· PATIENTS

The eligibility criteria for enrollment in the studies were: 1) a diagnosis of locally advanced pancreatic carcinoma, which was defined as a tumor with definite invasion of the celiac artery or the superior mesenteric artery and/or the portal vein on both sides of the tumor and no distant metastases on preoperative examinations; 2) no previous cancer treatment; 3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; 4) adequate bone marrow function (leukocyte count $\geq$ 4000 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3, and hemoglobin $\geq$ 10 g/dl), renal function (serum creatinine concentration < 1.1 mg/dl, blood urea nitrogen level < 22 mg/dl) and hepatic function (serum bilirubin level < 3.0 mg/dl, serum alanine and aspartate transaminase levels < 200 IU/l); 5) no serious complications; and 6) written informed consent of the patient.. Percutaneous biliary drainage was performed in patients with obstructive jaundice, and all patients were required to have a serum bilirubin level of less than 3.0 mg/dl before laparotomy.

A total of 346 patients with pancreatic carcinoma were treated in our institution between January 1993 and May 2001. The carcinoma was resectable in 98 patients (28.3%), unresectable locally advanced in 103 patients (29.8%), and metastatic in 145 patients (42.0%). Among the 103 patients with locally advanced pancreatic carcinoma, 54 patients satisfied the study criteria; 24 were enrolled in the IORT±EBRT alone study (Group A) and 30 in the IORT+EBRT with 5-FU study (Group B). Forty-nine patients were excluded from these studies because they did not meet the criteria or rejected the treatments. The patients' characteristics are shown in Table 1. There were no statistically significant differences in characteristics between group A and group B.

TREATMENT METHODS

Radiotherapy

IORT was delivered with 11 to 20 MeV of electron beams. Gross tumor volume (GTV) was determined using intraoperative ultrasonography. The energy of the electron beam was selected to deliver 90% of peak dose, i.e. 25 Gy, at the dorsal surface of the aortic wall. The diameter of the treatment cone was selected to cover the GTV with 1 to 2 cm lateral margin, and the circular treatment cones ranged from 6.0 to 10.0 cm in diameter. Following IORT, the gastrointestinal tract was carefully maintained outside the EBRT irradiation field by gastrointestinal bypass surgery in order to avoid radiation-induced gastrointestinal ulcers, and celiac plexus block with 50% ethanol was performed in all patients for pain control. Bilioduodenal or biliojejunal anastomosis was performed in patients with obstructive jaundice.

EBRT was started 2 to 4 weeks after IORT. Conformal treatment was performed with a coplanar arc rotation technique using a dynamic multi-leaf collimator (11 pairs of leaves; width of each pair, 2 cm) to minimize the volume irradiated around the planning target volume (PTV). Treatment was planned with a CT-based planning system. Clinical target volume (CTV) was defined as the GTV on the CT image plus a 1.5-cm margin to account for

subclinical tumor spread. PTV was defined as the CTV plus a 1.5- to 2.0-cm margin along the cranio-caudal axis and a 0.5- to 1.0-cm lateral margin to account for both physiological organ motion and daily set-up error. The prescribed dose was determined at the center of the PTV. The estimated dose at the margin of the CTV in each treatment plan was more than 90% of the prescribed dose, and the estimated dose to critical organs, such as the kidney and spinal cord, was less than 20% of the prescribed dose. A total of 40 Gy was delivered in 20 fractions: 2 Gy/fraction/day, 5 days/week for 4 weeks, with X-rays exceeding 10 MV.

Systemic chemotherapy

Systemic chemotherapy with 5-FU was performed in the patients enrolled in the second study, i.e. the study of IORT plus conformal EBRT with protracted infusion of 5-FU. 5-FU was administered intravenously at a dose of 200 mg/m2/day beginning on the first day of EBRT and continuing through the entire course of EBRT. Continuous infusion of 5-FU was administered 7 days a week.

Evaluation

Dynamic CT was performed to evaluate response at 2-month intervals after the start of therapy by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm, and tumor response was rated according to the WHO criteria. We used the National Cancer Institute common toxicity criteria, version 2, to evaluate adverse events.

The x^2 test was used to compare each variable of the patient characteristics in the two groups. Survival was calculated by the Kaplan-Meier method from the date of IORT. The statistical significance of differences between the survival curves was determined using the log-rank test. Differences with P values less than 0.05 were considered significant.

RESULTS

Cancer Spread in the Abdomen not Detected by CT Examination

All 54 patients underwent laparotomy to perform IORT, and the entire abdominal cavity was examined to determine whether the tumor had spread to the peritoneal surfaces, liver, or regional lymph nodes. Cancer spread was detected in the abdominal cavity in 20 of the 54 patients (37.0%): 9 of the 24 patients (37.5%) in group A and 11 of the 30 patients (36.7%) in group B. Metastasis to the liver was detected in 10 patients, to the peritoneum in 5 patients, to both sites in 4 patients, and to a distant lymph node in one patient. There were only 34 patients (63.0%) with true locally advanced disease.

Treatment

EBRT was performed in 16 patients in group A: all 15 patients without cancer spread in the abdomen and the patient with a distant lymph node metastasis. In B group, EBRT with 5-FU was used to treat 29 of the 30 patients, but it could not be used in the other patient because of massive ascites secondary to peritoneal dissemination of the carcinoma 2 weeks after IORT. The full 40-Gy irradiation dose was administered to 41 of the 45 patients (91.1%). Radiotherapy was discontinued at 30 Gy and 36 Gy because of nausea/vomiting and/or anorexia in 2 patients, at 34 Gy because of ileus in one patient, and at 8 Gy because of progression of brain metastasis in one patient.

Table 2. Comparison Grade 3 and 4 Toxicity between IORT+EBRT with and without 5-FU

	Without 5-FU (n=16)	With 5-FU (n=28)
Toxicity	n (%)	n (%)
Leukopenia	0	1 (3.6%)
Anemia	1 (6.3%)	0
Thrombocytopenia	1 (6.3%)	0
Anorexia	6 (37.5%)	14 (50.0%)
Nausea	4 (25.0%)	6 (21.4%)
Vomiting	1 (6.3%)	1 (3.6%)
Fatigue	2 (12.5%)	4 (14.3%)
GOT/GPT	3 (18.8%)	1 (3.6%)
Alkaline phosphatase	2 (12.5%)	0
γ-GTP	2 (12.5%)	0
GI bleeding	1 (6.3%)	0
Hepatic failure	0	1 (3.6%)
Total	9 (56.3%)	15 (53.6%)

IORT, intraoperative radiation therapy; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil; GOT, serum glutamic oxaloacetic transaminase; GPT, serum glutamic pyruvic transaminase; γ-GTP, γ-glutamyl transpeptidase.

Toxicity

The 44 patients who received an EBRT dose of 30 Gy or more were evaluated for treatment-related toxicity. The most common symptoms of toxicity during treatment were anorexia and nausea. Grade 3 or 4 toxicity was observed in 24 (54.5%) of the 4 patients

(Table 2). There were no differences in toxicity between group A and group B. Hematological toxicity was mild, and grade 3 toxicity was observed in only 2 patients.

Although there were no treatment-related deaths within 90 days after IORT, two patients died of late treatment-related causes. A gastric ulcer developed 6 months after IORT in one patient who was treated by IORT+EBRT alone, and the patient died of uncontrollable bleeding by hematemesis due to gastric ulcer 11 months after the start of treatment. At autopsy a few viable cancer cells remained in the irradiation field, but the pancreatic carcinoma had been controlled. The other patient who died had been treated by IORT+EBRT with 5-FU and developed ascites and jaundice about 19 months after the start of the treatment. The patient died of hepatic failure 25 months after the start of treatment. The autopsy revealed stiffening and stricture of the lower common bile duct induced by irradiation and marked liver atrophy. The pancreatic carcinoma had been controlled, however, a few cancer cells remained. We concluded that the patient died of hepatic failure due to late effects of irradiation.

Table 3. Response

	IORT+EBRT (n=24)	IORT+EBRT with 5-FU (n=30)
CR	1	0
PR	5	7
SD	8	17
PD	4	6
NE*	6	0
Response rate (%)	25.0%	23.3%

NE*: Not evaluated. The response after IORT was not evaluated in 6 patients with metastases who received IORT + EBRT. IORT, intraoperative radiation therapy; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Response and Progression

The overall response rate in group A was 25.0% (95% confidence interval (CI), 12.0% to 44.9%), and there was 1 complete response (CR) and 5 partial responses (PRs), 8 had stable disease (SD), 4 progressive disease (PD), and 6 patients were not evaluated (NE). The overall

response rate in group B was 23.3% (95% CI, 11.8% to 40.9%), and there were 0 CR, 7 with a PR, 17 with SD, and 6 with PD.

Disease progression was observed in 45 of the 48 assessable patients. Initial progression was observed in the form of distant metastasis, such as to the liver or peritoneum in 36 (75.0%) patients, and there was local progression alone in 9 (18.8%) patients (Table 4). There were no differences in progression between group A and B. Time to progression (TTP) ranged from 0.6 months to 31.0 months, and median TTP was 4.9 months in group A and 3.4 months in group B.

Table 4. Initial progression

	IORT±EBRT (n=18*)	IORT+EBRT with 5-FU (n=30)
No progression	1 (5.6%)	2 (6.7%)
Local progression	4 (22.2%)	5 (16.7%)
Distant	13 (72.2%)	23 (76.7%)
Liver	10	12
Peritoneum	3	8
Lymph node	0	1
Lymph node & peritoneum	0	1
Brain	0	1

* Progression after IORT was not examined in 6 patients with metastases who received IORT + EBRT.
IORT, intraoperative radiation therapy; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil.

Survival

The overall survival of the 54 patients is shown in Figure 1. The median survival time (MST) was 7.7 months, and the 1- and 2-year survival rates were 29.6% and 9.3%, respectively. Figure 2 shows survival curves for patients with and without cancer spread in the abdominal cavity, and MST in these 2 groups was 5.4 and 11.9 months, respectively. No patients with cancer spread survived more than one year, whereas the 1- and 2-year survival rates in the patients without cancer spread were 47.1% and 14.7%, respectively. There was a statistically significant difference in the survival curves between the 2 groups ($p<0.0001$).

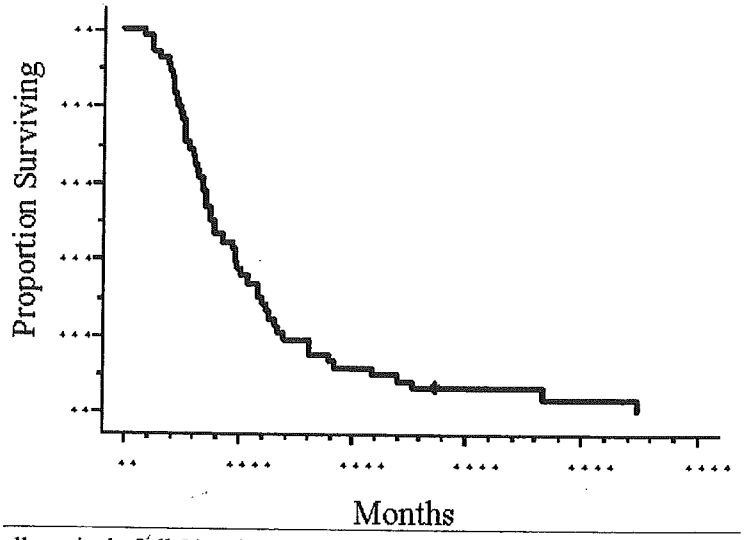

Figure 1. Overall survival of all 54 patients.

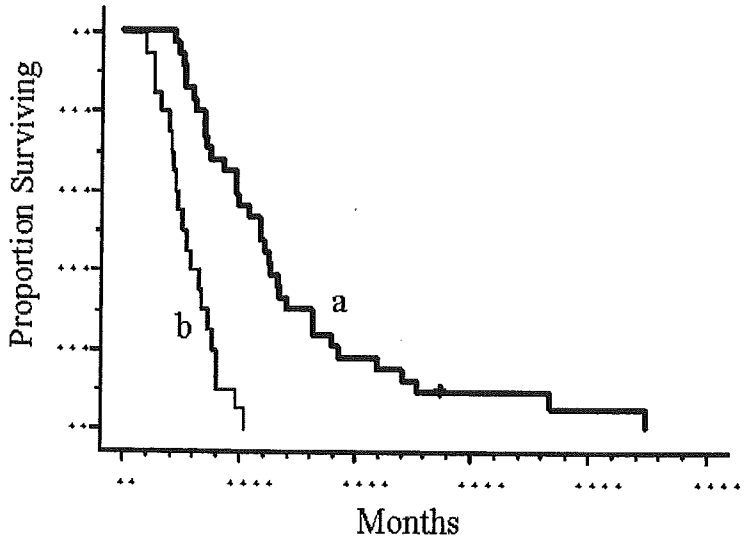

Figure 2. Curve "a" shows the survival of patients without cancer spread in the abdominal cavity (n=34), and curve "b" shows that of patients with cancer spread (n=20). There is a statistically significant difference between the 2 curves ($p<0.0001$).

Figure 3 shows the survival curves for the patients in group A and B. The MST for these 2 groups was 8.1 and 7.7 months, respectively. The 1-year survival rates were 20.8% and 36.7%, respectively, and the 2-year survival rate was 8.3% and 10.0%, respectively.There was no difference in the survival curves between the 2 groups (p=0.51).

There was no significant difference in the survival of the 34 patients without cancer spread in abdominal cavity according to whether they had been treated with or without 5-FU (Figure 4), and there was also no statistically significant difference in the survival of the 20 patients with cancer spread according to whether they were in group A or group B (Figure5).

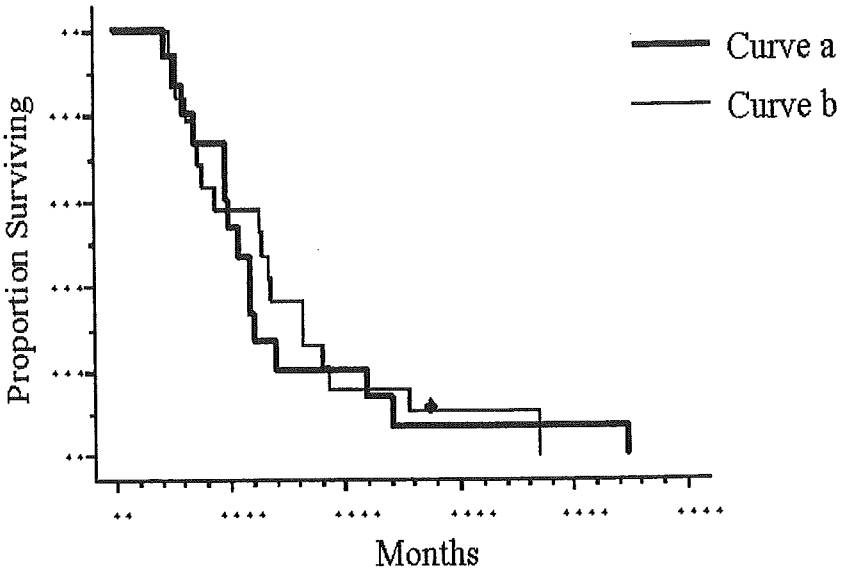

Figure 3. Curve "a" shows the survival of patients treated with IORT+EBRT without 5-FU (group A; n=24), and curve "b" shows that of patients treated with IORT+EBRT with 5-FU (group B; n=30). There is no significant difference between the 2 curves (p=0.51).

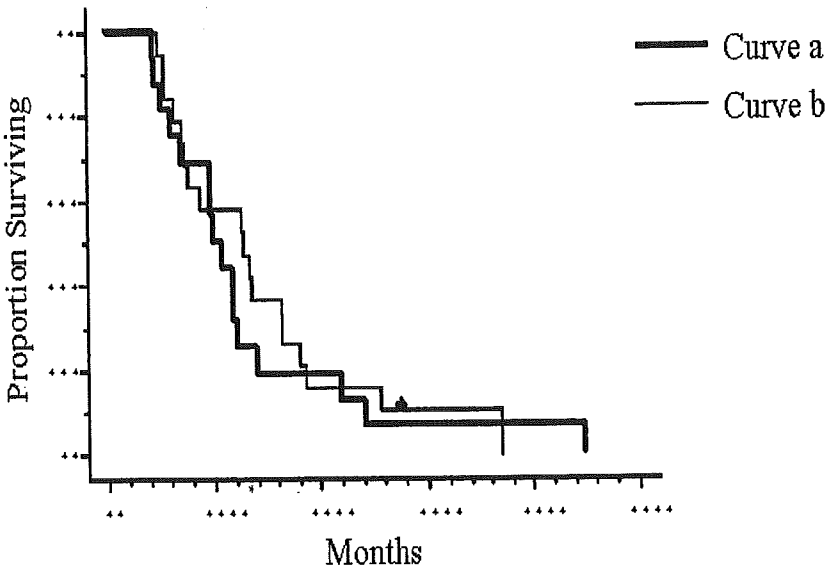

Figure 4. Overall survival of all 34 patients without cancer spread in abdominal cavity. Curve "a" shows the survival of patients with IORT+EBRT without 5-FU (n=15), and curve "b" shows that of patients treated with IORT+EBRT with 5-FU (n=19). There is no significant difference between the 2 curves (p=0.69).

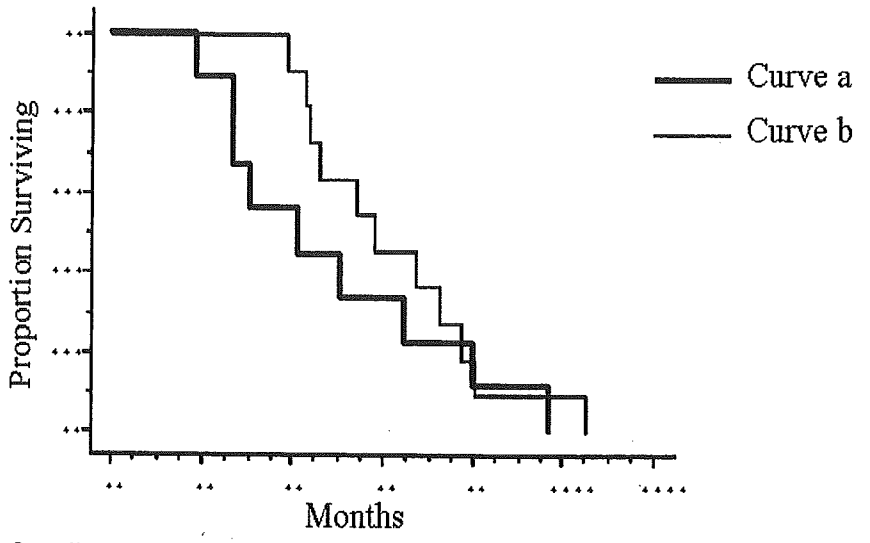

Figure 5. Overall survival of all 20 patients with cancer spread cancer spread in abdominal cavity. Curve "a" shows the survival of patients treated with IORT+EBRT (n=9), and curve "b" shows that of patients treated with IORT+EBRT with 5-FU (n=11). There is no significant difference between the 2 curves (p=0.31).

DISCUSSION

Locally Advanced Pancreatic Cancer is a Systemic Disease

We staged pancreatic carcinoma mainly on the basis of the dynamic CT findings, and the diagnosis was confirmed when the patients underwent laparotomy for IORT, which revealed that 37% patients already had metastasis in the abdominal cavity. It should be remembered that over one-third of even patients diagnosed with locally disease already have metastasis. We added MRI to the diagnostic methods in almost all patients in group B, but the accuracy of the diagnosis of metastasis did not improve. Other diagnostic methods, such as positron emission tomography or laparoscopy, may be required to diagnose metastasis more accurately.

Initial progression is also one of most important problems in treating patients with locally advanced pancreatic carcinoma. Metastasis to other sites, such as the liver or peritoneum, was initially observed in more than 70%, and the median time to progression was very short (3.3 months). Because of these two problems, more effective systemic chemotherapy is required to prolong survival even in patients with locally advanced pancreatic carcinoma.

Significance of IORT

In several studies, intensive irradiation consisting of a combination of EBRT and IORT has been performed to enhance the survival of patients with locally advanced pancreatic carcinoma.[7-13] However, Roldan et al.[11] reported finding no significant differences in

median or long-term survival between patients treated with EBRT alone and patients treated with a combination of IORT and EBRT (MST: 12.6 months versus 13.4 months).

To assess the effectiveness of IORT plus EBRT on survival, we can compare the results of the study of IORT plus EBRT with 5-FU (group B) with those of a study conducted at the National Cancer Center Hospital (NCCH) of Japan; it was a phase II trial of chemoradiation therapy consisting of EBRT (50.4 Gy in 28 fractions over 5.5 weeks) and concurrent protracted infusion of 5-FU at the same dose (200 mg/m^2/day).[6] Because there was little difference in subjects' characteristics or doses of 5-FU between these 2 studies, reasonable comparisons of their findings can be made. In the study of EBRT alone with 5-FU at the NCCH, MST was 10.3 months, and the 1- and 2-year survival rates were 41.8% and 0%, respectively. In our study (group B in this paper), MST was 7.7 months, and the 1- and 2-year survival rates were 36.7% and 10.0%, respectively. These results indicate that the addition of IORT to EBRT did not improve survival for patients with locally advanced pancreatic carcinoma. On the other hand, local progression was observed in 30% of patients in the study with EBRT alone with 5-FU and in 19% of patients in our study (IORT plus EBRT with 5-FU), and 5 long survivors (more than 2 years) were observed in only IORT plus EBRT with 5-FU. Some other studies using IORT plus EBRT reported a 2-year survival rate of about 20%.[9-11] Although those studies and our own were not randomized trials, the results indicate that the combination of IORT and EBRT yielded better local control and long-term survival (over 2 years) than EBRT alone.

The role of Concurrent 5-FU Chemotherapy in Intensive Radiotherapy

5-FU is generally accepted as a standard radiosensitizing agent for use in the chemoradiation therapy of pancreatic carcinoma, and we assessed the role of protracted infusion of 5-FU in this paper. Comparison between IORT+EBRT without and with 5-FU showed no difference in response, progression, or survival, contradicting the results of a randomized trial by the Gastrointestinal Tumor Study Group (GITSG) showing that chemoradiation therapy with 5-FU has advantages over radiation alone.[2] There are some possible explanations for the discrepancy: our studies were not randomized trials, we used more intensive irradiation with IORT plus EBRT, etc. Actually, the MST in the radiation alone arm in the GISTG study was only 5.3 months.

We expected systemic chemotherapy with 5-FU to suppress the progression and prolong the survival of patients with minimal metastasis not detected by conventional examinations and compared the results of radiation therapy alone and chemoradiation therapy with protracted infusion of 5-FU in those patients (Figure 5). Although it was a very small population, the survival of the patients treated with chemoradiation therapy seems to be prolonged during the first 6 months of therapy. Finally, the survival rates in the two studies were not statistically different, but more effective anticancer drugs for systemic chemotherapy may improve survival.

Chemoradiation Therapy with Gemcitabine

Since gemcitabine has proven to be effective in improving the survival of patients with advanced pancreatic carcinoma and to be a strong radiosensetizer,[14,15] it has become a candidate agent for use in the chemoradiation therapy of locally advanced pancreatic carcinoma. In phase I studies of gemcitabine dose escalation with concurrent radiation therapy, gemcitabine was administered at doses of only 40 to 90 mg/m^2 twice weekly and 250 to 500 mg/m^2 weekly, because gastrointestinal and hematologic toxicity was encountered.[16-20] The effects of concurrent gemcitabine administration on the survival rate of patients treated by chemoradiation therapy have been studied, but no evidence that gemcitabine is superior to 5-FU was found.[21] We think that early systemic administration of full-dose gemcitabine as part of sequential chemoradiation therapy with more compact irradiation, such as hypofractionated irradiation, may help prevent early development of distant metastasis.

CONCLUSIONS

The results of this review of our two studies do not suggest that chemoradiation therapy consisting of intensive irradiation by a combination of IORT and conformal EBRT with protracted infusion of 5-FU yields better survival of patients with locally advanced pancreatic cancer than conventional chemoradiation therapy with EBRT and 5-FU. However, the results indicate that locally advanced pancreatic cancer should be recognized as a systemic disease, and clinical trials of more promising systemic chemotherapy need to be conducted.

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Primary Tumor of Pancreatic Cancer as a Measurable Target Lesion in Chemotherapy Trials

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Background: It is unclear whether primary pancreatic cancer (PC) tumors can be accepted as measurable target lesions in chemotherapy trials. We reviewed recent PC patients to clarify the significance of their computed tomography (CT) responses of the primary tumor after chemotherapy.
Methods: The patient selection criteria were (i) having been admitted between January 2002 and December 2004, (ii) diagnosed as having histologically or cytologically proven adenocarcinoma of the pancreas, (iii) treated with chemotherapy with no previous anticancer treatment and (iv) having been evaluated by follow-up CT to assess the response according to the Response Evaluation Criteria in Solid Tumors criteria.
Results: A total of 143 patients met the selection criteria. It was possible to measure the largest diameter of the primary tumor in 119 (83%) of the 143, and primary tumor shrinkage was observed in 10 (8%) of the 119. When regarding the primary as measurable as opposed to non-measurable, the number of patients with measurable disease became 127 from 67, and the frequencies of partial response (PR), stable disease (SD) and progressive disease (PD) became 11, 74 and 15% of the 127 from 18, 52 and 30% of the 67, respectively. In the former situation, large primary tumor sometimes canceled the shrinkage or progression of small metastasis. In each setting, PR or SD represented a favorable prognosis compared with PD, however, there were no statistical differences between the PR and the SD.
Conclusion: Measuring the primary tumor is acceptable in ~80% of PC patients. However, we must be aware that the frequency of SD may increase compared with the PR or PD.

Key words: pancreatic neoplasm – RECIST – computed tomography – measurement – response

INTRODUCTION

The computed tomography (CT) response to treatment is an important indicator of the therapeutic effect of anticancer agents. In daily practice, response assessment is combined with other indicators of the patient's condition to contribute to the decision-making process. In clinical trials, it is widely used to identify and quantify the antitumor activity of investigational chemotherapy. A valid assessment of the response is based on an accurate measurement of the tumor on CT.

In pancreatic cancer (PC), however, it is difficult to accurately measure the size of the primary tumor mainly due to its invasive growth (1,2). In addition, the appearance of the tumor on a CT scan may not reflect the true proportion of the tumor response due to a vigorous desmoplastic reaction, including inflammation and fibrosis, within and around the tumor (3). Therefore, a primary PC tumor has been regarded as a non-measurable lesion in chemotherapy, and the antitumor effect of CT has been assessed mainly by measurable distant metastasis (4).

Recently, the consensus about the measurability of the primary PC tumor has become unclear. Shrinkage of the primary PC tumor has been more frequently observed since the introduction of gemcitabine (GEM)-based chemotherapy. There have been a number of trials that included not only patients with metastatic disease but also those with locally advanced disease, even though their end point is an objective CT response (5–7). In these reports, the primary PC tumor might be regarded as a measurable lesion, at least in locally advanced PC patients.

The current retrospective study was conducted to clarify whether the primary PC tumor could be accepted as a measurable target lesion in chemotherapy trials.

PATIENTS AND METHODS

The patient selection criteria were (i) having been admitted between January 2002 and December 2004, (ii) diagnosed as

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having histologically or cytologically proven adenocarcinoma of the pancreas, (iii) treated with chemotherapy with no previous anticancer treatment and (iv) having been evaluated by follow-up CT to assess the response. We listed all patients who met the above criteria and surveyed their records to clarify the significance of the primary tumor measurement in PC chemotherapy.

The tumor response was assessed by CT according to the Response Evaluation Criteria in Solid Tumors (RECIST) response criteria (8). In brief, a complete response was defined as the disappearance of all lesions. A partial response (PR) was defined as at least a 30% reduction in the tumor load, estimated as the sum of the longest diameters of all measurable lesions, taking as a reference the baseline sum of the longest diameters. Progressive disease (PD) was defined as at least a 20% increase in the tumor load, taking as a reference the smallest sum of the longest diameters recorded since the treatment started or development new lesions in a previously uninvolved site. Stable disease (SD) was defined as disease that showed neither sufficient shrinkage nor increase to qualify as either PR or PD.

CT scanning was performed with a four-section multidetector row CT scanner (Aquillion; Toshiba Medical System, Tokyo, Japan). Dynamic contrast-enhanced CT was performed in all patients with the mechanical injection of 100 ml of iopamidol (370 mg/ml of iodine) into the antecubital vein at a rate of 3 ml/s. CT scanning commenced 40–70 s after the start of injection of the contrast medium. Scanning parameters were as follows: 0.5 s gantry rotation time, a beam collimation of 4 × 2 mm, helical pitch of 5 and a reconstruction thickness of 5–7.5 mm.

The CT stage of each patient before chemotherapy was determined prospectively at our film conference held every Tuesday with the attendance of 2–4 staff from each section, i.e. diagnostic radiology, upper abdominal surgery and medical oncology. The measurability of the primary PC tumor on pretreatment CT was judged retrospectively (measurable or non-measurable) by three oncologists (H.I., J.F. and K.N) independently, with no clinical information of the patients. In this retrospective part, the radiologists did not participate in the judgment of measurability for primary lesions. The results were classified into three categories, i.e. 'measurable', 'marginal' or 'non-measurable', the definition of which was as follows: 'measurable' when three of the three judged the primary tumor as measurable, 'marginal' when two of the three judged the primary tumor as measurable and 'non-measurable' when one or none of the three judged the primary as measurable. Finally, the 'marginal' cases were determined to be measurable or non-measurable based on the consensus of the three (Fig. 1).

In the current study, responses were assessed by two methods, i.e. regarding the primary PC tumor as a non-measurable lesion (referential method) or as a measurable target lesion in cases with 'measurable' primary tumors (alternative method). In the latter, the maximum size of the pancreatic mass on CT was measured on the serial axial slices containing the largest portion of the mass. According to the RECIST criteria, shrinkage of the primary PC tumor was defined as 30% or greater reduction of the largest size, and PR was confirmed when the shrinkage continued for more than 4 weeks.

Survival curves were calculated using the Kaplan–Meier method (9). Overall survival was measured from the beginning of chemotherapy to the time of the final follow-up or death. Differences in survival were evaluated with log-rank tests. All analyses were performed using the statistical software SPSS 11.0J for Windows. Statistical significance was defined as a two-sided P-value of ≤ 0.05.

RESULTS

Between January 2002 and December 2004, a total of 327 histologically confirmed PC patients were admitted to our hospital. Of them, 63 underwent surgical resection, 20 were treated with chemoradiotherapy, 26 received best supportive care and 218 were treated with chemotherapy. Of the 218, 47 had anticancer treatment earlier, i.e. surgical resection of primary PC in 24 and chemotherapy in 23. Of the remaining 171, 28 were not evaluated by CT after chemotherapy because of their early deteriorations. Accordingly, the remaining 143 met the selection criteria in the current study.

The patient backgrounds are shown in Table 1. Of the 143, 67 had measurable metastasis and the remaining 76 had no measurable metastasis. Among them, 101 received GEM monotherapy as a clinical practice (1000 mg/m^2/30 min, Day 1, 8 and 15, every 4 week). The remaining 42 received chemotherapy as part of multicenter clinical trials: Phase 1/2 study of the fixed dose rate infusion of GEM (n = 11), and combination of GEM and S-1 (n = 11), Phase 2 study of combination of GEM and infusional fluorouracil (n = 5), S-1 (n = 6), NK911 (micelle forming polymeric doxorubicin, n = 6) and CPT-11 (n = 3).

Response by the Referential Method

Of 67 patients with measurable metastasis, 12 (18%) showed a PR, 35 (52%) remained SD, and 20 (30%) showed PD. All 12 PR cases showed liver metastasis shrinkage. Of 76 with no measurable metastasis, 68 remained SD and 8 showed PD. Therefore, the overall responses in the 143 were 12 PRs, 103 SD and 28 PD, according to a referential method, i.e. regarding the primary PC tumor as a non-target lesion.

Response by the Alternative Method

The frequencies of patients with a 'measurable' primary tumor in the 143 were 76, 85 and 87% according to each of the three blinded reviewers. As a result, the frequencies of 'measurable', 'marginal' and 'non-measurable' primary tumors were 74, 13 and 13%, respectively. Of the 19 'marginal' cases, 13 were reconsidered to be 'measurable' cases by discussion. Finally, 119 (83%) were diagnosed as having a measurable primary PC tumor. In the 119, the maximum size of the primary tumor ranged from 21 to 121 mm and the quartiles at 25, 50 and 75% were 37, 47 and 65 mm, respectively. Shrinkage of the primary tumor was observed in 10 of the 119. The relationship between the primary tumor measurability and presence

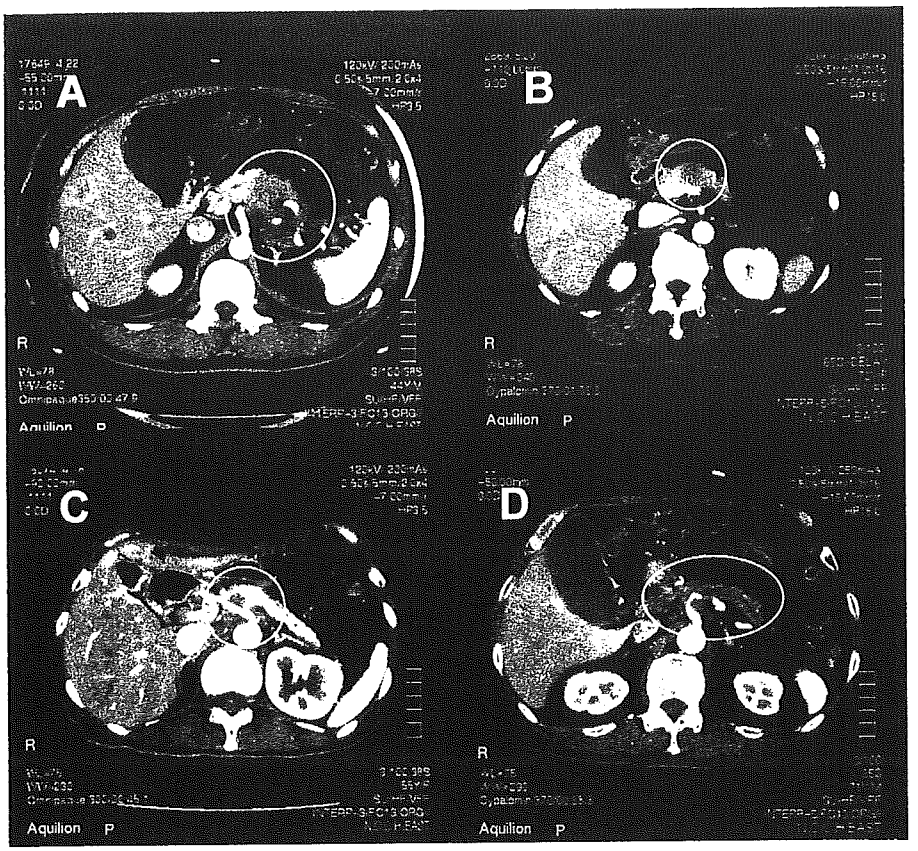

Figure 1. CT images of the 'measurable', 'marginal' or 'non-measurable' primary tumor (indicated in the center of an each white circle). (A) A case with the 'measurable' pancreatic body-tail tumor. (B) A case with the 'marginal' pancreatic body tumor, which was finally determined to be 'measurable'. (C) A case with the 'marginal' pancreatic body tumor, which was finally determined to be 'non-measurable' because of its irregular shape. (D) A case with the 'non-measurable' pancreatic tumor because of its indistinct margin.

Table 1. Patient characteristics in the 143 pancreatic cancer patients treated with chemotherapy

Gender (Man/woman)	76/67
Age [Median (range)]	63 (37–90)
Performance status (0/1/2/3)	101/37/4/1
Tumor location (Head/body-tail)	64/79
Stage	
Locally advanced disease	44
with measurable regional lymph node	2
without measurable regional lymph node	42
Metastatic disease	99
with measurable lesion	65
without measurable lesion	34
CA19-9† (U/ml)[Median, (25–75 percentile)]	713 (79-2,788)

†Carbohydrate antigen 19-9, cut-off index is less than 37 U/ml in our hospital.

Table 2. Relationship between the primary tumor measurability and the presence or absence of measurable metastasis

	Measurable metastasis		Total
	Absent	Present	
Primary tumor			
Non-measurable	16 (11%)	8 (6%)	24 (17%)
Measurable	60 (42%)	59 (41%)	119 (83%)
Total	76 (53%)	67 (47%)	143 (100%)

or absence of measurable metastasis is shown in Table 2. Of the 127 with measurable primary or metastatic tumors, 14 (11%) showed a PR, 94 (74%) remained SD and 19 (15%) showed PD. Of the remaining 16 with no measurable lesions, 13 remained SD and 3 showed PD. As a result, the overall responses in the 143 were 14 PRs, 107 SD and 22 PD, according to the alternative method.

Comparison of the Two Methods

The relationship between the referential and the alternative responses is shown in Table 3. A discrepancy between the responses was observed in 14 (10%) cases.

All five cases from SD (referential) to PR (alternative) had no target metastatic metastasis (locally advanced, 2; minute liver metastasis, 2; peritoneal dissemination, 1),

Table 3. CT response with or without measuring the primary tumor as a measurable target lesion

Response	Primary tumor as a measurable target lesion			
	PR[†]	SD[‡]	PD[§]	Total
Primary tumor as a non-measurable lesion				
PR	9	3		12
SD	5	98		103
PD		6	22	28
Total	14	107	22	143

[†]Partial response.
[‡]Stable disease.
[§]Progressive disease.

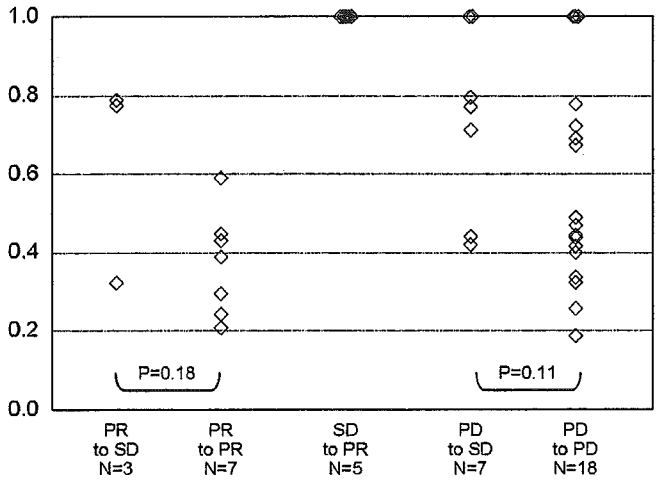

Figure 2. The proportion of the primary tumor size to all sum of the longest measurable lesion including the primary tumor. In cases from PR to SD, or from PD to SD, there was a trend to have a relatively large primary tumor compared with those from PR to PR, or from PD to PD, respectively. The *P*-values were calculated by Mann–Whitney *U*-tests.

i.e. shrinkage was observed in the primary tumor as the sole target lesion.

Cases from PR to SD, or from PD to SD, had relatively large primary tumors compared with metastasis (Fig. 2). In these cases, the primary tumor was so large to be set off against shrinkage or progression of small metastasis. Therefore, reduction of the total sum of the largest diameter of the targets did not reach over 30% in cases from PR to SD, or the enlargement of the total sum remained within 20% in cases from PD to SD, using the alternative method.

Survival curves of measurable cases according to each response are shown in Figs 3 and 4. They showed a situation that was commonly seen in a Phase 2 chemotherapy trial for advanced PC, i.e. a trial for metastatic PC using the referential method and for locally advanced or metastatic PC by the alternative method. PR and SD were superior to PD; however, there were no significant differences between PR and SD in both situations.

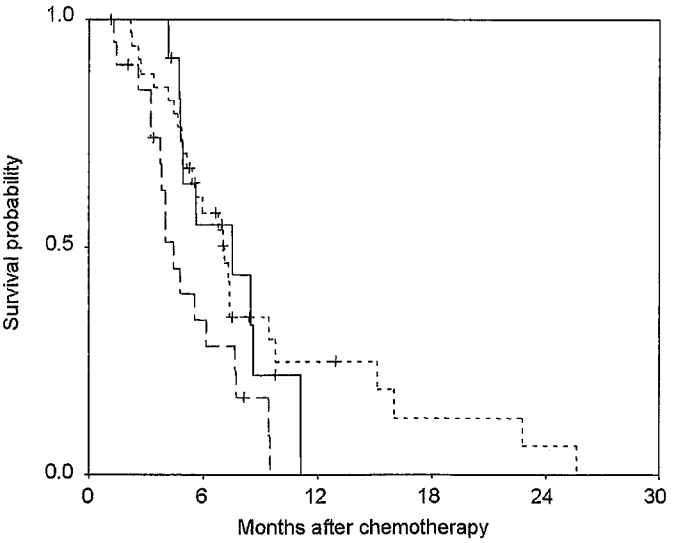

Figure 3. The overall survival curve of 67 patients with measurable metastasis according to the CT response when assessing the primary tumor as a non-target lesion (referential method). The plain line indicates cases with a PR, the fine dotted line indicates cases with SD and the dotted line indicates cases with PD. The *P*-values of the log-rank test for cases with PR versus SD, PR versus PD and SD versus PD were 0.80, 0.05 and 0.02, respectively.

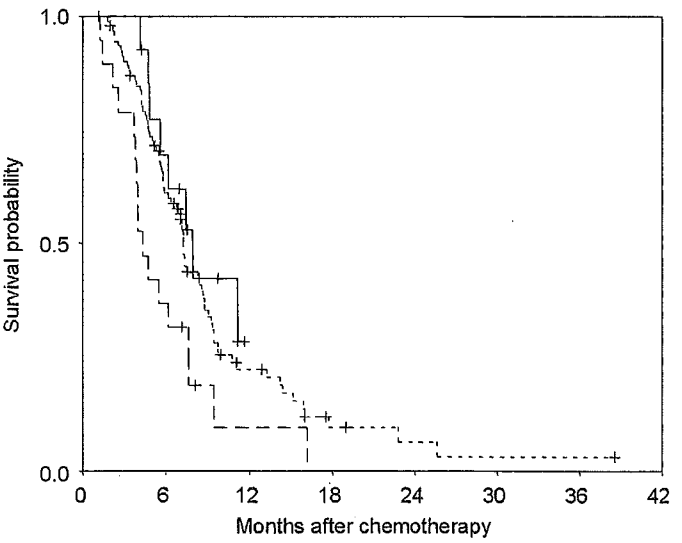

Figure 4. The overall survival curve of 127 patients with any measurable lesion according to the CT response when assessing the primary tumor as a target lesion (alternative method). The plain line indicates cases with a PR, the fine dotted line indicates cases with SD and the dotted line indicates cases with PD. The *P*-values of the log-rank test for cases with PR versus SD, PR versus PD and SD versus PD were 0.44, 0.03 and 0.02, respectively.

DISCUSSION

The newly introduced RECIST, which relies on the single largest dimension of the tumor, is intended to simplify the assessment of the tumor response and has become standard in the world. At the end of the preamble in the RECIST article, there is a statement that specific tumors or anatomic sites

presenting unique complexities will be considered in the future. In fact, clinical problems have already been reported in chemotherapy for malignant pleural mesothelioma (10,11) and gastric cancer (12,13) in adopting the unidimensional RECIST criteria. The main cause of the problems arises from the fact that those tumors represent a non-spherical, tridimensional shape at the primary site. PC also demonstrates a non-expanding, invasive growth pattern, and its accurate measuring on CT has been already reported to be difficult (1,2). Therefore, the antitumor effect in Phase 2 chemotherapy trials for PC has been mainly evaluated by the CT assessment of measurable distant metastasis, and primary tumors have generally been regarded as a non-measurable lesion (3).

However, recent reports of Phase 2 trials (5–7) sometimes include not only patients with metastatic disease but also those with locally advanced disease. In patients with locally advanced disease, the primary PC tumor must be measured and assessed using CT. Therefore, the current study focused on the validity of the primary PC tumor measurement and its assessment, because little attention has been given to this issue.

There must be some factors that influence the measurability of the primary PC tumor, such as the quality of CT images, the opinion of each physician and so on. The size of the primary PC tumor may change variously according to the contrast enhanced phase of dynamic CT (1). In the current study, however, an almost uniform method was used to obtain the CT images, thanks to an effort in our diagnostic radiology division. As for the disagreement of each physician's opinion, the current blind test showed a high frequency of agreement about the measurability of the primary tumor. Accordingly, we supposed the primary tumor to be measurable in ~80% of advanced PC patients, also in the other center hospitals.

The assessment of primary tumor shrinkage may be used for measuring the anticancer activity in Phase 2 trials for locally advanced PC. In the current study, however, we could not mention this issue because only two patients with locally advanced disease achieved a PR. Overall survival has been usually employed as the primary end point in Phase 2 trials for locally advanced PC (14,15), because standard chemoradiotherapy reproduced almost constant results, i.e. the median survival time of 10 months or 1 year survival rate of 40% (16–18). Accordingly, it may be unnecessary to measure the primary in trials for locally advanced disease.

Measuring the primary PC tumor may be an advantage for recruiting many patients into clinical trials. In fact, patients with measurable lesions increased from 67 to 127 patients. The result indicated candidates for Phase 2 trials may be doubled by measuring the primary tumor. In this manner, however, we should notice that the frequency of SD might increase compared with the PR or PD. As shown in the results, this phenomenon occurred because the large primary tumor sometimes canceled the shrinkage or progression of small metastasis. Accordingly, whether primary tumor can be accepted as a measurable target lesion or not should be determined strictly in each protocol to make an easy interpretation of anticancer activity. To date, the non-PD rate may be the best response indicator, because it is unnecessary to differentiate PR from SD until the development of a new effective chemotherapy superior to standard GEM in the treatment of PC. In this respect, we should be aware of regarding a non-PD rate as an end point, because it may tend to be high using the alternative method in the current study.

In conclusion, the measurement and assessment of the primary PC tumor may be accepted in Phase 2 trials, whereas a careful interpretation of the responses is needed for each protocol.

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Treatment Cost of Pancreatic Cancer in Japan: Analysis of the Difference after the Introduction of Gemcitabine

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Background: Recent advances in cancer chemotherapy have increased not only the survival rate but also the treatment cost, although there has been little interest in cost analyses in Japan.
Method: The actual cost of pancreatic cancer treatment was surveyed especially with respect to the difference after April 2001, which was the date that gemcitabine was introduced in Japan.
Results: A total of 113 patients were admitted consecutively from April 2000 to March 2002. Among the 113 patients, the total treatment cost over a lifetime was calculated in 54. In those 54 patients, the median treatment cost and survival time were $43 865 and 26.2 months for resectable disease ($n = 14$), $30 676 and 10.0 months for locally advanced disease ($n = 21$), and $29 255 and 4.8 months for metastatic disease ($n = 19$), respectively. Of the 54, 26 patients were admitted before April 2001 (Group A) and the remaining 28 were admitted thereafter (Group B). There were significantly more patients who received gemcitabine chemotherapy in Group B (19 of the 28) than in Group A (none of the 26). The median treatment cost and survival times were $35 744 and 7.4 months in Group A, and $35 226 and 8.8 months in Group B, respectively, whereas the total cost of anticancer agents was significantly higher in Group B than in Group A.
Conclusion: Although cost of gemcitabine is about 18-fold higher than 5-fluorouracil in Japan, the total costs after gemcitabine introduction did not tend to become higher in our hospital, probably because of simplification in examinations and shorter hospitalization.

Key words: pancreatic neoplasm – cost analysis – treatment cost – chemotherapy – investigational new drug application

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of death due to cancer in Japan, and in 2001 there were 19 397 deaths owing to this malignancy (1). Although surgical resection offers the opportunity for cure, only a small minority of PC patients are candidates for surgery. Moreover, even for these selected patients, the prognosis remains unfavorable because of post-operative recurrence. For a long time, chemotherapy for recurrent or unresectable PC had only limited value and there had been no regimen superior to 5-fluorouracil (5-FU) alone (2,3). However, in the late 1990s gemcitabine (GEM) showed significantly better results in survival time compared to 5-FU (4,5). Accordingly, GEM has been accepted as the first-line chemotherapy treatment for advanced PC in many countries, and in Japan GEM was introduced into hospitals in April 2000 (6). Although the incremental survival advantage of GEM over 5-FU is relatively small (median 1–2 months) (4,5,7), the cost of GEM is about 18-fold higher than 5-FU in Japan.

There has been little interest in cost analyses in cancer treatments in Japan, probably because Japanese people invariably join public health insurance programs and all hospital and doctor fees have been guarantied according to medical piecework (not a prospective payment system) by the government. However, total medical costs have increased year by year and the estimate of national medical care expenditure was $284 billion in 1999, i.e. $2240 per person, which represented 8% of the national income (8). Although the government has started to work on medical cost cutting and have tried a Japanese version of the Diagnosis Related Group/Prospective Payment System in a few model hospitals since 1998, most Japanese hospitals including National Cancer Center, employ the conventional payment system (the sum of piecework) at present. Because the prospective payment system will become widely prevalent in Japan, this may be the last chance to survey an actual cost of PC treatment according to the conventional payment system.

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