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# Prognostic Significance of Pretreatment Staging With $^{18}$F-FDG PET in Esophageal Cancer

## *A Nationwide Population-Based Study*

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**Purpose of the Report:** Without the routine use of $^{18}$F-FDG PET for initial staging of esophageal cancer, it may lead to inaccurate staging and suboptimal treatment. The purpose of this study was to evaluate the prognostic significance of pretreatment $^{18}$F-FDG PET in nonmetastatic esophageal cancer by comparing the survival between patients with and without pretreatment PET.

**Materials and Methods:** We selected newly diagnosed esophageal cancer patients without metastasis between 2009 and 2015 from Taiwan Cancer Registry and National Health Insurance Research Database. Pretreatment $^{18}$F-FDG PET staging was determined according to the implementation of PET within 90 days before starting treatment. Overall survival was calculated from the day of treatment initiation to the death from any cause. Survival curves were compared between patients with and without PET staging using the log-rank test.

**Results:** Of the 9078 patients included, 1765 (19.4%) and 7313 (80.6%) patients were staged with and without pretreatment PET, respectively. The median follow-up time for all patients and survivors was 1.29 years and 5.46 years, respectively. The pretreatment PET group had a lower risk of death than the no pretreatment PET group (hazards ratio, 0.74; 95% confidence interval, 0.70–0.79; $P < 0.001$). After adjusting for age, stage, histology, and tumor location, pretreatment PET remained significantly correlated with a lower risk of death (hazards ratio, 0.78; 95% confidence interval, 0.73–0.83; $P < 0.001$).

**Conclusions:** The utilization of pretreatment $^{18}$F-FDG PET for staging in nonmetastatic esophageal malignancy is associated with a lower risk of death even after adjusting for age, stage, histology, and tumor location.

**Key Words:** esophageal cancer, staging, FDG, PET, prognosis

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Esophageal cancer is the seventh most common malignancy and the sixth leading cause of cancer-related death worldwide, with approximately 572,034 new cases and 508,585 deaths recorded annually.[1] Squamous cell carcinoma accounts for 90% of all esophageal cancers in Eastern Asia,[2] whereas adenocarcinoma represents the major histology in Western countries.[3] The cause of this discrepancy is thought to arise from differences in ethnic profiles; lifestyle; and in the risk factors of smoking, alcohol, and betel nut chewing. Most esophageal cancer patients are diagnosed at an advanced stage, and these patients have poor prognosis despite aggressive management. Historically, the 5-year survival ranges from 15.6 to 47.4% for localized regional disease, and a dismal 5% for those with distant metastasis.[4,5] Early diagnosis and comprehensive disease staging are therefore imperative in improving prognosis.

Previous studies have suggested multiple staging modalities, such as endoscopy, endoscopic ultrasound (EUS), contrast-enhanced CT (CECT), and PET, and these individually contribute to accurate staging while complementing one another. The importance of $^{18}$F-FDG PET in staging of esophageal malignancy has been well established, especially in determining nodal status and detecting distant metastasis. A prospective study showed a higher accuracy of PET for diagnosing stage IV disease compared with the combination of CT and EUS (82% vs 64%; $P = 0.004$).[6] PET has also been prospectively found to have comparable accuracy to CECT for detecting regional lymph nodes (79% vs 82%) and have superior accuracy for detecting distant metastasis (100% vs 79%).[7] Despite having limited sensitivity, the value of PET mainly lies with its high diagnostic specificity. Therefore, the National Comprehensive Cancer Network Clinical Practice Guidelines for esophageal cancer recommend routine $^{18}$F-FDG PET/CT in staging workup for all esophageal cancer patients, with the exception of overt metastatic disease.[8]

Despite studies and guidelines suggesting routine $^{18}$F-FDG PET/CT staging for esophageal cancer, clinical adoption has been limited. It is currently unknown whether the potential suboptimal staging by omitting PET impacts clinical outcomes. Thus, this study aimed to investigate the prognostic significance of pretreatment PET in nonmetastatic esophageal malignancy.

## PATIENTS AND METHODS

### Study Design and Data Source

This retrospective study was conducted using data from the Health and Welfare Data Center (HWDC) established by the Ministry of Health and Welfare of Taiwan. The HWDC consolidates data gathered by the Taiwan government from various sources. These data are then deidentified and available for research based on case-by-case approval. Specifically, we used the Taiwan Cancer Registry, which includes detailed staging and treatment information of cancer patients; the Cause of Death database, which lists all death certificates issued in Taiwan; and the National Health Insurance Research Database, which includes billing information on all National

Health Insurance (NHI)–reimbursed examinations, medication, and treatment. The NHI system has been implemented since 1995 and covers more than 99% of all Taiwan citizens. Using $^{18}$F-FDG FDG PET for initial staging of esophageal cancer when optimal staging could not be achieved by conventional studies has been reimbursed since July 2004. All databases in the HWDC are linked through a common but anonymized identifier to preserve privacy.

This study received a certificate of exempt review from the institutional review board of our hospital. The requirement for informed consent was also waived owing to the retrospective and deidentified nature of the study.

## Study Population

We selected patients aged at least 20 years who were newly diagnosed with esophageal cancer (*ICD-O-3* site: C15) pathologically confirmed to be invasive carcinoma (*ICD-O-3* M-codes: 8010, 8070, 8071, 8072, 8083, 8140, and 8560) between 2009 and 2015. Patients with prior malignancy or metastatic disease were excluded from the analysis.

## Covariates and Outcome Definition

We extracted data on age, sex, clinical stage, histopathology, tumor location, tumor grading, treatment, and disease status at the last follow-up date from the Taiwan Cancer Registry. Age was analyzed as a continuous variable. We selected patients with squamous cell carcinoma (M-code: 8070, 8071, 8072, or 8083) or adenocarcinoma-like histologies (adenocarcinoma, adenosquamous, or unspecified carcinoma; M-code: 8140, 8560, or 8010). Treatment was classified into operation only, operation plus adjuvant radiotherapy or chemoradiotherapy, neoadjuvant therapy plus operation, concurrent chemoradiotherapy only, and others.

We searched the National Health Insurance Research Database for the presence of $^{18}$F-FDG PET performed within 0 to 90 days before the first day of treatment. Patients with a record of $^{18}$F-FDG PET were considered to have undergone pretreatment PET, whereas those without records were considered to have not undergone pretreatment PET.

The primary outcome of interest was overall survival (OS), calculated from the date of treatment initiation to the date of death. Information on OS was obtained from the Cause of Death database. Patients whose death record could not be found were considered alive and censored on the last day of the database records (December 31, 2018).

## Statistical Analysis

Continuous data were presented as the mean ± standard deviation or the median and interquartile range (IQR), as applicable. Meanwhile, categorical data were presented as numbers and percentages. The distributions of patient characteristics were compared using the $\chi^2$ test for categorical variables and the independent *t* test or Kruskal-Wallis test for continuous variables.

Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards models were used to estimate the hazards ratio (HRs) and 95% confidence interval (CIs) and determine the covariate effects on OS. Subgroup analysis was performed to evaluate the effect of pretreatment PET on OS across various subgroups. All statistical analyses were performed using R software, version 3.6.3 (http://www.r-project.org) and SAS (version 9.4; SAS Institution Inc, Cary, NC). A 2-sided $P$ value of less than 0.05 was considered statistically significant.

# RESULTS

## Patient Characteristics

In total, 9078 patients met the inclusion criteria (Fig. 1). The patients were predominantly male (93.5%), had a squamous cell carcinoma histology (96.2%), and had primary site in the thoracic esophagus (83.2%) (Table 1). The most common clinical disease stage was stage III (70.8%), followed by stage II (22.2%). The median follow-up time for all patients and the survivors was 1.29 years and 5.46 years, respectively. Overall, 1765 (19.4%) and 7313 (80.6%) did and did not undergo pretreatment PET. The baseline characteristics were comparable between the 2 groups.

## Predictors of Survival

On univariate analysis, pretreatment PET was associated with improved survival (HR, 0.74; 95% CI, 0.70–0.79; $P < 0.001$) (Fig. 2, Table 2). Known prognostic factors such as sex, clinical stage, and tumor location were also associated with OS in the univariate analysis. In the multivariable analysis adjusted for age, sex, clinical stage, histological type and grade, tumor location, and type of treatment received, pretreatment PET remained independently associated with OS. The pretreatment PET group had a lower risk of death than did the no pretreatment PET group (HR, 0.78; 95% CI, 0.73–0.83; $P < 0.001$).

Clinical stage was well correlated with prognosis in both groups (Figs. 3A, B; $P < 0.001$). Among the patients in the pretreatment and no pretreatment PET groups, the 5-year OS of

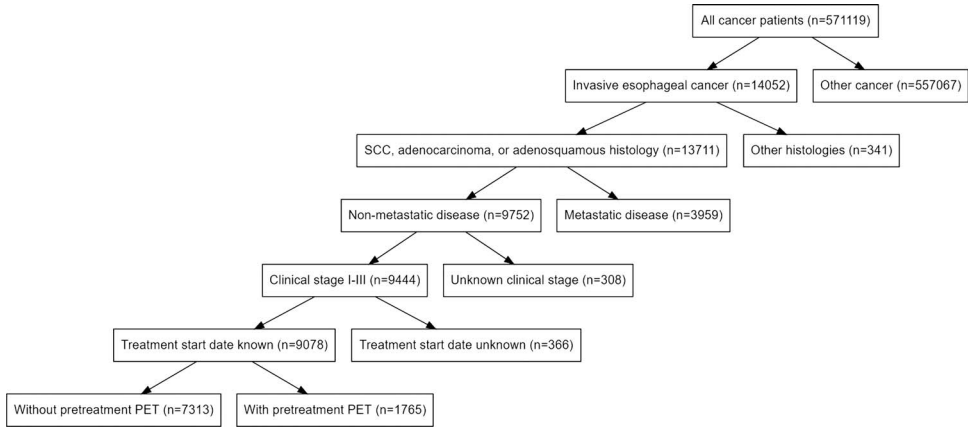


**FIGURE 1.** Patient inclusion flowchart.

**TABLE 1.** Patient and Tumor Characteristics by Pretreatment PET Groups (n = 9078)

| Characteristics | No Pretreatment PET Group (n = 7313) | Pretreatment PET Group (n = 1765) | *P* |
|---|---|---|---|
| Age, median (IQR), y | 56 (50–65) | 56 (50–63) | 0.021 |
| Sex, n (%) | | | 0.982 |
| Male | 6837 (93.5) | 1651 (93.5) | |
| Female | 476 (6.5) | 114 (6.5) | |
| AJCC stage | | | 0.006 |
| I | 481 (6.6) | 150 (8.5) | |
| II | 1608 (22.0) | 408 (23.1) | |
| III | 5224 (71.4) | 1207 (68.4) | |
| Tumor location | | | 0.907 |
| Unspecified | 962 (13.2) | 224 (12.7) | |
| Cervical | 257 (3.5) | 58 (3.3) | |
| Thoracic | 6075 (83) | 1478 (83.7) | |
| Abdominal | 19 (0.3) | 5 (0.3) | |
| Histological type, n (%) | | | 0.100 |
| Squamous cell carcinoma | 7026 (96.1) | 1711 (96.9) | |
| Adenocarcinoma like | 287 (3.9) | 54 (3.1) | |
| Treatment, n (%) | | | |
| Operation alone | 928 (12.7) | 207 (11.7) | <0.001 |
| Operation + (C)RT | 392 (5.4) | 108 (6.1) | |
| Neoadjuvant + operation | 1131 (15.5) | 368 (20.8) | |
| CCRT alone | 2248 (30.7) | 584 (33.1) | |
| Other | 2614 (35.7) | 498 (28.2) | |
| Median (IQR) follow-up, y | 1.21 (0.55–3.32) | 1.77 (0.76–3.99) | <0.001 |

Data are presented as the median (IQR) or n (%).

AJCC, American Joint Committee on Cancer; (C)RT, radiotherapy or chemoradiotherapy; CCRT, concurrent chemoradiotherapy.

those with stage I disease was 63.6% and 51.3%; stage II, 40.8% and 28.5%; and stage III, 23.5% and 16.7%, respectively. In the pretreatment PET group, the HRs for death of stage III patients compared with stage I patients was 3.72 (95% CI, 2.82–4.93; $P < 0.001$), whereas it was 2.89 (95% CI, 2.55–3.28; $P < 0.001$) in the no PET group.

## Subgroup Analysis on the Influence of Pretreatment PET

We performed an exploratory subgroup analysis to determine the influence of pretreatment PET in various subgroups. The effect of pretreatment PET was consistent across clinical stages (I, II, and III; most prominent effect on stage I), nodal status (negative and positive), and primary tumor sites (cervical, thoracic, and abdominal) (Fig. 4). Pretreatment PET was also consistently associated with improved survival across all treatment subgroups, albeit at varying degrees. The most prominent correlation with OS was observed in patients receiving surgery alone (HR, 0.48; 95% CI, 0.38–0.61; $P < 0.001$), followed by in patients without nodal involvement (HR, 0.59; 95% CI, 0.52–0.68; $P < 0.001$). We found progressively increasing rates of staging PET utilization in later years: 3% in 2009–2010, 23% in 2011–2013, and 29% in 2014–2016. However, the association of staging PET and survival remained relatively unchanged: 0.77 in 2009–2010, 0.76 in 2011–2013, and 0.75 in 2014–2016.

## DISCUSSION

$^{18}$F-FDG PET has been established to be a highly valuable staging modality for esophageal cancer, but it is not routinely performed for pretreatment staging. In this study, we conducted a nationwide population-based analysis to evaluate the association of pretreatment PET with survival in nonmetastatic esophageal cancer patients and found a significant correlation between pretreatment PET and improved survival. After adjusting for known prognostic factors including age, sex, tumor location, clinical stage, and treatment,[9] the correlation remained significant. This finding was also consistent across patient subgroups of clinical stage, nodal status, and tumor site.

Adherence to established guidelines has been reported to improve patient outcomes.[10] The National Comprehensive Cancer Network guidelines recommend routine pretreatment $^{18}$F-FDG PET/CT in the staging of all esophageal cancers patients except for those with overt metastatic disease.[8] In our study, we observed a trend of increasing use of this molecular imaging, as its advantages gradually become well recognized; however, ultimately less than 20% of patients actually underwent optimal staging with pretreatment PET. In a study by Barber et al,[11] a high rate of discordance was suggested between staging with conventional imaging alone and $^{18}$F-FDG PET/CT, with up to 40% of patients being downstaged or upstaged. Another prospective study showed that, compared with the combination of CT and EUS, a preoperative PET scan correctly upstaged 15% and downstaged 7% of patients.[6]

The clinical impact of pretreatment PET findings of esophageal cancer on management includes changes in treatment intent, treatment modality, and field of radiation. One of the most important roles of PET is the identification of undetected distant metastases. Most esophageal malignancies present with locally advanced disease, with approximately 20% to 30% of patients found with distant metastases at diagnosis, with the liver being the most common site, followed by the lung, bone, and brain.[12] The early detection of occult distant metastasis could prevent unnecessary radical treatment with surgery or radiotherapy and in turn avoid the resulting toxicities. Imdahl et al[13] reported that, in 66 operable patients, preoperative PET revealed metastases in 11 patients (16.6%) that were not noted by CT or ultrasound, and the management strategy was changed accordingly. Similar results showing that approximately 20% of distant metastases are found in a preoperative PET were reported.[14,15] These occult distant metastases would likely be overlooked in patients staged with conventional imaging alone. Conversely, patients whose pretreatment PET do not show distant metastasis were less likely to harbor occult distant metastasis and thus may have better outcomes after radical treatment. In our study, patients without pretreatment PET may have occult metastases not found by conventional imaging, thus resulting in a worse prognosis in across all stage subgroups in these patients.

In subgroup analysis by clinical stage, the association of pretreatment PET with improved survival was most prominent in stage I patients. PET was previously considered to have limited utility in early-stage patients due to the lower incidence of distant metastasis in this population.[16] Cuellar et al[17] even suggested PET/CT to be detrimental in cTis and cT1, N0 esophageal adenocarcinoma because of unwarranted biopsies in this group of patients with low rates of nodal and distant metastasis. However, another study reported a substantial impact of PET in this group. In patients who were planned for resection, the addition of PET to conventional modalities altered further management in up to 25% of patients.[18] Detecting occult lymph node or distant metastasis before surgery is important because patients upstaged pathologically might have less benefit from surgery. In our study, pretreatment PET had more substantial impact in stage I patients than in stage II and stage III

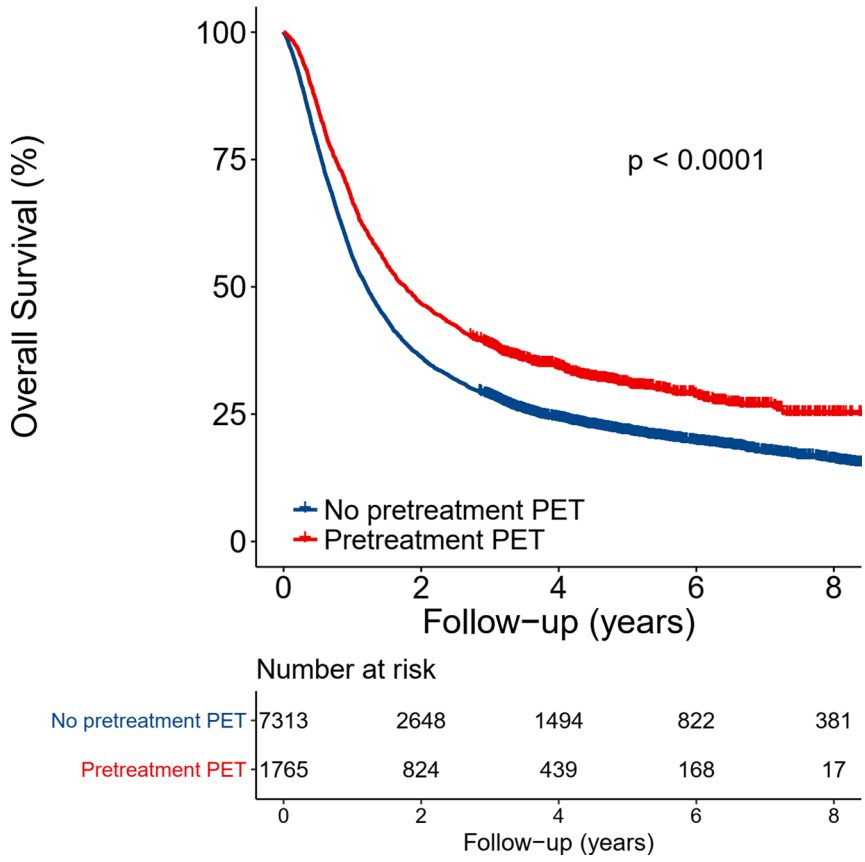


**FIGURE 2.** Kaplan-Meier curves of OS based on usage of pretreatment PET.

patients, possibly through precise staging and identification of true early-stage patients.

A parallel observation is that the impact of pretreatment PET is also more prominent in clinical N0 than that in clinical nodal-positive patients. The 5-year survival rate for N0 esophageal cancer patients is 47.1%, whereas it is only 25.3% for nodal positive patients. Accurate pretreatment diagnosis of lymph node metastasis is essential in both treatment selection and prognosis prediction. Although EUS combined with CECT is more sensitive than PET for detecting locoregional lymph nodes, the high negative predictive value of PET may be beneficial in identifying true early disease. A recent retrospective study demonstrated that lymph node status determined by PET is independently associated with recurrence-free survival (lymph node positive vs lymph node negative; HR, 1.90; $P = 0.045$) and OS (HR, 2.62; $P = 0.01$).[19] The usage of pretreatment PET likely resulted in more accurate staging of lymph nodes and hence optimal treatment strategies such as preoperative chemoradiation rather than surgery alone as well as the avoidance of adverse effect of unnecessary chemotherapy or radiotherapy.

Another possible means for the benefit of pretreatment PET is the influence of radiotherapy fields. Primary tumor localization and extent are usually defined endoscopically, but radiotherapy planning requires localization on CT. One study found that defining the tumor extent based on CT alone may exclude FDG-avid regions in up to 76% of patients.[20] A literature review focusing on the impact of PET/CT in radiation treatment of esophageal cancer demonstrated improved visualization of target structures and utility of PET SUV in the guidance of automatic gross tumor contouring.[21] The information provided by PET/CT allows radiation oncologists to more confidently designate the gross tumor area and therefore more accurately plan the radiation field accordingly. This may improve the outcomes of radiotherapy by lowering the possibility that the tumor is geometrically missed and by also decreasing toxicity by means of reducing the radiotherapy field margins needed for an uncertain tumor extent.

Pretreatment $^{18}$F-FDG PET has been established to have a prognostic value in esophageal malignancies. PET parameters, such as the SUV, total lesion glycolysis, and metabolic tumor value, predict resectability and curative effectiveness.[22,23] Previous studies showed that pretreatment $^{18}$F-FDG PET was able to differentiate superficial tumor infiltrations and correlated with clinicopathological prognosis.[24–26] $^{18}$F-FDG PET also has a clinical usage for prognostic stratification. Duong et al[27] showed that $^{18}$F-FDG PET altered the clinical management in esophageal cancer and enabled superior prognostic stratification over conventional modalities. In our study, staging and prognostic stratification was achieved in all patients regardless of the presence or absence of pretreatment PET. However, the 5-year survival rate was superior across all disease stages in the pretreatment PET group than that in the no pretreatment PET group and in previous studies, reflecting a more precise management for the patients in the PET group.

There are some limitations to our study. The usage of pretreatment PET was at the discretion of the treating physician. Although PET staging is included in the NHI, there may have been patients whose PET was paid out of pocket; these patients would erroneously be categorized under patients without staging PET. There may have been a minority number of studies that were performed with PET alone instead of PET/CT. Information on performance status, which is a known prognostic factor, was unavailable. Selection bias and residual or unmeasured confounding are likely, as in

**TABLE 2.** Univariate and Multivariable Cox Proportional Hazards Model for OS (n = 9078)

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| **Variable** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| Age, continuous | 1.02 (1.00–1.04) | 0.07 | 1.01 (1.01–1.01) | <0.001 |
| Sex | | | | |
| Male | Reference | | Reference | |
| Female | 0.79 (0.72–0.87) | <0.001 | 0.82 (0.74–0.90) | <0.001 |
| AJCC stage | | | | |
| I | Reference | | Reference | |
| II | 1.91 (1.69–2.16) | <0.001 | 1.76 (1.54–2.00) | <0.001 |
| III | 3.06 (2.73–3.43) | <0.001 | 2.68 (2.35–3.05) | <0.001 |
| Tumor location | | | | |
| Unspecified | Reference | | Reference | |
| Cervical | 0.88 (0.77–1.01) | 0.08 | 0.77 (0.67–0.88) | <0.001 |
| Thoracic | 0.76 (0.71–0.82) | <0.001 | 0.83 (0.77–0.88) | <0.001 |
| Abdominal | 0.37 (0.21–0.64) | <0.001 | 0.48 (0.28–0.84) | 0.01 |
| Histological type, n (%) | | | | |
| Squamous cell carcinoma | Reference | | Reference | |
| Adenocarcinoma like | 0.99 (0.88–1.12) | 0.86 | 1.03 (0.91–1.17) | 0.60 |
| Treatment, n (%) | | | | |
| Operation alone | Reference | | Reference | |
| Operation + (C)RT | 1.28 (1.13–1.47) | <0.001 | 1.00 (0.88–1.14) | 0.99 |
| Neoadjuvant + operation | 1.16 (1.06–1.28) | 0.002 | 0.70 (0.63–0.78) | <0.001 |
| CCRT alone | 2.60 (2.39–2.84) | <0.001 | 1.57 (1.42–1.73) | <0.001 |
| Other | 2.11 (1.94–2.30) | <0.001 | 1.31 (1.19–1.44) | <0.001 |
| Pretreatment PET | | | | |
| No | Reference | | Reference | |
| Yes | 0.74 (0.70–0.79) | <0.001 | 0.78 (0.73–0.83) | <0.001 |

AJCC, American Joint Committee on Cancer; (C)RT, radiotherapy or chemoradiotherapy; CCRT, concurrent chemoradiotherapy.

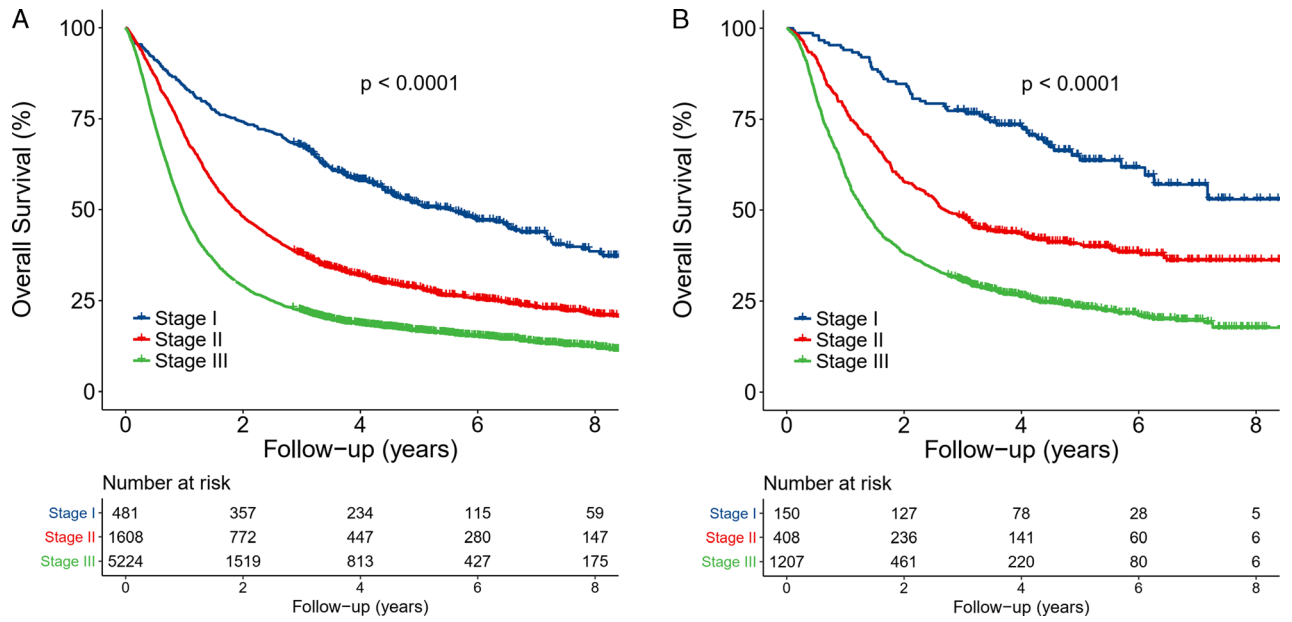


**FIGURE 3.** Kaplan-Meier survival curves by clinical stage subgroups in (**A**) the no pretreatment PET group and (**B**) the pretreatment PET group.

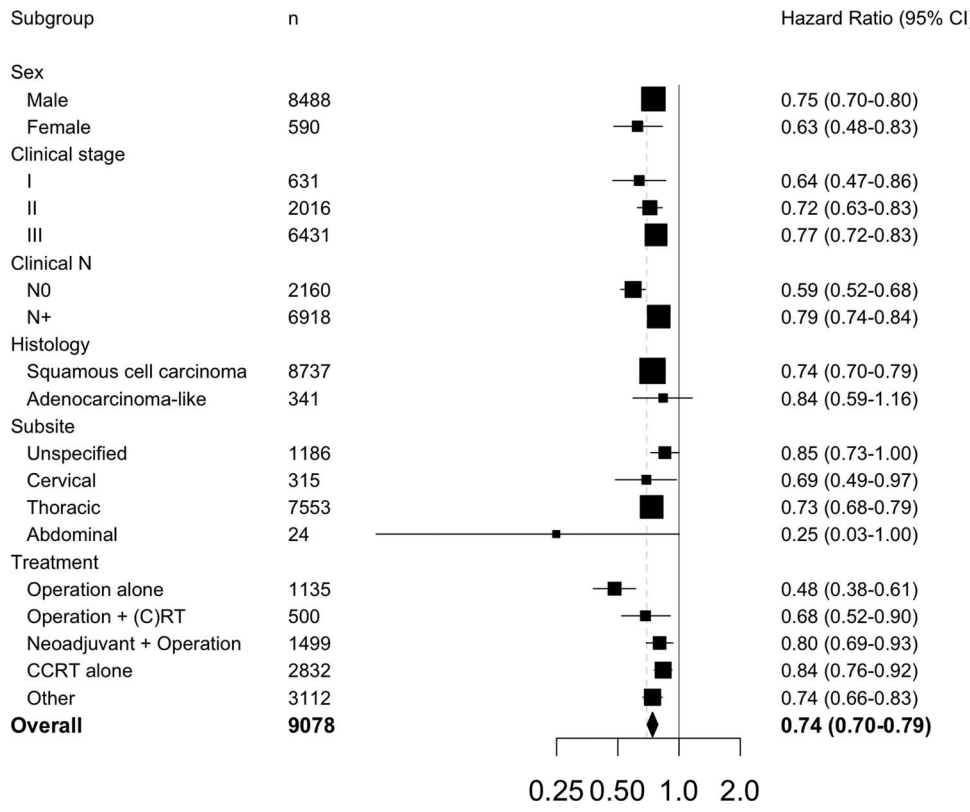


**FIGURE 4.** Forest plot of Cox proportional hazards regression illustrating the impact of pretreatment PET on OS by subgroup.

all retrospective studies. Despite these limitations, a major strength of this study is the use of a nationwide, population-based registry with detailed baseline and treatment information. Lifelong follow-up was possible with linkage with the national Cause of Death database.

In conclusion, utilization of pretreatment $^{18}$F-FDG PET was associated with improved OS in nonmetastatic esophageal cancer. Adhering to guideline suggestions and routine use of PET for staging and pretreatment evaluation may improve outcomes, owing to the established benefits of PET for a more accurate evaluation of nodal status, early detection of distant metastasis, and radiotherapy planning.

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