# Effectiveness of hyperthermia in clinical stage IV pancreatic cancer

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Although recent progress of chemotherapy for the pancreatic cancer provide improvement of the patients' prognosis, the advanced pancreatic cancer patients in clinical stage IV is still quite difficult to increase the survival rate. Hyperthermia is expected as an effective treatment for such patients in combination with chemotherapy. In order to investigate the effectiveness of hyperthermia using Thermotoron RF-8 combined with chemotherapy for clinical stage IV patients we examined the outcome of the patients in the periods until two years from the beginning of this therapy. The results were compared to the registered data of the multi-center of Japan in the patients of stage IV treated with chemotherapy alone. The aim of this study is to investigate whether hyperthermia contribute to improve the outcome of the pancreatic cancer patients in clinical stage IV.

**Material/Methods**
28 patients with advanced pancreatic cancer in clinical stage IV treated by more than 5 times of hyperthermia were examined. These patients had distant metastasis or peritoneal dissemination and were treated with several types of combination chemotherapy. Among them, 9 patients had the history of surgery for the primary tumour and 21 had no surgery. Hyperthermia using the Thermotron RF-8 heating device was administrated for 50 min each time just after chemotherapy 3 or 4 times in a month. The evaluation of outcome of the patients was expressed as CR, PR, SD, PD and overall survival. This evaluation was done at 3, 6, 12, 18 and 24 months after the beginning of this therapy.

**Results**
In the response to the treatment at 3 months, CR was 0 %, PR was 18%, SD was 39% and PD was 42%. Survival rate was 97%. At 6 months, CR was 0 %, PR was 16%, SD was 24% and PD was 40%. Survival rate was 80%. At 12 months, CR was 6%, PR was 0%, SD was 6% and PD was 59%. Survival rate was 41%. At 18 months, CR was 6%, PR was 0%, SD was 0% and PD was 19%. Survival rate was 25%. 2 patients survived more than 2 years. Among 12 patients observed for these two years, two patients survived, and one patient is still in the state of CR. The survival rate in 2 years was 17%. According to the Japanese Association of Clinical Cancer Centers, in the registered data in 2010, 1-year survival rate and 2 years survival rate of the stage IV pancreas cancer patients treated with chemotherapy alone, is 20% and 8% respectively. Although the number of the patients in our hospital is small, the outcome of them were superior to that of the registered patients in the Japanese Association of Clinical Cancer Centers, who were treated without hyperthermia.
Conclusion: The results in this study indicate that the treatment of hyperthermia combined with chemotherapy have a possibility to contribute to prolong the survival of the patients even in the clinical stage IV.

**Introduction**
In spite of the recent progress of the chemotherapy for the pancreatic cancer patients provide improvement of the patients' prognosis, the advanced pancreatic cancer in clinical stage IV with local recurrence, distant metastasis or peritoneal dissemination is still quite difficult to increase the survival rate. Hyperthermia is expected as an effective treatment for such patients in combination with chemotherapy (1,2,3). During 3 years and 5 months since 2016, 41 pancreatic cancer patients in various situations were treated in our hospital with hyperthermia using Thermotron RF-8. In this study, we evaluated the result of 28 patients treated more than 5 times by this therapy. In order to investigate the effectiveness of the hyperthermia using Thermotron RF-8 combined with chemotherapy for the patients in clinical stage IV, including tumour recurrence after surgery. We examined the outcome of the patients in the periods until two years after the beginning of this therapy. The results were compared to the registered data of the multi-center of Japan of the pancreas cancer patients in Stage IV treated with chemotherapy alone. The aim of this study is to investigate whether hyperthermia contribute to improve the prognosis of the pancreatic cancer patients in clinical stage IV.

**Material and Methods**
28 patients (from 40 to 79 years of age) with advanced pancreatic cancer in clinical stage IV treated by more than 5 times of hyperthermia combined with chemotherapy were examined. 16 cases were male patients, 12 cases were female patients. These patients had distant metastasis or peritoneal dissemination

and were treated with the several types of combination chemotherapy, FOLFIRINOX, Gemsitabin plus nab-Pacritaxel or S-1. Among them, 9 patients had the history of surgery for the primary tumour and 21 had no surgery (Table 1).

**Characteristics of the 28 patients**

| **Gender** | |
|---|---|
| Male | 16 |
| Female | 12 |
| **Age, years** | |
| Median | 64.3 |
| Range | 40-79 |
| **Metastic state** | |
| Liver | 18 |
| Lung | 7 |
| Peritoneum | 8 |
| **Pancreatic resection** | |
| No | 20 |
| Yes | 8 |

Heating device of Thermotron RF-8, which is widely used in Japan, was used for the hyperthermia treatment. Patients were administrated for 50 min each time just after chemotherapy 3 or 4 times a month. Most of the patients had the medical history of treatment, including surgery or standard chemotherapy in the other hospital before starting our therapy. Evaluation of outcomes of the patients was expressed as complete remission (CR), partial response (PR), stable disease (SD), progress disease (PD) and survival rate. This evaluation was done at 3, 6, 12, 18 and 24 months after the beginning of this therapy.

**Results**

In the response to the treatment at 3 months, CR was 0 %, PR was 18%, SD was 39% and PD was 42%. At 6 months, CR was 0 %, PR was 21%, SD was 24% and PD was 28%. At 12 months, CR was 6%, PR was 0%, SD was 6% and PD was 59%. At 18 months, CR was 6%, PR was 0%, SD was 0% and PD was 19% (fig 1).

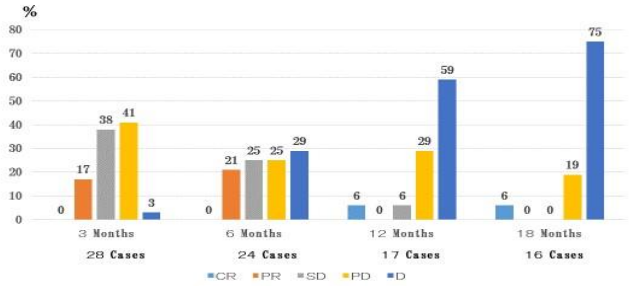


Figure 1: Outcomes were evaluated in 3, 6, 12 and 18 months after the beginning of hyperthermia therapy. Each number indicated the percentage of the patients in the same periods.

The outcome is getting worse, but at 6 months nearly 50% of the patients were keeping PR or SD, and at one year 41 % was still alive. Up to now, we observed 12 patients for more than two years. Among them, two patients were alive, and one of them is still in the state of CR. The survival rate of 1 year and 2 years were 41**%** and 15% respectively. According to the registered data in 2010 of Japanese Association of Clinical Cancer Centers, 1-year survival rate and 2 years survival rate of the stage Ⅳ pancreatic cancer patients treated with chemotherapy alone is 22.7 % and 6.1 % respectively (Fig 2).

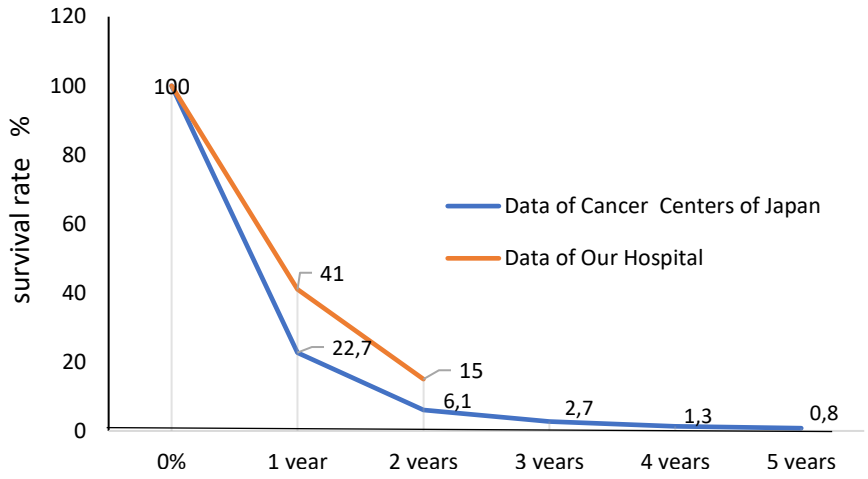


Figure 2: Survival rate until two years in our cases, and that of Japanese Association of Clinical Cancer Centers, (total 70 centers).

Even though the number of the patients in our study is small, the outcome of the patients were superior to that of the registered patients in Japanese Association of Clinical Cancer Centers, who were treated without hyperthermia. In our study, 3 cases showed the quite good response to this therapy.

**First case**

58 years old male patient. Diagnosis is invasive pancreas ductal carcinoma in the pancreas head with multiple liver metastasis. Chemotherapy was administered using the regimen of GEM + nabPTX by every 4 weeks for 2 years. Hyperthermia was started two months after the beginning of the chemotherapy. It was done on the same day after the chemotherapy. Before treatment, low density tumour was located close to the duodenum. After 1 year, the primary tumour disappeared, and after 2 years, the head of the pancreas was still tumour free. Liver metastasis was observed before the treatment, but 1 year later, those disappeared, and 2 years later the patient is still tumour free. Before the treatment, the CA19-9a tumour marker level was quite high; it was 26,494 unit/ml. But 3months after starting hyperthermia, the tumour markers (CEA, CA19-9) decreased within normal level. This situation continued at 2 years after starting this therapy. These results indicated that this patient is in clinical CR (Fig 3).

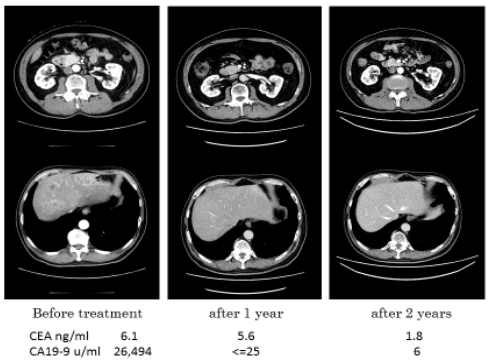


Figure 3: CT findings of the pancreas, liver and the tumour marker for two years in case 1

**Second Case**

The second case is a 65 years old male patient. The diagnosis is pancreatic cancer in the body to tail, with multiple liver metastasis. For the first chemotherapy, the regimen of GEM + nabPTX was administrated every 4 weeks and was continued for four months. After that, regimen was changed to GEM + S1. It was administrated every 3 weeks. This regimen is still continued until now. Hyperthermia was started at the same time as chemotherapy. The treatment was performed on the same day just after the chemotherapy. In the CT

findings, multiple liver metastasis and primary tumour is located in the pancreas body to tail as a low-density lesion before the treatment. In contrast,7 months later, metastatic tumour in the liver is markedly contracted. The primary tumour could not be detected. The level of tumour marker before the treatment, especially the level of CA19-9 was extraordinarily high, 551,790 U/ml, but 7 months after starting the hyperthermia, it decreased to 6,257. Therefore, the situation of this patient is considered to be PR (Fig 4).

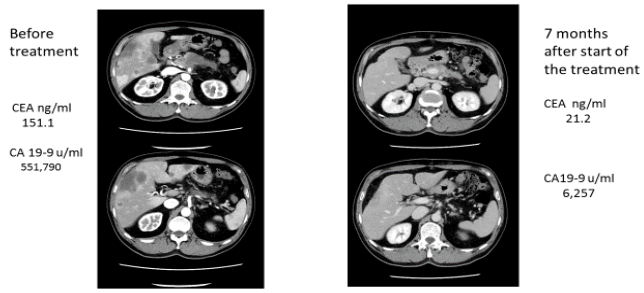


Figure 4: CT findings and the level of tumour marker before treatment and 7 months after the start of the treatment.

We estimated the temperature in the stomach during hyperthermia in this patient, using gastric catheter inserted sensor of temperature. The power of the radiofrequency for this patient was maintained about 1200 W. The maximal temperature was just over 44℃ by prone position.

**Third Case:**

58 years old male patient. The diagnosis is pancreatic cancer in the tail with invasion to the spleen and kidney with multiple liver metastasis. For the chemotherapy, the regimen of FOLFIRINOX was done during the first 3 months, after that it changed to GEM + nabPTX, and continued until now. FOLFIRINOX was done every 4 weeks for 3 months, GEM + S1 was done every 4 weeks. Hyperthermia was started at 2 months after the beginning of the chemotherapy. Treatment was done on the same day after the chemotherapy. In the CT findings, a big tumour was located in the tail of pancreas invading into the spleen and metastatic liver tumour was observed. 5 months after starting the therapy, the tumour was reduced and also the metastatic liver tumour was contracted. The tumour markers (CEA, CA19-9) were decreasing gradually during 6 months after starting hyperthermia. These findings indicate that this patient is also in the situation of PR (Fig 5).

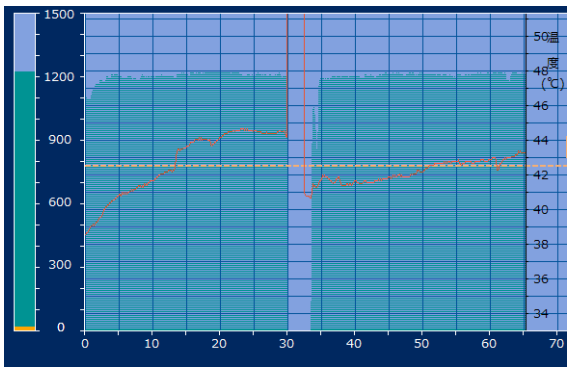


Figure 5: The record of estimation of temperature in the stomach during hyperthermia. Left axis is the power of RF (watt). Light green area indicates the change of the level of RF. Right axis is the temperature (℃). Horizontal shaft is time (min). Red line is the change of the temperature.

**Discussion**

It is generally important to decide the diagnosis in the early stage to provide good prognosis for malignant disease. Many cases of pancreatic cancer do not have the subjective symptoms in the early stage; therefore, patients do not always have a chance to receive surgery. According to the data of pancreatic cancer registry in Japan, respectable pancreatic cancer in the early stage account only 10% of all cases (4). The patients with no indication for surgery or recurrent cases after surgery are mainly treated with chemotherapy.

The regimen of the chemotherapy is on the way of progression (5,6), however it is still in the poor prognosis of the highly advanced cancer of stage IV, which have distant metastasis or peritoneal dissemination. Vascularity in the lesion of pancreatic cancer is relatively low in comparison with the other malignant tumour. That is one of the reasons why the effect of the treatment is limited, when the patients were treated with chemotherapy alone. Hyperthermia combined with chemotherapy is expected as an effective treatment for such patients to improve the outcome (7). In this treatment, the temperature of the target area is one of the important points to know the working situation of this treatment. It is not easy to estimate the temperature of the organ located in the deep part of the body directly. Pancreas is also quite difficult to do. We tried to estimate the temperature in the stomach during hyperthermia in a patient, using gastric catheter inserted sensor of temperature. Although this is not the temperature in the pancreas itself, it is considered to be nearly reflected the temperature of the deep area. In this case, the maximal temperature of the stomach was 43 to 44 ℃ during the treatment by RF power of 1200 Watt. These results were one of the evidences, which support the effectiveness of hyperthermia in this patient. The total outcome of our study is not yet satisfactory; however, the survival rate was improved in comparison with that of the registered data of the multi-center of Japan of pancreas cancer patients in stage IV treated with chemotherapy alone. Although the number of our cases were quite small to do the exact statistical analysis, the results indicated that hyperthermia treatment has a possibility to improve the prognosis even if in stage IV pancreatic cancer.

**Conclusion**

Hyperthermia treatment combined with chemotherapy have a strong possibility to contribute to prolong the survival of the patients even if in the clinical stage IV.

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