



# Prognostic Value of Primary Tumor and Immune Organ Metabolic Parameters Derived from Pretreatment <sup>18</sup>F-FDG PET/CT in Gastric Adenocarcinoma: A Retrospective Survival Analysis

Mide Adenokarsinomunda Tedavi Öncesi <sup>18</sup>F-FDG PET/BT ile Elde Edilen Primer Tümör ve İmmün Organ Metabolik Parametrelerinin Prognostik Değeri: Retrospektif Sağkalım Analizi

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## Abstract

**Objective:** To investigate the association of primary tumor volume-based parameters and immune organ (liver, spleen, bone marrow) metabolic parameters and their derived ratios [spleen-to-liver ratio (SLR), bone marrow-to-liver ratio (BLR), spleen-to-bone marrow ratio (SBR)], measured on pretreatment <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT), with overall survival in gastric adenocarcinoma.

**Methods:** 127 patients with histopathologically confirmed gastric adenocarcinoma who underwent pretreatment <sup>18</sup>F-FDG PET/CT were retrospectively evaluated. Maximum standardized uptake value, mean standardized uptake value, metabolic tumor volume, total lesion glycolysis (TLG) and immune-organ SUVs were measured and the ratios calculated. Survival analyses used the Kaplan-Meier method, log-rank test, and Cox regression.

**Results:** There were 91 death events (71.7%); the Kaplan-Meier median overall survival was 16.56 months, with 1-, 3-, and 5-year survival rates of 58.3%, 33.1%, and 28.1%, respectively. No significant independent association with overall survival was demonstrated for any of the primary-tumor or immune-organ PET/CT parameters; the SBR was lower in deceased patients (p=0.041) and showed a non-significant protective trend at the univariate level [hazard ratio (HR)=0.802 per 1 standard deviation (SD); 95% confidence interval (CI) 0.621–1.038; p=0.093], which was not supported by cut-off-based or multivariable analyses. In the primary multivariable model, distant metastasis independently increased the hazard of death (HR=1.798; 95% CI 1.187-2.723; p=0.006), whereas TLG SLR, and BLR showed no independent significance. In the stage-adjusted model, advanced stage remained independently associated with OS (HR=4.403; p=0.001).

**Conclusion:** In this gastric adenocarcinoma cohort with a high proportion of advanced-stage disease, no independent association with overall survival was demonstrated for any of the evaluated tumor- or immune-organ PET/CT parameters; established clinicopathological factors showed stronger prognostic associations than the PET-derived parameters. The prognostic role of immune organ metabolism in gastric cancer should be evaluated in large prospective studies.

**Keywords:** Stomach neoplasms, <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography prognosis, spleen, bone marrow

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## Öz

**Amaç:** Mide adenokarsinomlu hastalarda tedavi öncesi  $^{18}\text{F}$ -florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi ( $^{18}\text{F}$ -FDG PET/BT) ile ölçülen primer tümör volüm-tabanlı parametrelerinin (maksimum standartlaştırılmış tutulum değeri, ortalama standartlaştırılmış tutulum değeri, metabolik tümör hacmi, total lezyon glikolizi (TLG) ve immün organ (karaciğer, dalak, kemik iliği) metabolik parametreleri ile bunlardan türetilen oranların (dalak/karaciğer [SLR], kemik iliği/karaciğer [BLR]) genel sağkalım (GS) ile ilişkisinin araştırılması amaçlandı.

**Yöntem:** Histopatolojik olarak doğrulanmış gastrik adenokarsinomu bulunan ve tedavi öncesi  $^{18}\text{F}$ -FDG PET/BT yapılan 127 hasta retrospektif olarak değerlendirildi. Maksimum standartlaştırılmış tutulum değeri, ortalama standartlaştırılmış tutulum değeri, metabolik tümör hacmi, total lezyon glikolizi (TLG) ve immün organların standartlaştırılmış tutulum değerleri ölçüldü ve ilgili oranlar hesaplandı. Sağkalım analizlerinde Kaplan–Meier yöntemi, log-rank testi ve Cox regresyonu kullanıldı.

**Bulgular:** Toplam 91 ölüm (%71,7) gerçekleşti. Kaplan–Meier yöntemiyle hesaplanan medyan genel sağkalım 16,56 ay olup 1, 3 ve 5 yıllık sağkalım oranları sırasıyla %58,3, %33,1 ve %28,1 idi. Primer tümör veya immün organ PET/BT parametrelerinin hiçbirinin genel sağkalımla anlamlı bağımsız ilişkisi gösterilemedi. SBR, yaşamını yitiren hastalarda daha düşüktü ( $p=0,041$ ) ve tek değişkenli analizde istatistiksel olarak anlamlı olmayan koruyucu yönde bir eğilim gösterdi [bir standart sapma (SD) artış başına hazard oranı (HR)=0,802; %95 güven aralığı (GA): 0,621–1,038;  $p=0,093$ ]. Ancak bu bulgu, eşik değere dayalı veya çok değişkenli analizlerle desteklenmedi. Birincil çok değişkenli modelde uzak metastaz, ölüm hazardını bağımsız olarak artırırken (HR=1,798; %95 GA: 1,187–2,723;  $p=0,006$ ), TLG, SLR ve BLR bağımsız istatistiksel anlamlılık göstermedi. Evreye göre düzeltilmiş modelde ileri evre, genel sağkalımla bağımsız olarak ilişkili olmaya devam etti (HR=4,403;  $p=0,001$ ).

**Sonuç:** İleri evre hastalığın yüksek oranda temsil edildiği bu mide adenokarsinomu kohortunda değerlendirilen tümör ve immün organ PET/BT parametrelerinin hiçbirisi için bu kohortta genel sağkalımla bağımsız bir ilişki gösterilemedi; yerleşik klinikopatolojik faktörler, PET-türevi parametrelerden daha güçlü prognostik ilişkiler gösterdi. İmmün organ metabolizmasının mide kanserindeki prognostik rolü, geniş serili prospektif çalışmalarla değerlendirilmelidir.

**Anahtar Kelimeler:** Mide neoplazileri,  $^{18}\text{F}$ -florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi, z prognoz, dalak, kemik iliği

## Introduction

Gastric cancer is the fifth most common malignancy worldwide and remains a leading cause of cancer-related death; a substantial proportion of patients are diagnosed at an advanced stage and prognosis is poor (1).  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) is widely used for staging and the assessment of distant metastases in gastric cancer. The prognostic value of semiquantitative metabolic parameters of the primary tumor maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ), mean SUV ( $\text{SUV}_{\text{mean}}$ ), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) remains controversial; although high tumor uptake has been suggested to be associated with worse survival, considerable heterogeneity exists across individual studies. A recent study from our center likewise showed that distant metastasis, local invasion, and vascular invasion were associated with primary tumor metabolism regardless of HER2 status, while the prognostic role of PET parameters remained unresolved (2).

Meanwhile,  $^{18}\text{F}$ -FDG uptake in the organs of the reticuloendothelial system has been proposed as a non-invasive surrogate of the host systemic inflammatory/immune response to the tumor. In gastric cancer, the bone marrow-to-liver  $\text{SUV}_{\text{ratio}}$  bone marrow-to-liver ratio (BLR) was reported to be an independent predictor of recurrence-free and overall survival (OS) after curative resection (3). A high spleen-to-liver  $\text{SUV}_{\text{ratio}}$  spleen-to-liver ratio (SLR) has been associated with poor survival after ipilimumab in metastatic

melanoma (4), bone marrow uptake predicted distant recurrence in resected breast cancer (5), and bone marrow and spleen uptake were prognostic in colorectal cancer (6). Associations of secondary lymphoid organ metabolism with survival have also been reported in advanced lung cancer patients treated with immune checkpoint inhibitors (7,8), and similar findings have been shown in lymphoma (9,10), cervical cancer (11), and breast cancer (12). In gastric cancer, reticuloendothelial system uptake has been linked to the tumor immune microenvironment and prognosis (13), and diffuse splenic uptake to poor prognosis (14). These observations are consistent with growing evidence for the central role of systemic immunity in tumor progression (15,16,17,18). However, the prognostic value of these parameters in predominantly advanced-stage gastric adenocarcinoma has not been adequately investigated.

The aim of this study was to investigate the association of primary tumor volume-based parameters and immune organ (liver, spleen, bone marrow) metabolic parameters and their derived ratios, measured on pretreatment  $^{18}\text{F}$ -FDG PET/CT, with OS in patients with gastric adenocarcinoma.

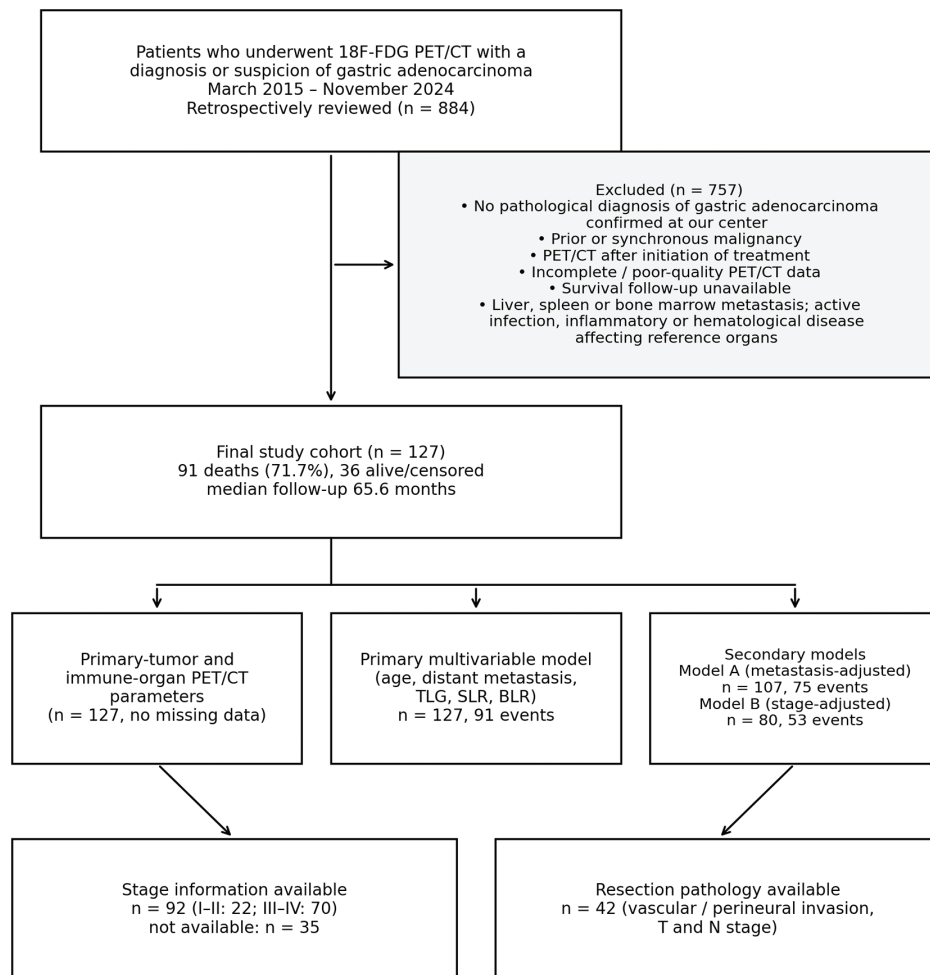
## Materials and Methods

### Patient Characteristics

This study consisted of 127 consecutive patients with histopathologically confirmed gastric adenocarcinoma referred to the Nuclear Medicine Clinic of University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye, for baseline  $^{18}\text{F}$ -FDG PET/CT

prior to treatment. Patients with complete pretreatment PET/CT data, physiological liver, spleen, and bone marrow measurements, and available survival follow-up were included; clinical and pathological variables were extracted when available. Between March 2015 and November 2024, 884 patients who underwent PET/CT with a diagnosis or suspicion of gastric adenocarcinoma at our hospital were retrospectively reviewed. The inclusion criterion was a pathological diagnosis of gastric adenocarcinoma confirmed at our center; all patients had endoscopic biopsy results, pathology specimens obtained at external centers were re-evaluated at our institution, and a subset also had pathological results from total resection material, in which perineural invasion, vascular invasion, local invasion (T stage), nodal status, and tumor size were evaluated.

Patients were excluded for the following reasons: absence of a pathological diagnosis of gastric adenocarcinoma confirmed at our center, prior or synchronous malignancy, PET/CT performed after the initiation of any oncological treatment, incomplete or poor-quality PET/CT data, and unavailable survival follow-up. To ensure that the reference-organ measurements reflected physiological uptake, patients with focal or diffuse liver, spleen, or bone marrow metastases, active infection or inflammatory disease, or known hematological disorders at the time of PET/CT were also excluded. After application of these criteria, 757 patients were excluded and the final study cohort comprised 127 patients; the patient selection process is summarized in Figure 1.



**Figure 1.** Flow diagram of patient selection. Of 884 patients who underwent  $^{18}\text{F}$ -FDG PET/CT with a diagnosis or suspicion of gastric adenocarcinoma between March 2015 and November 2024, 127 met the inclusion criteria and formed the final study cohort

$^{18}\text{F}$ -FDG: Fluorine-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

Retrospective data, covering the period from March 2015 to November 2024, were collected from institutional records, the hospital information system, and PACS. Data collection encompassed patient demographics (age, sex), tumor characteristics, including primary tumor location and histological subtype (Lauren classification), HER2 status, regional lymph node and distant metastatic status, serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9)], and documented therapeutic interventions. Total resection material was available in 42 patients, while the remaining 85 patients had only biopsy material. Tumor location was divided into four groups: esophagogastric junction (EGJ)-cardia, corpus-fundus, antrum, and diffuse; patients with tumors involving more than one region were classified as diffuse. Tumors involving the EGJ with an epicenter located >2 cm into the proximal stomach were staged as esophageal carcinomas and were not included, whereas cancers within the gastric cardia not involving the EGJ were staged as gastric carcinomas. The classification of tumor location was based on the region in which the tumor was pathologically proven, not solely on the areas of FDG uptake. The American Joint Committee on Cancer (AJCC) staging system was used to stage the tumor. The patient pool and imaging protocol were drawn from the gastric adenocarcinoma series previously published from our center (2). The treatment data was obtained through patient files and an electronic treatment archive system. OS was determined by calculating the months between the date of diagnosis and the date of death registered in the death notification system; surviving patients were censored at the date of last follow-up. The date of histopathological diagnosis was retained as the primary time origin for all survival analyses, in keeping with the conventional definition of OS in gastric cancer and to allow comparison with previous studies; because PET/CT was performed in close temporal proximity to the biopsy, the choice of origin was not expected to affect the results materially. The interval between the biopsy date and the PET/CT date was recorded for each patient, and, because the investigated parameters were derived from PET/CT, a sensitivity analysis in which OS was calculated from the date of PET/CT was additionally performed. Among treatment variables, surgical resection of the primary tumor (n=42) could be reliably ascertained from the pathology records and was used as the treatment covariate; detailed systemic treatment data were not available in the analysis dataset. Median follow-up (65.6 months) was estimated using the reverse Kaplan-Meier method. This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki following approval by the Clinical Research Ethics Committee of University of Health Sciences

Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 19, date: 09.01.2023). Owing to the retrospective design, the requirement for individual informed consent was waived.

### **<sup>18</sup>F-FDG PET/CT Imaging Protocol**

Imaging was conducted after a six-hour fast, provided patients' blood glucose level was  $\leq 150$  mg/dL. An intravenous dose of <sup>18</sup>F-FDG (0.09-0.14 mCi/kg, or 3.33-5.18 MBq/kg) was subsequently administered. Post-injection, patients rested in a quiet environment for 60 minutes before whole-body PET/CT imaging. Studies were acquired on either a GE Discovery MI 3-Ring system (GE Healthcare, Milwaukee, WI, USA) or a Siemens Biograph 6 LSO HI-REZ scanner (Siemens Medical Solutions, Chicago, IL, USA) employing LYSO and LSO crystal detectors, respectively. Low-dose CT was used for attenuation correction and anatomical localization, with acquisition parameters of 40–60 mAs, 140 kV, and 5 mm slice thickness on both systems. Of the 127 examinations, 53 were performed on the GE Discovery MI and 74 on the Siemens Biograph 6 system, using the manufacturers' standard iterative reconstruction protocols. Both systems employed manufacturer-standard ordered-subset expectation-maximization (OSEM) iterative reconstruction with CT-based attenuation correction and standard corrections for scatter, random coincidences, and decay; SUV values were normalized to body weight. Because acquisitions spanned a nine-year period, the exact reconstruction settings (number of iterations, number of subsets, and post-reconstruction Gaussian filtering) were not uniformly retrievable for every examination. The two systems were used in parallel over the study period without a formal cross-calibration or harmonization procedure. Because per-patient scanner assignment was not recorded in the study database, individual patients could not be linked to a specific scanner, and a scanner-stratified sensitivity analysis of the PET-derived parameters could not be performed. Imaging and SUV measurements were performed in accordance with the recommendations of the EANM procedure guidelines for tumour imaging (19).

### **Image Analysis**

A specialized workstation (GE Advanced Workstation, version 3.2, with the PET VCAR quantification module; GE Healthcare) was used to analyze the images. Maximum-intensity projection images were used to first locate the primary gastric tumor, and then the fused axial, sagittal, and coronal planes were employed for a thorough evaluation. Two experienced nuclear medicine physicians independently reviewed all PET/CT images; any discrepancies were resolved by consensus. Both readers reviewed all studies independently for lesion identification;

quantitative measurements were obtained from a single consensus VOI after joint review, and manual adjustment of the semiautomatic VOI was limited to excluding adjacent physiological or inflammatory uptake. Interobserver reproducibility of the quantitative measurements was not formally assessed. Both readers were blinded to the quantitative PET-derived measurements but had access to the relevant clinical information and cross-sectional imaging findings required for routine interpretation.

Primary-tumor volume of interest (VOI) delineation was performed semiautomatically on fused PET/CT images and manually adjusted in three orthogonal planes to encompass the whole metabolically active tumor while excluding adjacent physiological FDG uptake (gastric wall, bowel), non-tumoral inflammatory uptake, and unrelated hypermetabolic foci, with CT morphology used to confirm the anatomical extent of the lesion. Primary tumors with low or absent FDG uptake, in which the lesion could not be visually distinguished from physiological gastric wall activity, were delineated with reference to the CT-defined (mural thickening) extent of the tumor ( $n=10$ ); no patient was excluded on the basis of low tumor FDG avidity.  $SUV_{max}$  and  $SUV_{mean}$  were extracted from the final VOI. MTV was defined as the volume of all voxels within the primary-tumor VOI exceeding a fixed threshold of 40% of  $SUV_{max}$ , and total TLG was computed as the product of MTV and  $SUV_{mean}$ .

Physiological FDG uptake in immune-related organs was additionally measured to characterize the systemic immune-metabolic response. A spherical VOI of fixed diameter was placed in the right hepatic lobe (5 cm) and in the spleen (3 cm), avoiding focal lesions, vessels, and organ margins, to obtain the  $SUV_{max}$  values for the liver ( $SUV_{liver}$ ) and spleen ( $SUV_{spleen}$ ). For bone marrow uptake, separate spherical volumes of interest were placed in each of the L3, L4, and L5 vertebral bodies, avoiding degenerative or focal lesions;  $SUV_{BM}$  was defined as the highest of the  $SUV_{max}$  values measured across these three vertebrae. All organ measurements were thus consistently based on  $SUV_{max}$ , so that the numerator and denominator of each derived ratio relied on the same SUV metric. The liver was used as the reference tissue, owing to its relatively stable physiological FDG uptake, and the following ratios were derived: the SLR ( $SLR = SUV_{spleen} / SUV_{liver}$ ), the BLR ( $BLR = SUV_{BM} / SUV_{liver}$ ), and the spleen-to-bone-marrow ratio ( $SBR = SUV_{spleen} / SUV_{BM}$ ). Although both  $SUV_{max}$ - and  $SUV_{mean}$ -based reference-organ measurements have been used in the literature, a uniform  $SUV_{max}$ -based approach was adopted to avoid mixing different SUV metrics within a single ratio.

## Statistical Analysis

Data were analyzed using the Jamovi 2.6.19.0 program. Categorical variables are reported as frequency and percentage, and continuous variables as mean  $\pm$  standard deviation (SD) or median [(range/interquartile range (IQR))], as appropriate to their distribution. Differences in PET/CT parameters between patients who died during follow-up and those who remained alive were assessed using the independent-samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using the Pearson chi-square test, or Fisher's exact test when expected cell frequencies were low. Relationships between primary-tumor and immune-organ PET/CT metabolic parameters were assessed using Spearman's rank correlation coefficient.

Overall survival was estimated using the Kaplan-Meier method, with group comparisons by the log-rank test at both the median value and a data-optimized (maximally selected) cut-off for each parameter; p-values from the latter were corrected for multiple cut-point testing using a permutation procedure to avoid inflation of type-I error. One-, three-, five-, seven-, and nine-year OS estimates were reported with 95% confidence intervals (CIs). The association between each continuous PET/CT parameter and OS was evaluated using univariate Cox proportional-hazards regression. In the univariate analyses, hazard ratio (HR), 95% CIs, and p values were calculated. To test the independent prognostic value of the PET parameters, the pre-specified primary multivariable Cox model included age, distant metastasis, and the selected PET parameters (TLG, SLR, and BLR). TLG was selected as the representative volumetric tumor-burden metric, whereas SLR and BLR were selected a priori as the principal liver-referenced immune-organ ratios based on previous literature (2,3); the SBR was not part of this pre-specified model. A metastasis-adjusted model extended with additional clinical covariates (sex, CEA, CA19-9) (Model A) and a stage-adjusted model in which the AJCC stage group replaced distant metastasis (Model B) were constructed as secondary (exploratory) analyses in smaller complete-case subsets. To limit model complexity in these smaller subsets, the secondary models included TLG and SLR as representative tumor- and immune-organ PET parameters. The proportional hazards assumption of the Cox models was assessed based on the association of scaled Schoenfeld residuals with time. In the univariate analyses and in the primary multivariable model, continuous PET/CT parameters were evaluated per 1 SD increase. In the secondary models (Models A and B), TLG, CEA, and CA19-9 were  $\log_2$ -transformed owing to their right-skewed distributions; in these models, the HR

values for these variables were interpreted as the change in hazard per doubling of the respective parameter. Complete-case analysis was used for missing data. Two pre-specified sensitivity analyses were performed: (i) all survival analyses were repeated with OS calculated from the date of PET/CT instead of the date of diagnosis, and (ii) the primary multivariable model was additionally adjusted for surgical resection of the primary tumor (yes vs. no) as the available treatment covariate.

The discriminatory performance of the parameters for OS was evaluated at 1, 3, and 5 years using inverse-probability-of-censoring-weighted (IPCW) cumulative/dynamic time-dependent ROC analysis, which accounts for censoring; 95% CIs for the time-dependent area under the curve (AUC) values were obtained by bootstrapping (400 resamples). The time-dependent ROC analysis was defined as a secondary (exploratory) analysis. Correlations between primary-tumor and immune-organ metabolic parameters were assessed using Spearman's rank correlation coefficient. A two-sided  $p$  value  $<0.05$  was considered statistically significant.

## Results

A total of 127 patients were included in the analysis [median age 62.0 years (IQR 55.0-72.0); range 26-89]; advanced-stage disease was highly represented in the cohort (76% of patients with known stage were stage III-IV). There were 91 death events (71.7%) and 36 (28.3%) alive/censored observations. The median follow-up estimated by the reverse Kaplan-Meier method was 65.6 months. Baseline patient, tumor, and treatment characteristics are summarized in Table 1. Forty-two patients (33.1%) underwent surgical resection of the primary tumor, whereas 85 (66.9%) had endoscopic ( $n=74$ ) or external-center ( $n=11$ , re-evaluated at our institution) biopsy material only. The interval between the date of histopathological diagnosis and PET/CT did not exceed one month in any patient. The Kaplan-Meier median OS was 16.56 months, and the 1-, 3-, 5-, 7-, and 9-year survival probabilities were estimated at 58.3%, 33.1%, 28.1%, 28.1%, and 28.1%, respectively (Figure 2).

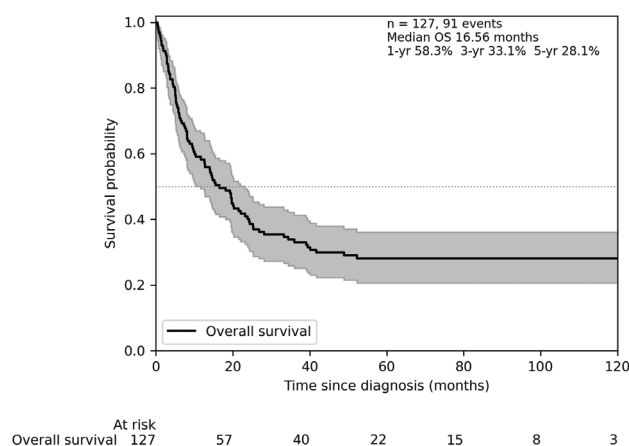
For the primary tumor, the median  $SUV_{max}$  was 8.86 (IQR 5.69-15.29),  $SUV_{mean}$  4.44 (2.94-7.16), MTV 30.64  $cm^3$  (16.61-54.40), and TLG 146.28 g (56.28-298.74). For the immune organs, the median liver  $SUV_{max}$  was 2.81, spleen  $SUV_{max}$  2.38, and bone marrow  $SUV_{max}$  2.65; the median SLR was 0.83, BLR 0.93, and SBR 0.85. Organ metabolisms were strongly and significantly inter-correlated: liver-spleen  $r=0.72$ , spleen-bone marrow  $r=0.55$ , liver-bone marrow  $r=0.54$  (all  $p<0.001$ ).

Apart from the SBR, no PET/CT parameter differed significantly between survivors and deceased patients; the SBR was significantly lower in deceased patients ( $p=0.041$ ), with a borderline trend for the SLR ( $p=0.089$ ). In univariate Cox models, primary-tumor  $SUV_{max}$ ,  $SUV_{mean}$ , MTV, and TLG; liver, spleen, and bone marrow  $SUV_{max}$  values; and the SLR, BLR, and SBR were not significantly associated with OS; the SBR showed a non-significant protective trend (HR=0.802 per 1 SD; 95% CI 0.621-1.038;  $p=0.093$ ) (Table 2). This trend was likewise not supported by the median cut-off analysis ( $p=0.112$ ), the permutation-corrected maximally selected cut-off analysis (corrected  $p=0.32$ ), or a multivariable model including the SBR (HR=0.805; 95% CI 0.613-1.056;  $p=0.117$ ); permutation-corrected cut-off analyses were non-significant for all parameters (lowest corrected  $p=0.086$ , for spleen  $SUV_{max}$ ) (Figure 3). In the secondary, time-dependent (IPCW) ROC analysis, discriminatory performance was low at all time points; the highest time-dependent AUC values (oriented so that values  $>0.50$  indicate discrimination in the direction of the observed association) were obtained for the SBR at 3 years (0.594; 95% CI 0.475-0.691) and for MTV at 5 years (0.595; 95% CI 0.461-0.734), and the CIs, included 0.50 for all parameters. In the primary multivariable Cox model (age, distant metastasis, TLG, SLR, BLR;  $n=127$ , 91 events), distant metastasis independently increased the hazard of death (HR=1.798; 95% CI 1.187-2.723;  $p=0.006$ ), whereas TLG, SLR, and BLR entered into the model showed no independent significance; a borderline protective trend was observed for the SLR (HR=0.813; 95% CI 0.644-1.026;  $p=0.081$ ) (Table 3). In contrast, advanced stage (III-IV), distant metastasis, and elevated CEA and CA19-9 were significantly associated with survival (Table 2); these findings support the internal clinical validity of the dataset. In Kaplan-Meier subgroup analyses, advanced stage ( $p<0.001$ ) and distant metastasis (median 9.6 vs. 22.0 months;  $p=0.007$ ) were associated with markedly shorter survival, whereas non-intestinal Lauren type ( $p=0.125$ ) and HER2 positivity ( $p=0.184$ ) did not reach statistical significance (Figure 4).

In the subgroup with available resection pathology ( $n=42$ ), the presence of vascular invasion was associated with markedly shorter survival (log-rank  $p=0.004$ ; univariate Cox HR=3.596; 95% CI 1.407-9.189;  $p=0.008$ ). Borderline trends were observed for perineural invasion ( $p=0.077$ ), T3-T4 local invasion ( $p=0.094$ ), and nodal positivity ( $p=0.189$ ) (Figure 5).

In the secondary, extended multivariable models, clinical variables and PET parameters were evaluated together (Figure 6). In the metastasis-adjusted Model A ( $n=107$ ,

| <b>Table 1. Baseline patient, tumor, and treatment characteristics (n=127)</b>                                                                                                                                                                                                                      |                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>Characteristic</b>                                                                                                                                                                                                                                                                               | <b>n=127</b>                                    |
| Age, years, median (IQR); range                                                                                                                                                                                                                                                                     | 62.0 (55.0-72.0); 26-89                         |
| Sex, male/female, n (%)                                                                                                                                                                                                                                                                             | 89 (70.1)/38 (29.9)                             |
| <b>PET/CT indication, n (%)</b>                                                                                                                                                                                                                                                                     |                                                 |
| Initial staging                                                                                                                                                                                                                                                                                     | 96 (75.6)                                       |
| Diagnostic work-up                                                                                                                                                                                                                                                                                  | 31 (24.4)                                       |
| <b>Primary tumor location, n (%)</b>                                                                                                                                                                                                                                                                |                                                 |
| EGJ-cardia                                                                                                                                                                                                                                                                                          | 28 (22.0)                                       |
| Corpus-fundus                                                                                                                                                                                                                                                                                       | 40 (31.5)                                       |
| Antrum                                                                                                                                                                                                                                                                                              | 38 (29.9)                                       |
| Diffuse (more than one region)                                                                                                                                                                                                                                                                      | 21 (16.5)                                       |
| <b>Lauren classification, n (%)</b>                                                                                                                                                                                                                                                                 |                                                 |
| Intestinal                                                                                                                                                                                                                                                                                          | 94 (74.0)                                       |
| Diffuse                                                                                                                                                                                                                                                                                             | 8 (6.3)                                         |
| Indeterminate                                                                                                                                                                                                                                                                                       | 2 (1.6)                                         |
| Not available                                                                                                                                                                                                                                                                                       | 23 (18.1)                                       |
| <b>Histological differentiation, n (%)</b>                                                                                                                                                                                                                                                          |                                                 |
| Well                                                                                                                                                                                                                                                                                                | 8 (6.3)                                         |
| Moderate                                                                                                                                                                                                                                                                                            | 47 (37.0)                                       |
| Poor                                                                                                                                                                                                                                                                                                | 35 (27.6)                                       |
| Signet ring cell/mucinous/mixed                                                                                                                                                                                                                                                                     | 7 (5.5)/5 (3.9)/2 (1.6)                         |
| Not available                                                                                                                                                                                                                                                                                       | 23 (18.1)                                       |
| HER2 status, positive/negative, n (%)                                                                                                                                                                                                                                                               | 19 (15.0)/108 (85.0)                            |
| <b>Pathological material, n (%)</b>                                                                                                                                                                                                                                                                 |                                                 |
| Total resection of primary tumor                                                                                                                                                                                                                                                                    | 42 (33.1)                                       |
| Endoscopic biopsy only                                                                                                                                                                                                                                                                              | 74 (58.3)                                       |
| External-center material (re-evaluated at our institution)                                                                                                                                                                                                                                          | 11 (8.7)                                        |
| <b>AJCC stage group, n (%)</b>                                                                                                                                                                                                                                                                      |                                                 |
| I-II                                                                                                                                                                                                                                                                                                | 22 (17.3)                                       |
| III                                                                                                                                                                                                                                                                                                 | 14 (11.0)                                       |
| IV                                                                                                                                                                                                                                                                                                  | 56 (44.1)                                       |
| Not available                                                                                                                                                                                                                                                                                       | 35 (27.6)                                       |
| Distant metastasis, present / absent, n (%)                                                                                                                                                                                                                                                         | 57 (44.9)/70 (55.1)                             |
| CEA, ng/mL, median (IQR)                                                                                                                                                                                                                                                                            | 4.35 (1.87-22.71); available n=110              |
| CA19-9, U/mL, median (IQR)                                                                                                                                                                                                                                                                          | 21.8 (7.8-89.3); available n=113                |
| <b>Treatment, n (%)</b>                                                                                                                                                                                                                                                                             |                                                 |
| Surgical resection of primary tumor                                                                                                                                                                                                                                                                 | 42 (33.1)                                       |
| Systemic treatment                                                                                                                                                                                                                                                                                  | Not uniformly available in the analysis dataset |
| <b>PET/CT scanner, n (%)</b>                                                                                                                                                                                                                                                                        |                                                 |
| GE Discovery MI                                                                                                                                                                                                                                                                                     | 53 (41.7)                                       |
| Siemens Biograph 6                                                                                                                                                                                                                                                                                  | 74 (58.3)                                       |
| Diagnosis-to-PET/CT interval                                                                                                                                                                                                                                                                        | ≤1 month in all patients                        |
| Follow-up, months, median (reverse Kaplan-Meier)                                                                                                                                                                                                                                                    | 65.6                                            |
| Death events, n (%)                                                                                                                                                                                                                                                                                 | 91 (71.7)                                       |
| IQR: Interquartile range, PET/CT: Positron emission tomography/computed tomography, EGJ: Esophagogastric junction, HER2: Human epidermal growth factor receptor 2, AJCC: American Joint Committee on Cancer, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, GE: General electric |                                                 |



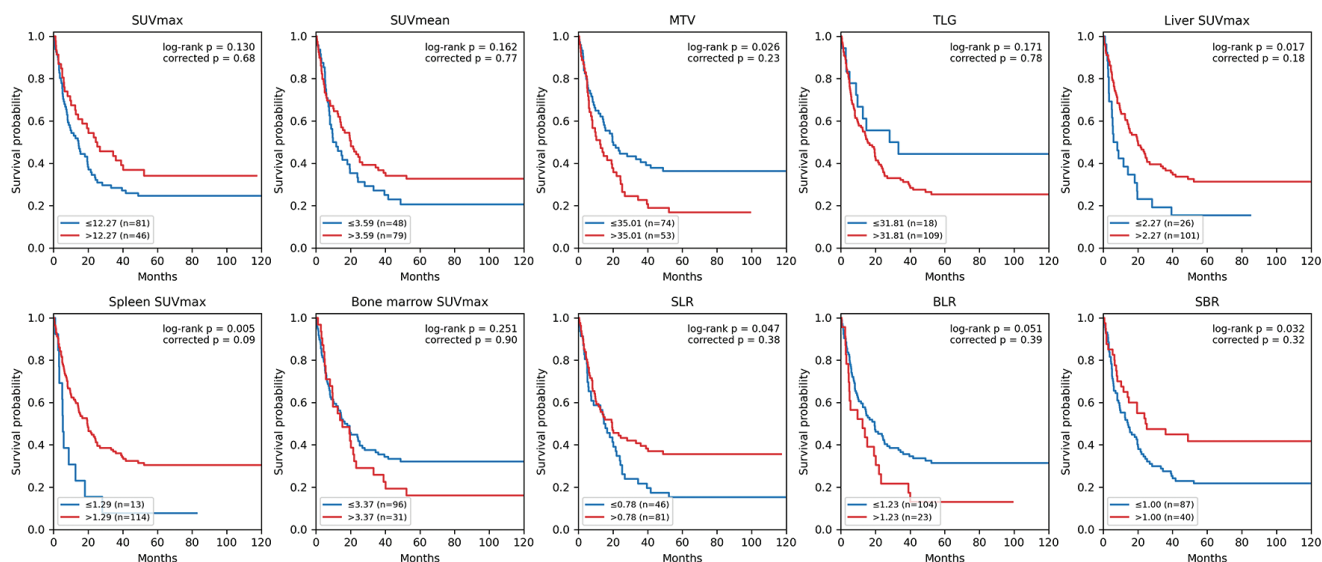
**Figure 2.** Kaplan-Meier overall survival curve for the entire cohort (n=127; 91 events) with numbers at risk. Survival was calculated from the date of histopathological diagnosis (biopsy date); the median overall survival was 16.56 months

75 events), no covariate retained independent statistical significance (distant metastasis: HR=1.384,  $p=0.262$ ; CA19-9: HR=1.063,  $p=0.116$ ; male sex: HR=1.577,  $p=0.090$ ) (Table 4). In the stage-adjusted Model B (n=80, 53 events), advanced stage was the only variable independently associated with OS (HR=4.403; 95% CI 1.781-10.890;  $p=0.001$ ) (Table 5); CEA ( $p=0.513$ ) and CA19-9 ( $p=0.291$ ) showed no independent significance. The PET parameters (TLG and SLR) remained non-significant in both secondary models. In the assessment based on Schoenfeld residuals, no evidence of violation of the proportional hazards assumption was found for any covariate in the primary model or in Models A and B (all  $p>0.05$ ). The variable-level distribution of missing data is summarized in Table 6; there were no missing observations for the PET/CT parameters. In both models, TLG and SLR provided no independent prognostic contribution. In the sensitivity analysis using the PET/CT date as the time origin (n=127, 91 events), the median OS was 15.93 months and the 1-, 3-, and

**Table 2. Univariate Cox regression analysis of PET metabolic and clinical parameters (n=127; events=91)**

| Parameter                              | Median (IQR)          | Deceased vs. alive, median (p) | HR (95% CI)          | p      | Optimal cut-off (corrected p) |
|----------------------------------------|-----------------------|--------------------------------|----------------------|--------|-------------------------------|
| <b>Primary tumor</b>                   |                       |                                |                      |        |                               |
| SUV <sub>max</sub>                     | 8.86 (5.69-15.29)     | 8.25 vs. 10.00 (0.514)         | 0.947 (0.770-1.166)  | 0.609  | 12.27 (0.678)                 |
| SUV <sub>mean</sub>                    | 4.44 (2.94-7.16)      | 4.37 vs. 4.70 (0.465)          | 1.006 (0.811-1.248)  | 0.956  | 3.59 (0.773)                  |
| MTV (cm <sup>3</sup> )                 | 30.64 (16.61-54.41)   | 33.87 vs. 28.00 (0.128)        | 1.137 (0.940-1.375)  | 0.187  | 35.01 (0.235)                 |
| TLG (g)                                | 146.28 (56.28-298.74) | 150.15 vs. 130.45 (0.526)      | 1.151 (0.941-1.407)  | 0.170  | 31.81 (0.780)                 |
| <b>Immune organs</b>                   |                       |                                |                      |        |                               |
| Liver SUV <sub>max</sub>               | 2.81 (2.41-3.33)      | 2.83 vs. 2.80 (0.991)          | 0.958 (0.774-1.185)  | 0.690  | 2.27 (0.182)                  |
| Spleen SUV <sub>max</sub>              | 2.38 (2.01-2.74)      | 2.34 vs. 2.41 (0.441)          | 0.862 (0.696-1.068)  | 0.175  | 1.29 (0.086)                  |
| Bone marrow SUV <sub>max</sub>         | 2.65 (1.98-3.29)      | 2.61 vs. 2.66 (0.716)          | 1.002 (0.825-1.218)  | 0.983  | 3.37 (0.896)                  |
| SLR                                    | 0.83 (0.71-0.93)      | 0.81 vs. 0.85 (0.089)          | 0.862 (0.696-1.067)  | 0.173  | 0.78 (0.383)                  |
| BLR                                    | 0.93 (0.76-1.16)      | 0.93 vs. 0.95 (0.558)          | 1.084 (0.887-1.325)  | 0.429  | 1.23 (0.391)                  |
| SBR                                    | 0.85 (0.71-1.07)      | 0.80 vs. 0.94 (0.041)          | 0.802 (0.621-1.038)  | 0.093  | 1.00 (0.317)                  |
| <b>Clinical variables</b>              |                       |                                |                      |        |                               |
| Distant metastasis (yes vs. no)        | –                     | –                              | 1.748 (1.157-2.640)  | 0.008  | –                             |
| Stage (III-IV vs. I-II)                | –                     | –                              | 4.585 (2.081-10.104) | <0.001 | –                             |
| CEA (per doubling)                     | –                     | –                              | 1.095 (1.009-1.188)  | 0.029  | –                             |
| CA19-9 (per doubling)                  | –                     | –                              | 1.098 (1.023-1.179)  | 0.009  | –                             |
| Sex (male vs. female)                  | –                     | –                              | 1.398 (0.876-2.229)  | 0.160  | –                             |
| Lauren (non-intestinal vs. intestinal) | –                     | –                              | 1.717 (0.853-3.457)  | 0.130  | –                             |
| HER2 (positive vs. negative)           | –                     | –                              | 0.664 (0.361-1.220)  | 0.187  | –                             |

For the continuous PET/CT parameters, HRs are per 1 standard deviation increase; for distant metastasis, yes vs. no; for stage, III-IV vs. I-II; for CEA and CA19-9, per doubling (log<sub>2</sub>-transformed). Deceased vs. alive comparison by Mann-Whitney U test. Optimal cut-off: maximally selected log-rank statistic (cut-points between the 10th and 90th percentiles) with permutation-corrected p (1000 permutations). HR: Hazard ratio; CI: Confidence interval; IQR: Interquartile range; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; SLR: Spleen-to-liver SUV<sub>rat</sub>; BLR: Bone marrow-to-liver SUV ratio; SBR: Spleen-to-bone-marrow SUV ratio



**Figure 3.** Kaplan-Meier overall survival curves according to maximally selected cut-offs of the primary-tumor ( $SUV_{max}$ ,  $SUV_{mean}$ , MTV, TLG) and immune-organ (liver, spleen, and bone marrow  $SUV_{max}$ ; SLR, BLR, SBR) PET/CT parameters. Uncorrected log-rank p values and permutation-corrected p values are given in each panel; none of the comparisons remained significant after correction for multiple cut-point testing

$SUV_{max}$ : Maximum standardized uptake value,  $SUV_{mean}$ : Mean standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SBR: Spleen-to-bone marrow ratio, PET/CT: Positron emission tomography/computed tomography

**Table 3. Primary multivariable Cox model (age, distant metastasis, TLG, SLR, BLR; n=127; events=91)**

| Variable           | Unit     | HR    | 95% CI      | p     |
|--------------------|----------|-------|-------------|-------|
| Age                | 10 years | 1.068 | 0.901-1.266 | 0.449 |
| Distant metastasis | Yes/No   | 1.798 | 1.187-2.723 | 0.006 |
| TLG                | 1 SD     | 1.137 | 0.915-1.413 | 0.245 |
| SLR                | 1 SD     | 0.813 | 0.644-1.026 | 0.081 |
| BLR                | 1 SD     | 1.140 | 0.908-1.432 | 0.260 |

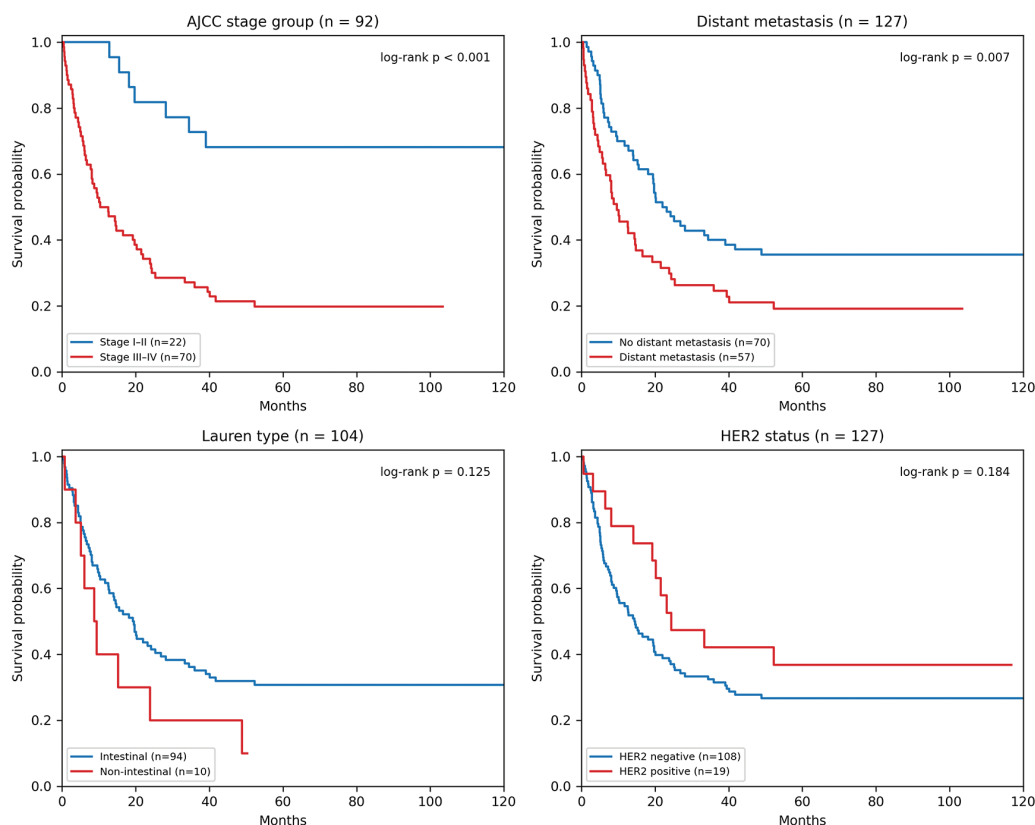
Pre-specified primary model; all variables were entered jointly. For the PET parameters, HRs are per 1 standard deviation (SD) increase; for age, per 10-year increase. Proportional hazards assumption (scaled Schoenfeld residuals): all  $p > 0.05$ . HR: Hazard ratio, CI: Confidence interval, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SD: Standard deviation

5-year survival rates were 58.3%, 33.9%, and 28.0%, respectively; no PET/CT parameter was significantly associated with OS in univariate Cox models (all  $p > 0.11$ ; SBR HR=0.816 per 1 SD; 95% CI 0.633–1.052;  $p=0.117$ ), and in the primary multivariable model distant metastasis remained independently associated with OS (HR=1.845; 95% CI 1.218–2.795;  $p=0.004$ ), whereas TLG ( $p=0.246$ ), SLR (HR=0.818;  $p=0.092$ ), and BLR ( $p=0.320$ ) did not. In the treatment-adjusted sensitivity model (age, distant metastasis, surgical resection, TLG, SLR, BLR;  $n=127$ ), surgical resection of the primary tumor was strongly associated with longer survival (HR=0.310; 95% CI 0.176–0.547;  $p<0.001$ ) and distant metastasis lost independent significance (HR=1.085; 95% CI 0.682–1.725;  $p=0.730$ ); in this model the SLR showed a protective association

(HR=0.729 per 1 SD; 95% CI 0.582–0.913;  $p=0.006$ ) and the BLR a nominal adverse association (HR=1.282; 95% CI 1.023–1.606;  $p=0.031$ ), while TLG remained non-significant (HR=1.217;  $p=0.085$ ). Because surgical resection is closely linked to stage and metastatic status, and these PET associations were not observed in the pre-specified models, they should be regarded as exploratory.

## Discussion

In this cohort of 127 gastric adenocarcinoma patients with a high proportion of advanced-stage disease, no independent association with OS was demonstrated for either primary tumor volume-based parameters or immune organ metabolic parameters measured on pretreatment  $^{18}F$ -FDG PET/CT, whereas the clinical prognostic signal



**Figure 4.** Kaplan-Meier overall survival curves according to AJCC stage group (I-II vs. III-IV;  $n=92$ ), distant metastasis status ( $n=127$ ), Lauren classification (intestinal vs. non-intestinal;  $n=104$ ), and HER2 status ( $n=127$ )

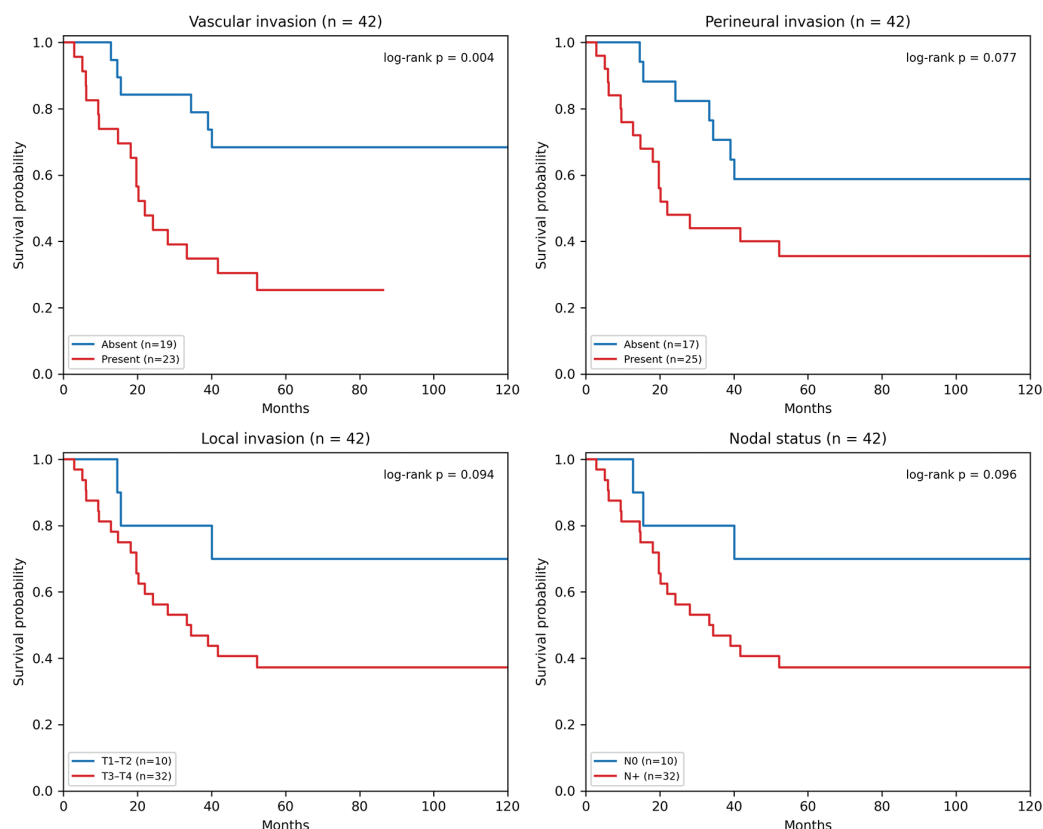
AJCC: American Joint Committee on Cancer, HER2: Human epidermal growth factor receptor 2

was preserved: distant metastasis was an independent prognostic factor in the primary multivariable model ( $HR=1.798$ ;  $p=0.006$ ), while advanced stage remained independently associated with OS in the subset with available stage information ( $HR=4.403$ ;  $p=0.001$ ). In Model A, extended with additional covariates, no single variable retained significance; this attenuation may partly reflect the smaller complete-case sample, fewer events, and covariance among clinical predictors. The significant associations observed for established clinical prognostic factors support the internal clinical validity of the dataset; however, they do not exclude the possibility that modest prognostic effects of PET-derived parameters could have remained undetected.

Our findings regarding primary tumor parameters are consistent with the heterogeneity of the literature. Although high tumor FDG uptake has been suggested to be associated with poor prognosis, this association has not been consistent across studies; the low FDG avidity of signet ring cell and mucinous subtypes is a well-recognized

factor weakening the link between uptake and biological aggressiveness in gastric cancer. In our center's previous HER2 series, metabolic parameters were cross-sectionally associated with distant metastasis and invasion, but their independent prognostic role remained unresolved (2); the present study tested this question directly, with a survival endpoint, in the same center's patient pool and found no independent association between these parameters and OS.

The negative finding for immune organ metabolism contrasts with parts of the literature. Lee et al. (3) reported that BLR was an independent predictor of recurrence-free and OS in 309 gastric cancer patients after curative resection, and diffuse splenic uptake has been associated with poor prognosis in gastric cancer (14). Similarly, immune-organ parameters have been found prognostic in melanoma (4), breast cancer (5,12), colorectal cancer (6), cervical cancer (11), and aggressive lymphoma (9,10). The most plausible explanation for this discrepancy is cohort composition: positive findings have largely been obtained



**Figure 5.** Kaplan-Meier overall survival curves in the resection-pathology subgroup (vascular invasion, perineural invasion, T stage, and N stage; n=42)

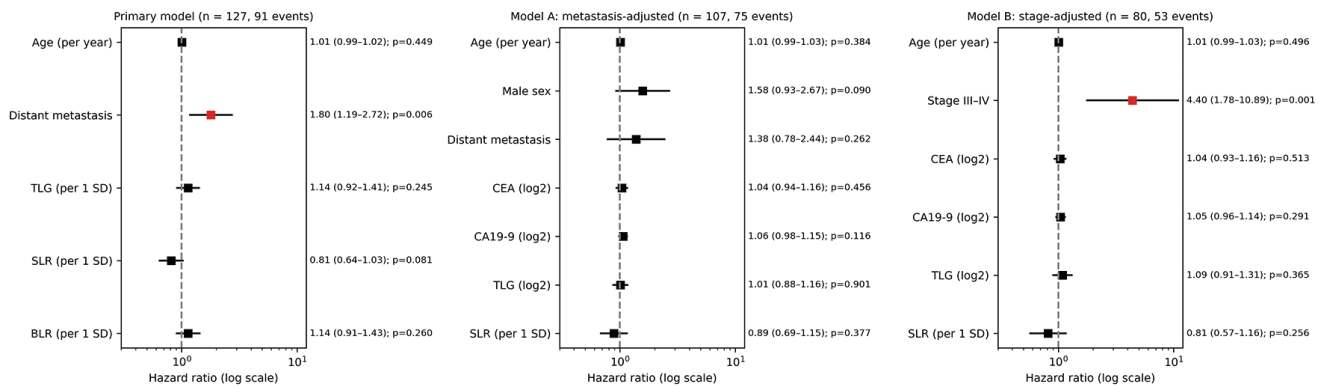
**Table 4. Metastasis-adjusted clinical-PET multivariable Cox model (Model A; n=107; events=75)**

| Variable           | Unit         | Adjusted HR | 95% CI      | p     |
|--------------------|--------------|-------------|-------------|-------|
| Age                | 10 years     | 1.089       | 0.899-1.318 | 0.384 |
| Male sex           | Male/Female  | 1.577       | 0.931-2.670 | 0.090 |
| Distant metastasis | Yes/No       | 1.384       | 0.785-2.439 | 0.262 |
| CEA                | Per doubling | 1.041       | 0.937-1.157 | 0.456 |
| CA19-9             | Per doubling | 1.063       | 0.985-1.148 | 0.116 |
| TLG                | Per doubling | 1.009       | 0.877-1.161 | 0.901 |
| SLR                | 1 SD         | 0.889       | 0.686-1.153 | 0.377 |

Model A jointly includes age, sex, distant metastasis, CEA, CA19-9, TLG, and SLR. The analysis was conducted on complete cases. Because CEA, CA19-9, and TLG were log2-transformed, their HRs are interpreted per doubling; the SLR HR is per 1 SD increase. Proportional hazards assumption: all p>0.05. HR: hazard ratio; CI: confidence interval, PET: Positron emission tomography, HR: Hazard ratio, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, SD: Standard deviation,

in early-stage, curatively resected (3) or immunotherapy-treated (4,7,8) populations. In our cohort, with its high proportion of advanced/metastatic disease, the prognostic impact of tumor burden and metastatic spread may have obscured the comparatively subtle signal of the host inflammatory response.

Moreover, the lack of independent significance of TLG, SLR, and BLR in the multivariable model was consistent with the lack of significant associations observed in the univariate analyses. The SBR was lower in deceased patients and showed a protective trend at the univariate level, but this trend did not reach statistical significance and was not supported by alternative analytical approaches; it



**Figure 6.** Forest plots of the primary pre-specified multivariable Cox model (age, distant metastasis, TLG, SLR, BLR), the metastasis-adjusted Model A, and the stage-adjusted Model B (hazard ratios with 95% confidence intervals, log scale; red squares indicate p<0.05)  
TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SD: Standard deviation, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9

| Table 5. Stage-adjusted clinical-PET multivariable Cox model (Model B; n=80; events=53) |              |             |              |       |
|-----------------------------------------------------------------------------------------|--------------|-------------|--------------|-------|
| Variable                                                                                | Unit         | Adjusted HR | 95% CI       | p     |
| Age                                                                                     | 10 years     | 1.080       | 0.865-1.349  | 0.496 |
| Stage III-IV                                                                            | III-IV/I-II  | 4.403       | 1.781-10.890 | 0.001 |
| CEA                                                                                     | Per doubling | 1.037       | 0.930-1.155  | 0.513 |
| CA19-9                                                                                  | Per doubling | 1.048       | 0.961-1.143  | 0.291 |
| TLG                                                                                     | Per doubling | 1.088       | 0.906-1.306  | 0.365 |
| SLR                                                                                     | 1 SD         | 0.814       | 0.571-1.161  | 0.256 |

Model B jointly includes age, stage group, CEA, CA19-9, TLG, and SLR. The analysis was conducted on complete cases with all model variables, including stage, available. Stage I-II is the reference group. Because CEA, CA19-9, and TLG were log<sub>2</sub>-transformed, their HRs are interpreted per doubling; the SLR HR is per 1 SD increase. Proportional hazards assumption: all p>0.05. HR: Hazard ratio, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, SD: Standard deviation

should therefore be considered hypothesis-generating. Methodological concerns about the type I error risk introduced by data-driven cutoffs have likewise been raised, and similar methodological concerns have been raised in lymphoma series (10). This observation underscores the importance of predefined cutoff values and multiple-testing corrections in prognostic biomarker studies.

Several biological mechanisms may underlie the protective trend observed for a higher SBR, although this signal did not reach statistical significance in the univariate analysis, was absent in the multivariable models, and should be interpreted with caution. Splenic FDG uptake reflects the metabolic activity of the white-pulp lymphoid compartment and of red-pulp macrophages and monocytes, whereas bone marrow uptake predominantly reflects granulopoietic activity and tumor-driven emergency myelopoiesis (15,16). In cancer, systemic release of interleukin-6, granulocyte- and granulocyte-macrophage colony-stimulating factors, and other tumor-derived mediators expands the myeloid compartment, mobilizes myeloid-derived suppressor cells

and neutrophils from the marrow, and is accompanied by contraction of adaptive lymphoid populations; this myeloid-skewed, immunosuppressive systemic state has been linked to disease progression (17,18) and to reticuloendothelial FDG uptake in gastric cancer (13). Within this framework, a relatively higher splenic than marrow uptake (higher SBR) may indicate a comparatively preserved lymphoid/reticuloendothelial immune activity relative to marrow myelopoiesis, whereas a lower SBR may reflect dominance of tumor-driven myelopoiesis over splenic immune activity, which would be consistent with the protective direction of the trend observed here. The absence of a comparable signal for the bone marrow parameters may be explained by several factors. First, lumbar bone marrow FDG uptake is influenced by non-immune determinants that are common in gastric cancer, such as chronic gastrointestinal blood loss and anemia with reactive erythroid hyperplasia, age-related changes in marrow cellularity, recent hemorrhage, and degenerative vertebral changes, which add measurement variability unrelated

**Table 6. Variable-level distribution of missing data**

| Variable                | Available (n) | Missing (n) | Missing % |
|-------------------------|---------------|-------------|-----------|
| Age                     | 127           | 0           | 0.0       |
| Sex                     | 127           | 0           | 0.0       |
| Biopsy type             | 127           | 0           | 0.0       |
| HER2 status             | 127           | 0           | 0.0       |
| Distant metastasis      | 127           | 0           | 0.0       |
| AJCC stage              | 92            | 35          | 27.6      |
| CEA                     | 110           | 17          | 13.4      |
| CA19-9                  | 113           | 14          | 11.0      |
| Lauren classification   | 104           | 23          | 18.1      |
| Histological grade/type | 104           | 23          | 18.1      |
| Tumor size              | 42            | 85          | 66.9      |
| Perineural invasion     | 42            | 85          | 66.9      |
| Vascular invasion       | 42            | 85          | 66.9      |
| T stage                 | 42            | 85          | 66.9      |
| N stage                 | 42            | 85          | 66.9      |
| PET/CT parameters (all) | 127           | 0           | 0.0       |

Percentages were calculated over the total of 127 patients. No imputation was applied to missing values; the corresponding analyses were conducted on complete cases. Resection-pathology variables (tumor size, invasion, T and N stage) were available only in the 42 patients with total resection material, HER2: Human epidermal growth factor receptor 2, AJCC: American Joint Committee on Cancer, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, T stage: Primary tumor stage, N stage: Regional lymph node stage, PET/CT: Positron emission tomography/computed tomography.

to antitumor immunity. Second, the spleen and the bone marrow respond to tumor-derived signals with different kinetics and cell populations: the spleen acts as a reservoir and site of extramedullary myelopoiesis and lymphoid activation, whereas the marrow response is dominated by granulopoiesis, so that the two organs may carry partly independent prognostic information (6,9,10,13). Third, the positive findings for BLR reported by Lee et al. (3) were obtained in a curatively resected, predominantly early-stage population; in our cohort dominated by advanced and metastatic disease, tumor burden and metastatic spread may have overwhelmed the comparatively subtle marrow signal. Finally, the SBR normalizes the two immune organs to each other rather than to the liver, thereby removing inter-patient variation in hepatic FDG uptake, which may have rendered it more sensitive to the balance between splenic and marrow activity than the liver-referenced ratios. Notably, the protective direction of the spleen-related ratios was also observed for the SLR in the exploratory resection-adjusted model, lending some internal consistency to this hypothesis, although the strong link between resectability and stage precludes causal interpretation. These considerations are hypothesis-generating and require confirmation in prospective studies incorporating concurrent hematological and immunological markers.

### Study Limitations

Our study has several limitations. First, its retrospective, single-center design carries a risk of selection bias and limits external validity. Second, two PET/CT systems were used without formal cross-calibration; the exact reconstruction settings and the per-patient scanner assignment were not retrievable, so scanner-adjusted modeling was not possible and residual scanner-related SUV variability cannot be excluded. Third, treatment was heterogeneous over the 2015-2024 period; only surgical resection could be included as a treatment covariate, whereas systemic treatment data were not uniformly documented, so treatment-stratified analyses and adjustment for era-related changes in treatment were not possible. Fourth, resection-pathology variables were available in only 42 patients and stage information was missing in approximately 28%, limiting the power of the subgroup and stage-adjusted analyses. Fifth, concurrent inflammatory markers such as CRP and the neutrophil-to-lymphocyte ratio were not available, and interobserver reproducibility of the PET measurements was not formally assessed. Sixth, the findings have not been externally validated, and the high proportion of advanced-stage disease limits generalizability to early-stage disease. Finally, the absence of a statistically significant association does not establish that the evaluated PET parameters

lack prognostic value; modest effects may have remained undetected owing to the sample size, number of events, and cohort composition.

## Conclusion

In this gastric adenocarcinoma cohort with a high proportion of advanced-stage disease, no independent association with OS was demonstrated for either primary-tumor or immune-organ metabolic PET/CT parameters. This finding does not establish the absence of prognostic value; rather, it indicates that no independent effect could be demonstrated in a cohort dominated by advanced-stage disease. In contrast, established clinical indicators, particularly distant metastasis and advanced AJCC stage, retained prognostic relevance. The prognostic role of immune-organ metabolism warrants evaluation in larger, stage-stratified prospective cohorts using predefined cutoffs.

## Ethics

**Ethics Committee Approval:** This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki following approval by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 19, date: 09.01.2023).

**Informed Consent:** Owing to the retrospective design, the requirement for individual informed consent was waived.

**Declaration on the Use of Artificial Intelligence:** Artificial intelligence-assisted tools were used solely for language editing and formatting support during the preparation of this manuscript. All study design, data collection, statistical analyses, interpretation of the results, and the final content were performed, verified, and approved by the authors, who take full responsibility for the manuscript.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: H.Ö., M.Ö.T., Concept: H.Ö., M.Ö.T., Design: H.Ö., Data Collection or Processing: M.N.A.T., M.Ö.T., H.Ö., Analysis or Interpretation: H.Ö., Literature Search: M.N.A.T., M.Ö.T., Writing: H.Ö., M.Ö.T.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial.

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