Difficulties and Prospects of Primary Liver Cancer Treatment

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Primary liver cancer occurs in hepatocytes and intrahepatic bile duct cells. As one of the common clinical tumors, it is associated with high degree of malignancy and rapid disease progression. Apart from that, the survival time of the patients with primary liver cancer is generally short, and the cancer is difficult to cure. Primary liver cancer is one of the major diseases that tremendously endanger human life and health. According to statistics, the global incidence of liver cancer ranks fifth among other malignant tumors each year, and 55% of these cases occur in China [1].

Surgery, interventional therapy, ablation therapy, localized ethanol injection, drugs, and radiotherapy are currently the commonly used methods for the treatment of primary liver cancer. Along with the development of molecular biology and molecular immunology, fundamental research continues to deepen our understanding of liver cancer, and the advances in technologies have indeed propelled the development of liver cancer treatment. Considering the complexity of tumor biology and the limitations of various treatment methods, comprehensive treatment involving multiple discipline collaboration which has become a consensus in the field of liver cancer treatment presents itself as a promising approach [2].

1 Surgical treatment

Surgery, including liver resection and liver transplantation, is the first choice for the treatment of primary liver cancer. Hepatectomy is the surgical removal of liver or part of the organ. The residual organ can maintain the liver function after hepatectomy. However, since a patient with severe liver cirrhosis cannot tolerate a surgery like hepatectomy, liver resection will not be performed on this patient, and unfortunately, the healthy parts of the liver will still not be able to maintain the liver function for long. On the other hand, liver transplantation is a method of radical cure of liver cancer, but a transplantation is permitted only if the strict indications in accordance with the commonly used Milan criteria and Hangzhou criteria are fulfilled. Furthermore, the patients need long-term immunosuppression after transplantation. Irrespective of either liver resection or liver transplantation, it is difficult to identify micrometastases before surgery due to the limitations of current imaging methods, and cancer recurrence will influence the prognosis of patients [3]. Therefore, to attain precision in liver surgery, imaging methods should also be improved along with surgical techniques.

2 Local treatment

Local treatment is the most important non-surgical treatment for primary liver cancer. It includes interventional, ablation, and radiation therapy. Compared with surgical treatment, local treatment which is minimally invasive does not involve complicated operations, and this therapy contributes to fewer complications. Moreover, the therapeutic outcomes of local treatment are highly reproducible. Particularly, the treatment of small liver cancer can achieve long-term effects which are comparable to those of surgical resection.

Transcatheter arterial chemoembolization and transcatheter arterial infusion chemotherapy are the main methods of interventional therapy for liver cancer at present.
However, interventional therapy is not a radical method for treatment, and essentially, it can only alleviate the pain and increase the chances for surgeries\(^4\).

Ablation treatment, including thermal ablation (radiofrequency, microwave, and laser), chemical ablation, and cryoablation,\(^[3]\) is used to treat liver cancer with a diameter of ≤3 cm. This treatment method can attain effects similar to liver resection. The appropriate ablation scheme is selected based on the size and location of the tumor, and it has gradually replaced localized ethanol injection, including the percutaneous ethanol injection and the ethanol injection under laparotomy. Ablation therapy is only suitable for smaller early tumors, and it is put at a disadvantage compared with surgery when tumor recurrence rate and patient survival rate are taken into account\(^6\).

Radiation therapy is an important method in the comprehensive treatment of liver cancer, but its clinical application is limited due to liver damage caused by radiation therapy and the low tolerated dose of the liver to radiation\(^7\). On the other hand, brachytherapy which is referred to as the implantation of radioactive particles is put in a predicament for extensive use for concerns such as radiation safety and pollution.

### 3 Medical treatment

Liver cancer has no obvious initial symptoms. That is the reason that most patients are already in the middle and advanced stages at the time of consultation and diagnosis and thus have lost the opportunity for surgery. Therefore, clinicians are required to accurately choose a treatment plan based on the patient’s condition, especially for patients with distant metastases. In recent years, drug therapy development has seen some fruitful progress that came up with systemic chemotherapy and targeted therapy.

Primary liver cancer is less sensitive to most chemotherapeutics. Systemic chemotherapy drugs such as doxorubicin, gemcitabine, cisplatin, 5-fluorouracil, or combined palliative therapy are only effective for treating <10% of primary liver cancer cases and these drugs are less tolerated in patients with cirrhosis\(^8\).

Sorafenib is a small-molecule targeted cancer drug that inhibits tumor cell proliferation and tumor angiogenesis. Sorafenib is an inhibitor of receptor tyrosine kinases such as those of vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor, and insulin-like growth factor. It is currently the only effective drug that has been proven to be useful for systemic treatment of advanced liver cancer, but the treatment involving sorafenib is costly and its mitigation is limited\(^9\). In addition, drugs targeting different targets have also been explored and tested for their potential use as the first-line and second-line treatments, but as of now, no drug (including sunitinib, brinib, and erlotinib) has proven to be superior to sorafenib.

With the advancements in genomic technologies, drug treatment based on gene targets has become more promising, and drug design has therefore started to gain momentum.

### 4 Immunotherapy

Immunotherapy based on immune recognition and effector mechanisms has become one of the important research avenues for liver cancer treatment. Programmed cell death protein-1 monoclonal antibody is recommended as a second-line treatment for advanced liver cancer by the Chinese Society of Clinical Oncology guidelines\(^[10]\). Tumor immunotherapy can enhance the body’s immune response, stimulate tumor-specific immunity, and break immune tolerance to achieve the purpose of delaying tumor progression, reducing tumor recurrence and metastasis, and even curing tumors. It is expected to become an important part of the comprehensive treatment regimen of liver cancer.

At present, some immunotherapy approaches and methods have been developed and being evaluated in clinical trials at different stages. The safety and efficacy of these treatments have been proven at clinical setting. In immunotherapy, the immune active cells are primed to kill the tumor cells. However, anti-tumor immune response will become lower if the patient has a larger tumor load. Therefore, immunotherapy can only remove a small number of scattered tumor cells and has limited effect on advanced solid tumors. At present, immunotherapy is used as an adjuvant therapy in combination with conventional therapies such as surgery and chemotherapy.

In summary, none of the known treatment methods for liver cancer is perfect, and each of them has certain limitations in delivering the optimal therapeutic result. Hence, comprehensive and sequential treatment involving multiple methods is still the most effective measure at present. Of note, the implementation of personalized treatment of multidisciplinary origin has become a treatment trend in recent years. Undoubtedly, tumor heterogeneity and individual differences are among the important factors that determine the effectiveness of a treatment regimen, and thus, a few practical issues, such as how to choose the most effective treatment and how to improve the standardized treatment for liver cancer, are awaiting resolution. For this reason, fundamental studies that focus on the precise identification of small liver cancer lesions, the role of oncogenes and tumor suppressor genes, the molecular mechanism of cancer recurrence and metastasis, tumor-specific targeted therapy, and immunotherapy should be the research spotlight for propelling treatment development.

### Acknowledgments

This work was supported by National Nature Science Foundations of China (No. 81000987), China Postdoctoral...
Science Foundation Funded Project (No. 201003744), Shaanxi Natural Science Basic Research Project (No. 2020JM-707), Xi’an Science and Technology Project (No. 201805094XYX2SF28 (3)), and Xi’an Health Commission Project (No. J201903071).

Conflicts of interest

The author declares no conflicts of interest.

References