The history of interventional therapy for liver cancer in China
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ABSTRACT

In China interventional therapy of liver cancer started in the 1980s. It is well-known that Professor Lin Gui is the founding father of Interventional radiology. Under the leadership of Lin Gui and other professors, interventional therapy of liver cancer has swiftly progressed in China. Indeed, TAI, TAE, TACE and ablation therapy have witnessed great innovations in hardware facilities, technical means, and therapeutic philosophy, while incorporating Chinese characteristics. As with the development of combined interventional therapy in China, interventional treatment of liver cancer has gradually started the process of precision and individualization. Actually, multidisciplinary, multimodal, and polymorphic treatments will be the most suitable pattern for liver cancer in the future, among which combination of interventional therapy with targeted, immunological treatments and information technology (IT) tools may bring a revolutionary breakthrough in liver cancer treatment.

Keywords: liver cancer; history; interventional therapy; embolization; ablation; multi-modal individualized treatment

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INTRODUCTION

Liver cancer is one of the most common malignancies in the world, with a high incidence of 780,000 new yearly cases. It is well-known that China is a country with a high burden of hepatitis. Meanwhile, the continuous rise of hepatitis incidence increases the hepatocellular carcinoma (HCC) burden, contributing to the fact that hepatocellular carcinoma patients in China account for about 50% of all cases worldwide. Therefore, liver cancer treatment has become the focus of medical investment in China (1). Most liver cancer patients show atypical progression, and are in advanced stage at diagnosis. Such cases can only receive non-surgical treatments, resulting in a surgical resection rate of only about 20% to 25%. Even in patients suitable for surgical resection, the 5-year recurrence rate is as high as 70% (2). Therefore, in recent decades, interventional therapy for liver cancer has emerged with the characteristics of minimal invasion, high efficiency, reduced side effects and good repeatability, and has gradually become an important treatment option in liver cancer. Although interventional therapy for liver cancer in China started relatively late, it quickly developed and now greatly influences the world. This article systematically reviews the development of interventional therapy for liver cancer in China.

In 1953 Seldinger invented arterial cannulation, and in 1964 Dotter reported the successful catheterization of the superficial femoral artery using coaxial catheterization, which represented the beginning of interventional radiology. However, it was in the 1970s that vascular intervention was introduced in China. In 1979, Lin Gui presented selective angiography for the diagnosis of hepatocellular carcinoma in China (3), and proposed that the interventional technique could also be used in the treatment of liver cancer. Then, Lin Gui carried out a series of animal and clinical studies on arterial embolization and published “Experimental liver and renal artery embolization and its clinical application” in 1981 in the Chinese Journal of Radiology (4), promoting interventional therapy for liver cancer in China. In 1985, Lin Gu proposed the dual blood supply theory of liver cancer (5-7), which laid the theoretical foundation for interventional therapy in liver cancer. In addition, Li Linsun in the 1980s multiple treatises and books on vascular intervention, attempting to promote the development of interventional therapy in China.

HEPATIC ARTERY INFUSION CHEMOTHERAPY (TAI)

TAI is the basic and one of the earliest techniques of interventional therapy in liver cancer. As early as the 1980s, TAI had become an important palliative treatment option for patients diagnosed with unresectable liver cancer (8). Its efficacy has been improved with the development of suitable regimens for arterial drugs and the understanding of their pharmacokinetics. For example, in 2017 hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin was applied in advanced hepatocellular carcinoma patients, and to some extent improved prognosis, with several patients even achieving complete remission (9). In addition (10), several guidelines have recommended TAI for colorectal liver metastases, establishing the irreplaceable usefulness of TAI in the treatment of liver metastases. Infusion pump implantation also made this therapeutic means more
HEPATIC ARTERY EMBOLIZATION (TAE) AND HEPATIC ARTERIAL CHEMOEMBOLIZATION (TACE)

Compared with TAI, TAE and TACE are more widely applied in the field of liver cancer in China. In 1990 Luo Pengfei proposed scheduling hepatic arterial chemoembolization (LP-TAE) with the administration of chemotherapeutic drugs, e.g. lipiodol and gelatin sponge (14, 15), and initially confirmed that lipiodol-based hepatic arterial chemoembolization (cTACE) is effective and safe in small HCC and could prolong survival in massive HCC. Based on these findings, he emphasized the advantages of super-selective chemoembolization (16), and proposed a complete filling method for interventional treatment (17), in order to improve efficacy in liver cancer. Jia Yuchen assessed treatment outcomes in 468 patients with primary liver cancer receiving different interventional treatments in 1993, and found significantly improved curative effect in the lipiodol and gelatin sponge embolization group compared with the artery perfusion chemotherapy group, confirming the important status of cTACE in the treatment of liver cancer (18). In 1994, Han Guohong systematically evaluated hepatic segmental arterial chemoembolization, which yields better a curative effect and less side effects during cTACE. In addition, Han Guohong further explored the mode and outcome of lipiodol deposition after chemoembolization (19-21), and found that lipiodol selectively accumulates in areas rich in blood supply, providing a theoretical basis for evaluating cTACE efficacy. In 2006 Cheng Yongde systematically discussed the issues related to TACE treatment of refractory liver cancer, which contributed to solving the clinical problems of interventional therapy in liver cancer, and earned the Shanghai Medical Science and Technology Award (22). Xu Ke applied the arsenious acid-lipiodol emulsion in the treatment of primary liver cancer in 2004 and showed a definite therapeutic effect, with less side effects; this is expected to further enhance the efficacy of cTACE (23, 24). In 2017, Zhao Ming proposed the concept of target-ed-intratumoral-lactic-acidosis (TILA) TACE, which is expected to achieve stronger and more effective tumor cytotoxicity by changing the acidic tumor microenvironment based on cTACE. It is therefore obvious that lipiodol constitutes a traditional embolic agent with good functions of embolism and angiography but lacks good drug-carrying ability, and its deposition in tissues is not stable.

To overcome the insufficiency of lipiodol embolism and further improve TACE efficacy, new embolic agents have gradually emerged, including microspheres, drug-eluted microspheres, radioactive microspheres, and others. Chen Qinghua is one of the first doctors studying microsphere embolization in the treatment of liver cancer. In 1994, it was confirmed in animal models that hepatic artery embolization of microspheres significantly affects liver cancer (25), and microsphere embolization has gradually been introduced into clinic. Compared with lipiodol, microspheres are more stable and present a better carrier-effect, which might lead to improved therapeutic effects. In 2015, Zou Yinghua developed iodipin-loaded microspheres, which allows their detection by X-ray and CT, making clinical interventions safer and more convenient (26). On the other hand, drug-eluted microspheres have been rapidly developed in China. Stable embolization and drug pump function make drug-eluted microspheres more cytotoxic to tumors. A number of clinical studies have shown that drug-eluted microspheres exhibit better efficacy in the treatment of liver cancer (27, 28). Many Chinese professors have assessed new drug-loaded microspheres/particles, with great success. Bletilla granules, Curcuma aromatica oil microspheres, pingyangmycin-loaded ion exchange microspheres and doxorubicin-loaded sodium alginate microspheres show certain therapeutic effects in animal experiments and clinical application (29-31). In 1996, Feng Gansheng assessed arterial embolization of bletilla granules in liver cancer therapy, and obtained better embolic efficacy compared with gelatin sponge particles, with an average survival period 19.8 months (32). Further studies found that bletilla granules might cure liver cancer by inhibiting tumor angiogenesis (33). In addition, arterial embolization of radioactive microspheres is of great significance for the treatment of metastatic colorectal cancer in the liver, and significantly improved the benefits of systemic chemotherapy. Indeed, radioactive microspheres have been studied for a long time in China. In 1992, Yan Zhiping summarized the rationale and application of radioactive microspheres (34), and performed embolization of yttrium glass microspheres in 18 patients diagnosed with liver cancer in 1994, obtaining good effects (35).

Based on the above findings, TACE treatment of liver cancer in China has been greatly developed and widely applied. The emergence of new materials, equipment and technologies, such as large digital plate DSA, microcatheter, guide wire, balloon microcatheter (36-38), makes precise TACE treatment of liver cancer possible. In recent years, driven by the development of biomaterials, many professors, e.g. Xu Ke, have developed nanoparticle drug delivery systems to selectively locate the tumor site and perform targeted therapy. Besides, such systems can also be combined with gene therapy to achieve greater effects (39).

ABLAUTION

In the 1980s, a group of doctors led by Luo Pengfei noticed that intratumoral injection of chemical agents, such as anhydrous ethanol and acetic acid, can achieve complete necrosis in small cell hepatocellular carcinoma; therefore, they gradually introduced chemical ablation in liver cancer. In the 1990s, physical ablation became a major tool for non-surgical treatment of liver cancer.
Chen Minhua introduced radiofrequency ablation for liver cancer in the late 1990s (40), and performed several studies to assess its efficacy and complications, also highlighting the significance of contrast-enhanced ultrasound in radiofrequency ablation of liver cancer. Meanwhile, Dong Baowei introduced the microwave tumor ablation technology in China and further improved it. Accordingly, Liang Ping further explored the value of ultrasound-guided microwave ablation in the treatment of liver cancer in 1997 (41). Compared with radiofrequency ablation, microwave ablation was shown to have higher efficiency and wider necrosis range, and was quickly developed. Lv Mingde and Xie Xiaoyan performed more in-depth studies of liver cancer ablation (42), and performed clinical trials from 2002 confirming that ultrasound-guided thermal ablation has good local therapeutic effects and improved three-year survival rate in early-stage liver cancer (43). In addition, although Chen Min-shan and Ma Kuan-sheng were hepatobiliary surgeons, they also attempted to promote thermal ablation therapy for liver cancer treatment in China. In 2005, Chen Min Shan carried out a randomized controlled study comparing surgery and percutaneous radiofrequency ablation. The final results showed that compared with surgical resection, percutaneous radiofrequency ablation has the same therapeutic effect in small cell hepatocellular carcinoma and even better short-term effects with tumor size ≤ 3 cm, thus laying an irreplaceable basis for thermal ablation in the treatment of liver cancer (44). Recently, Xu Xuenin combined cryoablation and radiofrequency ablation into a multi-modal ablation therapy system, allowing doctors to accurately control the range and effect of ablation; this is of great significance for liver cancer treatment. In 2014, Huang Jinhua used 30% hydrochloric acid infusion during radiofrequency ablation to efficiently expand the scope of ablation (45), for the treatment of large liver cell cancer and cancer originating from the caudate lobe.

As one of the physical ablation methods, cryoablation has its own advantages in the treatment of liver cancer. In 2005, Guo Zhi applied cryoablation in 26 cases of large cell hepatocellular carcinoma and obtained reduced tumor load in short term as well as increased quality of life (46-48). The latter authors suggested that cryoablation significantly improves the anti-tumor immune response in the human body and ameliorates liver function, promoting the development of cryoablation for liver cancer.

The HIFU ablation system invented independently by Chinese scientists could also be used for thermal ablation of tumors (49). Wang Zhibiao was one of the pioneer physicians using HIFU in China. Since the 1990s, he has explored the mechanism of HIFU, using it to treat liver cancer in 13 patients (50). Finally the latter study showed that treating liver cancer with HIFU was effective and feasible, indicating that applying this technology would provide a new non-invasive clinical treatment option for liver cancer, which could help strengthen the international influence of China in the field of interventional therapy for liver cancer.

In recent years irreversible electroporation technology (IRE) has gradually attracted interventional physicians. Actually compared with the radio frequency and microwave ablation methods, there is no heat sink effect during IRE. In addition, IRE would not cause injury to collagen rich tissues, including blood vessels, nerves and the bile duct, and is extremely suitable for ablation in dangerous sites (51). Because of these advantages, doctors like Zhang Xin, Ning Zhouyu and Lai Longxiang applied IRE in the treatment of advanced liver cancer, with accumulated clinical experience (52, 53).

Another non-vascular interventional therapeutic option for liver cancer also included brachytherapy, but had a short history in China and was not applied in clinical therapy until 1998 when the China Institute of Atomic Energy successfully developed radioactive I²⁵³ and PD¹⁰³. In spite of this, with help from researchers such as Zhang Fujun, liver cancer treatment with radioactive particles has been gradually promoted (54). Radioactive seed implantation has better safety than ablation and can be used to treat specific liver cancers such as tumor around the portal vein as well as portal vein tumor thrombosis (55-57), improving patient prognosis.

With the development of digital information technology represented by computers and network technologies, interventional therapy of liver cancer in China would become digitized and intellectualized in future. Digital three-dimensional reconstruction can transform two-dimensional CT and MRI images into three-dimensional images, which allow for preoperative visualization planning and may help achieve intraoperative real-time three-dimensional navigation. An intraoperative digital temperature control system can accurately monitor and adjust the ablation temperature, effectively enhancing treatment efficacy and ablation controllability. Indeed, medical big data is an important development direction in the future. Massive high-quality medical data on one hand can be used to guide and standardize operations in primary hospitals. On the other hand, data can be entered into artificial intelligence to construct robot operating systems for the interventional treatment of liver cancer; even full artificial intelligence diagnosis and treatment are expected to be feasible in the future.

INTerventional Combination Th-ERAPY

Liver cancers in China mainly consist of large cell liver cancer, and are prone to local recurrence and metastasis. Although interventional means are increasingly available to physicians, a single interventional therapy is usually unable to meet the clinical demands, and two or even more combined interventional techniques and sequential therapy have gradually become a breakthrough in improving pa-
tient prognosis. In the late 19th century, a dual intervention- 
al treatment strategy was proposed for large liver cell can-
cer, with repeated percutaneous transhepatic intratumoral 
 injection of anhydrous ethanol and lipiodol after arterial 
chemoembolization (58). Clinical studies revealed that 
such strategy significantly alleviate necrosis in large cell 
 liver cancer. In 2003 Wu Peihong confirmed the efficacy 
and advantages of TACE followed by radiofrequency abla-
tion in the treatment of patients with advanced liver cancer, 
providing a basis for combined interventional therapy in 
 liver cancer (59). Then, an increasing number of studies 
have shown that combined interventional therapy has ob-
vious advantages over single interventional therapy, e.g. 
TACE combined with brachytherapy for liver cancer, 
TACE combined with endovascular ablation for portal vein 
tumor thrombus. It is apparent that interventional combina-
tion therapy has become an important component of liver 
cancer therapy. What’s more, many researchers further 
completed and innovated this strategy. Wang Jianhua com-
bined $^{125}$ I radioactive particle scaffolds with TACE to treat 
liver cancer with portal vein tumor thrombus, with good 
short-term effects (60). To improve large cell liver cancer 
treatment, Huang Jinhua performed hepatic arterial embo-
lation and multi-source microwave ablation simultane-
ously under guidance by a three-dimensional visualization 
system (61). In this way, the side effects of chemotherapeu-
tic drugs could be avoided while increasing ablation effi-
ciency, providing a viable treatment regimen for patients 
with large cell liver cancer.

Because of progress in technology and concept, inter-
ventional therapy for liver cancer has gradually stepped 
into the door of individualized therapy; compared with 
drug treatment limited by gene polymorphism and variabil-
ity, interventional therapy has improved universality and 
stability.

**MULTI-MODAL INDIVIDUALIZED TREATMENT**

Although a diversity of techniques and methods in in-
terventional therapy for hepatocellular carcinoma allow 
physicians to achieve individualized treatment to some 
extent, interventional therapy has obvious defects. First, 
treatment cannot evaluate and address minimal 
residual disease. Currently, ablation therapy can only reach 
the evidence-based safety margin of the tumor, which is 
obviously not sufficiently "accurate". Secondly, intervenga-
tional therapy, after all, is only a partial or regional treat-
ment, and not suitable for liver cancer patients with multi-
ple metastases. Finally, some complications in patients 
could not be handled by interventional physicians. There-
fore, multidisciplinary, multimodal, and polymorphic ther-
apy will be the most suitable pattern for liver cancer in the 
future. Since early 21st century, many professors have em-
phasized that interventional therapy should be organically 
combined with radiotherapy, systemic chemotherapy, sur-
gical treatment, biological gene therapy, and traditional 
Chinese medicine to further improve patient prognosis in 
liver cancer (62). Professor Cheng Yongde explored the 
combination of interventional therapy and immunotherapy, 
using arterial perfusion of interleukin 2 (IL-2), lympho-
kine-activated killer cells (LAK), and tumor necrosis factor 
(TNF) to treat liver cancer for improved curative effects 
(63).

Targeted therapy is a powerful tool for interventional 
physicians in China. Sorafenib has been formally incorpo-
rated into treatment regimens for hepatocellular carcinoma 
by the China health and family planning commission. In 
2011, a study confirmed that TACE combined with Soraf-
enib has good long-term effects in advanced liver cancer 
(64), with the two therapeutic modalities complementing 
and reinforcing each other from a mechanistic angle (65).
In addition, a series of new targeted drugs, such as 
Regorafenib and Apatinib, could also be used in mono-
therapy or multimodality therapy of liver cancer.

In recent years, immunotherapy has attracted wide atten-
tion in the multimodality treatment of cancer. Indeed, as 
early as 2002, Chinese scientists reported the association 
of immunity and interventional therapy (66-68). Some even 
attempted to treat small cell hepatocellular carcinoma with 
radiofrequency ablation combined with arterial infusion of 
CIK cells (67), but beneficial responses from patients were 
not obtained. However, the development of immune 
checkpoint inhibitors (CTLA-4, PD-1/PD-L1) opened a 
new area for cancer immunotherapy. Currently, many med-
ical centers in China focus on the local (interventional) + 
systemic (immunomodulatory) treatment model. Although 
evidence is not strong for now, it is obvious that this model 
is revolutionizing the treatment of liver cancer.

With years of dedication and hard work of many pio-
neers, interventional therapy for liver cancer can be at-
tributed a glorious history, and excellent traditions and 
standards have been inherited. Currently, interventional 
therapy in China develops brightly and rapidly, but only 
caution and introspection could help solve the existent 
problems and achieve steady progress in the future. First, 
the clinical guidelines of interventional therapy and physi-
cians in China still need to be unified, to ensure proper 
qualification of interventional physicians and the applica-
tion of interventional therapy in primary hospitals. Mean-
while, interventional treatment of liver cancer remains an immature technique, with reduced usefulness 
in many cases. Therefore, interventional therapy 
should be closely combined with targeted/immunological 
therapies as well as information technology, to promote 
diagnosis and treatment in liver cancer for a new milestone.

**REFERENCES**

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA 
Cancer J Clin 2015; 65: 87-108.
1. Takayama T, Sekine T, Maknushi M, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet 2000; 356: 802-807.
2. Lin G. [Diagnosis of primary hepatic carcinoma by selective angiography (author's transl)]. Zhonghua Fang She Xue Za Zhi 1979; 13: 129-132.
3. Lin G. [Experimental embolization of hepatic and renal arteries and its clinical application (author's transl)]. Zhonghua Fang She Xue Za Zhi 1981; 15: 241-243.
4. Lin G. Blood supply and microvascular manifestations of metastatic liver tumors. Tumor 1984; 4: 152-154+190-194.
5. Zhang X, Feng Y, Wu T, et al. Therapeutic effect of hepatic artery infusion chemotherapy for unresectable primary liver cancer. Chinese Journal of Clinical Oncology 1986; 6.
6. Lyu N, Lin Y, Kong Y, et al. FOXAI: a phase II trial evaluating the efficacy and safety of hepatic arterial infusion of oxalaplatin plus fluorouracil/leucovorin for advanced hepatocellular carcinoma. Gut 2018; 67: 395-396.
7. Leal JN, Kingham TP. Hepatic artery infusion chemotherapy for liver malignancy. Surg Oncol Clin N Am 2015; 24: 121-148.
8. Jiang L, Shi L, Zhao J, et al. Efficacy and safety of continuous infusion of fluorouridine and dexamethasone in treatment of chemotherapy-resistant colorectal cancer liver metastases via arterial port-catheter system. Chinese Journal of Clinical Oncologists (electronic edition) 2014; 2: 211-215.
9. Li M, Wu W, Yin Z, et al. Clinical application of percutaneous artery port-catheter implantation in the treatment of abdominal tumor. Journal of Interventional Radiology 2014; 8: 739-742.
10. Wu Z, Li Q, Li L, et al. Application of percutaneous artery port-catheter implantation system in interventional therapy of advanced liver tumor. Journal of Practical Radiology 2000; 3: 173-174.
11. Luo P, Shao P, Guan Y, et al. Application of lipiodol hepatic arterial embolization in the treatment of 83 hepatocellular carcinoma patients. Cancer 1990; 4: 295-297.
12. Luo P, Shao P, Zhou Z, et al. Efficacy of LP-TAE in 18 cases of small liver cancer. Journal of Practical Radiology 1990; 4: 169-172+225.
13. Ye X, Wang S, Zhou D, et al. Superselective hepatic artery iodine chemotherapy embolization of hepatocellular carcinoma in 20 cases. J Oncol 2007; 2: 153-154.
14. Luo P, Chen X. Complete filling in interventional therapy of liver cancer. Chinese Journal of Radiology 1996; 2: 6.
15. Jia Y, Liu Q, Ye H, et al. Therapeutic effects of different interventional treatments for hepatocellular carcinoma (A report of 468 cases). Journal of Interventional Radiology 1993; 1: 5-8.
16. Han G. Hepatic segmental arterial chemoembolization in treatment of liver cancer. Foreign Medicine (Clinical Radiology Volume) 1994; 5: 258-261.
17. Han G, Guo Q, Guo Y, et al. Compare lipiodol accumulation, persistence and disappearance in liver cancer with angiography, CT and pathology after hepatic arterial chemoembolization. Chinese Journal of Medical Imaging 1994; 3: 158-162.
18. Jia Y, Liu Q, Ye H, et al. Therapeutic effects of different interventional treatments for hepatocellular carcinoma (A report of 468 cases). Journal of Interventional Radiology 1993; 1: 5-8.
19. Han G. Hepatic segmental arterial chemoembolization in treatment of liver cancer. Foreign Medicine (Clinical Radiology Volume) 1994; 5: 258-261.
20. Han G, Guo Q, Guo Y, et al. Compare lipiodol accumulation, persistence and disappearance in liver cancer with angiography, CT and pathology after hepatic arterial chemoembolization. Chinese Journal of Medical Imaging 1994; 3: 158-162.
21. Han G, Guo Q, Huang G, et al. Mechanism of lipiodol retention in hepatocellular carcinoma after hepatic arterial chemoembolization. Medical Journal of Chinese People's Liberation Army 1994; 2: 139-141.
22. Ji Y, Chen Y. Hepatic arterial chemoembolization in the treatment of refractory liver cancer. Journal of Interventional Radiology 2006; 12: 705-706.
23. Shao H, Xu K. Experimental research progress in the treatment of liver cancer with arsenic trioxide. China Journal of Cancer Prevention and Treatment 2005; 4.
24. Shao H, Xu K, Su H, et al. Clinical observation of arsenious acid-lipiodol emulsion in interventional treatment of hepatocellular carcinoma. China Journal of Cancer Prevention and Treatment 2004; 6.
25. Chen Q. Experimental study on therapeutic effect of hepatic artery embolization microspheres on transplanted hepatocellular carcinoma in rats. Journal of Interventional Radiology 1994; 2: 93-95.
26. Meng WJ, Lu XI, Wang H, et al. Preparation and evaluation of biocompatible long-term radiopaque microspheres based on polyvinyl alcohol and lipiodol for embolization. J Biomater Appl 2015; 30: 133-146.
27. Jiang S, Li G, Zhou Z, et al. Evaluation of the clinical effect of CalliSpheres drug-eluted embolic microspheres in advanced liver cancer. Chinese journal of interventional radiology (electronic edition) 2017; 3: 174-178.
28. Zhou G, Sun J, Zhang Y, et al. HepaSphere drug-eluted microsphere embolization in the treatment of 15 unresectable liver cancer cases Journal of Interventional Radiology 2015; 10: 869-872.
29. Xu K, Zou Y, Qi X, et al. Effect of transcatheter arterial chemoembolization with Alginate microspheres-Adriamycin on angiogenesis in rabbit hepatic VX2 carcinoma. Chinese Journal of Medical Imaging Technology 2010; 2: 217-220.
30. Yuan HY, Zhang Y, Fan TY. [Preparation and property study of ion-exchange embolic microspheres for delivering pingyangmycin]. Beijing Da Xue Xue Bao Yi Xue Ban 2009; 41: 217-220.
31. Zhou L, Yuan D, Zhang L, et al. Synergy and attenuation effect of compound curcuma aromatica oil microspheres in hepatic artery embolization of transplanted liver cancer in Rats. Journal of Nanjing University of Traditional Chinese Medicine 2010; 6: 447-449.
32. Feng G, Zhen C, Zhou R, et al. A comparative study on the curative effect of bletilla granules and gelatin sponge embolization in treating liver cancer. China National Journal of New Gastroenterology 1996; 3: 158-160.
33. Feng G, Li X, Zhen C, et al. Experimental study on inhibition of tumor angiogenesis by Chinese traditional medicine bletilla striata extract. National Medical Journal of China 2003; 5: 63-67.
34. Yan Z, Zhao H, Lin G. Radioactive microspheres brachytherapy in treatment of malignant liver tumors. Foreign Medicine (Radiation Medicine Nuclear Medicine Volume) 1992; 3: 130-134.
35. Yan Z, Lin G, Zhao H. Primary clinical application of 90yttrium glass microspheres therapy in hepatocellular carcinoma. Chinese Journal of Radiology 1994; 1: 55-57.
36. Nosher JL, Othman-Strickland PA, Jabbour S, et al. Changes in liver and spleen volumes and liver function after radioembolization with yttrium-90 resin microspheres. J Vasc Interv Radiol 2011; 22: 1706-1713.
37. van Malenstein H, Maleux G, Vandecavey V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011; 34: 368-376.

38. Bonomo G, Pedicini V, Monfardini L, et al. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. Cardiovasc Intervent Radiol 2010; 33: 552-559.

39. Zhen Y, Xu K. Development of nanoparticle vectors targeted therapy of hepatocellular carcinoma. Chinese Journal of Interventional Imaging and Therapy 2008; 4: 320-323.

40. Chen M, Li J, Li H, et al. Ultrasound-guided radiofrequency ablation of malignant hepatic tumors. Chinese Journal of Ultrasonography 2001; 7: 19-22.

41. Liang P, Dong B, Yu X, et al. Clinical application of ultrasound-guided microwave coagulation therapy for liver cancer. Chinese Journal of Oncology 1997; 6: 50-52.

42. Xie X, Lv M, Yin X, et al. Application of ultrasound-guided percutaneous radiofrequency ablation in treatment of liver cancer. Chinese Journal of Surgery 2003; 1: 26-29.

43. Lv M, Xuang M, Liang L, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial. National Medical Journal of China. 2006; 12: 801-805.

44. Chen M, Li J, Li H, et al. Comparison of effects of percutaneous radiofrequency ablation and surgical resection on small hepatocellular carcinoma. National Medical Journal of China 2005; 2: 12-15.

45. Yao W, Gu YK, Wang J, et al. Safety evaluation of a potential ablation agent-hydrochloric acid in the rabbits’ model. Ann Palliat Med 2014; 3: 250-262.

46. Guo Z, Ni H, Li B, et al. Experimental study about the effect of hepatic arterial blood flow on Argon-Helium cryoablation. In: The Fifth China Oncology Conference and the Seventh Cross-Strait Cancer Conference, International Tumor Cell and Gene Therapy Conference, The Second Sino-Japanese Conference on Tumor Ablation Therapy. Shijiazhuang, Hebei, China; 2008. p. 1. 2008.

47. Li X, Guo Z, Ni H, et al. Experimental study about the influence of cryoablation on immune function of liver cancer in mice. In: The Fifth China Oncology Conference and the Seventh Cross-Strait Cancer Conference, International Tumor Cell and Gene Therapy Conference, The Second Sino-Japanese Conference on Tumor Ablation Therapy. Shijiazhuang, Hebei, China; 2008. p. 2. 2008.

48. Guo Z, Xing W, Liu F, et al. Clinical application of Argon-Helium cryoablation system in the treatment of hepatocellular carcinoma. Chinese Journal of Radiology 2005; 2: 86-91.

49. Chen L, Wang K, Chen Z, et al. High intensity focused ultrasound ablation for patients with inoperable liver cancer. Hepatogastroenterology 2015; 62: 140-143.

50. Wu F, Chen W, Bai J, et al. Effect of high-intensity focused ultrasound on the patients with hepatocellular carcinoma: preliminary report. Chinese Journal of Ultrasonography 1999; 4: 20-23.

51. Lee EW, Loh CT, Kee ST. Imaging guided percutaneous irreversible electroproporation: ultrasound and immunohistological correlation. Technol Cancer Res Treat 2007; 6: 287-294.

52. Lai L, Su J, Lu H, et al. Clinical Efficacy of Ultrasound-Guided Irreversible Electroporation in Treatment of Advanced Hepatic Carcinoma. Chinese Journal of Bases and Clinics in General Surgery 2016; 6: 691-695.

53. Ning Z, Wang P, Chen H, et al. Pre-clinical Experimental Study of Animal Irreversible Electroporation Treatment for Liver Cancer. Journal of Chinese Oncology 2016; 1: 17-23.

54. Wei C, Yang W, Tan Q, et al. 125I radioactive seed implantation for primary liver cancer. Chinese Journal of General Surgery 2014; 7: 893-897.

55. Liu Y, Liu R, Wang P, et al. Percutaneous transcatheter implantation of 125iodine seeds for the treatment of liver cancer associated with portal vein tumor thrombus: initial experience in 19 cases. Journal of Interventional Radiology 2014; 1: 35-37.

56. Weng Z, Yang W, Jiang N, et al. Evaluation of CT-guided 125I seed implantation combined with transcatheter arterial chemoembolization in treating portal vein tumor thrombus associated with hepatocellular carcinoma. Journal of Interventional Radiology 2010; 7: 535-539.

57. Zhang F, Jiao D, Lu L, et al. CT-guided 125I seed implantation in the treatment of tumor thrombus in portal vein. In: The Fifth China Oncology Conference and the Seventh Cross-Strait Cancer Conference, International Tumor Cell and Gene Therapy Conference, The Second Sino-Japanese Conference on Tumor Ablation Therapy. Shijiazhuang, Hebei, China. 2008. p. 1.

58. Luo G, Su X, Luo P. long-term result of the repeated double interventional therapy in the treatment for massive hepatocellular carcinoma. Guangdong Medical Journal 1998; 10: 743-744.

59. Wu P, Zhang F, Zhao M, et al. Combination of transcatheter arterial chemoembolization and CT-guided radiofrequency ablation in treating advanced hepatocellular carcinoma. Chinese Journal of Radiology 2003; 10: 37-40.

60. Liu Q, Yan Z, Li S, et al. Linear 125I seed strand implantation combined with portal vein stenting and TACE for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Journal of Interventional Radiology 2009; 8: 593-595.

61. Huang S, Zhang T, Huang Z, et al. Initial Clinical Application of Transcatheter Arterial Chemoembolization Synchronously Combined with Multiple Microwave Ablation in the Treatment of Large Hepatocellular Carcinoma. Journal of Cancer Control and Treatment 2017; 2: 96-101.

62. Wu P. The role of radiofrequency ablation in multimodality therapy. Chinese Journal of Radiology 2002; 4: 6.

63. Yu X, Chen Y. Tumor necrosis factor in interventional treatment of advanced liver cancer Chinese Journal of Digestion 1993; 13: 309-310.

64. Chen S, Chen J, Xi W, et al. Transcatheter arterial chemoembolization combined with molecule-targeted sorafenib for the treatment of advanced hepatocellular carcinoma: observation of its long-term efficacy. Journal of Interventional Radiology 2011; 12: 958-960.

65. Wang W, Han G. Transarterial chemoembolization for hepatocellular carcinoma in the era of molecular targeted therapy. Infectious Disease Informatics 2012; 5: 308-312.

66. Li X. Experimental study about the influence of cryoablation on immune function of liver cancer in mice. Tianjin Medical University. 2008.

67. Wang Y, Chen M. Tumor immune escape and localized hyperthermia
68. Wu P, Zeng Y, Xia J, et al. Radiofrequency ablation combined with CIK transarterial infusion for the treatment of small hepatocellular carcinoma and micro hepatocellular carcinoma. In: The first Chinese conference on minimally invasive tumor therapy and the founding conference of minimally invasive tumor therapy committee in Chinese anti-cancer association. Guangzhou, Guangdong, China. 2005. p. 3.