

Evaluation of Gastric Carcinomas Histological Patterns in Relation to Tumors Aggressiveness Parameters

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ABSTRACT: Gastric carcinomas are frequent tumors with variable growth patterns that may interfere with the evaluation of histopathological prognostic parameters of the lesions. In this study we analyzed the incidence and statistical relation of histological growth patterns depending on the prognostic parameters of gastric carcinomas for 95 cases. Pure forms were present in 82.2% of cases, from which more frequent subtypes were low grade tubular carcinomas and poorly cohesive with signet-ring cells carcinomas. Mixed forms were present in 17.8% of cases, with the highest incidence of tumors containing well differentiated tubular carcinoma and poorly differentiated papillary carcinoma areas. Analysis of the identified types and subtypes in relation to the histological prognostic parameters indicated significant differences regarding the tumor stage, the mixed subtypes being more frequent in advanced stages. Although mixed subtypes were more commonly associated with vascular and perineural invasion, the aspects were statistically insignificant. Together with tumor stage, the lymphovascular and/or perineural invasion should be taken into consideration as prognostic indicators in the postoperative management of gastric cancer.

KEYWORDS: Gastric carcinoma, histological pattern, prognostic parameters

Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of mortality from this disease worldwide [1,2]. Although the incidence of gastric cancer has declined gradually over the last half century, the proximal gastric cancer incidence is growing [3].

Histopathologically, gastric carcinoma exhibits a marked architectural and cytological heterogeneity, often with the coexistence of multiple aspects. World Health Organization (WHO) classification recognizes four major histological patterns of gastric cancers: tubular, papillary, mucinous and poorly cohesive, along with some less uncommon histological variants [4]. The classification into these different subtypes is based on the dominant histological pattern, which often coexists with other histological patterns. The histopathological type is one of the major prognostic factors for carcinomas, which underlies the basic surgical management and consequently the extent of the surgical resection [5,6]. However, for gastric cancer, the prognostic value of the growth pattern has not been consistently recognized.

The mixed histological type accounts for about 25% of all gastric cancers, the coexistence of different histological patterns determining the

behavior and prognosis as compared to pure forms of this neoplasia [7,8].

The present study followed the association of various histological patterns of gastric cancer with prognostic severity factors such as vascular and perineural invasion as well as tumor stage.

Material and methods

The present study included a number of 95 cases of gastric carcinomas. The biological material was represented by surgical excision specimens obtained from the Surgical Clinics of the Emergency County Hospital of Craiova, which were fixed in 10% neutral buffered formalin, then processed by automated tissue processor (BioOptica) and hematoxylin-eosin stained. Interpretation and acquisition of images was performed using the Nikon E600 microscope. Tumors classification and staging was done according to the latest WHO classification [4].

The lymphovascular invasion was defined by the presence of cancer cells in the endothelium-lined area, and the peri/intraneural invasion was defined by the presence of peri/intraneural cancer cells.

The study was approved by the local ethical committee (no. 201/24th October 2017), and written informed consent was obtained from all the patients.

Results

The analyzed 95 cases of gastric carcinomas corresponded in 78 cases (82.2%) to pure forms and in 17 cases (17.8%) to mixed forms of the tumors (Table 1). The pure forms of tumors took the aspect of low-grade tubular carcinoma (35.7%) or poorly cohesive, with signet-ring cells carcinoma (18.9%) and poorly cohesive without signet-ring cells forms (12.6%). These were followed in the frequency order by high grade tubular carcinomas and papillary carcinomas of low or high grade. Mixed carcinoma forms have associated two tumor growth patterns in different proportions. Thus, we found more frequent tumors containing low grade tubular carcinoma areas and poorly differentiated papillary (9.5%) or high grade papillary and poorly cohesive areas (7.4%), and rarely the mucinous and poorly cohesive association pattern.

The classification of tumors analyzed in the pTNM staging system revealed for the pure forms carcinomas stage I eight cases (10.3%), 37 cases (47.4%) in stage II, 31 cases in stage III (39.7%) and two cases in stage IV (2.6%). Regarding the mixed forms, we found six cases in stage I (35.3%), nine cases in stage III (52.9%) and two cases in stage IV (11.8%). Tumor staging analysis based on the number of tumors with pure or mixed growth patterns indicated a higher incidence of the advanced

stages (III and IV) for mixed forms (58.8%) compared to pure forms (42.3%).

The lymphovascular invasion was identified in 32 cases, representing 33.6% of the investigated cases. This aspect was observed in 12 cases of tubular low grade carcinomas (33.3%), in three cases for each of papillary high grade carcinomas (60%), poorly cohesive carcinomas with and without signet-ring cells (20%) and in two cases of mucinous carcinomas (50%). For subtypes of tubular high grade, mucinous and mixed with papillary high grade and signet ring cells, we found two cases of lymphovascular invasion for each form, as well as for the mixed form with mucinous carcinoma and signet ring cell carcinoma areas.

Related to the number of pure or mixed growth pattern carcinoma cases, the incidence of lymphovascular invasion was slightly higher in mixed forms (35.2%) compared to the pure ones (32%).

The peri-or intraneural invasion was present in 29 cases with an aspect of fascicle disposal of cancer cells in peri-or intraneural areas. In most cases the tumors corresponded to pure forms, respectively in 23 cases and in six cases to mixed forms. However, related to the number of cases, we noticed that 29.5% of pure carcinomas associated the peri/intraneural invasion compared with the mixed tumors which had this aspect in 35.2% of cases.

Table 1. Histopathological parameters depending on carcinomas growth pattern

Growth pattern		TNM stage				Lympho-vascular invasion	Peri /intraneural invasion
		I	II	III	IV		
Pure (PGC)	tubular low grade (TGC-LG)	6	20	8	0	12	9
	tubular high grade (TGC-HG)	0	2	2	1	3	2
	papillary low grade (PGC-LG)	2	0	0	0	0	0
	papillary high grade (PGC-HG)	0	0	3	0	3	3
	mucinous (MGC)	0	2	2	0	2	2
	poorly cohesive without signet ring cells (PC-GC)	0	5	7	0	3	3
	poorly cohesive with signet ring cells (PC-GCS)	0	8	9	1	3	4
Mixed (MGC)	tubular low grade and papillary high grade (MGC-TP)	0	4	5	0	3	3
	papillary high grade and poorly cohesive signet ring cells (MGC-PS)	0	2	4	1	2	3
	mucinous and poorly cohesive signet ring cells (MGC-MS)	0	0	0	1	1	0
Total		8	43	40	4	32	29

In this study, the statistical analysis of histopathological parameters related to the mixed or pure type of lesions indicated insignificant differences ($p > 0.05$, χ^2 test), although the advanced stage, lymphovascular and peri-/intraneural invasion were more common in mixed carcinomas (Fig. 1A-C).

The statistical analysis of mixed and pure carcinomas subtypes depending on the histopathological parameters indicated

significant differences related to tumor stage ($p < 0.001$, χ^2 test), the mixed subtypes being more commonly diagnosed in stages II-IV compared to pure subtypes, frequently diagnosed in stages I-III (Fig. 1D).

On the contrary, although mixed subtypes were more often associated with lymphovascular and peri-/intraneural invasion, the aspects were statistically insignificant (Fig. 1E-F).

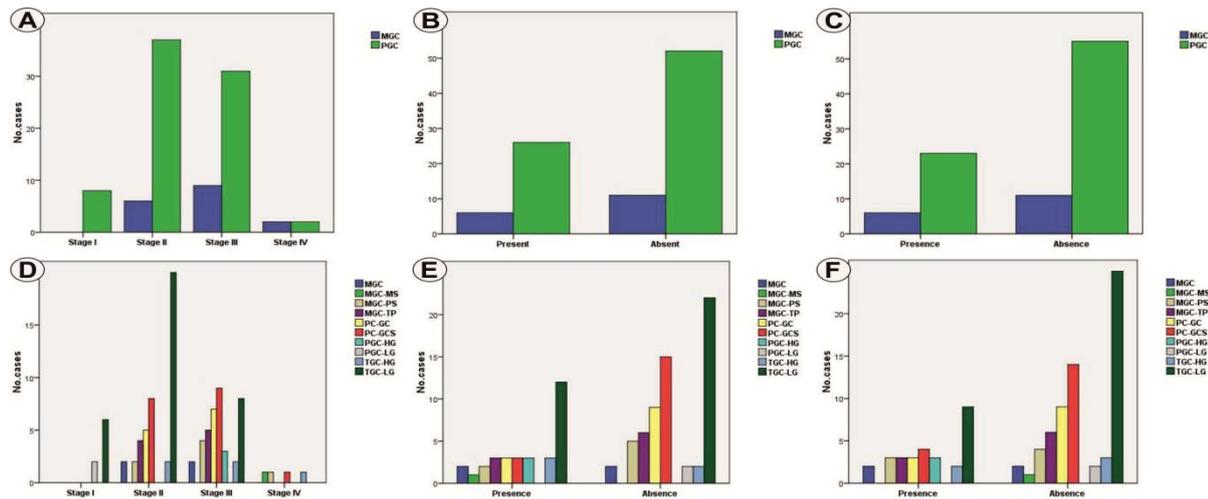


Fig.1. Cases distribution related to tumor type and stage (A), lymphovascular invasion (B) and peri-/intra-neural invasion (C). Cases distribution related to tumoral subtype and stage (D), lymphovascular invasion (E) and peri-/intra-neural invasion (F)

Discussions

The practical value of some of the histopathological variables is limited due to the histological complexity of the various growth patterns of gastric carcinomas, and especially of their coexistence, which often leads to an ambiguity in assessing the biological behavior [9,10].

It is generally accepted the fact that in the treatment guidelines the histological type is defined as one of the crucial factors in determining the need for practicing lymphadenectomy [11,12], as well as chemotherapy for advanced gastric cancer. Several studies have been concerned with identifying a more accurate stratification of prognosis for patients with gastric carcinoma based on morphological criteria [13-16].

A special place in the two most commonly used classifications of gastric cancer, WHO and Lauren classifications, is occupied by mixed carcinomas, which in various studies have been reported with variable incidence. Thus, in our study, mixed carcinomas represented 17.8% of all cases, compared to other studies that reported incidences of 21.9% [14], 13% [17], 14% [18], 14.1% [15], 27.2% [19] and 38.5% [20].

Concerning the results on mixed-type gastric cancer, several studies reported that it is associated with in lymph nodes metastasis [21-23] and large size tumors [24].

Analyzing the incidence of the histopathological negative prognostic factors, such as advanced stage, lymphovascular and peri-/intra-neural invasion related to the mixed or

pure tumor growth patterns, we observed for all the analyzed histopathological parameters a higher incidence in the mixed forms compared to the pure ones. Thus, the advanced stages (III/IV) of the tumors were present in 64.7% of the mixed forms cases and in 42.3% of the pure ones. For lymphovascular invasion, we found an incidence of 35.2% in mixed pattern cases, compared to 32% for pure ones, and for peri-/intra-neural invasion an incidence of 29.5% in pure carcinomas versus 35.2% in mixed forms. Moreover, for 25 cases we found the presence of both lymphovascular and peri-/intra-neural invasion, with an incidence of 29.4 in the mixed growth pattern tumors compared to 26.9% in the pure ones.

In gastric cancers, it was proven that the pTNM stage had a prognostic significance for both the 5 years survival rate and the local recurrence rate [25].

The lymphovascular invasion is an unfavorable prognostic indicator, its presence providing useful information for the prognosis and clinical management of patients with gastric carcinoma regardless of the disease stage [26].

Several studies have shown that the presence of lymphovascular invasion is correlated with tumor recurrence and a low survival rate independently of the lymph node status [27-32].

The incidence of lymphovascular invasion in gastric cancer ranges from 5.4% to 86%, the lowest incidence being reported in patients with lymph node negative tumors [33,34].

Several studies have shown that lymphovascular invasion is an unfavorable prognostic indicator independent of the

clinical-pathological factors of gastric cancer without lymph node metastasis, concluding that this parameter invasion can provide useful information for prognosis and clinical management in the subgroup of patients with gastric cancer and lymph node metastasis [33,35].

Kooby DA et al. reported that vascular invasion in patients with negative lymph node was an independent predictor of unfavorable evolution and identified more aggressive lesions independent of tumor size and depth of invasion [36].

The combination of traditional TNM staging and the assessment of lymphovascular invasion could lead to a more accurate indication for the patient's prognosis [37].

On the other hand, perineural invasion is an independent prognostic factor that affects overall survival and disease-free survival of gastric cancer patients undergoing curative resection, independently of lymph node status, tumor size, and depth of invasion [38].

Several studies have reported that lymphovascular or perineural invasion is associated with poor survival and/or early recurrences in gastric cancer, but only a small number of studies compared the prognostic superiority of lymphovascular and perineural invasion association [39-42].

Conclusions

In mixed type gastric carcinomas, the negative prognostic factors, represented by the advanced stage, lymph-vascular invasion and peri-/intra-neural invasion have a higher incidence compared to pure forms.

As a result, alongside the tumor stage, lymphovascular and/or intra-/perineural invasion should be taken into consideration in the postoperative gastric cancer management, and the concomitant presence of the two parameters may be used as a prognostic factor.

References

1. Parkin DM. International variation. *Oncogene*, 2004, 23(38):6329-6340.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 2010, 127(12):2893-2917.
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. *JAMA*, 1991, 265(10):1287-1289.
4. Lauwers GY, Carneiro F, Graham DY, Curado MP. Tumours of the stomach. In Bosman FT, Carneiro F, Hruban RH, Theise ND (Eds): *WHO Classification of Tumours of the Digestive System*, fourth edition, 2010, IARC Press, Lyon, 45-80.
5. Becker K, Langer R, Reim D, Novotny A, Meyer zum Buschenfelde C, Engel J, Friess H, Hofler H. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. *Ann Surg*, 2011, 253(5):934-939.
6. Liu GY, Liu KH, Zhang Y, Wang YZ, Wu XH, Lu YZ, Pan C, Yin P, Liao HF, Su JQ. Alterations of tumor-related genes do not exactly match the histopathological grade in gastric adenocarcinomas. *World J Gastroenterol*, 2010, 16(9):1129-1137.
7. Lee JH, Kim JH, Rhee K, Huh CW, Lee YC, Yoon SO, Youn YH, Park H, Lee SI. Undifferentiated early gastric cancer diagnosed as differentiated histology based on forceps biopsy. *Pathol Res Pract*. 2013, 209(5):314-318.
8. Takizawa K, Ono H, Kakushima N, Tanaka M, Hasuike N, Matsubayashi H, Yamaguchi Y, Bando E, Terashima M, Kusafuka K, Nakajima T. Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: how to manage the mixed histological type for endoscopic submucosal dissection. *Gastric Cancer*, 2013, 16(4):531-536.
9. Grundmann E, Schlake W. Histological classification of gastric cancer from initial to advanced stages. *Pathol Res Pract*, 1982, 173(3):260-274.
10. Lino-Silva LS, Salcedo Hernández RA, Molina-Frías E. Mixed gastric carcinoma with intestinal and cribriform patterns: a distinctive pathologic appearance associated with poor prognosis in advanced stages and a potential mimicker of metastatic breast carcinoma. *Int J Surg Pathol*, 2013, 21(1):6-14.
11. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*, 2011, 14(2):113-123.
12. Nakajima T. Gastric cancer treatment guidelines in Japan. *Gastric Cancer*, 2002, 5(1):1-5.
13. Zhu Z, Sun X, Wang J, Sun Z, Wang Z, Zheng X, Xu H. Histopathology-based prognostic score is independent prognostic factor of gastric carcinoma. *BMC Cancer*, 2014, 14:663.
14. Zheng H-c, Li X-h, Hara T, Masuda S, Yang X-h, Guan Y-f, Takano Y. Mixed-type gastric carcinomas exhibit more aggressive features and indicate the histogenesis of carcinomas. *Virchows Arch*, 2008, 452(5):525-534.
15. Stelzner S, Emmrich P. The mixed type in Lauren's classification of gastric carcinoma. Histologic description and biologic behavior. *Gen Diagn Pathol*, 1997, 143(1):39-48.
16. Komatsu S, Ichikawa D, Miyamae M, Shimizu H, Konishi H, Shiozaki A, Fujiwara H, Okamoto K, Kishimoto M, Otsuji E. Histological mixed-type as an independent prognostic factor in stage I gastric carcinoma. *World J Gastroenterol*, 2015, 21(2):549-555.
17. Borch K, Jonsson B, Tarpila E, Franzen T, Berglund J, Kullman E, Franzen L. Changing pattern of histological type, location, stage and outcome of surgical treatment of gastric carcinoma. *Br J Surg*, 2000, 87(2):618-626.

18. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand*, 1965, 64(1):31-49.
19. Park HK, Lee KY, Yoo MW, Hwang TS, Han HS. Mixed Carcinoma as an Independent Prognostic Factor in Submucosal Invasive Gastric Carcinoma. *J Korean Med Sci*, 2016, 31(6):866-872.
20. Carneiro F, Seixas M, Sobrinho-Simoes M. New elements for an updated classification of the carcinomas of the stomach. *Pathol Res Pract*, 1995, 191(6):571-584.
21. Watanabe G, Ajioka Y, Kato T. Pathological characteristics of differentiated-type early gastric carcinoma mixed with undifferentiated-type-Status of lymph node metastasis and macroscopic features. *Stom Int*, 2007, 42(11):1577-1587.
22. Tanabe H, Iwashita A, Haraoka S. Clinicopathological characteristics of differentiated mixed-type early gastric carcinoma with lymph node metastasis. *Stom Int*, 2007, 42(11):1561-1576.
23. Iwamoto J, Mizokami Y, Ito M, Shomokobe K, Hirayama T, Honda A, Saito Y, Ikegami T, Matsuzaki Y. Clinicopathological features of undifferentiated mixed type early gastric cancer treated with endoscopic submucosal dissection. *Hepatogastroenterology*, 2010, 57(97):185-190.
24. Hanaoka N, Tanabe S, Mikami T, Okayasu I, Saigenji K. Mixed-histologic-type submucosal invasive gastric cancer as a risk factor for lymph node metastasis: feasibility of endoscopic submucosal dissection. *Endoscopy*, 2009, 41(5):427-432.
25. Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg*, 2005, 24(1):127-139.
26. Du CY, Chen JG, Zhou Y, Zhao GF, Fu H, Zhou XK, Shi YQ. Impact of lymphatic and/or blood vessel invasion in stage II gastric cancer. *World J Gastroenterol*, 2012, 18(27):3610-3616.
27. Mete O, Asa SL. Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. *Mod Pathol*, 2011, 24(12):1545-1552.
28. Bu Z, Zheng Z, Li Z, Zhang L, Wu A, Wu X, Su Y, Ji J. Lymphatic vascular invasion is an independent correlated factor for lymph node metastasis and the prognosis of resectable T2 gastric cancer patients. *Tumour Biol*, 2013, 34(2):1005-1012.
29. Maehara Y, Kabashima A, Koga T, Tokunaga E, Takeuchi H, Kakeji Y, Sugimachi K. Vascular invasion and potential for tumor angiogenesis and metastasis in gastric carcinoma. *Surgery*, 2000, 128(3):408-416.
30. Cao F, Hu YW, Li P, Liu Y, Wang K, Ma L, Li PF, Ni CR, Ding HZ. Lymphangiogenic and angiogenic microvessel density in chinese patients with gastric carcinoma: correlation with clinicopathologic parameters and prognosis. *Asian Pac J Cancer Prev*, 2013, 14(8):4549-4552.
31. Kim JH, Park SS, Park SH, Kim SJ, Mok YJ, Kim CS, Lee JH, Kim YS. Clinical significance of immunohistochemically-identified lymphatic and/or blood vessel tumor invasion in gastric cancer. *J Surg Res*, 2010, 162(2):177-183.
32. Gresta LT, Rodrigues-Junior IA, de Castro LP, Cassali GD, Cabral MM. Assessment of vascular invasion in gastric cancer: a comparative study. *World J Gastroenterol*, 2013, 19(24):3761-3769.
33. Hyung WJ, Lee JH, Choi SH, Min JS, Noh SH. Prognostic impact of lymphatic and/or blood vessel invasion in patients with node-negative advanced gastric cancer. *Ann Surg Oncol*, 2002, 9(6):562-567.
34. Noguchi Y. Blood vessel invasion in gastric carcinoma. *Surgery*, 1990, 107(2):140-148.
35. Lee JH, Kim MG, Jung MS, Kwon SJ. Prognostic significance of lymphovascular invasion in node-negative gastric cancer. *World J Surg*, 2015, 39(3):732-739.
36. Kooby DA, Suriawinata A, Klimstra DS, Brennan MF, Karpeh MS. Biologic predictors of survival in node-negative gastric cancer. *Ann Surg*, 2003, 237(6):828-837.
37. Kikuchi E, Margulis V, Karakiewicz PI, Roscigno M, Mikami S, Lotan Y, Remzi M, Bolenz C, Langner C, Weizer A, Montorsi F, Bensalah K, Koppie TM, Fernández MI, Raman JD, Kassouf W, Wood C, Suardi N, Oya M, Shariat SF. Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. *J Clin Oncol*, 2009, 27(4):612-618.
38. Deng J, You Q, Gao Y, Yu Q, Zhao P, Zheng Y, Fang W, Xu N, Teng L. Prognostic value of perineural invasion in gastric cancer: a systematic review and meta-analysis. *PLoS One*, 2014, 9(2):e88907.
39. Hwang JE, Hong JY, Kim JE, Shim HJ, Bae WK, Hwang EC, Jeong O, Park YK, Lee KH, Lee JH, Cho SH, Chung IJ. Prognostic significance of the concomitant existence of lymphovascular and perineural invasion in locally advanced gastric cancer patients who underwent curative gastrectomy and adjuvant chemotherapy. *Jpn J Clin Oncol*, 2015, 45(6):541-546.
40. Scartozzi M, Galizia E, Verdecchia L, Berardi R, Graziano F, Catalano V, Giordani P, Mari D, Silva RR, Marmorale C, Zingaretti C, Cascinu S. Lymphatic, blood vessel and perineural invasion identifies early-stage high-risk radically resected gastric cancer patients. *Br J Cancer*, 2006, 95(4):445-449.
41. Li P, Ling YH, Zhu CM, Hu WM, Zhang XK, Luo RZ, He JH, Yun JP, Li YF, Cai MY. Vascular invasion as an independent predictor of poor prognosis in nonmetastatic gastric cancer after curative resection. *Int J Clin Exp Pathol*, 2015, 8(4):3910-3918.
42. Kim W, Park CH, Park SM, Park WB, Lim KW, Kim SN. Prognostic Significance of Lymphatic and Perineural Invasions in Patients with Gastric Cancer Who Have No Lymph Node and Serosal Involvement. *J Korean Gastric Cancer Assoc*, 2001, 1(2):77-82.

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