Editorial

The different routes of lymph node metastases in esophageal cancer and its significance

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Introduction

Patients with esophageal cancer generally have a guarded diagnosis, with an overall 5-year survival rate of 10%, and an overall post-esophagectomy 5-year survival rate between 15% and 40% (1). These tumors predominantly fall into two histologic subtypes: adenocarcinomas and squamous cell carcinomas. Esophageal adenocarcinoma is most commonly seen in the distal esophagus, while squamous cell carcinoma of the esophagus most often presents more proximally (2,3). For tumors of the esophagogastric junction, the Siewert classification system is helpful to classify the location of the tumor and subsequent treatment strategy. Cancers involving the esophagogastric junction, with a tumor center within 2 centimeters of the cardia, are defined as Siewert type I–II (4,5). Tumors of this classification are to be staged and treated as esophageal malignancies, while tumors with an epicenter greater than 2 centimeters from the esophagogastric junction are classified and treated as gastric malignancies even if involving this region (4).

In a study recently published by Ma *et al.* entitled "Comparison of lymph node metastasis pattern from esophagogastric junction adenocarcinoma versus very low thoracic esophageal squamous cancer: a propensity-matched analysis", the authors sought to compare patients presenting with very low thoracic esophageal squamous cell carcinoma (ESCC) to those presenting with esophagogastric junction adenocarcinoma (AEG) (6). In this study, the authors recorded the patterns of lymph node metastases with very low ESCC versus AEG and overall outcomes. Their goals were to understand better the metastatic capabilities of both tumors in this region and further understand how the distribution of lymph node metastases relate to survival outcomes in both groups. They selected patients with each tumor type fitting the anatomic location of Siewert I–II classifications and used propensity matched analysis to show the metastatic characteristics of the two groups. They identified initial groups of 120 very low ESCC patients and 156 AEG patients. Using propensity matching, the authors selected two groups of 60 patients and 61 patients respectively. The authors were able to use propensity matching to control for many of the demographic variables.

When controlled for age, sex, pathologic T stage, pathologic N stage, grade and tumor length, the authors showed that patients with very low ESCC had a statistically significantly higher prevalence of lymph node metastases than those with AEG. This trend was most dramatically represented in the lower mediastinal nodal basins and the paracardial nodal basins. There were no survival differences between these two groups, however. But the authors did observe that, in their initial data set, AEG patients with metastatic lower mediastinal lymph nodes had worse outcomes than patients without nodal metastases. Also, AEG patients with paracardial lymph node metastases had worse 5-year overall survival rates than those without these metastases. When looking at the entire cohort of both ESCC and AEG patients, the presence of paracardial

lymph node metastases was associated with a significantly worse survival. The survival of patients with positive lower mediastinal lymph nodes was also significantly worse in the entire cohort then those without positive lower mediastinal nodes.

This paper brings to light some important findings regarding distal ESCC and AEG with nodal metastases. Patients with very low ESCC were more likely to have locoregional node metastases than propensity matched patients presenting with AEG. Thus, we should not assume similar metastatic potentials between these two histologic subtypes even if they share the same anatomic location. Secondly, the authors note that when locoregional spread is present, very low ESCC patients demonstrated greater tendency for metastases in the lower mediastinum and paracardial nodes. AEG patients, conversely, demonstrated greater tendency for metastases in the lesser curvature of the stomach and left gastric artery basins. For AEG patients with lower mediastinal or paracardial lymph node metastases, they had statistically significant worse survival than the propensity matched group.

The study by the authors is interesting and focuses on differences in tumor behavior based on histology. The authors revealed a difference in the distribution of lymph node metastases of esophageal cancers not based on tumor location, but instead based on histology. When considering possible mechanisms for these differences, there is a possibility that different histologic variants will have different propensities to travel through specific lymph node channels. A wonderful corollary to this study would be to use a modality such as sentinel node evaluation or lymphoscintigraphy for all of these patients. Based on the results from this study, it would be interesting to see if the number of sentinel nodes and the pattern of spread differed in patients with ESCC versus AEG. Although not commonly used, sentinel node evaluation has been reported in the literature (7,8). We encourage research teams broadly to consider performing a study with this design. A multi-institutional approach would be even more impactful and address this question of impact of histology on nodal drainage pattern.

In review of the literature, a similar study examined broader outcome measures including overall survival and pathologic treatment response (9). In their study, they observed that histology was not a predictive factor for improved survival or pathologic treatment response. An important consideration to make, however, is that these investigators included patients who underwent neoadjuvant chemoradiation in addition to those who underwent surgery alone. In this current study, Ma and colleagues excluded all patients who had undergone neoadjuvant therapy. Further studies looking at all patients, including those who undergo preoperative treatment with chemotherapy, radiation treatment or immunotherapy would help garner better understanding of the overall survival trends of these patients.

There were some key elements from this study that would be helpful in interpreting the results. In particular, it would be helpful to know the number of total lymph nodes harvested in patients with ESCC versus AEG during their surgeries. Although the total number of lymph nodes harvested in the entire study was 14.1, were there differences in the number of nodes harvested in the ESCC group compared to the AEG group? It is possible that if one group had a significantly higher number of lymph nodes harvested compared to the other group, that may affect the percentage of patients with positive lymph nodes identified.

Also, the surgical approaches differed somewhat in each of these groups. Patients with squamous histology appeared to receive either an Ivor-Lewis or a McKeown esophagectomy exclusively. Patients with adenocarcinoma, alternatively, received an Ivor-Lewis or thoracoabdominal incision for their esophagectomy. Was there a difference in the surgical technique and the evaluation of the lower mediastinal nodes based on the surgical approach? The authors appropriately mention that the upper mediastinal nodes may not have been as well accessed with some of the surgical approaches compared to the other types of surgery. But it is also possible that the lower mediastinal lymph nodes may not have been harvested as thoroughly or as systematically based on surgical approach. This trend could possibly lead to differences in positive lymph nodes seen in this study. For follow-up, it would be helpful to list the surgical approaches in each group.

This study evaluated patterns of lymph node metastases and outcomes in these two groups of surgical patients. It would be interesting to see the patterns of lymph node metastases in patients who did not undergo surgery. Based on the results of this study, were patients with very low ESCC more likely not to be surgical candidates based on diffuse lymph node spread? Although we are told the number of surgical patients in this study, the authors may want to consider examining the overall number of patients who presented at their institution during the study period. Perhaps one group of patients were more likely to be candidates for surgery, compared to the other, based on

lymph node metastases. The authors have postulated that esophageal tumors may display different patterns of nodal drainage based on histology. The next step to research that ideology is to determine if histology confers a survival difference in patients with tumors in the same location. Evaluating all patients, not just surgical candidates, may help to answer that question more accurately.

Typically the location of lymph node metastases has been considered to be based on geographic location. Tumors in the distal esophagus would be expected to spread to the lower mediastinum, while tumors in the proximal esophagus would more likely have lymph node metastases in the superior mediastinum. The results of this study challenge that paradigm, however. This study showed that tumors in the same geographic location had different patterns of lymph node metastases based on histology. If not geographic location, then what were the reasons for these differences? To this end, other histopathologic criteria would give a broader picture. Were there differences in variables such as lymphovascular invasion, Ki-67 and other histopathological elements? These additional variables may add some information about possible causes of different patterns of lymph node metastases.

Another follow-up question to this study is to decide what modifications should be made to clinical practice. Given the information in the study, how do the authors recommend that treatment paradigms are changed? The authors do declare their recommendation and guidance that "*complete lower mediastinal and abdominal lymph node dissection should be performed in advanced AEG patients*". But do they feel that the surgical approach should vary based on their results? Also, should multi-modality treatment be more commonly considered in patients based on histology? An argument can be made for treating more patients with neoadjuvant treatment if the presence of lymph node metastases is greater in patients with squamous histology. But the counter-argument to be made is that overall survival did not differ in this study. Based on that fact, a very reasonable argument can be made not to base preoperative chemoradiation treatment solely on histology. Finally, do the authors feel that surveillance strategies should be altered based on histology? Should patients with a certain histology receive more frequent postoperative imaging, if the propensity for metastases is higher?

The authors have raised appropriate limitations in their study. It is a retrospective study and at one institution. Although it is a very busy institution, having increased diversity in medical centers would be helpful. The authors have performed a methodical analysis of this question and have shown some novel results. Having additional information presented, such as number of lymph nodes harvested, exact prevalence of surgical approaches in each group and histopathologic variables would also be helpful. But this study has raised some interesting questions. A multi-center, prospective study evaluating this question would be of interest broadly. Also, an experiment utilizing imaging studies such as lymphoscintigraphy would be useful to show potential differences in lymph node drainage.

Conclusions

We commend Ma and colleagues on their study to examine variation in lymph node metastases between EAG and very low ESCC. Understanding how tumors of varying histologies in the same anatomic region behave differently is a key step in recommending the best treatment strategy for curative intent in patients with esophageal cancer. We look forward to further work from this group to help improve our knowledge of lymph node metastases in esophageal carcinoma patients.

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