.8–44 Gy, both using a simultaneous integrated boost. Daily pretreatment imaging with cone-beam CT was performed for precise position correction before each fraction was delivered.

Approximately 5–8 weeks after the completion of nCRT, all patients underwent esophagectomy and LN dissection, with curative intent.

## 2.3. Gross tumor metrics in CT analysis

All primary tumors and involved LNs were delineated on pre- and post-CRT scans using MIM software (Mim Software Inc., Cleveland, OH, USA). A region-of-interest (ROI) was contoured from the pre- and post-CRT contrast-enhanced CT images. The ROI included the primary esophageal lesion and regional metastatic LNs. For primary lesions, the largest axial diameter, longitudinal tumor length, and tumor volume were measured, whereas for regional LNs, the largest axial diameter and tumor volume were measured. Changes in these measurements between the pre- and post-CRT CT scans were analyzed.

## 2.4. Metabolic tumor metrics in PET/CT analysis

PET/CT was performed using a Biograph TruePoint 40 PET/CT scanner (Siemens Healthcare, Erlangen, Germany). Before injection of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), every

patient fasted for at least 6 h, and their plasma glucose levels were maintained at < 140 mg/dL. $^{18}$F-FDG was injected intravenously at a dosage of 5.5 MBq/kg of body weight. After tracer uptake time (mean 56 ± 4 min), patients were subjected to PET/CT imaging. The patients were placed in a supine position with their arms facing up. Images were acquired from the skull base to the proximal thigh.

Overall, 74 patients underwent pre- and post-CRT PET/CT and were included in the metabolic change analysis. To evaluate metabolic tumor metrics in PET, primary tumor and metastatic LNs were delineated as ROIs on pre- and post-CRT PET/CT using the fixed absolute threshold method. The cutoff was set based on the most used value, the standardized uptake value (SUV) of 2.5 [12], and the adjacent normal organ structure was manually corrected. The parameters obtained for the PET analysis were SUVmax, mean SUV, metabolic tumor volume (MTV), and total lesion glycolysis (TLG). The SUVmax was defined as the maximum active concentration (injected dose/body weight) of FDG in the tumor. SUVmean was defined as the mean concentration (injected dose/body weight) of FDG in the tumor. MTV was calculated automatically using the software by summing the area with each two-dimensional transverse tumor outline and multiplying the value by the corresponding slice thickness. TLG was calculated by multiplying the SUVmean with the MTV.

### 2.5. Statistical analysis

The association between included factors and pCR was evaluated with Fisher's exact test or the $\chi^2$ test for categorical parameters and the *t*-test for continuous parameters. Univariate and multivariate analyses were performed using a logistic regression model to examine the association between clinicopathological factors and pCR. Odds ratios (ORs) and 95% confidence intervals (CIs) were also determined. Variables were selected for inclusion in multivariate analysis based on a p value significance of ≤0.1 in univariate analysis. The final model for the dataset was obtained by using the backward Wald stepwise selection method. OS was defined as the time from the date of surgery to death from any cause or to last follow-up. Recurrence-free survival (RFS) was defined as the time from the date of surgery until disease recurrence or death. Survival curves were evaluated using the Kaplan–Meier method. *P*-values less than 0.05 were considered statistically significant. Analyses were conducted using IBM SPSS version 25.0 (SPSS, Chicago, IL, USA).

## III. RESULTS

### 3.1. Patient characteristics

Overall, 103 patients who underwent nCRT followed by complete surgical resection of ESCC were included in this study. Table 1 shows all patient baseline and treatment characteristics. Most patients

(97.1%) had tumors located in the mid-to-lower thoracic region; 75.8% had a clinical T stage of T3 or higher, and 95.1% had regional LN involvement. Based on the AJCC/UICC 8th edition, 38 patients were classified as having stage IV disease. Among them, 24 patients were classified as stage IV due to SCL metastasis, and three patients had distant LN metastasis (two had abdominal para-aortic LN metastasis, and one had bilateral hilar LN metastasis). The most used chemotherapy regimens were paclitaxel plus carboplatin and 5-fluorouracil plus cisplatin, with a median total radiation dose of 44.1 Gy (range: 40–44.1 Gy).

**Table 1. Patient baseline and treatment characteristics**

| Characteristics | No. | % |
|---|---|---|
| Age, years (median, range) | 63 (31–77) | |
| Sex | | |
| Male | 86 | 83.5 |
| Female | 17 | 16.5 |
| Site | | |
| Upper thoracic (UI 20–25 cm) | 3 | 2.9 |
| Middle thoracic (UI 25–30 cm) | 46 | 44.7 |
| Lower thoracic (UI 30–40 cm) | 54 | 52.4 |
| Histological grade | | |
| Well differentiated | 6 | 5.8 |
| Moderately differentiated | 73 | 70.8 |
| Poorly differentiated | 12 | 11.7 |
| Unknown | 12 | 11.7 |
| Clinical T stage | | |
| T1 | 9 | 8.7 |
| T2 | 16 | 15.5 |
| T3 | 69 | 67.1 |
| T4 | 9 | 8.7 |
| Clinical N stage (AJCC/UICC 8th edition) | | |
| N0 | 5 | 4.9 |
| N1 | 40 | 38.8 |
| N2 | 50 | 48.5 |
| N3 | 8 | 7.8 |
| Clinical N stage (JES 11th edition) | | |
| N0 | 5 | 4.9 |

| | | |
|---|---|---|
| N1 | 22 | 21.3 |
| N2 | 49 | 47.6 |
| N3 | 17 | 16.5 |
| N4 | 10 | 9.7 |
| Stage (AJCC/UICC 8th edition) | | |
| I | 4 | 3.9 |
| II | 10 | 9.7 |
| III | 51 | 49.5 |
| IV | 38 | 36.9 |
| Stage (JES 11th edition) | | |
| I | 0 | 0 |
| II | 14 | 13.6 |
| III | 72 | 69.9 |
| IV | 17 | 16.5 |
| Chemotherapy regimen | | |
| Paclitaxel/carboplatin | 43 | 41.7 |
| 5-fluorouracil/cisplatin | 38 | 36.9 |
| Capecitabine/cisplatin | 8 | 7.8 |
| Pembrolizumab+ paclitaxel/carboplatin | 13 | 12.6 |
| Pembrolizumab+ capecitabine/cisplatin | 1 | 1 |
| Total radiation dose (Gy), (median, range) | 44.1 (40–44.1) | |
| Total radiation fractions, (median, range) | 21 (20–21) | |
| Time to surgery (weeks), (median, range) | 8.0 (5.0–13.4) | |

Abbreviations: UI: upper incisor, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control, JES: Japan Esophageal Society

## 3.2. Gross tumor metrics

Gross tumor changes in the primary esophageal lesions, metastatic LNs, and a combination of both are summarized in Table 2. Post-CRT tumor measurements were generally smaller than pre-CRT measurement. The median reductions in the axial diameter, length, and volume of the primary lesion were 28.63% (interquartile range [IQR], 18.23–33.67%), 36.20% (IQR, 14.43–55.93%), and 55.02% (IQR, 40.41–68.44%), respectively. In case of metastatic LNs, the median reduction in axial diameter and volume were 26.89% (IQR, 15.15–39.09%) and 50.76 (IQR, 36.42–66.30%), respectively. When primary tumor and LNs were combined, the median volume reduction was 54.11% (IQR, 40.68–68.28%).

**Table 2. Gross tumor metrics from the comparison between pre- and post-chemoradiotherapy computed tomography images**

| Parameters | Pre-CRT (median, IQR) | Post-CRT (median, IQR) | Reduction (%) |
|---|---|---|---|
| Primary esophageal lesion | | | |
| Axial diameter (cm) | 3.71 (3.13–4.24) | 2.76 (2.23–3.25) | 24.15 (18.23–33.67) |
| Longitudinal length (cm) | 6.68 (5.31–8.47) | 4.54 (2.89–5.97) | 28.08 (14.43–53.93) |
| Volume (mL) | 38.51 (20.33–58.64) | 15.49 (8.86–24.21) | 55.06 (40.41–68.44) |
| Metastatic LNs | | | |
| Axial diameter (cm) | 1.76 (1.37–2.33) | 1.24 (0.86–1.68) | 26.23 (15.15–39.09) |
| Volume (mL) | 4.83 (2.41–9.63) | 2.18 (0.93–4.75) | 54.89 (36.42–66.30) |
| Sum of primary lesion and LNs | | | |
| Volume (mL) | 45.46 (28.38–74.07) | 20.46 (10.73–30.83) | 54.67 (40.68–68.28) |

Abbreviations: LN: lymph node, IQR: interquartile range, CRT: chemoradiotherapy

## 3.3. Analysis of pathologic complete response and prognostic factors

After nCRT, 31 of 103 (30.1%) patients achieved a pCR (Table 3). In univariate analysis, age, clinical N stage according to the JES 11$^{th}$ edition, and preoperative tumor volume were significantly associated with pCR. In multivariate logistic regression analysis, age (OR 1.083, 95%CI 1.016–1.155), clinical T stage (OR 0.303, 95%CI 0.104–0.879), clinical N stage according to the JES 11$^{th}$ edition (OR 0.260, 95%CI 0.094–0.719), and Δtumor volume (OR 1.024, 95%CI 1.001–1.047) were associated with the likelihood of pCR (Table 4).

**Table 3. Pathological outcomes**

| Characteristics | No. | % |
|---|---|---|
| Total LN yield (median, range) | 57 (23–116) | |
| Pathologic T stage | | |
| T0 | 54 | 52.4 |

| | | |
|---|---|---|
| T1 | 12 | 11.6 |
| T2 | 15 | 14.6 |
| T3 | 21 | 20.4 |
| T4 | 1 | 1.0 |
| Pathologic N stage (AJCC/UICC 8th edition) | | |
| N0 | 44 | 42.7 |
| N1 | 36 | 35.0 |
| N2 | 17 | 16.5 |
| N3 | 6 | 5.8 |
| Pathologic stage (AJCC/UICC 8th edition) | | |
| I | 42 | 40.8 |
| II | 2 | 1.9 |
| III | 52 | 50.5 |
| IV | 7 | 6.8 |
| pCR | 31 | 30.1 |

Abbreviations: LN: lymph node, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control, JES: Japan Esophageal Society, pCR: pathologic CR

**Table 4. Univariate and multivariate analysis of pathologic complete response**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | OR | 95%CI | p-value | OR | 95%CI | p-value |
| Age | 1.077 | 1.013–1.144 | 0.017 | 1.083 | 1.016–1.155 | 0.015 |
| Sex (Male vs Female) | 1.808 | 0.617–5.297 | 0.280 | | | |
| Histological grade (W-MD vs PD) | 1.295 | 0.354–4.740 | 0.696 | | | |
| T stage (T1–2 vs T3–4) | 0.439 | 0.172–1.122 | 0.086 | 0.303 | 0.104–0.879 | 0.028 |
| N stage by AJCC/UICC 8th edition) (N0–1 vs N2–3) | 0.762 | 0.327–1.775 | 0.529 | | | |
| N stage by JES 11th edition (N0–1 vs N2–4) | 0.268 | 0.106–0.677 | 0.005 | 0.260 | 0.094–0.719 | 0.009 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Stage by AJCC/UICC 8th edition) (Stage I–II vs III–IV) | 1.089 | 0.314–3.779 | 0.894 | | | |
| Stage by AJCC/UICC 11th edition (Stage I–II vs III–IV) | 0.743 | 0.227–2.429 | 0.623 | | | |
| Tumor volume_initial | 0.988 | 0.974–1.003 | 0.121 | | | |
| Tumor volume_preop | 0.959 | 0.926–0.994 | 0.022 | | | |
| ΔTumor volume | 1.018 | 0.997–1.040 | 0.096 | 1.024 | 1.001–1.047 | 0.039 |

Abbreviations: OR: odds ratio, CI: confidence interval,
AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control,
JES: Japan Esophageal Society, W-MD: well to moderately differentiated,
PD: poorly differentiated, preop: preoperative

## 3.4. Overall survival and recurrence-free survival

OS and RFS were analyzed according to the pathological response status. As shown in Figure 1, patients who achieved a pCR showed superior survival; however, the difference was not statistically significant (5-year OS: 43.9% vs. 53.3%, p = 0.340). Recurrence was observed in 36 patients after nCRT and subsequent surgery. Among them, one patient had local recurrence, 10 had regional recurrence, and 16 had distant recurrence. Additionally, one patient had both local and regional LN recurrences, whereas eight patients had both regional and distant recurrences. Although RFS was higher in the pCR group, this difference was not statistically significant (5-year RFS: 42.0% vs. 47.2%, p = 0.352) (Figure 2).

The prognostic factors for OS and RFS are shown in Tables 5 and 6, respectively. In univariate analysis, initial tumor volume, preoperative tumor volume, ypT stage, and ypN stage were significantly associated with OS. In the multivariate model, the initial tumor volume (hazard ratio [HR] 1.011, 95%CI 1.001–1.020) and ypN stage (HR 2.674, 95%CI 1.392–5.136) were independent predictors of OS. Similarly, for RFS, the initial tumor volume, preoperative tumor volume, ypT stage, and ypN stage were significant factors in the univariate analysis. In the multivariate analysis, initial tumor volume (HR 1.009, 95%CI 1.000–1.019) and ypN stage (HR 1.986, 95%CI 1.064–3.707) remained significant predictors of RFS.

**Table 5. Univariate and multivariate analysis of overall survival**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95%CI | p-value | HR | 95%CI | p-value |

| | | | | | | |
|---|---|---|---|---|---|---|
| Age | 1.022 | 0.984–1.062 | 0.256 | | | |
| Sex (Male vs Female) | 1.387 | 0.545–3.531 | 0.493 | | | |
| Histological grade (W-MD vs PD) | 1.058 | 0.441–2.535 | 0.900 | | | |
| T stage (T1–2 vs T3–4) | 1.222 | 0.584–2.556 | 0.594 | | | |
| N stage by AJCC/UICC 8th edition (N0–1 vs N2–3) | 1.427 | 0.759–2.685 | 0.270 | | | |
| N stage by JES 11th edition (N0–1 vs N2–4) | 0.956 | 0.488–1.870 | 0.895 | | | |
| Stage by AJCC/UICC 8th edition (Stage I–II vs III–IV) | 1.115 | 0.437–2.842 | 1.115 | | | |
| Stage by JES 11th edition (Stage I–II vs III–IV) | 1.175 | 0.461–2.997 | 0.735 | | | |
| Tumor volume_initial | 1.011 | 1.002–1.020 | 0.016 | 1.011 | 1.001–1.020 | 0.030 |
| Tumor volume_preop | 1.039 | 1.019–1.060 | <0.0001 | | | |
| ΔTumor volume | 0.991 | 0.976–1.006 | 0.234 | | | |
| pCR (non-pCR vs pCR) | 0.716 | 0.359–1.428 | 0.343 | | | |
| ypT stage by AJCC/UICC 8th edition (T1–2 vs T3–4) | 2.333 | 1.140–4.373 | 0.019 | 1.550 | 0.766–3.134 | 0.223 |
| ypN stage by AJCC/UICC 8th edition (N0–1 vs N2–3) | 2.772 | 1.474–5.211 | 0.002 | 2.674 | 1.392–5.136 | 0.003 |
| ypStage by AJCC/UICC 8th edition (Stage I–II vs III–IV) | 1.751 | 0.919–3.337 | 0.088 | | | |

Abbreviations: OS: overall survival, HR: hazards ratio, CI: confidence interval, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control, JES: Japan Esophageal Society, W-MD: well to moderately differentiated, PD: poorly differentiated, preop: preoperative, pCR: pathologic complete response, yp: status post-neoadjuvant therapy

**Table 6. Univariate and multivariate analysis of recurrence-free survival**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age | 1.020 | 0.985–1.056 | 0.272 | | | |
| Sex (Male vs Female) | 1.149 | 0.516–2.559 | 0.734 | | | |
| Histological grade (W-MD vs PD) | 0.872 | 0.367–2.069 | 0.755 | | | |
| T stage (T1–2 vs T3–4) | 1.414 | 0.705–2.837 | 0.329 | | | |
| N stage by AJCC/UICC 8th edition (N0–1 vs N2–3) | 1.078 | 0.609–1.906 | 0.797 | | | |
| N stage by JES 11th edition (N0–1 vs N2–4) | 1.228 | 0.640–2.537 | 0.537 | | | |
| Stage by AJCC/UICC 8th edition (Stage I–II vs III–IV) | 1.446 | 0.573–3.650 | 0.435 | | | |
| Stage by JES 11th edition (Stage I–II vs III–IV) | 1.570 | 0.622–3.966 | 0.340 | | | |
| Tumor volume_initial | 1.010 | 1.002-1.019 | 0.018 | 1.009 | 1.000–1.019 | 0.040 |
| Tumor volume_preop | 1.033 | 1.014–1.053 | 0.001 | | | |
| ΔTumor volume | 0.994 | 0.980–1.007 | 0.360 | | | |
| pCR (non-pCR vs pCR) | 0.740 | 0.392–1.398 | 0.354 | | | |
| ypT stage by AJCC/UICC 8th edition (T1–2 vs T3–4) | 1.984 | 1.049–3.751 | 0.035 | 1.396 | 0.705–2.766 | 0.338 |
| ypN stage by AJCC/UICC 8th edition (N0–1 vs N2–3) | 2.089 | 1.145–3.811 | 0.016 | 1.986 | 1.064–3.707 | 0.031 |
| ypStage by AJCC/UICC 8th edition (Stage I–II vs III–IV) | 1.630 | 0.903–2.943 | 0.105 | | | |

Abbreviations: RFS: recurrence-free survival, HR: hazards ratio, CI: confidence interval, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control,

JES: Japan Esophageal Society, W-MD: well to moderately differentiated,
PD: poorly differentiated, preop: preoperative, pCR: pathologic complete response,
yp: status post-neoadjuvant therapy

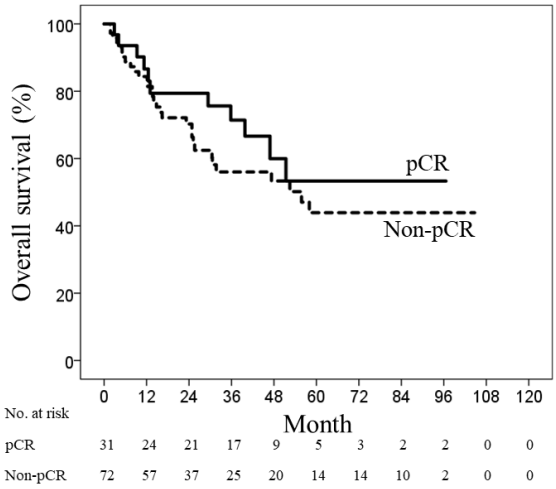


**Figure 1. Overall survival graphs for patients with and without pathologic complete response (p = 0.340)**

Abbreviations: no.: number, pCR: pathologic complete response

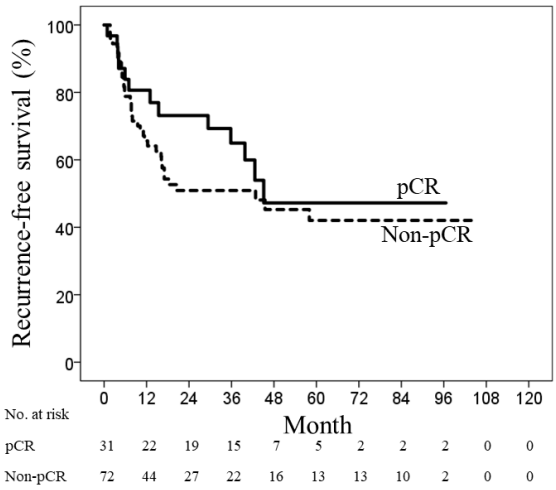


**Figure 2. Recurrence-free survival graphs for patients with and without pathologic complete response (p = 0.352)**

Abbreviations: no.: number, pCR: pathologic complete response

## 3.5. Patient characteristics of the metabolic analysis group

An additional analysis was conducted in the metabolic analysis group to predict pCR according to the metabolic tumor parameters, as assessed using PET/CT. The baseline characteristics and pathological outcomes of the 74 patients are summarized in Tables 7 and 8. Characteristics, such as tumor location and clinical stage, were generally similar to those of the overall cohort. In the metabolic analysis group, pCR was observed in 24 patients (32.4%).

**Table 7. Patient baseline and treatment characteristics of the metabolic analysis group**

| Characteristics | No. | % |
|---|---|---|
| Age, years (median, range) | 63 (31–77) | |
| Sex | | |
| Male | 61 | 82.4 |
| Female | 13 | 17.6 |

| | | |
|---|---|---|
| Site | | |
| Upper thoracic (UI 20–25 cm) | 1 | 1.4 |
| Middle thoracic (UI 25–30 cm) | 32 | 43.2 |
| Lower thoracic (UI 30–40 cm) | 41 | 55.4 |
| Histological grade | | |
| Well differentiated | 5 | 6.7 |
| Moderately differentiated | 53 | 71.6 |
| Poorly differentiated | 7 | 9.5 |
| Unknown | 9 | 12.2 |
| Clinical T stage | | |
| T1 | 8 | 10.8 |
| T2 | 11 | 14.9 |
| T3 | 48 | 64.9 |
| T4 | 7 | 9.4 |
| Clinical N stage (AJCC/UICC 8th edition) | | |
| N0 | 5 | 6.7 |
| N1 | 27 | 36.5 |
| N2 | 39 | 52.7 |
| N3 | 3 | 4.1 |
| Clinical N stage (JES 11th edition) | | |
| N0 | 5 | 6.8 |
| N1 | 17 | 23 |
| N2 | 33 | 44.6 |
| N3 | 12 | 16.2 |
| N4 | 7 | 9.4 |
| Stage (AJCC/UICC 8th edition) | | |
| I | 4 | 5.4 |
| II | 7 | 9.4 |
| III | 38 | 51.4 |
| IV | 25 | 33.8 |
| Stage (JES 11th edition) | | |
| I | 0 | 0 |
| II | 12 | 16.2 |
| III | 50 | 67.6 |
| IV | 12 | 16.2 |
| Chemotherapy regimen | | |

| | | |
|---|---|---|
| Paclitaxel/carboplatin | 27 | 36.5 |
| 5-fluorouracil/cisplatin | 34 | 45.9 |
| Capecitabine/cisplatin | 8 | 10.8 |
| Pembrolizumab+ paclitaxel/carboplatin | 5 | 6.8 |
| Pembrolizumab+ capecitabine/cisplatin | 0 | 0 |
| Total radiation dose (Gy), (median, range) | 44.1 (44.0–44.1) | |
| Total radiation fractions, (median, range) | 21 (20–21) | |
| Time to surgery (weeks), (median, range) | 8.0 (5.0–13.4) | |

Abbreviations: UI: upper incisor, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control, JES: Japan Esophageal Society

**Table 8. Pathological outcomes of the metabolic analysis group**

| Characteristics | No. | % |
|---|---|---|
| Total LN yield (median, range) | 58 (23–116) | |
| Pathologic T stage | | |
| T0 | 40 | 54.0 |
| T1 | 8 | 10.8 |
| T2 | 9 | 12.2 |
| T3 | 16 | 21.6 |
| T4 | 1 | 1.4 |
| Pathologic N stage (AJCC/UICC 8$^{th}$ edition) | | |
| N0 | 33 | 44.6 |
| N1 | 27 | 36.5 |
| N2 | 12 | 16.2 |
| N3 | 2 | 2.7 |
| Pathologic stage (AJCC/UICC 8$^{th}$ edition) | | |
| I | 32 | 43.2 |
| II | 1 | 1.4 |
| III | 37 | 50.0 |
| IV | 4 | 5.4 |
| pCR | 24 | 32.4 |

Abbreviations: LN: lymph node, AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control, JES: Japan Esophageal Society, pCR: pathologic complete response

## 3.6. Metabolic tumor metrics

Table 9 summarizes metabolic tumor changes before and after CRT. Metabolic tumor measurements, including SUVmax, SUVmean, TGL, and MTV, were generally lower after CRT than before CRT. The median reduction in TLG and MTV for primary lesion were 91.64% (IQR, 75.93–98.95%) and 83.36% (IQR, 69.67–96.57%), respectively. For metastatic LNs, the median reduction in TLG and MTV were 96.69% (IQR, 37.29–100.00%) and 95.74% (IQR, 51.94–100.00%), respectively. When combining primary lesion and metastatic LNs, the median reductions in TLG and MTV were 91.18% (IQR, 77.13–96.79%) and 82.81% (IQR, 68.56–95.08%), respectively.

**Table 9. Metabolic tumor metrics from the comparison between pre- and post-chemoradiotherapy positron emission tomography/computed tomography images**

| **Parameters** | **Pre-CRT** (median, IQR) | **Post-CRT** (median, IQR) | **Reduction** (median, IQR) |
|---|---|---|---|
| Primary esophageal lesion | | | |
| SUVmax | 16.38 (11.77–20.67) | 5.06 (3.54–6.65) | 10.41 (5.44–14.59) |
| SUVmean | 6.86 (5.12–8.05) | 3.46 (2.73–4.59) | 3.58 (1.64–5.13) |
| TLG | 179.01 (63.91–334.50) | 16.25 (2.21–31.14) | 91.64% (75.93–98.95%) |
| MTV (mL) | 25.70 (12.83–39.42) | 3.99 (0.65–8.48) | 83.36% (69.67–96.57%) |
| Metastatic LNs | | | |
| SUVmax | 5.35 (3.00–8.89) | 2.49 (1.76–3.49) | 2.60 (1.03–5.81) |
| SUVmean | 3.33 (2.73–4.49) | 0.00 (0.00–2.96) | 1.48 (0.00–3.25) |
| TLG | 5.69 (0.77–19.80) | 0.00 (0.00–1.58) | 96.69% (37.29–100.00%) |
| MTV (mL) | 1.69 (0.27–3.82) | 0.00 (0.00–0.53) | 95.74% (51.94–100.00) |
| Sum of primary lesion and LNs | | | |
| SUVmax | 16.38 (11.93–20.67) | 5.32 (3.58–6.93) | 10.48 (5.74–14.27) |
| SUVmean | 6.61 (5.10–7.82) | 3.30 (2.74–4.57) | 3.01 (1.36–4.45) |
| TLG | 212.63 (85.08–351.88) | 17.79 (3.56–34.72) | 91.18% (77.13–96.79%) |
| MTV (mL) | 30.51 (16.84–45.16) | 4.39 (1.17–9.18) | 82.81% (68.56–95.08%) |

Abbreviations: LN: lymph node, IQR: interquartile range, CRT: chemoradiotherapy, SUV: standardized uptake value, TLG: total lesion glycolysis, MTV: metabolic tumor volume

## 3.7. Analysis of pathologic complete response and prognostic factors in the metabolic analysis group

The results of the logistic regression analysis for the 74 patients with available PET metrics are summarized in Table 10. In the univariate analysis, only clinical N stage, according to the JES 11th edition was significantly associated with pCR. In the multivariate logistic regression model, both clinical N stage according to the JES 11th edition (OR 0.251, 95%CI 0.082–0.766) and preoperative MTV (OR 0.892, 95%CI 0.800–0.994) were significantly associated with pCR.

**Table 10. Univariate and multivariate analysis of pathologic complete response in the metabolic analysis group**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | OR | 95%CI | p-value | OR | 95%CI | p-value |
| Age | 1.061 | 0.991–1.137 | 0.088 | | | |
| Sex (Male vs Female) | 1.098 | 0.301–4.001 | 0.888 | | | |
| Histological grade (W-MD vs PD) | 0.965 | 0.170–5.466 | 0.968 | | | |
| T stage (T1–2 vs T3–4) | 0.417 | 0.142–1.225 | 0.112 | | | |
| N stage by AJCC/UICC 8th edition (N0–1 vs N2–3) | 0.856 | 0.321–2.280 | 0.755 | | | |
| N stage by JES 11th edition (N0–1 vs N2–4) | 0.250 | 0.087–0.721 | 0.010 | 0.251 | 0.082–0.766 | 0.015 |
| Stage by AJCC/UICC 8th edition (Stage I–II vs III–IV) | 1.333 | 0.320–5.552 | 0.693 | | | |
| Stage by JES 11th edition (Stage I–II vs III–IV) | 0.952 | 0.256–3.540 | 0.952 | | | |
| SUVmax_initial | 0.970 | 0.899–1.046 | 0.427 | | | |
| SUVmean_initial | 0.934 | 0.739–1.180 | 0.565 | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| TLG_initial | 0.998 | 0.996–1.001 | 0.221 | | | |
| MTV_initial | 0.976 | 0.952–1.002 | 0.069 | | | |
| SUVmax_preop | 0.891 | 0.733–1.083 | 0.246 | | | |
| SUVmean_preop | 0.972 | 0.678–1.393 | 0.877 | | | |
| TLG_preop | 0.982 | 0.962–1.003 | 0.089 | | | |
| MTV_preop | 0.890 | 0.802–0.987 | 0.028 | 0.892 | 0.800–0.994 | 0.038 |
| ΔSUVmax | 0.990 | 0.922–1.063 | 0.778 | | | |
| ΔSUVmean | 0.958 | 0.782–1.173 | 0.675 | | | |
| ΔTLG | 1.001 | 0.983–1.020 | 0.897 | | | |
| ΔMTV | 1.017 | 0.994–1.041 | 0.158 | | | |

Abbreviations: OR: odds ratio, CI: confidence interval,
AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control,
W-MD: well to moderately differentiated, PD: poorly differentiated,
SUV: standardized uptake value, TLG: total lesion glycolysis,
MTV: metabolic tumor volume, preop: preoperative

# IV. DISCUSSION

In this study, we investigated prognostic factors that predict pCR in patients with locally advanced ESCC who were treated with nCRT and subsequently with surgical resection. Clinical factors, including age, T stage, and N stage, based on the JES 11$^{th}$ edition classification, were associated with pCR. Additionally, a greater reduction in tumor volume after CRT was found to be a good prognostic factor. When metabolic tumor metrics were included in the analysis, the N stage based on the JES 11$^{th}$ classification and initial MTV were also identified as prognostic factors. To our knowledge, no previous study has analyzed clinical factors using both gross and metabolic metrics to predict pCR.

In our cohort, pCR was achieved in 30.1% of the patients. Previous studies have reported pCR rates ranging from as low as 10% to over 40%, with pCR rates being higher in patients with

SCC than in those with adenocarcinoma [3, 13, 14]. Our rate was slightly lower. Notably, our study included patients with a relatively high tumor burden, as more than 75% of the patients were classified as T3 or higher, and 27 patients had distant LN metastasis, including SCL involvement. Furthermore, the median LN yield was 57 (range 23–116), suggesting that radical LN dissection was performed more extensively in this study than in previous studies. In some instances, patients were treated by excluding the cervical area from the radiation field to enhance reconstruction success after esophagectomy, even in cases with positive LN metastasis present in that region. This may have contributed to lower pCR rates.

In this study, the general clinical factors associated with pCR were age, clinical T stage, and N stage, with the N stage evaluated based on the JES 11$^{th}$ edition criteria. Among the gross tumor metrics, a greater reduction in tumor volume was associated with higher odds of achieving pCR. Extensive LN metastasis and deeper invasion of the primary tumor indicates an advanced stage, suggesting that the effect of nCRT may be less significant than that in less advanced stages. This finding can be interpreted considering the finding that a greater tumor volume reduction is associated with a higher likelihood of achieving pCR. Although various clinical factors associated with pCR have been reported, controversy remains among studies. These factors include histological grade, T category, N category, overall stage, achievement of clinical complete response (cCR), time to surgery, and the number of LNs dissected [14-16]. In a large retrospective study, the factors associated with pCR in the overall cohort included histological grade (well to moderately differentiated vs. poorly differentiated), T stage (T1–2 vs. T3–4), and N stage (N0 vs. N+). When focusing specifically on ESCC, histological grade and N stage were identified as significant factors [14]. In our study, although T stage (T1–2 vs. T3–4) showed a significant association, N stage (N0 vs. N+) did not. A previous study assessed N stage based on the AJCC/UICC 7$^{th}$ edition [17], whereas our findings indicated no significant association with this factor. Instead, the N stage demonstrated differences between N0–1 and N2–4 according to the JES 11$^{th}$ edition. This suggests that the extent of LN metastasis at specific stations, as determined by the location of the primary tumor, may be more critical to treatment outcomes compared to the number of LN metastases. From the perspective of RT field, perilesional LNs (e.g., paresophageal LNs) near the primary lesion inevitably receive a higher radiation dose. Consequently, LN metastases located further away from the primary lesion may be of importance. Therefore, cases with more widespread LN involvement, rather than having LN involvement limited to the area close to the primary tumor, may be considered more advanced in terms of staging. Moreover, evaluation of pathological LN metastases is not straightforward. Assessment typically relies on imaging techniques, such as CT and PET/CT, as well as endoscopic ultrasonography. The reported sensitivities for these modalities are 0.50 (95%CI, 0.41–0.60), 0.57 (0.43–0.70), and 0.80 (0.75–0.84), respectively, while the specificities are 0.83 (0.77–0.89), 0.85 (0.7—0.95), and 0.70 (0.65–0.75), respectively [18]. Therefore, combining all modalities is essential. However, gray areas that pose clinical challenges remain.

Previous studies have aimed to predict clinical outcomes using PET parameters in esophageal cancer [19-22]. Venkat et al. evaluated the PET parameters of 76 patients with locally

advanced esophageal cancer who were treated with nCRT, followed by esophagectomy. Pre-CRT MTV < 33.1 and Pre-CRT TLG < 153 were independent prognostic factors for achieving pCR, whereas the percentage change in MTV was predictive of OS [19]. Tomoki et al. found that, in patients with ESCC who received neoadjuvant chemotherapy, a > 60% reduction in the MTV of the primary lesion was significantly associated with improved progression-free survival [21]. In our study, a low pre-CRT MTV was identified as a positive prognostic factor for achieving pCR, although TLG was not found to be significant. This may be due to the challenges in examining presurgical PET metrics in patients who received nCRT. A key issue is that post-CRT inflammation, particularly radiation esophagitis, can lead to increased FDG uptake, which may be misinterpreted as residual tumor activity [23, 24]. In our study, immediate preoperative PET/CT was performed at a median of 27 days (range 1–52 days) after the completion of CRT, when the effects of RT toxicity were still apparent. Currently, no clear guidelines for assessing PET metrics in such situations are available. In this study, we adjusted the MTV by referencing the mean SUV uptake of patients with clinically significant (G3 or higher) esophagitis who demonstrated clear signs of radiation esophagitis on PET/CT, as well as previously reported PET findings related to esophagitis [23-25]. At our institution, we have reported that comparing initial and mid-treatment PET/CT evaluation findings can effectively predict clinical outcomes [26, 27]. These studies have demonstrated significant predictive capabilities for treatment response and recurrence based on metabolic tumor metrics. Considering these factors, analyzing metabolic metrics using interim PET/CT during nCRT may be beneficial.

In our study, pCR was not associated with OS or RFS. Several studies have shown that achieving a pCR after nCRT offers survival benefits. Berger et al. and Ajani et al. reported that patients who achieved pCR following the induction of CRT had a longer median survival [9, 14, 28]. In a large cohort study from the Netherlands Cancer Registry, which involved 4,946 patients with esophageal cancer treated with the CROSS regimen, pCR was identified as a significant factor for survival [14]. However, in these studies, 70–80% of patients had adenocarcinomas. In a cohort of 284 patients from the M.D. Anderson Cancer Center, an OS and RFS benefit was associated with cCR, but no significant survival difference was observed based on pCR status [16]. Another study by Rohatgi et al., also from the M.D. Anderson Cancer Center, found a survival benefit for pCR in patients with adenocarcinoma, but not in patients with SCC. They suggested that this was due to the lack of a significant difference in metastasis rates between the pCR and non-pCR groups in patients with SCC, highlighting the importance of systemic therapy, even for patients with ESCC who achieve pCR [29]. On the other hand, several studies have reported the outcomes of nCRT followed by surgery, specifically for ESCC [30, 31]. A study conducted in Taiwan with 282 patients showed a pCR rate of 20.1%, with the pCR group demonstrating better OS than that of the non-pCR group (median OS: 98.8 months vs. 15.5 months, $p < 0.001$) [30]. In this study, RT was administered at a total dose of 30 Gy, consistently covering the supraclavicular fossa and the celiac and pericardial LN areas. Patients who achieved a pCR at this relatively low dose likely responded well to treatment and consequently had better prognoses. In our study, high-dose radiation was administered, and more extensive LN dissection was performed, representing a comparatively more radical treatment

approach. Notably, previous studies reported a 5-year OS of 2–30% in the non-pCR group, whereas our study showed a rate of 43.9%. This suggests that factors other than pCR achievement may have a greater impact on prognosis, which is potentially influenced by treatment intensity. In our data, the initial tumor volume and ypN stage were the most important prognostic factors for both outcomes. Although recurrence was more frequent in the non-pCR group, this difference was not statistically significant. In addition, most of the recurrences in the pCR group were caused by distant metastases. Ultimately, controlling LN metastasis is important, which is an important feature of ESCC spread. Based on the results of CheckMate-577, adjuvant nivolumab has become the standard treatment for patients who do not achieve pCR after nCRT [32]. However, these results suggest that, even if pCR is achieved in patients with ESCC, systemic therapy should be considered depending on individual factors.

Many studies aim to predict patients who can achieve pCR to explore less invasive treatment options, potentially avoiding radical surgeries such as esophagectomy, which carry high risks of complications and mortality. In the case of locally advanced rectal cancer, where neoadjuvant CRT followed by surgical resection is the standard treatment, promising oncological outcomes have been reported in patients who achieved cCR using a watch-and-wait strategy without surgery [33-35]. A meta-analysis indicated that for patients with esophageal cancer who achieved cCR after neoadjuvant CRT, additional surgery may affect the 2-year disease-free survival and OS but does not provide long-term survival benefits [36]. However, other retrospective studies have shown that cCR does not predict pCR [16], highlighting the necessity for future research that integrates various clinical factors to validate these findings.

A limitation of this study is its retrospective nature. While we explored the factors associated with pCR, achieving pCR did not result in a significant difference in prognosis. As previously mentioned, differences in patient characteristics and treatment approaches may have influenced our results. Additionally, since the study design focused on identifying factors associated with pCR, patients with shorter follow-up periods were also included, thus limiting the ability to assess long-term outcomes. A longer follow-up period will be necessary in future studies to identify precise prognostic factors. Although all patients underwent nCRT and curative surgery, the patient cohort had heterogeneous characteristics, including variations in chemotherapy regimens. Additionally, according to the most recent AJCC/UICC 8$^{th}$ edition criteria, 24 patients had SCL metastasis classified as distant LN metastasis, and three patients had non-regional LN metastasis under any staging system. These patients may have received alternative treatment options such as definitive CRT. Furthermore, only 31 patients achieved a pCR, which may be a small number for determining statistical significance when analyzing meaningful prognostic factors. However, the inclusion of clinical parameters along with gross and metabolic tumor metrics from PET/CT adds clinical value to the identification of prognostic factors.

# V. CONCLUSION

In conclusion, in patients with locally advanced thoracic ESCC undergoing nCRT followed by surgery, advanced T stages, wide LN metastasis, and low treatment response were associated with a reduced likelihood of achieving pCR. In addition, a low metabolic tumor burden in preoperative PET evaluation was associated with an increased chance of achieving pCR. Although further studies with a larger number of patients are warranted, our findings offer valuable insights for predicting clinical outcomes in patients with locally advanced ESCC receiving nCRT.

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## APPENDICES

None

Abstract in Korean

# 국소 진행성 흉부 식도 편평상피세포암에서 선행 항암화학방사선요법 후 수술 시 병리학적 완전 관해와 관련된 임상적 매개 변수 연구

국소 진행성 식도암에서 선행 항암화학방사선치료 후 수술을 시행하는 것은 표준 치료로 제시되고 있다. 선행 항암화학방사선치료 후 병리학적 완전 관해는 생존율 향상과 관련이 있는 것으로 보고되고 있으나, 병리학적 완전 관해를 예측하는 요인은 아직 불명확하다. 이에 이번 연구에서는 선행 화학방사선치료 후 수술을 시행한 국소 진행성 식도 편평상피세포암 환자에서 병리학적 완전 관해와 임상결과 간의 상관관계를 조사하고 병리학적 완전 관해의 예후 인자에 대해 확인하고자 하였다.

2011년 1월부터 2024년 3월까지 본 기관에서 선행 화학방사선치료 후 수술적 절제를 받은 국소진행성 식도 편평상피세포암 환자 103명을 분석하였다. 경부 식도에 위치한 종양이나 원격 전이가 있는 환자는 제외하였다. 선행 항암화학방사선치료 효과를 평가하기 위해, 진단 당시 및 수술 직전 영상에서 원발 종양 및 전이 림프절의 육안적 변화와 대사 변화를 평가하였다. 전체 환자 중 74명에서 치료 전/후의 양전자 방출 단층촬영을 통해 포도당 대사변화를 평가할 수 있었다. 병리학적 완전 관해와 관련된 요인은 로지스틱 회귀 방법을 사용하여 평가하였다.

선행 항암화학방사선치료 및 수술 절제 후, 31명의 환자(30.1%)에서 병리학적 완전 관해가 관찰되었다. 나이, 임상 T 병기, JES 11판에 따른 임상 N 병기, 종양 용적의 변화가 병리학적 완전관해와 관련이 있었다. 하지만 본 연구에서는 병리학적 완전 관해 달성 여부는 전체생존율과 무재발생존율의 차이를 보이지 않았다. 양전자방출 단층촬영 검사를 통한 대사 변화 분석 그룹에서는JES 11판에 따른 임상 N 병기와 수술 전 종양의 포도당대사용적 감소가 병리학적 완전 관해와 관련된 예후 인자로 확인되었다.

결론적으로 국소 진행성 식도암에서 선행 항암화학방사선치료 후 수술을 시행하였을 때 병리학적 완전 반응에 관련된 인자는 초기 T 병기, JES 11판에 따른 N 병기, 종양 용적 감소였고, 양전자방출단층촬영 검사상 수술 전 종양의 낮은 포도당대사율은 병리학적 완전 관해 가능성을 높게 하였다. 향후 예후 인자를 명확히 하기 위해 추가 연구가 필요하다.

**핵심되는 말** : 식도암, 항암화학방사선치료, 병리학적 완전반응, 양전자방출 컴퓨터 단층촬영