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Result of Multi-modality Treatment for Pancreatic Cancer

Noboru HARADA[1], Takashi YAMAGUCHI[2], and Ryoichi TSUCHIYA[2]

University of Shizuoka, College of Hamamatsu[1] and The Second Department of Surgery, Nagasaki University School of Medicine[2]

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ABSTRACT : We evaluated the results of cancer therapies rather than surgery in 167 patients with pancreatic cancer treated at our department during the past 17-year period after excluding those with islet cell tumor or cytoadenocarcinoma and those who died due to operation. In the group not treated by resection, survival was significantly longer in patients treated by combined modality treatment than in those not treated by any therapy. Prolongation of the mean survival rate for combined modality treatment was more marked in patients with bilio-enteric bypass operation without peritoneal dissemination or hepatic metastasis; the mean survival was 2.6 months in the group not treated by any therapy, 6.0 months in that treated by chemotherapy alone, and 7.2 months in that treated by combined modality treatment. As anti-cancer drug, 5-FU was the most effective. Better results were obtained in patients who received 4,000 rad radiation or more than in those who received less than4,000 rads. In the patients who underwent resection, better results were obtained in those who underwent combined adjuvant treatment.

INTRODUCTION

Marked advances have been made in the diagnosis of pancreatic cancer with a development of various tumor markers and improvement in pancreatic imaging techniques such as US and CT. However, this disease is rarely diagnosed at early curative stages, and in most patients, tumors are unresectable or only palliative resection are possible. Therefore, adjuvant chemotherapy has been used as a treatment to prolong the survival period of unresectable patients, and even for the patients with resectable tumors, adjuvant therapy has also been performed to enhance curability. However, response rates following single drug chemotherapy have been frequently reported to be lower in patients with pancreatic cancer than in those with cancer of other organs.

Therapies such as continuous administration or high dose regional infusion[1)] of anti-cancer drugs and new devices for hypoxic cell radiosensitizers[2)] in radiotherapy, and monoclonal antibody target immunotherapy[3)] are also in progress. In addition, systematic treatment that combines the effects of each modality including chmotherapy, immunotherapy, radiotherapy, and hyperthermia has become extremely important. We analyzed the results of our combined modality approach.

MATERIALS AND METHODS

During the past 17 years, we treated 179 patients with adenocarcinoma of the pancreas (107 males and 72 females). Their mean age was 60.1 years for males and 59.7 years for famales. The tumor was resectable in 41 of the 179 patients (22.9%); pancreatoduodenectomy was performed in 20 patients, total pancreatectomy in 15, distal pancreatectomy in 9.

Table 1. Modality of treatment for pancreatic cancer

	case	surgical only	chemo. only	rad. only	immuno. only	multimodality treatment
Resection (41)						
adenocarcinoma	38	9	17	0	0	12
cystadenocarcinma	3	1	1	0	0	1
Unresectable (126)						
adenocarcinoma	121	27	60	2	5	27
cystadenocarcinoma	3	3	0	0	0	0
others	2	1	0	0	0	1

Of 38 patients who underwent resction, chemotherapy alone was performed as adjuvant therapy in 17. Two adjuvant therapies or more were combined in 12 (combined modality treatment group), but adjuvant therapy was not performed in 9. Of 121 patients who did not undergo resection, 67 received either chemotherapy, radiotherapy, or immunotherapy alone, and 27 were treated by combination of these therapies (**Table 1**). The results of these treatments were compared by using mean survival period, and the differences were assessed by Wilcoxon test.

RESULTS

1. Unresectable Pancreatic Carcinoma

Chemotherapy alone was performed in 60 patients, of whom 37 received single durg chemotherapy and the remaining 23 were treated by combination chemotherapy. Of the patients who were treated by single drug chemotherapy, a fluoroprymidine derivative, primarily 5-fluorouracil (5-FU) was used in 22 patients, Neocacinostatin (NCS) in 7, and Mitomycin C (MMC) in 8. In the patients treated by combination chemotherapy, 5-FU was most frequentyly given in combination with NCS, MMC, Endoxan, or Adriamycin. The mean survival period of single drug treatment was 5.5 months in the patients with 5-FU, 2.3 months in those with MMC, and 2.9 months in those treated with NCS. 5-FU showed the most longest mean survival period among these drugs, but no significant defference was seen. No significant difference was also present between the patients treated by single chemotherapy and those treated by combination chemotherapy (**Table 2**).

Radiotherapy was performed on 17 patients in a dose ranging from 1,350 to 6,950 rads (mean 3,740 rads). Of them, 11 also received chemotherapy and 4 underwent chemotherapy plus immunotherapy with OK432 (picibanil) or PSK (Krestin). The mean survival period in 8 patients who received less than 4,000 rads was 4.0 months, but 6.8 months in 9 who received more than 4,000 rads (**Table 3**).

Immunotherapy was performed in 21 patients. Of them, 5 were treated by immunotherapy only. Chemotherapy was combined in 11, and chemotherapy plus radiotherapy were combined in 5. The mean survival period was almost same between the patients treated by immunotherapy alone and those treated in combination with chemotherapy, but longer in those with chemotherapy and raiotherapy. The mean

Table 2. Results of chemotherapy for unresectable pancreatic cancer

	no. case	mean survival period (mos.)
single Use	37	4.7±4.7
5-FU	22	5.5±5.9
MMC	8	2.3±1.0
NCS	7	2.9±1.2
combination use	23	3.9±2.3

Table 3. Result of ratiation therapy for unresectable pancreatic cancer

	no. case	mean survival period (mos)
radiation only	2	5.0±1.0
rad.+single chemererapy	7	4.4±3.4
rad.+combination chemo.	4	5.3±3.5
<4,000 rad	8	4.4±1.3
>4,000 rad	9	6.9±2.3

survival period was 5.7 months in patients treated with PSK and 3.1 months in those treated with OK432. PSK treated group showed a significant longer mean survival period as compared with that of OK432 group ($p<0.05$). The mean survival period in 2 patients treated both with OK432 and PSK was 8.5 months (**Table 4**).

Table 4. Result of immunotherapy for unresctable pancreatic cancer

	no. case	mean survival period (mos)
immunotherapy only	5	4.4±2.8
immuno.+chemothrapy	11	4.4±2.6
immuno.+chemo.+radio.	5	5.3±3.2
OK432	10	3.0±2.1
PSK	9	5.7±2.1
both	2	8.5±2.5

The therapeutic effects were compared among the patients, without any therapy, with chemotherapy alone, and with multi-modality treatment. The mean survival was 2.7 months in 27 patients without any therapy, 4.1 months in 60 patients who received chemotherapy alone, and 4.9 months in 27 patients who received multi-modality treatment. The patients with multimodality treatment showed a significantly higher cumulative survival rate than those of not treated by any therapy during the period between the 3rd and 6th months ($p<0.05$) and than those treated by chemotherapy alone at the 3rd month (**Fig. 1**).

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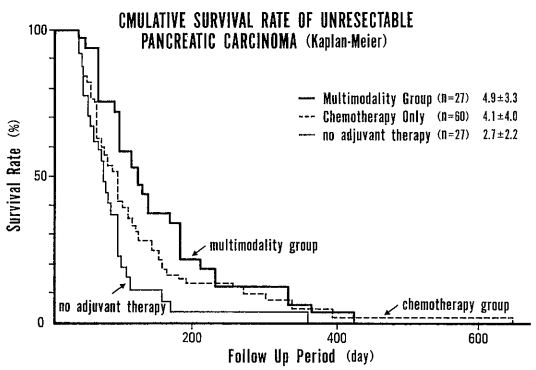

Fig. 1.

treatment on adjuvant therapy from evaluation of these results, survival was compared in the patients who underwent bilioenteric bypass operation for those locally advanced but without liver and peritoneal involvement (P_0H_0). The mean survival was 2.6 months in patients not treated by any adjuvant therapy. 6.0 months in those treated by chemotherapy alone, and 7.2 months in those treated by multi-modality treatment. Multi-modality treatment group showed a significantly longer survival ($p<0.01$) than the group not treated by any therapy (**Fig. 2**).

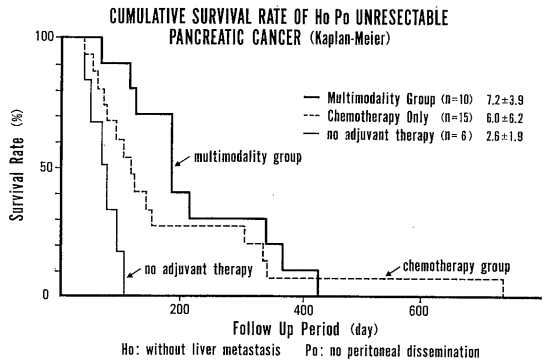

Fig. 2.

2. Resectable Pancreatic Cancer

In the 38 patients who underwent resection, the mean survival was 7.8 months in 9 patients without any adjuvant therapy, 16.2 months in those treated by single chemotherapy, and 15.4 months in 12 patients treated by combined adjuvant therapy. A significant difference was observed between the group treated by chemotherapy and that not treated by adjuvant therapy. However, no significant difference was observed between the group treated by combined adjuvant therapy and that without any adjuvant therapy (**Fig. 3**).

In patients with curative resection, the mean survival was 6.2 months in 3 not treated by adjuvant therapy, 26.1 months in 12 patients treated by immunochemotherapy, and 41.3 months in 2 patients treated by multi-modality therapy. A significant difference was observed in the patients of curative resection between the group with and without adjuvant therapy in survival during the period of from

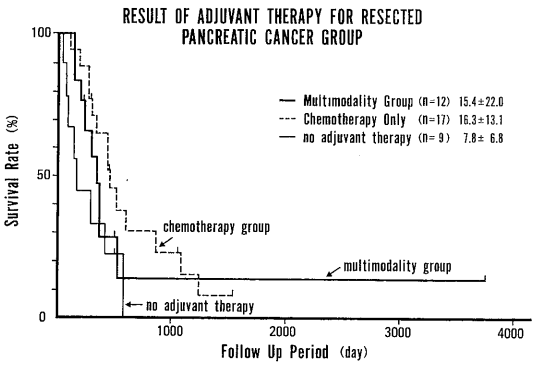

Fig. 3.

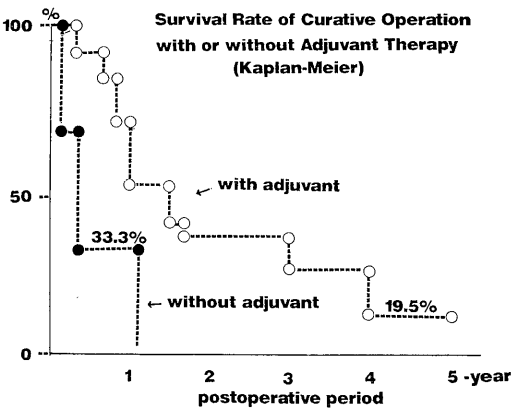

Fig. 4.

Table 5. Mean survival period in resected case

	Multimodality	Immunochemo.	Radiation	no adjuvant
curative (n=17)	41.3mos (n=2)	26.1±26.0 (n=12)	—	6.2±5.0 (n=3)
noncurative (n=35)	9.2±5.4 (n=9)	8.6±5.2 (n=13)	8.2 (n=2)	8.3±6.5 (n=11)

3 months to 13 months (**Table 5, Fig. 4**).

DISCUSSION

Since tumor is resectable, at present, only about in 30% of the patients with pancreatic cancer and curative resection in less than 10%, hope is placed in the effects of additional ajuvant therapy such as chemotherapy, radiotherapy, immunotherapy, or microwave hyperthermia. Harvery *et al*[4] reported in their review of the literature that only Streptozotocin, 5FU, and MMC showed respectively more than 20% response rates, but Adriamycin, NCS, Methyl-CCNU, and Cis-platinum showed only about 10% response rates. However, other reported response rates varied even with 5FU. Stolinsky[5] compared the effects of 5-FU between oral and intravenous administration, and observed higher response rates following intravenous administration. This date suggest that therapeutic effects seem to be associated with the doses and modes of administration.

We also used fluorapyrimidines, especially 5-FU, most frequently. The mean survival period in the patients treated with 5-FU revealed about two times longer than that in the patients treated with MMC or NCS. Fluoropyrimidine was suggested to be the most effective anti-cancer because back ground factors of the patients did not differ between these 3 drug groups.

MMC is the second most commonly used drug for pancreatic cancer. The response rates with this drug were reported to be 27%[6]. However, this drug has strong side effects such as myelosuppression, and the most of the patients with pancreatic cancer usually showing poor Perfomans Status can not tolerate adequate dose that may produce clinical anti-cancer effects. Among nitrosoureas, the response rates in patients with pancreatic cancer were reported to be 16% with CCNU, 6% with Methyl-CCNU[7], and 13% with Adriamicin used for the initial treatment[8]. DuPriest *et al.*[9] reported that the response rates following single chemotherapy with Streptozotocin were 36% in patients with adenocarcinoma of the pancreas, but we did not have any experience of this drug.

To enhance therapeutic effects of chemotherapy for advanced pancreatic cancer combination of drugs with different mechanisms of action was used in the treatment. Wiggans *et al.*[10] treated 23 patients with Streptozotocin+

MMC+5FU+(SMF therapy) and observed 48% responce (CR 1 patient, PR 9 patients). Smith *et al.*[11] treated 27 patients with 5FU+Adriamycin+MMC (FAM therapy) and obtained PR in 37% (10 patients). Mallinson *et al.*[12] reported the mean survival of 44 weeks in patients treated by combination chemotherapy (5FU + Cyclophosphamide + Methotrexate + Vincristine+MMC), but 9 weeks in control group. These studies strongly suggest the efficacy of combination chemotherapy as a treatment of pancreatic cancer. However, in contrast, Cullinan *et al.*[13] failed to show any advantage of combination chemotherapy when compared among the groups treated with 5-FU alone, 5-FU+doxorubicin, and 5-FU+doxorubicin+MMC.

Recently, usefulness of intraoperative irradiation developed by Abe *et al.*[14] has been evaluated actively. Komaki *et al.*[15] performed external irradiation for the patients with unresectable pancreatic cancer without distant metastasis and observed a median survival of 7 months in patients who received less than 4,500 rads and a median survival of 13 months in those who received 4,500 rads or more. Shipley *et al.*[16] perfromed intraoperative irradiation in combination with external irradiation in patients with unresectable pancreatic cancer and reported a median survival of 16. 5 months. Similar effects of radiotherapy were reported in the Western countries.[17,18] Shipley *et al.*[19] also observed high local control rates following local implantation of ^{13}I needles. Gunderson *et al.*[20] showed inhibitory effects of small doses preoperative irradiation on peritoneal seeding and preventive effects in combination of chemotherapy on distant metastasis. Cohen *et al.*[21] and Sindelar *et al.*[22] histologically evaluated the effects of radiotherapy and demonstrated marked reactive fibrosis in and around the tumor lesion. We recognized direct effects of irradiation on tumors, and also observed symptomatic improvements in general condition such as increased appetite resulting from relief of pain, which would be contributable to prolong survival. However, most of the patients treated by irradiation were H_0P_0 patients and usually performed in combination with chemo- or immunotherapy, therefore it was difficult to evaluate true effect on pancreatic cancer.

A randomized study conducted by the Gastrointestinal Tumor Study Group (GITSG)[23] that compares the therapeutic effects between patients treated by irradiation alone and those treated by irradiation+5FU chemotherapy showed prolongation of survival following the combined modality treatment. Kalser *et al.*[24] reported the mean survival in the group treated by irradi ation+chemotherapy (20 months) was significantly longer than that in the control group (10 months). Similar results were seen in our patients.

As the effects of PSK, a non-specific immunoactivator, Ebina *et al.*[25] showed the possibility that immunoactivator inhibits tumor proliferation at distant sites. In our patients treated with PSK, survival was singificantly prolonged, but further evaluation is needed in additional patients.

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