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ORIGINAL ARTICLE

Prognostic significance of computed tomography defined ascites in advanced gastric cancer

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Purpose: The aim of this study was to investigate the clinicopathologic features and prognosis in patients with computed tomography (CT) findings of ascites, with a focus on the correlation with peritoneal carcinomatosis. **Methods:** This study included a total of 157 patients who underwent surgery for advanced gastric cancer from 2003 to 2008 at the Department of Surgery, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea, which were analyzed retrospectively. **Results:** Fourteen patients (8.9%) presented ascites on their CT scan. Among them, 10 patients had peritoneal carcinomatosis, and showed significant difference with CT ascites positive group in the incidence of peritoneal carcinomatosis. The presence of CT ascites was significantly correlated with pathologic T stage, tumor size, histologic type, CT T and N stages, CT peritoneal nodularity and curability of surgery, statistically. The prognosis of CT ascites positive group was much poorer in the total advanced gastric cancer patients ($P < 0.001$), as well as in patients with pathologic T4 ($P = 0.002$). Also in patients without peritoneal carcinomatosis, CT ascites positive subgroup tended to have a worse prognosis than CT ascites negative subgroup ($P = 0.086$). Tumor size, CT T and N stages and the presence of CT peritoneal nodularity and ascites influenced the prognosis significantly; among which, if a tumor size larger than 5 cm, CT T4 stage and the presence of CT ascites were identified as independent prognostic factors. **Conclusion:** The presence of ascites was closely associated with peritoneal metastasis, and was the most significant independent prognostic factor in advanced gastric cancer in the present study.

Key Words: Ascites, Computed tomography, Stomach, Adenocarcinoma, Prognosis

INTRODUCTION

In the treatment of cancer patients, the preoperative assessment of patients' characteristics to determine the risk of poor prognosis is important for designing an optimal treatment strategy. Peritoneal carcinomatosis is known as one of the most potent negative prognostic factor in the gastric cancer [1-3]. An effort has been made to detect the peritoneal carcinomatosis preoperatively and the diagnostic imaging technique also has been advancing contemporary. However, the diagnosis of peritoneal metastasis is not yet to be often made before laparotomy [4,5].

Computed tomography (CT) scan is routinely performed in the gastric cancer patients preoperatively for the staging of the tumor, and has advantages in the diagnosis of distant metastasis to the solid organ such as liver, and in

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the assessment of the range of lymph node metastasis [6-8]. However, it has been reported that CT has a limited capability to find out peritoneal metastasis in spite of the advance of imaging technique [9-11].

Ascites is frequent detectable finding in CT scans for patients with advanced gastric cancer. And together with the increase of enhancement in peritoneal fat, the presence of nodules on the peritoneal and mesenteric surfaces, and the thickening of bowel walls, the presence of CT ascites has been regarded as one of the CT findings correlated with the peritoneal carcinomatosis [12-16]. Furthermore, CT finding of ascites has the merit of its objective finding.

Therefore, our study aimed to evaluate the possibility of CT ascites finding as a prognostic factor, and to compare this factor with the clinicopathologic features, through a retrospective review of all patients who underwent surgery for advanced gastric cancer.

METHODS

From January 2003 to December 2008, 334 patients with gastric adenocarcinoma underwent surgery at the Department of Surgery, Hallym University Kangdong Sacred Heart Hospital. All of their medical records were reviewed retrospectively, and the clinicopathologic and radiologic informations were retrieved. Of these, 177 patients were excluded for the following reasons: 1) They had not undergone CT at our hospital (n = 51). 2) They had a previous history of laparotomy, besides appendectomy and cholecystectomy (n = 13). 3) They had synchronous primary cancer in other organ (n = 6). 4) They had underlying medical diseases such as liver cirrhosis, congestive heart failure and chronic renal failure which could develop the ascites (n = 7). 5) They had confirmed an early gastric cancer pathologically (n = 125). 6) They presented peritonitis due to cancer perforation (n = 3); 7) Their medical records were missed (n = 5).

The remaining 157 patients were included in our study. Mean age was 61.39 years (range, 24 to 84 years), and male to female ratio was 2.49:1. Among them, curative resection could be performed in 119 patients. Another 38 patients underwent non-curative surgery such as palliative resection, bypass surgery, or "open-close" procedure with peritoneal biopsy only. Twenty-one patients showed peritoneal metastasis at laparotomy, and also were confirmed histologically. None of the patients underwent preoperative chemotherapy or radiotherapy, and patients who had medical problems which cause ascites were excluded; thus, any detected intra-abdominal fluid collections were considered to be a reflection of the intra-abdominal disease progress itself.

All of patients underwent routine esophagogastroduodenoscopy, and abdomino-pelvic CT scans before surgery for staging of cancer. Each patient performed endoscopic biopsy examination, and diagnosed with adenocarcinoma preoperatively.

Patients included in our study scanned using multi-detector CT (16-detector row; MX800IDT, Philips, Cleveland, OH, USA) in this period according to our protocol. Before the scanning, patients fasted for six hours. And they drank 450 mL of tab water immediate before performing the CT for achieving gastric distention. Contrast enhanced CT was performed on all patients except those who were allergic to the contrast material or had chronic renal disease. Contrast medium (Iopamidol; Radisense 300, Taejoon Pharm Co., Seoul, Korea) was injected intravenously at a rate of 3 mL/sec by using an automatic injector with a volume of 2 mL/kg. The abdomen and pelvis, from the level of diaphragm to the anus, were scanned routinely with a thickness of 5 mm, a pitch of 1.2, and a collimation of 16 × 1.5.

The original preoperative CT scans of all patients were reviewed by single gastrointestinal radiologist, whose experience was over 15 years. Radiologist was unaware of clinicopathologic informations of the patients.

Patients were considered to be positive for ascites on CT when any fluid was seen, regardless of the amount in perigastric area, subhepatic space, both para-colic gutters and the cul-de-sac, and these patients were named "CT ascites positive" group. Peritoneal seeding of cancer was suspected on CT scans if they demonstrated a parietal peritoneal or bowel wall abnormal thickening, enhancement, and nodularity, and also the patients with such findings were termed "CT peritoneal nodularity positive" group. Tumor invasion was also radiologically determined on CT,

based on the following criteria: T0, when the tumor mass was not shown; T4, when the high density irregularities of the outer space of the gastric wall with micronodularity or strands in the fat planes contiguous to the lesion were shown or the cleavage of fat planes between the gastric wall and the contiguous organs were lost. Others were classified as T1-3 group.

Nodal status of gastric cancer was also classified as N0 (no significantly enlarged lymph nodes), N1 (enlarged lymph nodes in perigastric area), and N2 or more (enlarged lymph nodes around the major arteries such as celiac trunk, common hepatic artery, and splenic artery, or abdominal aorta). Lymph nodes were considered involved when visible regardless of size, because usually normal lymph nodes are not seen on routine abdomen CT scan.

Results of the review such as CT defined tumor depth, lymph node metastasis, presence of ascites, and any other suspects of peritoneal metastases were compared to the clinicopathologic and surgical findings.

In patients of curative gastrectomy, final pathologic findings were used for staging of tumors based on tumor-node-metastasis criteria of the Union for International Cancer Control/American Joint Committee on Cancer 7th edition, and clinical and surgical stagings were determined in non-curative surgery group. In the histologic classification, the differentiated types included papillary adenocarcinomas, and well and moderately differentiated tubular adenocarcinomas, whereas the undifferentiated types included poorly differentiated tubular adenocarcinomas, mucinous adenocarcinomas, and signet-ring cell carcinomas.

Survival information was obtained from hospital records and results of a survey by the National Statistical Office. Mean follow-up period was 44.8 months (range, 2.0 to 103.1 months). The χ^2 test and Student's t-test were performed to compare clinicopathologic and radiologic features. Cumulate survival rates of CT ascites positive and negative groups were obtained by the Kaplan-Meier method and differences between the groups were evaluated by using the log-rank test. Since the CT ascites positive group showed more aggressive pattern in pathologic T stage and about 80% of ascites positive patients' T stages were T4 in our results, only serosal exposure (pT4) patients were selected and survival rate was also compaired among them according to the presence of ascites. Moreover, since the peritoneal seeding of cancer was frequently found in CT ascites positive group, the both groups were more stratified by the status of peritoneal carcinomatosis,

Table 1. Correlation between the presence of CT ascites and clinicopathologic and radiologic features

Variable	CT ascites (+) (n = 14)	CT ascites (−) (n = 143)	P-value
Age (yr)	53.6 ± 9.9	62.1 ± 12.4	0.032
Sex			0.541
Male	9	103	
Female	5	40	
Peritoneal carcinomatosis			<0.001
Positive	10	11	
Negative	4	132	
Tumor depth (pathologic T stage)			0.020
T2	1	32	
T3	2	59	
T4a	8	41	
T4b	3	11	
Tumor size (cm)			0.005
<5	1	78	
≥5	13	65	
Tumor location			0.001
Upper third	2	34	
Middle third	1	20	
Lower third	5	78	
Entire	6	11	
Histology			0.004
Differentiated	1	57	
Undifferentiated	13	84	
CT tumor depth			0.007
T0	0	27	
T1-3	3	64	
T4	11	52	
CT nodal status			0.032
N0	2	58	
N1	1	25	
≥N2	11	60	
CT peritoneal nodularity			<0.001
Positive	5	122	
Negative	9	21	
Curability of surgery			<0.001
Curative resection	2	117	
Palliative resection	2	8	
Bypass without resection	3	14	
Open-close procedure	7	4	

CT, computed tomography.

and analyzed the survival between the four sub-groups with same manner.

Multivariate analyses, using the Cox proportional hazards regression model, were performed to identify the independent risk factors for prognosis. Statistical analysis was performed using the SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA). A P-value less than 0.05 was considered statistically significant.

RESULTS

Fourteen (8.9%) out of the 157 patients presented ascites on preoperative CT. The locations of the ascites were cul-de-sac in 9, subhepatic space in 2, right paracolic gutter in 2, and left paracolic gutter in 1 patient. The clinicopathologic features of patients in this study are shown in Table 1. CT ascites positive group was significantly younger than ascites negative group. At laparotomy, 10 of CT ascites positive patients showed peritoneal carcinomatosis. The sensitivity, specificity, and positive predictive value of presence of CT ascites for the diagnosis of peritoneal carcinomatosis were 47.6%, 97.1%, and 71.4%, respectively.

The incidence of CT ascites was positively correlated with pathologic T stage (T2, 7.1%; T3, 14.3%; T4, 78.6%), tumor size (<5 cm, 7.1%; ≥5 cm, 92.9%), and histologic type (differentiated type, 7.1%; undifferentiated type, 92.9%). And also in the CT ascites positive group, CT findings such as CT T and N stages, and CT peritoneal nodularity, were showed more aggressive features than those of the CT ascites negative group. Almost of CT ascites positive patients performed non-curative surgery, such as bypass surgery or "open-close" procedure, and only two patients were able to undergo curative resection. Among the CT ascites positive patients, 6 patients had a tumor which located in distal part of stomach, whereas another 6 patients showed cancer which involved nearly whole stomach. When tumor is relatively confined in 1/3 part of stomach, the incidences of CT ascites are about 5% and nearly same despite of the different location of tumor. However, when the tumor is involved entire of stomach, the incidence of ascites is highly increased (39.3%), and showed significant difference.

The 5-years survival rates were 34.3% in the CT ascites positive group, and 72.5% in the CT ascites negative group, and significant differences were observed in both of groups ($P < 0.001$) (Fig. 1A). When only serosal exposure (pT4) patiens were selected and survival rate was compaired among them according to the presence of ascites (Fig. 1B), the prognosis of CT ascites positive with serosal exposure group was still poorer than that of CT ascites negative with serosal exposure group (36.4% vs. 52.2%, P = 0.002).

Moreover, when the groups were more stratified by the

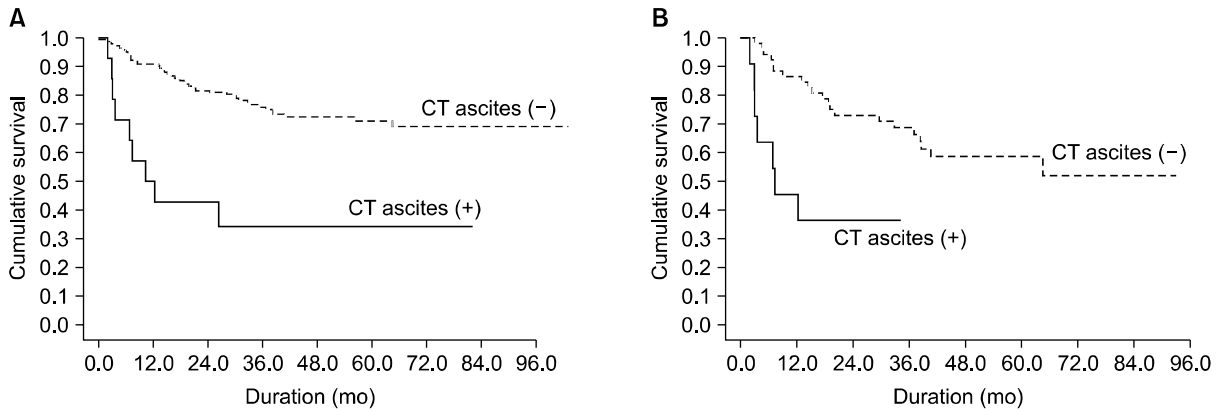

Fig. 1. (A) Cumulative overall survival of 157 advanced gastric cancer patients according to the status of computed tomography (CT) ascites ($P < 0.001$) (log rank test). (B) Cumulative survival of 63 patients with pathologic T4 (tumor invaded serosal surface or stomach or extended to adjacent organ across the serosal layer) in relation to the presence of CT ascites (P = 0.002) (log rank test). Group CT ascites (+), patients who had ascites regardless of the amount on their CT (n = 14); Group CT ascites (−), patients who did not showed ascites on CT (n = 143).

status of peritoneal carcinomatosis (Fig. 2), the survival of subgroups with peritoneal carcinomatosis (Fig. 2A, B) showed the almost similar pattern. Also, in the groups without peritoneal carcinomatosis (Fig. 2C, D), there's no significant difference between the subgroups, statistically. However, survival curves of subgroup C (CT ascites positive patients without peritoneal carcinomatosis) showed relatively close pattern to that of patients with peritoneal carcinomatosis, whereas, subgroup D (CT ascites negative patients without peritoneal carcinomatosis) tended to have a better prognosis (P = 0.086).

Univariate analysis of clinicopathologic features (Table 2) revealed that tumor size was significant factor associated with prognosis. Also, radiologic findings, such as presence of ascites and peritoneal nodularity, and T and N stage on their CT, were correlated with patients' survival significantly. However, age, sex, and histologic type were not correlated with the prognosis.

To determine the independent factors which could predict prognosis preoperatively, the factors, such as tumor size, CT T and N stages, and the presence of CT ascites and peritoneal nodularity, were selected for subsequent multivariate logistic regression analysis, among of the factors which associated significantly with survival at univariate analysis (Table 3). And, the presence of CT ascites, CT-T4 stage, and tumor size larger than 5 cm proved to be independent factors to predict poor survival. The relative risk of the presence of CT ascites was 2.991, and the presence of CT ascites had more influence on survival than the CT T4 stage and the tumor size larger than 5 cm.

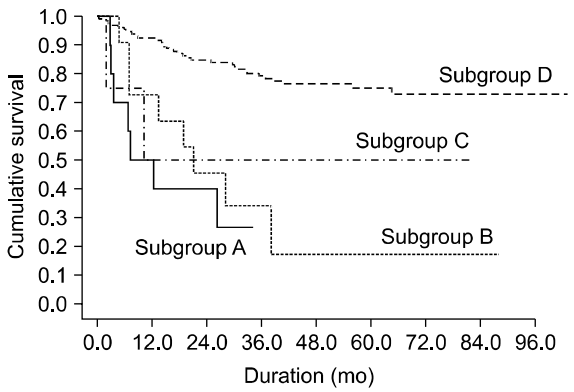

Fig. 2. Comparison of cumulative survival stratified by the status of peritoneal carcinomatosis and the presence of computed tomography (CT) ascites. Subgroup A, CT ascites (+) patients with peritoneal carcinomatosis (n = 10); Subgroup B, CT ascites (−) patients with peritoneal carcinomatosis (n = 11); Subgroup C, CT ascites (+) patients without peritoneal carcinomatosis (n = 4); Subgroup D, CT ascites (−) patients without peritoneal carcinomatosis (n = 132). Subgroups A vs. B (P = 0.388); subgroups B vs. C (P = 0.684), subgroups C vs. D (P = 0.086).

Table 2. Univariate analysis of clinicopathologic and radiologic features

Variable	Log-rank	P-value
Age	2.942	0.086
Sex	0.552	0.457
Tumor size	11.038	0.001
Histology	0.002	0.966
CT-T stage	10.795	0.029
CT-N stage	10.996	0.012
CT-peritoneal nodularity	8.994	0.003
CT-ascites	19.196	<0.001

CT, computed tomography.

DISCUSSION

Peritoneal metastasis is one of the most frequent causes that induce the useless surgery because of the difficulty of diagnosis without a direct vision [4,17]. Indeed, about 60% of unresectable patients have metastasis to the peritoneum or other organs that is not diagnosed until the surgical exploration [4]. Furthermore, the detection of peritoneal metastasis is extremely important clinically because the prognosis is directly related to the status of seeding [1,2]. At present, however, methods for visualization of the intraabdominal peritoneal surface and the assessment of the cancer status are limited.

Table 3. Multivariate analysis of prognostic factors, using Cox proportional hazard model

Factor	P-value	RR	95% CI
Tumor size larger than 5 cm	0.049	1.840	1.004-3.146
CT-T4 stage	0.035	2.148	1.127-3.726
CT-N2 or more stage	0.340	1.360	0.723-2.559
Presence of CT peritoneal nodularity	0.614	1.213	0.573-2.566
Presence of CT ascites	0.013	2.991	1.266-7.066

RR, relative risk; CI, confidence interval; CT, computed tomography.

Since beginning to use CT as preoperative workup in gastric cancer, it has been played a pivotal role in the detection of distant metastasis to the solid organs and the assessment of the range of lymph node metastasis [8,18]. And, CT was also used in diagnosis of peritoneal metastasis with the findings of the presence of nodules on peritoneal, omental or mesenteric surface, increase in density of peritoneal fat, thickening of bowel wall, and hydronephrosis [9,12-14]. However, the results in the diagnosis of peritoneal metastasis were relatively disappointment with low sensitivity and inaccurate staging [7,13,19,20]. The diagnostic accuracy is good enough in far advanced cases, whereas in the patients with tiny seeding nodule or cachexic state, it is difficult to find out the nodules on CT scan [12,19,21]. Efforts, such as rapid infusion of intravenous contrast medium, gastric water filling and fast scanning with multi-detector, are being made to overcome the limitations of CT in the evaluation of the transmural and extraserosal spread of disease. More recently, the spiral CT technique with thin section and multiplanar reconstruction has been used to provide better imaging details. In spite of the use of the advanced CT technique and the experience of the radiologist, however, the detection rate of peritoneal metastasis does not seem greatly improved as compared with those reported previous studies [22].

The ascites is another tool to diagnose the peritoneal metastasis in CT scan. Indeed, ascites is frequently found in advanced gastric cancer, and is more available than other CT findings which suspect peritoneal metastasis, because it is suitable for evaluation objectively. However, it also has a limitation that ascites is able to develop by other medical disorders such as liver cirrhosis, renal disease, congestive heart failure, and intraabdominal inflammations. Clinically, the higher sensitivity and positive predictive value of diagnostic tool about the peritoneal metastasis would help physicians to avoid unnecessary surgery. However, the sensitivity of CT ascites for the diagnosis of peritoneal metastasis was reported variously from 8 to about 50% [5,23,24]. And, like the preceding reports, the sensitivity, specificity, and positive predictive value of our result were 47.6%, 97.1%, and 71.4%, respectively, and also showed similarly low sensitivity, and dissatisfactory positive predictive value. Therefore, we still miss an opportunity to avoid needless laparotomy in more than half of patients when using CT scan for detecting fluid in abdominal cavity.

It is well known that ultrasonography is very useful in the diagnosis of intraabdominal free fluid. And, it is also very available to make an observation of lesion of liver, such as metastasis. Its result also was appeared variously, but in Kayaalp's report which compaired the ultrasound and CT for preoperative staging of gastric cancer, ultrasound is significantly more sensitive than CT for detecting ascites (64% vs. 36%, respectively) [25], and it also outperform our CT results of 47.6% of sensitivity. However, in detection of liver metastasis and peritoneal metastasis, there was no difference between two modalities. Moreover, the sensitivity of ultrasonography for detection of peritoneal metastasis ultrasonography is only 9%. And also in other report, ultrasound showed similar result that had a limitation in the detection of small peritoneal nodules [19], and showed weak point in detection of retroperitoneal invasion [25]. Therefore, their role for preoperative staging is complementary still now and if there is an expert for ultrasonography, it would be better to perform both modalities preoperatively in advanced gastric cancer. Chu et al. [26] also reported that the endoscopic ultrasonography (EUS) is useful for the detection of ascites with the result of 60.7% of sensitivity. However, in our cases, the location of ascites was cul-de-sac in more than half of patients, and EUS has an advantage to detect fluid only in perigastric area. Therefore, EUS is barely suitable for using this kind of purpose.

Positron emission tomography (PET) scan is also available and started to be used widely. However, in results of several studies, PET was not superior to CT scan in sensitivity and diagnostic performance [27], and still now, neither CT nor PET is thoroughly reliable method in the preoperative assessment of the extent of peritoneal involvement, in particular to predict small bowel involvement [28].

An important and clinically useful observation in our study is that the presence of CT ascites is confirmed as an independent prognostic factor in predicting survival, together with CT T4 stage and tumor size larger than 5 cm.

However, this study is a retrospective study, and has a limitation in the acquisition of detailed information of peritoneal metastasis, such as amount, size and location of seeding nodules. Therefore, it is difficult to measure the detailed diagnostic performance and characteristics of CT ascites against the surgical findings of peritoneal metastasis. In our study, more than half of ascites were found in cul-de-sac, and the amount was nearly scanty. Therefore, a prospective study about this concern may be needed.

In addition, in patients without peritoneal carcinomatosis, CT ascites positive subgroup has a tendency of poor survival than CT ascites negative subgroup, even though the survival was not significantly different statistically. Despite the patient's number of CT ascites positive, peritoneal metastasis negative subgroup was not sufficient to confirm, the early pattern of survival curves of CT ascites positive, peritoneal metastasis negative subgroup was nearly same with those of peritoneal metastasis positive groups. This finding may suggest that the operator missed the peritoneal metastasis or the seeding nodule which was too small to observe, or the number of cases in this study was too small to detect a significant difference in the group with respect to oncologic aspects. It is the limitation of this retrospective study, and we didn't perform the cytologic examination routinely. Therefore, to identify the influence the CT ascites finding on the survival, especially in patients who didn't show macroscopic peritoneal metastasis during exploration of intraperitoneal cavity, a large-scale prospective study will be needed, and the cytologic examination of peritoneal washing fluid may also be needed.

Laparoscopy is still generally accepted as diagnostic procedure of choice to compensate for the limited sensitivity of CT and other modalities for peritoneal metastasis [19,29]. Until now, no definite criteria have been suggested to perform staging laparoscopy. However, laparoscopy could be the initial operative procedure when the CT findings are doubtful, because it is a less invasive operation than a formal laparotomy, and it could make to avoid unnecessary surgical procedures [17,29,30]. Therefore, CT ascites finding may be the one of the criteria of diagnostic laparoscopy prior to the main surgical procedure.

Our results demonstrated that the presence of ascites on CT is positively correlated with the peritoneal carcinomatosis, and is an important independent prognostic factor in advanced gastric cancer. Furthermore, among the patients without macroscopic peritoneal carcinomatosis, CT ascites positive group has a tendency of poor prognosis than CT ascites negative group, even though the survival was not significantly different statistically. Therefore, in patients who detected ascites on their CT, diagnostic laparoscopy may be performed before the laparotomy, and more aggressive surgical resection and adjuvant chemotherapy might be needed.

CONFLICTS OF INTEREST

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

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