efficacy are important. Using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, evaluation of tumor regression effects on target lesions is recommended. However, in cases of severe infiltrative pancreatic carcinoma which includes multiple non-target lesions (*e.g.* in the surrounding lymph nodes and nervous plexus), examination of an overall tumor response is difficult to evaluate with computed tomography (CT). Even after successful treatments, tumor reduction may appear inadequate due to copious fibrillary elements present in pancreatic carcinomas. In addition to this, changes in tumor marker levels may be inconsistent in pancreatic carcinomas, adding to the difficulty of judging the efficacy of radiotherapy and hyperthermic chemotherapy.

Recently, fluorodeoxyglucose positron emission tomography (PET) has been used in diagnostic imaging for several types of pancreatic carcinomas[1-4]. PET examinations have been used, not only for initial evaluations of differential diagnosis[3-5] and diagnosis of distant metastasis and recurrences, but also for qualitative diagnosis[6]. Several studies have shown that PET is useful for the characterization of pancreatic tumors, as well as for assessments of the efficacy of chemotherapy and outcomes[7,8]. The increased uptake of fluorine-18 fluorodeoxyglucose, due to enhanced glucose metabolism in cancer cells, is a sensitive marker of tumor viability. Because PET examinations evaluate the activity of cancer cells rather than tumor size, the current study was designed to investigate the usefulness of PET examinations in the evaluation of therapeutic effects and prognosis of unresectable pancreatic head carcinomas. This differs from other recent reports because the subject cases examined here were limited to pancreatic head cancers in which excision was difficult and which were accompanied by massive local invasion without distant metastasis[8-11].

Subjects and methods

Characteristics of all the cases are shown in Table I. This study included 18 patients (6 females and

Table I. Response of tumor markers, CT, PET and overall survival times.

Case No.	Age/ Sex	Stage (UICC)	CRT (%)	CA19-9 (u/ml)		DUPAN-2 (U/ml)		SUV_{max}		RRS (%)	ST (months)	Prognosis
				BT	AT	BT	AT	BT	AT			
1	75M	III	6.3	5	5	386	99	5.5	1.3	76.4	38	Deceased
2	63M	III	-4.2	1,760	134	479	224	5.4	2.3	57.4	20	Deceased
3	61F	III	11	968	57	25	25	5.9	2.8	52.5	31	Deceased
4	77M	III	15	63	31	42	39	8.5	3.8	55.3	10	Deceased
5	64M	III	21	12	5	25	25	6.9	2.6	47.8	31	Deceased
6	71M	III	21	501	91	25	25	6.9	3.7	46.4	7	Deceased
7	57F	III	19	342	20	25	31	3.5	2.5	28.6	26	Deceased
8	64M	III	0	1,310	62	150	46	4.9	3.1	36.7	9	Deceased
9	49M	III	3.1	1,350	51	196	64	4.5	2.4	46.7	64	Living
10	79M	III	11	365	104	66	27	8.4	3.9	53.6	30	Deceased
11	72F	III	16	645	45	217	133	4.3	2.1	51.2	27	Deceased
12	74F	III	17	5	5	1,600	575	6.1	3.9	36.1	9	Deceased
13	72F	III	18	125	32	1,120	25	4	2.5	37.5	15	Deceased
14	81M	III	25	4,330	86	25	25	3.2	2.1	34.4	20	Deceased
15	62M	III	26	1,100	20	108	25	11.1	4.6	58.2	13	Deceased
16	66M	III	26	3,570	71	66	27	4.6	2.1	54.3	14	Deceased
17	70M	III	32	2,150	36	42	39	4.1	3.1	24.4	14	Deceased
18	73F	III	17	1,940	994	994	20,000	5.1	4.5	31.4	5	Deceased

CRT: Contraction rate of a tumor; RRS: Reduction rate of SUV_{max}; BT: before treatment; AT: after treatment; ST: survival time.

12 males). The patients' average age was 61 years old (range: 49 to 79 years), and the Karnofsky performance status (PS) at the baseline was ≧ 80%. Subject cases were unresectable pancreatic head cancers diagnosed as TNM classification stage 3 (T4 NX M0) from imaging and operative findings. All cases received the same multidisciplinary treatment and had a measurable pretreatment target lesion evaluated with both CT and PET imaging. Laparotomy was performed on all cases to clarify presence of metastases in the liver and peritoneum. Needle biopsies revealed adenocarcinoma in all cases. For cases with obstructive jaundice (17 cases) and duodenal wall invasion (16 cases), bypass surgery was performed. Blood glucose levels were measured three times per day, and controlled at 150 mg/dl or less with insulin. Outcome parameters in this study were the change in the longest axis of the tumor in multidirectional computed tomography (MDCT) imaging, the change of maximum SUV values (SUV_{max}) in PET imaging, and changes in tumor markers. These examinations were performed both prior to treatments and in the third month after treatments. The longest axis of the target lesion in the pancreatic head was measured using a horizontal section (3 mm slice thickness) in dynamic contrasting MDCT. All patients were examined with a high-resolution, whole-body PET scanner. The patients fasted for more than 4 h before an intravenous injection of ^{18}F-FDG, and the acquisition of whole-body PET images was started 50 min after the injection. Data acquisition was performed in a two-dimensional imaging mode. Cut-off values for SUV_{max} were defined as 3.0. With regard to tumor markers, CA 19-9 (normal < 37 U/ml) was used as the primary marker, and DUPAN-2 (normal < 150 U/ml) was used in cases where no rise of CA 19-9 was observed. Observations were continued for 4.5 years or until the patients died, excluding one example. In addition to the above measurements, the relationship between these variables and disease prognosis was examined using Pearson's coefficient and log-rank test.

Multidisciplinary treatments

Multidisciplinary treatments in this department were as follows: biliary and/or intestinal tract bypass surgery with intra-operative irradiation (8-12 cm in diameter, 20-25 Gy, 15 MeV); postoperative external irradiation (25 times, for a total of 50 Gy); hyperthermia treatments using a Thermotron-RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan) with CDDP (a total of 100-120 mg) and MMC (a total of 16-20 mg) (50 min, 1 time per week, 4-5 times); and systemic chemotherapy using 5-fluorouracil (5-FU) (a total of 14 g) for 28 days (Fig. 1). Second-line therapies were not initiated until therapeutic efficacies were evaluated at the 3rd month post-treatment.

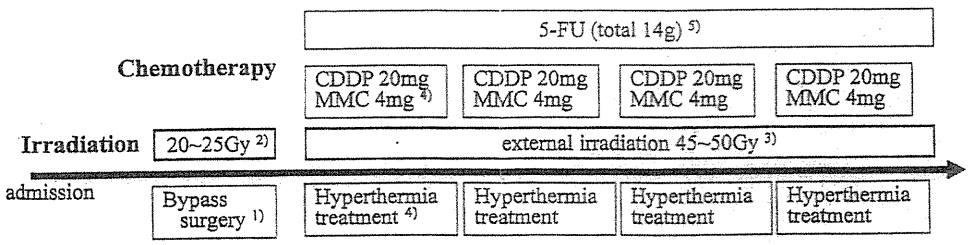

Fig. 1. 1) Biliary and/or gastric bypass surgery. 2) Intra-operative irradiation (20-25 Gy, 15 MeV). 3) Postoperative external irradiation (25 times, total of 50 Gy). 4) Hyperthermia treatment (RF-8) with CDDP (total of 100-120 mg) and MMC (total of 16-20 mg) (1 time per week, 4~5 times). 5) Systemic Chemotherapy using 5 FU (total of 14 g) for 28 days.

Hyperthermia treatments were delivered with an 8 MHz capacitive heating device. An electromagnetic field with power ranging from 1,200 to 1,400 W was used, depending on the patient's condition. This was applied between a pair of electrodes with diameters of 25 cm or 30 cm which were placed on the opposite sides of the target area. A saline solution maintained at 10 degrees Celsius degrees was circulated in boluses to avoid overheating of the skin.

Multidisciplinary treatments in this department appear to provide the following multiple advantages:

(A) Biliary bypass surgery helps prevent the occurrence of acute cholangitis and obstructive jaundice. Serious cholangitis developing during chemotherapy results in the interruption of treatment and adversely affects prognosis.

(B) Gastrointestinal anastomosis can help prevent duodenal stenosis or obstruction due to enterocolitis from radiation and tumor invasion.

(C) Hyperthermia is effective for hypoxic lesions with little effect on radiotherapy, and increases the uptake of anticancer drugs into tumor tissues.

(D) Irradiation (intra-operative and post-operative irradiation; total 75 Gy) provides not only antitumor effects, but also a reduction of cancer induced pain.

The therapeutic synergism of these multiple and complementary modalities appears to offer good results.

Results

No new metastases were found in any cases until treatment efficacy was evaluated at the 3rd month post-treatment. The average diameter of target lesions was 27 mm (range: 19 to 46 mm). Survival times ranged from 5 to 54 months. After undergoing multidisciplinary treatments, the average regression rate of the tumors was 15.6% (range: −4.2 to 32%) (Table I). A significant correlation between tumor reduction and prognosis was not observed (Pearson's r=-0.290, p-value=0.2636) (Fig. 2). Levels of CA

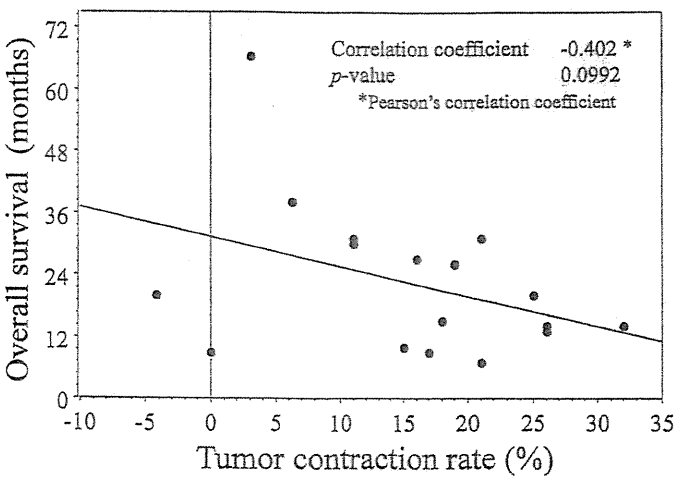

Fig. 2. Correlation of tumor reduction and prognosis. A significant correlation between the contraction rate of the pancreatic head cancer and overall survival was not observed (Pearson's r=-0.402, p-value=0.0992). *Pearson's correlation coefficient.

19-9 decreased in all cases post-treatment, and reached normal values in five cases (Table I). Similarly, no significant correlation was observed between the movement of tumor markers towards normal values and prognosis (Fig. 3). The average SUV_{max} value prior to treatment was 5.2 (Table I). After treatment, the SUV_{max} value decreased in all cases, and decreased to < 3.0 in seven cases. A significant correlation was found between post-treatment SUV_{max} values and a favorable prognosis (Pearson's r= -0.694, p-value=0.0014) (Fig. 4). In contrast, no correlation was found between reduced values of

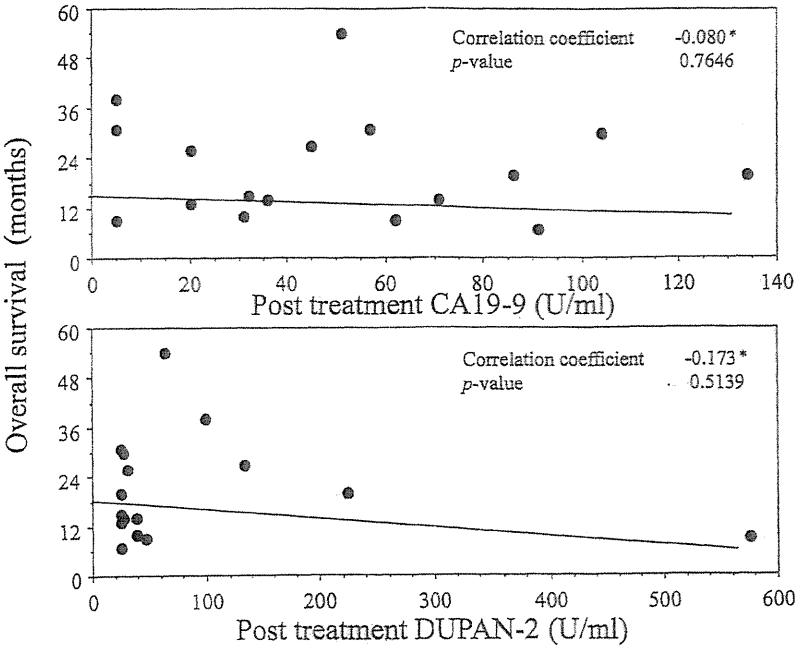

Fig. 3. Correlation of post-treatment tumor markers and prognosis. A significant correlation between post-treatment tumor markers (CA19-9 and DUPAN-2) and overall survival was not observed (Pearson's r=-0.402, p-value=0.0992). *Pearson's correlation coefficient.

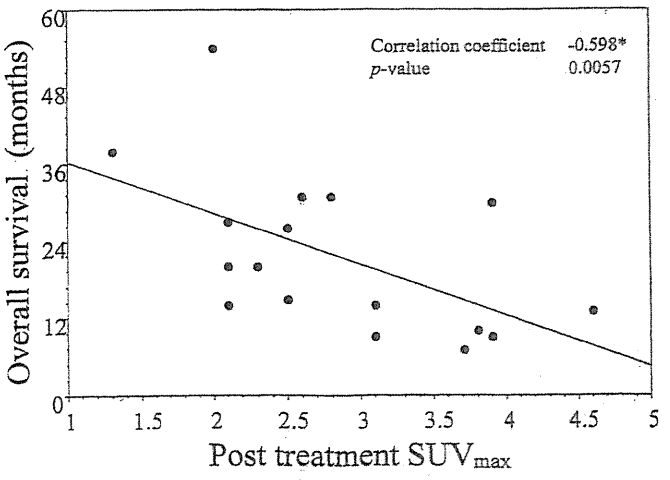

Fig. 4. Correlation of post-treatment SUV_{max} values and prognosis. A significant correlation was found between post-treatment SUV_{max} values and prognosis (Pearson's r=-0.598, p-value= 0.057). *Pearson's correlation coefficient.

SUV_{max} and the overall survival (OS) time (Fig. 5). Fig. 6 shows patient survival curves divided into regions for $SUV_{max} < 3.0$ and $SUV_{max} \geqq 3.0$. There were significant differences between overall survival times for patients with post-treatment values of $SUV_{max} < 3.0$, and for $SUV_{max} \geqq 3.0$ (log-rank test ; p-value=0.032). The median survival time for patients with post-treatment values of $SUV_{max} < 3.0$ increased compared to those with a value of $SUV_{max} \geqq 3.0$ (26 vs. 9 months).

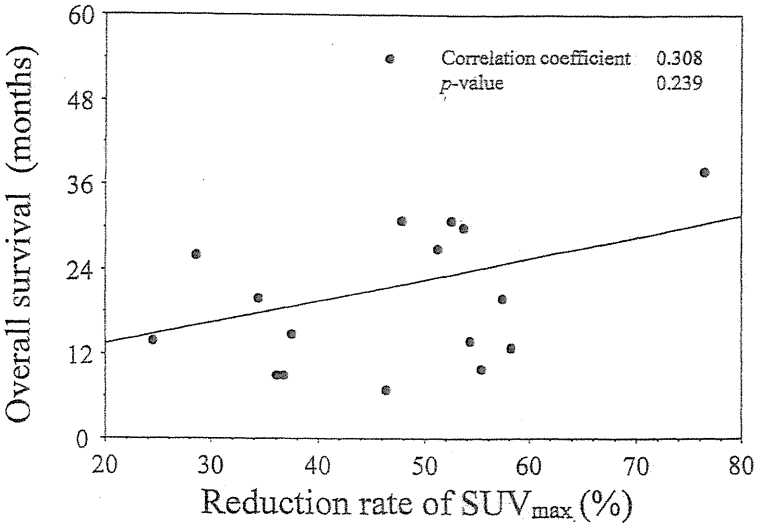

Fig. 5. Correlation of the reduction rate of SUV_{max} and prognosis. No significant correlation was found between the reduction rate of SUV_{max} and prognosis (Pearson's r=0.308, p-value=0.239).

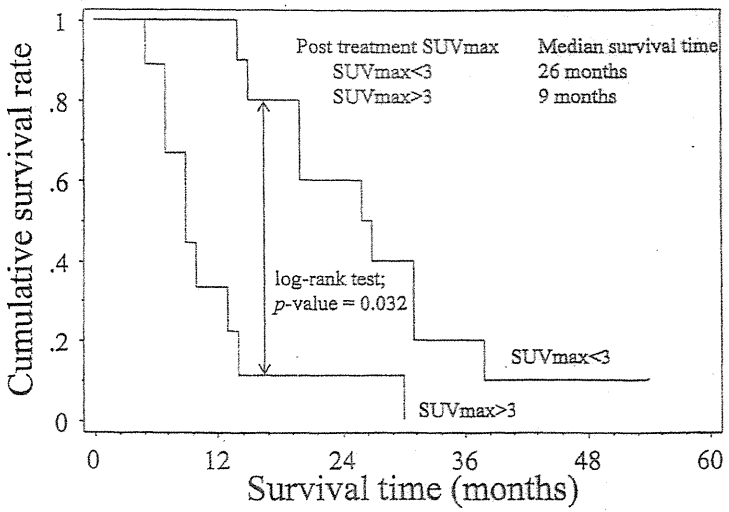

Fig. 6. Kaplan-Meier plot of overall survival times (OS) shows patient survival curves divided into $SUV_{max} < 3.0$ and $SUV_{max} \geqq 3.0$. There were significant differences between overall survival times (OS) for patients with post-treatment $SUV_{max} < 3.0$ and those with $SUV_{max} \geqq 3.0$ (log-rank test ; p-value=0.032). Median survival times of patients with post-treatment $SUV_{max} < 3.0$ increased compared to those with $SUV_{max} \geqq 3.0$ (26 vs. 9 months).

Discussion

Currently, the prognosis for unresectable pancreatic head carcinomas is dependent upon the degree of therapeutic response and the presence of distant metastasis. Following conventional treatment protocols, pancreatic carcinomas with distant metastases require systemic chemotherapy. In this study, multidisciplinary treatments were used for cases of pancreatic head cancer in which excision was difficult and which were accompanied by massive local invasions, including to the para-aortic lymph nodes. In short, these were severe cases for which a total, curative resection was considered impossible. The ultimate goal of this multidisciplinary treatment regimen was not simply tumor reduction with systemic chemotherapy, but rather annihilation of the primary carcinoma tissue itself. A sufficient control of the primary lesion is most important for reducing distant metastases and in obtaining long-term survival times. Currently, it is generally accepted that gemcitabine should be the standard first line chemotherapy drug for pancreatic cancer. However, 5-FU, platinum and MMC were used for these patients because using these drugs as the chemotherapeutic regimen of choice provided better hyperthermic sensitivity. Recently, studies have examined the hyperthermic sensitivity of GEM[12] and the timing of hyperthermia in relation to GEM treatments[13]. The question of whether hyperthermia using GEM provided improvements in tumor regression effect on target lesions was evaluated.

Following RECIST guidelines for solid tumors, tumor regression in the target lesions was evaluated, but in this study, no correlation was found between tumor reduction observed in CT and prognosis. PET examinations may be advantageous when compared to CTs for several reasons. First, retroperitoneal invasion and para-aortic lymph node metastasis often coalesce together in unresectable pancreatic cancer, making CT measurements of nearby target lesions difficult. With PET, this is done more accurately and reliably by measuring the SUV without concern for lesion positions. Second, even if a treatment achieves large-scale tumor cell destruction, because pancreatic carcinomas often have many fibrous components, the tumor may be difficult to shrink. In addition, there is a possibility that edema and inflammation due to irradiation and hyperthermia therapy may increase the tumor size. PET examination can evaluate carcinomatous metabolic activity without regard for potentially misleading issues of size. Finally, PET examinations allow the evaluation of distant metastasis simultaneously, and a more accurate disease localization can be achieved with PET/CT[14,15].

The evaluation method used to measure tumor markers and SUV_{max} is important. When the correlation with overall survival times is evaluated, measured values should be used, in contradiction to a previous study which used the response ratio of tumor markers and SUV_{max} according to European Organization for Research and Treatment of Cancer (EORTC) guidelines[14]. Cancer cells are certain to exist when the post-treatment SUV_{max} value is three or more, even if the response rate of SUV_{max} with treatment is 50%.

Reductions in tumor markers were thought to result from the efficacy of therapy, but CA 19-9 and DUPAN-2 were positive in 83.3% and 55.6% of the cases, respectively. PET examination was useful in cases of pancreatic carcinoma in which tumor markers did not rise. When tumor markers increase along with treatment, there is a high probability of distant metastases being present which were not seen in imaging. In addition, interpretation of a decrease state requires care and attention to the possibility that treatment of bile duct obstructions and acute cholangitis may have reduced tumor marker levels.

Pretreatment values of $SUV_{max} \geqq 3$ in PET imaging is necessary for the optimal evaluation of the therapeutic efficacy of pancreatic cancer treatments. In several studies, correlations between pre-treatment SUV_{max} values and the prognosis are still controversial[1,8], even though a significant correlation was not found in this study. Two studies showed that there was a significant correlation between a prognosis and FDG uptake after treatment, but that there was no relationship between prognosis and FDG uptake before treatment. Oku et al reported that FDG-PET imaging after radiotherapy is a good prognostic indicator for rectal cancer[16], and Brun et al reported the same results for head and neck squamous cell carcinomas[17]. Because PET examinations can simultaneously detect distant metastases (aside from intraperitoneal metastases) which may alter therapeutic strategies, such imaging should be strongly encouraged prior to treatment. With regard to prognostic predictions using SUV values of the primary lesion, SUV values should be evaluated in similar clinical stages and therapies. Even if the SUV_{max} value is less than 3 before treatment, a cancer with distant metastasis or a large size would show a worse prognosis. PET imaging has a sensitivity of 82-100% and a specificity of 67-100% for pancreatic carcinomas[18-22]. Previous several studies reported that the presence of tumors less than 2 cm in diameter and the presence of hyperglycemia may decrease diagnostic accuracy[23,24]. Tumor cellularity is one of factors influencing FDG uptake. Scirrhous tumors have a low cellularity, and thus should show lower accumulations of FDG[25,26]. In general, unresectable pancreatic carcinomas have a large size (in this study, the average tumor diameter was 27 mm) and severe local invasions, and the occurrences of false negatives from PET imaging may be low[27]. Blood glucose levels should be noted in evaluations of PET examinations. The effect of glucose levels in FDG-PET oncology is known, but the management of non-fasting patients or diabetic patients remains controversial. In this study, four subjects had diabetes mellitus, but no false negatives were found, suggesting that pre-examination glucose control may assist in the reduction of false negatives. In particular, in the presence of chronic hyperglycemia (not acute hyperglycemia), the adverse effect caused by high glucose levels was minimal in human adenocarcinoma cell models, except for small lesions (15 mm in size)[28,29]. Friess et al suggested that there was no significant difference between the high blood glucose group and the low one[30]. The only necessity is an instruction to patients to fast, and to check glucose levels immediately prior to FDG injection[31].

In order to avoid the influence of localized inflammation and edema from radiotherapy and hyperthermia treatments, PET imaging was performed during the 3rd month after the final treatment in the protocol. In addition, no additional chemotherapy was given during this period, because it is very likely that chemotherapy decreases carcinomatous carbohydrate metabolism, potentially altering PET accuracy. PET examination in the setting of recent chemotherapy may substantially increase the rate of false negative images.

In conclusion, FDG-PET examinations may be superior to tumor regression measured with CT and measurements of tumor markers after treatments. FDG-PET can be used to evaluate the efficacy and prognosis of unresectable pancreatic carcinoma (TNM classification stage3) cases in the 3rd month after a multidisciplinary treatment protocol. In addition, if post-treatment SUV_{max} values can be reduced to less than 3.0 by multidisciplinary treatments, this may translate to a more favorable prognosis.

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Abstract in Japanese

切除不能膵癌の集学的治療効果判定における ^{18}F-fluorodeoxyglucose positron tomography の有用性

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要　　旨: 通常，切除不能膵癌における原発巣の治療効果判定には CT 検査を用いることが多い．最近，^{18}F-fluorodeoxyglucose positron tomography (以下 PET) 検査は膵癌の存在診断だけでなく，腫瘍の質的評価が可能なため，遠隔転移や再発部位の検索にも用いられている．本研究では，集学的治療を受けた切除不能膵癌症例の治療効果と予後の判定に PET 検査が有用かを検討した．この研究は prospective cohort study である．対象の 18 症例全てが，TNM 分類 Stage3 の切除不能膵頭部癌である．集学的治療としてバイパス手術，放射線療法 (術中と術後)，温熱化学療法の全てを施行されている．効果判定の項目として，腫瘍マーカー値，腫瘍の縮小率，SUV_{max} (maximum standardized uptake value) を用い，それらと患者予後との関係を検討した．統計学的解析にはピアソン相関と Kaplan-Meyer 生存曲線を使用した．CT 検査による腫瘍サイズの縮小率と腫瘍マーカーの推移は患者予後と相関しなかった．治療後の SUV_{max} は予後と良く相関し，SUV_{max} 3 未満の症例は，特に生存期間が延長した．PET 検査は集学的治療を施行された切除不能膵癌の予後評価に有用である．

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and "Exact Test" produced by Prof. S. Aoki (http://aoki2.si.gunma-u.ac.jp/exact/exact.html). The χ^2 test, Fisher exact test probability, and Mann-Whitney U test were used as appropriate. $P \leq 0.05$ was considered as statistically significant.

RESULTS

The incidence of chyle leak was 8.0% (11/138) in all patients. The timing of start for enteral feeding was significantly earlier in the fast-track group (median, day 3; range, days 3–4) compared with the traditional group (median, day 5; range, days 3–16; $P < 0.001$). Incidence of chyle leak was significantly increased in the fast-track group compared to the traditional group (13.3% vs 1.6%, respectively, $P = 0.004$).

In comparison of clinical features, there were no significant differences between the patients with chyle leak and those without chyle leak except for early enteral feeding (timing of enteral feeding start was postoperative day 3 or 4; Table 1).

Five-day fast therapy with total parenteral nutrition was effective for all of our patients with chyle leak. No patients required the use of somatostatin analogs. Overall length of the hospital stay of the patients in the fast-track group without drain infection was significantly longer if there was a chyle leak (median hospital stay, 21 days; range, 15–28 days) compared with the patients without chyle leak (median hospital stay, 11 days; range, 5–23 days; $P < 0.001$).

DISCUSSION

In this study, we showed that the overall incidence of chyle leak in the patients who underwent DP was 8.0%. Only early enteral feeding was associated with the development of chyle leak. Chyle leak was one risk factor for prolonged hospital stay but could be successfully treated with dietary measures.

Several authors suggest lymph node dissection, neoplastic diseases, and chronic pancreatitis as risk factors for the development of chyle leak.[6–8] Malik et al[5] and van der Gaag et al[8] doubt that early enteral feeding affected the incidence of chyle leak in patients who underwent pancreatic resection (PD and DP). Our study showed that early enteral feeding was associated with chyle leak after DP.

Malik et al suggested that the mechanism of action leading to chyle leak may be due to the lipid content of the enteral feed, which may keep the visceral lymphatic channels that have been divided as part of the standard resection open, thus leading to the persistent chyle leak.[5] Chyle leak did occasionally occur despite a period of gut rest; however, it was during this period of early feeding that chyle leak became most problematic. This leads to the recognition that the likely source of this chyle was an early stimulation of the lymphatic drainage of the small intestine. Our results support this hypothesis. Our results also suggest that the visceral lymphatic channels may have remained open at least until 4 days postoperatively because all of our patients with chyle leak were started on enteral feeds on day 3 or 4.

There is little doubt that enteral nutrition carries advantages over total parenteral nutritional support. It is also easier to administer. There may be preservation of gut barrier function with enteral feeding, and it may prevent structural alterations induced by starvation and injury. However, several randomized controlled trials demonstrated that immediate postoperative enteral feeding through a jejunostomy tube is not beneficial in patients undergoing PD and is even associated with impaired respiratory mechanics and postoperative mobility.[10]

We did not deny a clinical benefit of the fast-track program for DP; however, further studies would be needed for establishing the appropriate time to start enteral feeding after pancreatic surgery.

Several authors have also shown that surgical devices such as ultrasound scissors or a vessel sealing system were not useful in preventing chyle leak.[5] In our study, we could not find benefit for using these devices in preventing chyle leak.

In conclusion, the overall incidence of chyle leak in the patients who underwent DP was 8.0% in our institute. Early enteral feeding may be associated with postoperative chyle leak. Further investigation is needed for establishing the appropriate time to start enteral feeding after DP.

The authors declare no conflict of interest.

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Long-Term Results of Surgical Resection After Preoperative Chemoradiation in Patients With Pancreatic Cancer

To the Editor:

We would like to report the long-term results of surgical resection after preoperative chemoradiation therapy (CRT) for patients with pancreatic cancer that extended beyond the pancreas.

Pancreatic cancer is a lethal disease with poor prognosis, even in patients who have undergone resection with curative intent. Bradley[1] proposed that further improvements in the numbers of long-term survivors are unlikely to result from modifications of current surgical techniques. To achieve a 5-year survival rate exceeding 50% in patients with pancreatic cancer, Traverso[2] advocated appropriate patient selection for curative resection by accurate staging, balanced resection, centralized treatment in high-volume centers, and the use of an effective adjuvant or neoadjuvant therapy. We previously reported that preoperative CRT was able to increase the resectability rate with clear margins and to decrease the rate of metastatic lymph nodes, resulting in improved prognosis of curative cases with pancreatic cancer that extended beyond the pancreas.[3,4] Herein, we investigate actual survival results at 5 years after surgical resection after preoperative CRT for patients with pancreatic cancer that extended beyond the pancreas.

PATIENTS

Among 175 patients with a clinical diagnosis of pancreatic cancer, 87 consecutive patients with pancreatic cancer were radiologically defined as having a resectable tumor between 2000 and 2005. Among them, 68 patients underwent pancreatic resection. The preoperative CRT was performed in 35 patients who had pancreatic cancer between 2001 and 2004 as described in the previous paper.[3,4] Of these 35 patients, 27 underwent surgical resection (preoperative CRT group). Among the other 52 patients, 41 underwent surgical resection, and these were classified as the surgery-alone group comprising patients with pancreatic cancer who had a tumor limited to the pancreas (T1/T2 TNM staging) between 2001 and 2004 and the resected cases from 2000 and from 2005. From these 68 resected patients, 48 (18 in the preoperative CRT group and 30 in the surgery-only group) with residual tumor staging of R0/1 were selected. The actual 5-year survival and disease-free survival rates were compared for the following 3 groups: (1) preoperative CRT and surgery-alone groups, including unresected patients; (2) preoperative CRT and surgery-alone groups, resected patients only; and (3) preoperative CRT and surgery-alone groups, selected patients who underwent curative resection (residual tumor grading; R0/1). No patient received adjuvant chemotherapy. Informed consent was obtained from all patients according to institutional regulations, and this study was approved by the local ethics committee. Actual 5-year survival and disease-free survival rates were calculated from the start of study treatment until death or the final date of follow-up and determined by the Kaplan-Meier method. All patients had a minimum follow-up of 65 months or were observed until death. Results were considered significant at $P < 0.05$.

RESULTS

Comparisons of Actual Survival and Disease-Free Survival Rates

As shown in Figure 1A, there was no significant difference in actual survival curves between the total preoperative CRT group (n = 35) and the surgery-alone group (n = 52). The difference in 5-year survival rates between the preoperative CRT and surgery-alone groups was 17%, in favor of the former. Figure 1B shows that the actual survival curve of the preoperative CRT group comprising resected patients only (n = 27) tended to be better relative to the surgery-alone group (n = 41), although the difference (23% at 5 years) did not quite reach statistical significance ($P = 0.053$). When the patients who underwent curative resection (R0/1) were selected, there was a significant difference in the actual survival curves between the preoperative CRT group (n = 18) and surgery-alone group (n = 30; $P = 0.0228$; Fig. 1C). The difference in 5-year survival rates reached 34%. As shown in Figure 1D, a significant difference in the disease-free

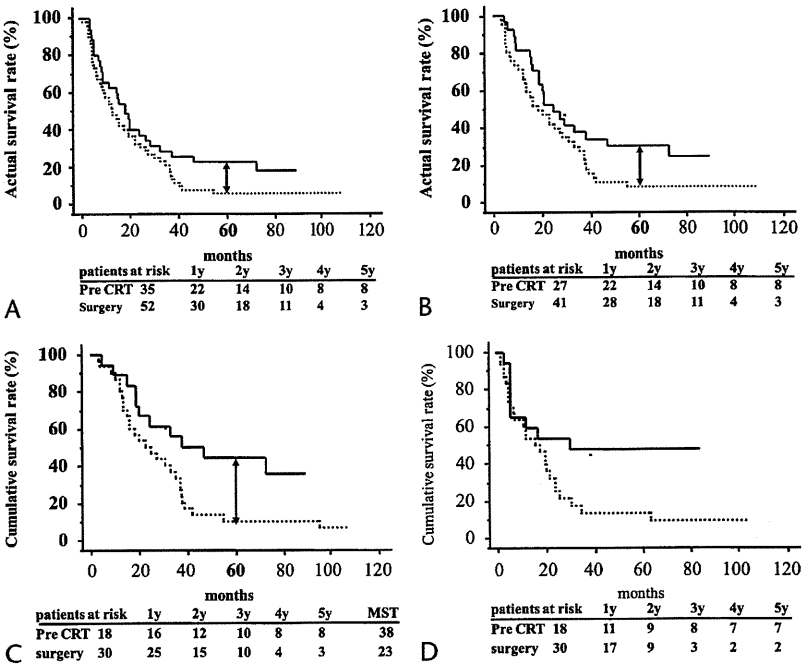

FIGURE 1. A, Actual survival curves of preoperative CRT (n = 27) and surgery-alone (n = 41) groups including unresectable patients. Solid line, preoperative CRT group; broken line, surgery-alone group. Actual survival rates at 1 year, 3 years, and 5 years were 66%, 40%, and 23% in the preoperative CRT group versus 58%, 33%, and 6% in the surgery-alone group; $P = 0.09$. The median survival time in preoperative CRT and surgery-alone groups were 19 and 13.5 months, respectively. B, Actual survival curves of the preoperative CRT and surgery-alone groups comprising resected patients. Actual survival rates at 1 year, 3 years, and 5 years were 82%, 37%, and 30% in the preoperative CRT group versus 66%, 27%, and 7% in surgery-alone groups, $P = 0.053$. The median survival time in the preoperative CRT and surgery-alone groups were 23 and 17 months, respectively. C, Actual survival curves of preoperative CRT (n = 18) and surgery-alone (n = 30) groups selecting patients who underwent curative resection. Actual survival rates at 1 year, 3 years, and 5 years were 89%, 56%, and 44% in the preoperative CRT group versus 80%, 33%, and 10% in the surgery-alone group; $P = 0.0228$. The median survival time in the preoperative CRT and surgery-alone groups were 38 and 23 months, respectively. D, Actual disease-free survival curves of the preoperative CRT and surgery-alone groups selecting patients who underwent curative resection. Actual disease-free survival rates at 1 year, 3 years, and 5 years were 61%, 44%, and 39% in the preoperative CRT group (n = 18) versus 57%, 10%, and 7% in the surgery-alone group (n = 30); $P = 0.024$.

survival curve was also found between the 2 groups ($P = 0.024$).

Clinicopathological Features of Long-Term Survivors

Eleven patients survived longer than 5 years after surgical resection. Among them, 9 patients had negative lymph node metastasis or R0 resection. Only one patient underwent pancreatic surgery with combined resection of the celiac axis. There were 2 patients surviving with distant organ metastasis but not local recurrence at 5 years of follow-up.

DISCUSSION

In most of the patients with pancreatic cancer, the tumor is classified as unresectable at diagnosis, and only approximately 20% of patients are indicated for surgery. Even after "curative" resection, patients with pancreatic cancer face a 50% to 80% local recurrence rate and a 25% to 50% chance of developing distant metastases in the peritoneum and liver, resulting in an actual 5-year survival rate of approximately 10%.[1] Recently, some randomized studies have shown favorable results in patients with pancreatic cancer who underwent curative resection followed by adjuvant therapy, reporting median survival times within the range of 20.1 to 23.6 months.[5,6]

This retrospective study showed that actual 5-year survival rate in the preoperative CRT group comprising of R0/1 resection patients only was 44%, which was significantly superior to the 10% seen in the surgery-alone group. It is important to note that no patient received adjuvant chemotherapy, but patients with recurrent disease underwent weekly gemcitabine administration on recurrence. Bradley[1] stated that actual 5-year survival rate was only 10% in resected patients with pancreatic cancer in some studies performed between 1972 and 2002. When actual long-term patient survival rates after pancreatoduodenectomy for pancreatic cancer have been reported, they have been disappointingly lower than the optimistic survival results predicted by those studies using actuarial analysis. Since the 1980s, neoadjuvant therapy has been introduced as one of the multidisciplinary treatments for pancreatic cancer. Recently, the MD Anderson cancer center group showed that actual 5-year survival rate of patients after multidisciplinary management including surgical resection was 27%,[7] and in patients with resectable pancreatic head cancer who underwent surgical resection after preoperative gemcitabine-based chemoradiation, actual 5-year survival rate was 36%.[8] In this study, actual 5-year survival rate was 44% in patients with pancreatic cancer who underwent curative resection (R0/1). Actually, the present study demonstrated a significant difference in the actual survival curve over 3 years between the preoperative CRT and surgery-alone groups who underwent curative resection. Furthermore, there was a similar disease-free survival rate within 1 year in the preoperative CRT and surgery-alone groups in the absence of adjuvant chemotherapy, but after 1 year, the difference in the disease-free survival curve became increasingly bigger. However, approximately half of the patients who underwent curative resection had disease recurrence at 1 year and died in 2 years in both groups. Preoperative CRT followed by surgical resection did not have enough power to improve the short-term survival rate and the frequency of early liver metastases, which was one of the major postoperative recurrence sites. In this respect, addition of adjuvant chemotherapy[5,6] or targeted chemotherapy to the liver[9,10] will be expected to improve the short-term survival rate. Ohigashi et al[9] reported that the actuarial 5-year survival rate of 31 patients who underwent pancreatectomy after neoadjuvant chemoradiation therapy plus postoperative liver perfusion chemotherapy was 53%, with low incidences of both local recurrence (9%) and liver metastasis (7%). Furthermore, Sho et al[10] evaluated the efficacy of postoperative combination therapy of high-dose 5-fluorouracil arterial infusion with systemic gemcitabine in 31 patients with pancreatic cancer who underwent surgical resection, resulting in low incidence of liver metastasis (10%). Thus, postoperative adjuvant chemotherapy targeted to the liver can be associated with a beneficial effect on early hepatic recurrence.

In conclusion, preoperative CRT followed by curative resection can improve the long-term survival rate in patients with pancreatic cancer that extended beyond the pancreas. A large-scale randomized controlled trial will be needed to confirm the clinical efficacy of preoperative CRT.

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ORIGINAL ARTICLE

A Prospective Randomized Controlled Trial of Preoperative Whole-Liver Chemolipiodolization for Hepatocellular Carcinoma

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Abstract
Background We previously reported that preoperative chemolipiodolization of the whole liver is effective for reducing the incidence of postoperative recurrence and prolonging survival in patients with resectable hepatocellular carcinoma (HCC). The present randomized controlled trial was performed to evaluate the influence of preoperative transcatheter arterial chemoembolization (TACE) on survival after the resection of HCC.
Methods Operative results and long-term outcome were prospectively compared among 42 patients who received only selective TACE targeting the tumor (selective group), 39 patients who received TACE targeting the tumor plus chemolipiodolization of the whole liver (whole-liver group), and 43 patients without preoperative TACE or chemolipiodolization (control group).
Results There were no serious side effects of TACE or chemolipiodolization and the operative outcomes did not differ among the three groups. Even though preoperative TACE induced complete tumor necrosis, there were no significant differences in the pattern of intrahepatic recurrence or the time until recurrence among the three groups. There were also no significant differences in disease-free survival or overall survival among the three groups, even among patients with larger tumor size.
Conclusion These results indicate that preoperative selective TACE and whole-liver chemolipiodolization plus TACE do not reduce the incidence of postoperative recurrence or prolong survival in patients with resectable HCC.

Keywords Hepatocellular carcinoma · Preoperative chemolipiodolization · Whole liver · Hepatectomy · Randomized controlled trial

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1]. Although the majority of patients are still found in Asia and Africa, recent studies have shown that the incidence and mortality rate of HCC are rising in North America and Europe [2, 3]. There has been an increase in reports of non-surgical therapeutic options for small HCC, such as percutaneous ethanol injection therapy [4], microwave coagulation therapy [5], and percutaneous radiofrequency ablation (RFA) [6], but there is ongoing controversy regarding the best method of treating small tumors. In Japan, liver transplantation is not a practical option for most HCC patients, because the national health insurance scheme only covers transplantation for patients with decompensated cirrhosis whose tumors fit the Milan criteria. Resection is, therefore, generally the first-line treatment for patients with small tumors and underlying chronic liver disease, but the long-term survival rate after

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potentially curative resection of HCC is still unsatisfactory because of the high rate of recurrence [7]. To improve prognosis, it is important to prevent the recurrence of HCC after its initial resection, but standard therapy for intrahepatic metastasis has not yet been developed.

With various improvements in interventional radiology, transcatheter arterial chemoembolization (TACE) has become an increasingly important palliative treatment for HCC. Initially, TACE was only performed for unresectable HCC, as well as for some early tumors that were extremely difficult to resect. More recently, TACE has been used as preoperative adjuvant therapy in patients who have resectable HCC with the hope that it may improve survival [8–13]. Based on the current evidence, however, preoperative TACE is not routinely recommended for patients undergoing hepatectomy to treat resectable HCC [14–16], and TACE may be contraindicated in patients with cirrhosis because it can lead to the progressive deterioration of liver function [14]. Whether preoperative TACE can improve the long-term survival of HCC patients is still unclear, and there have been only three randomized controlled trials evaluating the influence of preoperative TACE on survival [15, 17, 18]. We previously reported that preoperative chemolipiodolization of the entire liver is effective for reducing the incidence of postoperative recurrence and for prolonging survival in patients with resectable HCC [19]. Accordingly, the present randomized controlled trial was conducted to better assess the influence of preoperative TACE combined with whole-liver chemolipiodolization on survival after the resection of HCC.

Patients and Methods

Patients

Between January 2004 and June 2007, 124 patients with HCC underwent curative hepatic resection at our institution. A curative operation was defined as the resection of all detectable tumors. The eligibility criteria for inclusion in this study were as follows: (1) age 20–80 years; (2) a preoperative diagnosis of HCC with no previous treatment; (3) no other malignancies; (4) Child–Pugh score A or B; (5) leukocyte count $\geq$3,000/mm^3; (6) hemoglobin level $\geq$9.5 g/dl; (7) platelet count $\geq$50,000/mm^3; (8) serum creatinine level <1.2 mg/dl; (9) total bilirubin <2.0 mg/dl; (10) local nodular disease without extrahepatic metastasis; and (11) Eastern Cooperative Oncology Group (ECOG) performance status 0–1 [20]. The etiology of HCC (HCV-related or other [HBV-related or non-B, non-C-related]) and the size of the tumor on imaging were taken into consideration when dividing patients into the three groups. The sample size was estimated based on our previously reported 3-year disease-free survival rates in selective and whole-liver groups, being 25 and 60%, respectively [19]. We needed 37 patients in each group for a type I error rate of 5% and a type II error rate of 20% with a two-tailed test. Among the 124 patients, TACE was performed preoperatively in 81. Patients were randomized to receive chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization without gelatin sponge for the non-cancerous liver (whole-liver group, $n = 39$), or no preoperative TACE (control group, $n = 43$). The study protocol was explained to all patients, and they understood that they would be randomly selected for one of the above three groups. All patients gave written informed consent to participation in the trial. They were randomized by the envelope method and were informed of the result of the randomization before angiography. All operations were performed by the same surgeon, who had experience of over 700 hepatic resections. The protocol for this study was approved by the ethics committee of Kansai Medical University. The primary outcome measures were disease-free survival rate and overall survival rate. Secondary outcome measures included procedure-related complications and hospital mortality (Fig. 1).

Chemolipiodolization

A catheter was selectively inserted into the right or left hepatic artery, a segmental artery, or a subsegmental artery by Seldinger's method. In the selective group, TACE was performed via the right hepatic artery in 16 patients, the left hepatic artery in 10 patients, a segmental artery in 9 patients, and a subsegmental artery in 7 patients. In the whole-liver group, TACE (i.e., chemolipiodolization with gelatin sponge) was performed via the right hepatic artery in 18 patients and the left hepatic artery in 13 patients to target the tumor, while chemolipiodolization alone was performed on the non-cancerous side via the left or right hepatic artery. In a further 8 patients, TACE was performed via a right or left subsegmental artery to target the tumor and chemolipiodolization of the non-cancerous liver was performed via the right and left hepatic arteries as the catheter was withdrawn. The selective group was treated with epirubicin (Farmorubicin) at a mean ($\pm$ standard deviation [SD]) dose of 47.0 $\pm$ 17.8 mg, iodized oil (Lipiodol) at a mean volume of 3.8 $\pm$ 2.1 ml, and gelatin sponge particles. In the whole-liver group, epirubicin (28.1 $\pm$ 5.5 mg), Lipiodol (2.9 $\pm$ 1.4 ml), and gelatin sponge particles were used to treat the tumor, while only epirubicin (22.2 $\pm$ 6.2 mg) and Lipiodol (1.9 $\pm$ 0.8 ml) were infused into the non-cancerous liver. In the control group, only angiography was performed.

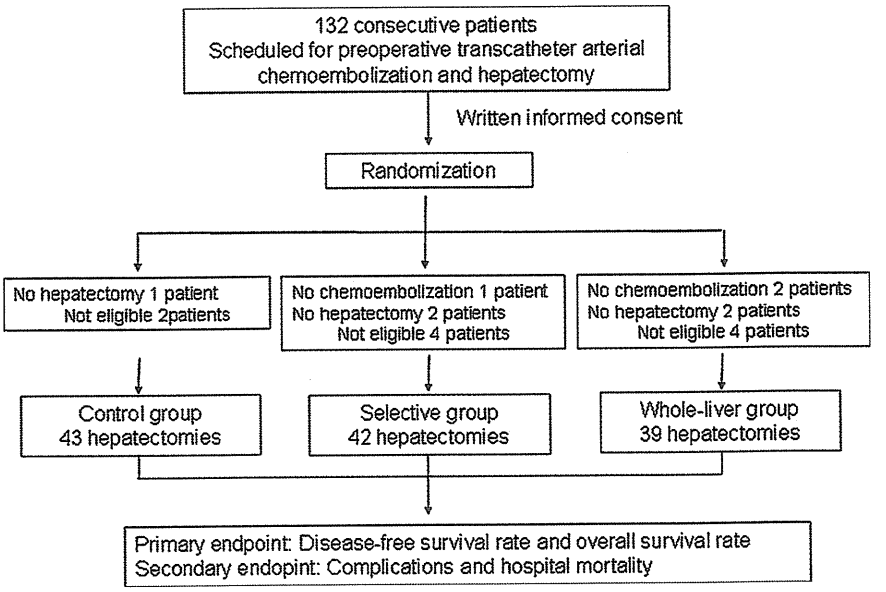

Fig. 1 Study design. We randomly divided patients into three groups: chemolipiodolization with gelatin sponge (equal to transcatheter arterial chemoembolization [TACE]) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization without gelatin sponge for the non-cancerous liver (whole-liver group, $n = 39$), or no preoperative TACE (control group, $n = 43$)

Clinicopathologic Variables and Surgery

Before randomization, each patient underwent conventional liver function tests, measurement of the indocyanine green retention rate at 15 min (ICGR15), and technetium-99m-diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy [21]. Hepatitis screening was undertaken by testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb). The levels of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were also measured. Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al. [22]. In brief, anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory, and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments [23]), or segmentectomy (resection of one Couinaud subsegment). All of the other procedures were non-anatomic and were classified as limited resection. Peripheral tumors and those with extrahepatic growth were managed by limited resection because this achieved adequate surgical margins. Central tumors located near the hepatic hilum or major vessels were treated by enucleation because it was too difficult or dangerous to remove enough of the liver to obtain an adequate margin. One senior pathologist reviewed all the specimens for histologic confirmation of the diagnosis. The width of the surgical margin was measured from the tumor border to the resection line. We evaluated the extent of necrosis on the largest tumor at its greatest diameter, even in cases with multiple tumors. The tumor stage was defined according to the TNM classification [24].

Follow-Up

Patients who survived were followed up after discharge, with physical examination, liver function tests, and ultrasound, computed tomography (CT), or magnetic resonance imaging being performed at least every 3 months to detect intrahepatic recurrence. Chest radiographs were also obtained to detect pulmonary metastases and chest CT was performed if the plain radiograph showed any abnormalities. Bone metastases were diagnosed by bone scintigraphy.

If the recurrence of HCC was detected by changes in the levels of tumor markers or by imaging, recurrence limited to the remnant liver was treated by TACE, lipiodolization, re-resection, or percutaneous local ablation therapy, such as RFA. If extrahepatic metastases were detected, active treatment was undertaken in patients with good hepatic functional reserve (Child–Pugh class A or B) and good performance status (0 or 1) who had a solitary extrahepatic metastasis and no evidence of intrahepatic recurrence, while other patients were treated only with radiation therapy to control symptoms caused by bone metastases.

Statistical Analysis

The results were expressed as the mean ± SD. Continuous variables were evaluated with the Mann–Whitney *U*-test or the Kruskal–Wallis test, as appropriate. Categorical data were compared with the Chi-square test or Fisher's exact test. The Kaplan–Meier method was used to calculate the

disease-free survival rate and the overall survival rate as of June 2010, and the significance of differences in survival rates was assessed with the generalized log-rank test. In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

There were no serious side effects of selective TACE or whole-liver chemolipiodolization. The interval between selective TACE, whole-liver chemolipiodolization, or angiography and hepatic resection was 21.2 ± 10.8, 23.0 ± 13.2, and 20.0 ± 13.2 days, respectively. Table 1 shows the preoperative characteristics of the patients in the three groups. There were no significant differences among the groups with respect to gender, age, Child–Pugh class, etiology of hepatitis or cirrhosis, alcohol abuse, preoperative liver function, or serum AFP and PIVKA-II levels. The operative results and pathologic findings in each group are listed in Table 2. The operating time, blood loss, requirement for transfusion, and operative procedures did not differ significantly among the three groups, nor did the rates of postoperative complications and hospital deaths. There were no significant differences in tumor size or the number of tumors detected on imaging before randomization among the groups. Although the tumor sizes measured in the surgical specimens were smaller in the selective group and the whole-liver group compared with the control group, the differences were not significant. In the selective, whole-liver, and control groups, complete tumor necrosis was confirmed in 9/42 patients (21%), 8/39 patients (21%), and 0/43 patients (0%), respectively. The other pathological characteristics of the tumors were comparable among the three groups.

Recurrence and Survival

The pattern of recurrence and time to recurrence in the three groups are shown in Table 3. A total of 27 patients in the selective group, 28 patients in the whole-liver group, and 26 patients in the control group developed recurrence of HCC. Extrahepatic recurrence was significantly less common in the selective and whole-liver groups compared with the control group. However, the percentage of intrahepatic recurrences due to multinodular/diffuse tumors and the incidence of recurrence within 6 months or 1 year following curative resection were not significantly different among the three groups.

The disease-free survival rates of the entire TACE group (selective and whole-liver groups) and the control group were 65 and 53% at 1 year, and 27 and 32% at 3 years, respectively (Fig. 2a). The overall survival rates of the entire TACE group and the control group were 88 and 83% at 1 year, 75 and 60% at 3 years, and 47 and 56% at 5 years, respectively (Fig. 2b). There were no significant

Table 1 Preoperative clinical characteristics of the three groups

	Control group ($n = 43$)	Selective group ($n = 42$)	Whole-liver group ($n = 39$)	*P*-value
Sex (male/female)	32/11	35/7	30/9	0.5921
Age (years)	66.1 ± 10.6	68.1 ± 5.7	66.8 ± 5.4	0.5122
Child–Pugh class (A/B)	39/4	37/5	34/5	0.8708
Etiology (HBV/HCV/NBC)	11/23/9	4/30/8	6/29/4	0.1663
Alcohol abuse (+/−)	17/26	19/23	19/20	0.6981
Platelet count ($10^4/\mu l$)	18.9 ± 10.6	15.2 ± 7.5	15.1 ± 6.9	0.2448
Total bilirubin (mg/dl)	0.89 ± 0.87	0.86 ± 0.32	0.89 ± 0.41	0.3861
Albumin (g/dl)	3.64 ± 0.57	3.67 ± 0.39	3.50 ± 0.47	0.2804
AST (IU/l)	47 ± 34	46 ± 23	47 ± 21	0.5452
ALT (IU/l)	44 ± 37	40 ± 25	45 ± 23	0.3158
Prothrombin time (%)	89 ± 14	86 ± 13	84 ± 14	0.3568
ALP (U/l)	353 ± 162	346 ± 165	365 ± 144	0.6605
γ-GTP (U/l)	99 ± 69	87 ± 95	101 ± 96	0.1859
ICGR15 (%)	15.5 ± 8.3	19.0 ± 9.5	19.2 ± 9.5	0.1384
GSA Rmax (mg/min)	0.554 ± 0.211	0.505 ± 0.194	0.584 ± 0.277	0.3985
Hyaluronic acid (ng/ml)	175 ± 165	199 ± 226	289 ± 385	0.3140
AFP (ng/ml)	858 ± 5,269	2,432 ± 11,638	1,791 ± 9,898	0.2750
PIVKA-II (mAU/ml)	2,385 ± 9,481	4,845 ± 17,126	1,124 ± 3,970	0.8634

The data represent the mean ± standard deviation (SD) or the number of patients
HBV hepatitis B virus, *HCV* hepatitis C virus, *NBC*, non-hepatitis B or C virus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyltransferase, *ICGR15* indocyanine green retention rate at 15 min, *GSA Rmax* maximum removal rate of technetium-99m-diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA), *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II

Table 2 Intraoperative and postoperative characteristics of the three groups

	Control group ($n = 43$)	Selective group ($n = 42$)	Whole-liver group ($n = 39$)	P-value
Operating time (min)	321 ± 124	300 ± 100	318 ± 135	0.8368
Operative blood loss (ml)	1,875 ± 1,841	1,418 ± 1,324	1,309 ± 1,218	0.3953
Blood transfusion (+/−)	20/23	15/27	13/26	0.4195
Operative procedure (limited/anatomic resection)	33/10	30/12	29/10	0.8545
No. of patients with complications	8 (19%)	3 (7%)	5 (13%)	0.2888
Hospital death	1 (2%)	1 (2%)	0 (0%)	0.6272
Postoperative hospital stay (days)	20 ± 18	16 ± 5	18 ± 12	0.1685
Tumor size on imaging before TACE (cm)	4.86 ± 4.12	4.30 ± 2.13	4.02 ± 3.88	0.7668
Tumor size in specimen (cm)	4.94 ± 3.52	3.66 ± 1.95	3.45 ± 2.15	0.1610
No. of tumors on imaging before TACE (single/multiple)	34/9	33/9	32/7	0.9156
No. of tumors in specimen (single/multiple)	32/11	32/10	31/8	0.8609
Histology (well/moderately/poorly/ complete necrosis)	3/34/6/0	3/30/0/9	1/29/1/8	0.0052
Microscopic capsule (+/−)	38/5	38/4	38/1	0.2940
Microvascular invasion (+/−)	28/15	31/11	24/15	0.4785
Microscopic surgical margin (+/−)	5/38	4/38	2/37	0.5763
Associated liver disease (normal/hepatitis/cirrhosis)	4/28/11	1/27/14	2/24/13	0.6581
Tumor stage (I + II/III + IV)	31/12	31/11	30/9	0.8807

The data represent the mean ± standard deviation (SD) or the number of patients

Table 3 Patterns and timing of recurrence

	Control group ($n = 26$)	Selective group ($n = 27$)	Whole-liver group ($n = 28$)	P-value
Extrahepatic recurrence	7/26 (27%)	3/27 (11%)	1/28 (4%)	0.0393
Intrahepatic recurrence				0.8829
Nodular recurrence	6/19 (32%)	6/24 (25%)	8/27 (30%)	
Multinodular/ diffuse recurrence	13/19 (68%)	18/24 (75%)	19/27 (70%)	
Timing of recurrence				
≤6 months	7/26 (27%)	6/27 (22%)	4/28 (14%)	0.5128
≤12 months	18/26 (69%)	13/27 (48%)	14/28 (50%)	0.2323

The data represent the number (percentage) of patients

differences in disease-free survival ($P = 0.6603$) or overall survival ($P = 0.4115$) between the two groups. Comparing the three groups, the disease-free survival rates of the selective group, whole-liver group, and control group were 67, 63, and 53% at 1 year, and 29, 27, and 32% at 3 years, respectively (Fig. 3a). The overall survival rates of the selective, whole-liver, and control groups were 91, 84, and 83% at 1 year, and 80, 70, and 60% at 3 years, respectively (Fig. 3b). There were no significant differences in disease-free survival ($P = 0.8303$) or overall survival ($P = 0.7126$) among the three groups.

When only patients with a solitary tumor measuring ≥5 cm in the greatest diameter were analyzed, the disease-free survival rates of the selective, whole-liver, and control groups were 50, 34, and 44% at 1 year, and 10, 11, and 9% at 3 years, respectively ($P = 0.8650$) (Fig. 4a). Among these patients, there were also no differences in the overall survival rate between the selective, whole-liver, and control groups, with survival rates of 82, 79, and 67% at 1 year, and 53, 68, and 47% at 3 years, respectively ($P = 0.7264$) (Fig. 4b).

Discussion

In our previous retrospective study, we found that preoperative chemolipiodolization of the whole liver achieved significant prolongation of both disease-free survival and overall survival for HCC patients [19]. The precise mechanism remains unclear, but some possible explanations are: (1) subclinical micrometastases due to portal vein dissemination or multicentric primary tumors are eliminated by whole-liver therapy and (2) reducing the tumor burden before surgery may lessen the chance of developing resistance to chemotherapy. TACE is a well-recognized treatment for HCC, either as adjuvant therapy or as a

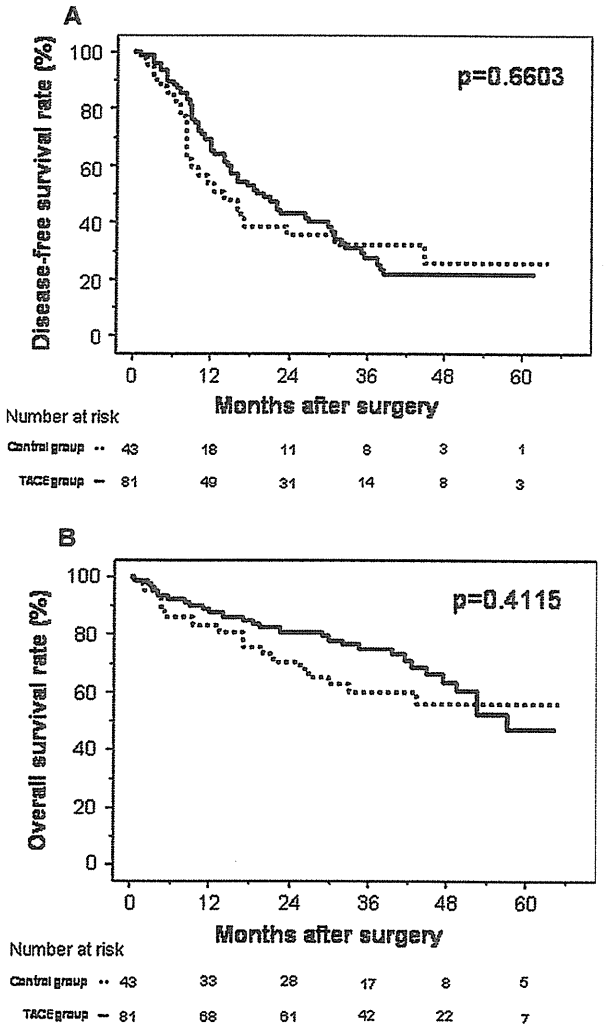

Fig. 2 **a** Comparison of disease-free survival after the resection of hepatocellular carcinoma (HCC) between patients receiving preoperative selective TACE and patients receiving preoperative TACE plus whole-liver chemolipiodolization (entire TACE group, $n = 81$, *solid line*) and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in disease-free survival between the two groups ($P = 0.6603$). **b** Comparison of overall survival after the resection of HCC between patients receiving preoperative selective TACE and patients receiving preoperative TACE plus whole-liver chemolipiodolization (entire TACE group, $n = 81$, *solid line*) and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in overall survival between the two groups ($P = 0.4115$)

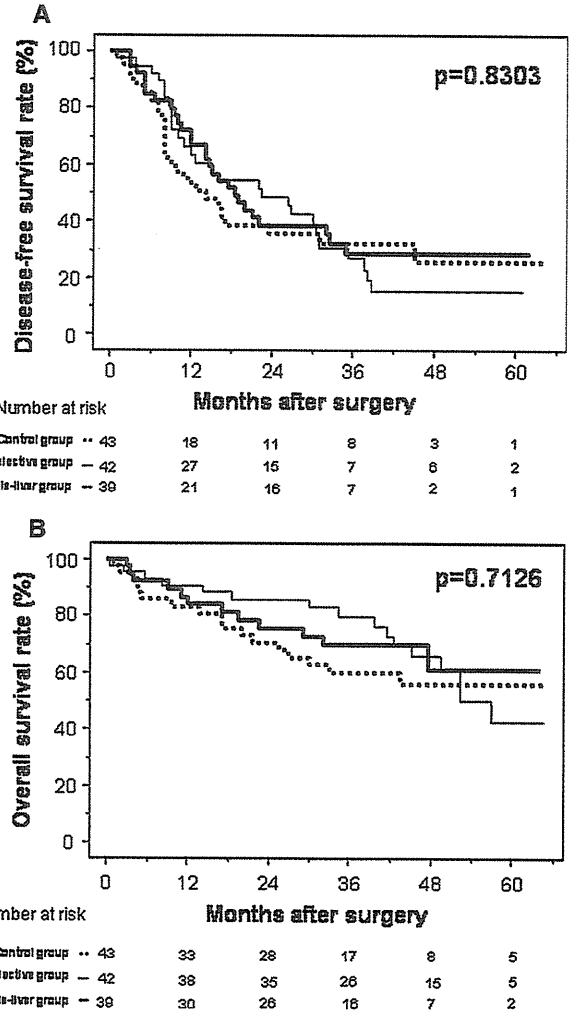

Fig. 3 **a** Comparison of disease-free survival after the resection of HCC among patients receiving preoperative selective TACE (selective group, $n = 42$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver group, $n = 39$, *thick solid line*), and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in disease-free survival among the three groups ($P = 0.8303$). **b** Comparison of overall survival after the resection of HCC among the selective group ($n = 42$, *thin solid line*), the whole-liver group ($n = 39$, *thick solid line*), and the control group ($n = 43$, *dotted line*). There were no significant differences in overall survival among the three groups ($P = 0.7126$)

definitive procedure in patients whose tumors are considered to be unresectable [25, 26]. Preoperative TACE is not only intended to prevent recurrence by controlling intrahepatic spread via the portal system, but also to facilitate surgery by reducing tumor bulk. In particular, minimizing resection of the non-tumorous liver is vital in patients with cirrhosis to avoid postoperative hepatic failure. Uchida et al. [14] reported a lower survival rate among cirrhosis patients who underwent TACE prior to the resection of HCC compared with patients who did not undergo TACE, and they recommended against preoperative TACE for patients with cirrhosis because the procedure could accelerate the deterioration of liver function. Lu et al. [11] performed a retrospective analysis of 120 HCC patients and concluded that preoperative TACE might benefit those with tumors >8 cm in diameter, but not those with tumors

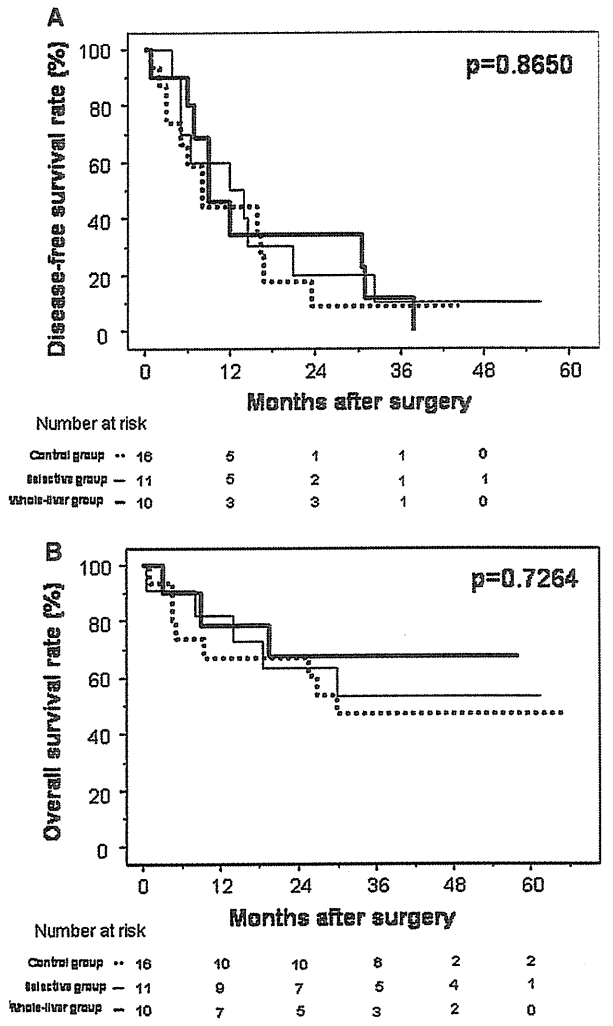

Fig. 4 **a** Comparison of disease-free survival after resection of a solitary HCC ≥5 cm in the greatest diameter among patients receiving preoperative selective TACE (selective group, $n = 11$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver group, $n = 10$, *thick solid line*), and patients without preoperative TACE (control group, $n = 16$, *dotted line*). There were no significant differences in disease-free survival among the three groups ($P = 0.8650$). **b** Comparison of overall survival after resection of a solitary HCC ≥5 cm in the greatest diameter among the selective group ($n = 11$, *thin solid line*), the whole-liver group ($n = 10$, *thick solid line*), and the control group ($n = 16$, *dotted line*). There were no significant differences in overall survival among the three groups ($P = 0.7264$)

2–8 cm in diameter. In contrast, it was reported that downstaging or total necrosis of the tumor was achieved by preoperative TACE in 62% of 103 HCC patients with cirrhosis, leading to an improvement of disease-free survival after liver resection and liver transplantation [13]. Thus, the value of preoperative TACE is still controversial.

A meta-analysis including seven randomized clinical trials was undertaken in the late 1990s to investigate the usefulness of TACE for treating unresectable HCC, which demonstrated an improvement in 2-year survival (odds ratio 0.53, $P = 0.017$) compared with control patients who were treated conservatively or received suboptimal management [27]. This established the role of TACE as the standard care for unresectable HCC, whether as palliative therapy or to improve resectability [27]. Subsequent investigations were directed towards the preoperative use of TACE as neoadjuvant therapy to prevent recurrence. To assess the clinical efficacy of preoperative TACE for resectable HCC, two randomized trials were conducted in 1995 and 1996 [15, 17] (Table 4). Both of these trials found no improvement in disease-free survival following neoadjuvant TACE, and Wu et al. [17] reported worse overall survival in the TACE group. In 2009, a randomized trial of neoadjuvant TACE for large resectable HCC was reported [18]. The results were similar, with no difference in disease-free survival or overall survival between the groups with or without TACE (Table 4). The present study is the fourth randomized trial to compare the long-term prognosis after the resection of HCC in patients with or without preoperative TACE. However, it is difficult to simply compare these trials. Zhou et al. [18] and Wu et al. [17] enrolled patients with large HCCs, whereas Yamasaki et al. [15] and the current trial enrolled patients with smaller HCCs. In the trial reported by Wu et al. [17], patients who received TACE underwent surgery a mean of 17.9 weeks after the detection of HCC, which was significantly longer than those not receiving TACE, who underwent resection 2.3 weeks after the detection of HCC ($P = 0.009$). In this study, patients in all groups underwent surgery in 20–23 days. Differences in the conclusions of the different trials could be attributed to the differences in the study designs or background characteristics.

We found no significant differences in disease-free survival or overall survival between the entire TACE group (selective and whole-liver groups) and the control group, or among the whole-liver, selective, and control groups, even among patients with tumor size >5 cm (Figs. 2, 3, and 4). The extrahepatic recurrence rate was significantly lower in the selective and whole-liver groups compared with the control group. However, even though preoperative TACE induced complete tumor necrosis, there were no significant differences in the pattern of intrahepatic recurrence or the time until recurrence among the three groups.

In conclusion, preoperative selective TACE or TACE plus whole-liver chemolipiodolization neither reduced the incidence of postoperative recurrence nor prolonged survival in patients with resectable HCC. Thus, despite its safety and feasibility, we cannot recommend preoperative TACE as a routine procedure before hepatectomy in patients with resectable HCC.