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REVIEW

# Carcinoma of the gastroesophageal junction in Chinese patients

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## Abstract

Carcinoma of the gastroesophageal junction (GEJ) is defined as carcinoma that crosses the GEJ line, irrespective of where the tumor epicenter is located. This group of cancer is rare but controversial. Based on study results from the majority of epidemiologic and clinicopathologic investigations carried out in Western countries, this cancer is believed to arise from Barrett's esophagus (BE) and includes both distal esophageal and proximal gastric carcinomas because of similar characteristics in epidemiology, clinicopathology, and molecular pathobiology in relation to BE. As such, the most recent American Joint Committee on Cancer staging manual requires staging all GEJ carcinomas with the rule for esophageal adenocarcinoma (EA). This mandate has been challenged recently by the data from several studies carried out mainly in Chinese patients. The emerging evidence derived from those studies suggests: (1) both BE and EA are uncommon in the Chinese population; (2) almost all GEJ cancers in Chinese arise in the proximal stomach and show the features of proximal gastric cancer, not those of EA; (3) application of the new cancer staging rule to GEJ cancer of Chinese patients cannot stratify patients' prognosis effectively; and (4) prognostic factors of GEJ cancer in Chinese are similar, but not identical, to those of EA. In conclusion, the recent evidence suggests that GEJ cancer in Chinese shows distinct clinicopathologic characteristics that are different from EA. Further investigations in molecular pathology may help illustrate the underlying pathogenesis mechanisms of this cancer in Chinese patients and better manage patients with this fatal disease.



**Key words:** Esophagus; Stomach; Cancer; Gastroesophageal junction; Staging; Barrett's esophagus

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## INTRODUCTION

Carcinomas of the gastroesophageal junction (GEJ) is defined by the World Health Organization (WHO) as tu-

mors "that cross the oesophagogastric junction... regardless of where the bulk of the tumours lies"[1]. Therefore, this cancer may arise from the distal esophagus, grow downward, cross the GEJ line, and invade the proximal stomach, or originate from the proximal stomach, grow upward, and invade the distal esophagus. For better surgical management of patients, Siewert and Stein classify this cancer into 3 types: Type I cancer shows epicenter in the distal esophagus 1-5 cm above the GEJ; Type Ⅲ cancer centers within the proximal stomach 2-5 cm below the GEJ; and Type Ⅱ tumor straddles the GEJ within a 3-cm longitudinal spread of 1 cm above and 2 cm below the GEJ[2-4].

At present, the underlying mechanisms of tumorigenesis for this uncommon cancer are poorly understood[5-7]. Several investigators from Western countries believe adenocarcinoma of the proximal stomach, i.e., gastric cardiac carcinoma, to be similar, or even identical, to Barrett's esophagus (BE)-associated distal esophageal adenocarcinoma (EA) on the basis of comparable characteristics in epidemiology[8-14], clinical presentations[15-23], molecular pathobiology[24], and histopathology[17,25-27]. This notion has been adopted by the American Joint Committee on Cancer that published the 7th edition of the cancer staging manual (AJCC 7) in 2009, requiring staging all GEJ cancers with the rule for EA[28].

Over the past decade, a growing body of evidence has been published on epidemiology[29-31] and clinicopathology[32-36] of GEJ carcinoma in Chinese patients with the standardized criteria. The emerging data suggest that GEJ carcinoma in Chinese is heterogeneous in histology and shows clinicopathologic features different from those of EA. This article critically reviews the most recent evidence on this fatal cancer in Chinese patients with the intention to promote clinical research and to better manage Chinese patients with this cancer.

## BE AND DISTAL EA REMAIN SCARCE IN CHINESE

Several recent population-based studies using the BE diagnostic criteria of the American Gastroenterology Association show a very low frequency of BE in the Chinese population[29,37-43]. In 2008, Tseng *et al*[29] reported a frequency of 0.28% of patients with columnar-lined esophagus out of 19 810 consecutive subjects at annual health check-up with upper endoscopy. By histology, among those with columnar-lined esophagus only 12 subjects had intestinal metaplasia and were qualified as BE patients, rendering a prevalence rate of 0.06% in the general population[29]. In referral patients for upper endoscopy, Kuo *et al*[30] reported only 1.8% of BE cases from 735 consecutive subjects. Similar results were also described in another upper endoscopy study of 5179 patients with a prevalence rate of BE at 1% and 0.35% for referral and screening cases at annual health check-up. These results have been repeatedly confirmed by several other endoscopy studies[40-42,44,45]. In addition to this very low prevalence rate, BE in most Chinese subjects is in the short- or ultra-short segment, i.e., shorter than 3 cm in the longitudinal length[40,46-49]. Chen *et al*[49] studied 4120 qualified BE cases in a meta analysis of 308 original research articles published over the period from 1997 to 2007. They reported overwhelming BE cases (78%) in the short-segment and most in tongue- and island-like endoscopic mucosal lesion patterns (78%). The long segment BE is infrequent and has not been reported in Chinese women. In a histopathology study of distal esophageal mucosa in patients with proximal gastric carcinoma, Sun *et al*[50] reported the finding of columnar-lined esophagus in up to 65% of the cases, 97% of which was confined within 1 cm above the GEJ line.

Similarly, EA remains rare in the Chinese population[51-57], unlike that in patients from the West where the incidence of EA has been rapidly rising in the most recent years and EA has outnumbered esophageal squamous cell carcinoma[58,59]. A population-based epidemiology study carried out in Taiwan over a 25-year period from 1979 to 2003 showed a steadily increasing trend for esophageal squamous cell carcinoma but not for EA[60]. In another study in Hong Kong, investigators even reported a decreasing trend for EA over a 20-year period from 1984 to 2003[31]. Among 10 751 new esophageal cancer cases reported to the Hong Kong Cancer Registry, the number of EA cases decreased from 224 in 1984 to 1988 to 131 in 1998 to 2003, a dramatic drop of over 40% in incidence[31].

By histopathology, investigators from a major tertiary medical center in Taiwan did not find a single case of EA over a 20-year period from 1987 to 2007[35]. Most recently, armed with the WHO diagnostic criteria[1] and the recently defined histological definition of the GEJ line[61,62], pathologists in Nanjing studied histopathologic features of consecutive 206 radical resections of tumors in the distal esophagus in a homogenous Chinese population and identified only 2 (1%) cases of true EA[34]. In that study, esophageal squamous cell carcinoma stays predominant[34].

These clinical study data suggest that BE-related diseases including EA remain uncommon in the Chinese population in the most recent years and may not be the source of their GEJ cancer[63].

## CLINICOPATHOLOGIC FEATURES ARE NOT THOSE OF EA

To answer the question as to where GEJ cancer in Chinese patients arises and what clinicopathologic differences in this cancer between Chinese and Westerners could be, a recent comparison study on clinicopathologic features of GEJ cancer with the WHO diagnostic criteria was conducted between Chinese patients treated in Nanjing, China, and American patients treated in Boston, the United States[33]. The researchers reported remarkable differences in almost all clinicopathologic characteristics of GEJ cancer between these two different ethnic

patient populations. In general, Chinese patients were 6-year younger, more in the female gender, and presented with tumors 1.5 cm larger in size. Their tumors were all centered in the proximal stomach and heterogeneous in histology with substantial proportions of the cases showing uncommon types such as adenosquamous cell carcinoma, neuroendocrine carcinoma, and pancreatic acinar-like adenocarcinoma[32,33,64]. In contrast in American patients, almost all tumors were centered in the distal esophagus and homogeneous as EA in histology[33]. As to the peri-tumor mucosal diseases in Chinese patients, although distal esophageal columnar metaplasia (14%) and dysplasia (0) were uncommon or absent, chronic gastritis (81%) and *Helicobacter pylori* (*H. pylori*) infection (35%) were widespread. Again, in a sharp contrast, distal esophageal columnar metaplasia (87%) and dysplasia (67%) in the Americans were overwhelming; but chronic gastritis (24%) and *H. pylori* infection (19%) were uncommon in the uninvolved proximal gastric mucosa[33]. The results suggest that GEJ cancer in American patients is indeed associated with BE and shows the clinicopathologic features of EA[25,65-68]. In contrast, GEJ cancer in Chinese is in fact primary proximal gastric cancer and different from EA.

Despite the fact that the results of this single comparison study confirm the rational on the AJCC 7 classification of this cancer as EA in American patients, the new AJCC 7 mandate for classification of all GEJ cancers as EA may be questionable and ineffective in Chinese patients.

## APPLICATION OF STAGING RULES ON EA CANNOT EFFECTIVELY PREDICT SURVIVAL IN CHINESE PATIENTS

The updated AJCC 7 staging guideline classifies all GEJ cancers as EA and requires staging these tumors as esophageal cancer[28]. The validity and effectiveness of this new mandate has been found problematic in Chinese patients. Researchers in Nanjing, China, investigated 142 cases of GEJ cancer and reported inferior stratification of survival prediction to survival stratification with the staging rule for gastric cancer, especially for pN and summary pⅢC stages, when these cases were staged with the scheme for EA based on the AJCC 7 new guideline[69]. They reported that the pN stage was more predictive in survival than the pT, which is consistent with the features of gastric cancer. In addition, they described a useful survival predictive value for celiac nodal disease and the lymph node ratio in patients with this cancer. In contrast, using the staging guideline for EA, they discovered illogical patient survival characteristics. For example, the Kaplan-Meier curves for patients staged at pⅢA predicted erroneously better survival than those staged at pIA and pIIB. Moreover, the survival curves also crossed in the cases staged at pⅡB and pⅢB, indicating the existence of intra-group heterogeneity. Importantly, even with the staging scheme for gastric cancer, the survival curves for patients with this cancer were not distinctive and showed incorrectly better survival prediction for patients staged at pⅠB and pⅡB than those at pⅠA and pⅡA. Interestingly enough, patients staged at pN3b had the 5-year survival rate worse than those with pM1 and pⅣ diseases[69]. These observations, taken along with the group clustering in pⅡA, pⅡB, pⅢA, and pⅢB, illustrate a poor discriminatory ability of the new AJCC 7 staging rule for this cancer in Chinese[70,71].

One of intriguing facts in Chinese patients with this cancer is that despite the larger tumor size and higher overall pathologic stage with stage pⅢ-Ⅳ in 70% of cases, the 5-year survival rate for patients with stage pⅢ tumors is significantly better in Chinese than in American patients[69]. A similar result for patients with proximal gastric cancer staged at pⅢ has been reported previously in an epidemiology study on the data derived from the Surveillance, Epidemiology, and End Results database[11]. In that study, although the overall patient survival curves are almost identical between EA and proximal gastric cancer groups, a distinct separation in survival curves between these two groups is demonstrated for patients with pⅢ diseases; importantly, the patients with proximal gastric cancer and staged at pⅢ show a much better survival trend than those with EA[11]. These results demonstrate a unique characteristic for proximal gastric cancer, which is distinctly different from that of EA[69].

The aforementioned preliminary data suggest that GEJ cancer in Chinese cannot be staged predicatively as EA with the new AJCC 7 guideline, as confirmed in a recent South Korean study[72]. Even staged with the rules for gastric cancer, these cases cannot be monotonically stratified for prognosis prediction[69], suggesting the existence of discrete pathobiological characteristics that set this cancer apart from EA and less characteristically from conventional gastric cancer[73]. Regardless, the study of GEJ cancer in Chinese patients treated in Nanjing is limited by a relatively small sample size, advanced pT3 disease in the majority of the cases, and a lack of consistent surgical lymphadenectomy procedure carried out in all cases[69]. Further investigation with defined criteria and a larger sample size is needed to validate those interesting results.

## PROGNOSTIC FACTORS AND SIRT1 GENE EXPRESSION

In the most recent reports on prognostic factors of EA with a large sample size, well-defined clinicopathologic characteristics, and robust follow-up from Western countries, the worse 5-year disease-specific prognostic factors are found to be associated with higher pT, pN stages, advanced age over 76 years, signet-ring cell histology, poor tumor differentiation, and extra-nodal diseases[74-77]. These prognostic factors for EA have been reported to

be similar, but not identical, to those in Chinese patients with GEJ cancer in recent publications[78-80]. However, because of the limited number of reports on this issue, the results are a bit inconsistent. For instance, in one report with 514 surgical resection cases of GEJ cancer at a major medical center in China, tumor gross and histology type, stage, vascular invasion, and extent of surgical resection were found to be significant prognostic factors[78]. In another detailed clinicopathology study report[79], patient age over 70 years, tumor size larger than 8 cm, poor differentiation, the number of positive lymph nodes over 16, and advanced summary pathology stage were shown to be associated with worse outcomes. In contrast, lymphovascular invasion, which is associated with worse survival in EA[80], is not shown to be a significant prognostic factor. Interestingly, celiac nodal metastasis and the lymph node ratio for the number of lymph node retrieved and nodal disease are reported to be significant prognostic factors[81-83]. The investigators further reported that the ratio of the number of positive nodes identified *vs* the number of total lymph nodes evaluated was related to significantly worse overall survival[79]. Furthermore, the patient survival rate becomes significantly worse for the lymph node ratio over 0.2, compared to the cases with negative nodal disease. The relative risk of worse prognosis for the ratio over 0.4 or 0.5 is 37-fold or 75-fold[79]. This powerful prognostic prediction by the lymph node ratio is very practical in clinical settings where nodal dissection by individual surgeons and nodal retrieval by pathologists vary and a unified nodal dissection protocol is not universally executed. This simple, easy-to-use, and objective prognostic indicator in gastric cancer has been repeatedly confirmed by many other investigators around the world[84-91].

Advanced age has been proven to be one of independent worse prognostic factors in GEJ cancer[74,75,79]. This may result from genetic abnormalities in aging associated genes such as Sirt1, which is a recently discovered, aging-related histone deacetylase involved in regulation of multiple critical steps of stress responses, nutrient metabolism, and aging through deacetylation of a variety of subcellular molecules such as p53, forkhead transcription factors, PGC-1α, NF-κB, Ku70, and histones[92-97]. An increasing body of evidence in molecular biology suggests a complex role for Sirt1 to play in tumorigenesis[96-101]. Feng *et al*[102] are the first to use tissue microarray and immunohistochemical methods to investigate the Sirt1 gene expression in proximal gastric cancer including GEJ cancer in Chinese patients. They reported that compared to normal controls, Sirt1 gene expression was significantly higher in a subgroup of GEJ cancer cases, which was significantly associated lymph node metastasis, higher pathologic stages, and worse survival prognosis with significantly lower 1- and 3-year survival rates (80% and 49%), compared to the Sirt1-negative cancer patient groups (89% and 71%), suggesting a prognostic predictive value for this molecule in patients with this cancer. It should be interesting to know how Sirt1 plays in the initiation and progression of GEJ cancer in Chinese patients.

## CONCLUSION

GEJ cancer is uncommon but poorly understood for its natural history, pathogenesis mechanisms, and prognosis. An increasing body of evidence accumulated in recent years suggests that GEJ cancer in Chinese patients arises mainly in the proximal stomach associated with chronic gastritis and shows a heterogeneous histology pattern. This cancer is distinctly different from EA and cannot be accurately stratified with the scheme for EA, as required by the updated AJCC 7 cancer staging guideline for patient survival prognosis prediction. Although the new AJCC 7 staging rule for gastric cancer may be used for this cancer, there exists considerable heterogeneity and indistinctive survival characteristics, suggesting the possibility of a distinct disease entity for this cancer.

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