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Original Article

FDG-PET Response After Induction Chemotherapy Can Predict Who Will Benefit From Subsequent Esophagectomy After Chemoradiotherapy for Esophageal Adenocarcinoma

Running title: PET RESPONSE PREDICTS SURGICAL BENEFIT

Mian Xi, MD[1], Zhongxing Liao, MD[2], Wayne L. Hofstetter, MD[3], Ritsuko Komaki, MD[2], Linus Ho, MD, PhD[4], Steven H. Lin, MD, PhD[2]

[1]Department of Radiation Oncology, Cancer Center, Sun Yat-sen University, State Key Laboratory of Oncology in South China, Collaborative Innovation Centre for Cancer Medicine, Guangzhou, Guangdong, China;

[2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;

[3]Cardiovascular and Thoracic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;

[4]Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Corresponding Author: Dr. Steven H. Lin, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030,

USA. Tel: 713-563-8490, Fax: 713-563-2366, Email: shlin@mdanderson.org

First Author: Dr. Mian Xi (not currently in training), Department of Radiation Oncology, Cancer Center, Sun Yat-sen University, No.651 Dongfeng East Road, Guangzhou 510060, China. Tel: +86-20-87343492, Fax: +86-20-87343385, E-mail: ximian@sysucc.org.cn

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ABSTRACT

This study aimed to determine whether ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) response after induction chemotherapy before concurrent chemoradiotherapy can identify patients with esophageal adenocarcinoma who may benefit from subsequent esophagectomy. **Methods:** We identified and analyzed 220 patients with esophageal adenocarcinoma who had received induction chemotherapy before chemoradiotherapy, with or without surgery, with curative intent; all underwent FDG-PET scanning before and after induction chemotherapy. FDG-PET responders were defined as patients who achieved complete response (CR) after induction chemotherapy (maximum standardized uptake value ≤ 3.0). The predictive value of FDG-PET response for patient outcomes was evaluated. **Results:** Overall, 86 patients had bimodality therapy (BMT; induction chemotherapy + chemoradiotherapy) and 134 had trimodality therapy (TMT; induction chemotherapy + chemoradiotherapy with surgery). Forty-eight patients (21.8%) achieved a FDG-PET-CR after induction chemotherapy. FDG-PET-CR was found to correlate with overall survival (OS) and progression-free survival (PFS) in BMT patients. For TMT patients, FDG-PET-CR predicted pathologic response (P = 0.003) but not survival. Among FDG-PET non-responders, TMT patients had significantly better survival than did BMT patients (P < 0.001). However, among FDG-PET responders, BMT patients had similar OS (P = 0.201) and PFS (P = 0.269) as did TMT patients. After propensity score-matched analysis, FDG-PET responders treated with BMT versus TMT still had comparable OS and PFS, but TMT was associated with better locoregional control. **Conclusion:** FDG-PET response to induction chemotherapy could be a useful imaging biomarker to identify

patients with esophageal adenocarcinoma who could benefit from subsequent esophagectomy after chemoradiotherapy. Compared with BMT, TMT can significantly improve survival in FDG-PET non-responders. However, outcomes for FDG-PET responders were similar after either treatment (BMT or TMT). Prospective validation of these findings is warranted.

Key Words: Esophageal cancer; induction chemotherapy; chemoradiotherapy; FDG-PET response; prognosis.

INTRODUCTION

Locally advanced esophageal cancer is typically treated with combined modalities, as the 5-year survival rates after surgery alone rarely exceed 20% *(1)*. Trimodality therapy (TMT), consisting of neoadjuvant chemoradiotherapy followed by surgery, is generally recommended as a standard care option for advanced esophageal cancer because of its positive effects on resectability, locoregional control, and long-term overall survival (OS) compared with surgery alone *(2-4)*. However, whether chemoradiotherapy and subsequent esophagectomy have an obvious advantage over definitive chemoradiotherapy is still debated. Two prospective randomized studies have challenged the role of surgery after chemoradiotherapy owing to the equivalent OS rates after these two approaches (chemoradiotherapy vs. chemoradiotherapy followed by surgery), especially in patients who showed a clinical response after chemoradiotherapy *(5,6)*. Notably, chemoradiotherapy followed by surgery was associated with significantly higher treatment-related mortality rates than chemoradiotherapy only, but the latter was associated with higher locoregional recurrence rates. The RTOG 0246 trial recently demonstrated that an organ-preserving selective-resection strategy for patients treated with definitive chemoradiotherapy had promising efficacy, with a 7-year OS rate of 31.7% *(7)*. Therefore, interest is growing in defining reliable criteria with which to identify which patients with chemoradiotherapy can safely defer or avoid surgery after chemoradiotherapy.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning is now commonly used in both the initial workup and the treatment response assessment in esophageal cancer *(8)*. However, the prognostic value of FDG-PET response after chemoradiotherapy has

not been definitively established, most likely because of the confounding effects of radiation-induced esophagitis *(9,10)*. On the other hand, FDG-PET response after induction chemotherapy seems to be a more dependable imaging marker for predicting survival *(11-13)*. Previous studies have suggested that FDG-PET response after induction chemotherapy could predict pathologic complete response (pCR) and were associated with survival outcomes in esophageal cancer patients treated with induction chemotherapy followed by neoadjuvant or definitive chemoradiotherapy *(11-13)*. Moreover, an early FDG-PET response could provide useful information for choosing a chemotherapy regimen to be used during radiation for those who do not show a FDG-PET response *(14)*. However, the value of FDG-PET response after induction chemotherapy in terms of identifying which patients will benefit from subsequent surgery after chemoradiotherapy has never been investigated. The aim of this study was to determine whether FDG-PET response after induction chemotherapy could identify patients with esophageal adenocarcinoma who may not benefit from esophagectomy after chemoradiotherapy.

MATERIALS AND METHODS

Patient Selection

We reviewed all consecutive patients with esophageal cancer seen at The University of Texas MD Anderson Cancer Center between January 2003 and June 2015 by using a prospectively maintained database. Patients who met the following criteria were included: (1) histologic documentation of esophageal adenocarcinoma; (2) disease stage I-III according to the 7th TNM staging system of the American Joint Committee on Cancer *(15)*; (3) thoracic or

gastroesophageal junction carcinoma; (4) induction chemotherapy before concurrent chemoradiotherapy (radiation dose ≥40 Gy); (5) baseline FDG-PET/computed tomography (CT) showing ^{18}F-FDG-avid tumors and FDG-PET rescanning obtained after induction chemotherapy at MD Anderson; (6) multidisciplinary evaluation before initiation of treatment; (7) complete and retrievable clinical records. On the basis of baseline characteristics, the patient whether receiving esophagectomy was at the discretion of multidisciplinary team and patients' intent. Patients with stage T1N0 or non-^{18}F-FDG-avid tumors at baseline were excluded. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

Treatment

All patients received induction chemotherapy followed by concurrent chemoradiotherapy, with or without subsequent surgery, with curative intent. The most common induction chemotherapy regimens included a fluoropyrimidine (5-fluorouracil or capecitabine), a platinum compound (oxaliplatin or cisplatin or carboplatin), and a taxane (docetaxel or paclitaxel). Two-drug combinations were also given to some patients (fluoropyrimidine/platinum, fluoropyrimidine/taxane, or platinum/taxane). The typical radiation dose was 50.4 Gy in 28 fractions given 5 days per week, given by three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy. The chemotherapy regimen given during radiation generally consisted of a fluoropyrimidine with either a platinum or a taxane.

Four to 6 weeks after completion of chemoradiotherapy, all patients underwent re-staging

procedures. Some patients then underwent esophagectomy by transthoracic (Ivor-Lewis), transhiatal, minimally invasive, or three-field technique, with the choice of technique at the discretion of the treating surgeon. Resection specimens were examined histopathologically, and pCR was defined as the complete absence of residual tumor in esophagus and lymph nodes. For patients who received chemoradiotherapy without surgery, clinical CR was defined as FDG-PET with only physiologic uptake and endoscopic biopsies without cancer cells as well as no evidence of distant metastasis.

PET Imaging

Whole-body PET/CT scans were obtained before and after the completion of induction chemotherapy by using an integrated PET/CT device (Discovery RX, ST, or STE; GE Medical Systems, Milwaukee, WI). All patients were required to fast for at least 6 h before being injected with ^{18}F-FDG. A non-contrast CT scan was obtained before PET for attenuation correction. PET scans were acquired 60-90 min after the intravenous administration of ^{18}F-FDG (dose 555-740 MBq). The maximum standardized uptake value (SUV_{max}) was calculated as described previously *(13)*. A FDG-PET-CR was defined as $SUV_{max} \leq 3.0$ after induction chemotherapy *(16)*. Patients were assigned to one of two groups: FDG-PET responders (FDG-PET CR) or FDG-PET non-responders (FDG-PET non-CR).

Statistical Analysis

Categorical variables were compared by using Chi-square or Fisher's exact tests. The

relationship between independent variables and FDG-PET response were quantified by logistic regression analysis. Propensity score matching analysis was used to reduce the effects of potentially confounding factors in the comparison of survival between treatment groups at a ratio of 1:1. Locoregional recurrence was defined as the persistence or recurrence of tumor at the primary tumor or regional lymph nodes, and distant recurrence was defined as systemic metastasis or non-regional lymph node recurrence. Recurrences were established on histologic, cytologic, or explicit radiologic proof.

Survival outcomes were defined from the date of diagnosis. All data were updated in August 2016 for censored data analysis. OS, progression-free survival (PFS), locoregional failure–free survival (LRFFS), and distant metastasis–free survival (DMFS) were analyzed by using the Kaplan-Meier method. Log-rank tests were used to examine the differences between groups, and a Cox proportional hazards regression model was applied in multivariate analysis. Variables with *P* values <0.2 in the univariate analysis were included in the multivariate analysis. Statistical analyses were done with Stata 12.0 and SPSS 22.0 software (SPSS Inc., Chicago, IL). *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Patient and treatment characteristics are shown in Table 1. A total of 220 patients with esophageal adenocarcinoma who met the inclusion criteria were selected for analysis, including 86 patients (39.1%) who received definitive chemoradiotherapy (bimodality therapy [BMT]) and

134 patients (60.9%) who received TMT. The median age of the entire group was 61 years (range 26–87 years), and the median length of the primary tumor was 6.0 cm (range 0.4–13.0 cm). Compared with patients treated with TMT, Patients who received BMT tended to be older, had worse performance status, had greater weight loss at baseline, had squamous cell carcinoma at proximal esophagus, and had more advanced disease.

All patients received induction chemotherapy; most patients (62.3%) received 1–2 cycles before chemoradiotherapy, and 37.7% received 3–8 cycles. The induction chemotherapy regimen comprised three drugs for 133 patients (60.5%) and two drugs for 87 (39.5%). The median radiation dose was 50.4 Gy (range 43.2–63.0 Gy), delivered by conformal techniques. After chemoradiotherapy, 127 of the 134 patients in the TMT group (94.8%) achieved R0 resection and 33 patients (24.6%) achieved a pCR.

Follow-Up and Survival

Median follow-up times were 34.1 months (range 3.9–145.5 months) for the entire group and 63.9 months (range 9.3–145.5 months) for patients who were alive at the time of this analysis. When these data were analyzed, 115 patients (52.3%) had recurrences and 124 patients (56.4%) had died in the whole cohort. A total of 59 patients (68.6%) in the BMT group experienced recurrences versus 66 patients (41.8%) in the TMT group (P<0.001). The TMT group demonstrated significantly lower locoregional recurrence rate (16.4% vs. 39.5%, P<0.001) and distant failure rate (41.0% vs. 60.5%, P=0.005) compared with the BMT group. As anticipated, patients in TMT group had significantly better 5-year OS rates (54.7% *vs.* 28.1%,

P<0.001) and 5-year PFS rates (51.4% *vs.* 20.6%, *P*<0.001) than did patients in the BMT group.

FDG-PET Response After Induction Chemotherapy

The median time from the completion of induction chemotherapy to the repeated FDG-PET scans was 17 days (range 9–27 days). The median baseline FDG-PET SUV_{max} for the entire group was 11.4 (range 3.1–60.3), and the median SUV_{max} for the entire group after induction chemotherapy was 5.1 (range 0.0–27.0). Of the 220 patients, 48 (21.8%) achieved a FDG-PET-CR after induction chemotherapy.

Among the BMT group, FDG-PET responders demonstrated a significantly higher clinical CR rate than FDG-PET non-responders (89.6% *vs.* 69.8%, *P*=0.006). The OS and PFS were also better among FDG-PET responders than FDG-PET non-responders (5-year OS rates, 43.5% *vs.* 21.9%, *P*=0.058; 5-year PFS rates, 34.8% *vs.* 15.7%, *P*=0.011; Fig. 1). Similarly, among the TMT group, FDG-PET responders had a higher pCR rate (48.0% *vs.* 19.3% for non-responders; *P*=0.003). However, FDG-PET response was not associated with OS or PFS in patients who received TMT (Fig. 1).

Univariate and multivariate logistic regression analysis to determine the relationships, if any, between prognostic variables and the probability of FDG-PET-CR revealed that primary tumor length was the only independent predictor of FDG-PET-CR (Table 2). Patients with tumors ≤6.0 cm long were more likely to achieve a FDG-PET-CR than those with tumors >6.0 cm long (odds ratio 0.426, *P*=0.023).

Survival Analysis in FDG-PET Responders

Among the 48 FDG-PET responders, 23 patients had BMT and 25 patients had TMT. As shown in Figure 2, no significant differences were found between the BMT and TMT groups in terms of 5-year OS rates (43.5% *vs.* 60.3%, *P*=0.201), 5-year PFS rates (34.8% *vs.* 55.1%, *P*=0.269), or 5-year DMFS rates (52.4% *vs.* 66.2%, *P*=0.606). However, LRFFS was better in the TMT group than in the BMT group (*P*=0.01). Multivariate analysis revealed that age was the only independent predictor of OS in this cohort (*P*=0.004; Supplemental Table 1).

Several pretreatment characteristics were not balanced between BMT and TMT groups in FDG-PET responders, and propensity score matching analysis was used to reduce this bias (Supplemental Table 2). After adjustment, the comparison demonstrated that OS (*P*=0.533), PFS (*P*=0.428), and DMFS (*P*=0.731) were still comparable between the two groups. Moreover, the TMT group still had significantly better LRFFS than did the BMT group (*P*=0.014; Supplemental Fig. 1).

Survival Analysis in FDG-PET Non-responders

Among the 172 FDG-PET non-responders, 63 patients had BMT and 109 patients had TMT. Patients receiving TMT had remarkably better OS, PFS, LRFFS, and DMFS than did the BMT group (*P*<0.001 for all; Fig. 3). Multivariate analysis identified sex and surgery to be independent prognostic factors for OS (Supplemental Table 3).

For propensity score matching analysis in this cohort, 57 patients who received BMT were matched with 57 patients who received TMT (Supplemental Table 4). With comparable

pretreatment characteristics after adjustment, the TMT group still had better OS, PFS, LRFFS, and DMFS survival than did the BMT group (P<0.05 for all; Supplemental Fig. 2).

DISCUSSION

We investigated the value of FDG-PET response after induction chemotherapy for identifying who would benefit (or not benefit) from subsequent esophagectomy after chemoradiotherapy in patients with esophageal adenocarcinoma. Our results demonstrated that among patients who did not show a FDG-PET response after induction chemotherapy, TMT could significantly improve survival compared with BMT. In addition, FDG-PET responders had similar outcomes regardless of whether the treatment was BMT or TMT after induction chemotherapy. Therefore, a FDG-PET response to induction chemotherapy could be useful as an early imaging biomarker for helping guide clinical decision-making for the treatment of esophageal adenocarcinoma.

Because 40%–50% of patients with esophageal cancer experience recurrence after either BMT or TMT *(4,17)*, the addition of induction chemotherapy before chemoradiotherapy is common in clinical practice as an attempt to eliminate occult micrometastases. Several retrospective studies and single-arm phase II trials suggested that induction chemotherapy before chemoradiotherapy could improve treatment response and survival, but the two prospective, randomized trials conducted to date failed to show a benefit from induction chemotherapy *(11,18-20)*. Despite these inconclusive results, several studies have demonstrated the predictive value of FDG-PET response after induction chemotherapy *(11-13)*. Unlike response after

chemoradiotherapy, the FDG-PET response after induction chemotherapy can be assessed earlier and would avoid the confounding influence of radiation-induced inflammation. Chhabra et al. investigated the prognostic significance of FDG-PET response in 52 esophageal cancer patients treated with definitive chemoradiotherapy *(12)*. They found that a pre-specified decrease in SUV_{max} of 35% after induction chemotherapy predicted both OS and DMFS. In our study, survival was also significantly better among FDG-PET responders than among non-responders in the BMT group, which confirmed the prognostic value of early FDG-PET response for this group of patients. Regarding patients treated with TMT, investigators from Memorial Sloan Kettering Cancer Center reported that FDG-PET response to induction chemotherapy was associated with pCR, R0 resection, and PFS *(11)*. This result was verified by van Rossum et al *(13)*. However, the Swiss Group for Clinical Cancer Research 75/02 trial revealed that survival among patients with a FDG-PET response to induction chemotherapy was similar to that of non-responders among patients who received TMT *(21)*. The differences in survival among the TMT group were also not statistically significant in our study. The lack of association between FDG-PET response and survival for patients undergoing TMT could be explained by several reasons. First, the prognostic value of FDG-PET response could be affected by the subsequent esophagectomy. Compared with patients receiving no surgery, the presence of residual disease after chemoradiotherapy was less important for patients treated with TMT *(16)*. Second, although FDG-PET response after induction chemotherapy did correlate with pCR, some FDG-PET non-responders could turn into pathologic responders after chemoradiotherapy, which might influence the accuracy of FDG-PET response to predict survival. Lastly, patients with distant

recurrences after chemoradiotherapy (i.e., before surgery) did not receive esophagectomy. Therefore, a subset of patients with poor prognosis were excluded from the TMT group, which may further limit the significance of FDG-PET response with regard to survival outcomes.

The predictive value of early FDG-PET response has prompted interest in using it to direct the choice of subsequent treatments in esophageal cancer. For FDG-PET responders in our study, patients who had BMT had promising and similar survival relative to the patients who had TMT, despite having worse baseline characteristics. The propensity score-matched analysis confirmed this result, suggesting that FDG-PET responders could be considered candidates for organ preservation without surgery. However, given the higher rate of locoregional recurrence among those given BMT, vigilant surveillance is indicated, especially during the first 2 years after chemoradiotherapy *(17)*. For patients who experience locoregional recurrence only after BMT, selective salvage surgery should be considered, because its long-term outcomes are comparable to those for patients undergoing planned esophagectomy after chemoradiotherapy *(22)*.

The current study also suggested that FDG-PET non-responders should be encouraged to receive esophagectomy because of the significant advantage in survival among those who receive TMT. Changing the chemotherapy regimen during radiation for FDG-PET non-responders might also be effective. Ku et al. reported that patients who did not respond on FDG-PET after induction chemotherapy whose chemotherapy was changed during the chemoradiotherapy had significantly better PFS than did patients whose chemotherapy regimen was not changed *(14)*. On the other hand, whether non-responders could proceed directly to surgery is unclear. The RTOG 8911 trial compared receipt of induction chemotherapy plus

surgery versus surgery alone for esophageal cancer and showed no difference in survival for FDG-PET non-responders after induction chemotherapy compared with the surgery-only group *(23)*. Therefore, prospective studies are needed to address the question of whether FDG-PET non-responders after induction chemotherapy should proceed to surgery directly or continue with chemoradiotherapy and subsequent surgery.

This study had several limitations. The number of patients was large, but the number of patients who achieved FDG-PET-CR was relatively small, which limited the number of patients in the propensity score–matched analysis. Another potential bias was the diversity of induction chemotherapy regimens and numbers of cycles among patients. However, this bias should have only minor effects on the results, as the type of induction agents and the number of cycles were not associated with the probability of FDG-PET-CR in logistic regression analysis. Finally, the timing at which FDG-PET scans were obtained after induction chemotherapy was not uniform among patients in this retrospective study.

CONCLUSION

FDG-PET response to induction chemotherapy could be a useful imaging biomarker to identify patients with esophageal adenocarcinoma who could benefit from subsequent esophagectomy after chemoradiotherapy. In fact, compared with BMT, TMT can significantly improve survival in FDG-PET non-responders. However, outcomes for FDG-PET responders could be similar regardless of whether they receive BMT or TMT after induction chemotherapy. Therefore, esophageal preservation strategies could be considered for this subset of patients.

Prospective validation of using FDG-PET findings to guide the choice of therapy is needed.

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DISCLOSURE

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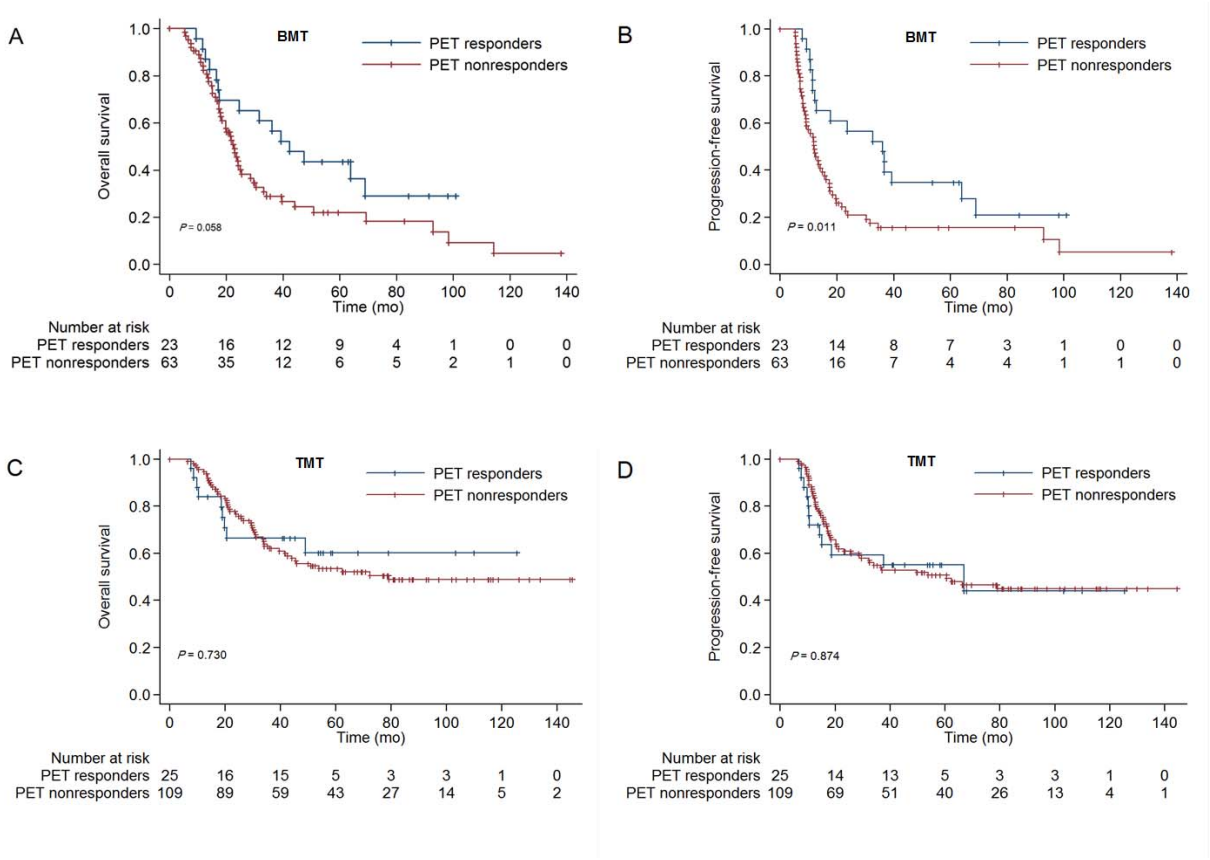


FIGURE 1. OS (A, C) and PFS (B, D) according to response or no response on FDG-PET after induction chemotherapy in patients receiving BMT or TMT.

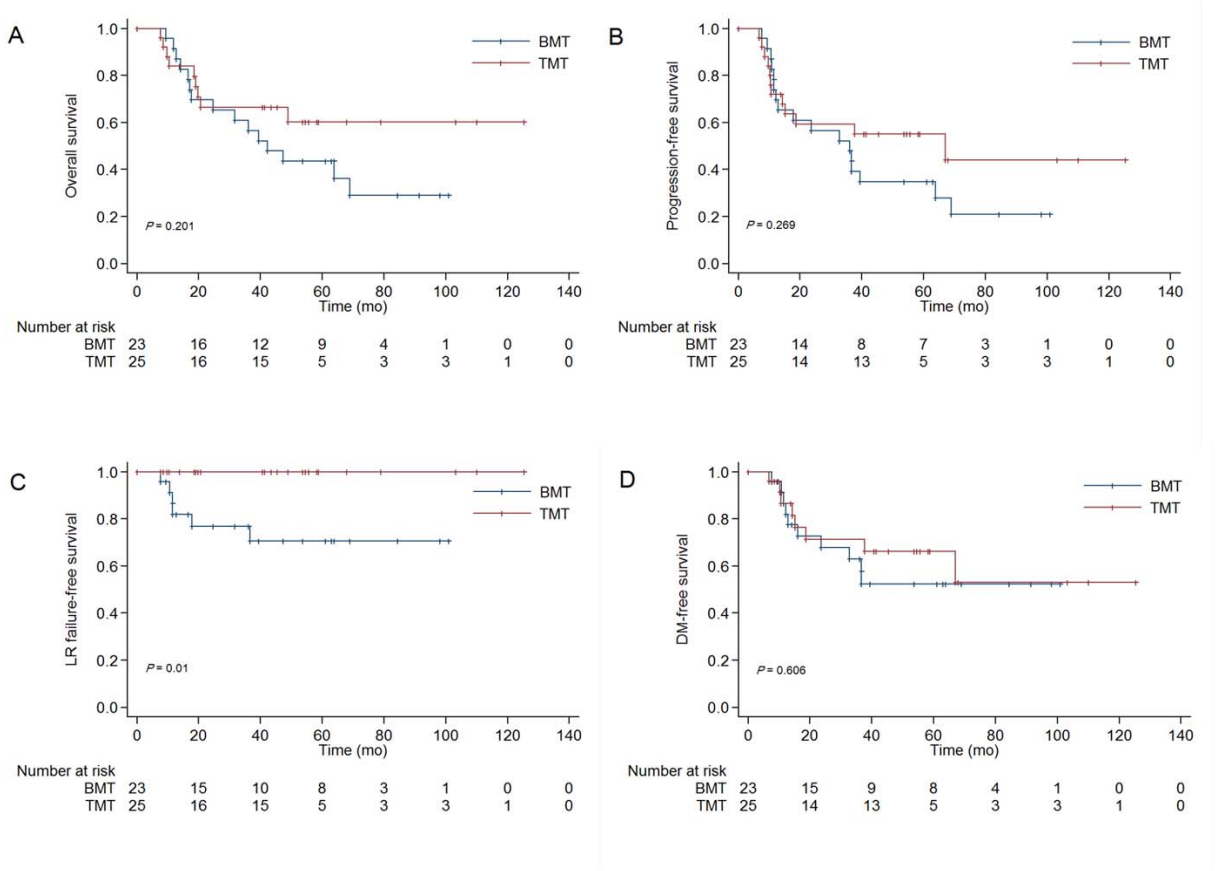


FIGURE 2. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 48 FDG-PET responders.

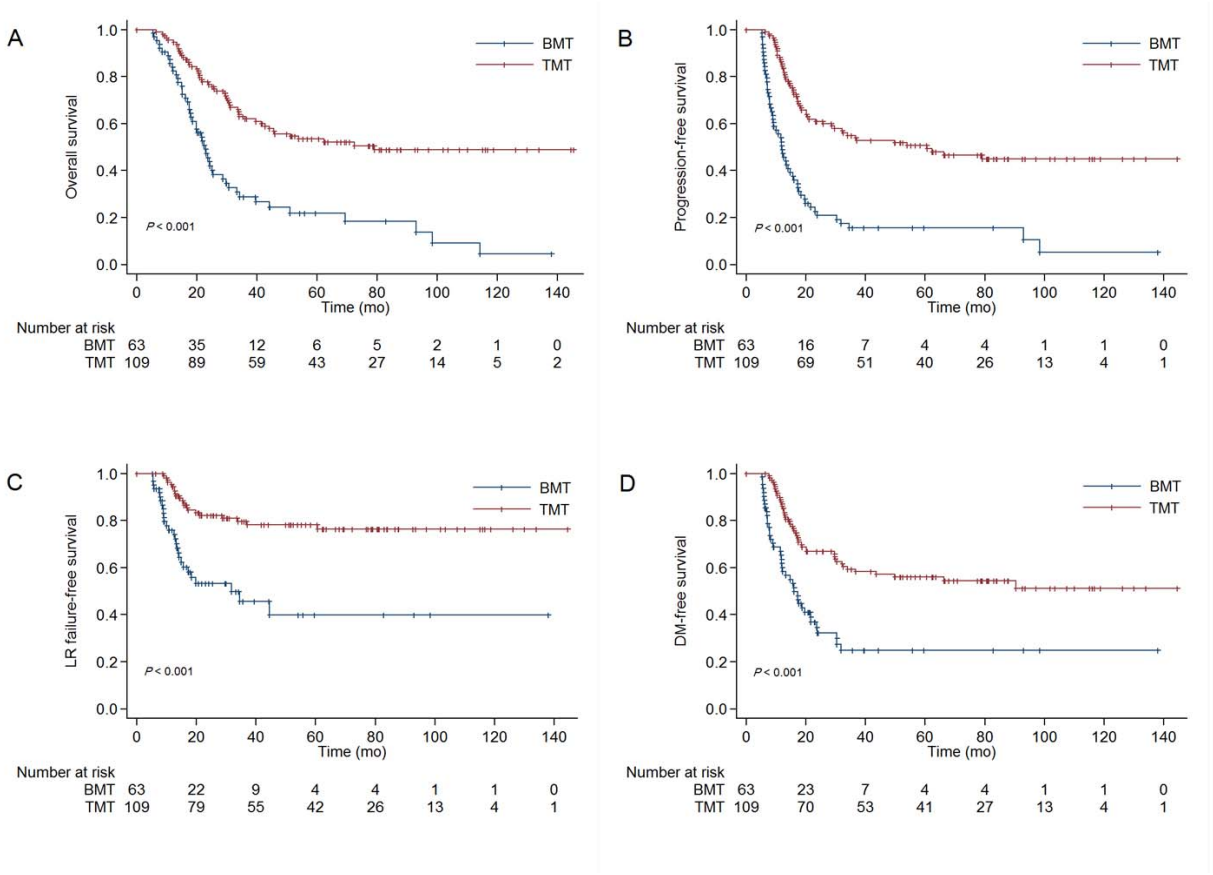


FIGURE 3. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 172 FDG-PET non-responders.

TABLE 1. Patient Characteristics

Characteristic	All Patients, n=220 (%)	BMT Patients, n=86 (%)	TMT Patients n=134 (%)	*P* Value
Age, years				0.002
<61	98 (44.5)	27 (31.4)	71 (53.0)	
≥61	122 (55.5)	59 (68.6)	63 (47.0)	
Sex				0.206
Male	201 (91.4)	76 (88.4)	125 (93.3)	
Female	19 (8.6)	10 (11.6)	9 (6.7)	
Ethnicity				0.439
Caucasian	201 (91.4)	77 (89.5)	124 (92.5)	
Others	19 (8.6)	9 (10.5)	10 (7.5)	
ECOG performance status				0.128
0	88 (40.0)	29 (33.7)	59 (44.0)	
1–2	132 (60.0)	57 (66.3)	75 (56.0)	
Weight loss				0.010
<10%	157 (71.4)	53 (61.6)	104 (77.6)	
≥10%	63 (28.6)	33 (38.4)	30 (22.4)	
Histologic subtype				0.381
Signet ring cell	35 (15.9)	16 (18.6)	19 (14.2)	
None	185 (84.1)	70 (81.4)	115 (85.8)	
Histologic grade				0.223
G1/G2	93 (42.3)	32 (37.2)	61 (45.5)	
G3	127 (57.7)	54 (62.8)	73 (54.5)	
Tumor location				0.645
Upper/middle	4 (1.8)	2 (2.3)	2 (1.5)	
Distal/GEJ	216 (98.2)	84 (97.7)	132 (98.5)	
Primary tumor length				0.874
≤6 cm	137 (62.3)	53 (61.6)	84 (62.7)	
>6 cm	83 (37.7)	33 (38.4)	50 (37.3)	
Clinical T stage				0.415
T1-2	15 (6.8)	4 (4.7)	11 (8.2)	
T3-4	205 (93.2)	82 (95.3)	123 (91.8)	
Clinical N stage				0.528
N0	43 (19.5)	15 (17.4)	28 (20.9)	
N1-3	177 (80.5)	71 (82.6)	106 (79.1)	
Clinical TNM stage				0.242
IB/II	50 (22.7)	16 (18.6)	34 (25.4)	
III	170 (77.3)	70 (81.4)	100 (74.6)	
Induction chemotherapy regimen				0.002
Fluoropyrimidine/platinum/taxane	133 (60.5)	63 (73.3)	70 (52.2)	

Two-drug combination*	87 (39.5)	23 (26.7)	64 (47.8)	
No. of induction chemotherapy cycles				<0.001
≤2	137 (62.3)	41 (47.7)	96 (71.6)	
>2	83 (37.7)	45 (52.3)	38 (28.4)	
Radiotherapy modality				0.111
3DCRT	28 (12.7)	16 (18.6)	12 (9.0)	
IMRT	138 (62.7)	50 (58.1)	88 (65.7)	
Proton therapy	54 (24.5)	20 (23.3)	34 (25.4)	

BMT, bimodality therapy; TMT, trimodality therapy; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

*Fluoropyrimidine/platinum or fluoropyrimidine/taxane or platinum/taxane.

TABLE 2. Influence of Baseline and Treatment Characteristics on FDG-PET Complete Response After Induction Chemotherapy

Characteristic		Univariate Analysis		Multivariate Analysis	
	No.	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years			0.435		
<61	98	Ref.			
≥61	122	1.297 (0.676–2.488)			
Sex			0.508		
Male	201	Ref.			
Female	19	0.65 (0.181–2.331)			
Ethnicity			0.620		
Caucasian	201	Ref.			
Others	19	1.312 (0.448–3.846)			
ECOG performance status			0.947		
0	88	Ref.			
1–2	132	0.978 (0.509–1.881)			
Weight loss			0.651		
<10%	157	Ref.			
≥10%	63	1.174 (0.586–2.354)			
Histologic subtype			0.467		
Signet ring cell	35	Ref.			
None	185	1.420 (0.552–3.648)			
Histologic grade			0.450		
G1/G2	93	Ref.			
G3	127	1.289 (0.668–2.487)			
Tumor location			0.877		
Upper/middle	4	Ref.			
Distal/GEJ	216	0.834 (0.085–8.207)			
Primary tumor length			0.042		0.023
≤6 cm	137	Ref.		Ref.	
>6 cm	83	0.474 (0.231–0.975)		0.426 (0.204–0.890)	
Clinical T stage			0.639		
T1-2	15	Ref.			
T3-4	205	0.752 (0.228–2.475)			
Clinical N stage			0.283		
N0	43	Ref.			
N1-3	177	0.66 (0.308–1.411)			
Induction chemotherapy regimen			0.048		0.059
Fluoropyrimidine/platinum/taxane	133	Ref.		Ref.	
Two-drug combination*	87	0.492 (0.243–0.995)		0.501 (0.244–1.026)	
No. of induction chemotherapy cycles			0.102		0.082

≤2	137	Ref.	Ref.
>2	83	1.717 (0.899–3.281)	1.814 (0.927–3.547)

Abbreviations: OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction.

*Fluoropyrimidine/platinum or fluoropyrimidine/taxane or platinum/taxane.

Supplemental Material for Online Publication

Number of Tables: 4
Number of Figures: 2

Supplemental Table 1. Univariate and Multivariate Analysis of Factors Related to Overall Survival in 48 FDG-PET Responders.

Supplemental Table 2. Pretreatment Characteristics for the 48 FDG-PET Responders by Therapy Type.

Supplemental Table 3. Univariate and Multivariate Analysis of Factors Related to Overall Survival in 172 FDG-PET Non-Responders.

Supplemental Table 4. Pretreatment Characteristics for the 172 FDG-PET Non-Responders by Therapy Type.

Supplemental Fig. 1. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 48 FDG-PET responders after propensity score-matching.

Supplemental Fig. 2. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 172 FDG-PET non-responders after propensity score-matching.

Supplemental Table 1. Univariate and Multivariate Analysis of Factors Related to Overall Survival in 48 FDG-PET Responders

Variable	Univariate	Multivariate	
	P-value	Hazard ratio (95% CI)	*P*-value
Age (years)			
<61 vs. ≥61	0.002	4.793 (1.633–14.063)	0.004
Sex			
Male vs. female	0.572		
Ethnicity			
Caucasian vs. others	0.188		
ECOG performance status			
0 vs. 1–2	0.299		
Weight loss			
<10% vs. ≥10%	0.499		
Histologic subtype			
Signet ring cell vs. none	0.287		
Histologic grade			
G3 vs. G1/G2	0.436		
Tumor location			
Upper/middle vs. distal/GEJ	0.016		
Primary tumor length			
≤6 cm vs. >6 cm	0.436		
Clinical T stage			
T1-2 vs. T3-4	0.750		
Clinical N stage			
N0 vs. N1-3	0.278		
Induction chemotherapy regimen			
Fluoropyrimidine/platinum/taxane vs. two-drug combination	0.396		
No. of induction chemotherapy cycles			
≤2 vs. >2	0.219		
Radiotherapy modality			
3DCRT vs. IMRT vs. Proton therapy	0.675		
Surgery			
Yes (TMT) vs. no (BMT)	0.201		

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; TMT, trimodality therapy; BMT, bimodality therapy.

Supplemental Table 2. Pretreatment Characteristics for the 48 FDG-PET Responders by Therapy Type

Characteristic	All Patients	Before Matching			After Propensity Score Matching		
	n=48 (%)	BMT n=23 (%)	TMT n=25 (%)	*P* Value	BMT n=16 (%)	TMT n=16 (%)	*P* Value
Age (years)				0.067			1.000
<61	19 (39.6)	6 (26.1)	13 (52.0)		4 (25.0)	4 (25.0)	
≥61	29 (60.4)	17 (73.9)	12 (48.0)		12 (75.0)	12 (75.0)	
Sex				0.102			/
Male	45 (93.8)	20 (87.0)	25 (100.0)		16 (100.0)	16 (100.0)	
Female	3 (6.3)	3 (13.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Ethnicity				1.000			0.484
Caucasian	43 (89.6)	21 (91.3)	22 (88.0)		14 (87.5)	16 (100.0)	
Others	5 (10.4)	2 (8.7)	3 (12.0)		2 (12.5)	0 (0.0)	
ECOG performance status				0.514			0.719
0	19 (39.6)	8 (34.8)	11 (44.0)		6 (37.5)	7 (43.8)	
1–2	29 (60.4)	15 (65.2)	14 (56.0)		10 (62.5)	9 (56.3)	
Weight loss				0.613			1.000
<10%	33 (68.8)	15 (65.2)	18 (72.0)		12 (75.0)	11 (68.8)	
≥10%	15 (31.3)	8 (34.8)	7 (28.0)		4 (25.0)	5 (31.3)	
Histologic subtype				0.407			1.000
Signet ring cell	6 (12.5)	4 (17.4)	2 (8.0)		2 (12.5)	2 (12.5)	
None	42 (87.5)	19 (82.6)	23 (92.0)		14 (87.5)	14 (87.5)	
Histologic grade				0.823			0.719
G1-2	18 (37.5)	9 (39.1)	9 (36.0)		6 (37.5)	7 (43.8)	
G3	30 (62.5)	14 (60.9)	16 (64.0)		10 (62.5)	9 (56.3)	
Tumor location				0.479			1.000
Upper/middle	1 (2.1)	1 (4.3)	0 (0.0)		1 (6.3)	0 (0.0)	
Distal/GEJ	47 (97.9)	22 (95.7)	25 (100.0)		15 (93.8)	16 (100.0)	
Primary tumor length				0.404			1.000
≤6 cm	36 (75.0)	16 (69.6)	20 (80.0)		13 (81.3)	13 (81.3)	
>6 cm	12 (25.0)	7 (30.4)	5 (20.0)		3 (18.8)	3 (18.8)	
Clinical T stage				0.338			1.000
T1-2	4 (8.3)	3 (13.0)	1 (4.0)		2 (12.5)	1 (6.3)	
T3-4	44 (91.7)	20 (87.0)	24 (96.0)		14 (87.5)	15 (93.8)	
Clinical N stage				0.868			1.000
N0	12 (25.0)	6 (26.1)	6 (24.0)		3 (18.8)	3 (18.8)	

N1-3	36 (75.0)	17 (73.9)	19 (76.0)	13 (81.3)	13 (81.3)

Abbreviations: BMT, bimodality therapy; TMT, trimodality therapy; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction.

Supplemental Table 3. Univariate and Multivariate Analysis of Factors Related to Overall Survival in 172 FDG-PET Non-Responders

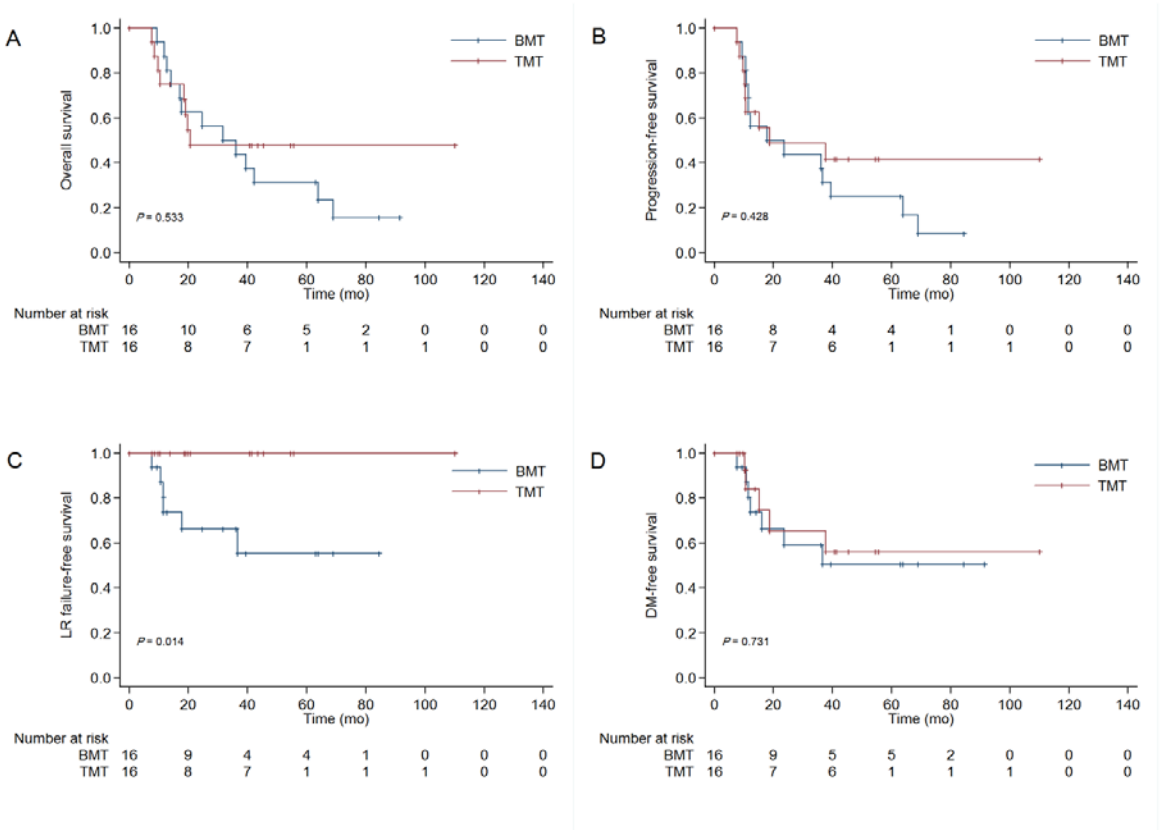
Variable	Univariate	Multivariate	
	P-value	Hazard ratio (95% CI)	*P*-value
Age (years)			
<61 vs. ≥61	0.075		
Sex			
Male vs. female	0.087	0.383 (0.166–0.884)	0.024
Ethnicity			
Caucasian vs. others	0.831		
ECOG performance status			
0 vs. 1–2	0.411		
Weight loss			
<10% vs. ≥10%	0.650		
Histologic subtype			
Signet ring cell vs. none	0.152		
Histologic grade			
G3 vs. G1/G2	<0.001		
Tumor location			
Upper/middle vs. distal/GEJ	0.923		
Primary tumor length			
≤6 cm vs. >6 cm	0.888		
Clinical T stage			
T1-2 vs. T3-4	0.411		
Clinical N stage			
N0 vs. N1-3	0.068		
Induction chemotherapy regimen			
Fluoropyrimidine/platinum/taxane vs. two-drug combination	0.533		
No. of induction chemotherapy			
≤2 vs. >2	0.280		
Radiotherapy modality			
3DCRT vs. IMRT vs. Proton therapy	0.646		
Surgery			
Yes (TMT) vs. no (BMT)	<0.001	2.895 (1.940–4.321)	<0.001

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; TMT, trimodality therapy; BMT, bimodality therapy.

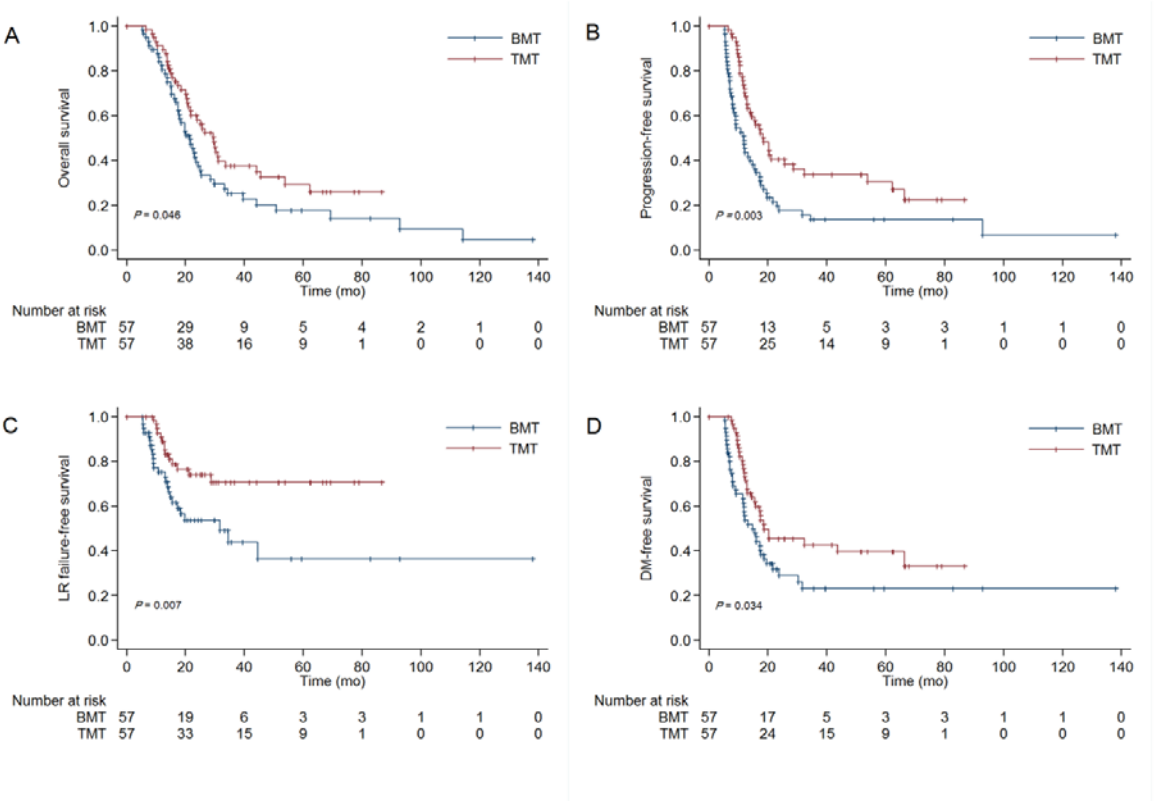
Supplemental Table 4. Pretreatment Characteristics for the 172 FDG-PET Non-Responders by Therapy Type

Characteristic	All Patients	Before Matching			After Propensity Score Matching		
	n=172 (%)	BMT n=63 (%)	TMT n=109 (%)	*P*-Value	BMT n=57 (%)	TMT n=57 (%)	*P*-Value
Age (years)				0.055			1.000
<61	79 (45.9)	21 (33.3)	58 (53.2)		21 (36.8)	21 (36.8)	
≥61	93 (54.1)	42 (66.7)	51 (46.8)		36 (63.2)	36 (63.2)	
Sex				0.041			0.542
Male	156 (90.7)	56 (88.9)	100 (91.7)		50 (87.7)	52 (91.2)	
Female	16 (9.3)	7 (11.1)	9 (8.3)		7 (12.3)	5 (8.8)	
Ethnicity				0.012			1.000
Caucasian	158 (91.9)	56 (88.9)	102 (93.6)		51 (89.5)	51 (89.5)	
Others	14 (8.1)	7 (11.1)	7 (6.4)		6 (10.5)	6 (10.5)	
ECOG PS				0.054			0.176
0	69 (40.1)	21 (33.3)	48 (44.0)		18 (31.6)	25 (43.9)	
1–2	103 (59.9)	42 (66.7)	61 (56.0)		39 (68.4)	32 (56.1)	
Weight loss				<0.001			1.000
<10%	124 (72.1)	38 (60.3)	86 (78.9)		38 (66.7)	38 (66.7)	
≥10%	48 (27.9)	25 (39.7)	23 (21.1)		19 (33.3)	19 (33.3)	
Histologic subtype				0.841			0.451
Signet ring cell	29 (16.9)	12 (19.0)	17 (15.6)		11 (19.3)	8 (14.0)	
None	143 (83.1)	51 (81.0)	92 (84.4)		46 (80.7)	49 (86.0)	
Histologic grade				0.398			0.329
G1-2	75 (43.6)	23 (36.5)	52 (47.7)		18 (31.6)	23 (40.4)	
G3	97 (56.4)	40 (63.5)	57 (52.3)		39 (68.4)	34 (59.6)	
Tumor location				<0.001			1.000
Upper/middle	3 (1.7)	1 (1.6)	2 (1.8)		1 (1.8)	1 (1.8)	
Distal/GEJ	169 (98.3)	62 (98.4)	107 (98.2)		56 (98.2)	56 (98.2)	
Primary tumor length				0.975			0.570
≤6 cm	101 (58.7)	37 (58.7)	64 (58.7)		34 (59.6)	31 (54.4)	
>6 cm	71 (41.3)	26 (41.3)	45 (41.3)		23 (40.4)	26 (45.6)	
Clinical T stage				0.073			1.000
T1-2	11 (6.4)	1 (1.6)	10 (9.2)		1 (1.8)	1 (1.8)	
T3-4	161 (93.6)	62 (98.4)	99 (90.8)		56 (98.2)	56 (98.2)	
Clinical N stage				0.139			0.568
N0	31 (18.0)	9 (14.3)	22 (20.2)		8 (14.0)	6 (10.5)	
N1-3	141 (82.0)	54 (85.7)	87 (79.8)		49 (86.0)	51 (89.5)	

Abbreviations: BMT, bimodality therapy; TMT, trimodality therapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; GEJ, gastroesophageal junction.



Supplemental Fig. 1. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 48 FDG-PET responders after propensity score-matching.



Supplemental Fig. 2. OS (A), PFS (B), LRFFS (C), and DMFS (D) according to type of therapy (BMT vs. TMT) among the 172 FDG-PET non-responders after propensity score-matching.