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Locally Advanced, Unresectable Pancreatic Cancer Treated by Stereotactic Radiation Therapy

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Purpose: In order to find out whether stereotactic radiation therapy (RT) using CyberKnife (CK) could improve survival rate and lower acute toxicity compared to conventional RT.

Materials and Methods: From April 2003 through April 2004, 19 patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤3 and locally advanced pancreas cancer without distant metastasis, evaluated by CT or PET/CT, were included. We administered stereotactic RT consisting of either 33 Gy, 36 Gy or 39 Gy in 3 fractions to 6, 4 and 9 patients, respectively, in an effort to increase the radiation dose step by step, and analyzed the survival rate and gastrointestinal toxicities by the acute radiation morbidity criteria of Radiation Therapeutic Oncology Group (RTOG). Prognostic factors of age, sex, ECOG performance score, chemotherapy, bypass surgery, radiation dose, CA19-9, planning target volume (PTV), and adjacent organ and vessel invasion on CT scan were evaluated by Log Rank test.

Results: The median survival time was 11 months with 1-year survival rate of 36.8%. During follow-up period (range 3~20 months, median 10 months), no significant gastrointestinal acute toxicity (RTOG grade 3) was observed. In univariate analysis, age, sex, ECOG performance score, chemotherapy, bypass surgery, radiation dose, CA19-9 level, and adjacent organ and vessel invasion did not show any significant changes of survival rate, however, patients with PTV (80 cc showed more favorable survival rate than those with PTV>80 cc (p-value<0.05). In multivariate analysis, age younger than 65 years and PTV>80 cc showed better survival rate.

Conclusion: In terms of survival, the efficacy of stereotactic radiation therapy using CK was found to be superior or similar to other recent studies achieved with conventional RT with intensive chemotherapy, high dose conformal RT, intraoperative RT (IORT), or intensity modulated RT (IMRT). Furthermore, severe toxicity was not observed. Short treatment time in relation to the short life expectancy gave patients more convenience and, finally, quality of life would be increased. Consequently, this could be regarded as an effective novel treatment modality for locally advanced, unresectable pancreas cancer. PTV would be a helpful prognostic factor for CK.

Key Words: Pancreatic cancer, Stereotactic radiation therapy, CyberKnife

Introduction

The incidence of pancreatic carcinoma has been continuously increasing worldwide in recent years. The 2002 Korean cancer statistics reported it to rank the 5th among common cancers to cause death.[1] Because of lacking clinical symptoms and signs, most patients have locally advanced, unresectable disease at the time of initial diagnosis. Without treatment in-

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tervention, the mean survival time is approximately 3 to 6 months.[2~4] Although surgery is considered to be the only curative treatment method, there are only 10~20% patients who have respectable tumors suitable for radical resection, and 30~85% patients treated by surgery have local recurrences.[5]

At present, there are no satisfactory treatment modalities for patients with locally advanced pancreatic carcinoma. Adenocarcinoma of pancreas is a disease characterized by resistance to cytotoxic therapy including chemotherapy and radiotherapy; response to systemic chemotherapy is relatively poor with only 20% response rate, which would last for only a short time, and most of the treatment effects are partial response. The conventional radiation dose to gross tumor volume is not large enough to cure patients with pancreatic carcinoma, because of the limited dose tolerant to the surrounding normal tissues such as gastrointestinal tract and kidneys.[6~9] Recent advances in computer technology and hardware of treatment machine have provided us with better radiation treatment and delivery systems, and intensity modulated radiation therapy (IMRT) technique or 3-dimensional conformal radiation therapy has increased radiation dose for pancreas cancer.[10] Also, CyberKnife (CK) could improve radiation dose distribution in cancer as a novel precise radiation treatment system, and allow safer delivery of radiation.

Our hospital installed CK in June 2002 and started stereotactic radiation therapy to pancreas cancer in October of that year. The first patient treated by the CK had locally advanced pancreas cancer and severe abdominal pain. Therefore, we administered CK therapy as palliative aim to promptly relieve pain. To define the first safe single radiation dose, we reviewed the data of the intraoperative radiation therapy (IORT), and found that Nishimura et al treated 71 unresectable pancreatic cancer patients by using 30~33 Gy dose of IORT with or without external beam radiation therapy. In their study, the median survival time was 8.2 months, which was not superior to other modalities. In terms of subacute and late toxicity, duodenal fibrosis and stenosis were noted in 3 patients. Two of them required reexploration and gastrojejunostomy. Gastrointestinal ulcers were noted in 7 patients (10%), and intestinal perforation was observed in 2 of the 7 patients. They recommended that gastric antacids should be administered for a long time after IORT, combined with external beam radiation therapy (EBRT).[11] Furthermore, Koong et al had earlier treated locally advanced, unresectable pancreatic cancer using CK. They gave single 25 Gy dose, which is equivalent to doses of 72.9 Gy and 140 Gy for the early and late responding tissues, respectively (for early responding tissue, α/β=10 Gy; for late responding tissue, α/β=3 Gy), and published their phase I experience of 15 patients, proving there was no severe toxicity.[12] Therefore, in order to reduce the severe toxicity, evidenced as duodenal bleeding, we used 33 Gy in 3 fractions at first, which is equivalent to 58 Gy when it is calculated by α/β=10 Gy for the early responding tissue or tumor, because single 30 Gy used in IORT is equivalent to doses of 100 Gy and 198 Gy for the early and late responding tissues, respectively (for early responding tissue, α/β=10 Gy; for late responding tissue, α/β=3 Gy). Consequently, our dose protocol would be safer than IORT with respect to severe complication.

The retrospective study on unresectable pancreas cancer treated by radiation therapy for 5 to 6 weeks (range of RT dose 40~50.4 Gy) combined with chemotherapy in our hospital from January 1998 to December 2001 showed that the median survival time was only 7 months (unpublished), and that 10 % of the patients could not complete the treatment because of poor tolerance. Since, Koong et al[12] proved it as a very safe treatment through the phase I study of radiosurgery, we speculated, therefore, that stereotactic radiation therapy using CK might provide higher radiation dose to tumor than conventional radiation therapy. Furthermore, short treatment period would give more convenience to the patients with short life expectancy and increase quality of life.

We report herein the survival rate and toxicity of stereotactic radiation therapy using CK in a group of patients with locally advanced, unresectable pancreatic carcinoma in order to determine the efficacy of this novel modality.

Materials and Methods

1. Selection of patients and characteristics

Since April 2003, we started protocol which is composed of stereotactic radiation therapy, starting 33 Gy in 3 fractions, for locally advanced pancreatic cancer. When mass size was more than 7 cm in the greatest dimension in a single plane or there was distant metastasis, they were not considered as candidates for stereotactic radiation therapy. We explained to patients, who were diagnosed as pancreas cancer or transferred from

other hospitals, treatment option for the pancreas cancer. The option for local modality was conventional radiation therapy for 5 weeks or stereotactic radiation therapy using CK in 3 fractions. Twenty one patients with pancreatic cancer chose the option of stereotactic radiation therapy using CK. Among them, two patients with distant metastasis, who received stereotactic radiation therapy as palliative aim to reduce pain during the same period, were excluded from this study. When we finished this protocol in April 2004, 19 patients were enrolled and the medical records of all patients who received stereotactic radiation therapy were retrospectively reviewed. Among them, 5 patients were pathologically confirmed as adenocarcinoma through biopsy, and the remaining patients were diagnosed with definite huge mass on CT, high CA19-9 level and/or lesion with high metabolism on PET/CT. The median age of patients was 60 (range 40～83), and the ratio of male to female patients was 13 : 6. As treatment prior to CyberKnife, 5 patients received chemotherapy and 2 patients received palliative bypass surgery. Fifteen patients underwent standard pretreatment staging studies, including history and physical examination, chemistry panel, CA19-9, and computed tomography (CT) scan. Fusion fluorodeoxyglucose positron emission tomography and CT (PET/CT) was done in 5 patients to confirm the diagnosis and obtain better tumor delineation.

2. Treatment method

We used gold fiducials with 4mm in length and 0.8mm in diameter as markers for tumor localization. We placed percutaneously a total of six fiducials using 18 gauged spinal needle under a fluoroscopy. Two gold fiducials were fixed to the transverse processes of 12th thoracic vertebral body, 1st and 2nd lumbar vertebral body, respectively. The home-made de-

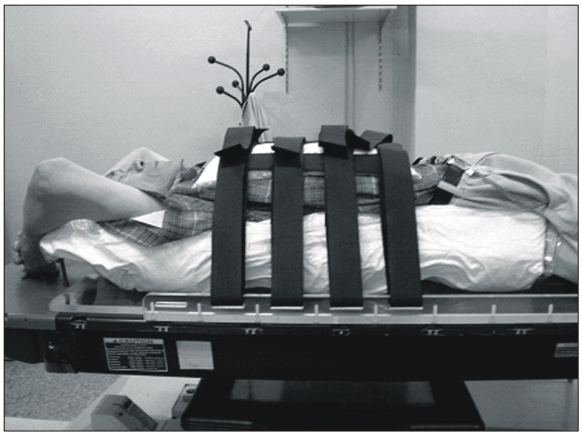

Fig. 1. Immobilization device was home-made for each patients to give comfortability on treatment position and to reduce respiratory motion. It is consisted of vacuum cradle, 4 belts, and small vacuum bag.

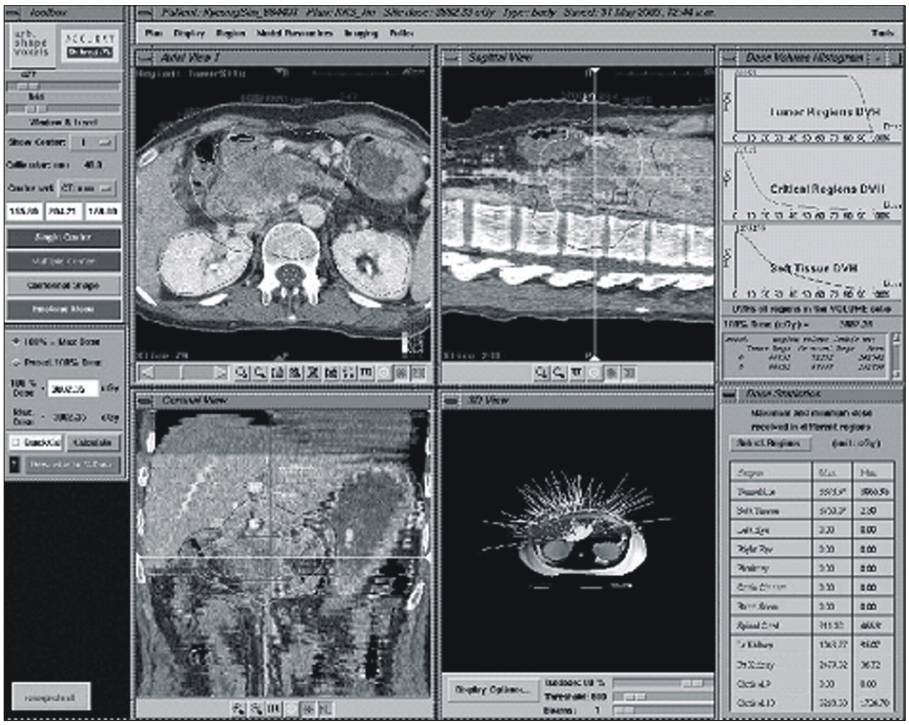

Fig. 2. Treatment plan for patient with 33 Gy. The tumor located in the head of pancreas is outlined in red. The sky blue line represents 85% isodose line.

vice, which was composed of an Alpha Cradle (Smithers Medical Products, North Canton, OH) and 4 belts to restrict respiratory motion, was made for each patient 3~10 days after fiducial placement (Fig. 1). The study of our institution indicated that it reduced the motion of the diaphragm in the range of 20~68% compared to the previously reported range of motion.[13] Next, a pancreatic protocol CT scan was performed with the patients in the treatment position, and these images were then processed for stereotactic radiation therapy planning system with an algorithm that was specifically developed for the CK.

The gross tumor volume (GTV) was defined as visible pancreatic mass and peripancreatic lymph node on cross sectional image of CT. Also the planning target volume (PTV) was defined as adding 4 mm margin to GTV on the planning CT scan (Fig. 2). All patients were treated within 2 days of their planning CT scan.

All treatments were continuously carried out as three fractions for 3 days. The fiducials were tracked by orthogonal X-ray to ensure reproducibility. Overall, the treatment time ranged from 30 minutes to 70 minutes. We administered stereotactic radiation therapy consisting of either 33 Gy, 36 Gy and 39 Gy in 3 fractions to 6, 4, and 9 patients in an effort to increase the radiation dose step by step with no dose-limiting toxicities. Radiation dose, fraction number, tumor volume, prescribed dose, and estimated conventional RT dose are described in Table 1.

3. Study end points

The patients were evaluated at follow-up intervals of 1 or 2 months. At each follow-up visit, standard evaluation consisted of history and physical examination, tumor marker assessment, and CT scan and/or PET/CT. Survival rate, toxic reactions, local disease control, and failure patterns were assessed. Survival rate was calculated from the time, when CK treatment was started, according to the Kaplan-Meier method. Also, we analyzed prognostic factors affecting overall survival rate by univariate and multivariate analysis according to log rank test and Cox's proportional hazards model, respectively. Acute and late toxicity were defined as symptoms developed within and after 3 months from treatment completion, respectively. The assessment criteria of tumor responses after treatment were described in Table 2. Local failure defined as increment of tumor size or new lesion develop in the radiation field. Meanwhile, if new lesion develop outside the radiation field, it is interpreted as distant metastasis.

Table 1. Radiation Dose, Fraction Number, Tumor Volume, Prescribed Dose and Estimated Dose to Conventional Radiation Therapy

Dose (cGX)/Fx*	No. of patients	Range of PTV† (cc)	Prescribed dose (%)	Estimated dose (Gy)	
				α/β=10	α/β=3
3,300/3	6	52~254 (67‡)	82~85	58	92
3,600/3	4	34~61 (36)	83~84	66	108
3,900/3	9	27~102 (49)	80~85	74	125

*fraction, † planning target volume, ‡ median value

Table 2. The Assessment Criteria of Tumor Responses

	PET/CT (SUV*)	CT (Volume)	CA19-9
CR†	No hot uptake	No tumor	Decreased into normal range
PR‡	>30% decreased	>50% regressed	>30% decreased
SD§	≤30% increased~≤30% decreased	≤50% enlarged~≤50% regressed	≤30% increased~≤30% decreased
PD‖	>30% increased	>50% enlarged	>30% increased

*standardized uptake value, † complete response, ‡ partial response, §stable disease, ‖progression disease

Table 3. RTOG Acute Radiation Morbidity

Grade	Upper GI*	Upper & Lower GI
0	No change	No change
1	Anorexia≤5% weight loss	Symptoms not requiring medication
2	Anorexia≤15% weight Loss	Symptoms requiring intermittent medication
3	Anorexia>15% weight loss	Symptoms requiring persistent medication
4	Symptoms requiring intensive medical or surgical intervention	

*gastrointestinal

Results

1. Acute toxicity

The RTOG acute radiation morbidity criteria (Table 3) were used for toxicity scoring.[12] Eight (42%) out of 19 patients were suffered from grade 1 or 2 acute toxicities (nausea, vomiting, or both) for a short period of time. However, there was no treatment related death or Grade 3 or 4 toxicity.

2. Late toxicity

After treatment, patients were closely followed at regular intervals. Within the 10-month median follow-up period (range 3～20 months) after CK, we observed no significant grade 3 or 4 toxicities. The grade 1 or 2 toxicities reported by 2 patients consisted of gastric ulcer and nausea/vomiting, respectively. None of the remainders suffered from treatment related toxicity.

3. Radiologic response

Fifteen patients underwent CT and/or PET/CT scans for 4 months duration after stereotactic radiation therapy. Four patients could not undergo CT and/or PET/CT scans within 4 months after CK, because 3 died earlier and a patient had lost follow-up for a year. Seven of 15 patients showed reduction of tumor size, 4 patients stable disease, and 4 patients local progression at that time. During follow-up duration (range 3～20 months, median 10 months), distant metastasis were detected in 3 patients (16%), both distant and local progression in 2 patients (11%), and local progression in 5 patients (26%). Ultimately, disease progression and local progression were seen in 10 and 7 patients, respectively. Thereafter, 9 (56%) of 16 patients did not progress locally during follow-up duration.

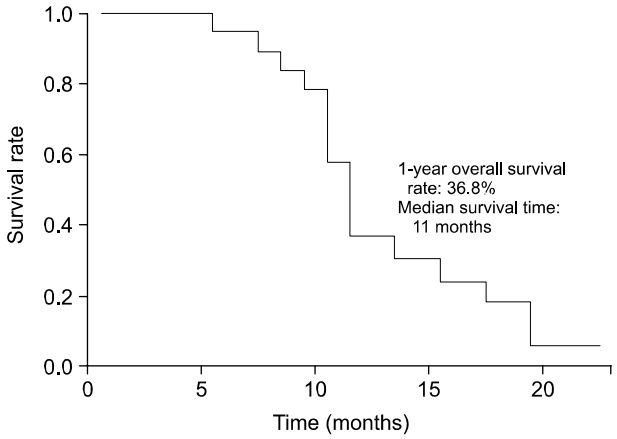

Fig. 3. Overall survival rate. The 1-year overall survival rate was 36.8%, and the median survival time was 11 months, calculated from the date of diagnosis.

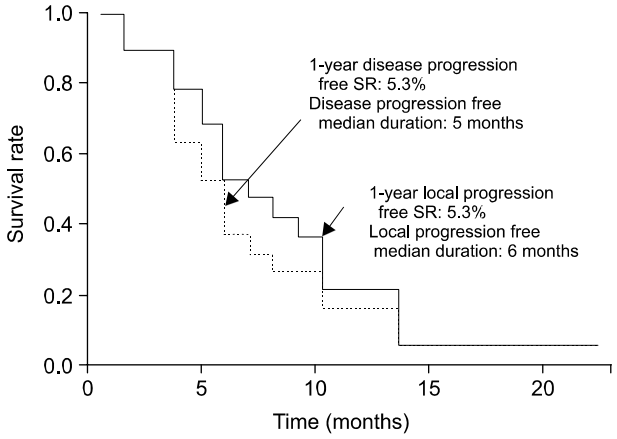

Fig. 4. The 1-year local progression free and disease progression free survival rate (SR) were 5.3% and 5.3%, respectively. The local progression free and disease free progression free median time were 6 months and 5 months, respectively.

4. Treatment outcome

Median survival time was 11 months (Fig. 3), and median disease progression free duration and local progression free duration were 5 months and 6 months, respectively (Fig. 4). The 1-year overall survival rate, disease progression free survival rate, and local progression free survival rate were 36.8%, 5.3%, and 5.3%, respectively.

In univariate analysis, patients with PTV 80 cc or less and no lymphadenopathy (LAP) had significantly longer median

Table 4. Prognostic Factors by Univariate Analysis

Prognostic factor		No of pts‡	MST* (months)	1-year SR† (%)	p-value
Age	≤65	12	11	42	NS§
	>65	7	10	29	
Sex	Male	13	11	38	NS
	Female	6	10	33	
Performance score	≤1	5	13	60	NS
	≥2	13	11	31	
Chemotherapy	(+)	5	11	20	NS
	(-)	14	11	43	
Bypass surgery	(+)	2	10	50	NS
	(-)	17	11	35	
CK dose (Gy)	<39	10	10	30	NS
	≥39	9	11	44	
CA19-9 (U/ml)	≤400	8	11	38	NS
	>400	10	10	10	
PTV (cc)	≤80	12	13	58	0.0048
	>80	7	10	0	
Stomach invasion	(-)	15	11	40	NS
	(+)	4	9	25	
Duodenum invasion	(-)	12	10	33	NS
	(+)	7	11	43	
SMA‖ invasion	(-)	13	11	31	NS
	(+)	6	11	50	
SMV¶ invasion	(-)	4	11	25	NS
	(+)	15	11	33	
Hepatic artery invasion	(-)	10	11	40	NS
	(+)	9	11	33	
LAP#	(-)	11	15	55	0.040
	(+)	8	10	13	

*median survival time, † survival rate, ‡ patients, §statistically not significant, ‖superior mesenteric artery, ¶superior mesenteric vein, #lymphadenopathy

Table 5. Prognostic Factors by Multivariate Analysis

Prognostic factors		p-value
Age	≤60 vs. >60	0.05
Sex	Male vs. female	NS*
Performance score	≤1 vs. ≥2	NS
Chemotherapy	(-) vs. (+)	NS
Bypass surgery	(-) vs. (+)	NS
CK dose (Gy)	≤36 vs. 39	NS
CA19-9 (U/ml)	≤300 vs. >300	NS
PTV† (cc)	≤80 vs. 80	0.001
Stomach invasion	(-) vs. (+)	NS
Duodenum invasion	(-) vs. (+)	NS
SMA‡ invasion	(-) vs. (+)	NS
SMV§ invasion	(-) vs. (+)	NS
Hepatic artery invasion	(-) vs. (+)	NS
LAP‖	(-) vs. (+)	NS

*statistically not significant, † planning target volume, ‡ superior mesenteric artery, §superior mesenteric vein, ‖lymphadenopathy

survival time (13 months for PTV ≤80 cc vs. 10 months for PTV>80 cc; p=0.0048, 15 months for no LAP vs. 10 months for LAP; p=0.040). Age, sex, ECOG performance score, chemotherapy, bypass surgery, radiation dose, CA19-9 level before CK, and invasion of adjacent organ and vessel such as stomach, duodenum, superior mesenteric artery and vein, or hepatic artery on CT scan, which was reviewed by specialist, were not significant prognostic factors in this study (Table 4). In multivariate analysis, age younger than 60 years and patients with PTV 80 cc or less were related to better overall survival (Table 5).

Table 6 lists the stereotactic radiation therapy parameters and site of first progression for the patients treated on this study. Local failures (4 patients) were predominant in 8 patients who received less than 39 Gy, and distant failure (4 patients) was predominant in 8 patients who were treated with 39 Gy.

Table 6. Parameters of Stereotactic Radiation Therapy and Site of First Progression

Patient	Dose (cGy)	PTV* (cc)	Site of first progression
1	3,300	66	(-)†
2	3,300	67	Local
3	3,300	165	Local
4	3,300	52	Distant
5	3,300	95	Not evaluable
6	3,300	254	Not evaluable
7	3,600	36	(-)
8	3,600	34	Local
9	3,600	39	Local
10	3,600	61	Local and distant
11	3,900	32	(-)
12	3,900	27	(-)
13	3,900	88	(-)
14	3,900	44	(-)
15	3,900	49	Local and distant
16	3,900	89	Distant
17	3,900	102	Distant
18	3,900	32	Distant
19	3,900	81	Not evaluable

*planning target volume, † (-): no progression was observed during follow-up period

Discussion

Unresectable pancreatic cancer has been considered as a miserable disease; the median survival is only 3 or 6 months, if conservative treatment was performed.[2~4] The recent standard treatments of locally advanced, unresectable pancreatic carcinoma consist of combination of radiation therapy and chemotherapy, and this concept is based on several randomized trials performed in 1980's. In 1981, the randomized prospective study of Gastrointestinal Tumor Study Group (GITSG) reported that radiation therapy combined with chemotherapy have better effect than radiation therapy alone: the median survival time was 10 months for combined therapy.[14] On the other hand, ECOG randomized study in 1985 showed no difference between 5-fluorouracil (5-FU) alone group and radiation plus 5-FU group; median survival was 8.2 and 8.3 months, respectively.[15] However, in other studies including GITSG randomized study in 1988, combined chemoradiation modality was proved to be more effective than radiation or chemotherapy alone.[16~19] Therefore, combined chemoradiation treatment was accepted as a standard therapy for locally advanced, unresectable pancreatic cancer.

However, a few recent studies revealed that single chemotherapy with radiation therapy failed to show survival gain. Ishii et al[20] treated 20 patients with unresectable pancreatic carcinoma in phase II study in which the combination of RT with protracted infusion of 5-FU was tested. The median survival was 10.3 months with grade 3 or worse acute toxicity in 20% of patients. Okusaka et al[21] treated 41 patients with the combination of RT and daily cisplatin infusion, and this combined therapy was completed in only 76% of patients and the median survival was 7.7 months. Also, Safran et al[22] used paclitaxel concomitant with RT in a phase II study in which 44 patients with unresectable pancreatic carcinoma were enrolled. The RT dose was 50.4 Gy and paclitaxel was administered weekly, and 12% of patients developed grade 3 acute toxicity and 5% grade 4 acute toxicity. Their median survival was 8 months. Crane et al[23] used concurrent gemcitabine, as radiosensitizer, and RT. During therapy, 24% of patients had severe acute toxicity and 33% of them had to be admitted to hospital for supportive therapy. They showed median survival was 11 months. However, Li et al[24] showed median survival of 14.5 months, when they used gemcitabine weekly and high dose RT (50.4～61.2 Gy). Nevertheless, there were severe toxicities. Four of 18 patients (22%) stopped RT during treatment and 4 patients (22%) did not receive maintenance chemotherapy after concurrent chemoradiotherapy due to toxicities. Also, Kim et al[25] showed median survival of 12 months, and 1 and 2-year survival rate of 46.7% and 17.0%, respectively, when they used gemcitabine or paclitaxel weekly concurrent with RT (45 Gy). However, there were grade 3 or 4 hematologic toxicities in 8 patients (19%), while grade 3 or 4 non-hematologic toxicities in 5 patients (12%). Although the results of Li et al and Kim et al appears to be particularly promising, the most results of concurrent single chemotherapy and radiation do not seem to provide major improvements, considering high rate of complication. Other authors have tested possible use of concomitant polychemotherapy[26~28]: RT combined with two or three drugs, including 5-FU, cistplatin or streptozotocin, showed better response and particularly high complete response. These results suggest that concomitant polychemotherapy with RT would have beneficial effect on

survival.[29] However, concomitant chemotherapy with RT was not well tolerated and some patients failed to complete the treatment due to toxicity. For example, in the study by Talamonti et al,[30] an unexpected toxicity occurred in a phase I ECOG study in which patients with locally advanced pancreatic carcinoma were treated with protracted 5-FU infusion (200 mg/m^2/d), weekly gemcitabine (50~100 mg/m^2), and EBRT of 59.4 Gy. Of 7 patients enrolled, 5 developed dose-limiting toxicity; 1 case of severe mucocutaneous reaction, 3 cases of severe duodenal ulceration with bleeding requiring blood transfusions, and 1 case of severe thrombocythemia which lasted for 4 weeks.

Most studies with concurrent chemoradiation therapy show that the median survival for unresectable pancreas cancer ranges from 7 to 14 months. There would be some debate on the above conclusion, and the standard treatment for unresectable pancreas cancer still remains to be established, considering that increasing survival rate might be expense of unexpected toxicity of many patients. The researches for combination method of radiation and chemotherapy, optimal dose of radiation and chemotherapy, and new treatment modality should be evaluated.

IORT is a new treatment modality for pancreas cancer. Nishimura et al[11] enrolled 71 patients for IORT and reported that the median survival was 8.2 months with many severe complications such as intestinal perforation. Therefore, this result indicates it not to be promising compared to other studies.

Recently, IMRT has been implemented for locally advanced pancreas cancer in order to increase the radiation dose to tumor and the local control rate. Bai et al[31] were able to escalate the total radiation dose of 60 Gy in 25 fractions in over 5 weeks, accompanied with tolerable acute radiation related toxicity for patients with advanced pancreatic cancer. The median follow-up period was 8 months and 1-year survival rate was 35%. More studies are needed, however, to answer whether IMRT could provide better survival and less toxicity than the conventional RT.

CK is also an another modality for pancreas cancer. Extracranial stereotactic radiosurgery or radiation therapy for lung and liver tumors have been well studied,[32,33] and about 90 % of complete response rate for lung tumor was reported.[32] As the first trial of CK for pancreas cancer, Koong et al[12] administered stereotactic radiosurgery of single 25 Gy to unresectable pancreas cancer. When α/β values were 10 Gy and 3 Gy for an early and a late effects, respectively, were used, this doses are biologically equivalent to 72.9 Gy and 140 Gy for the early and late response tissues, respectively. In their study, the median overall survival was 11 months with a median follow-up time of 5 months, and grade 3 toxicity was not observed. We started radiation dose of 33 Gy in 3 fractions and escalated to 36 Gy, and 39 Gy in 3 fractions, which are equivalent to 58 Gy, 66 Gy, and 74 Gy for the early response tissues, respectively. And, calculated biological effect doses (BED) for the late response tissues were 92 Gy, 108 Gy, and 125 Gy, respectively (Table 1). The 39 Gy in 3 fractions, which is equivalent to conventional radiation dose of 70 Gy, was nearly the same as 25 Gy in single fraction that Koong et al used. There was no severe complication such as grade 3 or 4 in Koong's as well as in our study. In our present study, 2 of 9 patients who received 39 Gy radiotherapy developed local progression, whereas, 5 of 10 patients who received less than 39 Gy radiotherapy developed local progression. Considering the study of Koong et al, in which patients treated with 25 Gy in single fraction did not show disease progression any more, more than 39 Gy used in our present study appears to have achieved total response of tumor. Though 25 Gy in single and 39 Gy in three fractions are equivalent to BED, when they were calculated according to α/β ratio, the total treatment time was different between the two. The dose rate effect during treatment time would be a considerable factor in regards to radiation biology of stereotactic radiotherapy.[34]

The median survival in our present study was 11 months, which is superior or similar to recent results obtained by using other modalities such as IMRT or high dose conformal RT. However, the present result does not suggest any significant improved benefit in terms of survival, compared with another modalities. Nevertheless, this new modality appears to be promising in terms of complication, and provides more capacity to combine with intensive chemotherapy. Furthermore, it could reduce the overall treatment time in relation to short life expectancy, thereby providing more convenience and high quality of life to patients.

In conclusion, stereotactic radiation therapy using CK for the patients with locally advanced pancreatic carcinoma is fe-

asible with low toxicity and short treatment time. To have survival gain, optimal integration of chemotherapy must be considered within acceptable side effect.

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국문초록

국소적으로 진행된, 절제 불가능한 췌장암에서 정위 방사선 치료

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목 적: 국소적으로 진행된, 절제 불가능한 췌장암 치료에 있어 고식적 방사선 치료와 비교하여 CyberKnife (CK)를 이용한 정위 방사선 치료의 생존율 및 급성 독성에 대해 분석하고자 하였다.
대상 및 방법: 2003년 4월부터 2004년 4월까지의, Eastern Cooperative Oncology Group (ECOG) 활동도 3 이하이며 CT 및 PET/CT로 평가하여 원격 전이 없는 국소 진행된 췌장암 환자 19명을 대상으로 하였다. 대상 환자는 점차 방사선량을 증가시키는 방법으로 33 Gy, 36 Gy, 39 Gy를 3분할로 각각 6명, 4명, 9명에서 CK를 이용한 정위 방사선 치료를 시행하였으며, 생존율 및 Radiation Therapeutic Oncology Group (RTOG) acute radiation morbidity criteria에 의한 위장관 독성을 분석하였다. 또한 나이, 성별, ECOG 수행 점수, 항암 치료, 우회로 조성술(bypass surgery) 여부, 방사선량, CA19-9, 계획용 표적 체적(planning target volume, PTV), CT상 주위 장기 및 혈관 침범 여부 등을 Log Rank test를 이용하여 예후 인자를 평가하였다.
결 과: 본 연구에서 중앙 생존 기간은 11개월, 1년 생존율은 36.8%였다. 추적 조사 기간 중(범위 3~20개월, 중앙값 10개월) 유의한 위장관 급성 독성은 관찰되지 않았다. 단일 인자 분석에서 계획용 표적 체적만이 유의한 예후 인자로 80 cc 이하인 경우가 80 cc 이상인 경우보다 생존율이 높았으며(p-value<0.05), 나이, 성별, ECOG 수행 점수, 항암 치료, 우회로 조성술, CA19-9 수치, 주위 장기 및 혈관 침범 여부 등에서는 통계적으로 유의한 차이를 보이지 않았다. 다인자 분석에서는 65세 이하인 경우와 PTV 80 cc 이하인 경우에서 생존율이 높았다.
결 론: 고식적 방사선 치료, 고선량 입체조형 방사선 치료(high dose conformal radiation therapy), 수술 중 방사선 치료(intraoperative radiation therapy) 또는 세기 조절 방사선 치료(intensity modulated radiation therapy, IMRT)를 이용한 최근의 결과와 비교하여 CK를 이용한 정위 방사선 치료는 생존율 측면에서 비슷하거나 나은 결과를 보였다. 또한 심각한 부작용은 관찰되지 않았으며 짧은 기간의 치료로 환자에게 편의를 제공할 수 있어 결과적으로 삶의 질을 향상시킬 수 있을 것이다. 따라서, 이 새로운 치료 방법은 국소 진행된, 절제 불가능한 췌장암 환자에서 심각한 부작용 없는 효과적인 치료가 될 것으로 생각된다. 또한 계획용 표적 체적은 CK 치료의 유용한 예후 인자로 사용될 것이다.

핵심용어: 췌장암, 정위 방사선 치료, CyberKnife