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Clinical significance of computed tomography-detected ascites in gastric cancer patients with peritoneal metastases

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Abstract

Patients with peritoneal metastases (PM) are generally considered incurable; therefore, the presence of PM is a critical factor in deciding between palliative surgery and curative resection as a therapeutic strategy. Previous studies have not determined the predictive value of ascites detected on computed tomography (CT) for the presence of PM. We aimed to analyze the factors that are associated with PM in patients with CT-detected ascites.

A total of 2207 consecutive patients who were diagnosed with gastric cancer between 2004 and 2013 were identified. Eleven patients with liver cirrhosis or chronic renal insufficiency with ascites and 57 patients who received previous treatment were excluded. Ninety-eight patients who had definite evidence of distant metastasis or PM on CT and 64 patients who did not undergo surgery were excluded. A total of 91 patients were enrolled in the study to analyze the association between CT-detected ascites and surgically confirmed PM.

Seventy-six patients underwent curative resection and 15 patients underwent palliative surgery. Twelve patients exhibited peritoneal seeding and 37 patients showed regional lymph node metastasis. Regional lymph node metastasis, advanced gastric cancer, undifferentiated pathology, and the amount of ascites were significantly associated with PM. Multivariable logistic regression analysis identified the amount of ascites to be an independent risk factor for the presence of PM.

Regional lymph node metastasis, advanced gastric cancer, undifferentiated pathology, and the amount of ascites were associated with PM. The amount of ascites was found to be an independent risk factor for PM.

Abbreviations: AGC = advanced gastric cancer, CT = computed tomography, EGC = early gastric cancer, EUS = endoscopic ultrasonography, PM = peritoneal metastases.

Keywords: ascites, computed tomography, gastric cancer, peritoneal metastases

1. Introduction

Gastric cancer is one of the leading causes of cancer-related deaths in the world,[1,2] and *Helicobacter pylori* infection is a major cause of gastric cancer.[3] Although the incidence and mortality rates have steadily declined over the past 4 decades, gastric cancer is still the second most common cancer in Korea.[4] As surgical resection is the only curative therapeutic option in the treatment of gastric cancer, accurate preoperative staging of gastric cancer is essential to determine the optimal therapeutic strategy. Computed tomography (CT) is an accurate and effective imaging technique for the preoperative staging of gastric cancer and has been used reliably to detect tumors and to assess metastases to regional lymph nodes, the liver, and distant metastases resulting from gastric cancer.[5–7] However, the sensitivity of CT for the detection of peritoneal metastases (PM) is lower (13%–30%) than its sensitivity for the detection of other distant metastases.[8,9] There are limitations in detecting PM by using CT, and therefore PM are often only detected intraoperatively.[8,10,11] Previous reports have suggested that nodules on the peritoneal surface, soft-tissue stranding in intraabdominal fat, omental cake, and peritoneal thickening with abnormal contrast enhancement are suggestive of PM.[12–14] Because patients with PM are generally deemed incurable, the presence of PM is a critical factor to be considered when choosing between palliative surgery and curative resection as a therapeutic

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strategy.[15] Some reports have suggested that the presence of ascites on a CT scan suggests the presence of PM and indicates a poor prognosis.[16–18] However, the predictive value of CT-detected ascites for the presence of PM has not been determined.[19] Some studies, which investigated the association between the volume of ascites detected by CT and PM, concluded that there was no significant association between the ascites and PM or survival outcomes.[20,21] However, those studies were limited by small sample sizes. In this study, we aimed to analyze the clinical significance of CT-detected ascites and determine if it is a predictive factor for PM in gastric cancer patients.

2. Materials and methods

2.1. Patients

This study was approved by the Institutional Review Board of Seoul National University Boramae Medical Center. A total of 2207 consecutive patients who were diagnosed with gastric cancer based on histological examinations of endoscopically biopsied gastric mucosal tissues between 2004 and 2013 were identified. Their electronic medical records and CT scans were retrospectively reviewed. Of the 2207 patients, ascites was detected on the CT scans of 321 patients. Eleven patients with liver cirrhosis or chronic renal failure with ascites and 57 patients who underwent previous treatment were excluded from the study. Ninety-eight patients whose CT images showed definite evidence of distant metastases or PM (contrast-enhanced density in peritoneal adipose tissues and nodules on the peritoneum, mesentery, and omentum) and 64 patients who did not undergo surgery were excluded. As a result, 91 patients were included in the study (Fig. 1).

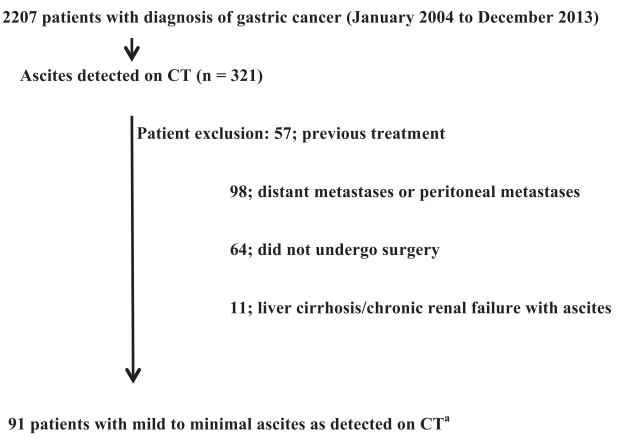

Figure 1. Patients enrolment.

2.2. Radiology

Contrast-enhanced CT examinations were performed on the 91 enrolled patients by using a Somatom Plus-4 scanner (Siemens Medical System, Erlangen, Germany). The helical technique was applied during the scanning of the abdomen and pelvis, and images were reconstructed with 10-mm-thick sections. A total of 80 to 120 mL of iopromide contrast medium (Ultravist 370, Schering, Berlin, Germany) was administered by using a mechanical power injector.

The CT findings were interpreted by an experienced radiologist (YHC). Tumor status, lymph node metastases, evidence of ascites, adjacent organ invasion, distant metastases, and PM were diagnosed. Ascites was diagnosed when a low radiologic density of $\leq$10 Hounsfield number was detected within the abdominopelvic cavity external to the abdominal or pelvic organs. The volume of ascites was calculated by applying ruler grids to the CT images, as described in previous reports.[19,21] Minimal ascites was defined as an ascites volume of $<$50 mL, and mild ascites was defined as a volume of 50 to 200 mL.

Based on a previous study, lymph nodes were considered significantly enlarged when the long axis diameter was $\geq$10 mm.[21] Other criteria for malignant involvement of the lymph nodes included a nearly round shape, loss of the normal fatty hilum, and marked heterogeneous enhancement. The lymph nodes located along the lesser or greater curvatures of the stomach or at the common hepatic, gastric, celiac, and splenic arteries were classified as regional, whereas intraabdominal nodes beyond these regions were defined as distant lymph nodes.[22]

2.3. Statistical analyses

Statistical analyses were performed by using IBM SPSS version 20.0 statistical software (IBM Corp., Armonk, NY). A 2-tailed $P<.05$ was considered statistically significant. The categorical variables of the CT findings were summarized as frequencies and proportions, and were evaluated by using the χ^2 test or Fisher exact test. Continuous variables were expressed as the mean $\pm$ standard deviation (SD) and were compared by performing a t test. To assess which variables were related to PM, we conducted a logistic regression analysis with Firth's penalized likelihood, which is used in the presence of small number of events.[23] First, a univariable logistic regression model was developed. Then, variables with $P<.20$ from the univariable analyses were included in the multivariable logistic regression analysis. The final model was developed using a backward elimination procedure.

3. Results

3.1. Baseline characteristics and clinical and surgical outcomes

A total of 91 patients (men, 59; women, 32; mean age, 61.8 yrs) were enrolled in the study to analyze the association between CT-detected ascites and surgically detected PM. Endoscopy results were available for 81 patients, of which 22 patients had early gastric cancer (EGC) and 59 patients had advanced gastric cancer (AGC). Of the 91 patients who underwent surgery, 76 patients underwent curative resection and 15 patients underwent palliative gastrectomy. Pathology findings revealed peritoneal seeding in 12 patients and regional lymph node metastasis in 37. No patient had distant lymph node metastasis (Table 1).

3.2. Factors associated with PM

The relationship between the detection of ascites on CT and PM at surgery is shown in Table 2. PM was detected during surgery in only 12 patients (13.2%). We found that endoscopic diagnosis of AGC ($P=.030$) and the presence of regional LN metastases ($P=.013$) were associated with PM. Further, the amount of ascites was higher in patients with PM than in those without PM ($P=.049$). The χ^2 test comparison indicated that the incidence of PM was higher in patients with mild ascites ($P=.015$) as

Table 1

Baseline characteristics of the patients with CT-detected ascites.

Variables	Patients with CT-detected ascites (N = 91)
Age, yrs	61.8 ± 12.6
Sex, male, n (%)	59 (64.8%)
Peritoneal metastases, n (%)	12 (13.2%)
Tumor marker elevation (N = 85), n (%)	12 (14.1%)
Amount of ascites, mL	13.36 ± 27.38
Endoscopy findings (N = 81)	
Early gastric cancer	22 (27.2%)
Advanced gastric cancer	59 (72.8%)
Pathology findings	
Well-differentiated adenocarcinoma	13 (14.3%)
Moderately differentiated adenocarcinoma	27 (29.7%)
Poorly differentiated adenocarcinoma	28 (30.8%)
Signet ring cell carcinoma	23 (25.3%)
CT-detected lymph node enlargement	
No lymph node enlargement	54 (59.3%)
Regional lymph node enlargement	37 (40.7%)
Staging	
I	33 (38.8%)
II	20 (23.5%)
III	32 (37.6%)
IV	0 (0.0%)
Ascites volume, mL	
<50	86 (94.5%)
50–100	3 (3.3%)
100–200	2 (2.2%)
>200	0 (0.0%)

CT = computed tomography.

compared with those with minimal ascites. Elevation of tumor marker levels was not significantly associated with PM. When a comparison was performed between patients with differentiated and undifferentiated pathology, PM was found to be significantly associated with undifferentiated pathology ($P = .043$) (Table 2).

3.3. Risk factors for PM

Univariable logistic regression analyses revealed that regional lymph node metastasis (OR, 4.905; 95% CI 1.424–20.556; $P = .011$), undifferentiated pathology on endoscopic biopsy (OR, 4.426; 95% CI 1.106–24.922; $P = .035$), and the amount of ascites (OR, 1.031; 95% CI 1.013–1.061; $P < .001$) were statistically significant factors associated with PM. In addition, endoscopic diagnosis of AGC was significantly associated with PM (OR, 10.670; 95% CI 1.286–1391.686; $P = .023$). In the multivariable logistic regression analysis with backward elimination, the amount of ascites was only identified as an independent risk factor for PM (OR, 1.089; 95% CI 1.018–1.193; $P = .001$; Table 3).

4. Discussion

Patients with PM are usually deemed incurable despite some recent studies showing survival benefits of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.[24,25] Therefore, the detection of PM is crucial in guiding therapeutic strategy. Previous studies have reported conflicting results on the association between CT-detected ascites and PM.[16,17,20,21] In our study, we found an association between the amount of ascites and the presence of PM in gastric cancer

Table 2

Comparison of clinical characteristics between patients with and without peritoneal metastases.

	Patients with PM (N = 12)	Patients without PM (N = 79)	*P*
Age, yrs	63.50 ± 9.59	61.52 ± 12.98	.613
Male sex	9 (75.0%)	50 (63.3%)	.530
Tumor marker elevation	3/11 (27.3%)	9/74 (12.2%)	.183
Amount of ascites	45.92 ± 58.48	8.41 ± 13.97	.049
Endoscopy findings			.030
Early gastric cancer	0 (0.0%)	22 (31.4%)	
Advanced gastric cancer	11 (100%)	48 (68.6%)	
Pathology finding			.201
Well-differentiated adenocarcinoma	1 (8.3%)	12 (15.2%)	
Moderately differentiated adenocarcinoma	1 (8.3%)	26 (32.9%)	
Poorly differentiated adenocarcinoma	5 (41.7%)	23 (29.1%)	
Signet ring cell carcinoma	5 (41.7%)	18 (22.8%)	
Pathology			.043
Differentiated	2 (20.0%)	34 (56.7%)	
Undifferentiated	8 (80.0%)	26 (43.3%)	
CT-detected lymph node enlargement			
No lymph node enlargement	3 (25.0%)	51 (64.6%)	.013
Regional lymph node enlargement	9 (75.0%)	28 (35.4%)	
Ascites, mL			.007
<50	9 (75%)	77 (97.5%)	
50–100	1 (8.3%)	2 (2.5%)	
100–200	2 (16.7%)	0 (0.0%)	
>200	0 (0.0%)	0 (0.0%)	
			.015
<50	9 (75.0%)	77 (97.5%)	
≥50	3 (25.0%)	2 (2.5%)	

CT = computed tomography, PM = peritoneal metastases.

Table 3

Univariable and multivariable analyses to determine risk factors of peritoneal metastases in patients with CT-detected ascites.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age, years	1.011	0.965–1.064	.640			
Male	1.586	0.460–6.757	.479			
Endoscopic diagnosis of AGC	10.670	1.286–1391.686	.023			
Undifferentiated pathology	4.426	1.106–24.922	.035			
Tumor marker elevation	2.839	0.614–11.291	.169			
Regional LN enlargement	4.905	1.424–20.556	.011			
Amount of ascites	1.031	1.013–1.061	<.001	1.089	1.018–1.193	.001

AGC = advanced gastric cancer, CT = computed tomography, LN = lymph node, OR = odds ratio.

patients who did not exhibit definite distant metastasis or PM on CT. As expected, univariable analysis revealed advanced gastric cancer and lymph node metastasis to be predictors. Similarly, undifferentiated pathology, which is a well-known factor associated with poor clinical outcome, was also found to be a factor.[26,27] In our study, which excluded patients with liver cirrhosis or chronic renal insufficiency, 10.5% of the patients with an ascites volume of < 50 mL had PM, whereas 60% of those with >50 mL of ascites had PM. Therefore, an ascites volume of >50 mL in gastric cancer patients without liver cirrhosis or chronic renal insufficiency may suggest PM.

CT-detected ascites was reported to be a specific indicator of PM in previous studies; however, the amount of ascites was not specified.[16–18] A recent study investigated patients with CT-detected ascites volume of <50 mL and concluded that there is no relation between minimal ascites and survival outcomes in patients with gastric cancer; however, patients with ascites volumes of >50 mL were not addressed in this study.[20] Chang et al[21] analyzed CT-detected ascites in gastric cancer patients, but the sample size was small. We investigated the factors associated with PM in gastric cancer patients and found the amount of ascites to be an independent risk factor. To our knowledge, this is the largest study to investigate the predictors of surgically proven PM in gastric cancer patients with ascites and without CT-detected distant metastasis or PM.

Preoperative identification of PM is critical in deciding therapeutic strategy. However, despite the recent developments in CT technology, the sensitivity of CT for PM detection is limited.[12] It is easy to diagnose PM when definite indicators such as soft tissue nodules, small bowel wall thickening, intra-abdominal fat stranding, and peritoneal thickening/enhancement are identified on CT,[22] and poor survival outcomes of patients with definite PM have been reported.[28,29] However, in cases where CT shows minimal ascites without additional indicators such as distant metastasis or PM, determining the therapeutic strategy is difficult. In cases with massive ascites, a cytological examination via paracentesis may aid in diagnosing PM. However, a cytological diagnosis cannot be performed in patients with minimal or mild ascites, making it more difficult for clinicians to establish a treatment plan in cases when CT does not show PM. Our study indicated that the risk of PM differs depending on the amount of ascites in patients with minimal or mild ascites. Our study may aid surgeons in deciding between curative resection and palliative surgery.

Previous studies have described that endoscopic ultrasonography (EUS) is a superior technique for the local staging of gastric cancer and the detection of ascites.[30–32] However, EUS is limited because of its low sensitivity in diagnosing liver or distant metastases.[19] In addition, the detection of fluid in the lower abdomen and the Douglas pouch by EUS is limited.[19,33] CT is very effective in the preoperative staging of gastric cancer, such as tumor detection and assessment of regional lymph node and liver metastases. However, CT has lower sensitivity in diagnosing PM as compared with diagnosing other distant metastases.[8,9] The findings of our study can be used by clinicians in cases where PM are not detected on CT.

Our study has some limitations. First, this study was a retrospective study. Because we included patients with CT-detected ascites and surgically confirmed PM, the size of this study is limited. Further, some of the enrolled patients lacked medical records such as endoscopic biopsy and tumor marker elevation results. However, this is the largest study to investigate the relation between CT-detected ascites and PM in patients with gastric cancer. Second, clinicopathological factors such as body mass index, *H. pylori* infection, and tumor size were not analyzed in this study. Third, the results of the peritoneal washing cytology performed during surgery were not available for most of the patients. Fourth, our study was conducted in a single academic teaching hospital.

5. Conclusions

Regional lymph node metastasis, advanced gastric cancer, undifferentiated pathology, and the amount of ascites were associated with PM. The amount of ascites was an independent risk factor for PM. Our study warrants further investigations with a larger sample size to elucidate the factors that are associated with PM in gastric cancer patients with ascites.

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