Multimodal approaches to the treatment of hepatocellular carcinoma

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SUMMARY

The prevalence of hepatocellular carcinoma in Europe and the US is increasing and is currently the leading cause of death in patients with cirrhosis. Surveillance programs for patients with cirrhosis aim to detect tumors at an early stage, when the greatest therapeutic benefits can be achieved. Curative treatments for early-stage tumors include liver transplantation, resection and percutaneous ablation. Transarterial chemoembolization (TACE) and sorafenib can improve survival for patients with intermediate and advanced tumors, respectively. In clinical practice, combination therapies are often used, despite limited evidence to support this approach from randomized controlled trials. Combination therapy with radiofrequency ablation (RFA) plus percutaneous ethanol injection can, however, improve survival for selected patients compared with RFA alone. Combined treatment with TACE and RFA also improves patients' survival compared with TACE or RFA monotherapy. TACE performed before or after surgical resection, however, is not beneficial. Prevention of tumor progression in patients awaiting liver transplantation requires nonsurgical treatments; however, the real advantages of the available treatment modalities are yet to be defined. The role of sorafenib administration in combination with TACE after the use of potentially curative treatments, for the treatment of intermediate hepatocellular carcinoma, or in selective settings after liver transplantation, requires further study.

KEYWORDS hepatocellular carcinoma, multimodal therapies, percutaneous ethanol injection, radiofrequency ablation, sorafenib, transarterial chemoembolization

REVIEW CRITERIA

Studies were retrieved from the MEDLINE database using the search terms "hepatocellular carcinoma", "liver cancer" and "primary liver carcinoma" individually and combined with the terms "randomized", "controlled clinical trials", "clinical trials", "phase III studies", "meta-analysis", "combined therapy", "treatment", "liver cancer", "TACE", "TAE", "chemoembolization", "embolization", "locoregional treatments", "PEI", "percutaneous ethanol injection", "RFA", "radiofrequency ablation", "liver transplantation" or "resection", as well as by a manual search and review of reference lists. The search included literature published in English up to September 2008.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a challenging malignancy in terms of its management and its complex etiology. It is also a malignancy of global importance—the sixth most common cancer and the third most common cause of cancer-related death worldwide.[1] The prevalence of HCC in the US and in Western Europe is increasing.[2,3] In most cases, patients with HCC have underlying cirrhosis, often secondary to HBV or HCV infection.[3] Primary preventative approaches involving vaccination against HBV have resulted in a decrease in the incidence of HBV-related HCC.[4] Vaccination against HCV is not yet possible, however, and prevention of HCV infection relies on the implementation of adequate public health measures. In patients with HBV or HCV infection, antiviral treatment might prevent progression to cirrhosis and the subsequent development of HCC; however, no clear evidence shows that antiviral therapy protects against the development of HCC in patients with HBV or HCV infection who have established cirrhosis, unless the virus is permanently cleared.[5]

Obesity and metabolic syndrome are considered risk factors for the development of nonalcoholic steatohepatitis (NASH) and NASH-related cirrhosis, and probably contribute to the increased prevalence of HCC.[6] Given the continuing increase in the prevalence of obesity and diabetes, the incidence of NASH-related HCC can also be expected to increase.[7]

Findings from clinical studies and cost-efficiency modeling analyses suggest that surveillance of well-defined groups of patients with cirrhosis may decrease tumor-related mortality.[8,9] Despite numerous efforts to screen for HCC in high-risk patients, such as carriers of hepatitis B surface antigen and patients with compensated cirrhosis, only 20–30% of patients are diagnosed as having HCC sufficiently early to benefit from curative treatments, for example, surgical resection and liver transplantation.[10,11]

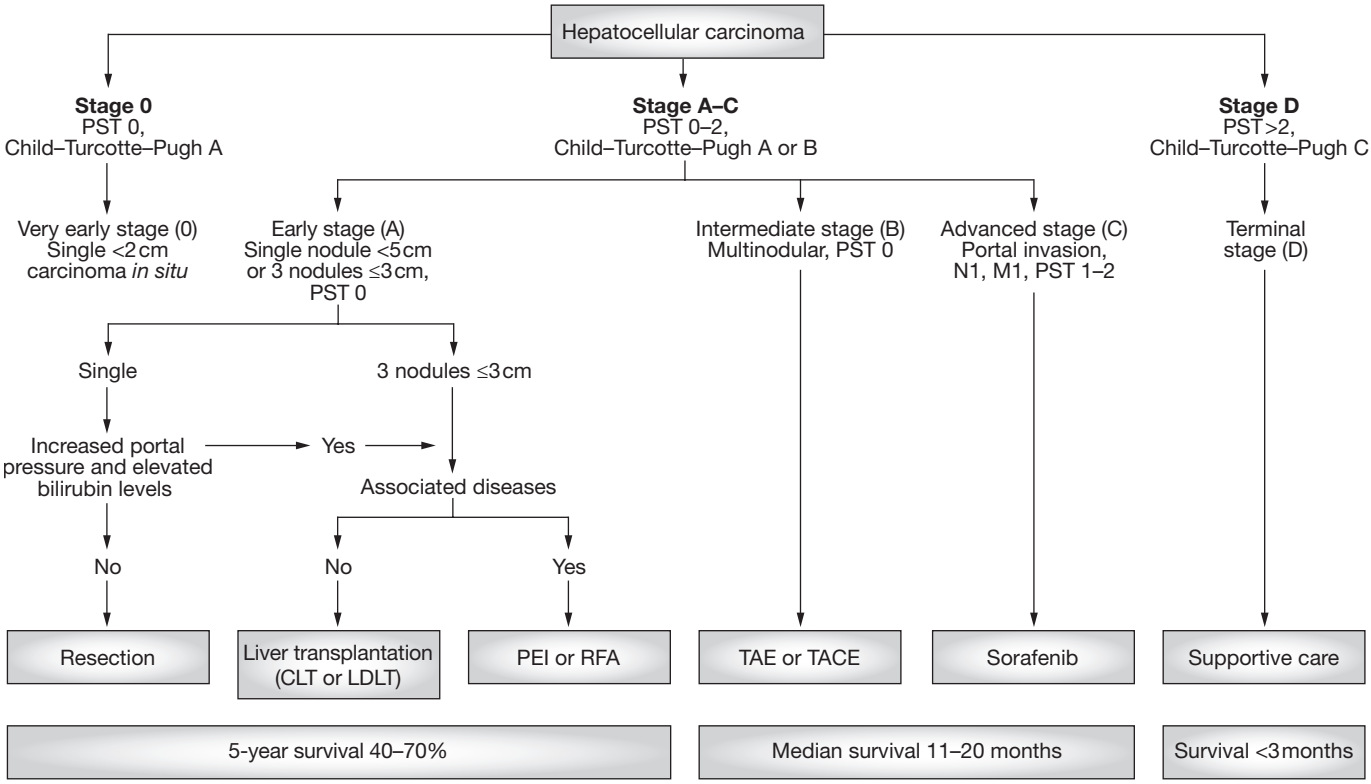

Figure 1 Algorithm for staging and treating patients diagnosed as having hepatocellular carcinoma. This algorithm is based on the Barcelona Clinic Liver Cancer guidelines. Hepatology, Vol 42, No. 5, 2005, 1208–1236.[9] Copyright (2005, Bruix J *et al*.); reprinted with permission of John Wiley & Sons, Inc. Abbreviations: CLT, cadaveric liver transplantation; LDLT, live donor liver transplantation; PEI, percutaneous ethanol injection; PST, performance status test; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization.

The prognosis of patients with HCC depends on several factors, including tumor stage, the patient's general health, liver function and the treatment options available.[9] Of the main prognostic models for staging HCC, only the Barcelona Clinic Liver Cancer (BCLC) classification[12] takes into account all the factors listed above.[13,14] Importantly, no prognostic model has yet demonstrated sufficient discriminative ability to predict survival accurately in an individual with HCC and cirrhosis[15] and, therefore, no system has been recommended worldwide for the evaluation of patients' prognosis in clinical practice.[9]

In the absence of an optimum prognostic model, treatment algorithms for patients with HCC in Europe and North America have been prepared on the basis of the BCLC classifications. The BCLC staging classification for HCC classifies patients as having stages of disease from 0 to D (Figure 1). Stage 0 is very early disease, which is defined as a solitary liver cancer that measures ≤2 cm without tumor invasion into surrounding tissues. Stage A is early disease, defined as patients who exhibit preserved liver function with a solitary HCC less than 5 cm in size, or up to three tumors each of which is ≤3 cm in size. Patients with stage 0 or stage A disease can be effectively treated by curative therapies, such as surgical resection, liver transplantation, or by percutaneous ablation methods, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). Patients with stage B (intermediate) disease can be treated with transarterial embolization (TAE) or transarterial chemoembolization (TACE). Previously, no standard systemic therapy existed for the treatment of patients with advanced (stage C) HCC; however, a randomized controlled trial (RCT) has now shown that sorafenib, an inhibitor of Raf kinase and vascular endothelial growth factor receptor, improves the overall survival of patients with stage C disease. Sorafenib is, therefore, now considered to be the standard treatment for advanced HCC.[16] Patients with stage D (terminal) disease do not benefit from

antitumor treatments and should only receive the best available supportive care.

Of note, evidence for the majority of therapeutic interventions used to treat patients with HCC was mostly obtained from investigations in small cohorts of patients. Very few RCTs have been performed in patients with HCC, and most of these studies were limited to the treatment of advanced disease. No RCTs have compared the efficacy of therapies that are considered to be effective for the treatment of early stage HCC (i.e. surgical resection, liver transplantation, percutaneous ablation) with that of no treatment.[9]

Another notable observation is that the management of HCC varies considerably between geographic regions.[17] We can speculate that this geographic variation in treatment approach might be influenced by the lack of a uniformly accepted, standardized staging system for HCC. An equally credible cause could be the significant increase in HCC cases associated with chronic hepatitis rather than with cirrhosis in areas in which HBV infection is endemic (e.g. Asian and Pacific regions). In regions in which HCC occurs in patients without underlying cirrhosis, resection is often preferred to transplantation or local-regional therapies. For example, the Japan Society of Hepatology guidelines recommend hepatectomy for patients with only one tumor, regardless of the tumor size.[18]

Different guidelines for the management of HCC[9,18] provide indications for the use of various treatments as monotherapies, but in clinical practice a multimodal approach that combines various techniques is used, either as first-line therapy or as a rescue (second-line) approach after the failure of a monotherapy. In our opinion, a multimodal approach is used because physicians and patients believe that combined interventional therapies will achieve effects that would be impossible to achieve by any single modality. Combined interventional therapies might enable the effective destruction of the tumor, with increased therapeutic efficacy over monotherapies.

This Review article critically discusses the available evidence that supports a multimodal treatment approach for HCC superimposed on cirrhosis. However, as mentioned before, the majority of studies that have investigated therapies for HCC were not randomized. Although findings from nonrandomized studies support the use of various multimodal treatment approaches for HCC, we must emphasize that RCTs must be performed so that firm conclusions and guidelines for the use of multimodal treatment strategies can be generated.

MONOTHERAPY FOR HEPATOCELLULAR CARCINOMA

Curative therapy

All available therapies for HCC, including liver transplantation,[19,20] are most efficacious when used to treat patients who have single tumors of 3 cm or below in size.[9] However, only a minority of patients with cirrhosis have tumors that meet this criterion at the time of their diagnosis of HCC and are eligible for potentially curative therapy.

Liver transplantation is the only treatment that can simultaneously eradicate the tumor and any underlying cirrhosis. In selected subgroups of patients who meet the Milan criteria[21] (a solitary tumor of <5 cm or up to 3 tumors each <3 cm in diameter), 5-year survival after liver transplantation is 70%, and the rate of recurrence is below 15%.[21,22] Unfortunately, the number of patients who undergo liver transplantation is minimal compared with the total number of patients with HCC, because of the shortage in donors and the stringent transplantation criteria for this indication, even for living donor liver transplantation.

Surgical resection of the tumor yields good results in candidates who present with single tumors and an excellent liver functional reserve, with reported 5-year survival of 60–70%.[10,23,24] The risk of tumor recurrence after resection is associated with several variables, including tumor size,[25] number of tumors[26,27] and the presence of vascular invasion.[28]

Percutaneous ablation methods, such as PEI or RFA, achieve a complete response in more than 80% of patients with tumors smaller than 3 cm in diameter, but in only 50% of patients with tumors of 3–5 cm in size.[29,30] After PEI or RFA, reported 5-year survival is 40–70%, depending on the tumor size, number of lesions, extent of response to treatment and Child–Turcotte–Pugh class.[30–32] RFA is preferred to PEI for treatment of tumors smaller than 4 cm in diameter because RFA is associated with lower recurrence rates, requires fewer treatment sessions and is associated with longer disease-free survival than PEI. However, no clear evidence exists for an overall survival advantage of RFA over PEI.[33–35]

Transarterial embolization, transarterial chemoembolization and other local-regional treatments

Progression of HCC is associated with intense angiogenesis. TAE and/or TACE are the most widely used first-line treatments for HCCs that cannot be resected. A meta-analysis has shown a beneficial effect of TAE and TACE on 2-year survival;[36] treated patients had a median survival of 20 months, compared with 16 months in untreated patients.[37] Although some clinicians might deem this effect of TAE and/or TACE on survival to be modest, our opinion is that better than modest effects would be difficult (if not impossible) to achieve in patients with unresectable neoplasms.

None of the other local-regional treatments, such as internal radiation with iodine 131 (^{131}I)-labeled oil or yttrium 90 (^{90}Y)-labeled microspheres, have been compared with the effects of no treatment in patients with unresectable HCC. One RCT, however, showed that ^{131}I-labeled poppy seed oil (lipiodol) was as effective as TACE in terms of patients' overall survival after 6 months, and after 1, 2, 3 and 4 years of treatment.[38] Findings from a cohort study by Kulik *et al*. suggested that ^{90}Y-labeled microspheres have a role in downstaging HCC before liver transplantation, RFA or resection.[39]

Systemic therapy

Before the development of sorafenib, first-line systemic therapies for the treatment of unresectable HCC were lacking. Many RCTs had demonstrated that the use of systemic chemotherapy, hormonal compounds, octreotide and interferon in patients with unresectable HCC did not improve survival compared with no treatment. Such agents are, therefore, discouraged for the treatment of unresectable HCC.[37] Sorafenib—a multitarget tyrosine kinase inhibitor with antiangiogenic and antiproliferative actions—prolongs the survival of patients with advanced HCC, with a median overall survival of 10.7 months reported for sorafenib users compared with 7.9 months for placebo-treated patients ($P=0.0006$).[16] The effect of sorafenib on patients' survival is probably related to both the antiangiogenic and antiproliferative properties of this agent.

Salvage transplantation

Salvage transplantation refers to the practice of listing patients for transplantation upon the development of tumor recurrence or liver decompensation after primary resection of the tumor. This approach was considered to be cost-effective in a theoretical decision analysis model.[40] The BCLC group proposed a policy of listing patients without evident HCC for liver transplantation on the basis of a high pathological risk of recurrence after resection (e.g. after identification of vascular invasion or satellite tumors).[41] The effects of this approach on patients' survival have not yet been examined.

MULTIMODAL TREATMENT FOR HEPATOCELLULAR CARCINOMA

Multimodal treatment for HCC can involve different modalities and treatment durations, and can be tailored according to the degree of liver function, the presence or absence of portal hypertension and the availability of different techniques. The number, location and size of lesions, the presence or absence of vascular invasion or extrahepatic spread and tumor aggressiveness are also important factors to consider. Combination therapies can be categorized as either concomitant, meaning that the different treatments are carried out during the same session or at essentially the same time, or sequential, meaning that the elements of the combined treatment are carried out one after another. Either strategy aims to increase the efficacy of treatment compared with monotherapy, for example to prevent tumor recurrence, or (in the case of sequential therapy) to slow tumor progression and reduce tumor size in patients who are awaiting liver transplantation (Box 1).

Combination therapies that include sorafenib

The hypervascular nature of HCC has led a number of investigators to explore the potential of antiangiogenic therapy to decrease intratumoral blood flow. As mentioned earlier, sorafenib improves the survival of patients with advanced HCC and is the current reference standard for the treatment of patients with this stage of disease.[16] Sorafenib decreases microvessel density and blood flow in the tumor, and increases the size of the RFA-induced coagulation zone.[42] In our opinion, this effect can reduce the risk of tumor persistence at the periphery of the lesion. Studies to investigate the effects of sorafenib as an adjuvant to potentially curative treatments such as resection or local ablation—where microscopic tumor residues must re-establish their blood supply

to regrow—will certainly be of interest. Indeed, an international RCT that aims to evaluate the effect of sorafenib versus placebo after resection or local ablation has already been initiated. This study will include patients with optimal general status, preserved hepatic function (Child–Turcotte–Pugh class A and B without ascites) and with different tumor characteristics (single lesions of any size in patients assigned surgical resection; single lesions of 2–5 cm in diameter, or up to 3 tumors each ≤3 cm in size in patients assigned local ablation). The primary end point of this RCT is recurrence-free survival. Studies to investigate the combination of sorafenib and TACE in patients with intermediate HCC, or combinations of sorafenib with other targeted therapies in patients with advanced HCC, will also be of interest.

Box 1 The proposed purpose of combination therapy.

Concomitant therapy
- Improved effectiveness over monotherapy for the treatment of large or difficult lesions
- Improved effectiveness over monotherapy for the treatment of multiple lesions
- Improved effectiveness over monotherapy for the prevention of tumor recurrence

Sequential therapy
- Improved effectiveness over monotherapy for the treatment of large or difficult lesions
- Improved effectiveness over monotherapy for the prevention of tumor recurrence
- To slow tumor progression for patients awaiting liver transplantation
- To reduce tumor size to meet orthotopic liver transplantation criteria
- To allow for salvage transplantation in patients without proven malignant disease after liver resection if pathological findings (e.g. evidence of vascular invasion) indicate the patient is at high risk of tumor recurrence

Radiofrequency ablation combined with percutaneous ethanol injection

As with many anticancer treatments, the therapeutic effect of RFA decreases with increasing tumor size.[29,30] Combination therapy with RFA and PEI may be an effective treatment for tumors larger than 3 cm or those that are difficult to treat using RFA alone, particularly for lesions that are located near large blood vessels (heat losses associated with the cooling effect of blood flow attenuate the efficacy of RFA) or near the Glisson capsule. In these instances, ethanol can be injected into parts of the tumor where RFA is likely to be ineffective. This concomitant use of PEI can reduce the risk of RFA-associated complications, such as intraperitoneal bleeding and intestinal perforation.

An RCT by Zhang *et al*. investigated the efficacy of concomitant RFA plus PEI ($n=66$) versus RFA alone ($n=67$) in patients with a solitary HCC of less than or equal to 7.0 cm in diameter, or with up to three HCCs of less than or equal to 3.0 cm in diameter. Participants had no evidence of extrahepatic metastasis or tumor invasion into the major portal or hepatic vein branches.[43] Compared with patients who received RFA alone, patients who received the combination therapy had significantly improved survival at 3 years (58.4% vs 75.8%, respectively; $P=0.01$) and at 5 years (35.9% vs 49.3%, respectively; $P=0.03$). However, subgroup analysis revealed that only patients who received combination treatment for tumors between 3.1 cm and 5.0 cm in diameter had a statistically significant improvement in overall survival. The authors of this study suggested that the survival advantage was evident only in this subgroup because tumors larger than 5.0 cm in diameter are too large to be treated adequately with percutaneous techniques. Overall recurrence rates in this study were similar in both treatment groups, but local recurrence was significantly reduced in patients treated with combination therapy compared with those who received RFA alone (6% vs 20%, respectively; $P=0.01$).[43]

Percutaneous ablation combined with transarterial embolization or transarterial chemoembolization

Local-regional techniques such as PEI, RFA, TAE and TACE all have limitations when used alone. As mentioned previously, the effectiveness of RFA is generally reduced by increased tumor size. This effect is probably attributable to increased blood flow in large lesions, which leads to heat loss and incomplete ablation. Administration of TACE before RFA might reduce or eliminate this heat loss[44,45] and lead to an increased volume of coagulation necrosis, which enables effective treatment of larger tumors than is possible with RFA

Table 1 Characteristics of RCTs that have investigated combination TACE plus percutaneous ablation for the treatment of HCC.

Study	Treatment arms	Number of patients	Number of patients with Child–Turcotte–Pugh class A/B/C tumor	Tumor status	Follow-up (years)	Overall survival (%)
Bartolozzi *et al*. (1995)[47]	TACE + PEI versus TACE	26 27	14/12/0 11/16/0	3.1–8 cm; 1 nodule and a maximum of 2 satellites <3 cm; no PVT or ES	3	14.5 14.2 (NS)
Koda *et al*. (2001)[48]	TACE + PEI versus PEI	26 26	19/5/0 14/8/0	<3 cm; no PVT or ES	5	40.4 37.7 (NS)
Akamatsu *et al*. (2004)[49]	TAE + PEI or RFA versus PEI or RFA	22 20	14/8[a] 16/4[a]	<5 cm	3	82.4 82.2 (NS)
Becker *et al*. (2005)[50]	TACE + PEI versus TACE	27 25	17/10/0 22/3/0	65% of patients had a tumor >5 cm; no ES	2	38.7 18.0 (NS)
Cheng *et al*. (2008)[51]	TACE + RFA versus TACE only and RFA only	96 95 100	55/41/0 57/38/0 60/40/0	3.1–7.5 cm; ≤3 tumors; no PVT or ES	5	31 13 8 (P <0.001)

[a]In both these studies, the first number refers to patients with Child–Turcotte–Pugh class A and the second refers to those with Child–Turcotte–Pugh classes B or C disease. Abbreviations: ES, extrahepatic spread; NS, not significant; PEI, percutaneous ethanol injection; PVT, portal vein thrombosis; RCT, randomized controlled trial; TACE, transarterial chemoembolization; TAE, transarterial embolization.

alone. The authors of a systematic review[46] found 15 studies that evaluated the efficacy of TAE or TACE combined with PEI or percutaneous acetic acid injection for the treatment of patients with HCC. Three of these studies were RCTs; another seven had evaluated the efficacy of TACE combined with RFA (one of which was another RCT), and one study had evaluated the efficacy of TACE combined with percutaneous acetic acid injection. A meta-analysis of the four RCTs[47–50] revealed significantly lower mortality in patients with HCC nodules of any size who had received combination treatment (TAE or TACE plus percutaneous ablation) than in similar patients treated with monotherapy (TAE, TACE or percutaneous ablation). One limitation of this meta-analysis was the small size of the studies included; consequently, no definitive conclusions can be drawn from its findings.

Results from a 2008, randomized, phase III trial that involved 291 consecutive patients with 1–3 lesions of 3.0–7.5 cm in diameter, however, supported the findings of the above meta-analysis. This study demonstrated that combination therapy with TACE and RFA was superior to TACE or RFA monotherapy, with better overall survival and a higher complete response rate in patients receiving combination therapy compared with those receiving TACE or RFA alone.[51] During follow-up (median 28.5 months), the median survival times for patients treated with combination TACE and RFA, TACE monotherapy or RFA monotherapy were 37 months, 24 months and 22 months, respectively (P <0.001 for either monotherapy versus combination therapy). No significant difference was observed in frequencies of adverse effects in the three treatment groups. This RCT had several strengths, including its prospective, randomized design and collection of data on long-term survival. Importantly, this study demonstrated comparable safety profiles for combination treatment and monotherapies, and provided evidence of improved disease control and survival benefits for combination therapy over monotherapy. Together, these findings support the use of combination TACE and RFA as a treatment option for HCC.

Our own meta-analysis of four RCTs, which included the large 2008 RCT described above, revealed a significant survival benefit that favors combination treatment with TACE plus percutaneous ablation over TACE or percutaneous monotherapy (G Cabibbo *et al*., unpublished data). An overview of data from the RCTs that have investigated the use of combined TACE and percutaneous ablation for the treatment of HCC is shown in Table 1.

Neoadjuvant and adjuvant transarterial embolization and transarterial chemoembolization

The purpose of preoperative and postoperative TAE or TACE is to destroy small, undetected, intrahepatic metastases.

Neoadjuvant transarterial embolization and transarterial chemoembolization

Only two RCTs have evaluated the effect of TAE or TACE performed before hepatic resection in patients with HCC. In one of these studies, 97 patients with a solitary HCC of 2–5 cm in diameter underwent hepatectomy with ($n = 50$) or without ($n = 47$) preoperative TAE.[52] The findings revealed no significant differences in mortality or tumor recurrence between the treatment groups. The second RCT investigated patients with tumors of up to and including 10 cm in diameter.[53] The findings from this study demonstrated that patients who received TACE before hepatectomy ($n = 24$) had reduced actuarial survival compared with those who received hepatectomy alone ($n = 28$, $P = 0.03$). This reduced survival was associated with an increased number of surgical complications and need for delayed surgery. Although no significant difference was observed in disease-free survival between the two treatment groups, the incidence of extrahepatic cancer recurrence was higher in the combined-therapy group.[53]

Together, these studies demonstrate that the use of preoperative TAE or TACE does not improve patient survival, nor does it reduce tumor recurrence. We do not, therefore, recommend the use of preoperative TAE or TACE for the treatment of patients with HCC.

Adjuvant chemoembolization

Transarterial oil-based chemoembolization (TOCE) is preferred to TACE (which uses a gelatin sponge for arterial embolization), because oil embolization is less likely than sponge embolization to cause hepatic failure secondary to massive ischemic necrosis.

Only two RCTs have compared the efficacy of hepatectomy alone and hepatectomy followed by TOCE.[54,55] The first of these studies demonstrated a significant increase in overall survival in patients who received the combined therapy compared with those who underwent radical resection only ($n = 47$ in both groups; 4-year survival was 56.9% and 35.1%, respectively; $P < 0.01$).[54] In the second, smaller RCT by Izumi and colleagues, 50 patients were assigned to undergo hepatectomy followed by TOCE ($n = 23$) or hepatectomy only ($n = 27$).[55] As in the above RCT, adjuvant therapy in this study was associated with a significant improvement in disease-free survival (32% vs 12% at 3 years; $P = 0.02$). The median disease-free interval for patients who received adjuvant treatment was 852 days compared with just 485 days for patients who underwent hepatectomy alone. No significant difference, however, was observed in overall survival between the two groups.

Although these findings suggest that postoperative chemoembolization benefits patients who undergo hepatectomy for HCC, the data were obtained from only two, small RCTs. Large RCTs should be performed to confirm the efficacy of this combination therapy.

Transarterial chemoembolization combined with radiotherapy

Patients with HCC and tumoral thrombosis of the main trunk of the portal vein are considered poor candidates for TACE because this therapy can worsen hepatic function. Local radiotherapy has some effect on the main tumor and on tumoral thrombosis of the portal vein and, therefore, combination therapy with local radiotherapy and TACE might be a reasonable therapeutic option for these patients.

The effects of combined TACE and local radiotherapy versus TACE alone have been compared in seven nonrandomized studies. A pooled analysis of data from these studies demonstrated that patients with neoplastic portal vein thrombosis who received combination therapy with TACE plus local radiotherapy had improved survival compared with those who received radiotherapy alone.[46] These data were not obtained from RCTs, however, and the lack of high-quality studies in this field makes firm conclusions difficult to reach.

MANAGEMENT OF PATIENTS AWAITING LIVER TRANSPLANTATION

The length of time that patients with HCC can wait before liver transplantation can be considerable, and while waiting they face the risk of developing contraindications to transplantation, or even death. Strategies have been devised to monitor and attempt to slow the growth and progression of tumors so that they stay within the accepted criteria for transplantation. Some management strategies for patients with HCC do not involve treatment, for example surveillance only or the prioritization of certain patients for transplantation; other options involve treatments such as

TACE, percutaneous ablation, or combinations of TACE and RFA, radiotherapy and resection. Management strategies that involve treatment are associated with risks, including vascular injury, invasion of the tumor into extrahepatic tissues, and liver decompensation. These risks should, therefore, be compared with the risk of cancer progression and tumor dissemination. The risk of tumor seeding after RFA, however, is very low,[56] and such seeding does not seem to worsen the prognosis of patients with HCC who are awaiting transplantation.

Several studies have shown the benefit of local-regional therapies, such as RFA, PEI, TAE and TACE, in containing tumor progression before liver transplantation. The guidelines of the American Association for the Study of the Liver Diseases recommend the use of such therapies (RFA or PEI for small tumors and TACE for compensated cirrhosis) if the expected waiting time is longer than 6 months.[9] However, we stress that no RCTs have investigated the use of these different strategies for the management of patients with HCC who are awaiting liver transplantation.

Transarterial chemoembolization before liver transplantation

The use of TACE before liver transplantation for HCC has been investigated by several groups;[57–59] however, at present the benefits of this approach have not been demonstrated. The popularity of the procedure can be attributed to its relatively minimal invasiveness and its demonstrated beneficial effects on survival in patients with unresectable HCC.[36]

In patients with decompensated HCC, TACE can induce liver failure and death and this treatment should, therefore, only be used in patients with relatively preserved liver function.[37] Furthermore, a study by Liou *et al.*[60] showed that lung metastases were more frequent in patients treated with TACE than in patients treated with the best supportive care, which suggests that TACE might not be the optimum first-line treatment in patients awaiting liver transplantation. In that study, however, factors that predisposed patients to lung metastases included the presence of a solitary tumor larger than 10 cm in diameter, multiple tumors with a main lesion larger than 5 cm in size, or diffuse HCC—all of which are conditions that preclude transplantation. In our opinion, additional studies with extended follow-up are needed to clarify the risk of extrahepatic tumor recurrence in patients after TACE.

Percutaneous ethanol injection before liver transplantation

No studies have systematically evaluated the potential benefit of PEI used before transplantation. One study has shown improved disease-free survival in patients who received a combination of PEI and TACE before transplantation compared with patients who did not receive such therapy (82% vs 65%, respectively, after 48 months).[61] Although no controlled studies have investigated the effects of PEI in patients awaiting liver transplantation, findings from theoretical models suggest that PEI may be a reasonable option for the management of patients who have been awaiting liver transplantation for longer than 6 months.[62]

Radiofrequency ablation before liver transplantation

As mentioned earlier, the risk of tumor seeding associated with RFA is minimal,[56] and should not affect tumor progression in patients with HCC. Although one report suggested that the rate of seeding after RFA was 12.5%,[63] this result has not been supported by findings from several subsequent studies. For example, a large, multicenter study reported an extremely low rate of tumor seeding in patients after RFA (0.5%).[64] Of note, any puncture-related seeding that occurs during RFA is usually restricted to poorly differentiated and peripheral tumors that cannot be approached via nontumoral liver tissue.[63–65]

Downstaging before liver transplantation

Downstaging is a controversial rationale for neoadjuvant treatment. The aim of downstaging is to achieve a partial tumor response, so that a tumor that initially exceeds the Milan criteria for liver transplantation is reduced and maintained within the transplantation criteria for at least 6 months.[66] Effective tumor downstaging may indicate the presence of a relatively nonaggressive tumor. A prospective study has successfully demonstrated the ability of TACE to downstage tumors that are initially larger than 3 cm in diameter, and to result in good post-transplantation survival.[67] Although

findings from this study are supported by those of a 2008 prospective trial[68] (which demonstrated excellent post-transplant outcomes achieved by tumor downstaging with resection, PEI, TACE, and percutaneous, laparoscopic or open RFA) this benefit has not been confirmed by other investigations that used TACE or RFA.[69,70] We believe several reasons account for these conflicting results, including the length of time before transplant, the extent of downstaging, the patient's age, and the duration of follow-up after transplantation.

CONCLUSIONS

Despite the use of aggressive local treatments such as PEI, RFA, TAE and TACE, tumor recurrence and the development of extrahepatic metastases continue to have a marked effect on survival for patients with HCC. Several steps are required to improve the effectiveness of HCC therapy, including the implementation of screening programs to increase the number of patients diagnosed in early stages of disease, improving patients' access to specialized, multidisciplinary treatments (i.e. pharmacological, interventional, radiological and surgical), and the utilization of staging systems to predict prognosis (Figure 1).

Combinations of local treatments, for example RFA plus PEI, or TACE plus PEI, have demonstrated survival benefits in some groups of patients. By contrast, the preoperative or postoperative use of chemoembolization has been shown to be ineffective, and may actually complicate surgical interventions. Local-regional treatments might, however, be useful to control tumor burden in patients who are awaiting liver transplantation. Many of these findings, however, are based on small, nonrandomized studies; consequently, an unmet need remains for prospective studies—and, in particular, RCTs—to evaluate the effects of these treatment modalities on HCC. The development of highly effective systemic therapies for patients with HCC also remains a challenge, and combinations of effective systemic therapies with local treatments such as RFA, TAE or TACE holds the promise of further improvements in patients' outcomes. The potential benefit of combining sorafenib with other promising approaches, including surgical resection, RFA, TACE and liver transplantation, is currently being investigated in RCTs, and their results are eagerly awaited.

KEY POINTS

- Hepatocellular carcinoma (HCC) is a malignancy that is difficult to treat, and is increasing in prevalence worldwide
- Curative treatment options for HCC (e.g. liver transplantation, surgical resection, percutaneous ablation) are available if the disease is diagnosed at an early stage
- Despite the use of aggressive local treatments, tumor recurrence and the development of extrahepatic metastases continue to have a significant effect on the overall survival of patients with HCC
- Combination treatment with radiofrequency ablation (RFA) plus percutaneous ethanol injection can achieve improved survival compared with the use of RFA alone in selected patients
- Combined treatment with transarterial chemoembolization and RFA improves survival compared with transarterial chemoembolization or RFA monotherapy
- Further, well-conducted, randomized controlled trials to examine the effectiveness of different multimodal approaches are urgently needed

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