Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/74/2024.LA19335

The Current Status and Prospects of Yttrium-90 Microsphere Radioembolization in the Treatment of Liver Cancer

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Abstract. Hepatocellular carcinoma (HCC), the world's most frequent primary liver cancer, affects millions of people. Since most patients are diagnosed with liver cancer at an advanced stage, the size of the tumor and the patient's physical condition often limit the feasibility of liver resection or liver transplantation. Therefore, many patients can only be treated with hepatic arterial chemoembolization (TACE) or sorafenib and so on. With the progress of glass and resin microspheres and the research of yttrium-90 microsphere radioembolization (Y-90 RE) technology, Y-90 RE has shown significant advantages in tumor control, tumor response, tolerance and side-effect management. Nowadays, Y90 microsphere radioembolization has become a key method in the treatment of HCC. This article reviews the mechanism, clinical application and comparison with other therapeutic methods of radioembolization with Y90 microspheres.

Keywords: Hepatocellular carcinoma, Yttrium-90, Y90 Microsphere Radioembolization.

1. Introduction

Liver cancer is one of the most frequent fatal solid malignancies and the leading cause of cancer death in the world. According to World Health Organization statistics in 2018, HCC ranks sixth globally in incidence and fourth in mortality, with approximately 840000 new cases per year and causing more than 780000 deaths [1]. The geographical distribution of HCC varied significantly, with more than 80% of cases occurring in less developed regions, particularly in East Asia (54.8%) and Southeast Asia (10.8%) [2]. The global cancer burden data published in 2020 showed that HCC ranked fifth globally in incidence and third in mortality, with 905,677 new cases and 830,180 deaths [3]. HCC is the fourth most prevalent form of malignant tumor in China and the third leading cause of death, accounting for 75% to 90% of primary liver cancer [4]. HCC is well known for its insidious onset and high invasiveness. Due to the insidious nature of HCC, most patients are already in the intermediate to advanced stages by the time they are discovered with liver cancer, and have a poor prognosis. Based on this, 39.0% to 53.5% of patients present with tumor vascular invasion or distant metastasis at initial finding with one year survival rate of only 12.0% to 38.3% [5].

Despite significant progress in the early found and treatment of HCC in recent years, patients' overall survival remains unsatisfactory due to its high relapse rate and limited therapeutic efficacy. At present, the treatment strategy of HCC is mainly based on the tumor staging system. Various staging systems for cancer have been developed to assess outcomes and develop treatment options for HCC, the most

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commonly used include the Barcelona Clinic Liver Cancer (BCLC) staging system and the Hong Kong Liver Cancer (HKLC) staging system [6]. The BCLC staging system, based on tumor burden, patient Performance Status (PS) and liver function Status, has good classification and prognostic ability. In this system, early-stage patients typically receive liver transplantation or local treatment, mid-stage patients undergo TACE, and late-stage patients are treated with systemic medication. However, despite these treatments, the survival of HCC patients remains low and more effective treatments are urgently needed [7]. In this context, Y-90 RE, as a local treatment, has gradually become an important choice in the treatment of advanced HCC [8]. Both basic research and clinical evidence suggest that Y-90 RE can effectively control tumor progression and improve patient survival. The technique has been recognized by many international guidelines and experts as an effective treatment for liver cancer, and has been widely used in more than 50 countries and regions around the world, this technique is being gradually introduced in many interventional diagnosis and treatment centers in China. The purpose of this study is to evaluate the efficacy and clinical application of Y-90 RE in the treatment of HCC, and to recommend it as a better treatment method for more patients with advanced HCC.

2. Current Treatment Status of Hepatocellular Carcinoma

As the most frequent malignant tumors globally, the incidence of HCC is particularly significant in the Asia-Pacific region. It is a leading cause of cancer-related deaths. Each year, there are approximately over 800,000 new cases globally, with the mortality rate closely approaching the incidence rate. It has become one of the significant challenges in public health. The primary risk factors for HCC include chronic infections with hepatitis B and C viruses, long-term alcohol abuse, and non-alcoholic fatty liver disease. Despite some progress in vaccination and antiviral treatment in recent years, the incidence of liver cancer continues to rise, particularly in certain developing countries.

Due to the high recurrence rate of HCC, patients who undergo successful resection or local ablation have a 50% chance of recurrence. The reasons for recurrence include the presence of micro-metastases within the liver, the impact of underlying liver diseases (such as cirrhosis), and the biological characteristics of liver cancer. Moreover, most patients are in the intermediate to advanced stages, which means that radical treatments such as surgical resection or liver transplantation are not applicable to the majority of patients. Therefore, reliance on conservative treatments, such as TACE and systemic drug therapy, is necessary. Although these treatment methods can extend survival to some extent, significant challenges remain in controlling recurrence and improving prognosis.

3. The mechanism of action of Yttrium-90 microsphere radioembolization

Y-90 RE is a form of localized internal radiation therapy that combines the dual effects of radiation therapy and local embolization. This technique involves the injection of Yttrium-90 radioactive microspheres into the microvasculature supplying blood to the tumor via the hepatic artery. Its mechanisms of action include the following: (1) Radiative effect: Yttrium-90 is a beta radiation emitter, and the released beta rays can damage the DNA of tumor cells and disrupt cellular structures, thereby killing tumor cells. (2) Ischemic effect: The microspheres, being small in diameter, can be selectively injected through the hepatic artery and deposit locally within the tumor, obstructing the microvasculature of the tumor tissue, blocking blood supply, and leading to hypoxia and nutrient deprivation in the tumor tissue. This, in turn, inhibits the growth and spread of cancer cells. The half-life of Yttrium-90 is 64 hours, allowing for sustained radiative therapeutic effects and enhancing control over the tumor.

4. Clinical applications of Y-90 microsphere radioembolization

4.1. Indications and Contraindications

Y-90 RE is suitable for patients with intermediate to advanced HCC, particularly those for whom surgical resection is not acceptable due to tumor size or location. Indications include: performance status scores of 0-2, Child-Pugh class A/B, presence or absence of portal vein tumor thrombus, and patients who have failed TACE or systemic therapy. Contraindications include severe liver dysfunction,

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pregnancy, and patients at high risk of significant bleeding. Additionally, the use of Y-90 RE should be approached with caution in patients with significant pulmonary shunting to avoid the occurrence of radiation pneumonitis. Contraindications include severe liver dysfunction, pregnancy, and patients at high risk of significant bleeding. Furthermore, the use of Y-90 RE should be approached with caution in patients with significant pulmonary shunting to avoid the occurrence of radiation pneumonitis**[9-15]**.

4.2. Considerations and Selection of Application Time

Y-90 RE should be implemented as early as possible in the treatment of intermediate to advanced liver cancer to maximize therapeutic efficacy. Research indicates that early intervention can more effectively control tumor progression and extend survival. In the acute and subacute phases, Y-90 RE can help reduce tumor progression and prolong progression-free survival (PFS), while in patients with advanced liver cancer, Y-90 RE can serve as a palliative treatment option. It is generally recommended to administer Y-90 RE every 3 to 6 months, with the specific frequency needing to be individualized based on the patient's condition and treatment response [9-15].

4.3. Clinical efficacy

As a local therapy, Y-90 RE has shown good efficacy in many clinical studies. The therapeutic effects include tumor reduction, improvement of liver function, decrease of liver cancer markers, prolongation of survival time and improvement of survival rate. Lee et al noted that patients with Y-90 RE-treated HCC had tumor shrinkage of 2% at 1 month, 14% at 3 months, and 28% at 6 months. In addition, Y-90 RE showed a synergistic effect with systemic drug therapy, which could improve the prognosis and prolong the survival time [16]. In a European multicenter study on Y90 RE, among a total of 325 patients, more than half were classified as BCLC-C (56.3%), and a quarter were classified as BCLC-B (26.8%). The overall median survival time for patients was 12.8 months (95% CI, 10.9 - 15.7), with a median survival time of 24.4 months (95% CI, 18.6 - 38.1) for BCLC-A patients, 16.9 months (95% CI, 12.8 - 28.0) for BCLC-B patients, and 10.0 months (95% CI, 7.7 - 10.9) for BCLC-C patients. Data from another European study involving 52 treated patients indicated that the presence or absence of portal vein thrombosis did not have a significant impact on overall median survival (18 months vs 13 months) [17].

5. Comparison of Y-90 microsphere radioembolization with other treatment methods

Compared to systemic drug therapies (such as sorafenib and lenvatinib) [18], the localized treatment effect of Y-90 radioembolization exhibits a stronger targeting capability, allowing for the direct delivery of radioactive microspheres to the microvasculature supplying the tumor, thereby reducing damage to healthy liver tissue. Although systemic drug therapies can inhibit overall tumor growth, they are associated with significant side effects, typically including hypertension, diarrhea, and hand-foot syndrome, which greatly impact the quality of life of patients. Furthermore, the efficacy of systemic drug therapies in controlling localized tumors is relatively limited, particularly in patients with treatment-resistant tumors. Y-90 radioembolization can effectively reduce tumor size through targeted radiotherapy, improving local control rates. Numerous clinical trials have demonstrated that the combination of Y-90 radioembolization with systemic drug therapies can produce a synergistic effect, not only controlling tumor growth but also significantly prolonging progression-free survival (PFS) and overall survival (OS), especially in patients unresponsive to conventional treatments. Therefore, the combined treatment modality of Y-90 radioembolization and systemic drugs offers an effective therapeutic option for patients with intermediate to advanced HCC. Additionally, in patients awaiting liver transplantation, Y-90 radioembolization serves as a bridging therapy that can help reduce tumor volume, increasing the likelihood of receiving a liver transplant and thereby improving long-term prognosis. The combination with systemic drugs can further control tumor progression in such patients, reducing the risk of tumor spread prior to transplantation. TACE employs a combination of embolic agents and chemotherapeutic drugs to obstruct tumor blood supply and directly kill tumor cells, while Y-90 radioembolization blocks tumor blood supply through radioactive microspheres and destroys

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tumor cell structures via radiation. Y-90 radioembolization has a stronger targeting capability, minimizing damage to normal liver tissue and is less likely to induce embolization syndrome, significantly improving patients' quality of life. Moreover, the radiation effect of Y-90 radioembolization can last for several weeks, providing a longer duration of antitumor activity, whereas the embolization effect of TACE is relatively short-lived and prone to tumor recurrence [19].

6. Strength & weakness of microsphere therapy

The advantages of Y-90 RE lie in its efficient targeted radioactive therapy, which can precisely act on tumor areas while minimizing the impact on normal tissues, resulting in a shorter recovery time post-treatment. Y-90 RE can also reduce the size of tumors in some patients to a degree that allows for surgical resection, providing opportunities for further treatment. However, Y-90 RE also has certain drawbacks, including high treatment costs, the need for specialized equipment and technical support, and potential radioactive side effects, such as radiation-induced liver damage. Additionally, for patients with significant pulmonary shunting, it may be necessary to adjust the dosage or choose alternative treatment options to avoid radioactive complications [20]. However, Y-90 RE also has certain drawbacks, including high treatment costs, the need for specialized equipment and technical support, and potential radioactive side effects, such as radiation-induced liver damage. Additionally, for patients with significant pulmonary shunting, it may be necessary to adjust the dosage or choose alternative treatment options to avoid radioactive complications.

7. Discussion

Despite demonstrating good efficacy in the treatment of advanced HCC, the application of Y-90 rE still faces several challenges. Firstly, radioactive liver damage is one of the common side effects of Y-90 RE, particularly pronounced in patients with poor liver function, which may affect the long-term prognosis of these patients. Secondly, the treatment costs associated with Y-90 RE are high, requiring expensive equipment and specialized technical support, which may not be feasible in resource-limited areas. Furthermore, the safe use of Y-90 relies on precise dosage calculations and operations; improper handling may lead to radioactive damage to non-target tissues. Therefore, optimizing the radiation dosage and precision, reducing side effects, while simultaneously enhancing efficacy, is an important direction for future research.

The future direction lies in enhancing the therapeutic efficacy of Y-90 RE through further technological advancements and synergistic effects with other treatment modalities. Firstly, improving the manufacturing process of microspheres and the precise control of radiation dosage can help reduce side effects while increasing the lethality against tumor tissues. For instance, developing new radioactive microsphere materials to enhance their targeting capability and radioactive payload can improve treatment efficiency and minimize the impact of non-targeted radiation. Secondly, integrating modern imaging technologies (such as CT, MRI, and PET-CT) for precise three-dimensional dose planning of Y-90 RE can assist in optimizing treatment protocols and increasing specificity towards tumors. For instance, developing new radioactive microsphere materials to enhance their targeting capability and radioactive payload can improve treatment efficiency and minimize the impact of non-targeted radiation. Secondly, integrating modern imaging technologies (such as CT, MRI, and PET-CT) for precise three-dimensional dose planning of Y-90 RE can assist in optimizing treatment protocols and increasing specificity towards tumors.

The development of multimodal integrated treatment strategies, including the combination of Y-90 RE with immunotherapy and targeted therapy, is likely to benefit patients. Bringing about a longer lifespan and better quality of life. Research shows that the combined application of immune checkpoint inhibitors with y-90 re is expected to produce a synergistic effect by increasing the release of tumor antigens and enhancing the body's immune response, thereby further improving treatment efficacy. In addition, the combined use of targeted therapy drugs can inhibit tumor angiogenesis and the proliferation of tumor cells, further enhancing the effects of localized radiotherapy.

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Personalized treatment plans tailored to different patients, particularly precision therapies based on molecular biomarkers, will contribute to improving treatment efficacy and reducing side effects For instance, by analyzing patients' genetic mutation profiles and molecular markers, suitable combination therapy strategies can be selected to achieve more precise treatment Concurrently, conducting large-scale clinical trials to validate the efficacy and safety of various combination therapies is crucial for promoting the widespread application of Y-90 RE.

Finally, the potential application of Y-90 RE in other types of tumors also warrants further exploration. In addition to HCC, the use of Y-90 RE in secondary liver tumors such as colorectal cancer liver metastases and gastric cancer liver metastases is gradually gaining attention. Future research could further investigate the application of Y-90 RE in other refractory tumors and develop comprehensive treatment plans in conjunction with other emerging therapies, such as CAR-T cell therapy, thereby providing new hope for more patients. With continuous technological advancements, exploration of combination therapies, and optimization of personalized treatment strategies, Y-90 RE is expected to become an important component in the treatment of advanced HCC and other liver tumors in the future, offering better treatment options and improved quality of life for patients.

8. Conclusion

Y-90 RE has become an important option for the treatment of intermediate to advanced HCC as a localized therapeutic approach. Through efficient targeted radioactive treatment, it can precisely act on the tumor area, reducing damage to surrounding healthy tissues, and has demonstrated significant efficacy compared to traditional therapies. Although Y-90 RE shows promising therapeutic prospects, further optimization of techniques, reduction of side effects, and expansion of its application range are still needed to play a greater role in the long-term management of liver cancer.

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