Journal Club

张丽英

2020-07-20

胃癌相关分类

胃癌组织学分类

Comparison of the Lauren, Nakamura, Japanese and WHO classification (histopathological classification schemes for gastric cancer)

Lauren(1965) 根据腺管分化水平	Nakamura et al.(1968) 中村分型	JGCA (2017)	WHO (2019)
Intestinal	Differntiated	Papillary: **pap** Tubullar1,well diffe Tubular2, moderately differentiated: **tub2**	Tubular, moderately differentiated
Indeterminate不确定	Undifferentiated	Poorly 1(solid type): **por1**	Tubular, poorly differntiated
Diffuse		Signet-ring cell: sig Poorly 2(non-solid type): **por2**	Poorly cohesive, signet-ring cell phenotye Poorly cohesive, other cell types
Intestinal/diffuse/indeterminate（根据成分）	Differntiated/Undifferentiated （根据成分）	**Mucinous**	Mucinous
Mixed		Description according to the proportion (e.g. por2>sig>tub2)	Mixed
Not defined 不能分类	Not defined	**Special type:** Adenosquamous carcinoma Squamous cell carcinoma Undifferntiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type	**Other histological subtypes:** Adenosquamous carcinoma Squamous cell carcinoma Undifferntiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type 其实日本分类 Micropapillary adenocarcinoma

这里需要注意的是，虽然乳头状癌划分到分化型胃癌中，但是出现脉管侵犯的概率很高，因此，淋巴结转移的风险远高于管状腺癌。也提示Lauren及中村分型有一定的局限性。

黏液腺癌需要根据黏液湖中的肿瘤细胞构成特定结构来进行划分

Digestive system tumours, WHO classification of tumours, 5th Edition, 2019

粘液表型分型

Phenotypic classification based on the presence of mucin, brush border, and Cdx2 expression

We classified lesions as having one of four phenotypes: gastric phenotype (G-phenotype), in which 10 % or more of the cancer cells were immunoreactive for HGM and/or MUC6, fewer cells were stained for MUC2 and CD10, and cancer cells were weakly positive or negative for Cdx2; intestinal phenotype (I-phenotype), in which 10 % or more of the cancer cells were immunoreactive for MUC2 and/or CD10, or strongly positive for Cdx2, and also in which fewer cells were stained for HGM and MUC6; mixed phenotype, in which 10 % of the cancer cells were immunoreactive for HGM and/or MUC6, and were also immunoreactive for at least one of MUC2, CD10, and Cdx2; and null phenotype (N-phenotype), in which fewer than 10 % of the cancer cells were immunoreactive for any of the five antigens. Further, the mixed phenotype was classified into two subgroups as follows: mixed gastric phenotype (MG-phenotype), in which cancer cells were predominantly immunoreactive for HGM and/or MUC6; and mixed intestinal phenotype (MI-phenotype), in which cancer cells were predominantly immunoreactive for MUC2 and/or CD10, and/or Cdx2. These definitions are based on the definitions of Egashira et al. [14], and according to the results of Mizoshita et al. [15, 16].

gland adenoma of the stomach. Gastric Cancer. 2006;9:177–84.
14. Egashira Y, Shimoda T, Ikegami M. Mucin histochemical analysis of minute gastric differentiated adenocarcinoma. Pathol Int. 1999;49:55–61.
15. Mizoshita T, Tsukamoto T, Inada K, Ogasawara N, Hirata A, Kato S, et al. Immunohistochemically detectable Cdx2 is present in intestinal phenotypic elements in early gastric cancers of both differentiated and undifferentiated types, with no correlation to non-neoplastic surrounding mucosa. Pathol Int. 2004;54: 392–400.
16. Mizoshita T, Tsukamoto T, Nakanishi H, Inada K, Ogasawara N, Joh T, et al. Expression of Cdx2 and the phenotype of advanced

MUC5AC
MUC6
MUC2
CD10
CDX2

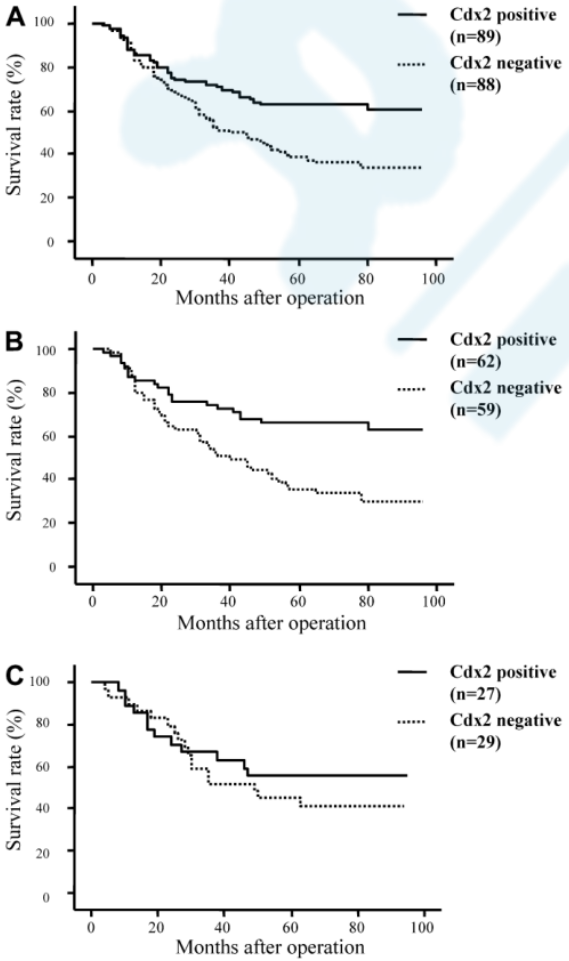


Fig. 4A–C Postoperative survival curves of gastric cancer patients with reference to the Cdx2 expression. **A** Note the better outcome with the Cdx2 positive cases in 177 advanced gastric cancers ($P = 0.0013$); **B** Note the better outcome with the Cdx2 positive cases in undifferentiated advanced gastric cancers ($P = 0.0009$); **C** The difference between two groups was not significant in differentiated advanced gastric cancers ($P = 0.43$)

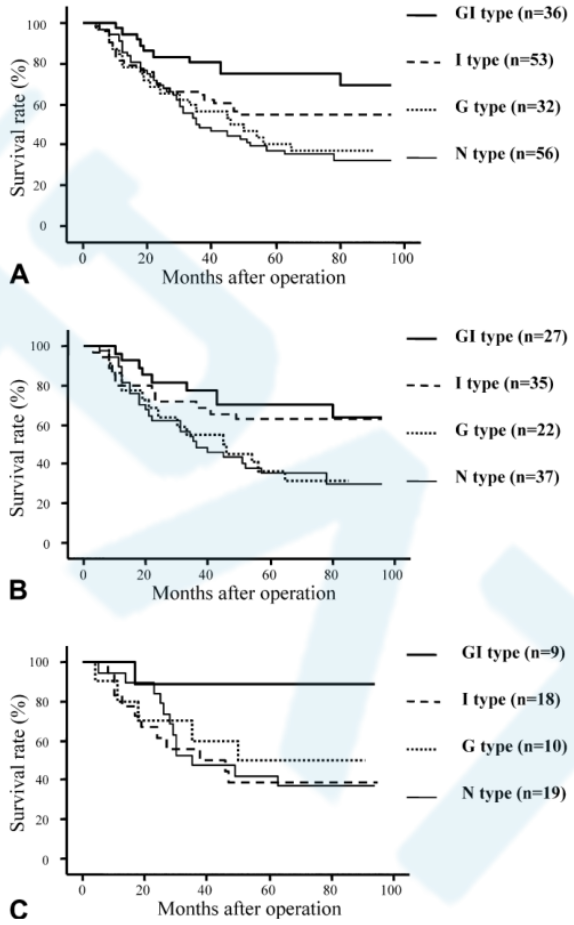


Fig. 5A–C Postoperative survival curves of gastric cancer patients with reference to the phenotypic classification. **A** Patients with GI type tumors have a better outcome than their N type counterparts in 177 cases ($P = 0.0052$); **B** Patients with GI type tumors have a better outcome than their N type counterparts in undifferentiated advanced gastric cancer cases ($P = 0.012$); **C** The difference between GI and N types was not significant in differentiated advanced gastric cancer cases ($P = 0.13$)

All advanced gastric cancer

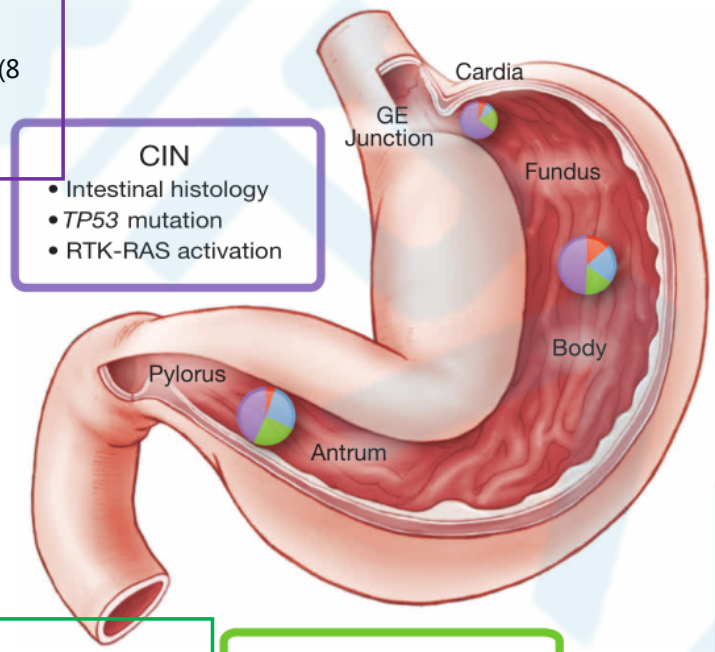
Undiffrentiated advanced gastric cancer

Differentiated advanced gastric cancer

J Cancer Res Clin Oncol (2003) 129: 727–734

分子分型

CIN(49.8%)
肠型为主
多发生于胃食管结合部或胃贲门
RTK-RAS扩增：**HER2(24%)**
EGFR(10%),HER3(8%),JAK2(5%),FGFR2(8%),MET(8%),PIK3CA(10%)和KRAS/NRAS(18%)
TP53高度突变（71%）



EBV(8.8%)
男性居多
肿瘤多位于胃底体
组织学是淋巴样间质或淋巴上皮样间质
PIK3CA突变（占该亚型80%）
CDKN2A基因沉默，
广泛的DNA启动子甲基化
JAK2，**PD-L1/L2基因扩增**
ARID1A(55%)和BCOR(23%)突变
免疫细胞信号增强

MSI(21.7%)
女性居多，诊断时多为老年患者
胃型CIMP
MLH1启动子区域高度甲基化
高突变率，如HER-25%）
,EGFR(5%),HER3(14%),JAK2(11%),FGFR2(2%),MET(3%),PIK3CA(42%)
PD-L1表达率高
有丝分裂通路激活

GS(19.7%)
弥漫型居多
诊断时多为年轻患者
细胞粘附相关通路被破坏相关：
CDH1(26%),**RHOA**(15%)和ARHGAP(15%)发生突变，
CLDN18染色体易位

国际癌症基因组图谱（TCGA）提议将胃癌分为4个亚型：EBV阳性型，微卫星不稳定（MSI）型，基因组稳定型（GS）和染色体不稳定型（CIN）

Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202-9.

Table 3.05 Key features of the four molecular gastric carcinoma subtypes proposed by The Cancer Genome Atlas (TCGA)

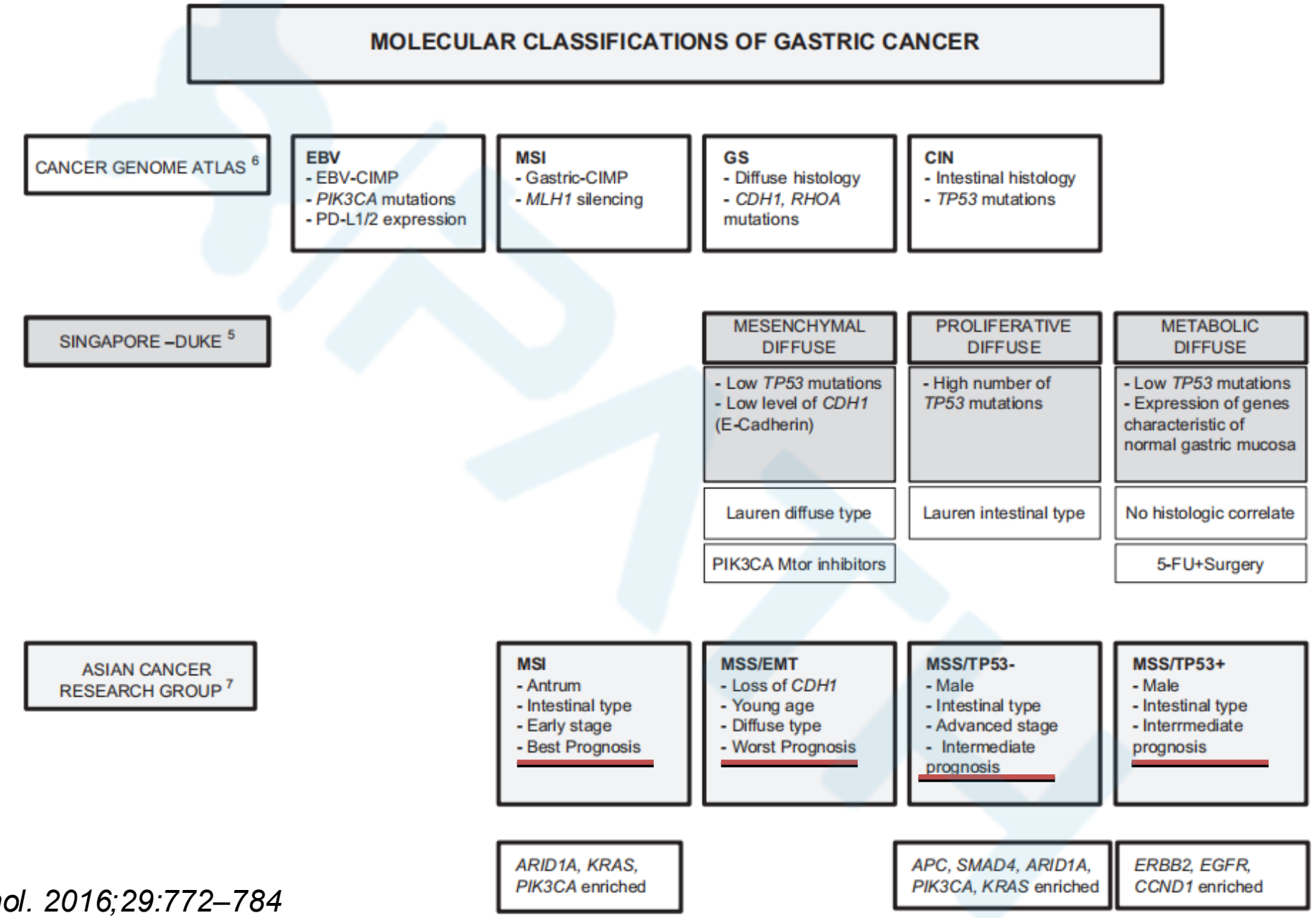
	EBV-positive	MSI	Genomically stable	Chromosomally unstable
Relative frequency	9%	22%	20%	50%
Representative histology	Gastric carcinoma with lymphoid stroma	None	Diffuse type[a]	Intestinal type[a]
Methylation				
	CIMP	CIMP	Rare	Rare
	MSI-high	Absent	All	Absent	Absent
Co	Rare	Rare	Rare	Frequent
Ge	Rare	Frequent	Rare	Rare
	Absent	Rare	Present	Rare
	Frequent	Present	Rare	Rare
RHOA	Rare	Rare	Present	Rare
CLDN18-ARHGAP fusion	Absent	Rare	Present	Rare
ARID1A	Frequent	Present	Rare	Rare
RTK amplification	Rare	Rare	Rare	Frequent
RTK mutation	Rare	Frequent	Rare	Rare
CD274 (*PD-L1*) and *PDCD1LG2* (*PD-L2*) amplification	Frequent	Rare	Rare	Rare

CIMP, CpG island methylator phenotype; MSI, microsatellite-instable; RTK, receptor tyrosine kinase.
[a]The Laurén histological classification used by TCGA; see Table 3.03 (p. 89) for the corresponding 2017 Japanese Gastric Cancer Association (JGCA) and 2019 WHO classifications.

WHO:
In routine pathology, immunohistochemistry of **mismatch repair proteins** (MLH1, etc.), **p53, and E-cadherin** combined with in situ hybridization for EBV-encoded small RNA (**EBER**) might allow molecular GC subtyping similar to the classification proposed by TCGA

Digestive system tumours, WHO classification of tumours, 5th Edition, 2019

Table 1 Current molecular classifications of gastric cancer[a]



Mod Pathol. 2016;29:772–784

Am J Surg Pathol .44(8):1017-1030, August 2020.

An Integrative Morphomolecular Classification System of Gastric Carcinoma With Distinct Clinical Outcomes

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Introduction---胃癌流行病学

Gastric carcinoma is one of the most common cancers worldwide and a leading cause of cancer-related death, particularly in eastern Asia.

In Taiwan, gastric carcinoma is a great burden on public health, with the medical and mortality-related costs accounting for ~0.08% of the Taiwanese economy.

This substantial burden from gastric carcinoma results from poor prognosis and poor response to current therapies. Because gastric carcinoma is a biologically and genetically heterogenous cancer with multifactorial pathogenesis, its management remains challenging.

A more robust classification system that can guide patient selection and therapeutic biomarker determination is urgently required.

Introduction---现行胃癌组织学分类(lauren及WHO)

Two current popular classification systems for gastric carcinoma, namely, Lauren classification and WHO classification, are based on morphologic patterns.

The Lauren classification system categorizes gastric carcinoma in a dichotomous manner into diffuse and intestinal subtypes.Diffuse-type gastric carcinoma is characterized by poorly cohesive cells in loose clusters or single cells with little or no glandular formation, whereas intestinal-type carcinoma is defined by glandular structures formed with variable degrees of differentiation.

The Lauren classification system is widely used in clinical practice because the diffuse and intestinal subtypes have distinct clinicopathologic features. Nevertheless, the intestinal type in the Lauren classification system is a histologically heterogenous group, and this histologic classification is insufficient to represent the divergent pathologic phenotypes of gastric carcinoma.

The WHO classification scheme provides more histologic classes, including poorly cohesive, tubular, papillary, and mucinous carcinomas. Poorly cohesive and tubular carcinoma are often used indiscriminately with the Lauren diffuse and intestinal histology, respectively. The papillary and mucinous subtypes largely rely on the concept of identifying predominant patterns of papillary architectures and mucinous differentiation in the tumor, respectively, but those patterns have not been commonly encountered in our clinical experience.

In addition, the clinicopathologic and molecular significance was unclear in those histologic classes.

Introduction---胃癌分子分型(TCGA)

In 2014, TCGA proposed a molecular classification encompassing 4 genetic subtypes of gastric cancer: Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomically stable (GS), and chromosomal instability (CIN).

EBV-positive gastric cancer is characterized by EBV infection and extensive DNA promoter hypermethylation.

MSI gastric cancer shows high levels of MSI and promoter hypermethylation of MLH1, and is associated with genetic hypermutation.

The other 2 subtypes GS and CIN are categorized by genomic aneuploidy.

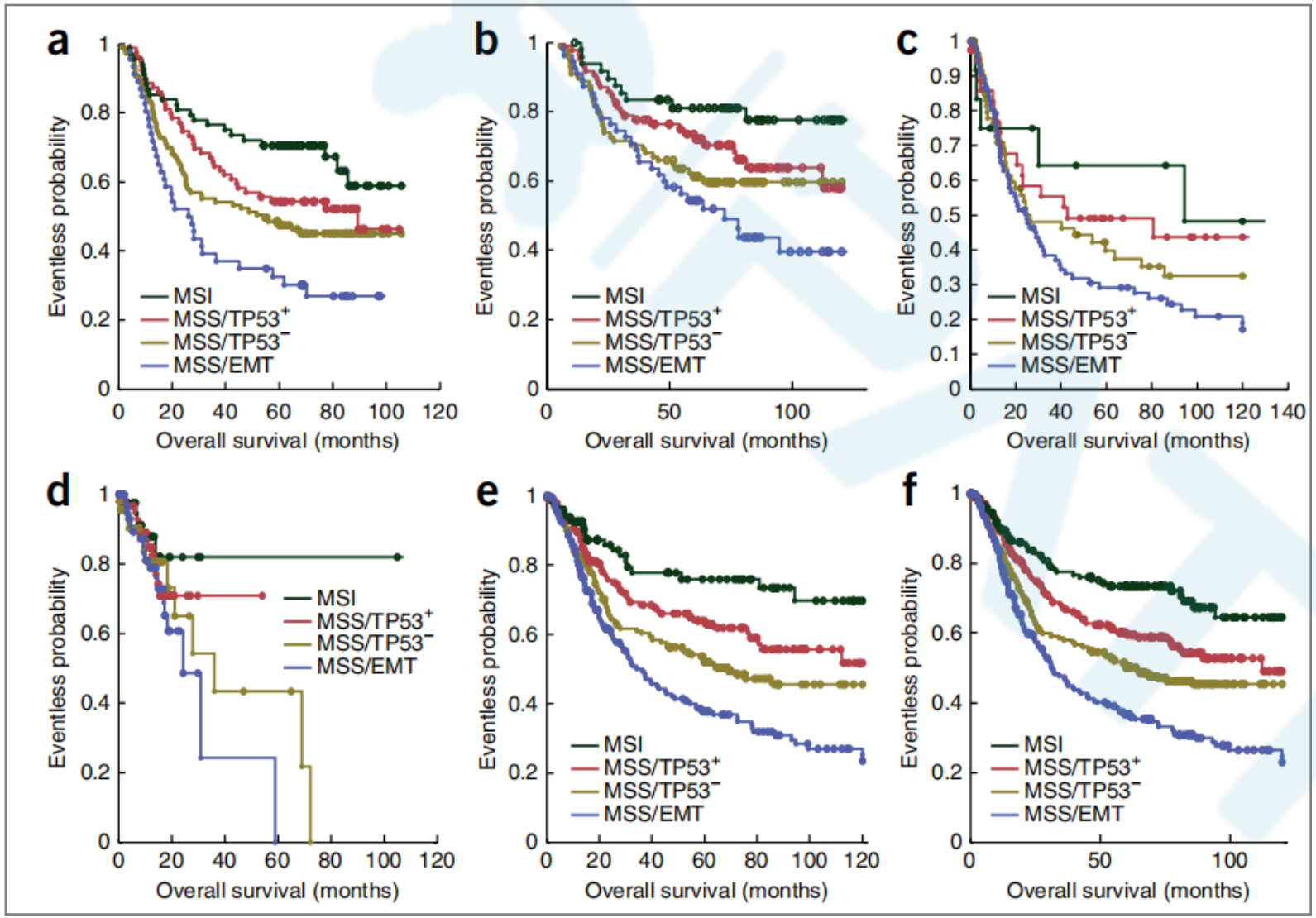
Although the 4 subtypes of TCGA classification are genetically distinct groups, they are not distinguishable in terms of clinical behavior and prognostic outcome.

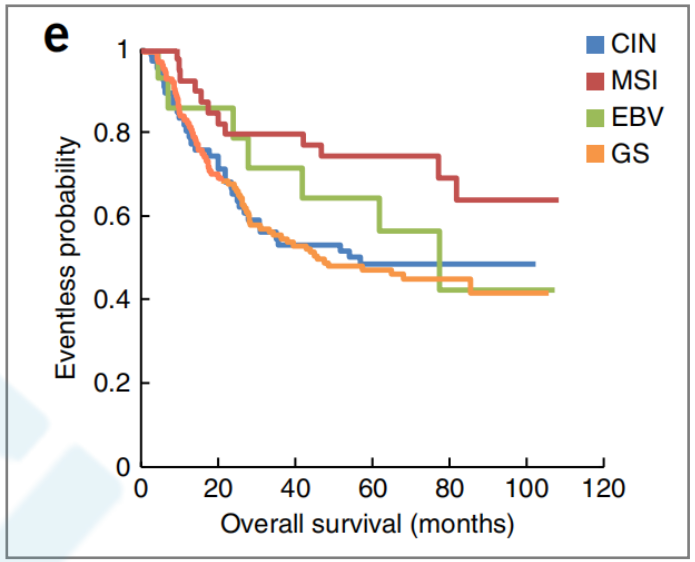
In addition, both the GS and CIN subtypes are composed of both the Lauren diffuse and intestinal histologies, indicating pathologic heterogeneity in this classification scheme.

Introduction---胃癌分子分型(ACRG)

Another promising and comprehensive molecular classification published by the Asian Cancer Research Group (ACRG) involves biological stratification of gastric carcinoma into MSI, microsatellite stable (MSS) with epithelial to mesenchymal transition, MSS tumors with active TP53 (MSS/TP53+), and MSS tumors with inactive TP53 (MSS/TP53−) types.

Introduction---胃癌分子分型(ACRG)





Nat Med . 2015 May;21(5):449-56.

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Although the ACRG classi-fication subtypes harbor different clinical outcomes, the complex methodologies and expensive molecular testing involved make the application of this scheme unsuitable in routine clinical practice.

Therefore, developing a more integral classification scheme with cost-effective diagnostic tools is essential in pathologic diagnostics.

Introduction---研究目的

The main goal of our study was to develop a practical classification scheme that segregates patients into prognostically relevant groups.

MATERIALS AND METHODS

Tissue Specimen

A total of 329 gastric adenocarcinomas from 2009 to 2011 were consecutively included in this study.

The exclusion criteria were carcinoma in situ, biopsy specimen, insufficient sample material, and metastatic carcinoma from other organs.

All of the patients received surgical resection with implication of complete tumor staging according to the 7th AJCC.

MATERIALS AND METHODS

Morphologic Review

Histologic sections from each case were reviewed by 2 pathologists (J.H.T. and J.Y.L.) to determine the morphologic patterns.

Because a tumor consists of a mixture of discrete histologic features, the patterns were classified according to the largest proportion of the tumor.

The presence of intestinal metaplasia and tumor-forming adenomatous precursor lesions was recorded during microscopic evaluation.

Conventional pathologic prognostic parameters were also analyzed, including grade of tumor differentiation (categorized into 2 tiers: low grade and high grade, based on whether the proportion of glandular formation is ≥ 50% of the tumor area), lymphovascular invasion, and TNM anatomic stage.

MATERIALS AND METHODS

Tissue Arrays and Immunohistochemistry

Antibody : MLH1 ; PMS2 ; MSH2 ; MSH6 ; E-cadherin ; HER2 ; ARID1A ; SATB2 ; PD-L1(clone: SP142)

- **Negative expression for mismatch repair proteins** (MLH1, PMS2, MSH2, and MSH6) was defined as complete absence of nuclear expression within tumor cells with concurrent positive labeling in stromal cells and lymphocytes.
- HER2 immunostaining was scored in accordance with the recommendation from the Trastuzumab for Gastric Cancer study.
- **HER2 overexpression** was positive when a tumor cell cluster with strong complete, basolateral, or lateral membranous reactivity (score 3) was present.
- The estimated percentage of expression for PD-L1 was recorded on the tumor cells and tumor-infiltrating and stromal immune cells. More than 5% of PD-L1 expression on the tumor cells and/or tumor-in- filtrating and stromal immune cells was considered positive.

MATERIALS AND METHODS

EBV-encoded Small RNA In Situ Hybridization

The signal was considered positive if strong and diffuse nuclear reactivity was observed under a negative background.

Fluorescence In Situ Hybridization

At least 30 nuclei per sample were counted.

PD-L1 amplification was defined as PD-L1/CEP9 ratio ≥2.0.

DNA Flow Cytometry

RESULTS

--- *Clinical Demographics*

A total of 157 (48%) and 172(52%) gastric carcinomas were located at the proximal and distal portions of the stomach, respectively.

A total of 123(37%) patients had Helicobacter infection.

Of all patients,44% (n=144) had lower TNM stages (I to II), whereas 56%(n=185) had higher TNM stages (III to IV).

Overall, 11%(n=36) of the patients presented with distant metastasis upon initial diagnosis.

The follow-up time for survivors ranged from 1 to 116 months, with mean and median survivals of 45 and 33 months, respectively.

Approximately 60% of patients die within 5 years.

TABLE 1. Clinicopathologic and Molecular Characteristics of the 329 Gastric Carcinomas

Clinical Features	N = 329, n (%)
Sex (male)	196 (60)
Age, mean (range)	65.4 (23-98)
Location—proximal	157 (48)
Cardia	36 (11)
Fundus	3 (1)
Body	103 (31)
Anastomosis	15 (5)
Location—distal	172 (52)
Antrum	158 (48)
Pylorus	14 (4)
Helicobacter infection	123 (37)
TNM anatomic stage	
Stage I	59 (18)
Stage II	85 (26)
Stage III	149 (45)
Stage IV	36 (11)
Morphologic patterns	
Diffuse	137 (42)
Intestinal	74 (22)
Tubular	53 (16)
Lymphoid	65 (20)
Intestinal metaplasia	238 (72)
Adenomatous precursor	56 (17)
Tumor differentiation	
Low grade	100 (30)
High grade	229 (70)
Lymphovascular invasion	265 (81)
HER2 overexpression	16 (5)
ARID1A loss	54 (16)
E-cadherin loss	20 (6)
SATB2 expression	32 (10)
PMS2/MLH1-deficiency	40 (12)
MSH6/MSH2-deficiency	0
Positive EBV in situ hybridization	17 (5)
PD-L1 expression	44 (13)
DNA content abnormality	175 (53)

RESULTS *--- Histologic Review*

Four most frequently encountered morphologic patterns at our institution are described, and the terms were **modified** from the Lauren and WHO classification systems(Table 2).

RESULTS

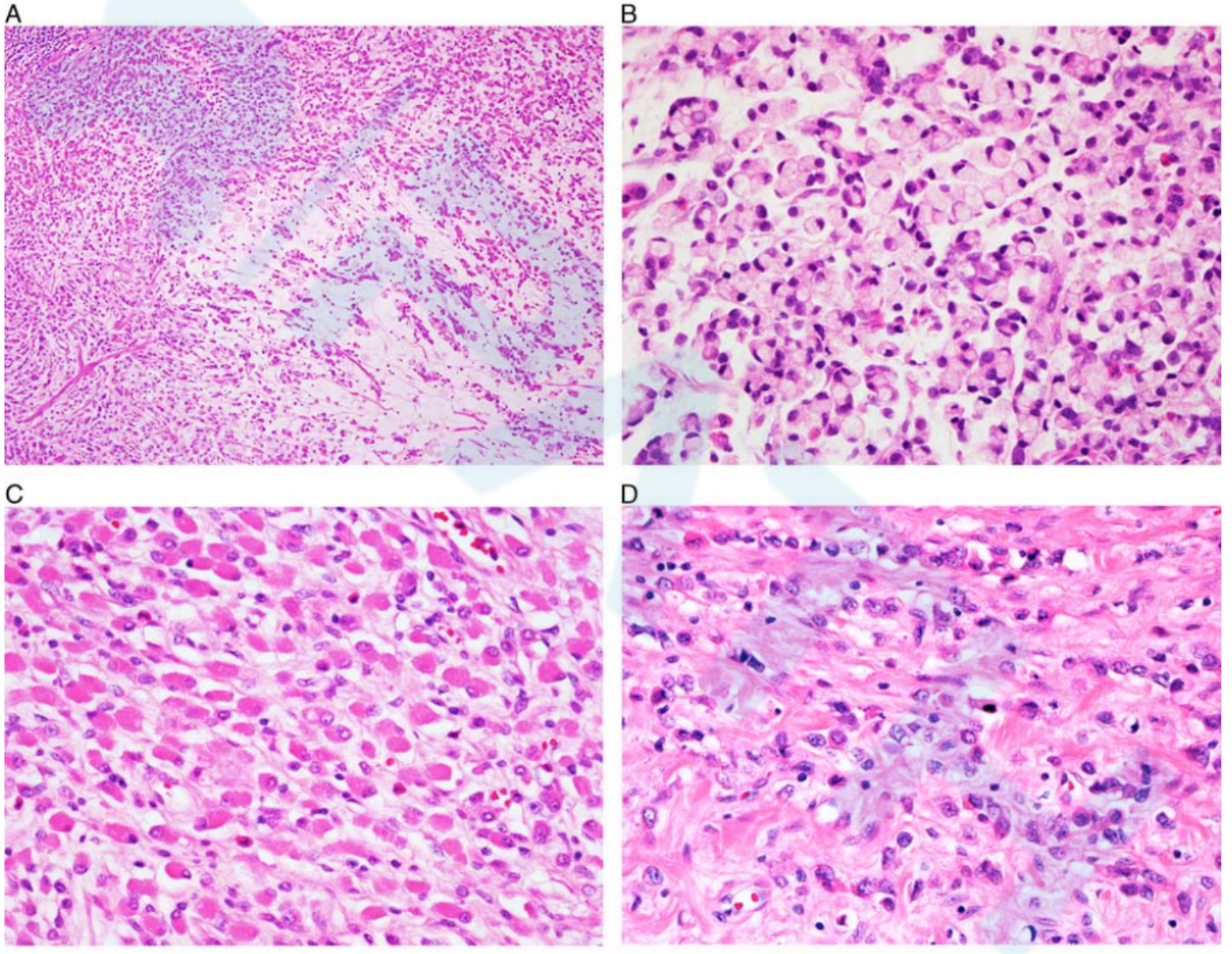
--- *Histologic Review*

The first category is the Lauren diffuse type, **corresponding to the poorly cohesive gastric carcinoma** of the WHO classification.

TABLE 2. Histologic Features of 4 Morphologic Patterns

Patterns	Histologic Features
Diffuse type	Poorly cohesive cells with single or in small aggregates, cords, and nests. Tumor cells may demonstrate a variable mixture of signet ring-like cells, plasmacytoid cells with eccentric eosinophilic cytoplasm, lymphohistiocytoid appearance, pleomorphic cells, and mucinous differentiation.
Intestinal type	Glandular structures, reminiscent of colorectal carcinoma. The dilated glands are lined by columnar epithelium with elongated, pseudostratified, and hyperchromatic nuclei. There are often luminal dirty necrosis and cribriform architectures.
Tubular type	Irregular tubular, microglandular, or acinar glands of varying diameters with cuboidal to columnar cells containing vesicular nuclei, nuclear irregularity, prominent nucleoli, and mucinous cytoplasm.
Lymphoid type	The tumor is well circumscribed and enriched with tumor-associated immune cells present within the tumor reactive stroma, between the tumor islands, and also invading the tumor proper. Tumor cells were often arranged in poorly differentiated cell nests, lobules, or syncytial aggregate, but other growth patterns were observed, including the diffuse, intestinal, or tubular histology

RESULTS --- *Histologic Review*



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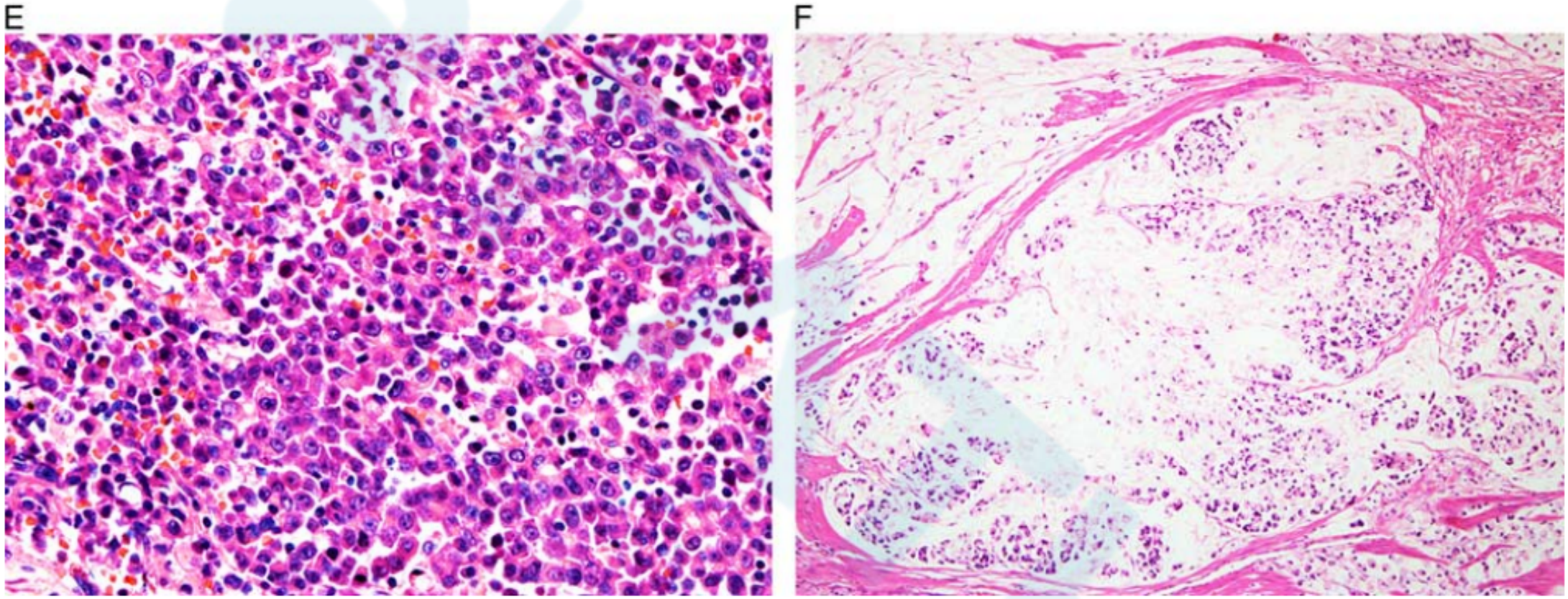

FIGURE 1. Diffuse-type gastric carcinoma. A, Diffuse infiltration of poorly cohesive cells arranged in the form of single cells or small aggregates, cords, and nests. Tumor cells may demonstrate a variable mixture of signet ring-like cells (B), plasmacytoid cells with an eccentric eosinophilic cytoplasm (C), lymphohistiocytoid cells (D), pleomorphic cells (E), and mucinous differentiation (F).

RESULTS

--- *Histologic Review*

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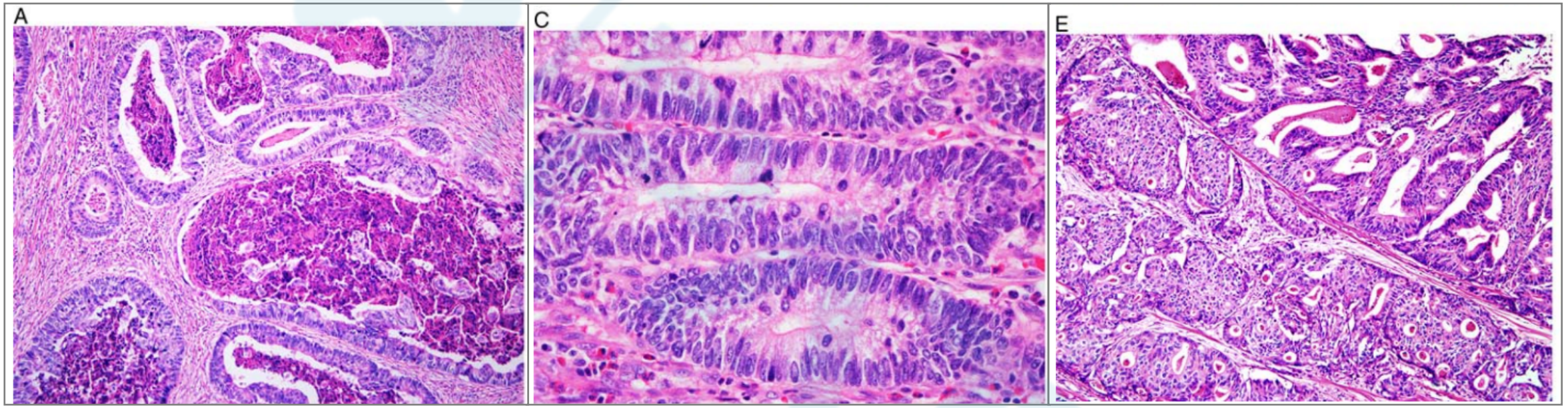

FIGURE 2. Intestinal and tubular morphologic types of gastric carcinoma. A, C, and E, The morphology of intestinal-type gastric carcinoma was reminiscent of that of colorectal carcinoma. Luminal dirty necrosis was commonly observed. The columnar epithelium contained elongated, pseudostratified, and hyperchromatic nuclei. B, C, and E, Tubular-type gastric carcinoma showed irregular diameters from the tubular, microglandular, to acinar glands of varying diameters. The glands were lined by cuboidal to columnar cells containing round to oval nuclei with vesicular chromatin, prominent nucleoli, and mucinous cytoplasm. E and F, Poor differentiation of the intestinal and tubular types, respectively.

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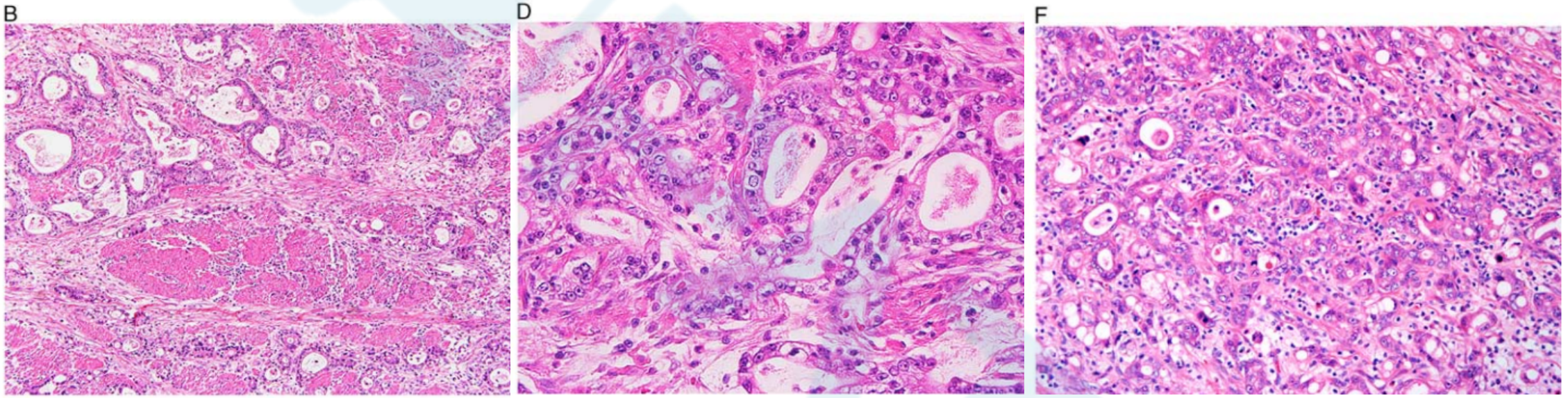

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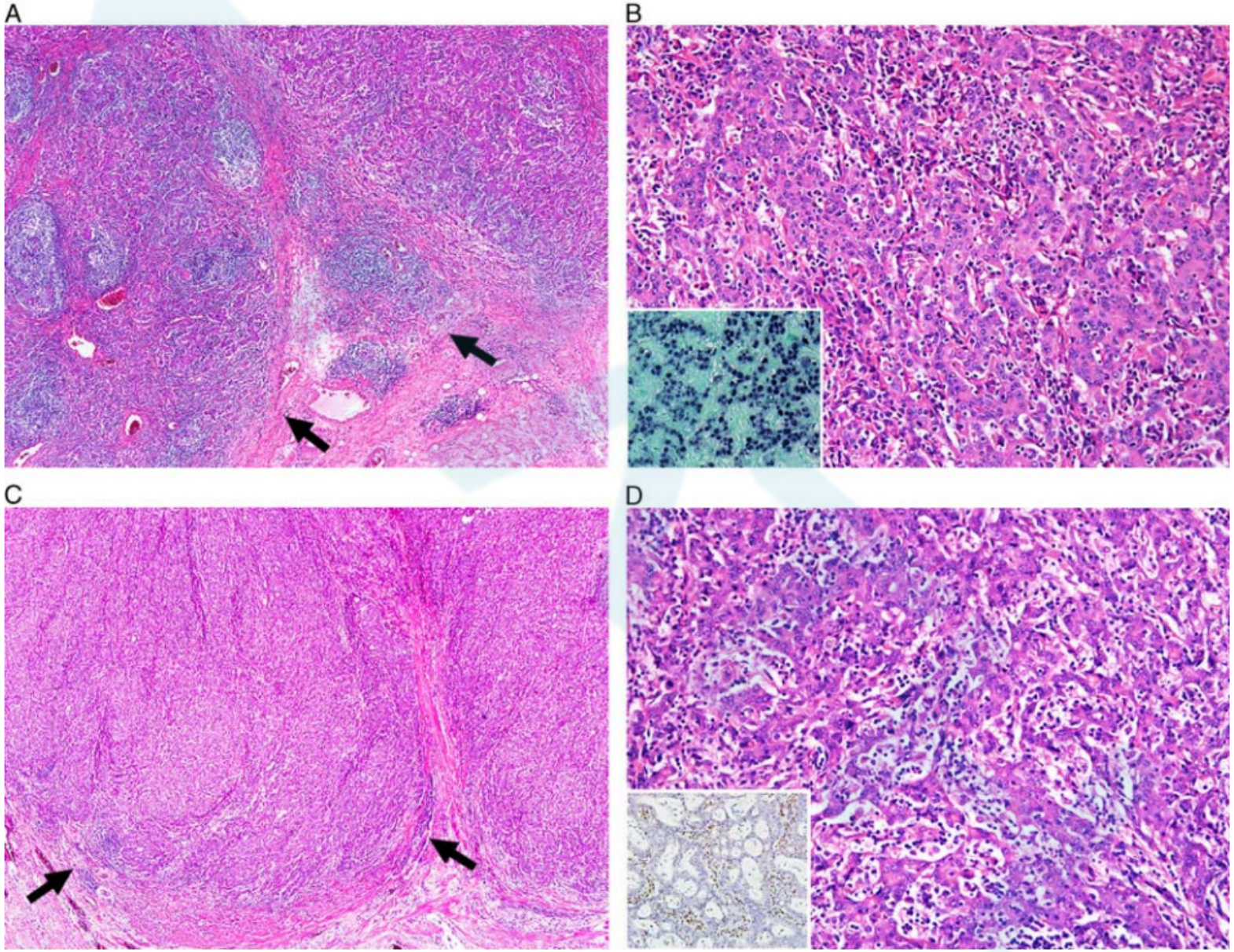

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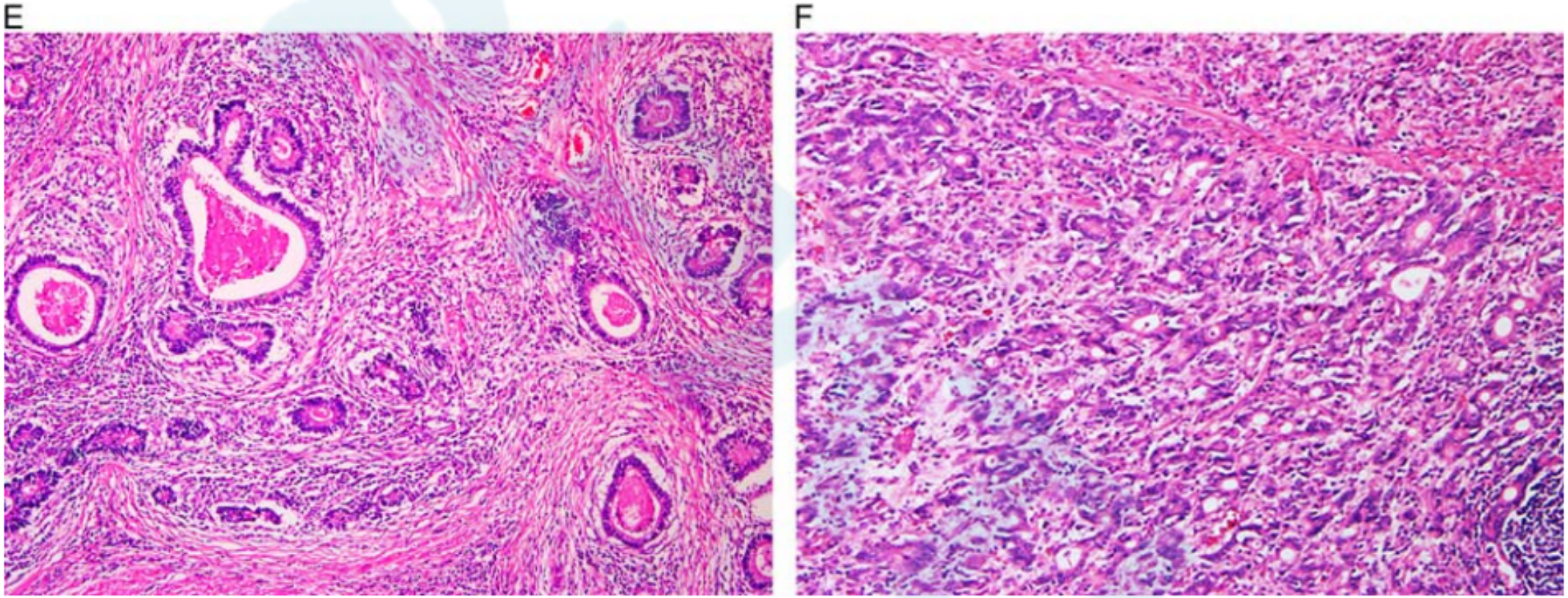

FIGURE 3. Lymphoid-type gastric carcinoma. The tumor is well circumscribed and enriched with tumor-associated immune cells (arrows). A and B, A EBV-positive gastric cancer. B, Inset: positive EBV in situ hybridization in tumor cells. C and D, A MSI gastric cancer. D, Inset: lost MLH1 expression in tumor cells. E and F, Tumor cells in lymphoid pattern may also demonstrate intestinal and tubular patterns, respectively.

RESULTS --- *Molecular Analysis*

- Immunohistochemical staining was performed on the tissue microarray.
- A total of 16 (5%) samples showed HER2 overexpression and membranous reactivity with a score of 3 (Supplementary Figs. 1A, B, Supplemental Digital Content 1, http://links.lww.com/PAS/A954).
- Loss of E-cadherin and ARID1A expression was identified in 20 (6%) and 54 (16%) gastric carcinomas, respectively (Supplementary Figs. 1C–E, Supplemental Digital Content 1, http://links.lww.com/PAS/A954).
- SATB2 was expressed in 32 (10%) samples (Supplementary Fig. 1F, Supplemental Digital Content 1, http://links.lww.com/PAS/A954).
- Concurrent loss of expression of PMS2 and MLH1 was identified in 39 (12%) gastric carcinomas, corresponding to high levels of MSI. One sample demonstrated isolated loss of PMS2 expression. MSH6/MSH2 expression was preserved in all samples.
- Overall, 17 (5%) gastric carcinomas were positive for EBV in situ hybridization, and these samples were mutually excluded from tumors with PMS2/MLH1-deficiency.
- PD-L1 expression was present in 44 samples (13%) (Supplementary Fig. 2A, Supplemental Digital Content 2, http://links.lww.com/ PAS/A955).

RESULTS --- *Fluorescence In Situ Hybridization*

- FISH analysis was carried out on lymphoid-type gastric cancer with no EBV infection or PMS2/MLH1 deficiency (n =17).
- PD-L1 gene amplification was detected in 2 (12%) samples (Supplementary Fig. 2B, Supplemental Digital Content 2, http://links.lww.com/PAS/A955). Both samples also demonstrated PD-L1 immunoexpression.
- DNA flow cytometry was performed successfully in 328 samples, and abnormalities were detected in 175 (53%) tumors (Supplementary Fig. 2C–F, Supplemental Digital Content 2, http://links.lww.com/PAS/A955).

RESULTS --- *Clinicopathologic Correlation With Morphologic Patterns*

TABLE 3. Clinicopathologic and Molecular Features Correlated With 4 Morphologic Classes

Features	Diffuse (n = 137)	Intestinal (n = 74)	Tubular (n = 53)	Lymphoid (n = 65)	*P*
Sex (male), n (%)	64 (47)	56 (76)	35 (66)	41 (63)	< 0.001
Age, mean (± SD)	59.4 (± 1.2)	69.1 (± 1.6)	70.2 (± 1.9)	69.7 (± 1.7)	< 0.001
Gastric location, n (%)					
Proximal	73 (53)	34 (46)	17 (32)	33 (51)	0.065
Distal	64 (47)	40 (54)	36 (68)	32 (49)	
Helicobacter infection, n (%)	54 (39)	27 (37)	26 (49)	16 (25)	0.049
TNM anatomic stage, n (%)					
I-II	41 (30)	40 (54)	22 (42)	41 (63)	< 0.001
III-IV	96 (70)	34 (46)	31 (59)	24 (37)	

- Diffuse-type gastric carcinoma presented female predilection (53%) and was a decade younger than the other histologic types (59.4 vs. ~69.4 y) (both P< 0.001).
- The intestinal and tubular types showed a tendency to be located at the distal part of the stomach (54% and 68%, respectively) in contrast to the predominant proximalsite most common for diffuse-type and lymphoid type gastric carcinomas (53% and 51%, respectively)(P = .065).
- Helicobacter infection was significantly associated with tubular-type gastric carcinoma (49%), but less significantly associated with lymphoid histology (25%, P = 0.049).
- Diffuse-type and tubular-type gastric carcinomas were strongly associated with a higher TNM stage (70% and 59%, respectively, with TNM stages III to IV), whereas intestinal-type and lymphoid-type gastric carcinomas were associated with a lower TNM stage (54% and 63%, respectively, with TNM stages I to II) (P < 0.001).

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Distal	64 (47)	40 (54)	36 (68)	32 (49)	
Helicobacter infection, n (%)	54 (39)	27 (37)	26 (49)	16 (25)	0.049
TNM anatomic stage, n (%)					
I-II	41 (30)	40 (54)	22 (42)	41 (63)	<0.001
III-IV	96 (70)	34 (46)	31 (59)	24 (37)	
Intestinal metaplasia, n (%)	82 (60)	59 (80)	43 (81)	54 (83)	<0.001
Adenomatous precursor, n (%)	8 (6)	29 (39)	7 (13)	12 (19)	<0.001
Tumor differentiation, n (%)					
Low grade	0	60 (81)	23 (43)	17 (26)	<0.001
High grade	137 (100)	14 (19)	30 (57)	48 (74)	
Lymphovascular invasion, n (%)	108 (79)	62 (84)	45 (85)	50 (77)	0.585

- Microscopically, intestinal metaplasia was less commonly detected in diffuse-type gastric carcinoma than in other histologic types.
- Intestinal-type gastric carcinoma more commonly harbored an adenomatous precursor than other types (39% vs. 11%, P<0.001) and also showed greater low grade tumor differentiation (81% vs. 16%, P<0.001).
- Lymphovascular invasion was present at similar frequencies in all histologic types (P=0.585).

PD-L1 indicates programmed death-ligand 1.

RESULTS --- *Clinicopathologic Correlation With Morphologic Patterns*

- HER2 overexpression was highly associated with the intestinal and tubular histologies (15% and 6%, respectively), but rarely occurred in diffuse and lymphoid histology (2% and 0%, respectively, P < 0.001).
- Loss of ARID1A expression was frequently observed in the lymphoid type (42%), less commonly observed in tubular and diffuse types (15% and 13%, respectively), and rarely observed in intestinal histology (1%, P < 0.001).
- Loss of E-cadherin expression was mostly identified in diffusetype gastric carcinoma (12% vs. 2%, P = 0.001), and SATB2 expression was mostly present in the intestinal histology (26%) and less commonly observed in other histologic subtypes (~5%, P < 0.001).

TABLE 3. Clinicopathologic and Molecular Features Correlated With 4 Morphologic Classes

Features	Diffuse (n = 137)	Intestinal (n = 74)	Tubular (n = 53)	Lymphoid (n = 65)	*P*
HER2 overexpression, n (%)	2 (2)	11 (15)	3 (6)	0	<0.001
ARID1A loss, n (%)	18 (13)	1 (1)	8 (15)	27 (42)	<0.001
E-cadherin loss, n (%)	17 (12)	0	1 (2)	2 (3)	0.001
SATB2 expression, n (%)	8 (6)	19 (26)	5 (9)	0	< 0.001
PMS2/MLH1-deficiency, n (%)	2 (2)	6 (8)	1 (2)	31 (48)	<0.001
Positive EBV ISH, n (%)	0	0	0	17 (26)	<0.001
PD-L1 expression, n (%)	7 (5)	8 (11)	2 (4)	27 (42)	<0.001
DNA content abnormality, n (%)	71 (52)	56 (76)	28 (54)	20 (31)	<0.001

PD-L1 indicates programmed death-ligand 1.

RESULTS --- *Clinicopathologic Correlation With Morphologic Patterns*

TABLE 3. Clinicopathologic and Molecular Features Correlated With 4 Morphologic Classes

Features	Diffuse (n = 137)	Intestinal (n = 74)	Tubular (n = 53)	Lymphoid (n = 65)	*P*
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Positive EBV ISH, n (%)	0	0	0	17 (26)	<0.001
PD-L1 expression, n (%)	7 (5)	8 (11)	2 (4)	27 (42)	<0.001
DNA content abnormality, n (%)	71 (52)	56 (76)	28 (54)	20 (31)	<0.001

PD-L1 indicates programmed death-ligand 1.

- According to molecular analysis, lymphoid histology was closely associated with EBV infection and PMS2/MLH1 deficiency (both P<0.001).
- Approximately 74% of lymphoidtype gastric carcinomas showed either EBV infection or PMS2/MLH1 deficiency. We observed that the tumor-associated immune cells were more intense and diffuse in EBV positive than in PMS2/MLH1-deficient gastric carcinomas.
- In fact, all EBV-positive gastric carcinomas (n=17) and 78% (31/40) of PMS2/MLH1-deficient gastric carcinomas showed lymphoid histology.

RESULTS --- *Clinicopathologic Correlation With Morphologic Patterns*

TABLE 3. Clinicopathologic and Molecular Features Correlated With 4 Morphologic Classes

Features	Diffuse (n = 137)	Intestinal (n = 74)	Tubular (n = 53)	Lymphoid (n = 65)	*P*
PD-L1 expression, n (%)	7 (5)	8 (11)	2 (4)	27 (42)	<0.001
DNA content abnormality, n (%)	71 (52)	56 (76)	28 (54)	20 (31)	<0.001

PD-L1 indicates programmed death-ligand 1.

- **PD-L1 expression was strikingly associated with lymphoid-type gastric carcinoma than other histologic subtypes (42% vs. 6%, P<0.001).**
- **PD-L1 expression was similar between lymphoid-type tumors with or without PMS2/MLH1 deficiency or EBV infection (P=0.591).**
- **DNA content abnormality was strongly associated with intestinal-type gastric carcinoma (76%), but was less frequently detected in the lymphoid histology (31%, P<0.001).**

RESULTS-*Clinicopathologic Correlation With DNA Content Abnormality*

- Tumors with abnormal DNA content were present more frequently in male patients, at the proximal gastric location, with high TNM stages, and at an older age of diagnosis than those with normal DNA content (P=0.003, 0.017,0.003, and 0.043, respectively) (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/PAS/A956).
- DNA content abnormality was not correlated with features of Helicobacter infection, intestinal metaplasia, adenomatous precursor, tumor differentiation, E-cadherin, SATB2, or PDL1 expression (P=0.983, 0.808, 0.358, 0.381, 0.440, 0.066, and 0.146, respectively).
- Abnormal DNA content was significantly associated with lymphovascular invasion and HER2 overexpression (P<0.001 and 0.022, respectively).
- Loss of ARID1A expression was strongly correlated with normal DNA content (P=0.009).
- Most gastric cancers with PMS2/MLH1 deficiency and EBV infection showed normal DNA content (P<0.001 and 0.011, respectively).
- Histologically, we subcategorized diffuse-type gastric cancers into signet ring-like (n=51), lymphohistiocytoid (n=41), pleomorphic (n=37), and mixed patterns (n=8) according to the largest morphologic components of the tumor.
- Interestingly, pleomorphic diffuse-type tumor (78%) most frequently showed cell aneuploidy, whereas the majority of signet ring-like tumors (61%) and mixed pattern (75%) showed normal DNA content (P=0.001).

RESULTS --- Clinical Features According to the TCGA Classification Scheme

TABLE 4. Comparisons of Clinical Features Between the Current Cohort and the TCGA Cohort

	Current Cohort (n = 329), n (%)				TCGA Cohort (n = 295), n (%)			
	MSI (n = 40) (12%)	EBV (n = 17) (5%)	GS (n = 108) (33%)	CIN (n = 163)* (50%)	MSI (n = 64) (22%)	EBV (n = 26) (9%)	GS (n = 58) (20%)	CIN (n = 147) (50%)
Sex (male)	25 (63)	14 (82)	49 (45)	107 (66)	28 (44)	21 (81)	36 (62)	97 (66)
Age (mean)	75	63	60	67	72	64	59	68

*One missing data due to unsuccessful flow cytometry.

- We reclassified our cohort according to the TCGA classification scheme. CIN (n=163, 50%) accounted for the largest group, followed by the GS (n=108, 33%), MSI (n=40, 12%), and EBV (n=17, 5%) groups.
- Table 4 presents a comparison of the clinical features between the current cohort and the TCGA cohort.
- Consistent with the study results of TCGA, patients with GS tumors were younger at diagnosis (mean, 60 y), whereas patients with MSI tumors were significantly older (mean, 75 y, P<0.001).
- GS tumors were more prevalent in women (55%), whereas EBV-positive tumors were more prevalent in men (82%, P=0.002).

RESULTS --- Clinical Features According to the TCGA Classification Scheme

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	Current Cohort (n = 329), n (%)				TCGA Cohort (n = 295), n (%)			
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Sex (male)	25 (63)	14 (82)	49 (45)	107 (66)	28 (44)	21 (81)	36 (62)	97 (66)
Age (mean)	75	63	60	67	72	64	59	68
Gastric location								
Proximal	9 (22)	12 (71)	47 (44)	88 (54)	30 (47)	20 (77)	29 (50)	94 (64)
Distal	31 (78)	5 (29)	61 (56)	75 (46)	31 (48)	6 (23)	28 (48)	49 (33)
TNM stage								
I-II	28 (70)	12 (71)	46 (43)	58 (36)	38 (59)	11 (42)	27 (47)	72 (49)
III-IV	12 (30)	5 (29)	62 (57)	105 (64)	19 (30)	15 (58)	28 (48)	69 (47)
Lauren class								
Diffuse	6 (15)	7 (41)	67 (62)	74 (45)	16 (25)	5 (19)	40 (69)	18 (12)
Intestinal	34 (85)	10 (59)	41 (38)	89 (55)	48 (75)	15 (58)	15 (29)	118 (80)

*One missing data due to unsuccessful flow cytometry.

- Most EBV tumors were present at the proximal part of the stomach (71%), and MSI tumors were primarily detected at the distal portion (78%, P=0.001).
- Helicobacter infection was not correlated with any molecular group (P=0.137).

RESULTS --- Clinical Features According to the TCGA Classification Scheme

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	Current Cohort (n = 329), n (%)				TCGA Cohort (n = 295), n (%)			
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Distal	31 (78)	5 (29)	61 (56)	75 (46)	31 (48)	6 (23)	28 (48)	49 (33)
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I-II	28 (70)	12 (71)	46 (43)	58 (36)	38 (59)	11 (42)	27 (47)	72 (49)
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Diffuse	6 (15)	7 (41)	67 (62)	74 (45)	6 (9)	5 (19)	40 (69)	18 (12)
Intestinal	34 (85)	10 (59)	41 (38)	89 (55)	48 (75)	15 (58)	15 (29)	118 (80)

*One missing data due to unsuccessful flow cytometry.

- Both MSI and EBV tumors tended to have a lower TNM stage (70% and 71%, respectively, stages I to II), whereas GS and CIN tumors had higher TNM stages (57% and 64%, respectively, stages III to IV, P<0.001).
- According to Lauren classification, only GS tumors showed predominant diffuse histology (P<0.001).
- These findings indicate that the clinical features of our cohort were similar to those of the cohort of TCGA, except that different classifying tools were used.

RESULTS -Pathologic and Molecular Features According to the TCGA Classification Scheme

- Supplementary Table 2, summarizes the pathologic and molecular features of our cohort according to the TCGA classification scheme.
- An evaluation of the histologic characteristics on the basis of our 4-tier classification revealed that most MSI and EBV tumors had a lymphoid histology (77% and 100%, respectively, P<0.001). Although diffuse histology was the most common morphologic pattern in GS (59%) and CIN gastric carcinomas (44%),other morphologic patterns were also prevalent.
- Therefore, histologic heterogeneity was recognized in these 2 molecular groups.
- Intestinal metaplasia occurred more frequently in MSI tumors (93%) than in other molecular groups (average, 70%, P=0.023).
- Adenomatous precursors tended to be present more often in MSI tumors than in the other groups (33%vs. 15%, P=0.017).
- EBV-positive gastric carcinomas had the lowest degree of tumor differentiation (12% vs. 32%,P=0.046), but less lymphovascular invasion (47% vs. 82%, P<0.001) compared with other molecular categories.
- A borderline association was observed between HER2 overexpression and CIN tumor (P=0.076).
- Loss of ARID1A expression was frequently noted in MSI tumors (55%, P<0.001).
- E-cadherin and SATB2 expressions were not correlated with any molecular classes (P=0.324 and 0.113, respectively).
- PD-L1 expression was more common in MSI and EBV (38% and 24%) tumors than in GS and CIN tumors (7% and 10%, P<0.001).
- DNA content abnormality was detected in 20% and 24% of MSI and EBV tumors, respectively.

RESULTS
--- Survival Analysis

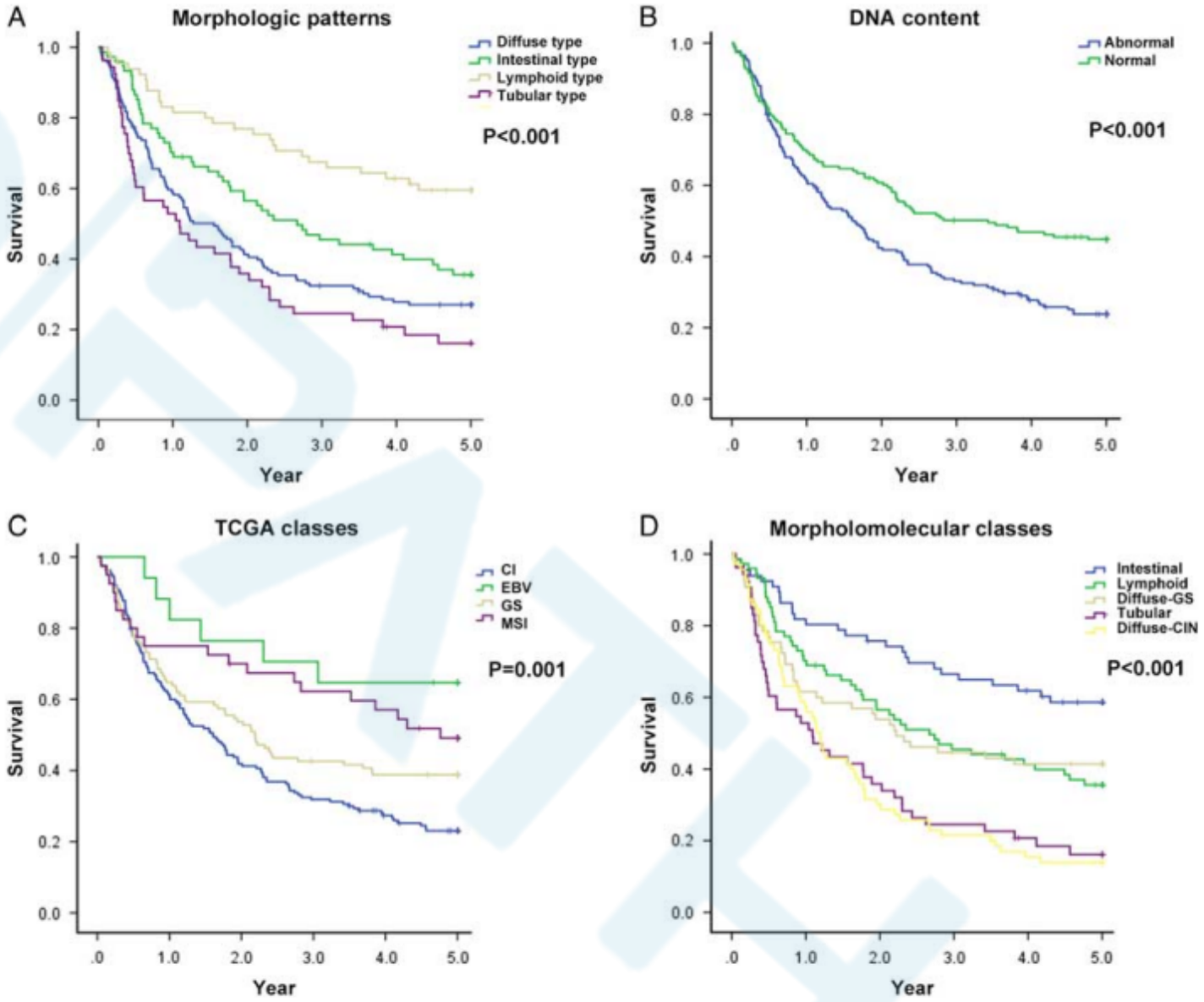
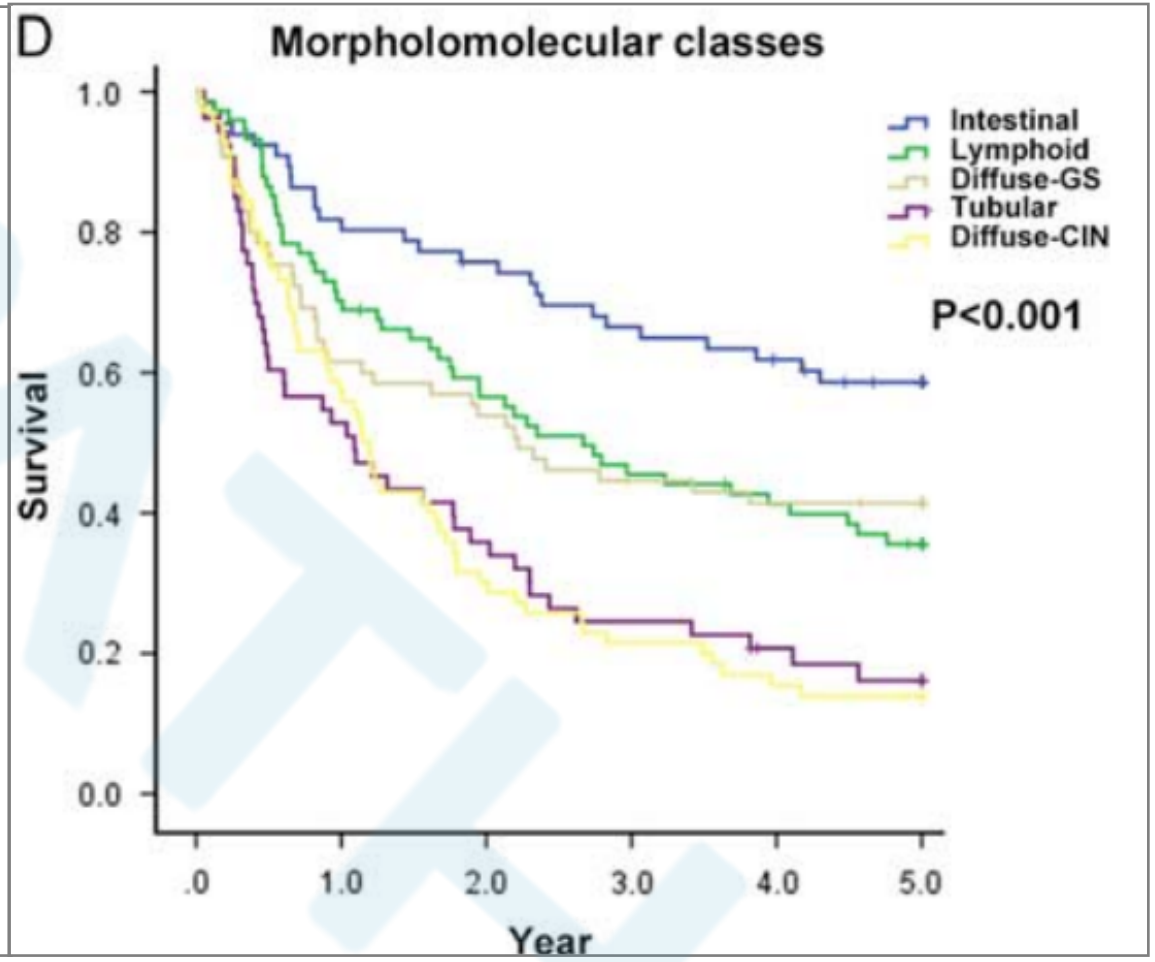


FIGURE 4. Univariate 5-year DFS analysis of gastric carcinoma. A, A strong significant correlation was observed between 5-year DFS and the 4-tier morphologic classification (A), DNA content abnormalities (B), TCGA molecular classification (C), and the proposed morphomolecular classification scheme (D).

RESULTS --- Survival Analysis

- Abnormal DNA content was a strong prognostic factor for overall survival only in diffuse-type gastric carcinoma (P =0.009).
- Therefore, we incorporated aneuploidy into the diffuse histologic class and proposed 5 morphomolecular phenotypes:

  intestinal, tubular, lymphoid, diffuse-GS type, and diffuse-CIN type.
- Figure 4D presents striking DFS differences among the 5 morphomolecular categories. The diffuse-CIN class had the worst survival among the classes.



RESULTS --- Survival Analysis

TABLE 5. Multivariate 5-Year DFS Analysis

	Morphomolecular Scheme		TCGA Scheme	
Features	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age at diagnosis (y)	1.012 (1.001-1.022)	0.027	1.011 (1.001-1.021)	0.033
Sex (male)	0.958 (0.718-1.278)	0.769	0.998 (0.746-1.335)	0.991
Anatomic stage		<0.001		<0.001
I	—		—	
II	1.410 (0.770-2.582)		1.502 (0.818-2.758)	
III	5.174 (2.940-9.105)		5.552 (3.125-9.865)	
IV	8.378 (4.346-16.153)		9.504 (4.883-18.499)	
Tumor differentiation		0.802		0.397
Low grade	—		—	
High grade	1.053 (0.705-1.571)		1.144 (0.838-1.561)	
Lymphovascular invasion		0.806		0.885
Absent	—		—	
Present	1.065 (0.644-1.760)		1.038 (0.629-1.711)	
TCGA classes				0.288
MSI			—	
EBV	—	—	0.551 (0.216-1.408)	
GS			0.998 (0.578-1.721)	
CIN			1.168 (0.706-1.932)	
Morphomolecular classes		<0.001	—	—
Diffuse-GS	1.671 (0.976-2.863)			
Diffuse-CIN	2.466 (1.502-4.049)			
Intestinal	1.832 (1.099-3.054)			
Tubular	2.911 (1.784-4.751)			
Lymphoid	—			

CI indicates confidence interval; HR, hazard ratio.

- **In the multivariate analysis for DFS and overall survival (Table 5 and Supplementary Table 3, Supplemental Digital Content 7, http://links.lww.com/PAS/A960, respectively), the morphomolecular classification was a strong independent prognostic factor in predicting patient outcome (P<0.001 and 0.007, respectively) in addition to age and anatomic stage, but sex, tumor differentiation, lymphovascular invasion, and TCGA classification were not.**

DISCUSSION

- Gastric carcinoma is characterized by its phenotypic divergence and histopathologic heterogeneity.
- In this study,we propose a morphomolecular classification to encompass 4 morphologic patterns and the molecular features described by the study of TCGA, including EBV infection, MSI, and aneuploidy status.

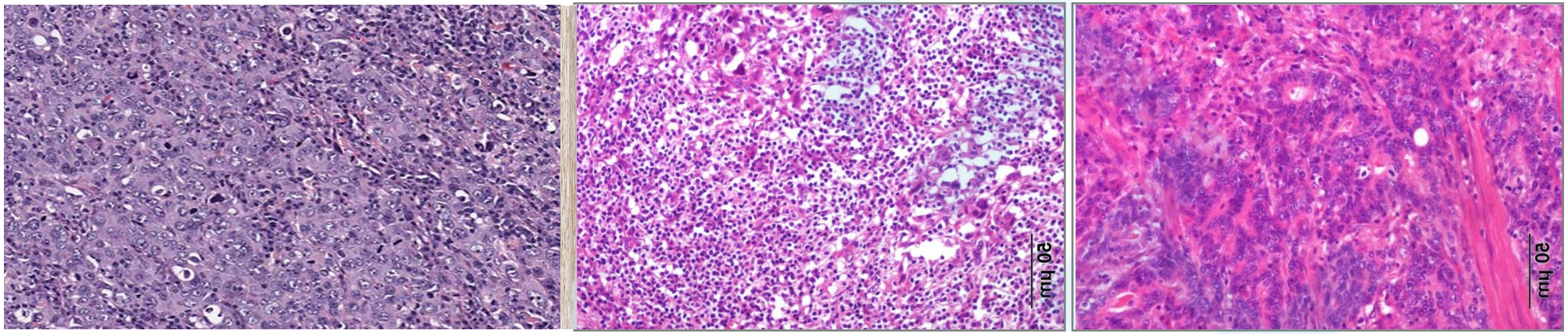
- Surprisingly, a lymphoid pattern corresponding to a rare variant described in the WHO classification, namely, gastric carcinoma with lymphoid stroma,was the third most common histologic pattern at our institute.
- Gastric carcinoma with lymphoid stroma was alsosynonymous with medullary carcinoma or lymphoepitheloma-like carcinoma and was reported to account for 1% to7% of all gastric adenocarcinomas.

DISCUSSION--关于EBV和MSI相关胃癌

- Histologically, the tumors demonstrate numerous tumor-infiltrating lymphocytes and a dense peritumoral lymphoid response.
- In addition to EBV infection, the morphologic feature of a dense lymphoid infiltrate is characterized in gastric carcinoma by high levels of MSI (ie, MSI gastric carcinoma).
- Because the EBV-positive and MSI gastric carcinomas together accounted for ~30% of the cohort of TCGA,we suggest that gastric carcinoma with lymphoid stroma is more frequently encountered than previously believed, and its prevalence may be greatly underestimated in the literature.
- Indeed, we classified ~20% of gastric carcinomas into this category, and a strong correlation of lymphoid histology with PMS2/MLH1 deficiency and EBV infection was noted(P<0.001).
- Consistent with previous reports,we found strong associations of early-stage (stage I or II) disease and prolonged survival with lymphoid-type gastric carcinoma, despite the fact that tumor differentiation was usually poor.

DISCUSSION--关于EBV和MSI相关胃癌

- Moreover, we identified a strong association of lymphoid-type gastric carcinoma with PD-L1 expression. PD-L1 expression predicts the response to immune checkpoint inhibitors and tumors with PD-L1 expression may bean eligible candidate for target therapeutics.
- Therefore,increased awareness of this morphologic pattern and the distinct clinical and molecular features can assist pathologists in classification, thereby facilitating clinical management.



DISCUSSION--对比其他胃癌分型

- In 2016, Setia et al performed a protein and mRNA expression-based classification and identified 5 groups of gastric cancers, including EBV, MSI, aberrant E-cadherin, normal p53 expression, or aberrant p53 expression.
- In the study, EBV-gastric and MSI-gastric cancers showed a trend for better survival than other groups of tumors.

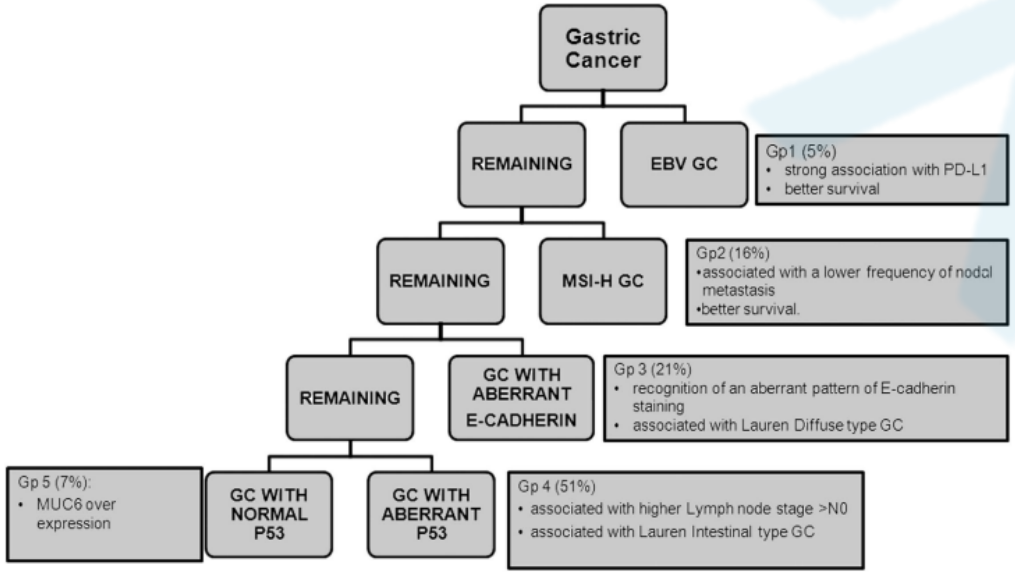


Figure 2 Summary of protein expression-based classification. The hierarchical clustering resulted in the determination of five groups of gastric adenocarcinomas. EBV, Epstein–Barr virus; GC, gastric cancer; MSI-H, high microsatellite instability.

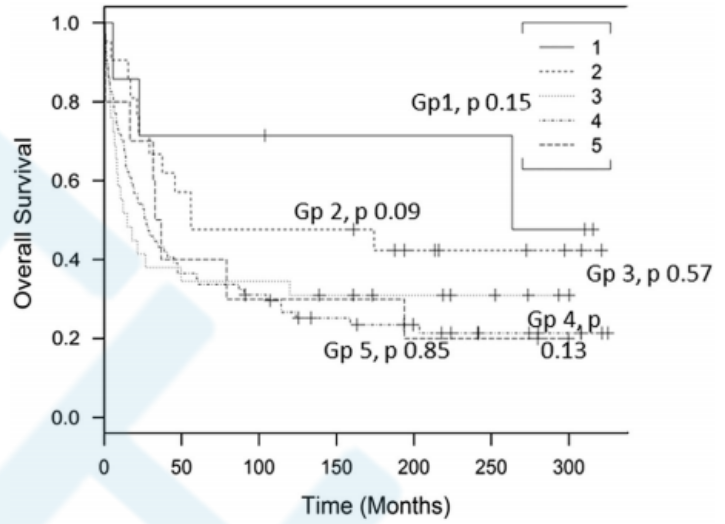


Figure 4 Kaplan–Meier curves for gastric cancer survival according to protein expression-based classification.

Mod Pathol. 2016;29:772–784

DISCUSSION--对比其他胃癌分型

- The authors subsequently analyzed correlations of morphologic patterns of gastric cancers with biomarker expression, including PD-L1, Her2/Neu expression, EBV, and MSI.
- The authors found a low predictive value of morphologic classification for biomarker expression.
- Several findings in the study were in line with ours.

✓ First, the authors observed a better survival of EBV-gastric and MSI-gastric carcinomas and a high proportion of gastric carcinoma with lymphoid stroma showed EBV infection or MSI.

✓ Second, loss of membranous E-cadherin expression was correlated with WHO poorly cohesive pattern.

- In more, tumor with aberrant p53 expression showed a predominant WHO tubular pattern, which corresponds to tubular-type and intestinal-type tumors in our classification.

DISCUSSION--对比其他胃癌分型

- However, the authors did not find positive predictive values of morphologic patterns for molecular biomarkers. This discrepancy may be attributed to different morphologic classification methods.
- In their study, the WHO classification scheme was used and a majority of EBV and MSI tumors were classified as tubular pattern, despite the fact that rich tumor-infiltrating lymphocytes were observed in the study.
- Although we also observed tubular structures in the EBV-gastric or MSI gastric carcinomas, lymphoid type was subtyped in our classification scheme.
- We consider that the presence of lymphoid stroma might be of greater importance and better correlated with molecular features.

DISCUSSION

---淋巴样型胃癌伴或不伴EBV or MSI

- Notably, ~25% of lymphoid-type gastric carcinomas in our classification showed no evidence of PMS2/MLH1 deficiency or EBV infection.
- The pathogenesis of rich lymphoid infiltrates in the tumor-associated stroma was unclear;
- however, we detected 2 samples (2/17, 12%) showing PD-L1 gene amplification. PD-L1 gene amplification was also detected in 15% of EBV-positive gastric cancers.
- PD-L1 immunoexpression was similar between lymphoid-type tumors with or without PMS2/MLH1 deficiency or EBV infection (P =0.591). Besides, the prognosis was similar between the 2 groups of tumors(P =0.716, data not shown).

- These findings suggested that lymphoid-type gastric cancer with or without PMS2/MLH1 deficiency or EBV infection may harbor similar molecular features and survival benefits. However, further research is required to verify this observation.

DISCUSSION--如何、为何鉴别EBV and MSI相关胃癌

如何

- Although histologic evaluation is an efficient and cost-effective method of identifying the lymphoid histology, confirming the status of MSI and EBV infection is essential.
- MSI gastric carcinomas harbor lower degrees of lymphoid in filtrates than do EBV-positive tumors, and 9 samples of PMS2/MLH1-deficient gastric carcinomas in our study lacked obvious lymphoid populations. Therefore, lymphoid histology may be easily missed through microscopic evaluation in some PMS2/MLH1-deficient tumors.

为何

- Moreover, MSI gastric carcinomas may not benefit from fluorouracil-based chemotherapy, but more likely respond to immunoregulatory agents compared with MSS tumors.
- In this respect, clarifying the status of MSI can accelerate initial diagnosis and decision-making on different therapeutic options.

DISCUSSION--建议EBV 和 MSI合并

- In the TCGA classification, EBV-positive and MSI gastric carcinomas are separate molecular classes;
- however, we observed that they showed similar clinicopathologic features.
- Most of the tumors of both classes were observed in older men, had lower TNM stages at diagnosis, showed lymphoid histology, had rare HER2 overexpression, and were frequently GS.
- Notably, both classes showed the most optimal prognosis in survival analysis.

- Therefore, it was reasonable to combine these 2 molecular classes into a single category (ie, lymphoid variant) to facilitate tumor classification.

DISCUSSION---CIN与DNA异常

- CIN gastric carcinoma constituted the largest subtype in TCGA classification, representing ~50% of the cohort.
- CIN indicates a status of abnormal DNA quantity in a tumor cell, engendering changes in chromosomal numbers with accelerated gain or loss of whole or large segments of chromosomes.
- In fact, abnormal DNA content is the molecular hallmark of many cancer types, including gastric carcinoma.
- CIN in cancer was also reported to have prognostic value in predicting patient survival.

DISCUSSION

---DNA异常与淋巴样组织型和弥漫型

- Our analysis revealed that aneuploidy was prevalent in diffuse, intestinal, and tubular types of gastric carcinoma, but not in the lymphoid type.
- However, aneuploidy predicted low survival mainly in cases of diffuse histology.
- Therefore, we combined aneuploidy and diffuse histology to form 2 categories: diffuse-GS and diffuse-CIN.
- We demonstrated that the morphomolecular classification was a strong and independent prognostic factor, but TCGA classification was not.
- These findings suggest that our morphomolecular classification system is effective in prognostic segregation.

DISCUSSION---CIN和DNA流式细胞分析

- To date, the pathogenesis of CIN in cancer remains unclear and may consist of multifactorial etiologies.
- Inactivation of tumor-suppressor genes, such as TP53 and RB genes, was also reported to disrupt genomic integrity and lead to CN.
- Several studies have used somatic copy number aberrations or gene expression profiles of different sets of genes to develop diagnostic indices of cellular aneuploidy. However, these tests are usually expensive and require complicated data analysis.
- In this study, we used DNA flow cytometric analysis to evaluate DNA content abnormality in gastric carcinomas. DNA flow cytometry has been applied in numerous studies for detecting CIN and is readily available in diagnostic laboratories;
- it is also an economical, efficient, and reliable method. According to our observations, using DNA flow cytometry to detect CIN is feasible.

DISCUSSION--肠型和管状型

- Finally, we proposed 2 morphologic patterns to describe glandular differentiation in gastric carcinoma: intestinal and tubular histologies.

✓ Intestinal-type gastric carcinoma was defined as having a morphology recapitulating colorectal carcinoma with a pseudostratified columnar epithelium, elongated, and hyperchromatic nuclei chromatin, and dirty necrosis.

✓ Glandular tumors without these features were classified into the tubular type, and they often showed an acinar or microglandular pattern. Tumor cells showed round or oval nuclei with an irregular and thickened nuclear membrane, vesicular chromatin, prominent nucleoli, and mucinous cytoplasm.

- We found that this binary approach could facilitate diagnosis and improve reproducibility.

DISCUSSION--肠型与 SATB2

- Notably, we observed that the expression of SATB2 was common in intestinal-type gastric carcinoma (26%), but uncommon in other histologic types (0% to 9%,P<0.001).
- SATB2 is a nuclear matrix-binding transcription factor and is involved in chromatin remodeling and epigenetic regulation.
- In one study, SATB2 expression was restricted to carcinomas of colorectal origin in the tissue microarrays of >1800 cases of colorectal carcinomas and >600 cases of other cancer tissues;
- therefore, SATB2 was considered a tissue-type-specific protein for tumors originating from the lower intestinal tract and a useful diagnostic marker for colorectal carcinoma.
- The expression of SATB2 was more frequently observed in intestinal-type than in tubular-type gastric carcinoma, which suggests that the cell lineage differed between the 2 glandular types of cancer cells.

DISCUSSION--肠型和管状型有不同的分子特征

- Moreover, HER2 overexpression was more common in the intestinal (15%) than in the tubular histology (6%), and loss of ARID1A expression was observed in 15% of tubular-type gastric carcinomas, but rarely in the intestinal type (1%).
- These findings provide evidence of distinct molecular features between the 2 classes.
- In addition, different prognostic outcomes were observed; therefore, it is reasonable to separate these 2 histologic patterns.
- The reason for the favorable prognosis observed in intestinal-type gastric carcinoma is unclear; however, the tubular histology harbored poorer tumor differentiation (57% vs. 19%, P<0.001) and higher TNM stages than the intestinal type (59% vs. 46%, P<0.001).
- Moreover, the intestinal histology morphologically showed intestinal cell lineage differentiation, whereas the tubular histology may be more related to the pancreatobiliary cell lineage. ????
- Extrapolating from the survival differences between cases of colorectal carcinoma and pancreatobiliary tract carcinoma, it is plausible that tubular-type gastric carcinomas have a significantly worse prognosis than intestinal-type gastric carcinomas. ????

DISCUSSION--本研究的局限性

- One limitation of our study is that gastric carcinoma with mixed or hybrid histology was classified according to its largest histologic component.
- In fact, mixed histologic patterns are commonly observed in gastric carcinoma.
- We recognized that mixed histology presents challenges and reproducibility problems in tumor classification; however, we did not find pertinent and distinct molecular features in gastric carcinoma with mixed histology.
- Further research may be required to develop other approaches that can be applied to the classification of gastric carcinoma with mixed histology.

Summary

- In summary, we propose a morphomolecular classification system for gastric carcinoma that is highly correlated with the molecular features described in the study of TCGA.
- The 4 morphologic patterns harbored specific and reproducible morphologic characteristics and improved the efficiency in pathologic classification, according to results of ancillary tests of mismatch repair immunohistochemistry, EBV in situ hybridization, and DNA content flow cytometry.
- Our analysis established distinguishable morphogenetic categories that not only differ in clinical and molecular characteristics but also segregate patients into prognostically distinct groups.


Thanks for your attention!

粘液表型分型

Table 4. Reported Datasets About Relationship Between Mucin Expression and Survival in Gastric Cancer					
Source, y	No.	Antibodies	Positivity, %	Phenotypes	Survival
Present study	412	MUC5AC, MUC6, MUC2, CD10	10	GC-GP, GC-IP, null	GC-GP and MUC5AC(+) has good survival in EGC
Toki et al,[5] 2010	95	MUC5AC, HGM, MUC6, M-GGMC-1, MUC2, CD10	5	G, GI, I, U	No correlation
Lee et al,[6] 2009	106	HGM, Con A, MUC2, MUC6	5	G, GI, I, U	I phenotype has good survival
Wakatsuki et al,[7] 2008	97	MUC5AC, MUC6, MUC2, CD10	10	G, GI, I, U	I phenotype has poor survival
Lee et al,[8] 2007	150	MUC1, MUC5AC, MUC6, MUC2, CD10	10	G, GI, I, U	G, GI phenotype have poor survival
Wang et al,[10] 2003	76	MUC1, MUC5AC	5	N/A	Muc1(+)/Muc5AC(−) has poor survival
Pinto-de-Sousa et al,[12] 2002	94	MUC5AC, MUC6, MUC2, MUC1	5	N/A	No correlation
Tajima et al,[13] 2001	136	HGM, MUC2, MUC6, CD10	10	G, GI, I, U	G phenotype has poor survival
Lee et al,[11] 2001	300	MUC5AC, MUC6, MUC2, MUC1	20	N/A	Muc1(+) has poor survival