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Original Article

The Clinicopathological Features of Mixed Carcinoma in 7,215 Patients with Gastric Cancer in a Tertiary Hospital in South Korea

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Background/Aims: There are few reports regarding mixed carcinoma, defined as a mixture of glandular and poorly cohesive components, in patients with gastric cancer (GC). The aim of this study was to evaluate the proportion and characteristics of mixed carcinoma in GC patients.

Methods: A total of 7,215 patients diagnosed with GC at Seoul National University Bundang Hospital were enrolled from March 2011 to February 2020. GC was divided into four groups (well-moderately differentiated GC, poorly differentiated GC, poorly cohesive carcinoma, and mixed carcinoma). The proportion of each GC type and the clinicopathological features were analyzed and divided into early GC and advanced GC.

Results: The proportion of mixed carcinoma was 10.9% (n=787). In early GC, submucosal invasion was the most common in poorly differentiated (53.7%), and mixed carcinoma ranked second (41.1%). Mixed carcinoma showed the highest proportion of lymph node metastasis in early GC (23.0%) and advanced GC (78.3%). In advanced GC, the rate of distant metastasis was 3.6% and 3.9% in well-moderately differentiated GC and mixed carcinoma, respectively, lower than that in poorly differentiated GC (6.4%) and poorly cohesive carcinoma (5.7%), without statistical significance.

Conclusions: Mixed carcinoma was associated with lymph node metastasis compared to other histological GC subtypes. And it showed relatively common submucosal invasion in early GC, but the rates of venous invasion and distant metastasis were lower in advanced GC. Further research is needed to uncover the mechanism underlying these characteristics of mixed carcinoma (Trial registration number: NCT04973631). **(Gut Liver 2023;17:731-740)**

Key Words: Stomach neoplasms; Pathology; Neoplasm staging; Lymphatic metastasis

INTRODUCTION

The incidence rates of gastric cancer (GC) are high,[1] mainly in the developing countries, especially in Eastern Europe, Eastern Asia, and South America.[2,3] In particular, 75% of patients with GC are Asian, with South Korea having the highest incidence of GC.[4,5]

There are several histological classifications of GC, including Lauren classification,[6] Japanese classification,[7] and World Health Organization (WHO) classification.[8] In 2010 WHO classification, mixed carcinoma was newly defined as a mixture of morphologically discrete glandular (tubular

or papillary adenocarcinoma) and signet ring cell carcinoma (SRC)/poorly cohesive carcinoma (PCC) histological components,[8] suggesting that there could be a unique entity, not just a mixture of GC.

Clinical pathological characteristics or prognosis of SRC/PCC were less invasive and better prognosis in early GC (EGC), whereas in advanced GC (AGC), more invasive and worse prognosis.[9-13] In EGC, mixed type GC was known to be more aggressive than pure SRC/PCC, thus lymph node (LN) metastasis or submucosal invasion was common.[14-17] However, there were few studies on the clinical pathological characteristics of mixed type GC in AGC. In addition, analysis on mixed carcinoma according to 2010 WHO classification definition has been very few. Our hypothesis was that mixed carcinoma could have different clinical pathological feature from PCC or glandular type not only in EGC but also in AGC. From this background, the aim of this study was to evaluate the clinical pathological features of mixed carcinoma GC patients depending on cancer invasion.

MATERIALS AND METHODS

1. Study population

This study was conducted on 10,021 patients diagnosed with GC at Seoul National University Bundang Hospital (SNUBH) from March 2011 to February 2020 (Fig. 1). The medical records of these patients, including age, sex, size of tumor, location, histological classification (Lauren and WHO classifications), initial treatment modality, tumor appearance, and TNM stage were collected from surgical, medical cohort.[18] In addition, clinical data warehouses, data search system in SNUBH and electronic medical records were reviewed as needed.

Patients were excluded if (1) the initial treatment modality was chemotherapy or conservative treatment, (2) the lack of pathological diagnosis, (3) the case of mucinous adenocarcinoma, papillary adenocarcinoma, or rare pathological type, or (4) PCC component was not identified (Fig. 1). The reasons of exclusion of those who did not receive operation or endoscopic treatment but received chemotherapy and conservative treatment in this study is as following: first, of the 2,162 patients who received chemotherapy or conservative treatment, only 15 patients (0.7%) were diagnosed as mixed carcinoma. In the remaining 2,147 patients, there is a possibility that some patients who might be diagnosed as mixed carcinoma with enough GC tissue. Division of Statistics, Medical Research Collaborating Center in our hospital and the pathologist (H.J.O.) advised us to exclude these patients who did not receive operation or endoscopic resection treatment due to possible serious selection bias. In addition, the accurate pathologically diagnosis of mixed carcinoma requires resected entire tissue of the tumor. Finally, we included 7,215 patients (Fig. 1) and analyzed GC patients into four groups (well-moderately differentiated [WMD], poorly differentiated [PD], PCC, and mixed carcinoma) by referring to 2010 WHO classification (Fig. 1).

This study was reviewed and approved by the Institu-

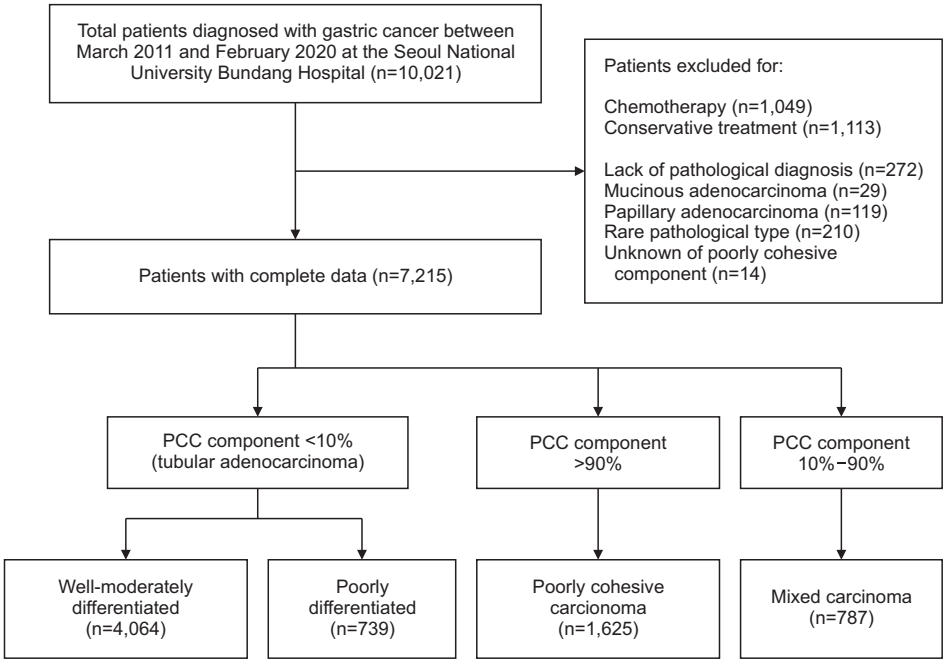

Fig. 1. Flowchart of the patient cohort definition.
PCC, poorly cohesive carcinoma.

tional Review Board of SNUBH (IRB number: B-2006-618-004). In accordance with Institutional Review Board guidelines for anonymous surveys, the need for written informed consent among participants was waived.

2. Data variable and assessment

The clinical characteristics in GC were analyzed depending on histological type, divided into four groups (WMD, PD, PCC, and mixed carcinoma). In 2010 WHO classification, tubular adenocarcinoma was also classified as well, moderately, or poorly differentiated. And PCC includes SRC which is defined as PCC that contains predominantly or exclusively signet ring cells. Mixed carcinoma is a mixture of tubulo-papillary and a poorly cohesive-SRC components, which means that each component must be clearly separated, and there is no cutoff defined in relation to the proportion of each component of the tumor classified as mixed carcinoma.[19] For example, if PCC components are rare at the edge of the tumor, the tumor cannot be classified as mixed carcinoma.[19] For example when one of the components is at least 10%, it could be diagnosed as mixed carcinoma. Accordingly, the professors at the Department of Pathology in SNUBH made a consensus to define mixed carcinoma if the distribution of PCC component is more than 10% and less than 90%. On the other hand, even in the form of mixture tumor, if the distribution of either granular or SRC/PCC component is exceeded 90%, it was defined as tubular/papillary adenocarcinoma and PCC, respectively. In case of pure SRC it was also included as a PCC group (Fig. 1). If the final diagnosis of GC at SNUBH is mixed carcinoma, PCC component was described as a percentage. We hypothesized that the prognosis of mixed carcinoma could be different depending on PCC components (10% to 90%), thus the mixed carcinoma was further categorized into four groups (10%≤PCC≤30%, 30%<PCC≤50%, 50%<PCC≤70%, and 70%<PCC≤90%). The location of GC was divided into three categories (upper, middle, and lower).[20] The tumor appearance of EGC was based on the Paris classification,[21] and AGC was based on the Borrmann classification system.

3. Statistical analysis

For categorical variables, frequency and percentage were calculated, and differences in distribution were estimated using the Pearson chi-square test. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and STATA version 17 (StataCorp LLC, College Station, TX, USA). Statistical significance was set at $p<0.05$. The Medical Research Collaborating Center of SNUBH supervised all the statistical analyses.

RESULTS

1. Baseline characteristics

The total patients enrolled in this study were 7,215, and mean age was 61.6 years. Among them, 4,810 (66.7%) were males, twice as many as 2,405 (33.3%) females. When analyzed by dividing into WMD, PD, PCC, and mixed carcinoma group, there were 4,064 (56.3%), 739 (10.2%), 1,625 (22.5%), and 787 (10.9%), respectively. Their mean age was 65.4 years for WMD and 62.6 years for PD, which was relatively old in comparison to 54.2 years for PCC and 56.8 years for mixed carcinoma. The sex distribution difference was also noticeable in the WMD (75.6% and 24.4% in males and females) and PD (70.5% and 29.5% in males and females), while the sex ratio in the PCC and mixed carcinoma was close to 1:1 (Table 1). The mean size of the tumor was the largest in PD (4.4 cm), the smallest in WMD (2.5 cm), and similar in PCC (4.1 cm) and mixed carcinoma (3.9 cm). In the analysis according to location, lower third was the most common among overall patients with 4,503 (62.4%), followed by middle third with 1,401 (19.4%) and upper third with 1,311 (18.2%). In the PD and PCC, the proportion of low third was relatively low, and the proportion of upper third was high. In the WMD group, the proportion of lower third was 2,870 (70.6%), the largest compared to other groups. In the mixed carcinoma, the distribution was similar to that in overall GC patients (Table 1). The distribution according to the Lauren classification was 4,595 (63.7%) of the internal type, 2,444 (33.9%) of the diffuse type, and 175 (2.4%) of the mixed type in overall patients. Among the mixed carcinoma, the internal type was 181 (23.0%), the diffuse type was 473 (60.1%), and the mixed type was 132 (16.8%). For the initial treatment modality, the WMD had 1,622 (39.9%) endoscopic treatments and 2,442 (60.1%) surgical treatments. In PD, PCC, and mixed carcinoma, 699 (94.6%), 1,574 (96.9%), and 748 (95.0%), respectively, were often treated surgically. Lymphatic invasion was the highest in PD (50.4%), followed by mixed carcinoma (30.6%). Venous inversion was high in PD (13.9%) and PCC (11.1%), and low in WMD (4.8%) and PCC (5.4%). Perineural invasion was high in PD (36.1%) and PCC (36.9%), followed by mixed carcinoma (24.6%). Node metastasis was positive, with the highest proportion of 330 (44.7%) in PD and the second-highest proportion of 308 (39.1%) in mixed carcinoma. Distant metastasis was also the most common with 27 (3.7%) in PD, followed by PCC with 39 (2.4%), and mixed carcinoma with only 10 (1.3%) (Table 1).

2. Subgroup analyses according to EGC and AGC

Of the total, 5,179 patients (71.8%) were EGC, and 2,036

Table 1. Baseline Characteristics of Patients with Gastric Cancer (n=7,215)

Characteristic	WMD	PD	PCC	Mixed carcinoma	Total	p-value*
No. of patients	4,064 (56.3)	739 (10.2)	1,625 (22.5)	787 (10.9)	7,215 (100)	
Age, yr	65.4±10.1	62.6±12.5	54.2±12.3	56.8±12.7	61.6±12.2	<0.001
Sex						<0.001
Male	3,071 (75.6)	521 (70.5)	790 (48.6)	428 (54.4)	4,810 (66.7)	
Female	993 (24.4)	218 (29.5)	835 (51.4)	359 (45.6)	2,405 (33.3)	
Size of tumor, cm	2.5±1.9	4.4±2.8	4.1±3.6	3.9±2.6	3.2±2.7	<0.001
Location						<0.001
Upper	583 (14.3)	204 (27.6)	384 (23.6)	140 (17.8)	1,311 (18.2)	
Middle	611 (15.0)	170 (23.0)	442 (27.2)	178 (22.6)	1,401 (19.4)	
Lower	2,870 (70.6)	365 (49.4)	799 (49.2)	469 (59.6)	4,503 (62.4)	
Lauren type†						<0.001
Intestinal	4,060 (99.8)	352 (47.6)	2 (0.1)	181 (23.0)	4,595 (63.7)	
Diffuse	2 (0.1)	352 (47.6)	1,617 (99.5)	473 (60.1)	2,444 (33.9)	
Mixed	2 (0.1)	35 (4.7)	6 (0.4)	132 (16.8)	175 (2.4)	
Treatment						<0.001
Endoscopic	1,622 (39.9)	40 (5.4)	51 (3.1)	39 (5.0)	1,752 (24.3)	
Operative	2,442 (60.1)	699 (94.6)	1,574 (96.9)	748 (95.0)	5,463 (75.7)	
Cancer type						<0.001
EGC	3,306 (81.3)	335 (45.3)	981 (60.4)	557 (70.8)	5,179 (71.8)	
AGC	758 (18.7)	404 (54.7)	644 (39.6)	230 (29.2)	2,036 (28.2)	
Lymphatic invasion	819 (20.8)	352 (50.4)	394 (25.2)	240 (30.6)	1,805 (25.9)	<0.001
Venous invasion	188 (4.8)	97 (13.9)	173 (11.1)	42 (5.4)	500 (7.2)	<0.001
Perineural invasion	410 (10.4)	252 (36.1)	576 (36.9)	193 (24.6)	1,431 (20.5)	<0.001
T stage‡						<0.001
1a	2,252 (55.4)	155 (21.0)	647 (39.8)	328 (41.7)	3,382 (46.9)	
1b	1,054 (25.9)	180 (24.4)	334 (20.6)	229 (29.1)	1,797 (24.9)	
2	284 (7.0)	92 (12.4)	139 (8.6)	83 (10.5)	598 (8.3)	
3	310 (7.6)	170 (23.0)	184 (11.3)	71 (9.0)	735 (10.2)	
4a	113 (2.8)	108 (14.6)	277 (17.0)	71 (9.0)	569 (7.9)	
4b	51 (1.3)	34 (4.6)	44 (2.7)	5 (0.6)	134 (1.9)	
Node metastasis						<0.001
Negative	3,424 (84.3)	409 (55.3)	1,112 (68.4)	479 (60.9)	5,424 (75.2)	
Positive	640 (15.7)	330 (44.7)	513 (31.6)	308 (39.1)	1,791 (24.8)	
Distant metastasis						<0.001
Negative	4,034 (99.3)	712 (96.3)	1,586 (97.6)	777 (98.7)	7,109 (98.5)	
Positive	30 (0.7)	27 (3.7)	39 (2.4)	10 (1.3)	106 (1.5)	

Data are presented as number (%) or mean±SD.
WMD, well-moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma; EGC, early gastric cancer; AGC, advanced gastric cancer.
*The p-values were calculated by the Student t-test (for continuous variables) and chi-square test (for categorical variables); †The total number was different because unknown or missing values were excluded from the percentage calculation; ‡The clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer.

patients (28.2%) were AGC (Table 1). In EGC, WMD was the most common with 3,306 (63.8%) (Table 2). And in AGC, WMD 758 (37.2%) and PCC 644 (31.6%), which were similar in distribution between the two groups (Table 3). The distribution ratio of mixed carcinoma was similar, with 557 EGC (10.8%) and 230 AGC (11.3%) (Tables 2 and 3). The sex ratio of mixed carcinoma was close to 1:1 (51.7% vs 48.3%) in EGC (Table 2). And about 1.5 times (60.9% vs 39.1%) more males in AGC (Table 3). The mean size of the tumor was the largest in mixed carcinoma of 3.2 cm among EGC (Table 2). In AGC, the mean size of tumor was the largest in PCC (6.8 cm), followed by PD and mixed cancer of 5.9 cm and 5.6 cm, respectively (Table 3). In the analysis of location, EGC was often distributed in lower third, and AGC was more distributed in upper third than EGC. This trend was similar in mixed carcinoma. In patients with EGC, 1,587 (48.0%) patients received endoscopic treatment for WMD, while only 49 (5.0%) and 35 (6.3%) patients received endoscopic treatment for PCC and mixed carcinoma, respectively (Table 2).

In EGC, the WMD group was almost 1:1 with 1,587 (48.0%) endoscopic treatment and 1,719 (52.0%) operative treatment. In contrast, most of the patients in PD, PCC, and mixed carcinoma groups received operative treatment,

Table 2. The Distribution of Patients with Early Gastric Cancer

Characteristic	WMD	PD	PCC	Mixed carcinoma	Total	p-value*	p-value†
No. of patients	3,306 (63.8)	335 (6.5)	981 (18.9)	557 (10.8)	5,179 (100)		
Age, yr	65.2±10.0	61±12.6	53.2±11.9	55.5±12.1	61.6±11.9	<0.001	<0.001
Sex						<0.001	<0.001
Male	2,484 (75.1)	231 (69.0)	453 (46.2)	288 (51.7)	3,456 (66.7)		
Female	822 (24.9)	104 (31.0)	528 (53.8)	269 (48.3)	1,723 (33.3)		
Size of tumor, cm	2.0±1.4	2.6±1.7	2.4±1.4	3.2±1.9	2.3±1.5	<0.001	<0.001
Location						<0.001	0.014
Upper	372 (11.3)	60 (17.9)	122 (12.4)	67 (12.0)	621 (12.0)		
Middle	488 (14.8)	90 (26.9)	267 (27.2)	128 (23.0)	973 (18.8)		
Lower	2,446 (74.0)	185 (55.2)	592 (60.3)	362 (65.0)	3,585 (69.2)		
Lauren type						<0.001	<0.001
Intestinal	3,302 (99.9)	166 (49.6)	0	141 (25.3)	3,609 (69.7)		
Diffuse	2 (0.1)	157 (46.9)	978 (99.7)	327 (58.7)	1,464 (28.3)		
Mixed	2 (0.1)	12 (3.6)	3 (0.3)	89 (16.0)	106 (2.0)		
Treatment						<0.001	<0.001
Endoscopic	1,587 (48.0)	39 (11.6)	49 (5.0)	35 (6.3)	1,710 (33.0)		
Operative	1,719 (52.0)	296 (88.4)	932 (95.0)	522 (93.7)	3,469 (67.0)		
Tumor appearance‡						<0.001	<0.001
0-I	125 (3.9)	3 (0.9)	2 (0.2)	7 (1.3)	137 (2.7)		
0-IIa	667 (21.0)	45 (14.1)	57 (6.1)	54 (9.7)	823 (16.5)		
0-IIb	424 (13.4)	54 (16.9)	232 (24.7)	87 (15.7)	797 (16.0)		
0-IIc	1,925 (60.7)	211 (65.9)	636 (67.7)	392 (70.8)	3,164 (63.5)		
0-III	32 (1.0)	7 (2.2)	12 (1.3)	12 (2.2)	63 (1.3)		
Lymphatic invasion	344 (10.7)	69 (21.4)	45 (4.8)	74 (13.3)	532 (10.6)	<0.001	<0.001
Venous invasion	28 (0.9)	4 (1.2)	4 (0.4)	2 (0.4)	38 (0.8)	0.246	0.177
Perineural invasion	37 (1.2)	14 (4.3)	51 (5.4)	23 (4.1)	125 (2.5)	<0.001	0.489
T stage§						<0.001	<0.001
1a	2,252 (68.1)	155 (46.3)	647 (66.0)	328 (58.9)	3,382 (65.3)		
1b	1,054 (31.9)	180 (53.7)	334 (34.0)	229 (41.1)	1,797 (34.7)		
Node metastasis						<0.001	<0.001
Negative	3,110 (94.1)	278 (83.0)	881 (89.8)	429 (77.0)	4,698 (90.7)		
Positive	196 (5.9)	57 (17.0)	100 (10.2)	128 (23.0)	481 (9.3)		
Distant metastasis						0.666	0.929
Negative	3,303 (99.9)	334 (99.7)	979 (99.8)	556 (99.8)	5,172 (99.9)		
Positive	3 (0.1)	1 (0.3)	2 (0.2)	1 (0.2)	7 (0.1)		

Data are presented as number (%) or mean±SD.

WMD, well-moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma.

*The p-values were calculated by Student t-test (for continuous variables) and the chi-square test (for categorical variables); †The p-values were calculated to compare the other three groups (except WMD) by Student t-test (for continuous variables) and the chi-square test (for categorical variables); ‡The total number was different because unknown or missing values were excluded from the percentage calculation; §The clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer.

88.4%, 95.0%, and 93.7%, respectively (Table 2). The tumor appearance of EGC was the most common 0-IIc type with 3,164 (63.5%), especially in mixed carcinoma, the 0-IIc type accounted for 392 (70.8%). Three groups were compared except for the WMD group, which had a large proportion of endoscopic treatment, and there was no significant difference between the three groups of venous invasion (p=0.177) and perineural invasion (p=0.489). Lymphatic invasion was the most common in PD (21.4%), while mixed carcinoma was the second most common at 13.3% (p<0.001). Submucosal invasion (T1b) was most common in PD (53.7%) and the second highest in mixed carcinoma (41.1%) (p<0.001) (Table 2). On the other hand, LN metastasis was most observed in mixed carcinoma (23%) in EGC (p<0.001) (Fig. 2A).

In AGC, the Borrmann type III tumors was the most common with 1,320 patients (68.7%). This was notable for 173 (76.5%) patients in mixed carcinoma (Table 3). Borrmann type IV tumors showed a large proportion of 168 patients (27.7%) in PCC patients, and the second highest proportion was 27 patients (11.9%) in mixed carcinoma. Venous invasion was significantly lower than the other three groups, with 40 (17.6%) patients in mixed carcinoma (p=0.016). In contrast, LN metastasis, like EGC, was most observed in mixed carcinoma (78.3%) (p<0.001) (Fig. 2B). In AGC, distant metastasis was 3.6% and 3.9% in WMD

Table 3. The Distribution of Patients with Advanced Gastric Cancer

Characteristic	WMD	PD	PCC	Mixed carcinoma	Total	p-value*
No. of patients	758 (37.2)	404 (19.8)	644 (31.6)	230 (11.3)	2,036 (100)	
Age, yr	66.2±10.7	63.9±12.3	55.8±12.8	60.1±13.5	61.7±12.9	<0.001
Sex						<0.001
Male	587 (77.4)	290 (71.8)	337 (52.3)	140 (60.9)	1,354 (66.5)	
Female	171 (22.6)	114 (28.2)	307 (47.7)	90 (39.1)	682 (33.5)	
Size of tumor, cm	4.6±2.3	5.9±2.7	6.8±4.2	5.6±3.1	5.7±3.3	<0.001
Location						<0.001
Upper	211 (27.8)	144 (35.6)	262 (40.7)	73 (31.7)	690 (33.9)	
Middle	123 (16.2)	80 (19.8)	175 (27.2)	50 (21.7)	428 (21.0)	
Lower	424 (55.9)	180 (44.6)	207 (32.1)	107 (46.5)	918 (45.1)	
Lauren type†						<0.001
Intestinal	758 (100)	186 (46)	2 (0.3)	40 (17.4)	986 (48.4)	
Diffuse	0	195 (48.3)	639 (99.2)	146 (63.5)	980 (48.1)	
Mixed	0	23 (5.7)	3 (0.5)	43 (18.7)	69 (3.4)	
Treatment						<0.001
Endoscopic	35 (4.6)	1 (0.2)	2 (0.3)	4 (1.7)	42 (2.1)	
Operative	723 (95.4)	403 (99.8)	642 (99.7)	226 (98.3)	1,994 (97.9)	
Tumor appearance†						<0.001
Borrmann I	35 (4.9)	9 (2.4)	4 (0.7)	6 (2.7)	54 (2.8)	
Borrmann II	130 (18.2)	81 (21.8)	10 (1.6)	14 (6.2)	235 (12.2)	
Borrmann III	482 (67.3)	256 (68.8)	409 (67.4)	173 (76.5)	1,320 (68.7)	
Borrmann IV	7 (1.0)	17 (4.6)	168 (27.7)	27 (11.9)	219 (11.4)	
Lymphatic invasion	475 (65.7)	283 (75.1)	349 (56.5)	166 (72.8)	1,273 (65.4)	<0.001
Venous invasion	160 (22.2)	93 (24.7)	169 (27.3)	40 (17.6)	462 (23.8)	0.016
Perineural invasion	373 (51.7)	238 (63.1)	525 (84.8)	170 (74.6)	1,306 (67.1)	<0.001
T stage‡						<0.001
2	284 (37.5)	92 (22.8)	139 (21.6)	83 (36.1)	598 (29.4)	
3	310 (40.9)	170 (42.1)	184 (28.6)	71 (30.9)	735 (36.1)	
4a	113 (14.9)	108 (26.7)	277 (43.0)	71 (30.9)	569 (27.9)	
4b	51 (6.7)	34 (8.4)	44 (6.8)	5 (2.2)	134 (6.6)	
Node metastasis						<0.001
Negative	314 (41.4)	131 (32.4)	231 (35.9)	50 (21.7)	726 (35.7)	
Positive	444 (58.6)	273 (67.6)	413 (64.1)	180 (78.3)	1,310 (64.3)	
Distant metastasis						0.091
Negative	731 (96.4)	378 (93.6)	607 (94.3)	221 (96.1)	1,937 (95.1)	
Positive	27 (3.6)	26 (6.4)	37 (5.7)	9 (3.9)	99 (4.9)	

Data are presented as number (%) or mean±SD.
WMD, well-moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma.
*The p-values were calculated by Student t-test (for continuous variables) and the chi-square test (for categorical variables); †The total number was different because unknown or missing values were excluded from the percentage calculation; ‡The clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer.

and mixed carcinoma, respectively, lower than PD 6.4% and PCC 5.7%, but there was no statistically significant difference (p=0.091) (Table 3, Fig. 3).

3. Subgroup analyses according to PCC component

We analyzed 787 mixed carcinoma patients by dividing them into four groups (10% to 30%, 31% to 50%, 51% to 70%, and 71% to 90%), to whether there were clinicopathological differences according to PCC component. The group with PCC component of 10% to 30% (mean age, 59.8 years) was older than the other groups (p<0.001), and the proportion of males (62.8%) was higher (p=0.022). However, there were no significant differences between the four groups according to size of tumor, location, initial treatment modality, lymphatic invasion, venous invasion, perineural invasion, T stage, LN metastasis, and distant metastasis (Table 4).

DISCUSSION

Pathologically, mixed carcinoma is a mixture of glandular and pure cohesive carcinoma histological components defined in the 2010 WHO classification, thus there have been few reports on this. Our study highlighted the independent clinical features of mixed carcinoma from glandu-

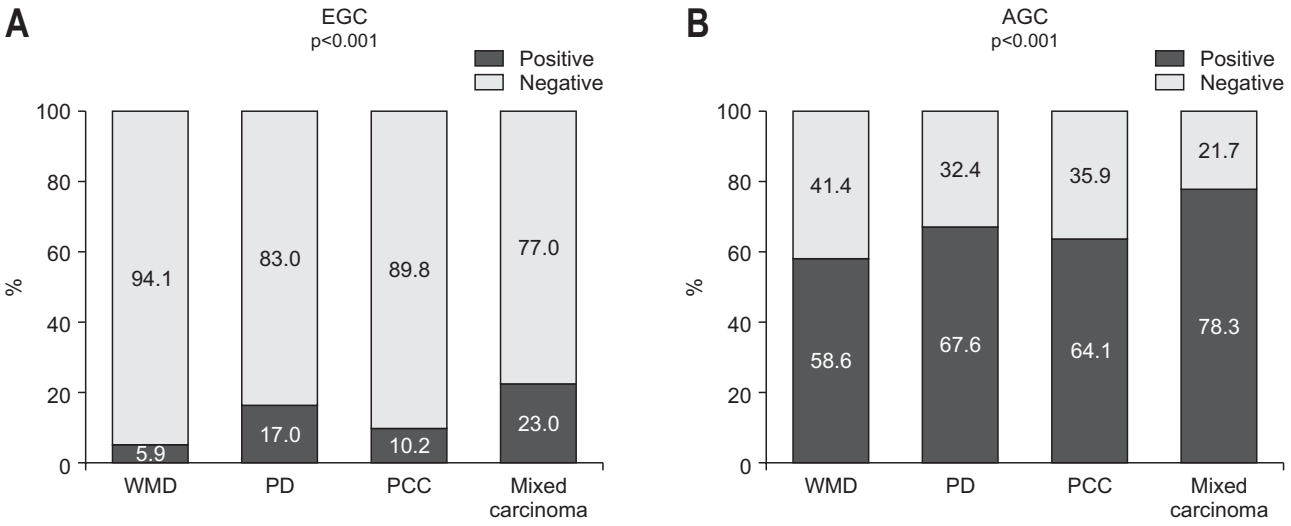

Fig. 2. Distribution of lymph node metastasis according to histological subtypes in EGC and AGC. (A, B) Lymph node metastasis was the highest in mixed carcinoma for both EGC (23.0%) and AGC (78.3%) (p<0.001). p-values were calculated by Student t-test (for continuous variables) and by the chi-square test (for categorical variables).
EGC, early gastric cancer; AGC, advanced gastric cancer; WMD, well-moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma.

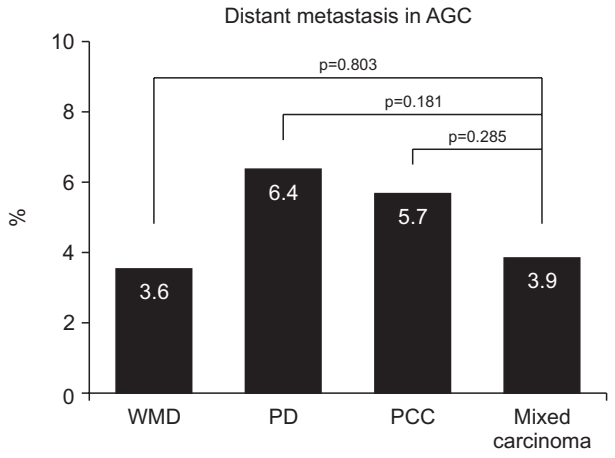

Fig. 3. Distant metastasis according to histological subtypes in advanced gastric cancer (AGC). The distant metastasis in AGC was relatively small in mixed carcinoma, but there was no statistically significant difference. p-values were calculated by Student t-test (for continuous variables) and by the chi-square test (for categorical variables).
WMD, well-moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma.

lar or pure cohesive carcinoma. Actually, mixed carcinoma was not rare (10.9%, 787/7,215). The diagnostic mean age of mixed carcinoma was about 5 years younger than the age of overall GC patients. The sex ratio of overall GC patients was twice that of males and females, whereas that in mixed carcinoma was similar. Mixed carcinoma showed more aggressive submucosal invasion and LN metastasis compared to other three subgroups in the GC. On the other hand, mixed carcinoma had less occurrence of venous invasion and distant metastasis in AGC. So far there was no clear mechanism regarding the less venous intrusion and distant metastasis in mixed carcinoma. It is reverse to that of SRC which shows the transition of prognosis as disease progressed. That is, SRC had better survival in EGC than non-SRC, but it becomes reverse in AGC which shows poor prognosis. A previous study suggested driver mutations that control the metastatic potential of SRC may occur late in the course of disease and acquire immune mechanisms or aggressive aspects.[9,13] Similarly, we guess that somehow mixed carcinoma has some potential to suppress metastasis. However, it is a simple hypothesis and further research should be performed for this puzzle.

Furthermore, it was also noteworthy that there was no clinicopathological difference according to the high and low PCC components in mixed carcinoma, indicating unique entity in the gastric carcinogenesis. Previous reports have suggested that mixed carcinoma has an even higher risk of LN metastasis than purely carcinoma.[16,22-24] However, they were based on the histologic type of the Japanese classification, defined mixed carcinoma as a mixture of differentiated and undifferentiated histological components partially overlaps with the 2010 WHO classification. Park *et al.*[17] reported that the presence of PCC histological components was an independent risk factor associated with LN metastasis in submucosal invasive EGC based on the 2010 WHO classification. However, this study has several limitations. That is, this study included 202 patients who received surgical treatment and only 56 were mixed

Table 4. The Distribution of Patients with Gastric Cancer According to the PCC Component

Characteristic	PCC component, %				Total	p-value*
	10≤PCC≤30	30<PCC≤50	50<PCC≤70	70<PCC≤90		
No. of patients	226 (28.7)	129 (16.4)	218 (27.7)	214 (27.2)	787 (100)	
Age, yr	59.8±12.1	55.8±12.7	55.6±12.5	55.5±13.0	56.8±12.7	<0.001
Sex						0.022
Male	142 (62.8)	67 (51.9)	107 (49.1)	112 (52.3)	428 (54.4)	
Female	84 (37.2)	62 (48.1)	111 (50.9)	102 (47.7)	359 (45.6)	
Size of tumor, cm	3.9±2.6	3.8±2.5	3.8±2.5	4.0±2.7	3.9±2.6	0.844
Location						0.135
Upper	50 (22.1)	25 (19.4)	33 (15.1)	32 (15.0)	140 (17.8)	
Middle	49 (21.7)	35 (27.1)	53 (24.3)	41 (19.2)	178 (22.6)	
Lower	127 (56.2)	69 (53.5)	132 (60.6)	141 (65.9)	469 (59.6)	
Treatment						0.241
Endoscopic	10 (4.4)	11 (8.5)	9 (4.1)	9 (4.2)	39 (5.0)	
Operative	216 (95.6)	118 (91.5)	209 (95.9)	205 (95.8)	748 (95.0)	
Lymphatic invasion	148 (65.8)	88 (68.8)	158 (72.8)	150 (70.1)	544 (69.4)	0.448
Venous invasion	209 (93.3)	121 (94.5)	207 (95.4)	204 (95.3)	741 (94.6)	0.745
Perineural invasion	176 (78.2)	94 (73.4)	161 (74.2)	160 (74.8)	591 (75.4)	0.694
T stage†						0.306
1a	91 (40.3)	51 (39.5)	97 (44.5)	89 (41.6)	328 (41.7)	
1b	79 (35.0)	38 (29.5)	57 (26.1)	55 (25.7)	229 (29.1)	
2	21 (9.3)	13 (10.1)	24 (11.0)	25 (11.7)	83 (10.5)	
3	23 (10.2)	14 (10.9)	18 (8.3)	16 (7.5)	71 (9.0)	
4a	12 (5.3)	11 (8.5)	21 (9.6)	27 (12.6)	71 (9.0)	
4b	0	2 (1.6)	1 (0.5)	2 (0.9)	5 (0.6)	
Node metastasis						0.296
Negative	148 (65.5)	80 (62.0)	129 (59.2)	122 (57.0)	479 (60.9)	
Positive	78 (34.5)	49 (38.0)	89 (40.8)	92 (43.0)	308 (39.1)	
Distant metastasis						0.115
Negative	224 (99.1)	129 (100)	212 (97.2)	212 (99.1)	777 (98.7)	
Positive	2 (0.9)	0	6 (2.8)	2 (0.9)	10 (1.3)	

Data are presented as number (%) or mean±SD.
PCC, poorly cohesive carcinoma.
*The p-values were calculated by Student t-test (for continuous variables) and the chi-square test (for categorical variables); †The clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer.

carcinoma, which was insufficient to explain statistically significant differences.[17] In contrast, our study enrolled 7,125 patients for long time who received endoscopic as well as surgical treatment, and evaluated LN metastasis by dividing into EGC and AGC. As a result, compared to the other histological three subgroups, the proportion of LN metastasis in mixed carcinoma was the highest in both EGC and AGC.

Huh *et al.*[14] reported that mixed SRC groups, defined as adenocarcinoma with a minor component (10% to 50%) of isolated carcinoma cells containing mucin in a based on the WHO International Histological Classification of Tumors, were associated with submucosal invasion (60.3%) compared to SRC groups (31.3%). In EGC, submucosal invasion was most common in the PD (53.7%) and the second most common in mixed carcinoma (41.1%). The proportion of submucosal invasion in mixed carcinoma was higher than that of WMD (31.9%) or PCC (34%),[14] This result was contrary to the previous reports probably the definition of mixed carcinoma was different.[14]

We assumed that the higher the PCC component, the more the clinical characteristics or prognosis could be different. However, when mixed carcinoma patients were divided into four subgroups according to PCC component in our study, there were no significant differences in size of tumor, location, initial treatment modality, lymphatic invasion, venous invasion, perineural invasion, T stage, LN metastasis, and distant metastasis.

Our study has several limitations. The first is the lack of information on *Helicobacter pylori* infection. Initially, we tried to fill up these data in the all the enrolled patients. However, we found that it was very difficult in reality. Second, our study did not touch the issue regarding how differences in histological types affect prognosis such as survival or recurrence rate. Another limitation was that most patients received surgical treatment in the histologi-

cal types except for WMD. This is originated from that the endoscopic therapy guidelines of Korea and Japan prohibit the PD including PCC.[25,26] Usually the GC patients with distant metastasis do not receive the operation but chemotherapy and only supportive care. Thus, the pathologists cannot get the enough tissue to make a diagnosis of "mixed carcinoma" by simple biopsy Therefore, we excluded patients who received chemotherapy and conservative treatment, but this study included a large number of mixed carcinoma patients which might overcome of this diagnostic problem.

In conclusion, mixed carcinoma was associated with LN metastasis compared to WMD, PD, and PCC in both EGC and AGC, and it showed relatively common submucosal invasion in EGC. However, mixed carcinoma shows relatively less venous invasion and distant metastasis in AGC. Further research is needed for the underlying mechanism regarding these characteristics of mixed carcinoma.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: N.K. Data acquisition: N.K., H.H.J. Data analysis and interpretation: H.H.J., H.J.O., D.H.S., Y.C., J.P. Drafting of the manuscript: H.H.J. Critical revision of the manuscript for important intellectual content: N.K., H.H.J. Statistical analysis: S.A. Obtained funding: N.K. Administrative, technical, or material support; study supervision: J.L., H.Y., C.M.S., Y.S.P., D.H.L., H.J.O., H.S.L., Y.S.P., S.H.A., Y.S.S., D.J.P., H.H.K., Ji-Won Kim, Jin Won Kim, K.W.L., W.C., J.H.P., Y.J.L., K.H.L., Y.H.K. Approval of final manuscript: all authors.

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