

New modalities of treatment for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide. Managing HCC is difficult. However, there are many treatment options available such as liver transplantation, radiotherapy, different ablative techniques, surgery, trans-arterial chemoembolization (TACE) and systemic therapy. These treatments did not show the promising responses and the recurrence rate is still high. On the other hand, there are some new treatments such as immunotherapy, gene therapy, combination of different therapies, Chinese traditional therapies and new targeted therapies. The aim of this study is to review both the recent changes in the common therapies and newly developed therapies of HCC.

Keywords carcinoma, hepatocellular, treatment, combined modality therapy

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide. It is the fifth most common cancer in men and the ninth in women. In addition, the incidence rate is almost equal to the mortality rate.¹ Many risk factors are known for HCC, such as age, gender, alcohol, HCV, HBV, and non-viral chronic liver disease. Moreover, currently among these risk factors HBV and HCV are the most important ones.² Managing HCC is difficult. However, there are many treatment options available such as liver transplantation, radiotherapy, different ablative techniques, surgery, trans-arterial chemoembolization (TACE) and systemic therapy.³ These treatments did not show the promising responses and the recurrence rate is still high.⁴ On the other hand, there are some new treatments such as immunotherapy,⁵ gene therapy,⁶ combination of different therapies, Chinese traditional therapies and new targeted therapies.⁷ The aim of this study is to review both the recent changes in the common therapies and newly developed therapies of HCC.

Methods and Materials

A focused literature review was performed in Medline, Embase and Cochrane Library to find the recent studies on the treatment of HCC. We limited our search to recent 5 years, although we bring a few numbers of older studies while we do forward-backward citation. In addition, we only evaluate the studies which were mainly about the human species and were published in English. For including studies in our review, we performed a double phase assessment. In the first phase, we considered only titles and abstract and in the second we assessed the full text to find out the relevance of the studies to our work. Based on this explanation, we included 4622 references. After removing duplicates, 3788 references were assessed in the first phase. Then, 1665 studies were excluded. As of the remaining studies, 387 of them were removed in the second phase. Among 1349 remaining ones, 173 studies were selected to include in this study. An adapted PRISMA flow diagram shows the process (Fig. 1). Our exclusion criteria for both phases were: complications, biomarkers, prediction and progression factors, case

reports, imaging, preclinical studies (in vitro and animal studies), cost and economy, risk factor and some other non-related subjects to the therapy of HCC.

Below, we briefly explain different therapies of the HCC considering new changes and recent modalities and treatment options.

Chemotherapy

One of the chemotherapy multi resistance tumours is HCC. It has a very low survival and despite the huge amount of scientific work in this matter, it appears that systemic chemotherapy is unsuccessful in HCC treatment.⁸ Doxorubicin is the chemotherapy of choice from past, but the effect of this drug on survival rate was equal or inferior, comparing with other chemotherapy drugs in several clinical trials.^{9,10} There were also a systematic review of 800 patients and 13 trials applying doxorubicin chemotherapy compare to other chemotherapies. The results showed chemotherapy in advanced HCC have poor effects. Doxorubicin monotherapy is not inferior to comparing with combination multiple drug chemotherapy or biological agents.¹⁰ Using Platinum-based chemotherapy with Oxaliplatin like PIAF schedule (Cisplatin + Interferon + Doxorubicin + 5-FU), minimizing toxicity and is better to be used for older patients. Though the overall survival (OS) is not significantly different from doxorubicin.¹⁰ Nonetheless, there are not randomized trials of Platinum agents in HCC systemic treatment, FOLFOX have uncertain benefits comparing with Doxorubicin.¹¹ Sorafenib therapy is an alternative palliative therapy that will be discussed later in this article.

TACE

TACE is a standard palliative, down staging therapy in patients with progressive inoperable HCC since 1970. It has been used in intermediate HCC that we have few choices of treatment.^{12,13} The main concept of chemoembolization is to emboli the hepatic artery which is the main hepatic tumour vessel. This procedure may cause tumour death without affecting normal tissue.¹⁴ In addition, a chemotherapy agent delivered to hepatic vessel. There are not a standard protocol for the choice of chemotherapy

drug or dosage, or rate of usage.¹⁵ Anthracyclines (daunorubicin, doxorubicin, epirubicin), platinum-based agents (cisplatin, lobaplatin, miriplatin), mitomycinC, and 5-fluorouracil is the chemotherapy drugs used in TACE. There are not noteworthy superiority reported on using specific chemotherapy agent in TACE.¹³ A systematic review of 15 studies comparing TACE with conservative management had reported that the patients with portal vein branch invasion and well liver function may achieve optimal advantage from treatment with TACE.¹⁶ Another systematic review on five randomized trials compared TACE with and without chemotherapy treatment. The results revealed no superiority of using chemotherapy with chemoembolization and the adverse effect of treatment is even higher in the TACE group compared to TAE.¹⁷ There are also alternative choices like balloon-occluded transarterial chemoembolization (B-TACE) using miriplatin (a lipo-philic anticancer drug) and gelatin particles. A significant higher local node treatment in B-TACE with the miriplatin group in comparison with routine TACE was reported in a non-randomized trial.¹⁸ In addition, no significant difference was reported, between TACE-miriplatin plus epirubicin and TACE-miriplatin group in the efficacy of therapeutic and adverse effects.¹⁹ Although lack of a randomized controlled trial (RCT) is noticeable in this issue.

DEB-TACE

Doxorubicin-eluting beads (DEBs) is an embolization device with TACE treatment. It is used in hypervascular tumours and emboli vessels with simultaneous administration of tumour located, controlled, sustain released dosage of chemotherapy which is mainly doxorubicin. These beads consist of vinyl alcohol and sulfonic acid groups with chemotherapy agents in different sizes.²⁰ This method is widely available since 2006, and the treatment effects are assumed to be superior compared to TACE.²¹ There are two systematic reviews on our search which compare the DEB-TACE with TACE. These studies, approximately include same studies with very inconsistent results. In addition, there are just few RCTs in this issue. These studies are not reporting a significant difference on survival rate.^{22,23} Other studies are non-randomized trials or retrospective researches assessing the registries or have a low sample size or could not evaluate survival rate, which makes the interpretation and decision of the reported results imprecise.^{24,25} However, a recent non-randomized controlled trial reported non-significant difference in survival rate between TACE and DEB-TACE in non-operable HCC patients. As the number of TACE treatment needed is higher than DEB-TACE with the same survival rate, DEB-TACE is more preferred by both clinicians and patients.²⁶ A meta-analysis in 2013 with seven studies (693 participants) reported no significant difference between the two procedures in hard outcomes. It has been also mentioned the need of running more RCT on this issue for better decisions,²⁷ while a meta-analysis in 2014 included seven studies (700 participants). It has reported a better tumour response with DEB-TACE. Although the survival rate was reported to not change significantly after 3 years and adverse side effects are also similarities between the two procedures.²¹

Gelatin Sponge Particle TACE

Gelatin sponge is an embolic agent generally used for embolization therapies of various diseases over 30 years. The size of embolic agent has direct influence on embolic effects. Gelatin

sponge particles are around $1-1.5 \times 1-1.5 \times 2$ mm. It has been made from either Spongel or Gelfoam sheets.²⁸ There are three embolization effect classifications named “short term”, “medium term” and “long term”. Gelatin sponge micro particles (GSMs) have medium effect.²⁹ Using the embolization component in TACE procedure increases the rate of necrosis of the main tumour and Gelatine sponge particles is used frequently in embolization procedures.³⁰ Gelatin sponge microparticles in a rabbit liver tumour were assessed in 2014. The results suggested the usage of GSMs-TACE comparing to c-TACE group and hepatic arterial infusion (HAI) group have higher concentration of chemotherapy drug with slow drug release.³¹ Human research also showed good tolerance on GSMs and the OS rate was 100% in six months and 87.5%, in one year.³² Other parallel studies confirmed the safety and effectiveness of gelatin sponge particle TACE for treatment of the Barcelona-Clinic Liver Cancer (BCLC) stage B HCC patients.³²

Hepatic Resection vs. TACE

Up to now, the curative choices of HCC are liver transplant, hepatic resection and radiofrequency ablation. Liver transplant appears to be gold standard treatment, but it is restricted because of the low number of donors. Hepatic resection is a better choice than radiofrequency ablation for the OS. In addition, for palliative treatment options we have TACE and sorafenib. TACE is generally used for HCC patients further than the BCLC stage A classification.³³ Two systematic reviews and meta-analysis compared the hepatic resection with TACE in OS of patients further than the BCLC stage A classification. The results of both are parallel and reported a significant overall one- and three-year better survival in hepatic resection group.^{33,34} Although, the lack of RCT in this issue was mentioned in both systematic reviews.

Cytokine Induced Killer Cell

Recently, immunotherapy is a new modality in cancer treatment. Cytokine-induced killer (CIK) cells are effective adoptive cell-based immunotherapy treatment. The concept of this treatment is to stimulate body immune response against tumour cells. So, the adverse side effects of chemotherapy and surgical procedures are minimized. CIK cells are natural killer like T cells and express both the T cell marker CD3 and the NK-cell marker CD56. The idea of applying CIK cells in cancer therapy was first reported by Schmidt-Wolf et al in 1991 on an animal model. In 2010, Stanford Medical University established an international registry on CIK cells (IRCC) for better application of this treatment based on clinical evidence;³⁵ particularly, researchers from china performed RCTs on combination CIK with TACE for HCC treatment. It is reported that the combination therapy improves quality of life and prevent cancer recurrence.³⁶ There is a systematic review comparing CIK-TACE with TACE alone in the HCC cancer treatment. Two RCTs and four non-RCT studies were included with 428 patients. The OS and progression-free survival (PFS) rates are better in the group treated with CIK-TACE.³⁵

Liver Transplantation

In the category of curative treatments for HCC and cirrhosis, liver transplant is a choice. In this procedure, liver tumour and underlying cirrhosis and possible risk of recurrence after resecting tumour will be removed. HCC patients will be

candidates for liver transplant based on tumour size and nodule numbers. Milan criteria are particularly used for choosing HCC patients for liver transplant (a solitary tumour nodule up to 5 cm or three nodules less than 3 cm). Because of the limited number of liver grafts, HCC patients must be selected. Vascular invasion, high alpha fetoprotein concentration, aggressive biology of tumour, multifocal large size tumour and having other comorbidities are the other exclusion criteria for this treatment.³⁷⁻⁴⁰ Fei Teng et al had described one-, three- and five-year survival rate of HCC patients after liver transplant: 78.9%, 53.2% and 46.4%, respectively.⁴¹ However, the lethal nature of HCC in addition to low source of liver graft makes it difficult to run RCTs and the lack of evidence is tangible in this concern. There are different criteria available for selecting HCC patients for liver transplant apart from Milan criteria. The most popular one is University of California, San Francisco (UCSF). No significant difference was reported between applying these two criteria. Other criteria are the United Network for Organ Sharing (UNOS), Tokyo, Kyoto, Kyushu, Hangzhou and Up-to-seven. The detail on these criteria are available elsewhere.^{10,42}

Down staging of HCC patient's candidate for liver transplant is unavoidable because of the high dropout rate for the duration of waiting for liver transplant. The main interventions for down staging are TACE, percutaneous ethanol injection (PEI), and radiofrequency ablation (RFA) and Sorafenib therapy in addition to TACE or DEB-TACE. However the lack of evidence in this area is obvious.⁴² However, current guidelines do not recommend a liver transplant for patients outside Milan criteria.⁴³

Salvage Liver Transplantation (SLT)

To minimize the waiting list dropout rate, alternative treatments are used in this period, such as local therapies and surgery. It has been proposed for patients with small HCC and preserved liver function. The efficacy of salvage transplantation that is primary resection before transplantation is assessed by Poon RT et al in 2002. Salvage transplantation reduces recurrence or worsening of liver function in waiting time for liver transplant.⁴⁵ The positive point of surgery specially laparoscopic surgery is the curative concentrating of resection, pathological analysis of tumour for vascular invasion, tumour differentiation, number of nodules affected and improving quality of life. The negative point of laparotomy is adhesion in the surgical site which makes next liver transplantation operation difficult. However, laparoscopic or robotic approaches result in lower adhesions in surgical site. Although liver function and size of tumour of patients do not let clinicians to use this approach in all patients.⁴⁶ A systematic review with 1508 patients was conducted in 2013 on short and long term outcomes of SLT. Although the short outcomes like duration of operation is significantly higher in SLT than primary liver transplant, the OS rate after 1, 3 and five years were not different.⁴⁷

Surgical resection

Liver resection surgery is performed for nearly six decades.⁴⁷ Surgical liver resection is a curative resection of the entire tumour in microscopic level with free of tumour cutting surface. Surgical resection is the treatment of choice in non-cirrhosis HCC in early stages. The frequency of non-cirrhosis HCC in Asia is about 8 times higher than western countries. In other HCC patients' surgical resection may cause liver failure. So, these patients must be selected carefully for surgical

treatment.⁴⁸ Prognostic factors for liver resection are tumour size, high level of alpha fetoprotein, micro and macro vascular invasion, and underlying liver disease such as cirrhosis.⁴⁹

There are two types of resection; anatomical resection, which is wide liver resection beyond the borders of tumour and non-anatomical resection which is used in hepatic dysfunction and remains the most possible liver residue. There are some controversies reported on the type of resection. Some studies suggested survival benefits from anatomic resection,⁵⁰ while the others reported no significant benefit.⁴⁹ A systematic review suggested anatomic resection of liver approves survival and diminish recurrence comparing to non-anatomical but the studies included in this meta-analysis are not randomized trials.⁵¹ Liu PH in 2014 showed surgical resection with TACE in HCC patients beyond Milan Criteria. They had reported a noteworthy improved long term survival with surgical resection.⁵²

LAPAROSCOPY

The first laparoscopic liver surgery was performed four decades after open surgical liver resection. Currently, with more technical improvement in laparoscopic surgery, more malignant liver tumour resection is carried out with this procedure.⁵³ There are few observational studies and a systematic review that compare open surgery and laparoscopic short-term and long-term outcomes on HCC and there are not noticeable differences between two surgical methods.⁵⁴ The systematic review was conducted in 2012 and included 10 observational studies. The overall complication rate was lower in the laparoscopic group. The recurrence rate of HCC, 5-year survival, and 3-year survival was not significantly changed between two procedures.⁴⁷

Radiotherapy

The role of radiotherapy (RT) is limited in patients with HCC due to low tolerance of normal liver tissue to radiation. However, new techniques in image guidance, breathing motion reduction strategies and appropriate dosimetry have been introduced for better local control and decreasing liver toxicity.

Radioembolization

Radioembolization (RE) delivers a high dose radiation through hepatic artery. Small microspheres loaded Yttrium-90, a B-emitter isotope is used in the case of RE. Two common 90Y devices are Thera-Sphere (BTG International, London, United Kingdom) which is a glass microsphere, and SIR-Sphere (SirtexMedical, Sydney, Australia) which is a resin microsphere. According to the literature, both microspheres have similar outcomes.⁵⁵ Radiation segmentectomy and boosted radioembolization are considered two novelties in the field of RE.

Radiation Segmentectomy

The combination of microcatheter technology and the localized radiation emission properties of 90Y microspheres introduce a novel treatment called radiation segmentectomy. Since ablation and resection are not suitable for the lesion located near critical structure, radiation segmentectomy is an appropriate way to overcome this drawback.⁵⁶ Michel et al conducted a follow up, multicenter study to assess the efficacy of radiation segmentectomy. Radiation segmentectomy was defined as 90Y microsphere infusion limited to ≥ 2 Couinaud

segments. Dosing was achieved by infusing a calculated lobar dose into a segmental tumour-feeding vessel. Therefore, segmental doses are higher than lobar doses by the ratio of lobar/segmental volumes. The results show, complete response (CR) in 47%, and partial response (PR) in 39% of patients.⁵⁷ A retrospective follow up study showed a CR of 95% of patients who received radiation segmentectomy.⁵⁸

Boosted Radioembolization

Boosted radioembolization is a novel concept for HCC. It is a personalized therapy in which the priority is given to tumour dosimetry rather than liver dosimetry. In this method, a predictive dosimetry model, based on technetium-99m microaggregated albumin (MAA), single-photon emission computed tomography/computed tomography (SPECT/CT), is utilized to identify tumours that need boosted microsphere dosing for better response rate.^{59,60} In another retrospective cohort study, Garin et al showed that boosted radioembolization based on MAA SPECT/CT caused prolonged OS for HCC portal vein thrombosis (PVT) patients, without increasing liver toxicity.⁶¹

Intensified modulated radiotherapy (IMRT)

IMRT is an advanced three-dimensional conformal radiotherapy (3D-CRT) that allows greater control of dose distribution. Since, it can change the intensity of individual rays within each beam, it can cover the treatment volume to concave tumour shape.⁶² Helical tomotherapy (HT) and volumetric-modulated arc therapy (VMRT) are two advanced forms of IMRT.

HT

It is a highly advanced radiotherapy, in which a gantry 6-MV linear accelerator is rotated continuously through 360° around the patient using tens of thousands of narrow beams. It integrates both IMRT and image guided radiotherapy (IGRT). IGRT system of HT is a daily mega-voltage computed tomography image guidance.⁶³ Three cohort studies showed a survival benefit and efficacy in utilizing HT for HCC patients.⁶⁴⁻⁶⁶ In a recent retrospective comparative study of 118 HCC patients, conducted in 2016, median survival in patients treated with HT was significantly more than with 3D-CRT.⁶⁷

VMRT

It is an advanced form of IMRT that unlike fixed-field radiation methods treat the tumour from all angles by rotating the beam around the patient. Rapid Arc TM (Varian Medical System, Palo Alto, CA) is a variation of VMRT.⁶⁸ In radiotherapy of HCC patients, targeted volume is greatly affected by respiratory motion. Active breathing coordinator (ABC) is a solution for gaining a better target volume. In order to determine the feasibility of rapid arc (RA) in association with ABC, Gong et al conducted a study of 12 HCC patients. 3D-CRT, IMRT and RA plans were designed and ABC was used for better assessment of target volume. The report resulted in better dose delivery and an accurate target volume besides shortening treatment time for RA.⁶⁹ 4D-CT is another solution to achieve better target coverage. 4D-CT scanning synchronizes CT image with respiratory cycle and is able to predict tumour movement. Another study involved 10 patients showed RA with 4D-CT or 3D-CT associated with ABC can effectively deliver accurate target volume compared with 3D-CT with free breathing.⁷⁰

Stereotactic Body Radiotherapy (SBRT)

When ablation or TACE fails, SBRT can be considered as an alternative therapy. SBRT delivers high radiation to focal HCC and decreases radiation induced liver toxicity by sparing other tissues.⁷¹ SBRT by Cyberknife® is a new technology for treatment of liver lesions that delivers 100 to 200 photon beams of 6 MV.⁷² For appropriate detection it requires gold fiducial markers in the periphery of tumour. A recent study, evaluated the possibility of implantation of gold fiducial markers and the imaging technique it requires. The important role of radiologist in implantation and applying sonographic guidance were concluded.⁷³

Helical Intensity-Modulated Radiotherapy-based Stereotactic body Radiotherapy

HT is an alternative for delivering SBRT, in a recent paper published in 2016, the phase I trial was conducted by Jun et al. to evaluate the feasibility and toxicity of helical intensity-modulated radiotherapy (HIMRT) based stereotactic body radiotherapy (SBRT) in eighteen HCC patients. At a median follow up of 28 months for living patients, an OS rate of 69.3% and a well-tolerated toxicity was concluded.⁷⁴

Differential Hepatic Avoidance RT (DHART)

In HCC patients with a high degree in the liver function heterogeneity as for cirrhosis patients, conventional RT methods cannot spare radiation to functional liver regions and it may lead to radiation induced liver disease (RILD) to overcome this drawback. Stephen et al. introduced a new modality for RT that is called differential hepatic avoidance RT (DHART). In this technique SC SPECT (Sulphur colloid Single photon emission tomography) images were used to spare region of functional liver through the use of dose painting techniques in proton pencil beam scanning (PBS) and photon volumetrically modulated arc therapy (VMAT) RT. This initial study indicated that DHART is achievable with either photon VMAT or proton PBS therapy in HCC patients.⁷⁵

Varian Trilogy™

Varian Trilogy™ is an RT delivery system that deliver a highly conformal radiation beam to a mobile target. It utilizes real-time Position Management™ (RPM) for respiratory control and On-Board Imager (OBI) for image guidance.⁷⁶ A prospective cohort study showed an excellent treatment outcome with minimal toxicity for this RT delivery system.⁷⁷

Ablation

Ablative therapy is considered a treatment with high safety profile and local control. Radiofrequency ablation (RFA), microwave ablation (MW), laser induced tumour therapy (LITT) - all parts of thermal ablation- ethanol or acetic acid injection - as part of chemical ablation- cryoablation, brachytherapy, irreversible electro-poration (IRE), and high intensity focused ultrasound (HIFU) are all considered as ablative therapies. Here we discussed technical advances in utilizing RFA, MWA, brachytherapy and HIFU with a major focus on RFA.

RFA

Poor visualization is one of the complications of ultrasound (US)-guide RFA. Contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography (CECT), and magnetic resonance imaging (MRI) are alternatives for the guidance of

RFA. However, the short durations of the different vascular phases, absence of real-time imaging guidance and increased radiation exposure are the disadvantages of using these imaging techniques.^{78,79} To overcome these problems a method called “fusion imaging” or “real time virtual sonography”, that synchronizes real-time US and CT or MRI, is introduced.⁸⁰ Two cohort studies showed an excellent technical success rate, safety and effectiveness for RFA using fusion imaging.^{81,82}

Reduced energy diffusion is a complication observed in RFA using conventional electrodes. Utilizing internally cold (IC) electrodes and saline-enhanced RFA are two techniques to overcome this drawback. However, these two techniques have their own problems, including the limitation of overheating and the risk of heating and ablation of non-tumour containing area, respectively.^{83,84} Internally cooled wet (ICW) electrodes that have the ability of both techniques (IC electrode and saline-enhanced RFA) are developed as a solution to compensate the limitations of these techniques. In a study, utilizing modified ICW electrode showed the safety and effectiveness of the technique and a successful local control.⁸⁵ In a retrospective comparative study, including 165 patients, mean ablation volume was significantly greater and local tumour progression was significantly lower in patients treated with ICW electrodes compared with patients treated with IC electrodes.⁸⁶

Conventional monopolar RFA devices have several problems including; systemic symptoms because of exposure to a wide area of the body, long ablation time and causing burns. In contrast to a monopolar device in which the electrical current flows between the electrodes and the grounding pad, in a bipolar device the current flows between two electrodes. Besides compensation for monopolar device complications, the bipolar device is more sufficient and makes a large thermo-coagulation volume in a single ablation procedure. A multi-center open-label trial confirmed the efficacy and safety of The CelonPOWER System, which is a bipolar RFA device.⁸⁷

Incomplete peripheral ablation of the tumour is another drawback of utilizing monopolar device;⁸⁸ while, multipolar technique provides a probe inserted outside the parameters of target lesion (no touch technique) and allows ablation of the tumours from margin to center. This causes complete margin ablation.⁸⁹ The pathological examination of 59 nodules in a retrospective study indicates an improvement in the rate of complete necrosis in no-touch multipolar radiofrequency ablation compared with monopolar technique.⁹⁰

Placement of sodium hyaluronate solution onto the liver surface can be used as a procedure for RF ablation of HCCs located on the liver surface. It causes separating of liver from other organs during the procedure and decreases the damage to adjacent organs. A phase one study was conducted to assess the safety of intraperitoneal injection of the sodium hyaluronate solution. Complete ablation and observation of tumour recurrence in one of 28 patients indicated the safety and efficacy of the technique.⁹¹

Microwave Ablation (MWA)

MWA is a locoregional therapy that can be conducted with the guidance of US, CT or MRI. In a follow-up study, MWA was performed by using a real-time virtual navigation system. The technique effectiveness was 94.44%.⁹² Low power output and small-diameter ablation is one of the complications of MWA.⁹³ Water or gas antenna cooling has introduced a solution for making higher power microwave system.

A retrospective cohort study reported that after utilizing a gas-cold system for MWA, overall primary technique effectiveness rate and OS rate were 91.6 and 76%, respectively. The results showed the safety and efficacy of the technique.⁹⁴ Risk of tumour seeding is considered for subcapsular tumours achieving thermal ablation.^{56,95} In order to reduce the probable risk of tumour seeding and local progression after thermal ablation for subcapsular HCC, a technique called NO-touch wedge ablation, was described by Premal et al. The technique involved probe placement at multiple oblique sites tangential and adjacent to the tumour, to create a sufficient ablation zone that is inclusive of the subcapsular tumour and the required peritumoural margins. After complete ablation of eight tumours, at an average imaging follow-up of 244 days, one case of local recurrence was observed.⁹⁶ One of the limitations for US guided thermal ablation is suboptimal conspicuity of some subcapsular tumours or tumours located in hepatic dome, that may lead to causing damage to adjacent tissues.^{97,98} Artificial ascites and plural effusion introduced a solution for this drawback.⁹⁹ In a case-control study that the efficacy of MWA with artificial pleural effusion was evaluated. The analysis showed no statistical differences between case and control groups in the primary technique effectiveness and local tumour progression rates.¹⁰⁰

Brachytherapy

Brachytherapy is an ablative therapy that utilizes interstitial implantation of radioactive seeds and delivers high dose radiation in the target area. Two types of radioactive seeds are applied, one of them is high energy gamma emitter (e.g., cobalt-60 and radium-226) and the other is low energy chemicals (e.g., iodine-125 and palladium-103). Because of the high energy irradiation of the first type, low energy seeds became more common in the past decades.¹⁰¹ CT-guided high-dose-rate brachytherapy (CT-HDRBT) is a new modality in ablative technique that uses iridium-192 seed, inserted through catheters with CT guidance.¹⁰² Two retrospective cohort study conducted by Colletini et al. evaluated the clinical outcome of CT-HDRBT in HCC patients and showed the effectiveness of this therapy in local tumour control of lesions unsuitable for resection or thermal ablation.^{103,104}

HIFU

HIFU is a new ablative therapy in which a unique frequency of US wave of 0.8 to 3.5 MHz is used and can be focused at a distance from therapeutic transducer. The high focused energy is able to induce necrosis by increasing tissue temperature.¹⁰⁵ Poor visualization of HCCs during HIFU treatment is an obstacle. Hiroyuki et al. reported a study of HIFU ablation assisted using color Doppler for the treatment of HCC. The usefulness of this method was concluded from the study.¹⁰⁶ In another study conducted by Michele et al. magnetic resonance-guided focused ultrasound (MRgFUS) was assessed as a treatment for solid tumour in abdomen. The study resulted in the safety and feasibility of the technique.¹⁰⁷

Chinese Herbal Medicine

Chinese herbal medicine is a type of traditional medicine used in cancer therapy for a long time ago.¹⁰⁸ In the case of HCC, studies evaluated the mechanism of action of this medicine and also this therapy has been used in vitro, in vivo, and also in recent clinical trials.

Ruanjianhugan

Oral Ruanjianhugan (RJH) tablets which were made up of ten medicinal materials are kind of Chinese herbal medicine used in a 22-year followed up clinical trial study. Results indicated that long-term intake of RJH increases OS in small HCC after resection. Also, it has preventive effects on small HCC recurrence.^{2,102,109,110}

Systemic Therapy

Antiangiogenesis Agents

Tyrosine Kinase Inhibitors: Sorafenib. In the Chinese subset of GIDEON study in 2015, 338 patients were followed prospectively to assess the efficacy and safety of SORAFENIB. Median OS of Child-Pugh A patients were longer than Child-Pugh B patients. Adverse effects (AE) comparison showed serious AEs (25.0% vs. 23.0%) in Child-Pugh B patients. In overall, this study indicated that Child-Pugh B patients would be safely healed with sorafenib.¹¹¹

Adjuvant sorafenib. Currently, sorafenib has been used as an adjuvant therapy after curative resection in BCLC-stage three patients. It has been indicated that adjuvant sorafenib was safe and well tolerated. OS and DFS had increased significantly in this study.¹¹³

Sorafenib Combination

a. Sorafenib Plus Cytotoxic Chemotherapy Agents

Doxorubicin: results of a phase II study indicated that median OS, PFS and time to progression (TTP) favored sorafenib.¹¹⁴
GEMOX (gemcitabine plus oxaliplatin): a randomized phase II trial showed no significant difference of the OS.¹¹⁵

Oxaliplatin: results of a phase II trial indicated that there is no considerable difference of OS and TTP between two groups.¹¹⁶

b. Sorafenib Plus EGFR Inhibitors

Erlotinib: no survival benefit favored this combination in a phase III trial.¹¹⁷

c. Sorafenib Plus mTOR Inhibitors

Everolimus: this combination failed to show significant advantages rather placebo in a phase III clinical trial on 546 patients.¹¹⁸

Temsirolimus: different phase I-II trials resulted in no favorable benefits of this combination.¹¹⁹⁻¹²¹

d. Sorafenib plus MEK inhibitors

Refametinib: results of first line study revealed good efficacy of this combination. Disease control rate (DCR) and overall response rate (ORR) were 43% and 5% respectively.¹²²

Regorafenib. Regorafenib is a multi-kinase inhibitor which inhibits kinases in angiogenesis and oncogenesis. It has been tried as a second line therapy after sorafenib in phase I and II clinical trials. The ORR and the DCR of regorafenib were 3% and 72% respectively. Drug-related adverse effects consisted of hand-foot skin reaction, diarrhea, fatigue, hypothyroidism, anorexia, hypertension, nausea and voice changes. Median OS was 13.8 months. Thoroughly, regorafenib was well tolerated and has antitumour activity on HCC.¹²³

Brivanib. Another TKI is brivanib which is a dual TKI receptor of VEGFR (VEGF receptor) and fibroblast growth

factor receptor (FGFR).^{110,124} BRISK-FL trial of 1150 patients was performed to compare brivanib and sorafenib. Results of this trial favored none of them. OS, TTP, ORR, DCR was the same. Somehow, brivanib showed more toxicity than sorafenib. BRISK-PS trial, which compared brivanib with placebo failed to give a significant increase in OS.¹²⁵

Axitinib. It is a selective Tyrosine Kinase Inhibitor of VEGFR-1,-2 and -3. Results of a clinical trial of 202 patients showed no significant improve in OS in comparison with sorafenib.¹²⁶

Sunitinib. Sunitinib, a multitargeted tyrosine kinase inhibitor, have been used in the treatment of HCC. Cheng et al. performed a phase III clinical trial on 1074 patients due to compare sorafenib and sunitinib. Their results showed no significant difference between OS in two groups while AEs of sunitinib were higher.¹²⁷

Linifanib. Linifanib is a new ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases, which presents no activity against representative cytosolic tyrosine kinases and serine/threonine kinase.¹²⁸ A phase III randomized clinical study on 1035 patients from 28 countries was performed to compare the efficacy and tolerability of linifanib versus sorafenib. The results showed similar OS of sorafenib and linifanib. Sorafenib showed more safety than linifanib but TTP and ORR advocated linifanib.¹²⁸

MET-TKI

Tivantinib. Tivantinib, a C-MET TK inhibitor, is used as a second line therapy of HCC in clinical trials. This drug is used as monotherapy and also in combination with sorafenib. In both types of monotherapy and in combination with sorafenib, safety results were acceptable.¹²⁹ Combination of tivantinib and sorafenib in phase II clinical trial turned back sorafenib resistance.¹³⁰ In another phase II clinical trial of tivantinib, survival and disease control, increased and AEs of the drug were manageable in addition, grade 3 neutropenia and myelotoxicity were observed as the side effects in some studies.¹³⁰

Cabozantinib. A randomized phase II trial used this drug as the second-line therapy. Results showed median OS as 15.1 months and DCR as 68%.¹³²

Monoclonal Antibodies

Bevacizumab. Bevacizumab attaches to VEGF-A which is the main form of VEGF in blood. Two phase II trial studies have been done in order to assess this monoclonal antibody effect on HCC. ORR was 13% and 14% interestingly, but this drug failed to develop because of safety concerns.^{133,134}

Ramucirumab. It is a human IgG1 monoclonal antibody. Ramucirumab targets VEGFR-2. In the REACH phase III trial on 565 patients, no significant OS improvement was observed except in patients with alpha fetoprotein (AFP) levels more than 400 ng/mL.¹³⁵

Chemotherapy

Doxorubicin. Doxorubicin has been recently compared to the oxaliplatin-flourouracil (FOLFOX regimen) combination in a phase III trial. OS benefits extended (6.5 versus 4.9 months) in the FOLFEX arm and ORR was significantly higher (8.2% versus 2.7%).¹¹⁴

GEMOX (gemcitabine plus oxaliplatin). Results of several phase II clinical trial studies showed that ORR (20%) and DCR (65%) were extended and drug safety profile was favorable.¹³⁶

Immunotherapy

Tremelimumab. Anti-CTLA4 monoclonal antibody, tremelimumab, is a novel immune-based therapy used in HCC patients. In addition to good safety profile, this drug showed acceptable ORR and DCR (18% and 76% respectively).¹³⁷

PD-1 Blocking Antibodies

Viral therapy. JX-594 has currently been used in a phase II study as an immunotherapeutic and oncolytic vaccine. High dose levels of this vaccine showed longer OS in comparison of low dose levels.¹³⁸

Lenalidomide. A phase II trial study has been tested Lenalidomide-a thalidomide analogue- in advanced HCC patients after sorafenib failure. Median OS and PFS were 7.6 and 3.6 months, respectively.¹³⁹

TGF- β inhibitors. TGF- β inhibitor was conducted on 109 patients in a phase II trial. Median OS and TTP were 9 and 3 months, respectively.¹⁴⁰

A. Personalized Therapy

Two different strategies can be used in this approach:

Liquid biopsy

Plasma DNA. We can identify cancer-associated changes by using both of these methods. Detection of point mutations, detection of aberrant DNA methylation, and the detection of chromosomal aberrations are detailed methods of molecular-change identification.¹⁴¹

Combination Therapies and Their Comparison

Combination of Minimally Invasive Therapies

Iodine-125 implantation plus radiofrequency ablation. Radiation therapy needs oxygen to destroy tumour cells. However, in the center of a tumour, lack of oxygenation reduces the effects of this therapy. This would be solved by heating the tumour area which makes more blood supply and more oxygenation.¹⁴² In a clinical trial of 136 patients, combination of radiofrequency ablation and iodine-125 implantation was evaluated. This combination therapy reduced the rate of recurrence ($P = 0.004$). The combination group had better results in survival rate than RFA-only group. The result of this study showed that the combination of iodine-125 and RFA would be an efficient option for patient with small HCC.¹⁴³

Combination of RFA and CIK

It was reported that hyperthermia can cause stimulation and activation of the immune system.¹⁴⁴ In a clinical trial, 62 patients with primary HCC (ranged in diameter from 2 to 8) were enrolled. This combination was compared with RFA alone. All the complications were related to RFA. Examined therapy had a better PFS rate ($P < 0.0001$). The risk of recurrence rate was significantly lower for new therapy (HR = 0.136, 95% CI: 0.049–0.379). The function of liver in combination group did not change and had the same functionality before CIT infusion. Based on the results of that study, the combination of CIK and RFA was a promising treatment for HCC.¹⁴⁵ In a clinical trial by Wang X et al, the combination of CIK and RF hyperthermia was evaluated. Thirty one patients with advanced HCC were enrolled. In this study instead of intravenous perfusion of CIK, the investigators use intraperitoneal perfusion of cytokine, because it leads CIK in to tumour tissue

and makes the treatment more effective. Median TTP was 6.1 months and median OS was 8.5 months. The results showed that this combination therapy was an effective therapeutic choice for patients with advanced HCC.¹⁴⁶

Radiofrequency Hyperthermia and Conformal Radiotherapy

Assessing the combination of radiotherapy and hyperthermia is a field of interest. Conformal radiotherapy elevates the dose of irradiation in tumour and decrease receiving doses in normal tissue of the liver and cause low damage to normal tissue. Also, hyperthermia causes more blood flow to the tumour tissue, which has an additive effect on the outcome of radiotherapy.¹⁴² In study by Dong Y, short and long term of radiofrequency hyperthermia combined with conformal radiotherapy was investigated. Data were collected from 80 patients with primary advanced HCC. The patients were randomly assigned into two groups: experimental group and control group, each with 40 patients. Bilirubin, albumin, ALT and PT levels were the same between two groups before the treatments. However, after treatments bilirubin, ALT and PT were reduced more significantly in the experimental group ($P < 0.05$). Albumin was elevated in both groups but this change was significant in experimental group ($P < 0.05$). Combined therapy was much more effective than the other therapy ($P < 0.001$). Follow-up results demonstrated that the experimental group had significantly better OS and also lower recurrence rate ($P < 0.001$). Based on these results, the combination of radiofrequency hyperthermia and conformal radiotherapy has low damage to the liver and it is an effective treatment option for advanced HCC patients.¹⁴⁷

Percutaneous Ethanol Injection and Radiofrequency Ablation

Li et al, in meta-analysis compared the combination of PEI + RFA with PEI and RFA as monotherapy. This study analysed the results of 13 studies from different parts of the world. First of all in this study RFA and PEI were compared. Results showed that RFA has better function than PEI in improving OS. Recurrence rate did not have significant difference in two therapies. On the other hand, PEI shows more complete tumour necrosis than RFA. In comparison of combination of these two therapies with themselves, overall the combination therapy shows better results than RFA. In spite of good result in complete tumour necrosis for combination group, this difference is not significant.¹⁴⁸

Chemotherapy and Minimally Invasive Ablative Therapies

TACE and RFA. In a study effectiveness of a combined therapy of RFA and DEB-TACE was compared with the DEB-TACE procedure alone in treatment of single HCC. CR at 1 month was achieved in 80% of tumours. The group treated with the combination therapy showed a significantly lower 2-year recurrence (48.1% vs. 78.2%, $P < 0.001$) and significantly higher survival (91.1% vs. 60.6%, $P = 0.004$) than the group treated with DEB-TACE alone.¹⁴⁹ In a retrospective analysis of 20 patients with intermediate size HCC, the combination of DEB-TACE and MR-guided RFA was evaluated. All of the cases had child-Pugh class A and B liver function, no tumour metastasis and HCC with tumour size >3 cm. No major therapy-related complications were observed except for a sub capsular hepatoma which was seen in one patient right after the RFA. Median OS was 37.4 months. This combination seemed to be an effective therapy for patients with medium size HCC.¹⁵⁰

TACE and CIK and RFA. Retrospective analysis of patients with HCC showed that RFA + CIK + TACE had more

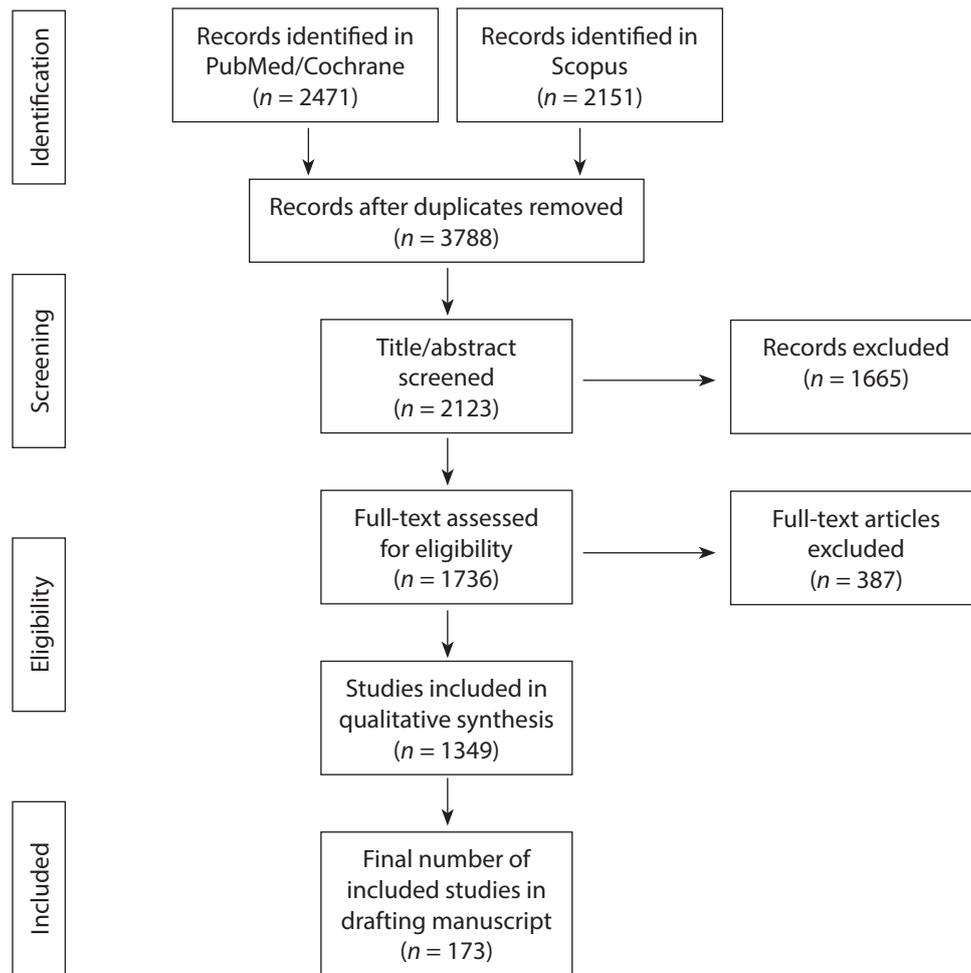


Fig. 1 The flowchart depicts the selection of studies for this review.

acceptable effect than RFA + TACE. Median survival time (ST) for the study group and the control group were 56 and 31 months, respectively which is statistically meaningful ($P = 0.023$). The results of this study demonstrated that CIK lower the risk of metastasis and recurrence in the study group and can improve the outcome of TACE + RFA.¹⁵¹

TACE and PVE and survival. In one RCT, 62 patients were divided into two groups, a group which had a combination of TACE and PVE and HIFU as a therapy and the other group had a combination TACE and PVE as a therapy. Nausea and vomiting were reported as a main side effect in both groups. However, in the experimental group after HIFU local pain was seen as a side effect in most of the cases. Response rate became 72% after adding HIFU to the therapy. This rate was higher than the response rate in control group (44%). Also, controlling time of HCC in study group was higher than the control group. Median survival for experimental and control group were 16 months and 10 months respectively. Also, the level of AFP was decreased in both groups, but in experimental group this happened in lesser scale than the control group and had significant difference ($P < 0.01$). This combination is a safe and effective treatment for advanced HCC.¹⁵²

Chemotherapy and Radiotherapy

One RCT conducted by Bush, et al. compared proton beam radiotherapy with TACE in treatment for HCC. Thirty six patients in TACE group received at least one TRACE with

additional TRACE for persistent disease and were treated with a mixture of ethiodol, carboplatin and doxorubicin with or without mitomycin. Thirty three patients in proton beam treatment group received the therapy to all parts of gross disease to a dose of 70.2 Gy. The 2-year OS for both groups was 59%. Median ST was 30 months (95% CI: 20.7–39.3 months). PFS survival was more in the proton beam treatment group (48% vs. 31%, $P = 0.06$).¹⁵³ In a meta-analysis conducted by Lobo, et al. clinical outcomes of transarterial radioembolization (TARE) and TACE in treatment of unresectable HCC were compared. In TACE group, 284 patients were injected chemotherapy into their liver tumours, while 269 patients in TARE group had an injection of β -emitting Yttrium-90. No significant difference was observed in survival for up to 4 years between the two groups (HR = 1.06; 95% CI: 0.81–1.46, $P = 0.567$). The patient treated with TACE needs at least one day of hospital stay, while TARE is an outpatient procedure.¹⁵⁴ In another meta-analysis by Zhang Y et al, different results were observed. They believed that TARE with Yttrium-90 had better OS, TTP and lower hospitalization time over TACE.¹⁵⁵ In a clinical trial, Jun Ma et al, evaluated the combination of TACE and Licartin on 341 patients. The major side effect of therapy in study group was thrombocytopenia, leucopenia and increased total bilirubin. All of the cases had stage III or IV HCC. It was reported that the efficacy of this combination therapy was higher in stage III patients. Researchers suggested this combination as a treatment for HCC patients.¹⁵⁶ In another

trial, this combination had acceptable outcomes for intermediate stage HCC and it was suggested as a therapeutic option for this stage.¹⁵⁷ In another study efficacy of the combination of TACE and brachytherapy was compared to TACE alone. The study group had combination of loboplatin-TACE and ¹²⁵I seeds as radiotherapy. DCR was higher in the study group ($P < 0.05$). Mean ST was 22.9 months for study group and 19.6 months for control group. Fever, pain and discomfort in liver area, nausea and vomiting and mild diarrhea were common complications in both groups. However, in the study group after ¹²⁵I implantation, liver function abnormalities and varying degrees of bone marrow suppression were observed. In this study, liver damage was low in the study group. This combination has efficacy for advanced HCC.¹⁵⁸ In another study combination of (DEBs)-based TACE and SBRT was evaluated. OS was remarkably higher in the TACE + SBRT group compared with the TACE-only group (33 and 20 months, respectively; $P = 0.02$). It can be a treatment for HCC with >3 cm tumour size.¹⁵⁹ In a retrospective study the effect of the combination of TACE + 3-DCRT + HIFU was evaluated. After the combination of TACE and 3-DCRT, HIFU was administered. Median ST and TTP were 26 and 9 months, respectively. Toxicity of this procedure was more common in cases with HBV and cirrhotic liver. Hepatic toxicities, gastrointestinal bleeding, and leukopenia were the major therapy-related toxicity of this combination, however for HIFU first- and second-degree skin burn were reported as major toxicity. This therapy is suggested for patients with unresectable HCC.¹⁶⁰

TACE and Gene Therapy

In two retrospective studies, the combination of adenovirus type 5 and TACE was compared to TACE monotherapy. Combination group had a better CR, PR and stable disease rate than monotherapy. In addition, this combination causes improvement in OS and PFS. It can be considered as an option for unresectable HCC.^{6,161}

Systemic therapy and Chemotherapy

Sorafenib and Chemotherapy

Recent studies have compared the effect of HIAC and sorafenib on advanced HCC. Results demonstrated that the median OS was better in HIAC-treated patients. HIAC can be a rational choice for patients with advanced HCC.^{162,163} However, it was observed that in cases with micro vascular invasion, sorafenib had a better outcome.¹⁶³ In a phase II trial by Cosgrove et al, safety and efficacy of sorafenib and DEB-TACE was evaluated. Fifty patients were enrolled. Most of them were male and had BCLC stage C HCC. Median survival for BCLC stages A, B and C was 45.6, 29.7 and 8 months, respectively. Cases within BCLC stage C HCC who had sorafenib therapy for more than 6 months had better ST. Complications of this combination were mostly related to sorafenib. The results demonstrated that this combination had safety and efficacy for patients with HCC, especially in cases with advanced HCC.¹⁶⁴

Other Systemic Therapies and TACE

In a clinical trial of 26 patients, the combination of Bevacizumab and TACE was evaluated. In this study, all of the cases had BCLC stage B or C HCC. In this study, median survival was 10.8 months. The result of this study demonstrated that this combination was an effective therapy for unresectable HCC.¹⁶⁵ In a retrospective analysis of 103 patients, combination

of sunitinib and TACE was assessed. Based on the results, this combination therapy elongates the survival period and postpones tumour progression and can be an option for advanced HCC.¹⁶⁶

Sorafenib and RFA

In a retrospective study the effect of Sorafenib and RFA was compared with RFA alone. Data were collected from 128 patients who had HCC within BCLC stage 0 to B1. Patients were equally divided in two groups. Sorafenib was administered after the RFA procedure. The recurrence rate was lower in the combination group. Median OS for RFA-sorafenib group and RFA group were 161.8 and 118.6 weeks, respectively. This combination reduced the recurrence rate. It may be an efficient therapeutic option for inoperable HCC.¹⁶⁷ In RCT the effect of Sorafenib and percutaneous radiofrequency ablation was examined. In another study, 62 patients were enrolled, and it was demonstrated that the effect of combination therapy was more efficient for medium-size HCC than RFA alone. This study showed the same results about recurrence rate.¹⁶⁸

Systemic Therapy and Radiotherapy

Radiotherapy and sorafenib. Nakazawa, et al. conducted a study to evaluate sorafenib and RT used in the treatment of unresectable HCC with major PVTT. OS was compared between cases with PVTT. There is no significant difference in the median survival (4.3 vs. 5.9 months; $P = 0.115$). After the propensity score matching ($n = 28$ per group), better survival was observed in the RT group than in the sorafenib group (median survival, 10.9 vs. 4.8 months; $P = 0.025$).¹⁶⁹ In another study YANG Y, et al evaluated the effect of cryotherapy plus sorafenib as a combination therapy for patients with advanced HCC. A total of 296 patients with HBV-related HCC in advance stage were enrolled and follow up for 2 years. The authors believe that the curative mechanism of sorafenib had a synergic effect on the effect of local cryoRx. Median OS was 12.5 months for cases in the combination group while median OS for sorafenib-only group was 8.6 months. This combination is safe and effective therapy for advanced HCC.¹⁷⁰

Sorafenib and Radioembolization. Radiation causes activation of intracellular signaling pathway. Also, it causes the increasing of VEGF in the body. In a phase two clinical trial of 29 HCC cases within BCLC stage B and C, safety and efficacy of the sorafenib plus radiembolization was examined. For radiembolization a form of brachytherapy, 90Y-microsphere was administered. Twenty five percent of cases showed the best overall response and among these cases, 28% showed CR. Median OS for cases in BCLC stage B was 15.2 months and for BCLC stage C was 6.5 months. The results of this study confirmed this combination as a safe and efficient option for advanced HCC.¹⁷¹

Surgical resection and minimally invasive ablative therapies. For small HCC, mainly there are two different therapeutic options. One of them is RFA and the other one is surgical resection (SR).^{172,173} In recent meta-analyses, it has shown that for small HCC (≤ 3 cm), SR is more efficient than RFA.^{172,173} In small HCC the one-, three- and five-year OS rate is higher in patients who had SR as a treatment option.^{172,173} The rate of local recurrence of HCC in SR group was lower than RFA group.¹⁷³ Also, for single nodular HCC, SR will be a suitable choice but for multi nodular HCC, RFA is a better choice, because of surgical complications.¹⁷² Performing RFA

by laparoscopic approach shows similar results in OS of patients as SR but the rate of local recurrence of HCC is still higher.¹⁷³

Conclusion

In summary, recent changes in managing of HCC have shown a trend in using minimally invasive and noninvasive options instead of hepatic resection and transplantation. New technologies in ablative devices, radiotherapy and chemotherapy have improved the accuracy and efficacy of these treatments. In addition, using immune system, gene therapy and new targeted

therapy agents have shown the high potential of cellular and molecular mechanisms in managing HCC. However, more RCTs are needed to evaluate the effect of these therapies. Moreover, the combination of different sort of therapy has become popular recently. Many researchers all over the world have reported the benefit of the majority of these combinations. However, in these cases more studies are needed to prove the advantage of this kind of therapy over current curative options.

Conflict of Interest

No one of the authors have any conflict of interest. ■

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