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Research Article

Using ^{18}F-FDG PET/CT to Predict Esophageal Cancer Survival: A Meta-Analysis

Wang J[1], Song J[2] and Li S[1]*

[1]Department of Nuclear Medicine, First Hospital of Shanxi Medical University, Taiyuan, China

[2]Department of Cancer Center, Shanxi Bethune Hospital, Taiyuan, China

***Corresponding author:** Sijin Li, 85 Jiefang South Road, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

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Abstract

Purpose: This study aimed to explore whether metabolic responses to ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography collected before, during, or after the treatment can predict the long-term survival rate of patients with esophageal cancer.

Patients and Methods: We searched for the following indices in articles listed in English and Chinese literature databases: the maximum standard uptake value (SUV_{max}), mean standard uptake value (SUV_{mean}), Metabolic Tumor Volume (MTV), and Total Lesion Glycolysis (TLG). If their values exceeded the thresholds, we defined them as responders; if they did not, we defined them as non-responders. We then performed a meta-analysis by extracting the Hazard Ratio (HR) and 95% confidence interval (95% CI) from each report to predict whether the status of responder or non-responder had an impact on prognosis.

Results: We identified 34 articles with a combined sample size of 2794 patients. HRs and 95% CIs were measured as follows: SUV_{max} = 1.15 (0.98-1.35), MTV = 3.45 (0.78-15.25), TLG = 1.04 (1.02-1.07), and SUV_{mean} = 1.85 (1.33-2.57) (before treatment); ΔSUV_{max} = 1.22 (1.06-1.39), Δ MTV = 1.07 (0.54-2.15), and ΔTLG = 1.09 (0.59-2.02) (during treatment); and SUV_{max} = 1.13 (1.05-1.22) and TLG = 1.05 (1.02-1.09) (after treatment). The results showed that the overall survival of the patients with low SUV (MTV, TLG) values was significantly higher than that of the patients with high SUV (MTV, TLG) values.

Conclusions: This meta-analysis shows that the prognoses of patients with PET metabolic responses are significantly better than those of non-responders. Our findings may help inform the clinical treatment and prediction of the prognoses of patients with esophageal cancer.

Keywords: Positron emission tomography; Esophageal neoplasms; Chemoradiotherapy

Abbreviations

95% CI: 95% Confidence Interval; CRT: Chemoradiotherapy; FDG: ^{18}F-fluorodeoxyglucose; HR: Hazard Ratio; MTV: Metabolic Tumor Volume; OS: Overall Survival; PET/CT: Positron Emission Tomography/Computed Tomography; SUV_{max}: Maximum Standard Uptake Value; SUV_{mean}: Mean Standard Uptake Value; TLG: Total Lesion Glycolysis

Introduction

Likely due to differences in economic development and living habits, the incidence of upper gastrointestinal cancer is high in economically underdeveloped areas, especially in East Asia and East Africa [1]. The annual incidence of upper gastrointestinal cancer in China, for example, accounts for 44.6% of the global incidence of the disease with a crude mortality rate of 13.68/100000 [2]. Esophageal cancer is one of the most common tumors of the upper digestive system. It is principally treated with a combination of surgery and neoadjuvants or definitive radiotherapy and chemotherapy. While this multimodal treatment has greatly reduced the mortality and improved the disease-free survival rate of patients with esophageal cancer, the accurate prediction of the prognoses of patients following the treatment has remained a challenge [3]. A superb supplement to traditional medical imaging, Positron Emission Tomography (PET) has partially replaced invasive examinations such as endoscopic biopsy as a method of delineating the target area in the early stages of tumor radiotherapy and thus holds a potential for improving the prediction of a patient's response to radiotherapy, chemotherapy, and even surgery [4].

In the past, CT was typically used to stage esophageal cancer. However, CT scans were not as useful 40 years ago as they are now. Despite its regional limitation, endoscopic ultrasound has become the best staging method (For stage of the primary tumor). New tools are still needed to predict the prognosis of esophageal cancer [5]. ^{18}F-FDG PET has recently gained popularity as a metabolic imaging modality. Many researchers have used it to evaluate the efficacy or to predict the outcomes of radiotherapy, chemotherapy, and surgery; ^{18}FDG-PET can thus help avoid the prescription of ineffective or unnecessary treatments.

In the present study, we identified responders as patients with PET parameters higher (e.g., $SUV_{max} > 9.6$) and lower (e.g., $SUV_{max} < 7.8$) than the standard threshold before and after treatment, respectively, as well as those with for whom the difference in parameters before

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and after treatment was greater than the standard percentage (e.g., ΔSUV_{max} > 23%). The values of PET parameters used as response thresholds differ greatly, and are primarily based on experience. Due to the differences in reported thresholds, we have not listed the values here.

As the literature featured no standardized guidelines, what changes in PET parameters across treatment are considered to indicate prognosis vary. Further, whether PET can predict the mortality and disease-free survival rate of patients remains controversial. To help inform the resolution of this controversy and contribute to a reference for clinical practice, the present meta-analysis of all relevant and available literature aimed to conduct a systematic, objective analysis of PET factors predictive of survival following esophageal cancer.

Patients and Methods

Literature search

We searched the Cochrane library MEDLINE, EMBASE, and China National Knowledge Internet for documents published in Chinese or English from any year. The following search query was used: "esophageal cancer" OR "carcinoma of esophagus" OR "esophageal carcinoma" OR "esophagus cancer" AND "positron emission tomography" OR "PET" AND "^{18}F-FDG" OR "fluorodeoxyglucose" AND "prognosis" OR "outcome" OR "prognostic" OR "existence" OR "survival" OR "predict" (Figure 1).

Selection of studies

The selected articles were independently evaluated by four researchers (three clinical doctors and one professor of statistics) who did not communicate with one another. Scores were tallied out of 36 points. Clear mention of indices in the article earned 2 points, unclear mention of indices earned 1 point, and no mention of indices earned 0 points (or based on the explanation in the comments). The average of the four scores awarded by the researchers was used as the final score. Disagreements were settled through discussion (Table 1). Further details regarding the method used to score each article are described in the Appendix.

Statistical methods

This paper selected four indices in each report to distinguish whether responding depends on each author's experience or practical results: the maximum standard uptake value (SUV_{max}), mean standard uptake value (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). When merging statistical results, it was necessary to perform a heterogeneity test to judge whether the statistics were heterogeneous. P-values of ≤0.100 were considered to indicate heterogenous statistical results.

In Revman software, I^2 can be used to describe the percentage of heterogeneity caused by various studies rather than sampling errors in the total heterogeneity. The formula used to calculate I^2 is as follows:

$$I^2 = [Q-(k-1)]/Q \times 100\%$$

where Q represents the chi-square value (χ^2) of the heterogeneity test, and k represents the number of included studies. I^2 values of ≤50% were considered to indicate statistical significance. The values of the four indicators of the survival rate selected in these papers were generated by the comparison of the Overall Survival (OS) rate, as calculated from the Hazards Ratio (HR) and 95% Confidence

Table 1: Standard for evaluation.

Project	Specific meaning	Comments (Score)
1	Define research objects clearly	The gender, age, pathological type, stage and so on of the subjects are clearly defined
2	Study types	Prospective (2) Retrospective(1)
3	Clearly define the outcome of the event	The optimal number of samples(2) Define the number of samples(1)
4	Application of statistical methods	
5	Description of Statistical method	
6	Criteria of patient included	
7	Characteristics of patient included	
8	Medical regulation and nursing convention	
9	Description of treatment	
10	Number and reasons of excluded patients	
11	Follow-up period	Including description of endings
12	Univariate survival analysis of prognostic factors	There is direct HR and 95% CI(2) There is not direct HR and 95% CI(1) There is noway we can get HR(0)
13	Multivariate survival analysis of prognostic factors	There is direct HR and 95% CI(2) There is not direct HR and 95% CI(1) No univariate analysis was performed or data could not be extracted(0)
14	PET report: Basic Information	
15	^{18}FDG-PET data acquisition	
16	^{18}FDG-PET technical parameters	
17	Using the double-blind method	
18	Clearly defined threshold	

HR: Hazard Ratio; CI: Confidence Interval.

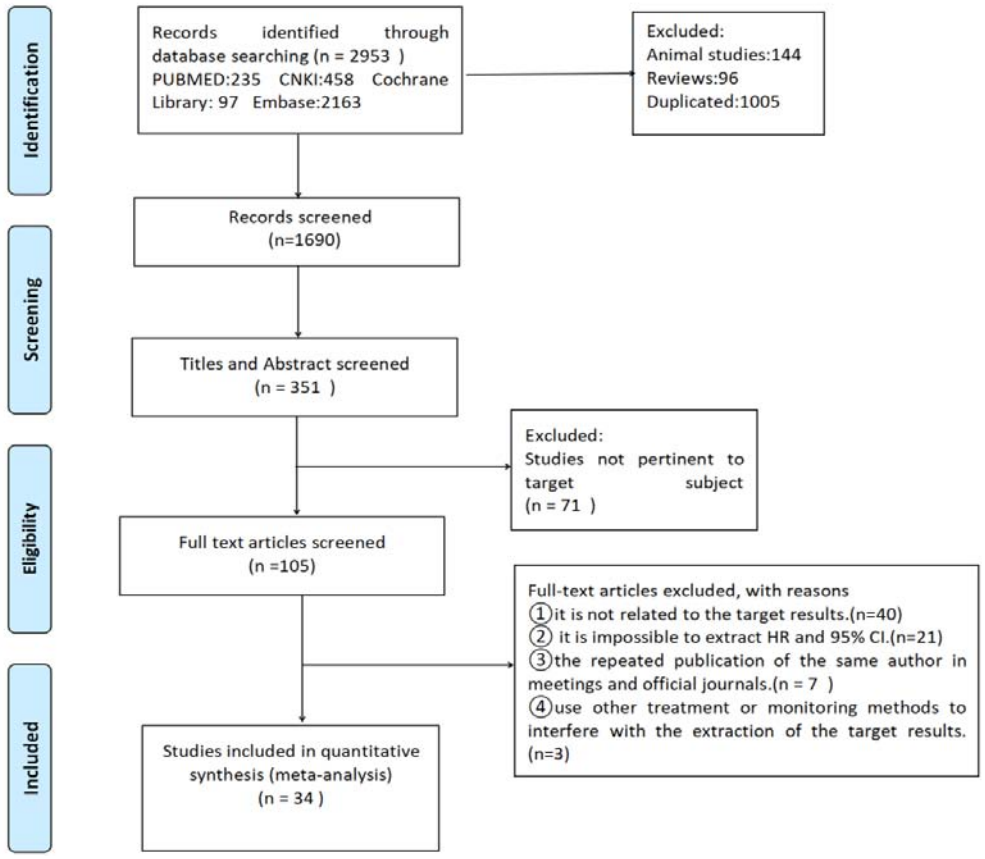

Figure 1: Flowchart of the selection of articles.

Interval (CI), between the two groups. The HR was calculated with the following formula:

$$\text{pooled lnHR}=\left[\frac{\sum \log rank \text{ Observed-Expected events}(O-E)}{\sum \log rank \text{ Variance}(V)}\right]$$

$$\text{pooled lnHR}=\left[\frac{\sum \frac{\ln HR}{\text{Variance of the lnHR}}}{\sum \frac{1}{\text{Variance of the lnHR}}}\right]$$

If HR and variance (V) were mentioned in the original text, they could be directly applied to the meta-analysis. The method of Jayne et al. [6] can be used to calculate the HR and 95% CI in any case from the K-M curve and P-value. First, the approximate value of each point on the curve is obtained by using Engauge Digitizer, and the approximate value of HR is calculated from the Excel table accompanying the manuscript published by Jayne et al. Revman is then used to calculate the upper and lower intervals of the 95% CI. If there are no censored data, the following formula can be used:

$$\text{HR}=\left[\frac{\text{Observed events research/logrank Expected events research}}{\text{Observed events control/logrank Expected events control}}\right]$$

The survival rate of patients with low SUV values (low MTV values/TLG values or high absolute value of ΔSUV) is generally higher than that of patients with high SUV values when HR >1.0. By contrast, the survival rate of patients with high SUV values (high MTV value/TLG value or low absolute value of ΔSUV) is higher than that of patients with low SUV values when HR ≤1.0.

If the results featured bias, we considered the subgroups analysis to confirm the presence of publication bias.

All the data were analyzed with Revman5.0 (The Nordic Cochrane Centre, Copenhagen, Denmark), MetaXL5.3 (EpiGear International Pty Ltd, Queensland, Australia), and Stata15.1 (StataCorp, Lakeway Drive, College Station, Texas, USA).

Results

Study selection and characteristics analysis

Hundreds of articles were retrieved from the aforementioned databases. After reading the titles and abstracts, 105 related articles were selected for analysis. Articles were subsequently removed on account of the following: 1) The content of the article was not related to the present study, 2) the study used other treatments or monitoring methods that interfered with the extraction of the target results (e.g., disease-free survival and progression-free survival were selected as prognostic factors instead of overall survival), 3) the article was published more than once by the same author, or 4) it was not possible to extract the HR and 95% CI. Finally, 34 articles remained. Articles containing only some of the target results and those featuring all of the target information were extracted separately. Of these 34 articles, 24 considered the effect of SUVmax before treatment [8-31]; nine, MTV before treatment [19,23,25,27-29,31-34]; seven, TLG before treatment [23,24,28,29,31,32,34]; three, SUVmean on OS before treatment [24,25,28]; four, SUVmax after treatment [10,16,20,29,31,35]; three, TLG after treatment [29,31,35]; 10, the

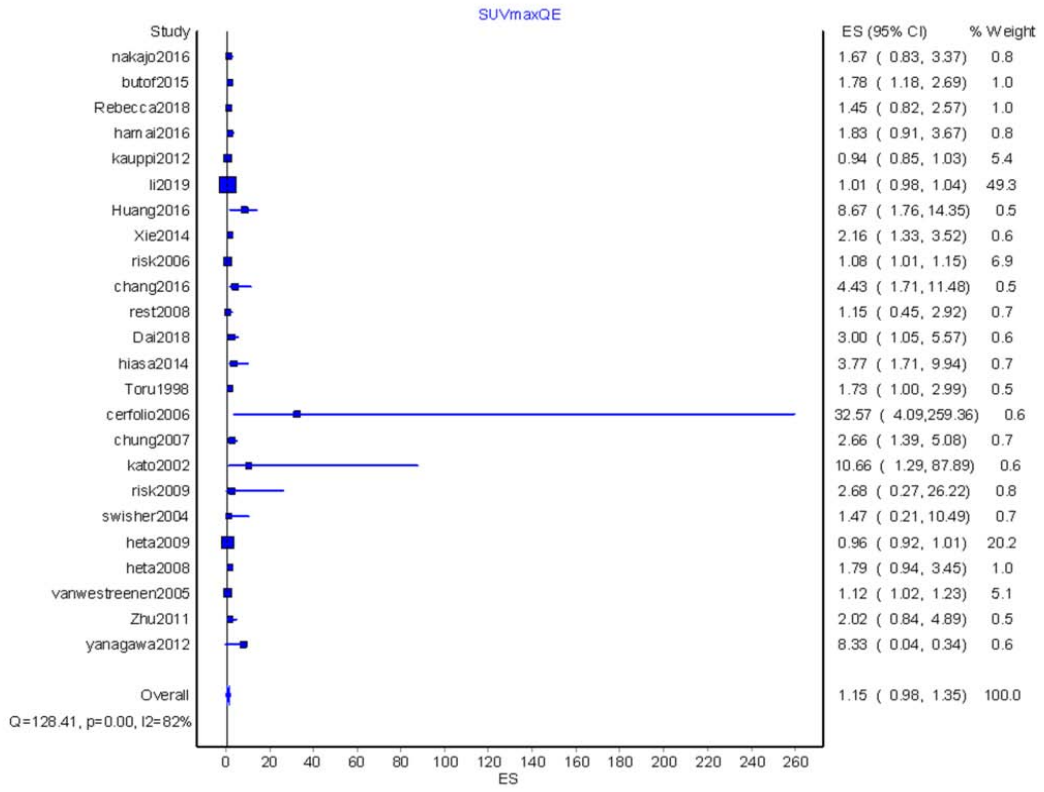

Figure 2a: Forest plots of SUV_{max} before treatment. SUV_{max}: The maximum standard uptake value.

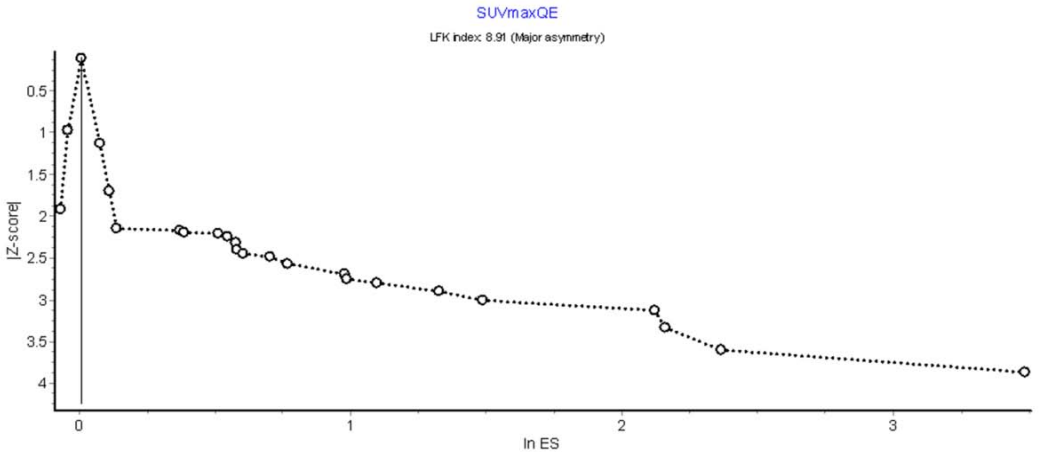

Figure 2b: Z-score of 24 studies before treatment. SUV_{max}: The maximum standard uptake value.

effect of ΔSUV_{max} before and after treatment [16,20,26,29,31,36-40]; four, ΔMTV before and after treatment [29,31,39,41]; and five, effect of ΔTLG before and after treatment (Table 2 and 3) [25,29,31,39,41].

Quality assessment

The lowest quality score of the 34 selected articles was 39, and the highest was 84. The scoring system adopted by the reviewers was relatively strict, and the document quality was relatively high. If an article lacked necessary information, the corresponding author of the article was contacted.

Meta-analysis before treatment

A meta-analysis of the four indicators (SUV_{max}, SUVmean, MTV, and TLG) before treatment was performed for OS. Twenty-four articles included the SUV_{max}. Because the I^2 = 82% >50%, these articles were analyzed with the QE model (HR = 1.15, 95% CI = 0.98-1.35). The results showed that the OS of the patients with low SUV_{max} was significantly higher than that of the patients with a high SUV_{max} (Figure 2a-2c).

The asymmetry of the funnel chart suggested publication bias.

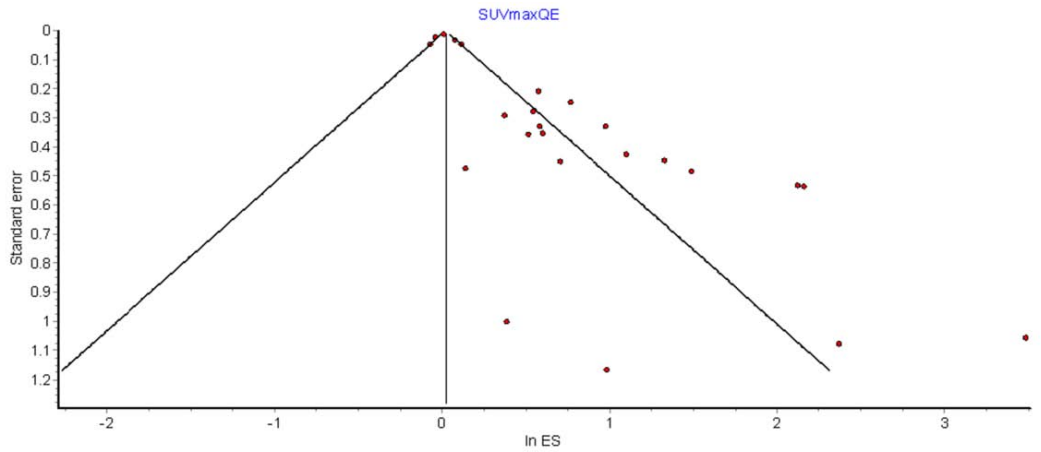

Figure 2c: Funnel Plots of SUV_{max} before treatment. These articles may be subject to publication bias. ES: Effect Size (hazard ratio); SUV_{max}: The maximum standard uptake value.

Table 2: Basic Information of studies included in the meta-analysis.

Study	Publication year	Number of patients	Pathological type	Stage	Score
Nakajo 2016	2016	52	NM	I-III	73
Butof 2015	2015	130	N	I-III	79
Rebecca 2018	2018	76	N	II-III	84
Hamai 2016	2016	111	NM	Ib-IV	73
Kauppi 2012	2012	66	A	I-IV	74
Li 2019	2019	134	S	T1-T4 N0-N2	78
Huang 2016	2016	82	S	T1-T4	53
Xie 2014	2014	60	N	I-IVb	50
Risk 2006	2006	50	N	T1-T3 N0-N1	50
Chang 2016	2016	61	S	LAEC	48
Rest 2008	2008	52	N	I-IV	64
Dai 2018	2018	167	S	I-III	53
Hiasa 2014	2014	101	S	I-IV	70
Toru 1993	1998	48	NM	III-IV	39
Cerfolio 2006	2006	89	N	I-IV	62
Chung 2007	2007	100	N	NM	65
Kato 2002	2002	32	S	I-IV	56
Lordick 2007	2007	110	A	T0-T4 N0-N1	80
Ott 2006	2006	65	A	IIa-IV	64
Risk 2009	2009	189	A	T0-T4	82
Roedl 2008	2008	51	A	NM	67
Swisher 2004	2004	83	N	IIa-IVa	73
Heta 2009	2009	151	A	NM	77
Heta 2008	2009	161	A	Excluded T1N0 and M1b	78
Vanwestreenen 2005	2005	40	N	I-IV	68
Weber 2001	2001	40	A	I-II	64
Zhu 2011	2011	49	S	I-IVa	50
Yu 2018	2018	80	NM	T1-T4	55
Lin 2018	2018	37	S	II-III	64

Hofheinz 2019	2019	147	S	I-III	77
Huang 2015	2015	49	N	T2-T4N0-N3M0	67
Kim 2016	2016	53	N	T2-T4N0-N1M0	69
Anna 2014	2013	79	N	NM	73
Yanagawa 2012	2012	51	S	LAEC	61

NM: Not Mentioned; S: Squamous Cell Carcinoma; A: Adenocarcinoma; N: Not Distinguish; LAEC: Locally Advanced Esophageal Cancer.

```
Number of studies =  24                          Root MSE      =   1.333

------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |  -.0426187   .0173397    -2.46   0.022    -.0785789   -.0066584
        bias |   2.249979    .317454     7.09   0.000     1.591619    2.908338
------------------------------------------------------------------------------

Test of H0: no small-study effects            P = 0.000
```

Figure 3a: Egger's test of SUV_{max} before treatment. SUV_{max}: The maximum standard uptake value.

```
Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard error

  adj. Kendall's Score (P-Q) =      64
        Std. Dev. of Score =   40.32
         Number of Studies =      24
                         z =    1.59
                   Pr > |z| =   0.112
                         z =    1.56 (continuity corrected)
                   Pr > |z| =   0.118 (continuity corrected)
```

Figure 3b: Begg's test of SUV_{max} before treatment. SUV_{max}: The maximum standard uptake value.

The two methods of Begg and Egger of Stata used to detect the publication bias indicated contradictory results. For a small sample, the Egger method (Figure 3a) is more sensitive than the Begg (Figure 3b) method. The result of P=0.000 indicated that the selected articles were subject to publication bias.

The heterogeneity of the 34 articles selected after manual review did not change greatly, indicating that the results are relatively robust; therefore, we performed subgroup analyses. The patients were categorized according to the following pathological types (articles that did not mention pathological types were excluded): squamous cell carcinoma, adenocarcinoma, and unsegmented. The HR and 95% CI of each subgroup were 3.69 (1.68-8.09), 0.96 (0.89-1.04) and 1.41 (1.16-1.71), respectively. These values were significantly different (p <0.00001).

The patients were further categorized according to the pathological stage of their cancer (articles that did not mention the stage were excluded): stage I or earlier, and stage II or earlier. The HR and 95% CI of each subgroup were 2.35 (1.59-3.48) and 1.52 (1.17-1.97), respectively. There was no significant difference between the two groups (p=0.07).

The patients were also divided according to treatment: radiotherapy and chemotherapy (S), operation (O), and undifferentiated treatment (N). The HR and 95% CI of each subgroup were 1.63 (1.32-2.02), 2.07 (1.20-3.55), and 1.19 (0.95-1.49), respectively. No significant difference was found between the three groups (P=0.06, Figure 4a-4c).

Nine articles included in our analysis considered MTV. Because the I^2 = 100% >50%, these articles were analyzed with the QE model (HR = 3.45, 95% CI = 0.78-15.25). Our results showed that the OS of the patients with low MTV values was significantly higher than that of the patients with high MTV values.

Seven articles included in our analysis considered TLG. Because the I2 = 81% >50%, these articles were analyzed with the QE model (HR = 1.04, 95% CI = 1.02-1.07). The results showed that the OS of the patients with low TLG values was significantly higher than that of the patients with high TLG values.

Three articles included in our analysis considered the SUVmean. Because the I^2 = 48% <50%, these articles were analyzed with the fixed-effect model (HR = 1.85, 95% CI = 1.33-2.57). The results showed that the OS of the patients with low SUVmean scores was significantly higher than that of the patients with high SUVmean scores.

Meta-analysis during treatment

Meta-analysis of the three indicators (Δ SUV_{max}, Δ MTV, and Δ TLG) measured during treatment was performed. Ten articles included in our analysis considered the ΔSUVmax. Because the I^2 =

Table 3: The index from the studies in the meta-analysis.

Study	Index	Time*	Threshold
Nakajo 2016	SUV_{max} SUV_{min} MTV TLG	Before CRT	NM
Butof 2015	SUV_{max} SUV_{min} MTV TLG	Before Radiotherapy	SUV_{max}>8.5 SUV_{mean}>8.14 MTV>8.5 TLG>12.4
Rebecca 2018	SUV MTV TLG	Before and after CRT (during the last week of RCT)	Pre: SUV>13.4 MTV>26.3 TLG>121 Post: SUV<5.33 MTV<6.6 TLG<30.2 ΔSUV >38.8% ΔMTV >35% ΔTLG>38.8%
Hamai 2016	SUV_{max}	Before and after CRT	Post: SUV_{max}>5.33 ΔSUV_{max}>75%
Kauppi 2012	SUV	Before and after CRT	Pre: SUVNM Post: SUVNM ΔSUV> 67%
Li 2019	SUV_{max} MTV TLG	Before (within 28 days) and after (when 40-50 Gy to the PTV had been delivered) radiotherapy	Pre: SUV_{max}>9.6 MTV>15.9 TLG>59.8 Post: SUV_{max}<7.8 MTV<10.5 TLG<44.3 ΔSUV_{max}>23% ΔMTV>7.5% ΔTLG>27%
Huang 2016	SUV_{max}	Before Radiotherapy	SUV_{max}>9.7
Xie 2014	SUV_{max} MTV TLG	Before Radiotherapy	SUV_{max}≥11.4 MTV≥8.27 TLG≥35.21
Risk 2006	SUV_{max}	Before Operation	SUV_{max}>4.5
Chang 2016	SUV_{max} SUV_{mean} MTV TLG	Before CRT	SUV_{max}>4.86 SUV_{mean}>2.37 MTV>8.93 TLG>20.42
Rest 2008	SUV_{max}	Before Operation	SUV_{max}>9
Dai 2018	SUV_{max}	Before Treatment	SUV_{max}>6
Hiasa 2014	SUV_{max}	Before Treatment	SUV_{max}>10.26
Toru 1993	SUV	Before Operation	SUV≥7.0
Cerfolio 2006	SUV	Before Operation	SUV≥6.6
Chung 2007	SUV	Before Operation	SUV≥15
Kato 2002	SUV	Before Operation	SUV≥3
Lordick 2007	SUV	Before (7 days) and after (14 days after the start of chemotherapy) treatment	ΔSUV≥35%
Ott 2006	SUV	Before and after treatment (14 days after initiation of therapy)	ΔSUV≥35%
Risk 2009	SUV	Before Chemotherapy	SUV_{max}≥4.5
Roedl 2008	SUV_{max} SUV_{mean} MTV TLG	Before (12.3 days ± 7.1) and after (16.9 days ± 6.8) treatment	ΔSUV_{max}≥43% ΔSUV_{mean}≥22% ΔMTV≥63% ΔTLG≥78%
Swisher 2004	SUV	Before and after CRT	Pre: SUV>9.5 Post: SUV<4
Heta 2009	SUV	Before and after treatment	ΔSUV>52%
Heta 2008	SUV	Before CRT	SUV>10.1
Vanwestreenen 2005	SUV_{max}	Before treatment	SUV_{max}≥6.7
Weber 2001	SUV	Before and after (14 days) Chemotherapy	ΔSUV≥35%
Zhu 2011	SUV_{max} MTV	Before Operation	SUV_{max}>11.6 MTV>14.5
Yu 2018	MTV	Before Operation	NM
Lin 2018	MTV TLG	Before Operation	MTV≥27.44 TLG≥166.2
Hofheinz 2019	SUV MTV TLG	Before Chemoradiotherapy	MTV>22.3 TLG>46 SUV NM
Huang 2015	SUV	Before and after (21 days) CRT	ΔSUV>60%
Kim 2016	SUV_{max} MTV TLG	Before (2-17 days) and after (45 Gy of radiotherapy with 3 cycles of chemotherapy) radiotherapy	ΔSUV_{max}>23.5 ΔMTV>25.5% ΔTLG> 44.8%
Anna 2014	SUV	after radiotherapy (14 days)	NM
Yanagawa 2012	SUV	Before and after chemotherapy (14 days)	NM

CRT: Chemoradiotherapy; NM: Not Mentioned; SUV_{max}: The maximum standard uptake value; SUV_{mean}: Mean Standard Uptake Value; MTV: Metabolic Tumor Volume; TLG: Total Lesion Glycolysis; PTV: Planned Target Volume; Δ: Means Differences Before and After Treatment. *Some articles did not specify the time of PET/CT examination, but based on clinical experience, we can reasonably infer that it was performed as soon as possible before and after the treatment of the patient.

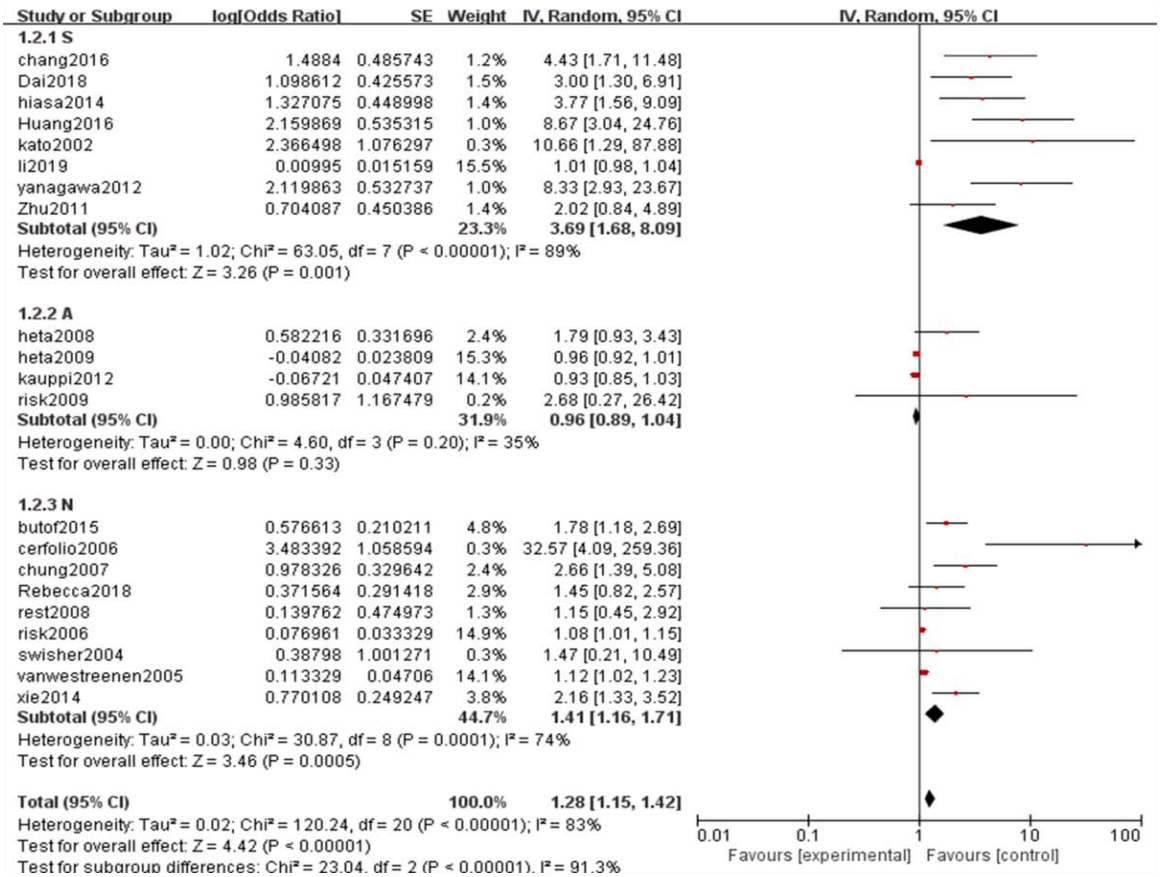

Figure 4a: Forest plots of the SUV_{max} subgroup according to pathological type. SUV_{max}: The maximum standard uptake value.

48% <50%, these articles were analyzed with the fixed-effect model (HR=1.22, 95% CI=1.06-1.39). The results showed that the OS of the patients with high absolute values of ΔSUV_{max} was significantly higher than that of the patients with low absolute values of ΔSUV_{max}.

Four articles included in our analysis considered the Δ MTV. Because the I^2 = 90% >50%, these articles were analyzed with the QE model (HR=1.07, 95% CI = 0.54-2.15). The results showed that the OS of patients with high absolute values of ΔMTV was significantly higher than that of the patients with low absolute values of ΔMTV.

Five articles included in our analysis considered the ΔTLG. Because the I^2 = 87% >50%, these articles were analyzed with the QE model (HR = 1.09, 95% CI = 0.59-2.02). The results showed that the OS of the patients with high absolute values of ΔTLG was significantly higher than that of the patients with low absolute values of ΔTLG.

Meta-analysis after treatment

Meta-analysis of the two indicators (SUV_{max} and TLG) measured after treatment was performed. Six articles included in our analysis considered the SUVmax. Because the I^2 = 58% >50%, these articles were analyzed with the QE model (HR = 1.13, 95% CI = 1.05-1.22). The results showed that the OS of the patients with low SUVmax values was significantly higher than that of the patients with high SUV_{max} values.

Three articles included in our analysis considered TLG. Because the I^2 = 91% >50%, these articles were analyzed with the QE model (HR = 1.05, 95% CI = 1.02-1.09). The results showed that the OS of the patients with low TLG values was significantly higher than that of the patients with high TLG values.

Discussion

The sixth leading cause of cancer-related death and the eighth most common cancer in the world, esophageal cancer is associated with a 5-year survival rate of less than 25% [42]. While endoscopy, CT, and MRI have conventionally been used to examine patients with esophageal cancer, the relatively new technique of PET has been increasingly used for the diagnosis, differential diagnosis, and clinical staging of patients with esophageal cancer. Imaging also helps to identify patients with significant complications who may respond to and benefit from more conservative treatment (i.e., without esophagectomy) after CRT is demonstrated to be fully or partially effective. Finally, PET/CT has demonstrated value as a follow-up tool for the timely detection of tumor recurrence after surgical treatment [43]. However, because ^{18}F-FDG PET can help to inform the metabolic diagnosis of esophageal cancer, it can compensate for the shortcomings of traditional methods and predict the prognosis of patients when combined with CT to construct a clear anatomical image. A study found ^{18}F-FDG PET/CT to be a powerful prognostic tool for evaluating OS in patients with esophageal cancer before, during, or after Chemoradiotherapy (CRT). PET parameters (TLG

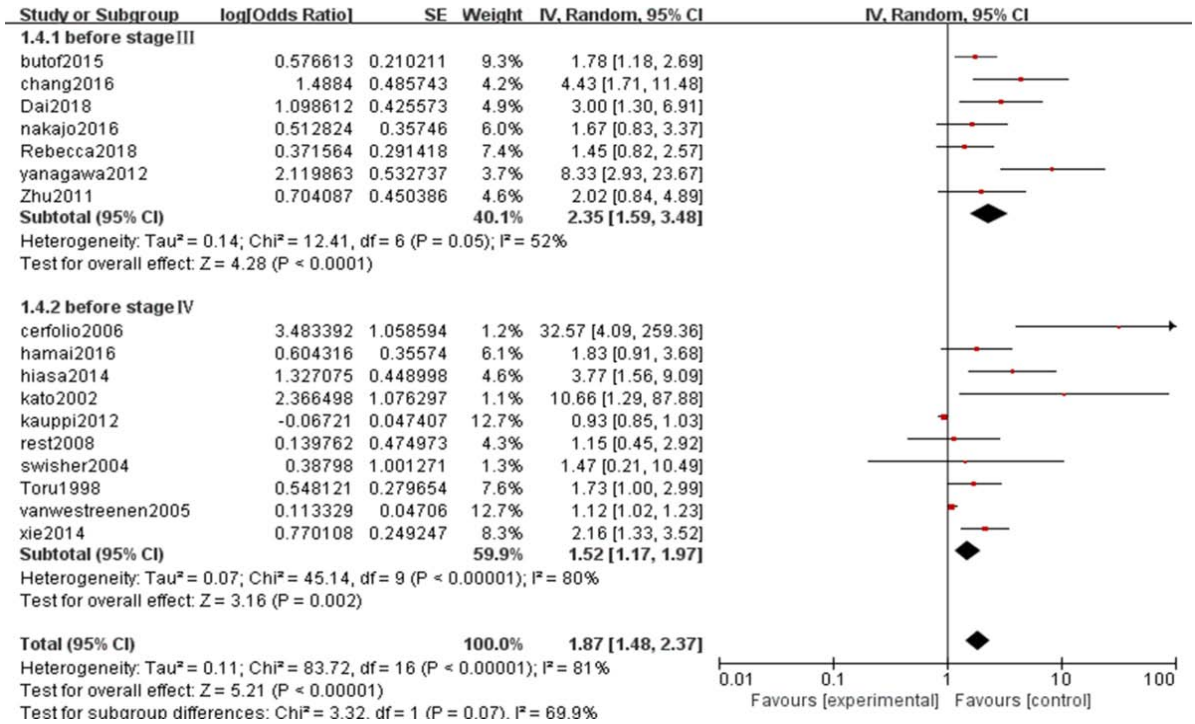

Figure 4b: Stage of cancer. SUV_{max}: The maximum standard uptake value.

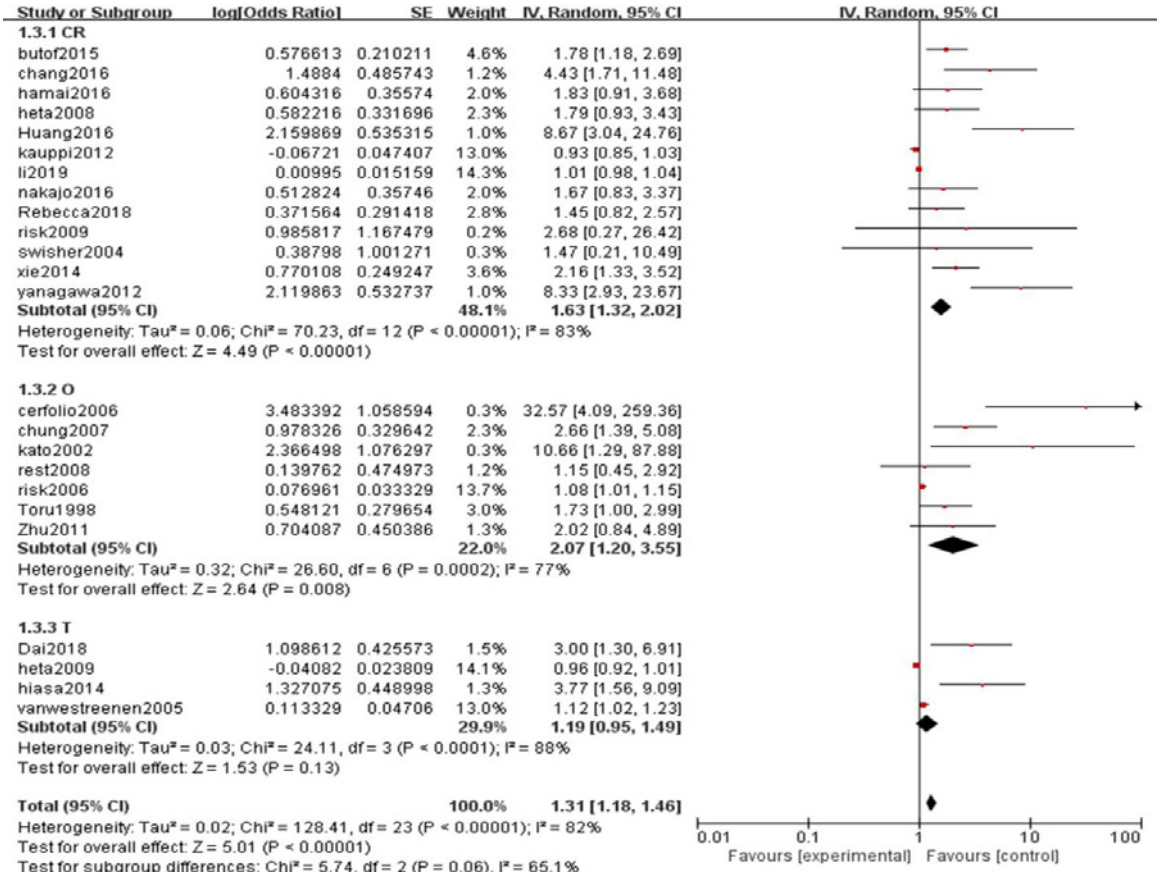

Figure 4c: Type of treatments. SUV_{max}: The maximum standard uptake value. SUV_{max}: The maximum standard uptake value.

= 50) can guide future treatment strategies by stratifying stage II/III patients who will receive CRT according to their predicted OS [44]. Another study showed that PET could reflect the response of esophageal cancer to neoadjuvant chemotherapy: the SUV values of the PET responders were significantly higher than those of the PET non-responders [45]. However, there are no large samples of clinical studies on the relationship between PET/CT metabolic response (or not) and prognosis to guide clinical treatment.

The articles selected in this meta-analysis featured considerable heterogeneity. The use of the traditional RE model and the square of tau (τ^2) to measure the differences between studies indicated large variance in the results of small samples, which leads to small weights. When calculating the weights in each study, the same τ^2 values are used for the denominators; hence, small studies will contribute a disproportionately large weight, while the weight of large studies will be reduced. The QE model is used to resolve the drawback of the RE model.

For cases with large heterogeneity, subgroup analysis was used to identify the source of heterogeneity. For studies providing the SUVmax before treatment, the possible causes of heterogeneity include, sex, age, treatment plan, clinical stage, pathological type, sample size, and article quality scores. However, as most articles did not make a clear distinction between sex and age, the present meta-analysis considered the patient's treatment plan, clinical stage, and pathological type as sources of heterogeneity.

When the patients were divided according to pathological type, the value of SUV_{max} could predict the OS of patients with squamous cell carcinoma and undifferentiated pathologies but not for those with adenocarcinoma pathologies. The difference between the three groups was statistically significant, indicating that the relationships between pathological type, the value of SUV_{max}, and OS are unclear and that the ^{18}F-FDG uptake of adenocarcinoma cells is not as effective as that of squamous cells (low or no uptake can be seen in 10% to 15% of undifferentiated adenocarcinomas). Hence, caution should be exercised when using the SUV_{max} to predict the OS of patients whose esophageal cancer follows the pathological pattern of adenocarcinomas.

When subgroups were divided according to stage, we found no significant difference between patients with cancer before or at stage I and those with cancer before or at stage II. However, it is possible that SUV_{max} is more effective as a predictor of esophageal cancer in the early and middle stages of cancer because the group of patients with cancer before or at stage IV includes patients with cancer before or at stage IV. More experiments are needed to confirm this hypothesis.

When the patients were sorted according to treatment, we found no significant difference between the four groups. While the methods of radiotherapy and chemotherapy, drug use, radiation dose, target delineation, and even surgical methods differed among the reviewed studies, the analyses of each subgroup confirmed that SUVmax could still be used to predict OS.

The overall analysis revealed that regardless of whether the indices were measured before or after treatment, SUV_{max}, MTV, TLG, and SUV_{mean} could perform well in predicting the OS of patients; the value of MTV is related to the size of the solid tumor, while the values of SUV_{max} and TLG are related to the pathological response. Hence, SUV_{max} and TLG can directly predict the efficacy of radiotherapy, chemotherapy, and surgery.

The results of this paper have important guiding significance for clinical work. However, due to the large heterogeneity in the articles included in this study, the prognostic value of PET/CT for the clinical response or choice of treatment should be used with caution. Further multi-center clinical studies with large sample size was conducted for verification.

Due to the high cost of PET/CT, many medical institutions do not perform PET/CT routinely in pre-treatment examinations in order to minimize the financial burden of patients. However, PET/CT improves the accuracy of tumor staging and target delineation as compared with simple CT. According to this paper, the response of parameters of PET/CT also plays a positive role in the prognosis. Especially for patients with locally advanced disease, continuing neoadjuvant chemotherapy may be beneficial if they respond well; however, if a patient responds poorly or weakly to neoadjuvant radiotherapy and chemotherapy, that treatment should be stopped as soon as possible [46-47]. This is of great value to therapeutic economics. For example, Angela and her groups have made a large number of statistics on the cost of patients with esophageal cancer with different treatment methods for a long time. For example, the average cost of radiotherapy for stage III patients is $7530, and the average cost of chemoradiotherapy is $11460 [48], if we can predict how well a patient will respond to treatments, it will save individuals and Medicare a lot of money.

At present, there are a variety of histopathological methods to evaluate the response of esophageal cancer to neoadjuvant radiotherapy and chemotherapy. however, there is no unified standard. As these methods are based on invasive procedures, they are not conducive to clinical application [49]. In contrast, the efficacy of ^{18}F-FDG PET/CT after neoadjuvant radiotherapy and chemotherapy is related to histopathological tumor regression and can reflect the prognosis of patients to some extent. According to this meta-analysis, we believe that PET/CT should be one of the routine tests performed before neoadjuvant radiotherapy, chemotherapy or surgery. If a patient responds well on PET/CT, treatment should proceed as planned; if the patient is non-responder, treatments other than neoadjuvant chemotherapy should be considered.

In clinical work, SUV_{max} is the most widely used parameter. As many radiologists ignore the significance of other parameters such as SUV_{mean}, MTV, and TLG, there are relatively few clinical studies with that data. In our study, parameters such as MTV and TLG may also be predictive of prognosis, and to a certain extent, may be more sensitive than SUV_{max}. In particular, when SUV_{max} is near the critical value, other parameters can be used as reference factors. Because it is not difficult to obtain these parameters, we suggest that they should be used as common predictive parameters in the clinic, in order to provide more support for the prognosis of esophageal cancer. In this paper, it can be seen that the critical value of SUV_{max} varies widely amongst the articles analyzed. While this is related, in part, to the different instruments and image processing methods used, it also highlights the lack of a unified standard to apply for the distinction between PET/CT responders and non-responders. Currently, SUV_{max}

thresholds are typically set between 4 and 10, but further research is needed to establish a unified standard.

This report is subject to several limitations. First, many of the included articles did not directly report HR values but instead extracted them through the K-M curve. This method inevitably results in mistakes. Second, the funnel chart of the reports collected from the literature was subject to publication bias, likely resulting in the overestimation of the presently identified predictive effect of the indices. Finally, all of the reports sourced from the literature are case-control or cohort studies, highlighting the need for large randomized controlled trials of the potential of PET/CT for predicting the prognoses of patients with esophageal cancer.

Conclusion

Our study demonstrates that the prognoses of patients who respond to PET/CT are significantly better than those of non-responders; however, the clinical courses for patients with esophageal cancer still need to be determined through a variety of examinations. Therefore, our study confirmed that ^{18}F-FDG PET/CT is helpful in predicting the prognosis of patients with esophageal cancer, thus guiding their treatment to a certain extent.

Declarations

Authors' contributions: Jingying Wang conducted data curation, performed formal analysis, and wrote this paper. Jianbo Song managed conceptualization and project administration. Sijin Li constructed the methodology, and reviewed and edited the paper.

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