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

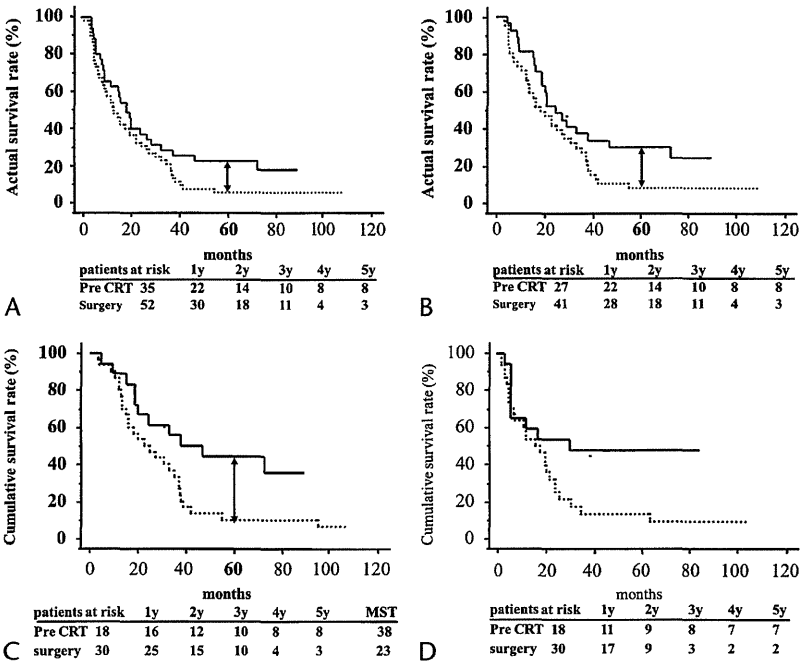

FIGURE 1. A, Actual survival curves of preoperative CRT (n = 27) and surgery-alone (n = 41) groups including unresectable patients. Solid line, preoperative CRT group; broken line, surgery-alone group. Actual survival rates at 1 year, 3 years, and 5 years were 66%, 40%, and 23% in the preoperative CRT 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.

The authors declare no conflict of interest.

Sohei Satoi, MD
Hiroaki Yanagimoto, MD
Hideyoshi Toyokawa, MD
Tomohisa Yamamoto, MD
Satoshi Hirooka, MD
Rintaro Yui, MD
So Yamaki, MD
Yoichi Matsui, MD
Hiroaki Kitade, MD
Department of Surgery
Kansai Medical University
Hirakata-City, Osaka, Japan
satoi@hirakata.kmu.ac.jp
Noboru Tanigawa, MD
Department of Radiology
Kansai Medical University
Hirakata-City, Osaka, Japan
Soichiro Takai, MD
A-Hon Kwon, MD
Department of Surgery
Kansai Medical University
Hirakata-City, Osaka, Japan

REFERENCES

1. Bradley EL III. Long-term survival after pancreatoduodenectomy for ductal adenocarcinoma. The emperor has no clothes? *Pancreas* 2008;37:349–351.
2. Traverso LW. Pancreatic cancer: surgery alone is not sufficient. *Surg Endosc* 2006;20:446–449.
3. Takai S, Satoi S, Yanagimoto H, et al. Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. *Pancreas* 2008;36:e26–e32.
4. Satoi S, Yanagimoto H, Toyokawa H, et al. Surgical results following pre-operative chemoradiation therapy for patients with pancreatic cancer. *Pancreas* 2009;38:282–288.
5. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–277.
6. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073–1081.
7. Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. *Ann Surg Oncol* 2009;16:836–847.
8. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3496–3502.
9. Ohigashi H, Ishikawa O, Eguchi H, et al. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. *Ann Surg* 2009;250:88–95.
10. Sho M, Tanaka T, Yamada T, et al. Novel postoperative adjuvant strategy prevents early hepatic recurrence after resection of pancreatic cancer. *J Hepatobiliary Pancreat Sci* 2011;18:235–239.

Dig Dis Sci
DOI 10.1007/s10620-012-2029-3

ORIGINAL ARTICLE

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

Masaki Kaibori · Noboru Tanigawa · Shuji Kariya · Hiroki Ikeda · Yoshitsugu Nakahashi · Junko Hirohara · Chizu Koreeda · Toshihito Seki · Satoshi Sawada · Kazuichi Okazaki · A-Hon Kwon

Received: 1 April 2011 / Accepted: 4 January 2012

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

M. Kaibori (✉) · A.-H. Kwon
Department of Surgery, Kansai Medical University, 2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan
e-mail: kaibori@hirakata.kmu.ac.jp

N. Tanigawa · S. Kariya · S. Sawada
Department of Radiology, Kansai Medical University, Hirakata, Osaka 573-1191, Japan

H. Ikeda · Y. Nakahashi · J. Hirohara · C. Koreeda · T. Seki · K. Okazaki
Department of Gastroenterology and Hepatology, Kansai Medical University, Hirakata, Osaka 573-1191, Japan

Published online: 24 January 2012

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.

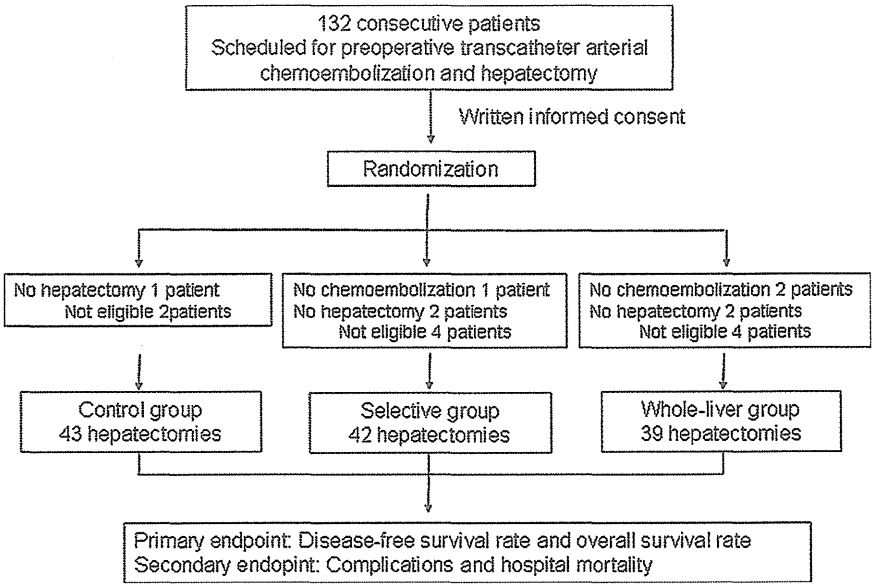

Fig. 1 Study design. We randomly divided patients into three groups: chemolipiodolization with gelatin sponge (equal to transcatheter arterial chemoembolization [TACE]) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization 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/μl)	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

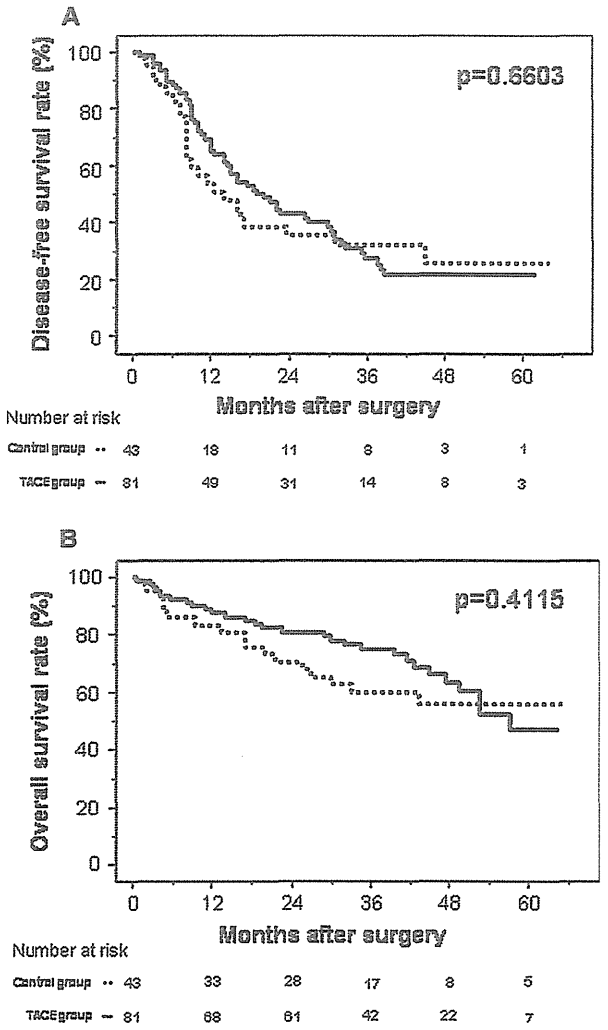

Fig. 2 **a** Comparison of disease-free survival after the resection of hepatocellular carcinoma (HCC) between patients receiving preoperative selective TACE and patients receiving preoperative TACE plus whole-liver chemolipiodolization (entire TACE group, $n = 81$, *solid line*) and patients not receiving 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 ($P = 0.4115$)

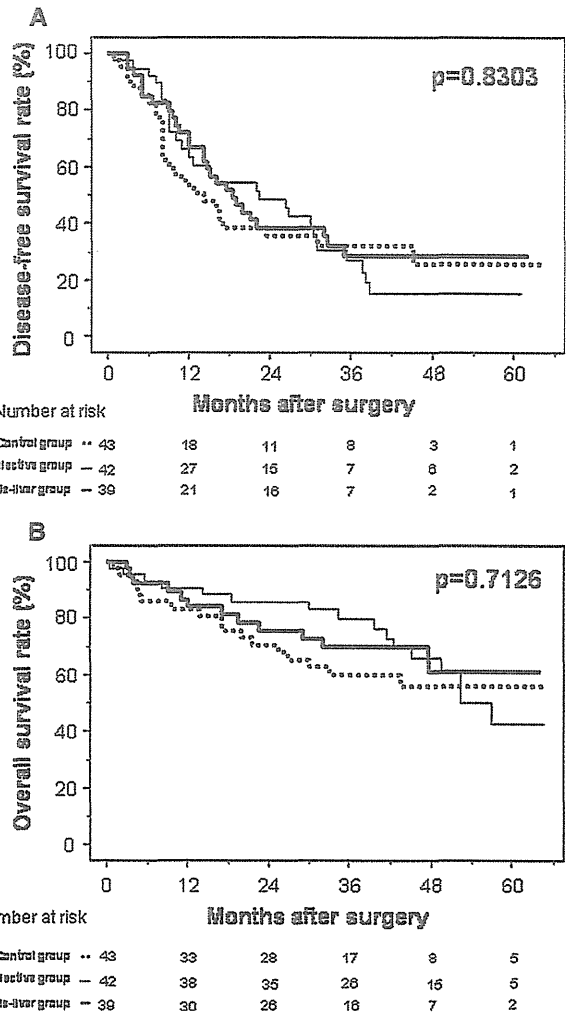

Fig. 3 **a** Comparison of disease-free survival after the resection of HCC among patients receiving preoperative selective TACE (selective group, $n = 42$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver group, $n = 39$, *thick solid line*), 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

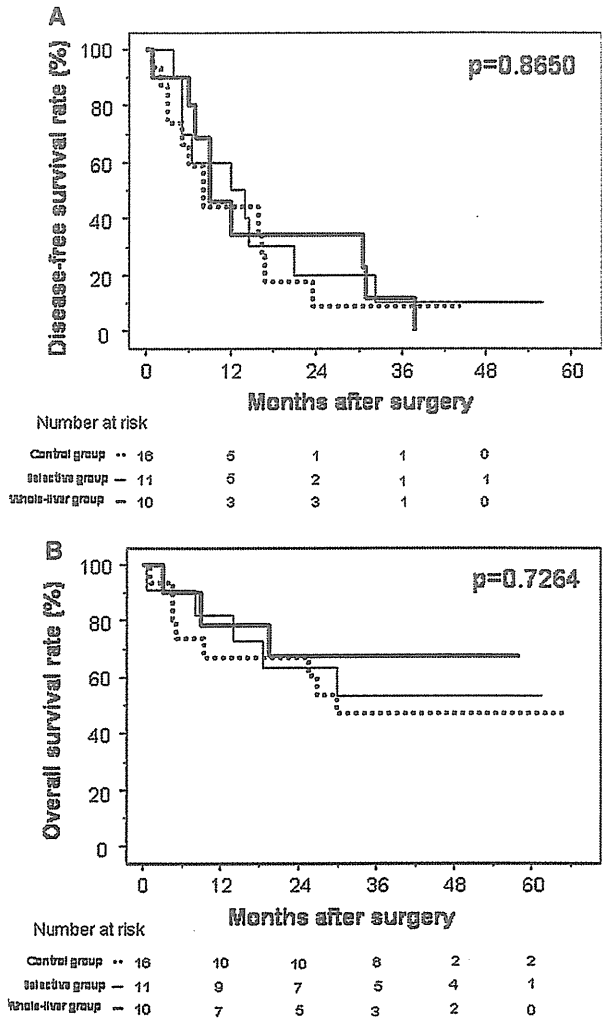

Fig. 4 **a** Comparison of disease-free survival after resection of a solitary HCC ≥5 cm in the greatest diameter among patients receiving preoperative selective TACE (selective group, $n = 11$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver 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.

Table 4 Results of randomized controlled trials on neoadjuvant transarterial chemoembolization and non-transarterial chemoembolization before hepatectomy for resectable hepatocellular carcinoma (HCC)

Study	Year	Total patients (*n*)	(TACE/non-TACE) patients (*n*)	Percentage of HBV (TACE/non-TACE)	Percentage of HCV (TACE/non-TACE)	Percentage of Child–Pugh class A (TACE/non-TACE)
This study		124	81/43	12/26	73/53	88/91
Zhou et al. [18]	2009	108	52/56	98/98	0/0	84/89
Yamasaki et al. [15]	1996	97	50/47	NR	NR	NR
Wu et al. [17]	1995	52	24/28	75/68	NR	92/86

Study	Mean preoperative tumor size (cm) (TACE/non-TACE)	Cytotoxic agent	TACE sessions per patient (*n*)	Complete necrosis (%) (TACE/non-TACE)
This study	4.1/5.0	EPI	1	**21/0**
Zhou et al. [18]	9.0/9.5	5FU, CDDP	1.5	**15/0**
Yamasaki et al. [15]	3.1/3.3	DOX	1	**16/NR**
Wu et al. [17]	14.3/14.5	DOX	3	NR/NR

Study	Morbidity (%) (TACE/non-TACE)	Mortality (%) (TACE/non-TACE)	3-year disease-free survival (%)	3-year overall survival (%) (TACE/non-TACE)
This study	10/19	1/2	28/32	75/60
Zhou et al. [18]	**Adhesions and longer operating time in TACE group**	0/0	26/21	40/32
Yamasaki et al. [15]	NR	6/9	54/42	91/88
Wu et al. [17]	NR	4/7	40/50	**33/60**

Significant differences are shown in **bold**. The number of patients receiving TACE in this study was 81 (42 patients in the selective group and 39 patients in the whole-liver group)

TACE transcatheter arterial chemoembolization, *NR* not reported, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *EPI* epirubicin, *5FU* 5-fluorouracil, *CDDP* cisplatin, *DOX* doxorubicin

Conflict of interest None.

References

1. Bosch FX, Ribes J, Borràs J. Epidemiology of primary liver cancer. *Semin Liver Dis.* 1999;19:271–285.
2. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979–94. *Lancet.* 1997;350:1142–1143.
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999;340:745–750.
4. Kotoh K, Sakai H, Sakamoto S, et al. The effect of percutaneous ethanol injection therapy on small solitary hepatocellular carcinoma is comparable to that of hepatectomy. *Am J Gastroenterol.* 1994;89:194–198.
5. Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer.* 1994;74:817–825.
6. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg.* 2006;243:321–328.
7. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg.* 2000;232:10–24.
8. Nakamura H, Tanaka T, Hori S, et al. Transcatheter embolization of hepatocellular carcinoma: assessment of efficacy in cases of resection following embolization. *Radiology.* 1983;147:401–405.
9. Sakurai M, Okamura J, Kuroda C. Transcatheter chemo-embolization effective for treating hepatocellular carcinoma. A histopathologic study. *Cancer.* 1984;54:387–392.
10. Harada T, Matsuo K, Inoue T, et al. Is preoperative hepatic arterial chemoembolization safe and effective for hepatocellular carcinoma? *Ann Surg.* 1996;224:4–9.
11. Lu CD, Peng SY, Jiang XC, Chiba Y, Tanigawa N. Preoperative transcatheter arterial chemoembolization and prognosis of patients with hepatocellular carcinomas: retrospective analysis of 120 cases. *World J Surg.* 1999;23:293–300.
12. Sugo H, Futagawa S, Beppu T, Fukasawa M, Kojima K. Role of preoperative transcatheter arterial chemoembolization for resectable hepatocellular carcinoma: relation between postoperative course and the pattern of tumor recurrence. *World J Surg.* 2003;27:1295–1299.
13. Majno PE, Adam R, Bismuth H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg.* 1997;226:688–703.
14. Uchida M, Kohno H, Kubota H, et al. Role of preoperative transcatheter arterial oily chemoembolization for resectable hepatocellular carcinoma. *World J Surg.* 1996;20:326–331.
15. Yamasaki S, Hasegawa H, Kinoshita H, et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of

hepatocellular carcinoma. *Jpn J Cancer Res.* 1996;87:206–211.
16. Nagasue N, Kohno H, Tachibana M, Yamanoi A, Ohmori H, El-Assal ON. Prognostic factors after hepatic resection for hepatocellular carcinoma associated with child-turcotte class B and C cirrhosis. *Ann Surg.* 1999;229:84–90.
17. Wu CC, Ho YZ, Ho WL, Wu TC, Liu TJ, P'eng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. *Br J Surg.* 1995;82:122–126.
18. Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. *Ann Surg.* 2009; 249:195–202.
19. Kaibori M, Tanigawa N, Matsui Y, Kwon AH, Sawada S, Kamiyama Y. Preoperative chemolipiodolization of the whole liver for hepatocellular carcinoma. *Anticancer Res.* 2004;24: 1929–1933.
20. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–655.
21. Kwon AH, Ha-Kawa SK, Uetsuji S, Inoue T, Matsui Y, Kamiyama Y. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy. *Hepatology.* 1997;25: 426–429.
22. Strasberg SM, Belghiti J, Clavn P-A, et al. The Brisbane 2000 terminology of liver anatomy and resection. Terminology Committee of the International Hepato-Pancreato-Biliary Association. *HPB.* 2000;2:333–339.
23. Couinaud C, ed. *Le Foie: Études Anatomiques et Chirurgicales.* Paris: Masson; 1957.
24. Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours.* 5th ed. New York: Wiley; 1997.
25. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology.* 1983;148:397–401.
26. Sato Y, Fujiwara K, Ogata I, et al. Transcatheter arterial embolization for hepatocellular carcinoma. Benefits and limitations for unresectable cases with liver cirrhosis evaluated by comparison with other conservative treatments. *Cancer.* 1985;55:2822–2825.
27. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology.* 2003;37:429–442.

J Gastrointest Surg
DOI 10.1007/s11605-011-1795-0

ORIGINAL ARTICLE

Neo-adjuvant Chemoradiation Therapy Using S-1 Followed by Surgical Resection in Patients with Pancreatic Cancer

Sohei Satoi · Hideyoshi Toyokawa · Hiroaki Yanagimoto · Tomohisa Yamamoto · Minoru Kamata · Chisato Ohe · Noriko Sakaida · Yoshiko Uemura · Hiroaki Kitade · Noboru Tanigawa · Kentaro Inoue · Yoichi Matsui · A-Hon Kwon

Received: 15 September 2011 / Accepted: 23 November 2011

Abstract
Objective The aim of this study was to compare short-term surgical results in pancreatic cancer patients who underwent surgical resection after neo-adjuvant chemoradiation therapy (NACRT) using S-1.
Methods The study population comprised 77 patients with pancreatic cancer between 2006 and 2010. Out of 34 patients who underwent staging laparoscopy between 2008 and 2010, 31 patients without occult distant organ metastasis underwent chemoradiation and of whom 30 underwent pancreatectomy (NACRT group). Of the other 43 patients, 36 underwent surgical resection in 2006–2008, followed by adjuvant therapy (adjuvant group). The primary endpoint was frequency of pathological curative resection (R0).
Results The new regimen of NACRT was feasible and safe. Twenty-eight of 30 (93%) patients in the NACRT group had R0 resection, which was significantly higher than in the adjuvant group (21 of 36 patients, 58%, $p=0.005$). The number and extent of metastatic lymph nodes in the NACRT group (1 (0–25), N0/1; 18 of 38) was significantly lower than in the adjuvant group (2 (0–19), N0/1; 23 of 30), $p=0.0363$). The frequency of intractable ascites in the NACRT group (eight of 30) was significantly higher than in the adjuvant group (two of 36, $p=0.035$).
Conclusion Neo-adjuvant chemoradiation therapy using S-1 followed by pancreatectomy can improve the rate of pathologically curative resection and reduces the number and extent of lymph node metastasis.

Keywords Chemoradiation · S-1 · Adjuvant chemotherapy · Residual tumor grading · Mortality and morbidity

S. Satoi (✉) · H. Toyokawa · H. Yanagimoto · T. Yamamoto · H. Kitade · K. Inoue · Y. Matsui · A.-H. Kwon
Department of Surgery, Kansai Medical University,
2-3-1, Shin-machi,
Hirakata City, Osaka 573-1191, Japan
e-mail: satoi@hirakata.kmu.ac.jp

M. Kamata · N. Tanigawa
Department of Radiology, Kansai Medical University,
2-3-1, Shin-machi,
Hirakata City, Osaka 573-1191, Japan

C. Ohe · N. Sakaida · Y. Uemura
Department of Pathology, Kansai Medical University,
2-3-1, Shin-machi,
Hirakata-City, Osaka 573-1191, Japan

Introduction

Pancreatic cancer is a lethal disease with a poor prognosis, even in patients who have undergone curative resection. The results of surgical therapy alone for ductal pancreatic adenocarcinoma are disappointing, and the 5-year actual survival rate ranges from 3% to 17%, even after surgical resection.[1–5] Bradley proposed that further improvements in the numbers of long-term survivors from this dread disease, or increases in the number of actual cures, are unlikely to result from modifications of current surgical techniques.[6] To achieve a 5-year survival rate exceeding 50% in patients with pancreatic cancer, Traverso[7] 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 neo-adjuvant therapy.

Published online: 09 December 2011

Neo-adjuvant chemoradiation therapy (NACRT) has several possibilities, such as improved patient selection after the re-staging evaluation, increased resectability rate with clear margins (R0 resection), and a decreased rate of metastatic lymph nodes (LN) and local relapse.[8] We previously reported that NACRT increased the resectability rate with clear margins and decreased the rate of metastatic spread to the lymph nodes, resulting in a significant improvement of the 5-year actual survival rate in curative cases with pancreatic cancer and who had not received adjuvant therapy.[9–11] However, there were three limitations and/or issues associated with our previous study that need to be addressed. Firstly, approximately 20% of patients who underwent NACRT did not undergo subsequent surgical resection because of tumor progression or newly developed distant organ metastases. Secondly, no partial or complete responses were observed after pre-operative chemoradiation using low-dose 5-fluorouracil and cisplatin or gemcitabine (400 mg/m^2, three times in 4 weeks). Finally, although the actual disease-free survival rate at 1 year was approximately 50%, this was similar to that of the surgery-alone group. To address these issues, we have introduced a new strategy of treating patients with pancreatic cancer.

The objective of this study was to investigate the short-term results in patients with pancreatic cancer after surgical resection following NACRT using S-1[12], an orally administered drug consisted of a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium.

Patients and Methods

Between January 2006 and September 2010, 103 consecutive patients with a clinical diagnosis of pancreatic ductal adenocarcinoma met our resectability criteria[9,10] and were regarded as potentially or borderline resectable or unresectable pancreatic cancer patients, as defined by the National Comprehensive Cancer Network (NCCN) guideline.[13] This diagnosis was made using cine-imaging multi-detector row CT (MDCT) at Kansai Medical University Hospital. The patients who were expected to achieve pathologically curative resection by Appleby operation[14] or distal pancreatectomy with the celiac axis (CA) resection[15] were also eligible for this study. Cases involving an endocrine tumor of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, anaplastic cancer, duodenal cancer, distal common bile duct cancer, or ampullary cancer were excluded. The period during which the patient was treated determined which group they were classified under, namely adjuvant (2006–2008) or NACRT (2008–2010) groups (Fig. 1).

Adjuvant Group Between January 2006 and September 2008, among 48 consecutive patients, 43 with T3/T4 pancreatic cancer (International Union Against Cancer (UICC) classification, sixth edition[16]) who met our resectability criteria[9,10] were classified as the adjuvant group, as shown in Fig. 1. Peri-operatively, all 43 patients had pathological evidence of pancreatic ductal adenocarcinoma. It was planned that all patients in the adjuvant group who underwent pancreatectomy would then receive adjuvant chemotherapy comprising weekly gemcitabine (1,000 mg/m^2) with three times in 4 weeks and a total of 18 times of gemcitabine administration.

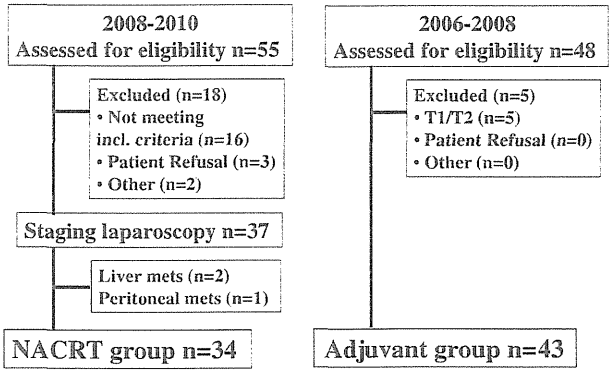

Fig. 1 Study profile

NACRT Group In October 2008, we introduced a new strategy for treating T3/T4 pancreatic cancer patients (UICC classification, sixth edition[16]) who met our resectability criteria,[9,10] and all patients since that date have been treated with this method, as described below. The main criteria for inclusion in this NACRT group were (1) T3/T4 pancreatic cancer (UICC classification, sixth edition[16]) and coincided with our resectability,[9,10] (2) confirmation of pathological evidence of pancreatic cancer, (3) no distant organ metastasis under the staging laparoscopy, and (4) introduction of adjuvant chemotherapy. There were 55 consecutive patients with clinically diagnosed pancreatic cancer between October 2008 and September 2010. Eighteen patients were excluded due to no pathological evidence (n=4), pre-operative diagnosis of lower bile duct cancer (n=4), localized tumor within pancreatic parenchyma (n=3), patients' refusal (n=3), poor performance status (n=2), and other reasons (n=2). The remaining 37 patients underwent staging laparoscopy, following which three additional patients with occult liver (n=2) and peritoneal (n=1) metastases were also excluded. Thus, eventually, 34 patients underwent the planned NACRT (described below) and were classified as the NACRT group (Fig. 1). The tumor extension in these patients was re-evaluated by cine-imaging MDCT 3 weeks after NACRT. It was planned that all patients in whom the MDCT did not show progressive disease or the development of newly distant organ metastasis would undergo

pancreatectomy at approximately 1 week after this re-evaluation. All patients who underwent pancreatectomy following NACRT were to undergo adjuvant chemotherapy with the same regimen as patients in the adjuvant group.

Regimen of NACRT Following the result of the phase I trial of S-1 with concurrent radiotherapy by Ikeda et al.,[12] radiotherapy was administered by 10 or 15 MV photons using three-dimensional treatment planning. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. The clinical target volume (CTV) included only the gross primary tumor and nodal involvement enlarged over 10 mm, as detected by computed tomography. Elective nodal irradiation was not used. The planning target volume was defined as CTV plus a 10-mm margin in the lateral direction and 10–20-mm margin in the craniocaudal direction to account for respiratory organ motion and daily setup error. The four-field technique was used. S-1 was administered orally, twice daily (80 mg/m^2/day) on the day of irradiation (Monday to Friday) during radiotherapy.

Extent of Lymph Node and Nerve Plexus Dissection LN dissection around the CA, superior mesenteric artery (SMA), middle colic artery (MCA), superior mesenteric vein (SMV), para-aortic region, and of the hepatoduodenal ligament and right-sided dissection of the nerve plexus around the CA and the SMA was carried out in patients who underwent pancreaticoduodenectomy. In patients who underwent distal pancreatectomy, LN dissection around the CA, SMA, MCA, SMV, and para-aortic region was performed in all patients, while left-sided dissection of the nerve plexus around the CA and the SMA was limited to patients with pancreatic body cancer. In a few cases, distal pancreatectomy with celiac axis resection was performed.

Post-operative morbidity and mortality, defined as in-hospital death due to any cause, were also recorded. Informed consent was obtained from all patients according to institutional regulations, and this study was approved by the local ethics committee. Patient data were obtained from the prospective database of pancreatobiliary disease at Kansai Medical University Hospital.

Endpoints and Statistical Analysis The primary endpoint was the frequency of pathological curative resection (R0) defined by residual tumor grading. The specimen was serially cut with the thickness of 5 mm. All of these were histologically examined according to "General Rules for the study of pancreatic Cancer[17]." Within the general rule, when all of surgical margin factors, such as the pancreatic and bile duct transection margins and dissected peripancreatic tissue margin, were negative, we determined no residual tumor (R0). If at least one of them was positive, pathological residual tumor (R1) was determined. Furthermore, the stumps of the nerve plexus and the retroperitoneal tissue were pathologically examined independently of the resected specimen, in order to evaluate, in detail, the extent of resection (namely R0 or R1) in the NACRT group. Secondary endpoints were feasibility of NACRT and its associated adverse effects, response rate defined by Response Evaluation Criteria in Solid Tumor,[18] pathological tumor grading defined by Evans classification,[19] and safety of pancreatectomy following NACRT. The study design to predict the number of patients necessary for statistical validity (two-sided) was based on the premise of improving the rate of pathologically curative resection from 70% to 90%, with the α set at 0.05 and the β set at 0.2, yielding a power of 80%. It was calculated that 30 patients were required in this study group. The countable data were expressed as the median and range. The countable data using Mann–Whitney U test or the category data using Fisher's exact test or chi-square test were compared between the NACRT and adjuvant groups. Results were considered significant at $p<0.05$.

Results

Clinical Courses of Patients in NACRT and Adjuvant Groups As shown in Fig. 2, among 34 patients in the NACRT group, one patient withdrew her consent to continue NACRT treatment due to grade 1 nausea and fatigue; she underwent pancreatectomy 19 days after discontinuation of NACRT. MDCT for re-evaluation showed the presence of multiple liver metastases in two patients, and one patient refused subsequent pancreatectomy due to poor performance status. Among 31 patients who underwent open laparotomy,

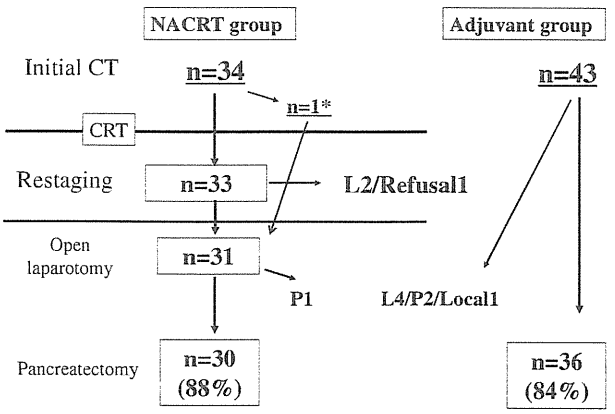

Fig. 2 Clinical course of NACRT and adjuvant groups. *Asterisk* the patient who had refused to continue this regimen underwent pancreatectomy without re-evaluation. *L* liver metastasis, *P* peritoneal metastasis, *Local* locally advanced tumor

one patient incidentally had occult peritoneal metastases. Consequently, 30 out of the 34 patients underwent pancreatectomy in NACRT group.

In the adjuvant group, seven patients did not undergo pancreatectomy because of liver metastasis (n=4), peritoneal metastasis (n=2), and progressive local disease (n=1) which became apparent during open laparotomy. Thus, eventually, 36 of 43 patients underwent surgical resection in the adjuvant group. There was no difference in the surgical resectability rate between the two groups.

Radiological Response and Adverse Effects of Chemoradiotherapy A total of 33 out of 34 patients completed the regimen of NACRT and were evaluated for efficacy in terms of radiological response at 3 weeks after the end of CRT. The patient who had refused to continue this regimen underwent pancreatectomy without re-evaluation. Complete response was not observed in any patient. Partial response and stable disease were achieved in six and 11 patients, respectively. The overall response rate and disease control rate were 18% and 88.0%, respectively. Twenty-five of 34 patients in NACRT group had pancreatic cancer with radiographic findings of portal or superior mesenteric vein (PV/SMV) invasion at pre-NACRT period. Six of nine patients with PV/SMV involvement demonstrating tumor abutment had tumor shrinkage with no radiographic evidence of PV/SMV abutment after NACRT. Three of 16 patients with PV/SMV involvement with impingement and narrowing of the lumen had tumor shrinkage with no radiographic evidence of PV/SMV abutment after NACRT. A total of 33 patients were evaluated for toxicity of NACRT as shown in Table 1. Adverse events were reported in 18 (55%) patients. No on-treatment deaths or grade 4 toxicity occurred. The most severe hematologic toxicity was leukocytosis (grade 3), reported in only one patient (3.0%). Grade 3 anorexia and fatigue were each seen in one patient (3.0%). Problems with biliary stenting were seen in seven patients (21%), who underwent procedures to replace the stenting. All toxicities were tolerable and reversible after temporarily withholding therapy.

Comparisons of Surgical and Pathological Results Between NACRT and Adjuvant Groups There were no significant differences in the clinical backgrounds between NACRT and adjuvant groups, apart from the resectability status defined by NCCN[12] as shown in Table 2. A significantly higher frequency of borderline resectable and unresectable pancreatic cancer was seen in the NACRT group relative to the adjuvant group (p=0.022). No significant differences were seen in operative factors between the two treatment groups, as shown in Table 3. Resection of other organs, including vascular resection, was carried out in 17 of 36 patients in the adjuvant group and 19 of 30 patients in NACRT group.

Regarding the rate of pathologically curative resection (R0), which was the primary endpoint in this study, 28 of 30 (93%) patients in NACRT group had R0 resection, which was significantly higher than the rate in the adjuvant group, where 21 of 36 (58%) patients had R0 resection (p=0.005). The reason of R1 resections of two patients in the NACRT group was the SMA margin.[20] The SMA margins were positive in 12 of 13 patients with R1 resections and in all patients with R2 resections (n=2). The neck margins were positive in the residual one of 13 patients with R1 resections and in one of two patients with R2 resections.

The number of metastatic lymph nodes in the NACRT group was significantly lower than the adjuvant group (p= 0.0363). When comparing the extent of metastatic lymph nodes, the frequency of N0/1 in the NACRT group was higher than in the adjuvant group (p=0.041). The lymph node ratio in the NACRT group was significantly lower than that in the adjuvant group (p=0.032). There was a tendency for a lower rate of negative lymph nodes in the NACRT group relative to the adjuvant group, but the difference did not reach statistical significance. In the NACRT group, there were three patients with T1/2 defined by pathological findings, with evidence of down-staging. Pathological effect, as defined by Evans classification[19], was grade IIA (n=21), IIB (n=7), and III (n=2).

Comparisons of Post-operative Mortality and Morbidity Between NACRT and Adjuvant Groups With one exception, there were no significant differences in mortality and morbidity between the two groups (Table 4). The exception was rate of intractable ascites, defined as drug resistance or ascites needed paracentesis, which was significantly higher in the NACRT group (eight of 30 patients, 27%) compared with the adjuvant group (two of 36 patients, 6%) (p=0.035). Diarrhea needing oral administration of loperamide hydrochloride and tincture of opium was reported in five of 36 (14%) patients in the adjuvant group and in nine of 30 (30%) patients in the NACR group, but the difference was not significant (p=0.138). There were three in-hospital deaths in the NACRT group. They had borderline resectable pancreatic cancer that needed vascular resection and/or other organ resection such as colon, adrenal gland, or stomach. They had adverse events of grade 2 anorexia and/or fatigue during NACRT. Postoperatively, three patients had anastomotic failure of the colon followed by liver failure, massive ascites followed by aspiration pneumonia, or fungemia followed by multiple organ dysfunction syndrome.

Discussion

In the majority of patients with pancreatic cancer, the tumor is classified as unresectable at diagnosis, and only

Table 1 Toxicity of NACRT

		0	1	2	3	4	G1–G4 (%)	G3–G4 (%)
Hematologic	Leucopenia	29	1	3	1	0	15	3.0
	Neutropenia	32	0	2	0	0	6.0	0
	Anemia	33	1	0	0	0	3.0	0
	Thrombocytopenia	34	0	0	0	0	0	0
Non-hematologic	Nausea	33	1	0	0	0	3.0	0
	Vomiting	33	0	1	0	0	3.0	0
	Anorexia	21	5	7	1	0	38	3.0
	Diarrhea	33	0	1	0	0	3.0	0
	Fatigue	27	0	6	1	0	21	3.0
	Weight loss	25	7	2	0	0	26.4	0
	Gastric ulcer	33	0	1	0	0	3.0	0
	DVT	33	0	1	0	0	3.0	0
	Skin rash	33	0	1	0	0	3.0	0
	Fever	26	8	0	0	0	23.5	0
	Stent trouble	28	0	0	7	0	20.8	20.8
No adverse events $n=15$								

Toxicity was graded according to Common Terminology Criteria for Adverse Events v4.0

DVT deep vein thrombosis

approximately 20% of patients are indicated for surgical resection. Even after "curative" resection, patients with pancreatic cancer face a 50–80% local recurrence rate and a 25–50% chance of developing distant metastases in the peritoneum and liver, resulting in an actual 5-year survival rate of approximately 10%.[1–5] Recently, some randomized studies have shown favorable results in pancreatic cancer patients who underwent curative resection followed by adjuvant therapy, reporting median survival times within the range of 20.1–23.6 months.[21–23] A systematic review and meta-analysis by Gillen et al. showed that an estimated median survival time of patients with resectable pancreatic cancer who underwent surgical resection following neo-adjuvant therapy was similar to those of patients who had adjuvant therapy.[24] Recently, a few centers have reported better actual survival rate in patients with pancreatic cancer who underwent surgical resection following NACRT. For example, the M.D. Anderson Cancer Center Group showed that the actual 5-year survival rate of patients after multidisciplinary management including surgical resection was 27%,[25] and in patients with resectable pancreatic head cancer who underwent surgical resection following preoperative gemcitabine-based chemoradiation, the actual 5-year survival rate was 36%.[26] Our previous study[9–11] demonstrated that the actual 5-year survival and disease-free survival rates in the pre-CRT group, who did not receive adjuvant chemotherapy, were significantly longer than in the surgery-alone group, in a sub-group analysis of patients who underwent curative resection. In fact, the actual survival curves in these studies demonstrated that a fall of the survival curve within 3 years after surgical resection, plateaued when it passed the 3-year mark. Thus, surgical resection following NACRT can be associated with improvement of long-term survival rate through good local disease control. In our previous study,

Table 2 Clinical background between NACRT and adjuvant groups

Parameter	Adjuvant ($n=36$)	NACRT ($n=30$)	p value
Sex (male/female)	25:11	15:15	0.133
Age (years)[a]	68 (51–81)	65.5 (36–79)	0.107
CA19-9 (U/ml)[a]	127 (6–1,729)	247 (1–2,232)	0.067
Diabetes mellitus (+/−)	10:26	11:19	0.596
Obstructive jaundice (+/−)	30:6	20:10	0.153
Albumin (g/dl)[a]	3.8 (1.9–4.4)	3.6 (2–4.3)	0.286
Hemoglobin (g/dl)[a]	12.1 (7.9–15.2)	11.4 (9.1–13.9)	0.142
Platelet count ($\times 10^4$)[a]	24 (12–43)	21 (13–40)	0.908
PR vs BR/UN	19:17/0	7:21/2	0.022
Stent exchange (+/−)	3:33	7:23	0.089

PR potentially resectable pancreatic cancer, *BR* borderline resectable pancreatic cancer, *UN* unresectable pancreatic cancer

[a]Values are median (range)

Table 3 Comparisons of surgical results between NACRT and adjuvant groups

Parameter	Adjuvant (n=36)	NACRT (n=30)	p value
Extent of blood loss (ml)	999 (324–5,238)	1,376 (438–3,853)	0.151
Op time (min)	514 (210–672)	531 (380–711)	0.146
Op type (PD/PpPD/DP/TP)	22:8:5:1	22:1:6:1	0.112
PV resection (+/−)	14:22	17:13[b]	0.216
CA/CHA resection (+/−)	0:36	2:28	0.203
Blood transfusion (none/auto/allo)	4:23:9	8:13:9	0.166
Location (Ph/Pbt)	31:5	22:8	0.227
Tumor size (mm)	32.5 (23–65)	30 (10–65)	0.341
Numbers of harvested LNs	26 (7–56)	33 (6–65)	0.340
Numbers of metastatic LNs	2 (0–19)	1 (0–25)	0.0363
Lymph node ratio[a]	0.07 (0–0.62)	0.02 (0–0.38)	0.032
N (−/+)	8:28	14:16	0.065
N 0/1:2/3	18:18	23:7	0.041
T 1/2:3/4	0:36	3:27	0.089
R0:1:2	21:13:2	28:2:0	0.005
Evans classification (IIA/IIB/III)	N/E	21:7:2	

TNM classification was defined by Japanese Pancreas Society

NACRT neo-adjuvant chemoradiation therapy, *Op* operation, *PD* pancreaticoduodenectomy, *PpPD* pylorus preserving pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *PV* portal vein, *CA* celiac axis, *CHA* common hepatic artery, *auto* autologous blood transfusion, *allo* allogeneic blood transfusion, *Ph* pancreatic head, *Pbt* pancreatic body and tail, *LN* lymph node, *R0* negative microscopic margin, *R1* positive microscopic margin, *R2* positive gross margin

[a] Lymph node ratio is calculated as number of metastatic lymph nodes/harvested lymph nodes

[b] One patient who underwent renal vein resection was included

approximately half the patients who underwent curative resection had disease recurrence at 1 year in both the NACRT and surgery-alone groups. NACRT 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 post-operative recurrence sites.

Table 4 Comparison of morbidity and mortality between NACRT and adjuvant groups

Parameter	Adjuvant	NACRT	p value
Overall complication (+/−)	12:24	10:20	1.000
Mortality (+/−)	0:36	3:27	0.098
Re-operation/no re-operation	0:36	1:29	0.455
DGE (+/−)	3:33	2:28	1.000
POPF (+/−)	7:29	1:29	0.063
Grade A/B/C	4:3:0	1:0:0	0.245
Wound dehiscence (+/−)	4:32	6:24	0.492
Intra-abdominal abscess (+/−)	1:35	1:29	1.000
Cholangitis (+/−)	0:36	2:28	0.203
Pneumonia (+/−)	0:36	2:28	0.203
Bile leakage (+/−)	0:36	0:30	–
PPH (+/−)	0:36	0:30	–
Intractable ascites (+/−)	2:34	8:22	0.035
Diarrhea (+/−)	5:31	9:21	0.138

DGE delayed gastric emptying, *NACRT* neo-adjuvant chemoradiation therapy, *POPF* post-operative pancreatic fistula, *PPH* post-pancreatectomy hemorrhage

There were several limitations and issues with our previous study that we aimed to resolve in this present study, namely (1) approximately 20% of patients who received pre-operative CRT did not undergo surgical resection because of progressive disease, resulting in a median survival time of 5.5 months (unpublished data); (2) surgical resection followed by pre-operative CRT only did not improve the short-term results; and (3) the previous regimen of pre-CRT was not aggressive enough to achieve tumor shrinkage. Therefore, we introduced (1) staging laparoscopy before patient recruitment to the new regimen of NACRT, (2) standard adjuvant chemotherapy, and (3) full dose of S-1 (80 mg/m^2) and radiotherapy (50.4 Gy).

S-1 is an orally administered drug, which is a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium. Very recently, the results of the gemcitabine and S-1 trial study (a randomized, prospective, open-label, three-arm, and phase III study) were presented to the public at the annual meeting of the American Society of Clinical Oncology 2011.[27] The results showed that oral S-1 provided

Table 5 Surgical results of neo-adjuvant chemoradiation therapy

Authors (reference number)	Year of publication	No of patients	Regimen of CRT	Resection rate; *n* (%)	Vascular resection rate; *n* (%)	R0 (%)	Negative LN mets rate (%)
White et al.[33]	2001	53	5-FU based (45 Gy)	28 (53)	2 (7)	71	19 (70)
Moutardier et al.[34]	2004	61	5-FU based (60 Gy)	40 (66)	5 (13)	95	30 (75)
Evans et al.[26]	2008	86	GEM (30 Gy)	64 (74)	13 (20)	89	40 (63)
Le Scodan et al.[35]	2009	41	5-FU based (50 Gy)	26 (63)	N/A	80.7	12 (46)
Ohigashi et al.[36]	2009	38	GEM (50.4 Gy)	31 (82)	17 (55)	97	28 (90)
Turrini et al.[37]	2010	34	Docetaxel-based (45)	17 (50)	N/A	100	13 (76)
Stokes et al.[38]	2011	40	Capecitabine (50 Gy)	16 (25)	4 (25)	88	13 (81)
Present study	–	34	S-1 (50 Gy)	30 (88)	17 (57)	94	14 (47)

CRT chemoradiation therapy, *5-FU* 5-fluorouracil, *GEM* gemcitabine, *LN* lymph node, *mets* metastasis, *N/A* not available

similar efficacy and tolerable toxicity to gemcitabine when used as first-line treatment for unresectable pancreatic cancer. The response rates of gemcitabine, S-1, and gemcitabine+S-1 were 13.3%, 21.0%, and 29.3%, respectively. In addition to the benefit of the oral drug on its own, the combination of S-1 and radiotherapy has been demonstrated to exert a synergistic effect against 5-FU-resistant cancer xenografts.[28,29] The response rate of CRT using S-1 was around 20% in phase I and II studies in patients with unresectable pancreatic cancer[12,30–32] As expected, our results showed that the response rate and disease control rate of NACRT using S-1 were 18% and 88.0%, respectively. To our knowledge, this is the first study of NACRT using S-1 and concurrent radiation for patients with resectable pancreatic cancer.

Despite the fact that we excluded patients with occult metastasis by using staging laparoscopy before study entry for NACRT, three of 34 patients had occult liver or peritoneal metastasis after NACRT. During the 9 weeks between study entry and surgical resection, approximately 10% of pancreatic cancer patients had progressive disease. In this study, the majority of patients who underwent NACRT using S-1 did not suffer from severe adverse effects, and 33 of 34 patients completed this regimen. However, seven of 34 (21%) NACRT patients required hospitalization because of cholangitis, resulting in a delay of the operation date. The primary endpoint of pathologically curative resection rate in this study showed a statistically significant difference in favor of NACRT over the adjuvant group, despite the fact that the NACRT group had a higher frequency of borderline resectable and unresectable pancreatic cancer cases. In this study, we pathologically examined the cut stump of the nerve plexus and retroperitoneal tissue independently in all cases, which was the main reason for a positive surgical margin (R1 resection). Moreover, there was a tendency for a higher rate of negative lymph node metastasis in the NACRT group than in the adjuvant group, but this did not reach statistical significance because of the small sample size. The frequency of N0 and N1 and number of metastatic lymph nodes in the NACRT group were significantly improved relative to those in adjuvant group. Most studies have reported that predictive factors for prognosis in patients with pancreatic cancer were pathologically curative resection and negative lymph node metastasis.[1–5] In addition to our results, some authors have reported the promising results of a higher rate of R0 resection (70–100%) and lower rate of metastastic lymph nodes (46–90%) in patients who underwent surgical resection following NACRT, as summarized in Table 5.[26,33–38]

We recognize that a limitation of our study was its prospective non-randomized design. Approximately 30% of patients were excluded before staging laparoscopy in the NACRT group due to no pathological evidence of pancreatic cancer, misdiagnosis of bile duct cancer, and so on. In contrast, 43 of 48 patients were included in the adjuvant group; the five excluded patients had T1/2 pancreatic cancer. Consequently, the frequency of borderline resectable pancreatic cancer in the NACRT group was significantly higher than in the adjuvant group. However, irrespective of this one important difference in the baseline characteristics between the two groups, the primary endpoint of this study was still reached.

Although there were no statistical differences in morbidity and mortality between the two groups, three in-hospital deaths were observed in the NACRT group. The common clinical features of these three patients were borderline resectable pancreatic cancer, grade 2 anorexia or fatigue during CRT, and other organ resection including vascular

resection. Gillen et al.[24] reported that in-hospital mortality after neo-adjuvant treatment and tumor resection was estimated at 2.2–6.0% in resectable patients and at 5.1–9.5% in non-resectable patients. In this present study, 23 of 30 (77%) patients in the NACRT group had borderline resectable and unresectable pancreatic cancer, and 17 of 30 (57%) patients underwent pancreatectomy with vascular resection. The patient population in the NACRT group had shifted to an advanced stage. Thus, special attention should be paid to patients with advanced pancreatic cancer who undergo this new type of surgical strategy.

In conclusion, in this study, NACRT using the orally administered drug S-1 resulted in a better response rate than was seen among the patients in the adjuvant group; it was also feasible and safe. Pancreatectomy after NACRT improved the rate of pathologically curative resection and reduced the number and extent of lymph node metastasis. A large-scale randomized controlled trial will be needed to confirm the clinical efficacy of NACRT.

References

1. Takai S, Satoi S, Toyokawa H, Yanagimoto H, Sugimoto N, Tsuji K, Araki H, Matsui Y, Imamura A, Kwon AH, Kamiyama Y. Clinicopathologic evaluation after resection for ductal adenocarcinoma of the pancreas: a retrospective, single-institution experience. Pancreas. 2003;26:243–9.
2. Conlon KC, Klimstra DS, Brennan MF. Long term survival after curative resection for pancreatic ductal adenocarcinoma. Ann Surg. 1996;223:273–279.
3. Adham M, Jaeck D, Le Borgne J, Oussoultzouglou E, Chenard-Neu MP, Mosnier JF, Scoazec JY, Mornex F, Partensky C. Long-term survival (5–20 years) after pancreatectomy for pancreatic ductal adenocarcinoma: a series of 30 patients collected from 3 institutions. Pancreas. 2008;37:352–7.
4. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, Gullerud RE, Donohue JH, Nagorney DM, Farnell MB. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg. 2008;247:456–62.
5. Han SS, Jang JY, Kim SW, Kim WH, Lee KU, Park YH. Analysis of long-term survivors after surgical resection for pancreatic cancer. Pancreas 2006;32:271–5.
6. Bradley III EL. Long-term survival after pancreatoduodenectomy for ductal adenocarcinoma. The emperor has no clothes? Pancreas 2008;37:349–351.
7. Traverso LW. Pancreatic cancer: surgery alone is not sufficient. Surg Endosc. 2006;20:446–9.
8. Crane CH, Varadhachary G, Pisters PW, Evans DB, Wolff RA. Future chemoradiation strategies in pancreatic cancer. Semin Oncol. 2007;34:335–46.
9. Takai S, Satoi S, Yanagimoto H, Toyokawa H, Takahashi K, Terakawa N, Araki H, Matsui Y, Sohgawa M, Kamiyama Y. Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. Pancreas 2008;36:e26-32.
10. Satoi S, Yanagimoto H, Toyokawa H, Takahashi K, Matsui Y, Kitade H, Mergental H, Tanigawa N, Takai S, Kwon AH. Surgical results following pre-operative chemoradiation therapy for patients with pancreatic cancer. Pancreas. 2009,38:282–8.
11. Satoi S, Yanagimoto H, Toyokawa H, Yamamoto T, Hirooka S, Yui R, Yamaki S, Matsui Y, Kitade H, Tanigawa N, Takai S, A-Hon Kwon. Long-term results of surgical resection following preoperative chemoradiation in patients with pancreatic cancer. Pancreas 2011; in press.
12. Ikeda M, Okusaka T, Ito Y, Ueno H, Morizane C, Furuse J, Ishii H, Kawashima M, Kagami Y, Ikeda H. A phase I trial of S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. Brit J Cancer 2007;96:1650–1655.
13. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology, ver 1. Fort Washington: NCCN; 2011.
14. Appleby LH. The celiac axis in the expansion of the operation for gastric carcinoma. Cancer 1953;6:704–7.
15. Hirano S, Kondo S, Hara T, Ambo Y, Tanaka E, Shichinohe T, Suzuki O, Hazama K. Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer: long-term results. Ann Surg. 2007;246:46–51.
16. Sobin L, Wittekind C, eds. TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.
17. Japan Pancreas Society. The general rules for clinical and pathological management of carcinoma of the pancreas, 6th ed. Tokyo: Kanehara; 2009.
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–216.
19. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Charnsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335–1339.
20. Raut CP, Tseng JF, Sun C, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007;246:52–60.
21. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210.
22. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–277.
23. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304:1073–81.
24. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267.
25. Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, Varadhachary G, Abbruzzese JL, Crane CH, Krishnan S, Vauthey JN, Abdalla EK, Lee JE, Pisters PW, Evans DB. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16:836–47.

26. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerkel GA, Charnsangavej C, Lano EA, Ho L, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008,26:3496–3502.
27. Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Chen JS, Mizumoto K, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi A, Cheng L, Okusaka T. Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (GEM) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study. J Clin Oncol 29: 2011 (suppl; abstr 4007)
28. Harada K, Kawaguchi S, Supriatno, Onoue T, Yoshida H, Sato M. Combined effects of the oral fluoropyrimidine anticancer agent, S-1 and radiation on human oral cancer cells. Oral Oncol 2004;40:713–719.
29. Nakata E, Fukushima M, Takai Y, Nemoto K, Ogawa Y, Nomiya T, Nakamura Y, Milas L, Yamada S. S-1, an oral fluoropyrimidine, enhances radiation response of DLD-1/FU human colon cancer xenografts resistant to 5-FU. Oncol Rep 2006;16:465–471.
30. Shinchi H, Maemura K, Noma H, Mataki Y, Aikou T, Takao S. Phase-I trial of oral fluoropyrimidine anticancer agent (S-1) with concurrent radiotherapy in patients with unresectable pancreatic cancer. Brit J Cancer. 2007;96:1353–1357.
31. Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Shirai Y, Nakagawa A, Kawakami H, Uno T, Ito H, Saisho H. Phase I study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer. Int. J. Radiation Oncology Biol. Phys 2008;67:219–224.
32. Kim HM, Bang S, Park JY, Seong J, Song SY, Chung JB, Park SW. Phase II trial of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer. Cancer Chemother Pharmacol. 2009;63:535–541.
33. White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, McGrath KM, Clary BM, Pappas TN, Tyler DS. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol 2001; 8: 758–765.
34. Moutardier V, Magnin V, Turrini O, Viret F, Hennekinne-Mucci S, Gonçalves A, Pesenti C, Guiramand J, Lelong B, Giovannini M, Monges G, Houvenaeghel G, Delpero JR. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys 2004;60:437–443.
35. Le Scodan R, Mornex F, Girard N, Mercier C, Valette PJ, Ychou M, Bibeau F, Roy P, Scoazec JY, Partensky C. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. Ann Oncol 2009;20:1387–1396.
36. Ohigashi H, Ishikawa O, Eguchi H, Takahashi H, Gotoh K, Yamada T, Yano M, Nakaizumi A, Uehara H, Tomita Y, Nishiyama K. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 2009;250:88–95.
37. Turrini O, Ychou M, Moureau-Zabotto L, Rouanet P, Giovannini M, Moutardier V, Azria D, Delpero JR, Viret F. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: New neoadjuvant regimen was safe and provided an interesting pathologic response. Eur J Surg Oncol. 2010;36:987–92.
38. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. Ann Surg Oncol. 2011;18:619–27.