Using 18F-FDG PET/CT to Predict Esophageal Cancer Survival: A Meta-analysis

Jingying Wang
Shanxi Medical University https://orcid.org/0000-0003-4128-8672
Jianbo Song
Shanxi Bethune Hospital
Sijin Li (lisjnm123@163.com)
First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China.

Research

Keywords: positron emission tomography, esophageal neoplasms, chemoradiotherapy

Posted Date: December 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-120613/v1

Using 18F-FDG PET/CT to Predict Esophageal Cancer Survival: A Meta-analysis

Type of manuscript: Research

Authors:

JingYing Wang，MSC

Department of Nuclear Medicine, First Hospital of Shanxi Medical University, Taiyuan, China.

JianBo Song, MD.PhD

Department of Cancer Center, Shanxi Bethune Hospital, Taiyuan, China.

SiJin Li, MD. PhD.

Department of Nuclear Medicine, First Hospital of Shanxi Medical University, Taiyuan, China.

Corresponding Author:

SiJin Li

Address: 85 Jiefang South Road, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China.

Fax:0351-4048123

Tel:+8613934519222

Email: lisjnm123@163.com

Abstract

Background: This study aimed to explore whether metabolic responses to positron emission tomography/computed tomography (PET/CT) collected before, during, or after the treatment can predict the long-term survival rate of patients with esophageal cancer.

Main body: 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.

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

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; for example, the annual incidence of upper gastrointestinal cancer in China accounts for 44.6% of the global incidence of the disease [1]. Esophageal cancer is one of the most common tumors of the upper digestive system. It is principally treated with a combination of surgery and neoadjuvant or traditional 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. 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.

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. New tools are still needed to predict the prognosis of esophageal cancer [2]. ^{18}F-fluorodeoxyglucose (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; FDG PET can thus help avoid the prescription of ineffective or unnecessary treatments. We identified responders as patients with higher standard uptake value (SUV) values before treatment and lower SUV values after treatment, as well as patients with greater differences in SUV values before and after treatment. The values of PET parameters used as response

thresholds differ greatly, and most are based on experience; due to these differences between articles, we have not listed the thresholds 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.

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 “18F-FDG” OR “fluorodeoxyglucose” AND “prognosis” OR “outcome” OR “prognostic” OR “existence” OR “survival” OR “predict” (Fig 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.

Table1. standard for evaluation

Project	**Specific meaning**	**Comments**
1	Clearly define the research object	
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 no direct HR or 95% CI (1) There is no way we can calculate HR (0)
13	Multivariate survival analysis of prognostic factors	There is direct HR and 95% CI (2) There is no direct HR or 95% CI (1) There is no way we can calculate HR (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

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

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

130 $$pooled \ln HR = \left[\frac{\sum \frac{\ln HR}{Variance\ of\ the \ln HR}}{\sum \frac{1}{Variance\ of\ the \ln HR}} \right]$$

131 If HR and variance (V) were mentioned in the original text, they could be
132 directly applied to the meta-analysis. The method of Jayne et al. [4] can be
133 used to calculate the HR and 95% CI in any case from the K-M curve and P-
134 value. First, the approximate value of each point on the curve is obtained by
135 using Engauge Digitizer, and the approximate value of HR is calculated from
136 the Excel table accompanying the manuscript published by Jayne et al.
137 Revman is then used to calculate the upper and lower intervals of the 95% CI.
138 If there are no censored data, the following formula can be used:

139 $$\mathrm{HR} = \left[\frac{Observed\ events\ research / \log rank\ Expected\ events\ reseach}{Observed\ events\ control / \log rank\ Expected\ events\ control} \right]$$

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

145 If the results featured bias, we considered the subgroups analysis to
146 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) contents were unrelated to the target results, 2) extracting the HR and 95% CI was impossible, 3) the article was published more than once by the same author, or 4) the study used other treatments or monitoring methods that interfered with the extraction of the target results. 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 SUV_{max} before treatment[5-28]; nine, MTV before treatment[16, 20, 22, 24-26, 28-31] ; seven, TLG before treatment[20, 21, 25, 26, 28, 29, 31]; three, SUV_{mean} on OS before treatment[21, 22, 25]; four, SUV_{max} after treatment[7, 13, 17, 26, 28, 32]; three, TLG after treatment[26, 28, 32]; 10, the effect of ΔSUV_{max} before and after treatment[13, 17, 23, 26, 28, 33-

167 37]; four, ΔMTV before and after treatment[26, 28, 36, 38]; and five, effect of

168 ΔTLG before and after treatment (Tables 2 and 3)[22, 26, 28, 36, 38].

169

Table1. standard for evaluation

Project	**Specific meaning**	**Comments**
1	Clearly define the research object	
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 no direct HR or 95% CI (1)
		There is no way we can calculate HR (0)

13	Multivariate survival analysis of prognostic factors	There is direct HR and 95% CI (2) There is no direct HR or 95% CI (1) There is no way we can calculate HR (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

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

A meta-analysis of the four indicators (SUV_{max}, SUV_{mean}, MTV, and TLG) before treatment was performed for OS. Twenty-four articles included the

181 SUV_{max}. Because the I^2 = 82% > 50%, these articles were analyzed with the
182 QE model (HR = 1.15, 95%CI = 0.98-1.35). The results showed that the OS of
183 the patients with low SUV_{max} was significantly higher than that of the patients
184 with a high SUV_{max} (Fig. 2A, 2B, 2C).

185 The asymmetry of the funnel chart suggested publication bias. The two
186 methods of Begg and Egger of Stata used to detect the publication bias
187 indicated contradictory results. For a small sample, the Egger method (Fig. 3A)
188 is more sensitive than the Begg (Fig. 3B) method. The result of P=0.000
189 indicated that the selected articles were subject to publication bias.

190 Because of the large heterogeneity, we performed subgroup analyses. The
191 patients were categorized according to the following pathological types (articles
192 that did not mention pathological types were excluded): squamous cell
193 carcinoma, adenocarcinoma, and unsegmented. The HR and 95% CI of each
194 subgroup were 3.69 (1.68-8.09), 0.96 (0.89-1.04), and 1.41 (1.16-1.71),
195 respectively. These values were significantly different (p<0.00001).

196 The patients were further categorized according to the pathological stage
197 of their cancer (articles that did not mention the stage were excluded): stage Ⅲ
198 or earlier, and stage Ⅳ or earlier. The HR and 95% CI of each subgroup were
199 2.35 (1.59-3.48) and 1.52 (1.17-1.97), respectively. There was no significant
200 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, Fig. 4A, 4B, 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 I^2 = 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 SUV_{mean}. 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 SUV_{mean} scores was significantly higher than that of the patients with high SUV_{mean} scores.

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

221 analysis considered the ΔSUV_{max}. Because the I^2 = 48%<50%, these articles
222 were analyzed with the fixed-effect model (HR=1.22, 95%CI=1.06-1.39). The
223 results showed that the OS of the patients with high absolute values of
224 ΔSUV_{max} was significantly higher than that of the patients with low absolute
225 values of ΔSUV_{max}.

226 Four articles included in our analysis considered the Δ MTV. Because the
227 I^2 = 90% > 50%, these articles were analyzed with the QE model (HR=1.07,
228 95% CI = 0.54-2.15). The results showed that the OS of patients with high
229 absolute values of ΔMTV was significantly higher than that of the patients with
230 low absolute values of ΔMTV.

231 Five articles included in our analysis considered the ΔTLG. Because the I^2
232 = 87%>50%, these articles were analyzed with the QE model (HR = 1.09, 95%
233 CI = 0.59-2.02). The results showed that the OS of the patients with high
234 absolute values of ΔTLG was significantly higher than that of the patients with
235 low absolute values of ΔTLG.

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

240 the patients with low SUV_{max} values was significantly higher than that of the
241 patients with high SUV_{max} values.

242 Three articles included in our analysis considered TLG. Because the I^2 =
243 91% > 50%, these articles were analyzed with the QE model (HR = 1.05, 95%
244 CI = 1.02-1.09). The results showed that the OS of the patients with low TLG
245 values was significantly higher than that of the patients with high TLG values.

246 **Discussion**

247 The sixth leading cause of cancer-related death and the eighth most
248 common cancer in the world, esophageal cancer is associated with a 5-year
249 survival rate of less than 25% [39]. While endoscopy, CT, and MRI have
250 conventionally been used to examine patients with esophageal cancer, the
251 relatively new technique of PET has been increasingly used for the diagnosis,
252 differential diagnosis, and clinical staging of patients with esophageal cancer.
253 Imaging also helps to identify patients with significant complications who may
254 respond to and benefit from more conservative treatment (i.e., without
255 esophagectomy) after CRT is demonstrated to be fully or partially effective.
256 Finally, PET/CT has demonstrated value as a follow-up tool for the timely
257 detection of tumor recurrence after surgical treatment [40]. However, because
258 ^{18}F-FDGPET can help to inform the metabolic diagnosis of esophageal cancer,
259 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 chemoradiation (CTRT). PET parameters (TLG = 50) can guide future treatment strategies by stratifying stage II/III patients who will receive CTRT according to their predicted OS [41]. 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 [42]. However, SUV changes and PET responses were not found by the study to be associated with prognosis.

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 SUV_{max} 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 Ⅲ and those with cancer before or at stage Ⅳ. 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

301 includes patients with cancer before or at stage Ⅲ. More experiments are
302 needed to confirm this hypothesis.

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

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

314 This report is subject to several limitations. First, many of the included
315 articles did not directly report HR values but instead extracted them through
316 the K-M curve. This method inevitably results in mistakes. Second, the funnel
317 chart of the reports collected from the literature was subject to publication bias,
318 likely resulting in the overestimation of the presently identified predictive effect
319 of the indices. Finally, all of the reports sourced from the literature are case-
320 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

Although our study is subject to limitations, it demonstrates that the prognoses of patients who respond to PET are significantly better than those of non-responders. Hence, our study can help to inform the prediction of the prognoses of patients with esophageal cancer and, therefore, their treatment.

List of abbreviations

^{18}F-fluorodeoxyglucose: FDG

95% confidence interval: 95% CI

Chemoradiation: CTRT

Hazard ratio: HR

Maximum standard uptake value: SUVmax

Mean standard uptake value: SUVmean

Metabolic tumor volume: MTV

Overall survival: OS

Positron emission tomography/computed tomography: PET/CT

Total lesion glycolysis: TLG

Declarations

Ethics approval and consent to participate：Not applicable

Consent for publication：Not applicable

Availability of data and materials：The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests：The authors declare that they have no competing interests.

Funding：There was no funding for this study.

Authors' contributions: JW conducted data curation, performed formal analysis, and wrote this paper. JS managed conceptualization and project administration. SL constructed the methodology, and reviewed and edited the paper.

Acknowledgements：Not applicable

Authors' information (optional)

REFERENCES

1. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global Burden of 5 Major Types Of Gastrointestinal Cancer. Gastroenterology. 2020.

2. Faigel DO. The Role of Endoscopic Ultrasound in Esophageal Cancer. Gastroenterol Hepatol (N Y). 2019;15:519-21.

3. Mantziari S, Pomoni A, Prior JO, Winiker M, Allemann P, Demartines N, et al. 18F- FDG PET/CT-derived parameters predict clinical stage and prognosis of esophageal cancer. BMC Med Imaging. 2020;20:7.

4. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

5. Fukunaga T, Okazumi S, Koide Y, Isono K, Imazeki K. Evaluation of esophageal cancers using fluorine-18-fluorodeoxyglucose PET. J Nucl Med. 1998;39:1002-7.

6. Kato H, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Ojima H, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. Cancer. 2002;94:921-8.

7. Swisher SG, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer. 2004;101:1776-85.

8. van Westreenen HL, Plukker JT, Cobben DC, Verhoogt CJ, Groen H, Jager PL. Prognostic value of the standardized uptake value in esophageal cancer. AJR Am J Roentgenol. 2005;185:436-40.

9. Cerfolio RJ, Bryant AS. Maximum standardized uptake values on positron emission tomography of esophageal cancer predicts stage, tumor biology, and survival. Ann Thorac Surg. 2006;82:391-4; discussion 394-5.

10. Rizk N, Downey RJ, Akhurst T, Gonen M, Bains MS, Larson S, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography standardized uptake values predict survival after esophageal adenocarcinoma resection. Ann Thorac Surg. 2006;81:1076-81.

11. Cheze-Le Rest C, Metges JP, Teyton P, Jestin-Le Tallec V, Lozac'h P, Volant A, et al. Prognostic value of initial fluorodeoxyglucose-PET in esophageal cancer: a prospective study. Nucl Med Commun. 2008;29:628-35.

12. Chung HW, Lee KH, Lee EJ, Lee SJ, Cho YS, Choi JY, et al. Comparison of uptake characteristics and prognostic value of 201Tl and 18F-FDG in esophageal cancer. World J Surg. 2008;32:69-75.

13. Javeri H, Xiao L, Rohren E, Komaki R, Hofstetter W, Lee JH, et al. Influence of the baseline 18F-fluoro-2-deoxy-D-glucose positron emission tomography results on survival and pathologic response in patients with gastroesophageal cancer undergoing chemoradiation. Cancer. 2009;115:624-30.

14. Javeri H, Xiao L, Rohren E, Lee JH, Liao Z, Hofstetter W, et al. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastroesophageal adenocarcinoma. Cancer. 2009;115:5184-92.

15. Rizk NP, Tang L, Adusumilli PS, Bains MS, Akhurst TJ, Ilson D, et al. Predictive value of initial PET-SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. J Thorac Oncol. 2009;4:875-9.

16. Zhu WQ, Yu JM, Sun XR, et al. The prognostic valHe of metabolic tumor volume in FDG PET ／ CT eva]uation of post—operative survival in patients with esophageal squamous cell cancer. Chin J Nucl Med.2011;31:378-81.

17. Kauppi JT, Oksala N, Salo JA, Helin H, Karhumäki L, Kemppainen J, et al. Locally advanced esophageal adenocarcinoma: response to neoadjuvant chemotherapy and survival predicted by ([18F])FDG-PET/CT. Acta Oncol. 2012;51:636-44.

18. Yanagawa M, Tatsumi M, Miyata H, Morii E, Tomiyama N, Watabe T, et al. Evaluation of response to neoadjuvant chemotherapy for esophageal cancer: PET response criteria in solid tumors versus response evaluation criteria in solid tumors. J Nucl Med. 2012;53:872-80.

19. Kajiwara T, Hiasa Y, Nishina T, Matsumoto T, Hori S, Nadano S, et al. Maximum standardized uptake value in 18F-fluoro-2-deoxyglucose positron emission tomography is associated with advanced tumor factors in esophageal cancer. Mol Clin Oncol. 2014;2:313-21.

20. Xie YT. Impact of F-FDG PET/CT before radiotherapy on treatment regimen and prognostic significance of PET/CT parameters in patients with esophageal cancer . Peking union medical college (department of medicine, tsinghua university) & Chinese academy of medical sciences, trans. In: zheng rong, Ed. Imaging medicine and nuclear medicine. ,2014.

21. Bütof R, Hofheinz F, Zöphel K, Stadelmann T, Schmollack J, Jentsch C, et al. Prognostic Value of Pretherapeutic Tumor-to-Blood Standardized Uptake Ratio in Patients with Esophageal Carcinoma. J Nucl Med. 2015;56:1150-6.

22. Chang S, Kim SJ. Prediction of Recurrence and Mortality of Locally Advanced Esophageal Cancer Patients Using Pretreatment F-18 FDG PET/CT Parameters: Intratumoral Heterogeneity, SUV, and Volumetric Parameters. Cancer Biother Radiopharm. 2016;31:1-6.

23. Hamai Y, Hihara J, Emi M, Furukawa T, Yamakita I, Kurokawa T, et al. Ability of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography to Predict Outcomes of Neoadjuvant Chemoradiotherapy Followed by Surgical Treatment for Esophageal Squamous Cell Carcinoma. Ann Thorac Surg. 2016;102:1132-9.

24. Huang CH, Shi DH, Cui XX, Xiao XC, Cai J. The maximum standard value of FDG before treatment was used to predict the radiotherapy effect of local advanced esophageal cancer. Med J of Communications. 2016;30:175-178.

25. Nakajo M, Jinguji M, Nakabeppu Y, Nakajo M, Higashi R, Fukukura Y, et al. Texture analysis of 18F-FDG PET/CT to predict tumour response and prognosis of patients with esophageal cancer treated by chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2017;44:206-14.

26. Bütof R, Hofheinz F, Zöphel K, Schmollack J, Jentsch C, Zschaeck S, et al. Prognostic value of SUR in patients with trimodality treatment of locally advanced esophageal carcinoma. J Nucl Med. 2018.

27. Dai L, Fu H, Wang F, Guo R, Yang YB, Lin Y, Lu KN. Analysis of relationship between18F-FDG PET/CT SUVmax of esophageal squamous cell carcinoma before treatment and postoperative survival. Natl Med J China. 2018;98:1707-1712.

28. Li Y, Zschaeck S, Lin Q, Chen S, Chen L, Wu H. Metabolic parameters of sequential 18F-FDG PET/CT predict overall survival of esophageal cancer patients treated with (chemo-) radiation. Radiat Oncol. 2019;14:35.

29. Lin XH. Progress of pretreatment metabolic parameters from18F-fluorodeoxyglucose positron Emission tomography/computed tomography in predicting the prognosis of esophageal cancer receiving radiotherapy. ANHUI MEDICAL UNIVERSITY,Trans. See: liting qian, Ed. Oncology. ,2018.

30. YU J, Li YS, Huang CR, Bo QZ, He SL, Wang CF. The predictive value of FDG PET/CT metabolic volume for postoperative prognosis of esophageal cancer. Journal of Imaging Research and Medical Applications. 2018;2:193-194.

31. Hofheinz F, Li Y, Steffen IG, Lin Q, Lili C, Hua W, et al. Confirmation of the prognostic value of pretherapeutic tumor SUR and MTV in patients with esophageal squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2019;46:1485-94.

32. Cervino AR, Pomerri F, Alfieri R, Sileni VC, Castoro C, Galuppo S, et al. 18F-fluorodeoxyglucose PET/computed tomography and risk stratification after neoadjuvant treatment in esophageal cancer patients. Nucl Med Commun. 2014;35:160-8.

33. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol. 2001;19:3058-65.

34. Ott K, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006;24:4692-8.

35. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8:797-805.

36. Roedl JB, Colen RR, Holalkere NS, Fischman AJ, Choi NC, Blake MA. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. Comparison to histopathologic and clinical response evaluation. Radiother Oncol. 2008;89:278-86.

37. Huang JW, Yeh HL, Hsu CP, Lu YY, Chuang CY, Lin JC, et al. To evaluate the treatment response of locally advanced esophageal cancer after preoperative chemoradiotherapy by FDG-PET/CT scan. J Chin Med Assoc. 2015;78:229-34.

38. Kim SJ, Koo PJ, Chang S. Predictive value of repeated F-18 FDG PET/CT parameters changes during preoperative chemoradiotherapy to predict pathologic response and overall survival in locally advanced esophageal adenocarcinoma patients. Cancer Chemother Pharmacol. 2016;77:723-31.

39. Then EO, Lopez M, Saleem S, Gayam V, Sunkara T, Culliford A, et al. Esophageal Cancer: An Updated Surveillance Epidemiology and End Results Database Analysis. World J Oncol. 2020;11:55-64.

40. Goense L, van Rossum PS, Reitsma JB, Lam MG, Meijer GJ, van Vulpen M, et al. Diagnostic Performance of ^{18}F-FDG PET and PET/CT for the Detection of Recurrent Esophageal Cancer After Treatment with Curative Intent: A Systematic Review and Meta-Analysis. J Nucl Med. 2015;56:995-1002.

41. Elimova E, Wang X, Etchebehere E, Shiozaki H, Shimodaira Y, Wadhwa R, et al. 18-fluorodeoxy-glucose positron emission computed tomography as predictive of response after chemoradiation in oesophageal cancer patients. Eur J Cancer. 2015;51:2545-52.

42. Weber MA, Bender K, von Gall CC, Stange A, Grünberg K, Ott K, et al. Assessment of diffusion-weighted MRI and 18F-fluoro-deoxyglucose PET/CT in monitoring early response to neoadjuvant chemotherapy in adenocarcinoma of the esophagogastric junction. J Gastrointestin Liver Dis. 2013;22:45-52.

Table3. Indices from the studies in the meta-analysis

Study	Index	Time	Threshold
Nakajo2016	SUVmax SUVmin MTV TLG	Before Chemoradiotherapy	NM
Butof2015	SUVmax SUVmin MTV TLG	Before radiotherapy	SUVmax>8.5 SUVmean>8.14 MTV>8.5 TLG>12.4
Rebecca2018	SUV MTV TLG	Before and after Chemoradiotherapy	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%
Hamai2016	SUVmax	Before and after Chemoradiotherapy	Post:SUVmax>5.33 ΔSUVmax>75%
Kauppi2012	SUV	Before and after Chemoradiotherapy	Pre:SUVNM Post:SUVNM ΔSUV> 67%
Li2019	SUVmax MTV TLG	Before and after radiotherapy	Pre:SUVmax>9.6MTV>10.5TLG>59.8 Post:SUVmax>7.8 MTV>15.9 TLG>44.3 ΔSUVmax> 23% ΔMTV> 7.5% ΔTLG>27%
Huang2016	SUVmax	Before radiotherapy	SUVmax>9.7
Xie2014	SUVmax MTV TLG	Before radiotherapy	SUVmax≥11.4 MTV≥8.27 TLG≥35.21
Risk2006	SUVmax	before operation	SUVmax>4.5
Chang2016	SUVmax SUVmean	before Chemoradiotherapy	SUVmax>4.86 SUVmean>2.37 MTV>8.93 TLG>20.42

	MTV TLG		
Rest2008	SUVmax	before operation	SUVmax>9
Dai2018	SUVmax	Before treatment	SUVmax>6
Hiasa2014	SUVmax	Before treatment	SUVmax>10.26
Toru1993	SUV	before operation	SUV≥7.0
Cerfolio2006	SUV	before operation	SUV≥6.6
Chung2007	SUV	before operation	SUV≥15
Kato2002	SUV	before operation	SUV≥3
Lordick2007	SUV	Before and after treatment	∆SUV≥35%
Ott2006	SUV	Before and after treatment	∆SUV≥35%
Risk2009	SUV	Before Chemotherapy	SUVmax≥4.5

484 Continued

485

Study	**Index**	**Time**	**Threshold**
Roedl2008	SUVmax	Before and after treatment	∆SUVmax≥43%
	SUVmean		∆SUVmean≥22%
	MTV TLG		∆MTV≥63% ∆TLG≥78%
Swisher2004	SUV	Before and after Chemoradiotherapy	Pre:SUV>9.5 Post:SUV>4
Heta2009	SUV	Before and after treatment	∆SUV>52%
Heta2008	SUV	Before Chemoradiotherapy	SUV>10.1
Vanwestreenen2005	SUVmax	Before treatment	SUVmax≥6.7

Weber2001	SUV	Before and after Chemotherapy	Δ SUV≥35%
Zhu2011	SUVmax	before	SUVmax>11.6
	MTV	operation	MTV>14.5
Yu2018	MTV	before operation	NM
Lin2018	MTV TLG	before operation	MTV≥27.44 TLG≥166.2
Hofheinz2019	SUV	Before Chemoradiotherapy	MTV>22.3 TLG>46
	MTV TLG		SUV NM
Huang2015	SUV	Before and after Chemoradiotherapy	Δ SUV>60%
Kim2016	SUVmax	Before and after radiotherapy	Δ SUVmax>23.5
	MTV TLG		Δ MTV>25.5% Δ TLG> 44.8%
Anna2014	SUV	after radiotherapy	NM
Yanagawa2012	SUV	Before and after chemotherapy	NM

NM, not mentioned; SUV_{max}, the maximum standard uptake value; SUV_{mean}, mean standard uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; Δ means differences before and after treatment.

Figure Legends

Figure 1 Flowchart of the selection of articles.

Figure 2 Forest plots of SUV_{max} before treatment (A). Z-score of 24 studies before treatment (B). Funnel Plots of SUV_{max} before treatment. These articles may be subject to publication bias (C). ES = effect size (hazard ratio), SUV_{max} = the maximum standard uptake value.

Figure 3 Egger's test of SUV_{max} before treatment (A). Begg's test of SUV_{max} before treatment (B). SUV_{max} = the maximum standard uptake value.

Figure 4 Forest plots of the SUV_{max} subgroup according to pathological type (A), stage of cancer (B), and type of treatments (C). SUV_{max} = the maximum standard uptake value.

Figures

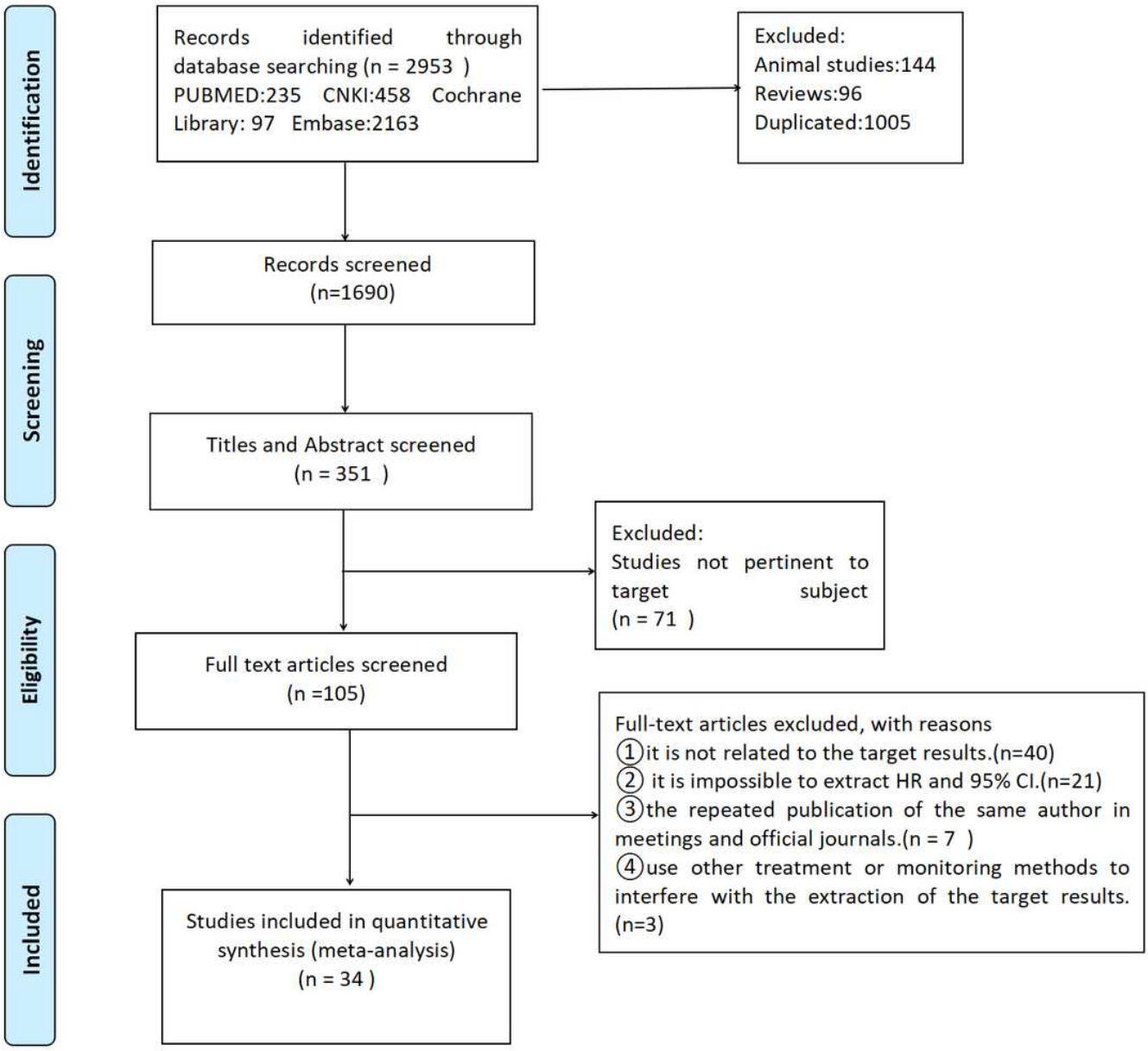

Figure 1

Flowchart of the selection of articles.

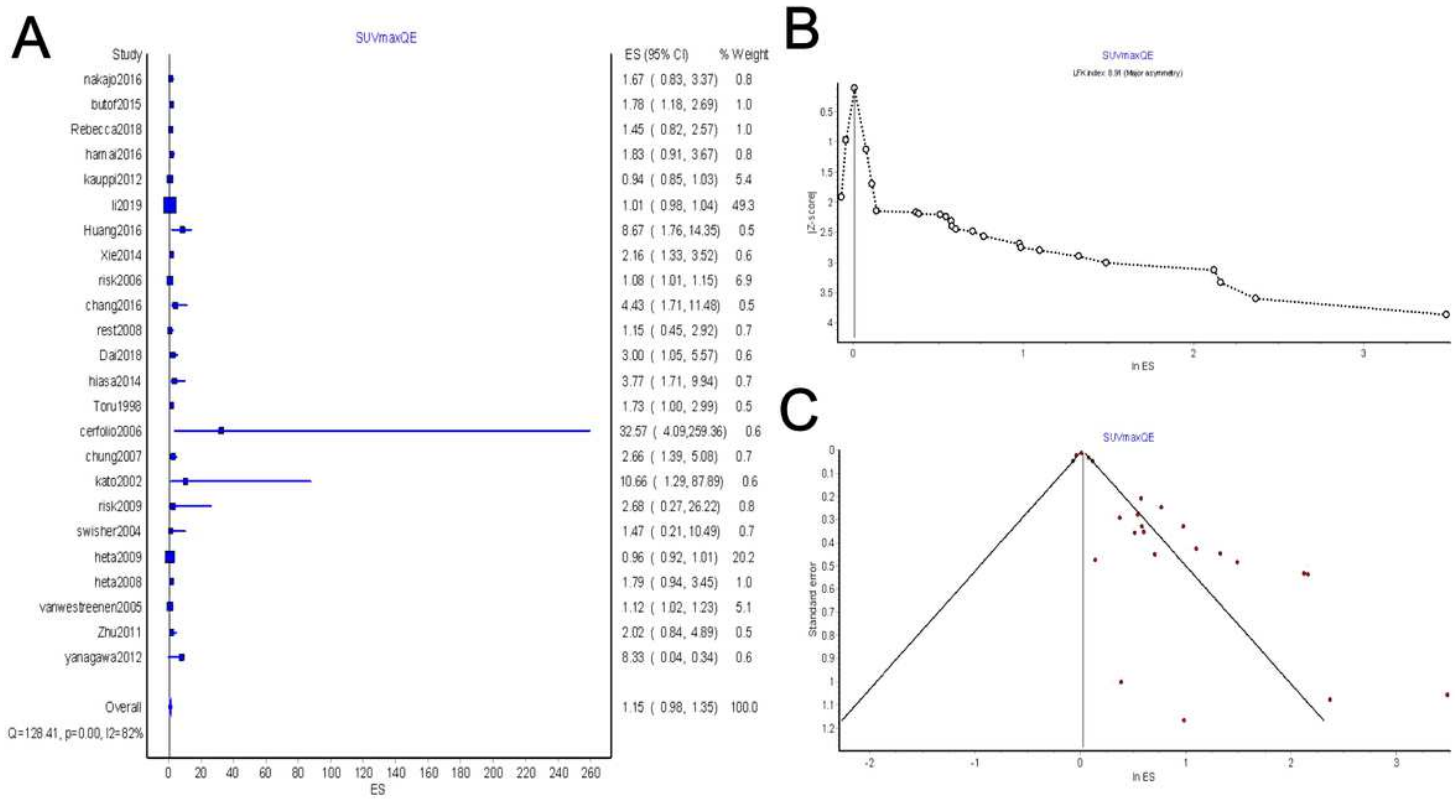

Figure 2

Forest plots of SUVmax before treatment (A). Z-score of 24 studies before treatment (B). Funnel Plots of SUVmax before treatment. These articles may be subject to publication bias (C). ES = effect size (hazard ratio), SUVmax = the maximum standard uptake value.

A

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

B

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 3

Egger's test of SUVmax before treatment (A). Begg's test of SUVmax before treatment (B). SUVmax = the maximum standard uptake value.

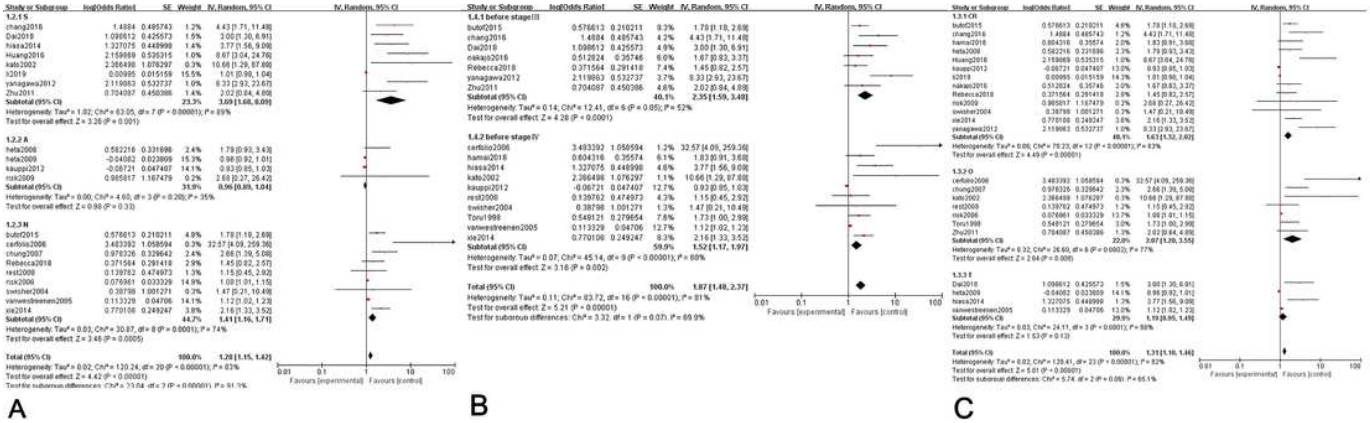

Figure 4

Forest plots of the SUVmax subgroup according to pathological type (A), stage of cancer (B), and type of treatments (C). SUVmax = the maximum standard uptake value.