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Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma

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Key words
HCC, hypervascular, SBRT, solitary, TACE.

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Abstact

Background and Aims: To compare the tumor control and safety of stereotactic body radiation therapy (SBRT) combined with transcatheter arterial chemoembolization (TACE) for small, solitary, and hypervascular hepatocellular carcinoma (HCC) with TACE alone.
Methods: Three hundred and sixty-five HCC patients who had solitary, ≤ 3 cm, and hypervascular nodule were treated with TACE. Among them, 30 patients followed by SBRT (SBRT group) and 38 patients without additional therapy and previous HCC treatment (control group) were enrolled in this retrospective cohort study. Local tumor progression, complication, and disease-free survival were compared between these groups.
Results: There was no difference in clinical background between these groups. Complete response to therapy was noted in 29 (96.3%) patients of the SBRT group, and in only one (3.3%) patient of the TACE group ($P < 0.001$). None of the patients developed acute hematologic toxicity of more than Common Terminology Criteria for Adverse Events Grade 3 during and after the treatment. Furthermore, none of the SBRT group developed radiation-induced liver damage. Disease-free survival of the 12 patients without previous HCC treatments in SBRT group was significantly superior to that in control group (15.7 months *vs* 4.2 months; $P = 0.029$).
Conclusion: The results indicated that SBRT combined with TACE is a safe and effective modality for locoregional treatment of small solitary primary HCC, and could be potentially a suitable option.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death in the world today. Based on the recent trend of periodic surveillance of patients with chronic hepatitis and liver cirrhosis, small HCC are occasionally detected during imaging examinations.[1–4] Transcatheter arterial chemoembolization (TACE) has been used widely and reported to be an effective treatment for patients with HCC.[5–7] Furthermore, TACE can be administered for any type of HCC, regardless of size, location, or number of tumors. Although repeated TACE is one of the most potent therapies for HCC, resistance to the therapy often ensues after several courses, and long-term survival rates are not high at present. Therefore, in early stages of HCC, TACE is not the first-line treatment option.[8]

Surgical resection is considered the first treatment option. However, it is usually limited because the majority of patients, even those with small HCC, have associated severe liver dysfunction.[9–11] In such cases, percutaneous ablation procedures are currently in clinical use as alternative treatment options for small HCC. Radio-frequency ablation is considered safe, effective, and reliable treatment for small HCC.[12–14] This treatment can generally be provided if HCC is detected by ultrasonography, present in the deep layers of the liver, and the patient is not at any risk of bleeding. In patients with early-stage disease, local radical cure is certain and with good convalescence, and thus the goal of any management program is to secure local tumor control. However, for patients with contraindications for hepatic resection or ablative therapy, or those in whom invasive locoregional treatments are deemed unsuitable for other reasons, the present trend is to select

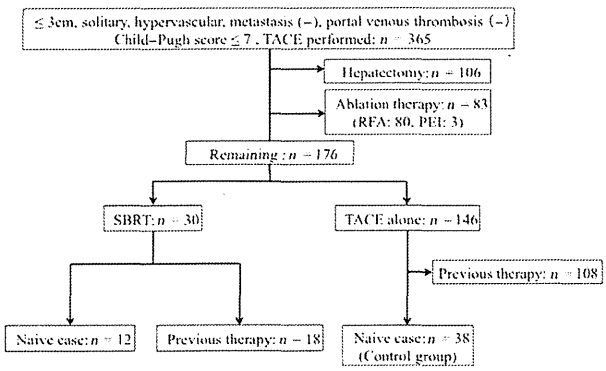

Figure 1 Treatment selection. PEI, percutaneous ethanol injection; RFA, radio-frequency ablation; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

repeat TACE or palliative therapy. Therefore, it is important to develop new treatment strategies for small HCC.

Historically, the role of radiation therapy for HCC has been limited by the risk of radiation-induced liver damage (RILD). However, technological advances in radiation planning, breathing motion reduction strategies, and image guidance have enhanced the feasibility of radiotherapy for HCC, with low risk of serious side-effects. Stereotactic body radiation therapy (SBRT) delivers high-dose radiation to HCC within a short period of time. SBRT procedures and treatment evaluation differ among the different facilities, but at least some studies have so far reported the efficacy and safety of SBRT for intrahepatic HCC.[15–17] In this cohort study, we demonstrate that SBRT combined with TACE can be considered a reliable treatment for small HCC in terms of therapeutic efficacy and safety, and can become an optional treatment for small HCC, similar to other locoregional treatments.

Materials and methods

Patients. Between June 2005 and August 2011, 365 consecutive Japanese HCC patients who met the following eligibility criteria were referred to our hospital and treated with TACE. The eligible criteria were (i) solitary hypervascular HCC nodule, up to 30 mm in diameter, without portal venous thrombosis or extrahepatic metastases and (ii) Child-Turcotte-Pugh (CTP) score ≤ 7. One hundred and six patients (29.0%) of them were followed by hepatic resection and 83 (22.8%) by ablative therapy. In the remaining 176 patients, 30 patients (8.3%) those who were not suitable or had no hope for hepatic resection or ablative therapy were followed by SBRT (SBRT group). The remaining 146 patients (38.9%) had not performed additional therapy after TACE, because they did not hope for additional treatment after TACE, had the HCC nearby the digestive tract, or had the underlying disease prior to HCC, for example, coronary heart disease, interstitial pneumonia, or dementia. In this group, 38 treatment-naive patients with TACE alone were defined as the control group (Fig. 1). All patients of SBRT group received comprehensive details about its benefits, treatment duration, and possible complication. The study protocol was approved by the Human Ethics Review Committee of Hiroshima University and a signed consent form was obtained from each subject.

Diagnosis of HCC. HCC was diagnosed based on imaging studies, including contrast-enhanced dynamic computed tomography (CT) and angiography combined with CT during arterial portography and hepatic arteriography. The diagnosis was based on the following classic imaging manifestations: (i) early enhancement at the arterial phase and hypoattenuation at the portal venous phase or at the equilibrium phase on contrast-enhanced dynamic CT, and (ii) hyperattenuation on CT during hepatic arteriography and hypoattenuation on CT during arterial portography.

TACE. TACE was performed in patients with hypervascular HCC nodules confirmed on CT during hepatic arteriography. TACE was performed through the femoral artery using the Seldinger technique under local anesthesia. An angiographic catheter was inserted into the hepatic feeding artery of a segment or subsegments containing the target tumor. Cisplatin (Randa; Nippon Kayaku, Tokyo, Japan) was used as the anticancer drug mixed with iodized oil (Lipiodol; Nihon Schering, Tokyo, Japan) at a concentration of 10 mg/mL and injected at a dose of 7–70 mg/body, or miriplatin (Miriplatin Hydrate; Dainippon Sumitomo Pharma Co., Tokyo, Japan) mixed with iodized oil (iodine addition products of the ethylesters of fatty acids obtained from poppy seed oil) at a concentration of 20 mg/mL and injected at a dose of 20–80 mg/body. In our institution, cisplatin was used before January 2010, but replaced with miriplatin since then. Cisplatin was used in 28 cases and miriplatin in 10 cases of TACE group, while cisplatin was used in 8 cases and miriplatin in 22 cases of SBRT group. The selected dose was based on tumor size and extent of liver damage. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels. A gelatin sponge was used after TACE.

SBRT. We performed SBRT at 1–2 months (median, 1 month) after TACE. SBRT entails the stereotactic delivery of ablative doses of radiation to a target tissue volume, and thus tight margins are typically used to minimize damage to fronting structures and organs. In all patients, a total dose of 48 or 60 Gy was delivered in four or eight fractions in 4–10 days. Patients were immobilized using a vacuum cushion (Vac-Lok, CIVCO, Kalona, IA, USA). The end-expiration phase has a better interbreath-hold reproducibility of organ position than the end-inspiration phase, and accordingly patients held their breath at end-expiration phase, using Abches (APEX Medical, Tokyo, Japan), a device that allows the patient to self-control the respiratory motion of the chest and abdomen.[18]

For treatment planning, CT volume data were transferred to a 3D treatment planning system (Pinnacle^3 ver. 9.0, PHILIPS, Amsterdam, Netherlands). Gross tumor volume (GTV) was defined as the volume of tumor and represented the remains of lipiodol at TACE and early enhancement of dynamic CT. A clinical target volume (CTV) margin of 3 mm was usually added to GTV for subclinical invasion. A planning target volume margin of 5–8 mm was usually added for reproducibility of respiratory motion and setup error to CTV. Eight noncoplanar ports were

Table 1 Patient characteristics

	SBRT group ($n = 30$)	TACE group ($n = 38$)	*P*-value
Age (years)†	70 (49–90)†	73 (48–92)†	0.082
Gender (male/female)	19/11	15/23	0.08
Tumor size (mm)	16 (10–30)†	21(6–30)†	0.051
Etiology (B/C/B+C/nonBnonC)#	4/24/1/1	4/31/1/2	0.637
T-bilirubin (mg/dL)	0.8 (0.2–1.6)†	0.75 (0.4–2.3)†	0.514
Albumin (g/dL)	4.1 (2.9–5)†	3.7 (2.8–4.9)†	0.112
Platelet ($\times 10^4/\mu L$)	9.9 (2.8–22.3)†	9.5 (5.1–21.4)†	0.246
Prothrombin time (%)	86 (50–109)†	82.5 (59–112)†	0.612
ICG-R (%)‡	16 (10.2–61.5)†	20 (6.2–86.4)†	0.532
Child–Pugh score (5,6/7)	24/6	31/7	0.391
Anticancer drug (miriplatin/cisplatin)	16/14	10/28	< 0.05
Accumulation rate of lipiodol (100–80%/80–50%)	29/1	38/0	0.441
Follow-up period (months)	12.3 (6.0–38.3)†	30.2 (7.4–54.4)†	< 0.05†

†Median (range).
#B, HBs antigen positive; C, HCV antibody positive; B+C, both HBs antigen and HCV antibody negative; HBV, hepatitis B virus; HCV, hepatitis C virus; ‡ICG-R, indocyanine green retention rate at 15 minutes; nonBnonC, both HBs antigen and HCV antibody negative.

selected in all patients, including four coplanar beams and four noncoplanar beams in a direction that avoided the intestine, gallbladder, esophagus, and spine, as much as possible. Treatment was delivered using 6–10 MV photons of the linear accelerator (Clinac iX, Varian Medical Systems, Palo Alto, CA, USA). In principle, tumors were delivered 12 Gy per fraction at the isocenter, and the total dose was 48 Gy with four fractions, with a voluntary breath-hold method. If the dose distribution to the normal liver or other adjacent organs was needed to be considered, tumors were delivered 7.5 Gy per fraction, with a total dose of 60 Gy in eight fractions.

Evaluation. The primary end-point in this study was the comparison of the local tumor control rate and safety between SBRT group and TACE group, while the secondary end-point was comparison of the overall survival rate and disease-free survival rate.

Follow-up dynamic CT was performed at 3 months intervals. The efficacy of treatment was evaluated by dynamic CT at 3 months after TACE in TACE group and at 6 months after SBRT in SBRT group, according to the Response Evaluation Criteria in Cancer of the Liver.[19] The CT findings were confirmed by consensus between two radiologists. We considered the necrotic area or the concentration of lipiodol as the effect of treatment. The necrotic area appeared as low-density area relative to normal hepatocytes, both on the arterial and equilibrium phases of the dynamic CT. When the irradiated nodule area showed this feature, SBRT or TACE, or their combination, was considered to have produced a complete effect. Local tumor progression was considered when a subsequent follow-up CT demonstrated tumor growth or enhancement in the irradiation zone, where complete effect had been noticed previously.

Complications were assessed according to version 4 of the Common Terminology Criteria for Adverse Events. RILD is the most important toxicity after liver irradiation and consists of anicteric hepatomegaly, ascites, and high serum alkaline phosphatase (> twice the upper limit of normal), typically occurring at 2 weeks to 3 months after treatment, or high serum transaminases (> 5 times the upper limit of normal), occurring within 3 months after completion of radiotherapy.[20,21] The blood test was measured regularly over a period of 6 months after the completion of radiotherapy. Physical symptoms were evaluated by asking patients to fill up a questionnaire every month.

Statistical analysis. The Statistical Package for Social Sciences version 9.0 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. The probability of survival was calculated by the Kaplan–Meier method and examined using the log–rank test. A *P*-value of less than 0.05 denoted statistical significance and all tests were two-tailed. In this study, the survival time was defined as the period from the date of SBRT to the date of death or the last follow up. The disease-free survival time represented the period from the date of SBRT to the date of disease progression.

Results

Clinical features. Table 1 lists the clinical characteristics of patients at baseline (before treatment). For SBRT group, the median age of patients was 70 years (range, 49–90), the median follow-up period was 12.3 months (range, 6.0–38.3), and 24 patients were classified as class A, while the remaining six were class B (score 7) by the Child–Pugh classification. For TACE group, the median age was 73 years (range, 48–92), the median follow-up period was 30.2 months (range, 7.4–54.4), and 31 patients were classified as class A, while the remaining seven were class B (score 7). The general condition of all patients was good, with Eastern Cooperative Oncology Group score of 0–1.

The location of targeted HCC was S1, S2, S3, S4, S5, S6, S7, and S8 in 0, 0, 0, 4, 2, 5, 7, and 12 patients in SBRT group, respectively.

TACE. For SBRT group, the median target size was 16 mm (range, 10–30). Miriplatin was used in 16 cases at a median dose of 27 mg (range, 10–80), and cisplatin in 14 cases at 25 mg (range, 5–40). The lipiodol accumulation rate in HCC after TACE was 100–80% in 29 cases and 80–50% in 1 case, but lipiodol was washed out and the accumulation rate became 100–80% in 4 cases,

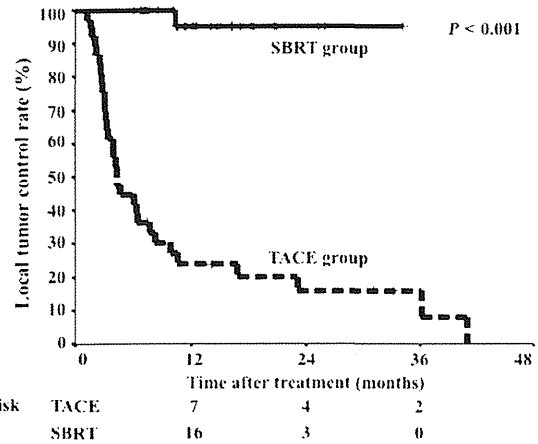

Figure 2 Local tumor control rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

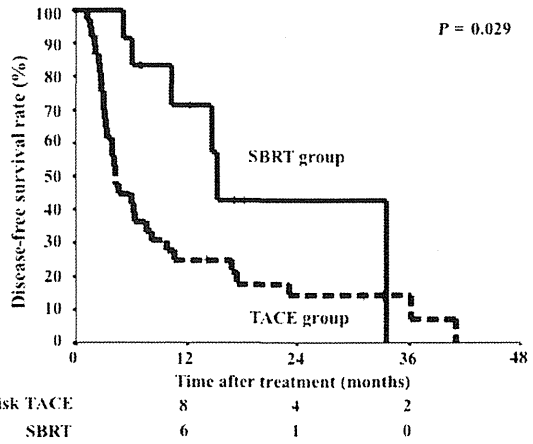

Figure 3 Disease-free survival rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

80–50% in 3 three cases, and 50–0% in 23 cases at 6 months after the end of SBRT.

For TACE group, the median target size was 21 mm (range, 6–30). Miriplatin was used in 10 cases at a median dose of 38 mg (range, 10–65), and cisplatin in 28 cases at 22.5 mg (range, 10–50). The lipiodol accumulation rate in HCC after TACE was 100–80% in 38 cases, but lipiodol was washed out and the accumulation rate became 100–80% in 12 cases, 80–50% in 4 cases, and 50–0% in 22 cases 3 months later at evaluation of the treatment efficacy.

SBRT. SBRT was performed 1–2 months after TACE in SBRT group. The radiation dose was 48 Gy per four fractions in 26 cases and 60 Gy per eight fractions in four cases. The reason for selecting 60 Gy in these four cases was to include the inferior cava vena or gallbladder within the irradiation field, and thus there was a need to reduce the radiation dose per fraction to prevent damage to these organs to levels weaker than the liver. In these four cases, two nodules were located in S7, one in S5, and the other in S4. The nodules in S7 and S5 were located near the inferior vena cava, whereas the nodule in S4 was located near the gallbladder and common bile duct. All cases showed local complete response.

Local tumor control rates. In 30 patients of SBRT group, 29 of 30 (96.3%) patients showed complete response. Although one patient was non-complete response (CR), the arterial phase enhancement of the tumor lasted 10 months only and then gradually disappeared. In 38 patients of TACE group, 1 of 30 (3.3%) patients showed complete response, but the others were non-CR (Fig. 2). We also evaluated local tumor control rates according to anticancer drugs. The local tumor control rate was not significantly affected by miriplatin or cisplatin.

Disease-free survival rates. We evaluated the disease free survival rate and overall survival rate between these two groups about the naive cases. In SBRT group, 12 of 30 patients were naïve

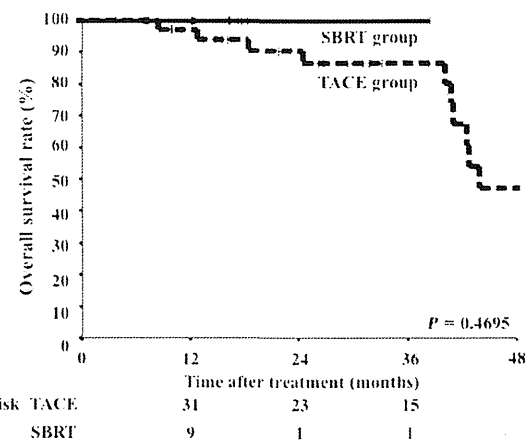

Figure 4 Overall survival rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

cases. In this group, the median disease-free survival time was 15.2 months, while the 1-, 2-, and 3-year cumulative disease-free survival rates were 71.4%, 42.0%, and 0%, respectively. The respective values in TACE group were 4.2 months, 24.8%, 14.2%, and 7.0% (Fig. 3). Disease-free survival in SBRT group was significantly superior to that in TACE group.

Overall survival rate. In SBRT group, the median overall survival time was not reached, because none of 12 patients died. The 1- and 3-year cumulative overall survival rates were 100% and 100%, respectively. In TACE group, the median overall survival time was 40.9 months. Of the 38 patients, four (10.5%) died due to HCC, four (10.5%) due to hepatic insufficiency, and four (10.5%) due to other reasons. The 1-, 2-, and 3-year cumulative overall survival rates were 88.9%, 73.6%, and 66.1%, respectively (Fig. 4).

Table 2 Hematologic and hepatic toxicity according to CTCAE ver.4

	SBRT group ($n = 30$)				TACE group ($n = 38$)			
	Post-SBRT grade				Post-TACE grade			
	1	2	3	4	1	2	3	4
Leukocytopenia	20	8	2	0	30	8	0	0
Thrombocytopenia	21	8	1	0	27	8	3	0
Low hemoglobin	27	3	0	0	36	2	0	0
Hyperbilirubinemia	27	3	0	0	34	2	2	0
High serum transaminases	30	0	0	0	33	5	0	0
High serum alkaline phosphatase	30	0	0	0	34	4	0	0

CTCAE, Common Terminology Criteria for Adverse Events; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

Complications. All patients of these groups completed the prescribed course of treatment. Evaluation of the results of blood tests in either group newly showed no cases of acute hematologic toxicity of more than Grade 3 (Table 2). Figure 5 shows the lack of significant changes in liver function in SBRT group. Furthermore, none of the patients experienced RILD. Within 6 months of the initiation of treatment, one patient of the SBRT group experienced an increase in CTP class, followed by progression in score from 6 to 8. However, there was no relationship between hepatotoxicity and the dose delivered to the normal liver.

Discussion

Following the Clinical Practice Guideline for Hepatocellular Carcinoma,[22] there are some potentially curative options for primary HCC, but they have some limitations.

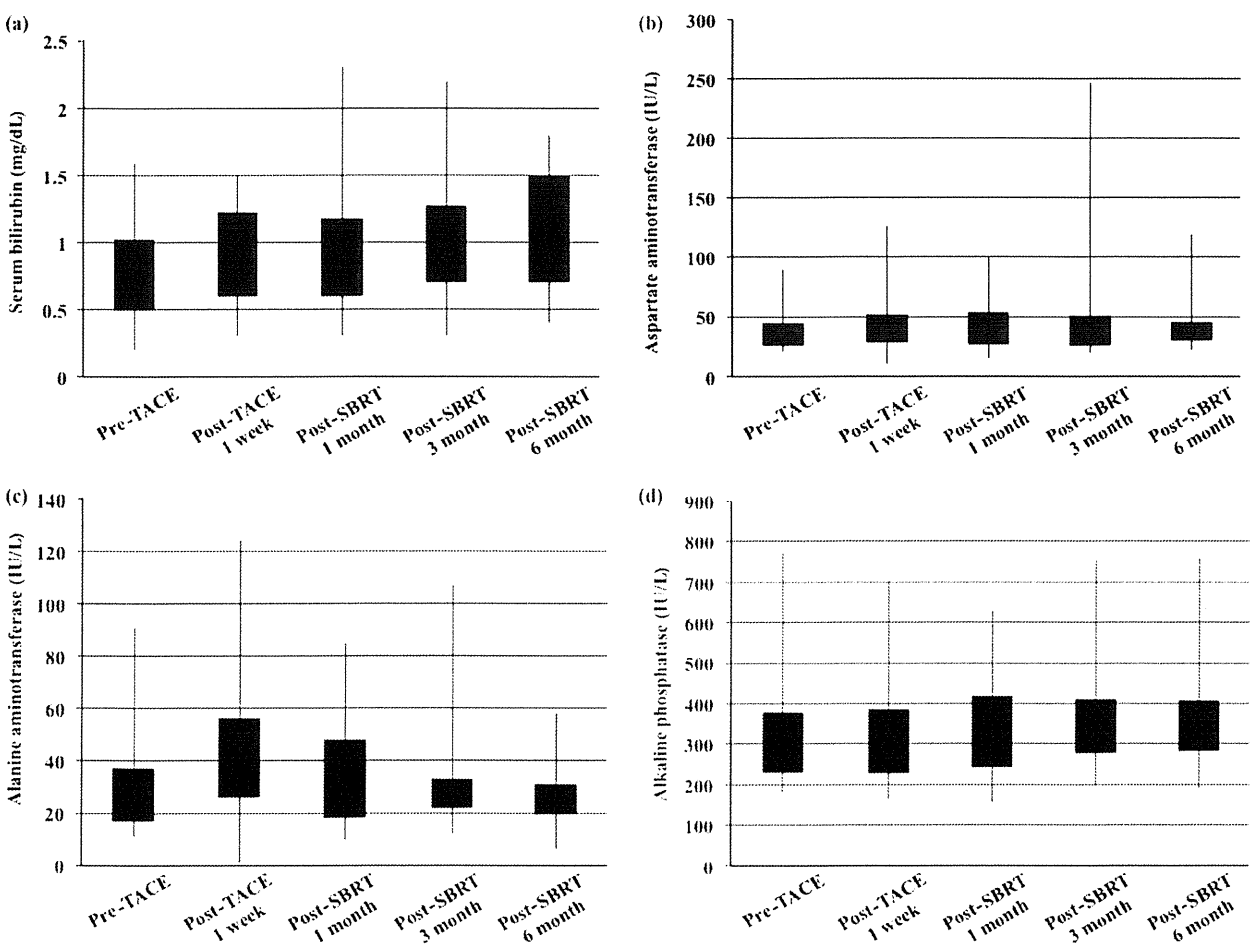

Figure 5 Serial changes in the levels of (a) total bilirubin, (b) aspartate aminotransferase, (c) alanine aminotransferase, and (d) alkaline phosphatase, from pre-TACE to 6 months after SBRT in SBRT group. Data are mean ± SD. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

The use of radiotherapy for HCC remains limited because of risk of RILD and the availability of more efficient or less time-consuming treatment options. However, recently, technological advances in radiation planning, breathing motion reduction strategies, and image guidance have enhanced the feasibility of radiotherapy for HCC, with low risk of toxicity. SBRT delivers a high dose of radiation to HCC within a short period of time and is an effective and less invasive for the delivery of high radiation doses to the tumor with hypofractionation. The role of radiotherapy in the treatment of small HCC has recently been emphasized in the context of the development of SBRT. Andolino *et al.*[23] examined patients with HCC and reported 2-year local tumor control and overall survival rates of 90% and 67%, respectively. Choi *et al.*[24] also reported that the 1- and 2-year survival rates after SBRT for primary HCC were 70.0% and 43.1%, respectively. The difference between these groups was the size of the HCC tumor. Similar results were reported by Sato *et al.*[25] and Herfarth *et al.*[26] But our result is better than theirs. We expect a better outcome free of adverse effects for TACE with SBRT based on the present results. Further large-scale clinical trials are required to confirm this hypothesis.

TACE and SBRT have limitations when used alone. TACE has the problem of incomplete necrosis due to dual blood supply around the HCC capsule or multiple collateral feeding circulation, and this seems to be one of the reasons for the incomplete response. Actually, in our study, the lipiodol accumulation rate in HCC has become decreased in about half of the cases 3 months later. On the other hand, SBRT can be problematic in relation to the irradiation dose and RILD. Several studies[27–29] demonstrated that the response of HCC to SBRT increased with increasing radiation dose, however, others showed that the use of lower dose (e.g. 24–48 Gy[30] or 44 Gy[23]) provided equal local tumor control. Andolino *et al.*[23] also suggested that SBRT might not be safe for patients with Child–Pugh score of ≥ 8. The exact mechanism of RILD remains elusive, but severe congestion of the sinusoids in the central portion of the lobules, reduced flow towards the portal areas, and death of large number of hepatocytes have been suggested.[31] Tumor recurrence and overlap of the surrounding area with the previously irradiation area should raise concern of impending heavier liver damage. Accordingly, we argue that a repeat SBRT to the neighboring recurrence is off-label. In addition, interstitial pneumonia and other pulmonary disorders are known radiation-induced complications.[32] So we particularly hesitate to irradiate in these cases. Further, if patients could not stop breathing because of cognitive function and so on, it is impossible to deliver the appropriate irradiation dose to the targeted region accurately.

SBRT combined with TACE may provide additional benefits. It is possible that radiation could interact with the chemotherapeutic agent while the drug remains in the tumors.[33] Rotman *et al.*[34] also reported that cis-diamminedichloroplatinum hindered the repair of DNA-chain damage and enhanced the sensitivity of tumor cells to irradiation.

In conclusion, our study demonstrated that SBRT combined with TACE is a safe and effective modality for locoregional treatment of small solitary primary HCC, even in patients with contraindication for hepatic resection and ablative therapy. Further large-scale studies are needed to assess the benefit of the combination therapy.

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Case Report

Case reports of portal vein thrombosis and bile duct stenosis after stereotactic body radiation therapy for hepatocellular carcinoma

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The aim of this study was to evaluate portal vein and bile duct toxicity after stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC). We retrospectively reviewed 63 patients who were administrated SBRT once for HCC. The prescribed doses were from 48 Gy in four fractions to 60 Gy in eight fractions. Portal vein thrombosis and bile duct stenosis were evaluated. The dose received by 2% of the volume (D_2) of the portal vein and bile duct was calculated. Portal vein thrombosis was observed in three patients (4.8%). Common points of these patients were Child–Pugh class B and D_2 of the portal vein 40 Gy or more (BED_3 ≥200 Gy). Bile duct stenosis was observed in one patient (1.6%). The patient had a history of cholangiocarcinoma and left hepatic lobectomy. Portal vein thrombosis may be necessary to be considered when SBRT for HCC is administrated to patients in higher Child–Pugh class with higher D_2 of the portal vein.

Key words: bile duct stenosis, hepatocellular carcinoma, portal vein thrombosis, stereotactic body radiation therapy

INTRODUCTION

THE CURATIVE THERAPY for hepatocellular carcinoma (HCC) is surgery. However, only 10–30% of patients with HCC are suitable for surgery. Ablation or transarterial chemoembolization (TACE) are recommended as alternative locoregional treatment. Radiation therapy is considered as an alternative to ablation or TACE.[1,2] Owing to recent advances in radiation techniques, stereotactic body radiation therapy (SBRT) enables accurate delivery of high radiation doses to a specific lesion. Preliminary data suggest that SBRT for HCC results in a good local control and rare treatment-related severe toxicity.[3–6]

The major toxicity of SBRT for HCC is radiation-induced liver disease (RILD). Tolerance doses to the liver were analyzed in a review using historical RILD data.[7] In the review, portal vein or biliary duct damage were also suggested, but dose constraints were not mentioned because there are few data on toxicity of these structures.[8–11] In this report, we focus on adverse effects of portal vein and biliary duct system after SBRT for HCC, and document three cases of portal vein thrombosis and one case of bile duct stenosis, which contain dose–volume information of the portal vein and bile duct.

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CASE REPORTS

WE RETROSPECTIVELY REVIEWED 63 patients who were administrated SBRT once for HCC, and those characteristics are shown in Table 1. The Model for End-Stage Liver Disease (MELD)-Na score was calculated as described by Kim *et al.*[12] Details of the inclusion criteria for SBRT and treatment procedure have been described previously.[13] The summary of treatment procedure was as follows. TACE was underwent before SBRT. If respiratory motion was greater than 5 mm, patients held their breath in the end-expiratory phase

Table 1 Patient characteristics

Age (years): median/range	73/49–90
Sex: male/female	38/25
ECOG PS: 0/1	59/4
Type of virus: HBV/HCV/NBNC	5/50/8
Child–Pugh class: A/B	52/11
MELD-Na score: median/range	10/6–21
Previous treatment: surgery/RFA/PEI/TACE	23/16/8/59
Tumor location: S1/S2/S3/S4/S5/S6/S7/S8	1/1/3/12/8/6/14/18
Tumor size (mm): median/range	19/3–54
Prescription dose:	
48 Gy in four fractions	52
50 Gy in five fractions	4
52.5 Gy in seven fractions	1
60 Gy in eight fractions	6

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NBNC, non-hepatitis B non-hepatitis C; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; S, segment; TACE, transarterial chemoembolization.

using a spirometer or Abches (APEX Medical, Tokyo, Japan). A fiducial marker was not used for targeting the tumor. An arterial phase of dynamic computed tomography (CT) scan was used for radiation treatment planning. Gross tumor volume (GTV) was defined by iodized oil and early enhancement. A clinical target volume (CTV) margin of 3 mm was usually added to GTV, and a planning target volume (PTV) margin of 5–8 mm was added to CTV. Eight non-coplanar ports were selected, and beams were delivered using 6–10-MV photons. The prescribed dose was calculated at the isocenter and was delivered on consecutive days. The prescribed dose was 50 Gy in five fractions until September 2004. Thereafter, 48 Gy in four fractions was usually used, and 60 Gy in eight fractions was used when the PTV included the portal vein, inferior vena cava or heart. The patient receiving 52.5 Gy in seven fractions was planned to receive 60 Gy in eight fractions, but the last fraction was discontinued because of a femoral neck fracture due to a fall.

Portal vein thrombosis, bile duct stenosis, blood bilirubin increase, ascites, gastrointestinal disorders and ulcers were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Portal vein thrombosis was non-tumoral as confirmed by dynamic CT scan or dynamic magnetic resonance imaging. We retrospectively delineated the portal vein and bile duct on the planning dynamic CT scan. The portal vein was delineated from the main trunk to the first branch. The common bile duct, cystic duct and the first branch of the hepatic duct were delineated as the bile duct. The dose received by 2% of the volume (D_2) of the portal vein and bile duct was calculated.

Results

The median follow-up duration was 17 months (range, 6–39).

Portal vein thrombosis

Median D_2 of the portal vein was 12.6 Gy (range, 0.4–58.7). Portal vein thrombosis was observed in three patients (4.8%), all of whom developed grade 3. Common points of these patients were Child–Pugh class B and D_2 of the portal vein of 40 Gy or higher (Fig. 1). Prescribed doses varied for D_2 of the portal vein; thus, the biological equivalent dose (BED) with α/β ratio of 3 Gy (BED_3) was calculated as an indicator. The BED_3 values of D_2 of the portal vein for patients 1, 2 and 3 were 217.4, 202.0 and 202.3 Gy, respectively.

Patient 1

A77-year-old man suffered from non-B, non-C liver cirrhosis and was in Child–Pugh class B. His MELD-Na

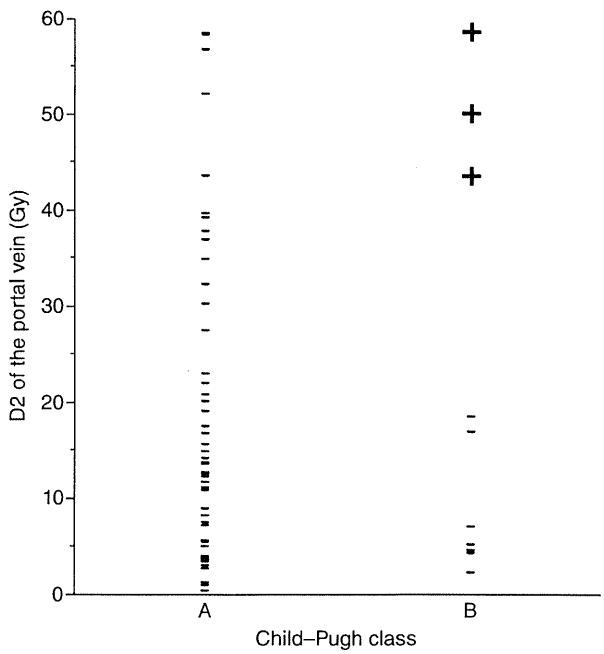

Figure 1 Relationship between Child–Pugh class and D_2 of the portal vein. Plus signs indicate the patients who experienced portal vein thrombosis.

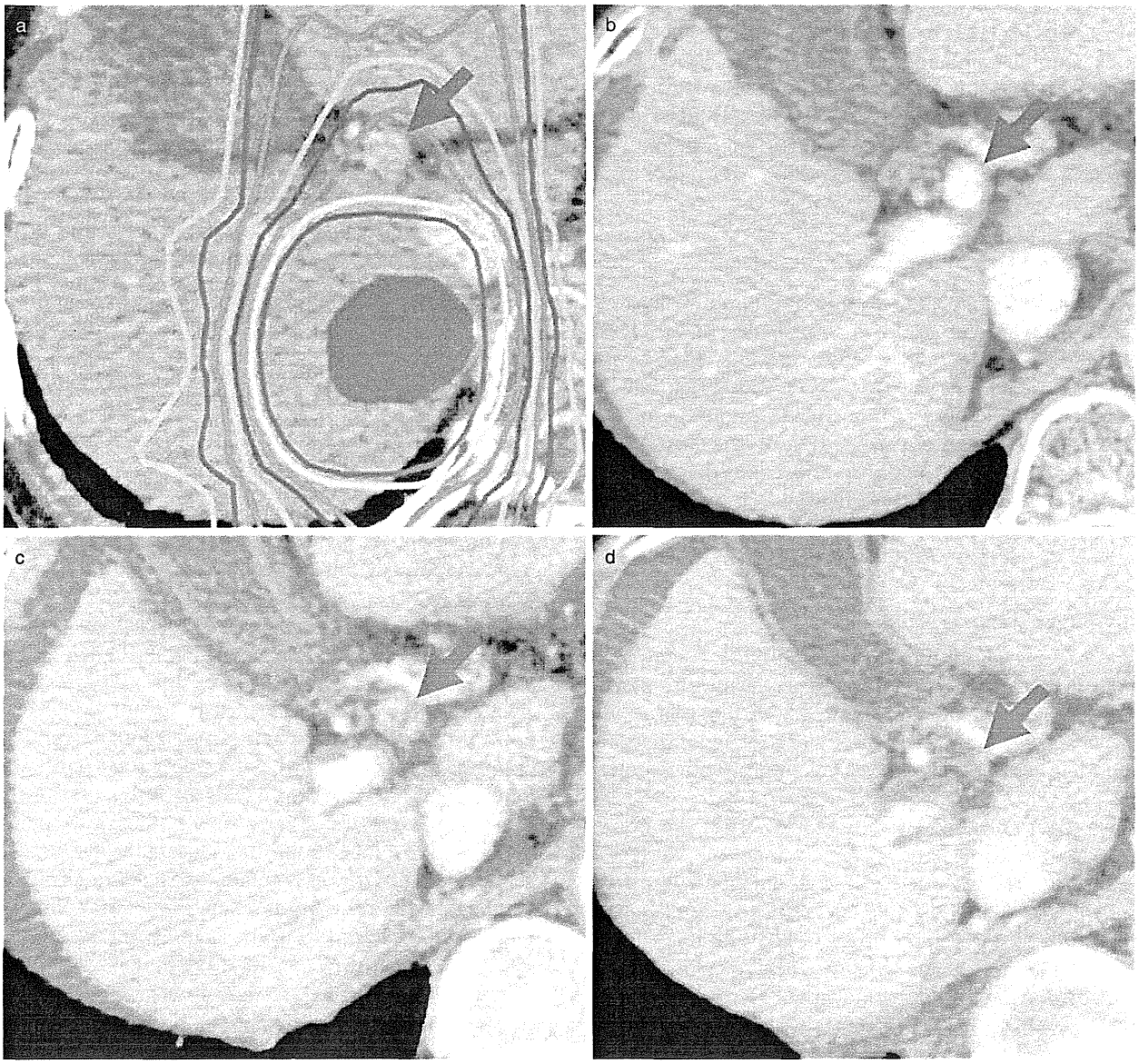

Figure 2 Red arrows indicate the left branch of the portal vein. (a) Dose distribution of the plan with 48 Gy in four fractions. Isodose lines from outer to inner represent 30%, 40%, 50%, 60%, 70%, 80%, 90% and 95% of the prescribed dose. Red circle indicates gross tumor volume. (b) No sign of portal vein thrombosis was observed at 5 months after stereotactic body radiation therapy (SBRT). (c) Poor enhancement of the left branch of the portal vein was observed at 7 months after SBRT. Portal vein thrombosis was diagnosed, and anticoagulation was started. (d) Portal vein thrombosis had progressed slightly at 14 months after SBRT, although anticoagulation was continued.

score was 11. He had received previous percutaneous ethanol injection and TACE for HCC. Recurrent HCC was diagnosed in segment 7. SBRT was administrated with 50 Gy in five fractions for recurrent HCC. D_2 of the portal vein was 50.1 Gy. Portal vein thrombosis was diagnosed 13 months later, and anticoagulation was started. He died from new intrahepatic recurrence at 17 months after SBRT.

Patient 2 (Fig. 2)

A 73-year-old woman suffered from cirrhosis caused by hepatitis C virus and was in Child–Pugh class B. Her

MELD-Na score was 14. She had received no previous treatment for HCC in segment 7. A total of 48 Gy SBRT was administrated in four fractions for HCC. D_2 of the portal vein was 43.6 Gy. Portal vein thrombosis was diagnosed 7 months later, and anticoagulation was started. Although the portal vein thrombosis had progressed slightly, she was alive without recurrence at 28 months after SBRT.

Patient 3

A69-year-old man suffered from non-B, non-C liver cirrhosis and was in Child–Pugh class B. His MELD-Na score was 15. He had received previous surgery and TACE for HCC. Recurrent HCC was diagnosed in segment 4. SBRT was administrated with 60 Gy in eight fractions for recurrent HCC. D_2 of the portal vein was 58.7 Gy. Portal vein thrombosis was diagnosed 10 months later, and anticoagulation was started. There was no progression of portal vein thrombosis, and he was alive without recurrence at 13 months after SBRT.

Bile duct stenosis

Median D_2 of the bile duct was 11.9 Gy (range, 0.2–58.6). Bile duct stenosis was observed in one patient (1.6%), who developed grade 2. The patient (Fig. 3) was a 70-year-old man with a history of cholangiocarcinoma and left hepatic lobectomy. Three months after surgery, a new solitary lesion was observed in segment 5, and histology confirmed HCC by biopsy. There was no evidence of recurrence of cholangiocarcinoma. SBRT was administrated with 48 Gy in four fractions. D_2 of the bile duct was 30.4 Gy. Bile duct stenosis was diagnosed as cholangitis at 8 months after SBRT and treated with an antibacterial agent. Although the cholangitis healed, he died from a new intrahepatic recurrence at 19 months after SBRT.

Blood bilirubin increase, ascites, gastrointestinal disorders and ulcer

Grade 3 blood bilirubin increase and ascites were observed in three patients (4.8%) and five patients (7.9%), respectively. There was no patient who showed gastrointestinal disorders or ulcer.

DISCUSSION

THIS IS THE first report of portal vein toxicity after SBRT with dose–volume metrics of the portal vein. Portal vein damage was suggested, but no constraints were mentioned because of few data.[7] Our report supplies important new information.

Three cases of portal hypertension have been reported as portal vein toxicity after SBRT.[9,10] The dose–volume metrics of the portal vein were not reported for these cases, so they were not comparable with our cases.

Portal vein thrombosis after SBRT has not been reported. The incidence of portal vein thrombosis was 4.8% in our report. Ogren *et al.*[14] showed that the overall risk for portal vein thrombosis during a lifetime is 1% in the general population. Janssen *et al.*[15] reported that the worst risk factor for portal vein thrombosis is a hepatic disorder including cirrhosis. Portal vein thrombosis is observed in 10–20% of patients with cirrhosis,[16] and increased with cirrhosis severity.[17] These data support our report that Child–Pugh class B was a common point of portal vein thrombosis. Zocco *et al.*[18] showed an association between portal vein thrombosis and high MELD score. Kim *et al.*[12] recently reported that MELD-Na score is more useful than MELD score alone. Guha *et al.*[19] recommended that the MELD-Na score should be measured when toxicity after radiation therapy to the liver is evaluated. The MELD-Na score of the patients experienced portal vein thrombosis was 11 of higher in our report.

Vascular injury is another risk factor for portal vein thrombosis.[20] Irradiation can cause vascular injury.[21,22] D_2 of the portal vein of 40 Gy or more was a common point of portal vein thrombosis in our report. High doses to the portal vein also may be a risk factor for portal vein thrombosis through vascular injury.

Bile duct toxicity after SBRT for liver tumors was evaluated with dose–volume metrics in one study.[11] Two cases of bile duct stenosis were reported. One patient was treated twice with SBRT and the high-dose area of more than 80 Gy corresponded to the biliary stenosis region. In another patient, the biliary tract was exposed to more than 20 Gy but did not correspond to the bile duct stenosis region. They concluded that SBRT with 40 Gy or less in five fractions for liver tumors was feasible with regard to biliary toxicity. In our report, bile duct of the patient who experienced bile duct stenosis was also irradiated with more than 20 Gy. Barney *et al.*[23] reported one case of grade 3 biliary stenosis after SBRT for cholangiocarcinoma. The patient was treated to a dose of 50 Gy in five fractions for positive resection margins after surgery for intrahepatic cholangiocarcinoma. In our report, the patient who experienced bile duct stenosis also had a history of cholangiocarcinoma and left hepatic lobectomy, although there was no evidence of recurrence of cholangiocarcinoma.

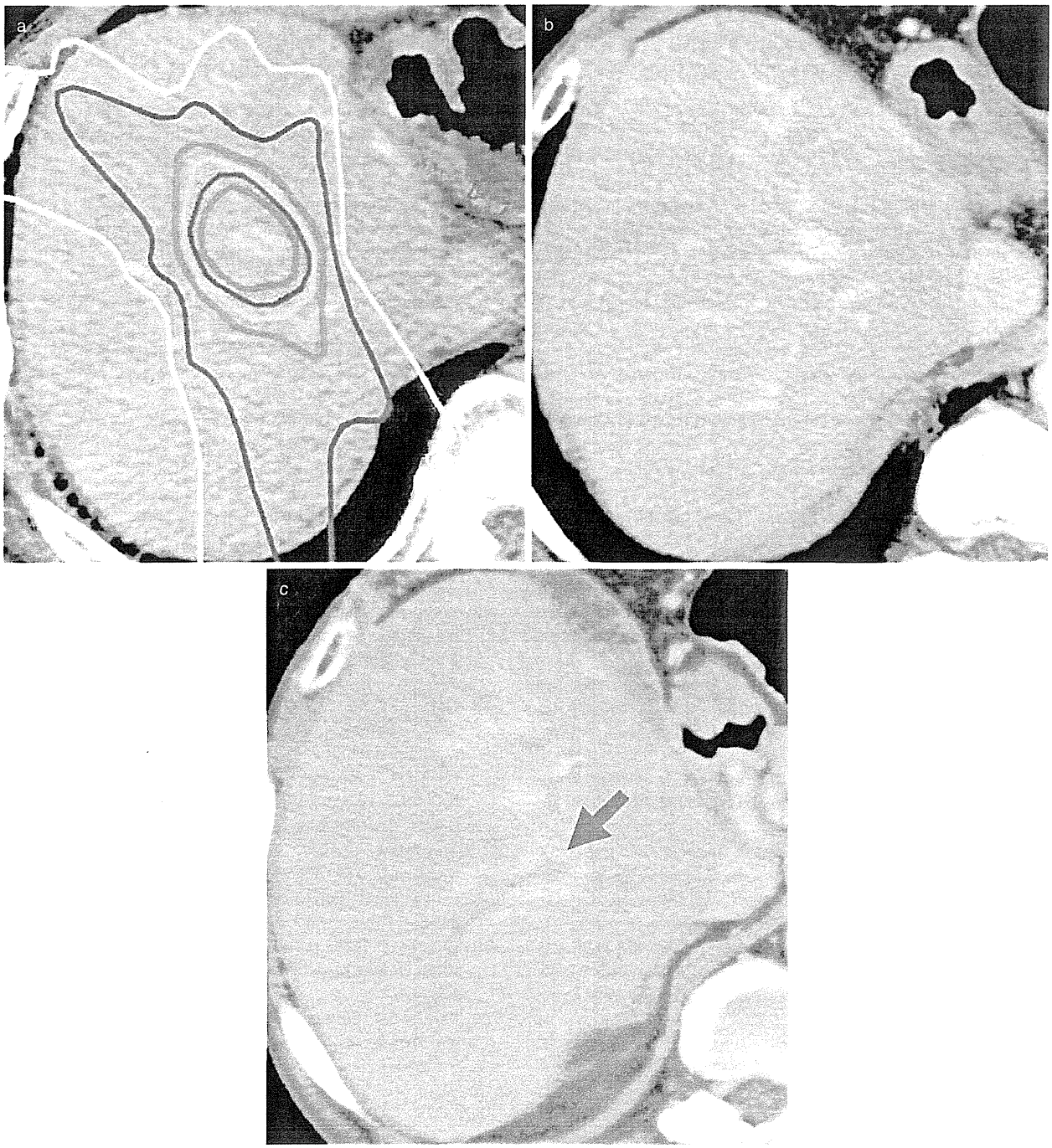

Figure 3 Peripheral slices from a gross tumor. (a) Dose distribution of a plan with 48 Gy in four fractions. Isodose lines from outer to inner represent 30%, 40%, 50%, 60%, 70% and 80% of the prescribed dose. (b) No sign of bile duct stenosis was observed at 6 months after stereotactic body radiation therapy (SBRT). (c) Red arrow indicates dilatation of the intrahepatic bile duct at 8 months after SBRT. Cholangitis was diagnosed with signs of infection and treated with an antibacterial agent.

In conclusion, portal vein thrombosis may be necessary to be considered when SBRT for HCC is administrated to patients in higher Child-Pugh class with higher D_2 of the portal vein.

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臨床放射線 58：649-650，2013

はじめに

永田 靖*

放射線治療の歴史は1895年にレントゲン博士がX線を発見した翌年の1896年に始まる。その後，わずか110年余りの間に放射線治療は目覚ましい進歩を遂げており，現在では，手術療法，化学療法と並ぶ，癌治療3本柱の1つに位置付けられている。

本邦での癌患者の数は増加の一途をたどっており，現在，国民の2人に1人が癌に罹患し，3人に1人が癌で死亡している。2009年の国内癌死亡数は34万人以上となり，癌治療の充実とさらなる進歩が要求されている。局所療法である放射線治療と手術療法とを比較した場合の放射線治療の特徴は，臓器の機能と形態の温存が可能であるということである。また，手術に比し，身体への負担が軽く，種々の合併症を有する患者や高齢者でも比較的安全に施行可能である。さらに，根治，緩和，予防といった様々な目的で用いられることも，放射線治療の重要な特長の1つである。

欧米ではすべての癌患者の約60%が放射線治療を受けている。一方，本邦の癌患者に放射線治療が施行される割合は30%程度であり，欧米とは大きな差がある。これは，本邦において放射線治療が適切な対象となる癌が少ないことも一因ではあるが，放射線治療を専門に行う放射線腫瘍医の数が少ないこと，癌治療の中での放射線治療に対する評価がいまだ不十分であることなども原因と考えられる。しかしながら，癌患者数の増加に加え，QOLを保ちながら癌を治癒させるという意識の高まりや，高齢者の増加がみられる現代社会の中で，本邦においても放射線治療の果たす役割が，今後ますます大きくなっていくことは確実である。

前述のように，放射線治療はわずか110年余りの間に目覚ましい進歩を遂げているが，この進歩は画像診断学，機械工学，コンピュータサイエンス，医学物理学，等の発展に寄与する部分が極めて大きい。特にX線CTやMRIを初めとする画像診断技術の進歩は，放射線治療を行ううえでの標的体積（以下ターゲット）の形状をより正確に把握することを可能にし，コンピュータ技術の進歩は，正確な三次元線量計算を可能とした。また，機械工学の進歩は治療装置の発展に大きく貢献し，原体照射や3D-CRT（three-dimensional conformal radiotherapy）といった現在ではルーチンに行われている治療技術が編み出されてきた。これらの関連技術のさらなる進歩が，高精度放射線治療の実現を可能とした。

本特集では高精度放射線治療のうち，体幹部定位放射線照射（stereotactic body radiation therapy：SBRT）および強度変調放射線治療（intensity modulated radiation therapy：IMRT）について検討した。すでに体幹部定位照射は200施設以上，強度変調放射線治療も120施設

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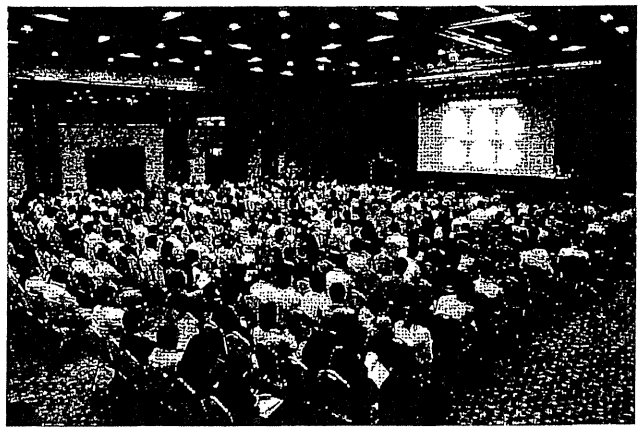
〔索引用語：高精度放射線治療，体幹部低位放射線照射，強度変調放射線治療〕



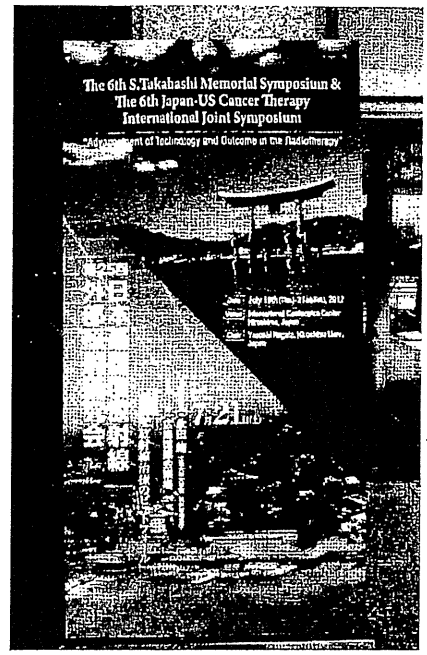


図　左：会場風景　右：会議案内　第6回高橋信次記念シンポジウムおよび第25回日本高精度放射線外部照射研究会（平成24年7月19～21日広島）

以上で行われるようになっている。そのため，すでに初期導入の時期を過ぎ，広く普及している時期といえる。しかし，このような時期に新たにこれらの高精度放射線治療を開始しようとする施設は，初期導入期の経過や当然クリアすべき問題点が欠落する可能性がある。そのために，初期の導入時よりの経験も含めて造詣の深い4名の先生がたに，高精度放射線治療のピットフォールとして原稿を頂戴した。

正常臓器を守りつつ，いかに癌を根治させるかという問題は放射線治療にとって根源的なテーマである。高精度放射線治療の実現は，このテーマをひたすらに探求することにより成し遂げられた大きな成果の1つである。放射線治療において高精度放射線治療の果たす役割は今後ますます増していくと思われる。

本特集は，平成24年7月19～21日に広島で開催された第6回高橋信次記念シンポジウムと第25回日本高精度放射線外部照射研究会（図）におけるシンポジウムの一部を誌上にまとめたものである。本企画をご提案いただいた「臨床放射線」編集委員会・編集室の滝沢氏に深謝するとともに，当日シンポジウムに出席いただいた500名以上の参加者の皆様にも当番世話人として重ねて御礼申し上げたい。

Forword：Pitfalls in the modern advanced techniques in radiotherapy

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ORIGINAL ARTICLE

Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

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Abstract

Purpose A multicenter survey was conducted to explore the role of adjuvant surgery for initially unresectable pancreatic cancer with a long-term favorable response to non-surgical cancer treatments.

Methods Clinical data including overall survival were retrospectively compared between 58 initially unresectable pancreatic cancer patients who underwent adjuvant surgery with a favorable response to non-surgical cancer treatments over 6 months after the initial treatment and 101 patients who did not undergo adjuvant surgery because of either unchanged unresectability, a poor performance status, and/or the patients' or surgeons' wishes.

Results Overall mortality and morbidity were 1.7 and 47 % in the adjuvant surgery group. The survival curve in the adjuvant surgery group was significantly better than in the control group ($p < 0.0001$). The propensity score analysis revealed that adjuvant surgery was a significant

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independent prognostic variable with an adjusted hazard ratio (95 % confidence interval) of 0.569 (0.36–0.89). Subgroup analysis according to the time from initial treatment to surgical resection showed a significant favorable difference in the overall survival in patients who underwent adjuvant surgery over 240 days after the initial treatment.

Conclusion Adjuvant surgery for initially unresectable pancreatic cancer patients can be a safe and effective treatment. The overall survival rate from the initial treatment is extremely high, especially in patients who received non-surgical anti-cancer treatment for more than 240 days.

Keywords Adjuvant surgery · Unresectable pancreatic cancer · Chemotherapy · Radiotherapy · Super-responder

Introduction

Pancreatic cancer is a lethal disease, and contributes to the increasing number of cancer deaths worldwide. Only 20 % of patients can be treated by surgery, and the overall 5-year survival rate is less than 5 % [1, 2]. Irrespective of the treatment strategy adopted, prognosis in patients with unresectable pancreatic cancer continues to be disappointing, with a median survival of 8–14 months [3–7]. These patients rarely have a chance to live more than 3 years.

Medical oncologists or pancreatic surgeons have identified candidates for surgical resection in patients with initially unresectable pancreatic cancer who favorably responded to multimodal treatment. Additional surgical resection during multimodal treatment is called "adjuvant surgery" [8]. The role of adjuvant surgery has not been fully determined because the number of patients who received this type of treatment was very small in each institution. Is adjuvant surgery a safe or effective treatment option for patients with unresectable pancreatic cancer? When should a shrunken tumor be removed in the process of maintaining chemotherapy and/or radiation therapy? There is no study indicating the clinical efficacy, safety and optimal timing of adjuvant surgery. There are long-term survivors and a comparable survival rate among this subset of patients after surgical resection following multimodal treatment [8–12]. However, the duration of multimodal treatment before pancreatectomy varies from a few months to several years in previous reports [8–12]. The clinical data on initially unresectable pancreatic cancer patients with a favorable response to chemo(radio)therapy over 6 months were collected as a project study of pancreatic surgery under the supervision of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS), to assess the role of adjuvant surgery in the clinical setting.

Patients and methods

A multicenter survey was conducted to collect clinical data on patients who underwent adjuvant surgery for initially unresectable pancreatic cancer following a favorable response to chemo(radio)therapy over 6 months from 2001 to 2009. Detailed data on 58 patients (adjuvant surgery group) were retrospectively collected from 39 out of 150 training institutes for highly advanced surgery registered by the committee of JSHBPS in 2009. The study criterion was initially unresectable pancreatic cancer patients who underwent surgical resection following the achievement of stable disease (SD), partial response (PR), or complete response (CR) defined by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1 [13]) over 6 months after initiating non-surgical anti-cancer treatments. The clinical data on 101 patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments who did not undergo surgical resection was collected as a control group from the same 39 centers. The unresectability of pancreatic cancer was based on the clinical criteria in each institute.

All patients had cytologically or pathologically proven ductal adenocarcinoma of the pancreas. The clinical variables shown in Table 1 were collected. Radiological assessment was performed according to RECIST version 1.1 [13]. The pathological parameters included residual tumor grading, Evans classification [14], and tumor staging according to TNM classification [15]. Serial data on tumor markers such as carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), DUPAN-2 or Span-1 were collected every 1–3 months during multimodal treatment. Post-operative follow-up data included serial data on tumor markers, adjuvant chemotherapy, the date and the primary site of disease recurrence, the date and cause of death, and the last follow-up date. The observation period was defined as the time from the initial treatment to the date of death for censored patients or the last follow-up date for non-censored patients. This study was performed in accordance with the precepts of the Helsinki Declaration, and was approved by the local ethics committee.

Statistical analysis

Continuous variables were expressed as median values and range. All parameters were compared between the adjuvant surgery and control groups. Statistical analyses, including the Mann–Whitney *U* test for continuous variables, and chi-squared statistics or Fisher's exact test for categorical variables, were performed using SAS software version 9.2 (SAS Institute, Cary, NC, USA). The primary outcome

Table 1 Clinical backgrounds in the adjuvant surgery and control groups

Parameters	Category	Adjuvant surgery ($n = 58$)	Control[a] ($n = 101$)	p value
Sex	Male	37 (63.8 %)	59 (58.4 %)	0.61
	Female	21 (36.2 %)	42 (41.6 %)	
Age (years)	Median (min–max)	62.5 (40–80)	65 (41–85)	0.01
Reason for unresectability	Local advance	41 (70.7 %)	56 (55.4 %)	0.07
	Distant organ metastasis			
	Overall	17 (29.3 %)	45 (44.6 %)	
	Peritoneal metastasis[b]	1 (1.7 %)	17 (16.8 %)	0.003
Tumor diameter	Median (min–max)	30 (16–75)	35 (13–76)	0.009
Tumor location	Ph	31 (53.4 %)	50 (49.5 %)	0.74
	Pbt	27 (46.6 %)	51 (50.5 %)	
Change in tumor marker[c]	Increase	4 (6.9 %)	4 (40 %)	0.46
	Decrease or no tumor marker	54 (93.1 %)	97 (96.0 %)	
Tumor marker (number of patients showing an increased level)	CA19-9	40 (69.0 %)	83 (82.2 %)	0.06
	Others	12 (20.7 %)	8 (7.9 %)	
	None	6 (10.3 %)	10 (9.9 %)	
CA19-9	Median (min–max)	313 (9–13080)	440 (11–144400)	0.13
Chemotherapy	GEM base	53 (91.4 %)	89 (88.1 %)	0.60
	Others	5 (8.6 %)	12 (11.9 %)	
Gemcitabine (g)	Median (min–max)	28.2 (0–173.6)	28.0 (0–168)	0.55
	≥28 g	29 (50 %)	50 (49.5 %)	1.00
	<28 g	29 (50 %)	51 (50.5 %)	
S-1 (mg)	Median (min–max)	3850 (0–53768)	6300 (0–64120)	0.19
	≥5650 mg	26 (44.8 %)	52 (51.5 %)	0.51
	<5650 mg	32 (55.2 %)	49 (48.5 %)	
Radiotherapy	Done	26 (44.8 %)	19 (18.8 %)	0.001
	None	32 (55.2 %)	82 (81.2 %)	
Immunotherapy	Done	2 (3.4 %)	6 (5.9 %)	0.71
	None	56 (96.6 %)	95 (94.1 %)	
TNM by UICC	II	10 (17.2 %)	14 (13.9 %)	0.63
	III	31 (53.4 %)	45 (44.6 %)	
	IV	17 (29.3 %)	42 (41.6 %)	
RECIST	CR	7 (12.1 %)	2 (2.0 %)	<0.0001
	PR	39 (67.2 %)	38 (37.6 %)	
	SD	12 (20.7 %)	61 (60.4 %)	
Duration until PR/CR[d]	Median (min–max)	151.5 (21–919)	174 (36–1669)	0.11

Data are the number (%) or median (range) unless otherwise specified

Met metastasis, *Ph* pancreas head, *Pbt* pancreas body and tail, *CA19-9* carbohydrate antigen 19-9, *GEM* gemcitabine, *RECIST* Response Evaluation Criteria In Solid Tumors, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease

[a] The reasons for initially unresectable pancreatic cancer in the control group were locally advanced tumors in 56 (54 %, 50 arterial invasions and 6 portal vein invasions with long segment) and distant organ metastases in 45 (46 %, 19 liver, 17 peritoneal metastasis or peritonitis carcinomatosa, 7 cervical or para-aortic lymph nodes, and 2 lung). Eighty-nine patients received gemcitabine-based chemotherapy, and 73 patients had S-1 chemotherapy

[b] Peritoneal metastasis includes peritonitis carcinomatosa

[c] Tumor marker: this category is divided into increased tumor marker and decreased or no tumor marker

[d] The days between the initiation of treatment and the identification of a partial/complete response of the tumor according to the RECIST criteria

variable was overall survival, defined as the time from non-surgical anti-cancer treatments to death or the last follow-up date. Comparisons of the overall survival between the two groups were made using the log-rank test. In addition, profound factors identified by the univariate analysis were further examined by multivariate Cox proportional-hazard

models to determine independent significant factors for survival.

A propensity score methodology was used to provide adjustments since a propensity score can calculate the conditional probability of receiving a treatment given all potential confounders measured. The propensity score analysis required calculation of the conditional probabilities for the adjuvant surgery group using a multivariate logistic regression to generate a propensity score [16]. The selection of variables for calculating the propensity score was based on the potential association with the overall survival results (sex, age, radiation therapy or not, tumor marker decrease or not during non-surgical anti-cancer treatment, PR/CR vs SD, tumor size, amount of gemcitabine administration, reason for unresectability). Model discrimination was assessed with C-statistics, and model calibration was assessed with Hosmer–Lemeshow statistics. The propensity score was subdivided into quartiles as shown in Table A (Electronic Supplementary Material). The treatment effect was separately estimated within each quartile, and quartile estimates were combined to give an overall estimate of adjuvant surgery. A survival analysis using Cox proportional-hazard models was used. The hazard ratio and 95 % confidence intervals were calculated for all estimates. A 2-tailed p value less than 0.05 was considered to be statistically significant.

Results

Clinical background in the adjuvant surgery and control groups

Tables 1 and 2 show that the reason for the initially unresectable pancreatic cancer was 41 locally advanced tumor and 17 distant organ metastases in the adjuvant surgery group. Fifty-three patients received gemcitabine-based chemotherapy, and 32 patients had S-1 chemotherapy. The radiological response of SD, PR, or CR was found in 7, 39, and 12 patients, respectively. The median duration between the initial therapy and the detection of PR/CR was 150 days (21–739). The median duration between the

Table 2 Type of surgery in the adjuvant surgery group

Reasons for UN	Locally advanced (n = 41)					Metastasis (n = 17)			Total number (%)
	SMA/(PV) (n = 16)	CHA/(PV) (n = 8)	CA/CHA/GDA (n = 9)	CA/SMA (n = 5)	PV (n = 3)	Liver (n = 13)	No 16 LN[a] (n = 3)	P (n = 1)	
Operation type									
PD[b]	13	7	0	1	2	7	0	0	30 (51)
TP	0	1	0	1	1	0	0	0	3 (5)
DP	3	0	3	0	0	5	3	1	15 (26)
DPCAR	0	0	6	3	0	1		0	10 (17)
Combined resections of other organs									
None	5	2	3	0	0	5	2	1	18 (31)
PV/SMV	9	4	2	1	3	4	0	0	23 (40)
Ad	0	0	6	3	0	1	1	0	11 (19)
CA/CHA	0	0	6	3	0	1	0	0	10 (17)
CHA	0	2	0	–	0	0	0	0	2 (3)
SMA	1	0	0	0	0	0	0	0	1 (2)
Liver	0	0	0	0	0	5 Bx2	0	0	5 (9)
Colon	1	0	0	0	0	1	0	0	2 (3)
Pathological findings									
CR[c]	1	1	2	1	0	1	1	0	7 (12)
R0/1/2[d]	36/5/0					12/4/1			

Data are the number (%) or median (range) unless otherwise specified

UN unresectability, *SMA* superior mesenteric artery, *CHA* common hepatic artery, *CA* celiac axis, *GDA* gastroduodenal artery, *PV* portal vein, *LN* lymph node, *P* peritoneal metastasis, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *DPCAR* DP with celiac axis resection, *TP* total pancreatectomy (TP), *SMV* superior mesenteric vein, *Ad* adrenal, *Bx* biopsy, *CR* complete response

[a] No 16 LN, paraaortic lymph node

[b] Includes pylorus preserving PD

[c] Complete pathological response was defined as the absence of identifiable tumor cells in the resected specimen. The pathological examination was done using 5-mm specimens slices according to the standard method defined by the Japan Pancreas Society

[d] Residual tumor grading; R0, negative microscopic margin; R1, positive microscopic margin; R2, positive gross margin

detection of PR/CR and surgical resection was 127 days (8–1335). Forty-six of 52 patients with available value of any tumor marker showed a decrease in the level of tumor marker before surgical resection, and only four patients had an increase, relative to the pre-initial treatment level.

The control group included 43 patients judged to have unresectable disease on laparotomy (18 locally unresectable, 13 peritoneal dissemination, 10 liver metastasis, and 2 distant lymph node metastasis), and 58 patients who did not undergo surgical resection because of either unchanged unresectability, a poor performance status, and/or the patients' or surgeons' wishes. Thirty-seven of 58 patients had SD on RECIST, and 21 patients had PR (8 distant organ metastases and 13 locally advanced tumors; Table 1).

There were significant differences in the age, presence of peritoneal metastasis, tumor size, concomitant use of radiotherapy, and frequency of PR/CR between the adjuvant surgery and control groups ($p < 0.05$).

Surgical background and post-operative complications in the adjuvant surgery group

The median time from initial therapy to surgical resection was 274 days (182–1418). Concomitant resections of other organs were performed in 40 patients (69 %; Table 2). As shown in Table 2, 23 patients underwent portal vein resection. The superior mesenteric artery, celiac axis and common hepatic artery were concomitantly resected in 1, 10, and 2 patients, respectively. There were 11 adrenal resections, 5 liver resections, 2 liver biopsies, and 2 colon resections. Post-operative mortality and morbidity are summarized in Table 3. There was no incidence of aspiration pneumonia, myocardial infarction, cerebral infarction, or pulmonary thrombosis.

Pathological findings in the adjuvant surgery group

Five of the 13 patients with liver metastases underwent surgical resection for metastatic lesions and two patients underwent liver biopsies. No liver tumors were found during surgery in the residual 6 patients with liver metastases. One patient had peritoneal metastasis diagnosed on computed tomography scan which was not found during surgical resection of the primary tumor. A pathological evaluation was done in 55 patients according to the Evans classification, and showed Grade I ($n = 17$), IIa (16), IIb (10), III (5), and IV (7). Pathological CR was found in 7 patients who had 5 locally advanced tumors, 1 para-aortic lymph node metastasis, and 1 liver metastasis. The 17 patients with distant organ metastases underwent R0 ($n = 12$), R1 ($n = 4$), and R2 ($n = 1$) resection, and 41 patients with locally advanced tumor had R0 ($n = 36$) and R1 ($n = 5$).

Table 3 Post-operative mortality and morbidity

In-hospital mortality: 1/58 (1.7 %)
Morbidity
Post-operative pancreatic fistula: 10 (17 %)
Delayed gastric emptying: 4 (7 %)
Post-pancreatectomy hemorrhage: 2 (3 %)
Intra-abdominal abscess or infection: 12 (21 %)
Wound dehiscence: 9 (16 %)
Bile leakage: 2 (3 %)
Deep vein thrombosis: 2 (3 %)
Superior mesenteric artery thrombosis: 1 (2 %)

Survival analysis in the adjuvant surgery and control groups

The median observation period was 51 months (20–122) in the control group. The overall survival rates at 1, 3, and 5 years in the control group were 88, 18, and 10 %, respectively, and the median survival time was 20.8 months. The median observation and post-operative observation periods in the adjuvant surgery group were 54 months (26–125) and 41 months (18–117), respectively. The overall survival rates at 1, 3, and 5 years were 95, 53, and 34 %, respectively, and the median survival time was 39.7 months. The overall survival rates after surgical resection at 1, 3, and 5 years were 76, 33, and 29 %, respectively, and the median survival time was 25 months. Figure 1 demonstrates that the survival curve in the adjuvant surgery group was significantly better than that in the control group ($p < 0.0001$). Five-year survival was observed in 9 patients in the adjuvant surgery group, and 4 patients in the control group. A multivariate analysis showed only a longer period of initial treatments to be a significant independent factor associated with survival in the adjuvant surgery group (Table 4). The disease-free survival rates at 1, 3, and 5 years were 54, 30, and 30 %, respectively. The primary site of recurrence was detected in a distant organ ($n = 21$; liver 11, lung 4, peritoneum 6, and liver and peritoneum 1) and in the loco-regional area ($n = 15$). One patient had an unknown site of recurrence. Twenty-one patients did not have any recurrence of disease. There was no significant difference in the primary site of recurrence and disease-free survival curve associated with the reason for unresectability.

Univariate and multivariate Cox proportion-hazard model analyses for overall survival in all patients

Table 5 shows metastatic disease, an increase in tumor marker, dose of gemcitabine <28 g, and stable disease on RECIST each increased the risk of death relative to those