

## Chemoradiotherapy with twice-weekly administration of low-dose gemcitabine for locally advanced pancreatic cancer

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### Abstract

**AIM:** To evaluate the chemoradiotherapy for locally advanced pancreatic cancer utilizing low dose gemcitabine as a radiation sensitizer administered twice weekly.

**METHODS:** We performed a retrospective analysis of chemoradiotherapy utilizing gemcitabine administered twice weekly at a dose of 40 mg/m<sup>2</sup>. After that, maintenance systemic chemotherapy with gemcitabine, at a dose of 1000 mg/m<sup>2</sup>, was administered weekly for 3 wk with 1-wk rest until disease progression or unacceptable toxicity developed.

**RESULTS:** Eighteen patients with locally advanced unresectable pancreatic cancer were enrolled. Three of those patients could not continue with the therapy; one patient had interstitial pneumonia during radiation therapy and two other patients showed liver metastasis or peritoneal metastasis during an early stage of the therapy. The median survival was 15.0 mo and the overall 1-year survival rate was 60%, while the median progression-free survival was 8.0 mo. The subgroup which showed the reduction of tumor development, more than 50% showed a tendency for a better prognosis; however, other parameters including age, gender and performance status did not correlate with survival. The median survival of the groups that died of liver metastasis and peritoneal metastasis were 13.0 mo and 27.7 mo, respectively.

**CONCLUSION:** Chemoradiotherapy with low-dose gemcitabine administered twice weekly could be effective to patients with locally advanced pancreatic cancer; however, patients developing liver metastases had a worse prognosis. Another chemoradiotherapy strategy might be needed for those patients, such as administering one or two cycles of chemotherapy initially, followed by chemoradiotherapy for the cases with no distant metastases.

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**Key words:** Advanced pancreatic cancer; Chemoradiotherapy; Gemcitabine; Radiosensitizer; Tumor marker

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### INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer death in the world and in most patients the tumor is surgically unresectable at the time of diagnosis<sup>[1]</sup>. Even in the patient with complete surgical resection, both distant and local patterns of recurrence are common<sup>[2]</sup>. In approximately 50% of resected pancreatic tumors, the surgical margins are involved with tumor cells, so it can be assumed that most patients are harboring occult metastases at the time of diagnosis<sup>[3]</sup>. Recently, studies for adjuvant chemotherapy or chemoradiotherapy, and those for neoadjuvant chemotherapy or chemoradiotherapy have been investigated<sup>[3-6]</sup>.

For patients with locally advanced pancreatic cancer, chemoradiotherapy has been accepted as a standard treatment<sup>[7]</sup>. The results of previous randomized trials

have indicated that external-beam radiation therapy and 5-fluorouracil (5-FU) therapy results in a significantly longer survival time than radiotherapy<sup>[8]</sup> or chemotherapy alone<sup>[9]</sup>. Gemcitabine, a deoxycytidine analog that functions as an antimetabolite, has been approved for use in patients with advanced pancreatic cancer<sup>[10,11]</sup>. In a randomized study, gemcitabine improved survival in inoperable pancreatic cancer in comparison with 5-FU<sup>[12]</sup>. Gemcitabine has also been shown to exert an effect in 5-FU-refractory pancreatic cancer<sup>[13]</sup>. Gemcitabine has also been shown to be a potent radiosensitizer, both *in vivo* and *in vitro*<sup>[14]</sup>. The vast majority of the reported phase I-III clinical trials have used gemcitabine as a single agent given weekly in a single dose<sup>[7,15,16]</sup> (i.e. 250 mg/m<sup>2</sup>).

Several preclinical data, including animal studies<sup>[17]</sup>, would suggest that maximum radiation sensitization with gemcitabine is observed at a lower dose administered twice weekly<sup>[15,17]</sup>. Blackstock *et al*<sup>[14,15]</sup> and Magnino *et al*<sup>[18]</sup> reported on a phase II study of chemoradiotherapy in which the patients were treated with gemcitabine twice weekly at 40 mg/m<sup>2</sup> and 50 mg/m<sup>2</sup>, respectively, associated with radiotherapy. Therefore, in the present study, we analyzed the results of retrospective analysis of chemoradiotherapy for locally advanced pancreatic cancer, utilizing gemcitabine as a radiation sensitizer administered twice weekly at a dose of 40 mg/m<sup>2</sup>, followed by maintenance systemic chemotherapy with gemcitabine.

## MATERIALS AND METHODS

Eligibility criteria included (1) locally advanced unresectable pancreatic cancer confirmed histologically or by imaging techniques including systemic computed tomography; (2) 20-74 years of age; (3) ECOG performance status of 0-2; (4) adequate hematological function, and adequate renal function, and (5) no prior anti-cancer treatment. A total dose of 40-50.4 Gy was delivered using 1.8-2.0 Gy daily fractions. Treatment planning was determined by a three-dimensional treatment planner. The targeted irradiation volume included the tumor, possible surrounding edema, and 1-cm margin. Gemcitabine, at a dose of 40 mg/m<sup>2</sup>, was administered as a 30-min intravenous infusion twice weekly (80 mg/m<sup>2</sup> per week) for 4-5 wk. Gemcitabine was given within 2 h before radiation treatment. At 2 wk after the completion of chemoradiotherapy, maintenance systemic chemotherapy of gemcitabine at a dose of 1000 mg/m<sup>2</sup> was administered as a 30-min intravenous infusion weekly for 3 wk with 1-wk rest until disease progression or unacceptable toxicity. Both radiation therapy and chemotherapy were suspended for grade 3 hematological toxicities or grade 2 non-hematological toxicities (according to the National Cancer Institute Common Toxicity Criteria) during the treatment course, and treatment was resumed when toxicity was resolved. The objective tumor response, as defined by the WHO criteria, was assessed every 2 mo or 3 mo by computed tomography scan or earlier if clinically indicated.

The Kaplan-Meier method was used to estimate the distribution of overall survival and progression free

Table 1 Patient characteristics

Number of patients completing the protocol	15
Gender	
Male	9 (60%)
Female	6 (40%)
Age (yr)	
Mean (range)	62.2 (50-73)
Tumor location	
Head	7 (46.7%)
Head-Body	1 (6.6%)
Body-Tail	7 (46.7%)
Total radiation dose	
40.0 Gy	12 (80%)
50.0 Gy	1 (6.6%)
50.4 Gy	2 (13.4%)
Response	
Complete response	1 (6.6%)
Partial response	4 (26.7%)
Stable disease	9 (60%)
Progressive disease	1 (6.6%)
Cause of death	
Liver metastasis	10 (66.7%)
Peritoneal metastasis	3 (20%)

survival. Progression free survival was calculated from the first day of treatment until there was evidence of clinical progression, tumor progression assessed by computed tomography scan measurement or death. Overall survival was calculated from the first day of treatment until the date of death. In this study, there is no control arm to treat the locally advanced pancreatic cancer.

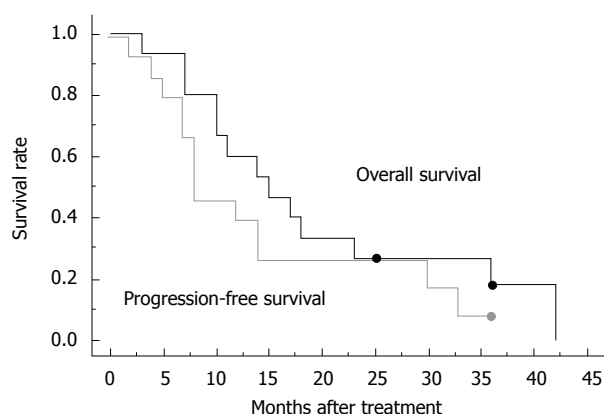
## RESULTS

### Clinical data

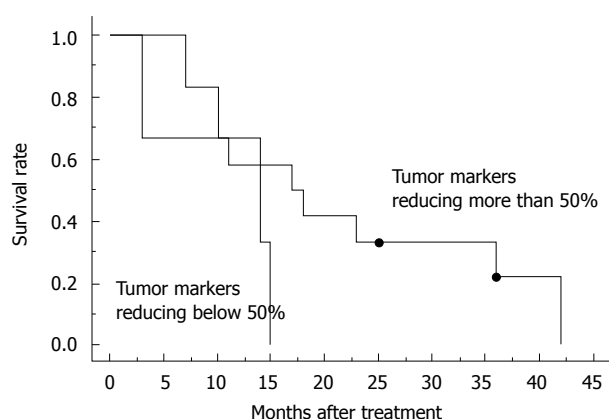
Eighteen patients were enrolled in this study. Three of those patients could not continue with the therapy under this protocol; one patient had interstitial pneumonia during radiation therapy and two other patients showed liver metastasis or peritoneal metastasis in an early stage of this protocol. Fifteen patients, including nine males and six females, completed therapy as planned and patient characteristics are shown in Table 1. The mean age was 62.2 years old (range, 50-73). The mean diameter of the tumor was 4.8-cm and the tumor was located in the pancreatic head in seven patients. Twelve patients received radiotherapy at a total of 40-Gy, two patients at a total dose of 50-Gy and one patient with 50.4-Gy. In general, therapy was well tolerated, one patient suffered AGML and another patient had an eruption. All the patients showed elevation of tumor markers, including CA19-9, Span-1 and DUPAN-2, at the enrollment for this study.

### Survival

Regarding overall response, there was one complete response, 4 partial responses, 9 stable diseases and one progressive disease; the response rate was 33%. No patients could undergo tumor resection even after the completion of chemoradiotherapy, because of infiltration

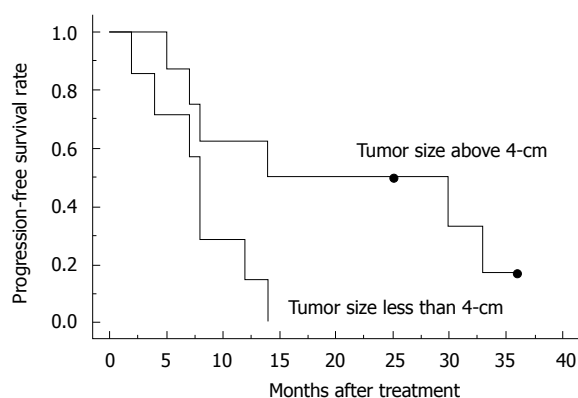


**Figure 1** Overall survival curve and progression-free survival curve for 15 patients who received chemoradiotherapy under this study protocol. Dot indicates censored cases.



**Figure 2** Overall survival curve for patients with tumor markers reducing more than 50% compared to that of pretreatment ( $n = 12$ ) and those reducing below 50% ( $n = 3$ ). Dot indicates censored cases.

of the adjacent large vessels. The median survival was 15.0 mo and the overall 1-year survival rate was 60%, while the median progression-free survival was 8.0 mo, estimated by the Kaplan-Meier method (Figure 1). In 80% of the patients, the level of tumor marker, including CA19-9, Span-1 and DUPAN-2, was reduced more than 50% compared to that of pretreatment. The subgroup where the tumor marker was reduced more than 50% had a tendency for a better prognosis (Figure 2), compared to the group with reduced tumor marker below 50% of pretreatment. Blackstock *et al*<sup>[15]</sup> postulated previously that the extended median survival observed in the CA19-9 responding patients might reflect the impact of the improved local control. However, a recent study demonstrated that pretreatment serum CA19-9 concentration was an independent prognostic factor for survival for advanced pancreatic cancer, but a decrease in concentration during chemotherapy was not significantly associated with lengthened survival compared with those who did not have a corresponding decrease<sup>[19]</sup>; therefore, the importance of decreasing in serum tumor marker concentration during therapy requires further discussion. In the subgroup with a tumor size less than 4-cm in diameter, median progression-free survival was 14.0 mo,



**Figure 3** Progression free-survival curve for patients with tumor size less than 4-cm ( $n = 6$ ) and those with a size above 4-cm ( $n = 9$ ). Dot indicates censored cases.

which was better than those above 4-cm in diameter (8.0 mo, Figure 3). Other parameters, including age, gender and performance status, did not correlate with survival. The major causes of death were liver metastasis and peritoneal metastasis. The median survival of the groups that died of liver metastasis and peritoneal metastasis were 13.0 mo and 27.7 mo, respectively.

## DISCUSSION

A recent retrospective comparison of the toxicity and efficacy of concurrent gemcitabine-based chemoradiotherapy with that of 5-FU based chemoradiotherapy for the patients with unresectable pancreatic cancer<sup>[20]</sup>, showed a significantly higher toxicity rate in patients treated with gemcitabine and similar median survival times between the two arms. Investigators in Taiwan<sup>[21]</sup> reported favorable results for chemoradiotherapy with concurrent gemcitabine administration (600 mg/m<sup>2</sup> once a week); however, this needs further confirmation by larger multi-institutional clinical trials.

Although this study, using a twice weekly gemcitabine infusion schedule for locally advanced pancreatic cancer was not a controlled study, the results of the median survival time, median disease free survival time and overall 1-year survival rate was found to be preferable compared to previous studies<sup>[7-9,15]</sup>. Okusaka *et al*<sup>[7]</sup> presented data of a phase II study for locally advanced pancreatic cancer treated with external-beam radiation (50.4 Gy) and weekly gemcitabine (250 mg/m<sup>2</sup> once a week) followed by maintenance chemotherapy using gemcitabine. The median survival time, median progression-free survival time and 1-year survival rate was 9.5 mo, 4.4 mo and 28%, respectively<sup>[7]</sup>. An expanded retrospective review of patients receiving gemcitabine-based chemoradiotherapy at the M. D. Anderson Cancer Center reflected the difficulties combining the systemic toxicities of 200-500 mg/m<sup>2</sup> doses of gemcitabine with the local-regional toxicities associated with chemoradiotherapy to the upper abdomen<sup>[22]</sup>. Furthermore, in the original GITSG trial of radiation and 5-FU based chemotherapy, 18% and 21% of the patients randomized into the

40-Gy and the 60-Gy treatment arms, respectively, were unable to complete all planned radiation<sup>[8]</sup>. For those patients completing the chemoradiotherapy, almost one-third were unable to initiate the planned maintenance 5-FU chemotherapy<sup>[8]</sup>. In this study, 15 of 18 patients could complete the planned protocol which might have come from the treatment with gemcitabine administered *via* a twice weekly infusion with radiation therapy and that most patients received radiation therapy at a total dose of 40-Gy. This might have resulted in the successful initiation in the maintenance of gemcitabine chemotherapy and to obtain a feasible survival rate in this trial. Some investigators did not propose maintenance chemotherapy after chemoradiotherapy<sup>[1]</sup>. Several studies of chemoradiotherapy used a therapeutic sequence with prior chemoradiotherapy and then chemotherapy until disease progression, but increased toxicity of chemotherapy after chemoradiotherapy limits this strategy<sup>[23,24]</sup>, which might partially contribute to the total dose of radiation.

Two of the three patients enrolled initially who did not continue with the therapy under this protocol showed liver metastasis or peritoneal metastasis in the early stage of this protocol. Blackstock *et al*<sup>[15]</sup> pointed out in their study that the radiation sensitizing properties of twice weekly gemcitabine were important for improving the local control, and did not impact the survival for patients harboring micrometastatic disease at the initiation treatment. Huguet *et al*<sup>[11]</sup> discussed that, an important concern about administering chemoradiotherapy as first-line treatment in patients with locally advanced pancreatic cancer was that approximately 30% of them had occult metastatic disease at diagnosis and thus, they would clearly not benefit from this locoregional treatment. Furthermore, another investigator demonstrated that a fraction of patients with locally advanced pancreatic cancer developed metastases within a few weeks and died very quickly despite the type of treatment<sup>[25]</sup>. In this study, the patients who developed liver metastasis had a worse prognosis, which might owe to the miss-diagnosis of the staging of the disease at the initiation of the therapy, because of failure to detect micrometastasis by conventional imaging modalities. In this situation, we might need another strategy for the chemoradiotherapy for locally advanced pancreatic cancer, such as one in which the patients receive one or two cycles of systemic chemotherapy using gemcitabine at a dose of 1000 mg/m<sup>2</sup> weekly for 3 wk with 1-wk rest, and then re-evaluated the staging of the disease, initiating the chemoradiotherapy under the protocol in this study. A recent study suggested that after control of disease by initial chemotherapy for at least 3 mo using combination of leucovorin, fluorouracil and gemcitabine, or gemcitabine and oxaliplatin, chemoradiotherapy with 5-FU, could significantly improve survival in patients with locally advanced pancreatic cancer compared with chemotherapy alone<sup>[1]</sup>.

In conclusion, chemoradiotherapy with low-dose gemcitabine given twice weekly could be effective to patients with locally advanced pancreatic cancer; however, patients developing liver metastases had a worse prog-

nosis. We might need another strategy for the chemoradiotherapy for those patients. Further investigations are required in the near future.

## COMMENTS

### Background

Pancreatic cancer is the fifth most common cause of cancer death in Japan. The prognosis is extremely poor because it is difficult to detect this disease in the early stage and also the postoperative incidence of recurrence is still high. We do not have any effective treatment for inoperable patients. Recently, chemoradiotherapy has been regarded as one of the standard therapies for locally advanced pancreatic cancer and it has improved the survival and presented a clinical benefit.

### Research frontiers

In the early 1980s, fluorouracil-based concomitant chemoradiotherapy was shown to be better than radiotherapy alone for patients with locally advanced pancreatic cancer. Gemcitabine has improved the outcome of patients with advanced disease by improving survival with a clinical benefit. Gemcitabine also has been shown to be a potent radiosensitizer, both *in vivo* and *in vitro*. The vast majority of the reported phase I - III clinical trials have used gemcitabine as a single agent given weekly in a single dose (i.e. 250 mg/m<sup>2</sup>), and there is no consensus of the protocol of the administration of gemcitabine.

### Innovations and breakthroughs

Several preclinical data, including animal studies, would suggest that maximum radiation sensitization with gemcitabine is observed at a lower dose administered twice weekly. In this study, we show that we could obtain the feasible results of survival compared to previous studies using our protocol. There existed some patients who could not continue the therapy, because of developing metastases. One reason could be the failure to detect micrometastasis by conventional imaging modalities at the beginning of chemoradiotherapy.

### Applications

Chemoradiotherapy, with low-dose gemcitabine given twice weekly, could be effective to patients with locally advanced pancreatic cancer. To improve this survival data, we may need stricter selection of the cases suitable for this chemoradiotherapy; however, using conventional imaging modalities, it seems to be hard to diagnose the micrometastasis, especially in the liver before this chemoradiotherapy. Another strategy that may be useful is where patients receive one or two cycles of systemic chemotherapy using gemcitabine at a dose of 1000 mg/m<sup>2</sup> weekly for 3 wk with 1-wk rest, and then be re-evaluated for the staging of the disease, and then initiating the chemoradiotherapy under the protocol in this study.

### Peer review

This is a nicely written paper that looks at the use of gemcitabine as a radiation sensitizer for pancreatic cancer. They report on twice-weekly doses. This dose contributes new information to the literature.

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