



Predicting liver and lung metastasis in esophageal cancer: does the site of primary tumor really matter?

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According to the GLOBOCAN, esophageal cancer is now the sixth leading cause of cancer-associated mortality with a death toll of 508,585 in year 2018 (1). Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) account for the majority of esophageal malignancies. While ESCC more commonly involves the proximal and middle esophagus with risk factors of alcohol drinking, tobacco smoking, hot beverage, and poor nutrition, EAC affects predominantly the lower esophagus and the gastroesophageal junction with strong association to tobacco smoking, obesity and gastroesophageal reflux disease. The epidemiology of ESCC is highly skewed with the highest incidence in countries along the so called “Asian Esophageal Cancer Belt” that includes eastern Turkey, Iran, Iraq, southern part of the former Soviet Union to Mongolia and northern part of China (2). On the other hand, EAC is more common in the Western population with increasing trend globally. Despite the vast differences between ESCC and EAC, both diseases have been treated with the same protocol and enrolled in same clinical trials under the empirical entity of “esophageal cancer” and the impact of the site of primary tumor has not been thoroughly studied. Nevertheless, both ESCC and EAC are notorious for poor prognosis due to their propensities for distant metastasis.

In an attempt to identify factors that predict the site of

metastasis in esophageal cancer, Ai *et al.* retrospectively analyzed patients with esophageal cancer from the Surveillance, Epidemiology and End Results (SEER) database (3). A total of 15,739 patients with esophageal cancer from 2010–2013 were reviewed and 8,927 patients were excluded due to incomplete information such as site of primary tumor or metastasis. At the end, the main analysis focused on the 900 patients with liver metastasis only and the 390 patients with lung metastasis only. By applying propensity matching with age, sex, histologic type and grade, they found that primary tumor location was an independent predictive factor for both liver and lung metastases. Liver metastasis was more likely to be associated with distal tumor while lung metastasis was more common for proximal tumor. In addition, patients with proximal tumor in the liver-metastasis group and patients with distal tumor in the lung-metastasis group had worse prognosis. They concluded that the findings were useful for guiding essential workup during diagnosis and follow-up, which hopefully should facilitate timely delivery of appropriate treatment. The authors should be congratulated for their meticulous effort in data collection and analysis from the SEER database. Their findings definitely served to start the ball-rolling for related research in tumor location by generating hypothesis and proposing patient stratification

factors for subsequent prospective studies. However, there are still unanswered questions regarding tumor location in esophageal cancer.

Is tumor location effect real in esophageal cancer?

Recognizing the importance of tumor location is practice-changing in the management of colorectal cancer (4). Indeed, the question of “left and right” has generated answers far beyond anatomical boundary and that tumor location is now known to be a composite of demographics, embryology, biology and even microbiome. Tumor location in colorectal cancer is not only prognostic but it is also predictive of benefit from various target therapies. On the contrary, tumor location of primary esophageal cancer and sites of metastasis is a less studied topic. Ai *et al.* proposed that the proximal tumors drain through the superior vena cava and azygous vein resulting in higher chance of lung metastasis while the distal tumors drains through the left gastric and portal veins resulting in more liver metastasis (3). Although this was a reasonable hypothesis, the data they had might not be able to support the hypothesis. Firstly, they have excluded patients with both liver and lung metastasis as well as those without liver or lung metastasis. This potentially created selection bias and for example those patients with a proximal tumor that first metastasized to liver and then lung, or vice versa, would have been excluded for a totally opposite conclusion. Secondly, the cohorts were dominated by lower esophageal cancer (liver metastasis group: 85.7%; lung metastasis group: 58.8%) that contributed to 88.0% liver metastasis and 54.2% lung metastasis. As such, the implications of tumor location as an independent factor in terms of prognostication and metastatic site prediction are still uncertain. Clearly, independent validation studies with large sample size particularly for upper esophagus will help.

Is tumor location the ultimate explanation for the observed association?

There may be a difference in biology between upper and lower esophageal cancers. As we all know, tumor location is strongly associated with the histologic subtype with ESCC predominantly proximal while EAC mostly confined to distal location. The tumor behavior and the metastatic cascade are likely governed by the respective histology subtype and thus genomic profile rather than the tumor

location. The Cancer Genome Atlas (TCGA) published the landmark paper in 2017 on comprehensive molecular profiling of 164 ESCC and EAC from both Eastern and Western populations (5). As expected, the molecular characteristics were distinctly different between ESCC and EAC with more frequent genomic amplifications of CCND1, SOX2 and TP63 in the former but more ERBB2, VEGFA, GATA4 and GATA6 amplifications in the latter. ESCC resembled more the squamous cell carcinoma of other anatomic sites than EAC while EAC showed strong resemblance to the chromosomal instable (CIN) gastric cancer. Wang *et al.* reported similar findings in 302 advanced esophageal cancers and highlighted the significance of distinct tumor biology according to the histologic subtypes (6). While we do agree anatomic drainage plays a role for the different patterns of metastasis, the current literature may also suggest that such a difference in metastatic behavior could be a result of the different tumor biology.

Although age, sex, histologic type and grade were included in the propensity matching, detailed information such as staging methods and treatment modalities were lacking. These information affect not only the accuracy of determining the site of the primary tumor and metastasis but also the course of disease and eventual development of metastasis as well as prognosis. For example, it is not clear whether the significantly better survival in patients with tumors of lower and middle esophagus of the liver metastasis group is a result of different treatment modality from that of the upper esophageal cancers. Nevertheless, these are known limitations to studies that utilize public database that may not contain all essential information.

Is liver or lung metastasis of esophageal cancer a potentially curable disease?

Aggressive management of metastatic disease in cancers like colorectal cancer and breast cancer has dramatically improved the clinical outcomes of these deadly disease. However, whether or not aggressive treatment results in better outcomes for metastatic esophageal cancer is still controversial. Patients with disseminated disease has a grave prognosis and expectancy is usually in terms of months despite the use of systemic therapy. On the other hand, most reports on aggressive management of oligometastatic disease showed favorable results but they are usually low level evidence without robust data from prospective randomized study (7,8). As such, the optimal management

of oligometastatic disease is currently ill-defined. It is hoped that the ability to predict the site of metastasis would help optimize timely detection and treatment in this aspect. Considering that the patients with lung metastasis had poor survival disregarding the location of the tumor, one would doubt whether lung metastasis could be a curable disease in esophageal cancer. Meanwhile, in patients with liver metastasis, differential survival outcomes of different tumor locations suggest a need of future study to test more aggressive or curative modality for these patients.

Beyond tumor location

A step further beyond prediction of the sites of metastasis would be the ability to prevent metastasis by deciphering the potential mechanism underlying the metastatic cascade. While efforts are being invested heavily in personalized therapy targeting at the respective signaling pathways, the roles of neutrophils in the tumor immune microenvironment are of emerging research interests in cancer metastasis (9). For instance, the importance of neutrophil extracellular traps (NETs) have been demonstrated in various cancers including colorectal, pancreatic and ovarian cancer (10-12). NETs are networks of extracellular neutrophil-derived DNA fibers and elevated circulating level is observed in inflammatory conditions, including tumor-associated inflammation. NETs support tumor metastasis by binding circulating tumor cells and promoting their proliferation in the metastatic sites. In pre-clinical murine models of advanced cancers including esophageal cancer, it was shown that the levels of NETs were elevated and that liver and lung metastasis could be inhibited by blocking NETs formation (13). It is envisaged that strategy to prevent metastasis will become an integral part of comprehensive cancer treatment in the future.

In conclusion, the work of Ai *et al.* has identified an important question in the management of esophageal cancer. The findings of more lung metastasis in upper esophageal cancers and more liver metastasis in middle/lower esophagus are hypothesis generating. Further concerted effort to decipher the molecular mechanism underlying tumor metastasis and to formula optimal management strategy for metastatic esophageal cancers of different locations are unmet clinical needs.

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Footnote

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