分担研究者　古瀬　純司					
Furuse, J., Ishii, H., Nakachi, K., Suzuki, E., Shimizu, S., Nakajima, K.	Phase I study of sorafenib in japanese patients with hepatocellular carcinoma.	Cancer Sci.	99	159-165	2008
Kobayashi, A., Takahashi, S., Ishii, H., Konishi, M., Nakagohri, T., Gotohda, N., Satake, M., Furuse, J., Kinoshita, T.	Factors predicting survival in advanced T-staged hepatocellular carcinoma patients treated with reduction hepatectomy followed by transcatheter arterial chemoembolization.	Eur. J. Surg. Oncol.	33	1019-24	2007
古瀬純司	進行肝細胞癌の化学療法 -Sorafenib plasebo- control randomized study (SHARP trial) を中心に	腫瘍内科	1	471-475	2007
Gotohda, N., Ishii, H., Konishi, M., Nakagohri, T., Takahashi, S., Furuse, J., Yoshino, M., Kinoshita, T.	Selection criteria for reduction hepatectomy in multiple advanced hepatocellular carcinoma.	Anticancer Res.	26	4671-4674	2006
Gotohda, N., Kinoshita, T., Konishi, M., Nakagohri, T., Takahashi, S., Furuse, J., Ishii, H., Yoshino, M.	New indication for reduction surgery in patients with advanced hepatocellular carcinoma with major vascular involvement.	World J. Surg.	30	431-438	2006
Ueno, H., Sato, T., Yamamoto, S., Tanaka, K., Ohkawa, S., Takagi, H., Yokosuka, O., Furuse, J., Saito, H., Sawaki, A., Kasugai, H., Osaki, Y., Fujiyama, S., Sato, K., Wakabayashi, K., Okusaka,T.	Randomized, double-blind, placebo-controlled trial of bovine lactoferrin in patients with chronic hepatitis C.	Cancer Sci.	97	1105-1510	2006
古瀬純司、鈴木英一郎、仲地耕平、清水　怜、石井　浩、吉野正曠	肝内胆管癌の化学療法 (動注を含む)	肝胆膵	53	1001-1007	2006
Kawashima, M., Furuse, J., Nishio, T., Konishi, M., Ishii, H., Kinoshita, T., Nagase, M., Nihei, K., Ogino, T.	Phase II Study of Radiotherapy Employing Proton Beam for Hepatocellular Carcinoma.	J. Clin. Oncol.	23	1839-1846	2005
Furuse, J., Ishii, H., Nagase, M., Kawashima, M., Ogino, T., Yoshino, M.	Adverse hepatic events caused by radiotherapy for advanced hepatocellular carcinoma.	J. Gastroen. Hepatol.	20	1512-1518	2005
石井　浩、古瀬純司、仲地耕平、鈴木英一郎	高度進行肝細胞癌に対するシスプラチン動注化学療法：重篤な有害事象は稀でない	肝臓	46	228-229	2005
古瀬純司、石井　浩、仲地耕平、鈴木英一郎、吉野正曠	臨床腫瘍学の現状と展望、がん薬物療法の実際、肝胆膵癌、	Progress in medicine	25	2087-2093	2005

分担研究者　　中面　哲也					
Yokomine, K., Nakatsura, T., Senju, S., Nakagata, N., Minohara, M., Kira, JI., Motomura, Y., Kubo, T., Sasaki, Y., and Nishimura, Y.	Regression of intestinal adenomas by vaccination with heat shock protein 105-pulsed bone marrow-derived dendritic cells in ApcMin/+ mice.	Cancer Sci.	98(12)	1930-1935	2007
中面哲也	Glypican-3(GPC3)ペプチドワクチンによる肝細胞癌の予防・治療法	G.I.Research	16(1)	17-23	2008
中面哲也	癌免疫療法	腫瘍内科	1(5)	449-453	2007
小森宏之、中面哲也、本村裕、別府透、石河隆敏、馬場秀夫、西村泰治	新規癌胎児性抗原 Glypican-3 を標的とした肝細胞癌の免疫療法	分子細胞治療	6(2)	57-61	2007
小森宏之、中面哲也、本村裕、別府透、 西村泰治、馬場秀夫	癌胎児性抗原 Glypican-3 を標的とした癌ワクチン療法	Biotherapy	21(1)	62-68	2007
Muchemwa, F.C., Nakatsura, T., Ihn, H., and Kageshita, T.	Heat shock protein 105 is overexpressed in squamous cell carcinoma and extramammary Paget disease but not in basal cell carcinoma.	Br. J. Dermatol.	155	582-585	2006
Komori, H., Nakatsura, T., Senju, S., Yoshitake, Y., Motomura, Y., Ikuta, Y., Fukuma, D., Yokomine, K., Harao, M., Beppu, T., Matsui, M., Torigoe, T., Sato, N., Baba, H., and Nishimura, Y.	Identification of HLA-A2- or HLA–A24-restricted CTL epitopes possibly useful for glypican-3-specific immunotherapy of hepatocellular carcinoma.	Clin. Cancer Res.	12	2689-2697	2006
Hosaka, S., Nakatsura, T., Tsukamoto, H., Hatayama, T., Baba, H., and Nishimura, Y.	Synthetic small interfering RNA targeting heat shock protein 105 induces apoptosis of various cancer cells both in vitro and in vivo.	Cancer Sci.	97	623-632	2006
Yokomine, K., Nakatsura, T., Minohara, M., Kira, JI., Kubo, T., Sasaki, Y., and Nishimura, Y.	Immunization with heat shock protein 105-pulsed dendritic cells leads to tumor rejection in mice.	Biochem. Biophys. Res. Comm.	343	269-278	2006
Motomura, Y., Senju, S., Nakatsura, T., Matsuyoshi, H., Hirata, S., Monji, M., Komori, H., Fukuma, D., Baba, H., and Nishimura, Y.	Embryonic stem cell-derived dendritic cells expressing glypican-3, a recently identified oncofetal antigen, induce protective immunity against highly metastatic mouse melanoma, B16-F10.	Cancer Res.	66	2414-2422	2006

影下登志郎、福島　聡、尹　浩信、西村泰治、中面哲也	悪性黒色腫の新しい血清マーカーGlypican-3 と SPARC	臨床皮膚科（増刊号）	60(5)	169-172	2006
小森宏之、中面哲也、別府　透、西村泰治、馬場秀夫	Glypican-3(GPC3)を標的とした免疫療法の有用性の検討	癌と化学療法	33(12)	1742-1744	2006
Ikuta, Y., Nakatsura, T., Kageshita, T., Fukushima, S., Ito, S., Wakamatsu, K., Baba, H., and Nishimura, Y.	Highly sensitive detection of melanoma at an early stage based on the increased serum SPARC and Glypican-3 levels.	Clin. Cancer Res.	11	8079-8088	2005
Matsuyoshi, H., Hirata, S., Yoshitake, Y., Motomura, Y., Fukuma, D., Kurisaki, A., Nakatsura, T., Nishimura, Y., and Senju, S.	Therapeutic effect of a-galactosylceramide-loaded dendritic cells genetically engineered to express SLC/CCL21 along with tumor antigen against peritoneally disseminated tumor cells.	Cancer Sci.	96	889-896	2005
Miyazaki, M.*, Nakatsura, T.*(*Equal contribution), Yokomine, K., Senju, S., Monji, M., Hosaka, S., Komori, H., Yoshitake, Y., Motomura, Y., Minohara, M., Kubo, T., Ishihara, K., Hatayama, T., Ogawa, M., and Nishimura, Y.	DNA vaccination of HSP105 leads to tumor rejection of colorectal cancer and melanoma in mice through activation of both CD4+ and CD8+ T cells.	Cancer Sci.	96	695-705	2005
Nakatsura, T., Nishimura, Y.	Usefulness of a novel oncofetal antigen Glypican-3 for diagnosis of hepatocellular carcinoma and melanoma.	(review) BioDrugs	19	71-77	2005
吉武義泰、中面哲也、西村泰治	癌免疫療法の新展開	日本臨床（増刊:『臨床免疫学(上)-基礎研究の進歩と最新の臨床-』）	63(4)	46-55	2005
分担研究者　千住　覚、　研究協力者　西村　泰治					
Senju, S., Suemori, H., Zembutsu, H., Uemura, Y., Hirata, S., Fukuma, D., Matsuyoshi, H., Shimomura, M., Haruta, M., Fukushima, S., Matsunaga, Y., Katagiri, T., Nakamura, Y., Furuya, M., Nakatsuji, N., and Nishimura, Y.	Genetically manipulated human embryonic stem cell-derived dendritic cells with immune regulatory function.	Stem cells	25	2720-2729	2007
Yokomine, K., Nakatsura, T., Senju, S., Nakagata, N., Minohara, M, Kira, J., Motomura, Y., Kubo, T., Sasaki, Y., and Nishimura, Y.	Regression of intestinal adenomas by vaccination with heat shock protein 105-pulsed bone marrow-derived dendritic cells in ApcMin/+ mice.	Cancer Sci.	98	1930-1935	2007

千住　覚、西村泰治	T 細胞応答の抑制性制御	免疫応答と免疫病態の統合的分子理解（南山堂、東京）		116-122	2007
千住　覚、西村泰治	MHC とは何か	アニテックス特集「動物 MHC」（研成社、東京）	19(2)	3-8	2007
小森宏之、中面哲也、本村　裕、別府　透、西村泰治、馬場秀夫	癌胎児性抗原 Glypican-3 を標的とした癌ワクチン療法	Biotherapy（癌と化学療法社）	21(1)	62-68	2007
小森宏之、中面哲也、本村　裕、石河隆敏、別府　透、馬場秀夫、西村泰治	新規がん胎児性抗原 Glypican-3 を標的とした肝細胞がんの免疫療法	分子細胞治療（先端医学社）	6(2)	57-61	2007
Motomura, Y., Senju, S., Nakatsura, T., Matsuyoshi, H., Hirata, S., Monji, M., Komori, H., Fukuma, D., Baba, H., and Nishimura, Y.	Embryonic stem cell-derived dendritic cells expressing Glypican-3, a recently identified oncofetal antigen, induce protective immunity against highly metastatic mouse melanoma, B16-F10.	Cancer Res.	66	2414-2422	2006
Komori, H., Nakatsura, T., Senju, S., Ikuta, Y., Yokomine, K., Yoshitake, Y., Motomura, Y., Beppu, T., Matsui, M., Torigoe, T., Sato, N., Baba, H. and Nishimura, Y.	Identification of HLA-A2- or HLA-A24-restricted CTL epitopes possibly useful for glypican-3-specific immunotherapy of hepatocellular carcinoma.	Clin. Cancer Res.	12	2689-2697	2006
Yokomine, K., Nakatsura, T., Minohara, M., Kira, J-I., Kubo, T., Sasaki, Y., and Nishimura, Y.	Immunization with heat shock protein 105-pulsed dendritic cells leads to tumor rejection in mice.	Biochem. Biophys. Res. Comm	343	269-278	2006
小森宏之、中面哲也、別府　透、西村泰治、馬場秀夫	Glypican-3(GPC3)を標的とした免疫療法の有用性の検討	癌と化学療法（癌と化学療法社）	33(12)	1742-1744	2006
影下登志郎、福島　聡、尹　浩信、西村泰治、中面哲也	悪性黒色腫の新しい血清マーカーglypican-3 と SPARC	臨床皮膚科（医学書院）	60(5) 増刊号	169-172	2006
Ikuta, Y., Nakatsura, T., Kageshita, T., Fukushima, S., Ito, S., Wakamatsu, K., Baba, H., and Nishimura, Y.	Highly sensitive diagnosis of melanoma at an early stage by detecting the serum SPARC and glypican-3 levels.	Clin. Cancer Res.	11	8079-8088	2005
Fukuma, D., Matsuyoshi, H., Hirata, S., Kurisaki, A., Yoshitake, Y., Sinohara, M., Nishimura, Y., and Senju, S.	Anti-cancer immunotherapy with semi-allogeneic embryonic stem cell-derived dendritic cells genetically engineered to express a model tumor antigen.	Biochem. Biophys. Res. Comm.	335	5-13	2005

Matsuyoshi, H., Hirata, S., Yoshitake, Y., Motomura, Y., Fukuma, D., Kurisaki, A., Nakatsura, T., Nishimura, Y., and Senju, S.	Therapeutic effect of α-galactosylceramide-loaded dendritic cells genetically engineered to express SLC/CCL21 along with tumor antigen against peritoneally disseminated tumor cells.	Cancer Sci.	96	889-896	2005
Miyazaki, M.*, Nakatsura, T.*, Senju, S., Monji, M., Hosaka, S., Komori, H., Yoshitake, Y., Motomura, Y., Yokomine, K., Minohara, M., Kubo, T., Ishihara, K., Hatayama, T., Ogawa, M., and Nishimura, Y. (*equal contribution)	DNA vaccination of HSP105 leads to tumor rejection of colorectal cancer and melanoma in mice through activation of both CD4+ and CD8+ T cells.	Cancer Sci.	96	695-705	2005
Guo , Y., Niiya, H., Azuma, T., Uchida, N., Yakushijin Y., Sakai, I., Hato, T., Takahashi, M., Senju, S., Nishimura, Y., and Yasukawa M.	Direct recognition and lysis of leukemia cells by WT1-specific CD4+ T lymphocytes in an HLA class II-restricted manner.	Blood	106	1415-1418	2005
Nakatsura, T., and Nishimura, Y.	[Review] Usefulness of a novel oncofetal antigen Glypican-3 for diagnosis of hepatocellular carcinoma and melanoma.	BioDrugs	19	71-77	2005
平田真哉、千住　覚、西村泰治	樹状細胞の移入による免疫抑制療法	臨床免疫	43(5)	603-607	2005
平田真哉、千住　覚、西村泰治	抗原提示細胞をターゲットとした免疫抑制療法	分子リウマチ	2 (1)	47-54	2005
吉武義泰、中面哲也、西村泰治	癌免疫療法研究の新展開	臨床免疫学（上）	63(4)	46-55	2005
分担研究者　　佐々木　裕					
佐々木　裕	特集　C 型肝炎の治療 新たな展開瀉血療法	モダンフィジシャン	28	72-75	2008
Yokomine, K., Nakatsura, T., Senju, S., Nakagata, N., Minohara, M., Kira , J., Motomura, Y., Kubo, T., Sasaki, Y. and Nishimura, Y.	Regression of intestinal adenomas by vaccination with heat shock protein 105-pulsed bone marrow-derived dendritic cells in ApcMin/+ mice.	Cancer Sci.	98	1930-1935	2007
Sasaki, Y.	Does oxidative stress participate in the development of hepatocellular carcinoma?	J Gastroenterol.	41	1135-1148	2006
Goto, H., Oda, Y., Murakami, Y., Tanaka, T., Hasuda, K., Goto, S., Sasaki, Y., Sakisaka, S. and Hattori, M.	Proportion of de novo cancers among colorectal cancers in Japan.	Gastroenterology	131	40-46	2006

Yokomine, K., Nakatsura, T., Monohara, M., Kira, J., Kubo, T., Sasaki, Y. and Nishimura, Y.	Immunization with heat shock protein 105-pulsed dendritic cells leads to tumor rejection in mice.	Biochem. Biophys. Res. Commun.	343	269-278	2006
長岡克弥、佐々木　裕	特集　肝癌の診療 –最新の進歩– 肝細胞癌における遺伝子異常	臨床消化器内科 増刊号	21	73-81	2006
Hamada, A., Aoki, A., Terazaki, H., Ito, K., Yokoo, K., Sasaki, Y. & Saito, H.	Pharmacokinetic changes of irinotecan by interstitial alkalinization in an advanced colorectal cancer patient.	Ther. Drug. Monit.	27(4)	536-538	2005
Nakanishi, F., Ohkawa, K., Ishida, H., Housui, A., Sato, A., Hiramatsu, N., Ueda, K., Takehara, T., Kasahara, A., Sasaki, Y., Hori, M., and Hayashi, N.	Alteration in gene expression profile by full length hepatitis B virus genome.	Intervirology	48	77-83	2005
Kawamura, K., Iyonaga, K., Ichiyasu, H., Nagano, J., Suga, M., and Sasaki,Y.	Differentiation, maturation, and survival of dendritic cells by osteopontin regulation.	Clin. Diagn. Lab. Immunol.	12	206-212	2005
佐々木　裕	特集　肝と酸化ストレス 酸化ストレスとシグナル伝達	臨床消化器内科	20	431-438	2005

書籍

著者氏名	論文タイトル名	書籍全体の編集者名 書籍名	出版社名 出版地	出版年 ページ
佐々木　裕	発癌機序	坪内博仁 「新しい診断と治療の ABC」 肝癌　消化器 7	最新医学社 東京	2007 pp33-42
佐々木　裕	アルコール過剰摂取は C 型慢性肝疾患における肝発癌率を高めるか？	跡見　裕、上村直実、 白鳥敬子、正木尚彦 「臨床に直結する肝･胆･膵 疾患治療のエビデンス」	文光堂 東京	2007 pp58-60
佐々木　裕	肝障害とその機序 酸化ストレスと肝疾患 （分担）	竹井謙之、川崎誠治 「別冊 医学のあゆみ 消化器疾患 Ver.3」 -state of arts II. 肝・胆・膵-	医歯薬出版 東京	2006 pp76-80
佐々木　裕	消化器疾患 NASH と酸化ストレス （分担）	吉川敏一 「別冊 医学のあゆみ 酸化ストレス」 -フリーラジカル医学生物学 の最前線-	医歯薬出版 東京	2006 pp294-298

IV. 研究成果の刊行物・別刷

主任研究者　木下　平
分担研究者　古瀬　純司
中面　哲也
千住　覚
佐々木　裕
研究協力者　西村　泰治

Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 33 (2007) 1019–1024
www.ejso.com

Factors predicting survival in advanced T-staged hepatocellular carcinoma patients treated with reduction hepatectomy followed by transcatheter arterial chemoembolization

A. Kobayashi [a], S. Takahashi [a,*], H. Ishii [b], M. Konishi [a], T. Nakagohri [a], N. Gotohda [a], M. Satake [c], J. Furuse [b], T. Kinoshita [a]

[a] *Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital East, Chiba, Japan*
[b] *Department of Hepatobiliary and Pancreatic Medical Oncology, National Cancer Center Hospital East, Chiba, Japan*
[c] *Department of Diagnostic Radiology, National Cancer Center Hospital East, Chiba, Japan*

Accepted 20 February 2007
Available online 30 March 2007

Abstract

Aims: To evaluate the efficacy of reduction hepatectomy followed by transcatheter arterial chemoembolization (TACE) for advanced T-Staged hepatocellular carcinomas (HCCs).
Methods: A retrospective analysis of 39 consecutive patients who underwent reduction hepatectomy followed by TACE for advanced T-Staged HCCs was undertaken.
Results: Reduction hepatectomies, including 20 major ones, were performed. After a median interval of 30 days, the hepatectomies were followed by TACE using farmorubicin. Actual overall 3-year survival after surgery was 32%. Indocyanine green $R_{15} \geq 15\%$, preoperative AFP ≥ 2000 ng/ml, and tumour reduction rate <98% were predictive of decreased overall survival. When the three prognostic factors were used in a scoring system, with one point assigned for each factor, the 3-year survival rates of patients with scores of 0, 1, 2, and 3 were 71%, 40%, 0%, and 0% respectively.
Conclusions: Reduction hepatectomy followed by TACE is effective in patients with advanced T-Staged HCCs who have none of the 3 poor prognostic factors. Reduction surgery followed by TACE is one of the options for controlling advanced T-Staged HCCs in patients who are not candidates for curative resection or TACE alone.

Keywords: Hepatocellular carcinoma; Resection; Transcatheter arterial embolization; Transcatheter arterial chemoembolization; Prognosis

Introduction

Multiple hepatocellular carcinomas (HCCs) with huge tumours or tumour thrombi are associated with a poor prognosis.[1–3] No effective treatment for the disease has yet been identified. Although surgical resection offers the best chance for long-term survival,[4–6] many of the patients are not candidates for curative resection due to underlying liver dysfunction or the extent of the tumour. Moreover, transcatheter arterial chemoembolization (TACE), which is thought to be the first option for unresectable HCC,[7,8] is sometimes ineffective for controlling such advanced T-staged HCCs, since a large tumour burden or portal tumour thrombi can frequently coexist with the disease.[9,10]

Reduction surgery is a potential treatment for advanced T-staged HCCs that cannot be treated by either curative resection or TACE alone. Several studies have reported long-term survivors after reduction surgery.[11–16] Previously, we reported the results of reduction surgery followed by TACE for treatment of advanced T-staged HCC patients with tumours greater than 10 cm in size with preserved liver function and residual tumour accounting for less than 10% of the remnant liver.[17] However, the efficacy of this strategy is still uncertain, since the optimal patient selection criteria for the strategy have not been determined.

* Corresponding author. Present address: Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Chiba, Japan. Tel.: +81 471 331 111; fax: +81 471 314 724.
E-mail address: shtakaha@east.ncc.go.jp (S. Takahashi).

0748-7983/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2007.02.023

The aims of this study were to confirm the efficacy of reduction surgery followed by TACE in the treatment of advanced T-staged HCC patients and to determine prognostic factors that could be used to identify those patients who would most benefit from reduction surgery. We focused particularly on the effect of the tumour volume ratio (volume of all tumours/volume of the whole liver × 100%) and the tumour reduction rate (volume of the resected tumours/volume of all tumours × 100%) on survival.

Patients and methods

Patient population

Three hundred and eighty-two patients with T3N0M0 HCC and 97 patients with T4N0M0 HCC were treated at the National Cancer Center Hospital East between November 1993 and November 2003. Among the T3N0M0 HCC patients, 173 had TACE, 122 had curative resection, 33 had ablation, 27 had hepatic arterial infusion (TAI), 15 had reduction hepatectomy followed by TACE, 8 had radiation, and 4 had systemic chemotherapy. Among the T4N0M0 HCC patients, 30 had TACE, 27 had TAI, 24 had reduction hepatectomy followed by TACE, 12 had curative resection, and 4 had radiation. The data of the 39 consecutive T3N0M0 HCC and T4N0M0 HCC patients who had reduction surgery followed by TACE were retrospectively examined. The patients consisted of 36 men and 3 women, ranging in age from 27 to 77 years (mean, 57 years). HCC staging was performed according to the staging criteria of the Japanese Liver Cancer Study Group.[18] The diagnosis of HCC was based on the pathological findings of the resected specimens.

The criteria for reduction hepatectomy were as follows: (1) the presence of multiple HCCs for which curative resection was not indicated and that appeared to be resistant to TACE due to tumour extent, tumour thrombus, or other factors; (2) no extrahepatic metastases; (3) sufficient liver function to tolerate the planned hepatectomy; and (4) written informed consent before treatment. All 39 patients had contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), hepatic angiography, abdominal ultrasonography, and chest X-Rays preoperatively to stage the HCCs and evaluate resectability. Liver function was assessed based on liver biochemistry tests, Child-Pugh grade,[19] and the indocyanine green retention rate at 15 min.[20] The patients' data were reviewed by hepatic surgeons, medical oncologists, and interventional radiologists during a conference to determine whether the patients met the aforementioned criteria.

Treatment procedure and follow up

First, large main tumours with satellite tumours that were obstacles for TACE were resected. Tumour thrombi in the portal or hepatic veins were also resected when they were recognized before or during the operation. Hepatic resection was performed by the forceps fracture method under inflow occlusion (Pringle's manoeuvre), and anatomic hepatectomy was performed whenever possible. All the resections were ultrasound-guided procedures.

Hepatectomy was followed by TACE as soon as liver function recovered during the postoperative period. TACE was repeated every 2–3 months until there was: complete remission of the remnant tumours; progressive disease despite treatment; or malfunction of the liver or other organs. The TACE procedure was performed by injecting a mixture of iodized oil (Lipiodol) 5 ml and farmorubicin 50 mg, followed by a gelatine sponge block (Gelfoam).

One month after treatment, the anti-tumour effects of TACE were assessed by CT. Subsequently, follow-up examinations, including CT, serum alpha-fetoprotein (AFP), and biochemistry assays, were conducted at least every 3 months. The median follow-up of the survivors was 23 months.

When disease progression was evident in the remnant liver, TACE was stopped and transcatheter arterial infusion chemotherapy with farmorubicin 50 mg was performed if possible. When disease progression was observed only outside the liver, TACE was continued if treatment to the hepatic tumour seemed to be beneficial.

Measurement of tumour volume ratio and tumour reduction rate

Tumour volumes were obtained from contrast-enhanced CT scans of the abdomen that were performed before hepatectomy using 5-mm collimation with administration of 120 cc of non-ionic intravenous contrast injected at 3 cc per second with 40-s, 60-s, and 3-min delays. Images were reconstructed at 5-mm intervals using a standard soft-tissue algorithm.

Tumours and the liver were outlined manually on each axial slice using a computer mouse. The tumour and whole liver volumes were calculated automatically by multiplying the sum of the areas from each slice by the reconstruction interval. Then, the tumour volume ratio (volume of all tumours/volume of the whole liver × 100%) and tumour reduction rate (volume of the resected tumours/volume of all tumours × 100%) were calculated. The resected part of the tumour was confirmed by both the surgical record and the findings of pre- and postoperative contrast-enhanced CT scans. All measurements were made by a radiologist.

Statistical analysis

Survival analyses were performed using the Kaplan–Meier method,[21] and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model.[22] A P value of less than 0.05 was considered significant.

Results

Patient characteristics and clinicopathological features of HCCs

Hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb) were positive in 10 and 18 patients, respectively. Twelve patients tested negative for both HBsAg and HCVAb. The mean results of the preoperative liver function tests were: ALT, 71.3 IU/L; serum albumin, 3.7 g/L; prothrombin time, 81.8%; and ICG R_{15} 16.2%. Based on the Child-Pugh grading system, 31 patients were stage A, and 8 were stage B. Twenty patients had liver cirrhosis. The median maximum tumour size was 11.5 cm (range, 4.5–21.5 cm); 20 patients had 10 or more tumours. The average tumour volume rate was 41%. The average preoperative AFP level was 802 ng/ml. Macroscopic portal vein invasion (thrombus) that involved a major branch was found in 12 patients. Four patients had tumour thrombus in the trunk of the portal vein. Based on the Japanese Liver Cancer Study Group classification of tumour growth extent, 31 cases had expansive tumour growth, and 8 had infiltrative growth.

Reduction hepatectomy

Four patients had tri-segmentectomies (Fig. 1), two had central bi-segmentectomies, 14 had lobectomies, 11 had segmentectomies, and 8 had partial resections; 7 patients had simultaneous direct removal of the portal tumour thrombus.

The average resected tumour volume was 1488 ml; the average tumour volume left in the remnant liver was 53 ml. The average tumour reduction was 94.7%.

One patient died on the 15th day after reduction hepatectomy due to liver failure. The morbidity rate was 41%: 8 cases had a biliary leak; 5 had ascites; 4 had a wound infection; 3 had an intra-abdominal abscess; 2 had bleeding; and 2 had liver failure.

Transcatheter arterial chemoembolization

All but one patient who underwent reduction hepatectomy received TACE; postoperative liver failure prevented the one patient from receiving TACE. The median interval from reduction hepatectomy to the first TACE treatment was 30 days, and the average number of TACE treatments was 3.6 (range, 1–15).

Survival

Survival time was calculated from the date of reduction hepatectomy. Actual overall 3-year survival was 32%, with a median survival of 11 months (Fig. 2). Six patients survived more than 3 years.

Among the 39 patients, 27 developed disease progression. The location of the initial progression included: remnant liver, 19 patients; lungs, 7; bone, 6; lymph nodes, 1; and brain, 1.

Correlation between clinicopathological factors and overall survival

To determine the prognostic factors related to survival after reduction hepatectomy in patients with advanced T-staged HCCs, the clinicopathological factors and overall survival of the 39 patients were analyzed (Table 1). Serum albumin level <3.5 g/L ($P = 0.03$), indocyanine green (ICG) $R_{15} \geq 15\%$ ($P < 0.01$), preoperative alpha-fetoprotein (AFP) ≥ 2000 ng/ml ($P = 0.04$), tumour reduction rate $<98\%$ ($P = 0.02$), macroscopic portal vein invasion ($P < 0.01$), and infiltrative growth ($P < 0.01$) were

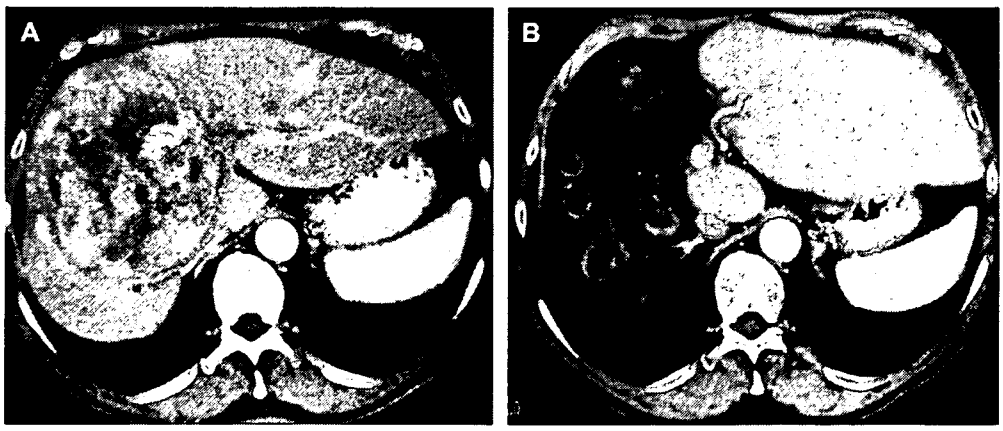

Figure 1. Contrast-enhanced computed tomography (CT) findings of a 66-year-old man with multiple hepatocellular carcinomas (HCCs). (A) CT before reduction hepatectomy demonstrates an HCC measuring 14 cm with many intrahepatic metastases throughout both lobes. The preoperative alpha-fetoprotein level was 6717 ng/ml, and no tumour thrombus was observed in the hepatic or portal veins. Liver function was preserved (ICG $R_{15} = 8.7\%$). The patient underwent reductive right tri-segmentectomy. (B) CT 4 years after reduction hepatectomy demonstrates small tumours well controlled by 10 successive transcatheter arterial chemoembolizations.

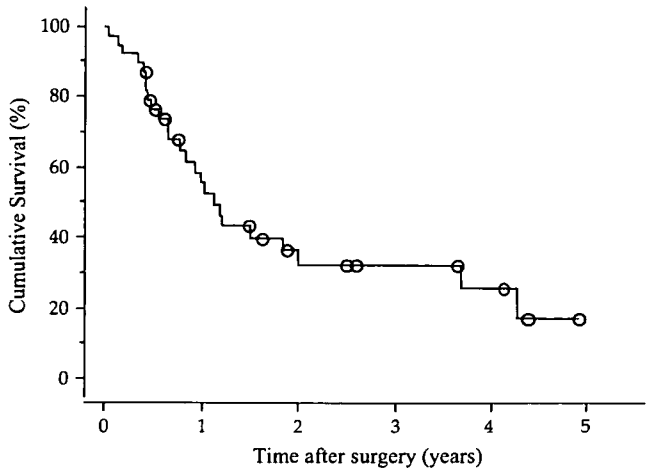

Figure 2. Cumulative survival curves after reduction hepatectomy followed by transcatheter arterial chemoembolization in patients with advanced T-staged HCCs.

significantly associated with poor overall survival. Neither the number nor size of tumours in the remnant liver was correlated with survival.

We examined the independent predictive value of the aforementioned factors for overall survival. The data were analyzed using a Cox regression model (Table 2). Serum albumin level <3.5 g/L was excluded from the analysis due to a possible correlation with ICG R_{15} ≥15%. ICG R_{15} ≥15% ($P < 0.01$; HR = 5.89; 95% CI, 1.98 to 17.5), preoperative AFP ≥2000 ng/ml ($P < 0.01$; HR = 5.85; 95% CI, 1.93 to 17.7), and tumour reduction rate <98% ($P < 0.01$; HR = 4.25; 95% CI, 1.55 to 11.7) were predictive for decreased overall survival.

When the three prognostic factors were used in a scoring system, with one point assigned for each factor, the total score was strongly correlated with survival after reduction hepatectomy ($P < 0.01$). The 3-year survival rates of patients with scores of 0 ($n = 7$), 1 ($n = 17$), 2 ($n = 13$), and 3 ($n = 2$) were 71%, 40%, 0%, and 0% respectively (Fig. 3). No patients with two or more criteria survived more than 15 months.

Table 1
Correlation between clinicopathologic factors and overall survival after reduction hepatectomy for multiple HCCs

	No. of patients	Median survival (mo)	P
HBsAg			
Negative	29	12.5	0.26
Positive	10	9.1	
HCVAb			
Negative	21	11.2	0.83
Positive	18	10.9	
ALT			
<70 IU/L	22	11.6	0.69
≥70 IU/L	17	9.3	
Albumin			
≥3.5 g/L	29	12.5	0.03
<3.5 g/L	10	5.0	
Prothrombin Time			
≥80%	22	11.0	0.65
<80%	17	11.2	
ICG R_{15}			
<15%	21	17.9	<0.01
≥15%	18	7.1	
Child-Pugh Stage			
A	31	11.9	0.61
B	8	7.3	
Tumor size			
<10 cm	19	7.9	0.17
≥10 cm	20	18.1	
Number of tumors			
<10	20	14.2	0.07
≥10	19	10.1	
AFP			
<2000 ng/ml	25	13.7	0.04
≥2000 ng/ml	14	6.1	
Tumor volume ratio[a]			
<50%	26	8.6	0.83
≥50%	13	12.5	
Tumor reduction rate[b]			
≥98%	21	17.9	0.02
<98%	18	7.1	
Macroscopical portal vein invasion			
Absent	27	13.7	<0.01
Present	12	5.8	
Growth type of tumor			
Expansive growth	31	13.7	<0.01
Infiltrative growth	8	6.9	

[a] Volume of all tumors/volume of whole liver × 100%.
[b] Volume of the resected tumors/volume of all tumors × 100%.

Discussion

The optimal treatment of patients with multiple HCCs who are not candidates for curative resection or TACE alone due to large tumours or tumour thrombi is unclear. Reduction surgery, which is also referred to as "debulking surgery", "tumour mass reduction surgery", and "tumour volume reduction surgery", is a potential treatment for patients with advanced T-staged HCCs.[11–17] Initially, large main tumours that are life-threatening and that can obstruct postoperative treatment are resected. Then, additional therapy, such as TACE or transcatheter arterial infusion chemotherapy, is given to treat the residual tumour in the remnant liver. Long-term survivors have been reported after reduction surgery for advanced HCCs. Several retrospective reports with small cohorts have shown that reduction surgery is superior to non-surgical treatment, such as TACE or transcatheter arterial infusion chemotherapy.[14,15] In a previous study, we reported the efficacy of reduction surgery followed by TACE in a small cohort of patients who had preserved liver function, tumour size greater than 10 cm, and residual tumour volume <10% of the remnant liver.[17] However, the indications for reduction hepatectomy followed by TACE are still unclear.

In the present study, all patients who underwent reduction hepatectomy were studied to confirm the efficacy of

Table 2
Multivariate analyses of factors affecting overall survival after reduction hepatectomy for multiple HCCs

	Hazard ratio	P
ICG R_{15} ≧15%	5.89 (1.98–17.5)	<0.01
AFP ≥2000 ng/ml	5.85 (1.93–17.7)	<0.01
Tumor reduction rate[a] <98%	4.25 (1.55–11.7)	<0.01
Macroscopical portal vein invasion	1.25 (0.38–4.07)	0.71
Infiltrative growth of tumor	2.19 (0.63–7.57)	0.22

Values in parentheses are 95 per cent confidence intervals.
[a] Volume of the resected tumors/volume of all tumors × 100%.

reduction surgery followed by TACE and to determine prognostic factors that might identify the patients who would most benefit from reduction hepatectomy. TACE was used as postoperative treatment since TACE is considered to be the first option for controlling unresectable multiple HCCs.

In this series, overall survival after reduction hepatectomy was 32% at 3 years and the results were not so much different from those of curative resection for stage IV HCC[23,24] while all our cases were classified as stage IVA according to the TNM classification system by UICC. Furthermore, patients who received the treatment were not a few because one quarter of patients with T4N0M0 HCC received the treatment.

Three factors associated with a poor prognosis were identified: ICG R_{15} ≥15%; preoperative AFP ≥2000 ng/ml; and tumour reduction rate <98%. These three factors capture the essence of the treatment strategy. First, the reduction hepatectomy tends to be a major hepatectomy due to the extent of tumour; however, postoperative liver failure or deterioration of liver function must be avoided, since this can delay the start of TACE. As well, sufficient liver function must be present preoperatively. Second, early

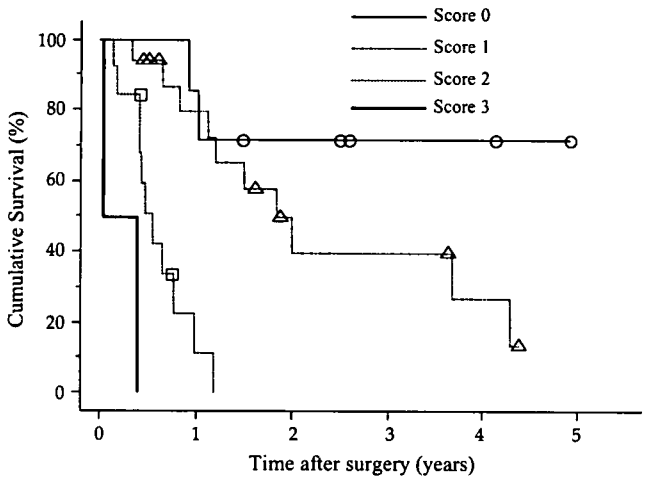

Figure 3. Cumulative survival curves after reduction hepatectomy followed by transcatheter arterial chemoembolization based on the scoring system. The scoring system was based on assigning one point for each of: ICG R_{15} ≥15%; preoperative alpha-fetoprotein ≥2000 ng/ml; and tumour reduction rate <98%.

progression is an issue with this treatment strategy; overall survival decreased to about 50% within a year in this series. A high preoperative AFP level has been reported to be a significant factor indicating a poor prognosis[2,25] and might be correlated with early death after reduction hepatectomy due to abrupt tumour progression inside or outside the liver. Third, control of the residual tumour in the remnant liver is necessary for long-term survival. A high tumour reduction rate indicates a low tumour burden in the remnant liver and may predict good control of the residual tumour with postoperative TACE.[9,10]

Extrahepatic disease,[12] residual tumour thrombus,[14] no effect of postoperative treatment,[14] and a remnant tumour index[13] have been reported as poor prognostic factors after reduction surgery for HCC. Yamamoto et al. proposed a remnant tumour index that is calculated based on the maximum diameter of the largest residual tumour (in cm) multiplied by the number of residual tumours; this index can be used to quantify the tumour burden in the remnant liver and select optimal candidates for reduction surgery.[13] The concept of a remnant tumour index is similar to that of the tumour reduction rate in the present study. However, the maximum diameter of the largest residual tumour, the number of residual tumours, and a remnant tumour index were not correlated with survival in the present study (data not shown). The tumour reduction rate may perhaps more accurately evaluate the efficacy of reduction surgery and the tumour burden in the remnant liver.

To select the best candidates for reduction hepatectomy, we would propose a scoring system that incorporates the aforementioned three factors for patients with multiple HCCs that are not treatable with curative resection. The score based on these factors was strongly correlated with survival after reduction hepatectomy; the 3-year survival rates of patients with scores of 0, 1, 2, and 3 were 71%, 40%, 0%, and 0% respectively. Patients with a score of 0 are good candidates for reduction hepatectomy followed by TACE. On the other hand, a score of 2 or 3 might be a contraindication for treatment, since there were no long-term survivors among patients who had scores of 2 or 3. Other non-surgical treatments, including experimental treatments, would be recommended for patients with a score of 2 or 3. Patients with a score of 1 sometimes survive a relatively long time; thus, patients with a score of 1 may be candidates for reduction hepatectomy, though other findings, such as cardiopulmonary function or performance status, should be considered in such patients.

Recently, intensive non-surgical treatments using transcatheter arterial infusion chemotherapy or systemic chemotherapy have improved the treatment of advanced T-staged HCCs.[26–31] A potential weakness of the present study is that our strategy using reduction hepatectomy followed by TACE did not take into account these new treatments. A clinical study comparing the efficacy of reduction hepatectomy followed by TACE with that of intensive non-surgical treatments in patients with advanced T-staged HCCs, especially

those with a score of 1, is needed. Moreover, the efficacy of reduction hepatectomy followed by one of these intensive non-surgical treatments should be investigated.

Since our study population was small, a prospective study is warranted to verify the validity of the scoring system.

In conclusion, reduction hepatectomy followed by TACE is effective in controlling advanced T-staged HCCs when the ICG R_{15} is <15%, the preoperative AFP is <2000 ng/ml, and the tumour reduction rate is ≥98%. Reduction hepatectomy followed by TACE is one of the options for controlling advanced T-staged HCCs in patients who are not candidates for curative resection or TACE alone.

References

1. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985;**56**:918–28.
2. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998;**28**:751–5.
3. Ikai I, Arii S, Kojiro M, et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. *Cancer* 2004;**101**:796–802.
4. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg* 1999;**229**:322–30.
5. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 1999;**134**:984–92.
6. Ng KK, Vauthey JN, Pawlik TM, et al. International Cooperative Study Group on Hepatocellular Carcinoma. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol* 2005;**12**:364–73.
7. Llovet JM, Real MI, Montaña X, et al. Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;**359**:1734–9.
8. Llovet JM, Bruix J. for the Barcelona-Clinic Liver Cancer Group. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003; **37**:429–42.
9. Mondazzi L, Bottelli R, Brambilla G, et al. Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma: a multivariate analysis of prognostic factors. *Hepatology* 1994;**19**:1115–23.
10. Taniguchi K, Nakata K, Kato Y, et al. Treatment of hepatocellular carcinoma with transcatheter arterial embolization. Analysis of prognostic factors. *Cancer* 1994;**73**:1341–5.
11. Shimamura Y, Gunven P, Ishii M, Ono M, Abe K. Debulking surgery and arterial embolization for unresectable liver cancer. *Hepatogastroenterology* 1993;**40**:10–3.
12. Yamamoto M, Iizuka H, Matsuda M, Nagahori K, Miura K, Itakura J. The indications for tumor mass reduction surgery and subsequent multidisciplinary treatments in stage IV hepatocellular carcinoma. *Surg Today* 1993;**23**:675–81.
13. Yamamoto K, Takenaka K, Kawahara N, et al. Indications for palliative reduction surgery in advanced hepatocellular carcinoma. The use of a remnant tumor index. *Arch Surg* 1997;**132**:120–3.
14. Nagashima J, Okuda K, Tanaka M, Sata M, Aoyagi S. Prognostic benefit in cytoreductive surgery for curatively unresectable hepatocellular carcinoma – comparison to transcatheter arterial chemoembolization. *Int J Oncol* 1999;**15**:1117–23.
15. Wakabayashi H, Ushiyama T, Ishimura K, et al. Significance of reduction surgery in multidisciplinary treatment of advanced hepatocellular carcinoma with multiple intrahepatic lesions. *J Surg Oncol* 2003;**82**:98–103.
16. Ku Y, Iwasaki T, Tominaga M, et al. Reductive surgery plus percutaneous isolated hepatic perfusion for multiple advanced hepatocellular carcinoma. *Ann Surg* 2004;**239**:53–60.
17. Inoue K, Nakamura T, Kinoshita T, et al. Volume reduction surgery for advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**:362–6.
18. Liver Cancer Study Group of Japan. *The general rules for the clinical and pathological study of primary liver cancer*. 2nd English ed. Tokyo, Japan: Kanehara & Co. Ltd.; 2003.
19. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**:646–9.
20. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* 1997;**84**:1255–9.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
22. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B* 1972;**34**:187–220.
23. Poon RT, Fan ST, Ng IO, Wong J. Prognosis after hepatic resection for stage IVA hepatocellular carcinoma: a need for reclassification. *Ann Surg* 2003;**237**:376–83.
24. Ikai I, Yamaoka Y, Yamamoto Y, et al. Surgical intervention for patients with stage IV-A hepatocellular carcinoma without lymph node metastasis: proposal as a standard therapy. *Ann Surg* 1998;**227**:433–9.
25. Nomura F, Ohnishi K, Tanabe Y. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. *Cancer* 1989;**64**:1700–7.
26. Ota H, Nagano H, Sakon M, et al. Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. *Br J Cancer* 2005;**93**:557–64.
27. Sakon M, Nagano H, Dono K, et al. Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002;**94**:435–42.
28. Leung TW, Tang AM, Zee B, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. *Cancer* 2002;**94**:421–7.
29. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005;**97**:1532–8.
30. Chung YH, Song IH, Song BC, et al. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. *Cancer* 2000;**88**:1986–91.
31. Ando E, Yamashita F, Tanaka M, Tanikawa K. novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer* 1997;**79**:1890–6.

Jpn J Clin Oncol 2007;37(3)186–192
doi:10.1093/jjco/hym006

Multiple Resections for Hepatic and Pulmonary Metastases of Colorectal Carcinoma

Shinichiro Takahashi[1], Kanji Nagai[2], Norio Saito[3], Masaru Konishi[1], Toshio Nakagohri[1], Naoto Gotohda[1], Mitsuyo Nishimura[2], Junji Yoshida[2] and Taira Kinoshita[1]

[1]Department of Hepato-biliary Pancreatic Surgery, [2]Department of Thoracic Surgery and [3]Department of Colorectal Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Received May 21, 2006; accepted November 8, 2006

Background: Resections are effective for some patients with both hepatic and pulmonary metastases of colorectal cancer, but the best selection criteria for the resections and effective treatment for recurrence after the resections have not been determined.
Methods: A retrospective analysis was performed for 30 consecutive patients who received aggressive multiple resections for both hepatic and pulmonary metastases of colorectal cancer. Recurrences after resections were surgically treated whenever resectable.
Results: For the 30 patients, 45 hepatectomies and 40 pulmonary resections were performed and 17 patients received three or more resections. No mortality was observed. Overall survival after the first metastasectomy for the second organ (liver or lung) was 58% and nine 5-year survivors were observed. Multivariate analyses revealed that primary colon cancer, stage IV in TNM classification and maximum size of hepatic tumor >3 cm at initial hepatectomy were poor prognostic factors, but several long-term survivors were observed even among patients with those factors.
Conclusions: Multiple resections for hepatic and pulmonary metastases of colorectal cancer are safe and effective. No single factor is considered to be a contraindication for the resections. For recurrence after the resections, surgical resection is also recommended if resectable.

Key words: colorectal cancer – hepatic metastasis – pulmonary metastasis – resection

INTRODUCTION

The liver and lung are the most common sites of distant metastases for colorectal carcinoma (1). Hepatic and pulmonary metastases may be detected sequentially or simultaneously in patients with colorectal carcinoma. Efficacy of resections for these two distant metastases has been reported in several studies (2–14). However, the criteria to select patients for those resections are still obscure.

In addition, although recurrence after those resections is one of the major problems of the strategy, further surgical approaches for recurrence after those resections are controversial.

The purpose of this study was to evaluate the efficacy of aggressive multiple resections for hepatic and pulmonary metastases of colorectal carcinoma and to find prognostic factors that might elucidate who would benefit most from hepatic and pulmonary resections for colorectal metastases.

PATIENTS AND METHODS

Two hundred and sixty-seven patients who had undergone hepatic resection and 98 patients who had undergone pulmonary resection, as the first treatment for colorectal metastasis at the National Cancer Center Hospital East between September 1992 and June 2005 were examined retrospectively. Eight patients had undergone surgical resections for both hepatic and pulmonary metastases as the first treatment for colorectal metastases. Metastases were synchronous with primary colorectal carcinoma in one of the eight patients. In the remaining 259 patients who had undergone hepatic resection as the first treatment for colorectal

For reprints and all correspondence: Shinichiro Takahashi, Department of Hepato-biliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Chiba, Japan. E-mail: shtakaha@east.ncc.go.jp

metastasis, 83 had the second recurrence in the liver, 29 in the lung, 12 in both liver and lung and 52 in the other organs. Sixteen of the 29 patients with pulmonary recurrence and one of the 12 patients with both hepatic and pulmonary recurrences were treated surgically. Two patients had undergone resections for both hepatic and pulmonary recurrences after more than two hepatic metastasectomies. In the remaining 90 patients who had undergone pulmonary resection as the first treatment for colorectal metastasis, three had the second recurrence in the liver, 27 in the lung, four in both liver and lung and 16 in other organs. All three patients with hepatic recurrence were treated surgically. However, all four patients with both hepatic and pulmonary recurrences underwent systemic chemotherapy as the second treatment.

As a result, 30 patients underwent both hepatic and pulmonary resections for colorectal metastasis. The patients consisted of 19 men and 11 women, ranging in age from 24 to 75 years with a mean of 59 years. Two of the patients had received adjuvant chemotherapy (tegafur/uracil and 5-fluorouracil/leucovorin) after primary colorectal resection and one patient had received preoperative chemoradiation for rectal cancer.

The criteria for hepatectomy were as follows: (1) metastatic lesions are confined to the liver and technically resectable, (2) no extrahepatic metastases except resectable pulmonary metastasis are detected, and (3) liver function is equal to complete resection of all hepatic tumors. The criteria for pulmonary resection were as follows: (1) metastatic lesions are confined to the lung and technically resectable, (2) no extrathoracic metastases except resectable hepatic metastasis are detected, and (3) cardiorespiratory function is equal to complete resection of all pulmonary tumors. The timing of the detection of hepatic and pulmonary metastases or the number of prior resections for metastases did not affect these criteria, so the selection criteria for further resections for recurrences after hepatic and pulmonary resections are the same as above.

At hepatectomy, intraoperative ultrasonography was performed to confirm tumor location and size of the lesions in all patients, and all of the resections were ultrasound-guided procedures. Hepatic resection was performed by the forceps fracture method under inflow occlusion (Pringle's maneuver). At pulmonary resection, hilar or mediastinal lymph node dissection was used to sample lymph nodes of most patients who had a lobectomy.

When hepatic and pulmonary metastases were detected simultaneously, hepatic resection was carried out first, followed by pulmonary resection.

No patient received adjuvant chemotherapy after hepatectomy or pulmonary resection.

After hepatic or pulmonary resection, patients were closely followed with diagnostic imaging [chest X-ray and abdominal computed tomography (CT)] and measurement of serum carcinoembryonic antigen (CEA) levels every 3 months; they also underwent an annual colonoscopy to detect any tumor recurrence. The median follow-up of survivors was 53 months.

Morphological Investigations

The resected specimens of colon or rectum, liver and lung were fixed in 10% phosphate-buffered formalin, cut at intervals of 5 mm and embedded in paraffin. Serial sections of 3-μm thickness were stained with hematoxylin and eosin for morphological examination. Each case was histologically classified according to the histological type, tumor size, location, number of metastases, presence of serosal invasion, nodal status and margin status. Histological diagnosis was performed according to the World Health Organization intestinal tumor classification (15).

Statistical Analysis

The student *t*-test was used to compare data between subgroups by the location of the primary tumor. The Mann–Whitney's U test was used to compare serum CEA levels between subgroups. Analyses of survival rates were performed using the Kaplan–Meier method (16) and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model (17). A P value of less than 0.05 was considered to denote significance.

RESULTS

Clinicopathological Features of Primary and Metastatic Tumors

The primary tumors were staged as I ($n = 1$), II ($n = 10$), III ($n = 15$) and IV ($n = 4$) according to TNM classification (Table 1). All patients at stage IV had hepatic metastasis at resection of the primary tumor.

At the initial hepatectomy, the average number of hepatic tumors was 2.1 (range, 1–12), the average maximum size was 3.2 cm (range, 0.3–9 cm) and the average preoperative CEA level was 19.9 ng/ml (range, 0.8–68.5 ng/ml). In all hepatectomies, the average number of hepatic tumors was 2.8 and the average maximum size was 3.3 cm. Lymph node metastasis at the hepatoduodenal ligament was shown in one patient.

Regarding pulmonary metastases, the average number of pulmonary tumors was 1.8 (range, 1–5), the average maximum size was 2.2 cm (range, 0.7–6.7 cm) and the average prethoracotomy CEA level was 12.4 ng/ml (range, 1.0–66.7 ng/ml) at initial pulmonary resection. In all pulmonary resections, the average number of pulmonary tumors was 2.1 and the average maximum size was 2.5 cm. Hilar lymph node metastasis of the lung was shown in two patients.

Surgical Resections for Hepatic and Pulmonary Metastases

Forty-five hepatectomies (30 partial resections, four subsegmentectomies, seven segmentectomies and four lobectomies

Table 1. Correlation between clinicopathologic factors and overall survival in patients with resected hepatic and pulmonary metastases from colorectal cancer

	No.	Median survival (mo)	*P* value
Primary colorectal lesion			
Location			
rectum	13	52.7	0.03
colon	17	38.6	
TNM classification			
I	1	88.9	0.02*
II	10	48.9	
III	15	38.8	
IV	4	14.6	
Lymph node metastasis			
absent	11	54.8	0.64
present	19	32.8	
Histological type of adenocarcinoma			
well or moderately differentiated	28	38.7	0.77
poorly differentiated and others	2	41.7	
Hepatic metastases			
First hepatectomy			
Number of tumors			
1	18	40.8	0.26
≥2	12	36.8	
Maximum size of the tumor (cm)			
<3	14	40.0	0.03
≥3	16	35.8	
Distribution of metastases			
unilobar	20	40.8	0.36
bilobar	10	36.8	
Lymph node of hepatoduodenal ligament			
negative	29	38.8	0.02
positive	1	13.9	
All hepatectomies			
Total number of tumors			
<3	19	38.6	0.79
≥3	11	38.8	
Maximum size of the tumor (cm)			
<3	13	38.8	0.08
≥3	17	38.6	
Distribution of metastases			
unilobar	17	43.0	0.49
bilobar	13	34.8	
Pulmonary metastases			
First pulmonary resection			
Number of tumors			
1	18	47.9	0.31
≥2	12	27.1	
Maximum size of the tumor (cm)			
<3	21	34.8	0.69
≥3	9	38.8	
Distribution of metastases			
unilobar	24	42.1	0.68
bilobar	6	27.1	
Hilar or mediastinal lymph node			
negative	28	36.7	0.89
positive	2	43.6	
All pulmonary resections			
Number of tumors			
<3	22	38.7	0.92
≥3	8	44.8	
Maximum size of the tumor (cm)			
<3	19	34.8	0.93
≥3	11	38.8	
Distribution of metastases			
unilobar	21	41.1	0.97
bilobar	9	30.8	
CEA level at initial recurrence (ng/ml)			
<50	25	38.7	0.34
≥50	5	33.0	
Disease-free interval from resection of primary tumor			
<1 year	19	38.8	0.23
≥1 year	11	38.6	
Simultaneous detection of hepatic and pulmonary recurrences			
yes	11	34.8	0.35
no	19	38.8	
Initial metastasis in the lung			
yes	3	54.8	0.72
no	27	38.6	
Total number of liver and lung resections			
2	13	33.0	0.50
≥3	17	54.3	

CEA, carcinoembryonic antigen.
*Stage I, II or III versus Stage IV.

according to Couinaud's anatomical classification (18)) and 40 pulmonary resections (32 partial resections, seven lobectomies and one pneumonectomy) were performed on the 30 patients. The average number of operations performed for hepatic or pulmonary metastases per patient was 2.8. Three operations were performed on 11 patients, four operations on four patients each and five operations on two patients each.

There was no perioperative mortality. Five complications were observed: two cases of biliary leak and one case each of portal vein thrombosis after hepatectomy, wound infection and air leak after pulmonary resection.

The location of initial metastasis was lung in three patients, liver in 19, and both liver and lung in eight. Eleven patients experienced hepatic and pulmonary metastases detected simultaneously.

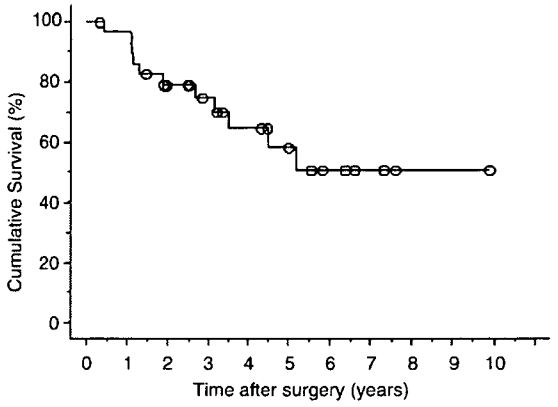

Figure 1. Cumulative survival curves for 30 patients who underwent resections for both hepatic and pulmonary metastases of colorectal cancer.

Recurrence after Surgical Resections for Hepatic and Pulmonary Metastases

Among 30 patients who underwent surgical resections for hepatic and pulmonary metastases, 25 developed recurrences when recurrence was defined as the first recurrent disease after at least one resection each for hepatic and pulmonary metastases. Locations of recurrences were as follows: lung in 11 patients, liver and lymph node in four each, both liver and lung in three, peritoneum, local recurrence and brain in one each. Re-resection could be performed in 15 of the 25 patients. Of the remaining 10 patients, eight received systemic chemotherapy, one each received radiation therapy and best supportive care.

Survival

Survival time was calculated from the date of the first metastasectomy for the second organ metastasized (liver or lung).

Actuarial overall survival was 58% at 5 years with a median survival of 39 months (Fig. 1). Disease-free survival was 56% at 1 year and 8% at 3 years, with a median recurrence-free survival of 13 months. Nine 5-year survivors were observed and eight of the nine patients are still alive without disease. Of the nine 5-year survivors, six had undergone three operations and one had undergone four operations.

When survival time was calculated from the date of the first metastasectomy for the first organ, actuarial overall survival was 70% at 5 years with a median survival of 60 months.

Correlation between Clinicopathologic Factors and Overall Survival

To find prognostic factors for survival after resection of hepatic and pulmonary metastases, clinicopathologic factors and overall survival calculated from the date of the first metastasectomy for the second organ were analyzed in 30 patients (Table 1). Primary colon carcinoma ($P = 0.03$), stage IV in TNM classification ($P = 0.02$), maximum size of hepatic tumor >3 cm at initial hepatectomy ($P = 0.03$), and lymph node metastasis of the hepatoduodenal ligament ($P = 0.02$) were significantly associated with poor overall survival. Whether hepatic and pulmonary metastases were detected simultaneously or sequentially was not correlated with survival ($P = 0.35$). Neither a disease-free interval of less than 1 year from resection of the primary tumor nor initial metastasis in the lung affected survival.

We examined the independent predictive value of the aforementioned factors on overall survival (Table 2). Lymph node metastasis of the hepatoduodenal ligament was excluded from the analysis because only one of the 30 patients had the factor. Primary colon carcinoma (Fig. 2A), stage IV in TNM classification (Fig. 2B), and maximum size of hepatic tumor >3 cm at initial hepatectomy (Fig. 2C) had predictive value for decreased overall survival after resection of hepatic and pulmonary metastases from colorectal cancer.

Comparing clinicopathological factors of patients with primary colon carcinoma and those of patients with primary rectal carcinoma, maximum size of pulmonary tumors (2.6 ± 1.6 cm versus 1.7 ± 0.7 cm) was significantly larger and prethoracotomy CEA level (18.2 ± 23.8 ng/ml versus 5.3 ± 5.4 ng/ml) was significantly higher in patients with primary colon carcinoma. The interval from primary resection to the first pulmonary resection tended to be longer in patients with primary colon carcinoma than in patients with primary rectal carcinoma (25.7 months versus 17.1 months, median).

DISCUSSION

Results of this study indicate that aggressive multiple resections for hepatic and pulmonary metastases of colorectal carcinoma are safe and contribute to long-term survival in some patients.

Hepatic and pulmonary metastases may be detected sequentially or simultaneously in patients with colorectal carcinoma. Although two distant organs are affected by the

Table 2. Multivariate analyses of factors affecting overall survival in patients with resected hepatic and pulmonary metastases from colorectal cancer

	Hazard ratio (95% CI)	*P* value
Location of primary tumor		
Rectum	—	0.01
Colon	8.74 (1.53—49.91)	
TNM classification of primary tumor		
I, II, III	—	0.03
IV	11.37 (1.34—96.53)	
Maximum size of tumor at first hepatectomy (cm)		
<3	—	<0.01
≥3	14.47 (2.33–89.85)	

CI, confidence interval; CEA, carcinoembryonic antigen.

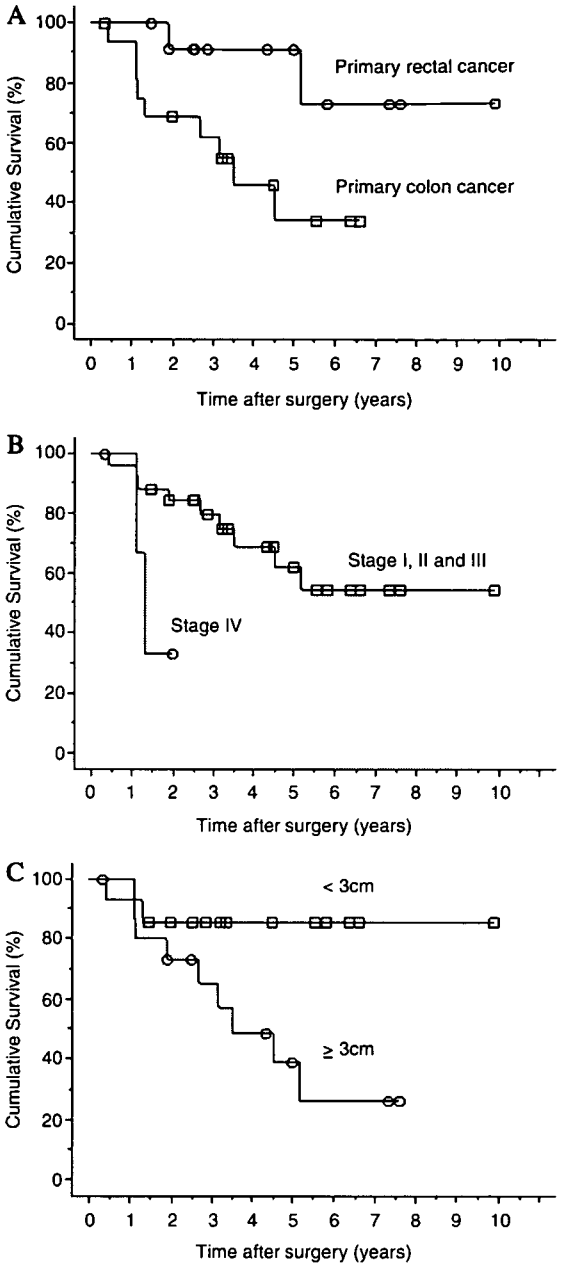

Figure 2. Cumulative survival curves after resections for hepatic and pulmonary metastases of colorectal cancer according to (A) location of primary tumor, (B) stage in TNM classification, and (C) maximum size of hepatic tumor at initial.

disease, several studies have demonstrated the efficacy of resections for both hepatic and pulmonary metastases (2–14). However, because of the frequent recurrences after resections, the best selection criteria for resection have not been established.

Lenhart *et al.* reported a disease-free survival of only 24% at 2 years in patients who underwent sequential hepatic and pulmonary resections for colorectal metastases (9). In the present study, the 2-year disease-free survival rate after the first metastasectomy for the second organ was also 24% with a median disease-free survival of only 13 months. The best treatment strategy for the recurrences after hepatic and pulmonary resections is obscure. However, only surgical removal of metastases offers a chance of cure. Aggressive repeat metastasectomy has been applied for recurrences after hepatic and pulmonary resections in our institution.

For the 30 patients of the present study, 45 hepatectomies and 40 pulmonary resections were performed and 17 patients received three or more resections with a maximum of five resections. Overall survival after the first metastasectomy for the second organ was 58% and nine 5-year survivors were observed. Surprisingly, seven of the nine 5-year survivors had undergone three or more resections. When survival time was calculated from the date of the first metastasectomy for the first metastasized organ, overall survival reached 70% at 5 years with a median survival of 60 months in the present study. Little is available on the result of repeat metastasectomy for recurrences after hepatic and pulmonary resections. Our results of long-term survival after hepatic and pulmonary resections in spite of frequent recurrences support the view that patients who can undergo resections for both hepatic and pulmonary metastases of colorectal cancer are in a selected population but can sometimes survive a long time with multiple metastasectomies. Interestingly, a recent study by Shah *et al.* also reported 74% 5-year survival rate after multidisciplinary surgical metastasectomies for colorectal cancer (19). The strategy and results of Shah *et al.* were similar to ours. However, while a majority of the patients received adjuvant chemotherapy after metastasectomies in Shah's study, no patient underwent adjuvant chemotherapy in the present study. These results indicate that the strategy of aggressive multiple metastasectomies count more than postoperative chemotherapies in the treatment for very restricted population of patients.

We found three factors for poor prognosis: size of hepatic tumor >3 cm at the first hepatectomy, primary colon carcinoma and stage IV tumor.

Maximum size of the hepatic tumor has been reported to be one of the important prognostic factors after hepatic resections for colorectal hepatic metastasis (20,21). This factor could affect prognosis in this population.

The reason for poor prognosis in patients with primary colon cancer is unknown. Patients with primary colon cancer had larger pulmonary tumors, higher CEA levels at the first pulmonary resection and relatively longer intervals from primary resection to the first pulmonary resection than patients with primary rectal cancer. A higher prethoracotomy CEA level was a factor of poor prognosis after hepatic and pulmonary resections in several studies (6,11). However, the reason why patients with primary colon cancer had more advanced pulmonary tumors than those with primary rectal cancer was unclear. A 'cascade' hypothesis based on the anatomy of the draining veins from the colon and rectum suggests that pulmonary metastasis in patients with primary colon carcinoma might come from hepatic metastasis with progressive site-induced change; however, pulmonary metastasis in patients with primary rectal carcinoma might come directly from the primary tumor, which seemed to be compatible with our results (22–24). However, the prognostic power of primary tumor location has not been demonstrated yet in patients with resected colorectal pulmonary metastasis (25–27); further examinations are needed to verify the hypothesis.

Neither the large size of the hepatic tumor nor primary colon carcinoma might influence the selection criteria for hepatic and pulmonary resections, because several long-term survivors were observed, even among patients with those factors.

Patients with stage IV disease had a poorer prognosis and showed no long-term survival. However, stage IV itself should not be considered as a contraindication for resections because the follow-up duration of patients with stage IV was short and the poor prognosis in stage IV was not consistent with the result that the disease-free interval from primary resection showed no correlation with prognosis.

Other factors such as synchronous metastasis (5), bilateral or multiple lung metastases (5,7), multiple liver metastases (8), short disease-free interval (8), simultaneous liver and lung metastases (10), mediastinal nodes involvement (11), primary histology (12) and high levels of both CEA and CA19-9 before metastasectomy (13) have been reported as prognostic factors after hepatic and pulmonary metastasectomy of colorectal cancer. Among those factors, whether the timing of the detection of hepatic and pulmonary metastases influences prognosis after resections has been an issue. In the present study, none of the aforementioned factors, including the timing of the detection of the metastases, showed any prognostic value. Based on our results, no single factor that contraindicated resections for hepatic and pulmonary metastases of colorectal cancer was identified. Thus, surgical resections might be the best option when both hepatic and pulmonary metastases are resectable in colorectal cancer. However, treatment for patients with several poor prognostic factors for multiple resections is still unknown.

The reason for the high survival rate 5 years after resections for hepatic and pulmonary metastases in our study might be partly explained by precise intrathoracic and abdominal examinations using helical computed tomography (28,29). However, it can not be denied that patients who can undergo both hepatic and pulmonary metastasectomy for colon cancer might have unique characteristics in some factors. For example, there may be some unique host-tumor interaction, considering the rare possibility of both hepatic and pulmonary resections for colorectal metastases and the surprisingly high survival rate after the metastasecomies in spite of multiple, multiphase and multi-organ metastases. The aforementioned hypothesis is supported by the fact that excellent survival in the present study was achieved, unexpectedly, without any help of adjuvant chemotherapy, although adjuvant chemotherapy after pulmonary or hepatic metastasectomy is a potential treatment for improving the prognosis of patients with colorectal cancer. Further investigation to clarify the reason for the good prognosis of this population might elucidate the mechanisms of metastases in colorectal cancer.

A limitation of our study is the relatively small population, because patients who can undergo resections for both hepatic and pulmonary metastases of colorectal carcinoma are rare. There is some possibility that correlations between several clinicopathological factors such as positive lymph nodes of the hepatoduodenal ligament, hilus pulmonis, or mediastinum and survival after resections could not be sufficiently validated because of the small cohort. A large multi-institutional study is recommended to verify the correlation.

In conclusion, multiple resections for hepatic and pulmonary metastases of colorectal cancer are safe and effective. Surgical resections could be the best option for resectable hepatic and pulmonary metastases in colorectal cancer.

Acknowledgments

This work was supported in part by grants from Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

References

1. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ, Jr, Pemberton JH, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1992;174:27–32.
2. Smith JW, Fortner JG, Burt M. Resection of hepatic and pulmonary metastases from colorectal cancer. *Surg Oncol* 1992;1:399–404.