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Original contribution

Predictive value of WHO classification for PD-L1 and Her2/Neu expression and distinct associations with protein expression based classification in gastric carcinoma☆,☆☆

Namrata Setia, MD[a,*], Sangjeong Ahn, MD[b], Hye S Han, MD, PhD[c], Do Youn Park, MD, PhD[d], Gregory Y Lauwers, MD[e]

[a]*Department of Pathology, University of Chicago, IL, USA 60637*
[b]*Department of Pathology, Catholic Kwandong University College of Medicine, International St. Mary's Hospital, Incheon, Republic of Korea 22711*
[c]*Konkuk University School of Medicine, Seoul, South Korea 501-600*
[d]*Department of Pathology, Pusan National University Hospital and Pusan National University School of Medicine, and BioMedical Research Institute, Busan, Republic of Korea 602-739*
[e]*Department of Pathology, H Lee Moffitt Cancer Center and Research Institute, Departments of Oncological Sciences, Pathology and Cell Biology, University of South Florida, Tampa, Florida, USA 33612*

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Summary The Cancer Genome Atlas data on gastric carcinoma has identified four biologic pathways as potential drivers of gastric carcinogenesis and suggested targeted therapies based on the genomic alterations underscoring each subset. The correlation between morphology, biologic groups and their corresponding biomarkers has been eluded in several previous studies; however, a comprehensive analysis in consideration of the recent advancements has not been performed. In this study we explored the predictive value of morphology for biomarker expression and its association with protein expression based classification of gastric carcinoma. Four hundred eighty six gastric carcinomas which had been classified into protein expression-based groups formed the case cohort. Upon analysis, we found a low positive predictive value of an individual morphologic pattern for biomarker-expression, indicating that an individual morphologic pattern alone cannot predict PD-L1, Her2/neu expression and EBV- or MSI-gastric cancer. A combination approach targeting the test in certain WHO patterns can be employed for maximizing the positive predictive values. These include, PD-L1 testing in tubular, carcinoma with lymphoid stroma, undifferentiated and poorly cohesive patterns and Her2/neu testing in tubular, mixed, papillary, mucinous and solid patterns. The predictive values and morphologic associations presented here have the potential to select patients for personalized therapy.

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* Corresponding author at: Department of Pathology University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637.
E-mail addresses: Namrata.Setia@uchospitals.edu (N. Setia, MD), vanitasahn@gmail.com (S. Ahn, MD), 20040002@kuh.ac.kr (H. S. Han, MD, PhD), pdy220@pusan.ac.kr (D. Y. Park, MD, PhD), Gregory.Lauwers@moffitt.org (G. Y. Lauwers, MD).

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1. Introduction

To this date, the therapeutic decisions in most malignancies are guided by the clinical and pathologic stage. However, additional prognostic factors may affect the treatment response in stage-matched individuals [1,2]. In gastric carcinoma, the prognostic significance of tumor histotype has been validated, and although not a staging parameter, tumor morphology has been used for guiding therapy [3]. The two commonly used histologic typing schemes include the Lauren and the World Health Organization (WHO) classification [4,5]. The Lauren classification is a simple three-tiered system that divides gastric carcinoma into intestinal, diffuse and indeterminate subtypes. The WHO classification reflects the "morphologic" heterogeneity of gastric carcinoma and recognizes several less common subtypes not identified in the Lauren classification.

Recent advances in the molecular pathogenesis of gastric carcinoma by The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) have emphasized the "molecular" heterogeneity of the disease [6,7]. The TCGA consortium identified four molecular subtypes of gastric carcinoma based on the biologic pathways involved. These include Epstein-Barr virus (EBV)-related, microsatellite instable (MSI), chromosomal instable (CIN) and genomically stable (GS) gastric carcinomas [6]. ACRG also reports four expression subtypes roughly corresponding to the TCGA subtypes and include MSS (microsatellite stable)/TP53−, MSS/TP53+, MSI, and MSS/EMT (epithelial-to-mesenchymal transition) [7].

Following the success of the ToGA trial, Her2 testing of gastric carcinoma has become routine after Food and Drug Administration (FDA) approved the use of Herceptin (trastuzumab) for treatment of advanced gastric and gastroesophageal carcinoma [8]. In May 2017, the FDA granted an accelerated site-agnostic approval for the use of immunotherapy in the treatment of any advanced mismatch repair-high or mismatch repair-deficient solid tumor [9]. This was followed by yet another accelerated approval of the use of immunotherapy in advanced gastric and gastroesophageal carcinomas in September 2017 [10]. Subsequently, pre-treatment Her2, MSI and PD-L1 testing are now incorporated in the routine diagnostic work-up of gastric carcinoma biopsies in many centers. Although certain morphologic/ biologic correlations have been implied in the TCGA and ACRG classifications, a comprehensive correlation between the exhaustive WHO classification and the molecular classification of gastric cancer has not been performed.

In a previous study, we were able to use *in situ* hybridization and immunohistochemical characterization of tumors to identify tumor subtypes similar to genomic profiling [11,12]. In the current study, we aimed to integrate morphologic subclassification into the protein- and mRNA-based stratification in an effort to pair the readily observable morphology with the biologic types of gastric cancers. We also explored the possibility of predicting biomarker expression in gastric adenocarcinoma based on morphology.

2. Materials and methods

2.1. Tissue samples

The study complied with the Helsinki Declaration and was approved by the Human Ethics Committee. The cohort comprised of 495 primary gastric carcinomas from Western and Korean patients analyzed in the previously reported studies [11,12]. The Western cohort included 146 primary gastric carcinoma resections performed at Massachusetts General Hospital from 1988 to 2007, and the Korean cohort included 349 primary gastric carcinoma resections performed at Pusan National University Hospital from 2005 to 2008. Tissue microarrays were constructed from diagnostic and representative areas after review by gastrointestinal pathologist (H.S.H. and D.Y.P.). The morphological assessment was performed by two GI pathologists (N.S. and G.Y.L.) on 2- to 3-mm cores and 1 to 3 cores per case were obtained. Three hundred forty-nine tumors were represented by two cores, 99 by one core and five by three cores. Tumors with one predominant pattern (forming at least 80% of tumor) were represented by one core only.

The morphologic classification was performed as endorsed by the 2010 WHO classification for gastric cancer. The tumors were subtyped into tubular, papillary, mucinous, poorly cohesive, mixed, carcinoma with lymphoid stroma and undifferentiated patterns. Given the limitation of using TMA, strict 50% rule for mucinous or papillary features and mixed (50% of each subtype) was not used. Tumor grade was assigned where appropriate as grade 1 (well differentiated), grade 2 (moderately differentiated), grade 3 (poorly differentiated), and grade 4 (undifferentiated). Finally, assessment was made for the presence of dense lymphocytic infiltrate in the tumor. The lymphocytic infiltrate was not quantified or further characterized.

The tumors were evaluated using a panel of biomarkers including, EBER-ISH and immunohistochemistry for MMR proteins, E-cadherin and p53. Subsequently, the tumors were classified into 5 protein expression subgroups: (1) EBV-related (EBER-ISH positive), (2) MSI (EBER-ISH negative *and* loss of MMR proteins), (3) Aberrant E-Cadherin (EBER-ISH negative *and* retained MMR proteins *and* loss of membranous E-cadherin expression), (4) Aberrant p53 (EBER-ISH negative *and* retained MMR proteins *and* retained expression of E-cadherin *and* complete loss or overexpression of p53) and, (5) Others (EBER-ISH negative *and* retained MMR proteins *and* retained expression of E-cadherin *and* normal p53).

Correlative analyses were performed between morphologic subtyping, protein expression classification and therapy-related biomarker expression, i.e., Her2/neu and PD- L1 in a subset of cases. The scoring of Her2/neu was performed using CAP/ASCP/ASCO criteria [13]; however, given the limitation of using TMAs, any membranous staining (score 1+ - 3+) was interpreted as positive. PD-L1 was scored as negative (0) if no staining was present and 1+ if any membranous staining of the tumor and/or inflammatory infiltrate at the interface was present. Antibody specifications,

scoring criteria and interpretation of the stains are listed in Supplementary Table 1.

2.2. Statistical analysis

Statistical analysis was performed using SAS statistical software version 9.4. Categorical variables were compared with Spearman correlation coefficients, and a 2-sided P value <.05 was considered statistically significant. The predictive values of each pattern for biomarker expression were calculated using frequency tables in SAS and Vassarstats (http://vassarstats.net/). In addition, pattern combinations with the best positive predictive value (PPV) for biomarker expression were identified.

3. Results

3.1. Distribution of WHO subtypes and protein expression (biologic) groups

Of the 495 tumors analyzed by protein expression classification, 486 tumors had adequate material for morphologic assessment and formed the study cohort. Nine tumors could not be assessed due to an insufficient amount of tissue on the TMA slides. The WHO morphologic patterns included 264 tubular (54.3%), 71 poorly cohesive (14.6%), 63 mixed (12.9%), 32 papillary (6.5%), 26 mucinous (5.3%), 17 carcinoma with lymphoid stroma (3.5%), 4 solid (0.8%) and 9 undifferentiated (1.8%) subtypes. The tumor subtypes, according to the Lauren classification included 311 intestinal (63.9%), 71 diffuse (14.5%) and 104 indeterminate (21.4%).

The 495 cases included 246 adenocarcinomas with aberrant expression of p53 (49.7%), 83 adenocarcinomas with aberrant expression of E-cadherin (16.7%), 33 EBV-gastric cancers (6.7%), 48 MSI-gastric cancers (9.7%) and 85 other (remaining) gastric cancers (17.1%).

3.2. Correlation between WHO subtypes and protein expression (biologic) groups

The distribution of WHO morphologic patterns and protein expression groups is shown in Fig. 1 and discussed below.

3.2.1. EBV-gastric carcinoma

The morphologic pattern of carcinoma with lymphoid stroma was significantly associated with the EBV-gastric carcinoma group ($P < .0001$). However, the morphology associated to this biologic subtype (EBV-gastric carcinoma) was not limited to carcinoma with lymphoid stroma. It also included gastric carcinomas with tubular (20/33; 60.6%), papillary (1; 3%), and undifferentiated carcinomas without lymphoid stroma (1; 3%) patterns. None of the gastric cancers in this group had a poorly cohesive (pure or mixed), mucinous or solid morphologic pattern. Tumor infiltrating lymphocytes (TILs) were prominent in this subgroup and were present in 26/33 cases (78.8% of all EBV-gastric carcinomas vs. 15.8% remaining, $P = .001$).

3.2.2. MSI-gastric carcinoma

MSI-gastric carcinomas characterized by loss of MMR nuclear immunostaining represented a heterogeneous group displaying a wide spectrum of morphologic patterns, including tubular (28/45, 62.2%), papillary (5/45, 11.1%), mucinous (5/45, 11.1%), carcinoma with lymphoid stroma (4/45, 8.9%), solid (2/45, 4.4%) and poorly cohesive (1/45, 2.2%) patterns. Tumor infiltrating lymphocytes were also prominent in this subgroup and were observed in 47% of MSI-gastric carcinomas (i.e., 32 of 45 cases) vs. 18% MSS-gastric carcinomas ($P = .001$).

3.2.3. Gastric adenocarcinoma with aberrant expression of E-cadherin

Adenocarcinomas with aberrant expression of E-cadherin, defined by loss of membranous E-cadherin expression, showed limited morphologic diversity with poorly cohesive or mixed (most common combination, poorly cohesive and tubular) patterns forming a significant proportion of cases (65/82; 79.2% cases, $P < .0001$). Less common morphologic patterns included mucinous (5/82, 6.09%), and rarely tubular (7/82, 8.53%), undifferentiated (4/82, 4.87%) and solid (1/82, 1.2%). Papillary and carcinoma with lymphoid stroma patterns were not observed in this group.

3.2.4. Gastric adenocarcinoma with aberrant expression of p53

Carcinomas with a tubular morphology (n = 156, 64.4%) formed the majority of the gastric cancers with aberrant expression of p53 (n = 242). Other less common morphologic

Others	Ab p53-GC	Ab E-cadherin-GC	MSI-GC	EBV-GC	WHO morphotype	EBV-GC	MSI-GC	Ab E-cadherin-GC	Ab p53-GC	Others
0.0622	<.0001	<.0001	0.4625	0.3817	Tubular	20	28	7	156	53
0.0199	<.0001	<.0001	0.0015	cbd*	Poorly cohesive	0	1	43	21	6
0.1463	0.1477	<.0001	cbd*	cbd*	Mixed	0	0	22	26	15
0.4505	0.0202	cbd*	0.2689	0.3632	Papillary	1	5	0	22	4
0.7778	0.4361	0.734	0.1195	cbd*	Mucinous	0	5	5	11	5
0.1562	<.0001	cbd*	0.0771	<.0001	Carcinoma with lymphoid stroma	11	4	0	1	1
cbd*	0.3014	0.6721	0.0198	cbd*	Solid	0	2	1	1	0
cbd*	0.7499	0.0377	cbd*	0.6145	Undifferentiated	1	0	4	4	0
cbd: cannot be determined as none of the cases demonstrate the morphotype					Total	33	45	82	242	84

Fig. 1 Association (P values, left) and distribution (number of cases, right) of WHO morphologic patterns and protein expression groups. Abbreviations: Ab E-cadherin-GC, adenocarcinoma with aberrant expression of E-cadherin; Ab p53-GC, adenocarcinoma with aberrant expression p53; EBV-GC, EBV gastric carcinoma; MSI-GC, microsatellite instable gastric carcinoma. Significant P values are highlighted in green.

	Tubular	Carcinoma with lymphoid stroma	Undifferentiated	Poorly cohesive	Mixed	Papillary	Mucinous	Solid
PD-L1	10	3	1	1	0	0	0	0
PPV	66.7	20	0	13.3	0	0	0	0
NPV	37.4	98.2	96.7	87.8	88.6	96.7	95.1	99.2

Fig. 2 Distribution (number of cases, row 2) and predictive values (rows 3 and 4) of PD-L1 expression by WHO patterns.

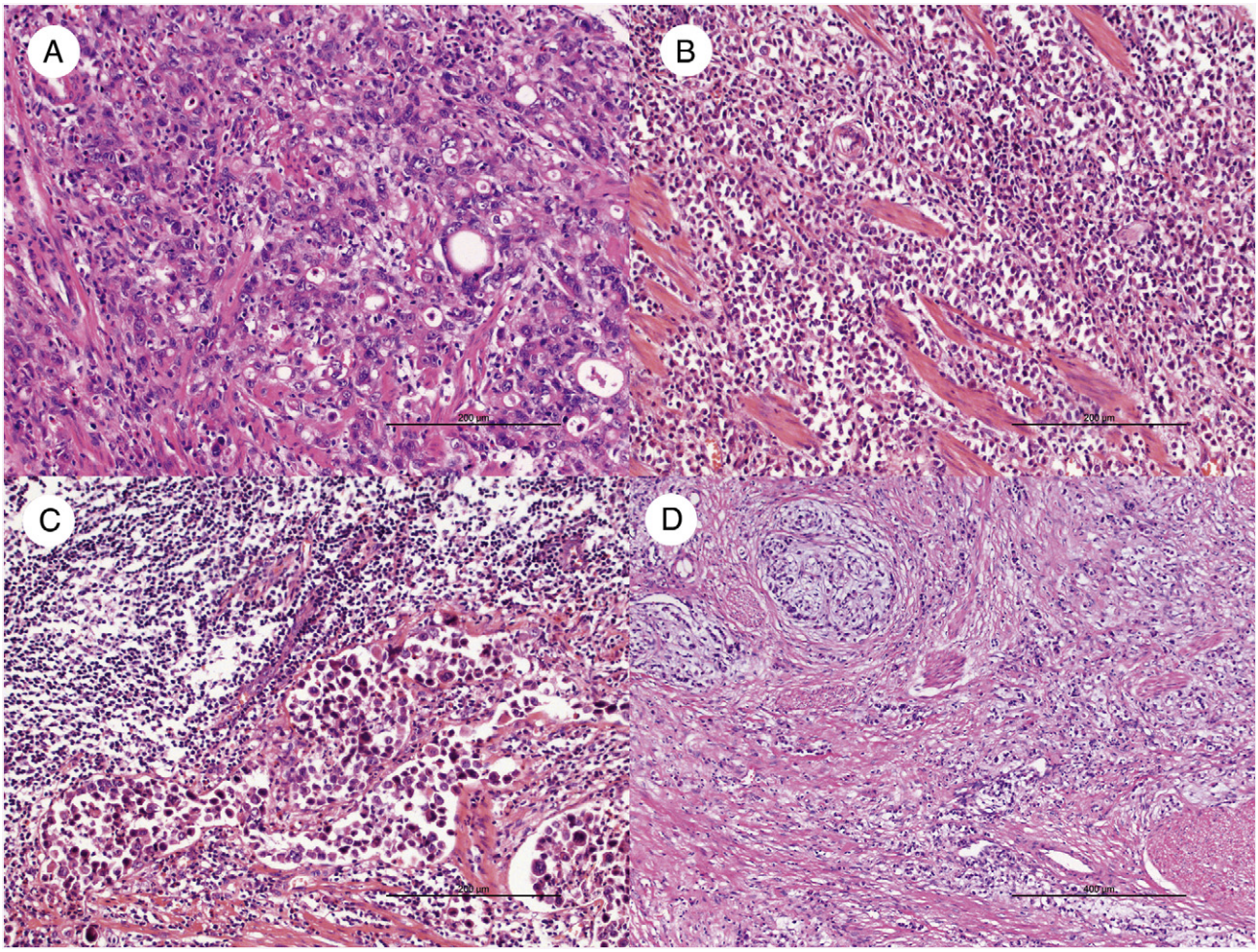

Fig. 3 WHO patterns with PD-L1 expression: A, tubular with lymphocytes; B, undifferentiated; C, carcinoma with lymphoid stroma; and D, poorly cohesive pattern (H&E stain, 200×).

	Tubular	Poorly cohesive	Mixed	Papillary	Mucinous	Carcinoma with lymphoid stroma	Solid	Undifferentiated
Her2	15	0	3	3	1	0	1	0
PPV	65.2	0	13	13	4	0	4	0
NPV	46.3	84.6	87	93.7	87	96.3	95.6	98

Fig. 4 Distribution (number of cases, row 2) and predictive values (rows 3 and 4) of Her2/neu expression by WHO patterns.

patterns included mixed (n = 26, 10.7%), papillary (n = 22, 9.1%), mucinous (n = 11, 4.5%), poorly cohesive (n = 21, 8.7%), undifferentiated (n = 4, 1.6%), solid (n = 1, 0.4%), and carcinoma with lymphoid stroma (1, 0.4%).

3.2.5. Others (remaining) gastric adenocarcinoma

This group, characterized by lack of EBER ISH, MSS status, normal expression of E- cadherin and p53, exhibited a broad morphologic diversity with 63.1% (53/84) tubular, 17.8% (15/84) mixed, 7.1% (6/84) poorly cohesive, 4.7% (4/84) papillary, and 1.2% (1/84) carcinomas with lymphoid stroma.

3.3. Predictive value of the WHO morphologic patterns for therapeutic biomarker expression

3.3.1. Predictive value of WHO patterns for PD-L1 expression

The positive predictive value (PPV) of any individual WHO pattern for identifying gastric cancers expressing PD-L1 was low (13.3%-66.7%). However, a 100% PPV for PD-L1 expression was seen with a combination of tubular, poorly cohesive, undifferentiated, and carcinoma with lymphoid stroma morphologic patterns (Figs. 2 and 3). Mixed, papillary, mucinous, and solid patterns of gastric cancers did not express PD-L1 in our cohort.

3.3.2. Predictive value of WHO patterns for Her2/neu expression

Similar to PD-L1 expression, the ability of any individual WHO pattern to correctly identify cancers with Her2/neu expression was low (13.3% - 65.2%). However, a 100% PPV for Her2/neu expression was seen with a combination of tubular, mixed, papillary, mucinous and solid morphologic patterns (Figs. 4 and 5). Poorly cohesive, undifferentiated and carcinoma with lymphoid stroma did not express Her2/neu in our cohort.

4. Discussion

The Lauren classification introduced in 1965 remains the most widely used histologic classification of gastric carcinoma [4]. Its simplicity and epidemiologic relevance has led to its endorsement by several cancer organizations as a predictive parameter in the management of gastric adenocarcinoma [14-17]. The advantage of the WHO classification, which was introduced in 2000 and later modified in 2010, is that it accommodates all 22 morphologic patterns of gastric carcinomas while recognizing that 'classic' subtypes such as tubular and poorly cohesive [roughly corresponding to Lauren 'intestinal' and 'diffuse' types] are more commonly encountered [5,18]. The identification of uncommon subtypes has furthered our understanding of gastric cancer pathogenesis; this is best exemplified by the association of carcinoma with lymphoid stroma with EBV infection. While the correlation of morphology, biologic characteristics and association with some biomarkers has been eluded in the past, their clinical significance was not broadly embraced until TCGA identified four biologic types of gastric cancers: EBV-related, MSI, GS and CIN. These four types roughly correlate with certain WHO morphologic patterns and distinctive targeted therapies in select instances. Herein we performed a comprehensive correlative analysis of WHO histologic patterns, biologic classification and biomarker

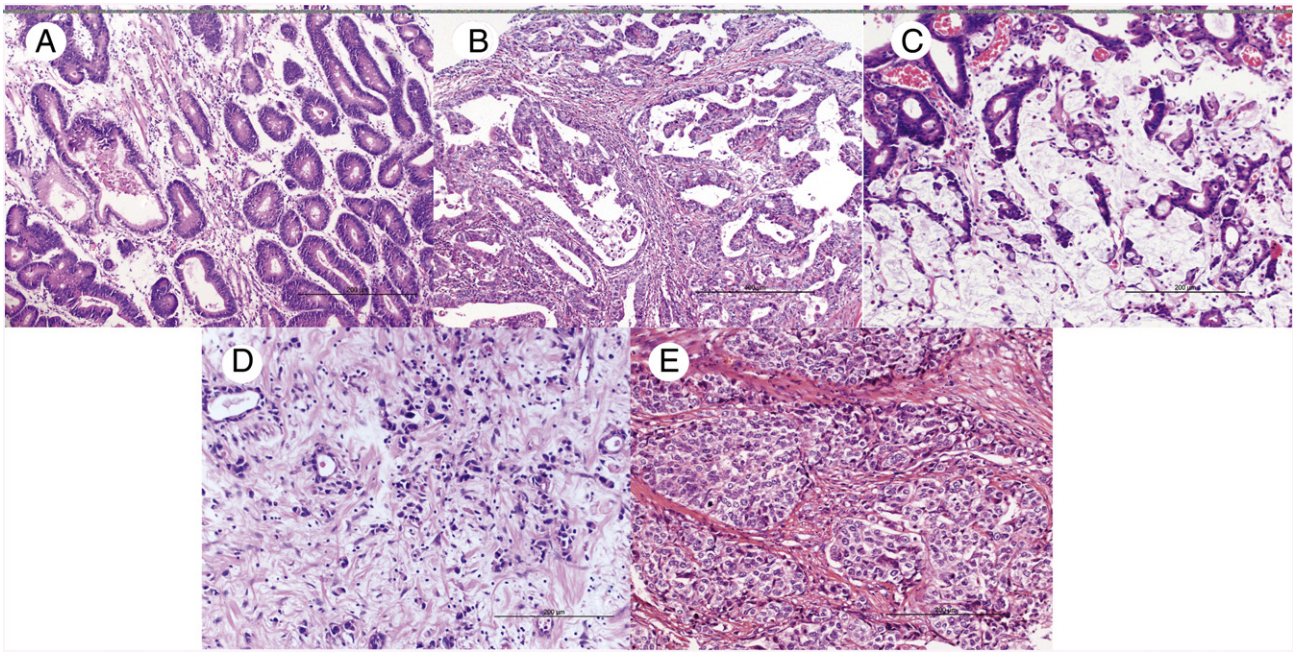

Fig. 5 WHO patterns with Her2/neu expression: A, tubular; B, papillary; C, mucinous; D, mixed; and E, solid pattern (H&E stain, 200×).

expression to explore the predictive value of morphology in a large cohort of gastric adenocarcinomas.

Some of the morphologic associations seen in our study have been reported in the literature. The association of carcinoma with lymphoid stroma and the presence of EBV in gastric cancer was first reported in 1990 and has been confirmed in several larger studies [19-21]. This association has recently gained interest after the identification of PD-L1 amplification in EBV-gastric carcinomas by TCGA [6]. Similar to the prior reports [19-21], we found a significant association of carcinoma with lymphoid stroma with EBV-gastric carcinomas; however, we also found that majority of EBV-gastric carcinomas have a conventional tubular morphology, albeit with increased lymphocytic infiltration. Tubular pattern (with increased lymphocytes) was seen in 61% (20/33) and carcinoma with lymphoid stroma pattern was seen in 33% (11/33) of EBV-gastric carcinomas in our study.

The reported literature on WHO patterns observed with MSI-gastric carcinoma is varied although a small proportion of carcinomas with lymphoid stroma have been reported to be microsatellite instable [20]. In the current study, 65% (11/17) of carcinomas with lymphoid stroma were EBV positive, and 24% (4/17) were microsatellite instable. Given the reported association with PD-L1 overexpression and immunotherapy with anti-PD-L1 and other check-point inhibitors, identification of this subtype of gastric carcinoma is also significant [22,23]. Besides carcinoma with lymphoid stroma, an association with Lauren intestinal subtype has also been reported [24]. Aria et al found well-differentiated MSI-gastric cancers to be associated with a papillary pattern and poorly/un-differentiated MSI-gastric cancers with solid pattern [24]. In this study, the MSI-gastric cancer subgroup was composed of diverse WHO patterns but tumors with infiltrating lymphocytes were significantly associated with microsatellite instability.

Poorly-cohesive (pure or mixed) morphology was not only seen in gastric cancers with aberrant E-cadherin expression, but also other in protein expression groups. These findings corroborate with the recent report that the mutational signature of poorly cohesive gastric cancer is broad and varied; the authors described mutations in several genes including *TP53, BRAF, PIK3CA, SMAD4* and *RHOA*, besides *CDH1* in a large cohort of poorly cohesive gastric carcinomas [25]. Tubular morphology was associated with gastric carcinoma with aberrant expression of p53 as has been previously reported [26,27].

FDA mandates the review of Her2/neu, MSI and PD-L1 testing in all patients with recurrent, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma. Herein, the overall prevalence of Her2/neu and PD-L1 detection cannot be accurately assessed given the limitation of using TMAs and the heterogeneity of biomarker expression. Both biomarkers show a low PPV with individual morphologic types. Since the objective of biomarker testing in clinical practice is to detect all cases that can potentially benefit from therapy, it is important to use an algorithm with a high PPV. From the above results, it is clear that an individual morphologic pattern alone cannot predict expression of PD-L1 or Her2/neu; however, a high PPV can be achieved with screening certain combinations of WHO patterns. These include, PD-L1 testing in tubular, poorly cohesive, carcinoma with lymphoid stroma and undifferentiated WHO patterns and Her2/neu evaluation in tubular, mixed, papillary, mucinous and solid WHO patterns.

The major limitation of our study is the sampling bias due to the use of TMAs for morphologic and biomarker analysis; however, the large sample size of the cohort may reduce this bias. In conclusion, we confirmed previously reported associations and identified additional significant associations of WHO types with biologic groups. Our analysis suggests that a targeted biomarker testing on a combination of WHO morphologic patterns is feasible and can be incorporated in routine clinical use for precision medicine screening.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2019.10.008.

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