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Review Article

Recent therapeutics in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a malignant tumor of hepatocytes. It is a common malignant tumor of the digestive system that often has initially hidden presentation followed by rapid progression. There are no obvious symptoms in the early stage of HCC. When diagnosed, most patients have locally advanced tumor or distant metastasis; therefore, HCC is difficult to treat and only supportive and symptomatic treatment is adopted. The prognosis is poor and survival time is short. How to effectively treat HCC is important clinically. In recent years, advances in medical technology have resulted in comprehensive treatment methods based on surgery.

Keywords: Hepatocellular carcinoma, recent therapeutics, medical oncology, surgery, treatment

Liver cancer is one of the most common malignant tumors worldwide. The incidence and mortality rates are ranked fifth and second, respectively [1]. There are about 750,000 new cases of hepatic carcinoma every year, with more than half occurring in China and the incidence is higher in men than in women. At present, treatment of HCC is divided into surgical and nonsurgical treatment [2].

The literature search strategy of the review was as follows: hepatocellular carcinoma, HCC, treatments, surgical treatment and nonsurgical treatment. Surgical treatment included resection, laparoscopic hepatectomy, robotic surgery, liver transplantation, transcatheter arterial chemoembolization (TACE), microwave ablation (MWA) and radiofrequency ablation (RFA). Nonsurgical treatments included proton therapy, immune-related therapy, molecular targeted drug therapy, chemotherapy, stereotactic body radiation therapy, traditional Chinese medicine, neoadjuvant therapy and nanotherapy. In recent years, advances in medical technology have resulted in comprehensive treatment methods for HCC. This paper reviews the latest therapeutics in related fields (**Figure 1**).

Surgical treatment

Resection

Early surgical resection is the first treatment for patients with noncirrhotic HCC, and the 5-year recurrence rate of small HCC without microvascular invasion is 50%-60% [3]. Lipoatrophy is one of the main features of nonalcoholic fatty liver disease [4]. Steatosis significantly increases the mortality and complication rate of patients after LR, making preoperative pathological evaluation of liver biopsy essential [5]. The European Association for the Study of the Liver (EASL) guidelines state that liver resection should be used for resectable isolated nodules without major vascular invasion and extrahepatic spread, regardless of size. The American Association for the Study of Liver Diseases (AASLD) guidelines advocate liver resection for patients with Child-Pugh class A disease with resectable T1 or T2 HCC (single tumor <5 cm, with or without vascular invasion, or multiple tumors <5 cm). The Asia Pacific Association for the Study of the Liver (APASL) consider all potentially resectable tumors to be free of extrahepatic metastases, regardless of vascu-

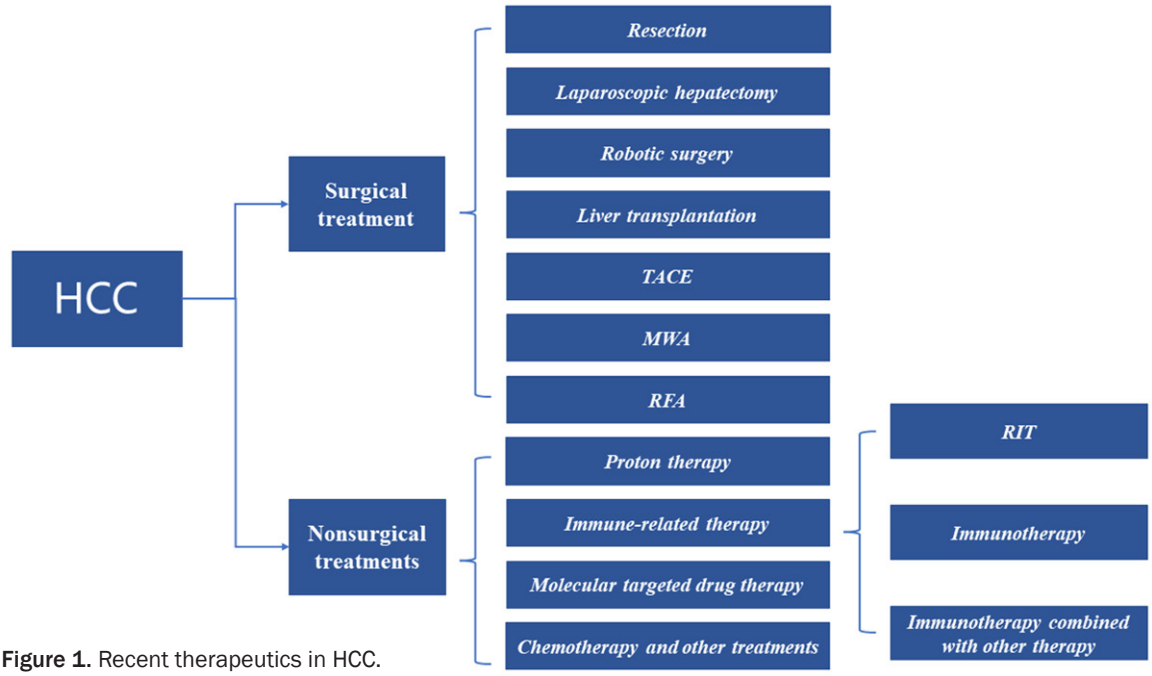

Figure 1. Recent therapeutics in HCC.

lar infiltration status, number and size of lesions (**Figure 1**) [5, 6]. At present, most scholars believe that hepatectomy should be considered first under the following conditions: liver function is Child-Pugh class A or B [7]; no vascular invasion or distant metastasis; single tumor diameter <5 cm or two or three tumors; and maximum tumor diameter ≤5 cm [8]. Accurate hepatectomy is a method to preserve residual liver function while resecting the tumor completely and controlling the amount of bleeding. The purposes are to reduce trauma and postoperative complications and accelerate postoperative recovery. Patients treated with accurate hepatectomy have less intraoperative blood loss, fewer postoperative complications, better postoperative liver function recovery, shorter hospital stays, and less postoperative recurrence compared with patients undergoing conventional hepatectomy (Pringle method) [9]. In the past, when anatomical hepatectomy was performed in China, the precise resection area was determined by the ischemic boundary of the liver surface after blocking the corresponding hepatic lobe or hepatic vasculature. In recent years, the proximal vessel was gradually blocked and methylene blue was injected into the distal vessel, to accurately determine the area of liver resection [10]. Researchers used three-dimensional (3D) reconstruction of anterior hepatic angiography, intraoperative blocking of regional blood flow and continuous injection of methylene blue staining to assist precise hepatectomy. Compared with patients with primary hepatocellular carcinoma (HCC) who undergo routine hepatectomy, accurate hepatectomy results in lower intraoperative bleeding volume, a shorter hospital stay, lower incidence of complications, less influence on liver function and coagulation, and early postoperative recovery [9, 10].

Laparoscopic hepatectomy

With the development of minimally invasive and laparoscopic techniques, laparoscopic liver resection is gradually being carried out and promoted in clinical practice. At present, most liver resections in the USA are performed under the assistance of laparoscopy. Laparoscopic hepatectomy is more complex than traditional abdominal surgery, and requires greater skills for the operator. However, laparoscopic hepatectomy has the following advantages [11]: incision length, intraoperative bleeding volume, postoperative liver function, gastrointestinal function recovery, and postoperative complication rate. Maintenance of a certain pneumoperitoneal pressure during laparoscopic hepatectomy can significantly reduce intraoperative blood loss [12]. A small incision in laparoscopic hepatectomy can reduce the chance of superfi-

cial infection at the surgical site [13]. Laparoscopic hepatectomy improves the clarity of the intrahepatic glissonean vertebral roots and hepatic veins, allowing greater surgical precision and reducing complications such as intraoperative bleeding and postoperative bile leaks [12]. There was no significant difference in perioperative mortality and postoperative 6-month and 1-year survival rates between the laparoscopic and open surgery groups. Laparoscopic surgery causes small local trauma and mild systemic response, and has rapid postoperative recovery. Isolated and focal lesions located in hepatic segments II, III, V and VI are the best indication for laparoscopic surgery. It is currently considered that it is safe and feasible to perform laparoscopic liver resection for treatment of HCC on the basis of strict control of resection and indications [14], and minimally invasive surgery is the developmental trend for treatment of HCC. Laparoscopic hepatectomy is safe and technically feasible compared with open surgery [15, 16]. Based on real-time tracking of organ shape and vessel locations for surgical navigation, laparoscopic hepatectomy can be performed using MEMS tri-axis magnetic sensors [17]. With the continuous progress in medical technology, laparoscopic techniques have gradually been applied in hepatectomy. In recent years [18], the continuous development of 3D technology has improved laparoscopic techniques, which have gradually been applied in clinical practice. The 3D laparoscopic system enables surgeons to obtain the same field of vision as with laparotomy, thus separating, ligating and lymphadenectomy of some important blood vessels. In the process of extensive excision, more precise results can be achieved. From the 3D perspective, surgeons can make more accurate judgments of the patient's condition [19], thereby ensuring the reliability and effectiveness of the surgical procedures. Compared with traditional laparotomy [20], 3D laparoscopy can improve the postoperative condition of patients, shorten length of hospital stay, and improve prognosis. The 3D laparoscopy can improve the feasibility of laparoscopic hepatectomy and reduce intraoperative complications without affecting the effectiveness of hepatectomy [21].

Robotic surgery

In the field of liver surgery, robotic surgery is still in the exploratory stage. Due to the particularity of liver surgery and the limitations of traditional laparoscopic equipment, laparoscopic hepatectomy has developed rapidly; however, it is still recognized as a difficult and high risk operation, and has been difficult to popularize in the short term. The robotic da Vinci Surgical System effectively overcomes the limitations of traditional laparoscopic techniques and equipment with its excellent 3D field of view and dexterous and stable operation of instruments, making feasible major operations such as right hemihepatectomy [22]. The da Vinci system has the advantages of enlarged 3D stereovision, multi-degree-of-freedom dexterous internal wrist instruments, hand tremor filtering, scaled-down operation range, better hand-eye coordination, and comfortable operating platform. It radically breaks through the limitations of traditional laparoscopic technology and achieves maximum operation. The dexterity and accuracy meet the needs of stable suturing in narrow spaces. The introduction of robotic surgical systems has optimized laparoscopic hepatectomy techniques and shortened the learning curve. The indications for robotic hepatectomy have rapidly expanded to right hepatectomy, donor right hepatectomy and portal biliary surgery. Laparoscopic contraindications such as hepatectomy for bile duct cancer and biliary tract reconstruction are discussed. Also contraindicated are patients with large tumors, multiple microscopic lesions, and lesions in close contact with hepatic veins [23]. Compared with traditional laparoscopy, the da Vinci Surgical System has achieved a revolutionary leap in complex gastrointestinal reconstruction, including biliary tract and pancreas, lymph node dissection, hemorrhage control, and vascular remodeling during complex hepatobiliary and pancreatic surgery [24]. The system is a brand new minimally invasive technology platform and has only been initiated by a few international centers in recent years. Therefore, in addition to the need to add matching auxiliary equipment, there is an urgent need for a lot of practice to improve and innovate key technologies such as hemostasis and surgical paths. Further research is needed on the indication and long-term efficacy of robotic hepatectomy. The path between robotic hepatectomy and traditional open surgery is different. This is because the robot arm holds the instrument through the mid-abdomen trocar hole, so that the lens and devices can only "bottom-up" their

dominant activities [25]. When the liver parenchyma is separated, there may be visually blind areas and potential risks when traditional open top-down surgery is attempted. Therefore, using the advantages of robots to create a suitable surgical path for hepatectomy can significantly shorten the operation time, and help surgeons with less laparoscopic experience to master robotic liver surgery more quickly [11]. When patients treated with minimally invasive surgery for stage I HCC over the past decade were counted and long-term outcomes were compared, survival rates at 1, 3 and 5 years after robotic surgery were higher than those after laparoscopic hepatectomy, thus improving long-term prognosis with robotic surgery in the treatment of early-stage HCC [26]. Despite the higher intraoperative cost of robotic access, the overall cost of robotic hepatectomy is lower because of its advantages of faster postoperative recovery and lower complication rate [23]. In summary, the da Vinci Surgical System overcomes the limitations and technical bottlenecks of traditional laparoscopic surgery. It can be predicted that it will improve the complexity and expand the indications of laparoscopic surgery, and achieve a leap forward in minimally invasive surgery.

Liver transplantation

Most patients with HCC have a history of cirrhosis. Therefore, liver transplantation is the best surgical treatment for resolving lesions and liver disease [27], and hepatic carcinoma is the only solid cancer that can be treated by transplantation. Before the 1990s, the results after liver transplantation were disappointing. The 5-year survival rate was between 30% and 40%. At present, the commonly used reference standards are Milan Criteria, Pittsburgh standard, and University of California San Francisco (UCSF). The Milan Criteria are the only globally recognized standard for small hepatic carcinoma transplantation [28]: single tumor diameter <5 cm, fewer than three tumors, and maximum tumor diameter <3 cm. There should be no macrovascular invasion or lymph node or extrahepatic metastasis. With the increasing number of liver transplants and the accumulation of experience in hepatic carcinoma, most scholars believe that the Milan Criteria are too strict [29], which makes some patients lose the chance of liver transplantation, and ignores factors such as vascular invasion, lymphatic metastasis, tumor grading and tumor markers. Some patients with hepatic carcinoma who may be cured will be excluded. Patients with hepatic carcinoma waiting for >1 year have a significantly lower long-term survival rate than patients with a waiting period <1 year. The model for End-Stage Liver Disease (MELD) score, tumor diameter, serum a-fetoprotein (AFP) level [30], and age are independent risk factors for increasing graft rejection. With the continuous improvement of living liver donor techniques, especially adult liver transplantation, the number of cases of liver live donor transplantations has increased annually in some countries with severe donor liver shortage. For patients with advanced hepatic carcinoma who have no other effective treatments, donors and recipients are willing to consider living donor liver transplantation. To prevent recurrence after hepatic carcinoma liver transplantation, the classical orthotopic liver transplantation is used to facilitate complete resection of the vena cava and posterior peritoneal lymphoid tissue [31]. Strict implementation of liver transplantation selection and application standards, improvement of living or marginal donor liver transplantation techniques, continuous optimization of pretreatment methods for hepatic carcinoma transplantation, and prevention and treatment of hepatic carcinoma recurrence and metastasis after liver transplantation are still the direction of unremitting efforts in the future.

Transcatheter arterial chemoembolization

TACE is the main treatment for patients with clinically unresectable HCC. It is also an adjuvant treatment before and after HCC resection. TACE does not take into account the location, size and number of tumors [32]. During the delivery of chemotherapeutic drugs, iodine oil is fed along with the embolic agent [33]; iodine oil is transported to the liver and deposited selectively in the tumor, reducing the blood supply to the tumor, and the chemotherapeutic drugs can control the growth of the tumor, thus preventing further deterioration of residual liver tissue [34]. TACE can be used either preoperatively or postoperatively. Preoperative TACE narrows the tumor size, expands the indications for surgical resection, and successfully transforms unresectable HCC into resectable

HCC. After TACE, the volume of the residual liver increases significantly, which improves the postoperative survival rate [35]. In addition, TACE can reduce tumor recurrence [36] and metastasis [37], and it can be used in combination with other methods [38]. The procedure for treating hepatic carcinoma mainly includes two aspects. (1) Increased drug concentration. The cytotoxic effect of drugs on cancer cells depends on the effective concentration of the drug and its duration of action. When drug concentration increases by one time, it can kill the cancer cells by 10-100 times. Reducing blood flow and vasoresistance therapy of target organs can increase the drug concentration to tens of times. Perfusion can reduce the binding of drugs to plasma proteins. Most randomized controlled trials were in patients with Child-Pugh class A (70%-100%), and no vessel invasion (>95%) in patients with multinodular HCC [39]. Patients with multinodular hepatic carcinoma are the best target for TACE. Transarterial radioembolization is a new therapeutic strategy using beta particles that can effectively treat unresectable primary and metastatic liver tumors [40, 41]. (2) Embolization of tumor blood vessels. This is mainly achieved through embolization of the arterial blood supply of the tumor, leading to tumor ischemia and hypoxia, which inhibits tumor growth and promotes tumor cell necrosis and apoptosis.

TACE involves insertion of a catheter into the tumor-supplying artery selectively or super-selectively, and injection of embolic agent at an appropriate rate to occlude the target artery and cause ischemic necrosis of the tumor tissue. Embolization with anticancer drugs or drug microspheres [42] can achieve chemoembolization. The classical TACE embolic agent is a mixture of ultra-liquid lipiodol and various chemotherapeutic drugs [43]. The lipiodol carries chemotherapeutic drugs into HCC to exert a local lethal effect. However, the mixed emulsion is unstable, and the chemotherapeutic drugs are released into the systemic circulation within a few hours to several days, which makes it difficult to achieve stable and sustained release. A number of DC beads (DEBDOX) loaded with doxorubicin have been used to treat HCC to evaluate their safety and efficacy. Recent drug-eluting bead transarterial chemoembolization replaces conventional iodine oil, and its indications are: (1) small HCC supplied by small hepatic arterioles; (2) repeated TACE for neovascular tumor-feeding arteries; (3) repeated TACE for residual viable tumors; (4) combined use of drug-eluting beads (DEB)-TACE with local RFA; (5) extrahepatic collateral blood supply to HCC tumors; (6) patients with poor liver function (Child-Pugh score 8-9); and (7) HCC with low or small vascularity [44]. Small-diameter DBEs (<100 μm) can completely embolize the tumor blood supply and reduce the recurrence rate. The study indicated that preoperative TACE is only effective when the mean tumor diameter is >5 cm, and preoperative TACE should be avoided in patients with small HCC. The prognosis of HCC patients depends on the degree of tumor necrosis induced by preoperative TACE, so the better the degree of necrosis, the better the prognosis [32]. The use of TACE in combination with portal venous embolizations (PVE) or portal vein chemoembolization (PVCE) in patients with HCC disease can improve the efficacy and reduce the recurrence rate [45]. In contrast, for patients with intermediate stage HCC, sequential treatment with lenvatinib (LEN)-TACE can achieve a better outcome and prognosis [46]. In conclusion, TACE can effectively control the local growth of HCC and improve patient survival, which is the preferred method for palliative treatment of HCC. Candidate criteria, chemotherapeutic drugs and interval cycles for TACE in the treatment of HCC need further study.

Microwave ablation

The basic principle of MWA is that the MW antenna is inserted into the tumor tissue, and a high-frequency electromagnetic field is introduced through the antenna. Under MW field radiation around the antenna probe, the molecules and ions in the tumor move back and forth with the constant change in the high-frequency electromagnetic field [47]. Molecules and ions move and contact each other, collide and generate heat energy, so that the local temperature rapidly rises above 60°C, causing coagulative necrosis of tumor cells. The frequency of MW therapy commonly used in clinical practice is 2450 and 915 MHz [48]. MWA heating is faster and more direct, and is superior to RFA in terms of time and thermal efficiency [49]. MWA does not need to connect

external negative plates and is less affected by thermal sedimentation effect. Compared with surgical resection, for small hepatic carcinoma in a good site [50], MWA can achieve complete clearance, but damage to the whole body and liver is less than that with surgical resection. For large HCC of 5-10 cm, in cooperation with other minimally invasive treatment, MWA can achieve high effectiveness and safety. Image-guided percutaneous MWA for HCC is simple, safe, practical and reproducible [51]. MWA has little pain, low cost, controllable heat field, and accurate results. Single ablation or multisite superposition ablation can inactivate a tumor ≤5 cm in diameter in one session. Due to reliable coagulation and larger ablation margins, MWA is suitable for subperitoneal HCC and has better local tumor control for HCC around small vessels [52]. There is no significant difference between the results after MWA and RFA, but the number of insertions of MWA is significantly less than that of RFA; therefore, for liver cancer with diameter >2 cm, MWA is more effective [53]. It can also reduce tumor mass, improve symptoms, and prolong survival of patients with advanced lesions [54]. Intraoperative and postoperative complications are few, and liver function and coagulation mechanism are not observably influenced, which is suitable for treatment of HCC in various stages. There is an urgent need to improve MWA devices and antennae, expand the MW coagulation zone, develop a new generation of image monitoring equipment, select new detection parameters, and explore metastasis and recurrence after MWA. However, the size and shape of the traditional MVA cauterization area are difficult to predict, which may lead to excessive ablation. The new generation of Emprint microwave cauterization improves the above-mentioned problems and becomes a promising method for the treatment of large HCC [55].

Radiofrequency ablation

RFA is a local minimally invasive treatment for hepatic carcinoma that cannot be surgically removed, or for patients waiting for a liver transplant to avoid tumor progression during transplantation [56]. The basic principle is that the RF therapeutic device emits medium-to-high frequency RF waves [57], and the electrode is inserted into the tumor tissue to emit RF current. This excites the tissue cells around the electrode to create ion oscillation, and the ions collide with each other to generate heat, thus killing the cells [58]. The cells are irreversibly necrotic, and at the same time, the blood vessel tissues around the tumor are coagulated, the blood supply is blocked, and tumor metastasis is prevented. The size of the lesion is the most important factor for local recurrence. At present, the clinical application of ablation-therapy-guided puncture technology is CT/MR technology, ultrasound or ultrasound fusion navigation technology, contrast-enhanced ultrasound and other related technology [59]. The multi-image fusion stereotactic positioning system can flexibly select the puncture route, avoid important blood vessels, guide bile duct structure needle insertion, guide the overall overlapping ablation, and can observe the position, depth and adjacent organ relationship of the electrode needle in real time, and the needle precision. RFA reduces damage of normal liver tissue. At present, the role of RFA in the radical treatment of hepatic carcinoma ≤3 cm and Child-Pugh class A or B liver function has been clearly defined [60], and it is widely used in tumors measuring 3-5 cm. However, there is a high risk of incomplete ablation of RFA in perivascular sites [52]. Treatment of larger hepatic carcinoma is in the exploration stage, and the prevention and treatment of adverse effects and complications should also be investigated.

Nonsurgical treatments

Proton therapy

The ideal effect of radiotherapy is to give the tumor cells a radical dose without damaging normal tissue. However, X-rays or gamma rays that are used in conventional radiotherapy inevitably damage normal tissues while treating tumors. Tumors cannot be treated radically [61]. With their superior physical properties, protons have achieved the ideal target of radiotherapy for cancer. In traditional radiotherapy, with increasing depth, the energy is gradually attenuated [62]. Protons, as positively charged particles, enter the human body at high speed, and the chance of interacting with normal tissues or cells is low. When a specific part of a cancer cell is detected, the speed suddenly drops and the protons stop, releasing the maximum energy, generating a Bragg peak, and killing the cancer cells [63]. During proton

therapy, the tissue at the front of the tumor is only exposed to a small amount radiation, and the normal tissue behind the tumor receives zero radiation and is not damaged. Compared to X-rays, proton beams have a limited range of energy deposition and lose most of their energy over a short distance at the end of the beam's range. These results cause a sharp rise and fall in energy absorption, known as the Bragg peak [64]. The Bragg peaks can be superimposed to provide a greater depth of coverage, the so-called extended Bragg peak beam. In addition, proton beam therapy (PBT) has a dosimetric advantage over 3D conformal radiotherapy and even intensity-modulated radiotherapy or volumetric-modulated arc therapy due to the absence of drug withdrawal dose. Therefore, PBT has the potential to reduce the risk of drug reactions [65]. The proton beam causes DNA damage and cytotoxicity by direct collision with the DNA molecules [66] and generation of oxygen free radicals. Traditional radiotherapy techniques may cause severe adverse reactions when treating tumors. Proton beams have unique Bragg peak physical properties and superior radiobiological characteristics compared with mainstream therapeutic photon therapy [61]. Proton therapy has broad application prospects and has been favored by academia. Especially in the past 5 years, protons have set off a new research boom in cancer treatment research. However, it is worth noting that even though proton therapy has broad application prospects, the cost of treatment is still higher than the existing radiotherapy techniques. However, the cost is likely to come down with advances in technology and research. This is a long process, and the cost-benefit ratio will inevitably affect the application of proton therapy in cancer.

Immune-related therapy

Radioimmunotherapy (RIT): RIT combines radionuclides with tumor-specific or related monoclonal antibodies to form radio-immunoconjugates that enter the body via certain pathways, specifically bind to tumor-cell-associated antigens, and form antigen-antibody complexes. The reaction-mediated cytotoxicity and the ionizing radiation of the released α and β rays kill tumor cells and play a role in treating tumors. The monoclonal antibodies currently used for RIT of HCC include an HCC monoclonal antibody fragment HAb18F (ab) 2, an AFP antibody, and a ferritin antibody [67]. To achieve targeting of intratumoral radiotherapy, radiopharmaceuticals can be directly injected into the tumor or via the circulation, such as an artery or peripheral vein. Since HCC is almost entirely connected to the hepatic artery, radiopharmaceuticals can directly reach the tumor tissue via this route. The intratumoral radiotherapy of HCC still needs combined with other therapy, and it has been shown to play a role in small lesions. RIT can prevent and alleviate dose-restricted organ adverse reactions, and it is safer to give tumors a high radiation dose. However, the sensitivity and specificity of monoclonal antibodies, the generation of human anti-mouse antibody response and poor long-term efficacy have limited their promotion and application. Improving the efficacy of RIT and reducing toxic adverse effects and promoting its wide range of clinical applications are the focus of future research.

Immunotherapy: Tumors can develop immune evasion and develop by regulating immunosuppressive mechanisms [68]. Glypican-3 (GPC3) is not expressed in normal liver, but only in HCC tissue [69], Programmed cell death (PD)-1/PD ligand (PD-L)1 immune checkpoints play an important role in the growth of tumors. PD-1 inhibitors can inhibit the immune evasion of tumors by blocking the PD-1/PD-L1 pathway and increase the number of tumors [70]. The antitumor immunity of the body can enhance T-cell toxicity, restore immune surveillance and immune clearance, and prevent $CD8^+$ T cells from transforming into T regulatory cells. However, in patients with liver cancer, the efficiency is <30%. This may be related to the tolerance of the immune microenvironment, inadequate exposure of tumor antigens, and insufficient T-cell infiltration in HCC. Nivolumab is an IgG4 monoclonal antibody that blocks PD-1 [71]. Clinical trials have shown that nivolumab for HCC is effective in reducing tumors and in treating advanced HCC, and patients treated with nivolumab are less likely to experience treatment-related adverse events and have a high safety profile, making it widely available for use in HCC [72]. Atezolizumab is an engineered IgG1 monoclonal antibody targeting PD-L1 [72]. PD-1/PD-L1 antibody and indoleamine 2,3 dioxygenase (IDO) inhibitor, as representatives of new immunological checkpoint inhibitor thera-

py [73], have many problems that need to be resolved before clinical application, such as timing of medication, course of medication and indications for drug withdrawal, formulation of new therapeutic evaluation criteria, combination with radiotherapy, chemotherapy and surgery, the most suitable drug population, and treatment after drug resistance. IDO inhibitors and PD-1 pathway blockers as targeted antibodies do not benefit all patients [74], and with the use of checkpoint inhibitors, the risk of immune-related adverse events increases accordingly. Therefore, appropriate biomarkers are the basis for accurate diagnosis and treatment. Biomarkers currently under study include PD-L1, tumor-infiltrating lymphocytes, clonality of T-cell receptors, mutation or new antigen load, peripheral blood markers, multiple immunohistochemical and combination of biological markers [75], but their application needs clinical verification. It is believed that in the near future, immunological checkpoint inhibitors will be used in cancer treatment in a more mature manner.

Immunotherapy combined with other therapy: Immunotherapy can be combined with other therapies. Hepatic arterial infusion chemotherapy plus targeted therapy and immunotherapy have good efficacy for advanced HCC [76]. TACE/RFA plus immunotherapy can improve immunity and prolong survival time [77]. Immunotherapy plus targeted therapy is a common strategy for unresectable HCC [78]. Immunotherapy plus tyrosine kinase inhibitors (TKIs) are also a good choice for unresectable HCC [79]. Immunotherapy plus anti-vascular endothelial growth factor (VEGF) antibodies have prominent synergistic effects [80]. Sintilimab (a selective anti-PD-1 antibody) plus bevacizumab (IBI305) showed good efficacy in Chinese patients with unresectable, HBV-associated HCC [81]. Atezolizumab plus bevacizumab also showed good efficacy with unresectable HCC in a phase 3 clinical trial [82].

Molecular targeted drug therapy

Molecular targeted drug therapy has unique advantages in controlling the proliferation of HCC, preventing and delaying recurrence and metastasis, and improving quality of life. Molecular targeted drug therapy inhibits the growth of HCC cells, thereby reducing the detrimental effects of drugs on normal liver cells.

There are two first-line TKIs (sorafenib and lenvatinib) and two second-line TKIs (regorafenib and cabozantinib) [83, 84]. Sorafenib is an oral multitarget [85], multikinase inhibitor that blocks tumor angiogenesis by inhibiting VEGF receptor and platelet-derived growth factor receptor. It is an effective target drug for the treatment of advanced HCC by blocking the Raf/MAPK/ERK signaling pathway and inhibiting the proliferation of tumor cells to exert dual-inhibition and multitarget blocking. In some Far Eastern regions, such as China and Korea, sorafenib has successfully reduced tumor recurrence rates and improved disease-free survival in HCC patients [86]. Patients with HCC with a pathological diagnosis of microvascular invasion also had improved survival with adjuvant treatment with sorafenib [87]. However, sorafenib has adverse reactions and is expensive, so its use has some limitations [88]. In addition to sorafenib, other molecular targeted drugs such as sunitinib and cedirib are also being studied, and have a good therapeutic effect. Apatinib as a VEGFR-2 targeted drug can improve overall survival of advanced HCC patients [89]. Lenvatinib is also used as a first-line drug for the treatment of HCC. Adequate doses of lenvatinib can protect liver function and improve the prognosis of HCC [90]. However, there is thyrotoxicity with lenvatinib, and even though this complication is rare, care should be taken to monitor thyroid function regularly when using lenvatinib [91]. Regorafenib is a second-line drug for the treatment of HCC, and it has been shown to have a significant therapeutic effect in patients with recurrent HCC after liver transplantation [92]. Long-term use of regorafenib has also been shown to reduce angiogenesis and improve portal hypertension and is therefore particularly indicated in patients with preserved liver function and portal hypertension [93].

GPC3 is a glycoprotein located on the cell membrane through a glycol-phosphatidylinositol anchor [94]. The expression of GPC3 can be found in various tumors and its expression in HCC is greater than in other tumors [95]. Recombinant monoclonal antibody codrituzumab (GC33) binds to the functional domain of GPC3 and exerts cytotoxicity and inhibits tumor growth [96]. CD47 is a suppressive innate immune checkpoint that helps cancer cells to escape from immune surveillance, and high

levels of CD47 are expressed in liver cancer to escape the immune system [97]. Recent studies have shown that BsAb, a combination of GPD3 and CD47, improves anti-HCC efficacy and safely enhances the innate immune response, and will be used more often clinically to improve treatment of HCC [98].

Chemotherapy and other treatments

Systemic chemotherapy is required for patients with HCC who are not suitable for surgery. Commonly used systemic drugs are fluorouracil and its derivatives, cisplatin, mitomycin, fluorouracil, doxorubicin and hydroxycamptothecin. HCC is less sensitive to most chemotherapeutic drugs. Therefore, combination chemotherapy is often used for HCC. For example, systemic chemotherapy is often combined with molecular targeted drugs and surgery to reduce the dose and reduce adverse effects, so as to improve the effectiveness for HCC.

Stereotactic body radiation therapy (SBRT) derives from the initial developments of intracranial stereotactic radiosurgery [99]. Whole-liver radiation is limited by the sensitivity of normal tissues to radiation, and the tolerable dose of whole liver is 30 Gy. 3D conformal techniques (3DCTs) can protect normal liver tissue and augment radiation dose; as an extension 3DCTs, SBRT has improved the therapeutic ratio [100]. Yanyan Long et al. reported that SBRT can ameliorate overall survival and local control of small HCC, even for pretreated patients or those with macrovascular invasion [101].

Although western medicine is the mainstay of treatment for HCC in China at present, Traditional Chinese medicine (TCM) can help reduce the toxicity of radiotherapy and chemotherapy, improve cancer-related symptoms and quality of life, and may prolong survival. TCM can be used as an important auxiliary treatment of HCC. The prescriptions commonly used in clinical treatments include Kang-ai injection [102], Yinchenhao decoction [103], and Shenling Baizhu powder [104].

Neoadjuvant therapy has been widely used in the treatment of lung cancer, gastric cancer, colorectal cancer, uterine cancer and other solid tumors. Treatment can reduce the stage of the tumor and unresectable tumor can become resectable. However, neoadjuvant therapy for liver cancer is not clear [105].

Nanotechnologies have been used recently in research in medical oncology, especially in HCC treatment. The main treatment strategy includes photothermal therapy and photodynamic therapy [106]. Nanotherapy can integrate gene therapy [107], chemotherapy [108] and targeted therapy [109]. Nevertheless, the above studies are limited to basic research and more clinical research should be performed.

Conclusion

HCC has high morbidity and mortality. Early HCC is usually treated with ablation or surgery, which can completely remove the tumor. When HCC progresses to the intermediate stage of the disease, TACE is usually chosen. At the advanced stage, there is a need to implement a systemic treatment plan, combined with immune-related therapy, radiotherapy and chemotherapy. Terminal HCC mainly receives symptomatic supportive treatment. Comprehensive treatment plays an important role in inhibiting the growth of tumor cells and improving survival rate. It is believed that, with further research, some more effective individualized comprehensive treatments will be applied clinically, and will also benefit HCC patients.

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Disclosure of conflict of interest

None.

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