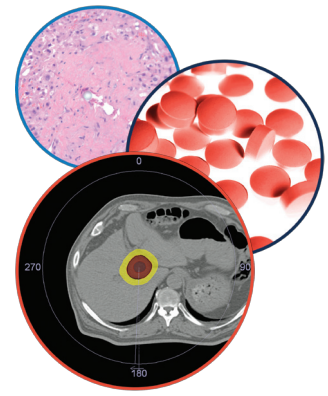
MANAGEMENT PERSPECTIVE



Hepatic Oncology

Nonsurgical multidisciplinary approach for recurrent hepatocellular carcinoma after surgical resection

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Practice Points

- Hepatocellular carcinoma (HCC) recurs very frequently after curative resection or local ablation (in more than 70% of patients at 5 years) but there is still no established treatment guideline for recurrent HCC.
- Individual recurrent HCC cases are very heterogeneous in terms of tumor factors (e.g., size, number, location, hypervascularity), host factors (e.g., age, comorbidities, reserve liver function) and treatment-related factors (e.g., invasiveness, cost, facilities).
- The current treatment options for recurrent HCC after surgical resection do not differ from the primary treatments for HCC, but potential tumor multiplicity and limited liver function in the recurrence setting needs to be considered when deciding therapies.
- Transarterial chemoembolization (TACE) is a mainstay treatment for patients with unresectable multiple intrahepatic recurrence and preserved liver function, and contraindicated in main portal vein invasion.
- Local ablation, such as radiofrequency ablation, is potentially curative and less invasive than re-resection, and could be applied very usefully in some selected cases with smaller sized recurrent HCC as a mono or combination therapy with TACE.
- Sorafenib is a first-line systemic therapy for advanced HCC but demonstrates marginal advantages for treating recurrent HCC according to subgroup analysis from a Western Phase III study.
- As a radiation therapy (RT) technology evolves, the role of RT in the treatment of HCC will increase as an effective locoregional therapy and as a part of multidisciplinary approaches.
- Given the breath of surgical and nonsurgical treatment options now available for recurrent HCC, the multidisciplinary approach is likely to be the best and most effective treatment strategy for these heterogeneous cases.

KEYWORDS
• drug-eluting bead transarterial chemoembolization • hepatocellular carcinoma • multidisciplinary approach • radiation therapy • radiofrequency ablation • re-resection • salvage liver transplantation • sorafenib • transarterial chemoembolization • transarterial radioembolization

SUMMARY Hepatocellular carcinoma (HCC) is characterized by frequent recurrence, even after curative resection and local ablation, and this represents a major challenge for HCC treatment. Although several treatment guidelines have been reported, they detail initial treatment choices and there are no established guidelines for recurrent HCC. The current treatment options for recurrent HCC do not differ from the primary treatments, but the unique characteristics of HCC recurrence should be considered when choosing treatments and each treatment should be individualized to different clinical situations. Furthermore, combinations of various treatments have been recently attempted. This review summarizes the current evidence for nonsurgical treatments of recurrent HCC after resection and suggests a multidisciplinary approach to improving the prognosis of recurrent HCC.

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Background

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer death worldwide and its incidence is rising in many countries [1,2]. The incidence and risk factors for HCC differ among different geographic regions and various scientific societies in each region have produced their own treatment guidelines for this disease [3–6]. According to these guidelines, surgical resection, liver transplantation and local ablation are the initial treatment options for early-stage HCC. However, after resection or local ablation, HCC recurs in up to 70% of patients because of undetected intrahepatic spreading or multicentric tumor occurrence, and recurrence has become the major challenge for improving survival outcomes in these patients [7]. All published treatment guidelines at present describe how to choose the initial treatment options but there are still no established guidelines or prospective studies that compare the efficacy of these different treatment options for recurrent HCC.

According to several retrospective reports, repeated hepatectomy for intrahepatic recurrence is recognized as an effective treatment modality that demonstrates an overall 5-year survival rate of 52% (range: 22–83%) [8–10]. Salvage liver transplantation (LT) could also be one of the most effective treatment options, demonstrating better disease-free and overall survival in comparison with repeated resection, but with higher rates of morbidity and mortality [11]. However, the number of candidates for repeated hepatectomy is limited in actual clinical practice because of the limited hepatic reserve after previous hepatectomy and potential multiplicity of recurrence [12]; the number of candidates for salvage liver LT is even more limited because of donor organ shortages and limited facilities. In contrast, nonsurgical locoregional treatments such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are indicated for unresectable recurrent HCC [13–15]. Although there is still no evidence to support RFA as an alternative to repeated resection or salvage liver transplantation, this intervention has been widely performed as a minimally invasive treatment for small recurrent HCC [13,16]. In real practice, TACE is the most widely performed treatment, especially for multinodular intrahepatic recurrent HCC [15–17]. Sorafenib is indicated for advanced HCC with or without extrahepatic metastasis [18,19], and a few Phase II/III studies on combination sorafenib and TACE treatment are currently underway.

This review summarizes the current evidence for the nonsurgical treatment of recurrent HCC after curative resection from literature review. Furthermore, I would like to share clinical experiences of treating recurrent HCC patients in our center and, finally, suggest a multidisciplinary approach to improving the prognosis of recurrent HCC.

Characteristics of HCC recurrence after resection or local ablation

Even after curative resection, HCC recurs very frequently: >70% of patients develop recurrence at 5 years after resection [7]. Mechanism of HCC recurrence after curative resection includes intrahepatic invisible metastasis at the time of initial resection and *de novo* primary HCC. Intrahepatic metastasis has been suggested as the main cause of early recurrence that occurs less than 2 years after an initial resection. Patients with early recurrence demonstrate more frequent extrahepatic metastases and multinodular intrahepatic recurrence and generally a poorer prognosis than patients with late recurrence. The risk factors for early recurrence are, reportedly, non-anatomical resection, microscopic vascular invasion and high serum AFP level. In contrast, *de novo* primary HCC can occur because of background liver disease and is considered to be another cause of HCC recurrence, especially 2 years after initial curative treatment. Because of this mechanism, HCC could continuously reoccur up to 5 years after an initial curative resection, and the risk factors for late recurrence, which include high-grade hepatitis activity, tumor multiplicity and gross tumor classification, may differ from the risk factors for early recurrence [7]. However, we cannot fully differentiate intrahepatic metastasis from *de novo* recurrent HCC by the time of recurrence, and the recurrence after curative resection in this review includes recurrences of both mechanisms.

Several retrospective studies have reported that the first recurrence site after curative resection is primarily intrahepatic (87–100%) [7,15,17]. Although extrahepatic recurrence and multiple (more than three nodules) intrahepatic recurrence is more common in early recurrence, which supports the notion that early recurrence is mainly due to metastasis, approximately 40–60% of early recurrence cases are still defined by three or more intrahepatic recurrent nodules and are thus considered potential candidates for local

treatment [17]. Extrahepatic recurrence is relatively rare at the initial presentation of recurrence (0–13%) although lung, bone, lymph node and brain metastasis could occur later in some patients [7,15,17]. Considering that the main cause of death of HCC patients is hepatic failure from intrahepatic HCC progression and/or liver function deterioration rather than distant metastasis [20], controlling intrahepatic lesions using combination locoregional therapies such as resection, local ablation, TACE and radiation therapy (RT) could have prognostic value in treating HCC recurrence, and these treatments have been widely performed in Asian countries [15,17]. Even in metastatic HCC patients, TACE could be combined with sorafenib to control intrahepatic HCC and/or obtain potential synergistic effects by adding sorafenib [21,22], and clinical trials are currently ongoing. However, the drawback of this strategy is that individual cases are so heterogeneous in terms of tumor factors (e.g., size, number, location, hypervascularity), host factors (e.g., age, comorbidities, reserve liver function), and treatment factors (e.g., invasiveness, cost, facility capability) that randomized controlled trials of treatment options are very difficult to design and perform in re-treatment settings. Hence, evidence has mainly been obtained from retrospective reports, and treatment is hard to standardize in recurrence settings although the clinical significance of patient prognosis is very high.

Nonsurgical treatment for recurrent HCC

Box 1 lists the current treatment options for recurrent HCC after surgical resection. These options are not different from the primary treatments used for HCC, but when making decisions about treatments for recurrence it is important to consider potential tumor multiplicity and limited liver function in comparison with primary treatment [12].

• Transarterial chemoembolization

Table 1 presents the clinical characteristics of postoperative recurrent HCC cases from Asan Medical Center (unpublished data), which is one of the largest referral hospitals in Asia, caring for over 2000 new HCC patients every year. Between 2000 and 2006, 290 consecutive HCC patients at Asan Medical Center were diagnosed to recur after curative resection and were subsequently analyzed. The main recurrence site was intrahepatic and more than 50% of the recurrences developed within 1 year of surgery. For the initial treatment of recurrent HCC, TACE was performed in 64.5% of patients, and RFA, re-resection and salvage transplantations were performed in 9.0, 7.2 and 0.3% of patients, respectively. Hence, when actually treating recurrent HCC, TACE is the most widely adopted intervention (~60% of patients), and the indications for TACE include an inability to receive re-resection due to impaired liver function, tumor multiplicity and a complicated location.

Although the efficacy of TACE has not been proven in randomized controlled trials for recurrent HCC, there are several retrospective studies that report good survival outcomes after repeated TACE [15,17]. At our center, of 635 HCC patients who received curative resection, 50% of cases developed recurrence after a median follow-up period of 37 months [15]. Among these cases, 68% were treated with repeat TACE; the median survival period after the first TACE was 39 months and the 5-year survival rate was >30%. Considering that the mean survival period was approximately

Box 1. Current treatment options for recurrent hepatocellular carcinoma after surgical resection.

Surgical treatments

- Re-resection for intrahepatic recurrent hepatocellular carcinoma
- Salvage liver transplantation
- Metastasectomy

Nonsurgical treatments

- Transarterial chemoembolization, transarterial radioembolization, drug-eluting bead transarterial chemoembolization
- Local ablation (radiofrequency ablation, ethanol injection)
- Sorafenib
- Systemic cytotoxic chemotherapy, hepatic arterial infusion chemotherapy
- Radiation therapy

Table 1. Example of clinical characteristics of consecutive postoperative recurrent hepatocellular carcinoma cases at an Asian referral center.

Characteristics	n = 290, n (%)
Location	
Intrahepatic	221 (76.2)
Extrahepatic	36 (12.4)
Intra- and extra-hepatic	33 (11.4)
Child–Pugh classification	
(A:B:C)	191:93:6 (65.9:32.1:2.1)
Time to recurrence	
<12 months	171 (59.0)
≥12 months	119 (41.0)
Initial treatment for recurrent HCC	
Repeat surgical resection	21 (7.2)
Salvage liver transplantation	1 (0.3)
TACE	187 (64.5)
RFA	26 (9.0)
Others	39 (13.4)
Lost to follow-up	16 (5.5)

Asan Medical Center, from 2000 to 2006, n = 290 [Unpublished Data].
HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization.

25.3 months after primary TACE for unresectable HCC [23], the results for TACE in recurrence settings are at least comparable with primary TACE for unresectable HCC. Moreover, when a recurrent tumor becomes completely necrotic after TACE, the median survival can be as high as 48.9 months, showing that some recurrent HCC with good TACE response could have much favorable survival. According to our data, the predictive factors for complete necrosis after TACE for recurrent HCC include small tumor size and a single tumor at recurrence [15].

A Japanese study has analyzed the recurrence patterns and survival of 211 cases of recurrent HCC after curative resection [17]. More than half of the patients in that report showed three or less intrahepatic recurrent nodules, 28% showed multiple intrahepatic recurrent nodules and 13% showed distant metastasis. Among all of those patients, TACE was performed most frequently, in 62% of patients, followed by local ablation in 19% of patients and re-resection in 6% of cases. When the researchers focused on patients with fewer intrahepatic recurrent nodules (i.e., three or less), TACE was still the most frequent treatment (50% of patients), followed by local ablation in 34% of patients and re-resection in approximately 10% of cases. The TACE patients demonstrated similar survival rates (5-year survival rate: 40.4%) to re-resection cases ($p = 0.3800$ according to the log rank test) and local ablation ($p = 0.2828$) [17]. These data are retrospective however and the results are not conclusive. Repeat hepatectomy is still recognized as the most effective treatment for recurrent HCC in suitable patients. However, in some patients with preserved liver function, TACE could demonstrate comparable survival in comparison with repeated resection or local ablation for recurrent HCC if it is effectively performed to produce complete necrosis. In addition, treatment decisions should be individualized according to liver function, tumor number, size and location, operator expertise and patient preference.

The drawbacks of conventional TACE include non-standardized methodology that widely varies between centers, including different drugs (e.g., doxorubicin, cisplatin, mitomycin and various mixtures), embolic agents, doses, and schedules. Recently, new transarterial techniques, such as drug-eluting bead TACE (DEB-TACE) which uses doxorubicin and transarterial radioembolization (TARE) using Yttrium-90-labeled spheres, have been developed [24,25]. These new transarterial treatments are better standardized and are reportedly better tolerated than conventional TACE. DEB-TACE demonstrates a significantly higher 6-month objective response rate in unresectable HCC patients, especially patients with Child–Pugh B, Eastern Cooperative Oncology Group performance status 1, bilobar disease, and recurrent disease, according to a unique Phase II

randomized controlled trial [26]. However, no randomized controlled trials have compared DEB-TACE and conventional TACE in terms of survival. TARE is a form of brachytherapy and differs from TACE in its antitumor mechanism. It consistently demonstrates similar survival rates across tumor stages compared with TACE or sorafenib in retrospective series or non-controlled prospective studies [27]. Relevant randomized controlled trials of TARE are currently ongoing, and the results of these studies will elucidate the potential and adequate indications for TARE to treat HCC.

Even in cases of advanced HCC with portal vein invasion or distant metastasis, TACE is still widely used as a palliative treatment, especially in Asian countries [20,21]. Several retrospective studies reported median survival periods >10 months in patients with portal vein tumor thrombus when TACE was combined with conformal RT confined to portal vein tumor thrombus and, if the radiation response was good, median survival reached almost 20 months [28–30]. Considering that the median survival of HCC patients with macrovascular invasion was 4.9 months in the SHARP trial [31], and the median survival of HCC patients with macrovascular invasion and/or extrahepatic spread (EHS) was 5.6 months in subgroup analysis from the Asian-Pacific trial [32], the on-demand TACE + RT combination strategy could be a promising option for certain patients with vascularly invading HCC, and several clinical trials are ongoing in this regard. However, in HCC with main portal vein thrombus, TACE should be considered a contraindication because of the risk of hepatic failure after embolization, and preserved only in very selected cases. The potential role of TACE in the treatment of HCC patients with EHS should also be elucidated in future clinical trials [22], and the TACE + sorafenib combination strategy is currently being studied.

As a treatment for recurrent HCC, TACE has been the mainstay for the treatment of unresectable multiple intrahepatic recurrence and preserved liver function, and is contraindicated by main portal vein invasion. Survival outcomes following TACE for recurrent HCC are quite good, especially if the tumors have become completely necrotic after repeated TACE. In the future, a combination TACE + RT approach could be a promising option for recurrent HCC with portal vein branch invasion. Although the efficacy of TACE remains unknown for HCC with EHS, a combination of TACE + systemic therapy (such as sorafenib) could be a potential option for future trials.

• Local ablation (radiofrequency ablation, percutaneous ethanol injection)

Several studies report that percutaneous local ablation therapy provides good local control of small HCC, demonstrating a comparable overall survival outcome in comparison with surgical resection as a primary treatment, although local recurrence remains slightly higher than surgical resection [33,34]. For recurrent HCC, a previous retrospective analysis of 102 recurrent HCC patients that received RFA as the initial treatment reported very good survival: 66-month median survival and 51.6% 5-year survival rate [13]. Local ablation is less invasive than surgery and could be applied to patients with more impaired liver function, but the candidate tumors for local ablation are generally smaller (i.e., <3 cm) than candidates for surgical resection, should be well visualized on ultrasonography and not located near major vessels. HCC recurrence is also common even after an initial RFA for recurrence, and a previous study has reported local recurrence and new HCCs in other parts of the liver in 8.4 and 66% of patients, respectively, after a median follow-up period of 31 months, with TACE performed on more than half of these cases [13]. Thus, previous retrospective results are not due to the efficacy of RFA alone, but rather that of combined treatments with other modalities.

Local ablation such as RFA is potentially curative and less invasive than re-resection. Although there are no data comparing ablation and re-resection, and local ablation could not be the alternatives to surgical resection in all resectable recurrent cases, it might show similar survival rates with more local recurrence in comparison with re-resection and could be applied very usefully in selected cases with small size HCC as a mono- or combination therapy with TACE. However, indications for local ablation will be limited to cases with a limited size and number of HCCs, and HCC location is also a very important factor because of technical feasibility. If HCC recurs again following local ablation, TACE is the most commonly used rescue therapy.

• Sorafenib

Sorafenib is indicated as a first-line systemic therapy for advanced HCC. Two milestone randomized controlled trials on sorafenib demonstrated significant median overall survival

benefits over the placebo in both Western (10.7 vs 7.9 months; hazard ratio [HR] = 0.69; p <0.001) and Eastern studies (6.5 vs 4.2 months; HR = 0.68; p = 0.014) [18,19]. The inclusion criteria for these studies included advanced HCC patients who were not eligible for surgery or other locoregional therapies, or demonstrated disease progression after these therapies in the SHARP trial, or who had unresectable or metastatic HCC in the Asian-Pacific trial. These criteria could have enabled some recurrent HCC patients to be included who are still candidates for TACE, which is a mainstay treatment in recurrence settings.

In subgroup analysis from the SHARP trial, 26% (158 of 602 patients) were cases of recurrence that developed after surgical resection or local ablation. In these patients, sorafenib demonstrated approximately 3 months of survival benefits in comparison with placebo, but this was not statistically significant (11.9 vs 8.8 months; HR = 0.79; 95% confidence interval [CI] = 0.51–1.22) [31]. In subgroup analysis from the Asian-Pacific trial, 31% (70 of 226 patients) were recurrent cases that developed after resection and no significant survival benefit of sorafenib over placebo was found (9.8 vs 10.5 months; HR = 0.94; 95% CI = 0.49–1.79) [32]. However, the number of recurrent patients was too small to determine the effects of sorafenib in this specific subgroup, and this drug still demonstrated a HR value <1 in subgroup analysis from the SHARP trial, although this finding was not statistically significant. More studies comparing the efficacy of various treatment options, including TACE, are warranted for recurrent HCC, and a combination TACE + sorafenib regimen could be another treatment option for HCC patients with EHS [22].

Another indication for sorafenib is TACE failure [3–6]. The definition of TACE failure is not generally agreed upon, but HCC progression despite two successive TACE sessions or tumor-supplying hepatic artery injury, which makes further TACE impossible, has been suggested [5,35]. However, the definition of progression after two TACE sessions according to modified Response Evaluation Criteria in Solid Tumors criteria is not based on scientific evidence and could be overly strict because some of these patients could still benefit from subsequent TACE. More data are needed in order to adequately define TACE failure, especially the time point at which further TACE is no longer beneficial or even harmful in terms of survival outcomes in comparison with sorafenib or the best supportive treatment.

Sorafenib is a first-line systemic therapy for advanced HCC but demonstrates a marginal advantage for treating recurrent HCC according to subgroup analysis from a Western Phase III study. Potential indications for sorafenib include an unresectable status, extrahepatic metastsis and contraindications for liver transplantation, TACE or RFA. Future prospective trials on sorafenib are needed to determine adequate indications and also combinations with other treatment modalities that are appropriate in recurrent settings. Another indication for sorafenib would be TACE failure, but more data are needed to adequately define this.

• Cytotoxic chemotherapy

Traditionally, advanced HCC shows a 10–20% response rate (complete + partial response) to conventional systemic cytotoxic chemotherapies such as doxorubicin, cisplatin, and 5-fluorouracil [36]. Combining these chemotherapies into the cisplatin/interferon-α-2b/doxorubicin/5-fluorouracil regimen (PIAF) fails to increase the median overall survival of advanced HCC patients in comparison with doxorubicin monotherapy (8.67 vs 6.83 months; p = 0.83), although the overall response rate is reported to be higher in the PIAF group than the doxorubicin monotherapy group (10.5 vs 20.9%; p = 0.058) [37]. With modest therapeutic efficacy, cytotoxic chemotherapy could more frequently induce treatment-related toxicity in HCC patients than in other types of cancer because advanced HCC patients often present with underlying impaired liver function, hypersplenism and coagulation abnormalities. According to previous reports neutropenia, thrombocytopenia, anemia, jaundice and even gastrointestinal bleeding develop in a considerable proportion of HCC patients who are treated with systemic cytotoxic chemotherapies [37]. Hence, systemic cytotoxic chemotherapies are not recommended as the initial standard treatment for advanced or recurrent HCC patients and should be considered only as a palliative or experimental treatment when other standard treatments are not possible or have failed.

Before the introduction of sorafenib, there were several retrospective reports of using hepatic arterial infusion chemotherapy and cytotoxic chemoregimens to treat locally advanced HCC patients with portal vein invasion in an attempt to reduce systemic toxicity and increase the local chemotherapeutic concentration [38]. However,

the number of patients included in these studies was too small to draw any meaningful conclusions regarding efficacy. These regimens are also too heterogeneous to be standardized. Further data will be needed to confirm and validate these results.

• Radiation therapy

External beam RT is conventionally used as a symptomatic palliation therapy to treat lymph node, bone and brain metastases. Because advanced RT technologies, such as conformal RT, intensity-modulated RT and stereotactic body RT (SBRT) facilitate RT-dose escalation to focal HCC, the role of RT as a HCC treatment option is expected to rapidly increase [39]. Although there are still no prospective randomized studies that show the survival benefits of external beam RT, several retrospective studies have reported a greater than 60% overall response to hypofractionated conformal RT and an approximately 70% overall response to SBRT when used to treat 5- to 6-cm-sized HCCs [40–44]. RT is widely performed in daily practice to treat HCC, especially in Asian countries [40–42,44]. In addition to symptomatic palliation, the tentative indications for using external beam RT as part of a multidisciplinary approach would also include portal-vein-invading HCC and intrahepatic HCC that fails to respond to repetitive TACE. SBRT could also be applied to small intrahepatic or metastatic HCCs with curative intent. However, future prospective studies are needed to determine the appropriate indications for RT in comparison with other treatment modalities in various clinical situations and to standardize RT methods before acceptance as a standard HCC treatment.

Multidisciplinary approach for recurrent HCC

Whenever re-resection or salvage LT is applicable in recurrent HCC, these treatments are considered to be the most effective treatment in terms of patients' survival [10,11]. However, the use of these procedures is uncommon in recurrence settings due to limited liver function after previous liver resection, potential multiplicity of recurrent HCC and donor organ shortages. Controlling the progression of intrahepatic recurrent HCC for as long as possible using combinations of various locoregional therapies, such as TACE, local ablation and RT, might delay hepatic failure of the patients which is the main cause of death in HCC [20]. In practice, TACE has become the most frequently performed rescue therapy for HCC recurrence [15,17], and RFA, RT and even sorafenib could be combined with TACE in various recurrent situations. Although prospective studies on this multidisciplinary concept are still lacking and hard to perform because of tumor heterogeneity and host- and treatment-related factors, a multidisciplinary approach is likely to be the best strategy for determining the most effective treatment at each decision point in HCC patients. The prerequisites for an effective multidisciplinary approach include free and thorough communication with the participants, respect for other opinions and a shared common treatment hierarchy. The outcomes of such approaches need to be periodically evaluated to modulate current treatment hierarchies for the best patient outcomes. Prospective studies (across different departments) could be designed more easily using this strategy.

As a suggestion for the treatment hierarchy for recurrent HCC we at first could consider whether the patient is eligible for re-resection, salvage LT or local ablation. If these treatments are not indicated we could perform on-demand TACE and, less frequently, TARE or DEB-TACE if there are no contraindications. Local ablation and RT could be combined with TACE for relevant cases. If these treatments are not applicable or extrahepatic metastasis is present, sorafenib can be considered **(Box 2)**.

Conclusion

HCC is characterized by a high rate of recurrence even after curative resection and local ablation, and this is a major challenge for clinicians. The knowledge required to select the most appropriate treatment for recurrent HCC includes the intrahepatic location of the lesions, any potential multiplicity, and limitations to the hepatic functional reserve. The current treatment options for recurrent HCC after surgical resection do not differ from primary HCC treatments, but the number of candidates for re-resection and salvage LT is limited in real practice. Nonsurgical treatment options for recurrent HCC include TACE, other transarterial treatments such as TARE and DEB-TACE, local ablation such as RFA and ethanol injection, sorafenib, cytotoxic chemotherapy and RT, and TACE is the most widely performed nonsurgical treatment for recurrent HCC. TACE, local ablation, RT and sorafenib have different

Box 2. Suggested treatment hierarchy for recurrent hepatocellular carcinoma.

- Re-resection for intrahepatic recurrent HCC
- Salvage liver transplantation
- Local ablation (radiofrequency ablation, ethanol injection)
- TACE (mainly), TARE (less frequently), DEB-TACE (less frequently), possibility of combination with local ablation or radiation therapy
- Sorafenib, possibility of combination sorafenib + TACE (current clinical trial)
- Other experimental treatments: hepatic arterial infusion chemotherapy, systemic cytotoxic chemotherapy (current clinical trials)

DEB-TACE: Drug-eluting bead transarterial chemoembolization: HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

efficacies, weaknesses and indications, and are, in fact, complementary to each other. Treatment for recurrent HCC should be individualized to the host, tumor characteristics and any treatment-related factors. Although prospective data are still lacking, various combinations of nonsurgical therapies have now being trialed, and multidisciplinary strategies are expected to become increasingly popular in the future for the treatment of HCC.

Future perspective

In addition to early detection of HCC by screening for high-risk patients and improvements to treatments, including the use of antiviral agents, the evolution of surgical and nonsurgical treatment options for HCC has dramatically improved patient survival outcomes over the past few decades. Recently, several combination treatments have been widely trialed in difficult-to-treat patients, including TACE + RT regimens for portal-vein-invaded HCC, curative-intent SBRT for small HCC cases that are not candidates for surgery or local ablation, TACE + sorafenib (or other novel systemic therapies) for advanced HCC, and downstaging TACE + surgical resection (or salvage LT). These treatment strategies could become the accepted standards if validated by future trials. The strengths and effectiveness of TARE and DEB-TACE in comparison with conventional TACE could be elucidated in ongoing and future studies, and these new transarterial treatments could become another option for HCC treatment. Many novel molecular targets for HCC are now being studied in preclinical and clinical trials, and molecular targeted agents that are more effective than sorafenib could be developed in the near future. These advances will hopefully lead to significant improvements in the prognosis of HCC in the future.

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