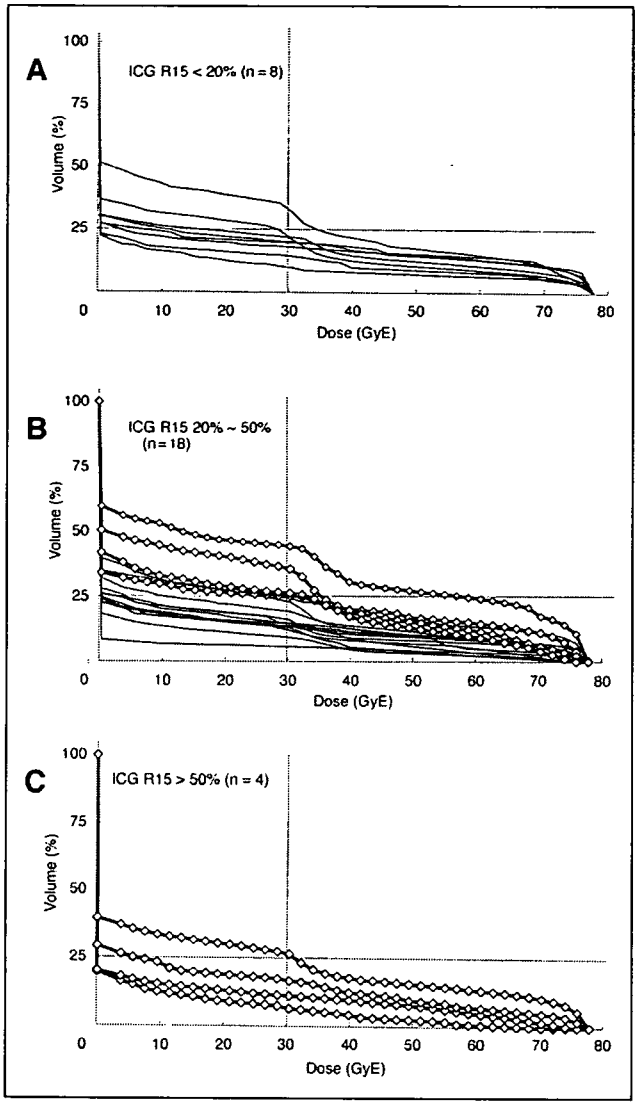

Fig 4. Dose-volume histogram (DVH) for all patients according to their pretreatment ICG R15 values, as noted in panels A, B, and C. Thick line with rhombi represents DVH for patients suffering from hepatic insufficiency within 6 months after completion of proton beam radiotherapy.

that seen in partial liver resection, rather than after 3-dimensional conformal or intensity-modulated radiotherapy delivering a low-dose of x-ray to a large proportion of noncancerous liver. Therefore, estimation of the risk of PRT-inducing hepatic insufficiency should be done with similar guidelines to evaluate liver tolerance to surgery, rather than that with normal tissue complication probability model using a mean dose administered to the entire liver.[21] Remnant liver volume and ICG R15 have been preferred indicators for that estimation, especially in Japan.[15] DVH analyses (Figs 4A to C) suggested that V_{30}% in combination with ICG R15 may be a useful indicator for estimation of liver tolerance to PRT, but no definite quantitative criteria emerged with the limited data obtained at present because of the small number of patients evaluated. The current staging system for HCC is based on survival data obtained in surgical series.[22] There is no reliable system to stratify the prognosis of patients with solitary but unresectable HCC on the assumption that they achieve good local control after PRT. Because of the limited availability of PRT at present, the establishment of particular criteria for patient selection using quantitative parameters of hepatic function such as ICG R15, and volume parameter like V_{30}%, is needed to maximize the cost-effectiveness of PRT.

Applicability of PRT instead of surgery for patients with early-stage disease should be considered with caution. Intraoperative ultrasonography (IOUS) has an important role in detecting small metastatic lesions, which could not be demonstrated in preoperative examinations. The high incidence of intrahepatic recurrences seen outside the PTV might be partly ascribable to the limit of pretreatment imaging studies. Infiltration of HCC to the portal vein and spread via portal blood flow is one of the mechanisms for the development of intrahepatic recurrence.[15] Actually, five recurrences occurred within the same segment of the primary tumor in this study. Although anatomic resection according to the architecture of the portal vein using IOUS offered a better chance of cure only for patients with noncirrhotic livers,[23] systematic segmental PRT based on multimodal imagings such as CT during arterial portography or MRI as well as image fusion technique[24] has a theoretical advantage compared with nonanatomic PRT confined to GTV only. Because there were few potentially curative approaches other than surgery for patients with HCC showing vascular invasion, further study is warranted to scrutinize an efficacy of PRT for patients with HCC of $\geq$ 5 cm in diameter, of which a large majority will demonstrate vascular invasion around the periphery of the tumor,[25] while giving attention to their V_{30}% values.

The risk of this aggressive dose-fractionation for sites such as the gastrointestinal loop, hepatic hilum, skin, or subcutanous tissues must be carefully considered, and more conventional fractionation must be adopted when these structures are critically involved in the PTV.

In conclusion, PRT for localized HCC using an aggressive dose-fractionation scheme (76 Gy_E for 5 weeks) achieved excellent local control rate regardless of vascular invasion or tumor size, if $\leq$10 cm, without devastating acute toxicity. Further study is warranted to scrutinize adequate patient selection according to quantitative parameter of hepatic function, such as ICG R15, and irradiated noncancerous liver volume in order to maximize survival benefit of this promising modality.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Scandinavian Journal of Gastroenterology, 2005; 40: 1378–1381

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CASE REPORT

Solitary bile duct hamartoma of the liver

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Abstract

Bile duct hamartomas, also known as von Meyenburg complexes, are benign liver malformations which usually present as multiple small nodules scattered in both lobes of the liver. We report a unique case of bile duct hamartoma. An asymptomatic 30-year-old man who had a solitary cystic lesion underwent partial hepatectomy. Macroscopically, the lesion, measuring 3.6 cm in diameter, was composed of a number of small grayish-white cysts measuring 0.1 to 1.2 cm in diameter. Histologically, the constituent cysts were embedded in a fibrous stroma and were lined by low columnar or cuboidal epithelium. By immunohistochemistry, the MIB-1 index was below 1%, and p53 and carcinoembryonic antigen (CEA) were negative. These findings lead us to conjecture that the lesion was a bile duct hamartoma, although its solitary nature and large size differed from those of typical bile duct hamartoma.

Key Words: *Bile duct hamartoma, ductal plate malformation, solitary*

Introduction

Recent advances in imaging modalities have resulted in more frequent detection of small cystic lesions in the liver. Bile duct hamartoma (BDH), also known as von Meyenburg complex, is one such lesion. A BDH is a focal, disordered collection of bile ducts; it is considered a benign ductal plate anomaly [1–7]. BDH commonly presents as small, whitish periportal nodules scattered in both lobes of the liver. The nodules are generally less than 0.5 cm in diameter, and a solitary lesion of BDH is rare [3,5–8]. We present an unusual case of solitary BDH.

Case report

In 2001 a 30-year-old man was referred with an asymptomatic cystic mass in the liver discovered incidentally during routine medical examination. He had no past history of serious illness. Physical and hematological examination was unremarkable. There was no serological evidence of hepatitis B or C virus infection. Contrast-enhanced computed tomography (CT) scans and magnetic resonance imaging (MRI) showed a multilocular cystic lesion, 3 cm in diameter, with enhanced septum under the surface of the right hepatic lobe (Figure 1). No other lesion was observed in the liver or other organs. Neither CT nor MRI revealed evidence of a mural nodule in the lesion.

The patient was submitted to laparotomy and underwent partial hepatectomy. He has been free of disease for two years.

Material and methods

Histological examination

The surgically resected specimen was fixed overnight in 10% formalin at 4°C, and the entire lesion was cut into slices 0.5 cm in thickness. Several histologic specimens were taken to adequately examine its histologic features. The paraffin blocks were retrieved and 4-μm slides prepared routinely, stained with hematoxylin and eosin and examined histopathologically.

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(Received 30 August 2004; accepted 17 February 2005)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365520510023387

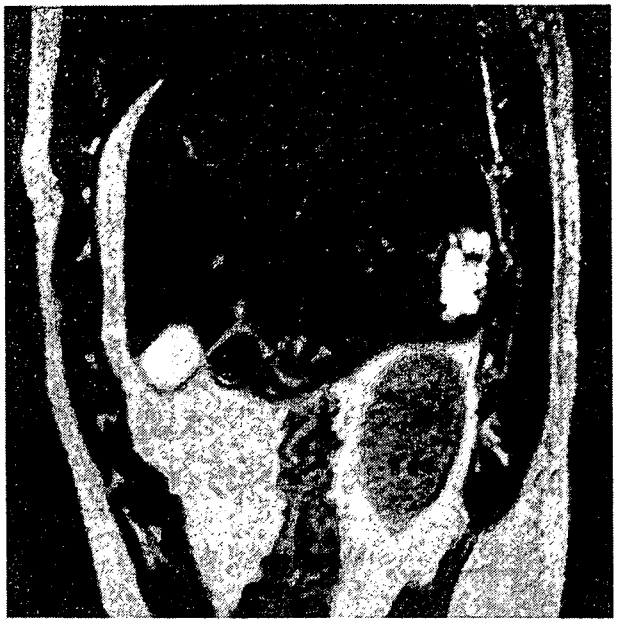

Figure 1. The cystic lesion has high signal intensity on the T2-weighted magnetic resonance image. No other lesion was observed in the liver.

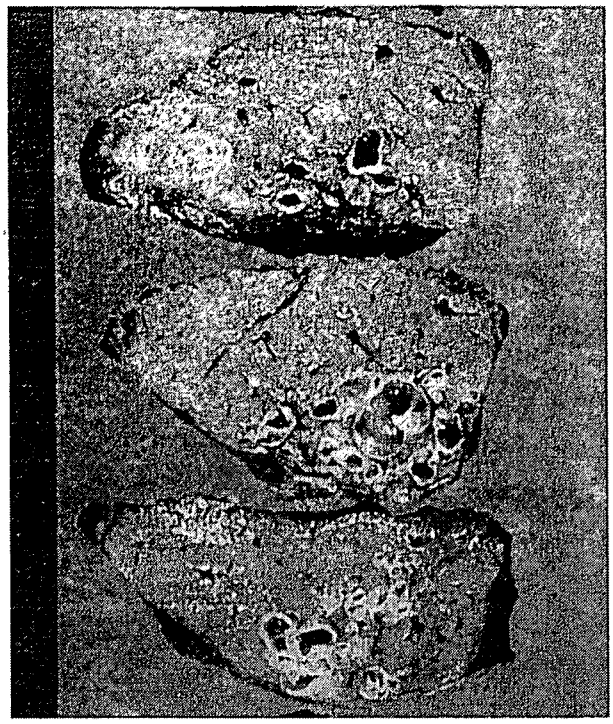

Figure 2. Cut surface of a resected specimen showed that the lesion is composed of a number of small, grayish-white cysts, 3 cm in size, with a green, viscous liquid content. No solid component was evident within the cystic lesion.

Immunohistochemistry

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections using the avidin-biotin complex method [9]. Sections were cut at 3 μm, deparaffinized in xylene, and the endogenous peroxidase activity was blocked with 0.3% H_2O_2 in methanol. The slides were treated with 0.05% pepsin for 60 min and microwaved [10] at 95°C for 20 min to recover antigenicity, then subjected to immunohistochemical staining for carcinoembryonic antigen (CEA) (1:1000; TAKARA BIO INC, Shiga, Japan), p53 (1:1000; NICHIREI, Tokyo, Japan), and Ki-67 antigen (MIB-1: 1:100; Dako, Glostrup, Denmark).

Results

Macroscopically, the lesion measured 3.6 cm in diameter and was composed of a number of small grayish-white cysts, the diameters of which ranged from 0.1 to 1.2 cm (Figure 2). Green and mucinous fluid was present in the cysts. Neither mural nodules on the cysts nor irregular septum was seen. Microscopically, the lesions were discrete, round in shape, and periportal in location. The constituent cysts were embedded in a fibrous stroma, and some of these cysts had dilated lumens (Figure 3A,B). The cysts were lined by a low columnar or cuboidal epithelium and contained bile-stained material (Figure 3C,D). Immunohistochemistry showed negative results for p53 and CEA monoclonal antibody. Fewer than 1% of cells showed proliferation activity, assessed by staining for Ki-67 antigen (clone MIB-1).

Discussion

Bile duct hamartomas consist of focal, disordered collections of bile ducts, lined with a single layer of low columnar or cuboidal epithelium, surrounded by abundant fibrous stroma [1–7]. The bile ducts within the lesions are round to irregular in shape, and contain pink amorphous material or actual bile.

In the present case, the lesion contained both small cysts (<0.5 cm) and larger cysts (0.5–1.2 cm), which were lined by a low columnar or cuboidal epithelium, contained bile-stained material, and were embedded in a fibrous stroma. Microscopic examination and immunohistochemistry did not show any potential for malignancy in the epithelium of the cysts. These findings lead us to conjecture that the lesion was a BDH. Two findings, however, differed from those of the typical BDH: the lesion was solitary and measured 3.6 cm in diameter, whereas typical BDH lesions are multiple and less than 0.5 cm in diameter. Thus, we believe this lesion is a previously unrecognized biliary lesion and propose to designate it as a solitary biliary hamartoma. Solitary BDH is characterized by a solitary nodule composed of small bile ducts of irregular shape, set in a fibrous stroma, and is distinct from typical BDH because of its large size, relatively

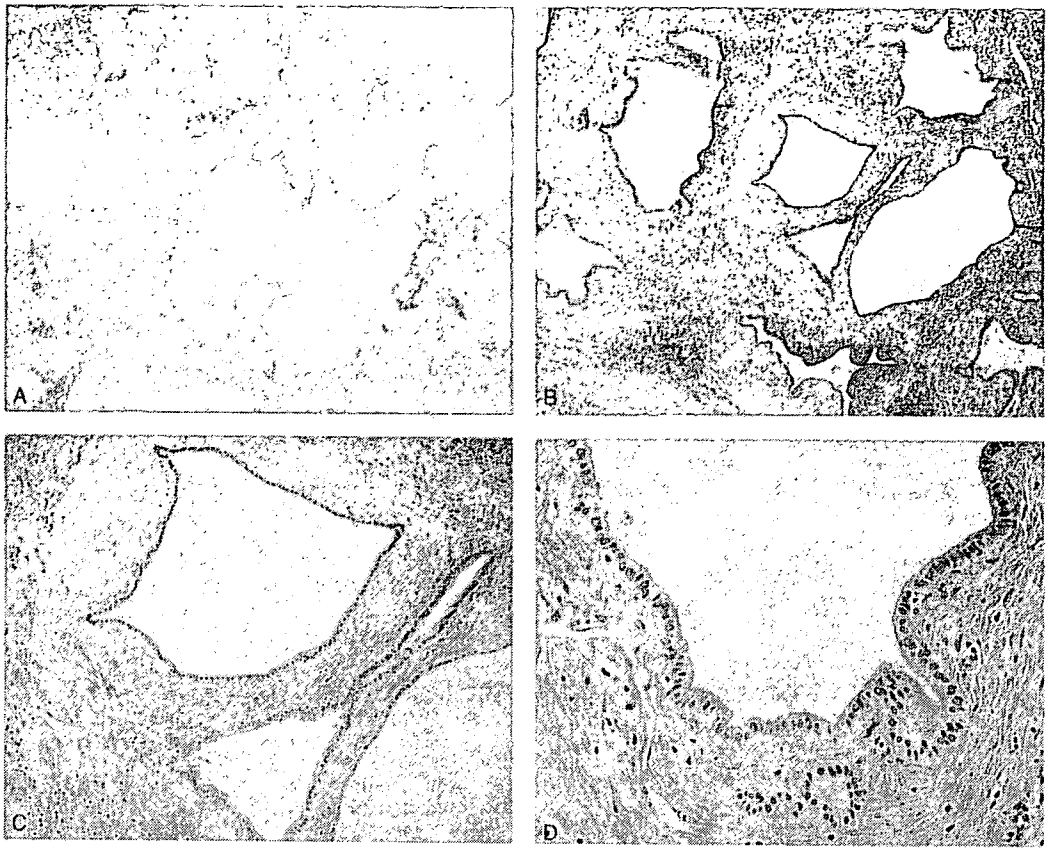

Figure 3. Distinctive features of solitary bile duct hamartoma. A. Microcysts of various size surrounded by fibrous stroma (hematoxylin & eosin; original magnification ×5). B. Microcysts are similar to bile ducts but show abnormal arrangement. Size of cysts tends to be larger than that of typical bile duct hamartoma (hematoxylin & eosin; original magnification ×40). C. & D. Epithelium lining of columnar cells and cuboidal cells shows no cytological abnormalities (hematoxylin & eosin; original magnification C: ×100, D: ×200).

larger bile ducts constituting the lesion, and absence of synchronous biliary hamartomas in the surrounding liver.

In our case, preoperative MRI, which is essential diagnostic imaging for detecting small cystic lesions [11–13], showed no cystic lesions other than the BDH in the liver. In the recent literature, no pathological study of solitary BDH confirmed by preoperative MRI has been reported.

The pathogenesis of BDH is obscure. Bile duct hamartoma is found frequently in patients with adult polycystic kidney disease, Caroli's disease, or congenital hepatic fibrosis [5,8,14–16]. The association with these congenital bile duct diseases suggests that BDH might be a genetic disease. V. J. Desmet hypothesized that BDH is a congenital disease of the intrahepatic bile ducts that results from abnormal remodeling of the embryonic ductal plate, and that BDH is associated with ductal plate malformation of the peripheral interlobular bile ducts in the late phase of bile duct embryogenesis [17]. However, it has been suggested that at least some BDHs are an acquired disease resulting from hepatic ischemia by arteriosclerosis or polyarteritis [18], or from alcoholic liver injury [19].

The pathogenesis of the present case is also unknown. However, ductal plate malformation might not be involved, because the patient had no other congenital bile duct disease, and furthermore the solitary lesion is not consistent with the concept of systemic malformation of the biliary tree. The lesion contained large cysts, and this feature resembles that of BDH resulting from hepatic ischemia reported by Popovsky et al. [18]. The morphological findings of the present case favor pathogenesis other than ductal plate malformation, such as hepatic ischemia, although no history of arteriosclerosis or polyarteritis was identified in the patient.

Bile duct hamartoma is a non-neoplastic lesion. Several papers reported cases of cholangiocarcinoma co-existing with BDHs [20,21]; however, association between cholangiocarcinoma and BDH is still a controversial idea. To date, no treatment is required when solitary BDH is correctly diagnosed. However, solitary BDH should be distinguished from other solitary hepatic lesions. Biliary cystadenoma is a primary cystic neoplasm in liver, and its radiological features resemble those of solitary BDH [22]. Biliary cystadenoma is defined as a multilocular lesion lined by a benign or atypical columnar cuboidal epithelium

usually with an "ovarian-like" stroma, and is rarely encountered in males. Many areas within biliary cystadenoma are composed of a combination of columnar to cuboidal mucinous epithelial cells, and the epithelial cells are positive to cytokeratin, epithelial membrane antigen, and CEA [13,22]. In contrast, neither atypical cells nor mucin-secreting cells were present in the epithelium of solitary BDH, and epithelial cells of solitary BDH were negative with antibody to CEA. The stroma of solitary BDH is relatively rich, but was different from "ovarian-like" stroma. Differentiation between biliary cystadenocarcinoma and solitary BDH is easier. Cystadenocarcinoma is a predominantly cystic but usually solid component macroscopically. Cystic lesions are lined by a proliferation of cytologically malignant epithelium in cystadenocarcinoma. Biliary adenofibroma is a rare benign biliary tumor characterized by microcystic and tubular formations embedded in a fibrous stroma [23,24]. Microscopic findings resemble those of solitary BDH, but its more solid appearance with honeycomb-cut surface is distinct from that of solitary BDH. Furthermore, the epithelium of biliary adenofibroma is positive to keratin AE.3/Cam5.2, CEA, and epithelial membrane antigen and has the marked nuclear p53 immunoreactivity and a low Ki-67 proliferative index ($\leq$10%). In contrast, the epithelium of solitary BDH was negative to CEA and p53, and showed a lower Ki-67 proliferative index ($<$1%).

Our patient underwent surgical resection because biliary cystadenoma could not be excluded in the preoperative diagnosis. Solitary BDH should be added to differential diagnoses of intrahepatic cystic lesions, however, the radiological diagnosis of solitary BDH might be difficult despite careful preoperative study.

In summary, on rare occasions solitary BDH may occur in the liver. Solitary BDH has to be considered as a differential diagnosis of intrahepatic cystic neoplasms.

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症例報告

術前診断に苦慮した肝血管筋脂肪腫の2切除例

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消 化 器 画 像
第7巻　第5号　別刷
2005年9月15日　発行

医学書院

症例報告

術前診断に苦慮した肝血管筋脂肪腫の2切除例*

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Key Words
肝血管筋脂肪腫
HMB-45

(要旨) 肝炎ウイルスや腫瘍マーカーがともに陰性であった2例を報告する．腹部USで比較的境界明瞭な内部不均一で血流が豊富な高エコー腫瘍として描出され，腹部CTにて，動脈相における不規則な濃染像と遅延相にて部分的に造影効果が遷延する所見を認め，血管造影では，動脈後期相より比較的均一に濃染され，門脈相においても造影効果は遷延していた．腹部MRIでは，T2強調像において高信号を示し，脂肪強調像で腫瘍内に明らかな脂肪成分は認めなかった．1例は生検を行ったが確定診断に至らず，肝細胞癌を否定できないため2例とも切除を行った．病理診断はともに肝血管筋脂肪腫であった．(消化器画像 2005;7:693-699)

はじめに

肝血管筋脂肪腫は比較的稀な腫瘍とされ，確定診断に至るのが困難であるとされている[3)]．今回，われわれは肝血管筋脂肪腫を2例経験し，その診断について文献的考察を含め報告する．

症　例

[症例1]

患者　51歳，女性．

主訴　特になし．

現病歴　2003年11月，検診にて肝腫瘍を指摘され当科へ紹介された．

既往歴・現症　特記事項なし．

血液生化学検査　肝炎ウイルスは陰性であり，腫瘍マーカーもCEAが軽度上昇しているほかは正常であった．

腹部US　肝S6に径3 cm大のhaloを伴う高エコー腫瘤を認めた．周囲との境界は明瞭で，内部は不均一であり，血流を認めた(図1)．また，腫瘍内部に径0.5 cm程度の嚢胞成分を認めた．

腹部CT　肝S6に径3.7 cmの中心部に嚢胞成分を有するダンベル状の腫瘍を認めた．造影効果は，動脈相で内部が不均一に濃染され，遅延相において遷延していた．周囲肝実質との境界は比較的不明瞭であり腫瘍被膜は認めなかった(図2)．

腹部MRI　T2強調像において，腫瘍全体が淡い高信号を呈し，中心部の嚢胞成分に一致して強い高信号域を認め，その周囲にも類円形の強い高信号領域を認めた．脂肪強調像におけるIn phase，Out of phaseで検索したが明らかな脂肪成分は認めなかった(図3)．

腹部血管造影　肝S6に動脈後期相にて濃染し門脈相

* Two Resected Cases of Hepatic Angiomyolipoma
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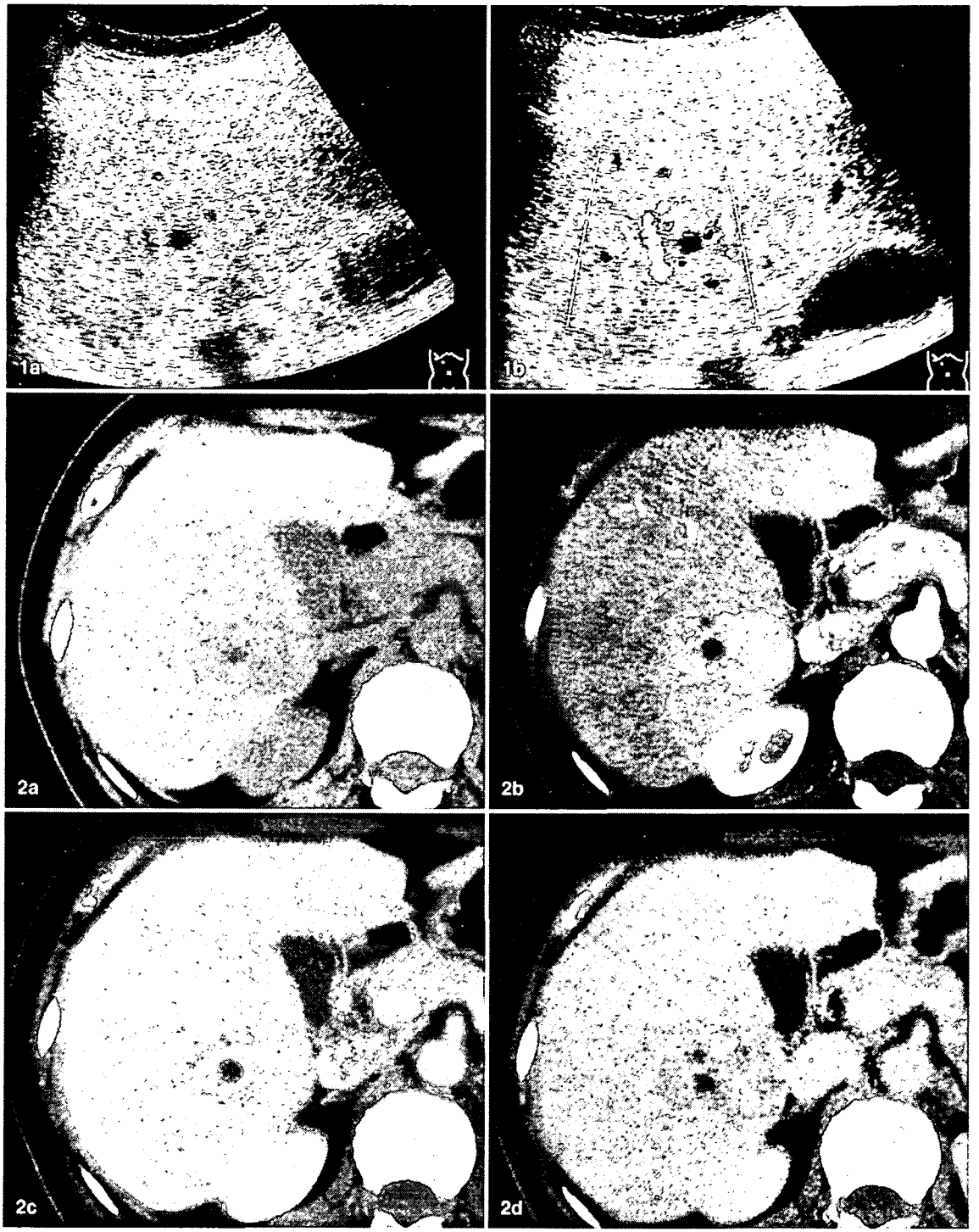
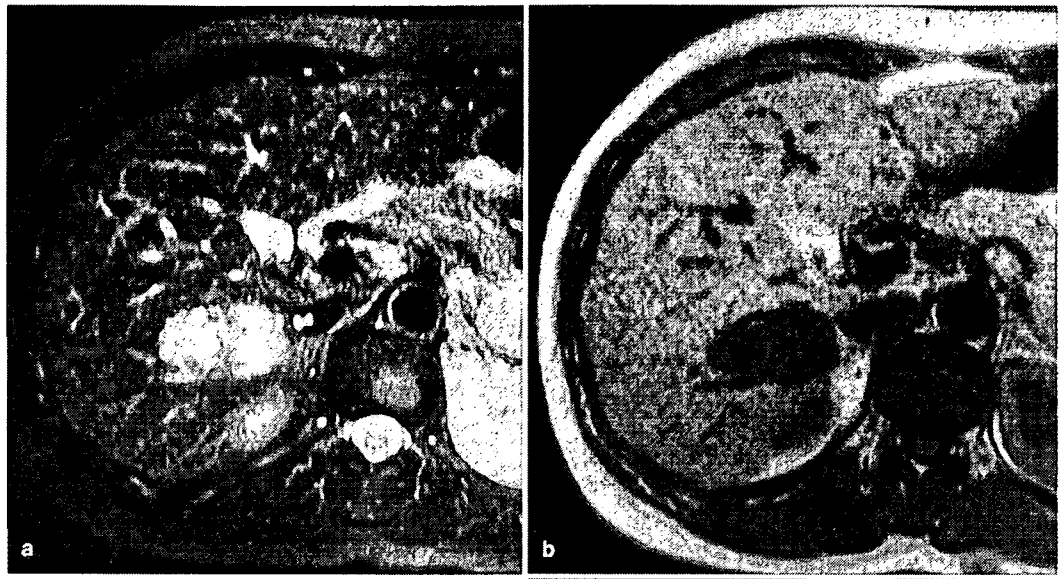


図1　US[症例1]
a. 肝S6に径3 cm大のhaloを伴う高エコー腫瘤を認めた．周囲との境界は明瞭で，内部は不均一であり，腫瘍内部に径0.5 cm程度の嚢胞成分を認めた．
b. 腫瘍内部に血流を認めた．

図2　CT[症例1]
a. plainで肝S6に低吸収域の腫瘤を認め，中心に嚢胞性病変を認める．
b. 動脈相で内部が不均一に濃染され，嚢胞性病変には造影効果は認めない．
c. 門脈相において，不均一な造影効果の遷延を認める．
d. 遅延相においても不均一に造影効果が遷延している．
周囲肝実質との境界は比較的明瞭であり被膜様構造は認めなかった．



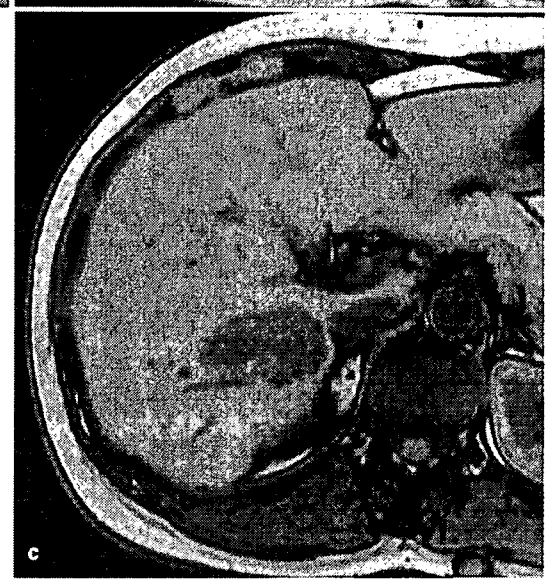
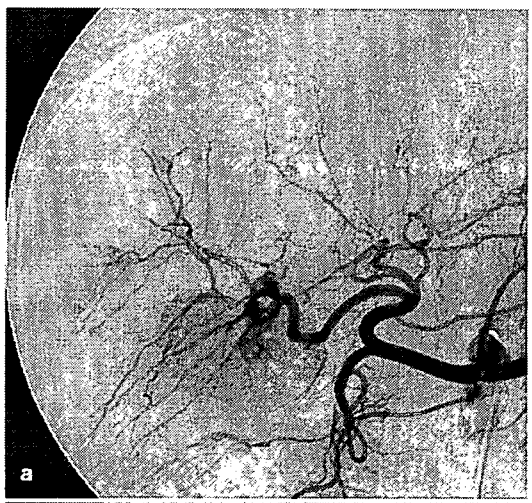
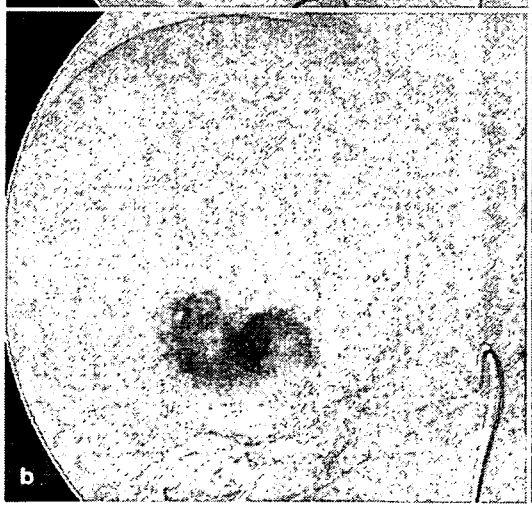


図3　MRI[症例1]
a. T2強調像において，腫瘍全体が淡い高信号を呈し，中心部の嚢胞成分に一致して強い高信号域を認め，その周囲にも類円形の強い高信号領域を認めた．
b，c. 脂肪強調像におけるIn phase，Out of phaseで検索したが明らかな脂肪成分は認めなかった．





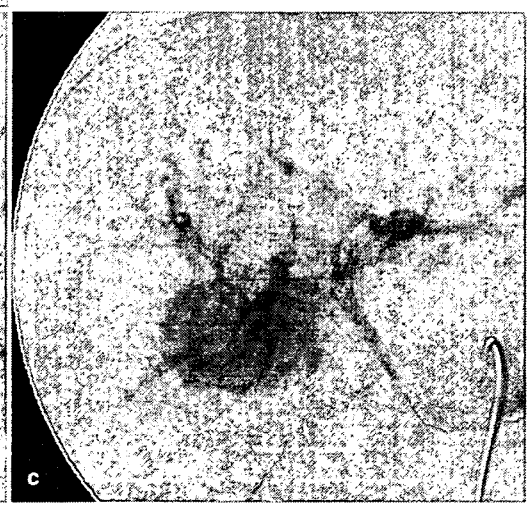


図4　血管造影[症例1]
a. 肝S6に動脈後期相にて濃染する腫瘍を認めた．
b. 実質相において肝S6腫瘍の造影効果は遷延し，肝S3，S7に腫瘤陰影を認めた．
c. 門脈相においても肝S3，6，7腫瘍の造影効果が遷延していた．

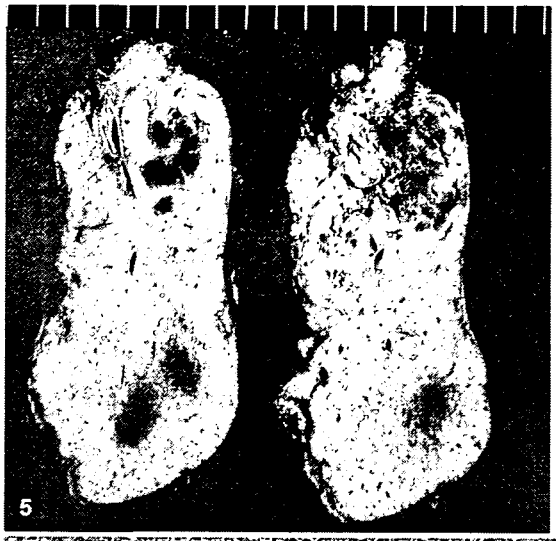
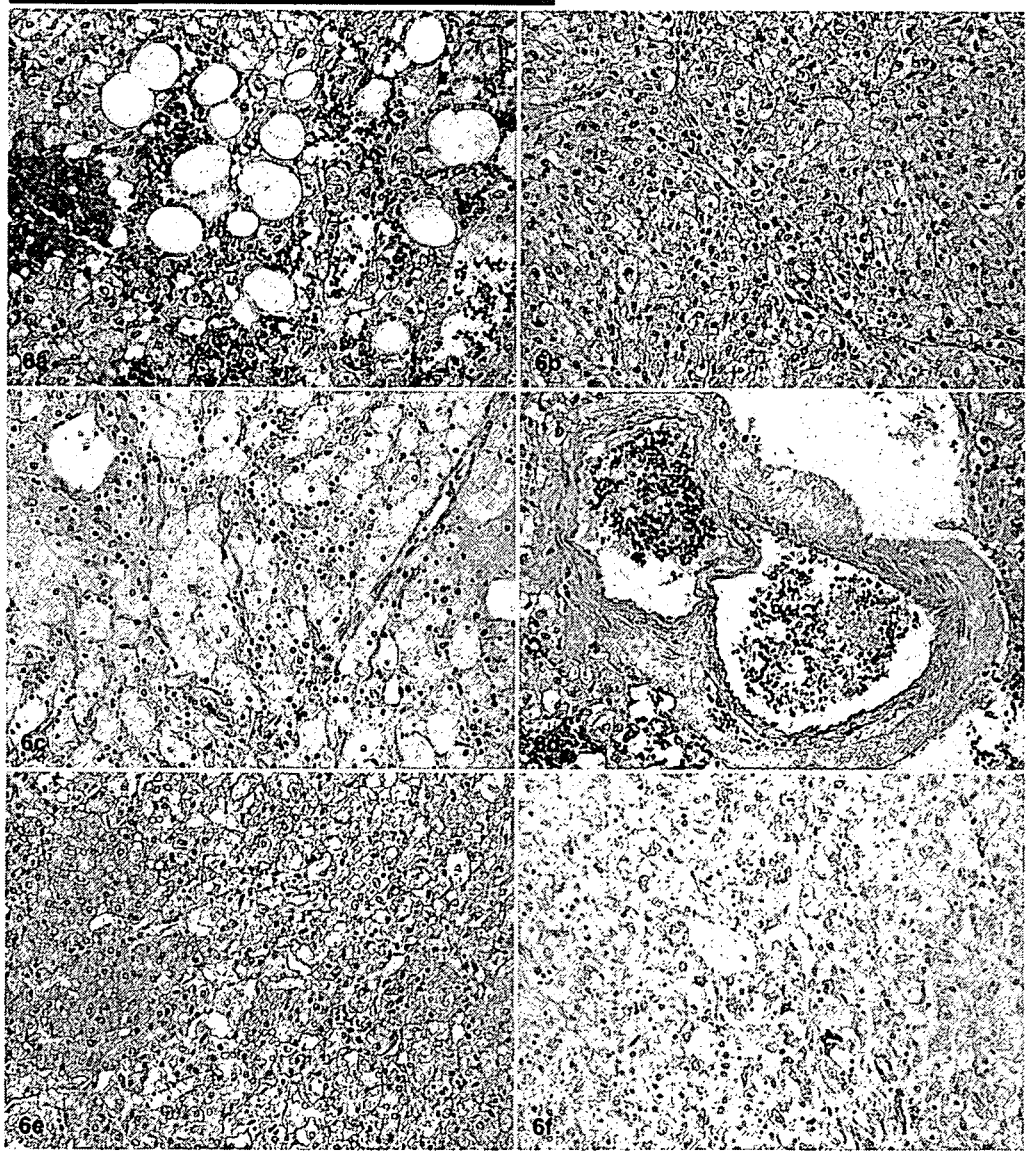


図5　摘出標本[症例1]
肝S6に大きさ4.1×4.1 cmで内部に出血を伴う褐色～白褐色調の腫瘍を認めた．弾性軟であり，周囲との境界は比較的明瞭であるが，明らかな被膜形成は認めなかった．

図6　病理組織所見[症例1]
a. 胞体に豊富な脂肪滴を含有する腫瘍細胞を認め，間質に血様性出血を認める．
b. 紡錘状の類上皮平滑筋様細胞．
c. xantomatous cell featureを示す腫瘍細胞．
d. 腫瘍辺縁に認められた壁肥厚を伴う動脈．
e. 腫瘍細胞は周囲の肝類洞内へ侵入するように増殖していた．
f. 免疫染色にてHMB-45がびまん性に陽性であった．



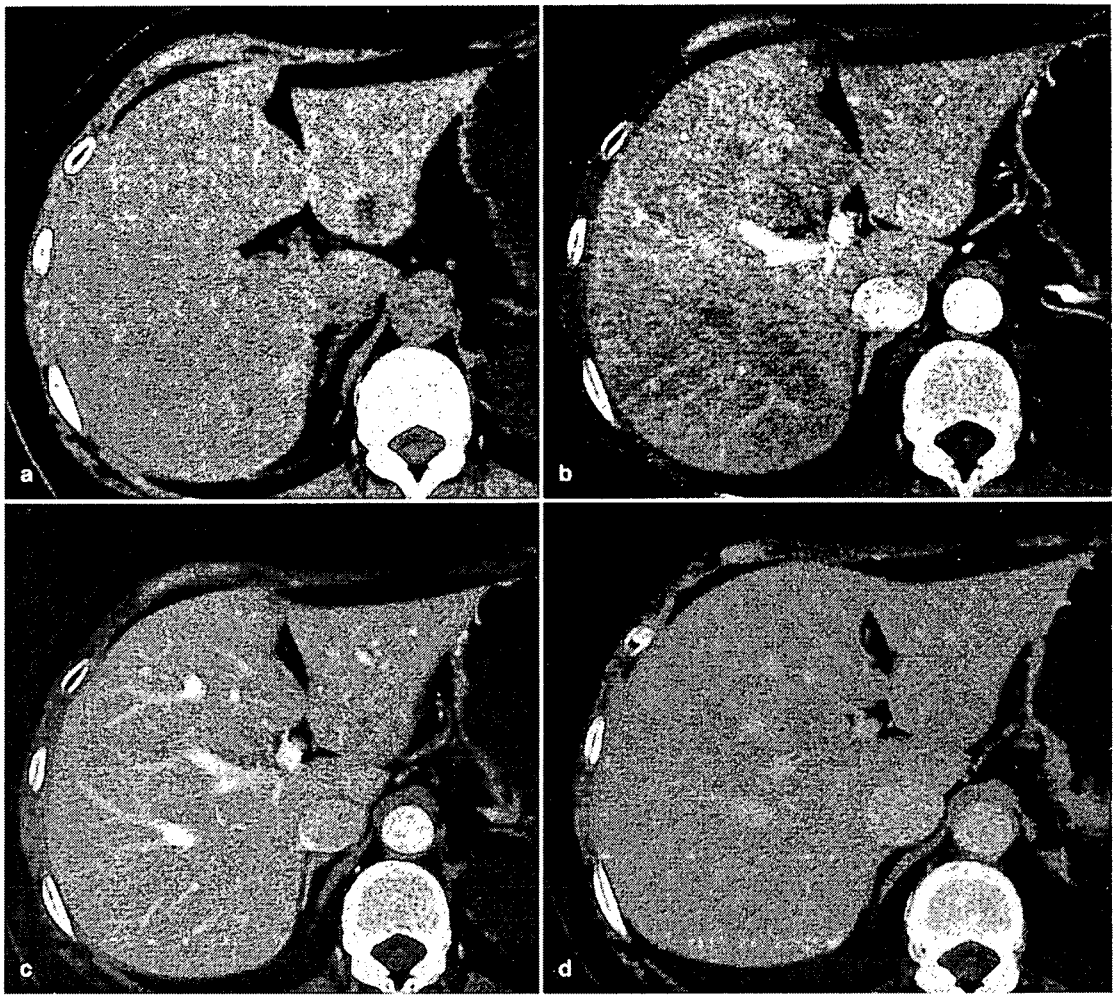


図7　CT[症例2]
a. plainにおいて肝S2に径2.5 cmの低吸収値である腫瘍を認めた.
b. 動脈相で内部が不均一に濃染さる.
c. 門脈相において内部に不均一な造影効果の遷延を認める.
d. 遅延相においても内部に不均一な造影効果の遷延を認める.
周囲肝実質との境界は比較的明瞭であり被膜様構造は認めなかった.

においても造影効果が遷延する腫瘍を認めた．また肝S3，S7にS6の腫瘍とほぼ同じ造影効果を有する小結節を認めた(図4)．

造影効果から検討すると典型的な肝細胞癌とは考えにくく，血管腫や血管筋脂肪腫なども考えられたが，肝内に多発病変を認めており肝細胞癌は否定できないとし，肝後区域切除＋S3部分切除を施行した．

摘出標本肉眼所見　肝S6に大きさ4.1×4.1 cmで内部に出血を伴う褐色～白褐色調の腫瘍を認めた．弾性軟であり，周囲との境界は比較的明瞭であるが，明らかな被膜形成は認めなかった(図5)．

病理組織所見　腫瘍細胞は，紡錘状の類上皮平滑筋様細胞，xantomatous cellと胞体に豊富な脂肪滴を含有する細胞からなり，周囲の肝類洞内へ侵入するように増殖していた．腫瘍辺縁には壁が肥厚した動脈を認めた．免疫染色にてHMB-45がびまん性に陽性であり，肝血管筋脂肪腫と診断された(図6)．腫瘍内出血は間質内に浸透するような出血であり，MR1 T2強調で強い高信号を呈した局面に一致し，組織学的特徴の1つである髄様性出血であった．肝S3，S7に認められた小結節はいずれも腺腫様過形成であった．

術後経過　現在無再発生存中である．

[症例2]

患者　61歳，女性．

主訴　特になし．

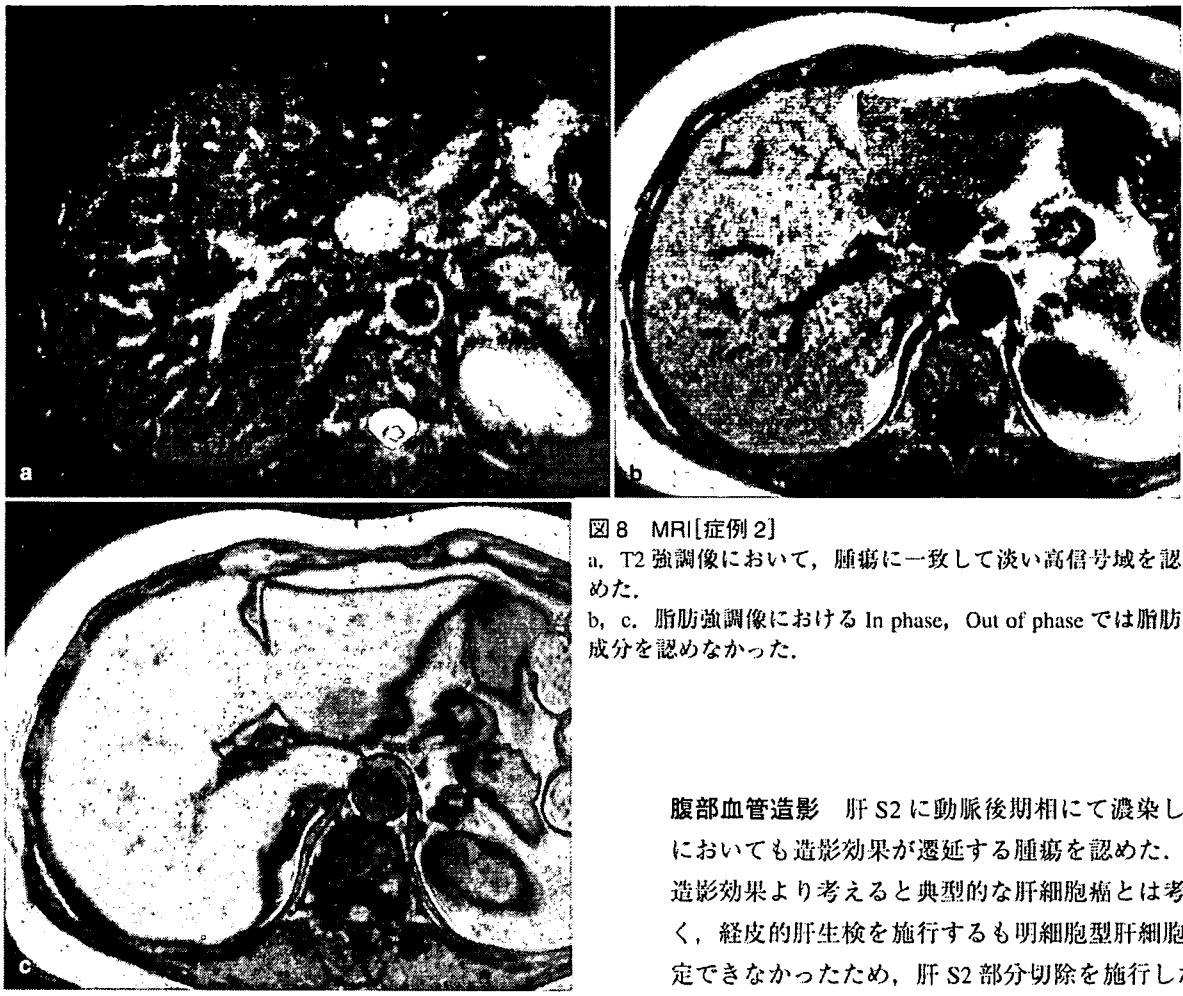


図8 MRI[症例2]
a. T2強調像において，腫瘍に一致して淡い高信号域を認めた．
b, c. 脂肪強調像における In phase，Out of phase では脂肪成分を認めなかった．

現病歴 2002年10月検診にて肝腫瘍を指摘され当科へ紹介された．

既往歴・現症 特記事項なし．

血液生化学検査 肝炎ウイルスは陰性であり，腫瘍マーカーも正常であった．

腹部US 肝S2に径2.5 cm，haloを伴う高エコー腫瘤を認めた．周囲との境界は明瞭で，内部は不均一であり血流を認めた．

腹部CT 肝S2に径2.5 cmの腫瘍を認めた．その造影効果は，動脈相で内部が不均一に濃染され，遅延相においても遷延していた．周囲肝実質との境界は比較的明瞭であり被膜様構造は認めなかった(図7)．

腹部MRI T2強調像において，腫瘍に一致して淡い高信号域を認めた．脂肪強調像における In phase，Out of phase では脂肪成分を認めなかった(図8)．

腹部血管造影 肝S2に動脈後期相にて濃染し門脈相においても造影効果が遷延する腫瘍を認めた．
造影効果より考えると典型的な肝細胞癌とは考えにくく，経皮的肝生検を施行するも明細胞型肝細胞癌を否定できなかったため，肝S2部分切除を施行した．

摘出標本肉眼所見 肝S2に大きさ3.0 × 1.5 cmの腫瘍を認め，その所見は[症例1]とほぼ同様であった．

病理組織所見 [症例1]と同様であった．肝血管筋脂肪腫と診断された．
術後経過現在無再発生存中である．

考 察

肝血管筋脂肪腫はIshakが1976年に初めて報告した稀な間葉系良性肝腫瘍である[1]．発症年齢は平均50歳であり，性差による差は認められず，通常は単発であるとされている[3]．

肝血管筋脂肪腫は画像診断で診断されることは少なく[3]，肝細胞癌，肝血管腫や脂肪を含むその他の間葉系腫瘍と診断されることが多い．肝血管筋脂肪腫は様々な割合の脂肪成分を有する特徴を持ち，個々の症例で10～90%以上のばらつきがあるとの報告もあるため[2]，脂肪成分は特異的な所見とはなりにくいと考

える．また自験例においては画像上脂肪成分は描出しえず，脂肪成分の所見は診断するうえで補助的な意味合いに過ぎないと考えられた．

Dynamic CTによる造影所見が有用であるとの報告があり，早期相で強く造影され，遅延相まで造影効果が遷延するとされている[5]．遷延する造影所見を持つ主な肝腫瘍は，肝血管腫，肝細胞癌と転移性肝癌であるとされ[6]，脂肪成分を有する腫瘍で考えると肝細胞癌との鑑別が問題になると考えられる．肝血管筋脂肪腫は造影効果が4分以上遷延することが特徴とされ[7]，肝細胞癌は遅延相にてほぼ造影効果が消失することを考えると[8]，鑑別診断に有用な所見と考えられる．造影効果のピークに着目すると，肝細胞癌のピークは10秒程であり[8]，肝血管筋脂肪腫は40～80秒であることから[7]，鑑別に有用である可能性が示唆される．しかし，フィルムに現像された画像所見から腫瘍における造影効果のピークや遷延を肝細胞癌の造影効果と比較して評価するのは，自験例の画像を観察する限り困難であると考えられ，あくまで腫瘍の造影効果をCT値として評価し，その増加や減衰を計測して初めて有用と考えられる．

病理組織診断においては，肝血管筋脂肪腫に特異的なHMB-45を用いた免疫染色は有用であったとの報告があり[1,3]，自験例においても確定診断に有力な情報であった．

おわりに

肝細胞癌と鑑別が困難であった肝血管筋脂肪腫の2例を経験した．単発で造影効果の遷延する肝細胞癌類似の造影パターンを示す肝腫瘍は肝血管筋脂肪腫も念頭に置いて診断することが必要と考えられた．

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Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma

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(Received July 31, 2007/Revised September 13, 2007/Accepted September 20, 2007/Online publication October 22, 2007)

Sorafenib is an orally active multikinase inhibitor that targets serine and threonine, and tyrosine kinases that are involved in tumor-cell signal transduction and tumor angiogenesis. This phase I trial was conducted to evaluate the pharmacokinetics (PK), safety, and preliminary efficacy of sorafenib in Japanese patients with hepatocellular carcinoma (HCC) with underlying liver dysfunction. Patients with unresectable HCC, Child–Pugh status A or B, and adequate organ functions were treated. A single dose of sorafenib was administered, followed by a 7-day wash-out period, after which patients received either sorafenib 200 mg (cohort 1) or 400 mg (cohort 2) twice daily. The PK were investigated after a single dose and during steady state. The efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors. A total of 27 patients were evaluated for PK, safety, and efficacy. Although both area under the concentration–time curve for 0–12 h and maximal concentration at steady state were slightly lower in Child–Pugh B patients than in Child–Pugh A patients, the difference was not considered to be clinically relevant. Common adverse drug events included elevated lipase, amylase, rash or desquamation, diarrhea, and hand–foot skin reaction. A dose-limiting toxicity of hand–foot skin reaction was observed in one patient (cohort 2). Among the 24 patients evaluable for tumor response, one patient (4%) achieved a partial response, 20 (83%) had stable disease, and three (13%) had progressive disease. Sorafenib demonstrated a favorable tolerability and safety profile in Japanese HCC patients. Moreover, promising preliminary antitumor activity has been observed. Finally, there were no clinically relevant differences in PK between Child–Pugh A and B patients. (*Cancer Sci* 2008; 99: 159–165)

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Surgery and local ablation therapy, including radiofrequency, are considered curative treatment for HCC.[1–3] Transcatheter arterial chemoembolization (TACE) has been applied to patients with advanced incurable HCC.[3–5] The majority of patients, however, have recurrence or metastasis after these treatments. Although systemic therapy, including chemotherapeutic agents, is available for metastatic or TACE-refractory advanced HCC, the prognosis remains poor. No standard systemic therapy that prolongs survival has been identified.

Sorafenib (BAY 43-9006; Bayer HealthCare Pharmaceuticals, West Haven, CT, USA) was discovered based on its potent activity against Raf kinase in a battery of biochemical, cellular, and *in vivo* assays.[6,7] Extensive mechanism of action studies have shown that sorafenib may inhibit tumor growth through multiple mechanisms: by inhibiting tumor-cell proliferation that is dependent on activation of the mitogen-activated protein kinase (MAPK) pathway, and by inhibiting tumor angiogenesis through inhibition of vascular endothelial growth factor receptor (VEGFR)-2 and platelet-derived growth factor receptor (PDGFR)-β. Some evidence points to the MAPK signal-transduction pathway as playing an important role in tumor growth and progression in HCC.[8] Published data suggest that vascular endothelial growth factor (VEGF) also plays a critical role in angiogenesis of HCC, which is important for the growth and progression of HCC.[9] Sorafenib has been investigated in various solid tumors in clinical studies[10–15] and has been approved in many countries for the treatment of renal cell carcinoma. Promising results with sorafenib were recently observed in a phase II study in HCC patients.[15]

Various factors, such as liver function or disease extension, influence treatment selection and prognosis for HCC.[2,3,16] Etiology, underlying condition, and treatment for HCC vary across countries or regions.[2,3,17] Most HCC patients in Japan have hepatitis or cirrhosis due to hepatitis B or C virus[2] and suffer from complications of liver dysfunction, with potential changes in the activity of metabolic enzymes, a reduction in blood flow in the liver, or protein-binding ability due to low serum albumin. However, the degree of influence of these factors on the pharmacokinetics (PK) and tolerability of sorafenib in Japanese patients with HCC is unknown. A phase I study in Japanese patients with advanced solid tumors was conducted before the present study,[18] and found that sorafenib at 400 mg b.i.d. was well tolerable and recommended for phase II studies based on safety and efficacy data. To investigate the effect of liver dysfunction and its complications on the PK, safety, and tolerability of sorafenib in Japanese patients with HCC, a phase I study was conducted. The primary objective of the present study was to evaluate the PK of sorafenib, and the secondary objectives were to evaluate the safety and tolerability of sorafenib, tumor response, time to progression (TTP), and overall survival in Japanese patients with HCC.

Materials and Methods

Patient eligibility. The eligibility criteria for enrolment in the study were: (1) histologically confirmed HCC; (2) unresectable and incurable with ablation therapy or TACE; (3) age ≥ 20 years; (4) Eastern Cooperative Oncology Group performance status of 0 or 1; (5) adequate bone marrow (absolute neutrophil count ≥ 1500 cells/mm^3, platelet count ≥ 75 000 cells/mm^3, and hemoglobin ≥ 8.0 g/dL), coagulation (prothrombin time ≤ 1.5 × upper limit of normal [ULN] and activated partial thromboplastin time ≤ 1.5 × ULN), renal function (serum creatinine concentration ≤ 1.5 × ULN), and hepatic function (serum total bilirubin level ≤ 3.0 mg/dL, serum aspartate and alanine transaminase levels ≤ 5.0 × ULN); (6) cirrhotic status of Child–Pugh A or B; (7) life expectancy of at least 12 weeks; and (8) written informed consent from the patient.

Exclusion criteria included clinically evident congestive heart failure, serious cardiac arrhythmias, active or symptomatic coronary artery disease or ischemia, active clinically serious infections, seizure disorder requiring medication, history of organ allograft, prior malignancy (any cancer treated curatively

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doi: 10.1111/j.1349-7006.2007.00648.x

>3 years prior to entry was not excluded), metastatic brain or meningeal tumors, anticancer therapy within 3 months of study entry, and pregnancy or lactation for women. This protocol was approved by the National Cancer Center's institutional review board for clinical investigation with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Treatment methods. The dose for the first cohort was 200 mg bid sorafenib, and the dose for the second cohort was escalated to 400 mg bid. To investigate the PK profile of sorafenib, including its elimination phase, a single dose was given as one-time administration followed by a 7-day wash-out period. Subsequently, the drug was given twice daily for 28 days without a resting period (cycle 1). Either 200 mg or 400 mg sorafenib was given to all patients orally twice daily, in the morning and in the evening (every 12 h as far as possible). Patients were allowed to continue on sorafenib after cycle 1 if they consented to continue, and no intolerable adverse event was experienced, as assessed by investigators. Treatment was continued until disease progression, intolerable adverse event, or consent of withdrawal.

Examination and observation for safety was conducted every 2 weeks, and administration of the drug was to be terminated immediately when the patient met the criteria for removal from the study, described in this protocol with due consideration for the patient's safety.

Study design. The present study was a non-randomized, uncontrolled, non-blinded, single-center phase I study to investigate the PK, safety, and tolerability of sorafenib in Japanese patients with HCC. The dose level investigated in this study was 200 mg bid for the first cohort and 400 mg bid for the second cohort. Twelve patients, including six with Child–Pugh A and six with Child–Pugh B, were to be enrolled in each cohort. Tolerability was evaluated at the end of cycle 1 by Child–Pugh classification. If less than two out of six patients experienced dose-limiting toxicity (DLT) in the 200-mg bid cohort, the study would proceed to the 400-mg bid cohort. DLT that needed dose modification was defined as: (1) grade 3 and grade 4 non-hematological toxicity, except for pancreatic enzyme abnormality and hand–foot skin reaction; (2) grade 4 pancreatic enzyme elevation with values that persisted on two consecutive determinations with a 3-day interval, or clinical and/or imaging findings of pancreatitis, or pancreatic adverse event considered to be life threatening, or having a high risk of serious or chronic disorders; (3) severe hand–foot skin reaction, moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that caused the patient to be unable to work or carry out the activities of daily living; (4) grade 4 neutropenia (absolute neutrophil count less than 500/μL) for 7 days duration; (5) grade 4 neutropenia of any duration with fever of 38.5°C and above; and (6) platelet count < 25 000 cells/mm^3. Toxicity was graded according to the National Cancer Institute common toxicity criteria version 2.0. The independent safety committee for this study gave advice on the evaluation of tolerability of the dose level and the cohort transition.

Pharmacokinetics. All patients who received at least one dose of study medication were included in the PK analysis. Blood samples for the determination of plasma concentrations of sorafenib (and its metabolites) were collected prior to drug administration, as well as 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h after single-dose administration. For the first cycle, blood was sampled prior to the first dosing on days 1, 4, 7, 10, 14, 21, and 28, along with 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h after the first dose on days 14 and 28. Urine voided up to 48 h after single administration was collected.

Concentrations of sorafenib and its metabolites in plasma and urine were determined using validated liquid chromatography and tandem mass spectrometry methods. Plasma PK parameters were calculated by non-compartment analysis by the KINCALC program (Bayer HealthCare Pharmaceuticals).[10] Primary plasma PK parameters were area under the concentration–time curve (AUC), AUC for 0–12 h (AUC_{0-12}), and maximal concentration (C_{max}). Plasma concentrations and PK parameters were analyzed by dose and Child–Pugh classification.

Clinical assessments. Physical examination, complete blood cell counts, serum chemistries, and urinalysis were carried out at baseline and at least twice monthly after initiating treatment with sorafenib. Patients underwent dynamic computed tomography (CT) to evaluate tumor response at baseline, the end of cycle 1, and every two cycles thereafter. CT was carried out by obtaining contiguous transverse sections with the helical scanning method at a section thickness of 5 mm. Tumor evaluation was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST).[19]

Statistical analysis. The data were analyzed using SAS (SAS Institute, Cary, NC, USA). The safety and efficacy were evaluated on an intention-to-treat basis. Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression, or death due to any cause. Overall survival was calculated from the first day of treatment until death due to any cause. Survival data were analyzed using the Kaplan–Meier method.

Results

Patient characteristics and treatments. From April 2004 through January 2005, a total of 27 patients were enrolled in the present study. Thirteen patients were enrolled at the treatment level of 200 mg (cohort 1) and 14 at the treatment level of 400 mg (cohort 2) twice daily (b.i.d.) for 28 days (cycle 1). One out of 13 patients in cohort 1 discontinued the study due to consent withdrawal after single-dose administration. One out of 14 patients in cohort 2 dropped out of this study due to adverse events during cycle 1. Patient characteristics are shown in Table 1. The median number of cycles administered per patient was five (range, 1–13 cycles). None of the patients from the 200-mg group reduced the dose of sorafenib, whereas two patients required dose reduction in the 400-mg group.

Evaluation of PK. Plasma drug concentrations were analyzed in 27 patients in the PK analysis. Plasma PK parameters of patients in the 200 and 400 mg bid groups are shown in Tables 2 and 3. There was a large interpatient variability in the PK of sorafenib. Geometric means of AUC, AUC_{0-12}, and C_{max} on day 1 of single-dose administration were not statistically different between 200 and 400 mg bid or between Child–Pugh A and B. Dose-dependent increases in AUC_{0-12} and C_{max} were observed at steady state (day 14) in the 200-mg bid and 400-mg bid patients; however, these increases were not dose proportional. Geometric means of AUC_{0-12} and C_{max} were slightly lower in the Child–Pugh B patients compared with the Child–Pugh A patients at steady state. The $t_{1/2}$ after single dose was similar between the Child–Pugh A and B groups for both dose levels.

Dose-dependent increases in the AUC_{0-12} and C_{max} of metabolites M-2 (*N*-oxide), M-4 (*N*-demethyl), and M-5 (*N*-oxide, desmethyl derivative) were observed. M-2 was the main metabolite in plasma. Ratios of each metabolite to the sum of all analytes were similar between the 200-mg bid and 400-mg bid patients and for baseline Child–Pugh class (Tables 2,3). M-7 (glucuronide of sorafenib) and M-8 (glucuronide of M-2) were detected in urine though no unchanged substance or M-2 was detected. There was no difference between the Child–Pugh A (1.21% for M-7 and 0.02% for M-8 at 400 mg) and B (1.18% and 0.02%, respectively, at 400 mg) groups in the urinary excretion rate of compounds at steady state. Interestingly, these PK results were similar to those obtained from the Japanese phase I study in non-HCC tumors.[18]

Adverse events. Adverse events of all 27 patients are shown in Table 4. Twenty-six out of 27 patients (96.3%) experienced an adverse event: 12 out of 13 patients (92.3%) in the 200-mg

doi: 10.1111/j.1349-7006.2007.00648.x

Table 1. Patient characteristics

Characteristic	200 mg bid (n = 13)	400 mg bid (n = 14)	Total (n = 27)
Sex (n)			
Male	12	13	25
Female	1	1	2
Median age (years)	69 (range 48–77)	70 (range 63–79)	70 (range 48–79)
Eastern Cooperative Oncology Group performance status			
0	13	14	27
Child–Pugh classification			
A	7	6	13
B	6	8	14
Viral markers			
HB antigen$^+$, HCV antibody$^-$	3	1	4
HB antigen$^-$, HCV antibody$^+$	9	11	20
HB antigen$^-$, HCV antibody$^-$	1	2	3
Previous treatment			
–	1	3	4
+	12	11	23
Tumor stage			
II	1	2	3
III	7	8	15
IVa	1	1	2
IVb	4	3	7
Portal vein tumor thrombus			
–	12	13	25
+	1	1	2
Metastasis			
–	9	11	20
+	4	3	7
Lung	3	1	4
Lung + lymph node	1	1	2
Lymph node	0	1	1

HB, hepatitis B; HCV, hepatitis C virus.

Table 2. Pharmacokinetic parameters of sorafenib and metabolites M-2, M-4, and M-5: sorafenib following single dose and multiple dose of 200 mg and 400 mg geometric mean (coefficient of variation)

Sorafenib	Parameter	Unit	200 mg bid				400 mg bid			
			Child–Pugh A		Child–Pugh B		Child–Pugh A		Child–Pugh B	
Single	n		7		6		6		8	
Dose	AUC	mg*h/L	28.29	190.29[‡]	18.64	74.1	20.33	90.31	26.87	96.97
Day 1	AUC_{0-12}	mg*h/L	5.02	190.36	2.75	61.06	3.82	86.06	3.11	88.16
	C_{max}	mg/L	0.81	195.96[‡]	0.49	67.85	0.55	83.75	0.53	86.68
	T_{max}	h[†]	7	3–12[‡]	18	4–24	8	6–24	24	4–24
	$T_{1/2}$	H	25.14	30.13[‡]	30.44	35.67	22.28	12.49	27.2	45.19
Cycle 1	N		6		6		6		6	
Day 14	AUC_{0-12}	mg*h/L	25.52	75.04	15.28	55.26	33.47	60.13	29.45	59.44[§]
	C_{max}	mg/L	3.36	87.29	1.89	62.14	4.66	66.12	3.04	94.39
Cycle 1	N		6		6		6		5	
Day 28	AUC_{0-12}	mg*h/L	31.63	101.64	20	73.4	28.91	86.79	20.71	72.06
	C_{max}	mg/L	4.22	92.32	3.32	78.65	3.32	113.47	4.01	79.12

[†]Median (range), [‡]n = 6, [§]n = 5. AUC_{0-12}, area under the concentration–time curve for 0–12 h.

group and 14 out of 14 patients (100%) in the 400-mg group. The most common drug-related adverse events were elevated lipase or amylase (88.9%), dermatological events (81.5%), and gastrointestinal events (70.4%). Common dermatological events were rash or desquamation (55.6%), and hand–foot skin reaction (44.4%). The incidence of adverse events in the 400-mg dose level was higher than that in the 200-mg dose level by ≥20%. These events fell under the categories of dermatology/skin (100.0 *vs* 61.5%), general cardiovascular (35.7 *vs* 7.7%), and renal/genitourinary (21.4 *vs* 0%).

Elevation of lipase and amylase was transient in most of the cases, and decreased gradually in all patients without treatment. One patient on 400 mg bid experienced acute pancreatitis that necessitated sorafenib withdrawal. The patient experienced abdominal pain 6 months after beginning treatment (cycle 6). Moreover, high lipase and amylase, as assessed by blood test,

Table 3. Pharmacokinetic parameters of sorafenib and metabolites M-2, M-4, and M-5: metabolites following multiple dose of 200 mg and 400 mg, measured at steady state (cycle 1, day 14) geometric mean (% coefficient of variation)

Parameter	200 mg bid			400 mg bid		
	M-2	M-4	M-5	M-2	M-4	M-5
Child–Pugh A						
n	6	6	6	6	6	6
AUC_{0-12} (mg × h/L)	4.18 (126)	0.92 (158)	0.79 (167)	6.18 (127)	1.68 (159)	1.22 (193)
Ratio† (%)	13.08 (30)	2.89 (60)	2.48 (81)	14.16 (39)	3.85 (55)	2.79 (85)
Child–Pugh B						
n	6	5	4	5	5	5
AUC_{0-12} (mg × h/L)	1.62 (173)	0.36 (131)	0.44 (351)	5.67 (90)	2.13 (142)	1.25 (117)
Ratio† (%)	9.05 (67)	1.85 (42)	1.95 (157)	14.46 (36)	5.44 (56)	3.19 (47)

†Median ratio of each metabolite to sum of all analytes. BAY 43-9006: M-2, BAY 67-3472; M-4, BAY 43-9007; and M-5, BAY 68-7769. AUC_{0-12}, area under the concentration–time curve for 0–12 h.

Table 4. Adverse events

Child–Pugh	Grade 3/4				All grades			
	200 mg bid		400 mg bid		200 mg bid		400 mg bid	
	A (*n* = 7)	B (*n* = 6)	A (*n* = 6)	B (*n* = 8)	A (*n* = 7)	B (*n* = 6)	A (*n* = 6)	B (*n* = 8)
Hematological								
Leukocytopenia	0	0	0	0	2 (29%)	0	1 (17%)	0
Lymphopenia	2 (29%)	1 (17%)	1 (17%)	1 (13%)	2 (29%)	1 (17%)	1 (17%)	2 (25%)
Platelets	0	0	1 (17%)	1 (13%)	0	1 (17%)	2 (33%)	3 (38%)
Non-hematological								
Hypertension	0	1 (17%)	1 (17%)	3 (38%)	0	1 (17%)	1 (17%)	3 (38%)
Fatigue	0	0	0	0	0	1 (17%)	0	0
Fever	0	0	0	0	1 (14%)	2 (33%)	0	1 (13%)
Weight loss	0	0	0	0	2 (29%)	1 (17%)	1 (17%)	4 (50%)
Hand–foot skin reaction	0	0	0	2 (27%)	2 (29%)	2 (33%)	5 (83%)	3 (38%)
Rash	0	0	0	2 (27%)	2 (29%)	3 (50%)	4 (67%)	6 (75%)
Alopecia	0	0	0	0	2 (29%)	1 (17%)	2 (33%)	0
Dry skin	0	0	0	0	0	0	0	3 (38%)
Pruritus	0	0	0	0	0	1 (17%)	4 (67%)	3 (38%)
Anorexia	0	0	0	0	2 (29%)	1 (17%)	1 (17%)	2 (25%)
Diarrhea	0	0	1 (17%)	0	4 (57%)	4 (67%)	2 (33%)	5 (63%)
Stomatitis	0	0	0	0	0	0	1 (17%)	2 (25%)
Lipase	3 (43%)	4 (67%)	4 (67%)	6 (75%)	6 (86%)	6 (100%)	6 (100%)	6 (75%)
Amylase	1 (14%)	1 (17%)	1 (17%)	1 (13%)	4 (57%)	3 (50%)	4 (67%)	5 (63%)

and swelling of the pancreas were observed. The patient's abdominal pain resolved 1 day after stopping sorafenib, and lipase and amylase normalized 2 days later. Sorafenib was restarted 20 days after resolution and continued over 122 days, without recurrence of pancreatitis.

Grade 3 or worse drug-related adverse events were observed in 23 patients (85.2%), the majority of which were related to laboratory abnormalities: 10 patients in the 200-mg group and 13 in the 400-mg group. One patient with Child–Pugh B in the 400-mg bid group experienced DLT of hand–foot skin reaction at the end of cycle 1. There were no drug-related deaths in either of the groups.

There was no major difference in the incidence and grade of drug-related adverse events between the Child–Pugh A and B groups. At the dose level of 200 mg, the drug-related adverse event whose incidence was at least 20% higher in the Child–Pugh B group than in the Child–Pugh A group was rash or desquamation (50.0 *vs* 28.6%). The differences at the 400-mg dose level were diarrhea (62.5 *vs* 33.3%), weight loss (50.0 *vs* 16.7%), hypertension (37.5 *vs* 16.7%), dry skin (37.5 *vs* 0%), and fatigue (25.0 *vs* 0%).

Table 5. Tumor response

Response	200 mg bid (*n* = 13)	400 mg bid (*n* = 14)	Total (*n* = 27)
Partial response	1	0	1 (3.7%)
Stable disease	10	11	21 (77.8%)
Progressive disease	1	2	3 (11.1%)
NA	1	1	2 (7.4%)

NA, not assessed because these patients did not complete cycle 1.

Tumor response and survival. Partial response was achieved in one of the 27 patients. No complete response was observed (Table 5; Fig. 1). The overall response rate was 3.7% (95% confidence interval, 0.1–14.0%). Stable disease was noted in 21 patients (77.8%) and the disease control rate (partial response + stable disease rate) was 81.5% in 27 patients. Progressive disease was noted in three patients (11.1%).

Disease progression or death was observed in all patients. Sixteen of the 27 patients died of disease progression, and two

doi: 10.1111/j.1349-7006.2007.00648.x

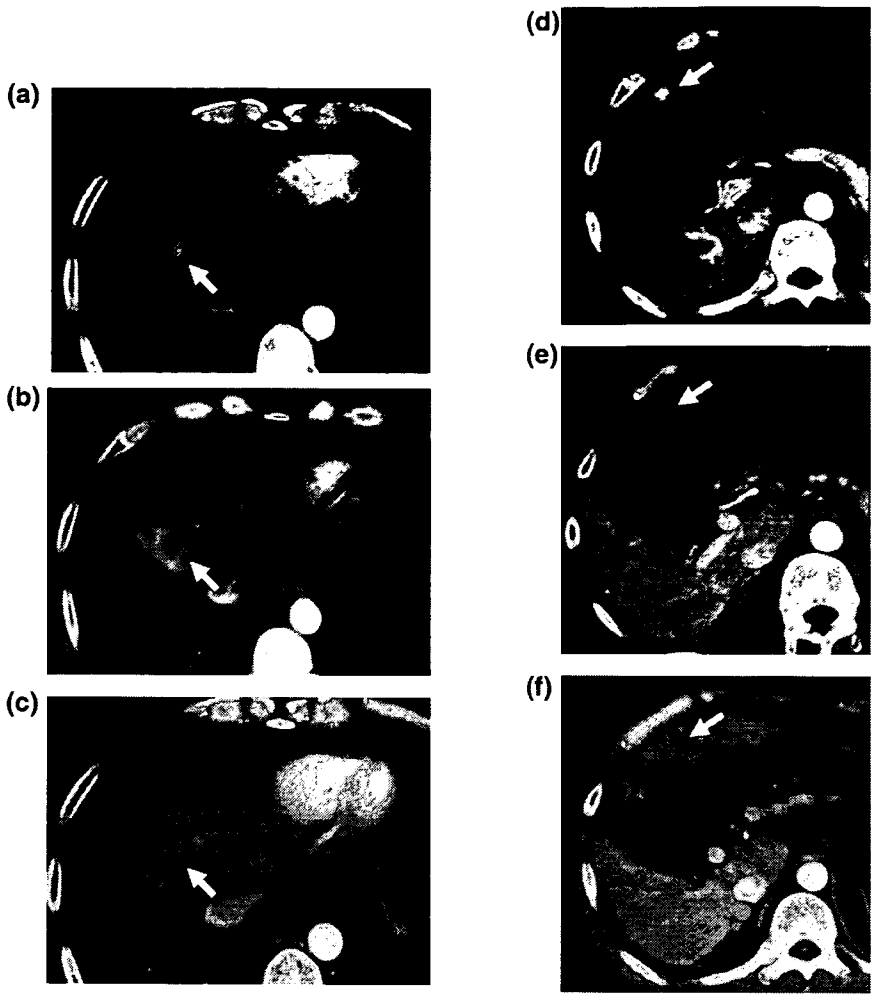

Fig. 1. A 48-year-old man with multiple tumors of hepatocellular carcinoma (HCC) after hepatectomy, percutaneous ethanol injection, and transcatheter arterial embolization. (a) Hypervascular HCC lesion, 1 cm in diameter, was revealed at the early phase of dynamic computed tomography (CT) before administration of sorafenib at the anterior superior segment of the liver (arrow). (b) The vascularity of this tumor disappeared 1 month after the administration of sorafenib. (c) The tumor was reduced 3 months after the administration of sorafenib. (d) Another hypervascular HCC lesion, 1 cm in diameter, was revealed at the early phase of dynamic CT before administration of sorafenib in the left lobe of the liver (arrow). (e) The vascularity of this tumor disappeared 8 months after the administration of sorafenib. (f) The tumor almost completely disappeared 10 months after the administration of sorafenib.

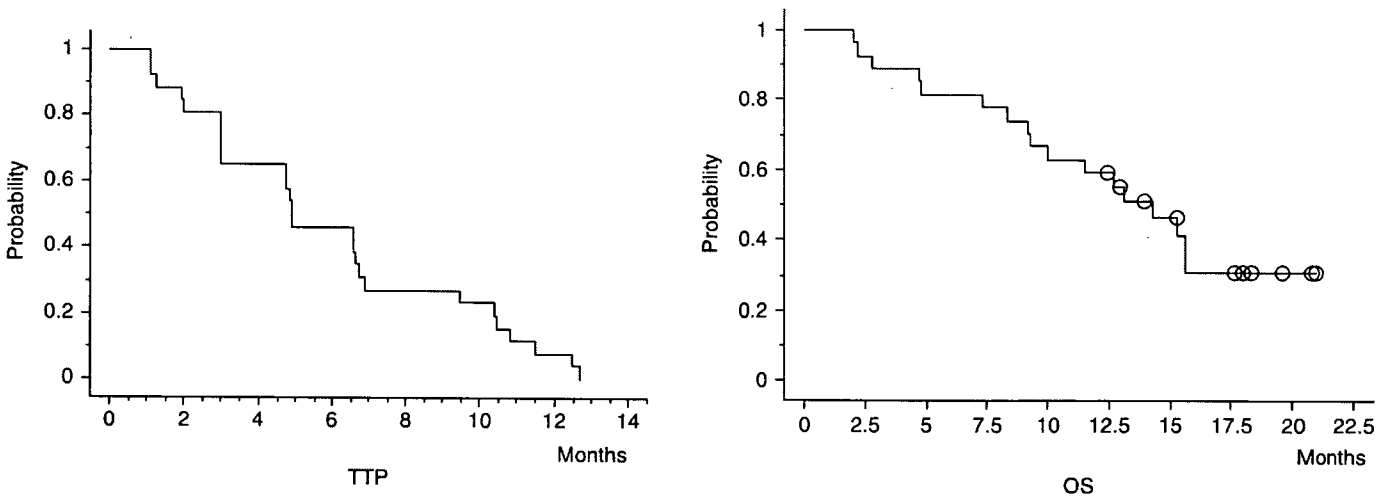

Fig. 2. Time to progression (TTP) in all 27 patients treated with sorafenib. The median TTP was 4.9 months, and the 6-month survival rate was 46.2%. Overall survival (OS) in the 27 patients treated with sorafenib. The median OS period was 15.6 months, and the 1-year survival rate was 59.3%.

died of cerebral infarction or myocardial infarction. Of the 27 patients, the median TTP was 4.9 months, and the median overall survival (OS) was 15.6 months (Fig. 2). The 6-month progression-free rate based on TTP was 46.2%, and 1- and 2-year OS were 59.3 and 30.9%, respectively.

Discussion

The PK, safety, and tolerability of sorafenib were investigated in Japanese patients with HCC treated with doses of 200 mg bid or 400 mg bid.

Most of the HCC patients had hepatitis or cirrhosis with underlying liver disorder and a reduction in hepatic blood flow to various degrees. Liver dysfunction in patients with HCC may affect the PK of sorafenib. When comparing the PK by Child–Pugh classification, geometric means of AUC_{0-12} and C_{max} at steady state were lower in the Child–Pugh B group than in the Child–Pugh A group, whereas after multiple doses of sorafenib, the mean plasma concentrations were highly variable and showed no clear dose dependency. Although the numerical differences in geometric means for PK parameters such as AUC, C_{max}, and $t_{1/2}$ were observed between Child–Pugh classifications, these differences were considered not to be clinically relevant in consideration of their large intersubject variability. No significant difference in clinical findings between these two groups was observed. There was also no major difference (i.e. over 20%) in the incidence of adverse events between Child–Pugh A and B groups. However, geometric means of AUC_{0-12} and C_{max} at steady state were slightly lower in the Child–Pugh B patients compared with the Child–Pugh A patients.

There were no remarkable differences in the overall incidence of adverse events for each dose level (92% for the 200-mg group and 100% for the 400-mg group). For a few drug-related adverse events, the incidences were at least 20% higher in the 400-mg group than in the 200-mg group, including rash or desquamation (71.4 *vs* 38.5%), hand–foot skin reaction (57.1 *vs* 30.8%), pruritus (50.0 *vs* 7.7%), decrease of platelets (35.7 *vs* 7.7%), hypertension (28.6 *vs* 7.7%), dry skin (21.4 *vs* 0%), and stomatitis or pharyngitis (21.4 *vs* 0%). DLT of hand–foot skin reaction was observed in a patient with Child–Pugh B at the end of cycle 1 with 400 mg bid, whereas no DLT was observed in the 200-mg bid group.

The most common drug-related adverse events were elevated lipase (88.9%) and amylase (59.3%). Twenty-four (88.9%) of the 27 patients showed high values of grade 3 or worse. Most of the patients were asymptomatic and only one patient had abdominal pain with findings to indicate pancreatitis on ultrasonography during cycle 6. His pancreatitis resolved shortly after discontinuation of sorafenib, and the patient restarted and continued with a reduced dose of sorafenib after recovery.

A separate phase I clinical study was carried out to evaluate the safety of sorafenib in patients with solid tumor, excluding HCC, at doses of 100, 200, 400, and 600 mg bid.[18] In that study, the most common type of adverse events included skin reaction, elevation of pancreatic enzyme, and gastrointestinal (GI) toxicity such as diarrhea. In the current study, a similar pattern of adverse events was observed. These results suggest that 'gastrointestinal' and 'dermatology/skin' are common adverse events regardless of cancer type and liver function status. One finding to note is that the incidence of elevation (grade 3/4) of lipase (63.0%) or amylase (14.8%) in the present study in HCC patients was higher than that observed in non-HCC patients (lipase 23% and amylase 10%).[18]

In summary, the present study showed no clinically significant difference in PK, safety, tolerability, or efficacy by Child–Pugh status or between HCC patients and non-HCC patients, whereas some dose dependency in adverse events was observed.

Investigations into cytotoxic agents for HCC have been conducted.[20,21] However, no standard chemotherapy has been established. Recently, a number of agents targeting growth factors were investigated in HCC. Through these investigations, it was indicated that epidermal growth factor receptor/human epidermal growth factor receptor 1 (EGFR/HER1) is actively expressed in human hepatoma cells.[22,23] Erlotinib, which is an EGFR/HER1 tyrosine kinase inhibitor, and lapatinib, which is an EGFR/HER1 and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, have been investigated in phase II studies in HCC patients.[24–26] For erlotinib, the response rate was 4–9%, the median TTP was 2.1–3.2 months, and the OS was 5.8–13 months,[24,25] whereas for lapatinib, the response rate was 0%, and the median progression-free survival time was 1.8 months.[26]

Hepatocellular carcinoma, given its hypervascular characteristics, may be sensitive to antiangiogenic agents.[9] It is known that VEGF augments the development and metastasis of HCC. Bevacizumab, a monoclonal antibody against VEGF, has been investigated in phase II studies.[27] The response rate with bevacizumab was 10% and the disease control rate was 80%. A combination of gemox (gemcitabine plus oxaliplatin) and bevacizumab showed a better response rate of 20%.[28]

Sorafenib, an orally active multikinase inhibitor, blocks tumor-cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGFR-2, VEGFR-3, and PDGFR-β tyrosine kinases. In phase II studies in non-Japanese and Japanese HCC patients, comparable median TTP of 4.2 and 4.9 months, respectively, and response rates of 2 and 4%, respectively, were shown.[15] However, OS in the two studies were different: 9.2 months in the non-Japanese study and 15.6 months in the Japanese study. Difference in backgrounds such as liver function or treatment after progression may play a role in this discrepancy in survival time.

In the current study, one patient achieved partial response (Fig. 1). The patient had several small viable HCC lesions after hepatectomy, percutaneous ethanol injection, and TACE. Following administration of sorafenib, tumor vascularity decreased dramatically preceding a gradual tumor reduction. Time to tumor shrinking varied across lesions, ranging from 1 to 8 months after initiation of treatment with sorafenib. It is likely that, with anti-VEGF agents such as sorafenib, it may take time to achieve tumor reduction to meet partial response by RECIST, whereas the duration of stable disease may persist due to its tumor stabilization activity.

With the relatively long TTP of VEGF pathway-targeting agents such as bevacizumab or sorafenib, these agents may have antitumor effects on HCC and prolong survival. With its profile of tumor stabilization and tolerability, sorafenib may be applicable not only for advanced HCC but also for the adjuvant setting after curative treatment, such as surgery or radiofrequency ablation therapy.

In conclusion, in the present phase I study, sorafenib demonstrated favorable safety and tolerability, and promising preliminary antitumor activity in Japanese HCC patients. Considering that DLT was observed in one of 14 patients treated with 400 mg bid, 400 mg bid could also be recommended for future studies in Japanese HCC patients, as well as non-HCC Japanese and Caucasian patients. However, as the number of patients was limited in this phase I study, a confirmatory study will be required with a larger number of patients.

Acknowledgments

This study was supported by Bayer Yakuhin.

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