Table 3
Level of distal sacrectomy and complications

Level of sacrectomy	Sepsis in pelvis	Ileus	Fistula[a]
Middle amputation			
S2 inferior margin (n = 12)	6	2	1
S2-3 (n = 26)	9	1	1
Low amputation			
S3 inferior margin (n = 16)	8	1	2
S3-4 (n = 10)	2	1	
S4 inferior margin (n = 5)	2		

[a] Fistula: enteroperineal fistula caused by anastomotic leakage.

Of 57 patients with R0 resection, 34 developed re-recurrence. The most common site was the lung (18 patients) followed by the pelvis (12 patients).

Oncologic outcomes reported in the literature

Factors such as type of surgery, combined therapy, and postoperative follow-up period are diversified, and comparison of reported oncologic outcomes for LRRC is of small significance. For example, a study that includes patients with recurrence after local excision naturally should show favorable outcome, whereas in a study conducted only with cases of FRT, unfavorable outcome can be predicted. Lopez-Kostner et al [33] reported a 5-year survival rate of 32% in 43 patients who underwent surgical treatment, 11 of whom developed recurrence after local excision. On the other hand, Bozzetti et al [18] showed a 5-year survival rate of less than 10% in patients who underwent surgery alone and pointed out a limitation of outcome after surgical treatment alone. Regarding 5-year survival after

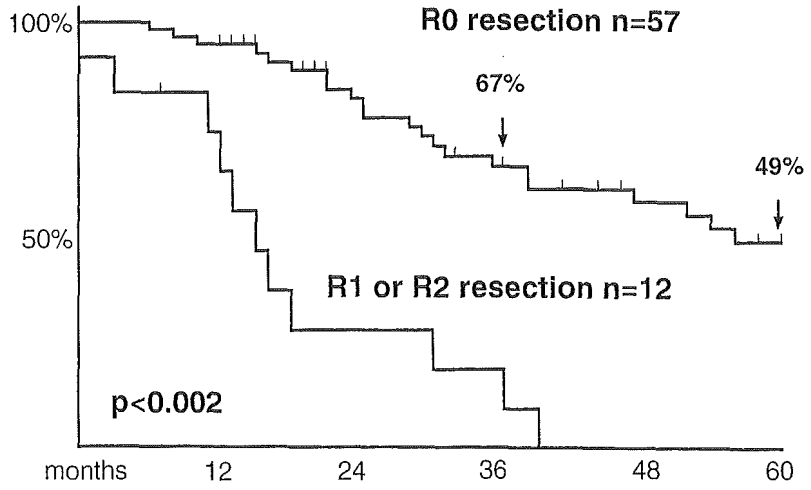

Fig. 5. Disease-specific survival curve. The difference between the two groups was significant ($P < 0.001$).

composite resection, Wanebo et al [19] reported a rate of 31%, Maetani et al [10] reported a rate of 25%, and Yamada et al [21] reported a rate of 18%. Those are not satisfactory outcomes. Incidence of local re-recurrence ranges from 27% to 61% [10,19,31].

As for outcome after multimodality therapy, there are many reports in which the ordinary dosages of radiation used preoperatively were 45 to 50 Gy. Intraoperative dosages of 10 to 15 Gy in R0 cases and 15 to 20 Gy in R-positive cases also were reported [24–29]. Valentini et al [24] reported a 5-year survival rate of 22%, and Mannaerts et al [23] reported a 3-year survival rate of 60%. In the series by Shoup et al [25], who investigated outcomes after resection plus intraoperative radiotherapy, patients with R0 had a median disease-free survival of 31 months and a median disease-specific survival of 66 months.

Lung metastasis and local re-recurrence account for nearly 90% of all re-recurrence patterns [31], and measures to prevent these two types of re-recurrence are important. Compared with 20 years ago, when the only effective antitumor agent was 5-fluorouracil, some effective antitumor agents (eg, CPT-11, UFT, capecitabine, and oxaliplatin) have become available. We think that surgical treatment, combined with composite resection and intraoperative radiotherapy, is indispensable for improving local control rates and that an effective chemotherapy regimen after re-resection is indispensable for inhibiting lung metastasis.

Prognostic factors and staging system

Several factors, such as type of initial surgery, tumor size, presence of symptoms, and serum carcinoembryomic antigen level, have been regarded as significant prognostic indicators, although a consensus has not been reached yet. Willet et al [11] and Wanebo et al [19] found improved resectability in patients who underwent initial low anterior resection compared with patients who had initial APR. If FRT developed after low anterior resection, however, there was no difference in resectability and survival between them [31]. Shoup et al [25] indicated that vascular invasion and R1/R2 resection are factors for poor prognosis. In either report, the most important factor is whether R0 resection was attained [19,24,25,27,31]. Researchers already have shown that in surgical treatment for primary rectal cancer, surgery-related and biologic factors are crucial [34]. Surgical margin status and complications are exclusively determined by a surgeon's technical skills. Complicated surgeries, such as TPES or abdominosacral resection, should be undertaken only in specialized centers with an experienced complex treatment team.

Suzuki et al [14] judged the degree of fixation to surrounding structures according to surgical and pathologic findings and proposed their own staging method. Valentini et al [24] also reported a similar staging system in

which they judged from CT scan imaging. They mentioned that degree of fixation is an independent prognostic factor. Wanebo et al [19] proposed a new staging system for stages TR1-2 to TR5, which are determined by extent of invasion. A staging system that uses degree of fixation or other prognostic factors is constructed so that treatment modalities for LRRC, especially surgical treatment, are placed in an appropriate position.

Summary

For primary rectal cancer, there is a difference in therapy between Western countries and Japan. In Western countries, initial surgery is total mesorectal excision or less limited surgery plus radiotherapy. For this reason, fibrosis caused by radiation occurs in the pelvis. On the other hand, in Japan, although preoperative radiotherapy is not given, total mesorectal excision or more extended surgery is performed as initial surgery, and the intrapelvic spaces are covered with postoperative scar tissue. In identifying an anatomic index and doing hemostasis, this scar tissue brings the surgeon more difficulty than the fibrosis caused by radiotherapy. Approximately half of our patients are irradiated preoperatively for recurrence. In those patients, operation is performed under an unfavorable condition because the fibrosis caused by radiation is added to the scar tissue caused by dissection. Composite resection, such as TPES, has been thought to be demanding and formidable because of high mortality and morbidity rates. Improvement of surgical techniques has allowed TPES to be completed with a blood loss of approximately 2000 to 3000 mL, however, which has resulted in a favorable learning curve with low morbidity and mortality rates.

We have excluded tumors that grow into the sacral promontory or sciatic notch from surgical indications. If high sacral amputation is performed, increased surgical invasiveness, more serious complications, and inevitable walking disorders are observed; as a result, a patient may have a remarkably deteriorated quality of life [6,9,12,19]. We have limited the level of sacral amputation in TPES to the S2 lower edge or below to preserve the second sacral nerve. Consequently, patients were able to have favorable quality of life after TPES, except for living with double stomas and temporary pain caused by resection of sacral nerves, and they were able to return to their original occupations [31,35].

If oncologic outcome obtained is superior to that after multimodality treatment, composite resection for FRT also may become an acceptable treatment. Finally, it should be noted that when extended surgeries, such as TPES, are performed for FRT, each of the departments concerned should review surgical indications and the surgeries must be worked on in the form of team medicine. One must realize that only through such process can negative resection margins be obtained as a great boon to patients.

References

[1] Gunderson LL, Sosin H. Area of failure found at reoperation following curative surgery for adenocarcinoma of the rectum. Cancer 1974;34:1278–92.

[2] McDermott FT, Hughes ES, Pihl E, et al. Local recurrence after potentially curative resection for rectal cancer in a series of 1008 patients. Br J Surg 1985;72:34–7.

[3] Pilipshen SJ, Heilweil M, Quan SH, et al. Patterns of pelvic recurrence following definitive resection of rectal cancer. Cancer 1984;53:1354–62.

[4] McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. Int J Colorectal Dis 1995;10:126–32.

[5] Wong CS, Cumming BJ, Brierly JD, et al. Treatment of locally recurrent rectal carcinoma: results and prognostic factors. Int J Radiat Oncol Biol Phys 1998;40(2):427–35.

[6] Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. Ann Surg 1981;194(4):458–71.

[7] Pacini P, Cionini L, Pirtoli L, et al. Symptomatic recurrences of carcinoma of the rectum and sigmoid: the influence of radiotherapy on the quality of life. Dis Colon Rectum 1986;29: 865–8.

[8] Takagi H, Morimoto T, Hara S, et al. Seven cases of pelvic exenteration combined with sacral resection for locally rectal cancer. J Surg Oncol 1986;32:184–8.

[9] Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. Cancer 1992;69:2876–83.

[10] Maetani S, Onodera H, Nishikawa T, et al. Significance of local recurrence of rectal cancer as a local or disseminated disease. Br J Surg 1998;85:521–5.

[11] Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for recurrent locally advanced rectal or rectosigmoid carcinoma. Cancer 1991;67:1504–8.

[12] Temple WJ, Ketcham AS. Sacral resection for control of pelvic tumors. Am J Surg 1992;163: 370–4.

[13] Wanebo HJ, Koness J, Vezeridis MP, et al. Pelvic resection of recurrent rectal cancer. Ann Surg 1994;220(4):586–97.

[14] Suzuki K, Gunderson LL, Devine RM, et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer 1995;75(4):939–52.

[15] Suzuki K, Dozois RR, Devine RM, et al. Curative reoperation for locally recurrent rectal cancer. Dis Colon Rectum 1996;39(7):730–6.

[16] Wiggers T, de Vries MR, Veeze-Kuypers B. Surgery for local recurrence of rectal carcinoma. Dis Colon Rectum 1996;39(3):323–8.

[17] Goes RN, Beart RW, Simons AJ, et al. Use of brachytherapy in management of locally recurrent rectal cancer. Dis Colon Rectum 1997;40(10):1177–9.

[18] Bozzetti F, Bertario L, Rossetti C, et al. Surgical treatment of locally recurrent rectal carcinoma. Dis Colon Rectum 1997;40(12):1421–4.

[19] Wanebo HJ, Antoniuk P, Koness J, et al. Pelvic resection of recurrent rectal cancer. Dis Colon Rectum 1999;42(11):1438–48.

[20] Mannaerts GHH, Rutten HJT, Martijn H, et al. Abdominosacral resection for primary irresectable and locally recurrent rectal cancer. Dis Colon Rectum 2001;44(6):806–14.

[21] Yamada K, Ishizawa T, Niwa K, et al. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. Br J Surg 2001;88:988–93.

[22] Magrini S, Nelson H, Gunderson LL. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. Dis Colon Rectum 1996;39:1–9.

[23] Mannaerts GHH, Martijn H, Crommelin MA, et al. Intraoperative electron beam radiation therapy for locally recurrent rectal carcinoma. Int J Radiat Oncol Biol Phys 1999;45(2): 297–308.

[24] Valentini V, Morganti A, De Franco A, et al. Chemoradiation with or without intra-operative radiation therapy in patients with locally recurrent rectal carcinoma. Cancer 1999; 86(12):2612–24.

[25] Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. Dis Colon Rectum 2000;45(5):585–92.
[26] Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. Surg Oncol Clin N Am 2003;12:993–1013.
[27] Kuehne J, Kleisli T, Biernacki P, et al. Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. Dis Colon Rectum 2003;46(79):895–9.
[28] Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg 2003;237(4):502–8.
[29] Rodel C, Grabenbauer GG, Matzel K, et al. Extensive surgery after high-dose preoperative chemoradiotherapy for locally advanced recurrent rectal cancer. Dis Colon Rectum 2000; 43(39):312–9.
[30] Temple WJ, Saettler EB. Locally recurrent rectal cancer: role of composite resection of extensive pelvic tumors with strategies for minimizing risk of recurrence. J Surg Oncol 2000; 73:47–58.
[31] Moriya Y, Akasu T, Fujita S, et al. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. Dis Colon Rectum, in press.
[32] Moriya Y, Hojo K, Sawada T, et al. Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 1989;32(4):307–15.
[33] Lopez-Kostner F, Fazio VW, Vignali A, et al. Locally recurrent rectal cancer: predictors and success of salvage surgery. Dis Colon Rectum 2001;44(2):173–8.
[34] Porter GA, Soskolne CL, Yakimets WW, et al. Surgeon-related factors and outcome in rectal cancer. Ann Surg 1998;227(2):157–67.
[35] Guren MG, Wiig JN, Dueland S, et al. Quality of life in patients with urinary diversion after operation for locally advanced rectal cancer. Eur J Surg Oncol 2001;27(7):645–51.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Hepatology Research 28 (2004) 41–48
Hepatology Research
www.elsevier.com/locate/ihepcom

A comparative study of the microcirculatory changes in the developing liver cirrhosis between the central and peripheral parts of the main lobe in mice

Pascal Niggemann [a,*], Satoru Murata [a], Zenya Naito [b], Tatsuo Kumazaki [a]

[a] *Department of Radiology, Center for Advanced Medical Technology, Nippon Medical School, 1-1-5 Sendagi, 113 8603 Tokyo, Japan*
[b] *Second Department of Pathology, Nippon Medical School, 1-1-5 Sendagi, 113 8603 Tokyo, Japan*

Received 14 January 2003; received in revised form 24 July 2003; accepted 20 August 2003

Abstract

A comparative study of the microcirculatory changes in the developing liver cirrhosis between the central and peripheral parts of the main lobe in mice. *Introduction:* To investigate whether a difference in microvascular vascular changes occurring in the peripheral and the central area of the main liver lobe exists and if, it can explain the liver atrophy observed predominantly in the peripheral part of the main liver lobe. *Materials and Methods:* Liver cirrhosis was induced in mice and the microvascular changes asserted using an intravital microscopy system after 1, 2, 3 and 8 weeks of treatment. *Results:* The mean blood velocity increased in the sinusoids; intrahepatic shunts appeared predominantly in the peripheral area and larger sized afferent terminal portal venules were rarefied in the peripheral area, with the central area being not affected. *Discussion:* The difference between the peripheral and central area shows a decreased direct and indirect reduction of the blood flow to the periphery of the main lobe, through the reduced number of afferent terminal portal venules and the development of intrahepatic shunting.

Keywords: Liver cirrhosis; Experimental; Liver circulation; Liver microcirculation; Liver atrophy

1. Introduction

The developing liver cirrhosis is characterized by a complex interaction of the extracellular matrix, cytogens, and the liver cells [1]. With advances in histological and molecular techniques, more about the underlying pathway of fibrogenesis is known. Vascular changes have been studied and it has been pointed out in animal studies that the vascular modifications are not the sole consequence of the fibrosis, but play a major role in the developing liver cirrhosis [2]. Besides analysis of the microvascular morphology, in more recent works in vivo microscopy has been used to characterize the altered blood flow in the developing liver cirrhosis [3].

However, no distinction between the blood flow in the central parts and the peripheral parts has been done. On cross-sectional imaging we frequently observe an atrophy of the liver that is more prominent in the peripheral parts of the main lobe then in the central parts [4]. A difference in the blood flow distribution in cirrhotic patients between the central and the peripheral area might explain the observed difference in atrophy as suggested elsewhere [5]. A mouse model, allowing the better visualization of the portal venous system [6], was used to conduct our in vivo microscopy study with the purpose to point out whether there are differences in the blood flow in the developing liver cirrhosis between the central and the peripheral parts of the main lobe in mice and to characterize those differences.

2. Materials and methods

2.1. Animal model

Eighty-nine ICR mice (Saitama Jikken, Japan), 6-weeks-old with a starting weight of 25–30 g were divided in three

* Corresponding author. Present address: Klinik für Radiologische Diagnostik, Universitätsklinikum der RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. Tel.: +49-241-80-88322; fax: +49-241-80-82411.
E-mail address: niggeman@rad.rwth-aachen.de (P. Niggemann).

1386-6346/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.hepres.2003.08.004

groups. Eleven mice were taken as the control group, 28 mice were assigned to group 1, and 51 mice to group 2. In order to induce liver cirrhosis, groups 1 and 2 received, respectively, 0.025 and 0.05 ml carbon tetrachloride diluted 1:1 with light white oil twice a week injected intraperitoneally. The two groups were subdivided in respectively three and four subgroups according to the duration of treatment. The duration of treatment was 1, 2 and 4 weeks for group 1 and 1, 2, 4, and 8 weeks for group 2. In the two groups respectively one and 26 animals died during the induction period, most probably due to the direct toxicity of carbon tetrachloride. In group 1, eight mice were analyzed after 1 week of treatment; 10 mice after 2 weeks and nine mice after 4 weeks. In group 2, eight mice were analyzed after 1 week of treatment; six mice after 2 weeks; six mice after 4 weeks and five mice after 8 weeks. A delay of 3 days was observed between the last carbon tetrachloride injection and the analysis with the in vivo microscopy technique.

Experiments were performed in compliance to the Japanese regulations and the Guide for the Care and Use of Laboratory Animals (National Academic Press, 1996). The animals were kept on a standard light cycle and fed with standard mice chow.

2.2. *Intravital fluorescense microscopy*

After sedation with pentobarbital injected intraperitoneally, the mouse was placed on an iron tray upon a warming pad and 0.3–0.4 ml (concentrated 0.8 mg/ml) Fluorescein Albumin (Sigma, Japan) was injected through a caudal vein. A medial laparatomy was performed and the liver surface exposed. While the liver remained in situ, a specially designed, freely movable tray was laid under the liver to limit respiratory movements. Great care was given to not compress or stretch any of the abdominal vessels. The liver surface was covered with a plastic film to prevent the drying out of the tissue. The iron tray was placed under the fluorescence microscope (BX 60, Olympus, Japan) and a blue fluorescence light (niba) obtained through a mercury lamp burner was applied using the epi-illumination technique to the liver surface. Using a magnification of 100×, 200× or 400× the obtained images of the microcirculation were captured with a 3 CCD Camera (M-3204 C, Olympus) at a rate of 30 pictures per second.

To ensure a high quality of the image, the RGB signal of the camera was used and the images were recorded to a Beta Cam Recorder (UVW 1400A, Sony, Japan) for off-line analysis. The total exposure time was limited not to exceed 10 min to avoid any damage through the fluorescence light. After completing the recording, the animals were killed through exsanguinations and the liver removed in randomly selected 28 animals belonging to all groups except the control group for histopathological analysis. The removed liver was analyzed by a pathologist specialized in liver pathology in regards to the degree the extent of fibrosis (the stage of the disease) and the activity of the necro-inflammatory activity (the grade of the disease) [7].

2.3. *Analysis*

Blood flow velocity, vessel size of the afferent terminal portal venules, sinusoids, draining efferent postsinusoidal venules, intrahepatic shunts and patterns of distribution of theses types of vessels were analyzed in the obtained sequences at a magnification of 200× or 400×. Quantitative analysis of the blood flow velocity was done off-line using a semi-automatic frame-to-frame technique with 60 half images of the interlaced NTSC video signal with a specially designed analysis system (Cap Image Version 7.0, Dr. Zeintl, Heidelberg, Germany) [3,8]. Shunts were identified as vessels that run straight with few or no branches from one afferent terminal portal venule to the efferent postsinusoidal venules.

The spatial distribution was of the vessels and shunts was analyzed during the recording and from the tape. To this purpose a belt shaped perimeter of the main lobe in the central and peripheral area at a 100× magnification was scanned. The size of the scanned area varied according to the size of the lobe.

The peripheral area was defined as the liver tissue being found near the hepatic capsule of the left main lobe at the lower edge of the left lobe and the central area was defined as being the liver tissue present near the hepatic capsule at a distance of at least 1 cm from the lower edge of the same lobe. If in that area an afferent terminal portal venule of a size greater than 20 μm, an efferent postsinusoidal venules or an intrahepatic shunt was found; the blood flow of this area was recorded. A negative finding for these vessels was noted if those vessels types could not be found in the visualized area.

For all those vessel types, the blood flow velocity was measured five times between two or more different frames. The mean of the results was taken as the mean blood flow velocity of the vessel. The diameter of the vessels was also measured.

The blood flow velocity in the sinusoids was analyzed in five different sinusoids in the analyzed area and the mean velocity of the measurements was taken as the mean velocity of the sinusoids in the area. It was known that the blood flow velocity is increased in some sinusoids, the so-called "fast sinusoids". This term was first employed by Sherman et al. [9] to characterize sinusoids, which have a high blood flow velocity of over 0.4 mm/s and still have a normal sinusoid appearance. Those sinusoids were included in the overall blood flow velocity when they were encountered in the studied area.

2.4. *Statistics*

Statistical analysis was performed with Statview (SAS, USA). Assuming the normality and homogeneity of variance across the groups, differences in the blood flow velocity

between the control group and the two carbon tetrachloride exposed groups were calculated using the Student's *t*-test. The values are shown as mean ± S.E. Data of the vessel distribution were calculated with binominal values whether a vessel type was present or not. The variance in the vessel distributions was calculated using the chi-square test. The significance of the observed histopathological changes was tested against the control group using the chi-square test.

In all cases a P value of <0.05 was taken to be significant.

3. Results

A mean velocity in five sinusoids in the peripheral area for the controls of 0.287 ± 0.12 mm/s and a mean velocity for group 1 of 0.426 ± 0.036, 0.407 ± 0.021, and 0.449 ± 0.026 mm/s (respectively, after 1, 2, and 4 weeks of treatment with carbon tetrachloride) was found. In group 2 a mean velocity of 0.480 ± 0.114, 0.412 ± 0.021, 0.419 ± 0.015 and 0.448 ± 0.26 mm/s, respectively, after 1, 2, 4, and 8 weeks of treatment with carbon tetrachloride was measured. A significant difference ($P < 0.01$) is found for all groups and week of treatment against the control group.

In the central area the mean velocity of the blood flow was 0.321 ± 0.14 mm/s for the control group and 0.497 ± 0.077 ($P < 0.05$), 0.474 ± 0.019, and 0.470 ± 0.019 mm/s, respectively, after 1, 2, and 4 weeks of treatment with carbon tetrachloride for group 1 (except for the first week $P < 0.01$ as compared to the control group). In group 2 the mean blood flow velocity was 0.392 ± 0.020, 0.476 ± 0.022, 0.509 ± 0.038, and 0.47 ± 0.032, respectively. After 1, 2, 4 and 8 weeks of treatment with carbon tetrachloride ($P < 0.01$ for all groups and week of treatment against the control group. No significant difference could be found between all groups and week of treatment).

Intrahepatic shunts have been observed in several mice after exposure to carbon tetrachloride, the percentage of mice with intrahepatic shunts in the observed area is shown in Fig. 1. The type of shunts observed were all portovenous shunts, arising from an afferent terminal portal venule and draining through an efferent postsinusoidal venules. There were no intrahepatic shunts visible in the control group, whereas shunts started to appear in the first week (Fig. 2) in both groups. After 2 weeks of treatment, there is no significant difference observed between the groups exposed longer than 2 weeks to carbon tetrachloride. However, shunts observed in mice longer exposed to carbon tetrachloride tended to be less tortuous and to run straighter (Figs. 3 and 4). Intrahepatic shunts were found more frequently in the peripheral part ($P < 0.01$) than in the central part. Intrahepatic shunts are more often found in animals treated with a higher dose of carbon tetrachloride after 1 week and that there is no significant difference to be found after 2 weeks between the two groups. The velocity of the blood flow in the shunt vessels was 1.02 ± 0.088 mm/s and hence close to the velocity observed in normal afferent terminal portal venules 0.915 ± 0.057 mm/s, but the diameters of the shunts vessels tended to be larger then any other vessel observed with shunts diameters up to 133.6 μm (mean 55.3 ± 12.3 μm). It is interesting to note, that in all mice in which an intrahepatic shunt was found in the central area, an intrahepatic shunt was also present in the peripheral area.

At least one afferent terminal portal venule with a size larger then 20 μm was found in every mouse of the control group in the peripheral part (Figs. 5 and 6) and at least one afferent terminal portal venule of that size could be found

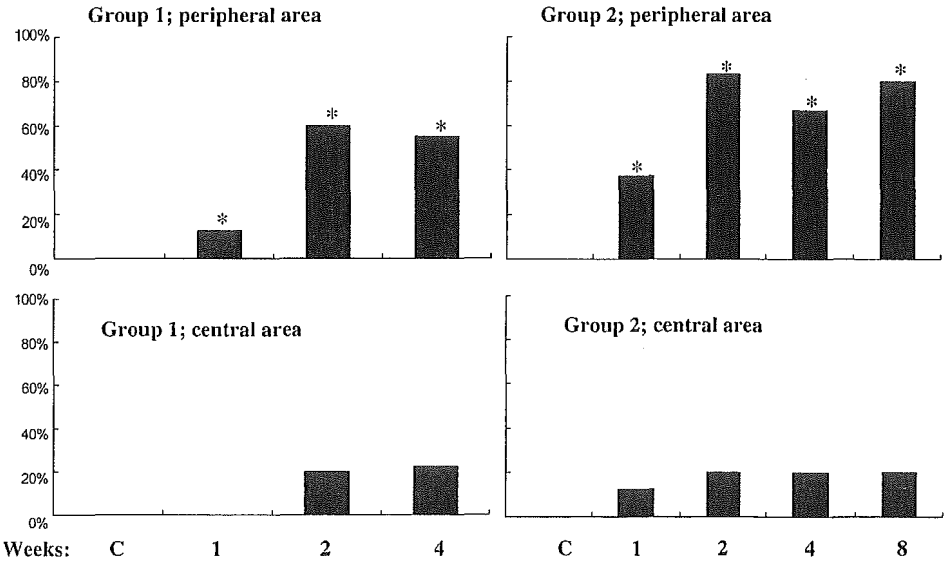

Fig. 1. Percentage of mice with portovenous shunts observed in the main lobe vs. the time of treatment. There are no intrahepatic shunts visible in the control group. Shunts start first to appear in the peripheral area and at a lesser rate in the central area only after a longer time of exposure to carbon tetrachloride (C: control group) (* $P < 0.05$).

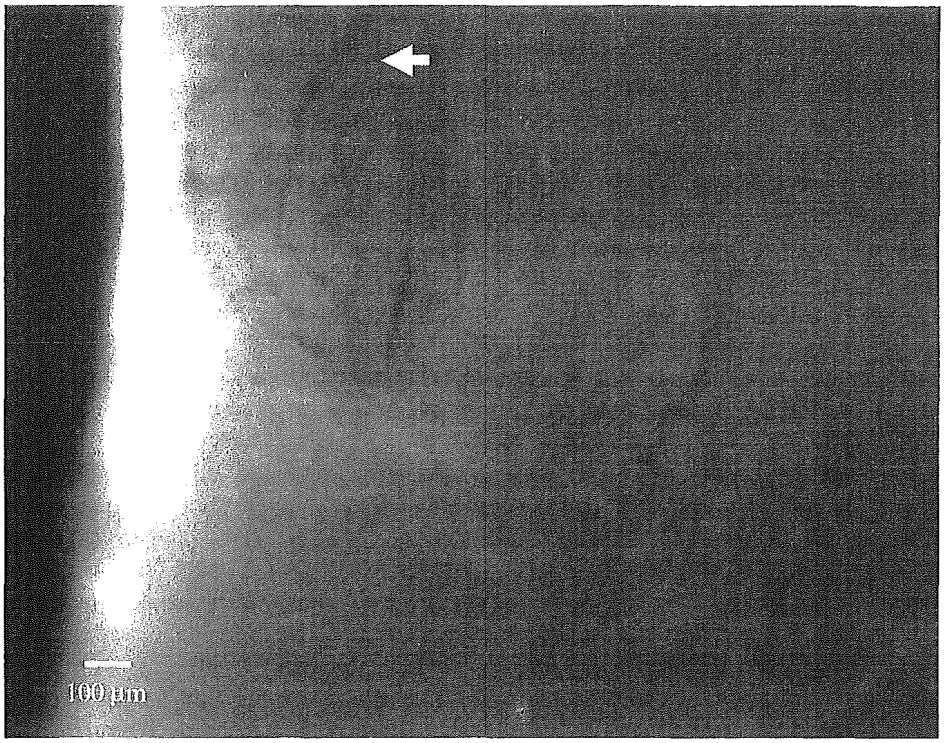

Fig. 2. Intrahepatic shunt observed in the peripheral part of the main lobe in a mouse after 1 week of treatment with 0.025 ml carbon tetrachloride injected twice a week i.p. The shunt consists of many small branches of the same size. Arrow: afferent terminal portal venule (magnification: 100×).

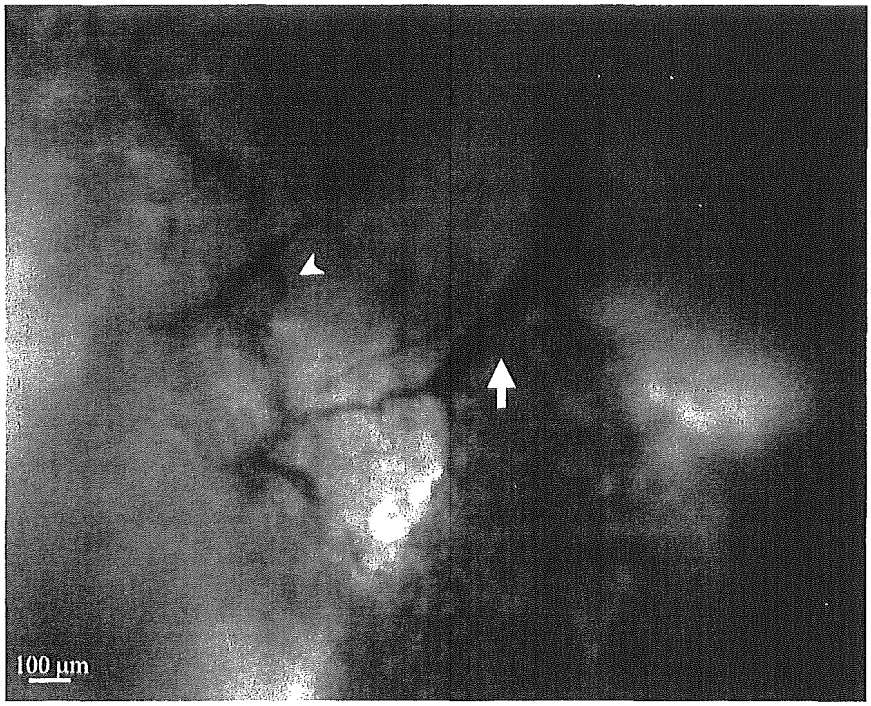

Fig. 3. Intrahepatic shunt observed in the peripheral part of the main lobe in a mouse after exposure to 2 weeks of 0.025 ml carbon tetrachloride twice a week i.p. Compared to the shunt in Fig. 2 there are fewer branches visible (arrowhead) and they are less homogenous in size. Arrow: afferent terminal portal venule (magnification: 100×).

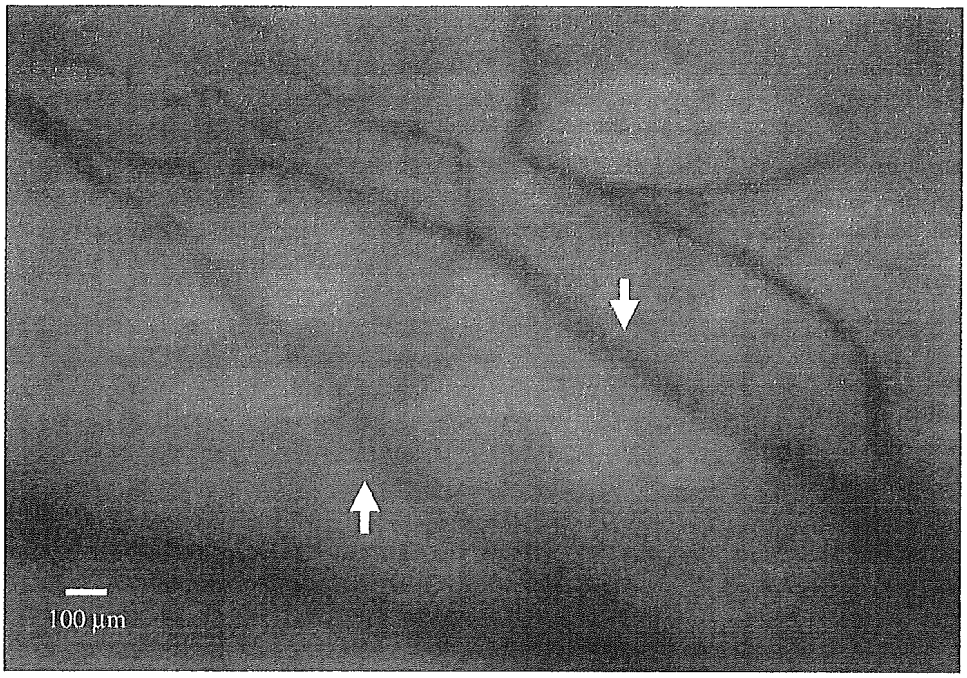

Fig. 4. Intrahepatic shunt (arrows) observed in the peripheral part of the main lobe in a mouse after 4 weeks of treatment with 0.025 ml carbon tetrachloride twice a week i.p. The vessels runs straighter then the shunts in Figs. 2 and 3 and there are fewer branches. (Magnification: 100×).

in 70% in the central part, too. With time of treatment, the number of afferent terminal portal venules of that size, which were found in the peripheral area, decreased, whereas still many mice remained with afferent terminal portal venules in the central area as shown in Fig. 7. But in all groups there were mice whose afferent terminal portal venules were still present in the peripheral part. The measured size of the afferent terminal portal venules larger than 20 µm in all groups did not vary from those measured in the control group (control group: 24.1 µm versus 34.2–38.7 µm for, respectively,

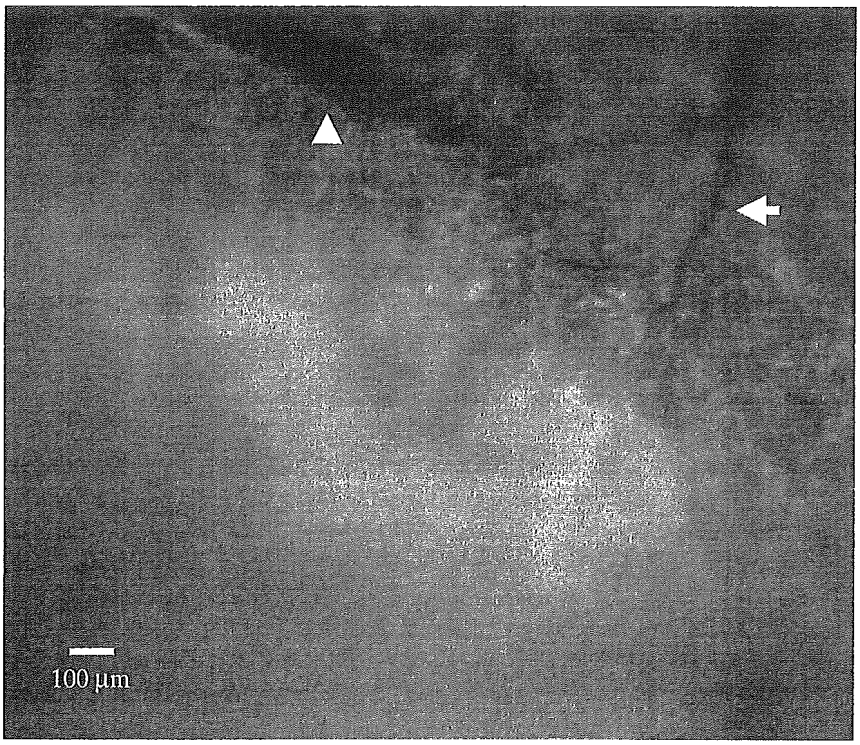

Fig. 5. Afferent portal venule (arrow) and draining efferent postsinusoidal venule (arrowhead) shown in the peripheral part of the main lobe in a mouse of the control group at a magnification of 100×. The splitting up of the afferent portal venule in several terminal branches is shown.

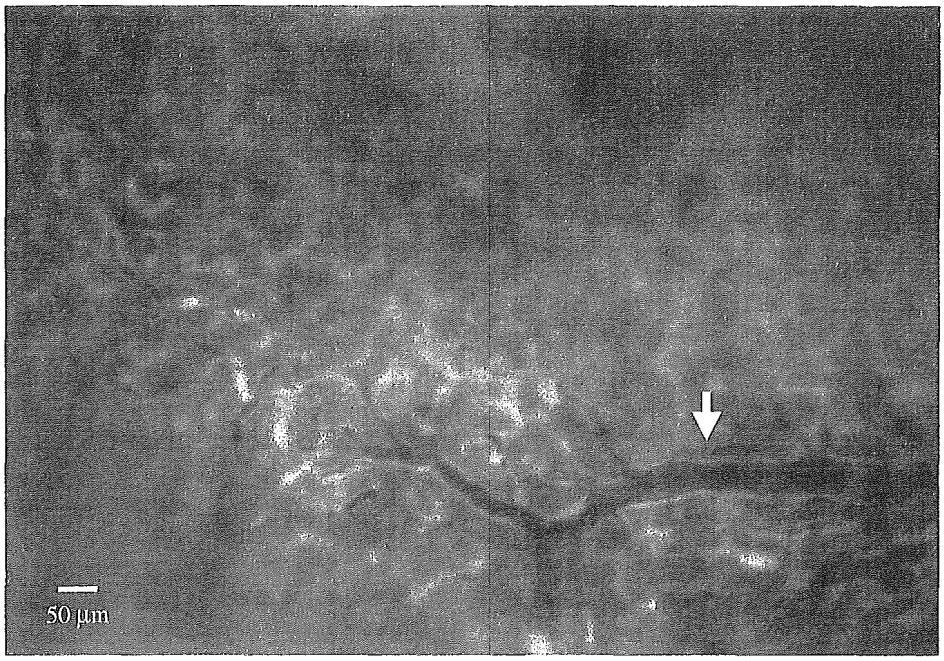

Fig. 6. Afferent terminal portal venule (arrow) observed in the peripheral part of the main lobe in a mouse of the control group at a magnification of 200×. The splitting up of the afferent terminal portal venule in the terminal branches before entering the sinusoids is shown.

group 2, 8 weeks of exposure and group 1, 1 week of exposure to carbon tetrachloride). The mean velocity in those vessels did not vary either (control group: 1.033 ± 0.081 mm/s versus 0.791 to 1.498 ± 0.222 mm/s for, respectively, group 2, 8 weeks of exposure and group 1, 1 week of exposure to carbon tetrachloride).

The histopathological analysis of the removed livers revealed characteristic pathological changes in all groups. We found a periportal fibrosis in two of four analyzed livers and a mild necro-inflammatory activity in four of four analyzed livers after 1 week of treatment with carbon tetrachloride in group and a bridging fibrosis in one out of four analyzed livers with a moderate to severe necro-inflammatory activity in four out of four livers after 8 weeks of treatment with carbon tetrachloride in group 2. The grade of the disease did not correlate with the duration of treatment in group 1, but it matched well with the duration of treatment in group 2 and as expected, we found a more severe necro-inflammatory

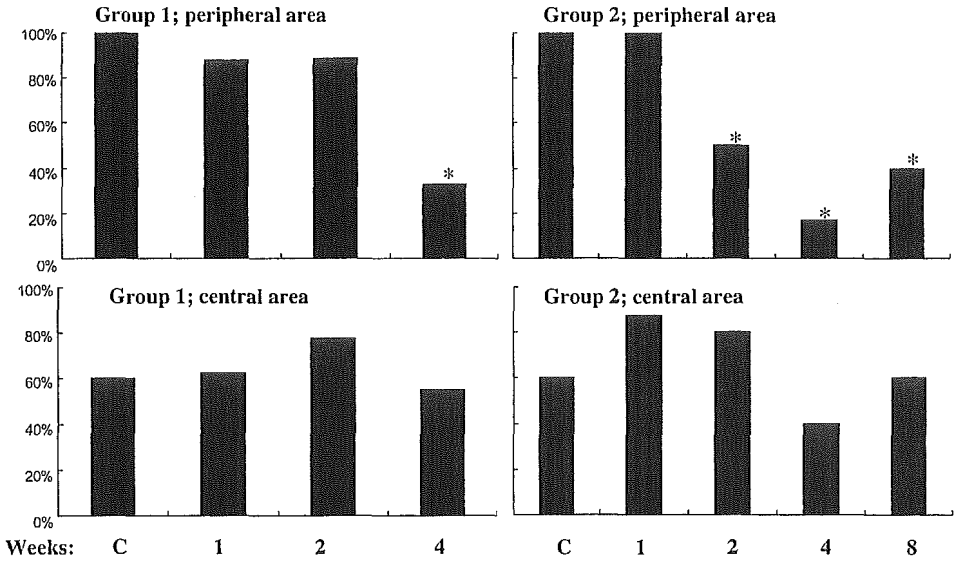

Fig. 7. Percentage of mice with at least one afferent terminal portal venule with a diameter >20 μm in the central or the peripheral area of the main lobe vs. the exposure time to carbon tetrachloride. Note a decrease of the number of mice with positive findings in the peripheral area whereas we cannot observe such a decrease in the central area. (C: control group) (*$P < 0.05$).

activity in mice of group 2 compared to those of group 1. No correlation in the duration of treatment and the stage of the disease was found. The decrease of afferent terminal portal venules and the development of intrahepatic shunts matched well with the grade of the disease.

4. Discussion

Many insights in the pathway of liver cirrhosis and fibrosis have been gained in the past years [1,10,11]. However, studies concerning the in vivo microcirculation in the developing liver cirrhosis are rare and the issue whether a difference exists between the distribution of vascular changes in the developing liver cirrhosis between the central and peripheral parts has not been addressed yet.

The total blood volume that passes the liver is the sum of the blood volume of the portal vein and the hepatic artery. The portal vein is the main vessel with the part of the hepatic artery being variable [12]. In the developing liver cirrhosis, portal hypertension starts to appear leading to a decrease of the blood flow in the portal vein [13]. The blood flow of the hepatic artery is therefore increased to maintain the total blood flow of the liver [14]. The reserve blood flow of the hepatic artery was found to be 22–100% [13,14]. With a greater decrease of the portal vein blood flow, the blood flow of the hepatic artery cannot be increase and therefore the total blood volume of the liver decreases [12].

Cross-sectional imaging studies [5,15] suggest that the blood reduction in the liver is not homogenous distributed. To study the areas that are more affected by the reduction of the total liver blood flow, we investigated whether there is a difference in the microcirculatory changes between the peripheral and central parts of the main lobe in mice.

It has been pointed out, that vascular changes in the developing liver cirrhosis occur at a very early stage [3], leading us to study the earliest stages of the developing liver cirrhosis. Several changes observed by using intravital microscopy in the developing liver cirrhosis have been described, such the appearance of fast sinusoids, the increase of the venous space, and the appearance of intrahepatic shunts [3,9]. The decrease of the number of afferent terminal portal venules with a size larger then 20 μm has not been described. Afferent terminal portal venules run up to the edge in normal liver tissue in mice and there are branches of variable size. Those branches up to the afferent terminal portal venules entering the sinus can be visualized. The size of was 20 μm chosen because an afferent terminal portal venule has usually a size greater than 20 μm before splitting up in the terminal branches [16] and because we wanted to focus on the analysis of the blood flow in amount of the sinusoidal circulation.

No statistical significant difference in the distribution of the "fast sinusoids" between the peripheral and central area could be found. "Fast sinusoids" started to appear already after 1 week of treatment leading to an increase in the mean velocity of the blood flow and thereafter no statistically significant difference of the mean velocity of the blood passing the sinusoids was found. This finding is concordant with results from other groups [3].

Two major differences were observed between the central and the peripheral parts. The appearance of portovenous shunts was more marked in the peripheral part. Functional shunts have been described before and it was thought that they might appear because of a reduced vascular resistance and being a more advanced state of the so-called "fast sinusoids". However, as the "fast sinusoids" appear equally in the central and peripheral parts, then the progression of the vascular changes must be faster in the periphery than in the central parts, this thesis being supported by the fact that shunts are only found in mice who have already developed "fast sinusoids". Therefore, the development of "fast sinusoids" represents a first step, being followed by the development of intrahepatic shunting. Shunting representing a functional decrease of the blood delivered to the liver tissue and as the shunts are present mainly in the peripheral parts, we can postulate a more marked functional decrease of the blood flow in the peripheral parts as compared to the central parts.

As compared to the control groups, less afferent terminal portal venules of a size greater than 20 μm in mice with developing liver cirrhosis were found. Branches of the afferent terminal portal venules visible up to the edge are of smaller size, but the velocity in those afferent terminal portal venules is not different from the velocity in afferent terminal portal venules of the same size in normal liver tissue. This same phenomenon of reduction of middle to large sized afferent terminal portal venules is not seen in the central part of the liver lobe.

The decrease of the middle to large sized afferent terminal portal venules and the intrahepatic shunt development could be connected in the following ways. Through the development of fibrosis and an increased vascular resistance of the sinusoidal vascular bed, the blood flow is redirected to the vessels with a smaller vascular resistance as compared to the remaining sinusoids. Those vessels are first the "fast sinusoids" and then the larger shunting vessels. An increased blood flow in the "fast sinusoids" would further increase the diameter and therefore will allow the development of large shunts as a compensatory mechanism. The vascular resistance of the shunts would be lower than the vascular resistance of the remaining afferent terminal portal venules and the sinusoidal vascular bed, but being a compensatory mechanism, still higher than the normal vascular resistance in a normal liver. Vollmar et al. [3] speculated, that in cirrhotic rats, the vascular resistance of the fast sinusoids would be lower than the resistance of the remaining normal sinusoids, which matches with our findings. However, the throughout visualization of the portal venous system is only possible in mice, so that the observation and the following interpretation differs.

The differences in the observation between the central and the peripheral part could be the consequence of an overall

blood flow reduction due to the development of portal hypertension. As portal hypertension develops and the vascular resistance being higher in the more peripheral part due to the more remote location (following the Hagen–Poiseuille equation), the vascular compensatory mechanisms should first start to appear here, which is just the case. Another important factor might be the difference in the number of peribiliary plexuses between the peripheral and the central part. As there are fewer peribiliary plexuses present in the peripheral part [17], the compensation of the reduced portal venous blood flow through the hepatic artery is hindered and changes in the vascular resistance should have a greater impact in the peripheral area, leading to trigger the compensatory mechanisms first in the peripheral part.

Therefore, the vascular changes observed in the developing liver cirrhosis are an active, compensatory process starting in areas located in the most peripheral part of the liver. The vascular changes observed are correlated to the grade of the developing liver cirrhosis, but it is important to note that even in several mice with no histopathological evidence of liver cirrhosis, we found the described vascular changes. Thus, the vascular changes could trigger or modify the fibrotic process, a hypothesis that has already been offered by other groups [3].

The consequence of all the findings taken together is that less blood is delivered to the still intact liver tissue in the peripheral part, which might be a valid explanation for the observed liver atrophy in advanced liver cirrhosis on cross-sectional imaging occurring mainly in the peripheral part of the main lobe.

Acknowledgements

Supported by the Center for Advanced Medical Technology grant from the Japanese Ministery of Education.

References

[1] Friedman SL. Seminars in medicine of the Beth Israel Hospital, Boston. The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. New Engl J Med 1993;328:1828–35.

[2] Rappaport AM, MacPhee PJ, Fisher MM, Phillips MJ. The scarring of the liver acini (cirrhosis). Tridimensional and microcirculatory considerations. Virchows Arch A Pathol Anat Histopathol 1983;402:107–37.

[3] Vollmar B, Siegmund S, Menger MD. An intravital fluorescence microscopic study of hepatic microvascular and cellular derangements in developing cirrhosis in rats. Hepatology 1998;27:1544–53.

[4] Dodd III GD, Baron RL, Oliver III JH, Federle MP. Spectrum of imaging findings of the liver in end-stage cirrhosis: part I gross morphology and diffuse abnormalities. AJR 1999;173:1031–6.

[5] Murata S, Itai Y, Asato M, Kobayashi H, Nakajima K, Saida Y, et al. Spatial and temporal alteration of the dual supply of the hepatic circulation with transient occlusion of the hepatic veins: spiral volumetric CT during arterial portography and arteriography. Nippon Igaku Hoshasen Gakkai Zasshi 1995;55:184–6.

[6] Kan Z, Ivancev K, Lunderquist A, McCuskey PA, Wright KC, Wallace S, et al. In vivo microscopy of hepatic tumors in animal models: a dynamic investigation of blood supply to hepatic metastases. Radiology 1993;187:621–6.

[7] Omata M, Shiratori Y. Long term effects of interferon therapy on histology and development of hepatocellular carcinoma in hepatitis C. J Gastroenterol Hepatol 2000;15:E134–40.

[8] Klyscz T, Junger M, Jung F, Zeintl H. Cap image-a new kind of computer-assisted video image analysis system for dynamic capillary microscopy. Biomed Tech 1997;42:168–75.

[9] Sherman IA, Pappas SC, Fisher MM. Hepatic microvascular changes associated with development of liver fibrosis and cirrhosis. Am J Physiol 1990;258:H460–5.

[10] Murawaki Y, Kawasaki H. Pathophysiology of hepatic fibrosis. Nippon Shokakibyo Gakkai Zasshi 1999;96:1143–52.

[11] Friedman SL, Hepatic Fibrosis. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's diseases of the liver. Philadelphia: Lippincott-Raven; 1999. p. 371–85.

[12] Groszmann RJ, deFranchis R, Portal Hypertension. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's diseases of the liver. Philadelphia: Lippincott-Raven; 1999. p. 387–442.

[13] Hanson KM, Johnson PC. Local control of hepatic arterial and portal venous flow in the dog. Am J Physiol 1966;21:712–20.

[14] Greenway CV, Oshiro G. Intrahepatic distribution of portal and hepatic arterial blood flows in anaesthetized cats and dogs and the effects of portal occlusion, raised venous pressure and histamine. J Physiol 1972;227:473–85.

[15] Itai Y, Murata S, Kurosaki Y. Straight border sign of the liver: spectrum of CT appearances and causes. Radiographics 1995;15:1089–102.

[16] Grisham JW, Nopanitaya W, Scanning electron microscopy of casts of hepatic microvessels: review of methods and results. In: Lautt WW, editors. Hepatic ciculation in health and disease. New York: Raven Press; 1981. p. 87–109.

[17] Kan Z, Ivancev K, Lunderquist A. Peribiliary plexa-important pathways for shunting of iodized oil and silicon rubber solution from the hepatic artery to the portal vein. An experimental study in rats. Investigative Radiology 1994;29:671–6.

Original Paper

Transcatheter Management for Multiple Liver Tumors after Hepatic Artery Obstruction Following Reservoir Placement

Satoru Murata, Hiroyuki Tajima, Yutaka Abe, Yasushige Komada
Tsuyoshi Fukunaga, Ken Nakazawa, Tatsuo Kumazaki
Department of Radiology/Center for Advanced Medical Technology, Nippon Medical School, Tokyo, Japan
Corresponding Author: Satoru Murata MD, PhD, Department of Radiology, Nippon Medical School
1-1-5 Sendagi, Bunkyou-ku, Tokyo, Japan
Tel: +81 35814 6240, Fax: +81 35685 1795, E-mail: murata satoru/radiology@nms.ac.jp

KEY WORDS:
Liver neoplasms; Hepatic artery; Obstruction; Reservoir; Treatment

ABBREVIATIONS:
Gastroduodenal Artery (GDA); Posterior Superior Pancreaticoduodenal Artery (PSPDA); Right Gastric Artery (RGA); Hepatocellular Carcinoma (HCC); Transcatheter Arterial Infusion (TAI); Transcatheter Arterial Chemoembolization (TACE); Dorsal Pancreatic Artery (DPA); Inferior Phrenic Artery (IPA); Inferior Thoracic Artery (ITA); Superior Mesenteric Artery (SMA)

ABSTRACT

Background/Aims: Hepatic arterial infusion chemotherapy via an implantable port system has been widely used to treat unresectable liver neoplasms. Complications of the hepatic artery occlusion following reservoir placement, however, makes it impossible to continue the infusion therapy. The purpose of our study was to assess the possibility of transcatheter treatment after the hepatic artery obstruction following reservoir placement.

Methodology: Between April 1999 and May 2002, 14 patients with liver tumors had the complication of hepatic artery obstruction following reservoir placement. We conducted a prospective trial to assess 1) the collateral pathways of feeding artery using angiography, 2) the possibility of transcatheter treatment or 3) re-reservoir placement for liver tumors.

Results: 1) Angiography revealed that the main collateral pathway of the feeding artery was the inferior phrenic artery in 7 patients (50%), the dorsal pancreatic artery in 4 patients (29%) and the anastomotic branch of the celiac axis in 1 patient (7%). The main collateral pathway could not be detected in 2 patients (14%). 2) Transcatheter treatment was successfully performed in all patients (100%). 3) Re-reservoir placement failed in all cases.

Conclusions: These results suggest that transcatheter treatment may be possible for patients with hepatic artery obstruction.

INTRODUCTION

For the last ten years, hepatic arterial infusion chemotherapy via an implantable port system has been widely used to treat unresectable malignant neoplasms of the liver (1-8). It has the advantage of increased local drug concentration, resulting in a high tumor response rate, with less systemic toxicity (1-8). However, it often causes occlusion of the hepatic artery; rates of occurrence of 10-40% have been reported (9-11).

Concerning the procedures of reservoir placement, aberrant hepatic arteries are usually embolized to permit global perfusion of the liver via a single hepatic artery that depends on development of the intrahepatic collateral circulation, and also the gastroduodenal artery (GDA) including the posterior superior pancreaticoduodenal artery (PSPDA) is embolized for preventing leakage of anticancer drug to the upper gastrointestinal region. The right gastric artery (RGA) is also embolized as much as possible. The complication of hepatic artery occlusion following reservoir placement makes it impossible to continue the infusion therapy.

We conducted a prospective trial to assess the collateral pathways of feeding artery to liver tumors and the possibility of transcatheter treatment for liver tumors after obstruction of the hepatic artery following reservoir placement.

METHODOLOGY

Between April 1999 and May 2002, 74 patients with liver tumors underwent reservoir placement. Twenty-one of the 74 patients had the complication of hepatic artery obstruction during hepatic arterial infusion chemotherapy via an implantable port system (n=18) or during procedures for performing reservoir placement (n=3). Fourteen of 21 patients resulted in tumor response (n=11) or had a complication of the procedures (n=3), and the subjects of our study were these 14 patients (eight men, 6 women; age range, 42-74 years; mean age, 61 years) with multiple liver tumors [5 hepatocellular carcinomas (HCCs), 9 metastatic tumors: 3 from colorectal cancer, 2 from gastric cancer, 2 from breast cancer, 1 from lung cancer and 1 from uterine cervical cancer] in whom we tried to perform transcatheter treatment again.

As shown in **Table 1**, of the 14 patients in this study, the GDA and the PSPDA were embolized in all patients, and the RGA was embolized in 12 patients during the reservoir placement. Four patients who had an aberrant hepatic artery underwent embolization of the aberrant hepatic artery.

Routine angiography was performed by using a 5-F pigtail catheter for abdominal aortic angiography, a

Hepato-Gastroenterology 2005; 52:852-856

TABLE 1 Embolization Sites of Arteries during Reservoir Placement

Patient No./ Age(y)/Sex	Primary	Occlusion of hepatic artery	Embolization site of Arteries for implantable port			
			GDA	PSPDA	RGA	Aberrant A
1/66/M	Lung ca.	CHA#	Done	Done	Done	None
2/62/M	Colon ca.	CHA-PHA‡	Done	Done	Done	Done
3/69/F	Gastric ca.	CHA-PHA	Done	Done	Done	None
4/66/M	Colon ca.	CHA-PHA	Done	Done	None	None
5/42/F	Breast ca.	CHA	Done	Done	Done	Done
6/52/F	Uterine cervical ca.	CHA	Done	Done	Done	Done
7/70/F	Gastric ca.	CHA-PHA	Done	Done	Done	None
8/50/F	Breast ca.	CHA	Done	Done	Done	None
9/74/M	Colon ca.	CHA-PHA	Done	Done	Done	None
10/51/M	HCCs	CHA-PHA	Done	Done	Done	None
11/67/F	HCCs	CHA-PHA	Done	Done	None	Done
12/67/M	HCCs	CHA-PHA	Done	Done	Done	None
13/60/M	HCCs	CHA-PHA	Done	Done	Done	None
14/68/M	HCCs	CHA-PHA	Done	Done	Done	None

#common hepatic artery; ‡proper hepatic artery.

TABLE 2 Collateral Pathways to the Tumors and Transcatheter Treatment

Patient No./ Age(y)/Sex	Primary	Occlusion of hepatic artery	Involvement of Arteries					TAE or TAI
			IPA	ITA	DPA	Periportal	Others	
1/66/M	Lung ca.	CHA#	Negative	Negative	Positive*	Negative	Negative	TAE
2/62/M	Colon ca.	CHA-PHA‡	Negative	Negative	Positive*	Negative	anastomotic br.	TAI
3/69/F	Gastric ca.	CHA-PHA	Negative	Right	Positive*	Positive	Negative	TAE
4/66/M	Colon ca.	CHA-PHA	Right	Negative	Positive	Positive	Negative	TAI
5/42/F	Breast ca.	CHA	Negative	Right	Negative	Positive	Anastomotic br.*	TAE
6/52/F	Uterine cervical ca.	CHA	Negative	Negative	Positive*	Positive	Negative	TAE
7/70/F	Gastric ca.	CHA-PHA	Right*	Negative	Positive	Positive	Duodenal br.	TAE
8/50/F	Breast ca.	CHA	Right	Negative	Negative	Positive	Negative	TAI
9/74/M	Colon ca.	CHA-PHA	Right*	Negative	Negative	Negative	Negative	TAE
10/51/M	HCCs	CHA-PHA	Bilateral*	Negative	Negative	Negative	Negative	TAE
11/67/F	HCCs	CHA-PHA	Right*	Negative	Negative	Negative	Negative	TAE
12/67/M	HCCs	CHA-PHA	Right*	Negative	Negative	Positive	Negative	TAE
13/60/M	HCCs	CHA-PHA	Right*	Negative	Negative	Negative	Negative	TAE
14/68/M	HCCs	CHA-PHA	Right*	Negative	Negative	Positive	Negative	TAE

#common hepatic artery; ‡proper hepatic artery, *main feeding artery.

5-F shephard hook catheter for celiac, superior mesenteric and inferior phrenic arteriography and a 5-F headhunter catheter for internal thoracic arteriography. When the 5-F catheter could not be inserted into the targeted artery, a 0.016-inch guidewire (Transend TM EX, Boston Scientific TARGET, US) was inserted into the targeted artery, and a 2.3-F microcatheter (Rapid Transit, Cordis, US) was advanced to it along the guidewire.

After performing routine angiography, tumor vessels, tumor stains and feeding arteries were evaluated by two radiologists (S.M., Y.A.). After reaching a consensus regarding the feeding arteries to liver tumors, we tried to advance a microcatheter to them for treatment.

Concerning transcatheter treatment, transcatheter infusion therapy (TAI) was performed in cases in which the periportal collateral arteries were the main feeding arteries because of preventing side effects such as cholangitis or gastrointestinal damage caused by embolization, or in the cases in which the main feeding artery was not revealed. Transcatheter arterial chemoembolization (TACE) with iodized poppy seed oil for HCCs or Amilomer (Spherex, Yakult Honsha Co.Ltd., Japan) with mitomycin C and contrast material for metastatic liver tumors was performed in the remaining cases. Then, when a microcatheter was advanced into the hepatic artery, we tried to place the long tapering type catheter (Anthron P-U catheter, Toray Medical Co., Ltd., Japan, Piolax W Spindle catheter, Piolax Medical Devices, INC., Japan) for an implantable port system. Informed consent was obtained from all patients.

RESULTS

These results are shown in **Table 2.**

Angiography revealed that: the main collateral pathway of the feeding artery was the inferior phrenic artery (IPA) in 7 of 14 patients (50%), the dorsal pancreatic artery (DPA) in 4 of 14 patients (29%) and the

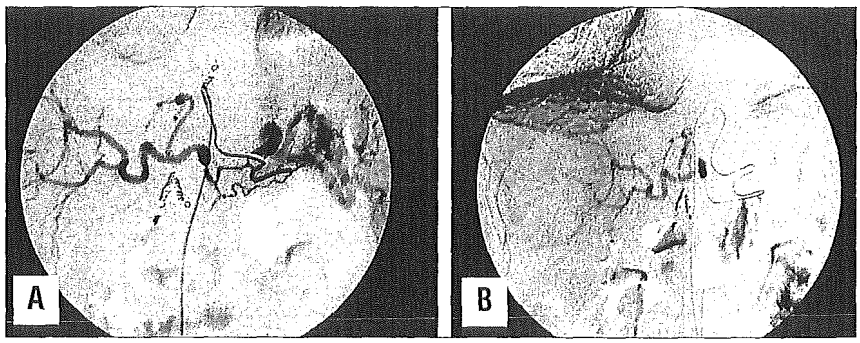

FIGURE 1
A 66-year-old man with liver metastases from lung cancer. **(A)** Arteriography via the DPA demonstrates the proper hepatic artery via the anastomosis of the DPA. **(B)** A microcatheter is advanced to the proper hepatic artery via the anastomosis of the DPA, and arteriography shows the global perfusion in the liver. We tried to change the microcatheter for the long tapered type catheter, but it failed because the long tapered type catheter could not be inserted into the anastomotic branch between the DPA and the proper hepatic artery.

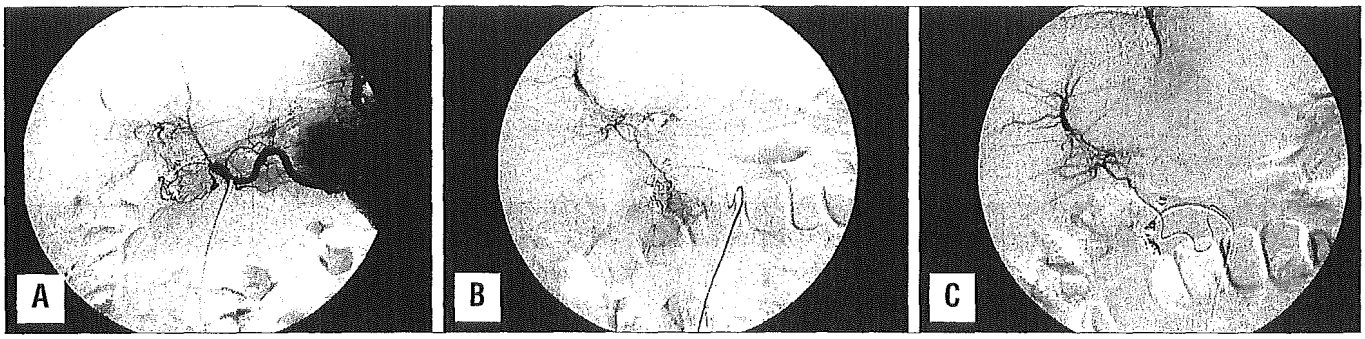

FIGURE 2 A 62-year-old man with liver metastases from colon cancer. **(A)** Celiac arteriography shows the common hepatic and the proper hepatic artery occlusion, and opacified intrahepatic collaterals. The catheter (Anthron PU catheter) is placed in the GDA for reservoir placement. **(B)** Angiography via the DPA demonstrates the intrahepatic collaterals via the pancreas arcade. **(C)** A microcatheter is advanced into the collateral artery near the intrahepatic arteries, and arteriography shows the intrahepatic arteries, not collaterals to the gastrointestinal area.

anastomotic branch of the celiac axis in 1 of 14 patients (7%). The main collateral pathway could not be detected in 2 of 14 patients (14%). Transcatheter treatment was successfully performed in all patients (100%). TACE was performed in eleven of 14 patients (79%) and TAI in the remaining 3 patients.
These results were shown in detail as follows:

Liver Metastases (n=9)

1) Collateral pathways of feeding artery

Main feeding arteries: the DPA **(Figures 1 and 2)** was in 4 of 9 patients, the right IPA was in 2 of 9 patients **(Figure 3)** and the anastomotic branch via the celiac axis was in 1 of 9 patients. The main collateral pathway could not be detected in 2 of 9 patients.

Other feeding arteries: the DPA was in 2 patients, the right IPA was in 2 patients, the right internal thoracic artery (ITA) was in 2 patients, the periportal collaterals was in 6 patients, the anastomotic branch via the celiac axis was in 1 patient and the duodenal branch in 1 patient.

2) Transcatheter treatment

Six of 9 patients successfully underwent TACE via the DPA in 3 patients, via the right IPA in 2 patients and via the anastomotic branch through the celiac axis in 1 patient. In the cases with TACE performed via the DPA and via the anastomotic branch, it was possible to advance a microcatheter into the proper hepatic artery (n=2) or the right hepatic artery (n=1) or the left hepatic artery (n=1) through the DPA or the

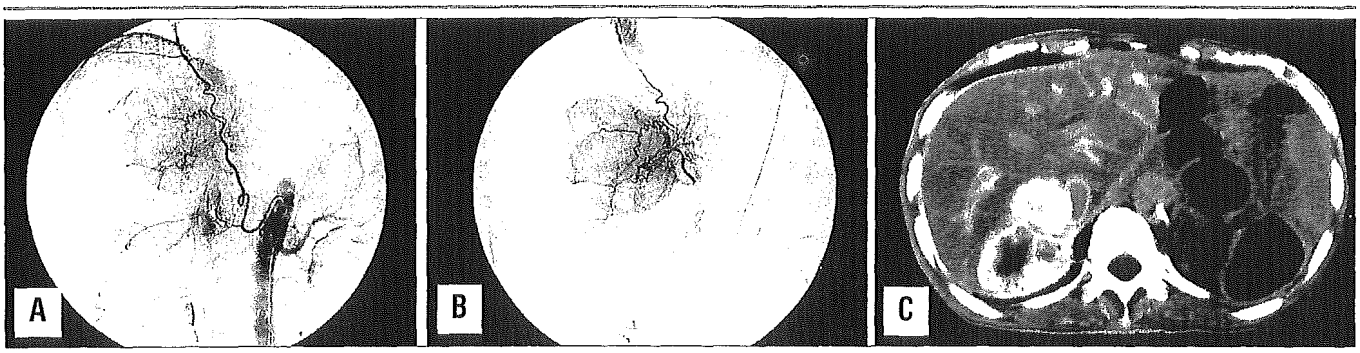

FIGURE 3 A 70-year-old woman with liver metastases from gastric cancer. **(A)** Selective right IPA arteriography reveals that the right IPA feeds the liver metastases. **(B)** A microcatheter is advanced to the distal site of the right IPA and TAE was performed via this site using Amilomer with mitomycin C and contrast material. **(C)** Nonenhanced CT image obtained after TAE shows accumulation of contrast material in the tumor.

anastomotic branch. In the remaining 3 patients, TAI was performed via both the DPA and the right IPA in 1 patient, via both the right IPA and the periportal collaterals in 1 patient and via the DPA in 1 patient. There were no complications related to TACE and TAI.

3) Re-reservoir placement

We tried to advance the long tapered type catheter for reservoir placement to one of the hepatic arteries via the collateral pathway in 4 cases, but it failed in all cases.

Hepatocellular Carcinomas (n=5)

1) Collateral pathways of feeding artery

Main feeding artery: the right IPA was in 4 patients and the bilateral IPAs were in 1 patient.

Other feeding arteries: the periportal collaterals were in 2 patients.

2) Transcatheter treatment

TACE was successfully performed only via the IPA in 4 patients and via the bilateral IPAs in 1 patient. Three of 5 patients had a complication of pleural effusion after TACE. However, pleural effusion diminished within 4 weeks in all 3 patients.

DISCUSSION

Obstruction of the hepatic artery after reservoir placement has been one of the most difficult problems of infusion chemotherapy. In this situation, the pancreaticoduodenal arcade thought to become a feeding artery in cases of obstruction of the common hepatic artery had been embolized already and also the aberrant hepatic artery had been embolized. Therefore, there are few pathways for advancing a catheter into the feeding artery to the tumors. Generally, systemic chemotherapy is the next step of treatment for liver tumors following such an obstruction of the hepatic artery. To our knowledge, there were no reports of transcatheter treatment in cases of obstruction of the hepatic artery after reservoir placement.

It is well known that the IPAs often play a role as feeding arteries in the patients with liver tumors adjacent to the liver surface (12,13). When HCCs are located in the ventral hepatic areas directly beneath the diaphragm, the ITAs serve as feeding arteries after hepatic artery occlusion caused by repeated TACE (14). Takeuchi *et al.* reported that the liver was supplied by the IPAs, by the superior mesenteric artery (SMA), by the celiac axis and the left gastric artery under temporary balloon occlusion of the proper hepatic artery (15). In our present cases, the GDA, the PSPDA and the RGA were already embolized by coils. Then, the SMA and the left gastric artery might be thought to become a feeding artery with lower frequency.

Our present study revealed that the IPAs serve as feeding arteries in the patients with HCCs and metastatic liver tumors as some researchers reported, but it was noted that the DPA had a tendency to be the feeding artery in cases of metastatic liver tumors. Before starting this study, we thought that the ITAs might be one of the main feeding arteries. There was no case that the ITA was the main feeding artery. This result could be disputed due to the fact that the time from initial TACE to ITA angiography was too short (ranged from 0 to 7 months, mean; 3.1 months) to develop anastomoses between the hepatic arteries and the ITAs.

Llovet *et al.* performed a randomized controlled trial in patients with unresectable hepatocellular carcinomas to assess the survival benefits of regular repeated TACE compared with conservative treatment and they obtained the results that TACE induced objective responses sustained for at least 6 months, and was associated with a significantly lower rate of portal vein invasion than conservative treatment (16). TACE should be performed for improvement of survival probabilities even though the hepatic artery is occluded following reservoir placement. In our present study, TACE was successful performed via the IPAs in all five cases with HCCs.

Concerning liver metastases from colorectal cancer, survival analyses showed a significant advantage for infusion chemotherapy compared with systemic chemotherapy by randomized controlled trial studies (3-5,7,8). On the other hand, there is no definite evidence of survival benefits in patients with liver metastases from other organs. We believe, however, that TACE or TAI may be effective in treatment even for liver metastases from other organs such as breast cancer, gastric cancer etc.

In our study, 6 of 9 patients had metastatic liver tumors and TACE was successfully performed via the DPA in 3 patients, via the right IPA in 2 patients and via the anastomotic branch through the celiac axis in 1 patient. It was noted that a microcatheter was advanced into the hepatic artery through the DPA. There has been no reports of TACE or TAI being performed via the DPA for liver tumors.

Though we tried to advance the long tapered type catheter for reservoir placement to one of the hepatic arteries via the collateral pathway in 4 cases, it was impossible in all cases. If the catheter for reservoir placement is developed as the same quality of a microcatheter, reservoir placement could be successfully performed again after occlusion of the hepatic artery following reservoir placement.

REFERENCES

1 **Arai Y, Endo T, Sone Y, et al:** Management of patients with unresectable liver metastases from colorectal and gastric cancer employing an implantable port system. Cancer Chemother Pharmacol 1992; 31:99-102.

2 **Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman** P: Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. Ann Intern Med 1989; 107:459-465.

3 **Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM:** A prospective randermized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal

liver metastases. Ann Surg 1987; 206:685-693.
4 **Hohn DC, Stagg RJ, Friedman MA, et al:** A randomized trial of continuous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. J Clin Oncol 1989; 7:1646-1654.
5 **Martin JK, O'Connell MJ, Wieand HS, et al:** Intraarterial floxuridine versus systemic fluorouracil for hepatic metastases from colorectal cancer: a randomized trial. Arch Surg 1990; 125:1022-1027.
6 **Meta-Analysis Group in Cancer:** Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst 1996; 88:252-258.
7 **Harmantas A, Rotstein LE, Langer B:** Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. Cancer 1996; 78:1639-1645.
8 **Benson AB 3rd:** Regional and systemic therapies for advanced colorectal carcinoma: randomized clinical trial results. Oncology 1998; 12:28-34.
9 **Oberfield RA, McCaffrey JA, Polio J, Clouse ME, Hamilton T:** Prolonged and continuous percutaneous intra-arterial hepatic infusion chemotherapy in advanced metastatic liver adenocarcinoma from colorectal primary. Cancer 1979; 44:414-423.
10 **Tsuji Y, Hamada H, Katsuki Y, et al:** Complication due to arterial infusion chemotherapy for liver metastasis from colorectal cancer. Jpn J Cancer Chemother 1997; 173:238-243. (Abstract in English; text in Japanese)
11 **Sadahiro S, Suzuki T, Tokunaga N, Tajima T, Makuuchi H, Ohtaki M:** Prevention of hepatic artery occlusion during continuous infusion of fluorouracil using liposteroid. AJR 2000; 175:1641-1642.
12 **Michels NA:** Collateral arterial pathways to the liver after ligation of the hepatic artery and removal of the celiac axis. Cancer 1953; 6:708-724.
13 **Seki H, Kimura M, Yoshimura N, Yamamoto S, Ozaki T, Sakai K:** Development of extrahepatic arterial blood supply to the liver during hepatic arterial infusion chemotherapy. Eur Radiol 1998; 8:1613-1618.
14 **Nakai M, Sato M, Kawai N, et al:** Hepatocellular carcinoma: involvement of the internal mammary artery. Radiology 2001; 219:147-152.
15 **Takeuchi Y, Arai Y, Inaba Y, Ohno K, Maeda T, Itai Y:** Extrahepatic arterial supply to the liver: observation with a unified CT and angiography system during temporary balloon occlusion of the proper hepatic artery. Radiology 1998; 209:121-128.
16 **Llovet JM, Real MI, Montana X, et al:** Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized trial. Lancet 2002; 359:1734-1739.

Technical Innovation

Temporary Occlusion of Two Hepatic Veins for Chemoembolization of Hepatocellular Carcinoma with Arteriohepatic Vein Shunts

Satoru Murata[1], Hiroyuki Tajima, Yutaka Abe, Tsuyoshi Fukunaga, Ken Nakazawa, Rabie Abdul Aziz Mohamad, Tatsuo Kumazaki

Treatments for hepatocellular carcinoma have conventionally been divided into curative and palliative. Recently, percutaneous ablation as palliative treatment was shown to induce complete response in a high proportion of patients with nonadvanced small hepatocellular carcinoma. In patients with unresectable hepatocellular carcinoma, however, transcatheter arterial chemoembolization is the most widely used palliative treatment.

Microscopic arteriovenous shunts usually are present in hepatocellular carcinomas [1]. Hepatocellular carcinoma tends to spread in the portal veins and, to a lesser extent, in the hepatic vein [1]. Involvement of intraportal and hepatic veins allows arteriovenous shunts to develop. Development of hepatic arteriovenous shunts prevents effective embolization of the tumor because anticancer drugs or mixtures of iodized oil and anticancer drugs easily go through the shunts [2]. Consequently, conventional transcatheter arterial chemoembolization causes liver dysfunction in patients with hepatocellular carcinoma with arterioportal venous shunts, because embolization of the portal veins induces ischemia of nontumorous liver parenchyma, or causes pulmonary embolism in patients with hepatocellular carcinoma with arteriohepatic vein shunts [3–5]. Therefore, a useful treatment for liver tumors with significant arteriovenous shunts is needed. We report successful transcatheter arterial chemoembolization using temporary occlusion of two hepatic veins for treatment of a huge hepatocellular carcinoma with significant intratumoral arteriohepatic vein shunts.

Subject and Methods

A 68-year-old man was admitted to our hospital for treatment of a liver tumor. His medical history was significant for hepatitis C, and he had been undergoing follow-up for 9 years. His α-fetoprotein level was 542 ng/mL (normal < 20 ng/mL).

A contrast-enhanced CT scan was obtained, and it revealed a 6-cm-diameter hepatocellular carcinoma at the upper portion of the superoanterior segment and bone metastases of the right ribs. The patient then underwent angiographic examination for further evaluation. CT during arteriography showed a hepatocellular carcinoma with an intratumoral arteriohepatic vein shunt and revealed that contrast medium drained directly from the hepatocellular carcinoma into the right hepatic vein during the early arterial phase (Fig. 1A). For CT arteriography, a total volume of 40 mL of diluted nonionic contrast material (100 mg I/mL diluted with physiologic saline) was injected into the proper hepatic artery at a rate of 2.0 mL/sec. CT arteriography was performed 5 sec after the onset of injection (table speed, 7 mm/sec). Selective proper hepatic arteriography showed the moderately hypervascular hepatocellular carcinoma with an intratumoral hepatic vein shunt during the early arterial phase (Fig. 1B).

For transcatheter arterial chemoembolization, we injected mixtures of iodized oil (total volume = tumor diameter [cm] + 1 mL; Lipiodol UF, Nihon Schering) and doxorubicin (40 mg) through a microcatheter (Rapid Transit, Cordis) into the anterior segmental branch of the hepatic artery. After that injection, particles of gelatin sponge (1 mm^2) were injected. On fluoroscopy, the accumulation of iodized oil in the hepatocellular carcinoma was poor, and iodized oil went through the arteriohepatic shunt into the inferior vena cava during the injection. Then, transcatheter arterial chemoembolization was stopped, and a small amount of particles of gelatin sponge was injected through the microcatheter. Proper hepatic arteriography after

Received October 21, 2003; accepted after revision June 1, 2004.

[1]All authors: Department of Radiology, Center for Advanced Medical Technology, Nippon Medical School, 1-1-5 Sendagi, Bunkyou-ku, Tokyo, Japan. Address correspondence to S. Murata (murata_satoru/radiology@nms.ac.jp).

AJR 2005;184:415–418 0361–803X/05/1842–415

embolization with gelatin sponge particles depicted an obstruction of the anterior segmental branch of the hepatic artery.

CT was performed to evaluate the efficacy of transcatheter arterial chemoembolization 3 weeks after treatment. It showed that the hepatocellular carcinoma had progressed (8 cm in diameter). Therefore, we attempted a second transcatheter arterial chemoembolization procedure with balloon occlusion of the right hepatic vein as a draining vein. We punctured the right femoral vein and inserted an 8-French sheath. The balloon catheter had a 6-French shaft and 20-mm-diameter balloon at the tip. We inserted it into the right hepatic vein and inflated the balloon by hand using 4 mL of diluted nonionic contrast material. Our method of confirmation of the right hepatic vein was that right and middle hepatic venography was performed by hand injection using occlusion of each hepatic vein with the patient in the right oblique position, and then the right hepatic vein was confirmed. Selective proper hepatic arteriography under balloon occlusion of the right hepatic vein, however, revealed the middle hepatic vein as a draining vein in the early arterial phase, a finding that angiography did not show without hepatic vein occlusion. Next, we punctured the left femoral vein and inserted a bal-

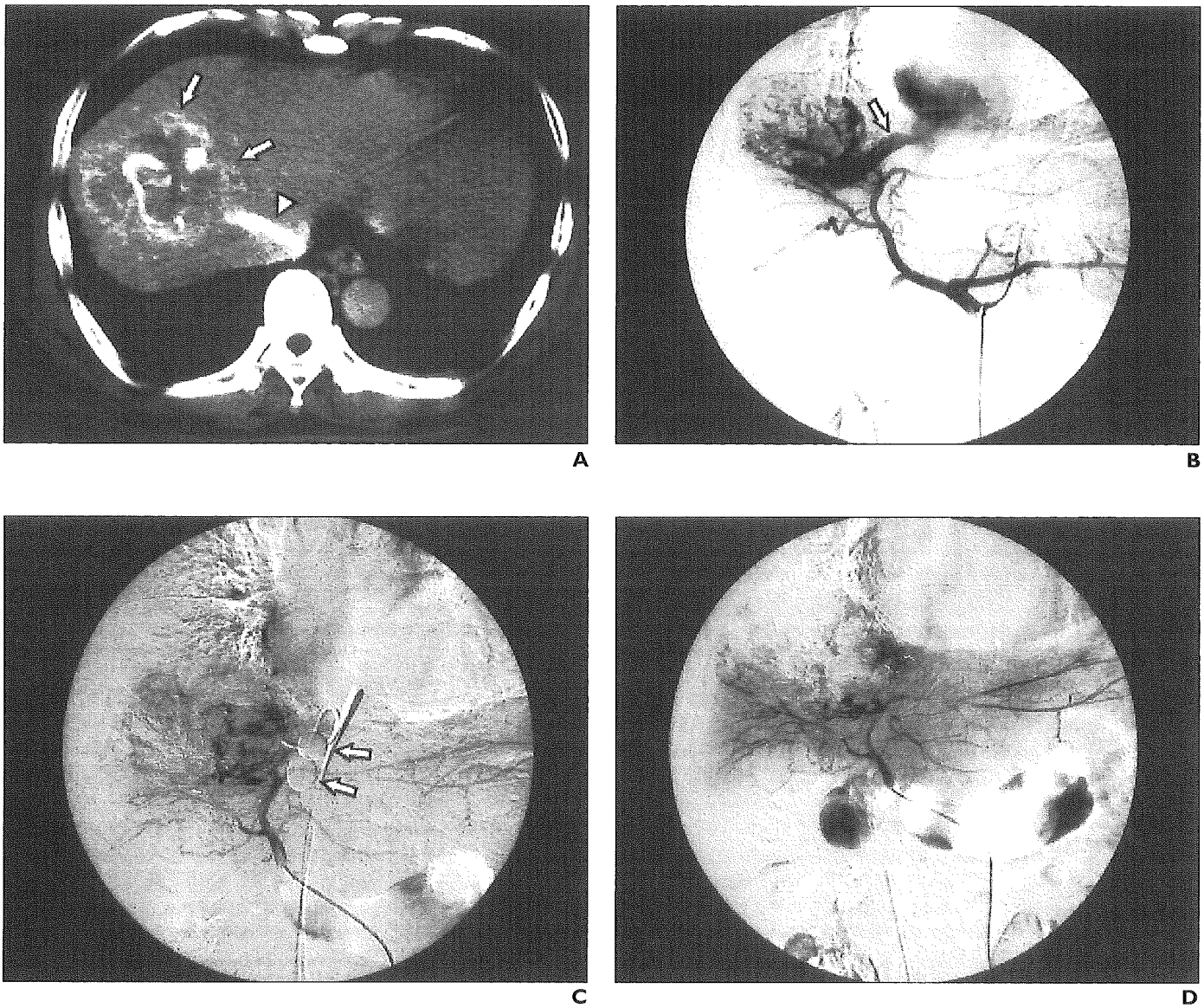

Fig. 1.—68-year-old man with huge hepatocellular carcinoma with intratumoral arteriohepatic vein anastomoses.
A, CT scan obtained during arteriography reveals 6-cm-diameter hepatocellular carcinoma (*arrows*) at upper portion of superoanterior segment with intratumoral hepatic vein shunts. Contrast medium is shown to drain directly from hepatocellular carcinoma into right hepatic vein (*arrowhead*).
B, Celiac arteriograph shows moderately hypervascular hepatocellular carcinoma with significant intratumoral arteriohepatic vein shunt (*arrow*).
C, Selective proper hepatic arteriograph with balloon occlusion of both right and middle hepatic veins shows no intratumoral arteriohepatic vein shunts. Arrows indicate two balloons.
D, Selective proper hepatic arteriograph 1 month after transcatheter arterial chemoembolization with hepatic vein occlusion shows disappearance of intratumoral arteriohepatic vein shunts.