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# Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: Results of feasibility study

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## Abstract

**AIM:** To explore whether intensity modulated radiation therapy (IMRT) in combination with chemotherapy could increase radiation dose to gross tumor volume without severe acute radiation related toxicity by decreasing the dose to the surrounding normal tissue in patients with locally advanced pancreatic cancer.

**METHODS:** Twenty-one patients with locally advanced pancreatic cancer were evaluated in this clinical trial. Patients would receive the dose of IMRT from 21Gy to 30Gy in 7 to 10 fractions within two weeks after conventional radiotherapy of 30Gy in 15 fractions over 3 weeks. The total escalation tumor dose would be 51, 54, 57, 60Gy, respectively. 5-fluorouracil (5-FU) or gemcitabine was given concurrently with radiotherapy during the treatment course.

**RESULTS:** Sixteen patients who had completed the radiotherapy plan with doses of 51Gy (3 cases), 54Gy (3 cases), 57Gy (3 cases) and 60Gy (7 cases) were included for evaluation. The median levels of CA19-9 prior to and after radiotherapy were 716 U/ml and 255 U/ml respectively ( $P < 0.001$ ) in 13 patients who demonstrated high levels of CA19-9 before radiotherapy. Fourteen patients who suffered from pain could reduce at least 1/3-1/2 amount of analgesic intake and 5 among these patients got complete relief of pain. Ten patients improved in Karnofsky performance status (KPS). The median follow-up period was 8 months and one-year survival rate was 35 %. No patient suffered more than grade III acute toxicities induced by radiotherapy.

**CONCLUSION:** Sixty Gy in 25 fractions over 5 weeks with late course IMRT technique combined with concurrent 5-FU chemotherapy can provide a definitely palliative benefit with tolerable acute radiation related toxicity for patients with advanced pancreatic cancer.

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## INTRODUCTION

The incidence of pancreatic carcinoma has been continuously increasing worldwide in recent years. The incidence in Shanghai of China has increased to 9.6 per 100 000 for males and 9.2 per 100 000 for females. Most patients have locally advanced unresectable disease at the time of initial diagnosis because of lacking clinical symptoms and signs. Without treatment intervention, the mean time of survival was approximately 4 to 6 months<sup>[1]</sup>. Although surgery was considered to be the only curative treatment method, there were only 10-20 % patients who had resectable tumors suitable for radical resection and 30-85 % patients would have local recurrences<sup>[2]</sup>.

At present, there are no satisfactory treatment modalities for patients with advanced pancreatic carcinoma. Adenocarcinoma of pancreas is a disease characterized by resistance to cytotoxic therapy including chemotherapy and radiotherapy. Treatment response of systemic chemotherapy is relatively poor with only 20 % response rate, which would last only a short time and most of the treatment effects are partial response. Meanwhile, the conventional radiation dose to gross tumor volume is not large enough to cure patients with pancreatic carcinoma because of the limited tolerant dose to the surrounding normal tissues such as gastrointestinal tract and kidneys. Many studies have shown that the local control and survival would be maximized if patients with pancreatic carcinoma were treated by surgery combined with chemoradiation therapy<sup>[3-6]</sup>. There were full laboratory and clinical evidences of potent radiosensitizing properties and significant systemic activity of 5-fluorouracil (5-FU) and/or gemcitabine (GEM) used in combination with radiotherapy in pancreatic carcinoma<sup>[7-12]</sup>.

In addition, since 1990's, radiation treatment equipments and related techniques have been developed dramatically. Especially, more attention has been paid to intensity modulated radiation therapy (IMRT), which is an approach with the aid of modern computer treatment planning system to conformal radiation therapy that conforms a high dose to the target (tumor) volume while restricting dose to the surrounding sensitive structures, and encouraging results have been achieved in clinical trials in head and neck carcinoma and thoracic carcinoma.

However, conventional radiotherapy can not give a higher dose needed to eradicate pancreatic carcinoma cells which are moderately sensitive to radiation due to the dose limited tissues adjacent to pancreas. In general, the dose adopted in conventional radiotherapy was approximately or less than 50Gy in 25 fractions over 5 weeks<sup>[5,11,12]</sup>. But the optimal dose of IMRT to treat patients with pancreatic carcinoma has not been established, especially in combination with chemotherapies such as 5-FU or GEM.

In this study, we reported our experience in the combination of IMRT and chemotherapy with 5-FU or GEM in a group of patients with locally advanced nonresectable pancreatic carcinoma. Our goal was to determine the feasibility of this treatment modality by evaluating the acute radiation toxicity and the treatment efficacy in this dose escalating trial. A second

purpose was to determine the palliation of symptoms, response rate and survival in this group of patients.

## MATERIALS AND METHODS

### *Eligibility*

From November 2001 to December 2002, patients with histologically proved pancreatic adenocarcinoma were enrolled into this study. Eligible patients included those with locally unresectable disease due to vascular invasion or extensive regional adenopathy, partial resection or local recurrence after operation. Patients with known metastasis to distant organs, ascites, Karnofsky performance status less than 70 were excluded. Required laboratory parameters included white blood cell count  $\geq 4 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , creatinine  $\leq 264 \mu\text{mol/L}$ . Patients with biliary or gastroduodenal obstruction must have had prior drainage before radiotherapy and chemotherapy were started. A complete history and physical examination were performed in all patients prior to scheduled treatment. Height, weight, performance status, tumor stage and serum level of tumor markers including carbohydrate antigen (CA) 19-9 were recorded. Required examinations for staging studies included a chest radiograph and abdominal computed tomographic (CT) scan or magnetic resonance image (MRI) scan, abdominal type B ultrasound and sometimes bone isotopic examination. All patients were required to sign a written informed consent according to national and institutional guidelines.

### *Radiotherapy*

Patients were CT simulated and treated in the supine position with their arms overhead. In order to make it easier to define tumor target volume from the stomach and duodenum, 300 ml of oral CT contrast with 2 % gastrografin solution was administered respectively one hour and half an hour before starting CT simulation scan with ACQsim spiral CT. For immobilization, a customized thermoplastic cast extending from the mid-thoracic spine to the mid-pelvis was made. Each patient was scanned from the upper dome of the right diaphragm (approximately at the level of T9-T10) to the bottom of the L4 vertebral body. The patient was imaged with overlapping CT slices that were 5 mm thick at 3 mm intervals. Center of CT scanning was marked on the thermoplastic cast. The gross tumor volume (GTV) and the surrounding critical structures of concern including the liver, kidneys, stomach, small intestine and spinal cord were defined after the data of CT scan were sent to the workstation of ACQsim (version 4.3) CT simulation software system. GTV represents tumor in the pancreas, the surrounding tissue infiltrated and adjacent lymph node metastasis. The clinical target volume (CTV) includes GTV plus any microscopic extension of disease that is suspected around GTV. The planning target volume (PTV) represents CTV plus any additional margins that are required to compensate for daily setup variations. Isocenter coordinate of radiotherapy was marked on the thermoplastic cast with the help of a laser mark system. Cadplan treatment plan system using Helios reverse treatment planning software was adopted to optimize the dose distribution after the images of CT scan and digitally reconstructed radiographs were transmitted. Then, the treatment data were sent to Varian 2100C/D accelerator by Varis network. Port films were taken at the first time and once every week of treatment to verify the radiation position.

Radiotherapy was divided into two phases. Conventional radiotherapy was delivered to a total of 30Gy in 15 fractions of 2Gy per fraction to the initial fields including the primary tumor plus the regional peripancreatic, celiac, and porta hepatis lymph nodes at the first phase. IMRT was given at the second

phase and GTV was covered by the 95 % prescribed isodose curve. The dose of IMRT ranged from 21Gy to 30Gy in 7-10 fractions of 3Gy per fraction. The total dose escalation levels were 51Gy, 54Gy, 57Gy and 60Gy respectively. Three patients were needed for each dose level. Dose-limiting toxicity (DLT) from radiotherapy was defined as grade IV hematologic toxicity or grade III nonhematologic toxicity according to common toxicity criteria (CTC, 2.0 version). Dose escalation continued to the next dose level if no patients suffered from DLT. Two or more instances of DLT among 3 patients occurred in the preceding dose level would declare it as the maximum tolerant dose (MTD). Another 3 patients would be needed for observation if one of them had DLT at a certain dose escalation level. If no one had DLT in these additional 3 patients, dose escalation would continue. However, if one patient developed DLT among the added 3 patients, the preceded dose level would be the MTD. In this study, the maximum escalation dose level was 60Gy.

### *Chemotherapy*

Gemcitabine (GM), 150 mg/d, was administered daily prior to radiotherapy on weeks 1, 3, 5, or 5-fluorouracil (5-FU), 250 mg/d, was given every week from Monday to Friday during the days of whole radiotherapy course.

### *Toxicity and response evaluation*

Toxicity was evaluated according to common toxicity criteria: version 2.0 (CTC 2.0)<sup>[13]</sup>. Hematologic parameters were assessed weekly, and all other adverse reactions were evaluated during the course of radiotherapy. Analgesic intake and weight were recorded at initial consultation and weekly during radiation therapy. Karnofsky performance status (KPS) was estimated prior to radiotherapy and recorded as it was improved, stable, or deteriorated after treatment. Weight change was classified as weight gain/loss if there was a weight increase/decrease  $\geq 5$  % over baseline value, otherwise it was classified as stable. Pain control was recorded when it was improved/deteriorated if there was a  $\geq 50$  % increase/decrease respectively in the daily intake of equivalent analgesic dose at least lasting for 4 weeks. The clinical response index was defined as a sustained improvement in at least one parameter (among three factors as KPS, weight and pain control) without the other two factors worsening for more than 4 weeks. Tumor volume response was assessed based on the tumor size pre- and postradiation CT scans. A complete response (CR) was defined as the disappearance of all clinical evidences of tumor without appearance of new lesions for more than 4 weeks. A partial response (PR) required a 50 % decrement in the maximal perpendicular tumor measurements, with no new lesion appearance for at least 4 weeks. No change (NC) was defined as less than 50 % reduction and less than 25 % increase of measurable tumor lesions. Progressive disease (PD) was defined as more than 25 % increase of measurable tumor lesions or new lesion developed. Response rate included the patients with CR and PR. Survival rate was calculated by the method of Kaplan Meier with the statistic software SPSS (version 9.0).

## RESULTS

### *Dose escalation*

Twenty-one patients were enrolled in this clinical study, 15 were unresectable as a result of major vascular invasion, 2 patients had partial tumor resected and other 4 patients had local recurrence at the primary site. Twelve were males and 9 females, and the median age of all patients was 64 years (range: 46-72 years).

Among these twenty-one patients, the primary lesions were

located at the head of 13 patients, at the body or tail of pancreas in 8 patients. Sixteen out of 21 patients completed the whole course of radiotherapy. The number of patients treated with different dose levels of 51Gy, 54Gy, 57Gy, 60Gy were 3, 3, 3 and 7 cases respectively. Dose volume histogram demonstrated that the median percentage of volume of small intestine received 80 % and 90 % of the prescribed dose was 10 % and 6 % respectively. Five out of 21 patients gave up the plan of radiotherapy because 4 patients had hepatic metastasis or ascites and another one had high fever, grade IV hematologic toxicity at the time of administration of GEM with a dose of 200 mg for the second time.

### Clinical benefit

Sixteen patients were analyzed. CA19-9 levels prior to radiotherapy were elevated in 13 patients with a median value of 716 U/ml. At the end of radiotherapy, the levels of CA19-9 decreased significantly with a median value of 255 U/ml ( $P < 0.001$ ). Compared with that before radiotherapy, the value of CA19-9 decreased more than half after radiation treatment in 10/13 patients. Fourteen out of 16 patients suffered from pain at the start of chemoradiation had a decrease of oral analgesic consumption at the end of radiotherapy by more than 1/3 of the total amount before treatment. Ten out of 14 patients had a reduction of analgesic consumption more than 50 % and 5 patients were virtually painless. KPS was improved in 10/16 patients while 4 patients deteriorated during treatment, the other 2 patients remained unchanged. Only one patient (1/16) gained weight  $\geq 5$  % during treatment and maintained it for more than four weeks. Nine patients suffered from weight loss in excess of 5 % of their pretreatment weight. The other 6 patients remained stable in weight during the treatment. In total, seven patients were improved in at least one parameter of KPS, analgesic consumption or weight without simultaneous deterioration of any other parameters. So the clinical benefit ratio was 33 % (7/21). If the 5 patients who did not complete the radiation schedule were excluded, the benefit ratio increased to 44 % (7/16).

### Radiological examination and survival rate

CT scanning after completion of radiotherapy demonstrated that no patient acquired CR, 5 out of 16 patients attained PR. Therefore, the response rate was 31 %. The median follow-up time was 8 months (range 3-17 months). One-year survival rate was 35 %.

### Toxicity

No patient had radiation-induced acute reactions such as nausea, vomiting, diarrhea of greater than grade II. Among the six patients (6/21) who received chemotherapy with GEM as radiosensitizer, 3 patients had grade II neutropenia, 1 patients had grade IV neutropenia, and one patient had grade IV hematologic toxicities of neutropenia, thrombocytopenia and anemia. The latter was excluded from the dose escalation study. For patients receiving 5-FU as a radiosensitizer, only 3 patients had grade II neutropenia and two other patients had grade II abnormal liver function. All of them were able to complete the radiotherapy schedule with the support of some medication.

## DISCUSSION

Locally advanced, surgically unresectable pancreatic carcinoma is a highly lethal disease. Its one-year survival rate is less than 10 %. Since diagnosis is usually made too late in the course of development of the disease to the chance of radical surgical resection, most patients experience progressive symptoms of pain, jaundice, weight loss, nausea, vomiting, or

anorexia. An effective locoregional treatment would be the only chance for such patients. GEM and 5-FU have been studied in clinical trials by Radiation Therapy Oncology Group (RTOG) as radiation sensitizers in pancreatic cancer<sup>[14,15]</sup>. Studies of 5-FU and radiation have demonstrated that 5-FU was an effective radiation sensitizer by inhibiting tumor cell DNA synthesis. Gemcitabine (GEM) is also a radiosensitizer. It requires intracellular phosphorylation resulting in accumulation of difluorodeoxycytidine triphosphate (dFdCTP). dFdCTP competed with deoxycytidine triphosphate (dCTP) for incorporation into DNA and subsequently inhibited DNA synthesis and decreased intracellular deoxynucleoside triphosphate pools by curbing ribonucleotide reductase<sup>[14,15]</sup>. Both 5-FU and GEM have significant radiosensitization effect on tumor cells in which DNA band breakage induced by radiation is more difficult to be repaired. The severe toxicity reported by Crane *et al*<sup>[16]</sup> was significantly higher in patients treated with gemcitabine-based chemoradiation than in those treated with 5-FU-based chemoradiation, in which 12 out of 53 patients (23 %) treated with gemcitabine and one out of 61 patients (2 %) treated with 5-FU suffered from severe acute toxicity ( $P < 0.001$ ). But in a phase II trial of protracted 5-fluorouracil (200 mg/m<sup>2</sup>/day) with concurrent radiotherapy, grade III or worse toxicity was observed in 20 % (4/20) patients<sup>[17]</sup>. In this study, among the 6 patients who were given GEM as a radiosensitizer with a dose of 200 mg/d on weeks 1, 3, 5, grade IV hematologic toxicities were found in two (33 %) patients. However, no one had acute toxicity greater than grade III in patients receiving 5-FU as a radiosensitizer. Therefore, in our study, 5-FU was the only drug used as a radiosensitizer at the later period of all cases. Boz *et al*<sup>[8]</sup> reported that it was relatively safe to use 5-FU through a central venous catheter at a dose of 300 mg/m<sup>2</sup>/d, 7 d/wk, from the first day of external beam radiotherapy throughout the entire course of radiation treatment. In our study, only 5 patients who received 5-FU had grade II acute reaction and it was considered safe to combine the treatment with radiotherapy. No patient had radiotherapy induced severe acute reactions that interrupted the completion of radiotherapy.

Most cases in our study were patients with locally advanced unresectable pancreatic carcinoma. The aim of this study was to find the optimal maximum dose of external beam radiation using IMRT technique, which would not result in severe acute reaction induced by radiotherapy while improving the life quality and prolonging the survival as long as possible. Among the patients who received a total dose of 60Gy, no one suffered from dose-limiting toxicities resulted from radiotherapy. However, the dose greater than 60Gy was not given because of the possible occurrence of severe late toxicities due to radiation to normal tissue. Therefore, this study did not acquire the MTD of radiotherapy. Normalized with conventional dose 2Gy per fraction, the biological equivalent dose of 60Gy with IMRT technique for the early response tissues and the late response tissues were 62.2Gy and 66Gy respectively (for early response tissue:  $\alpha/\beta = 10$ Gy, for late response tissue:  $\alpha/\beta = 3$ Gy). Consequently, this study suggested that the IMRT adopted in this trial surely could improve the biological dose to tumor volume. The analysis of dose volume histogram (DVH) showed that the median volume of small intestine receiving 80 % and 90 % prescribed dose was 10 % and 6 % respectively. Moreover, late complications of gastrointestinal tract such as intestinal perforation, hemorrhage and obstruction were not found during follow-up. But we were not sure that patients given total dosage of 60Gy would not have severe complications in the future even the expected survival was relatively short. Therefore, our maximum escalation dose was limited to 60Gy. The tolerance of the patients were quite good in terms of normal tissue acute toxicities induced by radiation

when 30Gy was given in 10 fractions with IMRT technique (PTV margin was 5 mm from GTV) in addition to the conventional dose of 30Gy over 15 fractions.

A recent study by Crane *et al*<sup>[16]</sup> demonstrated that weekly administration of GEM combined with radiation led to 1-year survival rate of 42 % and median survival duration of 11 months. The response rate and 1-year survival rate of this series were 31 % and 35 % respectively. The difference between our results compared with that in literature may be due to discrepancy of patient's selection. Up to now, no randomized prospective study in patients with pancreatic carcinoma compared the toxicities in gemcitabine-based *versus* 5-FU-based chemoradiation. Although the case number in our present study was relatively small, the primary results of our study indicated that the tolerance to 5-FU based chemoradiotherapy was much better than GEM based chemoradiotherapy.

In conclusion, for locally unresectable or recurrent pancreatic disease, this dose escalation clinical trial demonstrates that the dose level of 60Gy in 25 fractions over 5 weeks with IMRT technique combined with concurrent 5-FU is effective in improving survival, decreasing pain and the level of CA19-9 and promoting clinical benefit index without radiation-induced severe acute toxicities. Long term treatment effects and late toxicities remain to be evaluated.

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