

Two updates on adenocarcinoma of gastroesophageal junction from the fifth WHO classification of tumors of the digestive system: alteration of gastroesophageal junction definition and the emphasis on HER2 test.

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Research

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Abstract

Background: The incidence of gastroesophageal junction (GEJ) adenocarcinoma has increased rapidly but remains controversial over the last decades. There are two crucial updates of the fifth WHO classification including the alteration of GEJ location and the emphasize on human epidermal growth factor receptor 2 (HER2) test.

Methods: We retrospectively analyzed the clinicopathological features of 566 patients suffered from gastric adenocarcinoma. We comprehensively compared the clinicopathological features among GEJ and non-GEJ tumors, GEJ and proximal and distal gastric tumors with fourth and fifth edition, respectively. Besides, we discussed the correlation of the HER2 expression with clinicopathological features according to the fifth WHO classification.

Results: The results showed that the difference was mainly between GEJ and distal adenocarcinoma in the fourth edition, but some were between proximal and distal adenocarcinoma in the fifth edition. Tumors with longer invasion of the oesophagus were still mainly concentrated in GEJ tumors. The expression of HER2 in GEJ and proximal gastric adenocarcinoma was still higher than that in gastric body and distal site, which was basically consistent with the conclusion of the fourth edition classification.

Conclusions: The clinicopathological parameters of the GEJ tumors partly changed with the narrowing scope of the GEJ adenocarcinoma. The proximal gastric tumors rather than GEJ tumors tended to be more invasive. But the GEJ tumors with longer oesophageal invasion required additional management. The HER2-expression of GEJ adenocarcinoma is still higher than that of other gastric sites. The classification of the fifth edition is reasonable and worthy of recommendation.

Introduction

Gastric cancer is the fifth most common cancer worldwide and gastroesophageal junction (GEJ) carcinoma has drew considerable attention because of its remarkable increase in incidence [1]. Compared with oesophageal and gastric carcinoma, GEJ tumor need different surgical procedure and lymph nodes dissection. However, it's often unclear whether the tumor is of gastric or oesophageal origin even though examined with computed tomography or endoscopic. For example, the computed tomography just have a low specificity (44%) when classifying GEJ Siewert type II tumors [2][3]. The location of pathological anatomy seems the most accurate after operation, but the definition of GEJ adenocarcinoma (AEGs) remains controversial in last decades. Siewert et al. classified GEJ carcinoma into three types including type I with its center 1-5cm above the GEJ, type II with its center between 1 cm above and 2 cm below the junction, type III with its center 2–5 cm distal from the GEJ [4]. On the other hand, Nishi et al. proposed that the tumor is located 2 cm above and 2 cm below the GEJ carcinoma, regardless of its different histological subtype [5]. In the west and east, the Siewert's classification has

been widely used to distinguish the AEGs and adopted in the fourth WHO classification of tumors of the digestive system in past decades except in Japan.

In 2019, the fifth WHO classification of tumors of the digestive system changes the epicenter distance from the GEJ of the AEGs from 5 cm into 2 cm, showing no difference with Nishi's classification [6]. In virtually, the new definition of GEJ is similar to Siewert II and there are some studies have previously discussed the differences of clinicopathological features among the three Siewert types. A study demonstrates that patients with Siewert III tend to have later stages, more extensive lymph node involvement and worse survival than patients with type I or type II [7]. However, some data show the oncological outcomes of Siewert II tumors are similar to Siewert III in Eastern [8]. Moreover, when compared with distal gastric tumors, GEJ tumors are correlated with poor outcomes [9]. There is no consistent conclusion on the differences of clinicopathological features among GEJ subtypes. Therefore, a detailed and comprehensive analysis among the clinicopathological features is necessary not only between the fourth and the fifth edition of GEJ tumors, but also between the GEJ and other gastric tumors.

Besides, there is another significant point in fifth WHO of GEJ tumors that HER2 should be applied routinely to identify patients who may benefit from the target therapy of trastuzumb [6]. HER2 is a pro-oncogene encoded by erbB2 on chromosome 17 and its amplification might result in angiogenesis, tumorigenesis and excessive cell growth in several tissues such as colon, ovary, bladder, uterine and breast [10]. Although HER2 has been evaluated in many studies with gastric or GEJ adenocarcinomas, the scoring criteria and the definition of GEJ-location have varied, leading to discrepancies in HER2-amplification rates, which vary with an extremely wide range from 4–53% and a median rate of 20.2% [11][12]. Previous studies showed that HER2-positivity rates were higher in GEJ than gastric cancer [13][14], whereas some studies suggested that the presence of HER2-expression wasn't influenced by tumor location [15][16]. HER2-expression is heterogeneous in gastric or GEJ carcinoma, thus it's important to review the HER2 status by immunohistochemistry (IHC) or in situ hybridization and its correlating clinicopathological features according to the fifth WHO classification of tumors of the digestive system.

In the fifth edition, the two crucial updates are the alteration of GEJ adenocarcinomas' definition and the emphasis on HER2 test. There is no consistent conclusion about the differences of clinicopathological parameters between each GEJ adenocarcinomas with different location. The clinicopathological features related to HER2 status perhaps have a variation as well. In this study, we compared the clinicopathological features between AEGs and other gastric carcinomas (GCs) with fourth and fifth edition respectively. Then, we assessed the relationship between clinicopathological features and HER2-expression with fifth edition, to make an in-depth and comprehensive understanding about the GEJ adenocarcinomas of the fourth edition WHO of the digestive system.

Materials And Methods

Case Selection Study Design

We conducted a retrospective analysis including 566 cases that 464 of them were gastric carcinomas and 102 were GEJ adenocarcinoma (fourth edition of WHO). All patients were treated at Sichuan Cancer Hospital & Institute between 2016 and 2019 and this study received the approval from the ethics committee of Sichuan Cancer Hospital. The selected patients underwent radical resection of the tumor except for the ones who received radiotherapy or chemotherapy earlier.

The primary objective of this study was to compare the clinicopathological features of GEJ tumors with other gastric tumors such as proximal (excluding GEJ), body and distal gastric tumors. In addition, we also made a comparison of GEJ tumors between the fifth edition/Nishi classification and the fourth edition. The secondary objective was to discuss the correlation of HER2-expression with the clinicopathological features according to the fifth WHO classification of tumors of the digestive system.

Histological evaluation

Hematoxylin and eosin-stained (HE) sections from surgical excisions of specimen in all cases were reviewed by two pathologists using a multi-headed microscope. The histologic features were assessed as following: T classification (depth of tumor invasion), N-classification (nodal involvement), degree of tumor differentiation, lymphovascular invasion, nerve invasion and histologic type (Lauren's classification). The TNM classification was followed the AJCC eight edition [17]. Moreover, the sites of lymph nodes metastasis included four groups: lower mediastinal/periesophageal (No110-No.112), perigastric (No.1-No.6), suprapancreatic (No.7-No.11), para-aortic (No.16) [18]. The rate of lymph node metastasis was divided into three grades: score 1 means there was no lymph node metastasis, score 2 stood for 1-2 groups metastasis and score 3 stood for 3-4 groups metastasis.

Immunohistochemistry (IHC)

The rabbit monoclonal antibodies included anti-CDX-2 (RMA-0631, Maxim, Fuzhou, China), anti-CK7 (Kit-0021, Maxim), anti-CK20 (Kit-0025, Maxim) anti-KI67 (MIB-1, Maxim), anti-C-erbB-2 (EP3, Maxim) and antibodies for mismatch repair protein (MMR:MLH1, PMS2, MSH2 and MSH6). All procedures were performed in the EnVision System by a Benchmark-ULTRA automatic immunohistochemical staining instrument (Asia-core, China). HER2 scoring system proposed by Hoffman et al. was used as the criteria [19]. HER2 status was considered negative (HER2-) with scores of 0 and 1 (No membranous reactivity in <10% or faint or barely perceptible reactivity in $\geq 10\%$ of tumor cells). HER2 with score of 3 (strong and complete basolateral membranous reactivity in ≥ 10 of tumor cells). HER2 status with score 2 was considered positive unless tested for gene amplification. Microsatellite instability (MSI) was evaluated by four markers of MMR, including microsatellite stability with positive for all four markers and microsatellite and high frequency MSI (MSI-H) with deficiency for more than two markers [20].

Fluorescence in situ hybridization (FISH)

The levels of HER2 amplification were tested with the cases whose IHC score was two. FISH test of HER2-amplification was performed with PanthVysion kit (GSP, LBP, Guangzhou, China). The evaluation towards

HER2-amplification was based on the ratio of HER2 to centromere 17 copy number, according to the guidelines of 2007 ASCO/CAP [21]. Cases were considered as gene amplified for the HER2/CEP17 ratio of 2.2, equivocal with ratio less than 2.2 but more than 1.8 and negative with the ratio less than 1.8. The equivocal cases were not selected in our cohort.

Statistical analysis

Findings were analyzed using the SPSS software for Windows, Version 18. The clinicopathological parameters were collected according to a standardized protocol. The difference of clinicopathological features among GEJ and proximal and distal gastric tumors were tested using the Mann-Whitney U test and Kruskal-Wallis test. The difference of clinicopathological features between GEJ and non-GEJ tumors and the correlation between clinicopathological features and HER2-expression were tested using the Mann-Whitney U test and Fisher's exact test. Differences were considered to be significant with two-side and P-value of <0.05.

Results

Clinicopathological features of AEGs (5cm from GEJ) and GCs

The Clinicopathological features of AEGs(fourth edition/Siewert's classification) and GCs (proximal gastric excluding GEJ, gastric body and distal gastric) were summarized in Table1. There was no significant difference in patient age, histological type, degree of differentiation, M-classification and HER2-status between AEGs and GCs. In distal gastric cancer, female patients accounted for more than AEGs (P=0.005). AEGs had longer tumor diameter (P<0.001), higher T-classification (P<0.001), more frequent lymphovascular invasion (P=0.022) and more frequent nodal metastases (P=0.011) than distal gastric tumors. In addition, AEGs had higher rate of lymph node metastasis than gastric body (P=0.015) and distal gastric tumors (P=0.006). There was no difference in other parameters between AEGs and proximal gastric and gastric body. Her2 status was merely different between proximal and distal gastric (P=0.001).

Clinicopathological features of AEGs (2cm from GEJ) and GCs

According to the new fifth edition of tumors of the digestive system, the clinicopathological features of AEGs (Nishi's classification: 2cm from GEJ) and GCs were compared in Table2. There was no significant difference in patient age, histological type, N-classification, M-classification, rate of lymph node metastasis and HER2 status between AEGs and GCs. Compared with proximal gastric, AEGs had higher degree of differentiation (P=0.029). Besides, AEGs had shorter tumor diameter than proximal gastric (P=0.041) and gastric body (P=0.032), but showed higher T-classification than distal gastric (P=0.012). Her2 status was also merely different between proximal and distal gastric (P=0.021).

Comparison of AEGs' clinicopathological features between fourth edition and fifth edition groups.

In order to have a more comprehensive understanding of the impact of the change in the definition of AEGs, we compared the Clinicopathological features of the new fifth edition with the fourth edition of the AEGs. All AEGs were divided into two groups: 2cm-5cm group meant ones of 2cm to 5cm from GEJ and the 2cm group stood for the ones of 2cm from GEJ. There were 103 cases in fourth edition group (Siewert's classification) including 57 (56%) cases of 2cm from GEJ (the fifth edition) and 45 (44%) cases of 2cm to 5cm from GEJ. The 2cm group showed shorter in tumor diameter ($P<0.001$), lower T-classification ($P=0.021$) and lower N-classification ($P=0.035$) than tumors of 2cm-5cm group. There was no significant difference in other parameters between the two groups.

Correlation between HER2 status and clinicopathological characteristics

We evaluated the HER2 status and clinicopathological features among all 566 cases and the GEJ tumors were chosen with the new fifth edition. The incidence of HER2-expression in GEJ (25%) and proximal gastric (22%) were higher than gastric body (13%) and distal gastric (11%) tumors; this correlation was statistically significant ($P=0.001$). HER2-positivity was more common in low-moderate differentiation cases than high degree ones ($P<0.001$). Moreover, tumors of HER2-expression were distinctly associated with larger tumor diameter (0.001) and higher M-classification (0.039). Interestingly, there was no statistically difference in T-classification and N-classification. Although no difference in MMR status, there was merely one case of MSI-H in HER2-expression tumors.

Discussion

The Siewert's classification is widely used for surgical procedure of AEGs, while the Nishi's classification from Japan is almost the same as the Siewert II. Previous studies have been more focused on comparing the differences among Siewert I to Siewert III [22], or comparing the clinicopathological features between GEJ tumors with GCs. In the fifth WHO classification of tumors of the digestive system, Nishi's classification is used in the definition of AEGs. The change in the definition of GEJ tumors is significantly important for clinicopathological assessment and clinical management, such as the surgical choice and lymph node dissection.

In this study, we compared the clinicopathological features between AEGs and GCs with fourth and fifth edition respectively according to the fifth WHO classification. The difference between the AEGs and the GCs was mainly focused on the AEGs and distal gastric adenocarcinoma with the criteria of the fourth edition. The AEGs had higher T-classification than distal gastric with the criteria of both the fourth and fifth edition. This was in accord with previous studies, that proximal (GEJ and cardia) tumors were associated with poor outcomes [23][24]. However, when analyzed the N-classification and the rate of lymph node metastasis, the difference between AEGs and distal gastric with the fourth edition criteria turned into the difference between the proximal and the distal gastric adenocarcinoma with the fifth edition criteria. This was perhaps due to the tumors of 2cm-5cm from the GEJ classified to the proximal gastric tumors in the fifth edition. Moreover, the tumors of 2cm-5cm was same as the Siewert III.A multivariate analysis showed only lymph node metastases predicted the gastric carcinoma survival [25].

The majority of patients were found to have more lymph node involvement in the Siewert III [26], which was consistent with our results. From the results of this part, the Siewert III tumors were no longer included in GEJ adenocarcinoma, the treatment for GEJ tumors need update as well. Total gastrectomy or more extensive distal gastric lymph node dissection may not be required. On the other hand, the scope of proximal gastric tumors (excluding GEJ) was also changed with the update of the definition of GEJ. The proximal gastric adenocarcinoma statistically exhibited longer tumor diameter, higher T-classification and higher N-classification than distal gastric adenocarcinoma, that didn't appear in the fourth edition. What should be noted is that proximal gastric tumors rather than GEJ may have the worse survival and need to be treated especially and comprehensively. Besides, there was no significant difference in histologic types between AEGs and GCs, indicating that the tumor morphology could not help to distinguish AEGs from GCs.

Furthermore, we also compared the clinicopathological features between the AEGs (2cm from GEJ) and non-AEGs (2cm-5cm from GEJ) according to the fifth edition. The data showed AEGs of 2cm from GEJ had shorter tumor diameter, lower T-classification and lower N-classification than non-AEGs of 2cm to 5cm from GEJ. It seemed the AEGs were less invasive than non-AEGs. Notably, the extent of lymph node dissection in the mediastinum and the choice of distal esophagectomy made great important in GEJ tumors treatment. A multicenter retrospective study considered only the distance from the GEJ was significantly related to metastasis, and the longer the distance, the higher rate of lymph node metastasis [27]. In this study, AEGs were shorter in diameter than non-AEGs, which stood that AEGs were less likely to be lymph node involvement. Besides, some studies suggested lower mediastinal lymphadenectomy was recommended for oesophageal invasion of 3 cm or less; the extent of upper or middle mediastinal lymphadenectomy for oesophageal invasion of ≥ 3 cm [28][29]. Although shorter in diameter, the AEGs in our cohort had a higher rate than non-AEGs in terms of the length of oesophageal invasion more than 3cm, which showed AEGs need upper or middle mediastinal lymphadenectomy. Therefore, mediastinal lymph node dissection and surgical resection were not completely unified in AEGs, even though the scope of AEGs became narrowed under the fifth edition. The tumor's diameter and the length of oesophageal invasion both required special attention. What's more, we also compared the difference of mediastinal lymph node involvement between the two groups. The proportion of AEGs (57%) were slightly higher than non-AEGs, but with no statistical difference. This may be due to the lack of an accurate assessment of the length of oesophageal invasion before operation and the incomplete extent of lymph node dissection.

HER2 test is another significant point which was formally required in the fifth edition. This marker's expression and its relevant clinicopathological features were studied in previous researches with Siewert's classification [30][31]. On the basis of the fifth edition, we re-evaluated the clinicopathological features of total 566 cases and their HER2 status. The HER2-expression in GEJ and proximal tumors were statistically higher than that in body and distal tumors, which was consistent with other studies [30][32]. On the contrary, a study of 612 cases in Japan reported that the HER2-overexpression was not influenced by tumor location with Siewert's classification [16]. We assessed the HER2 status with both IHC and FISH and classified the tumor locations with Nishi's classification (fifth edition). Our results demonstrated GEJ tumors had a higher expression of HER2 than body and distal tumors even if the number of GEJ tumors

was decreased at the new criteria. This should be a crucial factor to emphasize the need for HER2 test in GEJ tumors. In addition, our analyses showed a statistically significant association between HER2-expression and pathological grade, tumor diameter and M-classification of gastric tumors. HER2-expression tumors had poor differentiation, longer diameter and more metastasis than HER2-negative ones, that meant HER2-expression tumors presented more invasive than HER2-negative ones. These results were agreed with other studies [33]. Therefore, the relevant clinicopathological features of HER2-expressing GEJ tumors were almost not changed in the fifth edition. Microsatellite instability was another significant molecular detection in gastric carcinoma, that was related to the contraction or expansion of microsatellite sequences owing to the replication errors caused by mutations in the mismatch repair (MMR) in most cases [34]. Patients with MSI-H were more than 30 percent likely to develop Lynch syndrome. Even though no statistically significant difference between MSI and HER2-expression, there was merely one of the 19 MSI-H cases showing positive for HER2, while other 18 cases were all negative for HER2. This demonstrated that the HER2-expression cases probably did not suffer from MSI-H, but more data were needed for further verification.

In conclusion, our study comprehensively compared the clinicopathological features among AEGs and non-AEGs tumors, GEJ and proximal and distal gastric tumors. The analyses showed that the difference was mainly between GEJ and distal adenocarcinoma in the fourth edition, but some of these differences were between proximal and distal adenocarcinoma in the fifth edition. And the invasiveness of proximal gastric tumors appeared to be relatively more invasive than GEJ and distal gastric tumors. The clinical management of proximal gastric tumors may need more attention and further research. In addition, the criteria of GEJ adenocarcinoma (fifth edition) are equivalent to the tumors of Siewert II (fourth edition). The Siewert III, with the worst prognosis, is no longer included in the category of the GEJ tumors. The treatment of the GEJ tumors does not have to be too aggressive. However, our data showed that tumors with longer invasion of the oesophagus were still mainly concentrated in GEJ tumors of fifth edition. It should be noted that these tumors require additional middle even upper mediastinal lymph node dissection and longer scope of esophagectomy. Besides, although the scope of GEJ carcinoma became narrowed after the revision, the expression of HER2 in GEJ and proximal gastric adenocarcinoma was still higher than that in gastric body and distal site, which was basically consistent with the conclusion of the fourth edition classification.

Conclusions

The clinicopathological parameters of the GEJ tumors change partly with the narrower scope of the GEJ adenocarcinoma. Although the treatment tends to be more unified and standardized. The GEJ tumors with longer oesophageal invasion required additional management. The HER2-expression in the fifth edition of GEJ adenocarcinoma is still higher than that of other sites of gastric. Therefore, the emphasis on the detection of HER2 in GEJ tumors is of great significance in clinical work. The overall analyses show the rationality with GEJ tumors criteria of the fifth WHO classification of tumors of the digestive system, which is worth recommending in pathological diagnosis and clinical work.

Declarations

Ethics approval and consent to participate

This article was approved by the Ethnic Committee of Sichuan Cancer Hospital & Institute.

Consent for publication

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Availability of data and materials

The data and materials are available to be shared.

Declaration of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

ML made the pathological diagnosis. JL provided the clinical information. YL drafted the manuscript. ML and JL participated in manuscript revision. All authors read and approved the final manuscript.

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Abbreviations

GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; AEGs, GEJ adenocarcinoma; GCs, gastric carcinomas; HE, hematoxylin and eosin-stained; MMR, mismatch repair protein; MSI, microsatellite instability; MSI-H, high frequency MSI; IHC, Immunohistochemistry; FISH, fluorescence in situ hybridization

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Tables

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