

Adenocarcinoma of esophagogastric junction: controversial classification, surgical management, and clinicopathology

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In recent years the world is witnessing an increasing incidence of adenocarcinoma of esophagogastric junction (AEG), which originates from epithelial tissue of esophagogastric junction (EGJ), and mainly derives from Barrett's esophagus. It's now gaining more and more attention due to the controversial etiology, classification and treatment.

Classification

There are two mainstreams to classify AEG: the Siewert (also called Munich) and Liverpool classifications. Based on the anatomical characteristics of EGJ, Siewert believes that adenocarcinomas locating within 5 cm from the cardia are an independent kind of tumor, and divides AEG into three types, which has been widely accepted by UICC, International Gastric Cancer Association (IGCA) and International Society for Disease of Esophagus (ISDE) (1). Type II/III is major, with type I uncommonly seen, and they differ greatly in etiology, epidemiology, origin, tumor biology, patient's medical history, and prognosis, making type II/III AEG considered an independent cancer. The 7th edition of American Joint Committee on Cancer (AJCC) recommends to categorize AEG into esophageal tumors. However, Suh *et al.* (2) report that the prognosis of AEG is similar to that of gastric carcinoma. Besides, even though AEG extending into the EGJ shows more advanced pathologic features than AEG not extending into the EGJ, the prognosis of both is not significantly different when stratified by T stage according to the 7th AJCC TNM classification; and compared with the classification of gastric cancer applied for AEG, esophageal classification for AEG from the 7th AJCC TNM classification shows a loss of distinctiveness

at each TNM stage. Thus they believe that to evaluate the prognosis of AEG within the stomach, type II/III AEG should be considered a part of gastric cancer irrespective of EGJ involvement. Through comparison of AEG staging via AJCC 6th gastric (G6) and 7th gastric (G7) and 7th esophageal (E7) staging systems, Kim *et al.* (3) recommend that AEG staging based on the current E7 staging which introduces histologic grading should be modified with accurate anatomical definition of tumor depth, removal of histologic grade from staging parameters, and classification of more than 15 lymph node metastases as a highly advanced stage with poorer survival. We'd always treat and investigate type II/III AEG as gastric carcinoma though there exist differences between them, while type I tumors are usually handled by thoracic surgeons in our center. Five-year survival rates are similar for Siewert types II and III AEG patients (50-60%).

Origin

Demico *et al.* (4) dichotomize AEG into intestinal-type and cardiac-type mucosa-associated adenocarcinomas, and find that the former type is more likely to be associated with younger age, reflux symptoms, proximal location, lower T stage, fewer nodal metastases, absence of lymphatic, venous or perineural invasion. Histologically, intestinal-type mucosa-associated tumors are more likely to be low-grade glandular tumors of intestinal or mixed immunophenotype and express nuclear beta-catenin, whereas tumors arising in a background of cardiac-type mucosa are more frequently associated with endothelial growth factor receptor (EGFR) amplification. Five-year overall survival rate is significantly

higher in patients with intestinal-type mucosa-associated tumors (28% *vs.* 9%). Their findings support the theory that multiple distinct pathways of tumorigenesis exist in the vicinity of the EGJ, including one in which tumors arise from dysplastic intestinal metaplasia (intestinal pathway), and one potentially involving dysplasia of the cardiac-type mucosa (non-intestinal pathway).

Neoadjuvant modality

Our meta-analysis based on randomized controlled trials (RCTs) reveals that: though neoadjuvant chemotherapy (NAC) followed by surgery tends to reduce the overall mortality compared with surgery alone (SA), and significantly lower the nodal stage for type II/III AEG, the other survival and surgical benefits are comparable between the two modalities; besides, the NAC-associated adverse effects are a significant drawback and the response rate varies (5). Therefore we think that NAC should not be recommended as a regular and routine intervention before obtaining abundant evidences of its efficacy and safety, and should be applied under the framework of clinical trials. Surgery without delay may remain the appropriate management for operable AEG. Besides, individuality should be focused on during comprehensive management of AEG patients, and systematic chemotherapy would be necessary among patients with micrometastatic disease already at diagnosis. A phase III study (6) comparing NAC with neoadjuvant radiochemotherapy (NRCT) in patients with locally advanced AEG reveals that: the number of patients undergoing R0 resection is not different between two groups; patients in NRCT arm have a significantly higher probability of showing pathologic complete response (15.6% *vs.* 2.0%) and tumor-free lymph nodes (64.4% *vs.* 37.7%) at resection; preoperative radiation therapy improves 3-year survival rate from 27.7% to 47.4% [hazard ratio (HR) 0.67; $P=0.07$]; postoperative mortality is non-significantly increased in the NRCT group (10.2% *vs.* 3.8%). The authors conclude that although statistical significance is not achieved, results point to a survival advantage for NRCT compared with NAC. Furthermore, Leibl *et al.* (7) report that after NRCT, the overall survival is 61% at 3 years. R0 resections are achieved in 94% of patients, and 71% of patients with pT3/pT4 tumors experience downstaging. The ypN0 rate is 67%. Regression grading reveals <10% viable cells in 44% of patients including 17% of cases with complete regression, 10-50% viable cells in 50% of cases and >50% viable cells in 6% of patients. Post operation,

35% of patients experienced pulmonary complications including pneumonia and/or pneumonitis. This study suggests that NRCT in patients with advanced AEG followed by surgery is a feasible approach with high efficacy. However, to avoid toxic pulmonary effects constraints for low-dose radiation volume parameters need specific attention.

Surgical management

Ways of gastrectomy

Thoracoabdominal surgery combined with dissection of lymph nodes above and below the phrenic is recommended for type I AEG. For type II/III AEG, total gastrectomy (TG) together with D2 lymphadenectomy is the common treatment, and the transthoracic approach is not preferred compared to the transabdominal operation for its leading to obvious weight loss, incision pain, limited respiration, poor prognosis and unsatisfactory lymphadenectomy, while some scholars believe that proximal gastrectomy (PG) is safe to treat type II/III AEG (8). Esophago-gastric anastomosis, jejunum interposition and the dual-path method are common post-PG reconstructions, with esophagojejunal Roux-en-Y anastomosis preferred post-TG. Based on data in our center, compared with those undergoing PG, type II/III AEG patients undergoing TG have significantly more R0 cutting edges, and superior radical degree, guaranteeing better prognosis. Patients undergoing TG could have more total and metastatic lymph nodes resected than those undergoing PG assuring the radical effect, and there exists a significant difference concerning the distal distance from cutting edge to tumor, suggesting the higher incidence of residual cancer cells post-PG. Patients undergoing TG could have better post-gastrectomy gastrointestinal function recovery including shorter bowel sounds recovery time, flatus and oral durations and days in hospital post-operation than those undergoing PG, reducing the incidence of nosocomial infection. Six months post-surgery, patients undergoing TG have lower RDQ and GERD-Q scores than those undergoing PG suggesting milder post-operation reflux, and serum CEA among patients undergoing TG is lower than that among individuals undergoing PG indicating less chance of recurrence, while the differences of nutritional status indexes including BMI, lymphocyte count, contents of albumin and prealbumin between two groups are not statistically significant, suggesting comparable post-surgical quality of life. Therefore we think that TG is

preferable to PG to treat Type II/III AEG concerned with radical effectiveness, perioperative recovery, quality of life and recurrence post-surgery.

Lymph node management

Number of residual lymph nodes is an independent prognostic risk factor of AEG. Endoscopic ultrasonography (EUS) could achieve a high accuracy of 75% when classifying T stage of type II/III AEG, and an ideal prediction of local lymph node metastasis, which is superior to CT scan. The incidence of lymph node metastasis is high in both type II (64.1%) and III (75.0%) AEGs. Concerning the lymphatic metastasis pattern, Yamashita *et al.* (9) find that No. 1 lymph nodes have the highest incidence of involvement (38.2%), followed by Nos. 3 (35.1%), 2 (23.1%) and 7 (20.9%) nodes. AEG mainly invades abdominal lymph nodes, with 15-30% cases involving mediastinal lymph nodes (only 1% invading the upper ones). Mine *et al.* (10) report that based on preoperative imaging, the incidence of upper/middle thoracic lymph node involvement is low in AEG having proximal ends below the vena cava foramen (VCF, 0%), when the tumors' proximal ends are above the VCF, patients have higher frequencies of upper/middle thoracic lymph node involvement (36.4%). The location of the proximal end of the tumor is an independent risk factor related to upper/middle thoracic lymph node involvement (odds ratio: 14.3, $P=0.013$), and could be useful in deciding the extent of thoracic lymphadenectomy. The priority of nodal dissection evaluated based on the therapeutic value index calculated by multiplying of metastasis frequency to each station and the 5-year survival rate of patients with metastasis to that station, Hasegawa *et al.* (11) find that among lymph nodes having a metastatic incidence exceeding 10%, the stations showing the first to fourth highest index are the paracardial and lesser curvature nodes (Nos. 1, 2, and 3) and the nodes at the root of the left gastric artery (No. 7), regardless of the Siewert subtype, suggesting them as the highest priority nodal stations to be dissected. The next station is the lower thoracic paraesophageal lymph node (No. 110), followed by the nodes along the proximal splenic artery (No. 11p) in type II, whereas it is the nodes along the proximal splenic artery (No. 11p) followed by the para-aortic nodes (No. 16a2), the nodes at the celiac artery (No. 9), and the nodes around the splenic hilum (No. 10) in type III. In type II AEG, Goto *et al.* (12) reveal that the incidence of splenic hilar lymph node metastasis is 4.8% and the 5-year survival rate of patients with splenic

hilar lymph node involvement is zero, causing the index of estimated benefit from lymph node dissection (IEBLD) of splenic hilar lymph nodes to be zero, which suggests that splenic hilar lymph node dissection may be omitted without decreasing curability in patients with type II AEG. They further reveal that the IEBLD of stations located near the EGJ is similar between type II and III AEGs and are generally high, while the IEBLDs of lower perigastric lymph nodes are higher in Siewert type III than in type II AEG cases. Thus they think that TG should be selected as a standard treatment for Siewert type III AEG, whereas in Siewert type II AEG, preservation of the distal part of the stomach may be an acceptable procedure.

Clinicopathology

Data from a single institution in Japan shows that larger, deeper tumors and nodal metastasis are more common in type III than type II AEGs. Depth of tumor and mediastinal lymph node metastasis are significant independent indicators for poor prognosis after R0 resection, and the recurrence rate for patients with mediastinal lymph node metastasis is 87.5%. The risk factors for mediastinal lymph node metastasis are length of esophageal invasion and histopathological grade (13). Based on data from our surgical center, local recurrences exist in 11.1% of cases, half of which are accompanied with distant metastasis; the median interval between surgery and relapse is 15 months; tumor invasion out of the myometrium, lymphatic metastasis, blood transfusion and absence of intraperitoneal chemotherapy are significant risk factors of local recurrence. In advanced AEG, the rate of vagus nerve invasion is 28.6%, and the tumor invasion is only limited to and will not exceed the same height as the upper malignancy margin, indicating that it's not necessary to expand the extent of nerve resection excessively; higher tumor position, formation of tumor thrombus and poor differentiation are independent risk factors of vagus nerve invasion.

Peri-operational management

Before surgery, gastric pH of patients with AEG is generally higher than the threshold of hypoacidity, and advanced malignancies are accompanied with higher pH compared with early ones; after operation, gastric pH significant rises and is of weak- or none-acidity, while it plays no significant role in determining post-surgical reflux symptom (14). Thus there is no need to further alkalinify gastrointestinal

juice both pre- and post-gastrectomy. Monitoring of peri-gastrectomy gastrointestinal juice markers might reveal much information about tumor and radical gastrectomy, and indicate prognosis as the case in distal gastrectomy (15). Peripheral blood neutrophil-lymphocyte ratio (NLR) could indicate tumor progression, and a support vector machine (SVM) based on peripheral CEA, carbohydrate antigen 19-9 (CA 19-9), lymphocyte percentage and platelet count could effectively indicate the inappropriateness for an AEG patient to undergo curative resection with high accuracy when the abovementioned four parameters elevate (16).

Endoscopic treatment

Yamada *et al.* (17) report that endoscopic resection of superficial AEG could achieve 5-year overall, recurrence-free, and cause-specific survival rates of 94.2%, 92.3% and 96.1%, respectively, and that en bloc, R0, and curative resection rates are 100%, 79% and 68%, respectively. In patients with curative resection, the cause-specific survival rate is 100 % with no recurrence or metastases detected. In patients with non-curative resection, recurrence is found in 17% patients. Therefore they believe that superficial AEG can be well controlled by endoscopic submucosal dissection (ESD) when curative resection is achieved. A study by Hirasawa *et al.* (18) finds that there are basically no major complications after ESD for superficial AEG and that the rates of en bloc resection and curative resection are 100% and 79%, respectively. Local or distant recurrences are not observed in any patient achieving curative resection during follow-up. Their results favor long-term outcomes for ESD to be a possible treatment for superficial AEG.

Biomarkers

Through analysis in our center, we find that: in AEG, extracellular matrix metalloproteinase inducer (CD147) and matrix metalloproteinases (MMPs), and tumor stem cell markers like Nanog and Oct-4 are more abundantly expressed compared to pericancerous and precancerous tissues. At the cellular level, Foxp3⁺ regulatory T cells (Tregs) are largely expressed. They are significantly more highly expressed in malignant tissues with poor differentiation grade than with good/moderate grade, with invasion out of the myometrium (pT3-4) than with lesion limited within the myometrium (pT1-2), with local lymphatic metastasis than without metastasis, with distant metastasis than without metastasis, in TNM III/

IV stages than in I/II stages, and with post-operational survival below 5 years than over 5 years, indicating them as potential biomarkers suggesting carcinogenesis, tumor invasion, metastasis, and prognosis, for diagnosis, and as therapeutic targets due to their vital role in tumor biological behaviors. Post operation, levels of interleukin (IL)-6, and its downstream signals including IL-10 and vascular endothelial growth factor (VEGF) significantly lower. They are highly expressed in malignant tissues, and their expressions are associated with TNM stage. There exists a correlation between signal transducers and activators of transcription 3 (STAT3) and IL-6 expression, suggesting that IL-6 may induce STAT3 activation, which positively correlates with tumor progression, and that inhibition of the IL-6/STAT3 signaling pathway may provide a novel therapeutic strategy against AEG (19).

Conclusions

For AEG, Siewert classification is preferred, and there are two possible origins. NRCT is superior to NAC, and TG is favorable for type II/III AEG with adequate lymphatic dissection. Peri-operational management should be focused on, and targeted therapy is worth investigation.

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References

1. Ajani JA, Barthel JS, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011;9:830-87.
2. Suh YS, Han DS, Kong SH, et al. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. *Ann Surg* 2012;255:908-15.
3. Kim HI, Cheong JH, Song KJ, et al. Staging of adenocarcinoma of the esophagogastric junction: comparison of AJCC 6th and 7th gastric and 7th esophageal staging systems. *Ann Surg Oncol* 2013;20:2713-20.
4. Demicco EG, Farris AB 3rd, Baba Y, et al. The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma. *Mod Pathol*

- 2011;24:1177-90.
5. Xu AM, Huang L, Liu W, et al. Neoadjuvant chemotherapy followed by surgery versus surgery alone for gastric carcinoma: systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014;9:e86941.
 6. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009;27:851-6.
 7. Leibl BJ, Vitz S, Schäfer W, et al. Adenocarcinoma of the esophagogastric junction: neoadjuvant radiochemotherapy and radical surgery : early results and toxicity. *Strahlenther Onkol* 2011;187:231-7.
 8. Rice TW, Rusch VW, Ishwaran H, et al. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. *Cancer* 2010;116:3763-73.
 9. Yamashita H, Katai H, Morita S, et al. Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. *Ann Surg* 2011;254:274-80.
 10. Mine S, Sano T, Hiki N, et al. Thoracic lymph node involvement in adenocarcinoma of the esophagogastric junction and lower esophageal squamous cell carcinoma relative to the location of the proximal end of the tumor. *Ann Surg Oncol* 2014;21:1596-601.
 11. Hasegawa S, Yoshikawa T, Rino Y, et al. Priority of lymph node dissection for Siewert type II/III adenocarcinoma of the esophagogastric junction. *Ann Surg Oncol* 2013;20:4252-9.
 12. Goto H, Tokunaga M, Sugisawa N, et al. Value of splenectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. *Gastric Cancer* 2013;16:590-5.
 13. Hosokawa Y, Kinoshita T, Konishi M, et al. Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. *Ann Surg Oncol* 2012;19:677-83.
 14. Huang L, Xu AM, Li TJ, et al. Should peri-gastrectomy gastric acidity be our focus among gastric cancer patients? *World J Gastroenterol* 2014;20:6981-8.
 15. Huang L, Xu A, Li T, et al. Detection of perioperative cancer antigen 72-4 in gastric juice pre- and post-distal gastrectomy and its significances. *Med Oncol* 2013;30:651.
 16. Xu AM, Huang L, Zhu L, et al. Significance of peripheral neutrophil-lymphocyte ratio among gastric cancer patients and construction of a treatment-predictive model: a study based on 1131 cases. *Am J Cancer Res* 2014;4:189-95.
 17. Yamada M, Oda I, Nonaka S, et al. Long-term outcome of endoscopic resection of superficial adenocarcinoma of the esophagogastric junction. *Endoscopy* 2013;45:992-6.
 18. Hirasawa K, Kokawa A, Oka H, et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. *Gastrointest Endosc* 2010;72:960-6.
 19. Wang Z, Si X, Xu A, et al. Activation of STAT3 in human gastric cancer cells via interleukin (IL)-6-type cytokine signaling correlates with clinical implications. *PLoS One* 2013;8:e75788.

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