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Hepatic irradiation in primary and metastatic liver cancer

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Summary. Between December 1973 and September 1987, 21 patients with primary liver cancer and 41 patients with metastatic liver cancer were treated with external irradiation, intra-arterial infusion chemotherapy and/or transarterial embolization (TAE) at the National Medical Center Hospital, the National South Kyushu Central Hospital and the National Kure Hospital. Of the patients with primary liver cancer, 13 cases were treated with intra-arterial infusion chemotherapy (30–40 mg adriamycin or 10 mg mitomycin C) and hepatic irradiation. Eight cases were treated by TAE and hepatic irradiation. In the Child A group, the survival period of the chemotherapy + hepatic irradiation cases (mean: 608 days) was longer than that of the TAE + hepatic irradiation cases (mean: 216 days). The median survival period of all the cases was 7.0 months (mean: 10.9 months). For 16 of the 21 patients (who had absorbed over 40 Gy), the median survival period was 11.9 months (mean: 11.7 months). For 5 of the 21 patients (who had absorbed below 40 Gy), the median survival period was 4.3 months (mean: 7.9 months). Of the patients with metastatic liver cancer, the median survival period was 7.2 months (mean: 8.0 months). For 22 of the 41 patients (who had absorbed over 40 Gy), the median survival was 7.9 months (mean: 12.6 months). For 19 of the 41 patients (who had absorbed below 40 Gy), the median survival period was 1.7 months (mean: 2.6 months). The pretreatment serum GOT (glutamate oxaloacetate transaminase) levels and the pretreatment Karnofsky performance status index were the factors governing the prognosis of the cases with metastatic liver cancer, while toxicity was generally mild.

Introduction

Primary and metastatic liver cancers are frequent causes of morbidity and mortality. Owing to recently developed technology, small liver cancers can be detected, although inoperable cases are often found. In advanced cases, hepatic arterial infusion chemotherapy, transarterial embolization (TAE) or intratumor injections of pure ethanol are commonly tried. However, it is sometimes impossible to treat by TAE cases which have already been treated repeatedly by TAE or those with tumor thrombosis of the main portal vein. We have carried out research into the use of external irradiation for the treatment of primary and metastatic liver cancer. We started treating these cases with external irradiation in 1973, and here we shall report on the results and some of the problems with this treatment.

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Materials and methods

Patient selection. The patients were required to have primary or metastatic liver cancer documented by echograms, computerized tomograph (CT) scans, radionuclide liver scans, angiograms and/or direct liver biopsies. All the patients were inoperable cases because of the size of the tumor, poor liver function test results or thrombosis of the main portal vein.

Patient characteristics. Between December 1973 and August 1987, 21 patients with primary liver cancer and 41 patients with metastatic liver cancer were treated with external irradiation, chemotherapy and/or TAE at the National Medical Center Hospital, the National South Kyushu Central Hospital and the National Kure Hospital. Table 1 shows the characteristics of the patients with primary liver cancer. Eighteen cases were male and 3 cases were female. The average age was 59.5 years. Fourteen patients (66.7%) had liver cirrhosis. Eleven patients (52.4%) were at stage 4, three patients (14.3%) were at stages 1 and 3 and four (19.0%) were at stage 2. Twelve patients were Child A, four patients were Child B and five were Child C. Thirteen patients were treated with intra-arterial infusion chemotherapy and hepatic irradiation, and eight patients were treated with TAE and hepatic irradiation. Table 2 shows the characteristics of patients with metastatic liver cancer. Of the total number of cases, 27 were male and fourteen were female. The average age was 59.5 years. The most frequent primary carcinoma site was the rectum while the other sites included the stomach, colon, breast, esophagus and lung. The most frequent primary histology was adenocarcinoma (66%), and they were all inoperable advanced cases.

Treatment. For most of our patients, local hepatic irradiation was carried out with AP-PA opposed fileds. Oblique fileds were occasionally utilized in patients with large hepatic volumes. The radiation field was established on a simulator determined by palpation, echograms, angiogra-

Table 1. Primary liver cancer: Patient characteristics

Characteristics	No. of patients
Sex	
Male	18
Female	3
Mean age: 59.5 (50–75) years	
Stage	
1	3
2	4
3	3
4	11
IAC+RT[a]	13
TAE+RT	8

[a] IAC, Intra-arterial one-shot chemotherapy; TAE, transarterial embolization; RT, radiation therapy

Table 2. Metastatic liver cancer: Patient characteristics

Characteristics	No. of patients
Sex	
Male	27
Female	14
Mean age: 59.5 (50–75) years	
Primary site	
Rectum	7
Stomach	6
Colon	6
Breast	6
Esophagus	4
Lung	3
Lymphoma	2
Others	7
Primary histology	
Adenocarcinoma	27
Squamous cell	4
Malignant lymphoma	2
Others	8

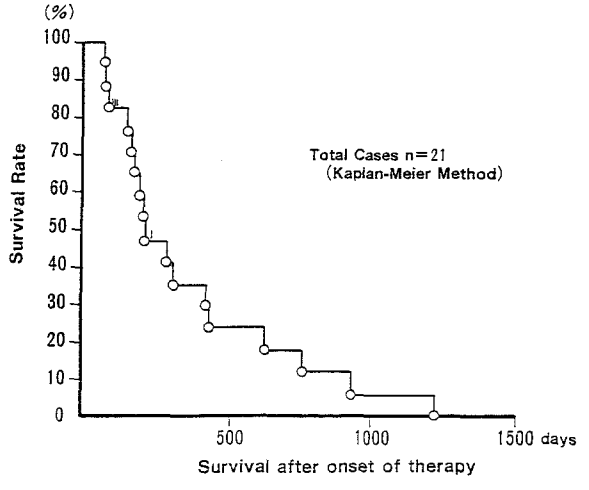

Fig. 1. Cumulative survival curve of all cases in primary liver cancer (n = 21) (Kaplan-Meier method)

phic films and either radionuclide scans or CT scans. Both fields were treated each day, using a 6-MV, 10-MV or 18-MV Linac X-ray apparatus for a dose in 1.8–3.0-Gy fractions. The mean dose absorbed was 43.8 Gy in all cases of primary liver cancer and 44.9 Gy in all cases of metastatic liver cancer. For the eight cases of primary liver cancer. TAE with lipiodol, adriamycin and Gelfoam was carried out. In these cases, irradiation was delivered after TAE. In the 11 cases of primary liver cancer, intra-arterial infusion chemotherapy (IAC) with adriamycin (30–40 mg) or mitomycin C (10 mg) was carried out. The white blood cell counts, platelet counts and chemistry profiles were obtained at the initiation of therapy and weekly during treatment for evidence of systemic toxicity. Once the therapy had been completed, the above checks were carried out at 1-week intervals. Four weeks after the treatment had been completed, the response of the patients was evaluated using the parameters previously described.

Results

Primary liver cancer

The cumulative survival curve of all the cases is shown in Fig. 1. The median survival period of all the cases was 7.0 months (mean: 10.9 months). The 1-year survival rate was 28.6%, the 2-year survival rate was 14.3%, and the 3-year survival rate was 4.7%. As for the cumulative survival curves of the two groups, the open circles represent the group that absorbed over 40 Gy, while the closed circles represent the group that absorbed below 40 Gy, as shown in Fig. 2. Table 3 is a comparison of these two groups. In

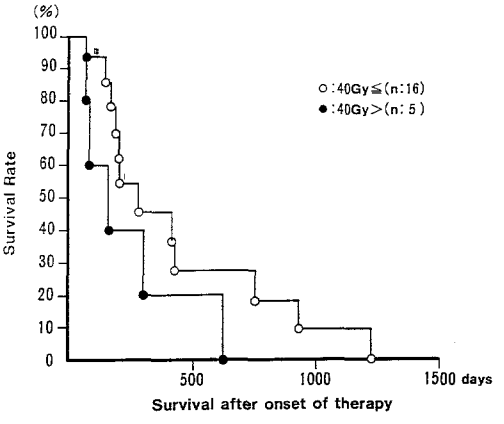

Fig. 2. Cumulative survival curves of the two groups in primary liver cancer. ○, the group that absorbed over 40 Gy (n = 16). ●, the group that absorbed below 40 Gy (n = 5)

Table 3. Primary liver cancer

Absorbed dose (Gy)	Number of cases	Mean absorbed dose (Gy)	Median survival (months)	Mean survival (months)	Median pretreatment KPS[a]
⩾40	16 (76%)	46.8	11.9	11.7	70
<40	5 (24%)	24.0	4.3	7.9	50
Total	21	35.4	7.0	10.9	50

[a] KPS, Karnofsky performance status index

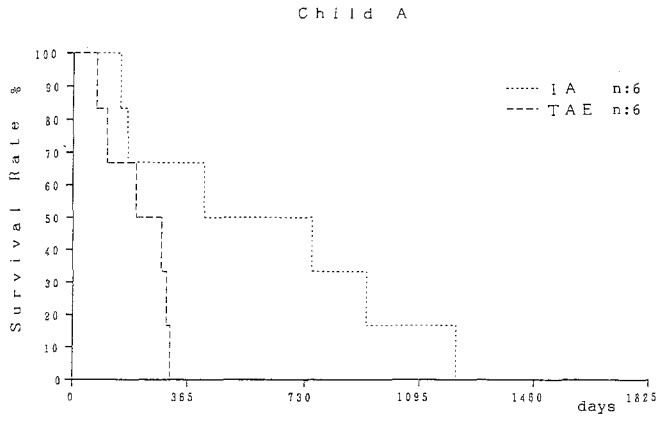

Fig. 3. Survival after onset of therapy

the group that absorbed over 40 Gy (16 cases out of the total: 76%), the mean dose absorbed was 46.8 Gy, and the median survival period was 11.9 months (mean: 11.7 months). As for the group that absorbed below 40 Gy (five cases of the total: 24%), the mean dose absorbed was 24.0 Gy, while the median survival period was 4.3 months (mean: 7.9 months). The median survival period of the first group was longer than that of the second. We then compared the two subsequent groups. The first group was treated with IAC and hepatic irradiation, while the second was treated with TAE and hepatic irradiation. The median survival period of the first group was longer than that of the second, but there was no significant difference between the two groups. Then we investigated the difference between these groups in the Child A group. There were six cases in each group and there was a significant difference between these two groups (Fig. 3). The mean survival period was 608 days in the first group and 216 days in the second one.

Metastatic liver cancer

In all the cases, the mean does absorbed was 36.0 Gy, while the median survival period was 7.2 months (mean: 8.0 months). The 1-year survival rate was 19.5%, and the 5-year survival rate was 2.4%. Table 4 shows the survival rate for cases that absorbed over 40 Gy, the mean dose absorbed, and median survival period for each primary site. The median survival periods for cases of rectum and colon carcinoma were the longest. Table 5 is a comparison of the

Table 4. Metastatic liver cancer

Primary site	Number of cases	Number of cases ⩾40 Gy	Mean absorbed dose (Gy)	Median survival (months)
Rectum	7	7 (100%)	51.4	7.8
Colon	6	5 (83%)	53.8	10.5
Stomach	6	3 (50%)	34.5	3.6
Esophagus	4	0 (0%)	17.5	1.3
Lung	3	2 (67%)	47.0	4.7
Breast	6	3 (50%)	33.4	4.6
Lymphoma	2	0 (0%)	10.0	2.2
Others	7	3 (43%)	28.5	5.9
Total	41	23 (56%)	36.0	7.2

Table 5. Metastatic liver cancer

Absorbed dose (Gy)	Number of cases	Mean absorbed dose (Gy)	Median survival (months)	Mean survival (months)	Median pretreatment KPS[a]
⩾40	22 (51%)	50.0	7.9 (4–68.6)	12.6	50
<40	19 (49%)	18.8	1.7 (1–10.4)	2.6	40
Total	41	36.0	7.2	8.0	40

[a] KPS, Karnofsky performance status index

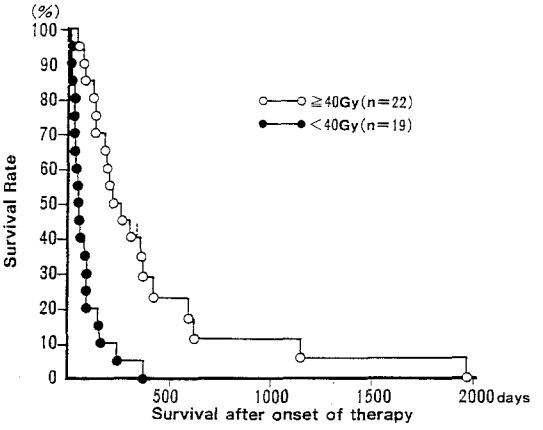

Fig. 4. Cumulative survival curves of the two groups in metastatic liver cancer. Twenty-two patients absorbed over 40 Gy (median survival, 7.9 months) and nineteen patients absorbed below 40 Gy (median survival, 1.7 months). $P = 0.001$ Wilcoxon test

two groups. In the first group, which absorbed over 40 Gy, the mean dose absorbed was 50.0 Gy, while the median survival period was 7.9 months (mean: 2.6 months). In the second group, which absorbed below 40 Gy, the mean dose absorbed was 18.8 Gy, and the median survival period was 1.7 months (mean: 2.6 months). The cumulative survival curves of these two groups are shown in Fig. 4. The cumulative survival rate of the first group was longer

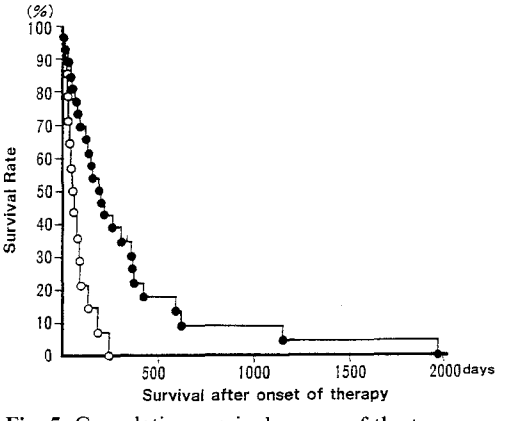

Fig. 5. Cumulative survival curves of the two groups in metastatic liver cancer. Twenty-six patients with normal serum GOT level (45 IU/l²) (median survival, 6.3 months) and 15 patients with abnormal serum GOT level (>45 IU/l) (median survival, 1.4 months). $P = 0.05$ Wilcoxon test. ●—● GOT ≦45 IU/l (n = 26), ○—○ GOT >45 IU/l (n = 15); $P = 0.05$

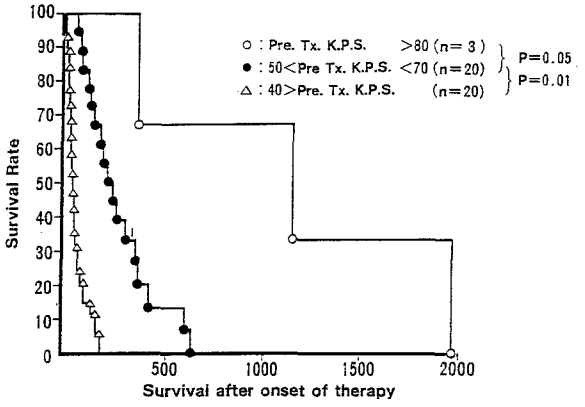

Fig. 6. Cumulative survival curves of the three groups in metastatic liver cancer. Three patients had Karnofsky performance status (KPS) index over 80 and 20 patients had KPS index between 50 and 70; $P = 0.05$ Wilcoxon test. Twenty patients had KPS index between 50 and 70, and 18 patients had KPS index below 40; $P = 0.01$ Wilcoxon test

than that of the second, and there was a significant difference between the two groups ($P = 0.001$). The cumulative survival rate of the patients whose pretreatment serum GOT levels were within the normal range was longer than those whose GOT levels were abnormal. There was a significant difference between the two groups ($P = 0.01$) Fig. 5, we have separated all the cases into three groups. For the first group, the pretreatment Karnofsky performance status index (KPS) was over 80, while for the second group $50 < KPS < 70$, and for the third group $KPS < 40$. Fig. 6 shows the cumulative survival curves of these three groups. The cumulative survival rate of the first group was longer than that of the second ($P = 0.05$), while that of the second group was longer than that of the third ($P = 0.01$).

Toxicity

Using this treatment modality, hematological toxicity was minimal. Most of the patients (69%) experienced nausea with or without vomiting, and this toxicity was seen to be more severe in cases with large radiation fields. One patient developed radiation hepatitis [6, 7, 9] owing to overdoses of radiation, we assume. One patient developed severe upper-gastrointestinal bleeding due to a radiation-induced duodenal ulcer, where the radiation dose to the hepatic portal region was over 70 Gy.

Discussion

Primary and metastatic liver cancers are frequent causes of morbidity and mortality. TAE, continuous arterial infusion chemotherapy and the intratumor injections of ethanol are the main treatment modalities for inoperable cases, and there have been numerous reports on their effectiveness. However, it is sometimes impossible to treat patients with these modalities. We have tried to treat such cases with external hepatic irradiation, but ideally this therapy should be used for the palliation of hepatic malignancy.

In 1954, Phillips et al. [13] reported on a series of 36 patients with liver metastasis who had received hepatic irradiation with 1000-kV X-rays. The total doses ranged from 2000 rad to 3000 rad. A symptomatic improvement was observed in 72% of the patients. In 1960, Phillips et al. [12] reported on a series of 26 patients with primary liver cancer. For this series, they reported that there was no significant effect on the group which had received less than 2000 rad, while the mean survival period was only 2 months. However, there was a significant effect on those who had received over 2000 rad, and their mean survival period was 12 months. Until the Phillips report, the treatment modality used was only hepatic irradiation. After 1980, the treatment modality changed to combined chemotherapy and hepatic irradiation [1–5, 8, 10–16]. In 1980, Friedman et al. [5] reported on a series of 20 patients with primary liver cancer who had been treated with combined intrahepatic arterial infusion chemotherapy and whole-liver irradiation. All the patients received an intrahepatic arterial infusion of 5-fluorouracil + adriamycin and 1500–2000 rad of whole-liver irradiation. Objective regression was observed in 45% of the patients, and the median survival period of the responders was 7 months.

In most reports concerning hepatic irradiation, the target volume was the whole liver. But for our cases the target volume was a certain part of the liver. In whole-liver irradiation, 2000–3000 rad has been reported to be the adequate radiation dose [1–5, 8, 10–14, 16]. We think that this is based on the Phillips report [12], the Ingold report [6] and the Kaplan report [7]. In 1965, Ingold et al. [6] reported on the relationship between radiation doses and radiation hepatitis. Radiation hepatitis was observed in 37% of the group that had received whole-liver irradiation of over 3000 rad, but in the group that had received less than 3000 rad, there were no cases of radiation hepatitis. In 1968, Kaplan et al. [7] reported on radiation hepatitis. They had observed radiation hepatitis in the cases who had received 2500–2700 rad on the whole liver, but all cases were reversible and there were no significant clinical problems. Of our cases, only one patient was documented as having radiation hepatitis. This patient had liver metastasis from gastric cancer, and had received irradiation of the right hepatic lobe somewhat over 60 Gy. The patient died from pneumonia. The autopsy showed evidence of radiation hepatitis but no viable cancer cells were observed.

In our study, the median survival period of cases with primary and metastatic liver cancer was longer in the group receiving over 40 Gy than that receiving below 40 Gy. The mean doses absorbed by the good responders were 46.8 Gy for those with primary liver cancer and 50.0 Gy for those with metastatic liver cancer. We think that the adequate radiation doses for partial hepatic irradiation is 50 Gy, and if the irradiated hepatic volume is small, 60 Gy is the tolerable dose. However, when the hepatic portal region is within the radiation field, the tolerable dose should be within 50 Gy. In 1978, Webber et al. [15] reported on which therapy was the more effective, radiation therapy alone or radiation therapy combined with chemotherapy for cases with metastatic liver cancer. In this series, all the cases were separated into three groups. The first group received a continuous arterial infusion of fluorodeoxyuridine, the second radiation therapy only, and the third received combined radiation therapy and continuous arterial infusion chemotherapy. The mean survival period of each group was 270 days, 140 days and 376 days. Among our primary liver cancer cases, 8 of the 21 patients were treated with combined TAE and hepatic irradiation, while the other 13 were treated with combined IAC and hepatic irra-

diation. The survival period of the IAC + hepatic irradiation group tended to be longer than that of the other groups. We therefore wonder whether the hypoxic cells increased in the tumor when TAE was performed, so that the tumor cells changed to radioresistant cells. We think that IAC is more useful for hepatic irradiation than TAE. For the cases of metastatic liver cancer, the pretreatment serum GOT levels and the pretreatment KPS were the factors governing the prognosis, but there were no examination factors for the cases of primary liver cancer. We think that our cases with primary liver cancer had liver cirrhosis as the basal disease, so the pretreatment serum GOT levels did not indicate pure tumor damage, but most of the cases with metastatic liver cancer had no basal disease of the liver, so the pretreatment serum GOT levels indicated the prognosis.

Although the toxicity of this therapy was generally mild, one patient died of panperitonitis due to duodenal perforation, while another patient developed radiation hepatitis. Each case received radiation doses of over 60 Gy.

We believe that the combination of intra-arterial infusion chemotherapy and external hepatic irradiation can be used in the treatment of a hepatic malignancy. We shall try to use tho combination therapy of hyperthermia and hepatic irradiation and intra-arterial infusion chemotherapy in the future.

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