Divergent Metastatic Patterns Between Esophageal Squamous-cell Carcinoma and Esophageal Adenocarcinoma: a Propensity-matched Analysis

Ganwei Liu
Peking University People's Hospital https://orcid.org/0000-0001-8090-9430
Feng Yang
Peking University People's Hospital
Shaodong Wang
Peking University People's Hospital
Jianfeng Li
Peking University People's Hospital
Zuli Zhou (zhouzulipkuph@yeah.net)
Peking University People's Hospital

Research

Keywords: Metastasis, esophageal squamous-cell carcinoma, esophageal adenocarcinoma, SEER database

Posted Date: May 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-499176/v1

Abstract

Background: To explore the different metastatic patterns between esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).

Methods: For this propensity-matched analysis, we used data from the latest iteration of the Surveillance, Epidemiology, and End Results (SEER) database and included patients diagnosed with esophageal cancer from 2010 to 2017.

Results: A total of 20,189 patients were identified, including 6,610 ESCC and 13,579 EAC. After propensity score matching, 4597 pairs were selected. Compared with ESCC, EAC had a higher rate of liver metastasis ($P < 0.001$) and brain metastasis ($P < 0.001$), and a lower rate of lung metastasis ($P < 0.001$), with no significant difference in bone metastasis ($P = 0.255$). The liver preferentially co-metastasized with lung in both cohorts. Brain metastasis was commonly observed in combination with other organ metastases in EAC.

Conclusions: There are major differences in metastatic patterns between ESCC and EAC. The patterns identified may reflect the underlying biology of metastatic esophageal cancer and have potential to influence future monitoring strategies depending on clinical settings.

Background

Esophageal cancer is the seven most common cancer worldwide and ranks sixth in terms of mortality among all types of cancer [1]. The detection and clinical management of esophageal cancer metastasis poses a critical global health challenge, since approximately 40% of patients with esophageal cancer are diagnosed with metastatic disease at the time of presentation [2]. As a disease entity, esophageal cancer principally comprises two major subtypes: esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). In spite of sharing an anatomical site, there are many differences between ESCC and EAC in terms of the etiology and clinical features [2, 3]. Meanwhile, according to the study conducted by the Cancer Genome Atlas Research Network, ESCC and EAC might belong to distinct molecular entities in view of their divergent genetic characterizations [4].

The process of tumor metastasis is fraught with complexity [5–7] and the metastatic patterns might be affected by cancer subtypes [8]. Two previous Surveillance, Epidemiology, and End Results (SEER) based studies had suggested some differences in metastatic patterns between ESCC and EAC [9, 10], but their findings were inconsistent. Moreover, patterns of combined metastases had not been fully illustrated in their study and propensity score matching was not performed to minimize potential selection biases. In addition, as the incidences of ESCC and EAC have been changed over the past several decades with an increasing of EAC and a decreasing of ESCC [2], this transformation should also be taken into consideration when assessing the characteristics of distant metastasis in esophageal cancer.

In the present study, we examined the metastatic patterns between ESCC or EAC, including both single-organ and multi-organ metastases, by utilizing the data extracted from the latest iteration of the SEER database.

Methods

Patients

The SEER program is a nationwide database that captures approximately 28% of the United States population. We searched the SEER for data on all patients who were primary histologically confirmed with ESCC (ICD-O-3 codes: 8070–8076) and EAC (ICD-O-3 codes: 8140,8144,8145) from 2010 and 2017. Data extracted included age, sex, race, tumor histology, tumor stage (T, N, and M), organ-specific metastasis, and use of surgery.

Statistical analyses

All characteristics of selected patients were included as categorical variables and determined using Pearson's $\chi 2$ test or Fisher's exact test. A nearest-neighbor 1:1 propensity score matching analysis with a 0.1-caliper width was used to reduce selection biases. Multivariable logistic regression analyses were done on the propensity-matched sample and were performed for each organ-specific metastasis. Results were considered significant if a two-sided p value of less than 0.05 was obtained. All analyses were conducted using Stata/SE 14.0 (Stata Corp., College Station, TX, USA).

Results

A total of 20,189 patients with esophageal cancer were enrolled, including 6,610 patients with ESCC and 13,579 patients with EAC. Compared with patients in the EAC group, those with ESCC tended to have older age, a higher rate of male, a lower incidence of white race, an earlier T stage, and a greater proportion of choice of surgery. Distant metastatic disease was present in 6502 (32.2%) patients and was found in 25.5% and 35.5% of patients with ESCC and EAC, respectively. Based on metastasis data extracted from the SEER database, the four metastatic lesions (bone, brain, liver, and lung) accounted for 78.1% (5,075/6,502) of all metastatic cases. After propensity score matching, 4597 pairs were selected. The distribution of baseline patient characteristics was well balanced with all values of standardized differences smaller than 10% after matching. The detailed clinicopathological data and standardized differences of baseline variables before and after propensity score matching were shown in Table 1 and Fig. 1.

Table 1
Clinicopathological features of patients with ESCC and EAC before and after propensity score matching.

Features	Before matching				After matching			
	ESCC	EAC	*p*	SD	ESCC	EAC	*p*	SD
Total number	6610	13579			4597	4597		
Age			< 0.001				0.271	
< 50	322 (4.9%)	986 (7.3%)		-0.111	277 (6.0%)	245 (5.3%)		0.042
50–65	3647 (55.1%)	7619 (56.1%)		-0.019	2419 (52.6%)	2403 (52.3%)		0.010
⩾65	2641 (40.0%)	4974 (36.6%)		0.068	1901 (41.4%)	1949 (42.4%)		-0.029
Sex			< 0.001				0.006	
Female	2345 (35.5%)	1832 (13.5%)		0.459	1440 (31.3%)	1320 (28.7%)		0.037
Male	4265 (64.5%)	11747 (86.5%)		-0.459	3157 (68.7%)	3277 (71.3%)		-0.037
Race			< 0.001				0.454	
White	4090 (61.9%)	12755 (93.9%)		-0.660	3745 (81.5%)	3802 (82.7%)		-0.028
Black	1690 (25.6%)	395 (2.9%)		0.519	430 (9.4%)	395 (8.6%)		0.018
OthersΔ	807 (12.2%)	387 (2.8%)		0.286	401 (8.7%)	378 (8.2%)		0.016
Unknown	23 (0.3%)	42 (0.3%)		0.007	21 (0.5%)	22 (0.5%)		0.011
T stage			< 0.001				0.027	
T1	1348 (20.4%)	3400 (25.0%)		-0.115	834 (18.1%)	943 (20.5%)		-0.063
T2	658 (10.0%)	1331 (9.8%)		0.005	451 (9.8%)	482 (10.5%)		-0.015

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander.

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SD, standardized difference.

Features	Before matching			After matching		
T3	2101 (31.8%)	4646 (34.2%)	-0.052	1568 (34.1%)	1520 (33.1%)	0.014
T4	999 (15.1%)	1159 (8.5%)	0.184	664 (14.4%)	632 (13.7%)	0.038
Unknown	1504 (22.8%)	3043 (22.4%)	0.008	1080 (23.5%)	1020 (22.2%)	0.023
N stage			< 0.001			0.039
N0	2588 (39.2%)	5366 (39.5%)	-0.007	1712 (37.2%)	1819 (39.6%)	-0.045
N1	2670 (40.4%)	5165 (38.0%)	0.048	1861 (40.5%)	1776 (38.6%)	0.026
N2	707 (10.7%)	1475 (10.9%)	-0.005	548 (11.9%)	510 (11.1%)	0.034
N3	213 (3.2%)	604 (4.4%)	-0.069	169 (3.7%)	148 (3.2%)	0.004
Unknown	432 (6.5%)	969 (7.1%)	-0.024	307 (6.7%)	344 (7.5%)	-0.008
M stage			< 0.001			0.276
M0	4922 (74.5%)	8765 (64.5%)	0.227	3277 (71.3%)	3324 (72.3%)	-0.023
M1	1688 (25.5%)	4814 (35.5%)	-0.227	1320 (28.7%)	1217 (27.7%)	0.023
Surgery			< 0.001			0.261
Yes	994 (15.0%)	4440 (32.7%)	-0.494	920 (19.6%)	841 (18.3%)	0.021
No	5602 (84.8%)	9087 (66.9%)	0.494	3681 (80.1%)	3743 (81.4%)	-0.022
Unknown	14 (0.2%)	52 (0.4%)	-0.037	14 (0.3%)	13 (0.3%)	0.009

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander.

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SD, standardized difference.

Distribution of metastasis according to histology

There were considerable differences in metastatic patterns between the two groups. As shown in Table 2, liver and lung were the primary sites of distant metastasis and brain was the least frequent metastatic lesion for both ESCC and EAC. The most common site of distant metastasis was lung for ESCC, whereas EAC markedly metastasized to liver more frequently. The metastatic rates of liver, bone, and brain in EAC were much higher than those in ESCC and the frequency of lung metastasis in ESCC was higher than that of EAC. To further validate this finding, multivariable analyses were performed to adjust for confounding variables including age, sex, race, T and N descriptors, and surgery in the matched cohorts. It was demonstrated that compared to ESCC, patients with EAC tended to have more liver metastasis ($P < 0.001$; 95% confidence interval (CI): 1.52–1.99) and brain metastasis ($P < 0.001$; 95% CI: 1.43–3.08), and a lower rate of lung metastasis ($P < 0.001$; 95% CI: 0.47–0.64), with no significant difference in bone metastasis ($P = 0.255$; 95% CI: 0.76–1.07) (Table 3).

Table 2
Frequencies of single-organ and multi-organ metastases in ESCC and EAC.

Features	**ESCC**		**EAC**		***P values***
	Number	(%)	Number	(%)	
One site					
Only liver	293	4.433	1466	10.796	< 0.001
Only lung	411	6.218	372	2.740	< 0.001
Only bone	178	2.693	531	3.910	< 0.001
Only brain	12	0.182	132	0.972	< 0.001
Two sites					
Liver and lung	150	2.269	530	3.903	< 0.001
Liver and bone	68	1.029	311	2.290	< 0.001
Liver and brain	2	0.030	46	0.339	< 0.001
Lung and bone	80	1.210	99	0.729	0.001
Lung and brain	7	0.106	18	0.133	0.613
Bone and brain	9	0.136	36	0.265	0.068
Three sites					
Liver and lung and bone	45	0.681	157	1.156	0.001
Liver and lung and brain	6	0.091	36	0.265	0.011
Liver and bone and brain	1	0.015	26	0.191	0.001
Lung and bone and brain	4	0.061	16	0.118	0.224
Four sites					
Liver and lung and bone and brain	7	0.106	26	0.191	0.158

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

Table 3
Multivariable logistic regression analyses of the impact of different histological subtypes on metastatic sites after matching.

Variable	Metastatic site	OR	95% CI	*P values*
EAC versus ESCC	Liver	1.74	1.52–1.99	< 0.001
	Lung	0.55	0.47–0.64	< 0.001
	Bone	0.90	0.76–1.07	0.255
	Brain	2.10	1.43–3.08	< 0.001
Adjusted for age, sex, race, T stage, N stage, and surgery.				
OR, odds ratio; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.				

Combination of metastases

Some patients showed metastatic disease at more than one site at the time of diagnosis. The frequencies of all possible combinations of the four metastatic lesions were listed in Table 2. The most frequent bi-organ metastasis was the liver and lung (ESCC: 2.3%, EAC: 3.9%) and the most frequent tri-organ metastasis was the liver, lung, and bone (ESCC: 0.7%, EAC: 1.2%). The potential interactions among these metastatic sites were further analyzed (Fig. 3, A-D). Liver preferentially co-metastasized with lung in both cohorts. Brain metastasis was commonly observed in combination with other organ metastases in EAC. In patients with bone metastasis, ESCC had a higher rate of co-metastasis to the lung and liver than brain while EAC was prone to co-metastasis with liver than lung and brain.

Discussion

This study is a comprehensive research for metastatic patterns in the two predominant subtypes of esophageal cancer (ESCC and EAC). Major differences between ESCC and EAC were observed, such as frequencies of single-site metastasis, patterns of combination of metastatic sites. These findings may help physicians implement better tailored screening modalities and follow-up strategies in future clinical settings.

Compared with ESCC, EAC had a higher rate of liver or brain metastasis and a lower rate of lung metastasis, with a similar trend in metastasis to bone. These results are partially consistent with findings from two previous SEER studies. Ai et al. found EAC was more likely to have liver, bone, or brain metastasis but had a lower rate of lung metastasis compared with ESCC [10]. The other study of SEER data from 2010 through 2014 reported that patients with EAC had a higher rate of liver or brain metastasis and those with ESCC were more likely to have lung metastasis, with similar proportions of bone metastasis among the two groups [9]. Diverse outcomes might partly be attributable to different

sample sizes and confounding clinical variables adjusted in the analysis. In addition, this discrepancy could also be the result of the transition of esophageal histology in the recent decades, which is an increase in the incidence of EAC because of the growing prevalence of obesity and the decline in ESCC incidence after promotion of smoking cessation [2, 11, 12].

Of note, the proportion of liver metastasis in EAC far outweighs that of in ESCC. This may in part be explained by differences in histological type and tumor location as well as pattern of lymphatic spread, as most cases of EAC are present in the lower esophagus where lymphatic flow tends to be downward, while ESCC is more common in the upper two thirds of the esophagus where lymphatic flow is inclined to be upward [13]. Furthermore, the relative short-distance from lower esophagus to liver might also facilitate the spread of esophageal cancer cells to this organ through the venous drainage of the gastrointestinal tract to the portal vein.

A concerning observation was that a large number of patients with metastatic disease exhibited multi-organ metastases. Among all combined metastases, the most frequent multi-organ metastatic pattern was the liver and lung in both ESCC and EAC groups. In concert with some published literatures, liver and lung are the two main drainage regions frequently colonized by a variety of cancers, targeting these sites of high vascular flow [7, 14]. Another observation is that liver or brain metastasis was commonly observed in combination with other organ metastases in EAC. These findings highlight the essential of regular imaging of chest and liver for all esophageal cancer patients and early PET-CT assessment of patients with EAC, especially in cases suspected with liver or brain metastasis. The mechanism of the propensity for a metastatic cell to spread to several anatomically distinct locations, either sequentially or synchronously, has not been demonstrated explicitly in previous literatures. In some extent, this phenomenon could be explained by the ‘seed and soil’ hypothesis that the microenvironment of two host organs bear a resemblance to each other thereby facilitating metastasis to the same degree [15].

To our best knowledge, this is the largest population-based study summarizing the metastatic patterns in ESCC and EAC by analyzing the recently released US SEER-18 cancer registry data. Nevertheless, our study is subject to a number of limitations. The first limitation is the retrospective nature of this study. Second, even though several studies have described molecular changes contributing tumor cells of esophageal cancer to a more aggressive biological behavior [16–19], the underlying mechanism for differences in metastatic patterns between histological subtypes remains unclear. Additionally, most metastatic lesions were clinically diagnosed without histologically confirmed, which might have resulted in misclassification.

Conclusion

In summary, this retrospective study showed that metastatic patterns were different between ESCC and EAC, which have potential to influence future monitoring strategies depending on clinical settings.

Declarations

Acknowledgments

The authors thank would like to thank Peking University People's Hospital scientific research program for the support of this study.

Author contributions

(I) Conception and design: Ganwei Liu, Feng Yang; (II) Administrative support: Jianfeng Li, Zuli Zhou; (III) Provision of study materials of patients: Shaodong Wang, Zuli Zhou; (IV) Collection and assembly of data: Ganwei Liu, Feng Yang; (V) Data analysis and interpretation: Ganwei Liu, Feng Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Funding

This work was supported by the Peking University People's Hospital scientific research program (RDE2019-24).

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

This research was based on publicly available database and a data use agreement was assigned. It was exempted from ethics approval by the ethics committee of Peking University People's Hospital as it was a retrospective study and no personal identification information was collected.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Rustgi AK, El-Serag HB. Esophageal carcinoma. N Engl J Med. 2014;371(26):2499-509.
3. Smyth EC, Lagergren J, Fitzgerald RC, et al. Oesophageal cancer. Nat Rev Dis Primers. 2017;3:17048.
4. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, Brigham, et al. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541(7636):169-75.

5. Chaffer C, Weinberg R. A perspective on cancer cell metastasis. Science (New York, NY). 2011;331(6024):1559-64.
6. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011;147(2):275-92.
7. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378-82.
8. Budczies J, von Winterfeld M, Klauschen F, et al. The landscape of metastatic progression patterns across major human cancers. Oncotarget. 2015;6(1):570-83.
9. Wu SG, Zhang WW, Sun JY, et al. Patterns of Distant Metastasis Between Histological Types in Esophageal Cancer. Front Oncol. 2018;8:302.
10. Ai D, Zhu H, Ren W, et al. Patterns of distant organ metastases in esophageal cancer: a population-based study. J Thorac Dis. 2017;9(9):3023-30.
11. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381-7.
12. Wang Q-L, Xie S-H, Li W-T, et al. Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis. JNCI: Journal of the National Cancer Institute. 2017;109(12).
13. Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Distribution of Lymph Node Metastases in Esophageal Carcinoma Patients Undergoing Upfront Surgery: A Systematic Review. Cancers (Basel). 2020;12(6).
14. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med. 2008;132(6):931-9.
15. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-8.
16. Liang Y, Chen X, Wu Y, et al. LncRNA CASC9 promotes esophageal squamous cell carcinoma metastasis through upregulating LAMC2 expression by interacting with the CREB-binding protein. Cell Death Differ. 2018;25(11):1980-95.
17. Cheng X, Wei L, Huang X, et al. Solute Carrier Family 39 Member 6 Gene Promotes Aggressiveness of Esophageal Carcinoma Cells by Increasing Intracellular Levels of Zinc, Activating Phosphatidylinositol 3-Kinase Signaling, and Up-regulating Genes That Regulate Metastasis. Gastroenterology. 2017;152(8):1985-97 e12.
18. Li Y, Fu L, Li JB, et al. Increased expression of EIF5A2, via hypoxia or gene amplification, contributes to metastasis and angiogenesis of esophageal squamous cell carcinoma. Gastroenterology. 2014;146(7):1701-13 e9.
19. Tseng RC, Chang JM, Chen JH, et al. Deregulation of SLIT2-mediated Cdc42 activity is associated with esophageal cancer metastasis and poor prognosis. J Thorac Oncol. 2015;10(1):189-98.

Figures

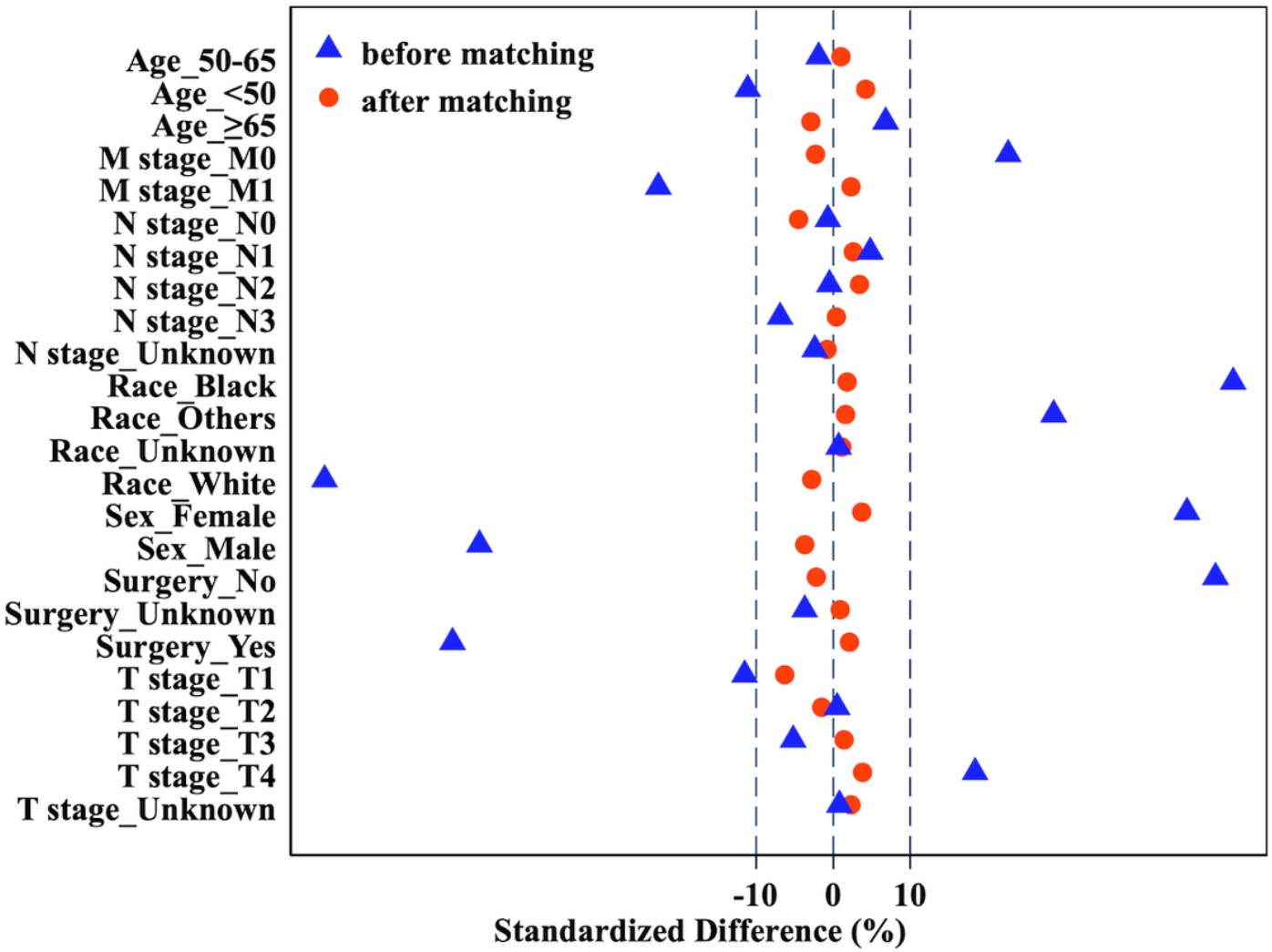

Figure 1

Standardized differences of baseline variables between patients with ESCC and patients with EAC before and after propensity score matching. ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

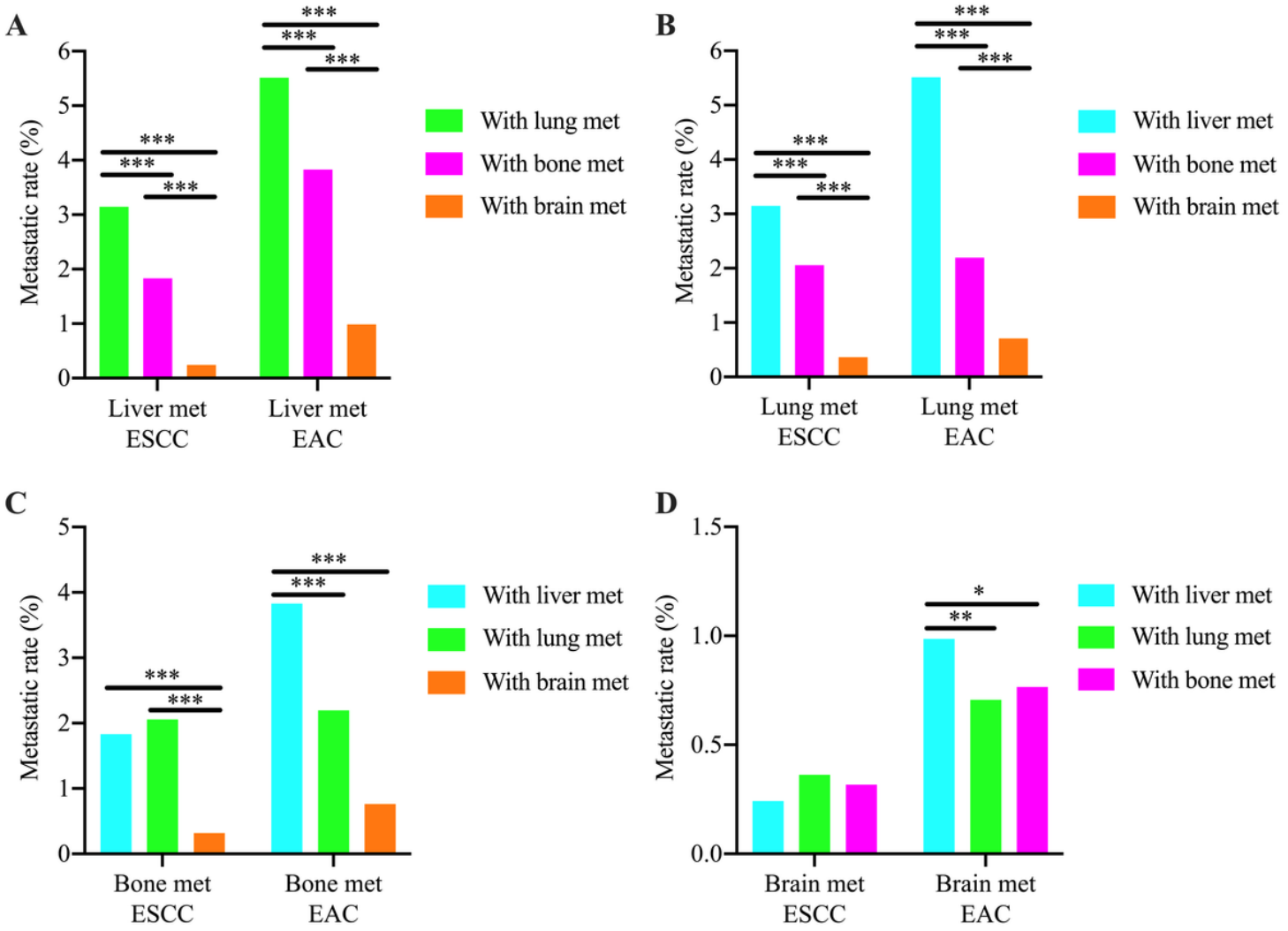

Figure 2

Comparisons of co-metastatic rates in ESCC and EAC. (A) Liver metastasis with other sites; (B) Lung metastasis with other sites; (C) Bone metastasis with other sites; (D) Brain metastasis with other sites. *p < 0.05, ** p < 0.01, *** p < 0.001. ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.