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Summary

Hepatic Arterial Infusion Chemotherapy for Liver Metastasis from Gastrointestinal Cancer

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Hepatic arterial infusion chemotherapy has been recognized as a hopeful therapeutic strategy for liver metastasis treatment in periods of underpowered systemic chemotherapy. However, clinical trials have failed to show survival benefits of hepatic arterial infusion chemotherapy. Thus, in a period when systemic chemotherapy is showing significant advances, the use of hepatic arterial infusion chemotherapy should be limited to uncontrolled liver metastasis by systemic chemotherapy and to special situations where it can be used due to evidence obtained from clinical studies. On the other hand, the results of clinical studies must be considered based on a deep understanding of techniques for hepatic arterial infusion chemotherapy. If advances in systemic chemotherapy fail to control liver metastasis, a reappraisal of hepatic arterial infusion chemotherapy may be required.

Key words : liver metastasis, hepatic arterial infusion chemotherapy, colorectal cancer, gastric cancer

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4 大腸癌肝転移に対する肝動注化学療法の位置づけ

荒井　保明

はじめに

肝転移は進行・再発大腸癌症例の予後を規定する重要な要因の一つである．肝動注化学療法はこの肝転移に対する治療法として，全身化学療法に比べ大きな可能性をもつと期待されてきた．しかし，これは5-fluorouracil（5-FU）以外に有効な薬剤のない時代における期待であり，irinotecan（CPT-11）やoxaliplatin（L-OHP），さらには分子標的治療薬などの出現により全身的薬物療法が著しく進歩している現在，その扱いもこのような状況の変化に対応して柔軟に変化させていく必要がある．

本稿では，種々の臨床試験で得られたエビデンス，ならびにこれらのエビデンスを解釈するうえで必要なこの治療のもつ特殊性を解説し，そのうえで激動しつつある大腸癌治療における肝動注化学療法の扱いを述べる．

I 肝動注化学療法の理論と技術

動注化学療法の薬理学的有利性については，局所薬剤濃度の上昇による効果の増強（increased local concentration without first pass effect）と注入された薬剤の全身循環への逸脱低下による副作用の軽減（first pass effect）の二点から説明されており，5-FUにおける経動脈的投与の有利性は静注投与の場合の約40倍とされている[1]．一方，実際の臨床において，この理論的な有利性を発現させるためには，技術的問題として以下の三点が必要となる．

第一点は，「至適薬剤分布の確保」である．標的とする腫瘍に薬剤が確実に分布することはこの治療が効果を上げるうえで必須であるが，他方，高濃度の薬剤が肝以外の隣接臓器に流入すれば重篤な合併症を惹起するため，これを避けることも必要である．この両者を満足する「至適薬剤分布の確保」，すなわち投与された薬剤が肝のすべての病巣に到達し，肝以外の隣接臓器に流入しないことはきわめて重要な条件である．

第二点は，「至適薬剤分布による投与を反復施行するための技術」である．肝動脈に薬剤投与を繰り返すためにはカテーテルの留置が必須であるが，その手法については欧米と本邦で大きな相違があり，欧米では開腹下での外科的カテーテル挿入留置が，本邦ではIVR技術を用いた経皮的カテーテル留置[2),3)]が標準となっている．

第三点は，「薬剤分布の評価と維持」である．肝転移病巣への動脈血供給は肝動脈のみからと誤解されがちであるが，実際には肝動脈以外に肝周囲の血管から種々の寄生動脈が動脈血を供

給することが知られており[4)~6)]，さらには治療の継続に伴いこれら寄生動脈の関与も変化する．このため，肝動注化学療法の施行にあたっては定期的に薬剤分布を評価し，必要があればこれを修正する技術が要求され，本邦では留置カテーテルからの造影下CT（CTA）による評価ならびに血管撮影手技による修正の必要性が広く認識されている．

薬理学的理論から示される肝動注化学療法の有利性は，あくまでこのような技術的裏づけのもとに成立するものであり，肝動注化学療法の位置づけを考えるうえでは，これら肝動注化学療法における技術の重要性を十分に理解して臨む必要がある．

II 臨床試験における結果

1. 欧米の臨床試験

1980年代後半から，肝外病変のない切除不能大腸癌肝転移症例を対象にフッ化ピリミジン系薬剤を用いた全身化学療法との比較試験七つ[7)~13)]が報告された（表I-4-1）．

米国で行われた五つの試験では，肝転移に対する奏効率42～62%と肝動注群が明らかに良好であったが，生存期間中央値（MST）は12.8～17カ月であり，全身化学療法群と有意差は認められなかった．仏，英で行われた比較試験では，肝動注群のMSTは前者が15カ月，後者が13.5カ月であり，前者では2年生存率で，後者ではMSTで，肝動注群が対照群に比べ有意に良好であると報告されたが，ともに対照群に無治療例が含まれており，仏の試験ではMSTに有意差がなかったこと，英の試験では対照群のMSTが7.5カ月とあまりに短かったことなどから，総合的には「肝動注は全身化学療法との比較において予後延長に寄与しない」と判断される結果となった．これら七つの比較試験については，メタ・アナリシスも行われたが，奏効率は肝動注群が明らかに優れていることが立証されたが，全身化学療法を受けた対照群との生存期間には有意差は認められなかった[14)]．

2000年代に入り，再び三つの報告がなされた．Lorenzらの168例を対象とした5-FUと

表I-4-1　大腸癌肝転移に対する肝動注（ia）対全身化学療法（iv）の比較試験結果概要

	報告年	症例数 (ia/iv)	薬剤 (ia/iv)	奏効率（%） (ia/iv)	生存期間中央値（月） (ia/iv)
City of Hope[7)]	1985	9/6	FUDR/5-FU	55/20 (0.2)	13.8/11.6 (NS)
NCCTG[8)]	1987	39/35	FUDR/5-FU	48/21 (0.02)	12.6/12.5 (0.53)
MSKCC[9)]	1987	46/49	FUDR/FUDR	62/20 (0.001)	17/12 (0.4)
NCI[10)]	1989	32/32	FUDR/FUDR	62/17(<0.003)	17/12 (0.27)
NCOG[11)]	1990	67/76	FUDR/FUDR	42/10 (0.0001)	16.7/16.1 (NS)
France[12)]	1992	81/82	FUDR/5-FU	49/49	15/11：2年生存率23/13% (<0.02)
UK-HAPT[13)]	1994	51/49	FUDR/－(control)		405日/226日 (0.03)
Germany[15)]	2000	57/57	FU-LV/FU-LV		18.7/17.6 (NS)
UK[16)]	2000	41/43	FUDR＋FU-LV/FU-LV		390/340日 (0.79)
UK[17)]	2003	145/145	de Gramont		14.7/14.8 (NS)

leucovolin（LV）の肝動注，fluorodeoxyuridine（FUDR）の肝動注，5-FUとLVの静注3群の比較試験では，MSTは5-FU/LV肝動注群で18.7カ月，FUDR肝動注群で12.7カ月，5-FU/LV静注群で17.6カ月であり，FUDR肝動注群は有意に不良で，5-FU/LV肝動注と5-FU/LV静注とでは差がなかった[15]．Allen-Mershらも84例を対象としたFUDR肝動注＋5-FU/LV静注と5-FU/LV静注との比較試験において，肝動注の併用が予後を改善することはないと報告し[16]，さらにKerrらは，290例を対象に5-FU/LVを初めに急速注入後，5-FUを2日間かけて持続注入するいわゆるde Gramontレジメンをベースとする投与法の肝動注と静注との比較試験を行い，MSTは肝動注群で14.7カ月，静注群で14.8カ月であり有意差はないと報告した[17]．

2. 本邦の臨床試験

全身化学療法との比較試験により大腸癌肝転移に対する1st-lineの治療法としての肝動注化学療法を評価しようとする試験は本邦では行われていない．本邦ではFUDRが承認されず，また欧米で用いられていた埋め込み型の持続注入ポンプの入手が困難であったため，5-FUの間欠的な投与法が検討され，Araiらにより大量5-FU週1回5時間持続肝動注化学療法（Weekly High-dose 5-FU：WHF肝動注療法）が開発され[18]，現在まで本邦における肝動注化学療法の標準的な投与スケジュールとして用いられている．

その治療成績は，あくまで第II相試験としての結果であるが，肝転移が予後規定因子と判断された肝外病変を有す11例を含む32例において，奏効率75%，MST 22カ月〔肝外病変（−）例では25カ月〕であった．続いて行われた画像上肝外病変のない30例を対象とした第II相試験では，奏効率83%，MST 26カ月であった[19]．他方，肝外病変（＋）例を含む133例を対象に行われたJapan Hepatic Arterial Infusion Study Group（JHAISG）による多施設共同研究では，奏効率52%，MST 16.3カ月〔肝外病変（−）例では17.9カ月〕であった[20]．

このように，本邦の試験では，上述の欧米の比較試験の動注化学療法の成績に比べかなり良好な結果が示されたが，いずれも第II相試験であり全身化学療法との比較試験が行われていないため，肝動注化学療法の扱いを示すエビデンスは得られていない．

III 臨床試験の結果に対する解釈

1. エビデンスとしての重み

欧米で行われた1980年代後半から現在までの10の比較試験のすべてにおいて，「肝動注は全身化学療法との比較において予後延長に寄与する」という評価は一度も下されていない．これはIaのエビデンスであり，少なくとも「肝動注化学療法を切除不能大腸癌肝転移に対する1st-lineの治療として扱うエビデンスはない」と言える．

一方，肝転移に対する腫瘍縮小効果に限るならば，肝動注化学療法は全身化学療法に比べ優れていることが確認されている[14]．

また，個々の比較試験は肝動注化学療法の劣性を証明したものではないため，肝動注化学療法が全身化学療法に比べ「生存期間の点で劣っている」と結論するものでもない．しかし，これらの試験における対照群の全身化学療法が，フッ化ピリミジン系薬剤の単独あるいはこれにロイコボリンを加えたものであり，MSTが12〜16カ月であった点を考慮すれば，infusional 5-FUをベースとしCPT-11やL-OHPを加えることにより奏効率が50%近く，MSTが20カ月前後に達している最近の全身化学療法に比べ，生存期間において肝動注化学療法が劣っていない可能性はより少なくなって

いると考えられる．

2. 技術面からみたエビデンスとしての問題点

他方，欧米におけるこれらの臨床試験については，前述した肝動注化学療法の技術的特殊性から以下の3点を指摘することができる．第一点は，肝動注のためのカテーテル留置がすべて全身麻酔下の開腹術により行われている点，第二点は，薬剤分布の評価がまったく行われていない点，第三点は治療継続期間の短い点である．

たとえば，Kerrらの試験[17]では，肝動注群の患者の37%がカテーテル留置不能や開腹術後の全身状態悪化で肝動注が開始されておらず，さらに29%では予定されていた2週間毎6コースの治療がカテーテルトラブルのため中央値で2コースしか施行できずに静注治療に変更されている．また，カテーテル留置後の薬剤分布についての評価も行われていない．これに対し，本邦で独自の発展を遂げた肝動注化学療法のための経皮的技術の場合，実行性についてはYamagamiらは93例に対し97%で肝動注が開始できたことを[21]，Tanakaらは426例を対象にカテーテル留置成功率99.8%と肝動脈の1年開存率81.4%，2年開存率58.1%[3]を，またSekiらは49例を対象に1年開存率78.4%[22]を報告している．すなわち，肝動注化学療法に必須のカテーテル留置手技の実行性については欧米と本邦の間に大きな乖離が存在している．加えて，本邦では薬剤分布についても入念な評価と修正の技術が一般化しているため，欧米の臨床試験における動注化学療法の成績を懐疑的に見る傾向が生じている．

3. 肝動注化学療法の限界

欧米[23]ならびに本邦の臨床試験[19),20]において共通しているのは，肝外病変の進展が予後を規定しているという点である．注入薬剤の全身循環への流出があるとはいえ，肝動注化学療法があくまで肝に対する局所療法であり，「肝外病変を制御しえない」という点で肝動注化学療法に明らかな限界のあることが確認されている．

以上より，臨床試験で示された結果ならびに肝動注化学療法の特殊性を考慮した臨床試験結果に対する上述の解釈に基づけば，現時点における肝動注化学療法は以下のように総括される．

1）施行には適切な技術が必要である．
2）肝転移に対する腫瘍縮小効果は全身化学療法に比べ高い．
3）肝外病変に対する効果はない．
4）肝外病変のない症例に対しても，1st-line治療とする根拠はない．

IV 肝動注化学療法の位置づけ

臨床試験で得られたエビデンスに基づくかぎり，大腸癌肝転移症例に対する肝動注化学療法の採用が許容される場面はきわめて限られている．しかし，実際には臨床試験における対象から逸脱するような，あるいは臨床試験の結果をそのまま外挿できないような状況も少なくない．そこで，可能なかぎり上述した臨床試験の結果に対する解釈に基づき，実臨床における肝動注化学療法の扱いが考慮される具体的な状況を列挙する．

1. 肝転移が予後規定因子で，かつ全身化学療法が無効の場合

肝動注化学療法を支持するエビデンスが示されていない現在，肝動注化学療法の採用がもっとも正当化されるのがこの状況である．全身化学療法が大きく進歩したとはいえ，その効果にも限界がある以上，この状況が生じる頻度は少なくない．ただし，「全身化学療法が無効」と判断するためには，少なくとも本邦で可能なinfusional 5-FUあるいは5-FU系薬剤による十分な治療とCPT-11による治療が前提とされるべきであろう．

なお，「無効」とは言えないまでも，肝転移による肝機能上昇などにより，これらの標準的全身化学療法の施行が困難な場合もこれに該当すると考えられ，肝動注化学療法の採用は許容されると考えられる．また，この状況下においては，肝外病変の有無は肝動注化学療法の採用に影響しないと考えられる．

2. 肝転移が切迫した予後規定因子の場合

前述のごとく，肝外病変がなく肝転移のみの場合であっても，肝動注化学療法を 1st-line 治療とするエビデンスはない．しかし，肝転移の程度が重度で，予後規定因子としての肝転移が切迫した状況にある症例を対象とした臨床試験があるわけではない．このため，「肝転移に対する腫瘍縮小効果が全身化学療法に比べ高い」ことを根拠に，このような症例に対し肝動注化学療法を 1st-line 治療として行うことは許容される可能性がある．この場合の肝動注化学療法は，肝転移に対する緊急避難的治療としての採用であり，肝外病変の有無は判断に影響しない．

ただし，肝転移に対する腫瘍縮小効果が低いとはいえ，全身化学療法によっても肝転移が制御される可能性はあるわけであり，エビデンスのない選択としての十分な説明と同意のうえで行うべきである．

3. 肝外病変の有無を問わず肝転移が主たる病巣の場合

肝転移が主たる病巣の症例に対し，肝転移ならびに肝外病変をともに制御しようとする観点から全身化学療法との併用で肝動注化学療法を採用することは，許容されるかもしれない．

ただし，実際的な投与法やその安全性，効果は確認されていない．このため，あくまで臨床試験，あるいはこれに準ずる試験的な治療として，十分な説明と同意の下に行われるべきである．

4. 肝転移が予後規定因子あるいは主たる病巣でない場合

肝転移に対する局所療法を支持する根拠は皆無であり，肝動注化学療法の適応とはならない．

V 考慮すべき事項

肝動注化学療法の適応を判断するうえでは，以下の点に注意を払うべきである．

1. 適切な技術で施行できるか否か

肝動注化学療法に必須の種々の技術は，本邦ではかなり普及しているが，なお特殊なものであり，治療として活用する場合にはかなりの完成度が要求される．不十分な技術で行われた場合には，きわめて重篤な合併症を惹起する可能性があり，単なる病態としての適応だけでなく，当該施設にこれを行う技術があるか否かを慎重に見極める必要がある．この場合，単なるカテーテル留置手技だけではなく，治療開始後の薬剤分布評価の体制が備わっているかも重要な点である．

2. 画像診断の不確実性

肝動注化学療法の適応を考えるうえで重要な肝外病変の評価は，通常画像診断で行われるが，部位ならびに活用する画像診断の種類によりその精度は著しく異なる．よって，原疾患の組織型や進行度，臨床経過などを含む，総合的な観点から判断する必要がある．いかなる画像診断法を用いても，検出不可能な微小病変が存在している可能性は常にあることを認識して臨む必要がある[24]．

3. 予後規定因子，肝転移重症度についての判断

肝動注化学療法の適応の判断にしばしば用いられる規準であるが，どの病巣が予後規定因子であるのか，あるいはどの程度の肝転移が切迫

した予後規定因子であるのかについては，明確な判断規準がなく，また，これを用いた臨床試験もない．将来的にはなんらかの規準の設定やこれによる評価が望まれるが，現時点では経験的な判断に頼らざるをえない．くれぐれも，独善的な判断に陥らぬよう，協議して判断する姿勢が必要と思われる．

おわりに

かつて全身化学療法の効果が不十分な時代に脚光を浴びたことのある肝動注化学療法であるが，現在は全身的薬物療法が跳躍している時代である．よって，肝動注化学療法は基本的にきわめて控えめに，ほかの方法がない場合の治療法の一つとして位置づけるのが妥当であろう．しかし，全身的薬物療法も到底治癒が期待できるわけではなく，自ずとその効果には限界がある．全身的薬物療法の評価が一定のレベルに達した段階で，もし必要があれば，その残された領域における肝動注化学療法の役割を改めて検討すればよいと思われる．

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GASTROENTEROLOGY

Late complication in patients undergoing pancreatic resection with intraoperative radiation therapy: Gastrointestinal bleeding with occlusion of the portal system

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Abstract

Background: There are few reports of late complications in patients who have undergone pancreatic resection with intraoperative radiation therapy (IORT), because carcinoma of the pancreas (PCa) and the bile duct (BCa) have a poor prognosis. The purpose of the present paper was to review gastrointestinal (GI) bleeding occurring with occlusion of the portal system (PVs) as a complication of IORT in patients surviving long term without recurrence.

Patients: From 1990 to 1999, 45 patients underwent surgical resection of the pancreas with IORT. Eleven of these patients survived >3 years without recurrence, and occlusion of PVs was recognized in five patients at follow-up examination. Three of these five patients received repeated blood transfusions for GI bleeding.

Results: One patient had BCa and two had PCa, and pancreatoduodenectomy was carried out. The delivered radiation doses of IORT were 30 Gy (two patients) and 35 Gy (one patient). The postoperative periods to initial GI bleeding were 36, 26 and 9 months, respectively. In all cases, angiography revealed occlusion of PVs and the collateral circulation. The bleeding points were esophageal varix (case 1), remnant stomach varix (case 2) and a jejunal ulcer (case 3), and blood transfusions were carried out totaling 44, 60 and 16 units, respectively. The GI bleeding disappeared spontaneously in case 1, developed sporadically in case 2 and was stopped by metallic stent insertion in PVs in case 3.

Conclusion: During long-term follow up after pancreatectomy with IORT, it is necessary to monitor patients for GI bleeding. A clinical trial on optimum doses, long-term safety and benefit of IORT is necessary.

Key words: bile duct cancer, complication, gastrointestinal bleeding, intraoperative radiation therapy, occlusion of the portal system, pancreatic cancer.

INTRODUCTION

Carcinoma of the pancreas (PCa) and the bile duct (BCa) have a poor prognosis.[1,2] The only therapy providing a possibility of cure is surgical resection. However, postoperative survival rate is low, and various kinds of adjuvant therapy have been attempted to improve the treatment outcome.[3–9] Many reports have discussed the benefit of intraoperative radiation therapy (IORT) as adjuvant therapy in PCa[5,10–14] and Bca,[15,16] but its efficacy remains controversial. Although it is reported that there are no short-term complications after IORT,[5,10–13] there are few reports on long-term safety because patient prognosis is extremely poor. In the present study we review the prevalence of gastrointestinal (GI) bleeding occurring with occlusion of the portal system as a complication of IORT in patients surviving long term without recurrence.

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METHODS

Patients

From January 1990 to December 1999, 139 patients underwent surgical resection of the pancreas at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan. Of these 139 patients, 41 with PCa and four with BCa underwent IORT (Table 1): a single dose of radiation ranging from 25 to 35 Gy (mean, 30.5 Gy) was delivered to the tumor bed just after resection. Eleven of the 45 patients survived >3 years without recurrence, but occlusion of the portal system was recognized in five of these 11 patients at follow up. In three of the five patients, repeated blood transfusions were carried out for GI bleeding, and the postoperative courses of these three patients are reviewed in detail.

RESULTS

One patient had carcinoma of the distal common bile duct and the other two had carcinoma of the head of the pancreas (PhCa). Pancreatoduodenectomy (PD) was carried out in all three patients and the reconstruction method of Imanaga was adopted, which entails an end-to-end gastrojejunostomy, end-to-side pancreatojejunostomy and choledochojejunostomy.[17] In one case (case 2), wedge resection of the superior mesenteric vein (SMV) was also performed. The delivered doses of IORT were 30 Gy in two patients and 35 Gy in one patient, and the postoperative periods to initial GI bleeding were 36, 26 and 9 months, respectively (Table 2).

Case 1

A 61-year-old man underwent PD with IORT for BCa. Gastrointestinal bleeding was recognized at 36 postoperative months (POM). Computed tomography (CT) at the time of initial bleeding showed an unclear SMV but contrast of the intrahepatic portal vein (PV). Increased blood flow from the remnant stomach wall to the esophagus wall was detected. Endoscopic examination (Fig. 1a) revealed esophageal varix, which was suspected of bleeding. Portography via the superior mesenteric artery (SMA) (Fig. 1b) showed occlusion of the SMV. The collateral circulation went through the elevated jejunum, and blood flowed into the intrahepatic PV around the choledochojejunostomy. The splenic vein (SV) could not be identified on portography via the splenic artery (SA) and we diagnosed that the SV blood was flowing back through the remnant stomach and esophagus walls.

Table 1 Patients with surgical resection of the pancreas

Procedure	Cases	Survivor >3 years without recurrence	GI bleeding with occlusion of the portal sysytem
Total pancreatic resection	139†	52†	3†
IORT (–)	94†	41†	0† (0)‡
PCa, PEn	20	7	0
PCy	40	26	0
BCa	16	2	0
VCa	18	6	0
IORT (+)	45†	11†	3† (5)‡
PCa	41	9	2† (4)‡
BCa	4	2	1† (1)‡

Bca, carcinoma the bile duct; Pca, carcinoma of the pancreas; GI, gastrointestinal; IORT, intraoperative radiation therapy; Pcy, cystic tumor of the pancreas; Pen, endocrine tumor of the pancreas; Vca, carcinoma of ampulla of Vater.

IORT (–), surgical resection without IORT; IORT (+), surgical resection with IORT.

†Total number of cases for procedure; ‡no. patients with occlusion of the portal system.

Table 2 Clinical features of three patients with GI bleeding

Patient no.	Sex	Age	Diagnosis	Surgical procedure/ reconstruction	PV resection	Radiation dose of IORT (Gy)	Initial bleeding (POM)
1	M	61	BCa	PD/Imanage	–	30	36
2	F	56	PhCa	PD/Imanage	Wedge resection	30	26
3	M	57	Phca	PD/Imanage	–	35	9

BCa, carcinoma of the bile duct; GI, gastrointestinal; IORT, intraoperative radiation therapy; PD, pancreatoduodenectomy; PhCa, carcinoma of the head of the pancreas; POM, postoperative months; PV, portal vein.

Case 2

A 56-year-old woman underwent PD with IORT for PhCa. Gastrointestinal bleeding was recognized at 26 POM. Computed tomography at the time of initial bleeding (Fig. 2) demonstrated occlusion of the SMV and collateral circulation. These findings were not noted at the follow-up examination and GI bleeding of unknown cause was therefore repeated. Endoscopic examination at 90 POM (Fig. 3a) revealed bleeding of remnant stomach varix. Angiography (Fig. 3b,c) showed occlusion of the SMV. The collateral circulation flowed back to the PV through the elevated jejunum, remnant stomach and SV.

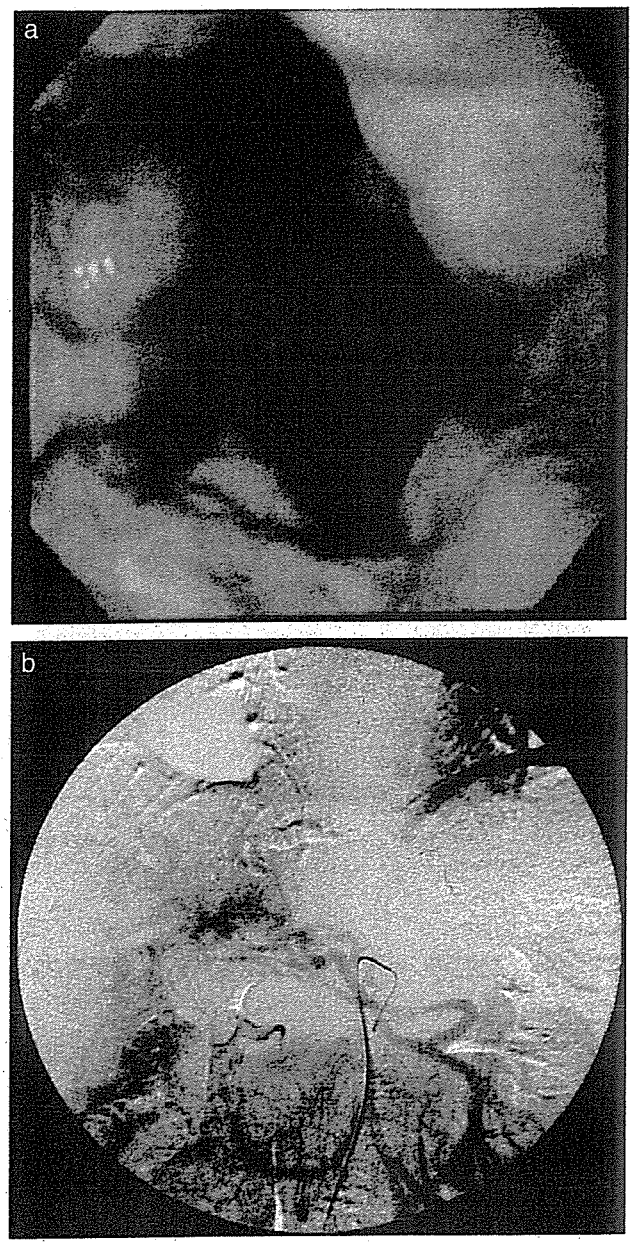

Figure 1 Case 1. Endoscopic examination revealing esophageal varix (a). Portography via the superior mesenteric artery (b) shows occlusion of superior mesenteric vein.

Case 3

A 57-year-old man underwent PD with IORT for PhCa. Gastrointestinal bleeding was recognized at 9 POM. Computed tomography at 11 POM demonstrated occlusion of the SMV and that the collateral circulation went through the elevated jejunum, anterior wall of the remnant stomach, splenic hilus and SV. Angiography (Fig. 4a) showed occlusion of the SMV, and percutaneous transhepatic portography (Fig. 4b) revealed stenosis of the SV at the portal confluence. The SV blood pressure had risen to 27 cmH_2O and PV blood pressure was 7.5 cmH_2O. Endoscopic examination at 20 POM (Fig. 4c) revealed a bleeding ulcer in the elevated jejunum.

Clinical course

Case 1 experienced repeated bleeding from 36 to 52 POM, and a total of 44 units of blood were transfused; however, there were no episodes of bleeding after 52 POM (Table 3). The patient had a relapse at 87 POM and died of cancer at 98 POM. In case 2, the first episode of GI bleeding was recognized at 26 POM and its cause was ascertained at 90 POM. During this period, a total of 60 units of blood were transfused; currently, at 98 POM, the patient is under close follow up. In case 3, the stenosis of SV at the portal confluence showed occlusion at 24 POM and a metallic stent was inserted between the PV and the SV. Gastrointestinal bleeding was not noted again until 54 POM.

DISCUSSION

In patients with PCa and BCa, the survival rate after surgical resection remains very low.[1,2] Intraoperative radiation therapy is a common adjuvant therapy to improve the treatment outcome, but its efficacy remains

Table 3 Patient clinical course

	GI bleeding (POM)	Blood transfusion (total units)	Clinical course	Recurrence	Follow-up months
1.	36–52	44	52 POM: GI bleeding (–)	+, 87 POM	98, DOD
2.	26–92	60	92 POM: close follow up	–	98, AW
3.	9–23	16	24 POM: GI bleeding (–)	–	54, AW

AW, alive and well; DOD, died of disease; GI, gastrointestinal; POM, postoperative months.

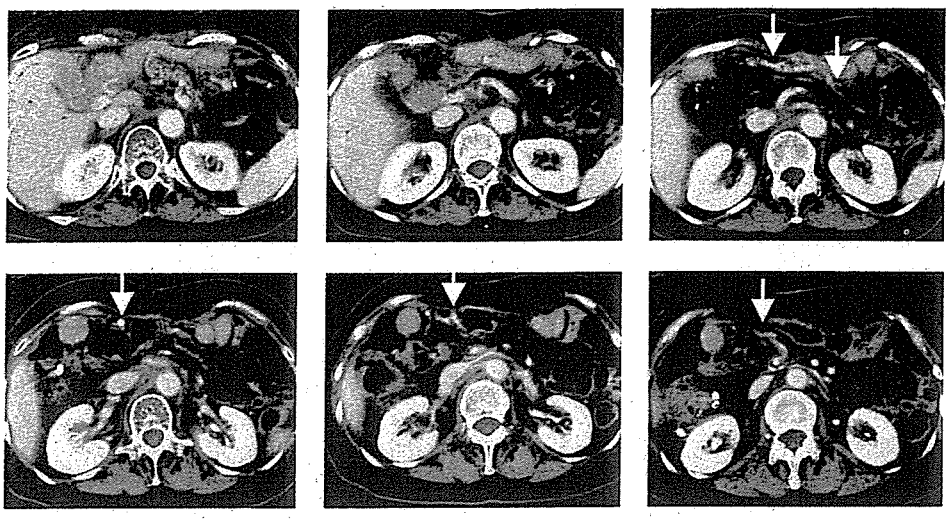

Figure 2 Case 2. Computed tomography showing occlusion of superior mesenteric vein and collateral circulation (arrows).

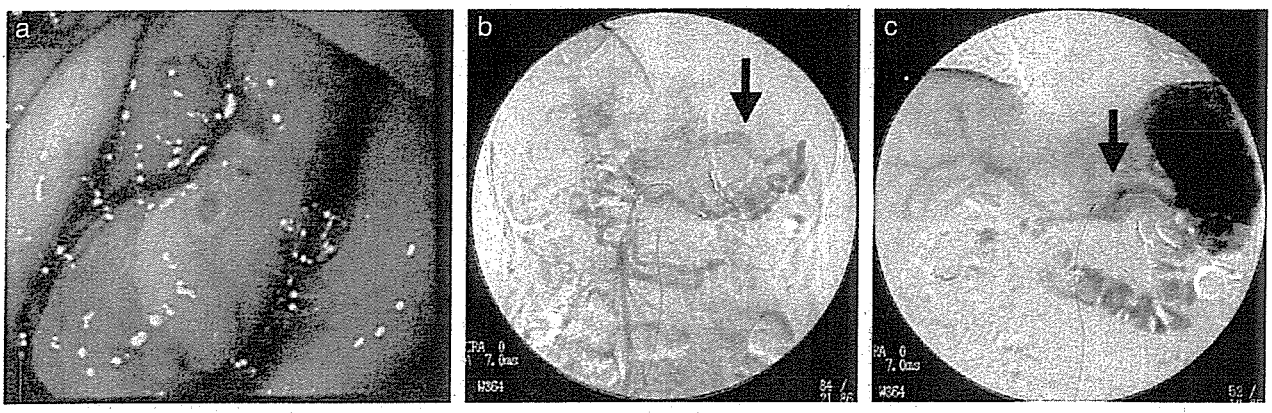

Figure 3 Case 2. Endoscopic examination demonstrating remnant stomach varix (a). Portography via superior mesenteric artery (b) and splenic artery (c) reveals occlusion of superior mesenteric vein and collateral circulation through splenic vein (arrow).

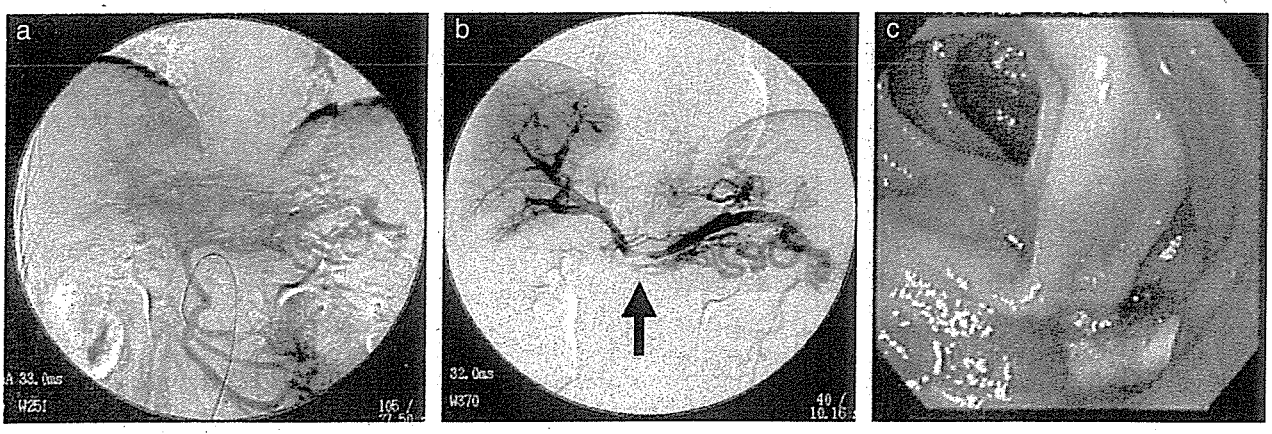

Figure 4 Case 3. Portography via superior mesenteric artery (a) and percutaneous transhepatic portography (b) at 14 post-operative months (POM) shows occlusion of superior mesenteric vein and stenosis of splenic vein (arrow). Endoscopic examination at 20 POM (c), reveals ulcer in the elevated jejunum.

controversial. While there have been reports of reduced local disease recurrence[10,11,13] and improved disease-free survival and survival rates,[12–15] it has also been reported that IORT does not extend survival time.[5,18]

Various series of trials were conducted in order to examine the benefits of IORT for PCa.[5,11–13] In all series, IORT was considered to have been safe in the short term following surgery.[5,11–13] However, because

treatment outcome of PCa is extremely poor, there are no reports of long-term safety following IORT. Autopsy analyses assessing radiation damage to various tissues after IORT have demonstrated fibrosis of the retroperitoneal soft tissues and the portal vein.[19,20] Fibrosis of tissues and occlusion of vessels in the radiation field are predicted late complications of IORT,[18] and one of the common clinical problems is GI bleeding caused by portal hypertension occurring with stenosis and/or occlusion of the portal system. Thus, in the present study we reviewed the prevalence of GI bleeding as a possible complication of IORT in patients who have survived for >3 postoperative years without disease recurrence.

Of our 11 patients who survived for >3 years without recurrence following resection of the pancreas and IORT, three (27.3%) of the five patients with subsequent occlusion of the portal system required repeated blood transfusions for GI bleeding. Unfortunately we were not able to determine whether the occlusion resulted from the operation or the influence of IORT. During the period of January 1990–December 1999, 41 of our 94 patients who underwent surgical resection of the pancreas without IORT were observed to survive for >3 years without recurrence (Table 1). Because CT is not always performed in patients with benign diseases, the precise frequency of portal occlusion in these 41 patients remains unknown. However, no occlusion of the portal system was observed in the follow-up period for these 41 patients and there were also no episodes of GI bleeding. Because lymph node dissection and nerve plexus excision were not always performed in these 41 patients, the influence of surgery on the development of portal occlusion cannot be compared simply between patients with and without IORT. However, taken together, our findings suggest that occlusion of the PV and GI bleeding occurred as a late complication of IORT.

Intraoperative radiation therapy at lower doses (up to 20 Gy) with or without fractionated external beam radiotherapy (up to total 60 Gy) has been reported to be safe, and there was no GI bleeding as a short-term complication.[5,11,12] While Reni *et al.* reported that GI bleeding was observed in five patients (6%), the doses of IORT ranged from 10 to 25 Gy (mean 17.5 Gy) in their series.[13] In the present series patients were treated with considerably high doses of radiation ranging from 25 to 35 Gy (mean 30.5 Gy), so the risk of this complication may have been raised.

In the clinical course of case 3, a metallic stent was inserted between the PV and the SV, causing SV blood pressure to fall dramatically. Gastrointestinal bleeding was not seen again until 54 POM. There have been no reports of stent insertion for GI bleeding caused by stenosis and/or occlusion of the portal system, but this treatment is thought to be remarkably effective.

Because GI bleeding occurred with occlusion of the portal system in three of the present patients, influence of the operation itself and high-dose radiotherapy on the development of this late complication cannot be excluded. We recommend that GI bleeding is considered by physicians during the long-term follow up of patients who undergo pancreatectomy with IORT. A clinical trial on optimum doses, long-term safety and benefit of IORT is necessary.

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CASE REPORT

Radiation Medicine: Vol. 23 No. 5, 371–375 p.p., 2005

Hepatic Hemangioma Presenting Atypical Radiologic Findings: A Case Report

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A 69-year-old woman was referred to our hospital due to a liver tumor that was incidentally noted on ultrasound (US). US revealed a pedunculated mass of 5 cm in diameter, with a heterogeneous echo pattern. On arterial phase dynamic contrast-enhanced computed tomography (CT), a tiny enhancing dot in the upper aspect of the mass was seen; whereas, the main portion of the lesion appeared as hypoattenuating. The tumor was of low intensity on T1-weighted magnetic resonance (MR) images, and showed slightly heterogeneous high intensity on T2-weighted MR images. The most characteristic feature of the tumor was its exophytic appearance. On post-gadolinium hepatic arterial dominant-phase MR images, the tumor showed nodular enhancement centrally, with progressive spread of enhancement on later images. Angiography showed dilatation of the right posterior inferior branch of the hepatic artery and C-shaped opacification. Since we could not rule out malignancy for these nonspecific radiologic findings, a partial resection of the liver was carried out, resulting in a pathological diagnosis of hepatic hemangioma. This hemangioma had marked hyalinization and fibrosis, causing a heterogeneous appearance on MR images. The tumor presented an exophytic appearance, which caused some diagnostic confusion.

Key words: hepatic hemangioma, exophytic appearance, hyalinization

Introduction

Hemangioma, the most common benign hepatic tumor, is frequently incidentally detected by ultrasound (US) and computed tomography (CT) in asymptomatic patients. It is therefore important to distinguish hemangioma from other hepatic neoplasms. In cases of typical hemangioma with characteristic findings, imaging modalities are highly reliable for diagnosis. However, there are a few atypical hemangiomas that may cause difficulties for radiologic diagnosis. We report the case of an atypical hepatic hemangioma presenting an exophytic appearance mimicking hepatic malignancy.

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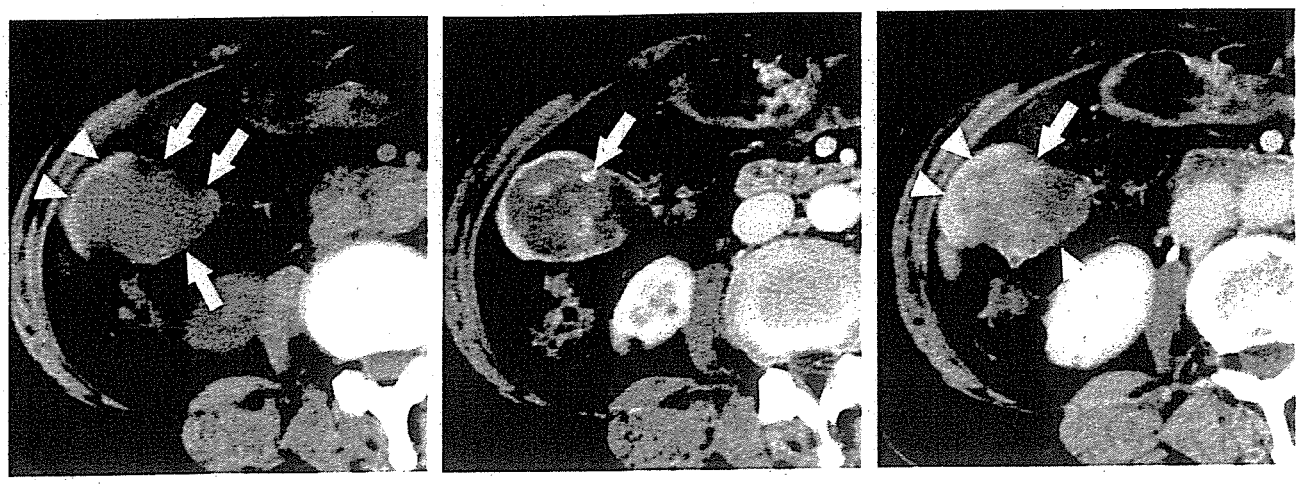
Case Report

A 69-year-old woman was referred to our hospital due to a liver tumor that was incidentally pointed out by US. On physical examination, the abdominal mass was not palpable. Liver function studies were normal. Serum levels of carcinoembryonic antigen, α-fetoprotein, and PIVKA-II were all within normal ranges. Hepatitis B surface antigen and hepatitis C antibody were negative.

US revealed a 5 cm pedunculated mass with heterogeneous echo pattern. Nonenhanced CT scan showed the exophytic mass in the right posterior inferior portion of the liver. After intravenous administration of contrast material, the arterial-phase CT showed minimal and no enhancement except for a tiny enhancing dot in the anterior aspect of the mass. Although the delayed-phase CT indicated more than half of the mass showing slight enhancement, the mass appeared hypoattenuating relative to the normal liver parenchyma (Fig. 1).

The tumor was of low intensity on T1-weighted MR images, and was moderately hyperintense on T2-weighted MR images. Hepatic arterial-dominant phase post-gadolinium MR images showed nodular enhance-



A | B | C

Fig. 1.
A: Nonenhanced CT scan shows an exophytic mass of 5 cm in diameter in the right posterior inferior portion of the liver (*arrows*), and the liver parenchyma (*arrowheads*).
B: After intravenous administration of contrast material, arterial-phase CT shows a tiny enhancing dot (*arrow*) isoattenuating to aortic enhancement.
C: The main part of the tumor (*arrows*) shows heterogeneous enhancement hypoattenuating compared to that of liver parenchyma (*arrowheads*) on delayed images.

ment centrally, with progressive enhancement on delayed images (Fig. 2).

Hepatic angiogram showed dilatation of the right posterior inferior branch of the hepatic artery and C-shaped opacification (Fig. 3).

Since we could not rule out malignant tumor based on these radiologic findings, partial resection of the liver was carried out. At surgery, a round tumor with capsule was seen, but no adhesion or peritoneal fluid was noted. The tumor was pedunculated and connected to the liver (subsegment 6) by a stalk of 3 cm in length. Macroscopically, the tumor measured 6.0×5.5×4.5 cm and was whitish, elastic, slightly firm, and well demarcated from the surrounding liver parenchyma. The cut surface of the tumor showed a whitish hyalinized area with dark red patches centrally and a tan-to-yellowish area peripherally (Fig. 4A). Histologically, there were multiple vessels of various sizes with marked hyaline-like degeneration in the central area, whereas small-sized vessels with rich fibrous stroma were predominant in the peripheral area (Figs. 4B, C). Somewhat large venous and arterial branches and large lymph vessels were seen in the border between the tumor and liver parenchyma. A pathological diagnosis of hepatic hemangioma was made.

The postoperative course was uneventful, and the patient was discharged 10 days after surgery.

Discussion

Hemangioma is the most common benign tumor of the liver. The incidence of hemangioma in the general population varies in published reports from 0.4% to 20%.[1]

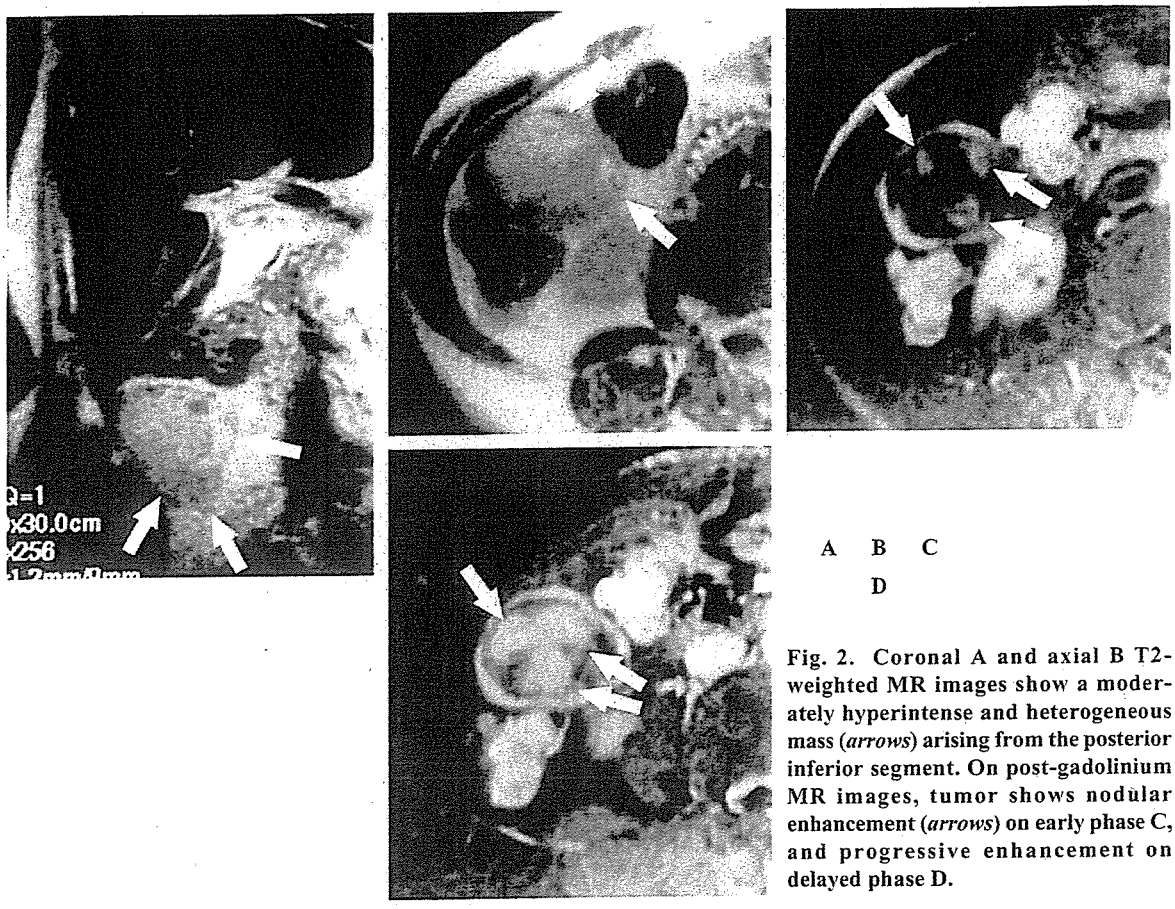
The typical radiologic features of cavernous hemangiomas have been well described, and it is usually easy to differentiate hemangioma from other liver tumors. However, the present case had atypical radiologic features, which caused some diagnostic confusion.

The typical US appearance is that of a homogeneous, hyperechoic mass with well-defined margins and some posterior echo enhancement.[2] In contrast to these features, in the present case, the internal echo pattern was partially hypoechoic and heterogeneous.

Strict criteria for the classic CT appearance of hepatic hemangioma include: relative hypoattenuation compared with normal liver on precontrast images, early peripheral enhancement, progressive spread of the opacified area towards the center of the lesion, and complete isoattenuating fill-in occurring not less than 3 minutes nor more than 60 minutes after contrast material administration.[3] Although the present tumor had a tiny enhancing dot in the arterial phase, early peripheral enhancement and progressive opacification towards the center of the lesion was not clear.

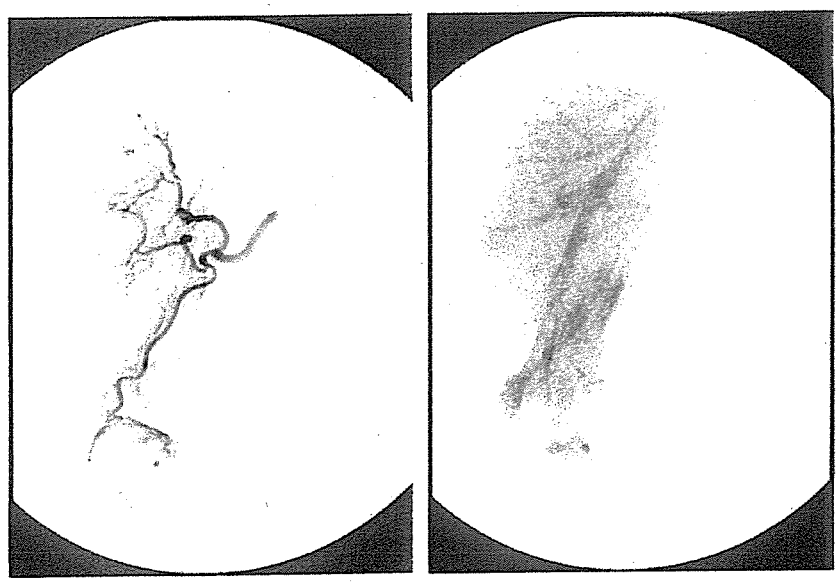
Hemangioma typically demonstrates marked high intensity on T2-weighted MR images and is usually spheroid or ovoid (87%).[3,4] However, the present tumor showed a moderately hyperintense and heterogeneous appearance on T2-weighted MR images.

In the present case, the hepatic angiogram showed dilatation of the right posterior inferior branch of the



A B C
D

Fig. 2. Coronal A and axial B T2-weighted MR images show a moderately hyperintense and heterogeneous mass (*arrows*) arising from the posterior inferior segment. On post-gadolinium MR images, tumor shows nodular enhancement (*arrows*) on early phase C, and progressive enhancement on delayed phase D.



A B

Fig. 3.
A: Selective hepatic angiogram shows dilatation of the right posterior inferior branch of the hepatic artery and C-shaped opacification.
B: Venous phase of hepatic angiogram shows mildly persistent peripheral enhancement.

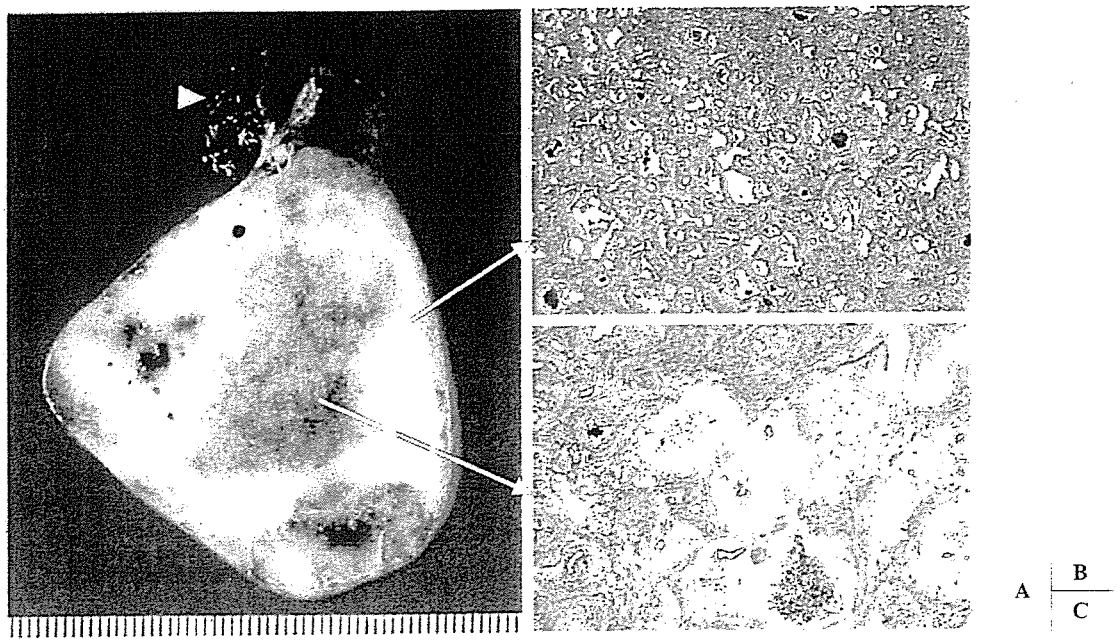


Fig. 4.
A: The resected tumor is a 6.0×5.5×4.5 cm mass with a 3-cm-long stalk. The cut surface of the tumor shows the whitish hyalinized area with dark red patches centrally and the tan-to-yellowish area peripherally. The stalk is seen (*arrowhead*).
B: The peripheral area of the tumor shows small-sized vessels with rich fibrous stroma.
C: The central area shows multiple vessels of various sizes with marked hyaline-like degeneration (Hematoxylin-eosin stain, original magnification ×40).

hepatic artery. Despite dilated feeding vessels, tumor vessels or vascular enhancement were not recognized. Dilated and tortuous feeding arteries are generally rare in hepatic hemangioma.[5]

The present tumor demonstrated radiologic findings inconsistent with those of typical hemangioma in all modalities. Nevertheless, this tumor showed a tiny enhancing dot in the arterial-phase CT scan that was considered to be consistent with the "bright dot" sign. Jang *et al.* advocated that this sign could be helpful in diagnosing small hemangiomas with nonspecific hypoattenuation at the arterial phase and portal venous phase of spiral CT.[6] In our case, there might have been a chance of a correct diagnosis preoperatively. However, the "bright dot" sign is characteristic of small hemangiomas (<2 cm in diameter), and it is uncertain whether this sign is reliable for large hemangiomas like our case (>4 cm in diameter). Further experience is needed.

The surgical procedure for benign hepatic tumors has been controversial. Terkivatan *et al.* reported that they advised surgery for any benign hepatic tumor that caused severe complaints and when there was an uncertain diagnosis.[7] In the present case, since the patient was asymptomatic, a radiologic follow-up or percutaneous needle biopsy might have been a reasonable option. However, we selected resection for the uncertain hepatic tumor because of its relatively large diameter, risk of rupture of the exophytic lesion, and the inability to exclude malignancy.

Histopathologically, multiple vessels of various sizes, remarkable hyalinization, and fibrosis of the stroma were present without a cavernous pattern in our case. The pathological diagnosis of hemangioma was based on the presence of variably sized, endothelial-lined vascular channels.

We considered various reasons for these atypical radiologic features. First, remarkable hyalinization and fibrosis without a cavernous pattern of the tumor can be causative of minimal enhancement. Some investigators reported that the reasons for nonenhancement of hemangioma were slow flow in the central sinusoids, central fibrosis, central thrombosis, and hemorrhage.[5,8] Yamashita *et al.* advocated that enhancement patterns and hemodynamic characteristics of hemangiomas could vary depending on the internal architecture of the lesion.[9] Second, the current tumor presented an exophytic appearance. According to Brancatelli *et al.*, 12% of hemangiomas demonstrate exophytic growth.[1] Moreover, pedunculated hemangiomas are very rare.[10] Third, the relatively large size of the present tumor could have