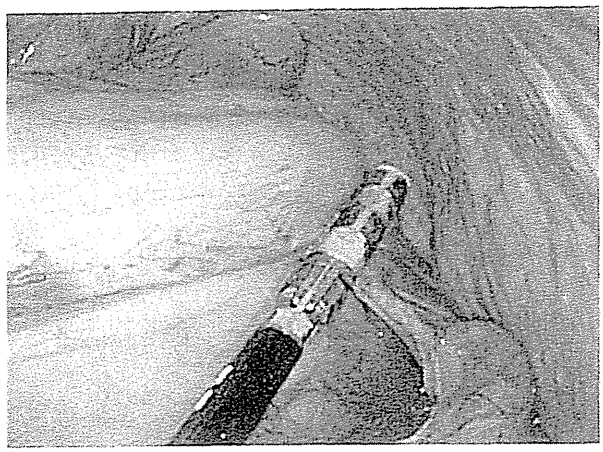

図1. 胃脾間膜切離
胃脾間膜切離は，食道胃周囲の血行遮断を加える場合は胃壁側でエネルギーデバイスで切離する．

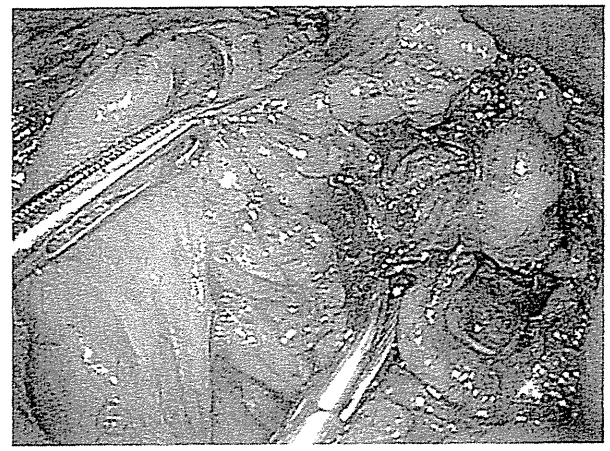

図2. 脾動脈の確認
脾門部が十分に視野展開されれば脾動脈の確保（結紮）を行う．

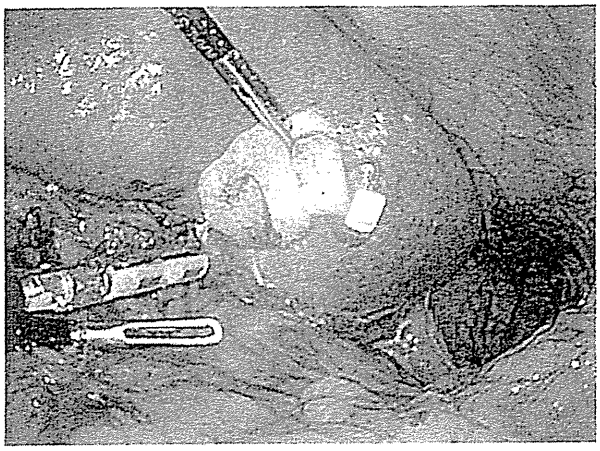

図3. 脾臓の展開
セクレアを用いて愛護的に脾臓を展開する．

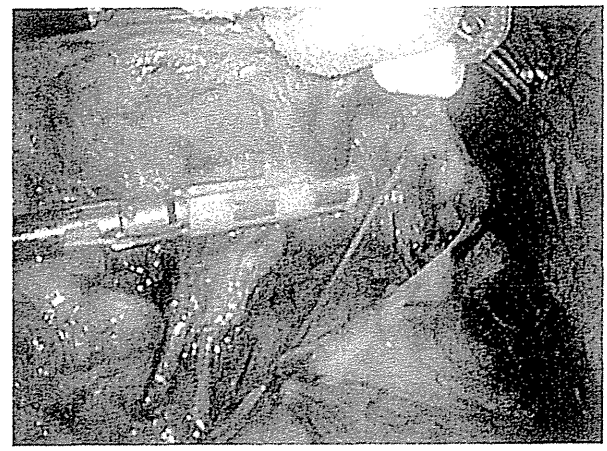

図4. 側副血行路の処理
脾結腸間膜の発達する側副血行路に対しVSSを使用し切離する．

b. 術中操作

切離に際しては，超音波凝固切開装置（HARMONIC：Ethicon社）やvessel sealing system（VSS）〔LigaSure：Covidien社，ENSEAL：Ethicon社〕を使用すると出血がおさえられる．また不意の出血に対してソフト凝固VIOシステム（アムコ社）を準備すると安心である．

開腹脾摘と同様に胃結腸間より網嚢内に入り左側に向かって大網を切離し，脾動脈結紮がむずかしい場合は脾動脈の確認のみにとどめて，良好な視野が得られてから脾動脈処理を行う．次に胃脾間膜の切離を行うが，食道胃周囲の血行遮断を加える場合は胃側で（図1），脾摘のみ行う場合は胃と脾臓の中間点でVSSを用いて切離を行う．巨脾の短胃動静脈はかなり太いので，胃側はクリップで結紮する場合もある．この切離を可及的に頭側にすすめることで脾門部の十分な視野展開が可能となる．ここで脾動脈の確保（結紮）を行う（図2）．

脾結腸間膜を後腹膜移行部まで切離する．ここで脾臓の展開が必要になるのであるが，当科では腹腔鏡下手術用に開発したセクレア[13]（ホギメディカル社）を用いて愛護的に展開している（図3）．門脈圧亢進症の場合は，側副血行路が発達していることが多いので，VSSで入念に止血しながら切離していく（図4）．

脾が十分に脱転・遊離したら，脾門部の処理に

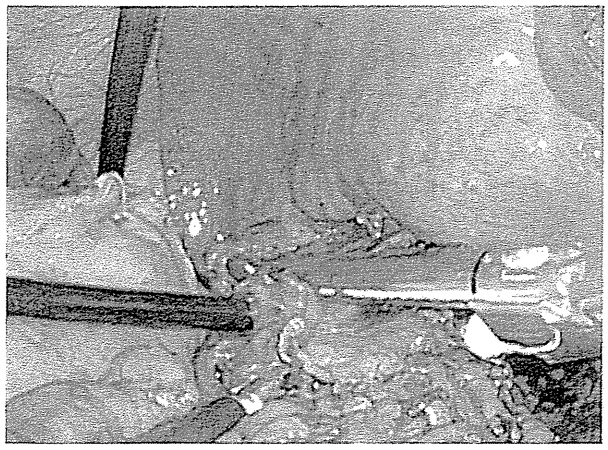

図5. 脾門部処理
脾が十分に脱転遊離したら，脾門部は自動縫合器を用いて一括で処理を行う．

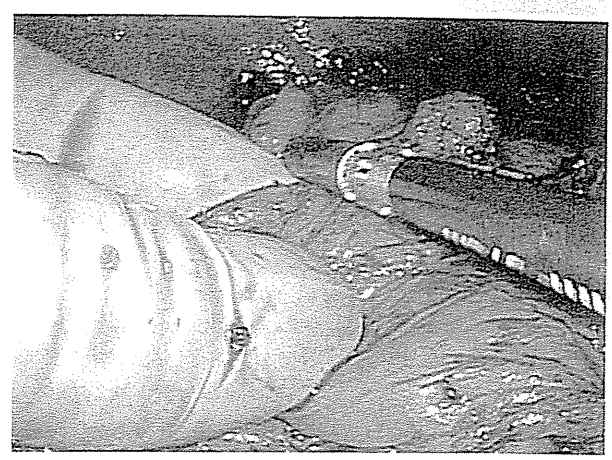

図6. 腹腔鏡補助下脾摘
Hand-assistによる腹腔鏡補助下脾摘

戻る．脾門部は自動縫合器を用いて一括で処理を行う（図5）．自動縫合器を挿入する際に，脾門部背側の血管を損傷する場合があるので，脾臓を十分に持ち上げて，特に背側を確認することが重要である．しかし巨脾の場合には，十分に持ち上げることがむずかしいことが多い．トロッカーを新たに挿入し鉗子を追加してでも十分に持ち上げて確認すべきである．

開腹脾摘と同様に手順にこだわらず，視野の良好な部分から処理をすることが重要である．

摘出にはビニール袋に脾臓を収納し摘出する．

巨脾摘出には最終的にある程度の皮膚切開が必要であるため，巨脾例ではhand-assistによる腹腔鏡補助下脾摘（図6）をすすめる．

Ⅳ．術　　後

術直後より抗凝固療法を開始する．術後第1日目より離床歩行，食事開始で腸管循環血液量が増加し血栓の予防となる．特に肝硬変の場合には禁食により血清アルブミン量が低下するため，早期の経口摂取は重要である．

脾摘後には門脈血栓も多く，特に特発性門脈圧亢進症では門脈血に占める脾静脈血の割合が73.8％と高く[15]，脾摘により急激に門脈血流が減少し高率に門脈血栓を発症する[14]．肝硬変における脾摘後の門脈血栓に関して，太い脾静脈径と白血球数低値が出現の独立因子と報告されている[16]．つまり巨脾例では術後門脈血栓発生率が高い．しかし近年，術後抗凝固療法で門脈血栓も減少傾向で，antithrombinⅢ投与が重要との報告がある[17]．

おわりに

腹腔鏡下脾摘では拡大視効果により，より丁寧な手術が可能となる．しかし巨脾例ではworking spaceの確保に難渋するため，脾の脱転，出血時の圧迫止血が容易である腹腔鏡補助下脾摘をすすめる．

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難治性腹水の治療

Management of refractory ascites

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Summary

利尿薬治療により軽減できない，あるいは早期再発を防止できない中等量以上の腹水は難治性腹水と定義され，患者のQOLを著しく低下させる。その成因には進行肝硬変に伴う門脈圧亢進症および神経体液性因子の著しい異常があり，循環血液量の増加，有効循環血液量の減少，腎でのNa・水排泄の著減を特徴とする。根本治療は肝移植であるが，QOLを改善しうる対症療法に腹水穿刺排液，腹腔ー静脈シャント術，経頸静脈的肝内門脈大循環シャント術，腹水濾過濃縮再静注法があり，治療にあたってはそれぞれの手技の適応，限界，有害事象をよく理解する必要がある。本稿では，これらの治療法の現状と問題点について文献的考察を加え検討した。症例ごとの肝機能，腎機能，合併症の程度を考慮して適切な治療法を選択し，難治性と判断した場合は早期に治療を切り替えて行うことがQOLの改善に最もつながると考える。

Keywords

難治性腹水　腹水穿刺排液　腹腔ー静脈シャント術　TIPS　CART

難治性腹水とは

肝硬変における難治性腹水の定義は1996年にArroyoらにより提唱された[1]。内科的治療により軽減できない，あるいは早期再発を予防できない中等量以上の腹水を難治性腹水（refractory ascites）と定義しており，これをさらに利尿薬抵抗性腹水（diuretic-resistant ascites）および利尿薬不耐性腹水（diuretic-intractable ascites）に分類した。その後，2003年に改訂が加えられている[2]。わが国における難治性腹水の診断および治療指針は確立

されておらず，各施設が独自に診断基準を設け治療を行っているのが現状である[3]。当院における難治性腹水の定義は，１日５ｇの塩分制限を行い，アルブミン値を2.5g/dL以上に維持し，フロセミド100mg，スピロノラクトン150mgを２週間投与しても，体重減少が1.5kg/週以内に止まる腹水（利尿薬抵抗性腹水），また利尿薬による副作用（Na 125mEq/L以下，K 5.5mEq/L以上，Cr 2 mg/dL以上，肝性脳症出現）のために利尿薬を制限せねばならず，体重減少が1.5kg/週以内に止まる腹水（利尿薬不耐性腹水）としている。難治性腹水の治療には一般的に肝移植，腹水穿刺排液，腹腔－静脈シャント術（peritoneo-venous shunt），経頸静脈的肝内門脈大循環シャント術（transjugular intrahepatic portosystemic shunt；TIPS），腹水濾過濃縮再静注法（cell-free and concentrated ascites reinfusion therapy；CART）が挙げられる[3]。肝硬変による難治性腹水に対する究極の治療は肝移植であるが，わが国の現状では難治性腹水に対し肝移植が標準治療として行われるとはいいがたい。本稿では，難治性腹水に対する治療の現状と問題点を解説する。

腹水穿刺排液

大量腹水症例に対する腹水穿刺排液は，一度は施行する方法であろう[4]。腹水の原因検索や悪性細胞の有無の判定など診断にも有用で，感染の有無なども検索できる[5]。また，穿刺液により漏出性腹水と滲出性腹水の鑑別を行える。漏出性腹水と滲出性腹水については，従来は腹水蛋白濃度が基準とされてきたが，現在では血清と腹水のアルブミン濃度差（血清・腹水アルブミン較差（serum ascites albumin gradient；SAAG））が1.1g/dL以上あれば漏出性腹水，それ未満であれば滲出性腹水とする基準が用いられることが多い[6]。また，腹水中の多核白血球数が250/μL以上で外科的に治療可能な腹腔内感染がない場合には，特発性細菌性腹膜炎（spontaneous bacterial peritonitis；SBP）と診断して治療を開始することが推奨されている[6]。難治性腹水に対して穿刺排液を頻回に行い，その都度血漿増量薬を静注投与する方法は，全身循環動態，肝・腎機能，生存率に悪影響を及ぼさず，利尿薬投与例に比べて入院期間が短縮し，肝性脳症，腎障害，電解質異常などの合併症の出現率が有意に低率であるとされる[7][8]。しかし，複数回の大量腹水穿刺排液を行い利尿薬投与を継続しても完全に腹水をコントロールできることは少なく，難治性腹水の治療法としては不十分であり，さらなる治療を要することが多い[4]。

腹腔–静脈シャント術

腹腔－静脈シャント術は1974年にLeveenらによって報告され[9]，その後さまざまな改良が加えられ，現在ではポンプチャンバーの付いたDenver shunt（ミハマメディカル社）が広く用いられている[10]。難治性腹水に対する代表的治療法の１つで，大量腹水を短期的に減少させ，腹部膨満による苦痛軽減に対し有用な手段である[11][12]。難治性腹水症例に対して比較的早期に腹腔－静脈シャント術を決断することで治療成績も向上し，安全に施行でき，QOLの改善につながるとされている[13]。また，肝硬変による難治性腹水のみではなく癌性腹膜炎による腹水も適応となる[14]。われわれの施設の検討でも，腹腔－静脈シャント術は腹水の成因や肝障害度に関わらず腹囲減少や尿量増加に寄与し，難治性腹水患者のQOLを改善すると考えられた。適応から外れるのは腹水の細菌培養陽性例，腹水中の白血球数500/μL以上，高度の出血傾向を認める場合とされる[13]。代表的な合併症にはシャント閉塞，播種性血管内凝固症候群（DIC）が挙げられる[15]。

TIPS

TIPSは，経皮経内頸静脈的に門脈と肝静脈との間に短絡路を形成させ，門脈系の減圧を図る方法である[16]。腹水出現の原因である門脈圧を低下させることにより病態改善を図るため，難治性腹水には有用な治療法である[17][18]。しかし，わが国ではウイルス性肝硬変が多く肝萎縮が高度なため，手技的難易度が高い点や保険診療未適応の問題から広く普及するには至っていない[16]。TIPS特有の合併症として肝性脳症が挙げられ，合併率

は32～52％とされる[17]。ただし，そのほとんどは内科的治療にてコントロール可能である[18][19]。TIPSの適応禁忌として肝性脳症，心肺疾患，腎不全（血清Cr 3.3mg/dL以上），肝不全（血清ビリルビン5.8mg/dL以上），敗血症，門脈血栓症などが挙げられる[20]。治療成績は良好で，90％の症例で腹水の改善を認める[18]。腹水穿刺排液と比較して有意に腹水を減少させ[21]，再発率も低い[22]。

CART

CARTは癌や肝硬変などによって貯留した腹水（または胸水）を最大孔径0.2μmの腹水濾過器で処理し，細菌や癌細胞，血球成分などを除去し，アルブミンやグロブリンなどの蛋白成分を回収して患者自身に静注する治療法である[23]。しかし，CARTは腹水を経静脈投与することに対する不安や発熱などの副作用などから難治性腹水治療の第一選択とはなっていない。さらに，CARTの適応基準や施行方法が確立されておらず，有効性に関する研究も少ない[24]。しかし，近年の報告では，CARTは腹部膨満を緩和させ，腹水中の蛋白を有効に血中に灌流でき血液製剤の投与を抑えられるとされている[24][25]。代表的な合併症に発熱があり，濃縮した腹水の灌流中に38～42℃に及ぶ発熱をきたすとされる[26]。Zaakらによると，CARTを施行した症例の43％に発熱が生じたと報告されている[26]。しかし，投与速度を減弱することやステロイドを用いることで十分にコントロール可能である[24]。

おわりに

難治性腹水に対する代表的な治療法を文献的考察もふまえて解説した。難治性腹水を腹水穿刺排液で治療した場合，１年生存率は約50％に過ぎず，その予後はきわめて不良である[27]。さらに，難治性腹水はQOLを著しく低下させる。難治性腹水に対してさまざまな治療法が開発されているが，根本的な治療は肝移植以外には望めない。そのため，難治性腹水に対する治療はQOLの改善が重視される。そのためには早期からの積極的な腹水治療が不可欠で，腹水穿刺排液を行っても腹水コントロールが困難な場合は積極的に腹腔－静脈シャント術やTIPSを検討すべきである。

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Preoperative Three-dimensional Virtual Simulation for Safe Liver Surgery

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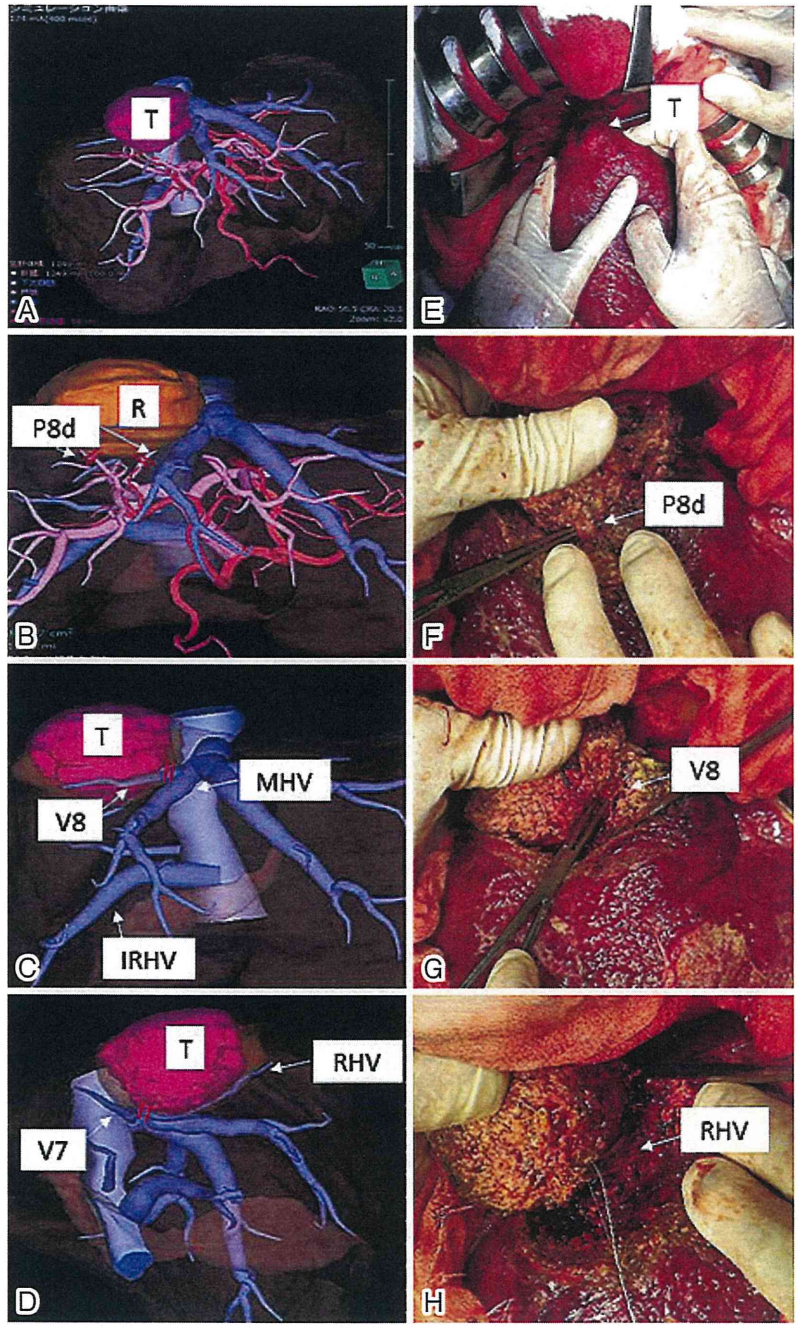

Fig. 1

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The recent progress of image analysis technology has been remarkable, and preoperative virtual simulation for liver surgery is necessary for safety hepatectomy[1,2]. It has become easy to grasp the complicated anatomical relationship between the portal triad, hepatic veins and a local tumor by volume rendering with multidetector-row computed tomography and a three-dimensional image analysis workstation (Synapse Vincent®; Fuji Photo Film Co. Ltd.).

In patients with damaged liver function or extended hepatectomies, the postoperative residual liver volume with preservation of blood supply and drainage vessels is very important for the prevention of liver failure. In this software, the surgeon can simulate various patterns of planned hepatectomy.

Case

A 79-year old female was referred for resection of a hepatocellular carcinoma. She suffered from chronic coughing and decreased respiratory function due to interstitial pneumonia with liver dysfunction due to chronic hepatitis C.

CT revealed a peripherally enhanced low-density mass 5.0 cm in diameter located in Segment VIII/VII. In consideration of her comorbidities, we simulated a safe liver resection using Vincent®. **Figure 1A–D** show the preoperative simulation of the hepatectomy. **Figure 1A** displays the perspective of the liver and the tumor. The tumor is located in segment VIII/VII just under the right diaphragm. In **Figure 1B**, two portal branches of the dorsal portion of segment VIII (P8d) were identified as main feeders of the resected liver area. The position of the tumor relative to a drainage vein in segment VIII (V8) and the right hepatic vein (RHV) are shown in **Figure 1C and D**. The distal portions of the V8 and the RHV after divergence from the middle hepatic vein (MHV) and the V7, respectively, were invaded by the tumor, and the V8 and the RHV needed to be resected. However, the MHV and the V7 were not directly influenced by the tumor, and the MHV and the V7 were thought to be able to be preserved. In consideration of these simulation images and her comorbidities, we selected a partial resection of segment VIII/VII with preservation of the MHV and the V7 as a recommended safe operation. **Figure 1E–H** show images from the operation. **Figure 1E** shows the local presence of the tumor and the liver according to the simulation image. Two P8ds were accepted according to the simulation of the liver excision line (**Fig. 1E**). The V8 (**Fig. 1G**) and the RHV (**Fig. 1H**) with invasion by the tumor were also identified during the hepatectomy and separated after ligation. The V7 and the MHV were confirmed to be preserved by intraoperative ultrasonography.

Conflict of Interest: The authors declare no conflict of interest.

Fig. 1 Preoperative three-dimensional virtual simulations (A–D) and images from the operation corresponding to these simulation images (E–H).
T: tumor, R: resected liver area, P8d: portal segment branches of the dorsal portion of segment VIII, V8: drainage vein of Segment VIII, MHV: middle hepatic vein, RHV: right hepatic vein, IRHV: inferior right hepatic vein

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RESEARCH ARTICLE Open Access

Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis

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Abstract

Background: This study investigated the survival benefits of sorafenib vs. radiotherapy (RT) in patients with unresectable hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) in the main trunk or the first branch.

Methods: Ninety-seven patients were retrospectively reviewed. Forty patients were enrolled by the Kanagawa Liver Study Group and received sorafenib, and 57 consecutive patients received RT in our hospital. Overall survival was compared between the two groups with PVTT by propensity score (PS) analysis. Factors associated with survival were evaluated by multivariate analysis.

Results: The median treatment period with sorafenib was 45 days, while the median total radiation dose was 50 Gy. The Child-Pugh class and the level of invasion into hepatic large vessels were significantly more advanced in the RT group than in the sorafenib group. Median survival did not differ significantly between the sorafenib group (4.3 months) and the RT group (5.9 months; $P = 0.115$). After PS matching (n = 28 per group), better survival was noted in the RT group than in the sorafenib group (median survival, 10.9 vs. 4.8 months; $P = 0.025$). A Cox model showed that des-γ-carboxy prothrombin <1000 mAU/mL at enrollment and RT were significant independent predictors of survival in the PS model ($P = 0.024$, HR, 0.508; 95% CI, 0.282 to 0.915; and $P = 0.007$, HR, 0.434; 95% CI, 0.235 to 0.779; respectively).

Conclusions: RT is a better first-line therapy than sorafenib in patients who have advanced unresectable HCC with PVTT.

Keywords: Hepatocellular carcinoma, Overall survival, Portal venous tumor thrombosis, Radiotherapy, Sorafenib

Background

Hepatocellular carcinoma (HCC) recurs frequently after curative treatment [1-4]. Advanced HCC sometimes causes macroscopic hepatic vascular invasion, including portal vein tumor thrombosis (PVTT) in the main portal trunk or the first branch and venous thrombosis in the hepatic vein trunk or inferior vena cava. These conditions can be life threatening, and the prognosis of patients with PVTT remains very poor, with a median survival of only approximately 3 months without treatment [5-8]. Therefore, identification of effective treatments that are not associated with significant adverse effects would be of benefit for this patient population. Transarterial chemoembolization (TACE) is one treatment for advanced HCC and is associated with an increased risk of ischemic necrosis of the liver and of treatment-related death in patients with PVTT. Therefore, this strategy is limited to a select group of patients with good hepatic function, patients with PVTT other than in the main or the first branch, and those with

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adequate collateral circulation around the occluded portal vein. Other treatment options include hepatic infusion chemotherapy mainly with 5-fluorouracil and cisplatin with or without interferon [9-11]. However, the efficacy of such treatments is limited, and this regimen can cause considerable stress for patients.

The use of molecular targeted therapy continues to increase. Sorafenib is an oral multikinase inhibitor with antiangiogenic and antiproliferative effects that significantly improves time-to-tumor progression and overall survival (OS) of patients with advanced HCC and is widely used to treat advanced HCC in which curative therapy is not indicated [12-14]. Sorafenib inhibits several tyrosine kinase receptors, including vascular endothelial growth factor (VEGF) receptor (R)-2, VEGFR-3, platelet-derived growth factor receptor β, FLT-3, and C-kit [15]. Although the use of sorafenib is limited to a select group of patients with good hepatic function, it can also be effective for patients with advanced HCC and a poor prognosis, including those with worse ECOG performance status, extrahepatic spread, vascular invasion, older age, and presence of macroscopic vascular invasion or extrahepatic spread [12]. However, care must be exercised due to the fact that sorafenib frequently causes various adverse events (AEs) such as hand-foot syndrome, gastrointestinal hemorrhage, and use-limiting anorexia [12-14].

Radiotherapy (RT) can produce survival benefits in patients with advanced HCC and macroscopic hepatic vascular invasion [7,16-18]. We previously reported that the use of three-dimensional conformal RT (3D-CRT) resulted in a good disease control rate and prolonged survival in these patients. Because of a high induction rate of stable disease (SD), both responders and nonresponders had improved outcomes when compared with patients who received supportive care alone [8,17]. Another advantage of 3D-CRT is that treatment can be administered on an outpatient basis without the difficulties associated with TACE or hepatic infusion chemotherapy, and RT did not produce grade 3 or higher liver, gastrointestinal, or hematological toxicity [8,17].

The goal of the present study was to compare the survival benefit of sorafenib versus RT in two retrospective cohorts of patients with advanced HCC and PVTT in the main trunk or the first branch. Propensity score analysis was used to reduce biases, and potential predictors of survival were analyzed using a Cox model.

Methods

Study population

Ninety-seven patients with macroscopic hepatic vascular invasion were retrospectively reviewed following approval by the institutional review board at Kitasato University East Hospital. Study protocols were conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written, informed consent. HCC with macroscopic hepatic vascular invasion included patients with portal tumor invasion involving first-order branches and the main trunk of the portal vein, and venous thrombosis in the hepatic vein trunk or inferior vena cava. A diagnosis of tumor invasion and macroscopic hepatic vascular invasion was established in all patients by computed tomography (CT) on the basis of the following criteria: (i) a low-attenuation intraluminal filling defect with expanded macroscopic hepatic vascular invasion adjacent to the primary tumor during the portal phase, and (ii) an enhanced inner side of the filling defect during the arterial phase. Forty patients treated with sorafenib enrolled in the Kanagawa Liver Study Group (four institutes in Kanagawa Prefecture in Japan) and 57 consecutive HCC patients treated with RT in Kitasato University East Hospital (Sagamihara, Kanagawa, Japan) were examined. Overall survival (OS) and AEs were compared between the two groups of the entire cohort and in a PS-matched cohort. Factors potentially associated with OS were analyzed statistically in a PS-matched model. Treatment response was not compared, because the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) and the modified RECIST criteria, which are commonly used for patients with HCC treated with sorafenib, were not adapted for use in patients with macroscopic hepatic vascular invasion [19,20]. The follow-up period was from initiation of treatment to the time of death. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Sorafenib group

From July 2009 through November 2011, a total of 40 patients with advanced HCC with macroscopic hepatic vascular invasion and chronic liver disease of mainly Child-Pugh (C-P) class A received sorafenib at four institutes in Kanagawa Prefecture in Japan (Kitasato University East Hospital, Sagamihara; Yokohama City University Hospital, Yokohama; St. Marianna University Hospital, Kawasaki, and Kanagawa Cancer Center, Yokohama). Eligibility criteria for treatment with sorafenib were as follows: (i) unresectable advanced HCC without HCC rupture; (ii) no effect of TACE; (iii) no previous sorafenib therapy for the liver tumor; (iv) C-P class A or B (up to a score of 7 points) hepatic function; (v) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 [21]; and (vi) the following laboratory findings: neutrophil count above 1500/μL, platelet count above 7.5×10^4 mm^3, and serum hemoglobin level above 8.5 g/dL. Patients initially received a standard dose of sorafenib, 400 mg twice daily (800 mg/day) or 200 mg twice daily (400 mg/day) for those with low body weight. The dose

was reduced or treatment was temporarily suspended in patients who had drug-related grade 2–4 toxicities (until recovery to grade 1 or less) or at the discretion of the treating physician. The initial reduced dose of sorafenib was 400 mg/day. The dose was increased to the standard dose level in accordance with each patient's tolerance. Treatment was continued until radiologic progression or recurrence of HCC, unacceptable toxicity associated with the study drug, or withdrawal of consent.

RT group

From July 2001 through November 2011, 57 consecutive patients with advanced HCC and macroscopic hepatic vascular invasion initially received 3D-CRT at Kitasato University East Hospital, Sagamihara, Japan. Inclusion criteria for patients who received RT were as follows: (i) unresectable HCC with macroscopic hepatic vascular invasion; (ii) C-P class A or B hepatic function; (iii) an ECOG performance status of 0–2; (iv) no refractory ascites; and (v) no previous radiation therapy of the liver. The RT procedure was performed as described previously [8,17]. Briefly, macroscopic hepatic vascular invasion was mainly irradiated, regardless of the presence or absence of multinodular HCC. RT doses and treatment angles were determined with the use of a 3D-view technique to minimize critical organ injury. CT planning was used to determine radiation fields and the clinical target volume (CTV), which was defined as only the macroscopic hepatic vascular invasion. The main HCC was also irradiated together with hepatic vascular invasion if the tumor was directly involved. Other multiple nodules were not always included in the CTV. 3D-CRT was planned according to tentative guidelines to ensure that the normal liver volume irradiated with more than one half of the prescribed dose did not exceed 50% of the total liver volume. A daily radiation dose of 1.8 to 2.0 Gy was administered with a 6- or 10-MV X-rays using two- to four-port combinations. Five fractions were administered per week to deliver a total dose of around 50 Gy.

Statistical analysis

The overall survival rates of patients who underwent sorafenib or RT were calculated from the date of diagnosis of macroscopic hepatic vascular invasion. The primary end point was all-cause mortality. The Chi-square or Fisher's exact test was used to compare categorical variables, whereas Student's *t*-test or the Mann–Whitney *U* test was used for continuous variables. The Kaplan-Meier method was used to obtain the cumulative survival rate. PS analysis was performed using multiple logistic regression to analyze patients treated with sorafenib or RT. Variables associated with treatment decisions were entered in the PS model. The PS model was then used to provide a one-to-one match between the sorafenib and RT groups by the nearest-neighbor matched method [22]. In each matched subgroup, survival curves were compared using the log-rank test. Variables that achieved significance ($P < 0.05$) or those that were close to significance ($P < 0.15$) by the log-rank test were subsequently included in the multivariate analysis using a forward stepwise Cox regression model for the analysis of factors associated with OS, with adjustments for confounding factors. A two-tailed $P < 0.05$ was considered significant. All statistical analyses were performed

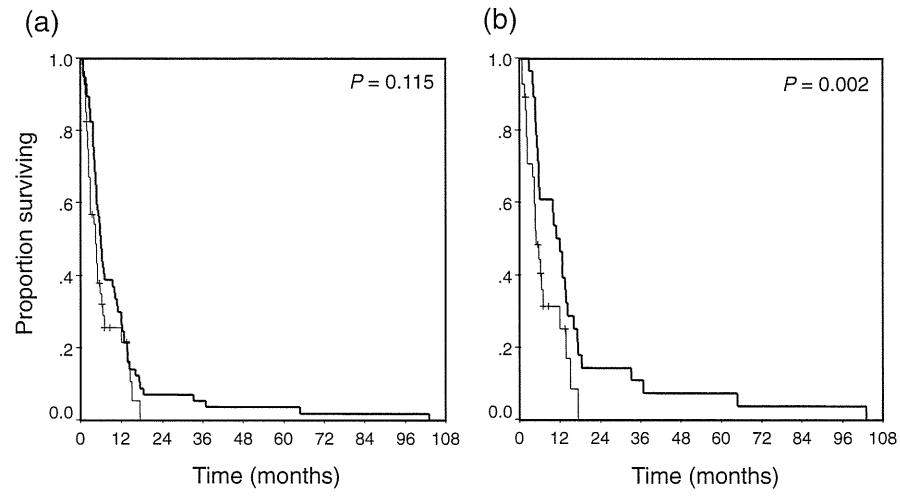

Figure 1 Kaplan-Meier curves for OS of the RT (bold lines) and sorafenib (solid lines) groups. (a), all patients (n = 97) and **(b)**, PS-matched patients (n = 56). Although no significant difference between the two groups is observed in **(a)** ($P = 0.115$), OS in the PS-matched patients is significantly longer in the RT group (median 10.9 months) than in the sorafenib group (median 4.8 months), as shown in **(b)** ($P = 0.002$, log-rank test).

Table 1 Baseline characteristics of 64 patients with Child-Pugh class A and 56 patients matched by propensity score

	Entire cohort			PS-matched cohort		
	Sorafenib	RT	*P* value	Sorafenib	RT	*P* value
Covariates	n = 36	n = 28		n = 28	n = 28	
Age (years)	70 (62–78)	67 (61–71)	0.069	70 (61–78)	67 (61–70)	0.04
Sex (male/female)	31/5	19/9	0.127	23/5	19/9	0.355
HCV	19/17	17/11	0.615	16/12	17/11	1.0
*Main/first branch	7/29	9/19	0.262	7/24	9/19	0.205
Metastases (present/absent)	7/29	2/26	0.278	6/22	2/26	0.252
Previous Treatments (present/absent)	26/10	20/8	1.0	18/10	20/8	0.775
TACE/TAI	21	20		15	20	
RFA	3	0		2	0	
RT	2	0		1	0	
AFP (ng/dL)	1047 (44–5919)	43 (10–1096)	0.005	680 (37–3708)	43 (10–1096)	0.144
DCP (mAU/mL)	2915 (111–19706)	224 (33–2880)	0.013	2151 (58–10775)	224 (33–2880)	0.488

Data are presented as medians (range).
Abbreviations: *TACE* transarterial chemoembolization, *TAI* transarterial infusion chemotherapy, *RFA* radiofrequency ablation, *RT* radiotherapy, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PS* propensity score.
*Portal tumor invasion to the main trunk or first branch.

using the Statistical Package for Social Sciences (SPSS 17.0 for Windows, SPSS, Inc. Chicago, IL).

Results

Patient characteristics and crude OS in response to sorafenib versus RT

All patients (n = 97) underwent either sorafenib (n = 40) or RT (n = 57) treatment. In the sorafenib group, 28 patients initially received a dose 400 mg of sorafenib twice daily (800 mg/day), while 12 received a dose of 200 mg of sorafenib twice daily (400 mg/day) because of older age, low body mass index, or anorexia. The mean duration of treatment with sorafenib was 45 days (range, 7–400 days).

A total radiation dose of 30 to 56 Gy (median 50 Gy) was delivered, and a combination of PVTT and hepatic vein tumor thrombosis (HVTT) was observed in 10 patients in the RT group. The sorafenib group had significantly better hepatic function of C-P class A/B (sorafenib 36/4 and RT 34/23 patients, respectively, $P = 0.001$) and median platelet counts than the RT group (sorafenib 15.1 and RT $11.8 \times 10^4/mm^3$, respectively, $P = 0.004$). Tumor thrombosis in the main portal trunk was significantly more common in the RT group than in the sorafenib group (main/first branch: sorafenib 7/33 and RT 22/35 patients, respectively, $P = 0.021$). Otherwise, age, sex, the proportions of anti-hepatitis C virus-positive and of extrahepatic spread, and the median values of laboratory findings including α-fetoprotein and des-γ-carboxy prothrombin were not significantly different between the two groups. Thirty-three patients treated with sorafenib died (83%), while 57 treated with RT died during the observation period. Despite the fact that the RT study population had significant worsening of hepatic function and tumor progression in comparison with the sorafenib group, crude OS was not significantly different between the two groups [$P = 0.115$, 4.4 months (range, 0.7-17.5) in the sorafenib group, and 5.9 months (range, 0.6-103) in the RT group], as shown in Figure 1a.

OS and factors related to OS in the PS-matched population

A total of 64 patients with C-P class A hepatic function and PVTT only. (sorafenib; n = 36, RT; n = 28) was extracted for PS analyses, as shown in Table 1 and Figure 2. Six of the 34 RT group patients with C-P class A were excluded because they had a combination of PVTT and HVTT. Significant differences between these two groups were observed in baseline levels of the tumor markers α-fetoprotein and des-γ-carboxy prothrombin (DCP). PS analysis with the one-to-one nearest-neighbor matching

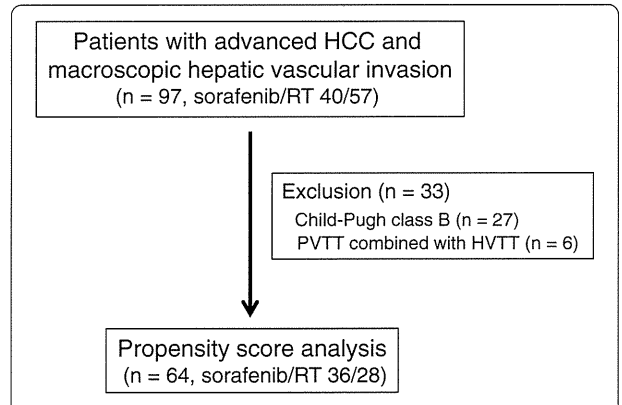

Figure 2 Enrollment of patients. HCC: hepatocellular carcinoma; RT: radiotherapy; PVTT: portal vein tumor thrombosis; HVTT: hepatic vein tumor thrombosis.

Table 2 Cox regression analysis of factors potentially related to overall survival

	Log-rank test		Cox		
Covariates	n	*P* value	*P* value	HR	95% CI
Age (≥70/<70 y)	33/23	0.355			
Sex (male/female)	42/14	0.424			
HCV (present/absent)	34/22	0.58			
*Main trunk (present/absent)	16/40	0.612			
Extrahepatic spread (present/absent)	5/51	0.278			
Previous treatments (present/absent)	38/18	0.546			
AFP ≥ 100 (ng/dL)	28/28	0.073			
DCP ≥ 1000 (mAU/mL)	27	0.066	0.024	1	
<1000	29			0.508	0.282, 0.915
Sorafenib	28	0.002	0.007	1	
RT	28			0.434	0.235, 0.779

Abbreviations: *HCV* hepatitis C virus, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *RT* radiotherapy, *HR* hazard ratio, *CI* confidence interval.
*Portal invasion to the main trunk.

method was conducted to minimize selection bias and to adjust backgrounds. The two PS-matched groups (28 patients per group) were well balanced, as shown in Table 1. The PS-matched model was validated by the Hosmer and Lemeshow goodness-of-fit test ($P = 0.091$) and by the value of the area under the curve (0.719; 95% CI, 0.594-0.844). In the PS-matched cohort, the median OS was significantly shorter in the sorafenib group (4.8 months; range, 0.7-17.3) than in the RT group (10.9 months; range, 2.8-103; $P = 0.002$, log-rank test), as shown in Figure 1b. Cox regression analyses showed that DCP <1000 mAu/mL at pretreatment and RT were independent contributors to OS ($P = 0.024$; HR, 0.508; 95% CI, 0.282 to 0.915; $P = 0.007$; HR, 0.434; 95% CI, 0.235 to 0.779, respectively) (Table 2).

Treatment tolerability

Treatment tolerability was analyzed by comparison of the AEs between the sorafenib and RT groups matched according to PS score. In the sorafenib group, 25 (90%) of 28 patients permanently discontinued sorafenib (due to AEs, n = 15; disease progression, n = 10). There was no radiographic or clinical evidence of pancreatitis, and there were no drug-related deaths. As shown in Table 3, AEs of grade 3 or more were observed in 19 patients, and almost all AEs were related to the liver (AST/ALT increase in six patients, anorexia/nausea in four patients, hepatic failure in one patient, and ascites in one patient). In the RT group, there was no grade 3 or higher gastrointestinal or hepatic toxicity, including anorexia/nausea, gastric ulcer, increase in AST/ALT, or hepatic failure. Grade 3 leukocytopenia was observed in only one patient. There were no long-term sequelae.

Discussion

PS analysis demonstrated that RT was associated with better survival than sorafenib in patients with advanced unresectable HCC and PVTT. PVTT occurs in a substantial portion of HCC patients and is evident in up to approximately 40% of HCC patients at the time of death [7,9,23]. Sorafenib is an oral multikinase inhibitor that prolongs survival and the time to progression in patients with advanced HCC. This drug is also effective in patients with advanced HCC and poor prognosis, including those with worse ECOG performance status, extrahepatic spread,

Table 3 Comparison of AEs between sorafenib and RT

	Sorafenib	RT
Grade 3/4 toxicity		
Total (n)	19	1
AST/ALT increased	6	0
Anorexia/nausea	4	0
HFSR	3	0
Hepatic Failure	1	0
Ascites	1	0
Hypertension	1	0
Proteinuria	1	0
Sepsis	1	0
Thrombocytopenia	1	0
Anemia	0	0
Leukocytopenia	0	1
Pancreatitis	0	0
Discontinuation, n (%)	15 (54)	1 (4)

Abbreviations: *AEs* adverse events, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *RT* radiotherapy, *HFSR* hand-foot-skin reaction.

vascular invasion, older age, and the presence of macroscopic vascular invasion or extrahepatic spread [12]. In a recent PS analysis of sorafenib alone versus sorafenib combined with TACE for advanced HCC (in which 20-30% of the patient population had major trunk PVTT), neither regimen produced a significant benefit in OS [24]. We previously reported that RT produced favorable survival benefits without the hardships associated with conventional treatment for macroscopic hepatic vascular invasion [8,17].

The current study demonstrated that DCP <1000 mAu/mL at pretreatment and RT were independently related to OS, according to a Cox model in a PS analysis. The serum DCP level correlates with intrahepatic vascular invasion, and the DCP level might reflect expansion of macroscopic hepatic vascular invasion [25]. These findings suggest that the first goal of therapy for advanced HCC with major PVTT should consist of intensive treatment to recanalize the PVTT. RT is more effective than sorafenib, because major PVTT is intensively irradiated by RT. In fact, the overall objective response rate (complete response plus partial response) for PVTT by RT reached 45%, and the response rate was even better in patients with C-P class A [17]. In addition, 3D-CRT for PVTT can minimize liver-related AEs (Table 3). Almost all patients receiving sorafenib discontinued therapy (due to AEs or disease progression), while only one patient discontinued RT. Involvement of the main PVTT is associated with poor prognosis, possibly because of increased risk of tumor spread, elevated portal venous pressure causing variceal hemorrhage, and decreased portal flow resulting in ascites, jaundice, hepatic encephalopathy, and liver failure [7,9,23,26]. Sorafenib can compromise hepatic function by decreasing portal blood flow, as we previously demonstrated that sorafenib induced significant vasoconstriction of the portal venous area and significantly reduced portal venous flow, according to Doppler ultrasonography in patients with unresectable HCC [27]. Other investigators have used magnetic resonance imaging to show similar results [28]. Therefore, we believe that sorafenib should be administered only after recanalization of major PVTT by other treatments [9].

The optimal treatment regimen for patients with unresectable HCC and PVTT remains to be established. C-P class A hepatic function is likely related to the treatment response and survival, because it was previously identified as one of the factors contributing to OS in various treatments for HCC. Furthermore, we previously reported that C-P class A hepatic function was related to the response to RT [17]. Conversely, patients with C-P class B hepatic function tend to have a poor response to treatment, because treatments often further impair hepatic function.

Limitations of the current study include the small study population, as the number of patients with HCC and major PVTT is relatively small in the general population. Furthermore, this was a non-prospectively randomized study, and the evaluation of responsiveness to sorafenib may have been incomplete due to the involvement of different institutions. Therefore, OS and contributing factors were analyzed by PS analysis.

Conclusions

First-line therapy for unresectable HCC with PVTT should consist of RT rather than sorafenib. Sorafenib should be introduced after recanalization of PVTT by other treatments, including RT. Multidisciplinary therapies based on individual hepatic function are expected to improve outcomes in the future.

Abbreviations

RT: Radiotherapy; HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombosis; HVTT: Hepatic vein tumor thrombosis; PS: Propensity score; TACE: Transarterial chemoembolization; OS: Overall survival; VEGF: Vascular endothelial growth factor; AE: Adverse event; 3D-CRT: Three-dimensional conformal RT; RECIST: Response Evaluation Criteria in Solid Tumors; C-P: Child-Pugh; ECOG: Eastern Cooperative Oncology Group; CTV: Clinical target volume.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: TN, HH, YO, YT, and JT; analysis: TN and YO; treatment and data collection: TN, HH, YO, YT, JT, and TM; drafting article: TN and AS; critical revision: MW, SK, and KW. All authors read and approved the final manuscript.

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Original Article

Radiofrequency ablation combined with chemolipiodolization in a porcine liver: Comparison of the pharmacokinetic analysis with cisplatin powder and miriplatin

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Aim: To compare the pharmacokinetics of radiofrequency (RF) ablation with chemolipiodolization using cisplatin (CDDP) powder and miriplatin (MPT) in a porcine liver.

Methods: Twelve pigs were divided equally into four groups. After each CDDP powder-lipiodol suspension (n = 6; groups A and B) or MPT-lipiodol suspension (n = 6; groups C and D) was injected into the lateral left artery, one RF ablation was performed at the lateral left lobe of each pig. Six pigs (groups A and C) were killed on the same day as treatment, whereas the other pigs (groups B and D) were killed 7 days after the treatment. The platinum concentrations in venous blood were assayed at 15, 60 and 120 min, and 7 days after treatment. The platinum concentrations in the ablated area and the surrounding liver were also examined.

Results: Plasma platinum concentrations of the CDDP group peaked at 15 min, and then gradually diminished over time (μg units), while plasma platinum levels in the MPT group gradually increased over time (ng units). Liver tissue platinum concentrations of the CDDP group were significantly lower in non-ablative areas than in ablated areas at days 0 and 7, while liver concentrations of the MPT group were significantly higher in non-ablative areas than in ablated areas at day 7.

Conclusion: MPT may be a suitable chemotherapeutic agent to stagnate platinum in the surrounding liver.

Key words: chemolipiodolization, cisplatin, hepatocellular carcinoma, miriplatin, pharmacokinetics, radiofrequency ablation

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignant diseases in Asia and Africa.[1] Radiofrequency (RF) ablation is a useful procedure for treating unresectable HCC,[2] and good outcomes have been obtained with respect to survival and local control. Several reports have also demonstrated that transcatheter arterial chemoembolization (TACE) combined with RF ablation is superior to RF ablation alone because of expansion of the ablation size.[3–7]

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Transcatheter arterial chemoembolization is also an effective procedure for unresectable HCC.[8] Several intra-arterial anticancer drugs including platinum and anthracycline agents are used for chemolipiodolization in HCC. However, the optimum anticancer drug for HCC remains unclear. In Japan, a fine-powder formulation of cisplatin (CDDP) (DDPH, IA-call; Nippon Kayaku, Tokyo, Japan) and miriplatin (MPT) (Miripla; Dainippon Sumitomo, Osaka, Japan)[9–11] is presently used as a platinum agent for intra-arterial infusion. CDDP powder is rather hydrophilic and barely soluble in iodized oil (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France). Several studies have demonstrated the benefits of hepatic arterial injection chemotherapy with CDDP suspended in lipiodol for HCC.[12,13] MPT is a lipophilic agent, and is easily suspended in lipiodol. The platinum component is released gradually over a long

period. However, the optimal antitumor agent for RF ablation combined with TACE remains unknown. Furthermore, there are little comparative data on the pharmacokinetics of these two platinum agents at treatment. Thus, in the present study, we evaluated the pharmacokinetics of two platinum agents (CDDP and MPT) at RF ablation combined with chemolipiodolization.

METHODS

Animal study

THE STUDY DESIGN was approved by the ethics committee of Juntendo University Nerima Hospital. Animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals published by the Juntendo University School of Medicine. Twelve pigs with an average weight of 61 kg (range, 59–68) were equally divided into four groups. Group classification into CDDP powder and MPT treatment is shown in Table 1.

Animals were anesthetized by i.m. injection of medetomidine (80 μg/kg) and ketamine (5 mg/kg). After intubation, dexamethasone (0.1 mg/kg) was i.m. injected. Oxygen and nitrous oxide (1:1 ratio) inhalation was performed, and anesthesia was maintained with halothane. Cardiac and respiratory parameters and oxygen saturations were monitored throughout the experiments. With the animals in the supine position, an electrode pad was attached to the flank, and a laparotomy was performed by a median abdominal incision. A 4-Fr sheath was inserted into the right femoral artery by cutting down the inguinal skin of the animal. Another 4-Fr sheath was placed into the right femoral vein for blood sampling. A 4-Fr catheter (Cobra; Terumo Clinical Supply, Gifu, Japan) was then placed into the celiac artery and the inferior vena cava.

A suspension of CDDP powder (35 mg; equivalent to 19.5 mg platinum content) plus lipiodol (3 mL) (groups A and B) or MPT 70 mg (equivalent to 17.5 mg platinum content) plus lipiodol (3 mL) (groups C and D) was injected slowly under fluoroscopic monitoring into the lateral left hepatic artery using a 2.7-Fr microcatheter (Gadelius Medical, Tokyo, Japan). Subsequently, one RF ablation was performed at the lateral left lobe in each porcine liver. In this experiment, we used an RF3000 radiofrequency ablation system (Boston Scientific, Natick, MA, USA) with an expansion-type electrode. All pigs were treated with a 15-cm long, 17-G, 2.0-cm expandable eight-hook needle electrode under inspection.

Six pigs (groups A and C) were killed with an overdose of pentobarbital sodium 120 min after administration, and the other six pigs (groups B and D) were killed by the same method at 7 days after the treatment. Subsequently, the treated livers were explanted.

Platinum concentration of blood samples

The blood sampling schedule is shown in Figure 1. Blood samples were obtained just beneath the right atrium via the vena cava inferior prior to the treatment at 15, 60 and 120 min, and 7 days after treatment. The samples were collected into Na-ethylenediaminetetraacetic acid-coated tubes. Plasma was separated by centrifugation, and an aliquot of plasma then immediately transferred to an Amicon ultrafiltration system (Millipore, Billerica, MA, USA)

Table 1 Group classification

Group	Pig no	Bodyweight (kg)	Date of death	Anticancer drug	Lipiodol (mL)
	1	65	0		3.5
A	2	63	0	CDDP 35 mg	3.5
	3	65	0		3.5
	4	69	7		3.5
B	5	63	7	CDDP 35 mg	3.5
	6	60	7		3.5
	7	68	0		3.5
C	8	65	0	MPT 70 mg	3.5
	9	60	0		3.5
	10	66	7		3.5
D	11	62	7	MPT 70 mg	3.5
	12	59	7		3.5

CDDP, cisplatin; MPT, miriplatin.

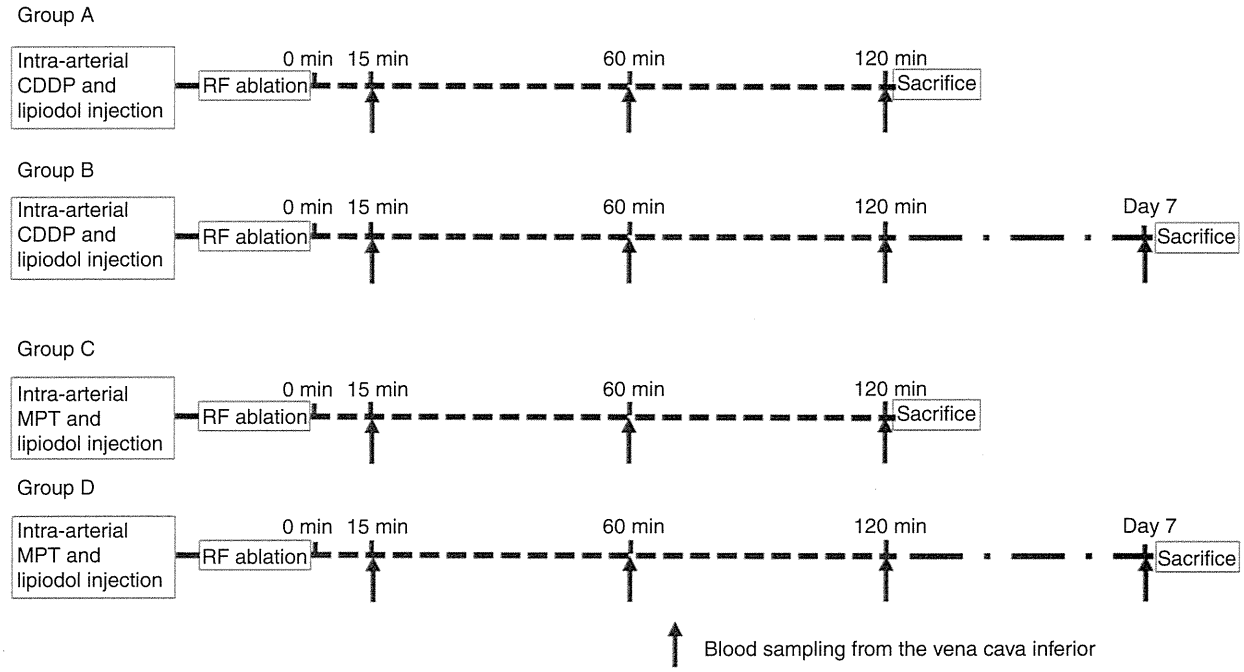

Figure 1 Study protocol of radiofrequency ablation (RF) ablation following chemolipiodolization and blood sampling. CDDP, cisplatin. MPT, miriplatin.

and centrifuged for another 10 min. The plasma and filtered plasma were stored at −80°C until platinum analysis. Subsequently, the total (protein-bound and unbound) and free (protein unbound) platinum concentrations of blood samples were measured by atomic absorption spectroscopy (SIMAA 6000; Perkin Elmer, Waltham, MA, USA). Measurements of the plasma platinum concentrations of the MPT-treated groups were also made by inductive coupled plasma atomic emission spectrometry (ICP-AES; Perkin Elmer)[14] as the detection limit of the atomic absorption spectrometer was 0.05 μg/mL.

Platinum concentration of liver specimens

The total platinum concentrations were determined in two samples from the ablated areas and two samples from each of two non-ablated surrounding liver tissues (1 and 3 cm distant to the portal hepatic side from the ablated area). The platinum concentrations of liver specimens were also measured by atomic absorption spectroscopy.

Statistical analysis

Data are presented as individual data points or means ± standard deviation. Statistical significance was evaluated with one-way ANOVA. The homogeneity of the variances was analyzed by the Levene test. In cases in which the variances were unequal, post-hoc multiple comparisons were made using the Games–Howell method. All statistical analyses were performed using PASW Statistic software (version 17.0 for Windows; SPSS Japan, Tokyo, Japan). All tests were two-sided and values of $P < 0.05$ were considered statistically significant.

RESULTS

Plasma platinum concentrations

THE TIME COURSES of total and free platinum in venous blood are shown in Figure 2(a). Total and free platinum concentration of the CDDP group peaked at 15 min (1.09 ± 0.17 and 0.147 ± 0.055 μg/mL, respectively), and then gradually diminished over time in the μg range. By contrast, total platinum concentration of the MPT group was undetectable at all times in the μg/mL range. However, as shown in Figure 2(b), total platinum concentration in the MPT group gradually increased over time in the ng range, and levels were approximately sixfold higher at 7 days than at 15 min.

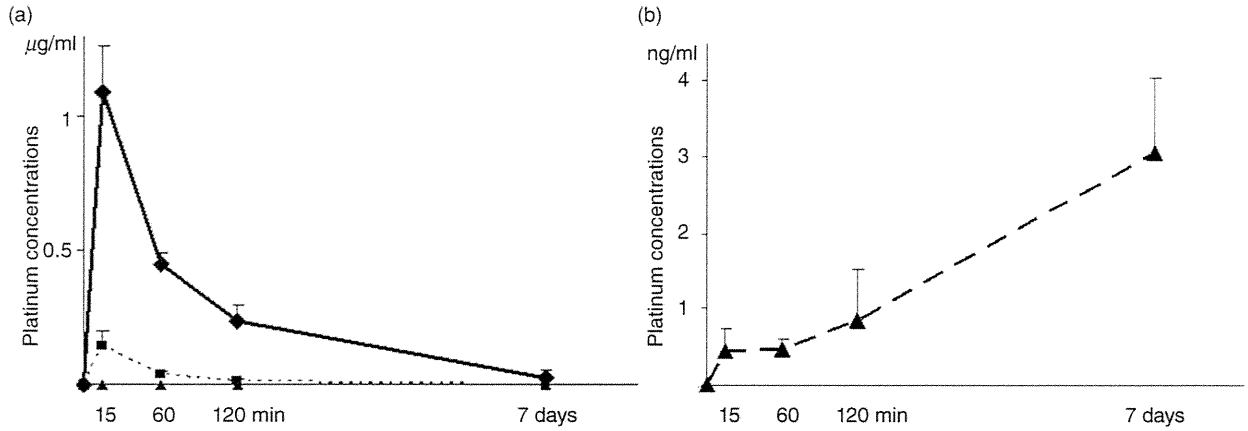

Figure 2 Time course of the plasma platinum (Pt) concentrations. (a) In the cisplatin (CDDP)-powder group, total and free Pt concentration peaked at 15 min after radiofrequency ablation and then gradually decreased over time in μg units. In the miriplatin (MPT) group, total Pt concentration was undetectable level at any blood sampling points in the μg range. (b) Plasma platinum concentrations of miriplatin increased gradually over time in the ng range. Data represent mean ± standard deviation. $n = 6$ per group at 15, 60 and 120 min and $n = 3$ per group at 7 days. —•—, total Pt of CDDP group; ···•···, free Pt of CDDP group; --•--, total Pt of MPT group; —•—, total Pt of MPT group.

Platinum concentrations of liver specimens

As shown in Figure 3(a), the total platinum concentrations of liver tissue treated with CDDP powder were significantly higher in the ablated area than at 1 and 3 cm away from the ablated zone at days 0 and 7 ($P < 0.05$). By contrast, the total platinum concentrations of liver tissue treated with MPT were significantly higher at 1 and 3 cm away from the ablated zone than in the ablated area at day 7 ($P < 0.05$) (Fig. 3b). The ratios of total platinum concentrations of the surrounding liver at 1 and 3 cm away from the ablated zone compared with the ablated area at day 7 were 0.33 and 0.29, respectively, for the CDDP powder group, and 1.78 and 2.69, respectively, for the MPT group.

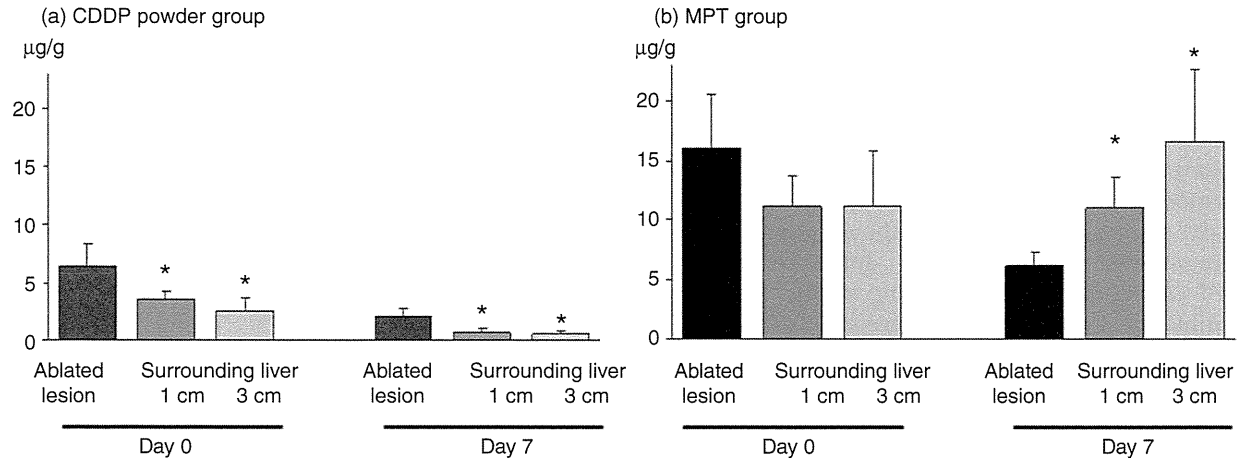

Figure 3 Platinum (Pt) concentrations of liver specimens at day 0 and day 7. (a) In the cisplatin (CDDP)-powder group, there were significant differences between Pt concentrations at ablated areas versus non-ablated areas at day 0 and day 7. (b) In the miriplatin (MPT) group, significant differences in the Pt concentrations were found between ablated areas and 1 or 3 cm away from the ablated areas. Data represent the mean ± standard deviation. $n = 6$ (from three animals) per group at each point. *$P < 0.05$ vs ablated areas.