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Onset of Liver Metastasis After Histologically Curative Resection of Pancreatic Cancer

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Abstract

Purpose. We assessed the possibility of predicting the time of onset of liver metastases by measuring the postoperative changes in serum carbohydrate antigen (CA)19-9 after curative resection of pancreatic cancers.

Methods. Among 28 patients who underwent histologically defined curative resection of pancreatic cancer between 1984 and 1999, liver metastasis developed in 11 patients with elevated serum CA19-9 levels. We plotted the serum CA19-9 levels against time on a semilogarithmic graph. Over the linear part of the curve, the time when log[CA19-9] equaled zero was defined as the time of onset of liver metastases. The log[CA19-9] level doubling time was then calculated and evaluated in relation to the survival period.

Results. The serum CA19-9 levels increased linearly in 10 of the 11 patients. The predicted time of onset of liver metastasis ranged from preoperative day 163.0 to postoperative day 27.1, being preoperative in eight patients. The doubling time until death correlated strongly with survival in the eight patients with maintained log[CA19-9] linearity.

Conclusion. The onset of liver metastases might be preoperative in patients with advanced pancreatic cancer. Therefore, neoadjuvant chemotherapy should be mandatory even if there is no sign of liver metastases.

Key words Pancreatic cancer · Tumor marker · Carbohydrate antigen 19-9 · Doubling time · Liver metastasis

Introduction

The results of treatment for pancreatic cancer are extremely poor, despite intensive efforts. We use a combination of extended radical pancreatectomy and intraoperative radiation therapy to achieve histologically defined curative resection for pancreatic cancer, and prevent local recurrence.[1,2] Although this treatment helps to control local recurrence, survival has not improved dramatically because of the frequency of deaths associated with hematogenous metastases, especially in the liver. Almost all of these patients die within 2 years of surgery. Although liver metastases might exist before resection, in the form of latent lesions, to our knowledge there is no report providing evidence of this.

To improve the results of treatment for pancreatic cancer, we need more detailed information on the development of liver metastases. As yet, there is no reliable marker of liver metastases; thus, we investigated whether postoperative changes in carbohydrate antigen (CA)19-9 levels correlated with the predicted time of onset of liver metastases, and with prognosis.

Patients and Methods

Between 1984 and 1999, 41 patients with pancreatic cancer underwent a combination of extended resection and lymphadenectomy plus intraoperative radiation at Kumamoto University Hospital. The extended operation for pancreatic cancer consisted of pancreatectomy with almost complete dissection of the lymph nodes around the porta hepatis, the celiac axis, the mesenteric radix, and the aorta, from the level of the diaphragm down to the inferior mesenteric artery. After the tumor was resected, intraoperative radiation was delivered to an area of 6 × 10–14 cm, including the tumor bed, to a dose of 30 Gy with 8–12 MeV of an electron beam.[1]

Among 28 patients who underwent histologically confirmed resection of pancreatic cancer, 13 died of liver metastases, 11 of whom had positive serum CA19-9 levels. We retrospectively analyzed these 11 patients,

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Table 1. Clinical characteristics of the 11 patients

Patient No.	Age (years)	Sex	Stage	Preoperative CA19-9
1	48	M	II B	354.0
2	70	M	II B	72.1
3	40	F	IV	110.0
4	68	M	IV	1006.0
5	60	M	II B	85.0
6	70	F	II A	488.2
7	62	M	II B	1083.8
8	44	M	II B	2226.2
9	65	F	I A	51.7
10	73	F	II B	4700.0
11	71	F	II A	426.7

Mean age: 61.0 ± 3.3 years; M:F = 6:5
CA, carbohydrate antigen

who had no sign of local recurrence on postoperative computed tomography (CT) scanning or ultrasonographic examination. Their mean age was 61.0 years (range, 40–73 years), and there were six men and five women. The cancer stage at the time of resection was p-Stage IA in one patient, p-Stage IIA in two, p-Stage IIB in six (54.5%), and p-Stage IV in two. Although both of the patients with p-Stage IV cancer had metastases in the lymph nodes around the aorta, these were resected and the operation was judged to be curative. The mean preoperative serum CA19-9 level in the 11 patients was 964.0 (range, 51.7–4700) (Table 1).

We plotted the postoperative changes in CA19-9 levels on a semilogarithmic scale. The time when log[CA19-9] equaled zero was defined as the time of onset of liver metastases, on the linear part of the curve. The influence of the local lesion was excluded if follow-up CT scans showed no sign of local recurrence after curative resection. We judged that the change in log[CA19-9] reflected the status of liver metastasis exactly. Thus. the zero point on this line represented the time of onset of the liver metastases. Furthermore, if liver metastases were the cause of death, the number of days it took for the log[CA19-9] levels to double within the period of exponential increase was defined as the doubling time. We then investigated the correlation between the prognosis and the doubling time.

Hepatic metastases were evaluated preoperatively by CT scanning and ultrasonography, intraoperatively by ultrasonography, and postoperatively every 3 months by CT scanning and ultrasonography. Serum CA19-9 levels were also measured once a month postoperatively.

Statistical analysis was performed with a statistical software program (Statview; Abacus Concepts, Berkeley, CA, USA). Fisher's exact test and Wilcoxon's test were used for statistical evaluation with $P < 0.05$ considered significant. All results are expressed as mean ± SEM.

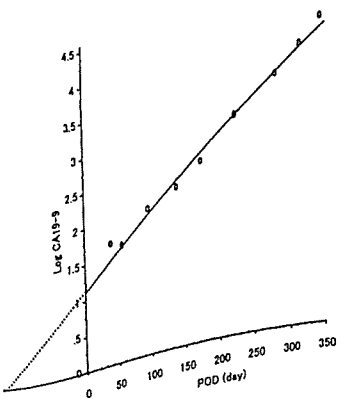
Results

Prediction of the Time of Onset of Liver Metastases

The actual 5-year survival rate of the 28 patients who underwent curative resection was 21.8%. Thirteen (65.0%) of the 20 deaths were caused by liver metastases, but 2 of these 13 patients were excluded from the analysis because their preoperative CA19-9 levels were negative. The CA19-9 levels decreased in the remaining 11 patients, but returned to within the normal range 1–2 months postoperatively in only 5. Ten patients had a linear increase in the postoperative log[CA19-9], which correlated well with the postoperative time (Fig. 1). The postoperative CA19-9 level did not increase in the other patient after liver metastases appeared. The predicted time of onset of liver metastases in ten patients ranged from preoperative day 163.0 to postoperative day 27.1, with preoperative metastases being confirmed in eight patients (mean preoperative day 62.7) (Table 2).

Prediction of Prognosis and Survival Based on Doubling Time

In the eight patients with a constant linear relationship throughout the observation period, postoperative survival and the doubling time were well correlated (Fig. 2) The mean CA19-9 doubling time was 20.8 days in the eight patients who died of liver metastases (Table 3). One of the remaining two patients suffered postoperative complications, which may have affected their survival. The other patient showed a biphasic change in the CA19-9 level, which increased rapidly during the postoperative course. Therefore, the doubling time was calculated twice from the plotted line of this patient, who died of blood-borne metastases. The doubling time increased from 150.5 to 301.0 within about 1 year after the operation. We think that tumors with different grades



Patient No.	R (Coefficient of correlation)	p
No. 1	0.964	<0.0001
No. 2	0.969	0.0006
No. 3	0.911	<0.0001
No. 4	0.969	0.0054
No. 5	0.973	0.0041
No. 6	0.999	<0.0001
No. 7	0.999	<0.0001
No. 8	0.973	<0.0001
No. 9	0.999	<0.0001
No.10	0.962	<0.0001
No.11	0.09	0.535

Fig. 1. Postoperative change in log[CA19-9] levels showed a linear increase in 10 of 11 patients who underwent curative resection of pancreatic cancer. The zero point of the log[CA19-9] was considered the day of onset of liver metastasis. *POD*, postoperative day

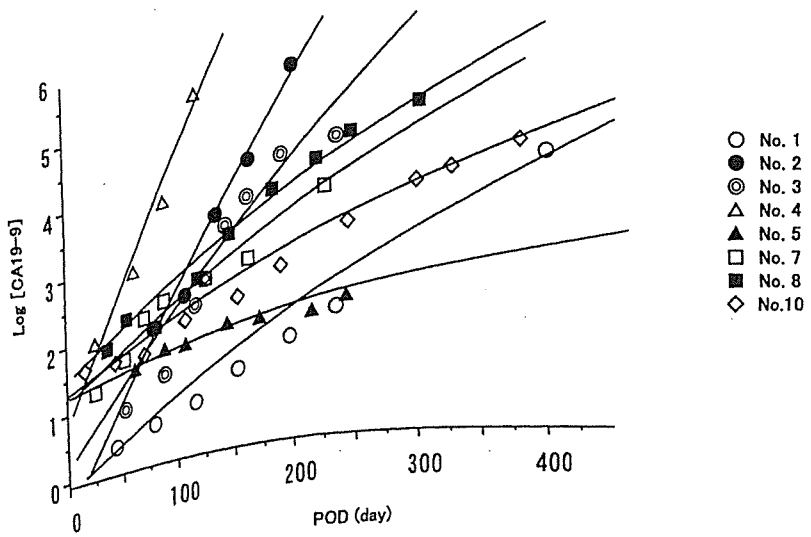


Fig. 2. Postoperative changes in the log[CA19-9] level showed a constant increase in 8 of 10 patients during the observation period. *POD*, postoperative day

Table 2. Predicted time of onset of liver metastasis in the 10 patients

Patient no.	Predicted time of CA19-9 levels at zero (operation day = 0)
1	27.1
2	19.8
3	−13.0
4	−30.5
5	−45.7
6	−58.4
7	−106.8
8	−121.6
9	−134.0
10	−163.4
Average	−62.7

of malignancy gained power while repeating the division.

The correlation coefficient between the survival period and the CA19-9 doubling time was 0.877, with a P value of 0.0023 in these eight patients (Fig. 3). Patient no. 5 underwent transcatheter arterial embolization (TAE) and patient no. 8 received a transarterial infusion of anticancer drugs for the metastatic liver lesions. However, the linearity of the CA19-9 curve during the observation period was hardly affected. None of the other patients received adjuvant chemotherapy. All liver metastatic nodules appeared fully developed on CT scans. When the survival time was replaced with the length of time after onset of liver metastasis, the correlation coefficient was 0.906, with a P value of 0.0008, yielding an even higher correlation (Fig. 3).

Discussion

To control local recurrence of pancreatic cancer, we routinely performed a combination of extended radical pancreatectomy with intraoperative radiation therapy.[1] Unfortunately, this approach has failed to achieve great improvement in the treatment results. We examined the factors affecting prognosis by conducting autopsies,

Table 3. Log[CA19-9] doubling times and survival periods in the 8 patients

Patient No.	Doubling time (days)	Survival period (months)
1	27.4	16.0
2	15.1	7.6
3	10.4	6.9
4	8.4	6.0
5	20.1	9.0[a]
7	20.1	11.3
8	27.4	17.5[b]
10	37.6	15.0
Average	20.8 ± 9.75	11.2 ± 4.5

[a]Transarterial embolization
[b]Transarterial infusion

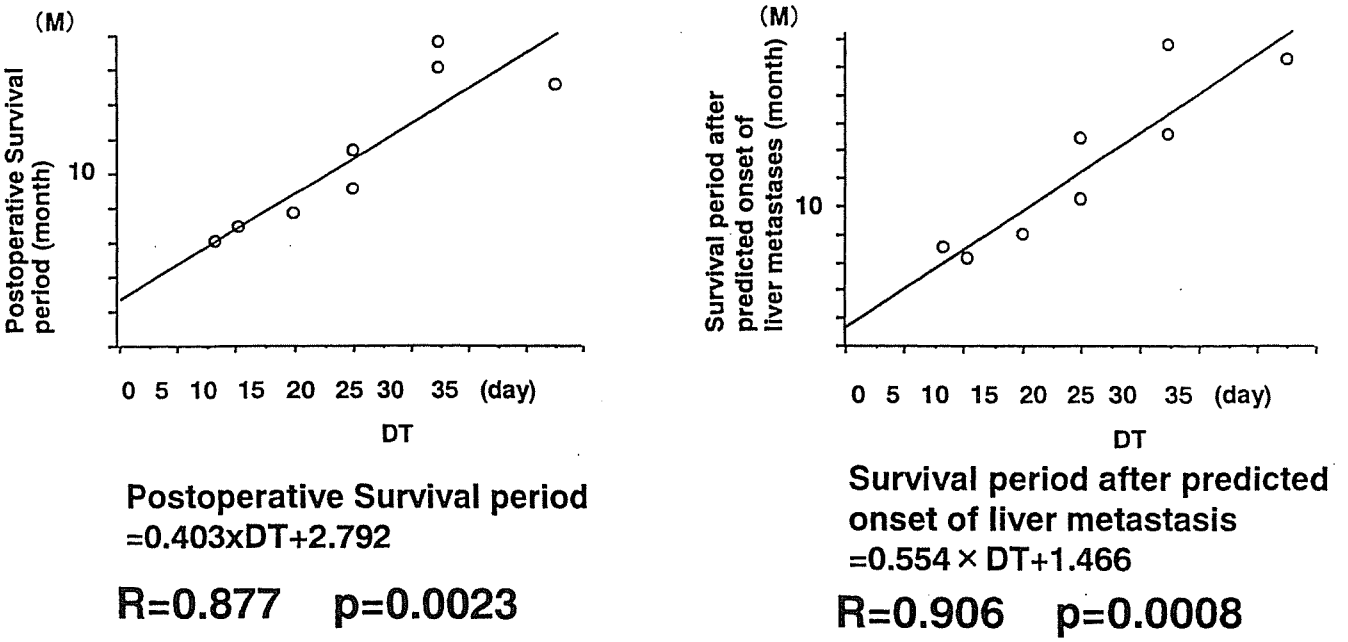


Fig. 3. We examined the relationship between the log[CA19-9] doubling time (DT) and the survival period. The survival period after surgery and that after the onset of liver metastases were both significantly related to the doubling time

which revealed that although the treatment effectively prevented local recurrence, blood-borne metastases, especially to the liver, greatly affected the overall prognosis.[2]

To improve the results of treatment for pancreatic cancer, effective measures against blood-borne metastases, especially liver metastases, are urgently required. However, few studies have been done on the time of onset of liver metastases in relation to surgery. It has been suggested that the liver metastases emerging postoperatively originate from undetected liver micrometastases,[3] intraoperative dissemination of cancer cells, and local recurring lesions. Safi et al. reported that CA19-9 measurement is a simple test, which can be used for diagnosis as well as for predicting resectability, survival after surgery, and the potential for recurrence.[4] Montgomery et al. reported that measuring postoperative levels of CA19-9 was the best predictor of disease-free survival and median survival.[5]

Staab et al. examined time-related changes in levels of carcinoembryonic antigen, another tumor marker, in patients with gastrointestinal tract cancer, and analyzed the relationship between those changes and prognosis.[6] Takahashi et al. reported that changes in tumor markers correlated strongly with an increase in tumor size, representing an exponential increase, and demonstrated a correlation between doubling time and survival periods.[7] Although some reports suggest that changes in CA19-9 levels were useful for predicting the prognosis of patients with pancreatic cancer,[8-11] or as a

marker of hepatic metastases,[12,13] the usefulness of monitoring changes in CA19-9 levels based on theoretical calculations has not been analyzed. Our findings reinforce the need for liver metastases. The CA19-9 levels were negative in 2 of our 13 patients, both of whom died of liver metastasis within 2 years, indicating a high possibility that liver metastasis had already existed before the operation. Even if CA19-9 is negative in the early postoperative period in patients with advanced cancer, recurrence is likely, so regular postoperative examination is mandatory.

There is little doubt that the rate of tumor growth is a prognostic factor. In the present study, we found that the doubling time of the serum CA19-9 levels was closely correlated with the postoperative survival period, and even more closely correlated with survival after the onset of liver metastases. These results suggest that liver metastases greatly affect the prognosis of pancreatic cancer; thus, we must establish measures to prevent metastasis. Even if an advanced pancreatic cancer is resectable, occult liver metastases may already exist at the time of surgery and neoadjuvant chemotherapy is necessary to prevent postoperative hepatic recurrence. Otherwise, the existence of micrometastasis would contraindicate surgery.

In conclusion, the onset of liver metastases might be preoperative in patients with advanced resectable pancreatic cancer. Thus, we must find effective neoadjuvant chemotherapy to prevent liver metastases. Otherwise, these patients should be excluded from resection by preoperative selection. These important issues need to be resolved in the search for more effective treatment against pancreatic cancer.

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Evaluation of the Efficacy of Combined Continuous Arterial Infusion and Systemic Chemotherapy for the Treatment of Advanced Pancreatic Carcinoma

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Abstract

Purpose: To evaluate the effects of combined continuous transcatheter arterial infusion (CTAI) and systemic chemotherapy in patients with advanced pancreatic carcinoma.
Methods: CTAI was performed in 17 patients with stage IV pancreatic cancer with (n = 11) or without (n = 6) liver metastasis. The reservoir was transcutaneously implanted with the help of angiography. The inferior pancreatic artery (IPA) was embolized to achieve delivery of the pancreatic blood supply through only the celiac artery. The systemic administration of gemcitabine was combined with the infusion of 5-fluorouracil via the reservoir. Treatment effects were evaluated based on the primary tumor size, liver metastasis, and survival time and factors such as tumor size, tumor location, and stage of pancreatic carcinoma; the embolized arteries were analyzed with respect to treatment effects and prognosis.
Results: A catheter was fixed in the gastroduodenal artery and splenic artery in 10 and 7 patients, respectively. Complete peripancreatic arterial occlusion was successful in 10 patients. CT showed a decrease in tumor size in 6 of 17 (35%) patients and a decrease in liver metastases in 6 of 11 (55%) patients. The survival time ranged from 4 to 18 months (mean ± SD, 8.8 ± 1.5 months). Complete embolization of arteries surrounding the pancreas was achieved in 10 patients; they manifested superior treatment effects and prognoses ($p < 0.05$).
Conclusion: In patients with advanced pancreatic cancer, long-term CTAI with systemic chemotherapy appeared to be effective not only against the primary tumor but also against liver metastases. Patients with successfully occluded peripancreatic arteries tended to survive longer.

Key words: Chemotherapeutic infusion—Interventional procedure—Pancreas neoplasm

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Due to advances in diagnostic imaging techniques, the detection rate of curatively resectable small pancreatic carcinoma has increased. However, resection at the time of diagnosis is possible in only 5–22% of patients [1–3], not only because patients with small pancreatic carcinomas demonstrate normal values on blood examination and manifest few clinical symptoms, but also because intraoperatively found cancers greater than 2–2.5 cm in diameter tend to have already invaded the lymph nodes, liver, and peritoneal surface [1–4].

Among the chemotherapeutic agents evaluated in patients with pancreatic cancer, 5-fluorouracil (5-FU) yielded response rates ranging from 0 to 27% [5–7]. The anticancer activity of gemcitabine (2′-2′-difluorodeoxycitidine) and its clinical benefits have been demonstrated [8–11]. To deliver anticancer drugs more selectively to the cancer tissue, thereby achieving higher concentrations of the antineoplastic agents in the tumor mass, intra-arterial chemotherapy has been tested; its sensitivity was dose-dependent [12].

The pancreas is supplied by numerous vessels that derive from the superior mesenteric artery (SMA) and the celiac, dorsal pancreatic, great pancreatic, and caudal pancreatic

arteries arising from the splenic artery [13, 14]. When an indwelling catheter is placed in the gastroduodenal artery (GDA) or splenic artery (SPA) during surgery [15], the inferior pancreatic artery (IPA) arising from the SMA starts to function as a pancreatic carcinoma-feeding vessel. As radiation therapy is often associated with local recurrence, it should be combined with other treatments to address metastatic lesions of the liver [16, 17].

This study was designed to examine the effects of the combination of gemcitabine and 5-FU, delivered by intra-arterial continuous infusion via a transcutaneous arterial port implanted into the gastroduodenal or splenic artery, in patients with advanced pancreatic cancer.

Materials and Methods

Between January 2001 and December 2002, we treated 17 chemotherapy-naive patients with advanced pancreatic carcinoma (pancreatic ductal carcinoma). Their diagnosis was established based on typical results at ultrasonography, multidetector helical computed tomography (MD-CT), and endoscopic retrograde cholangiopancreatography (ERCP). To assess the hemodynamic status around the pancreas, selective angiograms were obtained. In 8 of the 17 patients, adenocarcinoma of the pancreas was confirmed histologically or cytologically by aspiration under ERCP. In other patients, primary pancreatic cancer was diagnosed by a elevation of tumor marker including CA19-9, SPAN1, and DU-PAN-2.

Patient Characteristics

The study population consisted of 17 patients (10 men, 7 women) ranging in age from 42 to 74 years (average 64 years). All carried a diagnosis of advanced stage IV pancreatic cancer including 4 patients with stage IVa disease and 13 patients with stage IVb. The size of the primary pancreatic tumors, measured by pretreatment MD-CT, ranged from 2 to 10 cm (mean 4.7 cm). In 10 patients they were located in the pancreatic head and in 7 in the body or tail. Eleven patients had multiple liver metastases. All patients gave written prior informed consent before entering the study.

Technique for Hemodynamic Modification

In general, the arterial system in the head of the pancreas consists of the anterior or posterior superior pancreaticoduodenal artery (ASPD or PSPD) that arises from the GDA and IPA that branches off the SMA. These arteries combine to form a pancreaticoduodenal arcade that surrounds the pancreatic head. In the arterial system of the pancreatic body and tail, the dorsal pancreatic artery (DPA), greater pancreatic artery (GPA), and caudal pancreatic artery (CPA) that branch directly off the SPA are combined within the pancreatic parenchyma to form the transverse pancreatic artery (TPA). Accordingly, the blood flow to the pancreatic head neoplasm is mainly supplied from the ASPD, PSPD, and IPA whereas blood to the pancreatic body and tail derives from the DPA, GPA, and CPA. Therefore, in our treatment strategy against advanced pancreatic carcinoma, we superselectively embolized the pancreatic arteries, leaving only the GPA and CPA to simplify the potential branches that flow into the pancreatic parenchyma (Fig. 1). A complete occlusion was defined as embolization of the peripancreatic arteries including ASPD, PSPD, GDA, DPA, and IPA and gastric arteries including the right (RGA) and left (LGA) gastric arteries.

First, a 4-Fr-catheter was inserted from the femoral artery using the Seldinger technique. The RGA and LGA, ASPD, PSPD, and IPA were occluded with microcoils to prevent gastroduodenal injury from anticancer agents. With the patient under local anesthesia, the catheter for arterial infusion was introduced from a branch of the left subclavian artery in 9 patients and a branch of the right femoral artery in 8 patients. The catheter was fixed in the GDA in 9 patients and in the SPA in 8 patients (Figs. 1, 3A). In all patients, a catheter was introduced into the celiac axis; this carried a side hole at a site appropriate for the distribution of anticancer agents not only to the pancreatic tumor but also to the whole liver. An arterial port was implanted at a subcutaneous site; the patients were fully ambulatory throughout the term of treatment.

We used a 4 Fr catheter (Medikit, Tokyo, Japan) for angiography and a 2.4 Fr microcatheter (Target, Boston Scientific, Watertown, MA, USA). Placement of the 4 Fr catheter was aided by a 0.035-inch diameter torque Radifocus guidewire (Terumo, Tokyo, Japan). To place the microcatheter, we used a Dasher-14 guidewire (outside diameter 0.014 inch) with a free transformation tip (Boston Scientific) and a GT wire (outside diameter 0.014 inch) with a fixed-angle tip (Terumo). Vortex embolization microcoils (Boston Scientific) and interlocking detachable coils (IDC) (Boston Scientific) were the metallic coils for embolization. The intra-arterial indwelling catheters were 3.3 Fr polyurethane catheters coated with a hydrophilic heparinized polymer (Anthron PU catheter; Toray Medical, Tokyo, Japan) and 3.3 Fr W-spiral catheters (Piolax Medical Devices, Yokohama, Japan); BardPort (Bard, Salt Lake City, UT, USA) was used as the port for arterial infusion.

Drug Administration

Gemcitabine diluted in normal saline was intravenously administered for 30 min once a week for 3 consecutive weeks (Fig. 2). 5-FU was delivered via the arterial port at a dose of 250 mg/day on days 1–5 every week as a continuous infusion (Fig. 2). In patients manifesting toxicity of WHO grade 2 or greater, the drug infusion was interrupted until recovery. In patients with disease progression, chemotherapy was discontinued.

Assessment of Blood Chemistry Response Rate

All patients underwent urinalysis, peripheral blood examination, biochemical analysis, and renal and hepatic function tests before each course of arterial infusion chemotherapy. Tests for tumor marker CA 19-9 (0–35 U/ml) were conducted every 4 weeks. The tumor response was evaluated every 4 weeks using multislice helical CT according to WHO criteria. Complete response (CR) was defined as the disappearance of all evidence of cancer for 4 weeks or longer, partial response (PR) as a 50% or greater reduction in the sum of the products of the perpendicular diameter of all lesions for 4 weeks or longer in the absence of any evidence of new or progressive lesions, and no change (NC) as a less than 50% reduction or a less than 25% increase in the sum of the products of the perpendicular diameters of all lesions in the absence of any evidence of new lesions. Progressive disease (PD) was recorded when there was a more than 25% increase in one or more lesions or the appearance of new lesions. In patients who achieved CR and PR, the procedure was regarded as effective.

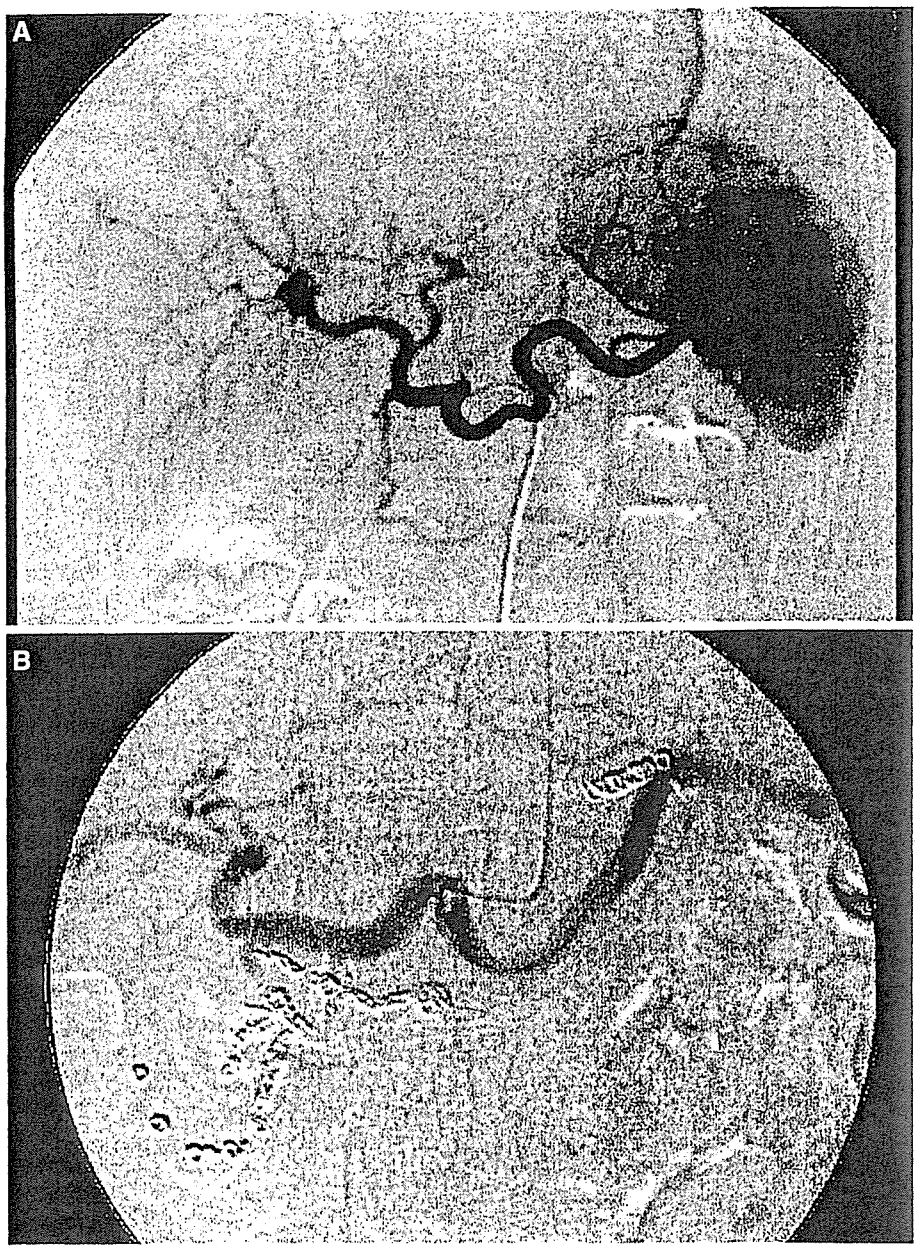

Fig. 1. **A** Angiographic study before hemodynamic changes in the peripancreatic artery in patients with advanced pancreatic carcinoma. A celiacangiogram visualized the right and left gastric, gastroduodenal, and posterior and anterior superior pancreaticoduodenal arteries. **B** Angiographic study after percutaneous port implantation showing hemodynamic changes in the peripancreatic artery in patients with advanced pancreatic carcinoma. A catheter with a side hole at the celiac trunk was fixed in the splenic artery. Arterial occlusion of the inferior pancreatic, right and left gastric, gastroduodenal, and posterior and anterior superior pancreaticoduodenal arteries was completely successful.

Statistical Analysis

Treatment effects were evaluated based on tumor size (<4 cm vs. >4 cm), tumor location (pancreatic head vs. pancreatic body or tail), stage of pancreatic carcinoma (stage IVa vs. IVb), and degree of arterial occlusion of the peripancreatic arteries (complete vs. incomplete). For statistical analysis we used the chi-square test; survival was evaluated by the Kaplan–Meier method (log-rank test).

Results

Arterial Occlusion

The results of complete or incomplete arterial occlusion are summarized in Table 1. Arterial occlusion was completely successful in 10 patients including 3 patients with stage IVa and 7 patients with stage IVb pancreatic carcinoma (Figs. 1, 3A). In the other 7 patients, the IPA, GDA, LGA, RGA, ASPD, or PSPD could not be embolized because multiple feeders originated at these arteries. Arterial occlusion of the peripancreatic arteries including the IPA and GDA was incompletely successful in 5 and 3 patients, respectively. Arterial occlusion of the gastric arteries including the LGA and RGA was incompletely successful in 1 and 4 patients, respectively. We were able to infuse the anticancer agents into the primary tumor and liver metastases.

Of 11 patients with liver metastasis, 1 had a replaced anomalously located right hepatic artery (RHA). Therefore, the RHA was embolized with a microcoil so that the liver was perfused only through the common hepatic artery.

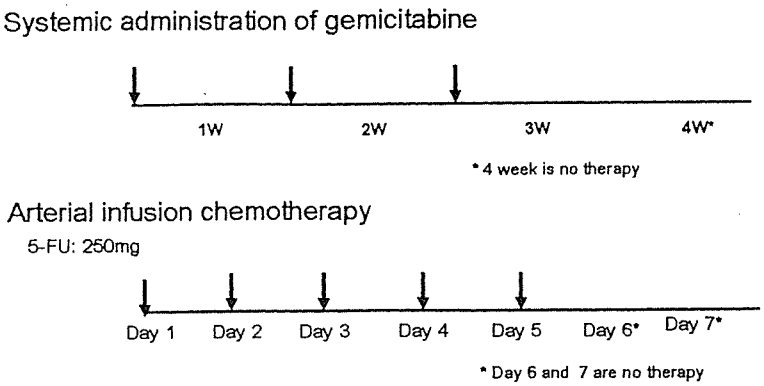

Fig. 2. The therapeutic regimen used. W, weeks; 5-FU, 5-fluorouracil.

Table 1. Arterial occlusion

Artery		Complete occlusion	Incomplete occlusion
Peripancreatic artery	IPA	12	5
	PSPD	17	0
	ASPD	17	0
	GDA	17	0
	DPA	14	3
Gastric artery	LGA	16	1
	RGA	13	4

IPA, inferior pancreatic artery; PSPD, posterior superior pancreaticoduodenal artery; ASPD, anterior superior pancreaticoduodenal artery; GDA, gastroduodenal artery; DPA, dorsal pancreatic artery; LGA, left gastric artery; RGA, right gastric artery

Table 2. Response rates

	CR	PR	NC	PD	Total
Primary pancreas tumor	2 (12%)	4 (24%)	7 (40%)	4 (24%)	17
Metastatic liver tumor	2 (18%)	4 (36%)	4 (36%)	1 (9%)	11

CR, complete response; PR, partial response; NC, no change; PD, progressive disease

Treatment Efficacy and Survival

As shown in Table 2, 2 patients (12%) had CR, 4 (24%) had PR, 7 (41%) had NC, and 4 (24%) manifested PD. On CT, 6 patients (35%) showed a decrease in the size of the tumor (Fig. 3B–D). The tumor size and location, and the arteries not embolized, had no significant effect on the efficacy of treatment (Table 3).

Of the 11 patients with liver metastasis, 2 (18%) were judged as CR, 4 (36%) as PR, 4 as NC (36%), and 1 (9%) as PD (Table 2). On CT, 6 (55%) showed a decrease in their metastatic liver tumors (Fig. 3C, E). Patients with complete occlusion of arteries surrounding the pancreas manifested the better treatment results ($p < 0.05$) (Table 3).

We used the Kaplan–Meier method to determine the effect of tumor size, tumor location, stage of pancreatic carcinoma, and degree of arterial occlusion on survival (Fig. 4). Survival ranged from 4 to 22 months (mean ± SD, 11.3 ± 1.4 months) and patients with complete arterial occlusion manifested the better outcomes ($p < 0.01$, Fig. 4).

Evaluation of Tumor Marker

Compared with pretreatment levels, tumor marker levels were markedly decreased at 4 weeks after the start of arterial infusion in 13 of the 17 patients (77%). In all patients with PD, they were increased on week 4.

Complications

One patient with dislocation of the infusion catheter required reimplantation. In 6 other patients, the dislocated catheter was removed at the time progressive disease became apparent.

No patients died from side effects attributable to chemotherapy (Fig. 4A, E). The most common toxicities presented as hematologic events. All patients developed anemia during treatment; 3 patients with grade 3 anemia required blood transfusions. However, we encountered no potentially life-threatening toxicity.

Severe non-hematologic side effects were observed in 4 patients; these were one each of duodenal ulcer, cholangitis, partial splenic embolization, and mild cerebral infarction with a partial visual field defect. One patient developed diabetes mellitus after arterial infusion chemotherapy. Two patients with pre-existing diabetes mellitus manifested aggravation of the blood sugar level; however, this was controlled by increasing the insulin dose.

Treatment Outcomes

Only 4 of the 17 patients were alive at the time of this report. The causes of death included liver failure resulting from the development of liver metastases (6 patients) or superior mesenteric vein–portal vein thromboses (1 patient), disseminated intravascular coagulation due to direct tumor invasion into the duodenum (1 patient), cancerous peritonitis (2 patients), and cerebral infarction (1 patient); 2 patients died of unknown causes.

Discussion

Compared with other gastrointestinal cancers, pancreatic carcinomas have very unfavorable treatment results; the

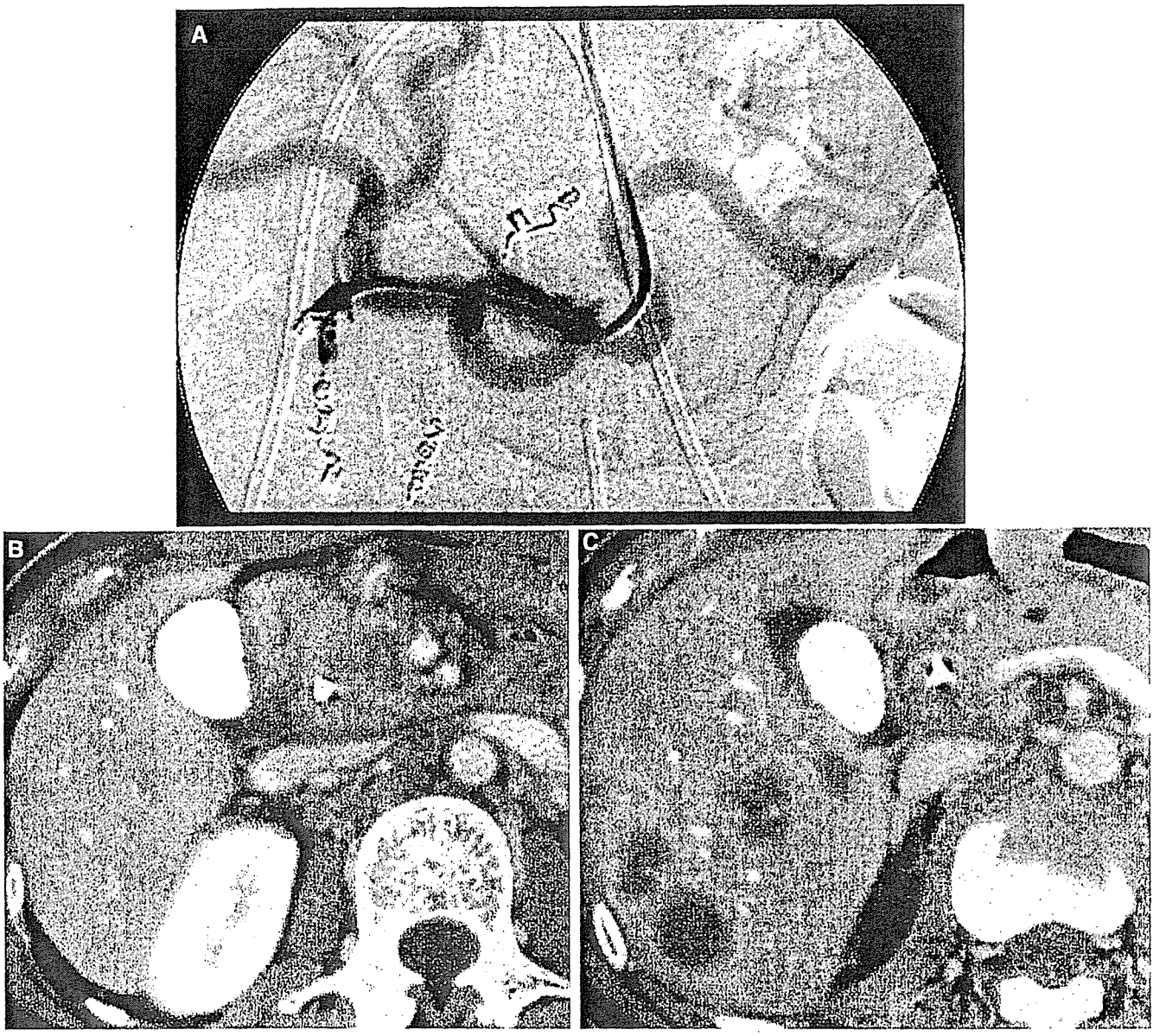

Fig. 3A–E. In this 46-year-old woman with stage IV advanced pancreatic carcinoma and multiple liver metastases a complete response of the primary tumor and liver metastasis was obtained. **A** Angiographic study after percutaneous port implantation. A catheter with a side hole at the celiac trunk was fixed in the gastroduodenal artery. **B** Before arterial infusion therapy. Note the extensive tumor involving the pancreatic head. **C** Before arterial infusion therapy. Multiple liver metastases are present. **D** Nine weeks after the first course of arterial infusion therapy. The primary tumor cannot be detected in the pancreatic head. **E** Nine weeks after the first course of arterial infusion therapy. The liver metastases are remarkably reduced.

surgical resection rate is reportedly 14.2% [18, 19]. Systemic adjuvant chemotherapy for pancreatic carcinoma has not increased the 5-year survival rate [20, 21], and the addition of adjuvant chemotherapy to radiation treatment failed to provide any significant increases in survival [22, 23]. The cause of death in patients with advanced pancreatic carcinoma is primarily local cancer progression and distant metastases [17, 24, 25], and pancreatic carcinomas larger than 2 cm are frequently associated with lymph node, liver, and retroperitoneal metastases [13, 26]. Gudjonsson [27] contended that surgical resection of pancreatic carcinoma represents a waste of resources. As patients with advanced pancreatic cancer that cannot be resected have poor treatment results, the mean survival being 6 months or less for patients with stage IV disease and at most 1 year for stage II/III patients [24, 25, 28, 29], it has been suggested that only symptomatic support should be given in patients with stage IV pancreatic carcinoma [25, 30]. On the other hand, patients receiving palliative chemotherapy showed better overall survival than did those who received no treatment,

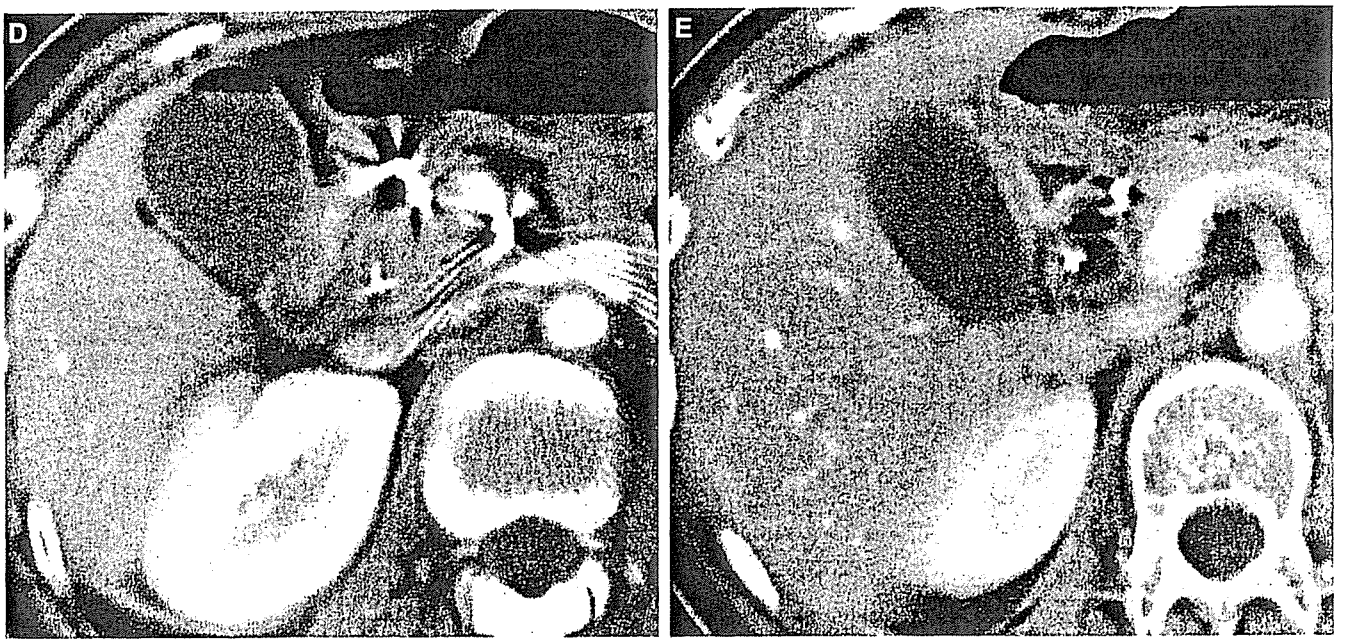

Fig. 3. Continued

Table 3. Factors for response rate

	Tumor size	Tumor location	Stage of pancreatic cancer	Complete artery embolization
Primary pancreas tumor	NS	NS	NS	NS
Metastatic liver tumor	NS	NS	NS	$p < 0.05$

NS, not significant

without impairment of their quality of life [14, 15, 22, 23, 25, 26, 28, 30–35].

Intra-arterial infusion delivers higher drug concentrations to the tumors, thereby overcoming the problem of poor blood flow to the tumor mass [36]. Pancreatic carcinomas are dose-dependently sensitive to locoregional chemotherapy [37, 38]. In previous reports, intra-arterial chemotherapy [39–44] was delivered through a Seldinger catheter introduced at each session via the femoral artery into the celiac axis. Despite the attendant discomforts, regional chemotherapy appeared to be sufficiently effective and tolerable to warrant testing in an adjuvant setting [41, 43, 44]. The results were promising with respect to lowering the occurrence of liver metastasis and increasing survival time.

The rationale for the intra-arterial infusion of chemotherapeutic agents appears to be promising from the perspective of drug concentration-response because most liver metastases (3 mm or more) receive arterial blood supply [45, 46]. Intra-arterial infusion is thought to take advantage of the first-pass effect of the drug, thereby delivering higher local drug concentrations to the tumor cells at lower rates of toxicity. Continuous intra-arterial infusion has the advantage of maintaining the drug concentration when a time-dependent chemotherapeutic agent such as 5-FU is used. On the other hand, the systemic blood concentration of 5-FU may be too low to be effective against occult extrahepatic metastases, because the first-pass effect of 5-FU is up to 50% [47].

There is currently no evidence that in patients with pancreatic carcinoma, intra-arterial infusion chemotherapy provides advantages over systemic therapy with respect to progression-free survival or overall survival [48], although in patients with colorectal liver metastases a significantly higher response rate was observed [49]. Local and hepatic therapy for pancreatic cancer is not satisfactory because even after curative resection of pancreatic carcinoma, most patients suffer from recurrence at the local site and in the hepatic and/or peritoneal cavity. Moreover, extra-abdominal metastases were documented in 27% of cases [50]. Therefore, systemic chemotherapy with gemcitabine added to regional and hepatic intra-arterial infusion therapy is necessary in patients with pancreatic carcinoma.

We introduced the catheter for arterial infusion from a branch of the left subclavian and femoral artery that was exposed in all patients under local anesthesia. Direct surgical implantation of an intra-arterial catheter in the hepatic artery has been proposed to deliver drugs as a continuous infusion, avoiding the risks and discomforts of iterative artery puncture. However, this approach is suitable only in patients undergoing surgical intervention, and the appropriateness of its use in patients with unresectable stage III pancreatic carcinomas and stage IV liver metastasis has been questioned [51].

Honma et al. [52] reported the utility of arterial infusion chemotherapy after vascular supply redistribution via superselective embolization in patients with advanced pan-

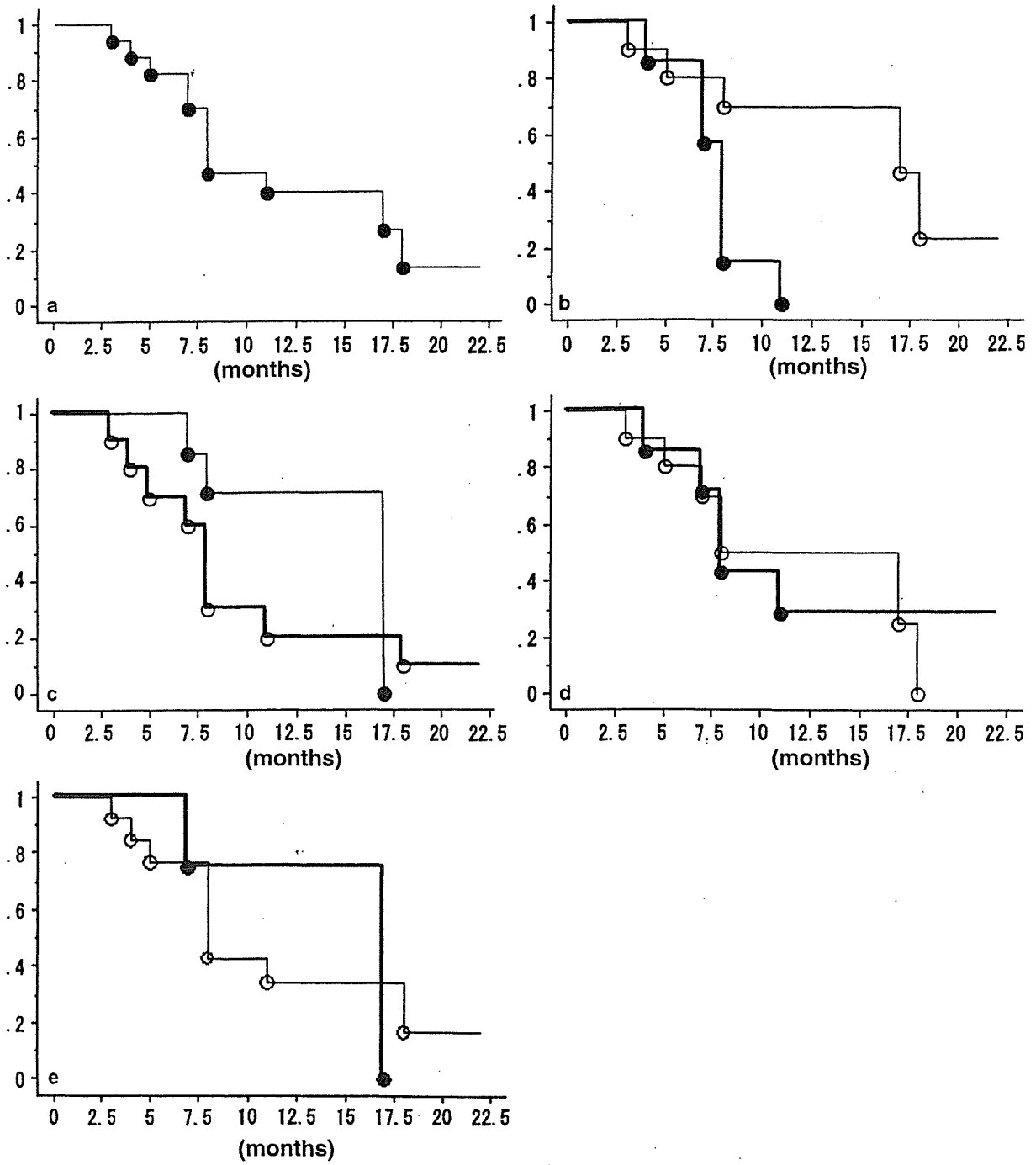

Fig. 4. **A** Overall survival for patients receiving 5-FU intra-arterial infusion and systemic gemcitabine therapy for stage IV pancreatic cancer. **B** Survival rates of patients with embolized arteries. Patients with successful arterial occlusion survived longer than did patients with incomplete occlusion ($p < 0.01$). Open circles, complete artery occlusion; filled circles, incomplete artery occlusion. **C** Relationship between survival rates and pancreatic tumor size. There was no significant difference between patients with large and small primary tumors. Open circles, large primary tumor; filled circles, small primary tumor. **D** Relationship between survival rate and tumor location. There was no significant difference between patients with cancer at the pancreatic head and those whose cancer involved the pancreatic body or tail. Open circles, cancer of the pancreatic head; filled circles, cancer of the body or tail of the pancreas. **E** Relationship between survival rate and pancreatic cancer of the stage. There was no significant difference between patients with stage IVa and stage IVb disease. Open circles. stage IVb; filled circles, stage IVa.

creatic carcinoma. The definition of complete occlusion differs between Honma et al.'s paper and ours. They defined complete occlusion as disappearance of enhancement of the whole pancreas. We defined complete occlusion as actual arterial occlusion of the peripancreatic arteries. In order to avoid gastric complications, we embolized gastric arteries. Their study did not evaluate gastric arteries, but we included the RGA and LGA.

In our study, arterial occlusion of the peripancreatic arteries including the IPA was incompletely successful in 5 patients. This may have resulted in heterogeneous drug distribution into the pancreatic parenchyma. Honma et al. reported that gastrointestinal symptoms including transient nausea and mild anorexia occurred during administration of anticancer agents in 9 and 13 patients, respectively. In our study, arterial occlusion of the gastric arteries including the RGA was incomplete in 4 patients, resulting in gastrointestinal symptoms such as transient nausea and mild anorexia during administration of anticancer agents. In order to raise the success rate of the peripancreatic arteries, we modified the embolization technique, so that the RGA and IPA were embolized through a microcatheter advanced through the LGA and the arcade of the PSPD and ASPD, respectively.

Honma et al. reported that efficacy of the treatment against primary pancreatic carcinoma was 68.8%, while in ours it was 35%. However, Honma et al. used a different regimen for arterial infusion chemotherapy. They reported that the total dose of anticancer agents was 500 mg/m^2 for 5-FU and 20 mg/m^2 for CDDP. In our study the total dose of anticancer agent was 250 mg/m^2 for 5-FU; CDDP is not permitted for use against pancreatic carcinoma in our country. Second, in our primary trials using their regimen the side effects were not acceptable. For these reasons, our results were inferior to those in Honma et al.'s study but the frequency of side effects was much less.

Patients in whom arterial infusion chemotherapy had to be stopped after several courses, primarily due to dislocation of the infusion catheter, were excluded from our study. One patient with dislocation of the infusion catheter required reimplantation. However, in another 6 patients who experienced catheter dislocation the drug was distributed normally, and reimplantation was not necessary.

Our study has limitations. Because it was a preliminary investigation, the need for strict inclusion staging limited the number of patients enrolled and precluded meaningful statistical data analysis. Due to our small sample size, the effect of selection bias may have been magnified. Of our 17 patients diagnosed with stage IV pancreatic carcinoma; 4 patients had stage IVa and 13 had stage IVb. Those with stage IVa had a significantly better course than did patients with stage IVb.

In conclusion, in patients with advanced pancreatic carcinoma, long-term CTAI with systemic chemotherapy appeared to be effective not only against the primary tumor but also especially against liver metastases. Patients with successful occlusion of the peripancreatic arteries including the IPA survived longer. More accurate evaluation of the perfusion of anticancer agents using fusion imaging of RI flow study and CT images would be necessary. A more effective regimen of arterial infusion chemotherapy should be attempted.

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CLINICAL TRIALS ARTICLE

Clinical Trials 2006; 3: 1–9

Estimation of the average causal effect among subgroups defined by post-treatment variables

Yutaka Matsuyama[a] *and Satoshi Morita*[b]

Background In clinical trials, when comparing treatments in a subgroup of patients defined by an event that occurred after randomization is required, the standard estimator that adjusts for the post-treatment variable does not have a causal interpretation.

Purpose To address this problem, we formulate clinically relevant causal estimands using the principal stratification framework developed by Frangakis and Rubin [3], and propose a new estimation method for the principal causal effect.

Methods We consider the comparison of the duration of response among patients who responded to chemotherapy in a cancer clinical trial. Our goal is to estimate the local average treatment effect, that is, the treatment difference among patients who would have responded to either treatment. In order to identify this estimand, we make the assumption that the value of the counterfactual indicator of response is independent of both the actual response status and the outcome variable of interest conditional on the covariates. The proposed estimator is a weighted average of the standard estimators for responders where weights are the probability that the response would have occurred had the patient received the other treatment.

Results The proposed method is applied to data from a randomized phase III clinical trial in patients with advanced non-small-cell lung cancer. The average difference for the duration of response among responders estimated by the proposed method and the standard one was 16.1 (days) and 9.5 (days), respectively. We also evaluate the performance of the proposed method through simulation studies, which showed that the proposed estimator was unbiased, while the standard one was largely biased.

Conclusions We have developed an estimation method for the local average treatment effect. For any type of outcome variables, our estimator can be easily constructed and can be interpreted as the treatment effect among patients who would have had the event in either treatment group. *Clinical Trials* 2006; 3: 1–9. www.SCTjournal.com

Introduction

In clinical trials, it is conceptually difficult to make a treatment comparison in a subgroup of patients defined by an event that occurred after randomization. For example, in cancer clinical trials, one would like to compare the duration of response among patients who responded to chemotherapy. One scientific question behind such analyses is that responses to different treatment regimens will have different response durations, so responders are the primary group of interest. However, such comparison is problematic if the treatment has any effect on response, because the subgroup of responders under the standard treatment and the subgroup of responders under the new treatment are not the

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same group of patients. This problem is known to epidemiologists as post-treatment selection bias [1,2], which implies that a comparison of the duration of response among responding subgroups does not have a causal interpretation.

Recently, Frangakis and Rubin [3] have proposed a principal stratification framework with respect to post-treatment variables. The principal stratification approach is a cross-classification of patients defined by the joint potential values of the post-treatment variable under each of the treatments that are being compared. As with the example of the chemotherapy responder described above, patients can be classified into four potential subgroups:

1) those who would respond under either treatment assignment, the true responders;
2) those who would not respond under the standard but would respond under the new treatment, the new treatment only responders;
3) those who would respond under the standard but would not respond under the new treatment, the standard treatment only responders;
4) those who would not respond under either treatment assignment, the non-responders.

The principal causal effect is defined as a comparison of potential outcomes of primary interest within a principal stratum. In a comparison of the duration of response among responders, the treatment difference among patients who would have had a response in either treatment assignment, that is, true responders, is a matter of concern, because the potential values for the duration of response under two treatments are defined only for this subgroup. The key property of the principal stratification is that it is based on the stratification by the baseline potential characteristics of each patient and is not affected by treatment. Rubin [4,5] has called this causal parameter the survivor average causal effect in the context of censored quality-of-life (QOL) data due to death.

In this article, we propose an estimation method for the average causal effect among subgroups defined by a post-treatment variable, the responder average causal effect (RACE). It is important to note that we cannot directly observe the principal stratum to which a patient belongs because the indicator of whether a patient would have responded to the other treatment is a counterfactual variable. Therefore, our approach to this problem is to attempt to predict the probability of a response in each treatment group as a function of covariates and estimate the treatment difference among patients who would have responded to either treatment.

A closely related estimation method for the principal causal effect has been proposed by Gilbert *et al.* [6]. Zhang and Rubin [7] have considered the problem of truncation by death in randomized experiments and derived large sample bounds for the principal causal effect, with or without various identification assumptions. Our approach differs from their approaches in incorporating information from variables related to the post-treatment variable (response) and outcome (duration of response). Furthermore, our approach does not require the assumption which rules out the existence of patients who would respond under control treatment but would not respond under new treatment. This assumption, which is similar to the monotonicity assumption [8], may be reasonable in a placebo controlled study, but is not reasonable in an active controlled study.

Estimation of the average causal effect among responders

The definition of principal causal effects

Consider a randomized clinical trial for cancer treatments with two drug treatment conditions – a standard treatment and a new treatment, and two outcomes: an indicator of response to the drug and the duration of response. We assume that the prerandomization or time-dependent covariates are available. We also assume that there is full compliance and no unintended missing data. The objective is to draw inferences about the effect of treatment on the duration of response. Some patients, however, will not respond to the treatment, with the result that the duration of response is not defined.

We define the potential outcomes of the study patients. Let $\boldsymbol{Z}$ be the vector of treatment assignments for the N randomized patients, with ith element Z_i ($Z_i = 1$ for a new treatment; $Z_i = 0$ for a standard treatment). Let $\boldsymbol{R}(\boldsymbol{Z})$ be the N-vector with ith element $R_i(\boldsymbol{Z})$, which is the indicator of whether the ith patient would respond given $\boldsymbol{Z}$. For patients with $R_i(\boldsymbol{Z}) = 1$, let $Y_i(\boldsymbol{Z})$ be the duration of response given $\boldsymbol{Z}$. In order to limit the possible potential outcomes for each patient, we adopt Rubin's [9] stable unit treatment value assumption (SUTVA) throughout. It states that $R_i(\boldsymbol{Z}) = R_i(\boldsymbol{Z}')$ whenever $Z_i = Z_i'$, and $Y_i(\boldsymbol{Z}) = Y_i(\boldsymbol{Z}')$ whenever $Z_i = Z_i'$ and $R_i(Z_i) = R_i'(Z_i) = 1$. SUTVA implies that potential outcomes for each patient i are unrelated to the assignment $Z_j (j \neq i)$ of other patients, and allows $R_i(\boldsymbol{Z})$ and $Y_i(\boldsymbol{Z})$ to be written as $R_i(Z_i)$ and $Y_i(Z_i)$, respectively. Therefore, under SUTVA, each patient has two potential outcomes for response ($R_i(1)$, $R_i(0)$), and at most two potential outcomes for duration of response ($Y_i(1)$, $Y_i(0)$). For each patient, only one of $R_i(1)$ or $R_i(0)$ is observed. Note that $Y_i(1)\{Y_i(0)\}$ is defined only if $R_i(1) = 1$ $\{R_i(0) = 1\}$. We will also

assume the consistency assumption that, for every individual i, if the actual value of Z_i turns out to be z_i, then the value that R (or Y) would take on if Z_i were z_i is equal to the actual value of R (or Y). This assumption relates the observed outcome to the potential outcomes.

The definition of the average causal effect of treatment on the response is straightforward: $E[R_i(1) - R_i(0)]$, that is, the difference between the average of the response had all patients taken the new treatment and the average of the response had all patients taken the standard treatment [9–11]. This unobservable quantity can be obtained from the observable parameter by $E(R_i|Z_i = 1) - E(R_i|Z_i = 0)$, when the random assignment of treatments is carried out correctly.

Drawing causal inferences about the effect of the treatment on Y is more problematic. A standard method adjusts for the post-treatment variable (R) using the difference between the distributions $E(Y_i|Z_i = 1,\ R_i = 1)$ and $E(Y_i|Z_i = 0,\ R_i = 1)$. This comparison, however, is not a causal parameter, because the two subgroups, $Z_i = 1,\ R_i = 1$ and $Z_i = 0,\ R_i = 1$, will not be comparable unless the event of response is random [1]. To overcome this problem, Frangakis and Rubin [3] have proposed the principal causal effect that is defined as a comparison of potential outcomes under standard versus new treatment within a principal stratum:

$$E[Y_i(1) - Y_i(0) \mid R_i(1) = R_i(0) = 1] \tag{1}$$

As was suggested in Rubin [4,5], the most meaningful inferences about the causal effects on Y can be drawn only for this subgroup, because both $Y_i(1)$ and $Y_i(0)$ are defined only for this subgroup. This population level causal parameter is the effect of the treatment on the duration of response (Y) for a common set of patients, that is, patients who would respond under both treatments. Therefore, this parameter does not suffer from the complications of the standard post-treatment-adjusted one.

Potential values $R_i(1)$ and $R_i(0)$ were also used by Robins and Greenland [2], but, like Rosenbaum [1], they did not use those values to define causal effects adjusted for the post-treatment variable. Instead, they used a framework where both the treatment and the post-treatment variable are controllable, and defined counterfactual values of outcomes Y that would have been observed under assignment to treatment Z and if the post-treatment variable somehow were simultaneously forced to attain a value. In such an approach, the duration of response is "missing" among patients who have not responded, and causal estimands can be defined by comparing the distribution between the randomized groups. This framework is not compatible with the studies we consider, which do not directly control the post-treatment variable. Specifically, the duration of response among patients who have not responded to chemotherapy is not really missing data, which would imply a hidden value, but is nonexistent and is simply undefined.

Proposed estimation method

The primary estimand of interest is the difference in outcome Y in the group of patients that would have responded under both treatments, defined by Equation (1). This local average treatment effect can be written as follows:

$$\mu = \frac{E[\{Y_i(1) - Y_i(0)\}R_i(0)R_i(1)]}{E[R_i(0)R_i(1)]} \tag{2}$$

The quantity $R_i(0)R_i(1)$ in both the numerator and denominator of Equation (2) takes the value of one for any patient who would have responded under both treatments and takes the value of zero for all other patients. It is not possible to estimate Equation (2) without introducing assumptions, because the joint distributions involved in the numerator and denominator of Equation (2) are not observable. For example, when the treatment has no effects on response, that is, $R_i(z) = R_i(1 - z)$, we can estimate Equation (2) from the observed data as

$$\frac{\sum_j Y_j(1)R_j(1)}{\sum_j R_j(1)} - \frac{\sum_k Y_k(0)R_k(0)}{\sum_k R_k(0)} \tag{3}$$

where j indexes over patients assigned to group $z = 1$ and k indexes over patients assigned to group $z = 0$. However, if the treatment has any effect on response, the estimator Equation (3) from the observed responders will in general be a biased estimate of the causal parameter owing to the post-treatment selection bias.

In order to identify Equation (2), we make the following assumption about the potential outcomes:

$$\Pr[R_i(1-z) = 1 \mid R_i(z), Y_i(z), X_i] = \Pr[R_i(1-z) = 1 \mid X_i] \tag{4}$$

where X_i represents the prerandomization or time-dependent covariates. This assumption means that the probability that the response would have been observed had the patient received the other treatment can be explained only by measured covariates X_i. Let $w_i(z) = E[R_i(z)|X_i]$ be the expected value of $R_i(z)$ conditional on X_i for $z = 0,1$. Then, under the assumption of Equation (4), we have

$$\begin{aligned} &E[Y_i(z)R_i(z)R_i(1-z) \mid X_i] \\ &= E[Y_i(z)R_i(z) \mid X_i]E[R_i(1-z) \mid X_i] \\ &= E[Y_i(z)R_i(z) \mid X_i]w_i(1-z) \\ &= E[Y_i(z)R_i(z)w_i(1-z) \mid X_i] \end{aligned}$$

From this equation, conditional on X_i and with a consistent estimator $\hat{w}_i(z)$ of $w_i(z)$ for $z = 0,1$, an estimator of Equation (2) is given by

$$\hat{\mu} = \frac{\sum_j Y_j(1)R_j(1)\hat{w}_j(0)}{\sum_j R_j(1)\hat{w}_j(0)} - \frac{\sum_k Y_k(0)R_k(0)\hat{w}_k(1)}{\sum_k R_k(0)\hat{w}_k(1)} \quad (5)$$

where j indexes over patients assigned to group $z = 1$ and k indexes over patients assigned to group $z = 0$.

Although the probabilities of response under the other treatment are unknown, we can predict them from the data in each treatment group. Therefore, our proposed estimation procedure for Equation (2) consists of the following three steps:

1) Modelling: A model such as logistic regression is used to predict the probability of response in each treatment group as a function of covariates.
2) Prediction: Using the estimates of the regression parameters in the other treatment group estimated in step (1), the probability that the response would have occurred had the patient received the other treatment is predicted in each patient.
3) Weighting: The usual analysis comparing the duration of response between treatment groups (ie, estimation of the difference in means) is conducted among the observed responders using the individual-specific weight, which is the estimated probability in step (2).

We provide an alternative explanation of the above step (3). We assume the following causal model for the potential outcomes on principal stratum of the true responders:

$$E[Y_i(z) \mid R_i(1) = R_i(0) = 1] = \beta_z \quad (6)$$

where β_z ($z = 0,1$) is the mean duration of response in each treatment group. We contrast the causal model (6) with the following association model for the observed responders:

$$E[Y_i \mid R_i = 1, Z_i] = \beta_0'(1 - Z_i) + \beta_1' Z_i \quad (7)$$

Assuming no other bias such as measurement error, we can unbiasedly estimate the associational parameter $\beta' = (\beta_0', \beta_1')$ by fitting Equation (7) to the observed data. If there is no post-treatment selection bias, the parameters of models (6) and (7) are equal. As a consequence, associational estimate of β' is also an unbiased estimate of the causal parameter $\beta = (\beta_0, \beta_1)$. If the treatment has any effect on response, then $\beta \neq \beta'$ and unweighted estimate of β' is a biased estimate of the causal parameter β owing to the post-treatment selection bias. However, even when event of response is not random, if the assumption (4) is true, one can obtain unbiased estimate of the causal parameter β of model (6) by fitting the association model (7) using individual-specific weights $\hat{\Pr}(R_i(1 - Z_i) = 1|X_i)$. Again, in practice, individual-specific weight is unknown and one must estimate it from the data by specifying a model.

The use of estimated weights induces within-individual correlation, which invalidates the model-based standard error estimates outputted by many standard statistical packages. Two methods are used to construct the confidence intervals for the weighted estimator. The first is based on a robust variance estimate [12,13]. The robust variance estimator provides conservative confidence intervals for the parameter of interest θ, that is, the 95% Wald confidence intervals calculated as $\theta \pm 1.96 \times$ (robust standard error) is guaranteed to cover the true value θ at least 95% of the time in large samples [14,15]. The robust intervals are conservative because they do not account for the fact that the weights are estimated, and estimating the weights shrinks the variance of our weighted estimator. The second method is based on robust variance that accounts for the variability of the weights (see Appendix). The observation that a weighted estimator that uses the estimated weights has smaller variance than one that uses the true weights has been discussed by Robins *et al.* [16] and a series of papers by Rubin and Thomas [17–19].

Simulation studies

To evaluate the performance of the proposed estimation method, we carried out simulation studies. We simulated data from two treatment groups, coded as $z = 0$ (standard treatment) or $z = 1$ (new treatment). The simulations were based on 1000 replications, so that the estimated coverage probability of a true 95% confidence interval would have a simulation accuracy of approximately 1.35%. For each subject i, a potential outcome variable under the assigned group z, $Y_i(z)$, was generated via the linear model, $Y_i(z|x_i, \varepsilon_i) = \beta_{0,z} + x_i + \varepsilon_i$, where $(\beta_{0,0}, \beta_{0,1}) = (50,60)$. A covariate X_i was generated from a normal distribution with a mean of 10 and a standard deviation of 20. The random error ϵ_i was generated from a normal distribution with a mean of zero and a standard deviation of 5. For each subject i, a potential outcome variable under the other treatment, $Y_i(1 - z)$, was also generated from the above model.

For each subject i, a potential response indicator $R_i(0)$ under the standard treatment was generated via the logistic regression model

$$\Pr(R_i(0) = 1 \mid x_i) = \frac{\exp(\alpha_{0,0} + \alpha_1 x_i)}{1 + \exp(\alpha_{0,0} + \alpha_1 x_i)} \quad (8)$$

In model (8), $\alpha_1 = \log(1.07)$, so that 10-fold increases in X_i produces two-fold increases in the odds of response. $\alpha_{0,0} = -0.08, -0.69, -1.28, -1.93$ and -2.70, so that the probability of response under the standard treatment was nearly 60%, 50%, 40%, 30% and 20%, respectively. For the potential response under the new treatment, the following logistic regression model was assumed

$$\Pr(R_i(1)=1 \mid x_i, y_i(0)r_i(0)) = \frac{\exp(\alpha_{0,1} + \alpha_1 x_i + \alpha_2 y_i(0)r_i(0))}{1+\exp(\alpha_{0,1} + \alpha_1 x_i + \alpha_2 y_i(0)r_i(0))} \quad (9)$$

$\alpha_{0,1} = 1.35, 0.58, -0.08, -0.69$ and -1.28, so that the probability of response under the new treatment was nearly 80%, 70%, 60%, 50% and 40% when $\alpha_2 = 0$, respectively. In model (9), two situations were considered: $\alpha_2 = 0$ (situation A), corresponding to the assumption (4), and $\alpha_2 \neq 0$ (situation B), corresponding to a departure from the assumption (4). The selection bias parameter α_2 can be interpreted as the conditional log-odds ratio for response under the new treatment between subjects who differ by 1 in $y_i(0)r_i(0)$. In situation B, $\alpha_2 = 0.1$, which implies that, after conditioning on a covariate X_i, a 10-fold increase in the duration of response under the standard treatment produces an $\exp(1) = 2.72$ times increased odds of response under the new treatment. We are interested in the situation $\alpha_2 > 0$, because among subjects with the same covariate X, those with longer duration of response might be more likely to respond under the other treatment than those with shorter duration of response.

An equal sample size of 100 for each group was randomly generated (total sample size was 200). In situation A, we compared the results from the standard method whose analysis model is given in Equation (7) with those from the proposed method in which weights were estimated by the logistic regression model that included X_i as a covariate. In situation B, only the proposed method was applied. For both situations, the result from the subjects who had a response under both treatments, that is, a true responder stratum, was regarded as a true value in each replication. Therefore, the average true treatment effect for duration of response was $10(=\beta_{0,1} - \beta_{0,0} = 60 - 50)$.

Table 1 shows the results for the case of $\alpha_2 = 0$ in model (9). Each row of Table 1 reports the Monte Carlo mean bias, mean squared error (MSE), and coverage probability of the nominal 95% large sample confidence intervals, for the estimate of difference in Y_i according to the combinations of the response rate in each group. Examining rows 1–5 of Table 1, one can see that under the assumption (4) the proposed estimator is nearly unbiased, while the standard one is largely biased. For both methods, MSE is increasing with the decrease of the numbers of responders. The coverage probabilities for the proposed estimator based on the robust variance, which accounts for the variability of the weights, are close to the nominal level of 95%. One can also see that ignoring the fact that the weights are estimated leads to conservative coverage probability in all situations. Under-coverage rate in row 5 is due to small sample sizes of responders. The bias of the standard estimator is also reflected in the smaller coverage probabilities. Examining rows 6–7 of Table 1, we observe that both methods give unbiased estimators, as expected, when the response rates are equal between the treatment groups.

Table 2 shows the results for the case of $\alpha_2 = 0.1$ in model (9). Examining rows 6–7 of Table 2, we observe that, even in situation B, the proposed estimator is unbiased when the response rates are equal between the treatment groups. The coverage probabilities based on the robust variance, which accounts for the variability of the weights, are close to the nominal level of 95%. However, examining rows 1–5 of Table 2, one can see that the proposed estimator is slightly biased when the assumption (4) is not satisfied. The small degree of bias was due to the fact that, in the above simulation, the weight

Table 1 Simulation results (Ignorable missingness)

	Response rate		Proposed method				Standard method		
No	New	Standard	Bias	MSE	95% coverage[a]	95% coverage[b]	Bias	MSE	95% coverage
1	80%	60%	0.01	11.87	94.5%	96.2%	−4.01	29.88	87.6%
2	70%	50%	0.03	14.74	95.6%	96.8%	−4.21	36.15	83.8%
3	60%	40%	−0.05	18.50	95.8%	96.7%	−4.35	41.43	82.9%
4	50%	30%	−0.12	29.35	95.3%	95.5%	−4.97	61.10	81.0%
5	40%	20%	−0.01	52.92	92.6%	93.4%	−5.57	94.55	81.0%
6	60%	60%	−0.06	13.90	95.3%	96.8%	0.01	16.17	97.1%
7	40%	40%	−0.15	25.63	95.2%	96.7%	−0.18	31.54	96.4%

[a]Robust 95% confidence intervals, which account for variability of weights.
[b]Robust 95% confidence intervals, which do not account for variability of weights.

Table 2 Simulation results (Non-ignorable missingness)

		Response rate		Proposed method			
No	α_2	New	Standard	Bias	MSE	95% coverage[a]	95% coverage[b]
1		80%	60%	0.35	12.45	98.3%	98.9%
2		70%	50%	0.84	16.32	97.6%	98.2%
3		60%	40%	1.02	20.25	98.2%	98.6%
4	0.1	50%	30%	1.36	32.68	96.5%	97.2%
5		40%	20%	0.98	42.36	94.8%	95.6%
6		60%	60%	0.05	15.41	97.1%	97.6%
7		40%	40%	−0.07	23.51	97.8%	98.2%

[a]Robust 95% confidence intervals, which account for variability of weights.
[b]Robust 95% confidence intervals, which do not account for variability of weights.

prediction model was misspecified in only standard treatment group. The bias of our estimator will, in general, be larger as the weight prediction model is mis-specified in both groups. To reduce this bias of our estimator, it is important to collect covariates which satisfy the assumption (4), and to include these covariates as explanatory variables in the weight prediction model.

Application to advanced non-small-cell lung cancer trial data

Our illustrative application is a randomized phase III clinical trial of advanced non-small-cell Lung cancer (NSCLC) Full details on the design, conduct, and the main clinical results have been reported [20]. A total of 398 patients with previously untreated NSCLC were randomized to receive Cisplatin + Irinotecan (CPT-P), Cisplatin + Vindesine (VDS-P), or Irinotecan alone in order to compare the survival rate. Here we used the first two treatment groups to compare the duration of response among responders. The response rate was 43.7% (55/126) for patients in the CPT-P group and 31.7% (38/120) for those in the VDS-P group. The difference in response rates was 12.0% with the 95% confidence interval (−0.03%, 24.0%).

We used a logistic regression model to predict the probability of response in each treatment group. Sex, age, stage and performance status were used as the covariates. Figure 1 shows the distribution of estimates of weight in each group, which is the probability of response that would have occurred had the patient received the other treatment.

Table 3 shows the average duration of response among responders estimated by the proposed method and the standard one. The average difference for the duration of response estimated by the standard method was 9.5 (days), which would be biased because of the difference in response rates between the treatment groups. The estimated difference by the proposed method was 16.1 (days) with the robust 95% confidence interval (−14.6,46.7). The narrower intervals were obtained by accounting for the variability of the weights.

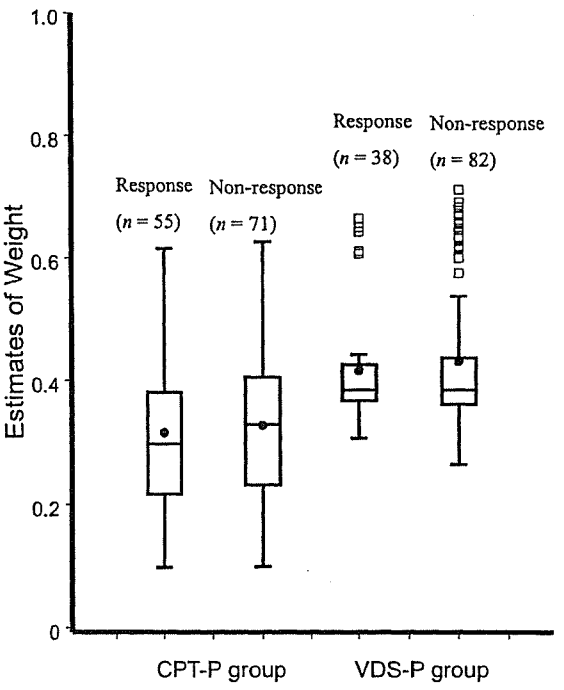

Figure 1 Distribution of weights (the probability of response that would have occurred had the patient received the other treatment) according to the response status in each treatment group. Each box shows the location of the mean (●), median (middle horizontal bar), and quartiles (border horizontal bars). Vertical lines extend to the most extreme observations which are no more than 1.5 × IQR (interquartile range) beyond the quartiles. Observations beyond the vertical lines are plotted individually (□)