RESEARCH COMMUNICATION

Gemcitabine-based Concurrent Chemoradiotherapy Versus Chemotherapy Alone in Patients with Locally Advanced Pancreatic Cancer

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Abstract

Objective: To explore improved treatment by retrospectively comparing survival time of gemcitabine-based concurrent chemoradiotherapy (GemRT) versus chemotherapy (Gem) alone in patients with locally advanced pancreatic cancer (LAPC). Methods: From January 2005 to June 2010, 56 patients with LAPC from Subei People's Hospital were treated either with Gem (n=21) or GemRT (n=35). Gem consisted of 4-6 cycles gemcitabine alone (1000 mg/m^2 on Days 1, 8, 15, 28-day a cycle). GemRT consisted of 50.4Gy/28F radiotherapy with concurrent 2 cycles of gemcitabine (1000 mg/m^2 on days of radiation 1, 8, 15, 21-day a cycle). Radiation was delivered to the gross tumor volume plus 1-1.5 cm by use of a three-dimensional conformal technique. The follow-up time was calculated from the time of diagnosis to the date of death or last contact. Kaplan-Meier methodology wes used to evaluate survival. Results: Patient characteristics were not significantly different between treatment groups. The disease control rate and the objective response rate of GemRT versus Gem was 97.1% vs 71.4%, 74.3% vs 38.1%. The overall survival (OS) was significantly better for GemRT compared to Gem (median 13 months versus 8 months; 51.4% versus 14.3% at 1 year, respectively). Conclusion: Radiation therapy at 50.4Gy with 2 concurrent cycles of gemcitabine results in favorable rates of OS. Concurrent chemoradiotherapy should be the first choice for patients with LAPC.

Keywords: Locally advanced pancreatic cancer - concurrent chemoradiotherapy - gemcitabine

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Introduction

Pancreatic cancer is one of the most malignant cancer type in digestive system with increasing incidence, fast progression and poor prognosis. Only 10-20% of the patients have resectable tumours at diagnosis and resection is a prerequisite for cure but even with adjuvant therapy five-year median overall survival of resected patients is still at about 20% (Brunner et al., 2010). While the other patients cannot receive operation because of local invasion or distant metastasis. LAPC, defined as unresecetable and local invasive disease at diagnosis, is a challenging malignancy to treat. Treatment purpose is to alleviate symptoms, improve quality of life, raise progression-free survival and overall survival rate. Our hospital began to apply 3D-CRT in combination with concurrent gemcitabine to treat patients with LAPC since 2005. In this clinical study, we retrospectively compare survival time of gemcitabine-based concurrent chemoradiotherapy (GemRT) versus chemotherapy (Gem) alone in patients with LAPC to explore the better treatment.

Materials and Methods

Patient eligibility

This is a retrospective study identifying all patients treated at Subei People's Hospital. The following eligibility criteria were used: 1. Cytologica or histologic proof adenocarcinoma of pancreatic cancer 2. Evidence of greater than 180 degrees SMA encasement, any celiac abutment, unreconstructible SMV/portal occlusion, aortic invasion or encasement and metastases to lymph nodes beyond the field of resection 3. Unequivocal tumor size measured by CT, a minimal diameter ≥ 1.0cm 4. minimal Karnofsky performance score ≥ 60% 5. No serious heart and lung diseases 6. Absolute granulocyte count of ≥ 3.5×10^9/L, hepatic function and renal function level less than 1.5 times upper limit of normal 7.Patients received Gem (1000 mg/m^2 on Days 1, 8, 15, 28-day a cycle, 4-6 cycles in total) or GemRT (50.4Gy in 28 fractions with concurrent 2 cycles of gemcitabine on days of radiation) schema. Exclusion criteria included: Clinically significant cardiovascular or peripheral vascular disease; Child, pregnant or lactating women; Evidence of distant metastasis; Prior radiation to the upper abdomen; History of other chemotherapy protocols; Parents with unmeasured tumor size.

Treatment Plan

Patients of Gem group received 4-6 cycles of gemcitabine, 1000 mg/m^2 on Days 1, 8, 15, 28-day a cycle. Patients of GemRT group received 50.4 Gy in 28

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fractions on Monday through Friday over 5.5 weeks with concurrent 2 cycles of gemcitabine, 1000 mg/m^2 on days of radiation 1, 8, 15, 21-day a cycle.

Protocol-Specified Conformal Radiation Technique

Three-dimensional conformal RT was used in GemRT group. Patients were immobilized by thermoplastic sheet in a supine position and 3-D conformal treatment planning was applied on IV and oral contrast enhanced planning CT scans. The gross primary tumor and any regional lymph nodes greater than 1 cm identified on CT scans were treated. CTV (clinical target volume) was GTV margin plus 1-1.5cm, PTV (planning target volume) comprised CTV margin plus 1-1.5 cm and covered by 90% isodose line. A three or four-field technique with equal beam weighting was suggested, but customization of beam angles and weighting was allowed. The dose was prescribed to 1.8Gy per fraction, 5 times per week and 50.4Gy in total. Concurrent 2-cycle gemcitabine was on days of radiation 1, 8, 15, 21-day a cycle. Figure 1 shows graphs of dose and field distribution of a representative patient.

Efficacy, treatment evaluation and statistical analysis

CT abdomen were performed 1 month before and after treatment to identify efficacy. The primary end point was overall survival (OS), measured from the date of study entry to the date of death or last follow-up. Kaplan-Meier methodology was used to evaluate OS. Response and progression were based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria, including complete remission (CR), partial remission (PR), stable disease (SD) and progression disease (PD). Disease control rate (DCR) was equal to CR+PR+SD, while objective response rate (ORR) was CR+PR. Statistical analyses were carried out with SPSS Version 16.0 software.

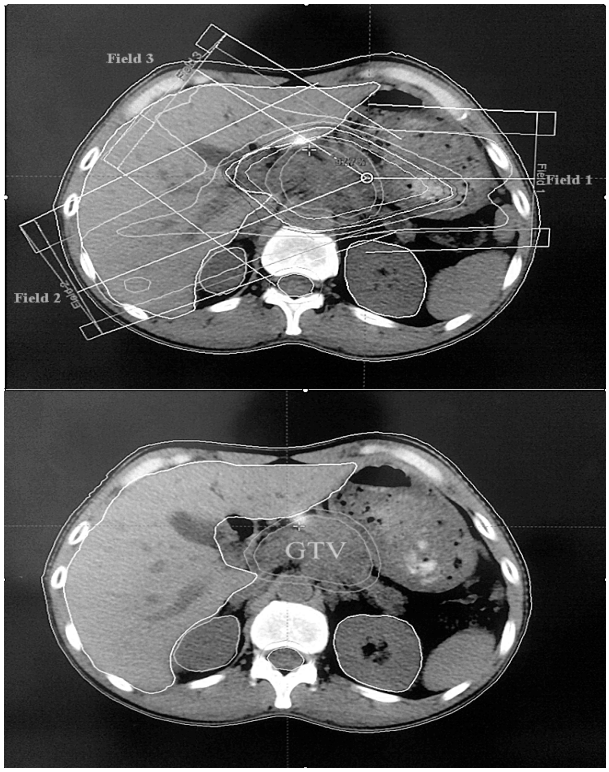

Figure 1. An Example of Dose Distribution and Field Distribution

Table 1. Patient Characteristics

		Gem		GemRT	
		patients	%	patients	%
All patients		21		35	
Age	Median(Range)	61(39-71)		61(44-71)	
Gender	Male	13	65	17	49
	Female	7	35	18	51
Tumor location	Head	17	81	29	83
	Body	4	19	5	14
	Tail	-	-	1	3
AJCC 2002	II	10	48	17	49
	III	11	52	18	51

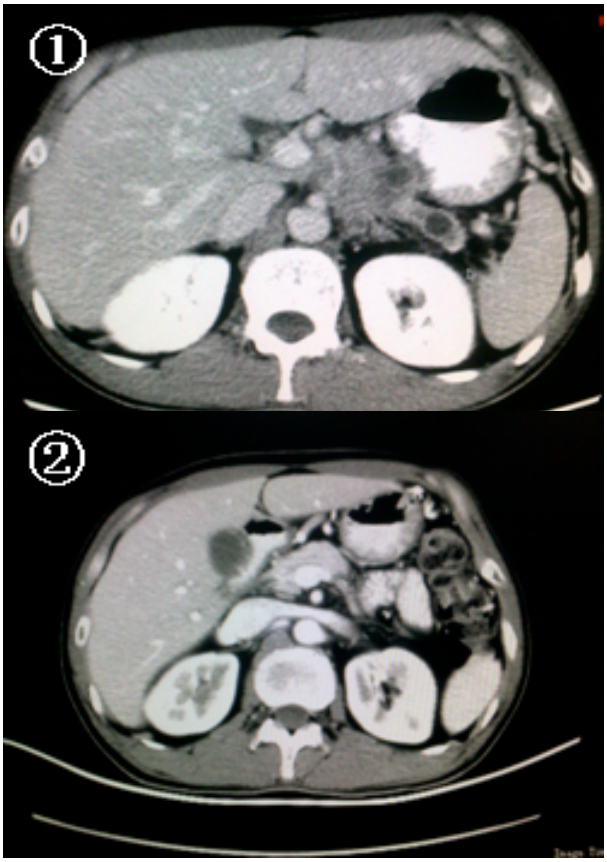

Figure 2. A patient's Tumor Variation Before and After Treatment. The tumor size was 36*49 mm before treatment, but tumor vanished at last

Results

Patient characteristics

We retrospectively analyzed the data of 72 patients with LAPC treated in our hospital from Jan 2005 to Jun 2010. Finally, 56 patients were eligible for this study, 30 males while 26 females. Median age was 60.5-year (range 48-73). The disease was staged according to AJCC 2002 TNM staging system. Patients characteristics are listed in Table 1.

Treatment and outcome

The last follow-up date was 28th Feb.2011, the follow-up ranged 8-24 months. Twenty-one patients were treated with Gem, and thirty-five patients treated with GemRT.

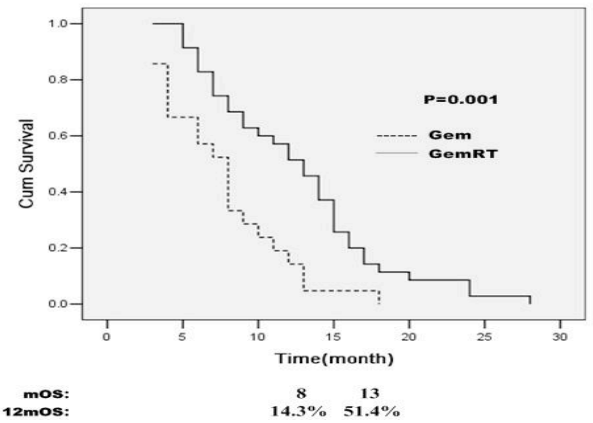

Figure 3. Kaplan-Meier Plot of Overall Survival of Patients. GemRT (n = 35) versus Gem (n = 21). Y-axis = percentage of patients surviving. Median overall survival time 8 vs 13 months; 1-year overall survival rate: 14.3% vs 51.4%

In Gem group, number of CR, PR, SD, PD was 0, 8, 7, 6, while in GemRT group was 9, 17, 8, 1. The ORR of Gem and GemRT were 38.10% and 74.29% respectively. Combined DCR was 71.43% vs 97.14%, respectively in the Gem and GemRT groups. Figure 2 shows tumor variation before and after treatment of a patient in GemRT group.

At last follow-up, all patients in Gem group (21 patients in total) have died, and the median survival time (MST) was 8 months (ranged from 3-18 months), 1-year overall survival (OS) was 14.3%. 23 of 35 patients in GemRT group (23/35) have died, and the median survival time (MST) was 13 months (ranged from 5-28 months), 1-year overall survival (OS) was 51.4%. Figure 3 shows Kaplan-Meier plot of overall survival of patients.

Discussion

The incidence of pancreatic cancer varies greatly around the world, especially remains higher in developed countries. Pancreatic cancer ranks 4th most lethal cancer in absolute patient numbers in t America (Jemal et al., 2007). In China, the latest data revealed that the incidence was 5.1/100,000 and gradually ascended over past decades (Ni et al., 2006). Patients with pancreatic cancer have short overall survival and 92% would die in a year after diagnosis. And 5-year OS is as low as 3%, the median survival time is 3-6 months. National Cancer Database (NCD) statistically analyzed 100,000 data of patients with pancreatic cancer and discovered that OS did not improve over past twenty years (Sener et al., 1999).

Surgery is deemed as the optimal choice for pancreatic cancer. Unfortunately, it is hard to diagnose early and about 80% of patients lost chance of operation (Li et al., 2010). Surgery, chemotherapy and radiotherapy are the most important strategies dealing with malignant tumor, which has already become consensus. Pancreatic cancer is moderate sensitive to radiation, and with the development of radiation technique, three-dimensional conformal technique enhances the dose of tumor area, improve the uniformity of dose distribution and finally increase local control rate. Chemotherapy is an essential element in the treatment of LAPC to fight the high tendency of distant spread. Therefore, concurrent chemoradiotherapy is widely used to cure pancreatic cancer. With current treatments, the median survival of LAPC patients is about 9-10 months (Hidalgo, 2010).

Many phase I–II trials using gemcitabine-based CRT have been evaluated for LAPC. Since Brurris firstly reported that gemcitabine could improve OS for advanced pancreatic cancer in 1997, gemcitabine monotherapy or gemcitabine-based chemotherapy combinations was considered as first-line therapy for advanced pancreatic cancer (Burris et al., 1997; Banu et al., 2007; Bria et al., 2007; Sultana et al., 2007). Zhu et al. reported a meta-analysis about the role of gemcitabine in the chemoradiotherapy for LAPC, which consisted of 4 studies from 1999-2009 to make sensitivity analysis (Zhu et al., 2011). Their conclusion was that on the basis of the evidence evaluated in the present meta-analysis, gemcitabine-based CRT seemed to be superior to 5-FU-based CRT in the treatment of LAPC. Hunter et al. completed a Phase I trial of gemcitabine and oxaliplatin with concurrent radiotherapy in patients with LAPC in 2011. This trial resulted in favorable rates of local tumor response (median survival was 11.8 months) and 1-year freedom from local progression (93.8%,95% confidence interval, 63.2-99.1) (Hunter et al., 2011). Loehrer et al. also published an Eastern Cooperative Oncology Group trial named gemcitabine alone versus gemcitabine plus radiotherapy in patients with LAPC. The median survival was 9.2 months and 11.1 months for GEM alone and GEM plus radiation, respectively((one-sided P = 0.017 by stratified log-rank test), which demonstrated improved overall survival with the addition of radiation therapy to gemcitabine (Loehrer et al., 2011). We underwent 3D-CRT concurrently with gemcitabine-based chemotherapy to explore the better treatment by comparing survival time of Gem and GemRT groups. The disease control rate and the objective response rate of GemRT versus Gem were 97.14% vs 71.43%, 74.29% vs 38.10%. The overall survival (OS) was significantly better for GemRT compared to Gem (median 13 months versus 8 months; 51.4% versus 14.3% at 1 year, respectively).

The results reveled that for patients with LAPC, radiation therapy to 50.4Gy with concurrent 2 cycles of gemcitabine has better rates of OS than gemcitabine monotherapy. Concurrent chemoradiotherapy should be the first choice for patients with LAPC.

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