Multidisciplinary approach to the treatment of advanced hepatocellular carcinoma in the era of new biologic agents

Junichi Shindoh, MD, PhD
Department of Gastroenterological Surgery, Toranomon Hospital

Affiliation:
1. Hepatobiliary-pancreatic Surgery Division, Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, JAPAN
2. Okinaka Memorial Institute for Medical Disease, Tokyo, JAPAN

Correspondence and reprint requests to:
Junichi Shindoh MD, PhD.
Surgeon-in-chief, Hepatobiliary-pancreatic Surgery Division
Department of Gastroenterological Surgery, Toranomon Hospital
2-2-2 Toranomon, Minatoku, Tokyo 105-8470, Japan
Tel: +81-3-3588-1111
E-mail: shindou-tky@umin.ac.jp

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Abstract

With the recent advances in the field of 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 rather 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 the initial treatment, systematic removal of the 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 issue in HCC, aggressive treatment for recurrence is also important, because a prolonged cancer-free interval is reported to be associated with improved overall survival. For patients with advanced disease, recently introduced molecular-targeted agents may potentially 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. In this report, the theoretical bases for the management of HCC are revisited and the currently used strategies to maximize the survival outcomes in patients with advanced HCC is discussed.
**Introduction**

Hepatocellular carcinoma (HCC) accounts for 70% to 90% of all cases of primary liver cancer,\(^1\) and is reported as 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 the recent developments in the screening methods for HCC, the 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 rather 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 the recognition of aberrant signaling pathways, which has facilitated the 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 the treatment of HCC,\(^11-15\) and the recent rapid progress in the field of chemotherapy is changing the landscape of multidisciplinary treatment for patients with advanced HCC.

In this article, the theoretical bases and strategies for successful management of advanced HCC are discussed, with special attention paid to the recent advances in systemic therapies and their efficacy to allow conversion surgery.

**Clinical decision and fate of a patient with hepatic malignancy**

The baseline oncological status at presentation is a strong predictor of the 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 rather tailored to the oncological aggressiveness of tumor, anatomical considerations, and/or response to chemotherapy to maximize the clinical outcomes with a “test of time”(16) (Figure 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 with the potential to enjoy prolonged survival or even cure with surgery is regarded as an important approach in the field of colorectal liver metastases.(17, 18) Even though various clinical trials serve as evidence to guide our clinical practice, the clinical decision making is actually complex and heavily dependent on the conditional probability based on the reported data and our experiences.(16) As such, a multidisciplinary team approach is important to take the appropriate path, avoiding unnecessary/inefficient ways, for maximizing the survival outcomes 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 the management of HCC difficult.(19, 20) When looking at the trend of instantaneous probability of recurrence after the 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, inevitably, there is a clear difference in the patterns of tumor extension/dissemination between these two disease entities, which may affect the chronological changes in the risk of recurrence. Considering the sustained risk of neocarcinogenesis in the underlying liver, it is difficult to literally “eradicate”
the risk of recurrence even after complete removal of entire tumors in the management of HCC. Therefore, clinical management of HCC is rather complex, and it would be impossible to simply apply the treatment theory for colorectal liver metastases in the management of HCC.

Over the long run, treatment for HCC gradually progresses from curative-intent to palliative-intent. During this process, the choice of treatment gradually narrows after multiple sessions of treatment according to the oncological status of the tumor and underlying liver function (Figure 3). Given these typical clinical courses of HCC, optimization of each treatment step would be important to maximize the survival outcomes.

1. Importance of the initial choice of treatment for hepatocellular carcinoma

   Based on the high propensity of HCC to invade the intrahepatic vascular structures and spread via the closest portal branches,(21, 22) systematic removal of the tumor-bearing portal territories, known as anatomic resection (Figure 4), was proposed as a theoretically optimal surgical maneuver in the 1980s,(22) and various studies have validated the efficacy of anatomical resection.(23-32) In patients with primary solitary HCC, anatomic resection may affect the pattern of recurrence and post-progression clinical course, which may, in turn, affect the overall survival (OS) of the patients. Our group previously demonstrated the prognostic impact of the initial choice of surgical procedure in patients with primary solitary HCC, using a Markov model.(33) Although anatomic resection significantly decreased the yearly probability of tumor recurrence, in line with various previous reports, successful complete removal of the tumor-bearing portal territory was also correlated with prolonged survival through “delayed stage progression” after recurrence.(32) Given that time-to-interventional failure (TIF) is an important surrogate measure for predicting the OS in HCC,(34) it would be important to select the most suitable surgical maneuver at initial hepatectomy to maximize the TIF, especially in patients with solitary HCC.
Meanwhile, for patients with small, oligo HCCs, several randomized controlled trials (RCT) have demonstrated that RFA may show similar efficacy to that of surgery. (35-39) However, these observations need to be interpreted carefully, because the analysis of the outcomes is based on the findings in a selected population of patients with small HCCs, which are supposed to be curable by either surgery or RFA. In actual clinical settings, the technical feasibility of RFA, in terms of the tumor location or proximity to major vessels should be carefully evaluated before selecting the initial treatment. On the other hand, these outcomes do suggest that there exists a group of patients that benefits from less invasive procedures than surgery, and the prognostic impact of complete removal of the tumor-bearing portal territory might be smaller in this subgroup of patients. Given that the prognostic impact of microvascular invasion is relatively low among patients with small (<2 cm) HCCs (40) and that 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 alternate option for selected patients with small, oligo HCCs.

2. Prognostic impact of treatment for recurrence

Despite curative-intent treatment for the primary lesion, a relatively high incidence of recurrence remains a major issue in the management of HCC. However, several studies have reported that aggressive treatment of recurrences is also associated with improved survival of the patients, (41-43) and a prolonged cancer-free interval after curative-intent treatment for recurrence is empirically associated with a prolonged OS. For patients with colorectal liver metastases, it is well-known that an aggressive surgical approach for recurrence is associated with improved survival, and the concept of the “time to surgical failure” is an emerging new surrogate endpoint for the OS. (44) According to one previous study, a similar concept is also applicable to patients
with HCC, and based on an analysis of the data of 1,175 patients, we confirmed that the time to interventional (curative-intent) failure was, in fact, associated with the OS.(34) When patients with resectable and/or ablatable recurrences were analyzed, the survival outcomes were significantly better when a curative-intent therapy had been selected, suggesting that curative-intent treatment should be considered where possible to promote better survival outcomes. Although the actual optimal choice of treatment is dependent on both the oncological status of the tumor and physical status of the patients, the aforementioned observations suggest that an aggressive approach to treatment of recurrent lesions may be one of the important steps to maximize the survival outcomes of patients with HCC.

3. Is systemic therapy just a means of prolonging life?

HCC is intrinsically resistant to chemotherapy, because of overexpression of drug transporter proteins, including the multi-drug resistance gene, MDR1. Underlying liver disease also contributes towards reducing the efficacy of cytotoxic chemotherapy.(45) Therefore, molecular-targeted agents have been actively developed for the treatment of HCC.

Sorafenib was the first biologic agent developed with clinical evidence of efficacy as a 1st-line treatment agent for HCC. However, because its efficacy in terms of the size-based response remains unsatisfactory, it is difficult to expect an impressive response that would allow conversion surgery in the conventional management of advanced HCC. Recently, new molecular-targeted agents and immune check point inhibitors have been introduced and intensive systemic therapy is becoming a standard of care for advanced HCC.(11-15) A RCT conducted to investigate the efficacy of atezolizumab plus bevacizumab showed significant improvement of the survival outcomes in the study treatment arm as compared to the sorafenib arm.(13) Nowadays, systemic therapy is not just a means of prolonging life, but is becoming a sword for fighting advanced HCC.
Although HCC is a cancer with a generally poor prognosis, optimization of the treatment strategies from the initial choice of treatment to systemic therapies for advanced cases would maximize the OS on the conventional track of “irreversible” clinical course (Figure 5).

New resectability criteria for advanced HCC

In the field of colorectal liver metastases, conversion surgery for initially unresectable disease is reported to be associated with improved survival.(17, 18) According to an expert consensus statement in the United States,(46) the indication for surgery in patients with colorectal liver metastases should be determined from both the technical and oncological standpoints.(46) 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 is dependent on the disease control probability with surgery, which is determined by adequate radiological staging and behavior of the metastatic lesions during preoperative chemotherapy.

To expect a further significant prolongation of the survival in patients with advanced HCC, a similar aggressive surgical approach as for cases of colorectal metastases would be inevitable. However, one of the reasons why the clinical management principle applied for cases with colorectal liver metastases is not applicable to HCC is that we need to consider the “condition” of HCC patients, who often have underlying liver disease, in addition to the “anatomy” of the liver lesions that determines technical resectability and “biology” of the tumors that defines oncological resectability. To simply define potential resectability in cases of advanced HCC, our group has proposed original resectability criteria (Table 1),(47) and applied them for 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 in patients with advanced HCC have increasingly been reported. Our group has recently reported the clinical outcomes of 107 consecutive patients who received treatment with lenvatinib for initially unresectable HCC (see Supplemental Table 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 7 patients, the surgery had to conclude with R2 resection due to interim progression of the disease or a palliative-intent procedure. Analysis of the survival outcomes revealed that the disease-specific survival rate was significantly better in the patients in whom R0 resection was achieved as compared to that in the patients 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 treatments.

Although our current experience with combined tyrosine kinase inhibitor plus immune checkpoint inhibitor therapy for HCC remains insufficient, Zhu et al. recently reported the preliminary outcomes of 63 consecutive patients who received combined TKI plus anti-PD-1 antibody therapy as first-line treatment. Of these, R0 resection could be 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. These encouraging results may warrant further multicenter prospective studies to investigate the efficacy of combined tyrosine kinase inhibitor plus immune checkpoint inhibitor
Does conversion surgery truly improve the 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 still remain several unresolved questions, such as the optimal situation 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. A retrospective review of the clinical data was performed in accordance with the ethical guidelines for clinical studies under 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 using similar analytic methods reported in previous studies.

Figure 6 shows the results of the analysis. Imbalance of pretreatment confounders between the patients who underwent R0 resection and those who received no or other treatments were adjusted by inverse probability of treatment weighting using propensity scores estimated by a pooled logistic regression model. The date was handled likewise as a cross-over 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). With excluding one patient who underwent curative resection after 3 years of lenvatinib treatment as an outlier, adjusted survival analysis clearly indicates that successful conversion to R0 resection after lenvatinib treatment in carefully selected patients may be associated with improved survival, even after statistical adjustment to minimize the immortal-time bias.
In regard to the optimal situation and timing of conversion surgery after lenvatinib treatment, a multicenter prospective study, LENS-HCC (jRCTs031190057), has been performed recently. The results, expected in the near future, could be 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 perspective**

With recent advances in the field of systemic therapies, surgery is becoming a potential treatment option for patients with advanced HCC as part of a multidisciplinary approach. However, as compared to colorectal liver metastases, for which various highly efficacious (60%-70% response rates) 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%) (Figure 7).

Since the response rate to systemic therapies is known to be closely associated with the rate of successful conversion in patients with hepatic malignancies,(57) additional strategies to further improve the response rate to systemic therapy would be 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 regimens, given the recent encouraging results of hepatic arterial infusion chemotherapy (HAIC),(58-61) combined systemic therapy plus HAIC could be a potentially useful option in the management of advanced HCC.

**Conclusions**

This report revisited the theoretical bases for the management of HCC and discussed the potential benefits and efficacy of conversion surgery from our current standpoint. With recent
advances in the field of systemic therapies, an increasing number of patients are expected to benefit from surgery. However, given that the management of HCC is rather complex and the reported response rates to systemic therapies remain unsatisfactory, further investigations are needed to obtain higher success rates of conversion to curative-intent surgery and maximize the treatment benefits in patients with advanced HCC through a multidisciplinary approach.
FIGURE LEGENDS

Figure 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 who presented with 20 HCC nodules in the liver 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 the serum alpha fetoprotein level (E). After portal vein embolization, R0 resection was achieved in this patient with two-stage hepatectomy, and the patient survived for 13 months without recurrence.

Abbreviations. SOR, sorafenib; LEN, lenvatinib; AFP, alpha fetoprotein.

Figure 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)

Figure 3. Typical clinical course of hepatocellular carcinoma

Figure 4. Anatomic resection and non-anatomic resection

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

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

**Figure 7. Response rate for systemic therapies and expected conversion rate**
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Figure 2

Hepatocellular carcinoma (N=1013)

Colorectal liver metastases (N=350)
Resection/Ablation

- Resection
- RFA (Radiofrequency Ablation)
- TACE (Transarterial ChemoEmbolization)
- TAI (Transarterial Ablation)

Without Resection/Ablation:

- Systemic therapies/
- Best supportive care

≥4 nodules

≥4 nodules

Vp4

Up to 3 nodules, ≤3 cm each
Resection  
RFA  
TACE  
TAI

Conventional approach

≥4 nodules

Vp4

Up to 3 nodules,
≤3 cm each

① Prolonged RFS with optimal initial treatment

② Aggressive therapy for resectable/ablatable recurrence

③ Optimized systemic therapy

New approach

Up to 3 nodules,
≤3 cm each

≥4 nodules

Vp4

Prolonged survival through optimization of treatment strategy
Figure 6

Cox proportional hazards analysis revealed that R0 resection achieved a significantly better disease-specific survival rate, compared to other treatments (P<0.0001).
Figure 7

The graph shows the relationship between conversion rate and response rate for different treatments. The treatments include:

- Colorectal liver metastases
- Cytotoxic + anti-VEGF/anti-EGFR
- HCC
- TKI + ICI + ?
- TKI + ICI
- TKI

The graph indicates that TKI + ICI + ? shows the highest conversion rate and response rate among the treatments.
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
### Supplemental Table. Baseline characteristics of the 107 patients

(adopted from Shindoh J, et al. An Surg Oncol 2021;28(2):844-853 with permission)

| Characteristic                                    | Value |
|--------------------------------------------------|-------|
| N                                                | 107   |
| Age                                              | 73 (35-93) |
| Male gender                                      | 82 (76.6%) |
| Etiology (HB/HC/HB+HC/nBnC)                      | 16 (15.0%)/ 54 (50.5%)/ 1 (0.9%)/ 36 (33.6%) |
| BCLC stage (A/B/C)                               | 7 (6.5%)/ 40 (37.4%)/ 60 (56.1%) |
| Performance status (0/1/2)                       | 94 (87.9%)/ 12 (11.2%)/ 1 (0.9%) |
| Child-Pugh class (A/B)                           | 99 (92.5%)/ 8 (7.5%) |
| ALBI grade (1/2/3)                               | 34 (31.8%)/ 72 (67.2%)/ 1 (0.9%) |
| CONUT undernutrition grade a                     | 21 (19.6%)/ 64 (59.8%)/ 19 (17.8%)/ 3 (2.8%) |
| History of MTA administration                    | 16 (15.0%) |
| Refractoriness to TACE b                         | 76 (71.0%) |
| Intrahepatic disease                             | 94 (87.9%) |
| Extrahepatic disease                             | 44 (41.1%) |
| Maximum size (mm)                                | 31 (11-175) |
| Number of tumor                                  | 4 (1-200) |
| Macroscopic portal invasion c                     | 87 (81.3%)/ 3 (2.8%)/ 9 (8.4%)/ 2 (1.9%)/ 6 (5.6%) |
| Macroscopic venous invasion c                     | 99 (92.5%)/ 1 (0.9%)/ 1 (0.9%)/ 6 (5.6%) |
| Type 4 enhancement pattern d                     | 23 (21.5%) |
| AFP level (ng/mL)                                | 88 (1-61041) |
| DCP level (mAu/mL)                               | 215 (8-96035) |
| Duration of treatment with lenvatinib (months)   | 5.6 (0.1-34.9) |
| Discontinuation of lenvatinib due to adverse event during the treatment course | 29 (27.1%) |

Figures represent median (range) unless indicated.

*a* Undernutrition grade defined based on the CONUT score

*b* Defined based on the consensus statement

*c* Macoroscopic vascula invasion defined by Liver Cancer Study Group of Japan

*d* Heterogeneous arterial enhancement pattern suggestive of poor differentiation

**Abbreviations.** HB, hepatitis B; HC, hepatitis C; BCLC, Barcelona Clinic Liver Cancer; CONUT, controlling nutritional status; MTA, molecular targeted agent; TACE, transarterial
chemoembolization; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin;