—Review—

Multidisciplinary Approach to the Treatment of Advanced Hepatocellular Carcinoma in the Era of New Biologic Agents

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With recent advances in systemic therapy, an increasing number of patients with advanced hepatocellular carcinoma (HCC) are expected to benefit from surgery. However, given the complex background of the disease and frequent presence of underlying liver injury, treatment of advanced HCC is complex and the treatment principle applied to colorectal liver metastases, for which conversion surgery has been actively performed, is often not applicable to patients with HCC. To maximize the survival outcomes of patients with HCC, optimization of each step of treatment through a multidisciplinary approach is inevitable. As initial treatment, systematic removal of tumor-bearing portal territory is associated with improved survival in patients with solitary HCC, and radiofrequency ablation is also effective for small, oligo HCCs. Although the high incidence of recurrence even after curative-intent treatment is a major concern in HCC, aggressive treatment for recurrence is important, because a prolonged cancer-free interval is associated with improved overall survival. For patients with advanced disease, recently introduced molecular-targeted agents may be effective for successful conversion to surgery in initially unresectable cases, although the overall response rate of HCC to systemic therapies remains unsatisfactory as compared to that of colorectal liver metastases. This report revisits the theoretical bases for management of HCC and discusses current strategies for maximizing survival of patients with advanced HCC. (J Nippon Med Sch 2022; 89: 145–153)

Key words: hepatocellular carcinoma, surgery, hepatectomy, chemotherapy

Introduction

Hepatocellular carcinoma (HCC) accounts for 70% to 90% of all cases of primary liver cancer[1] and is the third leading cause of cancer-related death worldwide[2]. HCC is potentially curable by surgical resection[3,4], radiofrequency ablation (RFA)[5,6], or liver transplantation[7,8], if it is diagnosed in its early stage. However, despite recent developments in screening for HCC, diagnosis is often made only in the intermediate or advanced stage of the disease.

Although various treatment options, including transarterial chemoembolization (TACE), radioembolization with yttrium-90, radiotherapy, and systemic therapies are available for advanced HCC, it remains difficult to expect excellent responses to these conventional approaches that would allow conversion surgery to be successfully performed in patients with unresectable disease at diagnosis. However, molecular characterization of hepatocarcinogenesis has led to identification of aberrant signaling pathways, which has facilitated development of targeted agents as potentially useful treatment agents for HCC. Since the introduction of sorafenib in 2007[9,10], various molecular-targeted agents and immune checkpoint inhibitors have been introduced for treatment of HCC[11–15], and recent rapid progress in chemotherapy is changing the landscape of multidisciplinary treatment for patients with advanced HCC.

This article discusses the theoretical bases and strategies for successful management of advanced HCC, particularly recent advances in systemic therapies and their

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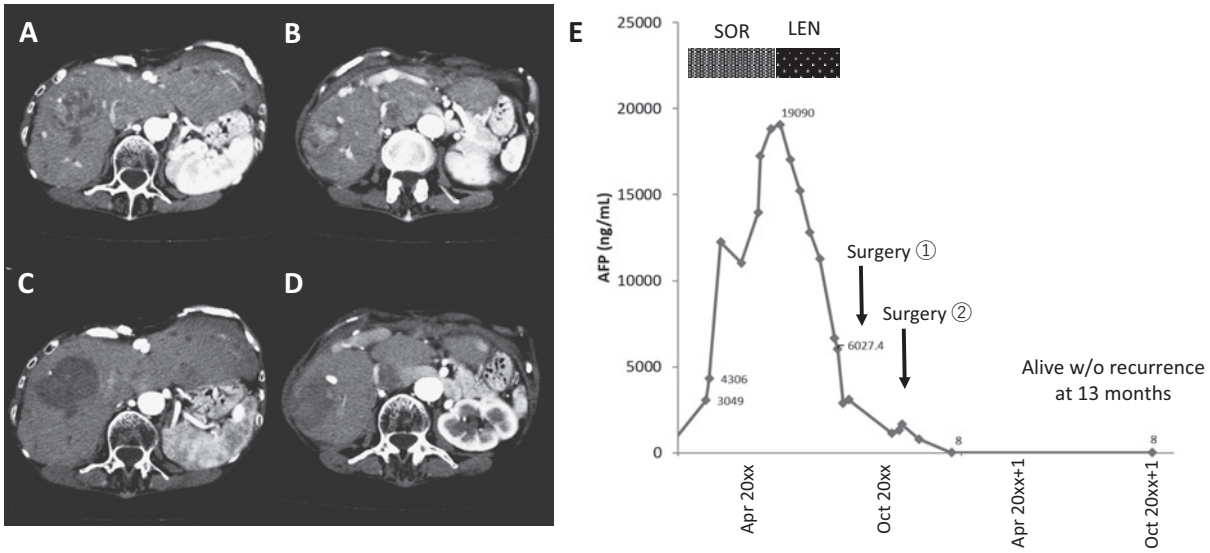

Fig. 1 A case of successful conversion surgery for initially unresectable hepatocellular carcinoma after lenvatinib treatment (Adopted from Shindoh J, et al. Ann Surg Oncol 2021 doi: 10.1245/s10434-021-09974-0 with permission)
A 53-year-old woman presented with 20 HCC nodules in the liver and underwent lenvatinib treatment after failure of sorafenib (A, B). Imaging analysis at 8 weeks after the initiation of lenvatinib treatment showed significant response (RECIST SD and mRECIST PR) (C, D), with a significant decrease in serum alpha fetoprotein level (E). After portal vein embolization, R0 resection was achieved with two-stage hepatectomy, and the patient survived for 13 months without recurrence.
Abbreviations. SOR, sorafenib; LEN, lenvatinib; AFP, alpha fetoprotein.

efficacy in allowing conversion surgery.

Clinical Decisions and the Fate of a Patient with Hepatic Malignancy

Baseline oncological status at presentation is a strong predictor of prognosis in patients with hepatic malignancies. However, it is also true that accurate prediction of the fate of each patient is difficult, because our clinical practice is tailored to the oncological aggressiveness of tumor, anatomic considerations, and/or response to chemotherapy, to maximize clinical outcomes with the "test of time"[16] (**Fig. 1**).

Among the various treatment approaches, the efficacy of multidisciplinary treatment for colorectal liver metastases has been well described, and an aggressive approach to avoid missing patients who might enjoy prolonged survival or even cure with surgery is regarded as an important approach in treating colorectal liver metastases[17,18]. Although clinical trials serve as evidence to guide our clinical practice, clinical decision-making is complex and depends heavily on the conditional probability, as indicated by reported data and clinician experience[16]. As such, a multidisciplinary team approach is appropriate to avoid unnecessary/inefficient treatments and maximize survival of patients with advanced hepatic malignancies.

Complexity of Multidisciplinary Treatment for Hepatocellular Carcinoma

Because HCC usually arises in an already injured liver, a high incidence of tumor recurrence due to *de novo* carcinogenesis, even after curative-intent treatment, makes management of HCC difficult[19,20]. When looking at the trend of instantaneous probability of recurrence after initial hepatectomy, a clear difference was observed between colorectal liver metastases and HCC, as shown in **Figure 2**. Since colorectal liver metastases originally arise outside of the liver, while HCC arises/disseminates within an already injured liver, there are clear and inevitable differences in the patterns of tumor extension/dissemination between these two disease entities, which may affect chronological changes in the risk of recurrence. Because of the sustained risk of neocarcinogenesis in the underlying liver, it is difficult to eliminate the risk of recurrence even after complete removal of entire tumors in the management of HCC. Therefore, clinical management of HCC is complex, and it would be impossible to simply apply the treatment theory for colorectal liver metastases to the management of HCC.

Over the long run, treatment for HCC gradually pro-

gresses from curative-intent to palliative-intent. During this process, the choice of treatment gradually narrows, after multiple sessions of treatment, in accordance with the oncological status of the tumor and underlying liver function (**Fig. 3**). Given the typical clinical course of HCC, optimization of each treatment step would help maximize survival.

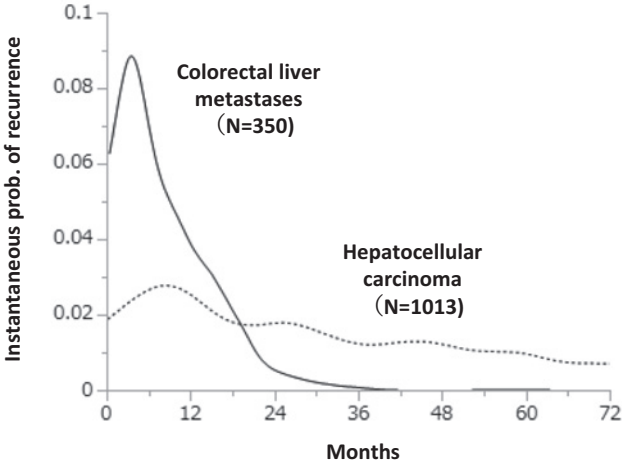

Fig. 2 Time trend of instantaneous probability of recurrence after initial hepatectomy (Adopted from Shindoh J, J Hepatobiliary Pancreat Sci 2021; 28 (6): 461-469 with permission)

Importance of Initial Choice of Treatment for Hepatocellular Carcinoma

Because of the strong propensity of HCC to invade intrahepatic vascular structures and spread via the closest portal branches[21,22], systematic removal of tumor-bearing portal territories, known as anatomic resection (**Fig. 4**), was proposed as a theoretically optimal surgical maneuver in the 1980s[22], and studies have validated the efficacy of anatomic resection[23–32]. In patients with primary solitary HCC, anatomic resection may affect the pattern of recurrence and post-progression clinical course, which

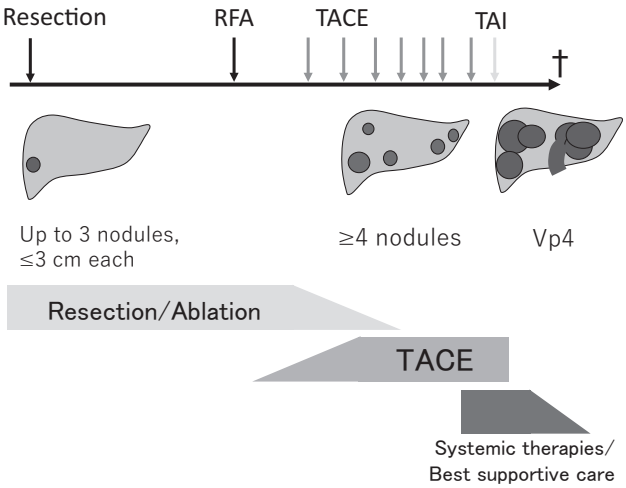

Fig. 3 Typical clinical course of hepatocellular carcinoma

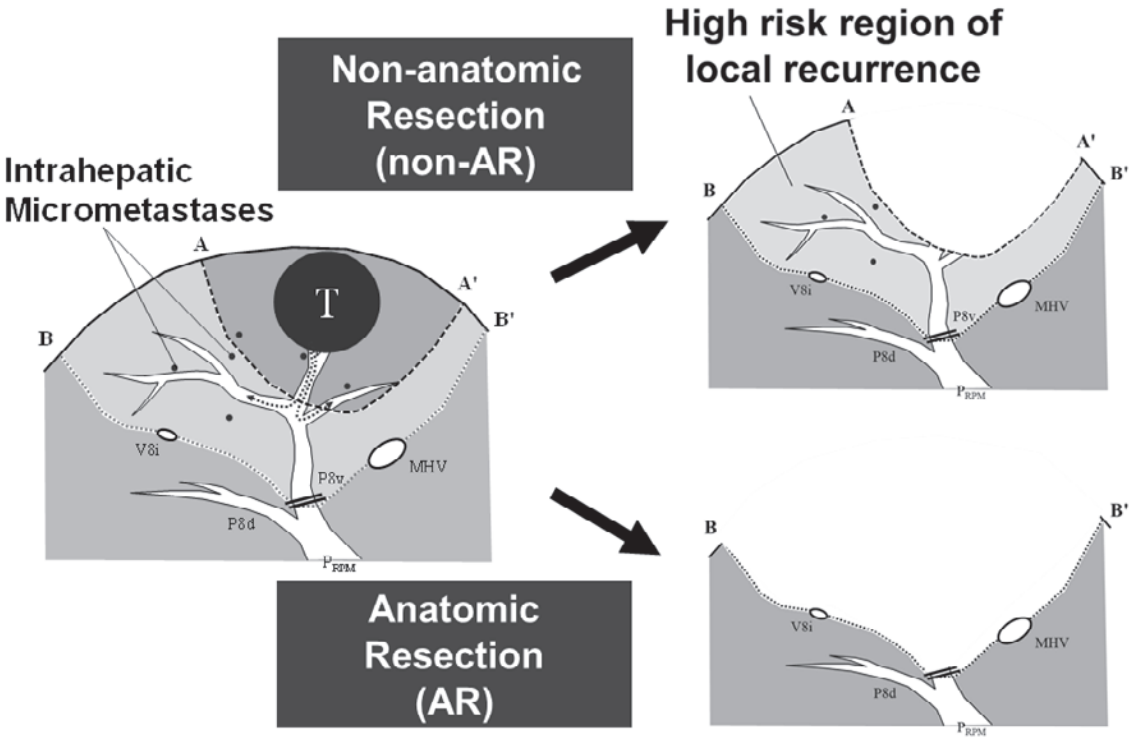

Fig. 4 Anatomic and non-anatomic resection

may in turn affect overall survival (OS). Using a Markov model, our group previously investigated the prognostic impact of the initial choice of surgical procedure in patients with primary solitary HCC[32]. Although anatomic resection significantly decreased the annual risk of tumor recurrence, in line with previous reports, successful complete removal of the tumor-bearing portal territory was associated with prolonged survival through "delayed stage progression" after recurrence[32]. Given that time to interventional failure (TIF) is an important surrogate measure for predicting OS in HCC[33], it is important to select the most suitable surgical maneuver at initial hepatectomy, to maximize TIF, especially in patients with solitary HCC.

For patients with small, oligo HCCs, several randomized controlled trials (RCT) reported that RFA has efficacy similar to that of surgery[34–38]. However, these observations need to be interpreted carefully because the analysis of outcomes was based on findings from a select population of patients with small HCCs, which are believed to be curable by surgery or RFA. In actual clinical settings, the technical feasibility of RFA, in terms of tumor location or proximity to major vessels, should be carefully evaluated before selecting the initial treatment. Nevertheless, these outcomes suggest that some patients may benefit from procedures less invasive than surgery and that the prognostic impact of complete removal of the tumor-bearing portal territory might be smaller in such patients. Given that the prognostic impact of microvascular invasion is relatively low among patients with small (<2 cm) HCCs[39] and that the efficacy of anatomic resection could theoretically be obtained among patients who actually have microscopic cancer spread (i.e., microvascular invasion and/or intrahepatic micrometastasis), RFA could also be an option for selected patients with small, oligo HCCs.

Prognostic Impact of Treatment for Recurrence

Despite curative-intent treatment for the primary lesion, the relatively high incidence of recurrence remains a major concern in the management of HCC. However, several studies have reported that aggressive treatment of recurrences is associated with improved survival[40–42] and that a prolonged cancer-free interval after curative-intent treatment for recurrence is empirically associated with prolonged OS. For patients with colorectal liver metastases, an aggressive surgical approach for recurrence is associated with improved survival, and the concept of "time to surgical failure" is an emerging surrogate endpoint for OS[43]. A previous study found that a similar concept was applicable to patients with HCC and, in an analysis of data from 1,175 patients, we confirmed that time to interventional (curative-intent) failure was, in fact, associated with OS[33]. When patients with resectable and/or ablatable recurrences were analyzed, survival outcomes were significantly better when a curative-intent therapy had been selected, suggesting that curative-intent treatment should be considered, when possible, in order to achieve better survival outcomes. Although the actual optimal choice of treatment depends on the oncological status of the tumor and physical status of the patients, the above observations suggest that an aggressive approach to treatment of recurrent lesions may be an important step in maximizing survival of patients with HCC.

Is Systemic Therapy Just a Means of Prolonging Life?

Because of overexpression of drug transporter proteins, including the multi-drug resistance gene *MDR1*, HCC is intrinsically resistant to chemotherapy. Underlying liver disease also contributes towards reducing the efficacy of cytotoxic chemotherapy[44]. Therefore, molecular-targeted agents have been actively developed to treat HCC.

Sorafenib was the first biologic agent developed that had clinical evidence of efficacy as a 1st-line treatment agent for HCC. However, because its efficacy with respect to size-based response remains unsatisfactory, it is difficult to expect an impressive response that would allow conversion surgery in conventional management of advanced HCC. New molecular-targeted agents and immune checkpoint inhibitors have been introduced, and intensive systemic therapy is becoming a standard of care for advanced HCC[11–15]. An RCT investigating the efficacy of atezolizumab plus bevacizumab showed significantly better survival outcomes in the study treatment arm than in the sorafenib arm[13]. Systemic therapy is no longer just a means of prolonging life, but is becoming a sword for fighting advanced HCC.

Although HCC generally has a poor prognosis, optimization of treatment strategies, from initial choice of treatment to systemic therapies for advanced cases, would maximize OS on the conventional track of "irreversible" clinical course (**Fig. 5**).

New Resectability Criteria for Advanced HCC

For colorectal liver metastases, conversion surgery for initially unresectable disease was associated with improved survival[17,18]. According to an expert consensus statement

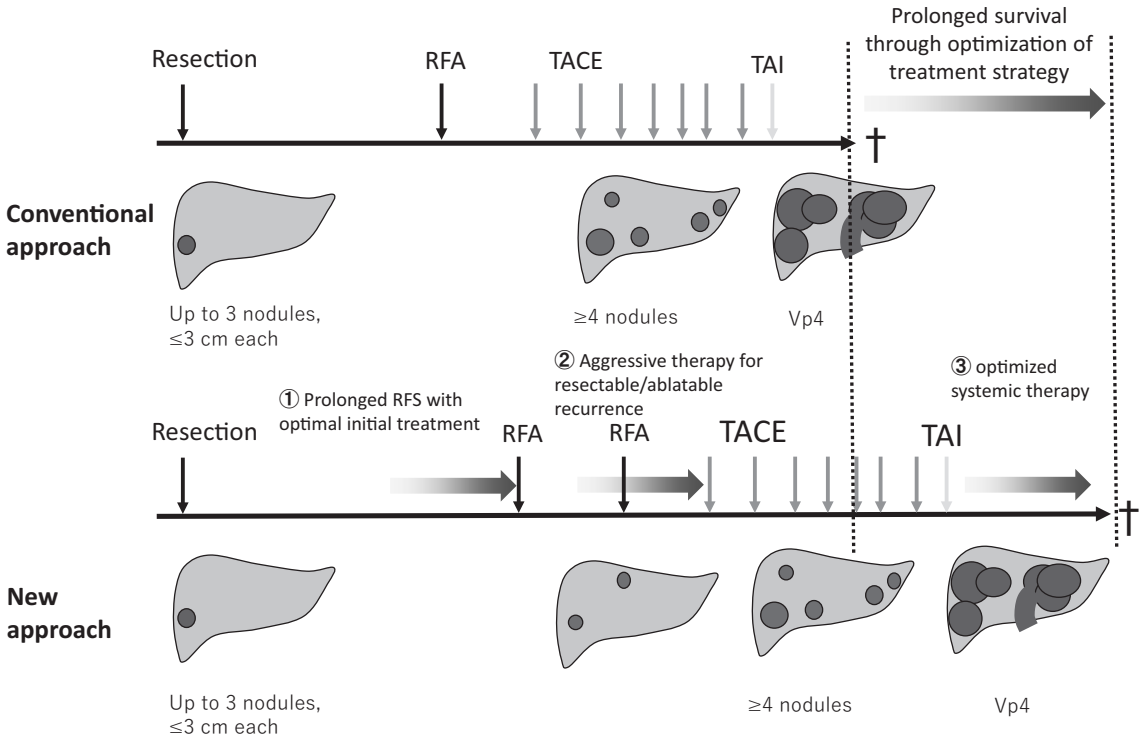

Fig. 5 Optimization of treatment approach and potential extension of survival outcomes of patients with HCC.

in the United States[45], indications for surgery in patients with colorectal liver metastases should be determined from technical and oncological perspectives[45]. The technical resectability criteria include 1) expectation of margin-negative resection (i.e., R0 resection) and 2) expectation of preserving a sufficient future liver remnant volume. Oncological resectability depends on the probability of disease control with surgery, which is determined by adequate radiological staging and the behavior of metastatic lesions during preoperative chemotherapy.

To achieve further significant prolongation of survival in patients with advanced HCC, a surgical approach as aggressive as that used for colorectal metastases is needed. However, one reason why the clinical management principle applied to cases with colorectal liver metastases is not applicable to HCC is that we must consider the "condition" of HCC patients, who often have underlying liver disease, in addition to the "anatomy" of liver lesions, which determines technical resectability, and the "biology" of tumors, which defines oncological resectability. To develop straightforward standards for potential resectability of advanced HCC, our group has proposed original resectability criteria (**Table 1**)[46] and applied them to clinical decision-making in conversion surgery after intensive systemic therapies for advanced HCC.

Efficacy of a New Molecular-targeted Agent in Allowing Conversion Surgery among Patients with Advanced HCC

Outcomes of conversion surgery after intensive systemic therapy have increasingly been reported for patients with advanced HCC[46–53]. Our group recently reported clinical outcomes for 107 consecutive patients who received lenvatinib for initially unresectable HCC (see **Supplementary Table** (https://doi.org/10.1272/jnms.JNMS.2022_89-223) for details of baseline characteristics). After lenvatinib treatment for a median of 5.6 months, the overall response rate was 36.4% according to RECIST 1.1 and 63.6% according to the modified RECIST. Of the 107 patients who were initially unsuitable for curative-intent therapy or TACE, 54 (50.5%) patients received additional therapies after treatment with lenvatinib, including surgery in 16 patients; R0 resection was achieved in 9 (8.4%) patients, and in the remaining seven patients, surgery had to concluded with R2 resection because of interim disease progression or a palliative-intent procedure. Analysis of survival outcomes revealed that the disease-specific survival rate was significantly better for patients in whom R0 resection was achieved than for those in whom the surgery had to be concluded with R2 resection, those who received other additional treatments, and those who did not receive any additional treatment[46].

Table 1 Definition of resectability for hepatocellular carcinoma

Technical criteria for resectability
1. Resectable: i) and ii)
i) Margin-negative resection is expected to be feasible (i.e., R0 resection)
ii) Child-Pugh class A/B patients fulfilling the safety criteria for hepatectomy (e.g., ICG-Krem≥0.05)
2. Marginally resectable: i) or ii)
i) Expected ability to preserve an adequate future liver remnant with portal flow modulation procedures (e.g., ICG-Krem<0.05)
ii) Child-Pugh class A/B patients with controllable portal hypertension with medication or intervention
3. Unresectable: i) or ii)
i) Margin-negative resection cannot be achieved (i.e., R2 resection)
ii) Child-Pugh class A/B patients with uncontrollable portal hypertension, or Child-Pugh class C patients
Oncological criteria for resectability
1. Resectable: i) and ii) and iii)
i) Patients with up to 3 HCCs
ii) No macroscopic vascular invasion beyond the 2nd order portal branch or the main trunk of the hepatic vein (i.e., Vp0-2 or Vv0-2)
iii) No nodal involvement or extrahepatic disease (i.e., N0M0)
2. Marginally resectable: at least one of the following
i) Patients with 4 or more HCCs
ii) Presence of major vascular invasion up to the 1st order portal branch or IVC (i.e., Vp3-4 or Vv3)
iii) Regional nodal involvement (i.e., N1)
iv) Distant metastasis limited to the right adrenal gland or lung
3. Unresectable: i) or ii)
i) Distant nodal involvement
ii) Extrahepatic metastasis other than in the right adrenal gland or lung

Although our experience with combined tyrosine kinase inhibitor plus immune checkpoint inhibitor therapy for HCC is limited, Zhu et al. recently reported preliminary outcomes of 63 consecutive patients who received combined TKI plus anti-PD-1 antibody therapy as first-line treatment. R0 resection was successfully accomplished in 10 (15.9%) patients after a median treatment duration of 3.2 months, and a relatively high pathological response rate was confirmed, especially among patients with large tumors[47]. These encouraging results warrant further multicenter prospective studies of the efficacy of combined tyrosine kinase inhibitor plus immune checkpoint inhibitor therapy toward conversion surgery among patients with unresectable HCC.

Does Conversion Surgery Truly Improve Survival in Patients with Advanced HCC?

While successful conversion to curative-intent resection after intensive systemic therapy for advanced HCC has been increasingly achieved, there remain several unresolved questions, such as the optimal conditions for conversion, optimal timing of conversion surgery, and true prognostic advantage of conversion surgery for HCC.

So, here, an exploratory analysis was conducted using updated data from our previous study[46]. A retrospective review of the clinical data was performed in accordance with the ethical guidelines for clinical studies, with the approval of the institutional review board at Toranomon Hospital (No.1438-H/B). Survival curves were constructed by the Kaplan-Meier method and compared using the log-rank test. To account for immortal time bias as a result of inappropriate accounting of follow-up time and treatment status, an exploratory analysis was added that used analytic methods similar to those reported previously[54,55].

Figure 6 shows the results of the analysis. An imbalance in pretreatment confounders between patients who underwent R0 resection and those who received no or other treatments was adjusted by inverse probability of treatment weighting, using propensity scores estimated by a pooled logistic regression model. The date were handled likewise as a crossover study in which every patient starts out with medical therapy and, at various times, some patients cross over to surgical arm (i.e., R0 resection). After excluding one outlying patient who underwent curative resection after 3 years of lenvatinib treatment, adjusted survival analysis clearly indicates that successful conversion to R0 resection after lenvatinib treatment in carefully selected patients is associated with improved survival, even after statistical adjustment to minimize immortal time bias.

In regard to the optimal conditions and timing of con-

version surgery after lenvatinib treatment, a multicenter prospective study, LENS-HCC (jRCTs031190057), was performed recently. The results, expected in the near future, are expected to clarify the actual conversion rate and short-term surgical outcomes of intended surgical intervention for advanced HCC after lenvatinib treatment.

Unmet Needs in Current Clinical Practice and Future Perspectives

With recent advances in systemic therapies, surgery is becoming a potential treatment option for patients with advanced HCC, as part of a multidisciplinary approach.

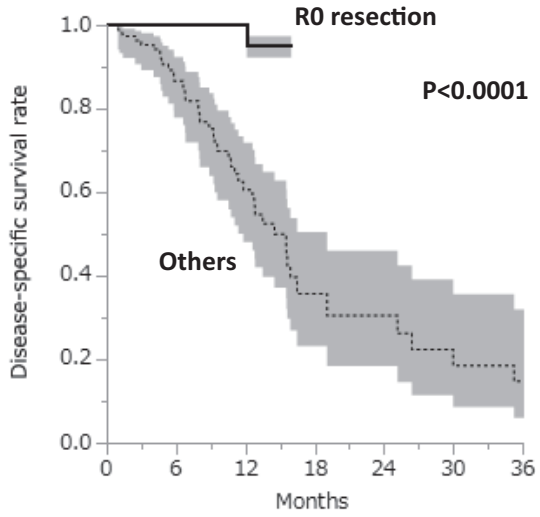

Fig. 6 Adjusted disease-specific survival of patients who successfully underwent R0 resection after treatment with lenvatinib
Shaded areas indicate 95% confidence intervals.

However, as compared to colorectal liver metastases, for which various highly efficacious (response rate, 60-70%) chemotherapy regimens are available, the overall response rates of HCC to systemic therapies, including combined tyrosine kinase inhibitor plus immune checkpoint inhibitor therapy, remain unsatisfactory (20-30%) (**Fig. 7**).

Since the response rate to systemic therapies is closely associated with the rate of successful conversion in patients with hepatic malignancies[56], additional strategies that further improve response rate to systemic therapy are needed to obtain a higher success rate of conversion surgery and improved survival in patients with advanced HCC. Although HCC is generally refractory to systemic cytotoxic therapy, recent encouraging results of hepatic arterial infusion chemotherapy (HAIC)[57–60] and combined systemic therapy plus HAIC suggest that they could be potentially useful options for managing advanced HCC.

Conclusions

This report revisited the theoretical bases for management of HCC and discussed the potential benefits and efficacy of conversion surgery under current conditions. With recent advances in systemic therapies, greater numbers of patients are expected to benefit from surgery. However, because management of HCC is complex and reported response rates to systemic therapies remain unsatisfactory, further investigations are needed in order to obtain higher success rates of conversion to curative-intent surgery and maximize treatment benefits for pa-

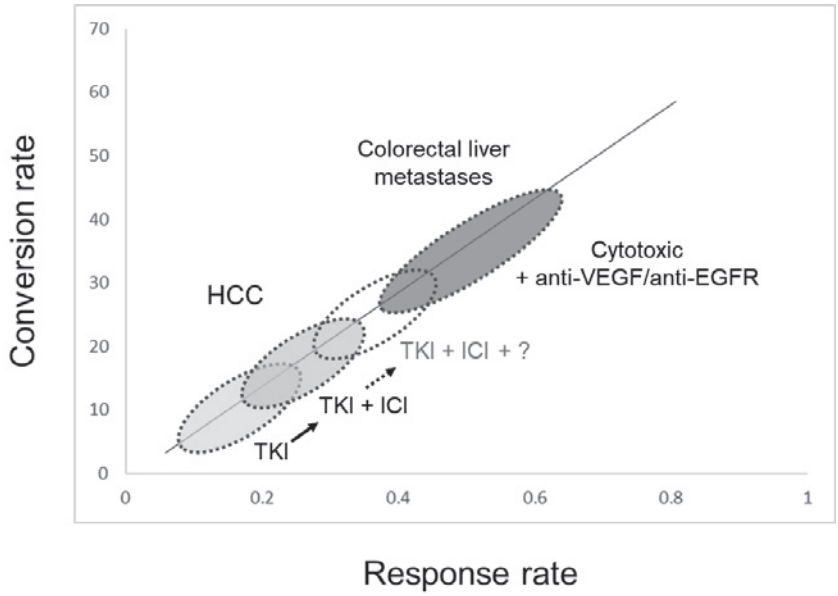

Fig. 7 Response rate for systemic therapies and expected conversion rate

tients with advanced HCC treated through a multidisciplinary approach.

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References

1. Villanueva A. Hepatocellular carcinoma. N Engl J Med. 2019;380(15):1450–62.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
3. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology. 2000;32(6):1224–9.
4. Takayama T, Makuuchi M, Hirohashi S, et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology. 1998;28(5):1241–6.
5. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology. 2008;47(1):82–9.
6. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol. 2012;107(4):569–77; quiz 78.
7. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012;13(1):e11–22.
8. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg. 2004;240(3):451–9; discussion 9-61.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359 (4):378–90.
10. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10(1):25–34.
11. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379(1):54–63.
12. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064): 56–66.
13. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905.
14. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–73.
15. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–96.
16. Shindoh J. Risk stratification and goal of systemic therapy for successful surgical management of colorectal liver metastases: Oncological optimization. J Hepatobiliary Pancreat Sci. 2021;28(6):461–9.
17. Adam R, De Gramont A, Figueras J, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist. 2012;17(10):1225–39.
18. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27(22):3677–83.
19. Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg. 1991;214(2):114–7.
20. Imamura H, Matsuyama Y, Miyagawa Y, et al. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg. 1999;86(8):1032–8.
21. Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. Semin Liver Dis. 1986;6(3):259–66.
22. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet. 1985;161 (4):346–50.
23. Kaibori M, Kon M, Kitawaki T, et al. Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2017;24 (11):616–26.
24. Kakazu T, Makuuchi M, Kawasaki S, et al. Repeat hepatic resection for recurrent hepatocellular carcinoma. Hepatogastroenterology. 1993;40(4):337–41.
25. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol. 1993;9(4):298–304.
26. Regimbeau JM, Kianmanesh R, Farges O, Dondero F, Sauvanet A, Belghiti J. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. Surgery. 2002;131(3):311–7.
27. Shindoh J, Hasegawa K, Inoue Y, et al. Risk factors of post-operative recurrence and adequate surgical approach to improve long-term outcomes of hepatocellular carcinoma. HPB (Oxford). 2013;15(1):31–9.
28. Shindoh J, Makuuchi M, Matsuyama Y, et al. Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. J Hepatol. 2016;64(3):594–600.
29. Tanaka S, Mogushi K, Yasen M, et al. Surgical contribution to recurrence-free survival in patients with macrovascular-invasion-negative hepatocellular carcinoma. J Am Coll Surg. 2009;208(3):368–74.
30. Vigano L, Procopio F, Mimmo A, et al. Oncologic superiority of anatomic resection of hepatocellular carcinoma by ultrasound-guided compression of the portal tributaries compared with nonanatomic resection: An analysis of patients matched for tumor characteristics and liver function. Surgery. 2018;164(5):1006–13.
31. Wakai T, Shirai Y, Sakata J, et al. Anatomic resection independently improves long-term survival in patients with T1-T2 hepatocellular carcinoma. Ann Surg Oncol. 2007;14 (4):1356–65.
32. Shindoh J, Kobayashi Y, Umino R, Kojima K, Okubo S, Hashimoto M. Successful anatomic resection of tumor-bearing portal territory delays long-term stage progression of hepatocellular carcinoma. Ann Surg Oncol. 2021; 28(2):844–53.

33. Shindoh J, Kawamura Y, Kobayashi Y, et al. Time-to-interventional failure as a new surrogate measure for survival outcomes after resection of hepatocellular carcinoma. J Gastrointest Surg. 2020;24(1):50−7.
34. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321−8.
35. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794−802.
36. Huang GT, Lee PH, Tsang YM, et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. Ann Surg. 2005;242(1):36−42.
37. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010; 252(6):903−12.
38. Izumi N, Hasegawa K, Nishioka Y, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial). J Clin Oncol. 2019;37(15suppl): 4002.
39. Shindoh J, Andreou A, Aloia TA, et al. Microvascular invasion does not predict long-term survival in hepatocellular carcinoma up to 2 cm: reappraisal of the staging system for solitary tumors. Ann Surg Oncol. 2013;20(4):1223−9.
40. Mise Y, Hasegawa K, Shindoh J, et al. The feasibility of third or more repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg. 2015;262(2):347−57.
41. Meniconi RL, Komatsu S, Perdigao F, Boelle PY, Soubrane O, Scatton O. Recurrent hepatocellular carcinoma: a Western strategy that emphasizes the impact of pathologic profile of the first resection. Surgery. 2015;157(3):454−62.
42. Yang W, Chen MH, Wang MQ, et al. Combination therapy of radiofrequency ablation and transarterial chemoembolization in recurrent hepatocellular carcinoma after hepatectomy compared with single treatment. Hepatol Res. 2009;39(3):231−40.
43. Oba M, Hasegawa K, Matsuyama Y, et al. Discrepancy between recurrence-free survival and overall survival in patients with resectable colorectal liver metastases: a potential surrogate endpoint for time to surgical failure. Ann Surg Oncol. 2014;21(6):1817−24.
44. Shindoh J, Kaseb A, Vauthey JN. Surgical strategy for liver cancers in the era of effective chemotherapy. Liver Cancer. 2013;2(1):47−54.
45. Adams RB, Aloia TA, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB (Oxford). 2013;15(2):91−103.
46. Shindoh J, Kawamura Y, Kobayashi Y, et al. Prognostic impact of surgical intervention after lenvatinib treatment for advanced hepatocellular carcinoma. Ann Surg Oncol. 2021;28(12):7663−72.
47. Zhu XD, Huang C, Shen YH, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. Liver Cancer. 2021;10(4):320−9.
48. Matsuki R, Kawai K, Suzuki Y, et al. Pathological complete response in conversion hepatectomy induced by lenvatinib for advanced hepatocellular carcinoma. Liver Cancer. 2020;9(3):358−60.
49. Ohya Y, Hayashida S, Tsuji A, et al. Conversion hepatectomy for advanced hepatocellular carcinoma after right portal vein transection and lenvatinib therapy. Surg Case Rep. 2020;6(1):318.
50. Sato N, Beppu T, Kinoshita K, et al. Conversion hepatectomy for huge hepatocellular carcinoma with arterioportal shunt after chemoembolization and lenvatinib therapy. Anticancer Res. 2019;39(10):5695−701.
51. Tomonari T, Sato Y, Tanaka H, et al. Conversion therapy for unresectable hepatocellular carcinoma after lenvatinib: Three case reports. Medicine (Baltimore). 2020;99(42):e 22782.
52. Wang Y, Lu LC, Guan Y, et al. Atezolizumab plus bevacizumab combination enables an unresectable hepatocellular carcinoma resectable and links immune exclusion and tumor dedifferentiation to acquired resistance. Exp Hematol Oncol. 2021;10(1):45.
53. Salem R, Li D, Sommer N, et al. Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave 150 trial. Cancer Med. 2021;10(16):5437−47.
54. Gatzoflias S, Beier MA, Ning Y, et al. Efficacy of primary surgical versus medical intervention for treatment of left-sided infective endocarditis. Ann Thorac Surg. 2020;110 (5):1615−21.
55. Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R. Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. Kidney Int. 2010;77(7):630−6.
56. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol. 2005;16(8):1311−9.
57. Ando E, Tanaka M, Yamashita F, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer. 2002;95(3):588−95.
58. Kudo M, Ueshima K, Yokosuka O, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3(6):424−32.
59. Nagamatsu H, Hiraki M, Mizukami N, et al. Intra-arterial therapy with cisplatin suspension in lipiodol and 5-fluorouracil for hepatocellular carcinoma with portal vein tumour thrombosis. Aliment Pharmocol Ther. 2010;32(4): 543−50.
60. 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(2):435−42.

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