Table 3. Preoperative Therapy (n = 15) and Details of Hepatic Resection (n = 34) in Patients with Hepatocellular Carcinoma with Vp3/4 or Vv3

Variable	n
Preoperative TACE	15
TE4 (tumor reduction or necrosis 100%)	0
TE3 (tumor reduction or necrosis 50–100%)	6
TE2 (other than TE3 or TE1)	9
TE1 (tumor growth more than 25%)	0
Liver resection	34
Major liver resection (3 or more segments)	25
Minor liver resection	9
Sectionectomy	5
Segmentectomy	4

TACE, transcatheter arterial chemoembolization; TE, therapeutic effect.

minutes) and the median operative blood loss during surgery was 1,983 mL (range 189 to 25,491 mL). The median THVE time was 15 minutes (range 7 to 48 minutes). One hospital death (2.9%) occurred in 1994. Three patients had postoperative complications related to hyperbilirubinemia (total bilirubin > 5 mg/dL), and 1 patient had disseminated intravascular coagulation syndrome. These severe postoperative complications occurred only in patients who underwent liver resection during the first decade in our 20-year experience. The other postoperative complications are shown in Table 4.

Survival and prognostic factors

To determine whether a hepatic resection provided patients with improved prospects for survival, the overall survival of

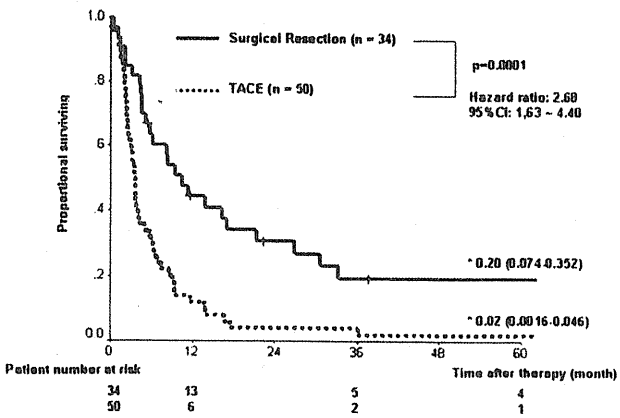

Figure 1. Overall survival after treatment. Two groups were compared by the Kaplan-Meier method. Patients with hepatocellular carcinoma (HCC) with tumor thrombus were divided into hepatectomy (n = 34) and transcatheter arterial embolization (TACE) (n = 50) groups. We calculated the hazard ratio and 95% CI. *Indicates the proportional surviving rate and 95% CI for the 60-month time point.

Table 4. Postoperative Morbidity and Mortality in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma with Vp3/4 or Vv3 (n = 34)

Complication	n (%)
Morbidity	15 (44)
Hyperbilirubinemia (T-Bil > 5 mg/dL)	3
Pneumonia	1
Pleural effusion	2
Ascites	3
Biliary leakage/fistula	3
Disseminated intravascular coagulation	1
Intra-abdominal hemorrhage	1
Upper gastrointestinal bleeding	1
Pulmonary thromboembolism	1
Mortality	1 (2.9)
Hospital death	1
Operative death	0

all 34 patients who underwent hepatic resection was compared with that of the 50 patients who underwent TACE alone. Patient characteristics are shown in Table 2. Although our results showed that the incidence of patients with multiple tumors and that of patients with ICGR15 >15% in the TACE only group were higher than those in the resection group, the overall survival was significantly different between patients undergoing hepatic resection (n = 34) and TACE (n = 50; p = 0.0001; Fig. 1). We also calculated the hazard ratio and 95% CI between the 2 groups. The hazard ratio was 2.68 and 95% CI was 1.63 to 4.40. The proportional survival rate for the 60-month time point was 0.20 (95% CI 0.074 to 0.352) in the resection group and 0.02 (95% CI 0.0016 to 0.046) in the TACE group (Fig. 1).

To determine the prognostic factors for survival, we performed a variable selection procedure in the Cox proportional hazards regression model in the 34 patients who underwent hepatectomy. The efficacy of preoperative TACE (TE2 or less), the tumor diameter (10 cm or greater), the surgical margin (positive), and the blood loss during surgery were selected as prognostic factors for overall survival in patients who underwent hepatic resection for HCC with a tumor thrombus invading the major vasculature in the univariate Cox analysis (Table 5). We selected the variables that were significant in the univariate Cox analysis. Then, including selected variables, we performed the Cox proportional hazard model with a stepwise selection procedure. A positive surgical margin was not significant in the first step. Preoperative TACE (TE2 or less), tumor diameter (10 cm or greater), and the blood loss during surgery were selected as significant favorable prognostic factors (Table 6).

Table 5. Univariate Analysis of Prognostic Factors Using Cox Proportional Hazards Regression Model in Patients with Hepatocellular Carcinoma (Vp3/4 or Vv3) Who Underwent Hepatic Resection (n = 34)

Variables/categories	n	MST, mo	Hazard ratio	95% CI		p Value
				Lower	Upper	
Age, y			0.86	0.37	1.79	0.60
≥ 60	20	11.4				
< 60	14	8.2				
Sex			1.51	0.44	5.15	0.51
Male	29	9.5				
Female	5	10.5				
Virus status			1.83	0.77	4.35	0.17
HBV or HCV (+)	23	23.0				
NBNC	11	16.9				
ICGR15, %			0.84	0.38	1.86	0.67
≥ 15	14	6.2				
< 15	20	10.5				
AFP, ng/mL			1.0	0.43	2.34	>0.9
≥ 10,000	12	5.7				
< 10,000	22	11.4				
Preoperative TACE			2.98	1.01	8.80	0.048
TE3	6	33.1				
TE2 or less	28	8.2				
No. of tumors			1.96	0.87	4.39	0.10
Solitary	16	16.9				
Multiple	18	5.2				
Tumor diameter, cm			3.11	1.36	7.13	0.007
< 10	21	16.2				
≥ 10	13	5.2				
Surgical margin			2.62	1.12	6.11	0.026
Positive	18	8.2				
Negative	16	21.3				
Operation time, min			1.71	0.80	3.67	0.17
< 355	18	13.8				
≥ 355	16	5.2				
Blood loss, mL			2.88	1.30	6.37	0.009
< 1,983	17	21.3				
≥ 1,983	17	4.6				

AFP, α-fetoprotein; HBV, hepatitis B virus antigen positive; HCV, hepatitis C virus antibody positive; ICGR15, indocyanine green retention rate at 15 minutes; MST, median survival time; NBNC, non-B nor non-C; TACE, transarterial chemoembolization; TE, therapeutic effect.

To determine which patients had better survival, we examined survival by dividing 3 subgroups stratified by the 2 favorable factors (maximal tumor diameter and the effectiveness of TACE) identified in the Cox proportional hazard model. Patients with a tumor diameter less than 10 cm and a favorable effect of preoperative TACE (TE3) had more favorable survival compared with patients with a tumor diameter 10 cm or greater and a worse effect of preoperative TACE (TE2) or no performance of preoperative TACE. The median survival time in patients with a tumor size 10 cm or greater and a worse effect of preoperative TACE (TE2) or no performance of preoperative TACE was 4.7 months, so these patients seemed to be contraindicated for hepatic resection (Fig. 2).

DISCUSSION

This study suggests that aggressive surgical treatment to achieve extirpation of HCC with major vascular invasion may prolong survival in selected patients. Our study included a relatively large number of patients who had undergone hepatectomy for HCC with Vv3 compared with previous reports.[9,11] Major vascular invasion such as a tumor thrombus of the portal vein or hepatic vein has been

Table 6. Prognostic Factors Identified in the Stepwise Multivariable Cox Proportional Hazards Regression Model in Patients with Hepatocellular Carcinoma (Vp3/4 or Vv3) Who Underwent Hepatic Resection (n = 34)

Variables (category)	Hazard ratio	95% CI		p Value
		Lower	Upper	
Tumor diameter (≥10 cm)	2.78	1.16	6.64	0.022
Blood loss (≥1,983 mL)	3.32	1.39	7.94	0.007
Preoperative TACE (≤TE2)	4.65	1.39	15.5	0.013

Surgical margin (positive) was not selected as statistically significant in the first step of multivariable Cox model.
TACE, transcatheter arterial chemoembolization; TE, therapeutic effect.

reported to be one of the most important prognostic factors for HCC.[3,7] Pawarode and colleagues[19] demonstrated the natural history of HCC to be only 9.7 weeks in patients with HCC and major vascular invasion. Furthermore, portal trunk tumor thrombus may cause portal hypertension, leading to liver failure and a poor prognosis, and HCC with Vv3 may cause various complications such as pulmonary embolism and metastases.[20,21] Therefore, an appropriate strategy for treatment of these highly advanced HCC patients needs to be elucidated.

Some reports have documented that the results after hepatic resection for HCC with major vascular invasion have been disappointing.[6,7] The 5-year survival rate after resection was approximately 10% in patients with HCC with major vascular invasion.[22-24] In our study, patients with

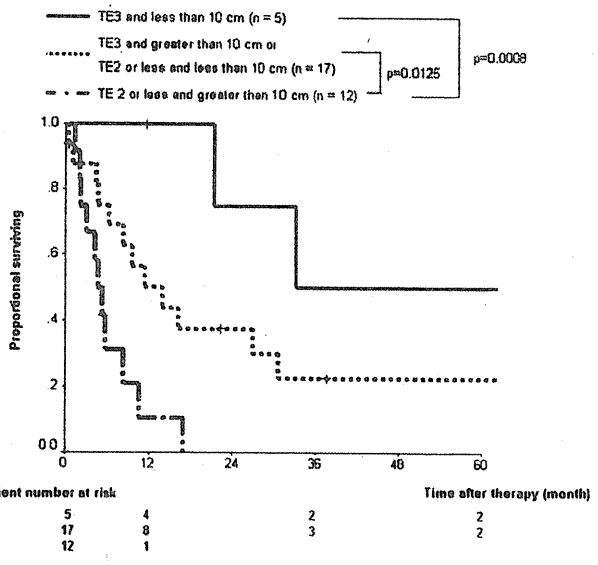

Figure 2. Overall survival after liver resection. Patients with hepatocellular carcinoma (HCC) with tumor thrombus were divided into 3 groups: patients with a tumor size of less than 10 cm and preoperative transcatheter arterial embolization (TACE) efficacy of therapeutic effect (TE)3 (n = 5); patients with a tumor size of less than 10 cm and preoperative TACE efficacy of TE2 or less (n = 16) or preoperative TACE efficacy of TE3 and a tumor size of greater than 10 cm (n = 1); and patients with a tumor size of 10 cm or greater and preoperative TACE efficacy of TE2 or less (n = 12).

HCC and Vp4/3 or Vv3 had better survival after hepatectomy compared with patients treated by TACE alone. However, TACE and transarterial chemotherapy may prolong survival in comparison to the natural history of these advanced HCC patients.[25,26] These findings suggested that TACE is likely to contribute to the control of tumor progression and that combination therapy using hepatectomy and preoperative or postoperative adjuvant therapy may be required for the successful treatment of HCC with major vascular invasion.

The real need is to be able to identify which patients with advanced HCC will require an operation. Our surgical indication for hepatectomy is to proceed to surgery regardless of the number of metastases whenever a remnant functional liver volume is preserved and a potentially curative resection can be performed. Several studies have reported that a large tumor (10 cm or greater in diameter) may be associated with a poorer survival and intrahepatic metastases related to venous invasion, positive surgical margin, and blood loss.[27-29] Consistent with these findings, in our study, the Cox proportional hazards model with a stepwise selection procedure showed a tumor diameter of 10 cm or greater, the blood loss during surgery, and the effectiveness of preoperative TACE, which were selected by referencing previously published reports, to all be prognostic factors for survival.[27-29] It therefore seems likely that a huge tumor is relatively difficult to cure by a resection alone. In this study, the morbidity and mortality rates were not significantly worse compared with those from other reports, suggesting that our surgical indication may be justified.[7,22,23] The results of our study are consistent with those in the report by Minagawa and associates,[14] which showed that preoperative TACE was a useful strategy for the treatment for HCC with portal venous invasion. Their study demonstrated the 5-year survival after hepatic resection to be better than that in other previous and our current reports.[7,22-24,30] In our personal observation, patients with HCC and Vp4/3 or Vv3 had poorer survival after hepatectomy compared with patients with HCC and tumor thrombus invading the more peripheral branch of the portal vein or hepatic vein. The favorable results reported by Minagawa and cowork-

ers[14] may be explained by the fact that their study included HCC with tumor thrombus in the second-order branch of the portal vein (Vp2), which is known to be associated with better survival.[3] On the other hand, our report focused on the treatment for HCC with Vp3/4 and Vv3. Our data showed that patients with HCC who had good treatment results from preoperative TACE (TE3) and a tumor size less than 10 cm in diameter appeared to have a favorable outcome after hepatectomy. Although no significant difference was observed in overall survival in regard to the number of tumors, the median survival time in patients with multiple tumors tended to be short. This suggested that careful attention is required to proceed to surgery in patients with multiple HCC. Patients who had HCC with both a tumor size 10 cm or greater and a less than TE3 result of preoperative TACE may be contraindicated for surgery, suggesting that these patients are likely to undergo palliative therapy.

Sorafenib, an oral multikinase inhibitor, was reported to prolong the survival of patients with advanced HCC in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Asian-Pacific study.[31,32] The outcomes of treating HCC with tumor thrombus in the major vasculature with sorafenib have not yet been well described, but combination therapy using sorafenib and TACE might be another possible neoadjuvant therapy for advanced HCC. Lau and colleagues[33] demonstrated that other neoadjuvant modalities, such as radiation therapy, also improve survival. Ku and associates[34] demonstrated that percutaneous isolated hepatic perfusion for multiple advanced HCC is a promising treatment. A combination of 5-FU and interferon treatment has been reported to be effective for advanced HCC.[35] These findings are consistent with our finding that effective treatment with neoadjuvant therapy may be an important factor for patient selection and surgical indication to prolong survival in these advanced HCC patients.

CONCLUSIONS

In conclusion, a combination of aggressive surgical treatment and effective preoperative TACE for HCC and tumor thrombus invading the major vasculature may be a beneficial treatment strategy in selected patients. Extremely large tumors with major vascular invasion may be currently contraindicated for surgery alone but may be treated by palliative therapy, and such tumors may need to be downstaged by several modalities before resection is performed.

Author Contributions

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Analysis and interpretation of data: Yoshidome, Kimura, Shimizu, Ohtsuka

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肝動脈化学塞栓療法により長期生存したVp4門脈内腫瘍栓を伴う肝細胞癌の1例

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Transcatheter Arterial Chemoembolization Prolonged Survival in a Patient with Advanced Hepatocellular Carcinoma Accompanied by Tumor Thrombus of the Portal Vein Trunk: Shingo Kagawa, Hiroyuki Yoshidome, Fumio Kimura, Hiroaki Shimizu, Masayuki Ohtsuka, Atsushi Kato, Hideyuki Yoshitomi, Katsunori Furukawa, Dan Takeuchi, Tsukasa Takayashiki, Kosuke Suda, Shigetsugu Takano, Satoshi Kuboki and Masaru Miyazaki (*Dept. of General Surgery, Chiba University Graduate School of Medicine*)

Summary

A 50-year-old man having an advanced hepatocellular carcinoma (HCC) was admitted to our institution. An abdominal computed tomogram showed infiltrative mass in the right liver with tumor thrombus invading into the main trunk and contralateral branch of the portal vein. Repetitive transcatheter arterial chemoembolization reduced a tumor size and shrunken portal vein tumor thrombus. The tumor marker levels such as AFP and PIVKA-II decreased. During follow-up, he was diagnosed as having an impending rupture of HCC with acute abdominal pain. He was successfully treated with interventional technique. He died of liver failure 66 months after the first treatment. Although he had a highly advanced HCC with tumor thrombus of the portal vein, repetitive transcatheter arterial chemoembolization therapy may prolong survival. **Key words:** Hepatocellular carcinoma (HCC), Portal vein tumor thrombus, Transcatheter arterial chemoembolization (TACE)

要旨 症例は50歳，男性。発熱を主訴に受診。肝機能障害を認め精査したところ，腹部造影CTにて肝前区域を中心とした境界不明瞭なびまん性の肝細胞癌を認め，両側の門脈枝および門脈本幹に及ぶ門脈内腫瘍栓（Vp4）を伴っていた。肝予備能と予測残肝容積から切除不能と判断し，肝動脈化学（塞栓）療法（Lip-TAI，TACE）を繰り返し施行し，腫瘍の縮小およびAFP，PIVKA-IIの著明な低下を認めた。初回治療後3年目にimpending ruptureを認めたが，TACE施行により止血を得た。以後もTACEを継続し治療した。初回治療後5年6か月にて胆管内腫瘍栓に伴う胆道出血により肝不全が進行し死亡した。本症例はVp4門脈腫瘍栓を伴う肝細胞癌であったが，残肝機能に留意した肝動脈カテーテル療法により長期生存し得る症例も存在することが示唆された。

はじめに

肝細胞癌の治療においては，腫瘍進展度と残肝予備能を考慮した治療法の選択が重要である。門脈腫瘍栓を有した肝細胞癌は予後不良であり，特に高度門脈侵襲例においては根治的治療が不能となる例も少なくない。今回われわれは，Vp4門脈内腫瘍栓を伴う肝細胞癌に対し，肝動脈カテーテル療法（Lip-TAI，TACE）を繰り返すことにより長期生存した1例を経験したので報告する。

I. 症　例

患者: 50歳，男性。

主訴: 発熱。

現病歴: 発熱を主訴に前医受診。血液検査にて肝機能障害を指摘され，精査にて肝細胞癌ならびにC型肝硬変の診断となり精査加療目的に当科紹介となった。輸血歴はなく，アルコールは焼酎4杯/日であった。

入院時現症: 肝を3横指触知した。血液検査所見では肝

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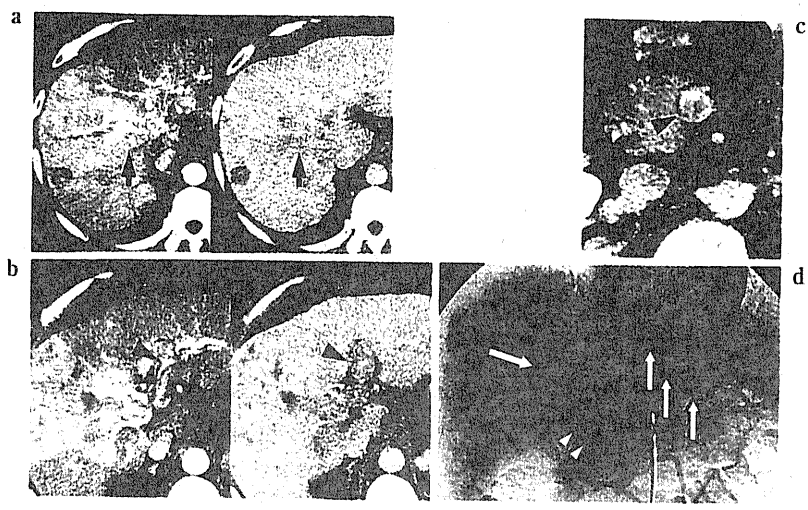
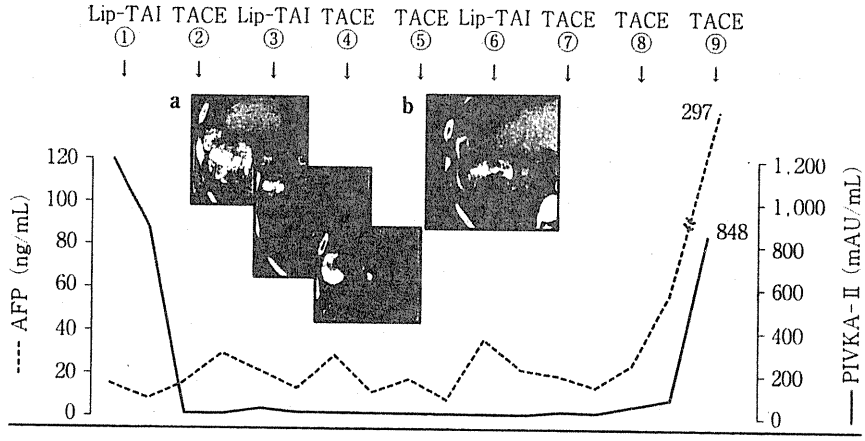


図 1

a,b,c: 腹部造影 CT。前区域に動脈相で濃染する境界不明瞭な，びまん性の腫瘍を認める（黒矢印）。腫瘍栓は門脈臍部，上腸間膜静脈にまで及ぶ（黒矢頭）。
d: 腹部血管造影。前区域および左葉にも腫瘍濃染像を認め（白矢印），門脈本幹は thread and streaks sign を呈する（白矢頭）。



	2004.7	2005.8	2006.4	2007.2	2007.7	2008.2	2008.11	2009.5	2009.11
ICG R_{15} (%)	29.2	39.1	41.9	52.3	—	54.4	57.4	54.3	62.3
Plt ($\times 10^4/\mu L$)	13.8	12.6	12.8	11.4	11.9	10.9	9.3	8.4	9.9
GOT/GPT(IU/L)	156/106	150/141	78/72	130/118	80/83	79/66	99/66	74/53	125/52
T-Bil (mg/dL)	1.4	1.2	1.4	2.0	1.4	1.9	2.0	1.9	2.4

図 2　治療経過

a: 肝動脈カテーテル療法 4 回施行後。肝 S8，S5 肝細胞癌へのリピオドールの集積を認め，門脈内腫瘍栓は縮小している。
b: 肝 S8 腫瘍近傍の被膜下に extravasation を認める。

酵素の異常を認めた。liver damage A，Child-Pugh A（6 点）であったが，肝予備能は ICG R_{15} 29.2% と低下を認めた。腫瘍マーカーは AFP 15.2 ng/mL，PIVKA-II 1,215 mAU/mL と高値であった。

腹部造影 CT（図 1a～c）: 前区域に不整形の enhanced area を認めた。対側門脈枝，門脈本幹に及ぶ腫瘍栓を認めた（Vp4）。

腹部血管造影（図 1d）: 右葉に不整形の腫瘍濃染像を認め，左葉にも約 1 cm 大の腫瘍濃染像が散在していた。門脈本幹は thread and streaks sign を呈していた。

治療経過: 以上から，両側の門脈枝および門脈本幹に及ぶ門脈内腫瘍栓（Vp4）を伴う両葉多発肝細胞癌の診断となり，肝予備能と予測残肝容量から切除不能と判断した。リピオドールと塩酸アクラルビシン（ACR）にメイ

ロンを添加した混合液を使用し肝動脈化学療法（Lip-TAI）を施行した。初回治療後に腫瘍マーカーの著明な低下を認めた。以後は腫瘍選択的に肝動脈化学塞栓療法（TACE）を加えることにより，4回目肝動脈カテーテル療法後には標的結節治療効果度はTE2とコントロールされ，門脈腫瘍栓の縮小も認めていた（図2a）。2007年7月，突然の腹痛を認め，造影CTにてimpending ruptureと診断し緊急TACEにより制御した。その後も肝機能に配慮し，肝動脈カテーテル療法を継続した（図2）。最終的には胆管内侵襲による繰り返す胆道出血のために肝不全が進行し2010年に死亡したが，初回より5年6か月の長期生存が得られた。

Ⅱ. 考　察

門脈腫瘍栓を伴う肝細胞癌は予後不良であり，Vp3/4症例では無治療で生存期間中央値（MST）2.7～4か月，TACEを行った例でもMST 3.8～9.5か月と報告されている[1-4]。また当科における50例の切除不能Vp3/4症例に対する検討においても，TACE治療成績は1年生存率10%と極めて不良であった。2009年版の肝癌診療ガイドラインの治療アルゴリズムにおいても，脈管侵襲を有する症例の場合には，肝障害度Aの症例においては肝切除，肝動脈塞栓療法，肝動注化学療法が示されており，個々の症例に応じた治療の選択が必要である[5]。

われわれは高度脈管侵襲例でもTACEによりdown-stagingし，かつ切除可能であれば長期予後が期待できることを報告している[6]。また，Minagawaらも門脈腫瘍栓を伴う（Vp2症例を含む）肝細胞癌において，TACEと手術の組み合わせにより5年生存率42%，MST 31か月と良好な治療成績を報告している[7]。Kuらによる減量肝切除と経皮的肝灌流療法を併用した2段階療法でも長期生存が報告されており[8]，適応は限られるが，このような症例には積極的な外科治療を中心とした集学的治療が望まれる。

本症例は，Vp4門脈腫瘍栓を伴っていたが，初回Lip-TAIにより抗腫瘍効果が認められ，残肝機能に留意した腫瘍選択的TACEの継続が長期生存に寄与したと考えられた。

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テーマ●多様化する転移性肝癌の治療—大腸癌肝転移

多様化する大腸癌肝転移例に対する外科治療

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要旨：大腸癌肝転移は大腸癌症例の予後を規定する重要な因子であり，肝切除はその予後を改善する有効な治療法である．両葉多発肝転移例や大血管浸潤例に対しても，さまざまな外科手術手技を併施し肝切除の適応は拡大されているのが現状である．一方，大腸癌に対する新規抗癌剤併用療法や分子標的治療薬の進歩はめざましく，切除不能肝転移例を切除可能へと移行させる治療戦略となりつつあり，また切除可能例に対してもより根治性を高めることで，予後向上につなげることを目的として術前化学療法が施行されるようになってきている．外科的治療は以前に比してより集学的治療戦略として行われ，今後これらの進歩を踏まえた新たな治療戦略が今後期待される．

索引用語：肝転移，血管合併切除，肝切除，予後因子

はじめに

大腸癌肝転移は大腸癌症例の予後を規定する重要な因子であり，その治療法として肝切除が第一選択であることには議論の余地がない[1)~6)]．大腸癌肝転移症例に対する肝切除の適応は拡大されてきており，両葉多発肝転移例や大血管浸潤例に対しても，術前門脈枝塞栓術による肝実質温存や血管合併切除再建などの積極的な外科治療が施行されるようになってきている[7)~10)]．

一方，進行再発大腸癌に対してFOLFOX，FOLFIRIなど新規抗癌剤併用療法や分子標的治療薬bevacizumab，cetuximabの有効性が報告されており，切除不能進行再発大腸癌症例における生存中央値は20カ月を超す報告がなされるようになってきた[11)~13)]．Adamらは大腸癌肝転移肝切除不能例に対してdownstageを目的としたneoadjuvant chemotherapyにより，1104例中138例（12.5%）に肝切除が施行可能となり，その予後は初回肝切除例と比べても遜色のないことを報告しており[14)]，切除不能肝転移例に対して新規抗癌剤を投与することで切除可能へconvertする新たな治療戦略は切除例数の増加や予後の向上には不可欠であると考えられる．また最近は切除可能例に対してもより根治性を高め予後向上につなげることを期待して術前化学療法が施行されるようになってきており，外科的治療は以前に比してより集学的治療として行われるようになってきた．

I　外科切除適応

外科切除適応を決定するに当たり実地臨床として考慮する点としては，腫瘍の個数や大きさ・腫瘍の占拠部位・大血管浸潤の有無・肝門ダリソン浸潤の有無・肝外転移併存の有無・肝門リンパ節転移の有無が一般的にあげられる[15)~21)]．腫瘍の個数や大きさに関しては，大腸癌取り扱い規約（第7版）において，これらの因子を考慮したH分類が規定されている．以前は腫瘍個数が4個以上の

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Advances in surgical treatment for colorectal liver metastases

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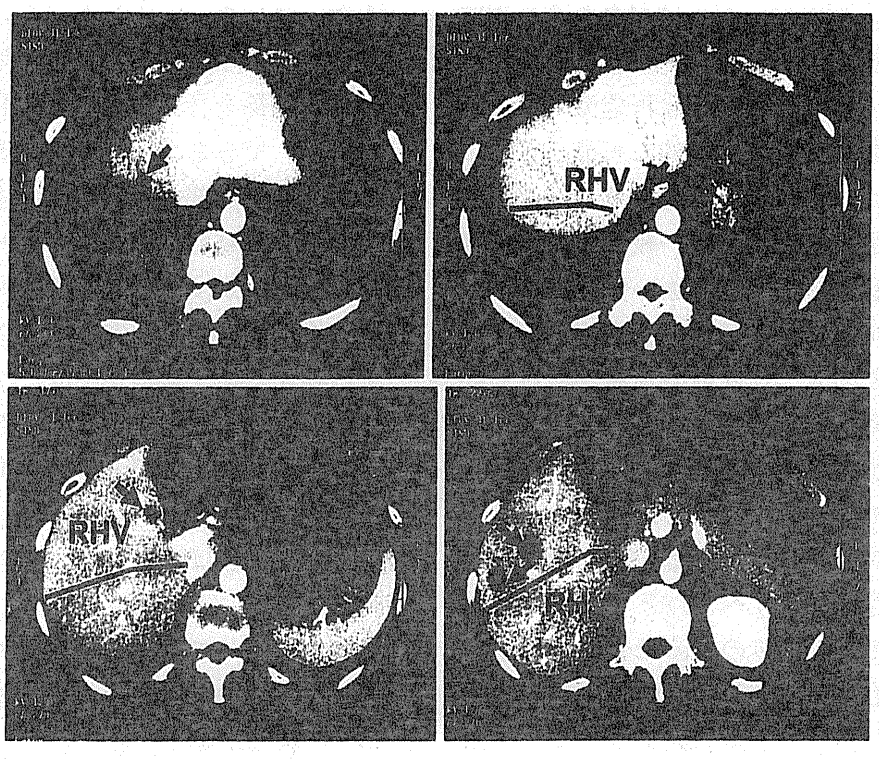

Figure 1. 肝転移巣による肝切除術式の volumetry のための切除ライン（左3区域切除）.

症例では予後が不良であるとの報告から[19)20)]，切除適応となる腫瘍個数に制限をつけることが一般的であった．しかしながら肝切除の安全性の向上と画像診断の進歩から，現在では肝臓外科医からみた手術適応を考える際には，根治的肝切除施行において腫瘍個数には制限をつけていないことが一般的である．これは欧米での切除率25%に対して，本邦ではH1・2で80～90%，H3でも約40%の切除率であることからも理解される．また切除の方法に関しても，海外では葉切除や区域切除が主流であるのに対し，本邦では部分切除が多く行われていることもその一因である．切除適応に当たっての重要な点としては，予測残肝容積の測定結果とICG15分停滞率や肝合成能などからみた肝予備能評価の結果を総合的に判断し，耐術可能の範囲にあるかを判断することである．つまり術式決定に際しては，肝切除後に残る肝実質量が術後の肝不全などの致死的合併症を回避するために機能的に十分に残ることが必要である．肝切除術式を決定する方法としては，ICG15分停滞率・術前総ビリルビン値・腹水の有無から切除可能範囲を予測するいわゆる幕内基準が一般的でかつ簡便である[22)]．実際の予測残肝率の測定としては，われわれはFigure 1のように腫瘍の存在範囲より予想される術式を想定して，腫瘍の体積を除いた機能的全肝体積と機能的残肝体積を測定して行っている．また同時に身長・体重よりstandard liver volume（SLV）を計測する．これらの方法で予測した残肝量が，施設間で差はあるものの全肝およびSLVの30～40%の範囲であれば，一期的に肝切除を施行している．これより少ない場合には門脈枝塞栓術を施行して，2～3週後の残肝量の増大後に手術を施行している．一般に転移性肝癌の場合には肝機能は正常であることが多く，通常は残肝量のみで規定されることが多い．high volume centerで行われる転移性肝癌に対する肝切除時のmortalityは2%未満であるのが一般的であり，後で述べる血管合併切除などの拡大切除を施行しても，現在はほぼmortalityは0%に近くなっている．

ここで先に述べた切除適応決定因子を検討してみると，腫瘍の個数や大きさ・腫瘍の占拠部位な

どは残肝量不足が切除適応からはずれる主な理由である．残る肝臓の唯一のドレナージとなる肝静脈浸潤例における肝静脈合併切除再建や下大静脈合併切除再建は施設により手技的に可能か否かによって切除適応が決定される．肝門リンパ節転移や制御できない肝外転移併存は一般的には肝切除を施行しても予後が悪く，肝切除の意義が少ないと考えられがちである．抗癌剤・分子標的治療剤の詳細は他稿に譲るが，これらの進歩があっても肝転移が予後規定因子となることが多く，抗癌剤単独での5年以上の生存の可能性はこのような症例に対して極めてまれとなることからも，可及的に肝切除施行を考慮すべきである．そこで，切除不能を決定する際に留意すべき点としては，消化管専門内科医・外科医のみの判断で肝切除不能を判断しないことも必要である．肝切除が施行可能な場合にもかかわらず，腫瘍個数が多いことや腫瘍の大きさが大きいことだけで切除不能と安易に判断してしまうことは，避けなければならない．特に抗癌剤治療が進歩してきている現状であるからこそ逆に，いずれかのタイミングで肝切除が施行可能であれば，予後を延長できる可能性が高くなる．術前抗癌剤併施肝切除については後に述べるが，長期に抗癌剤を投与しSD，PDと判断され紹介された症例でも切除が可能である場合が多いのも事実であり，肝切除を加えることで初回肝切除症例とほぼ同等の予後が期待できる．しかしながら，また同時に長期に抗癌剤の投与を施行した症例では，肝障害のみならず肝切除後の肝再生不全がおこりうることからも，抗癌剤投与と切除をどのタイミングで行うかが今後重要な解決すべき問題点である．

II 肝切除の手技的問題

肝切除の方法としては，portal triadを処理しその区画を切除する系統的肝切除と腫瘍からの一定のmarginをとり切除を施行する部分切除に分けられる[23][24]．肝細胞癌では系統的切除を行うことが肝癌診療ガイドラインでも推奨されている[25]．転移性肝癌でも約30%の症例に微小肝転移が門脈内に存在することが基礎的検討でわかっており，当科では以前は可能な限り系統的肝切除を行っていた．しかしながら現在の両葉多発肝転移症例に対する肝切除例数の増加にともない，根治的肝切除を行いながら術後肝不全を回避するためには，できるだけ肝実質を温存することが必要と考えられ，部分切除を選択することが増えてきている．本邦では先に述べたとおり部分切除を選択する施設が多く，また最近の再肝切除の施行例数の増加にともない安全性からも可及的に肝実質を温存する術式選択が主流となってきている．以上のことからも現在では転移性肝癌では，どちらの切除の方法を選択するかは大きな問題とされない．腫瘍とのmarginに関しては，以前は5ミリ以上，できれば1センチとることが必要と考えられていたが，占拠部位が肝門に近い症例や両葉多発症例において，5ミリ以上のmarginをすべてにとることは不可能である場合も多い．現在，本邦では腫瘍が露出しないように肝切除することで十分であると考えられており，一方欧米でのいわゆるR0手術では1ミリ以上のmarginが必要と考えられている．またKokudoらは基礎的検討を踏まえ2ミリ程度のmarginの必要性を報告しており，肝切除時の腫瘍露出は多変量解析でも予後因子となっていることからも，これが現実的であると考えられる[26]．いうまでもないが，十分にmarginを取りうる症例でいたずらに縮小することは慎むべきである．

手技的な問題点としては肝静脈合併切除再建や下大静脈合併切除があげられる[27)~30)]．肝静脈合併切除再建の適応となる症例は，一般には限られておりhigh volume centerでも症例数は多くないと思われるが，下大静脈合併切除再建は現在十分安全に施行可能な手技である．Figure 2が当科での下大静脈合併切除施行・未施行の肝切除後の生存曲線であるが，その生存曲線には有意差を認めていないことと術後合併症にも差を認めないことからも，下大静脈浸潤例といえども根治的肝切除が可能である症例は積極的に適応とすべきである．MD-CTやMRIにて癌の浸潤範囲が診断されるが，最終的には術中の判断により浸潤範囲を推定している．下大静脈を切除する際は肝動脈・門脈などの流入血行遮断と肝上・下部での下大静

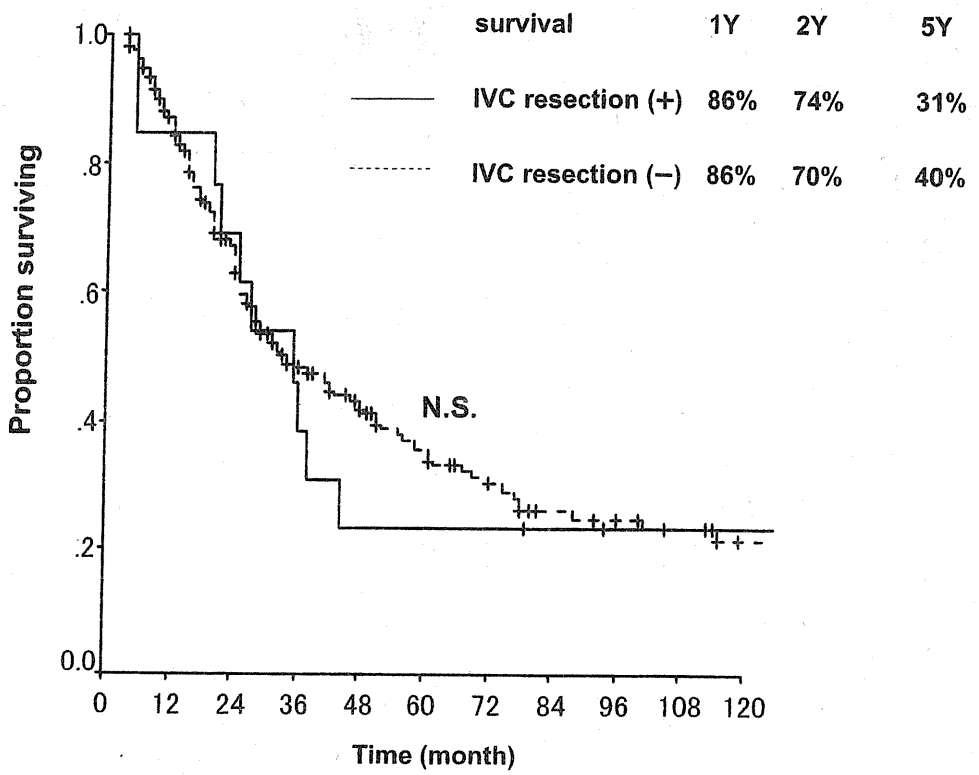

Figure 2. 下大静脈浸潤併存肝転移例に対する下大静脈合併切除の有無別の切除後累積生存率.

脈遮断が必要であることが多く，切除方法は部分的に切除か環状に切除かで分けられる[29)30)]．その再建方法は単純縫合閉鎖や自家静脈を用いたパッチ再建や e-PTFE グラフトを用いた全置換に分かれるが[29)30)]，いずれにせよ血管外科手技の発達した今日では，下大静脈浸潤例を切除することは十分に安全に可能である．

両葉多発肝転移例に対して適応は限られているが，two-stage hepatectomy という治療戦略も新たに登場している[31)~33)]．ひとつの例として，まず左肝にある肝転移を切除して術中に多発している右肝に対して，術中右門脈枝塞栓術を施行して残肝量肥大後に右肝切除（右葉切除）を施行して根治的に肝切除を行う方法である．この方法により，肝切除適応はさらに拡大することとなり，化学療法と組み合わせるなど，今後は適応の決定・安全性を含めた症例の集積結果が待たれる治療戦略である．

III　転移の時期を考慮した肝切除

本邦では一般に大腸癌発見時に存在した肝転移を同時性とし，原発巣切除後に存在するものを異時性肝転移と定義することが多い．本邦では以前より原発巣と同時に肝切除を施行することが多く，当科でも以前は原発巣と同時に切除を行っていた．一方海外では6カ月ないし1年以内までの転移を同時性と考える場合があり，この点で定義に差があるものの，Scheel らは同時性肝転移症例の予後不良の一因として微小肝転移の存在を指摘しており[34)]，われわれの retrospective な検討でも転移の時期は独立した有意な予後規定因子であることから，同時性肝転移では微小肝転移の存在が示唆される．つまり切除後残肝に微小肝転移が存在するために，肝再生シグナルとともに肝切除後早期に病変が再発として顕在化する場合があり，このことは消化器専門医にとって，肝切除施行が無用であったと考えさせる一因となる．そこでわれわれは2004年より同時性多発肝転移症例は原則的に原発巣の切除を先行し，一定の観察期間の後に，微小肝転移巣の顕在化の有無と原発巣の治癒切除を病理組織学的に確認した後に，転移

巣を切除する方針へ変更した．観察期間中に約43％の症例で肝転移巣の腫瘍の増大や腫瘍個数の増加が認められ，以前の原発巣との同時切除を施行した症例と比較してみると，術後早期の残肝再発率は有意に抑制された[35]．このように待機的肝切除施行は同時切除にともなう縫合不全などに起因する感染症やそれによる肝不全などの重篤な合併症のリスクが回避できること[36]と，微小転移の出現の有無を確認できることにより根治的肝切除が施行可能となる利点がある[37)38]．特に肝実質を大量に肝切除を行う場合に，感染性合併症は術後の肝不全に対しての危険因子であり注意を要する．また今後は切除不能症例のみならず術前化学療法施行症例の増加が予想され，分子標的治療剤としてbevacizumabを併用投与する場合が考えられる．bevacizumabの出血・縫合不全（創傷治癒遅延）のリスクから考えても，原発巣と分けて肝切除を施行することも新たな治療戦略である．

肝外転移に関して，その中で特に肺転移は外科切除が有効な病変である[16)~18)]．以前はその適応はやはり限られていたが，手術術式も鏡視下肺部分切除が一般的な切除の方法であり，現在では術前術後管理の進歩により両葉肺転移症例や多発症例に対しても安全に切除施行可能となり，肺切除の適応は拡大されつつある．同時性肺転移の場合は以前より肝切除と分けて施行されることが多く，肝切除後の根治性確認後に施行されてきた．現在は特に原発巣を含め肝・肺の3臓器に病変がある場合には，1臓器ごとの切除の間に抗癌剤投与を施行しながら根治性・適応を確認して，待機的にselectionを行いながら外科切除を施行していけば治癒にいたる症例も存在するようになっており，制御可能な肺転移併存は肝切除適応外ではなくなっている．

IV 術前抗癌剤併施肝切除

他稿に詳述されているとおり大腸癌に対する抗癌剤の進歩はめざましく，これを併用することでその予後は向上できると考えられる．その投与方法としては術前に用いる場合と術後に補助療法として投与する場合に大別される．肝転移に関してはすでにステージIVであり切除率も低いことから，これまでのところ切除不能症例に対して投与した検討の報告が多い．Adamらの報告[14]のように切除不能の肝転移症例に対して抗癌剤投与により切除可能へとconvertする治療戦略は，肝切除の対象とならない症例において少なくとも10％の症例が肝切除に移行可能となり，これらの対象症例において肝切除を施行した場合の予後は，切除可能症例に対する初回肝切除後の予後とは差異を認めないことから，積極的に行われるべき治療戦略であると考えられる．切除適応基準が施設間でばらつきが多く存在する現状では，いまだ切除不能とされる症例が存在する大腸癌肝転移症例にとって，結果としてこの治療戦略は有益なものであろう．肝切除不能の判断は先に述べたとおり，①腫瘍結節数多発などにより切除後の残肝量が不足する場合，②腫瘍の占拠部位が肝門グリソン鞘のため残肝量不足となる場合や残肝の唯一のドレナージとなる肝静脈に腫瘍浸潤が及びその再建が不能である場合，③切除不能の肝外転移併存の場合，の3点が考えられる．

一方，術前抗癌剤投与による肝障害の報告もなされており，oxaliplatin-basedの投与ではいわゆるblue liver（sinusoidal obstruction syndrome）が，irinotecan-basedではyellow liverつまり脂肪肝の報告がなされている[39]．Vautheyらは FOLFIRIの先行投与によるsteatohepatitisの存在する症例では術後在院死例が多かったことを報告をしているが[40]，われわれはこれまでのところ経験していない．しかしながら，Kaouriら[41]の報告のように抗癌剤の術前投与回数が多いほど術後合併症の頻度が高くなることが報告されており，術前抗癌剤投与と肝障害の観点からは，より効果の早い治療法を選択することが今後重要であろう．FOLFOX，FOLFIRIに分子標的治療薬bevacizumabを併用した治療戦略が現在主流になりつつあり，またbevacizumabの併用によりblue liverの軽減が認められたとの報告もあり[42]，今後投与方法・投与期間を含めさらに詳細な検討が必要となるであろう．本邦ではcetuximabのfirst lineでの投与はまだ認可されていな

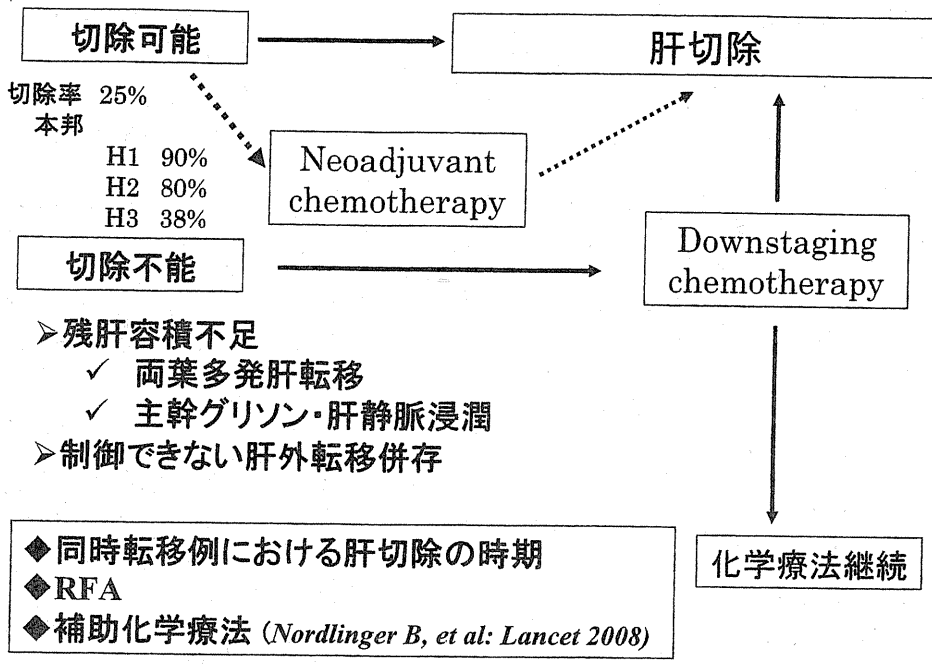

Figure 3. 現在の肝転移例に対する治療戦略.

いが，NCCN ガイドライン 2009 においては first line での投与が推奨されており，報告をみても cetuximab の併用は肝切除移行を早期に可能とする可能性が示唆され，今後の検討が待たれるところである.

われわれの経験を踏まえて考えると，一般に抗癌剤投与後の肝切除症例の組織学的効果は画像上 Complete response (CR) や Partial Response (PR) の部位においても Grade 1a～2 にとどまっており，腫瘍の切除は必要であることが推測される. ここで肝切除に際して，特に画像上 CR になっている病変の扱いが問題になっている[43]. われわれの経験でも瘢痕になっていた部位には cancer cell は認められないことはあるが，画像上 CR となっている部位が初回肝切除後に再燃し，再肝切除標本において cancer cell を認めることは経験されることであり，画像上 CR の部分は可及的に切除されることが望ましいと現状では考えられる. 実際，画像上 CR 病変が病理組織学的に CR となっている頻度は 10～20% 程度と報告されており[14][43]，また画像上 CR となった部位の経過を観察した報告においても，術中所見で癌の存在を確認し切除を施行した病変と切除を施行せずに術後経過を観察し再燃を認めた病変を合わせると，CR 病変全症例の中で 83% に癌の存在や再燃があったと報告されている[43]. つまり画像上 CR 病変であってもどのタイミングかで切除ないし RFA 施行が必要になるであろう. これら術前の CT, MRI での CR 病変は実地臨床においては，ソナゾイドを用いた術中超音波検査が今後有効な方法と考えられる. しかしながら，抗癌剤投与が長くなると，術中ソナゾイドを用いた超音波検査でも CR 病変は同定ができない場合も考えられ，存在が不明の病変は切除をすることは不可能である. また一方全肝区域に存在する肝転移の場合には，残肝量の問題から画像上 CR 病変を切除できずに経過観察せざるをえない場合もある. 以上の点からも術前抗癌剤投与症例の治療戦略として 1 つの考え方は，初回肝切除前に切除不能と判断された責任病変が CR/PR となり切除可能と判断されれば，その時点で切除を考慮することが重要である. 現在は再肝切除の手技も確立されており，画像上 CR 病変に対して再燃後に再度治療を考慮することも 1 つの戦略であろう. 抗癌剤による肝障害の点からも投与を施行してからどのタイミングで肝切除を施行するべきかという問題は，今後詳

細に検討することが必要であろう．

肝切除可能な肝転移症例において，微小転移を消失させ根治性を向上させるという目的で，術前抗癌剤投与を施行後に肝切除を施行するべきかという議論がなされている．術前化学療法の病理組織学的効果が肝切除後の生存期間の予後因子となったとの報告や[44)~46)]，また術前化学療法施行により欧米でのいわゆるR1手術となった肝切除症例の予後とR0症例の予後に差異はなかったとの報告[47)]がなされたことから，術前化学療法施行症例はますます増えてくると考えられる[48)~51)]．現時点での補助療法を含めた大腸癌肝転移例に対する治療戦略をシェーマに示すが（Figure 3），先に述べた微小肝転移の問題を含め，まだ一定の結論は出ていないが，肝切除後の早期肝再発抑制のためには待機的肝切除か術前化学療法併用肝切除を施行するかなど，今後さらなる検討が必要と考えられる．また消化器専門医にとって肝転移はすでにステージIVであることから考えても，新規抗癌剤と分子標的治療剤の投与はますます増えてくると考えられる．肝切除は予後を有意に伸ばしうる治療法であることから肝臓外科医側からみると肝障害や術後の合併症や肝再生の点からも適切な抗癌剤投与方法・期間と切除の可否を含めそのタイミングを考慮することが肝要であることを注記したい．

おわりに

大腸癌肝転移に対する肝切除は手術手技や周術期管理の進歩により，安全に施行可能であり，肝切除・新規抗癌剤・分子標的薬を合わせた新たな治療戦略は今後ますます進歩していくであろう．

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Carbon Ion Radiotherapy for Treatment of Prostate Cancer and Subsequent Outcomes after Biochemical Failure

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Abstract. *Background/Aim: Carbon ion radiotherapy is expected to be suitable to treat localized prostate cancer because it yields great biological and physical effects. The aim of this study was to examine long-term results and subsequent outcomes after biochemical failure. Patients and Methods: A total of 254 patients were treated from the beginning of 2003 and followed through 2009. Long-term hormone therapy was also used for some intermediate-risk and high-risk patients. Results: Among the patients examined, 54 patients experienced biochemical failure. Failure-free survival was 76%, 91% and 76% at eight years in low-risk, intermediate-risk and high-risk patients, respectively. Clinical progression occurred only in high-risk patients, with 89% progression-free survival at eight years. After biochemical failure, diseases of most patients were well controlled by salvage therapy but twelve high-risk patients (5%) died of prostate cancer. Conclusion: Carbon ion radiotherapy had an excellent effect on localized prostate cancer. Factors influencing salvage therapy included PSA kinetics and duration between radiation and failure.*

In 2005 in Japan, 42,997 men were diagnosed with prostate cancer (an incidence of 42.0 per 100,000 men), and 9,264 men died of prostate cancer (1). The proportion of patients with cancer at a localized stage has increased and radiotherapy and surgery are critical curative treatments for such patients. Carbon ion beam is characterized by high cytocidal effects, high linear energy transfer and excellent radiation dose distribution. Based on its biological and physical effects, carbon ion radiotherapy is considered as a new treatment modality for solid tumors. The National Institute of Radiological Sciences in Japan constructed the Heavy Ion Medical Accelerator in Chiba (HIMAC) in 1993 and started to use carbon ion radiotherapy to treat localized and locally advanced prostate cancer in 1995. Preliminary short-term results have been reported (2-4). Since then, this is the first study to assess the long-term outcomes of patients who received carbon ion radiotherapy between 1995 and 2003. Because some patients experienced biochemical failure, the present study examined the influence of adjuvant therapy on the subsequent outcome.

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Key Words: External beam radiation therapy, PSA-doubling time, carbon radiotherapy, prostate cancer.

Patients and Methods

Patients. Patients with confirmed histological adenocarcinoma and T1b-T3N0M0 cancer were enrolled in the study. Between the start of treatment (October 1995) and October 2003, 254 consecutive patients had received carbon ion radiotherapy. Patients had not received previous treatment for prostate cancer. Clinical records for all patients were collected in 2009. The follow-up period lasted for a mean of 98 months, with a median of 96 months and a range of 5-178 months. To establish the radiation modality, the three following Protocols were adapted sequentially (2): 35 cases used Protocol 9402 with a dose escalation of 54.0-72.0 Gy equivalent (GyE), 62 cases used Protocol 9703 with a dose escalation of 60.0-66.0 GyE and a fixed dose of 66.0 GyE, and 157 cases used Protocol 9904 with a fixed dose of 66.0 GyE in 20 fractions. Stages were defined using the UICC (2002). Before treatment, prostate biopsy with eight or more cores was performed and Gleason scores were estimated by a central pathologist (MH). Patients were divided into low-risk, intermediate-risk and high-risk groups using the NCCN classification system (5).

Hormone therapy was used according to risk classification as follows: no hormone therapy for low-risk and intermediate-risk patients with T2ab, and two to six months of neoadjuvant hormone therapy and one year or more of adjuvant hormone therapy for other intermediate-risk patients with T2c or with Gleason score of 7 and all high-risk patients. Hormone therapy generally consisted of a luteinizing hormone-releasing hormone agonist and a daily dose of 80 mg of bicalutamide. After biochemical failure, conventional hormone therapy, second-line hormone therapy and chemotherapy were successively employed.

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Patients underwent digital rectal examinations and determination of prostate-specific antigen (PSA) every three to six months. If abnormal findings were suspected, an imaging examination including a bone scan and magnetic resonance imaging scan was carried out along with frequent PSA assays. The primary endpoint was biochemical failure, and overall and clinical progression-free survival rates were calculated.

Rates of acute and late morbidities were estimated using the RTOG/EORTG system (6).

PSA kinetics. Total PSA (PSA) was determined using commercial kits (AxSYM PSA Dainapack; Abbot, Chiba Japan). Biochemical failure was judged by Phoenix criteria, when PSA was elevated by 2 ng/ml or more over baseline (7). PSA-doubling time (PSA-DT) and velocity before biochemical failure were calculated by linear regression. A slope was obtained from three or more points by the least-squares fitting method using the natural logarithm (ln) of PSA (for calculation of PSA-DT) or PSA (for calculation of velocity). Consequently, PSA-DT was calculated as ln 2/slope (8) and velocity was determined as the difference in PSA increase per year (9). The response to salvage hormone therapy was evaluated as follows: a partial response (PR) was defined as a decrease in PSA ≥50% from baseline, progressive disease (PD) was designated as an increase in PSA ≥25% over baseline, and no change (NC) was denoted as any change between PR and PD.

Carbon ion radiotherapy. The technique of carbon ion radiotherapy was previously reported (2). Briefly, the head and feet of the patients were positioned in a customized cradle and the pelvis was immobilized with a thermoplastic sheet. The bladder was filled with 100 ml of sterilized water in the anterior direction at a computed tomography (CT) planning and at each session from the anterior direction. The rectum was emptied with a laxative or enema, if necessary.

The clinical target volume was designed for the prostate and seminal vesicle after referring to a 5-mm thick CT scan. The initial planning target volume was created by adding 10-mm anterior and lateral margins and 5-mm posterior margin. After the first 10 fractions, the posterior margin was set on the anterior wall of the rectum to limit the dose received by the rectum to <50 GyE. Radiation was performed with one anterior-posterior port and a pair of lateral ports which were alternated at each session once a day in four fractions per week for five weeks.

Statistical analysis. Survival was calculated with the Kaplan-Meier method. Statistical differences were determined by the unpaired two-group *t*-test and *p*-value of ≤0.05 was considered statistical significant. All calculations were performed with SPSS statistical computer program (SPSS Inc, Tokyo, Japan).

Results

Risk groups and outcomes. The risk distribution of the patients was 11%, 26% and 63% in the low-risk, intermediate- risk and high-risk groups, respectively (Table I).

Five patients showed local recurrences (2%), some of which were due to insufficient radiation doses in the initial protocols. Distant metastases were detected in a total of 15 patients (6%) distributed as follows: ten in bone, three in abdominal lymph nodes, one in liver and one in lung. Twelve patients (5%) died of cancer-specific causes, all of them were high-risk patients (8% of the high-risk group). Forty-three patients (17%) died of other diseases: four (14%), nine (14%) and thirty (19%) belonged to the low-, intermediate- and high-risk groups, respectively. These patients showed no signs of biochemical failure until death.

Table I. *Risk classification. The number of patients with biochemical failure is shown in parentheses.*

		Low-risk	Intermediate-risk	High-risk
No. of cases		29 (7)	66 (7)	159 (40)
Age (years)	≤60	2	7	10
	61-65	6	12	22
	66-70	8	15	52
	71-75	10	23	54
	76-80	3	8	18
	≥81	0	1	3
Stage	T1bc	19	27	14
	T2ab	10	12	9
	T2c	0	27	37
	T3	0	0	99
Gleason score	≤6	29	26	27
	7	0	40	73
	≥8	0	0	59
Initial PSA (ng/ml)	≤4	4	1	0
	>4-<10	25	21	17
	≥10-20	0	49	29
	>20-50	0	0	69
	>50-100	0	0	31
	>100	0	0	13

The rates of overall survival in all patients at five and eight years after radiotherapy were 90% and 84%, respectively, while the respective rates of biochemical failure-free survival were 85% and 79%. Three-, five- and eight-year overall survival rates were 93%, 93% and 93% in the low-risk group, 96%, 94% and 90% in the intermediate-risk group, and 95%, 88% and 79% in the high-risk group, respectively (Figure 1). The respective rates for biochemical failure-free survival were 93%, 85% and 76% in the low-risk group, 97%, 95% and 91% in the intermediate-risk group and 85%, 79% and 76% in the high-risk group, respectively (Figure 2). No clinical progression was detected in the low-risk and intermediate-risk groups. Three-, five- and eight-year progression-free survival rates in the high-risk group were 96%, 93% and 89% (Figure 3, p=0.005).

At G0, G1, G2, G3 and G4, the incidence of morbidities in the bladder/urethra were 70%, 27%, 3%, 0% and 0% (acute morbidities) and 70%. 21%, 6%, 3% and 0% (late morbidities), respectively, and the incidence of morbidities in the rectum were 97%. 3%, 0%, 0% and 0% (acute morbidities) and 85%. 9%, 4%, 2% and 0% (late morbidies), respectively.

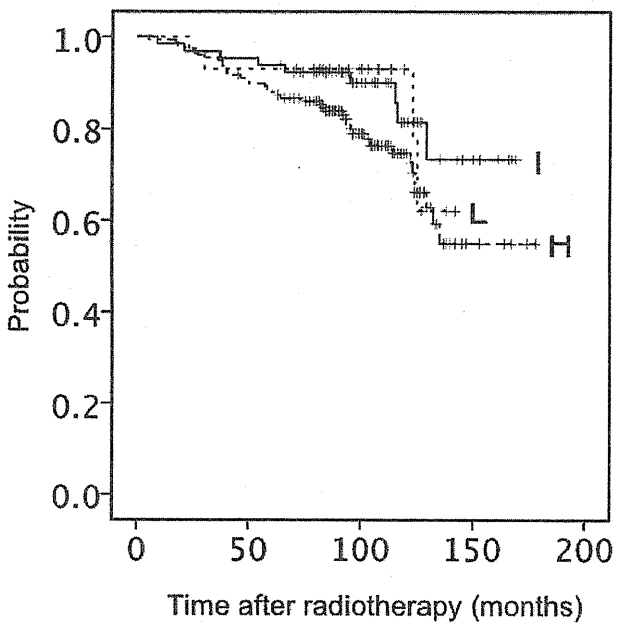

Figure 1. *Overall survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates overall survival probability.*

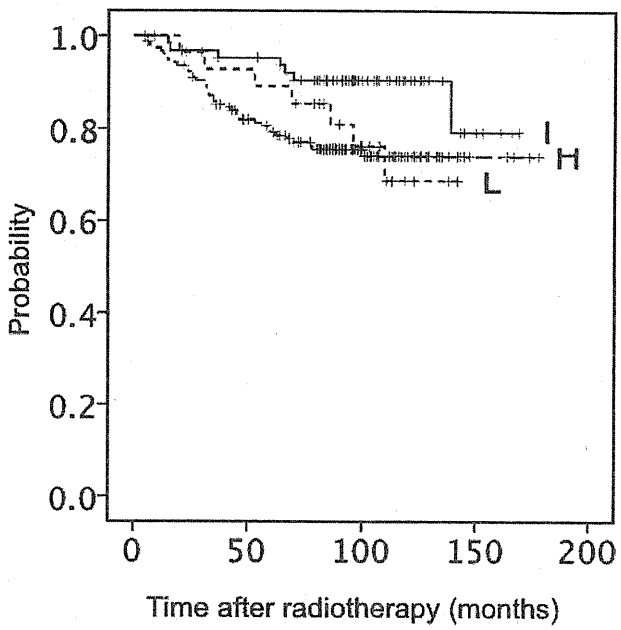

Figure 2. *Biochemical failure-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates biochemical failure-free survival probability*

Effect of hormone therapy. Patients were treated with hormone therapy or left untreated according to the risk classification (Table II). Of 254 patients, 54 (21%) experienced biochemical failure; 24%, 11% and 25% in the low-, intermediate- and high-risk groups, respectively. The relatively high rate of biochemical failure in the low-risk patients may be partially due to the small number of patients in this group compared to the others; moreover, the low-risk group may contain underdiagnosed cases without adjuvant hormone therapy. Biochemical failure occurred infrequently in the intermediate-risk patients, due perhaps to the long-term adjuvant hormone therapy provided to T2c patients. In contrast, no hormone therapy was scheduled for T2ab patients. As the failure rate was rather low in the high-risk patients, hormone therapy seemed to be beneficial and a two-year treatment duration appeared to be better for avoiding biochemical failure compared to shorter treatments.

After biochemical failure, the patients without or after adjuvant hormone therapy were treated with conventional hormone therapy for two years or more. Most patients in the low- and intermediate-risk groups responded well with PR. No cancer deaths were observed in these groups.

Of 159 high-risk patients, 40 (25%) experienced biochemical failure. Twenty-six patients showed failure without or after

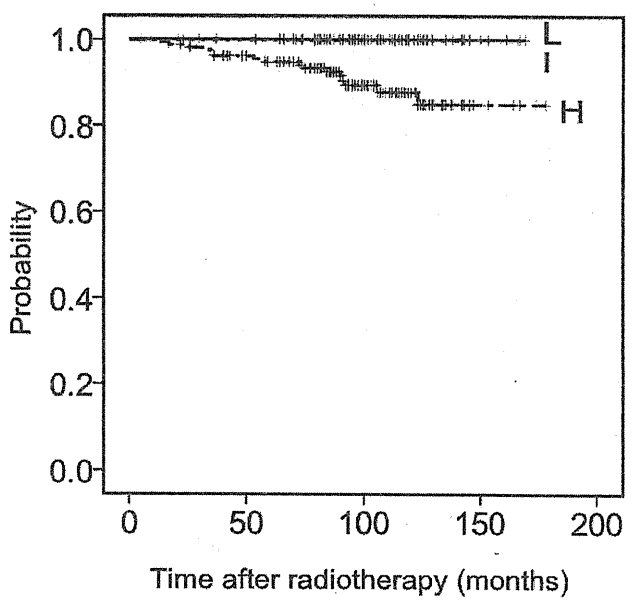

Figure 3. *Clinical progression-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates clinical progression-free survival probability.*

Table II. *Relationship between hormone therapy and biochemical failure. Other failures occurred after termination of hormone treatment.*

	Low risk		Intermediate risk		High risk	
Hormone therapy	No failure	Failure	No failure	Failure	No failure	Failure
None or <1 year	21	7	22	6	15	10
1-2 years	1	0	13	0	32	12
>2 years			24	1	72	4
During treatment[a]						14

[a]Biochemical failure during hormone treatment.

Table III. *Response to salvage therapy after biochemical failure. Data are shown as mean, median (range).*

	PR (37)[a]	NC and PD (17)[a]	*p*-value
Low: intermediate: high risk	7 : 7 : 23	0 : 0 : 17	
Initial PSA (ng/ml)	31.0, 19.0 (2-174)	50.2, 29.1 (8.2-260)	0.24
Radiation-failure (months)	47, 43 (6-112)	33, 19 (6-139)	0.15
Nadir PSA (ng/ml)	0.81, 0.24 (0.003-10.3)	0.62, 0.2 (0.06-2.8)	0.60
PSA-DT (months)[b]	8.9. 6.5 (1.2-24.9)	4.5, 2.9 (0.65-17.5)	0.009
Velocity (ng/ml/year)[b]	5.4, 1.7 (0.34-68.2)	29.8, 3.0 (0.6-205.2)	0.12

PR: PSA decrease ≥50%, PD: PSA increase ≥25%, NC: any change between PR and PD; [a]number of cases; [b]Value from one case (a patient with lymph node metastasis) was excluded.

adjuvant hormone therapy. These patients were treated with conventional hormone therapy repeatedly and 23 patients showed PR and three showed PD. Of these patients, three died of prostate cancer after an average period of 62 months (range 32-106 months) after radiotherapy.

Fourteen high-risk patients progressed to a castration-resistant state despite continuous hormone treatment, nine of whom died of prostate cancer after an average period of 43 months (range 16-91 months) from radiotherapy (Figure 4). The period between radiotherapy and biochemical failure was shorter for these patients (average 20 months: range 6-38 months) than for the other high-risk patients who experienced biochemical failure (average 42 months: range 6-95 months; p=0.0002).

The factors influencing the salvage therapy for biochemical failure were examined (Table III). PSA-DT was found to significantly affect response, and a PSA-DT greater than ten months indicated a good response to salvage hormone therapy (data not shown).

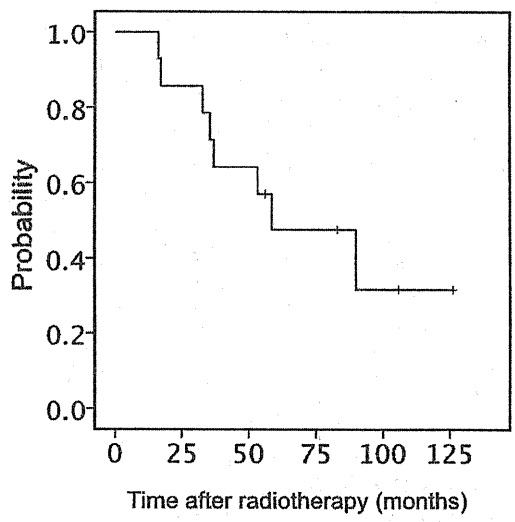

Figure 4. *Cause-specific survival of fourteen high-risk patients with disease progression under continuous hormone treatment after radiotherapy.*

Discussion

Radiotherapy for prostate cancer in Japan is generally reserved for rather advanced stages of the disease. Based on the results determined from 162 patients with prostate cancer at 50 facilities in 1999-2000, 80% of the patients were high-risk, and overall and biochemical failure-free survival rates at three years were 86.7% and 86.1%, respectively. Two-thirds of patients received hormone therapy (10). In the present study, 63% of patients were high-risk.