Treatment Algorithms for Managing Hepatocellular Carcinoma

Vivek A. Saraswat, Gaurav Pandey, Sachin Shetty

Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Early diagnosis and aggressive therapy improves outcome in hepatocellular carcinoma (HCC). Several potentially curative as well as palliative treatment options are available for patients. The choice of therapy is influenced by factors such as extent of tumor and severity of underlying liver dysfunction as well as availability of resources and of expertise. A systematic, algorithmic approach would ensure optimal therapy for each patient and is likely to improve outcomes. Even after receiving therapy for HCC, patients remain at risk for recurrent HCC as well as progression of underlying cirrhosis. Proper assessment and monitoring is needed for the underlying liver disease, which may progress to liver failure and have a major impact on long-term survival. Comprehensive care for patients with cirrhosis includes interventions such as antiviral therapy for HBV and HCV, abstention from alcohol, management of fatty liver disease, endoscopic surveillance and treatment for complications of portal hypertension and, if indicated, immunization against HAV and HBV. An algorithmic approach is useful for choosing the most appropriate treatment option for the individual patient from among the various options that are available. The general consensus is that the BCLC system should be preferred for staging HCC as it is useful in predicting outcomes and planning treatment. The BCLC system classifies patients with HCC into five categories: very early, early, intermediate, advanced, and terminal. It incorporates data on tumor status (number and size of nodules, vascular invasion, extra-hepatic spread), liver function (CTP status, presence of portal hypertension) and overall health status (constitutional symptoms, cancer symptoms, performance status). Treatment allocation according to sub-class of patients is a merit of the BCLC system; a few limitations have been noted, particularly with respect to patients with BCLC stage B and C disease. The treatment algorithm as per BCLC system is summarized in this review. (J CLIN EXP HEPATOL 2014;4:S80–S89)

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Address for correspondence: Vivek A. Saraswat, Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. Tel.: +91 9415004007 (mobile), +91 522 2494407, +91 522 2494408

E-mail: profviveksaraswat@gmail.com

Abbreviations: AJCC–UICC: American Joint Committee on Cancer and Union for International Cancer Control; ALT: alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; bm-JIS: biomarker JIS; CEUS: contrast-enhanced ultrasound; CLIP: Cancer of the Liver Italian Program; CTP: Child–Turcotte–Pugh criteria; CUPI: Chinese University Prognostic Index; EASL: European expert panel; EBRT: external beam radiotherapy; HCC: hepatocellular carcinoma; JIS: Japanese integrated system; LT: liver transplantation; MAA: macro-aggregate albumin; MCT: microwave coagulation therapy; MWA: microwave ablation; NCCN: National Comprehensive Cancer Network; PAI: percutaneous acetic acid injection; PEI: percutaneous ethanol injection; PLT: primary LT; RBV: ribavirin; RECIST: response evaluation criteria in solid tumors; RFA: radiofrequency ablation; SIRT: Selective Internal Radiation Treatment; SLT: salvage liver transplant; TACE: trans-catheter arterial chemo-embolization; TACE-DEB: TACE with drug eluting beads; TAE: transarterial embolization; TAI: trans-catheter hepatic arterial infusion; TARE: transarterial radio-embolization; TNM: Tumor–Node–Metastasis; WHO: World Health Organization

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Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Typically, diagnosis is late and median survival following diagnosis is approximately 6–20 months.¹ This highlights need for early diagnosis and aggressive therapy in order to improve outcome in this.

Several potentially curative as well as palliative treatment options are available for patients with HCC (Table 1). Although surgical resection is the mainstay of therapy, this is possible in fewer than 5% of patients. The choice of therapy is influenced by factors such as extent of tumor and severity of underlying liver dysfunction as well as availability of resources and of expertise. A systematic, algorithmic approach would ensure optimal therapy for each patient and is likely to improve outcomes.

Even after receiving therapy for HCC, patients remain at risk for recurrent HCC as well as progression of underlying cirrhosis. Proper assessment and monitoring is needed for the underlying liver disease, which may progress to liver failure and have a major impact on long-term survival. Comprehensive care for patients with cirrhosis includes interventions such as antiviral therapy for HBV and HCV, abstention from alcohol, management of fatty liver disease, endoscopic surveillance and treatment for complications

Table 1 Treatments for HCC.

Surgical therapy	Local ablative therapy	Loco-regional therapy	Systemic therapy
Resection	Radiofrequency ablation (RFA)	Trans-catheter therapy	Systemic chemotherapy
Liver transplantation	Percutaneous ethanol injection (PEI)	Chemo-lipiodolization	Hormone therapy
	Percutaneous acetic acid injection (PAI)	Bland transarterial embolization (TAE)	Immune therapy
	Microwave ablation (MWA)	Transarterial chemo-embolization (TACE)	Molecular targeted therapy
	Cryoablation	TACE with drug eluting beads (TACE-DEB)	
	Irreversible electroporation	Radiotherapy	
	HIFU	Transarterial radio-embolization (TARE)	
	Photodynamic therapy	External beam radiotherapy (EBRT)	
		Stereotactic radiotherapy	

of portal hypertension and, if indicated, immunization against HAV and HBV.

The questions posed by the INASL taskforce were

- What should be the treatment algorithm based on the preferred staging system?
- How should the response to treatment be assessed?
- What should be the treatment algorithm for recurrence of HCC?

PREFERRED STAGING SYSTEM AND TREATMENT ALLOCATION FOR HEPATOCELLULAR CARCINOMA

To answer the first question, a word about the various staging systems that have been used for HCC is in order. Staging systems in cancer are generally used for prognostication but may also be useful for choosing appropriate therapy. HCC presents a unique situation among solid tumors where the staging system is required to assess risk from two life-threatening conditions present at the same time ie. cancer

and cirrhosis of the liver. Hence, it is understandable that any staging system used for HCC must incorporate prognostic indicators not only for tumor status but also for liver function and overall health status.² When choice of 'curative' therapies is being debated (eg. local ablation vs. resection vs. transplantation), more detailed anatomical information, as provided in the TNM staging system, as well as more accurate prediction of the risk of HCC recurrence, which is likely to be provided in the near future by biomarkers and molecular classification systems, is needed.

Over the years, several systems have been proposed for staging HCC including Okuda staging,³ Pugh's modification of Child-Turcotte criteria (CTP),⁴ TNM staging,⁵ the French staging system,⁶ the Cancer of the Liver Italian Program (CLIP),¹ the Chinese University Prognostic Index (CUPI),⁷ the Japanese integrated staging system (JIS)⁸ and biomarker JIS (bm-JIS),⁹ Barcelona Clinic Liver Cancer (BCLC) staging,^{10,11} etc. Different staging systems used for HCC are compared in Table 2. However, these staging systems have not been compared in randomized trials and recommendations rely on observational studies.

Table 2 Comparison of Staging Systems for HCC.

System	Tumor status	Liver function status	General health status	External validation	Remark
Okuda	Yes	No	No	No	May be useful in advanced HCC
Child-Turcotte-Pugh (CTP) criteria	No	Yes	No	No	Useful only for medically treated patients
Tumor-Node-Metastasis (TNM, AJCC)	Yes	No	No	Yes, for liver resection and LT	Pathology and operative details needed
Cancer of liver Italian Program (CLIP)	Yes	Yes	No	Yes	Includes PVT, AFP Useful at advanced stages, few effectively treated
Chinese University Prognostic Index (CUPI)	Yes	Yes	Yes	Yes	Useful at advanced stages, few effectively treated
Japanese Integrated System (JIS)	Yes	Yes	No	No	
Biomarker JIS (bm-JIS)	Yes	Yes	No	Yes	Includes AFP, DCP, AFP-L3
Barcelona Clinic Liver Cancer system (BCLC)	Yes	Yes	Yes	Yes	Treatment allocation as per sub-stage

Figure 1 Updated BCLC Staging system and Treatment Strategy (EASL-EORTC Clinical Practice Guidelines, 2012).

Some of them have been found to suffer from drawbacks that limit their applicability [Okuda, CTP, TNM], only a few have been externally validated (BCLC, CUPI, CLIP, and bm-JIS), even fewer include all three types of prognostic indicators mentioned above (BCLC, CUPI) and only one (the BCLC system; [Figure 1](#)) allocates treatments to specific prognostic sub-classes. The AHPBA/AJCC Second Consensus Conference on HCC (2010) concluded that no single staging system was applicable to all patients with HCC.¹² The ongoing debate about the choice of the optimal staging system mainly pertained to patients who did not undergo hepatic resection. The consensus document urged that use of regional staging systems should be avoided, since this precluded comparison of results. It advised that the BCLC classification should be used in patients with advanced liver disease who were not candidates for liver transplantation or resection, though it cautioned that judgment needed to be exercised since some patients with BCLC stage B and C disease might be candidates for resection or transplantation. For staging HCC among patients undergoing liver resection, it recommended the American Joint Committee on Cancer and Union for International Cancer Control (AJCC-UICC) classification.

The general consensus, supported by EASL² and AASLD,^{13,14} is that the BCLC system should be preferred for staging HCC as it is useful in predicting outcomes and planning treatment choices, is flexible, has been updated once,¹⁰ and is likely to be updated again to incorporate new biomarkers for better prognostication and novel therapies for specific subsets. Other staging systems, alone or in combination with BCLC, are not recommended in clinical practice.² Molecular classification systems¹⁵ are

likely to advance prognostication as well as treatment allocation but are not yet ready for clinical use.

INASL clinical practice guidelines endorse the BCLC system for treatment allocation in HCC.

ALGORITHMIC APPROACH TO TREATMENT ALLOCATION FOR HEPATOCELLULAR CARCINOMA ACCORDING TO THE BARCELONA CLINIC LIVER CANCER SYSTEM

An algorithmic approach is useful for choosing the most appropriate treatment option for the individual patient from among the various options that are available.^{2,16} Attempts to generate algorithmic approaches for the treatment of HCC are difficult since indications for various treatment modalities are evolving rapidly, new treatments are being developed and the therapeutic approach tends to vary depending upon expertise available at individual centers.

The BCLC system ([Figure 1](#)) classifies patients with HCC into five categories: very early, early, intermediate, advanced, and terminal.^{10,11} It incorporates data on tumor status (number and size of nodules, vascular invasion, extra-hepatic spread), liver function (CTP status, presence of portal hypertension) and overall health status (constitutional symptoms, cancer symptoms, performance status). Treatment allocation according to sub-class of patients is a merit of the BCLC system; a few limitations have been noted, particularly with respect to patients with BCLC stage B and C disease. The treatment algorithm as per BCLC system is summarized below.

Very early stage HCC or Stage 0 (PST 0, Child-Pugh A) refers to a single tumor <2 cm or carcinoma *in situ*.

Table 3 Assessment of Response Comparing RECIST and m-RECIST (EASL-EORTC).

Response category	RECIST	m-RECIST
Target lesions		
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
m-RECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD	
Porta hepatitis lymph node	Lymph nodes detected at the porta hepatitis can be considered malignant if the lymph node short axis is at least 2 cm	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth	

When portal pressure and bilirubin are normal, resection is indicated. In case portal pressure and/or bilirubin are increased, in the absence of important co-morbidities, liver transplantation is the therapy of choice while, in the presence of associated diseases, radiofrequency ablation (RFA) is the therapy of choice.

For **early or stage A HCC** (≤ 3 nodules ≤ 3 cm each, PS 0), the same algorithm applies as for stage 0 HCC in case of a single nodule. In case there are no more than 3 nodules, each ≤ 3 cm, liver transplantation should be performed in the absence of associated diseases while RFA is recommended in the presence of associated diseases.

Currently, 5-year survival rate after surgical resection and transplant is 70–80% while it is $\sim 70\%$ after local ablative procedures.^{17–20}

For **intermediate or stage B HCC** (multi-nodular, PS 0), transarterial chemo-embolization (TACE) is advised. Median survival in Stage B is 20 months and ranges from 14 to 45 months, highlighting the need for further refinement and sub-stratification in this category.

For **advanced or stage C HCC** (invasion, N1, M1; PS 1–2), sorafenib is recommended. Median survival is 11 months (range 6–14 months).

Patients with **terminal or stage D disease** (PST > 2 , Child–Pugh C) have very poor performance (ECOG 3–4), and short survival (median survival 3 months or 11% at 1-year). Only palliative treatment with best supportive care is recommended.²

Treatment Stage Migration

If patients do not fulfill criteria for a particular stage, or do not respond to therapy offered according to their stage, they should be offered the next most suitable option within the same stage or in the next prognostic stage.^{2,10}

Limitations of the Barcelona Clinic Liver Cancer System

A few limitations have been noted in the BCLC system. An area of major concern is that allocation to curative therapy (tumor ablation, liver resection and LT) according to BCLC

criteria appears to be unduly restrictive. If followed strictly, many patient subgroups being offered LT according to current practices, as detailed below, are likely to be deprived of the benefits of this life-saving therapy. The Milan criteria²¹ for liver transplantation in patients with HCC (ie. solitary tumor ≤ 5 cm or ≤ 3 tumors, all ≤ 3 cm), are followed throughout the world and form the benchmark for LT in HCC. According to the simplified AJCC classification for HCC, tumor size does not impact survival in T1 stage when vascular invasion is absent.²² Even patients with T2 tumors (solitary tumor with vascular invasion or multiple tumors, none more than 5 cm) may be suitable candidates for resection when liver function permits. Some patients with stage A HCC (single tumor, >2 cm or multiple nodules) but with associated diseases as well as some with stage B HCC (multi-nodular tumors) but with a good performance status are likely to benefit from LT; however, they are deprived of this option under the BCLC algorithm.² Even CTP class C patients undergo liver transplantation successfully with a low risk of recurrence if they are within Milan criteria. However, the BCLC algorithm restricts liver resection to stage 0 disease (single tumor, ≤ 2 cm) and liver transplantation to stage A disease (3 nodules, ≤ 3 cm, no associated diseases).² In an era when most workers are contemplating expansion of criteria for LT in HCC, these recommendations appear unduly restrictive.

With advances in surgical and radiological techniques, neo-adjuvant therapies are increasingly being used to downstage HCC so as to make curative interventions possible. Use of portal vein thrombosis to enhance remnant liver size before hepatectomy may increase the scope for resection of larger HCCs. Improving liver function by optimizing medical therapy may further decrease morbidity. However, these strategies find no mention in the BCLC system. As results with these strategies become available, BCLC guidelines for treatment allocation may need to be revised. Finally, criteria for allocation to LT have been developed only for cadaveric LT programs and extrapolation to the LDLT situation awaits validation.

HOW SHOULD THE RESPONSE TO TREATMENT BE ASSESSED?

Follow-up after Therapy for Early Detection of Recurrence in Hepatocellular Carcinoma

Measurement of Response Rate

Though the standard outcome parameter in cancer research is overall survival, surrogate endpoints such as response rate and time to progression are also useful. However, assessing response to therapy for HCC has been problematic. It was realized that the World Health Organization (WHO) criteria underestimated the actual response rate for HCC. These were amended in 2000 by a European expert panel (EASL) which took into account

treatment-induced tumor necrosis and proposed response evaluation criteria in solid tumors (RECIST) guidelines based on tumor shrinkage.²³ However, to the limitations of assessment modalities, anatomic tumor response metrics are insufficient in HCC and can be misleading when assessing response to molecular targeted or loco-regional therapies. In order to provide a common framework for designing clinical trials, AASLD developed modified RECIST (m-RECIST)²⁴ guidelines in 2008 (Table 3). These are based on measurement of the maximum diameter of viable tumor tissue in the target lesion as determined by contrast uptake in the arterial phase of contrast-enhanced radiologic imaging techniques. The hyper-enhancing area must be measurable (at least 1 cm), clearly delineated and reproducible at later examinations.

Follow-up of Hepatocellular Carcinoma Patients after Therapy or Transplant

Post-treatment Surveillance

Even patients who have a good response to treatment are at risk for disease recurrence and second primary HCCs. 30–50% patients with HCC recur within 2 years while approximately 20% do so by 3 years after LT. One in three patients with recurrent HCC after LT are amenable to treatment with curative intent. Therefore active surveillance for HCC is advocated after LT. Imaging modalities for hepatic and extra-hepatic staging used in the pre-transplant setting are applicable for monitoring recurrence after LT. Although there is no consensus on the optimal approach for post-treatment surveillance in patients undergoing loco-regional therapy for HCC, various groups of experts have proposed surveillance programs.

National Comprehensive Cancer Network (NCCN)¹² guidelines have proposed the following monitoring schedule after ablation or resection:

- Imaging every three to six months for two years, then annually,
- Assay of serum AFP, if initially elevated, every three months for two years, then six-monthly,
- Monitoring and appropriate treatment of all patients with underlying liver disease.²⁵

The International Consensus Conference for HCC recommends that post-transplant monitoring should include 6- to 12-monthly contrast-enhanced CT or MRI imaging and α -fetoprotein measurements.¹⁶

ESMO Clinical Practice Guidelines²⁶ propose response evaluation and follow-up as follows:

- Response assessment should be based on dynamic CT or MRI studies [III, A] using the modified RECIST criteria.
- Serum tumor markers such as alpha-fetoprotein levels may be helpful, particularly in the case of not easily

Figure 2 An algorithm for management of recurrent HCC.

measurable disease, but should not be used as the only determinant for treatment decision.

- Follow-up of patients who underwent radical treatments should consist of the clinical evaluation of liver decompensation and the early detection of recurrence by dynamic CT or MRI studies every 3 months during the first 2 years and every 6 months after that.
- Patients with more advanced stages of HCC who were treated with TACE or systemic agents (e.g. sorafenib) must be evaluated every 2 months for signs of liver decompensation clinically and for tumor progression by dynamic CT or MRI, to guide decisions.

Early detection of recurrence and surgical management may lead to increased survival. In HCC, tumor recurrence is related to factors such as vascular invasion, tumor differentiation, number of tumors and AFP slope. Patients who have increased risk of recurrence such as size beyond Milan criteria at listing, microvascular invasion and microsatellitosis at histopathology in the explanted liver, and AFP >400 mg/dL should have cross-sectional imaging studies at least every 6-monthly for 3–5 years post-transplant.^{12,27} m-RECIST criteria specify that post-therapeutic evaluation of patients with cirrhosis and HCC is based exclusively on contrast-enhanced dynamic imaging criteria. Recommended techniques are contrast-enhanced spiral CT scan (5 mm thickness and 5 mm reconstruction interval) or contrast-enhanced MRI. Other imaging techniques, such as angiography, contrast-enhanced ultrasound (CEUS)

and PET-CT are likely to be more widely used in future but, due to lack of adequate data, are considered controversial at present.²⁴

Contrast-enhanced ultrasound (CEUS) represents a viable alternative for follow-up after treatment for tumors >2 cm as it has diagnostic accuracy similar to that of the CT/MRI, avoids radiation and is devoid of hepatic and renal toxicity. However experience with CEUS is insufficient and it is recommended for use together with CE-CT and CE-MRI during follow-up after treatment.

Although utility of serum tumor markers in the diagnosis of HCC and in following progression of disease remain under investigation, they are useful during follow-up after treatment, especially in those where it was elevated initially.

Finally, it is also important that patients with advanced liver disease have proper monitoring for esophageal varices and treatment of their underlying liver disease, which may have a major impact on long-term survival.

- What should be the treatment **algorithm for recurrence of HCC**?

RECURRENT HEPATOCELLULAR CARCINOMA

Cancer recurrence, generally in the hepatic remnant, occurs in 70–100% of cases after liver resection for HCC.^{11,25,28} Cumulative 5-year recurrence rate after ‘curative’ partial

hepatectomy averages above 70% in both Eastern and Western centers. Recurrence is not necessarily failure of therapy. It may be treated with curative intent in almost 40% of cases and prolonged survival may result from aggressive management with iterative resection and percutaneous ablation.¹² Recurrent HCC has been categorized based on morphology of recurrences¹² or timing of recurrence.²⁹

Based on morphology, recurrent HCC may be

- a) **marginal** (type 1) when recurrence is located near the resection margin
- b) **nodular** (type 2) when the single or double recurrent lesion is located more than 3 cm from the surgical scar and
- c) **multi-nodular or diffuse** (type 3) when the recurrence consists of many nodules scattered throughout the remaining liver or as an infiltrative lesion.

Nodular and marginal recurrences are suitable for curative procedures ie. surgery, PEI and RFA, in more than 80% of cases; no difference in survival was noted related to the different treatments employed. The results of radical treatment of the recurrence are quite good; 5-year survival in 55 cases of cured recurrences was 64.3%, not significantly different from 72.9% observed in the 58 patients who never recurred.¹²

Based on timing of recurrence, two major patterns of recurrent HCC within the liver have been reported viz. intra-hepatic metastasis from the primary resected tumor and multi-centric occurrence of a new tumor in the liver remnant.²

Intra-hepatic metastases represented early recurrence, within 1 year after hepatectomy, were often diffuse and were rarely treatable, with unsatisfactory long-term survival.¹² They were directly related to macroscopic and microscopic neoplastic vascular infiltration and subsequent intra-hepatic venous spread, resulting in the worst type of recurrence, the multi-nodular-diffuse type.² Cirrhosis, HCV positivity and elevated transaminases were significantly associated with this type of recurrence.¹²

Multi-centric occurrence is associated with the underlying liver status, is usually late, with ≤ 3 lesions and is associated with better survival than early recurrence.² Cirrhosis was a major risk factor for recurrence in this subgroup.¹² It is generally agreed that presence of ≤ 3 lesions is probably associated with multi-centric occurrence, for which resection or radiofrequency ablation are indicated while presence of ≥ 4 lesions is probably associated with intra-hepatic metastasis, for which TACE is indicated.²⁹⁻³¹

TREATMENT STRATEGIES FOR RECURRENT HEPATOCELLULAR CARCINOMA

Modes of presentation at recurrence together with the feasibility of radical treatment are the best determinants

of prognosis.¹² Various therapeutic modalities such as repeat hepatectomy, local ablation therapy and transcatheter arterial chemo-embolization (TACE) have been used to treat recurrent HCC. There is no standard strategy for choosing between different modalities. Regardless of the timing of recurrence, marginal and nodular recurrences should be considered for radical treatment, which may restore life expectancy to the same level as in patients who never recurred.¹²

Treatment Strategy for Multi-centric Cancers

Though the principles of treatment for recurrent HCC are essentially similar to those for treating primary HCC, modalities should be selected according to the degree of progression (number and size of tumors, presence or absence of tumor embolus, etc.), severity of hepatic impairment and multi-centric occurrence or intra-hepatic metastasis.^{12,15} Efforts to improve functional liver reserve with optimizing medical therapy should be made before radical treatment is planned, so that a curative treatment strategy can be planned for multi-centric occurrence. Preliminary data from Japan have shown that a combination of TACE and RFA for large lesions, to convert them to resectable disease wherever possible, even for highly advanced, recurrent cancer, results in increased survival.²

Treatment Strategies for Intra-hepatic Metastasis

It is important to select treatment not only for overt lesions, but also for micro-metastases. Combination therapy, including TACE, is required for initial or recurrence treatment.

Liver Transplantation

Theoretically, liver transplantation would be the optimal treatment for recurrent HCC within Milan criteria but organ shortage makes LT controversial for recurrent HCC and experience is restricted to a few reports.²⁷ An Italian study of liver transplantation (LT) as a salvage procedure (SLT) in the event of HCC recurrence found comparable overall (62% vs. 73%, $P = \text{NS}$) and disease-free (48% vs. 71%, $P = \text{NS}$) 5-year survival rates for SLT and primary LT (PLT) for HCC.²⁹ However, literature reports about SLT are conflicting. While Belghiti and Durand²⁸ found that both 3-year and 5-year overall survival rates in PLT and SLT recipients were similar (82% vs. 82% and 59% vs. 61%), as did Del Gaudio et al²⁹ and Vennarecci et al,²⁵ others reported an increased risk of recurrence (54% vs. 18%), with a poorer 5-year overall (41% vs. 61%) as well as disease-free survival (29% vs. 58%) for SLT than for PLT.²⁷ Since multiple challenges including shortage of organs, waiting list time, tumor biology, stage of tumor etc. remain to be addressed, the International Consensus

Conference for HCC has stated that re-transplantation is not an appropriate treatment for recurrent HCC.¹⁶ A small subset of patients who develop *de novo* HCC as a part of progression or recurrent disease may merit consideration for LT.

Repeat Hepatectomy

Repeating the resection is the treatment of choice if oncological clearance can be achieved, in suitable patients with good performance status and adequate liver functional reserve.³² The main consideration remains the likelihood of patients developing post-hepatectomy liver failure. Though surgery is technically demanding due to adhesions, anatomical disorientation caused by the rotation of liver remnant following regeneration and due to limited liver reserve, safety and long-term results of repeated resection have been well-documented, with operative mortality ranging from 0% to 8.5% and reported cumulative 5-year survival rate after a second hepatectomy being comparable to survival after initial hepatectomy for primary HCC. However, it is noteworthy that, in the reported series, the majority of patients had good liver reserve and small tumors.^{32,33}

In a recent systematic review of 1149 patients in 29 series of repeat hepatectomy for recurrent HCC with a curative intent, 1-, 3- and 5-year survival rates were reported to range between 69–100%, 21–87% and 25–87% respectively.³⁴ These data support the use of repeat resection for recurrent HCC.³² The International Consensus Conference for HCC has recommended that recurrence after liver transplantation may be treated by surgery for resectable lesions or by loco-regional or systemic therapy, including sorafenib, for unresectable lesions.¹⁶

Local Ablation Therapies

Radiofrequency ablation (RFA), microwave coagulation therapy (MCT) and percutaneous ethanol injection (PEI) are the three most commonly used local ablative treatment modalities for treatment of small primary HCC. They are also useful interventions in patients with recurrent HCC, >80% of whom have impaired liver function or multicentric tumors, which precludes repeat hepatectomy.³⁵ Reports on the use of PEI in treating HCC recurrence are scarce.

Radiofrequency Ablation

RFA is suitable for recurrent HCC after hepatectomy when detected at an early stage, while the nodules are still small. RFA is minimally invasive, is applied percutaneously and can be used repeatedly. It achieves complete ablation in over 90% and long-term survival is comparable to results achieved with hepatectomy. The reported 3-year survival rate averaged above 60% and the 5-year overall survival rate ranged from 18% to 51.6%.^{35–37} Liang et al³⁸ found similar overall survival after percutaneous RFA and repeat

partial hepatectomy for recurrent HCC in comparable patients within Milan. Further, RFA was less invasive and less morbid.

In a study of 41 recurrent HCC treated with RFA after hepatectomy, Yang et al reported that the late recurrences group (>1 year) had significantly longer overall survival than the early recurrence group (mean overall survival 42.9 vs. 16.4 months).³⁷ The important issue of RFA needle track seeding by the tumor has been studied by various groups and a relatively high risk of up to 12.5% has been reported.³⁹

Transarterial Chemo-embolization (TACE)

Among patients with recurrent HCC, TACE is reserved for those with unimpaired function of the liver remnant and in those with multiple nodules.⁴⁰ Although TACE improves survival in patients with unresectable HCC and is regularly used in patients with intra-hepatic HCC recurrence,^{40,41} due to lack of comparative studies, TACE protocols for recurrent HCC are not standardized for optimal time interval between treatments and for choice, dosage, concentration and rate of injection of the chemotherapeutic and embolizing agents.⁷

There are a few unresolved issues with TACE.⁴² It is always problematic in patients with compromised liver reserve. Anatomic changes due to previous operation such as neovascularisation, fresh collaterals that feed the recurrent tumor and risk of embolization of non-tumorous liver tissue make TACE technically demanding. Cumulative drug toxicity may ensue from repeated TACE sessions. Finally, TACE cannot be regarded as a curative treatment for recurrent HCC, though it may prolong survival.

Transarterial Chemo-embolization with Radiofrequency Ablation

Preliminary data from Japan demonstrated that TACE with RFA improved the prognosis of multiple recurrent HCC even in cases beyond Milan criteria, suggesting that, even with multi-centric occurrence, treatment should aim at cure by attempting to downgrade highly advanced, recurrent cancer to resectable disease wherever possible.

Selective Internal Radiation Treatment (SIRT) involves intra-arterial administration of Yttrium⁹⁰ (⁹⁰Y) microspheres into the hepatic artery via the trans-femoral route. Microspheres are trapped within the microvasculature and are concentrated selectively in the tumor due to its rich arterial supply. Thus, effective tumoricidal radiation is delivered to the tumor while radiation injury to normal liver is limited. SIRT requires optimal perfusion to enhance free radical dependent cell death. It is a safe and effective option for palliative therapy of large or multifocal HCC without major portal vein invasion or extra-hepatic spread, bridging therapy before liver

transplantation, tumor downstaging and for treating patients who are not fit for surgery.⁴³ In chronic liver disease, porto-systemic shunting allows a fraction of the ⁹⁰Y microspheres to reach the pulmonary bed, resulting in radiation pneumonitis. ^{99m}Tc macro-aggregate albumin (MAA) scintigraphy helps to determine the arterial anatomy and to calculate the shunt fraction, which should be below 15% to reduce risk of radiation pneumonitis.

Extra-hepatic recurrence is seen in 5–20% of the patients. Sorafenib has shown marginal survival benefits in large, placebo-controlled phase III trials in Europe and Asia for patients with advanced HCC.⁴⁴ Prolonged survival after surgical resection may be achieved in selected patients with solitary extra-hepatic recurrence at the sites of the abdominal lymph node, adrenal gland, lung, and peritoneum. Surgical resection might be an effective option in patients with one or two isolated extra-hepatic metastases if the patient otherwise has good performance status, good hepatic functional reserve and well-controlled intra-hepatic HCC recurrence.^{43,45}

PREVENTION

Till date there is no universally accepted form of adjuvant therapy for preventing recurrence after hepatic resection.⁴³ Antiviral therapy wherever indicated and trans-catheter hepatic arterial infusion (TAI) may prevent appearance of intra-hepatic metastasis.

Antiviral Therapy

Asian studies in chronic hepatitis B showed that tumor recurrence after curative treatment for HCC increased with increasing levels of HBV-DNA and alanine aminotransferase (ALT), suggesting that viral replication played a role in development of tumor recurrence. In a recent meta-analysis of nine cohort studies involving more than 500 patients with HBV-related HCC, Wong et al concluded that antiviral therapy could significantly reduce the risk of HCC recurrence after curative treatment and might also allow salvage therapy in case of HCC recurrence by preserving liver function.⁴⁶

A study evaluated the treatment response and hepatic functional reserve in patients who received combination therapy with PEG-IFN α -2b and ribavirin (RBV) after radical treatment of HCV-related HCC. The 1-year and 3-year cumulative survival rates were 100% and 90.2% in the secondary treatment group, and 96.0% and 61.2% in the no-secondary treatment group, respectively, showing a significant difference between the groups. Multivariate analysis identified secondary interferon treatment as a significant factor.

Role of Adjuvant Regional Therapy

In patients with high risk factors for recurrence, adjuvant TACE after hepatic resection demonstrated survival

benefit but the effect in those with a low risk of recurrence remains unclear.⁴³ Though initial studies had shown promise with adjuvant transarterial ¹³¹I-lipiodol treatment and adjuvant immunotherapy with interferon, their role in preventing early intra-hepatic recurrence remains to be confirmed.^{41,46,47}

Current evidence suggests that adjuvant regional chemotherapy with or without embolization or combined with systemic chemotherapy does not provide any additional survival benefit.⁴³

CONFLICTS OF INTEREST

All authors have none to declare.

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