Prognostic Significance of a Minute Amount of Ascites During Chemoradiotherapy for Locally Advanced Pancreatic Cancer

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Abstract. *Aim: The aim of this study was to investigate the clinical factors for predicting overall survival (OS) and the significance of a minute amount of ascites on computed tomography (CT) in patients with locally advanced pancreatic cancer (LAPC) treated with chemoradiotherapy (CRT). Patients and Methods: Between 2003 and 2011, 48 consecutive patients with LAPC were treated with CRT. Various clinical factors, including ascites, were evaluated for correlation with OS. A subset analysis of 16 patients with a minute amount of ascites was also performed. Results: The median survival duration and the 1-year OS rates were 11.5 months and 50%, respectively. A minute amount of ascites on CT and elevated carbohydrate antigen 19-9 (CA19-9) level were significantly associated with poorer OS. In 16 patients with ascites, the amount of ascites increased in the course of the disease, and these were considered to be cancerous clinically, regardless of the amount. Conclusion: A minute amount of ascites and CA19-9 were important prognostic factors in CRT. Any amount of ascites was considered an early indicator of peritoneal carcinomatosis in LAPC.*

Chemoradiotherapy (CRT) is a standard treatment for locally advanced pancreatic cancer (LAPC). Nevertheless, there is surprisingly little evidence on the impact of the addition of radiation therapy to systemic chemotherapy in LAPC. Most previous studies have failed to demonstrate that CRT improved survival or provided additional benefit compared to gemcitabine alone, although the comparisons were indirect (1-3). The effect of CRT compared to chemotherapy alone is controversial: pancreatic cancer is extremely hypoxic and radioresistant, whereas it is surrounded by radiosensitive organs, such as the gastrointestinal tract, kidney, spinal cord, and liver (4). The combination of gemcitabine and radiation therapy sacrifices the dose reduction of gemcitabine or the target volume reduction of the radiation field in order to avoid excessive toxicities because gemcitabine acts as a radiosensitizer (5, 6). Another reason why the survival benefit of CRT has hardly been shown in the treatment for pancreatic cancer is that pancreatic cancer has a high propensity to metastasize to other organs. Huguet *et al*. reported that approximately 30% of LAPC patients had occult metastatic disease at diagnosis and thus would clearly not benefit from locoregional treatment (7). Recently, progress in radiation technology such as intensity-modulated radiation therapy, stereotactic radiotherapy, and carbon-ion radiotherapy can reduce the dose to organs at risk and allow increased dose intensity to the target (8-10). The next step to improve survival is to select appropriate patients whose disease is truly localized and who would benefit from locoregional treatment.

In the present study, we investigated the role of previously reported prognostic factors in overall survival (OS). In addition to these reported factors, we focused on the presence of a minute amount of ascites on computed tomographic (CT) images. Although a certain amount of ascites is well known as a prognostic factor, the argument as to what extent ascites represents peritoneal carcinomatosis or not has not been resolved because a minute amount of ascites might occasionally also be seen in non-cancer patients. We hypothesized that even a minute amount of ascites is an early sign of peritoneal dissemination in LAPC. Herein, we also report on the impact of a minute amount of ascites in LAPC.

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Table I. *Patients' characteristics.*

Number of patients	43
Gender, n	
Male	32 (74%)
Female	11 (26%)
Median age (range), years	64 (35-81)
PS: 0/1/2, n	13/29/1
Tumor location: Head/body or tail, n	22/21
Median tumor size (range), mm	40 (20-65)
N Stage: N0/N1, n	14/29
Median CA19-9 (range), U/ml	244 (0.6-4503)
Pathological confirmation: Yes/no, n	27/16
Ascites: Yes/no, n	16/27

PS: Performance status; CA19-9: carbohydrate antigen 19-9.

Patients and Methods

Patients. This was a retrospective study of patients with LAPC treated at Kyushu University, Japan. Between December 2003 and December 2011, we reviewed 48 consecutive patients who underwent definitive CRT. Eligibility criteria included (a) locally advanced unresectable pancreatic cancer confirmed histologically or clinically by diagnostic imaging including CT, (b) without distant metastasis and peritoneal carcinomatosis, (c) Eastern Cooperative Oncology Group performance status of 0-2, (d) adequate hematological and renal functions, (e) intent of definitive CRT, and (f) no combination therapy involving radiation therapy and surgery. Staging was according to the seventh edition of the TNM classification of the Union for International Cancer Control (11). We excluded five patients due to insufficient pretreatment evaluation in that the CT scan range was outside of the pelvic region. Eventually, 43 patients were included in this analysis.

Radiation therapy. Of 43 patients, four underwent a combination of intraoperative radiation therapy (IORT) and external beam radiation therapy (EBRT), and 39 patients underwent EBRT alone. The median dose of IORT was 20 Gy (range=15-20 Gy), and the subsequent EBRT dose was set at 40 Gy. The median dose of EBRT alone was 50 Gy (range=40-50.4 Gy) and the daily fractional dose was 1.8 or 2.0 Gy. EBRT was performed with a 10-MV X-ray machine using mainly four beams for the primary tumor and regional lymph nodes. Treatment was planned using a three-dimensional treatment planner.

Chemotherapy. For all patients, chemotherapy was performed concurrently with EBRT. Before 2009, gemcitabine was mainly administered at a dose of 250-1000 mg/m^2 weekly for 3 weeks with a 1-week rest, or at a dose of 40 mg/m^2 twice weekly for 4-5 weeks. Since 2009, S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) has mainly been used orally, twice a day at a dose of 60-80 mg/m^2/day. One patient was given cisplatin and etoposide concurrently because of gemcitabine and S-1 resistance before radiation therapy. Two weeks after completion of CRT, maintenance systemic chemotherapy with gemcitabine or S-1 was administered until disease progression or unacceptable toxicity. Thirteen patients had undergone chemotherapy before radiation therapy.

Table II. *The characteristics of patients with ascites partitioned into groups A and B (group A, only in the pelvic region; and group B, in both pelvic region and the upper abdomen).*

	Group A	Group B
Number of patients	7	9
Alive/dead, n	2/5	1/8
Gender: MaIe/femaIe, n	5/2	5/4
Median age (range), years	68 (58-77)	65 (57-74)
PS: 0/1-2	2/5	2/7
Tumor location: Head/body or tail	4/3	7/2
Median tumor size (range), mm	40 (23-50)	40 (20-60)
N Stage: N0/N1, n	3/4	7/2
Median CA19-9 (range), U/ml	243 (0.6-824.6)	290 (23.5-3588)
Pathological confirmation: Yes/no, n	6/1	4/5
Chemotherapy: GEM/S-1, n	4/3	7/2

PS: Performance status; CA19-9: carbohydrate antigen 19-9; GEM/S-1: gemcitabine/S-.

Statistical analysis. OS was calculated from the initiation of radiation therapy until either the last follow-up or death using the Kaplan–Meier method. Differences between survival curves in the subsets of patients were analyzed using the log-rank test. Prognostic factors were age (≥64 *vs.* <64 years), gender (male *vs.* female), performance status (0 *vs.* 1-2), tumor site (head *vs.* body/tail), tumor size (≥40 mm *vs.* <40 mm), lymph node metastasis (N0 *vs.* N1), baseline carbohydrate antigen 19-9 (CA19-9) (≥244 *vs.* <244), and ascites (yes *vs.* no). In 16 out of the 43 patients, a minute amount of ascites was observed on the pre-treatment CT image. To estimate the significance of a minute amount of ascites, we divided the patients with ascites into two groups: those with ascites only in the pelvic region on the CT image (group A), which would hardly suggest peritoneal carcinomatosis, and those with ascites not only in the pelvic region but also in the upper abdominal region (group B), in which case the possible existence of peritoneal carcinomatosis cannot be denied.

Statistical significance was defined as a value of $p<0.05$ in the present study. All statistical calculations were performed using statistical analysis software (JMP version 8.0.2, SAS, Cary, NC, USA; and Prism version 5.0, GraphPad, San Diego, CA, USA).

Results

The patients' characteristics are presented in Table I. The median age was 64 years (range=35-81 years). The tumors were partially equally distributed by site. Twenty-seven patients were confirmed to have adenocarcinoma of the pancreas pathologically. The remaining patients failed a pathological confirmation but were diagnosed by clinical examination. A small amount of ascites was observed in 16 patients; however, there was no seeding of suspected peritoneal carcinomatosis. Seven patients were categorized as group A and nine patients as group B. The characteristics of group A and B are presented in Table II.

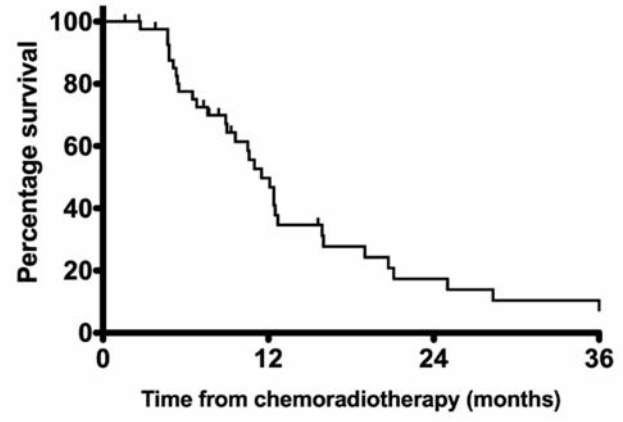

Figure 1. *Kaplan–Meier estimate of overall survival in all 43 patients.*

Table III. *Univariate and multivariate analysis of overall survival (OS).*

Factor	N	1-Year OS	Univariate *p*-Value	Multivariate *p*-Value
Age, years				
<65	24	55%	0.1514	0.0095
≥65	19	42%		
Gender, n				
Male	32	56%	0.1024	0.7808
Female	11	32%		
PS, n				
0	13	23%	0.3104	0.0653
1-2	30	59%		
Tumor site				
Head	22	49%	0.5048	0.8518
Body/tail	21	50%		
Tumor size, mm				
<40	18	60%	0.2918	0.2744
≥40	25	42%		
N Stage, n				
N0	29	57%	0.1791	0.5329
N1	14	35%		
CA19-9, U/ml				
<244	22	65%	0.0006	0.0004
≥244	21	33%		
Ascites, n				
No	27	66%	0.0383	0.032
Yes	16	24%		

PS: Performance status; CA19-9: carbohydrate antigen 19-9.

At last analysis, 32 (74%) patients had died. The median follow-up time for patients overall was 9.6 (range=1.6-79.7) months. The median survival duration and 1-year OS rate for patients overall were 11.5 months and 50%, respectively (Figure 1). On univariate analysis, factors associated with poor prognosis were a high baseline CA19-9 value and the presence of ascites. On multivariate analysis, CA19-9, ascites, and age were independently associated with OS. The results of the univariate and multivariate analysis of OS are shown in Table III. In patients with CA19-9 <244 U/ml and without ascites (n=15), the median survival duration and 1-year OS rate were 20.7 months and 77%, respectively. There was no significance in OS regardless of differences in therapeutic regimen, such as the presence or absence of IORT, or the regimen of concurrent chemotherapy (data not shown).

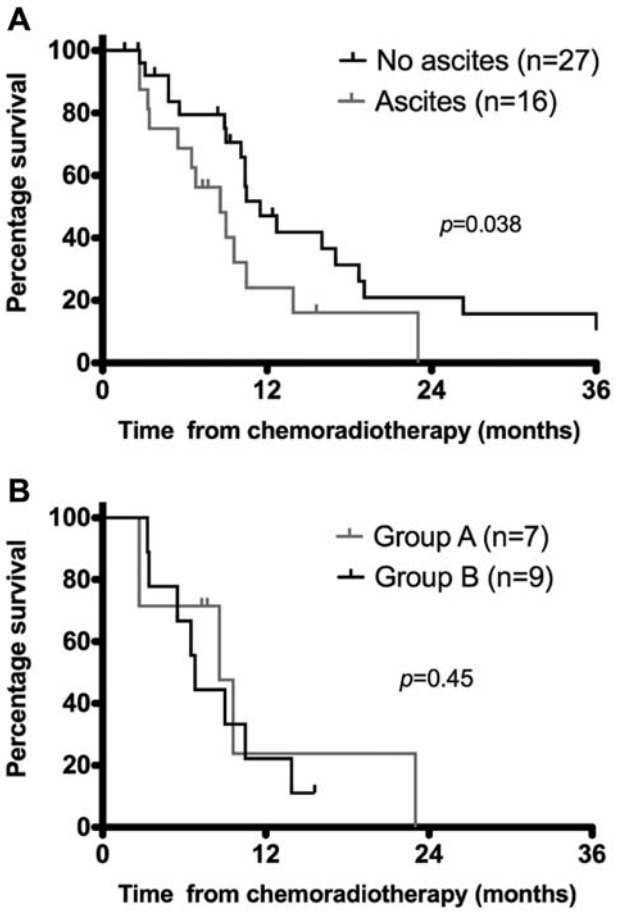

Figure 2. *A: Kaplan–Meier estimate of overall survival in patients without ascites (n=27) and with ascites (n=16) included in subset analysis. B: Kaplan-Meier estimate of overall survival in 16 patients included in subset analysis by the amount of ascites. Group A includes patients with ascites only in the pelvic region (n=7). Group B includes patients with ascites in not only the pelvis but also the upper abdomen (n=9).*

We performed a subset analysis of 16 patients whose pre-treatment CT images revealed ascites. The patients with pre-treatment ascites tended to have poorer prognoses than those without ascites on CT images (p=0.038; Figure 2A). The median survival in groups A and B were 9.6 *vs*. 6.8 months, respectively (p=0.44; Figure 2B). In all 16 patients, ascites increased over time and was considered to be apparent peritoneal carcinomatosis with peritoneal seeding on CT images or cytological examination of ascites (Figure 3).

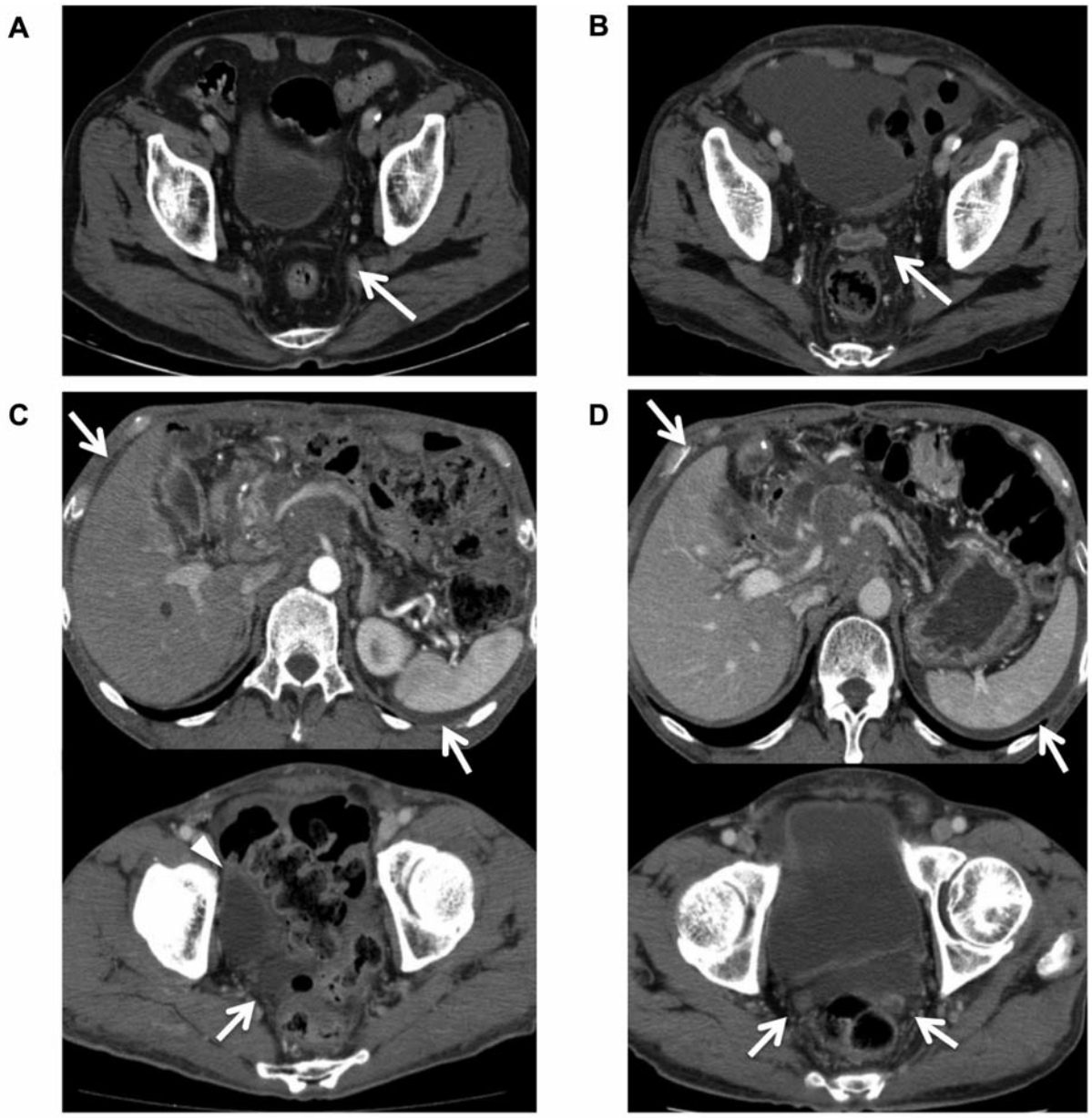

Figure 3. *Computed tomographic (CT) images of two patients with minute amounts of ascites (group A, only in the pelvic region; and group B, in both pelvic region and the upper abdomen) before and after chemoradiotherapy (CRT). A: CT image of a patient in group A before CRT, showing a minute amount of ascites only in Douglas' pouch. B: One year after CRT, the amount of ascites had increased in this patient and peritoneal seeding had appeared. C: CT image of a patient in group B before CRT, showing a minute amount of ascites in the pelvic area and upper abdomen. Arrowhead indicates the bladder. D: Six months after CRT, the amount of ascites had increased in the same patient and peritoneal seeding had appeared.*

Discussion

Since gemcitabine was introduced, many phase III trials have suggested that gemcitabine chemotherapy yields good survival outcomes, almost equivalent to the historical survival data for CRT of LAPC. Ishii *et al*. reported that gemcitabine monotherapy led to a median OS of 15.0 months and a 1-year OS rate of 64%, clearly better than the historical data for CRT with 5-fluorouracil (3). On the other hand, a recent randomized trial by Loehrer *et al*. demonstrated improved OS with the addition of radiation therapy to gemcitabine in patients with LAPC (12). They reported 1- and 2-year OS rates of 50% and 12% in the CRT group. This is not considered conclusive because they failed

to complete their planned analysis due to poor recruitment. Although our results, with 11.5 months of median survival and 1-year OS of 50%, are comparable to those of the previous reports, it is not a satisfactory outcome. As radiation techniques have advanced, local tumor control has improved by use of specialized techniques such as stereotactic radiation therapy or intensity-modulated radiation therapy (8, 13). While local control may impact survival in some way, no prospective data strongly support this statement, given the lack of phase III data showing a direct link from radiation therapy to local control to OS. One reason for this is that LAPC has a proclivity toward metastasis, and most patients with LAPC have microscopic metastases before treatment, which are not detected on standard imaging evaluation. In those cases, systemic chemotherapy contributes substantially to overall survival, whereas radiation therapy does not. However, for long-term survival, radiation therapy is inherently expected to be significantly superior to chemotherapy alone, as Loehrer *et al*. (12) showed. To establish the superiority of radiation therapy, we have to discriminate between candidates whose disease is truly localized from those who have sub-clinical metastases.

CA19-9 is the most widely used tumor marker and a well-known prognostic factor for LAPC (14). In our study, baseline CA19-9 values retained independent prognostic significance. This effect was particularly dramatic when patients were stratified by a cutoff value of 244 U/ml (1-year OS: 33% *vs*. 65% for patients with CA19-9 ≥244 U/ml *vs*. <244 U/ml, respectively). The prognostic impact of baseline CA19-9 has been demonstrated in patients with all stages of disease treated with varying modalities (14-16).

In additional analysis, we found that the presence of ascites prior to treatment is also a significant independent prognostic factor for LAPC. The presence of ascites and that of peritoneal seeding are generally considered to be associated with poor outcomes in patients with locally advanced or metastatic pancreatic cancer (17). However, a minute amount of ascites only in the pelvic region without seeding of soft-tissue implants along the peritoneum and omentum on a CT image does not always represent peritoneal carcinomatosis (18). There are many potential causes of ascites in patients with cancer, including peritoneal carcinomatosis, portal vein thrombosis, elevated portal venous pressure, congestive heart failure, nephrotic syndrome, and peritoneal infections. A minute amount of ascites shown in group A patients in our study may not be considered malignant peritoneal carcinomatosis. Usually there has been little to discuss concerning such a minute amount of ascites. In all patients in our study, the amount of ascites increased and was determined as peritoneal carcinomatosis during the disease course. Although not all ascites were confirmed pathologically, it is considered that the presence of any amount of ascites in patients with pancreatic cancer is an early indicator of peritoneal carcinomatosis. Even a minute amount of fluid collection within the abdominal cavity is relatively easy to detect on a CT image and is useful for decisions about treatment strategy. In contrast, occult metastasis in the liver, which often comes to a head after CRT and also worsens prognosis, is difficult to distinguish on conventional imaging modalities before treatment. We have reported the usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography as a predictor of distant metastasis in patients with operable pancreatic cancer (19). Distant metastasis-free survival rates in a group with a low standardized uptake value (SUV) and in a high-SUV group were 91% and 20%, respectively, at 1 year. Patients with high SUV had a high frequency of developing obvious distant disease and tended to have a poor prognosis. It is most important to identify patients who would benefit from locoregional treatment by taking advantage of various prognostic modalities. The addition of radiation therapy has the demerits of increasing the risk of toxicity and the necessity for reducing the dose of systemic chemotherapy (5). This might not benefit patients with micrometastases. Radiation therapy with concurrent chemotherapy would be advocated for patients who are not at a high risk of distant metastasis in the treatment strategy for LAPC.

This study had several limitations. Pathological confirmation was not sufficient in some patients. Concerning peritoneal carcinomatosis, pathological or cytological diagnosis was also not performed in most cases. Furthermore, this was a retrospective study performed at a single institution. The radiation method and the selected chemotherapy agents were decided under various strategies. The conclusions revealed here are suitable for generating hypotheses and should be verified by larger prospective studies.

Conclusion

CA19-9 and a minute of ascites were important prognostic factors for patients with LAPC undergoing CRT. In particular, the presence of ascites in any amount was easy to detect on CT images and may be an early indicator of peritoneal carcinomatosis for LAPC. The addition of radiation therapy is expected to improve survival in patients without ascites and with a low CA19-9 level.

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