広島大学学術情報リポジトリ
Hiroshima University Institutional Repository

Title	Outcomes and Prognostic Analysis of Surgical Resection for Oligometastasis from Hepatocellular Carcinoma
Author(s)	OSHITA, KO; KOBAYASHI, TSUYOSHI; TADOKORO, TAKESHI; NAMBA, YOSUKE; FUKUHARA, SOTARO; MATSUBARA, KEISO; TAKEI, DAISUKE; HONMYO, NARUHIKO; KURODA, SHINTARO; KAWAOKA, TOMOKAZU; AIKATA, HIROSHI; OHDAN, HIDEKI
Citation	Anticancer Research , 43 (11) : 5189 - 5196
Issue Date	2023-11-01
DOI	
Self DOI	
URL	https://ir.lib.hiroshima-u.ac.jp/00056130
Right	Copyright © 2023 International Institute of Anticancer Research (Dr. George J. Delinasios), All rights reserved. This is not the published version. Please cite only the published version. この論文は出版社版ではありません。引用の際には出版社版をご確認、ご利用ください。
Relation	

Outcomes and Prognostic Analysis of Surgical Resection for Oligometastasis from Hepatocellular Carcinoma

KO OSHITA[1], TSUYOSHI KOBAYASHI[1], TAKESHI TADOKORO[1], YOSUKE NAMBA[1], SOTARO FUKUHARA[1], KEISO MATSUBARA[1], DAISUKE TAKEI[1], NARUHIKO HONMYO[1], SHINTARO KURODA[1], TOMOKAZU KAWAOKA[2,3], HIROSHI AIKATA[2,3] and HIDEKI OHDAN[1]

[1]Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan;

[2]Medical Center for Translational and Clinical Research, Hiroshima University Hospital, Hiroshima, Japan;

[3]Department of Gastroenterology and Metabolisms, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

***Correspondence to*:** Tsuyoshi Kobayashi,

Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551 Japan.

Tel: +81 0822575222, Fax: +81 0822575224,

e-mail: tsukoba@hiroshima-u.ac.jp

Key Words: Hepatocellular carcinoma, oligometastasis, surgical resection.

Running title: Surgery for Oligometastasis from Hepatocellular Carcinoma

Article type: Clinical study

Date of submission: 08/09/2023

Abstract

Background/Aim: This study aimed to evaluate the outcomes of patients who underwent resection for oligometastasis from hepatocellular carcinoma (HCC) and identify the prognostic factors associated with poor survival.

Patients and Methods: Patients who underwent resection for oligometastasis from HCC between January 2000 and April 2021 were retrospectively investigated. Oligometastasis was defined as 1–5 single organ metastases that were detected preoperatively in this study. Clinical characteristics and treatment outcomes were analyzed, and independent risk factors for poor prognosis were identified using cox proportional hazards model.

Results: A total of 33 patients were included in this study. Eleven oligometastases were located in the intraabdominal lymph node, 8 in the adrenal gland, 5 in the lung, 4 in the peritoneum, 3 in the

pleura, and 1 each in the supraclavicular lymph node and abdominal wall. No re-operation or operative death occurred in this study. The median OS was 44.6 months (range=5.1–150.6 months), and the median survival after primary HCC diagnosis was 116.5 months (range=7.1–253.6 months). The median cumulative incidence of recurrent HCC was 7.2 months (range=0.3–94.7 months). The multivariate analysis showed that an alpha-fetoprotein level ≥ 20 ng/ml and multiple primary HCC tumors were independent poor prognostic factors.

Conclusion: Clinical characteristics and treatment outcomes of patients who underwent resection for oligometastasis from HCC were demonstrated. A high alpha-fetoprotein level and multiple primary HCC tumors were independent poor prognostic factors. Surgical resection can be one of the treatment options for oligometastasis from HCC.

Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related death worldwide. Extrahepatic metastasis from HCC indicates an advanced disease stage and is generally associated with poor prognosis in HCC (1). Systemic chemotherapy with or without locoregional therapy for intrahepatic lesions has been widely applied in patients with extrahepatic metastasis (2, 3). However, several investigators have demonstrated the efficacy of resection in prolonging survival of selected patients with extrahepatic metastasis from HCC (4-6).

In metastatic disease, oligometastasis has been proposed as an intermediate state between local and systemic metastasis and is considered a condition that can benefit from locoregional therapy (7). The definition of oligometastasis has not been clearly established but is generally defined as the presence of 1–5 distant metastases that can be safely treated by a local approach (8, 9). The efficacy of local therapy for oligometastasis in the treatment of various cancers, including colorectal, pancreatic, and lung cancers, has been demonstrated (10-12). Although several reports have been published on the outcomes of resection of extrahepatic metastases of HCC, most of these reports are either comprehensive analyses of all resected metastases or they focus only on recurrent metastases after primary HCC resection; in contrast, few reports have examined results limited to oligometastasis.

The aim of this study was to evaluate the clinical characteristics and treatment outcomes of patients who underwent resection for oligometastasis from HCC and to identify the prognostic factors

associated with poor survival.

Patients and Methods

Patients. Clinical data of 39 patients who underwent surgical resection for extrahepatic metastasis from HCC at our institution from January 2000 to April 2021 were retrospectively collected. The diagnosis of metastasis was confirmed by contrast-enhanced computed tomography (CT), and ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) was performed in combination as needed. In addition, coexisting intrahepatic tumors were evaluated by contrast-enhanced CT, magnetic resonance imaging (MRI), or hepatic arterial angiography.

This study was performed in accordance with the 1975 Declaration of Helsinki and approved by the institutional review board of Hiroshima University (Provided ID Number: E-2014-0922-01). Informed consent was obtained from all patients.

Inclusion and exclusion criteria. In this study, oligometastasis was defined as follows: (i) 1–5 extrahepatic metastases in a single organ, (ii) metastases that could have been detected preoperatively, except for those incidentally discovered during surgery. Among patients who

underwent resection of oligometastasis, except those with polymetastasis, which is defined as more than six metastases, during the observation period, those who met the following criteria were determined to be candidates: 1) metastasis without intrahepatic tumors or metastasis with an intrahepatic tumor that was potentially resectable or controllable by non-surgical treatments, such as radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE), 2) sufficient liver function as defined by Child-Pugh classification grade A or B, and 3) Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who underwent diagnostic, palliative, or non-radical surgery and those who did not meet the criteria described above were excluded from the study. In addition, patients followed up for less than 12 months were excluded.

Surgical procedure and follow-up. The treatment strategy for metastasis was determined by a multidisciplinary team consisting of surgeons, hepatologists, and radiologists, who considered radiological images and the clinical course of the disease. Surgery was indicated when the metastasis was not progressive and when radical resection was feasible.

Metastatic lesions were resected from each metastatic site, while metastases concomitant with intrahepatic tumors were resected simultaneously during hepatectomy. After discharge, all patients were followed up for tumor recurrence and metastasis by measuring tumor markers, including alpha-

fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), every 3 months and by performing abdominal ultrasound, CT, or MRI every 6 months (13). In cases of suspected recurrence, ^{18}F-FDG-PET was performed.

Data collection. To identify factors associated with poor prognosis, the following baseline patient characteristics, primary HCC characteristics, and preoperative and postoperative patient and oligometastasis data were collected. Baseline patient characteristics included age at oligometastasis resection, sex, and background liver etiology. Primary HCC characteristics included maximum tumor size, tumor number, histological differentiation, and vascular invasion. Preoperative factors included timing of metastasis development, the maximum size and number of metastases, the presence of coexisting intrahepatic lesions, preoperative therapy for metastasis, Child-Pugh grade, platelet count, and the creatinine, AFP, and DCP levels. Metastases detected at ≤ 6 and > 6 months after treatment of the primary tumor were classified as synchronous and metachronous, respectively. Overall survival (OS) was defined as the time from the date of resection of oligometastasis to the date of death from any cause or the date the patient was last known to be alive. The albumin-bilirubin (ALBI) grade consists of three grades (grades 1–3), which are divided according to the following method: log10 bilirubin (μmol/l) × 0.66 + albumin (g/l) ×0.085 (cut-off values of grades ½ and 2/3 were −2.60 and

−1.39, respectively.

Statistical analysis. Continuous variables are expressed as medians. Survival analysis was performed using the Kaplan–Meier method. Univariate analyses were performed using the log–rank test, while a multivariate analysis was performed using the Cox regression model for variables for which $p<0.05$ in the univariate analysis to assess independent risk factors associated with poor OS. Cut-off values for continuous variables were determined based on clinically significant values. All statistical analyses were performed using JMP software (version 16.0; SAS Institute Inc., Cary, NC, USA); statistical significance was defined as $p<0.05$.

Results

Baseline characteristics. During the study period of January 2000 to April 2021, 39 patients underwent surgical resection for extrahepatic metastasis of HCC at Hiroshima university hospital. Six patients were excluded for the following reasons: two underwent resection for polymetastasis, three underwent non-radical or palliative resection, and one was followed up for less than 12 months. Finally, 33 patients were enrolled in this study. The demographic characteristics of the study

population are shown in Table I. The median age of patients at the time of resection of oligometastasis was 66 years (range=42–85 years), and 28 patients were male (84.8%) and 5 were female (15.2%). Twenty-five patients (75.8%) had hepatitis B or hepatitis C as a background liver etiology.

The median maximum size of the primary HCC was 36 mm (range=10–128 mm), and the median number of tumors was two (range=1–10). Twenty-three patients (69.7%) had tumors with well to moderately differentiated histology, and 10 patients (30.3%) had tumors with poorly differentiated to undifferentiated histology. Seventeen patients (51.5%) had vascular invasion, and no patient had a history of tumor rupture. The treatment for primary HCC was surgery in 27 patients, resection in 26 patients, and liver transplantation in 1one patient. Of the patients not treated with surgery, RFA, hepatic arterial infusion chemotherapy, and TACE were performed in two, three, and one patient, respectively.

Characteristics of oligometastasis. Table II showed the details of the oligometastasis. Oligometastases were located in the intraabdominal lymph node (n = 11, 33.3%), adrenal gland (n = 8, 24.2%), lung (n = 5, 15.2%), peritoneum (n = 4, 12.1%), pleura (n =3, 9.1%), supraclavicular lymph node (n = 1, 3.0%), and abdominal wall (n = 1, 3.0%). Four patients had synchronous

metastasis (12.1%) and 29 patients (87.9%) had metachronous metastasis. The metastasis was solitary in 22 patients (75.8%) and multiple in seven patients (24.2%). The median maximum size of the metastasis was 30 mm (range=6–115 mm), and the median number of metastases was 1 (range=1–4).

Eight patients (24.2%) had received preoperative treatment for oligometastasis including chemotherapy (n = 7) and TACE (n = 1), and the median duration of preoperative treatment was 7.3 months (range=2.6–26.4 months). Preoperative chemotherapy included lenvatinib in one, S-1 or 5-fluorouracil plus cisplatin combination therapy in four, and S-1 plus interferon combination therapy in two, while TACE was performed for the adrenal gland. Thirteen patients (39.4%) had coexisting intrahepatic lesions at the time of metastasis resection, and all intrahepatic lesions were judged to be controlled. In 11 patients (33.3%), oligometastasis was resected during hepatectomy for coexisting intrahepatic lesions.

Short-term outcome. Table III shows the short-term outcomes after resection of oligometastasis. Nine patients (27.3%) had postoperative complications of Clavien-Dindo classification grade 2 or higher. Of those nine patients, two (6.1%) experienced complications of Clavien-Dindo grade 3, one underwent endoscopic hemostasis for esophageal hemorrhage, and one underwent percutaneous

drainage for biliary leakage. No re-operation or operative death occurred in this study.

Survival analysis. The median OS was 44.6 months (range=5.1–150.6 months), and the cumulative 1-, 3-, and 5-year OS rates were 84.9%, 54.8%, and 39.4%, respectively (Figure 1A). In addition, the median survival time after diagnosis of primary HCC was 116.5 months (range=7.1–253.6 months), and the cumulative 1-, 3-, and 5-year survival rates were 100%, 80.9%, and 63.7%, respectively (Figure 1B). The median cumulative incidence of recurrent HCC was 7.2 months (range=0.3–94.7 months) and the cumulative 1- and 3-year rates of incidence of recurrent HCC were 36.8% and 92.2%, respectively (Figure 1C). Recurrence after resection for oligometastasis was noted in 29 patients (87.9%) and included intrahepatic recurrence as well as lung, adrenal gland, bone, and myocardial recurrence and peritoneal dissemination. The median time to recurrence was 6.7 months (range=0.3–94.6 months). Eight patients (24.2%) underwent repeat resections for recurrence: four for the adrenal gland, two for lung, and two for intrahepatic recurrence. Of the patients with recurrence who did not undergo resection, ten received chemotherapy, nine received radiotherapy, four underwent TACE, and one received microwave ablation.

Predictors of OS. Table IV shows the results of the univariate and multivariate analyses of

prognostic factors of OS. In the univariate analysis, an AFP level ≥20 ng/ml and multiple primary HCC tumors were each significantly predictive of poor prognosis. In the multivariate analysis, an AFP level ≥20 ng/ml [hazard ratio (HR) = 3.181, 95% confidence interval (CI)=1.255–8.064; *p*=0.015] and multiple primary HCC tumors (HR = 3.248, 95%CI=1.228–8.592; *p*=0.018) emerged as independent predictors of poor survival.

Discussion

In the present study, we retrospectively investigated the outcomes of patients with oligometastasis from HCC who underwent surgical resection to determine the impact of surgery on clinical outcomes. Patients who underwent resection for oligometastasis exhibited a median survival time of 44.6 months and the 5-year OS rate was 39.4%. In the multivariate analysis, a high AFP level and multiple primary HCC tumors were independent prognostic factors for poor OS. Although several reports of HCC oligometastases in specific organs, such as the adrenal gland and lung, have been published, to the best of our knowledge, this is the first study that focused on the treatment outcomes of patients with whole-body oligometastasis from HCC.

Extrahepatic metastasis from HCC is associated with poor prognosis, and patients with extrahepatic metastasis are typically treated with systemic chemotherapy. Patients treated with sorafenib, a multi-

kinase inhibitor, have a median survival of 10.7–11.0 months (14, 15). With the advances of highly effective chemotherapy, a recent nationwide Japanese analysis reported an increase in survival to 25.5 months for patients treated with lenvatinib, a new multi-kinase inhibitor approved in 2018 (16). To improve prognosis, it is necessary to develop evidence not only for chemotherapy but also for multimodality treatment. Several surgeons have shown that appropriately selected patients who underwent resection for recurrent extrahepatic metastases had a significantly better prognosis than those who did not undergo resection (4, 6, 17). Chua *et al*. suggested that indications for resection of extrahepatic HCC were patients with limited isolated metastases, preserved liver function, and primary tumors that were adequately controlled (18). The definition of oligometastasis is similar to this proposal; however, the reference to the number of tumors makes it a clearer indicator. There have been a few reports of resection of oligometastases from HCC, with seven reports affecting the lung and adrenal glands (Table V) (19-25). Among these, five investigators have shown that patients who undergo resection for oligometastases have a better OS than those who undergo non-surgical treatment. The OS after resection for oligometastases ranged from 15.0-69.8 months, and the 5-year survival rate ranged from 20.3-33.3%. The results of this study were comparable to those of previous studies. Kim *et al*. compared the prognosis of patients treated with locoregional therapy and chemotherapy for pulmonary oligometastasis from HCC using propensity score matching; they

reported a significantly better 2-year OS rate in patients treated with local therapy than in those treated with chemotherapy (66.6% *vs*. 31.2%, $p<0.001$) (26). Our results may provide useful data for future studies on the efficacy of resection for oligometastasis in other organs in addition to that in the adrenal gland and lung.

The multivariate analysis revealed that a high AFP level and multiple primary HCC tumors were significant prognostic factors for OS. A high AFP level plays an important role in HCC development and progression and is a well-known biomarker that predicts poor prognosis (27). AFP has been reported to be a prognostic factor after resection of primary HCC and lung metastases from HCC (28, 29). HCC cases with high AFP levels show marked activation of VEGF signaling, and trials of chemotherapy targeting patients with HCC and high AFP levels have also been conducted (30, 31). In this study, a high AFP level was also found to be a poor prognostic factor, and it was suggested that AFP is an important biomarker after resection for oligometastasis. DCP, another common HCC tumor marker, was not a significant prognostic factor in this study.

In addition, the presence of multiple primary HCC tumors was also shown to be a prognostic factor. The number of tumors has a significant impact on the treatment strategy and prognosis of patients with HCC (3). The presence of multiple tumors has also been reported to be an independent predictor that affects long-term survival and contributes to high recurrence rates in patients with HCC who

undergo resection. Saito et al. reported that more than three tumors as a risk factor for the postoperative recurrence of HCC (32). Our previous study showed that multiple tumors were a significant risk factor for extrahepatic recurrence after hepatectomy, and the presence of multiple tumors is an important factor in the development and treatment of extrahepatic metastases (13). A significant relationship between AFP and tumor number has been reported, and these two factors may correlate with each other as poor prognostic factors (33). The number of primary HCCs may also influence patient prognosis after resection for oligometastasis, which suggests that primary HCC-related factors should be considered when treating oligometastasis. In contrast, the number of metastases was not associated with poor prognosis, which may be due to the limitation of the number of tumors that met the definition of oligometastasis.

In this study, the postoperative recurrence rate was high at 87.9%. Due to the high recurrence rate, resection should be considered a treatment option as part of a multimodal approach that also includes non-surgical treatments. Although systemic therapy is the standard treatment modality for patients with extrahepatic metastasis, multidisciplinary therapy including resection is considered feasible in patients with oligometastasis. Since the organs in which metastasis develop are diverse and often require the opinion of specialists in each field, the approach to managing patients with metastatic HCC should consistently involve a multidisciplinary team comprising not only hepatologist and liver

surgeons, but also physicians with expertise in various organ-specific conditions.

The limitations of this study include its retrospective nature, long study period of inclusion, small sample size, and single-institution involvement, which may have resulted in biases. Due to the rarity of extrahepatic metastasis from HCC, these limitations were often observed in previous studies. Furthermore, the patients with HCC oligometastasis in this study were carefully selected; they had undergone resection and were not compared to patients treated with non-surgical therapies. To overcome these limitations, future studies with a larger number of patients from multiple institutions are required.

Conclusion

In conclusion, clinical characteristics and treatment outcomes of patients who underwent resection for oligometastasis from HCC was demonstrated. A high AFP level and multiple primary HCC were independent preoperative predictors of poor prognosis; such patients should be carefully followed up. Surgical resection can be one of the treatment options for patients with oligometastasis from HCC.

Conflicts of Interest We have no conflicts of interest to declare in association with the present study.

Authors' Contributions: KO and TK designed the study, analyzed the data, and drafted the manuscript. TT, YN, SF, KM, DT, NH, SK, TK, HA and HO contributed to the study design and revised the manuscript. All Authors reviewed the manuscript and revised it critically for intellectual content. All Authors approved the final version of the manuscript and agreed to be accountable for the work.

Acknowledgements: The Authors would like to thank Enago (www.enago.jp) for the English language review.

Funding: This work was supported in part by the Japan Agency for Medical Research and Development (AMED) [grant number JP22fk0210108). The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

References

1 Yang Y, Nagano H, Ota H, Morimoto O, Nakamura M, Wada H, Noda T, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Dono K, Umeshita K, Nakamori S, Wakasa K, Sakon M, Monden M: Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. Surgery 141(2): 196-202, 2007. DOI: 10.1016/j.surg.2006.06.033

2 Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS: Hepatocellular carcinoma. Nat Rev Dis Primers 7(1): 6, 2021. DOI: 10.1038/s41572-020-00240-3

3 EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 69(1): 182-236, 2018. DOI: 10.1016/j.jhep.2018.03.019

4 Yoh T, Seo S, Taura K, Iguchi K, Ogiso S, Fukumitsu K, Ishii T, Kaido T, Uemoto S: Surgery for recurrent hepatocellular carcinoma: achieving long-term survival. Ann Surg 273(4): 792-799, 2021. DOI: 10.1097/sla.0000000000003358

5 Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M, Yoshida H, Koike K: Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 117(19): 4475-4483, 2011. DOI: 10.1002/cncr.25960

6 Berger Y, Spivack JH, Heskel M, Aycart SN, Labow DM, Sarpel U: Extrahepatic metastasectomy for hepatocellular carcinoma: Predictors of long-term survival. J Surg Oncol 114(4): 469-474, 2016. DOI: 10.1002/jso.24340

7 Hellman S, Weichselbaum RR: Oligometastases. J Clin Oncol 13(1): 8-10, 1995. DOI: 10.1200/jco.1995.13.1.8

8 Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, Dingemans AC, Fournier B, Hurkmans C, Lecouvet FE, Meattini I, Méndez Romero A, Ricardi U, Russell NS, Schanne DH, Scorsetti M, Tombal B, Verellen D, Verfaillie C, Ost P: Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 21(1): e18-e28, 2020. DOI: 10.1016/s1470-2045(19)30718-1

9 Szturz P, Vermorken JB: Oligometastatic cancer: key concepts and research opportunities for 2021 and beyond. Cancers (Basel) 13(11), 2021. DOI: 10.3390/cancers13112518

10 Chandy ETJ, Saxby HJ, Pang JW, Sharma RA: The multidisciplinary management of oligometastases from colorectal cancer: a narrative review. Ann Palliat Med 10(5): 5988-6001, 2021. DOI: 10.21037/apm-20-919

11 Kandel P, Wallace MB, Stauffer J, Bolan C, Raimondo M, Woodward TA, Gomez V, Ritter AW,

Asbun H, Mody K: Survival of patients with oligometastatic pancreatic ductal adenocarcinoma treated with combined modality treatment including surgical resection: a pilot study. J Pancreat Cancer 4(1): 88-94, 2018. DOI: 10.1089/pancan.2018.0011

12 Schlachtenberger G, Doerr F, Menghesha H, Heldwein MB, Lauinger P, Wolber P, Klussmann JP, Wahlers T, Hekmat K: Pulmonary metastasectomy for metastatic head and neck cancer prolongs survival significantly compared to non-surgical therapy. Eur J Cardiothorac Surg10.1093/ejcts/ezac098, 2022. DOI: 10.1093/ejcts/ezac098

13 Hashimoto M, Kobayashi T, Ishiyama K, Ide K, Ohira M, Tahara H, Kuroda S, Hamaoka M, Iwako H, Okimoto S, Honmyo N, Ohdan H: Predictive independent factors for extrahepatic metastasis of hepatocellular carcinoma following curative hepatectomy. Anticancer Res 37(5): 2625-2631, 2017. DOI: 10.21873/anticanres.11609

14 Llovet JM, Bruix J: Molecular targeted therapies in hepatocellular carcinoma. Hepatology 48(4): 1312-1327, 2008. DOI: 10.1002/hep.22506

15 Kawaoka T, Aikata H, Kan H, Fujino H, Fukuhara T, Kobayashi T, Naeshiro N, Miyaki D, Hiramatsu A, Imamura M, Kawakami Y, Hyogo H, Chayama K: Clinical outcome and prognostic factors of patients with hepatocellular carcinoma and extrahepatic metastasis treated with sorafenib. Hepatol Res 44(13): 1320-1328, 2014. DOI: 10.1111/hepr.12307

16 Tsuchiya K, Kurosaki M, Sakamoto A, Marusawa H, Kojima Y, Hasebe C, Arai H, Joko K, Kondo M, Tsuji K, Sohda T, Kimura H, Ogawa C, Uchida Y, Wada S, Kobashi H, Furuta K, Shigeno M, Kusakabe A, Akahane T, Narita R, Yoshida H, Mitsuda A, Ide Y, Matsushita T, Izumi N, On Behalf Of Japanese Red Cross Liver Study G: The real-world data in Japanese patients with unresectable hepatocellular carcinoma treated with lenvatinib from a nationwide multicenter study. Cancers (Basel) 13(11), 2021. DOI: 10.3390/cancers13112608

17 Midorikawa Y, Takayama T, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Teramoto K, Yoshida N, Kobayashi N, Tsuji S, Higaki T: Favorable outcomes of surgical resection for extrahepatic recurrent hepatocellular carcinoma. Hepatol Res 50(8): 978-984, 2020. DOI: 10.1111/hepr.13526

18 Chua TC, Morris DL: Exploring the role of resection of extrahepatic metastases from hepatocellular carcinoma. Surg Oncol 21(2): 95-101, 2012. DOI: 10.1016/j.suronc.2011.01.005

19 Staubitz JI, Hoppe-Lotichius M, Baumgart J, Mittler J, Lang H, Musholt TJ: Survival after adrenalectomy for metastatic hepatocellular carcinoma: a 25-year institutional experience. World J Surg 45(4): 1118-1125, 2021. DOI: 10.1007/s00268-020-05909-0

20 Teegen EM, Mogl MT, Pratschke J, Rayes N: Adrenal metastasis of hepatocellular carcinoma

in patients following liver resection or liver transplantation: experience from a tertiary referral center. Int J Surg Oncol 2018: 4195076, 2018. DOI: 10.1155/2018/4195076

21 Ha TY, Hwang S, Ahn CS, Kim KH, Lee YJ, Moon DB, Song GW, Jung DH, Park GC, Lee SG: Resection of metachronous adrenal metastasis after liver resection and transplantation for hepatocellular carcinoma. Dig Surg 31(6): 428-435, 2014. DOI: 10.1159/000370078

22 Chen F, Sato K, Fujinaga T, Sonobe M, Shoji T, Sakai H, Miyahara R, Bando T, Okubo K, Hirata T, Date H: Pulmonary resection for metastases from hepatocellular carcinoma. World J Surg 32(10): 2213-2217, 2008. DOI: 10.1007/s00268-008-9684-8

23 Park JS, Yoon DS, Kim KS, Choi JS, Lee WJ, Chi HS, Kim BR: What is the best treatment modality for adrenal metastasis from hepatocellular carcinoma? J Surg Oncol 96(1): 32-36, 2007. DOI: 10.1002/jso.20773

24 Tomimaru Y, Sasaki Y, Yamada T, Eguchi H, Takami K, Ohigashi H, Higashiyama M, Ishikawa O, Kodama K, Imaoka S: The significance of surgical resection for pulmonary metastasis from hepatocellular carcinoma. Am J Surg 192(1): 46-51, 2006. DOI: 10.1016/j.amjsurg.2005.12.006

25 Momoi H, Shimahara Y, Terajima H, Iimuro Y, Yamamoto N, Yamamoto Y, Ikai I, Yamaoka Y: Management of adrenal metastasis from hepatocellular carcinoma. Surg Today 32(12): 1035-

1041, 2002. DOI: 10.1007/s005950200210

26 Kim K, Kim TH, Kim TH, Seong J: Efficacy of local therapy for oligometastatic hepatocellular carcinoma: a propensity score matched analysis. J Hepatocell Carcinoma 8: 35-44, 2021. DOI: 10.2147/jhc.s290197

27 Zucman-Rossi J, Villanueva A, Nault JC, Llovet JM: Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology 149(5): 1226-1239.e1224, 2015. DOI: 10.1053/j.gastro.2015.05.061

28 Ridder DA, Weinmann A, Schindeldecker M, Urbansky LL, Berndt K, Gerber TS, Lang H, Lotz J, Lackner KJ, Roth W, Straub BK: Comprehensive clinicopathologic study of alpha fetoprotein-expression in a large cohort of patients with hepatocellular carcinoma. Int J Cancer 150(6): 1053-1066, 2022. DOI: 10.1002/ijc.33898

29 Ohba T, Yano T, Yoshida T, Kawano D, Tsukamoto S, Shoji F, Taketomi A, Saitsu H, Takeo S, Maehara Y: Results of a surgical resection of pulmonary metastasis from hepatocellular carcinoma: prognostic impact of the preoperative serum alpha-fetoprotein level. Surg Today 42(6): 526-531, 2012. DOI: 10.1007/s00595-011-0090-8

30 Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, Bruix J, Qin S, Thuluvath PJ, Llovet JM, Leberre MA, Jensen M, Meinhardt G, Kang YK: SEARCH: a phase III,

randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 33(6): 559-566, 2015. DOI: 10.1200/jco.2013.53.7746

31 Chau I, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Kudo M, Pfiffer T, Hatano E, Chung HC, Kopeckova K, Phelip JM, Brandi G, Ohkawa S, Li CP, Okusaka T, Hsu Y, Abada PB, Zhu AX: Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: an analysis of the phase 3 REACH study. Br J Cancer 119(1): 19-26, 2018. DOI: 10.1038/s41416-018-0103-0

32 RYO SAITO, HIDETAKE AMEMIYA, NAOHIRO HOSOMURA, HIROMICHI KAWAIDA, SUGURU MARUYAMA, HIROKI SHIMIZU, SHINJI FURUYA, HIDENORI AKAIKE, YOSHIHIKO KAWAGUCHI, MAKOTO SUDO, SHINGO INOUE, HIROSHI KONO and DAIDUKE ICHIKAWA Prognostic Significance of Treatment Strategies for the Recurrent Hepatocellular Carcinomas After Radical Resection. In Vivo 2020, 34(3) 1265-1270. DOI: 10.21873/invivo.11900

33 Carr BI, Kanke F, Wise M, Satomura S: Clinical evaluation of lens culinaris agglutinin-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin in histologically proven hepatocellular carcinoma in the United States. Dig Dis Sci 52(3): 776-782, 2007. DOI: 10.1007/s10620-006-

Figure legends

Figure 1. Survival outcomes of patients with hepatocellular carcinoma (HCC) oligometastasis. (A) Overall survival after resection for HCC oligometastasis. (B) Overall survival after diagnosis of primary HCC. (C) Cumulative incidence of recurrence after resection for HCC oligometastasis.

Table I. Baseline characteristics of 33 patients who underwent surgical resection for oligometastasis from hepatocellular carcinoma (HCC).

Variables	n = 33
Clinical factors	
Age (years) at metastasectomy	66 (42–85)
Sex (Male/Female)	28/5
Viral hepatitis/Non-B and non-C	25/8
Factors in primary HCC	
Maximum size (mm)	36 (10–128)
Number of tumors	2 (1–10)
Histological differentiation (well-moderate/poor-undifferentiated)	23/10
Vascular invasion	17 (51.5)
Factors in oligometastasis	
Timing (synchronous/metachronous)	4/29
Maximum size (mm)	30 (6–115)
The number of metastases	1 (1–4)
Coexisting intrahepatic lesion	13 (39.4)
Preoperative therapy	8 (24.2)
Clinical data at metastasectomy	
Child-Pugh classification grade (A/B)	29/4
Platelet count ($\times 10^4/mm^3$)	10.2 (3.5–24.5)
Creatinine (mg/dl)	0.86 (0.52–9.35)
AFP (< 20 ng/ml/ ≥ 20 ng/ml)	17/16
DCP (<40 mAU/ml/ ≥ 40 mAU/ml)	8/25
ALBI grade (1/2–3)	22/11

Variables are expressed as median (range) or n (%). AFP: Alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; ALBI: albumin-bilirubin.

Table II. Details of oligometastasis.

Variables	n = 33
Intraabdominal lymph node	11 (33.3)
1	8
2	2
3	1
Adrenal gland	8 (24.2)
1	10
Lung	5 (15.2)
1	2
2	1
3	1
4	1
Peritoneum	4 (12.1)
1	2
Pleura	3 (9.1)
1	2
4	1
Supraclavicular lymph node	1 (3.0)
1	1
Abdominal wall	1 (3.0)
1	1

Variables are expressed as n (%).

Table III. Short-term outcomes after surgical resection.

Variables	n = 33
Postoperative complications	9 (27.3)
Clavien–Dindo classification grade 2	
Ascites	3 (9.1)
Pleural effusion	1 (3.0)
Surgical site infection	1 (3.0)
Delayed gastric emptying	1 (3.0)
Pneumonia	1 (3.0)
Clavien–Dindo classification grade 3	
Esophageal hemorrhage	1 (3.0)
Bile leakage	1 (3.0)
Reoperation	0 (0.0)
Mortality in hospital stay	0 (0.0)
Hospital stays (days)	13.5 (4–54)

Variables are expressed as median (range) or n (%).

Table IV. Prognostic factors for survival identified by univariate and multivariate analyses (n = 33).

	Univariate		Multivariate		
Variables	n (%)	*p*-Value	HR	95%CI	*p*-Value
Age at metastasectomy, ≥ 70 years	13 (39.4)	0.328			
Sex, male	28 (84.8)	0.060			
Viral hepatitis	25 (75.8)	0.934			
Maximum size of primary HCC, ≥ 50 mm	12 (36.4)	0.330			
Multiple primary HCC tumors	18 (54.5)	0.036	3.248	1.228–8.592	0.018
Histological differentiation, poor-undifferentiated	10 (30.3)	0.533			
Vascular invasion	17 (51.5)	0.445			
Timing, metachronous	29 (87.9)	0.335			
Maximum size of metastases, ≥ 30 mm	15 (45.6)	0.738			
Multiple metastases	16 (48.5)	0.738			
Coexisting intrahepatic lesion	13 (39.4)	0.214			
Preoperative therapy for metastasis	8 (24.2)	0.326			
Child-Pugh classification grade B	4 (12.1)	0.075			
ALBI grade ≥ 2	11 (33.3)	0.854			
Platelet count, $< 8.0\times10^4/mm^3$	10 (30.3)	0.259			
Creatinine, ≥ 1.5 mg/dl	4 (12.1)	0.963			
AFP, ≥ 20 ng/ml	16 (48.5)	0.031	3.181	1.255–8.064	0.015
DCP, ≥ 40 mAU/ml	25 (75.8)	0.127			

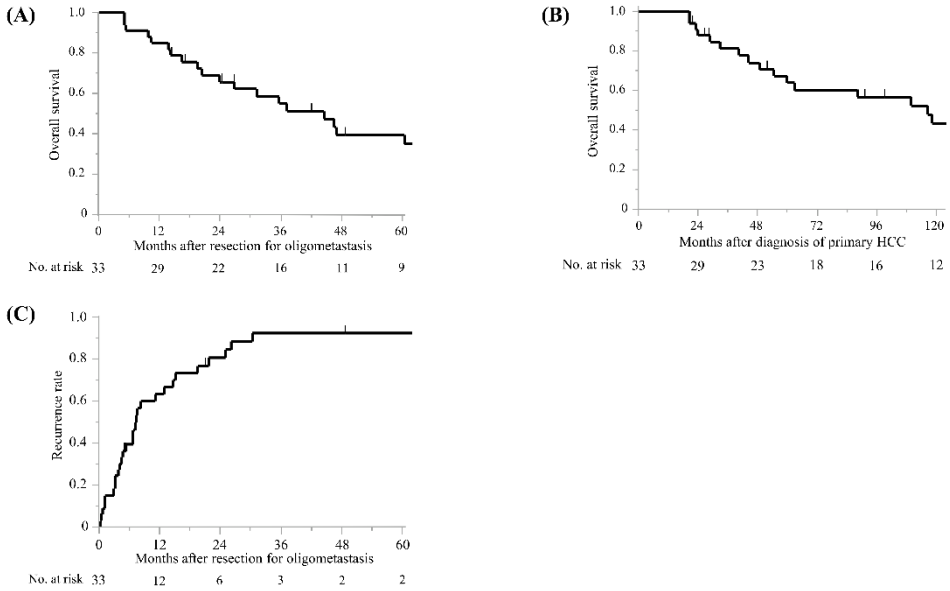
HR: Hazard ratio; CI: confidential interval; HCC: hepatocellular carcinoma; ALBI: albumin-bilirubin; AFP: alpha-fetoprotein; DCP: des-γ-carboxy prothrombin.

Table V. Previous studies on outcomes of resection for oligometastasis from hepatocellular carcinoma.

No.	Author	Year	Study period (years)	Location of oligometastasis	n	Median OS after resection for oligometastasis (months)	Survival rate after resection for oligometastasis (%)
1	Staubitz *et al.* (19)	2021	25	Adrenal gland	16	15.0	N/A
2	Teegen *et al*. (20)	2018	10	Adrenal gland	8	69.8	N/A
3	Ha *et al.* (21)	2014	15	Adrenal gland	26	N/A	20.3 (5-year)
4	Chen *et al.* (22)	2008	12	Lung	12	N/A	28.9 (5-year)
5	Park *et al*. (23)	2007	14	Adrenal gland	5	21.4	N/A
6	Tomimaru *et al*. (24)	2006	15	Lung	8	29.0	33.3 (5-year)
7	Momoi *et al.* (25)	2002	13	Adrenal gland	13	N/A	25.0 (5-year)

OS: Overall survival; N/A: not applicable.

Figure 1


(A)
Overall survival
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
Months after resection for oligometastasis
No. at risk 33 29 22 16 11 9
(B)
Overall survival
1.0
0.8
0.6
0.4
0.2
0
0
24
48
72
96
120
Months after diagnosis of primary HCC
No. at risk 33 29 23 18 16 12
(C)
Recurrence rate
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
Months after resection for oligometastasis
No. at risk 33 12 6 3 2 2