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Intraoperative Radiation Therapy for Carcinoma of the Pancreas

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Abstract Intraoperative radiation therapy (IOR) was performed on 13 patients with carcinoma of the pancreas. Seven cases were resectable and 6 cases wre unresectable. Tumor regression was observed in 5 of 6 unresectable tumors. Relief of abdominal pain was achieved in all 6 cases. The median survival of 13 patients was 145 days.

Intraarterial infuson of hypoxic cell radiosensitizer RK28 was examined as a model of future clinical application for IOR using a rabbit VX2 tumor system. The tumor regression slopes were statistically different ($P<0.01$). But the difference in long-term survivals was not statistically significant ($P<0.10$). Intraarterial infusion of RK28 is clinically promising in the future.

Key Words : Intraoperative Radiation Therapy(IOR), Carcinoma, Pancreas, Intraarterial Infusion, Radiosensitizer, RK28, Rabbit, VX2 tumor

Introduction

Thirteen pancreatic carcinoma patients were treated with intraoperative radiation therapy(IOR) in our hospital during July 1988 to Feb.1990. This paper summerizes the finding of the experienced cases and also the effect of hypoxic cell radiosensitizer RK28 is shown in the future clinical application for IOR using rabbit VX2 tumor system.

Material and Methods

Thirteen patients with pancreatic adenocarcinomas, 9 men and 4 women ranging in age from 36 to 75years, were treated with IOR during July '88 to Feb.'90. Clinical staging followed the General Rules for Cancer of the Pancreas(Japan Pancreas Society, 1986)(Table 1). Four patients were in stage Ⅲ, 9 patients in stage Ⅳ. There were 7 resectable and 6 unresectable tumors. Five patients had liver metastases and 5 had peritoneal metastases. The IOR was delivered to the tumor or the tumor bed. Electron beams of 12 MeV and 15 MeV at doses of 25 Gy were single-irradiated using cone-shaped applicators of 6cm, 8cm and 10cm in diameter. Additional external radiation therapy (ERT) was given to 8 patients with 10 MV of X-rays in 200cGy fractions up to 60 Gy. Hyperthermia therapy was added to 7 patients using 13.5 MHz of RF with 400 watts for 40 min at once (Table 2). A survival curve was determined using Kaplan-Meier method.

In animal experiments, rabbit VX2 tumor was maintained by serial transplantation. Solid tumors of 3cm in diameter (n=6) were irradiated with 15 Gy of X-rays (200 kVp, 10 mA, 70 cGy/min) a minute after intraarterial infusions of

Table 1 Patients characteristics

Case			C.C.	Stage
1.	42yo	F	jaudice	III ($Ph \cdot T_3 \cdot N(-) \cdot S_0 \cdot Rp_0 \cdot PV_0 \cdot CH_3 \cdot A_0 \cdot Plx(-) \cdot H_0$)
2.	59yo	M	(melena)	III ($Pb \cdot T_2 \cdot N_1(+) \cdot S_2 \cdot Rp_1 \cdot PV_1 \cdot CH_0 \cdot H_0$)
3.	60yo	M	jaudice	III ($Ph \cdot T_3 \cdot N(+) \cdot S_2 \cdot Rp_2 \cdot PV_0 \cdot CH_3 \cdot Plx(-) \cdot H_0$)
4.	75yo	F	jaudice	III ($Phb \cdot T_2N_1(+) \cdot S_0 \cdot Rp_2 \cdot PV_2 \cdot CH_3 \cdot Plx(-)H_0$)
5.	56yo	M	jaudice	IV ($Ph \cdot T_3 \cdot N_3(+) \cdot S_2 \cdot Rp_1 \cdot PV_1 \cdot CH_3 \cdot A_3 \cdot Plx(-) \cdot H_0$)
6.	72yo	M	jaudice	IV ($Phb \cdot T_2 \cdot N_3(+) \cdot S_2 \cdot Rp_2 \cdot PV_2 \cdot CH_3 \cdot A_1 \cdot Plx(-) \cdot H_0$)
7.	46yo	M	back pain	IV ($Ph\text{-}b \cdot T_3 \cdot S_3 \cdot Rp_3 \cdot PV_3 \cdot A_3 \cdot Plx(-) \cdot P_2 \cdot H_2$)
8.	55yo	M	epigastralgia	IV ($Ph\text{-}b \cdot T_4 \cdot N_1(+) \cdot S_3 \cdot Rp_3 \cdot PV_3 \cdot CH_3 \cdot A_3 \cdot H_1$)
9.	53yo	M	epigastralgia	IV ($Phbt \cdot T_4 \cdot N_3(+) \cdot S_3 \cdot Rp_3 \cdot PV_3 \cdot A_3 \cdot P_3 \cdot H_0$)
10.	68yo	F	epigastralgia	IV ($Pb \cdot T_2 \cdot N_3(+) \cdot S_1 \cdot Rp_1 \cdot PV_1 \cdot A_0 \cdot P_0 \cdot H_0$)
11.	36yo	M	epigastralgia	IV ($Ph \cdot T_3 \cdot N_2(-) \cdot S_3 \cdot Rp_3 \cdot PV_3 \cdot CH_3 \cdot A_2 \cdot Plx(-) \cdot P_2 \cdot H_1$)
12.	56yo	F	epigastralgia	IV ($Pb \cdot T_4 \cdot N_3(+) \cdot S_3 \cdot Rp_2 \cdot PV_3 \cdot A_3 \cdot P_2 \cdot H_3$)
13.	67yo	M	jaundice	IV ($Ph \cdot T_3 \cdot N_2(+) \cdot S_3 \cdot Rp_3 \cdot PV_3 \cdot CH_2 \cdot \cdot Plx(+) \cdot P_1 \cdot H_1$)

Table 2 Treatment characteristics

Case	Surgery	IOR	External Radi.therapy	Hyper-thermia	pain relief	outcome
1.	abs.cur.	25 Gy, ϕ8cm 10MeV Elec.	30 Gy, 9×7cm 10 MV X-ray	10 times		20 month alive
2.	abs.cur.	25 Gy, ϕ8cm 12MeV Elec.	none	none		0.5 month dead
3.	abs.cur.	25 Gy, ϕ6cm 12MeV Elec.	none	none		13.5 month dead
4.	abs.cur.	25 Gy, ϕ8cm 12MeV Elec.	40 Gy, 7×6cm 10 MV X-ray	10 times		13 months alive
5.	rel. non-cur.	25 Gy, ϕ8cm 12 MeV Elec.	4 Gy, 6×8cm 10 MV X-ray	none		3 month dead
6.	rel. non-cur.	25 Gy, ϕ8cm 12 MeV Elec.	none	none		3.5 month dead
7.	unresec.	25 Gy, ϕ10cm 15 MeV Elec.	none	none	+	4 month dead
8.	unresec.	25 Gy, ϕ8cm 15 MeV Elec.	58 Gy, 6×7cm 10 MV X-ray	10 times	+	2.5 month dead
9.	unresec.	25 Gy, ϕ6cm 12 MeV Elec.	50 Gy, 6×7cm 10 MV X-ray	9 times	+	5 month dead
10.	abs. non-cur.	25 Gy, ϕ8cm 12 MeV Elec.	none	none	+	8.5 month alive
11.	unresec.	25 Gy, ϕ8cm 12 MeV Elec.	40 Gy, 14×10cm 10 MV X-ray	5 times	+	6.5 month dead
12.	unresec.	25 Gy, ϕ8cm 12 MeV Elec.	(pre) 30 Gy (post) 30 Gy	3 times	+	5 month dead
13.	unresec.	25 Gy, ϕ8cm 12 MeV Elec.	(pre) 60 Gy 10 MV X-ray	10 times		0.5 month dead

RK28[1),2)] (80mg/kg b.w., 50mg/ml in saline) via the saphenous artery[3)]. The CT scans were performed to evaluate a tumor volume with 8-mm thickness at 10-mm intervals. Statistical comparisons were made with tests for tumor regression slopes. Survival curves were determined using Kaplan-Meier method, then statistical comparisons were made using the generalized Wilcoxon test.

Results

Tumor regression of pancreatic cancer was observed 5 of 6 unresectable tumors except case 13. Relief of pain was achieved in all 6 patients. The midian survival was obtained

of 145 days (Fig.1). Five patients (cases 5, 7, 9, 11 and 12) died due to hepatic metastases and/or peritoneal metastases, 3 patients (case 3, 8 and 13) due to gastro-intestinal bleedings, a patient(case 2) due to pancreatic fistula and a patient (case 6) due to sepsis. Three patients are alive. Case 9 was shown in Fig. 2. The tumor almost disappeared 4 months after IOR. The effect of intraarterial infusion of RK28 was shown in Fig.3. The tumor regression slopes were statistically different($p<0.01$). The radiosensitizing effect was observed. But survival curves were not statistically different ($p<0.10$) (Fig. 4).

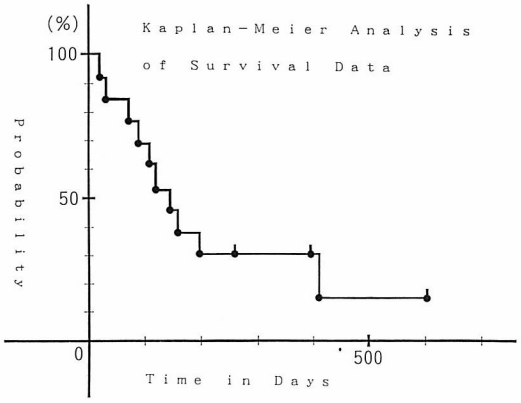

Fig.1 Survival curve of 13 patients

Discussion

It is well known that IOR improves local tumor control though it does not contribute survival rates[4),5)]. In this study, we cannot show if IOR works well or not because ERT alone, which means control, was not done.

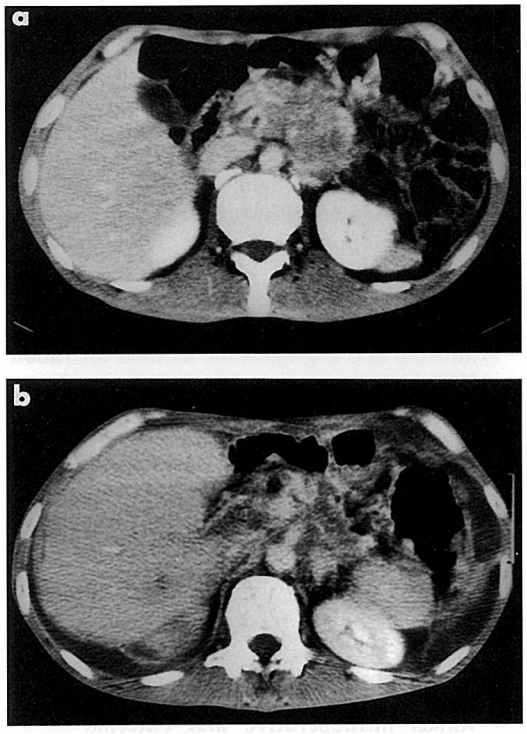

Fig.2 Case 9.
a) before treatment
b) Four months after treatment

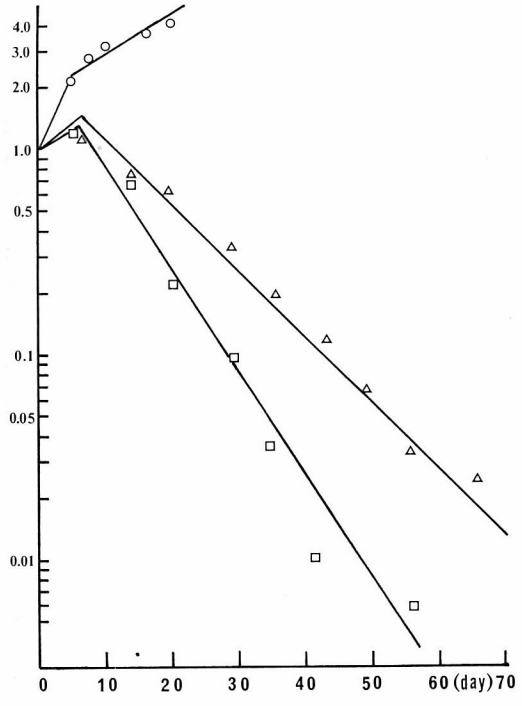

Fig.3 Tumor regression curves in rabbit VX2 tumor system.
group A;control n=6 (○), B;15 Gy alone n=6 (△), C;15 Gy+RK28 i.a. n=6 (□).
B vs C($p<0.01$).

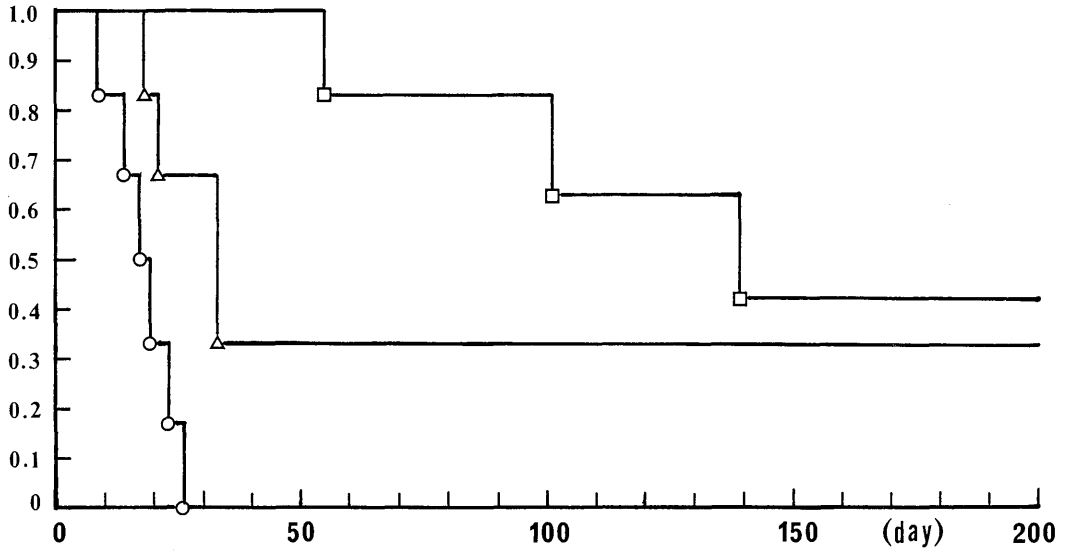

Fig. 4 Survival curves in rabbit VX2 tumor system.
group A;control n=6 (○), B;15 Gy alone n=6 (△), C;15 Gy+RK28 i.a. n=6 (□). B vs C($p<0.10$).

However, it is clear that irradiation including both IOR and ERT is effective since tumor regression was observed in 5 out of 6 unresectable tumors except case 13 who died within a half month. It is believed that IOR destroys only tumor tissue and minimizes damages of normal tissues. If additional ERT is delivered, tumor cell killing by irradiation will be increased. Our results shows that survival benefits seems to be low. One of the reasons may be hematogenous and/or peritoneal spread of tumor cells rather than local failures. Effective treatments for distant metastases are storongly expected.

In animal experiments, the radiosensitizing effect of RK28 was found by means of its intraarterial infusion which provides twice concentration in tumor tissue as much as intravenous infusion (data not shown). Intraarterial infusion of RK28 is clinically promising in the future, though misonidazole was not effective[6].

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