J Gastric Cancer. 2024 Apr;24(2):185-198
https://doi.org/10.5230/jgc.2024.24.e14
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Peritoneal Washing Cytology Positivity in Gastric Cancer: Role of Lymph Node Metastasis as a Risk Factor

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Received: Sep 7, 2023
Revised: Oct 28, 2023
Accepted: Nov 12, 2023
Published online: Jan 9, 2024

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Funding
This study was supported by the National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (Nos. 2020R1A2C1012007 and RS-2022-00166271), the Catholic Medical Center Research Foundation in the program year 2021, the Research Supporting Program of

ABSTRACT

Purpose: Peritoneal washing cytology (PWC) is a widely used diagnostic tool for detecting peritoneal metastasis of advanced gastric cancer. However, the prognosis of patients with positive PWC remains poor even after gastrectomy, and treatments vary among institutions and eras. In this study, we identified the clinical factors that can help predict cytology-positive (CY(+)) gastric cancer.
Materials and Methods: We retrospectively reviewed the national data of patients with gastric cancer from 2019, as provided by the Information Committee of the Korean Gastric Cancer Association. Of the 13,447 patients with gastric cancer, 3,672 underwent PWC. Based on cytology results, we analyzed the clinicopathological characteristics and assessed the possibility of CY(+) outcomes in relation to T and N stages.
Results: Of the 3,270 patients who underwent PWC without preoperative chemotherapy, 325 were CY(+), whereas 2,945 were negative. CY(+) was more commonly observed in patients with Borrmann type IV gastric cancer, an undifferentiated histological type, and advanced pathological stages. Multivariate analysis revealed Borrmann type IV (odds ratio [OR], 1.821), tumor invasion to T3–4 (OR, 2.041), and lymph node metastasis (OR, 3.155) as independent predictors of CY(+). Furthermore, for circular tumor location, the N stage emerged as a significant risk factor for CY(+), particularly when the tumor was located on the posterior wall (PW) side.
Conclusions: Lymph node metastasis significantly affects CY(+) outcomes, particularly when the tumor is located on the PW side. Therefore, PWC should be considered not only in suspected serosal exposure cases but also in cases of lymph node metastasis.

Keywords: Gastric cancer; Cytology; Risk factor; Lymph node metastasis

INTRODUCTION

The incidence of early gastric cancer is increasing, and gastric cancer remains a major health concern because it significantly contributes to cancer-related morbidity and mortality [1-3]. The propensity of advanced gastric cancer (AGC) to metastasize to the peritoneal cavity is well-known; this frequently results in the development of disseminated tumor nodules and a markedly worse prognosis compared with localized gastric cancer [4,5]. Therefore, timely identifying peritoneal metastasis is of paramount importance because it offers a window of opportunities for prompt interventions that can substantially improve patient outcomes [6-8].

the Korean Gastric Cancer Association (Nos. KGCA2022IC2 and KGCA2022IC3), and the Korean Society of Endo-Laparoscopic & Robotic Surgery for 2022 (No. KSERS-22-04). The study sponsors were not involved in the study design, analysis, data interpretation, report writing, or the decision to submit the study results for publication.

Conflict of Interest

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

Author Contributions

Conceptualization: S.H.S.; Data curation: K.S., S.H.S., Information Committee of the KGCA; Formal analysis: K.S., S.H.S.; Investigation: K.S., S.H.S.; Validation: L.H.H., S.H.S.; Writing - original draft: K.S.; Writing - review & editing: L.H.H., S.K.Y., S.H.S.

Peritoneal washing cytology (PWC) is a valuable and minimally invasive technique [9-12]. It plays a dual role in the staging and prognostic assessment of AGC by detecting free cancer cells or tumor clusters in the peritoneal fluid. The information obtained from PWC is important for providing crucial evidence regarding the extent of peritoneal invasion. However, because the incidence of positive PWC results varies among patients, ongoing research and discussion are warranted to identify the clinical variables that can consistently predict PWC. The guidelines from Korea and Japan recognize the prognostic significance of positive PWC results [13,14]. Positive PWC, even in the absence of macroscopic peritoneal dissemination, suggests stage IV disease, indicating a disseminated disease. Although guidelines generally recommend the application of PWC for patients with AGC, particularly those being considered for curative resection, specific guidelines on when to perform PWC remain unavailable. At present, gastric cancer specialists perform PWC in patients with advanced cancer or suspected distant metastases at their discretion.

Therefore, in this study, we identified the clinicopathological characteristics associated with PWC positivity using national data collected from patients with gastric cancer and established indications for performing PWC.

MATERIALS AND METHODS

Data collection

We retrospectively reviewed nationwide data collected by the Information Committee of the Korean Gastric Cancer Association (KGCA) in 2019. The data, which included 54 variables, were collected from 68 institutions and comprised information on 14,076 patients who underwent surgery for gastric adenocarcinoma between January 2019 and March 2020. The Information Committee of the KGCA developed a case report form for the 2019 nationwide survey by using data from previous Korean surveys [2,15]. The case report form included information on patient demographics, medical history, pathological findings, operative methods, and surgical outcomes [2]. The Information Committee of the KGCA reviewed the collected data and removed incorrect or missing data. In total, 13,447 patients who could undergo PWC were identified, 3,672 of whom underwent PWC. After excluding the patients who had undergone preoperative chemotherapy, 3,270 patients who had undergone PWC were analyzed. Based on the PWC results, the patients were categorized into 2 groups: cytology-positive (CY(+)) and cytology-negative (CY(−)). The following clinicopathological characteristics and postoperative outcomes were collected: age, sex, body mass index, preoperative Eastern Cooperative Oncology Group (ECOG) scores, first relative family history of gastric cancer, history of other malignancies, surgical approach, extent of gastrectomy and lymphadenectomy, macroscopic tumor type, histological classification, pathological tumor invasion, lymph node metastasis (pT and pN), and tumor location (tubular and circular).

The Institutional Review Board of the Ethics Committee of the College of Medicine, Catholic University of Korea approved this study (approval No. XC20RIDI0049). Patient records were anonymized and de-identified before analysis.

Intraoperative PWC

Upon entering the peritoneal cavity via open or minimally invasive surgery, it was exploratorily assessed to determine tumor operability. If the peritoneal fluid was present, it was aspirated for pathological analysis. If the fluid volume was insufficient for cytological

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analysis, the pelvic and left subphrenic area was lavaged with 200 mL of normal saline. PWC was selectively performed when computed tomography (CT) or positron emission tomography (PET) indicated peritoneal seeding or when invasion into the serosa or adjacent organs was a concern.

Statistical analyses

The Student's t-test or Mann–Whitney U-test was performed for parametric continuous variables. The data were presented as mean±standard deviation. The chi-squared or Fisher's exact test was performed for categorical data. Univariate and multivariate analyses were performed to identify the risk factors for CY(+) using a logistic regression model. p-values less than 0.05 were considered significant. SPSS (ver.24; SPSS, Inc., Chicago, IL, USA) for Windows was used to perform statistical analysis.

RESULTS

Baseline characteristics and PWC trends of the study cohort

Table 1 presents the trends in which Korean surgeons performed PWC in patients with gastric cancer. PWC was more frequently performed in patients who underwent preoperative chemotherapy (69.2%, P<0.001), those with confirmed distant metastases, except CY(+), preoperatively (53.5%, P<0.001), those who underwent open surgery (54.2%, P<0.001), those with Borrmann type IV cancer (55.4%, P<0.001), and those with undifferentiated histological type cancer (29.1%, P<0.001) than in those without. In terms of tumor location, PWC was more frequently performed in patients with a whole tubular location (60.3%, P<0.001), 2 or more circular locations (43.5%, P<0.001), and whole circular location (52.9%, P<0.001). Furthermore, in terms of pathological T and N stages, PWC frequency increased as the stage progressed. Interestingly, PWC was even performed in patients with T1 (17.4%) or N0 (19.6%) cancer.

Table 1. Baseline characteristics of the entire study cohort

Variables (n=13,447)	Performed cytology (n=3,672)	Not performed cytology (n=9,775)	P-value
Age	63.1±12.1	62.8±11.8	0.165
Sex			<0.001
Male	2,499 (28.4)	6,309 (71.6)	
Female	1,173 (25.3)	3,466 (74.7)	
BMI	23.5±3.4	24.1±3.4	<0.001
ECOG score			<0.001
0–1	3,178 (40)	4,772 (60)	
2–4	413 (60.8)	266 (39.2)	
Unknown	81 (1.7)	4,737 (98.3)	
Family history			<0.001
Yes	415 (25.8)	1,194 (74.2)	
No	2,856 (26.6)	7,892 (73.4)	
Unknown	401 (36.8)	689 (63.2)	
Preoperative chemotherapy			<0.001
No	3,270 (25.4)	9,594 (74.6)	
Yes	402 (69.2)	179 (30.8)	
Unknown	0 (0)	2 (100)	
History of other malignancy			<0.001
Yes	191 (26.5)	530 (73.5)	
No	3,080 (26.4)	8,603 (73.6)	
Unknown	401 (38.4)	642 (61.6)	
Distant metastasis except CY(+)			<0.001
Yes	343 (53.5)	298 (46.5)	
No	3,329 (26)	9,477 (74)	

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https://doi.org/10.5230/jgc.2024.24.e14

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Table 1. (Continued) Baseline characteristics of the entire study cohort

Variables (n=13,447)	Performed cytology (n=3,672)	Not performed cytology (n=9,775)	P-value
Approach			<0.001
Laparoscopic	1,622 (18.2)	7,314 (81.8)	
Open	1,946 (54.2)	1,646 (45.8)	
Robotic	97 (12.3)	689 (87.7)	
Unknown	7 (5.3)	126 (94.7)	
Extent of resection			<0.001
STG	2,422 (23.6)	7,820 (76.4)	
TG	1,055 (38.6)	1,675 (61.4)	
No resection or other	195 (41.1)	280 (58.9)	
LN dissection			<0.001
No resection	14 (7.9)	164 (92.1)	
D1+ or less	958 (18.4)	4,239 (81.6)	
D2 or more	2,521 (32)	5,345 (68)	
Unknown	179 (86.9)	27 (13.1)	
Number of lesions			<0.001
1	3,523 (27.5)	9,274 (72.5)	
2 or more	147 (26.5)	408 (73.5)	
Unknown	2 (2.1)	93 (97.9)	
Tumor location (tubular)			<0.001
GEJ/upper	917 (33)	1,864 (67)	
Mid	945 (23.6)	3,057 (76.4)	
Lower	1,589 (25.8)	4,573 (74.2)	
Whole	158 (60.3)	104 (39.7)	
Unknown	63 (26.3)	177 (73.8)	
Tumor location (circular)			<0.001
LC	1,349 (26.5)	3,734 (73.5)	
GC	575 (25.8)	1,657 (74.2)	
AW	534 (24.4)	1,651 (75.6)	
PW	681 (24.6)	2,085 (75.4)	
2 or more	70 (43.5)	91 (56.5)	
Circular	359 (52.9)	320 (47.1)	
Unknown	104 (30.5)	237 (69.5)	
Macroscopic type			<0.001
Borrmann type IV (–)	3,244 (26.3)	9,113 (73.7)	
Borrmann type IV (+)	315 (55.4)	254 (44.6)	
Unknown	113 (21.7)	408 (78.3)	
Tumor size (cm)	5.1±3.3	3.5±2.6	<0.001
Histological type			
Differentiated	1,439 (25.3)	4,248 (74.7)	
Undifferentiated	2,116 (29.1)	5,164 (70.9)	
Unknown	117 (24.4)	363 (75.6)	
Lymphovascular invasion			<0.001
Yes	1,674 (39.7)	2,546 (60.3)	
No	1,827 (20.8)	6,973 (79.2)	
Unknown	171 (44.0)	256 (60.0)	
pT			<0.001
T1	1,453 (17.4)	6,900 (82.6)	
T2	384 (30.1)	893 (69.9)	
T3	733 (43.2)	964 (56.8)	
T4	986 (56.3)	766 (43.7)	
Unknown	116 (31.5)	252 (68.5)	
pN			<0.001
N0	1,817 (19.6)	7,431 (80.4)	
N1	476 (35.5)	863 (64.5)	
N2	400 (40.5)	587 (59.5)	
N3	751 (54.6)	625 (45.4)	
Unknown	228 (45.9)	269 (54.1)	

Data are represented as numbers (%) and mean±standard deviation.
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; CY(+); cytology-positive; STG = subtotal gastrectomy; TG = total gastrectomy; LN = lymph node; GEJ = gastroesophageal junction; LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall.

https://doi.org/10.5230/jgc.2024.24.e14

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Clinicopathological characteristics of patients based on PWC results

After applying our exclusion criteria, we focused on patients who underwent PWC; **Table 2** summarizes their clinicopathological characteristics. Of the 3,270 patients, 325 were CY(+), whereas 2,945 were CY(−). Several factors, including the ECOG score, surgical approach, resection extent, lymph node dissection, macroscopic type, tumor size, histological type, and pathological T and N stages, exhibited significant differences between both groups. A particularly interesting observation pertained to tumor location. The CY(+) rate peaked at 24.4% for tumors located in the circular region, except for unknown locations. However, tumors located on the posterior wall (PW) had a relatively low CY(+) rate of 4.5% (P<0.001).

Table 2. Clinicopathologic characteristics based on the PWC results

Variables (n=3,270)	CY(+) (n=325)	CY(−) (n=2,945)	P-value
Age	63.9±12.3	63.1±12.1	0.236
Sex			0.950
Male	222 (9.9)	2,017 (90.1)	
Female	103 (10.0)	928 (90.0)	
BMI	22.6±3.5	23.6±3.4	<0.001
ECOG score			0.038
0–1	274 (9.5)	2,603 (90.5)	
2–4	51 (13.0)	342 (87.0)	
Family history			0.048
Yes	42 (11.3)	330 (88.7)	
No	259 (10.3)	2,267 (89.7)	
Unknown	24 (6.5)	348 (93.5)	
History of other malignancy			0.039
Yes	21 (12.4)	149 (87.6)	
No	280 (10.3)	2,448 (89.7)	
Unknown	24 (6.5)	348 (93.5)	
Approach			0.023
Laparoscopic	155 (10.6)	1,305 (89.4)	
Open	168 (9.8)	1,545 (90.2)	
Robotic	2 (2.1)	95 (97.9)	
Extent of resection			<0.001
STG	143 (6.7)	2,004 (93.3)	
TG	107 (11.3)	842 (88.7)	
No resection or others	75 (43.1)	99 (56.9)	
LN dissection			<0.001
D1+ or less	44 (5.2)	806 (94.8)	
D2 or more	206 (9.2)	2,040 (90.8)	
No LN dissection	75 (43.1)	99 (56.9)	
Number of lesions			0.016
1	320 (10.2)	2,821 (89.8)	
2 or more	5 (3.9)	124 (96.1)	
Tumor location (tubular)			<0.001
GEJ/upper	58 (7.0)	771 (93.0)	
Mid	71 (8.2)	792 (91.8)	
Lower	147 (10.7)	1,224 (89.3)	
Whole	25 (16.7)	125 (83.3)	
Unknown	24 (42.1)	33 (57.9)	
Tumor location (circular)			<0.001
LC	108 (9.2)	1,070 (90.8)	
GC	40 (7.9)	467 (92.1)	
AW	38 (8.2)	425 (91.8)	
PW	28 (4.5)	590 (95.5)	
2 or more	3 (4.3)	67 (95.7)	
Circular	82 (24.4)	254 (75.6)	
Unknown	26 (26.5)	72 (73.5)	

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Table 2. (Continued) Clinicopathologic characteristics based on the PWC results

Variables (n=3,270)	CY(+) (n=325)	CY(−) (n=2,945)	P-value
Macroscopic type			<0.001
Borrmann type IV (−)	212 (7.3)	2,675 (92.7)	
Borrmann type IV (+)	74 (26.4)	206 (73.6)	
Unknown	39 (37.9)	64 (62.1)	
Tumor size (cm)	7.5±3.8	4.9±3.2	<0.001
Histological type			<0.001
Differentiated	75 (6.0)	1,182 (94.0)	
Undifferentiated	217 (11.4)	1,692 (88.6)	
Unknown	33 (31.7)	71 (68.3)	
pT			<0.001
T1	37 (3.0)	1,214 (97.0)	
T2	18 (5.2)	328 (94.8)	
T3	47 (7.0)	628 (93.0)	
T4	181 (20.2)	716 (79.8)	
Unknown	42 (41.6)	59 (58.4)	
pT			<0.001
T1–2	55 (3.4)	1,542 (96.6)	
T3–4	228 (14.5)	1,344 (85.5)	
Unknown	42 (41.6)	59 (58.4)	
pN			<0.001
N0	38 (2.4)	1,533 (97.6)	
N1	27 (6.4)	398 (93.6)	
N2	38 (10.4)	329 (89.6)	
N3	141 (20.2)	556 (79.8)	
Unknown	81 (38.6)	129 (61.4)	
pN			<0.001
N−	38 (2.4)	1,533 (97.6)	
N+	206 (13.8)	1,283 (86.2)	
Unknown	81 (38.6)	129 (61.4)	
Subgroups			<0.001
pT2N−	4 (2.2)	177 (97.8)	
pT2N+	14 (8.6)	148 (91.4)	
pT3–4N−	21 (5.7)	346 (94.3)	
pT4–4N+	186 (16.4)	948 (83.6)	
Others	100 (7.0)	1,326 (93.0)	

Data are represented as numbers (%) and mean±standard deviation.
PWC = peritoneal washing cytology; CY(+); cytology-positive; CY(−); cytology-negative; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; STG = subtotal gastrectomy; TG = total gastrectomy; LN = lymph node; GEJ = gastroesophageal junction; LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall.

Identification of the risk factors for CY(+)

To identify the risk factors associated with CY(+), we conducted logistic regression analysis of 2,019 patients who underwent PWC. The pT1 group was excluded before analysis because the incidence of CY(+) is low in this group in real-world clinical settings. In addition, variables such as tumor size, pathological stage, and lymphovascular invasion were excluded because they were the final pathological results. Multivariate analysis revealed several independent risk factors for CY(+) (**Table 3**). Notably, patients with Borrmann type IV tumors had an odds ratio (OR) of 1.821 (95% confidence interval [CI], 1.288–2.576; P=0.001). Patients with advanced pathological tumor stages, specifically pT3–4, had an OR of 2.041 (95% CI, 1.213–3.435; P=0.007). The presence of lymph node metastasis had the highest OR of 3.155 (95% CI, 2.030–4.903; P<0.001). In contrast, D2 or more dissection decreased the risk of CY(+); this may be because palliative gastrectomy with minimal lymph node dissection was categorized into the D1+ or less lymph node dissection group. Interestingly, among circular locations, the PW side had a significantly lower risk, with an OR of 0.568 (95% CI, 0.344–0.939; P=0.027).

https://doi.org/10.5230/jgc.2024.24.e14

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Table 3. Risk factors for CY(+) (excluding T1 cases)

Variable (n=2,019)	Univariate				Multivariate			
	HR	LCI	UCI	P-value	HR	LCI	UCI	P-value
Age	1.001	0.991	1.011	0.841				
Sex								
Male	Reference							
Female	0.967	0.737	1.270	0.811				
BMI	0.947	0.912	0.983	0.004				
ECOG score								
0–1	Reference							
2–4	1.449	1.029	2.039	0.034				
Approach								
Laparoscopic	Reference				Reference			
Open	0.667	0.518	0.860	0.002	0.857	0.631	1.165	0.324
Robotic	0.300	0.071	1.271	0.102	0.480	0.109	2.101	0.330
Extent of resection								
STG	Reference							
TG	1.233	0.933	1.630	0.142				
No resection	5.123	3.528	7.438	0.000				
Extent of LN dissection								
D1+ or less	Reference				Reference			
D2 or more	0.777	0.521	1.157	0.214	0.614	0.399	0.944	0.026
No LN dissection	3.756	2.300	6.133	0.000				
Tumor location (circular)								
LC	Reference				Reference			
GC	0.981	0.653	1.473	0.926	0.974	0.641	1.482	0.903
AW	0.851	0.550	1.316	0.468	0.994	0.635	1.557	0.979
PW	0.453	0.277	0.741	0.002	0.568	0.344	0.939	0.027
2 or more	0.424	0.129	1.389	0.156	0.492	0.148	1.639	0.248
Circular	2.146	1.531	3.007	0.000	1.364	0.944	1.971	0.098
Unknown	3.064	1.819	5.160	0.000	0.698	0.321	1.519	0.365
Macroscopic type								
Borrman type IV (–)	Reference				Reference			
Borrman type IV (+)	2.533	1.839	3.488	0.000	1.821	1.288	2.576	0.001
Unknown	6.236	3.993	9.738	0.000	3.090	1.445	6.608	0.004
Histologic type								
Differentiated	Reference							
Undifferentiated	1.503	1.121	2.016	0.007				
Unknown	4.174	2.556	6.815	0.000				
pT								
T2	Reference				Reference			
T3–4	3.091	1.885	5.070	0.000	2.041	1.213	3.435	0.007
Unknown	12.972	6.993	24.061	0.000	2.526	0.994	6.418	0.052
pN								
N–	Reference				Reference			
N+	3.847	2.506	5.905	0.000	3.155	2.030	4.903	0.000
Unknown	12.297	7.403	20.425	0.000	3.215	1.531	6.752	0.002

CY(+) = cytology-positive; HR = hazard ratio; LCI = lower confidence interval; UCI = upper confidence interval; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; STG = subtotal gastrectomy; TG = total gastrectomy; LN = lymph node; LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall.

Assessing the possibility of CY(+) based on T and N stages stratified by circular tumor location

Table 4 presents the outcomes of the chi-squared analysis of the CY(+) ratio, taking into account the pathological T stage, stratified by the pathological N stage and the circular tumor location. Among the patients who underwent PWC (n=3,270), we excluded those with T1 cancer and without information on T or N stages or tumor location. In particular, both T and N stages distinctly affected the possibility of CY(+). **Fig. 1** provides a schematic illustration of the essence of these findings.

https://doi.org/10.5230/jgc.2024.24.e14

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Table 4. Possibility of CY(+) based on T and N stages stratified by circular tumor location (excluding T1 and unknown T and N stage or tumor location cases)

Location/LN metastasis	pT2 (n=341)	pT3–4 (n=1,482)	Total (n=1,823)	P-value
All (n=1,823)				
N–	2.2% (4/179)	5.8% (21/361)	4.6% (25/540)	0.044
N+	8.6% (14/162)	16.6% (186/1,121)	15.6% (200/1,283)	0.004
Total	5.3% (18/341)	14% (207/1,482)	12.3% (225/1,823)	<0.001
LC (n=688)				
N–	0% (0/70)	7% (9/129)	4.5% (9/199)	0.018
N+	8% (4/50)	16.2% (71/439)	15.3% (75/489)	0.089
Total	3.3% (4/120)	14.1% (80/568)	12.2% (84/688)	<0.001
GC (n=269)				
N–	0% (0/23)	9.6% (5/52)	6.7% (5/75)	0.151
N+	10.7% (3/28)	15.7% (26/166)	14.9% (29/194)	0.364
Total	5.9% (3/51)	14.2% (31/218)	12.6% (34/269)	0.077
AW (n=251)				
N–	7.1% (2/28)	3.4% (2/58)	4.7% (4/86)	0.393
N+	8.8% (3/34)	16% (21/131)	14.5% (24/165)	0.220
Total	8.1% (5/62)	12.2% (23/189)	11.2% (28/251)	0.261
PW (n=313)				
N–	4.7% (2/43)	3.4% (3/88)	3.8% (5/131)	0.531
N+	7.1% (3/42)	9.3% (13/140)	8.8% (16/182)	0.472
Total	5.9% (5/85)	7% (16/228)	6.7% (21/313)	0.473
2 or more (n=49)				
N–	0% (0/5)	11.1% (1/9)	7.1% (1/14)	0.643
N+	0% (0/3)	6.3% (2/32)	5.7% (2/35)	0.834
Total	0% (0/8)	7.3% (3/41)	6.1% (3/49)	0.579
Circular (n=253)				
N–	0% (0/10)	4.0% (1/25)	2.9% (1/35)	0.714
N+	20.0% (1/5)	24.9% (53/213)	24.8% (54/218)	0.638
Total	6.7% (1/15)	22.7% (54/238)	21.7% (55/253)	0.123

CY(+) = cytology-positive; LN = lymph node; LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall.

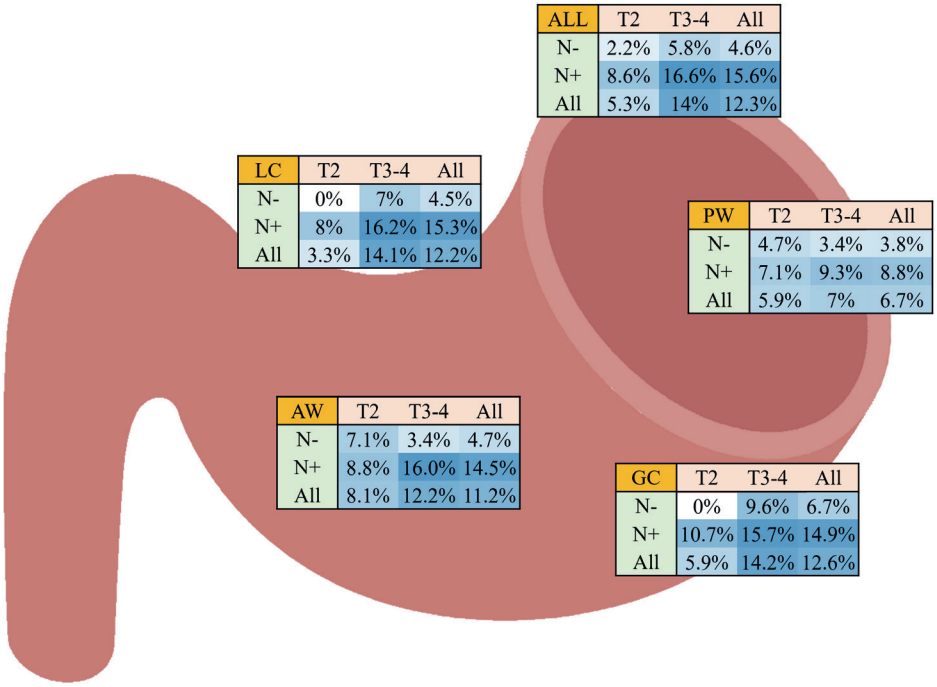

Fig. 1. Schematic diagram of the cytology-positive rate based on T and N stages stratified by circular tumor location. LC = lesser curvature; PW = posterior wall; AW = anterior wall; GC = greater curvature.

https://doi.org/10.5230/jgc.2024.24.e14

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Importance of T and N stages in CY(+) based on circular tumor location

Multivariate analysis was conducted to elucidate the effect of T and N stages on CY(+) based on circular tumor location in the same cohort (**Table 4**). For tumors located on the lesser curvature (LC) side, both T and N stages were independent determinants of CY(+). However, differences were observed based on specific tumor locations. In particular, for tumors on the PW side and circular location, only the N stage was identified as an independent risk factor, with ORs of 3.489 (95% CI, 1.170–10.409; P=0.025) and 11.195 (95% CI, 1.497–83.738; P=0.019), respectively. On the other hand, for tumors located on the greater curvature (GC) or anterior wall (AW) and the circular location, the N stage affected CY(+); however, the difference was not statistically significant (**Table 5**).

Subgroup analysis of patients with T3–4N0 based on PWC results

We conducted a focused chi-squared analysis of patients diagnosed with T3–4N0 to determine whether the cytology results varied depending on the tumor location (**Supplementary Table 1**). Notably, the differences for tumors located on the AW and PW sides were not statistically significant; however, their CY(+) ratio tended to be lower compared with that of other locations. Furthermore, patients with Borrmann type IV cancer exhibited significantly elevated CY(+) rates.

DISCUSSION

When identifying the predictive factors for CY(+) results among patients with gastric cancer who did not receive preoperative chemotherapy, several key determinants emerged, including the Borrmann type IV classification and lymph node metastasis. Our multivariate analysis, as summarized in **Table 3**, revealed that lymph node metastasis significantly affected the CY(+) outcomes of all patients who underwent PWC, except for T1 cases, with an OR of 3.155. Furthermore, among circular tumor locations, only the PW side significantly decreased the risk of CY (+), with an OR of 0.568. In addition, a closer examination of CY(+) probabilities (**Table 4**) revealed a nuanced picture: the effect of the T stage was less pronounced than that of the N stage for tumors located on the PW side compared with those located on other locations, including LC and GC. However, this does not suggest that gastric cancer on the PW side has a decreased propensity for peritoneal metastasis when deeply rooted and with minimal or absent lymph node metastasis. This observation probably stems from the stomach anatomy. The PW side, anatomically enclosed by the pancreas, greater omentum, and lesser omentum, is present in a relatively confined space [16,17]. Therefore, even if the tumor is deeply embedded, the cells may not disperse far from their origin. However, considering the multifaceted nature of the peritoneal metastasis of tumor cells, PWC should be performed even if the possibility of CY(+) is relatively low [18]. Hence, in patients with AGC on the PW side, opening the omentum and actively performing PWC are vital. Additionally, while tumor depth is typically considered a primary risk factor for peritoneal metastasis of gastric cancer, our findings suggest that the significance of lymph node metastasis varies based on the tumor location [19]. Collectively, our results underscore the pivotal role of tumor location and specific clinicopathological features in predicting CY(+) outcomes, offering invaluable insights for clinicians.

Peritoneal metastasis of gastric cancer is a multifaceted process. It involves the migration of tumor cells from the stomach to the peritoneal cavity, a space that envelops the abdominal organs [20]. While the exact mechanism underlying peritoneal seeding remains unknown,

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Table 5. Importance of T and N stages in CY(+) stratified by circular tumor location (excluding T1 and unknown T and N stage cases)

Variable (n=1,823)		Multivariate analysis			
		HR	LCI	UCI	P-value
All					
	pT				
	T2		Reference		
	T3–4	2.228	1.344	3.695	0.002
	pN				
	N–		Reference		
	N+	3.348	2.169	5.167	0.000
LC					
	pT				
	T2		Reference		
	T3–4	3.423	1.208	9.705	0.021
	pN				
	N–		Reference		
	N+	3.095	1.500	6.386	0.002
GC					
	pT				
	T2		Reference		
	T3–4	-	-	-	-
	pN				
	N–		Reference		
	N+	2.461	0.915	6.618	0.074
AW					
	pT				
	T2		Reference		
	T3–4	-	-	-	-
	pN				
	N–		Reference		
	N+	2.429	0.867	6.807	0.091
PW					
	pT				
	T2		Reference		
	T3–4	-	-	-	-
	pN				
	N–		Reference		
	N+	3.489	1.170	10.409	0.025
2 or more					
	pT				
	T2		Reference		
	T3–4	-	-	-	-
	pN				
	N–		Reference		
	N+	0.533	0.043	6.655	0.625
Circular					
	pT				
	T2		Reference		
	T3–4	-	-	-	-
	pN				
	N–		Reference		
	N+	11.195	1.497	83.738	0.019

CY(+) = cytology-positive; HR = hazard ratio; LCI = lower confidence interval; UCI = upper confidence interval; LC = lesser curvature; GC = greater curvature; AW = anterior wall; PW = posterior wall.

the presence of malignant cells in the peritoneum can initiate peritoneal seeding [21,22]. This metastatic route is particularly prevalent in gastric cancer and often leads to advanced disease stages and poor prognosis. In the peritoneal cavity, cancer cells interact with the microenvironment, leveraging adaptive mechanisms for survival, subsequently attaching to

https://doi.org/10.5230/jgc.2024.24.e14

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peritoneal mesothelial cells or the lymphatic stomata [20,23,24]. After successful invasion, they proliferate, and along with blood vascular neogenesis, form new blood vessels that support their growth. These steps underscore the intricate series of events facilitating the metastasis of gastric cancer cells within the peritoneal environment and highlight potential therapeutic intervention targets [25,26].

Several factors can affect the risk and pattern of peritoneal metastasis of gastric cancer, including primary tumor location in the stomach [19,27,28]. A previous study has revealed that tumors in different stomach regions exhibit varied metastatic behaviors, emphasizing the complex interplay between anatomical positioning and metastatic tendencies [28]. Such differential metastatic patterns accentuate the intricacies of tumor location and their effect on peritoneal dissemination [27]. These insights emphasize the need to consider tumor location when devising treatment strategies, predicting outcomes, and planning interventions for patients with gastric cancer.

The biggest challenge in diagnosing patients with AGC and suspected peritoneal metastasis is the absence of relevant guidelines for diagnosis. Guidelines may vary among surgeons; however, at our hospital, PWC is performed when seeding is suspected. Moreover, even if peritoneal seeding is not clearly confirmed via CT or PET, PWC is performed before gastrectomy when serosal invasion is suspected, or when further invasion to adjacent organs beyond serosal invasion is suspected. Additionally, even if serosal invasion is unclear, cytology is performed if a lesion resembling a seeding nodule is identified during surgery. In a Korean study, the authors selectively performed PWC in patients in whom overt peritoneal metastasis was strongly suspected; however, they did not provide any clear criteria [29]. In the present study, nationwide data were collected; therefore, individual PWC protocols were not available. The protocol used by most institutions, including ours, is as follows: the peritoneal cavity is accessed via open or minimally invasive surgery, followed by exploration to confirm tumor operability. If the peritoneal fluid is present, it is aspirated for analysis; however, if the amount is insufficient, irrigation is performed using 200 mL of normal saline to rinse the pelvic cavity and left subphrenic area before gastrectomy [29].

However, the clinical utility of PWC for patients with AGC remains controversial. The European Society for Medical Oncology views this procedure as optional [30]. Furthermore, the current National Comprehensive Cancer Network guidelines do not explicitly incorporate peritoneal cytology into the gastric cancer treatment algorithm, despite considering CY(+) as a criterion for curing unresectable cancers [31]. In fact, in actual clinical settings, CY(+) and stage IV do not perfectly align. However, CY(+) has been classified as Stage IV based on the Japanese classification of gastric carcinoma [32] or UICC/AJCC 8th TNM classification [33]. The 5-year overall survival of patients with CY(+) without gross peritoneal seeding who receive gastrectomy is 26% [34,35]. Because it has been confirmed that stage and prognosis can vary based on CY(+), this alone signifies that CY(+) holds significant clinical importance. Furthermore, by performing PWC first and confirming the absence of peritoneal dissemination, patients can avoid the unfortunate scenario of receiving unnecessary systemic therapies and missing the optimal surgical time. However, if CY(+) is confirmed, the patient can be saved from undergoing unnecessary surgery that could potentially delay the appropriate timing for systemic therapy, thereby avoiding inappropriate treatment strategies. Importantly, for patients with unresectable or metastatic gastric cancer, additional therapies such as targeted therapy using trastuzumab or immunotherapy using nivolumab may be administered. These agents have exhibited prognostic benefits in third-line or subsequent

https://doi.org/10.5230/jgc.2024.24.e14

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treatment in an Asian patient population or first-line treatment combined with standard cytotoxic agents [36-38].

This study has several limitations. First, it was limited by its retrospective nature. This approach inherently introduces challenges, including potential biases in data collection and the inability to establish causal relationships between variables, affecting the overall validity and reliability of the findings. In particular, owing to the lack of clear standards for conducting PWC, a high possibility of selection bias remains when performing retrospective analysis. Upon reviewing the latest version of the Japanese Gastric Cancer Treatment Guidelines published in July 2021, the members of the Japanese Gastric Cancer Association have mentioned that they weakly recommend staging laparoscopy as a treatment strategy for patients with AGC and suspected peritoneal metastasis [39]. Another limitation that warrants consideration is the imbalance in the number of participants between both groups; this introduces a potential source of bias in the comparison. Implementing a matching technique would be preferable to ensure that the groups are comparable in size and other key characteristics. This will help minimize the differences that can confound the results and provide a more accurate reflection of the true effects under investigation. Third, because no information on the clinical stage before surgery was available, analysis was performed based on the postoperative pathological stage. However, this approach is disadvantageous because information on the clinical stage is required to determine beforehand whether the cytology is positive. Finally, survival information was lacking, making it impossible to analyze the results based on the survival prognosis of patients. Nevertheless, to the best of our knowledge, this study is the first and the largest to analyze the effects of the depth of cancer and lymph node metastasis on the possibility of peritoneal metastasis of gastric cancer. Furthermore, our study results are significant because they present all data from Korea, a country with a high incidence of gastric cancer.

Lymph node metastasis may be a significant determinant of CY(+) outcomes, particularly when the tumor is located on the PW side. As such, PWC should be considered not only in cases where serosal exposure is suspected but also when lymph node metastasis is suspected.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Subgroup analysis of patients with T3–4N0 according to the results of PWC

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