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Effects of multimodal treatment and hyperthermia on hepatic tumors*

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Summary. The therapeutic results of Lp-TAE (transcatheter arterial embolization in the presence or absence of Gelfoam particles preceded by the infusion of a mixture of lipiodol and an anticancer drug via the proper hepatic artery) or DSM-TAE (transcatheter arterial embolization with degradable starch microspheres and the arterial injection of anticancer drugs via the hepatic artery) combined with hyperthermia were evaluated in 30 patients with hepatocellular carcinoma (HCC), 5 subjects with hepatic cholangiocarcinoma, and 22 patients with metastatic liver carcinoma. Hyperthermia was performed using an 8-MHz Thermotron RF-8. Tumor temperatures could be measured in 31 patients (54.4%) with malignant lesions of the liver who had undergone hyperthermia. The mean maximal temperature (T_{max}) was 41.5° C in the metastatic liver cancers. The efficiency of heating in HCC was unfavorable, i. e., the mean T_{max} was only 40.7° C. The rise in tumor temperature was greater in either HCC or metastatic liver carcinoma associated with portal invasion of the lesion. The tumor-temperature elevation was also excellent in HCC that had been subjected to embolization with DSM in combination with hyperthermia. The response rate (complete response plus partial response) was as high as 40% (4/10) in the group in which the tumor temperature could be raised to 42° C or more. Among the 52 patients who had shown a high pretreatment level of tumor marker, that value decreased in 34 cases (65.4%), and the decrease was greater than 50% in 22 cases (42.3%).

Introduction

Hyperthermia, a new treatment for cancer, has been shown to be effective when performed in combination with radiation therapy or chemotherapy. Among various malignant tumors involving the digestive organs, hepatic carcinoma and esophageal cancer are frequently treated by hyperthermia. The liver is a nearly homogeneous parenchymal organ, and since it is rather uninfluenced by intestinal gas, this organ can be said to be suitable for hyperthermia. However, the liver receives its blood supply not only from the hepatic artery but also from the portal vein. Therefore, the efficiency of hyperthermia for hepatic carcinoma seems to be reduced by the cooling effect of the blood circulation.

Accordingly, the effects of hyperthermia may be enhanced by embolization since a decrease in the tumor blood flow is thought to increase the temperature and lower the pH more in the tumor than in the normal tissue [2, 3]. In the present study, hyperthermia was performed in combination with intra-arterial injection of either anticancer drugs together with embolization materials (lipiodol and DSM [1, 4, 6–8, 11, 15]) or anticancer drugs alone in patients with unresectable HCC and metastatic liver carcinoma to evaluate the effectiveness of the therapy.

Subjects and methods

The subjects who participated in this multimodal treatment study were 57 patients with unresectable liver carcinoma who were treated in our department during the period from August 1985 through July 1990. They consisted of 30 patients with HCC, 5 with hepatic cholangiocarcinoma, and 22 with metastatic liver carcinoma. The number of cases treated with hyperthermia are shown in Table 1.

Hyperthermia was induced with an RF heating device (Thermotron RF-8) using an electric current of 8 MHz at an RF output ranging from 800 to 1500 W. An electric current was applied between two plate electrodes positioned on both sides of the target site (Fig. 1). The temperature was monitored at four different sites by four thermometers. Degradable starch microspheres (DSM, Spherex, Pharmacia, Sweden), which are cross-linked starch particles measuring 20–70 μm in diameter (mean, 45 μm) and are degraded by amylases in the blood, were used as

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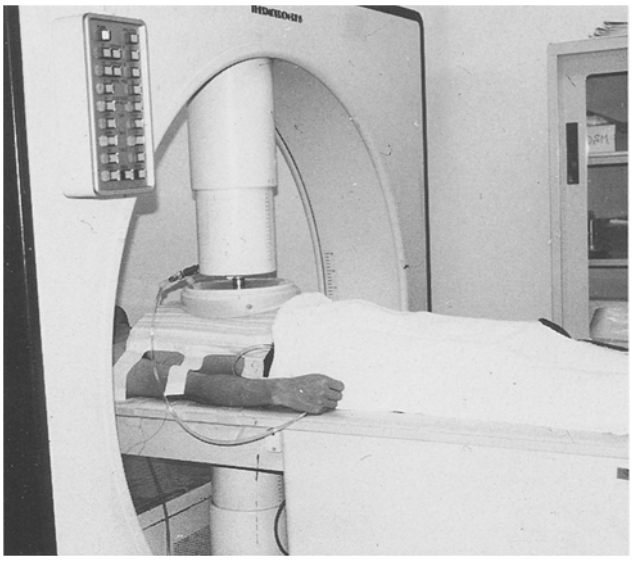

Fig. 1. A general view of treatment of a patient with liver carcinoma using a Thermotron RF-8. The patient is placed in the supine position on the treatment table, and an electric current is applied betweeen two plate electrodes positioned on both sides of the target site

Table 1. Number of cases treated with a combination of hyperthermia and chemotherapy, chemoembolization, or radiotherapy

Treatment combined with hyperthermia	HCC	Metastasis	Cholangio-carcinoma	Totals
1. Intravenous injection	1	0	0	1
2. Intra-arterial injection	5	17	1	23
3. Lipiodol embolization	13	0	0	13
4. DSM embolization	10	5	0	15
5. Combined radiotherapy	1	0	4	5
Totals	30	22	5	57

the embolization material. If these microspheres are injected intra-arterially, the arterial blood flow is blocked transiently and reversibly. Lipiodol was also mixed with an anticancer drug and injected via the proper hepatic artery. Anticancer drugs such as Adriamycin (10–20 mg), mitomycin C (10–20 mg), or 5-FU (500–750 mg) were mixed with DSM or lipiodol and injected into the peripheral portion of the hepatic artery by Seldinger's method.

Hyperthermia was performed twice a week over a period of 2–3 weeks for a total of 4–6 treatments. The effect of the therapy was evaluated on the basis of the percentage of reduction in the tumor area as determined from CT images and angiograms. A partial response (PR) was defined as a reduction of 50% or more in the size of the tumor; a minor response (MR), as a reduction of 25%–50% in the tumor mass; and no change (NC), as a reduction of less than 25% in the tumor area.

Results

Table 2 shows the differences in the tumor temperature obtained using various treatment methods for HCC and metastatic liver carcinoma. The mean T_{max} was lower in the HCC group than in the metastatic group (40.7° vs 41.5°C). However, even in HCC cases, remarkable increases in tumor temperature were obtained when hyperthermia was combined with DSM embolization; the mean T_{max} was 41.4°C.

Table 2. Tumor temperatures achieved by various treatment modalities in HCC and metastatic liver carcinoma

Tumor temperature	HCC			Metastasis		Total
	DSM	Lip	(–)	DSM	(–)	
≧42°C	3	0	2	1	4	10 (32.3%)
<42°C	5	6	3	3	4	21 (67.7%)
Totals	8	6	5	4	8	31
Mean temperature	41.4°C	39.7°C – 40.7°C	40.6°C	41.3°C – 41.5°C	41.6°C	41.0°C

Table 3. Relationship between the existence of portal vein thrombosis and T_{max}

Tumor temperature	HCC		Metastasis	
	+ PV invasion	– PV invasion	+ PV invasion	– PV invasion
≧42°C	4 (40.0%)	1 (12.5%)	3 (60.0%)	2 (28.6%)
<42°C	6 (60.0%)	8 (87.5%)	2 (40.0%)	5 (71.4%)
Totals	10	9	5	7
Mean temperature	41.3°C	39.9°C	41.9°C	41.2°C

Table 4. Relationship between tumor temperature and efficacy rate

Tumor temperature	HCC	Metastasis	Cholangio-carcinoma	Totals
≧42°C	1/5 (20.0%)	3/5 (60.0%)	(–)	4/10 (40.0%)
<42°C	0/14 (0)	1/7 (14.3%)	(–)	1/21 (4.8%)
Not measured	4/11 (36.4%)	3/10 (30.0%)	0/5 (0)	7/26 (26.9%)
Totals	5/30 (16.7%)	7/22 (31.8%)	0/5 (0)	12/57 (21.1%)

Table 3 shows the relationship between the existence of a portal vein thrombus and the T_{max}. In both the HCC group and the metastatic group, the rise in the temperature was greater in patients who had a portal vein thrombus than in who did not.

Table 4 presents the response rates, defined as the percentage of subjects in whom a PR or a better improvement was achieved. The response rates were 16.7% (5/30), 31.8% (7/22), and 0 (0/5) in the HCC group, the metastatic group, and the cholangiocarcinoma group, respectively, for an overall response rate of 21.1% (12/57). In the group

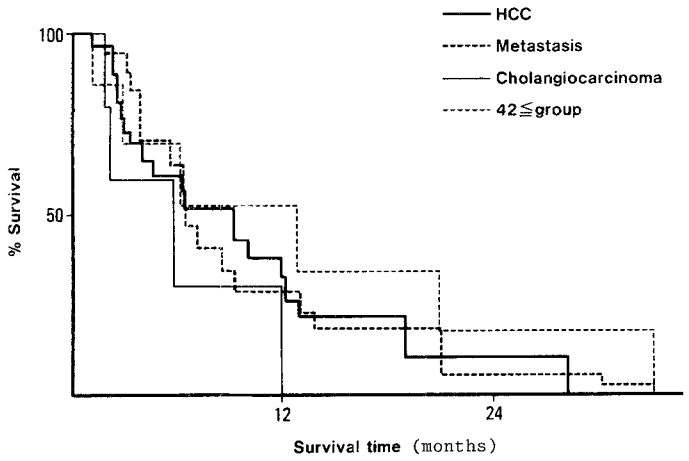

Fig. 2. Survival curves generated for 57 patients treated with hyperthermia, showing that survival was prolonged to 13.5 months in the group with a T_{max} of 42° C or more

Table 5. Changes in tumor marker levels after treatment

Change in tumor marker	HCC	Metastasis	Cholangiocarcinoma	Totals
50%–100%	13/29 (44.8%)	7/20 (35.0%)	2/3 (66.7%)	22/52 (42.3%)
0–50%	7/29 (24.1%)	5/20 (25.0%)	0/3 (0)	12/52 (23.1%)
Increase	9/29 (31.0%)	8/20 (40.0%)	1/3 (33.3%)	18/52 (34.6%)

with a T_{max} of 42° C or more, the response rate was as high as 40% (4/10). In contrast, the treatment was effective for only one case in the group with a lower T_{max}.

Table 5 shows the data on the change in tumor marker levels caused by the treatment. Among the 52 cases who had a high value before the therapy, it was decreased in 34 cases (65.4%, and the decrease amounted to 50% or more in 22 cases (42.3%).

Figure 2 presents the survival curves drawn according to the method of Kaplan-Meier. The average duration of survival was 10.1 months in HCC, 6.3 months in cholangiocarcinoma, and 9.8 months in metastatic liver carcinoma. Survival was prolonged to 13.5 months in the group with a T_{max} of 42° C or more, but this prolongation was not statistically significant.

Case report

In a 53-year-old man with HCC, a low-density area was seen in the right lobe on the CT scan (Fig. 3a). It was shown to be HCC (diffuse type) by needle biopsy. The alpha-fetoprotein level was 4500 units before treatment. Mitomycin C (10 mg) and Adriamycin (10 mg) were mixed with DSM (300 mg) and injected through a catheter, and hyperthermia was then performed twice a week for a total of seven treatments. After treatment, the alpha-fetoprotein value decreased to 300 units and the low-density area on the CT scan diminished in size (Fig. 3b).

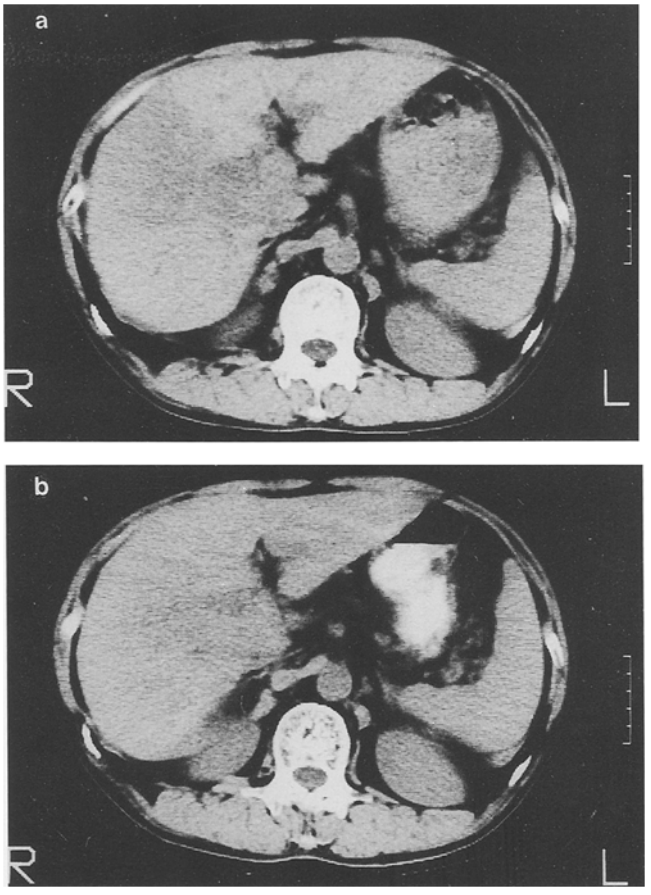

Fig. 3a, b. CT scans obtained in a 58-year-old man with HCC. **a** In the right love, a low-density area is seen; it was shown to be HCC by needle biopsy. **b** After multimodal treatment combined with hyperthermia, the low-density area on the CT scan was diminished in size

Discussion

Some reports have described the combined use of hyperthermia and chemotherapy. Storm et al. [13] reported that the survival of patients with malignant melanoma could be prolonged by hyperthermia combined with arterial injection of an anticancer drug. Moffat et al. [9] also reported that hyperthermia plus systemic or intra-arterial administration of an anticancer drug improved the response rate and the survival value obtained in patients with liver metastasis of colon cancer. Both of these research groups suggested the usefulness of chemohyperthermia, although they pointed out that some problems remained to be solved in relation to the methods applied for heating and thermometry.

Temperature elevations to 42° C or more have been attained in nearly half of the subjects treated thus far, e.g., in 44% (71/161) of the series of patients studied by Storm et al. [13]. These investigators reported that the overall response varied according to the minimal tumor temperature. On the other hand, Moffat et al. [9] stated that the mean T_{max} at the center of the tumor was only 39.5 ± 1.2° C in patients who had been subjected to hyperthermia and that they found no correlation between the temperature and the therapeutic results. A great majority of

these reports involved cases of metastatic liver carcinoma, and the effectiveness of heat treatment did not differ between histological types.

The problems encountered in hyperthermia for cancer are how to heat the tumor uniformly and how to minimize the loss of heat to the tissue blood flow [5, 10, 12, 14]. There are three purposes in performing hyperthermia with intra-arterial injection of anticancer drugs together with DSM or lipiodol [1, 4, 6, 7, 11, 15]: (1) to decrease the intratumoral pH, which enhances the heat sensitivity, while (2) increasing the temperature in the tumor, and (3) to retain anticancer agents in the liver by temporarily blocking the supply of blood to the tumor with DSM.

In conclusion, local hyperthermia for liver cancer was introduced only recently, and there are many difficulties to be overcome. First, the currently available heating methods are far from ideal. Therefore, we think that there is a pressing need to make improvements in the heating techniques. Second, the conventional method of tumor-temperature measurement is invasive, because the thermosensor has to be inserted directly into the tumor. In fact, about half of our patients could not tolerate this procedure. Consequently, a much less invasive method must be developed. Third, we must make every effort to minimize the risk of damage to the surrounding normal tissues. Fourth, it goes without saying that precise control of the local blood flow is one of the factors essential to the success of the treatment. It is considered useful to perform arterial embolization concomitantly. However, better embolization materials are needed. We must develop an optimal protocol for local hyperthermia for liver cancer, including embolization, chemotherapy, and/or radiotherapy.

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