# Treatment outcomes of concurrent hyperthermia and chemoradiotherapy for pancreatic cancer: Insights into the significance of hyperthermia treatment

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**Abstract.** Patients with locally advanced unresectable pancreatic cancer (LAUPC) have a poor prognosis. In addition their quality of life impaired by cancer pain and biliary tract infections. Therefore, multimodality therapy and selection of optimal treatment methods are essential for achieving prolonged survival. The present study investigated the significance of using hyperthermia concurrently with multimodality therapy to improve treatment outcomes in patients with LAUPC. In total, 13 patients receiving concurrent hyperthermia and chemoradiotherapy (HCR) or chemoradiotherapy (CR) alone for LAUPC between 2002 and 2013 were analyzed retrospectively. Of the 13 patients, 5 received concurrent HCR and 8 received CR. The chemotherapy regimens were 5-fluorouracil (5-FU) in 5 patients and gemcitabine hydrochloride (GEM) in the other 8. Patients who gave consent for hyperthermia treatment received GEM plus CR. The median overall survival period for all patients was 12 months and the 1-year survival rate was 55%; the corresponding values were 12 months and 57% in the GEM CR group, and 15 months and 80% in the HCR group. Univariate analyses was perfomed to identify factors predicting recurrence after treatment. The potential prognostic factors analyzed were: Age, sex, performance status, location, tumor size, the tumor marker CA 19-9, total radiation dose, chemotherapy and hyperthermia. Univariate analysis for factors associated with outcomes revealed a significant difference favoring the HCR group [relative risk=15.97 (95% confidence interval: 12.87-19.83) P=0.021]. In conclusion, hyperthermia merits active recommendation to pancreatic cancer patients who have a positive attitude toward this treatment and whose performance status is satisfactory.

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*Key words:* pancreatic cancer, chemoradiotherapy, hyperthermia, gemcitabine hydrochloride, 5-fluorouracil

## Introduction

Complete surgical cure of pancreatic cancer is possible. However, Japanese patients with early-stage disease have few symptoms, and only 10% of pancreatic cancer cases are diagnosed at a resectable stage (1). Most patients present with unresectable advanced disease at the time of diagnosis, and the recurrence rate is high even when aggressive resection is performed (2). In Japan, the number of deaths from pancreatic cancer per year has steadily risen, to approximately 30,000 at present, making it the fourth (7.4%) leading cause of cancer deaths (3). In recent years, patients with borderline resectable pancreatic cancer have been treated with surgery following preoperative chemoradiotherapy or intensive multi-agent chemotherapy. However, quality of life is often impaired by cancer pain and biliary tract infections in patients with locally advanced unresectable pancreatic cancer, which has a poor prognosis. Therefore, multimodality therapy and selection of optimal treatment methods are essential for achieving prolonged survival in these patients. Chemoradiotherapy with fluorouracil (5-FU) was formerly the standard therapy for advanced pancreatic cancer. However, Burris *et al* (4). Reported that chemotherapy with gemcitabine hydrochloride (GEM) produced significant benefits in terms of the symptom-alleviating effect and the survival rate. Thereafter, GEM replaced 5-FU as the standard chemotherapy for pancreatic cancer. Furthermore, a randomized comparative study of chemoradiotherapy with 5-FU vs. GEM, conducted by Li *et al* (5), showed significantly prolonged survival in the GEM group. Although these therapies are effective, the survival rate in patients with pancreatic cancer is significantly lower than that in patients with other carcinomas. Thus, we investigated the significance of using hyperthermia concurrently with multimodality therapy for improving the outcomes

Table I. Patient characteristics.

| Characteristics | n=13 |
|---|---|
| Follow-up (months) | |
| Median | 12 |
| Range | 4-8 |
| Sex | |
| Male | 4 |
| Female | 9 |
| Age | |
| Median | 78 |
| Range | 48-80 |
| Pathology | |
| Adenoca | 4 (31) |
| Unknown (CT and MRI) | 9 (69) |
| PS | |
| 1 | 11 (85) |
| 2 | 2 (15) |
| Location | |
| Pancreatic head | 7 (54) |
| Pancreatic body | 8 (46) |
| Tumor size (cm) | |
| Median | 5.5 |
| Range | 3-9 |
| Tumor marker (CA 19-9 U/ml) | |
| Median | 5.5 |
| Range | 0.1-13,850 |
| Stage (UICC 7th) | |
| cT4 cN0 cM0 stage III | 9 (69) |
| cT4 cN1 cM0 stage III | 3 (23) |
| cT2 cN1 cM0 stage III | 1 (8) |

Follow-up periods, sex, age, pathology, location, tumor size, tumor markers and stage with percentages indicated in parentheses. Other data are presented as the number of patients, with percentages in parentheses. Adenoca, adenocarcinoma; PS, performance status.

of patients with locally advanced unresectable pancreatic cancer.

## Materials and methods

*Patient selection*. We retrospectively studied 13 patients who received concurrent hyperthermia and chemoradiotherapy (HCR) or chemoradiotherapy (CR) alone during the period from 2002 to 2013 (Table I). Documentation of informed consent for treatment was signed by each patient and placed in the patient's medical record. These patients were diagnosed as having locally advanced unresectable pancreatic cancer based on histopathological and imaging findings. Among the 13 patients, five received concurrent HCR and eight were given CR. The drugs used for chemotherapy were 5-FU in five patients and GEM in the other eight. GEM was used in all 5 patients who received

Table II. Five patients received concurrent hyperthermia and chemoradiotherapy.

| No. | Age (years)/sex | Pathology | Location | CA19-9 (U/ml) | Tumor size (cm) | Stage | Hyperthermia | Gemcitabine dose | Radiation dose (Gy) | Adverse event | Survival time (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 64/M | Adenoca | Pancreatic body | 511 | 5 | cT4cN0 | 6 times | 500 mg/m$^2$ (3 times/month) | 60 | Grade 3 Gastric ulcer | 18 |
| 2 | 62/F | No | Pancreatic body | 85.3 | 6 | cT4cN0 | 5 times | 600 mg/m$^2$ (3 times/month) | 50 | Grade 2 Gastritis and enterocolitis | 17 |
| 3 | 49/F | No | Pancreatic body | 173.2 | 7 | cT4cN0 | 5 times | 1000 mg/m$^2$ (1 time/month) | 50 | Grade 2 Gastritis and enterocolitis | 15 |
| 4 | 62/F | Adenoca | Pancreatic head | 68 | 6 | cT4cN1 | 6 times | 600 mg/m$^2$ (3 times/month) | 50 | Grade 2 Gastritis and enterocolitis | 12 |
| 5 | 73/M | No | Pancreatic body | 140.8 | 5 | cT4cN1 | 5 times | 500 mg/m$^2$ (3 times/month) | 50 | Grade 3 neutropenia | 18 |

Five patients received concurrent hyperthermia and chemoradiotherapy. Adenoca, adenocarcinoma.

Table III. Summary of RT approaches.

| Approach | Details |
|---|---|
| Chemoradiation | 13 cases |
| Radiation dose | |
| 1.4 Gy x 2 fractions/day, total 60.8 Gy | 1 case |
| 1.6 Gy x 2 fractions/day, total 51.6 Gy | 2 cases |
| 2 Gy/fraction, total 50 Gy | 9 cases |
| 2 Gy/fraction, total 60 Gy | 1 case |
| Radiation field | |
| CTV | Pancreatic tumor only or pancreatic tumor with LN meta + 10-15 mm |
| PTV | CTV + 5-8 mm |
| 50 Gy over | CTV + less than 5 mm on the small bowel surface |

Data for each procedure are presented as the number of patients, with percentages in parentheses. CTV, clinical target volume; LN, lymph node; PTV, planning target volume.

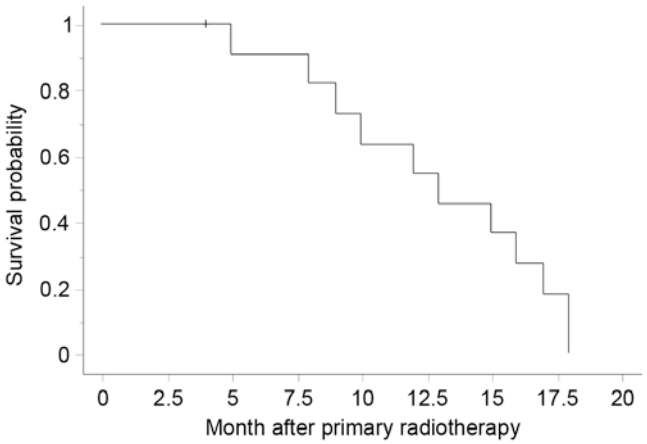


Figure 1. Overall survival curve of all patients. CR, chemoradiotherapy; HCR, hyperthermia and chemoradiotherapy.

concurrent HCR (Table II). Patients who consented to undergo hyperthermia treatment were given GEM CR. As for the selection of chemotherapeutic agents, 5-FU was used at our hospital until the approval of GEM in Japan.

*Radiotherapy*. The device employed for radiotherapy was the SIEMENS PRIMUS KD2 (SIEMENS Oncology Care Systems, Concord, CA, USA). For treatment planning, the XiO (version 4.4.0-4.6.0; Elekta, Hamburg, Germany) was employed and the isocenter dose was calculated by Clarkson's method. Irradiation fields were determined as follows: First, a 1.5-cm margin was added to the clinical target volume (CTV), which was the planning target volume (PTV), and then a 5-mm margin was added to the PTV, which was the irradiation field. Irradiation was performed using 10MV X-rays; irradiation with opposed anterior and posterior beams was performed on two patients and 4- or more field irradiation was performed on the others. Hyperfractionation was applied in three cases and 2 Gy/fraction in the others (including all 5 patients who received concurrent HCR). Total doses were 60 Gy in two patients and approximately 50 Gy in the others. In the two patients given 60 Gy in total, localized irradiation of tumor sites was performed as boost radiation after the dose had exceeded 50 Gy (Table III).

*Chemotherapy*. Treatment regimens were as follows: 5-FU, 300 mg/m$^2$ 3 times/month (3 weeks of treatment followed by a 1-week treatment-free period); GEM, 1,000 mg/m$^2$ once/month or 500 to 600 mg/m$^2$ 3 times/month (3 weeks of treatment followed by a 1-week treatment-free period).

*Hyperthermia*. In combination with radiotherapy, hyperthermia was administered for 50 min/session once or twice a week, 5 to 6 times in total, employing an 8-MHz RF-capacitive heating device (Thermotron-RF8; Yamamoto Vinita Co., Ltd., Osaka, Japan). The 25- or 30-cm electrodes of the Thermotron-RF8, with output settings ranging from 800 to 1,200 W, were applied to lesions. The lesions were heated to 41˚C or higher and then evaluated using images obtained with the Thermotron-RF8 thermo-simulator.

*Statistical analysis*. Survival was calculated by the Kaplan-Meier method, and differences were expressed at a 5% significance level with a two-tailed log-rank test. All calculations and survival displays were conducted using the SPSS 21.0J statistical software package (SSPS Inc., Chicago, IL, USA). Acute and late complications were graded according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC), version 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf).

## Results

*Overall survival*. The median overall survival period of all patients was 12 months and the 1-year survival rate was 55% (Fig. 1); the corresponding values were 10 months and 50% in the 5-FU CR group, 12 months and 57% in the GEM CR group, and 15 months and 80% in the HCR group. Univariate analysis for factors associated with outcomes revealed a significant difference favoring the HCR group (P=0.021) (Fig. 2) and no significant difference in the GEM or the 5-FU CR group (P=0.263) (Fig. 3).

*Adverse events*. Ten patients (10/13, 77%) developed gastroenteritis (acute adverse events ≥ Grade 2) including five (5/13, 38%) with Grade 3 gastroenteritis. Of these five patients, three developed enteritis, necessitating hospitalization for medical therapy, and two developed duodenal ulcers (corresponding to Grade 2 severity) requiring medical therapy. Thus, there were no occurrences of adverse events ≥ Grade 4. In the HCR group, two patients (2/5, 40%) developed Grade 3 gastroenteritis; one each with enteritis and duodenal ulcers.

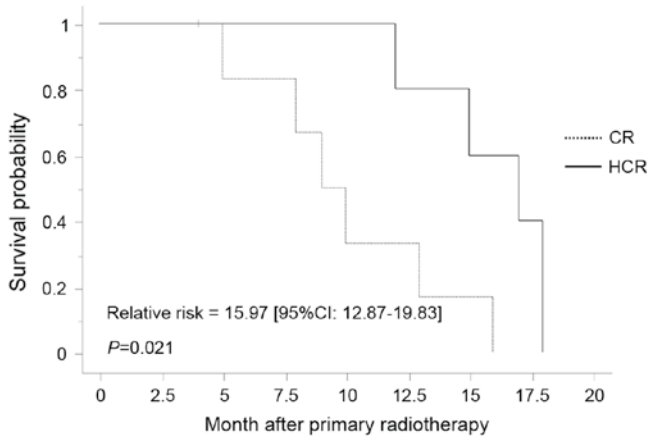


Figure 2. Overall survival in the HCR and CR groups. P-values were calculated by the log-rank test stratified according to the radiation therapy treatment group. HCR, hyperthermia and chemoradiotherapy; CR, chemoradiotherapy; CI, confidence interval.

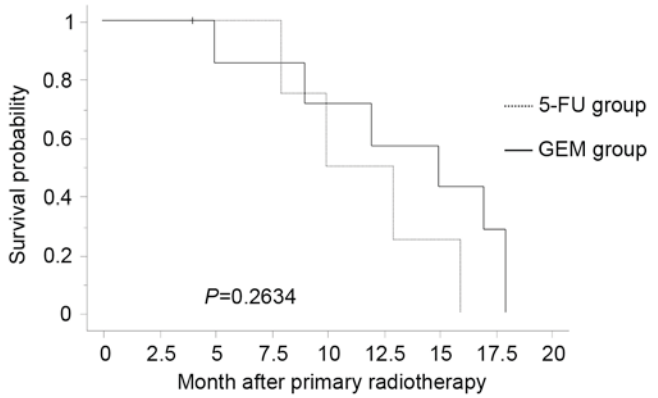


Figure 3. Overall survivals in the 5FU and GEM groups. P-values were calculated by the log-rank test stratified according to the radiation therapy treatment group. 5-FU, 5-fluorouracil; GEM, gemcitabine hydrochloride.

Hematotoxicity ≥ Grade 2 occurred in nine patients (9/13, 69%) including three with Grade 3 and one (in the 5-FU CR group) with Grade 4 hematotoxicity. All five patients in the HCR group developed hematotoxicity ≥ Grade 2: Grade 2 in three patients and Grade 3 in two. No serious late adverse events were noted.

## Discussion

Surgery is the only treatment by which complete cure of pancreatic cancer can be achieved. However, according to data from the pancreatic cancer registry in Japan, early-stage resectable pancreatic cancer accounts for only 10% of all cases (1). As for lymphadenectomy, there is thought to be no significant difference in outcomes between radical and standard lymphadenectomy (6,7). Since surgery is the only radical therapy for pancreatic cancer, increasing the percentage of pancreatic cancer cases diagnosed at a stage when tumors are still resectable is essential. In the NCCN guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#pancreatic), pancreatic cancer is classified into 3 types: Resectable, unresectable, and borderline resectable. Surgical treatment of borderline resectable pancreatic cancer after neoadjuvant chemotherapy is a promising approach.

As for chemotherapy, marked advances in postoperative adjuvant chemotherapy have improved the outcomes of cancer patients (8), and postoperative treatment strategies are an area of ongoing research with promising new developments. However, for patients with unresectable pancreatic cancer, satisfactory prognostic improvement has not yet been achieved, despite advances obtained with the use of GEM, which was approved in Japan in 2001. In recent years, therapies with FOLFIRINOX (9) and with the combination of GEM plus Abraxane have improved the outcomes of these patients (10). However, in Japan, these therapies appear to be associated with higher incidences of adverse events (11,12).

It has long been accepted that radiotherapy in combination with 5-FU chemotherapy (5-FU CR) is the standard treatment regimen for unresectable pancreatic cancer since greater improvement of outcomes was noted in patients given CR as compared to those receiving radiotherapy alone (13). A comparative study of GEM CR vs. GEM chemotherapy (14) showed that the former had significantly better outcomes, though the incidence of adverse events was high. In contrast, a clinical study comparing concurrent FP (5-FU plus CDDP) CR vs. GEM chemotherapy (15) found that the latter showed a significant difference in outcomes with a low incidence of adverse events. Another study demonstrated concurrent TS-1 (tegafur, gimeracil, and oteracil potassium) CR to be useful (16). Incidences of adverse events are relatively high with CR and there was no significant difference in outcomes between chemotherapy alone and that with concurrent CR. Accordingly, at our hospital, we tend to use chemotherapy alone for pancreatic cancer.

In a previous clinical study of 5-FU CR, the median survival was 11 months and the 1-year survival rate was approximately 30%. These results showed concurrent 5-FU CR to yield better outcomes than radiotherapy alone, leading to the establishment of 5-FU CR as a first-line treatment (11). After the advent of GEM, Crane *et al* (17). Reported that GEM CR achieved a median survival of 11 months and a 1-year survival rate of 42%, while Gillen *et al* (2). Reported that GEM CR achieved a median survival of 14.5 months.

At our institution, the median survival period is 15 months and the 1-year survival rate is 80% with concurrent GEM HCR; these outcomes are better than those in previous studies of CR. Comparison of concurrent GEM vs. 5-FU CR revealed no difference in outcomes. Pancreatic cancer is generally a hypovascular tumor and is thus more difficult to visualize with tumor staining than other carcinomas. One of the reasons for prolonged survival in our patients given concurrent HCR is considered to be the larger doses of drugs delivered to tumor sites. This is because concurrent HCR increases the blood supply to tumors. In GEM chemotherapy, nuclear factor kappa B (NF-κB), a transcription factor, is activated through immunological mechanisms, and this is regarded as one of the causes of GEM resistance development. Heat shock protein induced by concurrent HCR reportedly exerts inhibitory actions on NF-κB activity (18,19), which is regarded as being a mechanism underlying the antitumor effect of HCR. Accordingly, for patients whose performance status is satisfactory, hyperthermia is considered to contribute to prolonged survival

regardless of whether or not HCR, concurrent hyperthermia or maintenance GEM chemotherapy is also administered.

HCR is also considered to be useful in patients who have developed drug resistance after receiving chemotherapy alone. However, patients who agree to receive HCR generally have a positive attitude toward treatment, as well as a satisfactory performance status, and this may bias outcomes. We plan to collect more data on patients given HCR in future studies.

Although the sample size was small, there appeared to be no difference in the incidence of adverse events between CR and HCR. The safety of HCR in our study is thus considered to be similar to that in previous studies (20).

However, there are several issues and challenges, which must be addressed, before widespread adoption of hyperthermia treatment. First, the procedure is time-consuming as it involves application site pain despite cooling of the skin surface, and there is a risk of heat transfer to stents placed in patients with bile duct or pancreatic tumors. No specific methods for reducing this discomfort have yet been devised. As for the latter problem, the informed consent procedure for hyperthermia treatment is carefully carried out at our hospital, with detailed explanations, and patients thus undergo hyperthermia treatment safely. To date, there have been no problems associated with the metallic stents. Emaciation is widely recognized as occurring in patients with pancreatic cancer; hyperthermia treatment is considered to be suitable for emaciated patients.

Given the difficulty at present in achieving marked improvement of outcomes in unresectable pancreatic cancer, measures against the development of adverse events and drug resistance during chemotherapy are considered to be essential. Such measures can be applied with the use of hyperthermia; if the search for application sites for hyperthermia is successful, this treatment can provide benefits for cancer patients whose performance status is satisfactory (21).

Concurrent HCR is reportedly effective for various carcinomas as well as for pancreatic cancer. A significant difference in outcomes was noted in patients with cervix carcinoma who received hyperthermia treatment in addition to Chemoradiotherapy (20). Another study showed hyperthermia application to be useful for rectal cancer as preoperative therapy (22). These reports provide evidence of hyperthermia being a useful treatment for various carcinomas.

Molecular targeted drugs are expected to achieve improved outcomes in patients with locally advanced unresectable pancreatic cancer whose performance status is satisfactory, while modified or advanced hyperthermia techniques are also expected to contribute to improving the outcomes of patients with various carcinomas.

In conclusions, we studied multimodality therapy for pancreatic cancer in a small patient sample, confirming the efficacy and safety of concurrent hyperthermia and chemoradiotherapy. Thus, hyperthermia treatment merits active recommendation to pancreatic cancer patients who show a positive attitude toward treatment and whose performance status is satisfactory.

All clinical procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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