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# Alternating chemoradiotherapy in patients with nasopharyngeal cancer: prognostic factors and proposal for individualization of therapy

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The purpose of this study is to assess the efficacy of alternating chemoradiation in patients with nasopharyngeal cancer. From 1990–2006, 100 patients with nasopharyngeal cancer were treated with alternating chemoradiation at the Aichi Cancer Center. Of these, 4, 2, 23, 34, 13 and 23 patients were staged as I, IIA, IIB, III, IVA and IVB, respectively. The median radiation doses for primary tumors and metastatic lymph nodes were 66.6 Gy (range, 50.4–80.2 Gy) and 66 Gy (range, 40.4–82.2 Gy), respectively. A total of 82 patients received chemotherapy with both cisplatin and 5-fluorouracil (5-FU), while 14 patients received nedaplatin (CDGP) and 5-FU. With a median follow-up of 65.9 months, the 5-year rates of overall survival (OAS) and progression-free survival (PFS) were 78.1% and 68.3%, respectively. On multivariate analysis (MVA), elderly age, N3, and WHO type I histology proved to be significantly unfavorable prognostic factors of OAS. As for PFS, there were T4, N3, and WHO type I histology in MVA. Acute toxicities of hematologic and mucositis/dermatitis ≥ Grade 3 were relatively high (32%); however, they were well-managed. Late toxicities of ≥ Grade 3 were three (3%) mandibular osteomyelitis and one (1%) lethal mucosal bleeding. Results for alternating chemoradiation for nasopharyngeal carcinoma are promising. In order to improve outcomes, usage of intensity-modulated radiation therapy and application of active anticancer agents are hopeful treatments, especially for groups with poor prognosis factors with WHO type I histopathology, T4 and/or N3 disease.

**Keywords:** nasopharyngeal carcinoma; alternating chemoradiation; WHO type I histopathology

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common disease among Southern Chinese, Southeast Asian, Northern African and Inuit populations. In Japan, the USA and Western European countries it is relatively rare. Because of anatomical characteristics, surgical treatment is very difficult. In addition, the majority of NPC patients revealed undifferentiated carcinoma, which is relatively sensitive to radiation therapy. Therefore, radiotherapy is widely accepted as the first choice of therapy for NPC. In recent years, by randomized-control trials, chemoradiotherapy has shown significant survival benefits over radiotherapy alone, improving both local and distant control [1–4]. In addition, meta-analysis of eight randomized trials showed significant benefits for OAS and event-free survival [5]. The pooled hazard ratio of death was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 y from the addition of chemotherapy. Thus, the standard treatment for locally advanced NPC is now believed to be concurrent chemoradiotherapy. However, several key factors need further clarification. Firstly, the chemotherapy used in the Intergroup 0099 study (IGS) consisted of three courses each of concurrent administration of cisplatin (CDDP) and adjuvant chemotherapy with both CDDP and 5-fluorouracil (5-FU). However, about two thirds (63%) of patients could receive concurrent chemotherapy, and about half (55%) could receive the full course of adjuvant chemotherapy. Secondly, a higher incidence of adverse events ≥ Grade 3 was observed in the chemoradiation group than in the radiation alone group (59% vs 34%). Finally, chemoradiation reduced distant metastasis; however, it did not reach sufficient levels. Of the 18 patients with recurrence in the

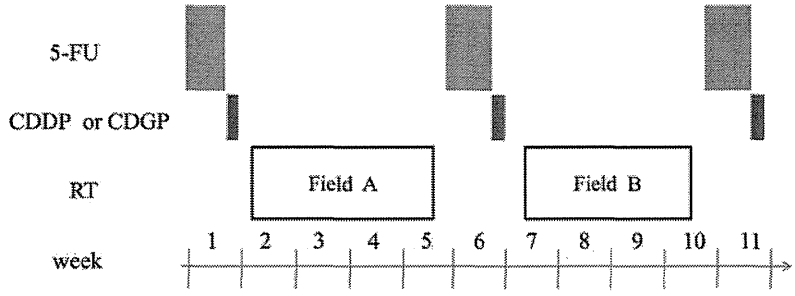


**Fig. 1.** Study design of alternating chemoradiotherapy. 5-FU = 5-fluorouracil 800 mg/m$^2$ on Days 1–5 continuous infusion, CDDP = cisplatin 50 mg/m$^2$ Day 6–7, CDGP = nedapatin 130 mg/m$^2$ on Day 6, RT = radiotherapy, Field A = large field including from the skull base to supraclavicular fossa, Field B = boost field including the nasopharynx and metastatic lymph nodes.

chemoradiation arm, 10 (56%) developed distant metastasis (DM) in the IGS. A considerable incidence of DM still developed in the IGS due to insufficient dose intensities of chemotherapy, instead of increasing adverse events.

In the Aichi Cancer Center, we conducted alternating chemoradiotherapy for advanced NPC patients from 1987 and reported promising results with sufficiently better compliance (94%), of which the 5-year OAS and PFS rates were 75% and 63%, respectively [6]. In the present study, we analysed the efficacy of alternating chemoradiotherapy for NPC with relatively longer follow-up and sought to refine our treatment strategy according to data regarding failure patterns.

## MATERIALS AND METHODS

### Patient characteristics

Between 1990 and 2006, a total of 100 consecutive patients with newly diagnosed histology-proven nasopharyngeal carcinoma underwent definitive chemoradiotherapy (CRT) in the Aichi Cancer Center. All patients underwent fiberoptic nasopharyngoscopy and magnetic resonance imaging (MRI) to assess the extent of primary and cervical lymph nodes. Evaluation of distant metastasis was done by chest X-ray, computed tomography (CT), liver ultrasonography, and bone scintigraphy. After 2002, positron emission tomography (PET) or PET-CT was also used to evaluate the extent of the disease. In addition, laboratory data, electrocardiograms, and 24-h creatinine clearance were evaluated to assess general condition. For this analysis, all patients were restaged according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system [6].

### Treatment schedule

#### *Chemotherapy*

The treatment scheme is shown in Fig. 1. Details of the treatment regimen have been reported in another article [7]. Chemotherapy regimens were a combination of CDDP and 5-FU (FP) or nedaplatin (CDGP) and 5-FU (FN) regimens. In the FP regimen, 5-FU was administered continuously at a dose of 800 mg/m$^2$ on Days 1–5 and CDDP at a dose of 50 mg/m$^2$ on Days 6–7. In the FN regimen, 5-FU was administered continuously at a dose of 800 mg/m$^2$ on Days 1–5 and CDGP at a dose of 130 mg/m$^2$ on Day 6. Chemotherapy was performed in principal three times at 4-week intervals. However, when a WBC count <3000/mm$^2$ or a platelet count <100 000/mm$^2$ was obtained at the scheduled date of drug administration, chemotherapy was postponed and radiation therapy was alternately prescribed. When hematological data obtained two weeks after radiotherapy did not meet the inclusion criteria (WBC count >3000/mm$^2$ and platelet count >100 000/mm$^2$), the next cycle of chemotherapy was withdrawn. When the WBC count decreased to <1000/mm$^2$ or the platelet count decreased to <25 000/mm$^2$ after chemotherapy, doses of both 5-FU and CDDP were decreased by 25% at the next cycle. In addition, the dose of CDDP only was decreased by 25% when serum creatinine levels >1.5 mg/dl were noted.

#### *Radiotherapy*

Using a 6–10 MV photon beam by linear accelerator, external beam radiotherapy commenced 2–3 d after the completion of previous chemotherapy. At simulation and daily treatment, the head, neck and shoulder were immobilized in a hyperextended position using a thermoplastic mask. Radiotherapy was performed with a daily fraction of 1.8–2.0 Gy. The initial radiation field covered the nasopharynx and upper and middle cervical regions using bilateral opposing portals and lower cervical, and supraclavicular region using anterior single field irradiation at a dose of 36–40 Gy. Then, a shrinking field of 26–30 Gy was boosted to the nasopharynx and involved lymph nodes using the dynamic conformal rotational technique. In the shrinking field, we kept enough margins of primary tumors and involved lymph nodes from the edge of field. Those margins were mainly decided dependent on proximity to

critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes. During the second period of chemotherapy, radiotherapy was temporarily interrupted to spare the increasingly acute toxicity of 5-FU. Additional boosts of up to 10 Gy with stereotactic multiple arc treatment were also permitted, if residual tumors existed at primary sites.

### Follow-up and statistical consideration

Toxicities of CRT were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [8]. During the treatment period, complete blood counts and biochemical examinations were performed at least once a week. After completion of CRT, the treatment response was assessed by fiberoptic nasopharyngoscopy, MRI and/or PET/CT. The frequency of follow-up was every month for the first year, once every two months between the second and third post-treatment year, and once every three months after the third post-treatment year. Fiberoptic nasopharyngoscopy was performed at every visit, and post-treatment MRI scans were obtained every three months for the first year and then every six months thereafter. The survival period was calculated from the start of treatment to death or the last follow-up examination, and progression-free survival was defined as the period from the start of treatment to the progression of tumors or death by any cause. Overall survival and progression-free survival curves were calculated by the Kaplan-Meier method [9]. The log-rank test was used to compare survival curves. A Cox-proportional hazard model was used for multivariate analysis. Differences in the ratios between the two groups were assessed by the chi-square test.

## RESULTS

### Patient characteristics

Between June 1990 and March 2005, 100 patients with NPC received definitive CRT in the Aichi Cancer Center. Table 1 shows patient characteristics in this cohort. We analysed all patients who were treated with CRT. The median age was 55 years old (range, 28–80). Performance status was distributed as 2 of 0, 93 of 1, 3 of 2, and 2 of 3, respectively. Of these, 8 patients (8%) had histopathology with keratinizing squamous cell carcinoma (WHO type I), and 70 patients (70%) had Stage III–IVB disease. During this period the number of patients with NPC who were treated with radiotherapy alone was 13. The common reasons for radiotherapy alone were advanced age or poor general condition.

**Table 1.** Patient characteristics

| Characteristics | | | *n* |
|---|---|---|---|
| Age, years: median (range) | | 55 (28–80) | |
| Gender: | | | |
| | Male | | 72 |
| | Female | | 28 |
| Performance status | | | |
| | | 0 | 2 |
| | | 1 | 93 |
| | | 2 | 3 |
| | | 3 | 2 |
| Histology | | | |
| | | type I | 8 |
| | | non type I | 90 |
| | | others | 2 |
| T stage | | | |
| | | 1 | 37 |
| | | 2a | 15 |
| | | 2b | 15 |
| | | 3 | 15 |
| | | 4 | 18 |
| N stage | | | |
| | | 0 | 11 |
| | | 1 | 31 |
| | | 2 | 34 |
| | | 3a | 9 |
| | | 3b | 15 |
| Stage | | | |
| | | I | 4 |
| | | IIA | 2 |
| | | IIB | 24 |
| | | III | 34 |
| | | IVA | 12 |
| | | IVB | 24 |

### Treatment contents

The median dose to the primary site was 66.6 Gy (range, 50.4–80.2 Gy), and the median dose to involved lymph nodes was 66 Gy (range, 40.4–82.2 Gy), respectively. The median period of the whole course of alternating CRT was

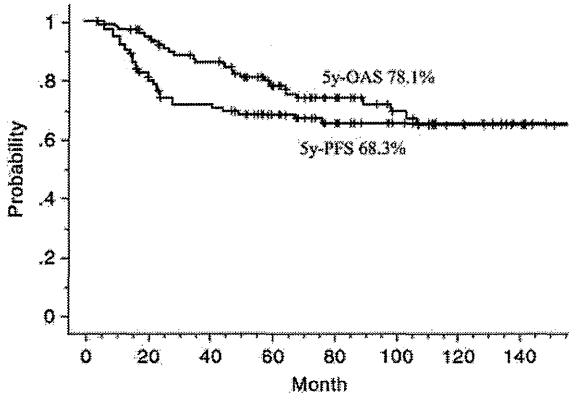


**Fig. 2.** Overall survival (OAS) and progression-free survival (PFS) curves.

85 days (range, 47–147 days), and the median period of overall treatment time of radiation therapy (OTT) was 69 days (range, 42–110 days).

## Treatment outcomes

The 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively (Fig. 2). The 5-year rates of OAS of the group divided by stage were 100, 100, 86.1, 77.6, 91.7 and 60.3% for Stage I, IIA, IIB, III, IVA and IVB, respectively. The 5-year rates of OAS and PFS of 96 patients who received alternating CRT were 78.2% and 68%, respectively. As for initial response after completion of CRT, complete remission (CR) rates of primary and nodal lesions were 86% and 83%, respectively. At a median follow-up of 65.9 months (range, 3.9–22.9 months), 62 were alive without disease, 11 were alive with disease, 18 died from the disease, 2 died from other diseases (both esophagus carcinoma) and 7 died from unknown reasons.

The 5-year rates of loco-regional progression-free survival (LRPFS) and distant metastasis-free survival (DMFS) were 77.9% and 87.8%, respectively.

A total of 32 patients (32%) developed treatment failure at one or more sites. Disease progression developed in 19 for primary, 9 for regional and 11 for distant sites at the last follow-up. Among 11 patients with distant failure, the most frequent site was the lung in 8, followed by bone in 4 and the liver in 2.

Of 21 patients who developed locoregional recurrence, 13 were treated with additional chemoradiation. Of the remainder, 2 patients were re-treated with radiotherapy alone, and 4 with only chemotherapy. One patient received neck dissection for regional failure, and another did not receive any treatment because of the patient's refusal for treatment.

Out of 11 patients who developed distant metastasis, 9 were treated by chemotherapy, and 2 patients received palliative radiotherapy only.

## Univariate analysis

Univariate analysis (UVA) results are listed in Table 2.

Elderly age, male, WHO type I histology, and N3 were revealed as significant unfavorable prognostic factors of OAS. The 5-year rate of OAS of the group with WHO type I histology was significantly lower than that with non-type I histology (33.3% vs 81.6%, $P<0.0001$, Fig. 3). The group with N3 lesions had significantly worse 5-year OAS (60.3%) than that with N0–2 (84%; $P=0.0017$). The 5-year rates of OAS of patients who received reduced dose and planned dose chemotherapy were 76.6% and 78.6%, respectively ($P=0.75$).

As for PFS, significantly unfavorable factors were revealed as WHO type I histology, T4 and N3.

The 5-year PFS rate of the group with N3 was significantly lower than that with N0–2 (41.5% vs 76.5%, $P=0.001$). The 5-year PFS rate of the group with T4 was significantly lower than that with T1–3 (54.5% vs 71.4%, $P=0.014$). The 5-year rates of PFS of patients who received reduced dose and planned dose chemotherapy were 69.7% and 66.7%, respectively ($P=0.59$).

The 5-year rate of LRPFS of the group with WHO type I histology was significantly lower than that with non-type I histology (21.4 % vs 84.5 %, $P<0.0001$).

The 5-year rate of DMFS of patients with N3 was significantly lower than that with N0–2 (62.8% vs 95.1%, $P<0.0001$). The 5-year LRPFS of patients with T4 was significantly lower than that with T1–3 (63.3% vs 81.1%, $P=0.027$).

## Multivariate analysis

Multivariate analysis (MVA) results are listed in Table 3. On MVA, significantly unfavorable prognostic factors of OAS were elderly age, WHO type I histology and N3, respectively. As for PFS, they were WHO type I histology, T4 and N3, respectively.

## Treatment compliance

Regarding the contents of chemotherapy, 82 patients received FP, while 14 received FN. Four patients had other chemotherapy regimens, as described below. One patient with Stage I (cT1N0M0) received two courses of CDDP/5-FU followed by definitive radiotherapy. One patient received six courses of weekly docetaxel (TXT) because of elderly age and poor medical condition. One patient received chemotherapy with both CDGP and TXT because 5-FU was inappropriate due to a past history of myocardial infarction. One patient received concurrent administration with decreased doses of CDGP and 5-FU due to elderly age. Chemotherapy compliance is shown in Table 4. In 96 patients who received alternating CRT, over 90% of patients received three courses of chemotherapy and 70% of patients received the planned dose of three courses. In

**Table 2.** Univariate analyses for overall survival and progression-free survival

| Factors | No. | 5-year OAS (%) | *P*-value | 5-year PFS (%) | *P*-value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Female | 28 | 88.7 | 0.017 | 77.9 | 0.15 |
| Male | 72 | 73.8 | | 64.4 | |
| Age (years) | | | | | |
| <51 | 48 | 93.4 | 0.0006 | 73.6 | 0.26 |
| ≥51 | 52 | 64.2 | | 63.4 | |
| PS | | | | | |
| 0, 1 | 95 | 79.1 | 0.148 | 69.9 | 0.1 |
| 2, 3 | 5 | 60 | | 30 | |
| Histology | | | | | |
| WHO non type I | 90 | 81.6 | $P<0.0001$ | 72.1 | $P<0.0001$ |
| type I | 8 | 33.3 | | 14.3 | |
| T stage | | | | | |
| T1–3 | 82 | 78.2 | 0.79 | 71.4 | 0.014 |
| ≥T4 | 18 | 77.4 | | 54.5 | |
| N stage | | | | | |
| N0–2 | 76 | 84 | 0.001 | 76.5 | 0.001 |
| N3 | 24 | 60.3 | | 41.5 | |
| Total treatment duration (day) | | | | | |
| <85 | 48 | 69 | 0.0615 | 62.3 | 0.135 |
| ≥85 | 52 | 85.6 | | 73.8 | |
| OTT (day) | | | | | |
| <69 | 49 | 78.2 | 0.884 | 72.2 | 0.36 |
| ≥69 | 51 | 78.2 | | 64.8 | |
| Dose for primary site (Gy) | | | | | |
| <66 | 30 | 76.7 | 0.712 | 70 | 0.7 |
| ≥66 | 70 | 78.7 | | 67.5 | |
| Dose for metastatic LN (Gy) | | | | | |
| <66 | 35 | 77.5 | 0.683 | 71.8 | 0.78 |
| ≥66 | 54 | 74.8 | | 65.1 | |

OAS = overall survival, PFS = progression-free survival, PS = performance status, WHO = World Health Organization, OTT = overall treatment time of radiotherapy, LN = lymph node.

detail, 29 patients received reduced dose chemotherapy while 67 patients received the planned dose of three courses. The most common reason for dose reductions was renal dysfunction (47%), followed by severe mucositis (20%). The median total dose of CDDP was 300 mg/m$^2$ (range, 150–340 mg/m$^2$), CDGP was 375 mg/m$^2$ (range, 80–400 mg/m$^2$), and for 5-FU was 12 000 mg/m$^2$ (range, 3050–12 000 mg/m$^2$). In the cohort of patients who received reduced dose chemotherapy, the median total doses of CDDP, CDGP and 5FU were 250 mg/m$^2$, 330 mg/m$^2$ and 9400mg/m$^2$, respectively. Unplanned interruption of RT was experienced in 14 patients (14%), and 2 out of 14 patients required a break in RT over seven days. Severe mucositis (36%) was the most common reason for interruption of RT, followed by infection of the hyperalimentation catheter (29%).

## Treatment toxicity

Acute toxicities observed during treatment are listed in Table 5. The most common toxicity was leukopenia. Grade

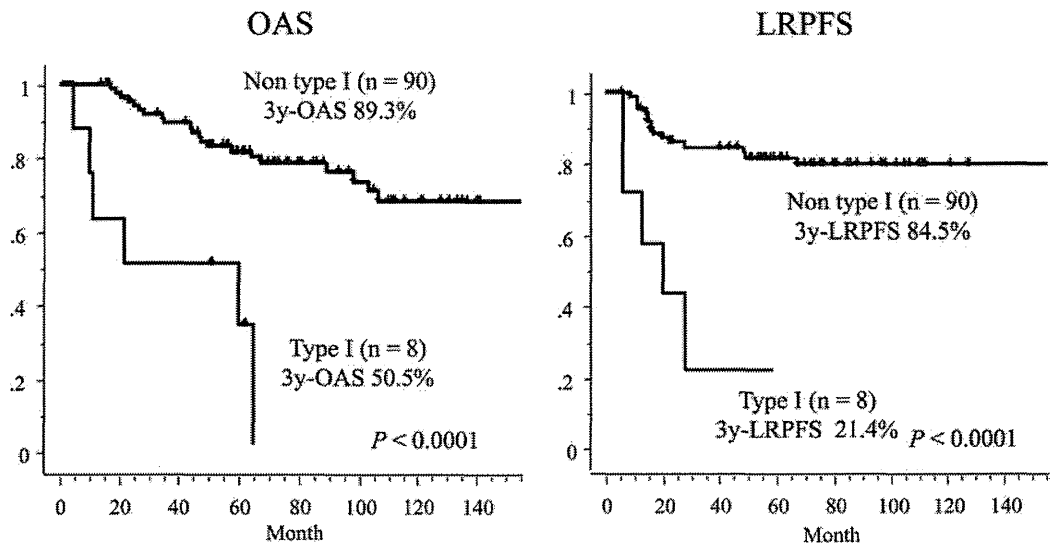


**Fig. 3.** Overall survival (OAS) and locoregional progression-free survival (LRPFS) curves of groups divided by WHO histopathological types.

**Table 3.** Multivariate analyses for overall survival and progression-free survival

| | | OAS | | PFS | |
|---|---|---|---|---|---|
| **Factors** | **No.** | **HR (95% CI)** | ***P*-value** | **HR (95% CI)** | ***P*-value** |
| Gender | | | | | |
| Female | 28 | | 0.109 | | 0.5 |
| Male | 72 | 2.76 (0.104–1.257) | | 1.36 (0.291–1.836) | |
| Age (years) | | | | | |
| <51 | 48 | | 0.0018 | | 0.198 |
| ≥51 | 52 | 4.92 (0.074–0.551) | | 1.62 (0.294–1.290) | |
| Histology | | | | | |
| WHO non type I | 90 | | 0.0034 | | 0.0004 |
| type I | 8 | 4.62 (0.077–0.603) | | 5.747 (0.067–0.454) | |
| T stage | | | | | |
| T1–3 | 82 | | 0.555 | | 0.023 |
| T4 | 18 | 1.36 (0.264–2.047) | | 2.5 (0.181–0.881) | |
| N stage | | | | | |
| N0–2 | 76 | | 0.0076 | | 0.0025 |
| N3 | 24 | 3.03 (0.147–0.745) | | 3.012 (0.163–0.680) | |
| OTT (day) | | | | | |
| <69 | 49 | 1.10 (0.395–2.065) | 0.8092 | | 0.605 |
| ≥69 | 51 | | | 1.215 (0.393–1.724) | |

HR = hazard ratio, CI = confidence intervals, OAS = overall survival, PFS = progression-free survival, WHO = World Health Organization, OTT = overall treatment time of radiotherapy.

3 or higher leukopenia, neutropenia, thrombocytopenia and anemia occurred in 37, 22, 11 and 18 patients, respectively. Grade 3 or higher mucositis and dermatitis developed in 20 and 18 patients, respectively.

Late toxicities are listed in Table 6. Three Grade 3 osteomyelitis of the mandible occurred in this series. One patient died because of late toxicity due to lethal mucosal bleeding. The patient diagnosed as cT3N1M0 with histology of Type I received 80 Gy to the primary site including additional SRT boosts of 10 Gy due to an insufficient response at the planned 70 Gy. The patient developed active mucosal bleeding in the nasopharynx, and died five years later. We experienced no Grade 3 or higher late toxicity of brain necrosis, visual disturbance or swallowing disturbance.

## DISCUSSION

A randomized control trial showed survival advantages of concurrent chemoradiotherapy over radiation alone, thus it is believed to be the standard treatment for locally advanced NPC. In the IGS, Stage III–IVB patients with NPC were randomized to CRT or RT, and the combined CRT group was treated with radiation and concurrent triweekly CDDP followed by three adjuvant cycles of FP [1]. The 3-year rate of OAS of the RT-only group was significantly lower than that of the CRT group (46% vs 76%; $P < 0.001$), and the same results were noted for the 3-year rate of PFS (24% vs 69%; $P < 0.001$). However, some problems with the results from the IGS were identified. Firstly, results of the RT arm in the IGS seem to be unacceptably bad because the reported 3-year rates of OAS for the same stages were over 70%. One of the reasons for this discrepancy is that the rate of WHO type I histology in the IGS series (24%) is larger than that of endemic regions, which is believed to have adversely impacted on clinical results. Secondly, the compliance of chemotherapy was insufficient in the IGS. The completion rates of planned chemotherapy of concurrent and adjuvant series were reported as 63% and 55%, respectively. In order to confirm this result, the IGS should be extrapolated in endemic regions [4]. In Hong Kong, the NPC-9901 trial on patients with T1-4N2-3M0 disease was designed to confirm the therapeutic ratio achieved by the IGS regimen. Regarding the compliance of chemotherapy, 65% of patients completed all six cycles, and 79% had five cycles. The CRT arm achieved significantly higher failure-free survival (72% vs 62% at 3 years, $P = 0.027$), mostly as a result of improvements in locoregional control. However, DMFS did not improve significantly (76% vs 73%, $P = 0.47$) and OAS was identical (78% vs 78%, $P = 0.97$). In other RCTs reported by Lin and Chen, the CRT arm significantly improved PFS and OAS [2, 3].

There is also evidence by meta-analysis dealing with eight randomized trials of 1753 patients regarding locally advanced NPC. In this analysis, the pooled hazard ratio of death for adding chemotherapy was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years (56% vs 62%). A

**Table 4.** Compliance of chemotherapy

| | *n* | median (range) |
|---|---|---|
| **Total cycles given** | | |
| 1 | 2 | |
| 2 | 7 | |
| ≥3 | 87 | |
| **Total dose given** | | |
| Cisplatin (mg/m$^2$) | | 300 (150–340) |
| Nedaplatin (mg/m$^2$) | | 375 (80–400) |
| 5-fluorouracil (mg/m$^2$) | | 12 000 (3050–12 000) |

**Table 5.** Acute, severe and life-threatening toxicities due to chemoradiotherapy

| Toxicity | Gr 0 | Gr 1 | Gr 2 | Gr 3 | Gr 4 | Gr 5 | unknown | ≥ Gr 3 |
|---|---|---|---|---|---|---|---|---|
| Leukopenia | 4 | 12 | 43 | 32 | 5 | 0 | 4 | 37 |
| Granulocytopenia | 18 | 27 | 28 | 17 | 5 | 0 | 5 | 22 |
| Anemia | 6 | 33 | 39 | 14 | 4 | 0 | 4 | 18 |
| Thrombocytopenia | 28 | 37 | 10 | 8 | 3 | 0 | 4 | 11 |
| Liver dysfunction | 71 | 20 | 5 | 1 | 0 | 0 | 1 | 1 |
| Renal dysfunction | 71 | 28 | 0 | 0 | 0 | 0 | 1 | 0 |
| Vomiting | 33 | 14 | 50 | 3 | 0 | 0 | 0 | 3 |
| Mucositis | 0 | 13 | 67 | 19 | 1 | 0 | 0 | 20 |
| Dermatitis | 0 | 37 | 45 | 17 | 1 | 0 | 0 | 18 |
| Salivary gland changes | 1 | 13 | 86 | 0 | 0 | 0 | 0 | 0 |

**Table 6.** Late, severe and life-threatening toxicities due to chemoradiotherapy

| Toxicity | Gr 0 | Gr 1 | Gr 2 | Gr 3 | Gr 4 | Gr 5 | ≥ Gr 3 |
|---|---|---|---|---|---|---|---|
| Swallowing dysfunction | 95 | 4 | 1 | 0 | 0 | 0 | 0 |
| Visual dysfunction | 99 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hearing impairment | 81 | 5 | 14 | 0 | 0 | 0 | 0 |
| Osteomyelitis | 96 | 0 | 1 | 3 | 0 | 0 | 3 |
| Brain necrosis | 99 | 1 | 0 | 0 | 0 | 0 | 0 |
| Bleeding | 99 | 1 | 0 | 0 | 0 | 1 | 1 |

significant interaction was observed between the timing of chemotherapy and overall survival ($P = 0.005$), with the highest benefit resulting from concomitant chemotherapy [5]. However, increasing acute toxicities caused by administration of chemotherapy were also reported in this analysis. In the IGS, acute toxicities of ≥ Grade 3 were reported as 50% and 76% for RT and CRT arms, respectively. Similarly, in the NPC-9901 trial, toxicities of ≥ Grade 3 were observed as 53% and 84% for RT and CRT arms, respectively ($P < 0.01$). The 3-year actuarial rate of late toxicity was slightly higher in the CRT arm than in that of the RT arm, although it was not significant (28% vs 13%, $P = 0.24$).

In our institute, we adopted alternating CRT for NPC from 1987. In a previous report, 32 patients with NPC received alternating CRT, and the 5-year rates of OAS and PFS were 75% and 63%, respectively. A Phase II study of alternating chemoradiotherapy for patients with NPC was performed in four medical institutions including our institution from 1997 and reported promising results with high compliance (91%), of which the 2-year OAS and PFS rates were 94% and 83%, respectively [10]. In the present study with longer follow-up and a larger cohort, the 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively. We think these data are comparable with previous series. In addition, we believe that acute and late complication rates were sufficiently low according to longer follow-up with 65.9 months.

We believe alternating chemoradiotherapy has several advantages in CRT for NPC. Because the radiation field has to be large, severe mucositis and dermatitis sometimes develops and leads to a treatment break. In addition, late complications, such as disturbances in swallowing or hearing sometimes become significant problems. Alternating chemoradiotherapy has the potential benefit in reducing acute toxicities. As for reported data of the NPC-9901 trial, acute mucositis and skin reactions over Grade 3 were observed in 62% and 20% patients in the CRT arm, respectively. In the present study, acute mucositis or dermatitis of ≥ Grade 3 developed in 20% and 18%, respectively. By alternating chemotherapy and radiotherapy, we could also use intensive multi-agent chemotherapy regimens such as FP or FN without increasing acute and late complications. Although our data is a retrospective analysis in a single institute, the 5-year rate of OAS in the present study (78.1%) was more promising than that of the IGS trial (67%). Regarding the compliance of chemotherapy, over 90% patients in the present study could receive three courses of chemotherapy and 70% of our cohort had completed planned full doses. As a result the total dose of chemotherapy in patients who received a reduced dose was still about 80% of the planned dose. Our data is thought to be more encouraging than that of the IGS, in which only 55% patients completed the planned chemotherapy. Failure patterns in CRT for NPC patients are thought to be both loco-regional, but also in distant sites. In the present study, DMFS at 5-years was 87.8%, which was higher than that of the reported series. The 3-year DMFS rate of the NPC-9901 study was reported as 76%. We believe that it was caused by the advantages of intensive chemotherapy in the present study. An unexpected RT break was needed in 14 patients (14%), of which only 2 patients needed RT breaks longer than one week.

The argument against alternating CRT is that planned RT interruptions may lead to sacrifices in treatment efficacy. In many studies, it is well known that prolongation of overall treatment time negatively influences clinical outcomes. *In vitro*, accelerated repopulation occurred 28 days after the start of RT; thus, prolongation of treatment time led to the development of radiation resistance. In the present study, OTT was not significantly related to clinical outcome. One of the reasons is that the high compliance of the present study would have helped avoid essential prolongation of OTT in our cohort.

In the present series, WHO type I histopathology was a significantly unfavorable factor of both OAS and PFS. The incidence of WHO type I histology in Western countries is very different from East Asian countries. In the IGS series conducted in North America, the rate of WHO type I histology was 22%, which was higher than the rates in studies

conducted in endemic regions. WHO type I histopathology, keratinizing squamous cell carcinoma, was reported to be much less related to EBV infection than non-keratinizing carcinoma. It was also reported to be less sensitive to RT [11]. However, there are not so many reports regarding clinical results. One of the reasons is that the proportion of type I histopathology is very low in endemic regions. In Japan, the proportion of type I histopathology is about 20%, which was similar to North America. Kawashima *et al.* reported a Japanese multi-institutional survey of 333 NPC patients, in which the proportion of type I histopathology was 19% [12]. In that series, type I histopathology proved to be a significantly worse prognostic factor of OAS and PFS on both UVA and MVA. In the present study, the population of type I histopathology was 8%; however, these eight patients had remarkably poor prognosis. Six of the eight patients developed treatment failure. In our series, WHO type I histopathology was a significantly worse factor of both OAS (3-year rates; 50.5% vs 89.3%; $P < 0.0001$) and LRPFS (3-year rates; 21.4% vs 84.5%, $P < 0.0001$). The majority of failure patterns of these patients were in loco-regional sites. In order to improve treatment outcomes of these patients, dose escalation without increasing adverse events is believed to be promising. In recent years, intensity-modulated radiation therapy (IMRT) is widely used for head and neck cancer because of its dose conformity ability for PTV, reducing doses to normal tissue. RTOG 0225, a multi-institutional Phase II trial was conducted to test the feasibility of IMRT with or without chemotherapy for NPC. A 90% LRPF rate was reported as well as an acceptably low incidence of Grade 3 adverse events without xerostomia of Grade 4 [13]. In our institution, we started IMRT for NPC patients using Helical Tomotherapy until June 2006, and we have reported our preliminary clinical results [14]. In the future, dose escalation for patients with type I histopathology using IMRT will be helpful for improving clinical results.

The 5-year rates of PFS and LRPFS of patients with T4 were significantly inferior to those with T1–3, even though there was no significant difference in the 5-year rates of DMFS between these two groups. Because of the proximity of tumors to critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes, the radiation fields and dose coverages for primary tumors are often compromised. Preliminary results of radiation dose escalation for patients with T3–T4 NPC show good local control (2-year rate of locoregional control; 95.7%) and survival (2-year rate of OAS; 92.1%) [15]. For these patients, dose escalation using IMRT is also promising improved clinical results.

The 5-year rates of OAS and DMFS of patients with N3 were significantly inferior to those with N0–2 in the present series. On the other hand, N3 showed no apparent correlation with worsening LRPF. From this result, patients with N3 are expected to have a higher incidence of distant metastasis. Thus, a more effective regimen of chemotherapy should be considered to overcome limitations. In fact, TAX 324, a randomized Phase III trial, has shown the distinct survival advantages of multi-agent intensive chemotherapy including docetaxel and FP over PF for locally advanced head and neck cancer [16].

We believe that the present results for alternating chemoradiotherapy are promising compared to previously reported series of concurrent chemoradiotherapy. However, several subgroups with some risk factors proved to have insufficient outcomes. In order to refine clinical results without increasing adverse events, there is room for modification especially in patients with high-risk factors. Dose escalation using IMRT for type I histopathology and/or T4 disease and more intensive modifications of chemotherapy for N3 disease should be considered in future.

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Hepatology Research

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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 $\alpha/\beta$ 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

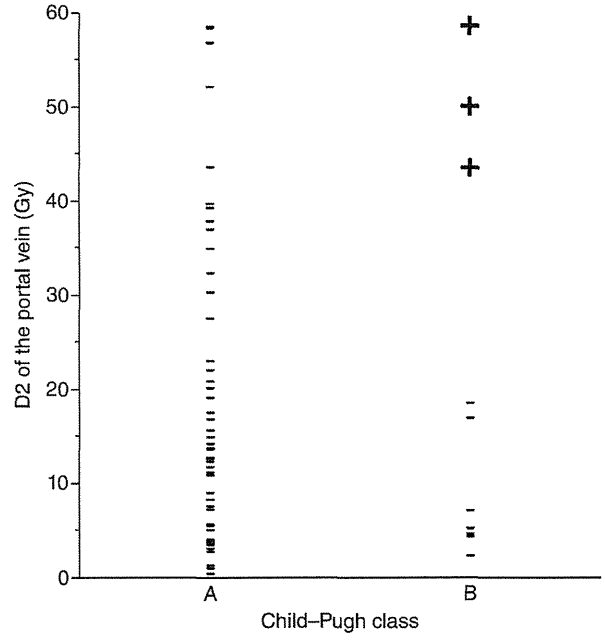


Figure 1 Relationship between Child–Pugh class and $D_2$ of the portal vein. Plus signs indicate the patients who experienced portal vein thrombosis.

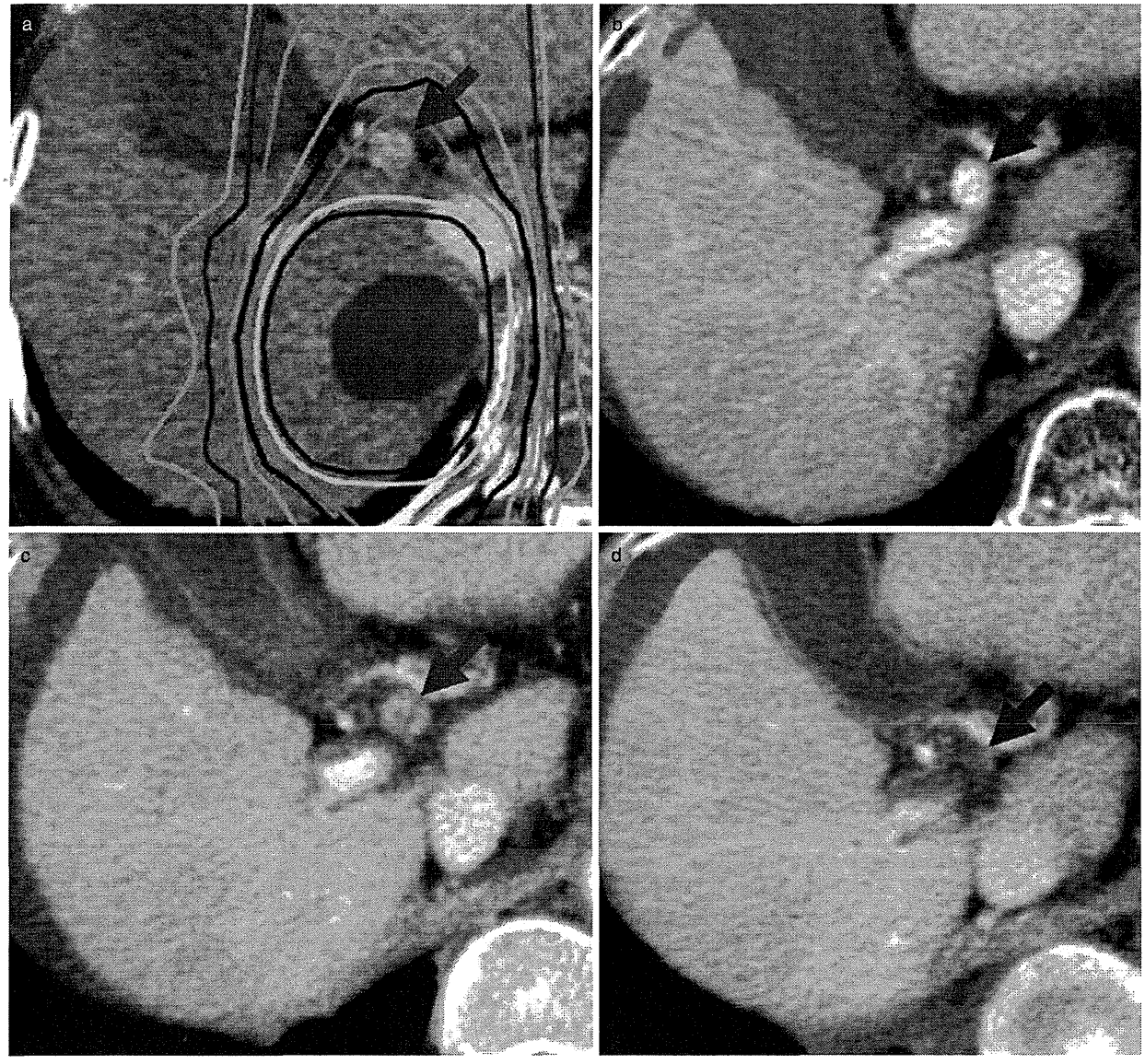


**Figure 2** Red arrows indicate the left branch of the portal vein. (a) Dose distribution of the plan with 48 Gy in four fractions. Isodose lines from outer to inner represent 30%, 40%, 50%, 60%, 70%, 80%, 90% and 95% of the prescribed dose. Red circle indicates gross tumor volume. (b) No sign of portal 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.

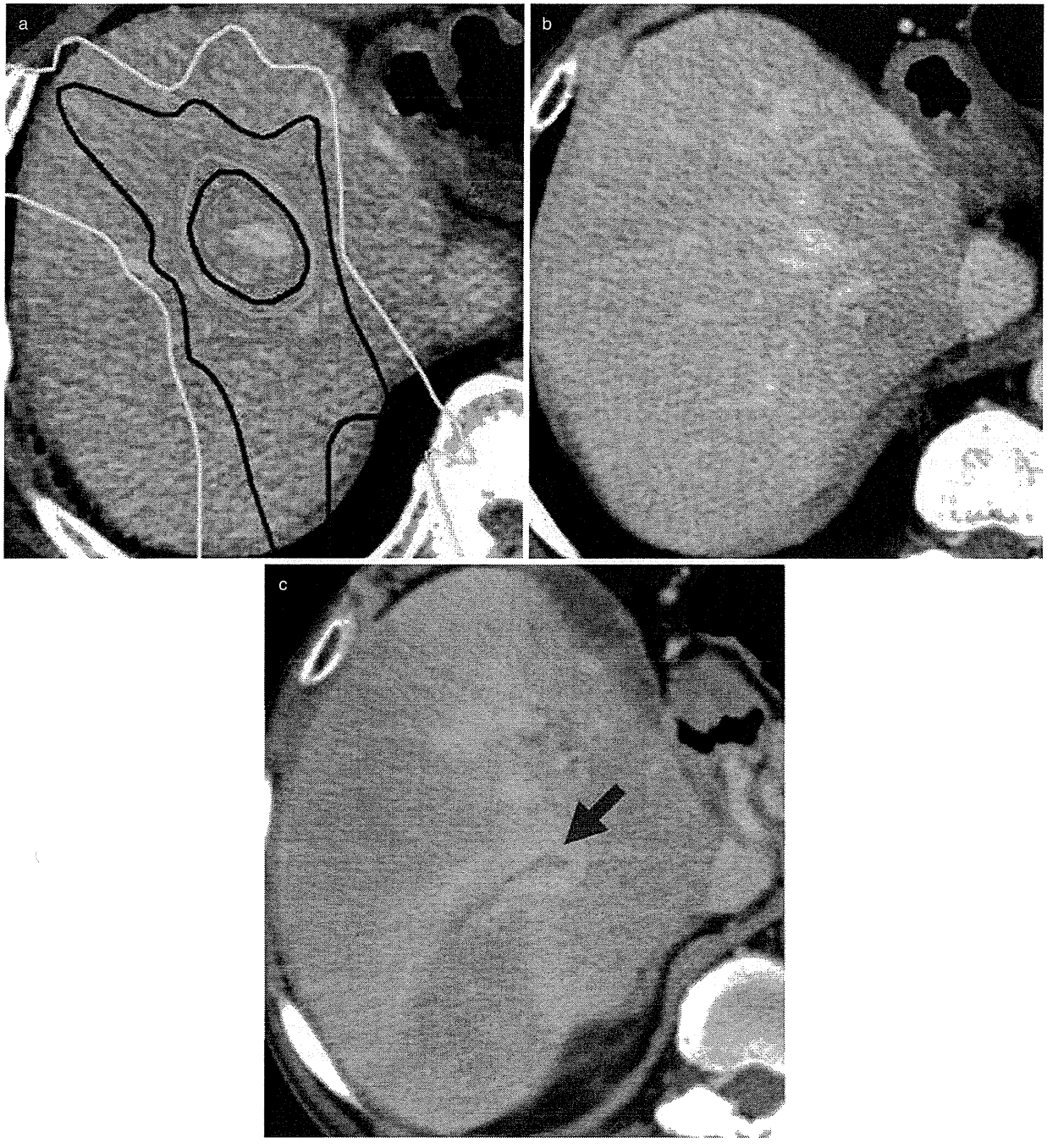


**Figure 3** Peripheral slices from a gross tumor. (a) Dose distribution of a plan with 48 Gy in four fractions. Isodose lines from outer to inner represent 30%, 40%, 50%, 60%, 70% and 80% of the prescribed dose. (b) No sign of bile duct stenosis was observed at 6 months after stereotactic body radiation 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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HEPATOLOGY

# 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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Conflict of interest: The authors declare no conflict of interest.

## 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, $\leq 3$ 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

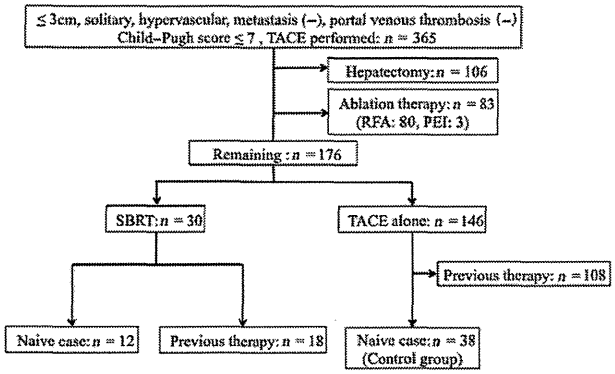


**Figure 1** Treatment selection. PEI, percutaneous ethanol injection; RFA, radio-frequency ablation; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

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,

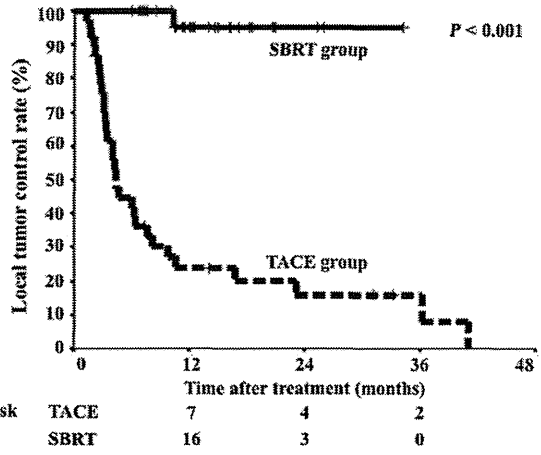


**Figure 2** Local tumor control rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

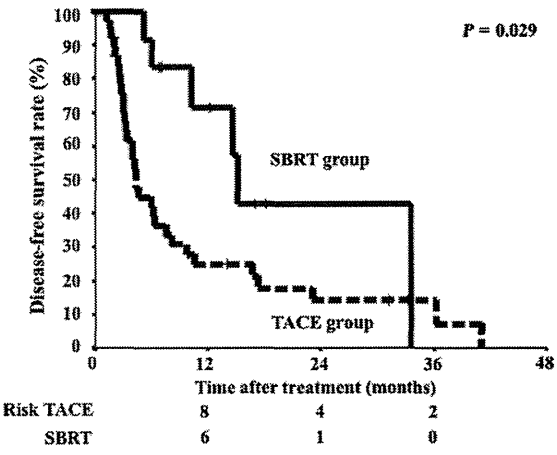


**Figure 3** Disease-free survival rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

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

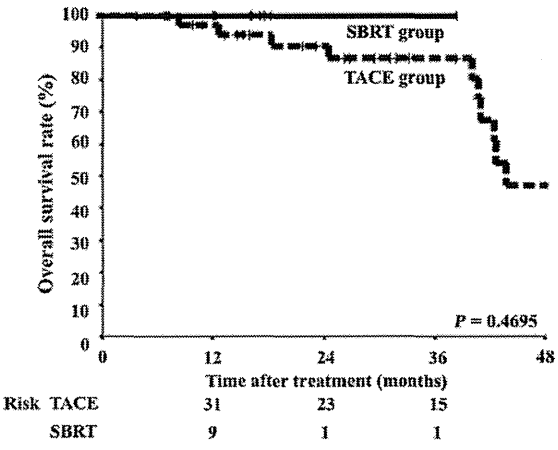


**Figure 4** Overall survival rate according to treatment modality. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

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).