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Two updates on oesophagogastric junction adenocarcinoma from the fifth WHO classification: Alteration of definition and emphasis on HER2 test

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Summary. Introduction. The incidence of oesophagogastric junction adenocarcinoma has increased rapidly but remains controversial over the last decades. There are two crucial updates of the fifth World Health Organization (WHO) classification, including the alteration of its definition and the emphasis on the human epidermal growth factor receptor 2 (HER2) test.

Methods. A total of 566 clinicopathological samples from patients who were diagnosed with gastric adenocarcinoma were retrospectively analyzed. We comprehensively compared the clinicopathological features of oesophagogastric junction adenocarcinoma between the fourth (V4.0) and fifth (V5.0) WHO versions. The clinicalpathological features among oesophagogastric junction, proximal and distal gastric tumors with fourth and fifth edition were also compared, respectively. Also, we discuss the correlation of HER2-expression with clinicopathological features according to the V5.0.

Results. The results showed that the difference was mainly between oesophagogastric junction and distal adenocarcinoma in V4.0, while some were found between proximal and distal adenocarcinoma in V5.0. Tumors invading the oesophagus more than 3cm were still mainly oesophagogastric junction tumors. The expression of HER2 in oesophagogastric junction and proximal gastric adenocarcinoma was still higher than that in gastric body and distal sites.

Conclusions. The clinicopathological parameters of the oesophagogastric junction tumors changed to some extent in the updated WHO version. The proximal gastric tumors tended to be more invasive than those located in oesophagogastric junction. But the latter with oesophageal invasion required additional management. The HER2-expression of oesophagogastric junction adenocarcinoma is the highest. The classification of V5.0 is reasonable and worth recommendation.

Key words: Oesophagogastric junction adenocarcinoma, Siewert's classification, Nishi's classification, The fifth WHO classification, Epidermal growth factor receptor 2 (HER2)

Introduction

Gastric cancer is the fifth most common cancer worldwide and adenocarcinoma of the oesophagogastric junction has drawn considerable attention because of its remarkable increasing incidence (Cowan et al., 2018). Compared with oesophageal and gastric carcinoma, oesophagogastric junction adenocarcinoma requires different surgical procedures, as well as lymph node dissection. The location of pathological anatomy was considered the most accurate after operation, but the definition of oesophagogastric junction adenocarcinoma remains controversial in the last decades. Siewert (Siewert and Stein, 1998) has classified oesophagogastric junction adenocarcinoma into three types, including type I with its epicentre 1-5 cm above the oesophagogastric junction, type II with its epicentre between 1 cm above and 2 cm below the junction, and type III with its epicentre 2-5 cm distal from the junction. Meanwhile, Nishi (Nishi et al., 1978) proposed

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Abbreviations. WHO, World Health Organization; HER2, human epidermal growth factor receptor 2; V4.0, fourth version; V4.0, fourth version; CT, computed tomography; HE, hematoxylin and eosin-stained; MMR, mismatch repair protein; MSS, microsatellite stability; MSI-H, microsatellite instability of high frequency; FISH, Fluorescence in situ hybridization.

that oesophagogastric junction tumor is located 2 cm above and 2 cm below the oesophagogastric junction, regardless of its different histological subtype. Except in Japan, Siewert's classification has been widely used to distinguish the oesophagogastric junction adenocarcinoma and recommended in the fourth World Health Organization (WHO) classification (V4.0) of tumors of the digestive system.

In 2019, the fifth WHO classification (V5.0) of tumors of the digestive system redefined the oesophagogastric junction adenocarcinoma as having its epicentre from 5 to 2 cm, showing almost no difference with Nishi's classification (Nagtegaal et al., 2020). The new definition of oesophagogastric junction adenocarcinoma is similar to Siewert II. Efforts have been made to discuss the difference of clinicopathological features among the three Siewert subtypes, but with no consistent conclusion (Feith et al., 2006; Suh et al., 2012). Moreover, when compared with distal gastric tumors, oesophagogastric junction adenocarcinoma was associated with worse outcome (Costa et al., 2016). Therefore, a detailed and comprehensive analysis among the clinicopathological features is necessary, not only between the V4.0 and the V5.0 for oesophagogastric junction adenocarcinoma, but also between the gastric and oesophagogastric junction adenocarcinoma.

Besides, it is now increasingly clear that human epidermal growth factor receptor 2 (HER2) should be detected routinely to identify patients who may benefit from the target therapy of trastuzumab, which has been proposed in the V5.0 (Nagtegaal et al., 2020). HER2 is a pro-oncogene encoded by erbB2 on chromosome 17 and its amplification may result in angiogenesis, tumorigenesis and excessive cell growth in several tissues (Roskoski, 2014). The HER2-amplication rate exhibits a great discrepancy, which varies with an extremely wide range, from 4 to 53% (median, 20.2%) (Maresch et al., 2012; Abrahao-Machado et al., 2016). Previous studies showed that HER2-expression was heterogeneous in gastric or oesophagogastric junction adenocarcinoma (Oono et al., 2018; Roy et al., 2019), thus it is important to review HER2 status and its correlating clinicopathological features according to V5.0.

In this study, we compared the clinicopathological features between gastric and oesophagogastric junction adenocarcinoma with V4.0 and V5.0, respectively. With that, we sought to assess the relationship between clinicopathological features and HER2-expression with V5.0, aiming to make an in-depth and comprehensive understanding about the V5.0 for oesophagogastric junction adenocarcinoma.

Materials and methods

Case Selection

A retrospective analysis was conducted. A total of 566 patients were included, among which, 464 were gastric adenocarcinoma and the remainder were oesophagogastric junction adenocarcinoma (V4.0). All patients received radical resection of the tumor at Sichuan Cancer Hospital & Institute between 2016 and 2019. Patients who received neoadjuvant therapies were excluded. The study was approved by the ethics committee of Sichuan Cancer Hospital.

Histological evaluation

Using a multi-headed microscope, hematoxylin and eosin-stained (HE) sections from surgical excisions of specimens in all cases were reviewed by two pathologists. 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 consistent with the AJCC eighth edition (Agnes et al., 2020). Moreover, the sites of lymph node metastasis included four groups: lower mediastinal/periesophageal (No110-No.112), perigastric (No.1-No.6), suprapancreatic (No.7-No.11), para-aortic (No.16) (Yamashita et al., 2017). The sites of lymph node metastasis were divided into three classifications: none (0), periesophageal (1), more than periesophageal and perigastric (≥2).

Immunohistochemistry

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 (Hofmann et al., 2008) was set as the criteria. HER2 status was considered negative (HER2-) with scores of 0 and 1 (No membranous reactivity in <10% or faint or barely perceptible reactivity in ≥10% of tumor cells). HER2 with a score of 3 (strong and complete basolateral membranous reactivity in ≥10 of tumor cells) was considered HER2-amplification (Fig. 1). HER2 status with the score of 2 was considered positive unless tested for gene amplification. The status of microsatellites was evaluated by four markers of mismatch repair protein (MMR), including microsatellite stability (MSS) with four positive markers and microsatellite instability of high frequency (MSI-H) with deficiency of more than two markers (Chaves et al., 2000).

Fluorescence in situ hybridization (FISH)

The levels of HER2 amplification were tested with

the cases whose immunohistochemistry 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 (Wolff et al., 2007). Cases were considered gene amplified for the HER2/CEP17 ratio of more than 2.2 (Fig. 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

Data was analyzed with SPSS software for Windows, Version 20. The clinicopathological parameters were collected according to a standardized protocol. The Mann-Whitney U test and Kruskal-Wallis test were performed to assess the difference of clinicopathological features among oesophagogastric junction adenocarcinoma, proximal and distal gastric tumors. The difference of clinicopathological features between oesophagogastric junction adenocarcinoma of V4.0 and V5.0, and the correlation between clinicopathological features and HER2-expression were evaluated with the Mann-Whitney U test and Fisher's exact test. P-value <0.05 was considered significantly different.

Results

Comparison of the clinicopathological features of gastric (proximal gastric, gastric body and distal gastric) and oesophagogastric junction adenocarcinoma between V4.0 and V5.0

All 566 patients were divided into different groups according to the location of the disease. The clinicopathological features of gastric (proximal gastric, gastric body and distal gastric) and oesophagogastric junction adenocarcinoma (V4.0 and V5.0) are summarized in Table 1. In V4.0, there was no significant difference in patient age, histological type, degree of differentiation, M-classification and HER2-status between gastric and oesophagogastric junction adenocarcinoma. Compared with distal gastric cancer, oesophagogastric junction adenocarcinoma was associated with larger tumor (P<0.001), higher T classification (P<0.001), and more frequent nodal metastases (P=0.011). In addition, oesophagogastric junction adenocarcinoma had more lymph node metastasis than gastric body (P=0.015) and distal gastric tumors (P=0.006). There was no difference in other parameters among oesophagogastric junction, proximal gastric and gastric body adenocarcinoma. HER2 status was merely different between proximal and distal gastric (P=0.001).

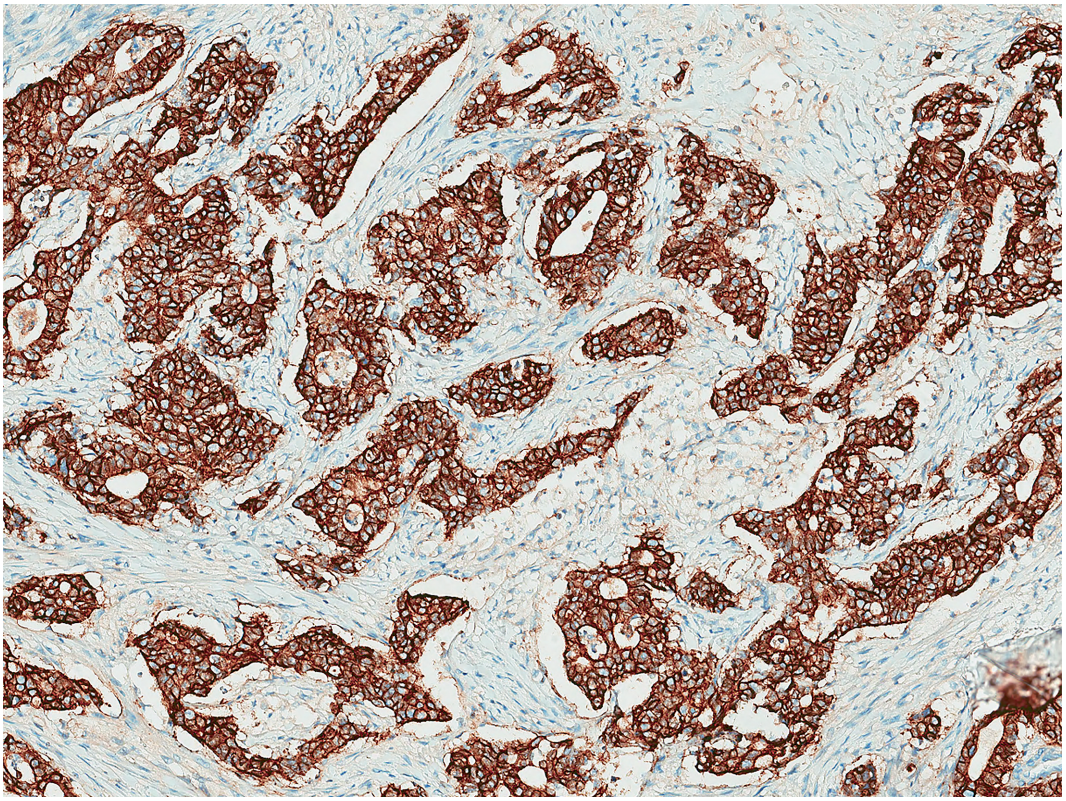

Fig. 1: HER2-immunohistochemistry of score 3 showed strong and complete basolateral membranous reactivity in 90% adenocarcinoma cells (≥10 of tumor cells), which was considered as HER2-amplification. × 100.

According to the new version (V5.0), there was no significant difference in patient age, histological type, N classification, M classification, sites of lymph node metastasis and HER2 status between gastric and oesophagogastric junction adenocarcinoma. Compared with proximal gastric, oesophagogastric junction adenocarcinoma had a higher degree of differentiation (P=0.029). Besides, although oesophagogastric junction tumors were smaller than proximal gastric (P=0.041) and gastric body (P=0.032), it had more advanced T classification than distal gastric (P=0.012) tumors. The comparison of HER2 status was consistent with that in V4.0, suggesting significant difference was only detected between proximal and distal gastric adenocarcinoma (P=0.021).

Difference of clinicopathological features of oesophagogastric junction adenocarcinoma between V4.0 (group 1) and V5.0 (group 2)

In order to have a more comprehensive understanding of the impact of the change in the definition of oesophagogastric junction adenocarcinoma, we selected 103 patients with oesophagogastric junction adenocarcinoma and compared the clinicopathological features between the fourth and fifth edition of oesophagogastric junction adenocarcinoma (Table 2). All cases of oesophagogastric junction adenocarcinoma were divided into two groups: group 1was diagnosed with V4.0 criteria, within 2 to 5 cm from oesophagogastric junction, while group 2 was diagnosed with V5.0 criteria, within 2 cm from oesophagogastric junction. There were 45 (44%) cases of group 1 and 57 (56%) cases of group 2. Candidates in group 2 showed smaller tumor (P<0.001), earlier T classification (P=0.021) and N classification (P=0.035). There was no significant difference in other parameters between the two groups.

Correlation between HER2 status and clinicopathological characteristics of all 566 cases

We evaluated the association between HER2 status

Table 1. Comparison of the clinicopathological features of gastric (proximal gastric, gastric body and distal gastric) and oesophagogastric junction adenocarcinoma between V4.0 and V5.0.

	Location				P value			
	EGJ (V4.0/V5.0)	Proximal (V4.0/V5.0)	Body	Distal	EGJ vs Proximal (V4.0/V5.0)	EGJ vs Body (V4.0/V5.0)	EGJ vs Distal (V4.0/V5.0)	Proximal vs Distal (V4.0/V5.0)
Age								
≤59	29/15	29/43	57	103	1.000/1.000	0.411/1.000	0.082/0.693	0.052/0.012
>59	73/42	82/113	81	112				
Sex								
Male	85/11	93/132	101	152	1.000/1.000	0.258/0.304	0.005/0.018	0.001/0.000
Female	17/46	18/24	37	63				
Lauren histologic								
Intestinal	57/33	73/97	84	117	0.181/0.900	0.737/0.826	0.489/0.264	0.183/0.102
Mixed	28/18	22/32	25	47				
Diffuse	17/6	16/27	29	51				
Degree of differentiation								
Low-Moderate	34/15	55/82	43	78	0.087/0.029	1.000/1.000	1.000/1.000	0.113/0.169
High	68/42	56/82	95	137				
Tumor diameter								
≤4	44/36	58/64	57	154	1.000/0.041	1.000/0.032	0.000/1.000	0.005/0.000
>4	58/21	53/90	81	61				
T-classification								
≤T2	11/10	27/28	36	82	0.164/1.000	0.053/1.000	0.000/0.012	0.049/0.000
≥T3	91/47	84/128	102	133				
N-classification								
≤N1	46/31	65/80	72	137	0.288/0.690	1.000/0.779	0.011/0.198	1.000/0.017
≥N2	56/26	46/76	66	78				
M-classification								
M0	87/9	12/138	121	195	0.394/0.410	0.592/0.518	0.152/0.159	0.665/0.484
M1	15/48	99/18	17	20				
Sites of lymph node metastasis								
None	18/12	37/42	47	94	1.000/1.000	0.015/0.250	0.006/0.188	0.125/0.009
Periesophageal	70/38	47/79	86	86				
More than two	14/7	27/34	5	35				
HER2								
Negative	84/43	81/123	120	24	0.575/1.000	1.000/0.280	0.548/0.087	0.001/0.021
Positive	19/14	30/35	18	24				

and clinicopathological features among all 566 cases and the cases were divided according to the criteria of V5.0 (Table 3). The incidence of HER2-expression in oesophagogastric junction (25%) and proximal gastric (22%) were dramatically higher than gastric body (13%) and distal gastric (11%) tumors (P=0.001). HER2-positivity was more common in low-moderate differentiation cases than the higher ones (P<0.001). Moreover, tumors of HER2-expression were distinctly associated with larger tumor (P<0.001) and more advanced M classification (P=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

In V5.0, the definition of oesophagogastric junction adenocarcinoma was the same as Nishi's classification in addition to emphasis on adenocarcinoma. The change in the definition of oesophagogastric junction tumors is very important for clinicopathological assessment and clinical management, such as the surgical dissection procedure.

In this study, we compared the clinicopathological features between gastric and oesophagogastric junction adenocarcinoma with V4.0 and V5.0, respectively. The oesophagogastric junction adenocarcinoma had more advanced T-classification than distal gastric adenocarcinoma with the criteria of both the V4.0 and V5.0. This was concurred by previous studies, that proximal (oesophagogastric junction and cardia) tumors were associated with poor outcomes (Kattan et al., 2003; Talamonti et al 2003). However, there were still some changes between the clinicopathological features of V4.0 and V 5.0. When compared with V4.0, the differences of N-classification and the sites of lymph node metastasis were mainly focused on oesophagogastric junction and distal gastric adenocarcinoma. But these differences were mainly found on proximal gastric and distal gastric adenocarcinoma with the V5.0. This was perhaps because the oesophagogastric junction tumors of 2cm-5cm from the oesophagogastric junction with V4.0 were classified to the proximal gastric tumors in the V5.0. The majority of patients were found to have more lymph node involvement in the Siewert III (Barbour et al., 2007), which was consistent with our results. Based on these findings, the Siewert III tumors were no longer included in oesophagogastric junction adenocarcinoma and the treatment for oesophagogastric junction tumors needs to be updated. Total gastrectomy or more extensive distal gastric lymph node dissection may not be considered. On the other hand, the scope of proximal gastric tumors also changed, which statistically exhibited larger tumor, more advanced T-classification and N-classification than distal gastric adenocarcinoma. Thus,

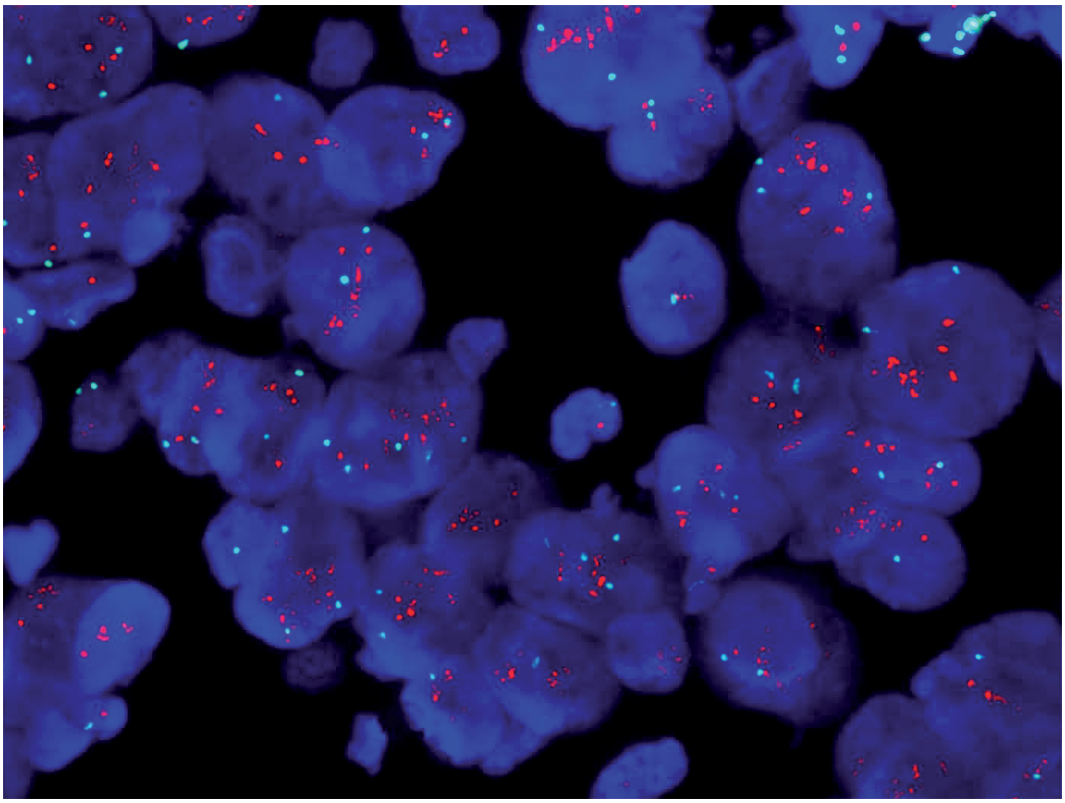

Fig. 2. FISH result showed case with HER2/CEP17 ratio of more than 2.2 was considered HER2 gene amplified. The red signal represented HER2, the blue signal represented CEP17. x 1,000.

proximal gastric tumors, rather than oesophagogastric junction adenocarcinoma, may have worse survival and need more aggressive treatment.

Furthermore, we also compared the clinicopathological features between the V4.0 (group 1) and V5.0 (group 2) of oesophagogastric junction adenocarcinoma. The data showed the group 2 had smaller tumor, and earlier T-classification and N-classification than group 1. It seemed that group 1 was less invasive. Notably, the extent of lymph node dissection in the mediastinum and the choice of distal esophagectomy were of great importance in the treatment for oesophagogastric junction adenocarcinoma. A multicenter retrospective study indicated only the distance from the oesophagogastric junction was significantly related to metastasis. The longer the distance is, the higher rate of lymph node metastasis is (Hosokawa et al., 2012). In the newer version, the distance of oesophagogastric junction adenocarcinoma was smaller, which supported that oesophagogastric junction adenocarcinoma was less likely to have lymph node involvement. Besides, some studies suggested the extent of upper or middle mediastinal lymphadenectomy was for oesophageal invasion of ≥ 3 cm (Koyanagi et al., 2018; Kumamoto et al., 2020). Group 2 had a higher rate than older ones in terms of the extent of oesophageal invasion of ≥ 3 cm, which showed that oesophagogastric junction adenocarcinoma need upper or middle mediastinal lymphadenectomy. With that, we compared the difference of mediastinal lymph node involvement between the two groups. The proportion of group 2 (57%) were slightly higher than group 1, but with no statistical difference. This may be due to the lack of an accurate assessment of the extent of oesophageal invasion before operation and the incomplete extent of lymph node dissection.

Table 2. Difference of clinicopathological features of oesophagogastric junction adenocarcinoma between V4.0 (group 1) and V5.0 (group 2).

	Overall 103	Group 1 (%) 45 (43.7)	Group 2 (%) 57 (55.3)	P-value
Age				0.596
≤59	29	14 (48.3)	15 (51.7)	
> 59	73	31 (42.5)	42 (57.5)	
Sex				0.424
Male	85	39 (45.9)	46 (54.1)	
Female	17	6 (35.3)	11 (64.7)	
Lauren histologic				0.337
Intestinal	57	24 (42.1)	33 (57.9)	
Mixed	28	10 (35.7)	18 (64.3)	
Diffuse	17	11 (64.7)	6 (35.3)	
Degree of differentiation				0.092
Low-Moderate	34	9 (26.5)	15 (44.1)	
High	68	26 (38.2)	42 (61.8)	
Tumor diameter				0.000
≤4	44	8 (18.2)	36 (81.8)	
>4	58	37 (63.8)	21 (36.2)	
Esophageal invasion				
≤3	91	44 (48.4)	47 (51.6)	0.011[a]
>3	11	1 (9.1)	10 (90.9)	
T-classification				0.021[a]
≤T2	11	1 (9.1)	10 (90.9)	
≥T3	91	44 (48.4)	47 (51.6)	
N-classification				0.035
≤N1	46	15 (32.6)	31 (67.4)	
≥N2	56	30 (53.6)	26 (46.4)	
M-classification				0.729
M0	87	39 (44.8)	48 (55.2)	
M1	15	6 (40)	9 (60)	
Sites of lymph node metastasis				0.323
0	18	6 (33.3)	12 (66.7)	
1	70	32 (45.7)	38 (54.3)	
≥2	14	7 (50)	7 (50)	
Periesophageal lymph node metastasis				0.897
Negative	81	36 (44.4)	4 5(55.6)	
Positive	21	9 (42.9)	12 (57.1)	
Lymphovascular invasion				0.989
Negative	25	11 (44)	14 (56)	
Positive	77	34 (44.2)	43 (55.8)	
HER2 status				0.085
Negative	83	40 (48.2)	43 (51.8)	
Positive	19	5 (26.3)	14 (73.7)	

[a]: Fisher's exact test

Table 3. Correlation between HER2 status and clinicopathological characteristics of all 566 cases.

	Overall	HER2+	HER2-	P-value
Lauren histologic				0.181
Intestinal	331	58 (17.5)	273 (82.5)	
Mixed	122	13 (10.7)	102 (83.6)	
Diffuse	113	20 (17.7)	100 (88.5)	
Degree of differentiation				0.000
Low-Moderate	210	50 (23.8)	160 (76.2)	
High	356	41 (11.5)	31 5(88.5)	
Tumor diameter				0.001
≤4	313	36 (11.5)	277 (88.5)	
>4	253	55 (21.7)	198 (78.3)	
T-classification				0.120
≤T2	156	19 (12.2)	137 (87.8)	
≥T3	410	72 (17.6)	338 (82.4)	
N-classification				0.137
≤N1	320	45 (14.1)	275 (85.9)	
≥N2	246	46 (18.7)	200 (81.3)	
M-classification				0.039
M0	502	75 (14.9)	427 (85.1)	
M1	64	16 (25)	48 (75)	
MMR				0.337[a]
negative	19	1 (5.3)	18 (94.7)	
positive	547	9 (1.6)	457 (83.5)	
KI67				0.246
1	212	39 (18.4)	173 (81.6)	
2	354	52 (14.7)	302 (85.3)	

[a]: Fisher's exact test

HER2 test is another significant point which was formally recommended in the V5.0. Its expression and relevant clinicopathological features have been well studied in previous research with Siewert's classification (Madani et al., 2015; Grillo et al., 2016). A Japanese study indicated that HER2-overexpression was not associated with tumor location with Siewert's classification (Oono et al., 2018). An Italian study also showed HER2 amplification was not correlated with tumor location and prevailed in intestinal-type and low-grade tumors (Cappellesso et al., 2015). On the contrary, we re-evaluated the clinicopathological features of the 566 cases with their HER2 status, using V5.0. The HER2-expression in oesophagogastric junction and proximal tumors were statistically higher than that in body and distal tumors, which was consistent with some studies (Shan et al., 2013; Madani et al., 2015). This was perhaps because we used the latest classification to compare the HER2 status of different sites and chose a small sample size. Our results demonstrated oesophagogastric junction tumors had a higher expression of HER2 than body and distal tumors even if the scope of oesophagogastric junction adenocarcinoma was narrowed with the new criterion. This should be critical to emphasize the HER2 test in oesophagogastric junction adenocarcinoma. In addition, our analyses showed a statistically significant association between HER2-expression and pathological grade, tumor diameter and M-classification for gastric tumors. HER2-expression tumors had poor differentiation, larger diameter and more metastasis than HER2-negative ones, which indicated that HER2-expression tumors were more aggressive. These results were consistent with previous studies (Rajagopal et al., 2015). Therefore, the relevant clinicopathological features of HER2-expressing oesophagogastric junction adenocarcinoma remained unchanged in the V5.0. The status of microsatellites was another significant molecular test in gastric carcinoma, which was related to the contraction or expansion or of microsatellite sequences owing to the replication errors caused by mutations in the mismatch repair (MMR) in most cases (Shokal and Sharma, 2012). Patients with deficiency of more than two markers of mismatch repair protein were considered microsatellite instability of high frequency (MSI-H). More than 30% patients with MSI-H were likely to develop Lynch syndrome. Even though there was no statistically significant difference between microsatellite status and HER2-expression, only one of the 19 MSI-H cases showed positive for HER2, while another 18 cases were all negative for HER2. This demonstrated that the HER2-expression cases probably did not suffer from MSI-H, but further verification is required.

Conclusions

The clinicopathological parameters of the oesophagogastric junction adenocarcinoma changed in the updated WHO classification. The analyses showed that the difference was mainly between proximal and distal adenocarcinoma and the proximal gastric tumors seem to be more invasive than oesophagogastric junction in the newer version. Although the treatment tends to be more unified and standardized, the oesophagogastric junction tumors with extent of oesophageal invasion more than 3cm required additional management. The HER2-expression of oesophagogastric junction adenocarcinoma is still higher than that of other sites of gastric adenocarcinoma in the updated version. Therefore, the emphasis on the detection of HER2 in oesophagogastric junction tumors is of great significance in clinical practice. The overall analyses showed it is reasonable to recommend the updated V5.0 in pathological diagnosis, as well as clinical practice.

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Competing interests. The author(s) declared no potential conflicts of interest.

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