OncoTargets and Therapy

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REVIEW

Applications of Yttrium-90 (^{90}Y) in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, affecting millions of people worldwide. Due to the lack of systemic radiation therapy in hepatocellular carcinoma, researchers have been investigating the use of yttrium-90 (^{90}Y) radioembolization for local-regional tumor control since the 1960s. With the development of glass and resin ^{90}Y microspheres and the durable local control, good long-term efficacy, and equivalent tumor responsiveness and tolerability of ^{90}Y-selective internal irradiation compared with alternative therapies such as transarterial chemoembolization (TACE) and sorafenib, ^{90}Y radioembolization has gradually been applied in the treatment of hepatocellular carcinoma of all stages. In this article, we summarize the latest progress of ^{90}Y in the treatment of hepatocellular carcinoma in terms of its principle, advantages, indications, contraindications, efficacy and adverse effects.

Keywords: yttrium-90, hepatocellular carcinoma, internal radioembolisation

Liver cancer, ranking as the sixth most prevalent malignant tumor globally, poses a significant global health challenge due to its high mortality rate. The World Health Organization projects that over one million individuals will succumb to liver cancer by 2030 based on current projections.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer, accounting for 75% to 80% of all liver cancers. Its onset is often linked to various liver diseases such as viral hepatitis, alcoholic fatty liver, and non-alcoholic fatty liver.[2] Primary treatment modalities for liver cancer include traditional surgical resection, percutaneous anhydrous ethanol injection, transarterial chemoembolization (TACE), ablation therapy, liver transplantation, and chemotherapy, among others. Surgical intervention is effective for early-stage liver cancer, achieving complete cure. However, a significant proportion of liver cancer patients, around 70%, are diagnosed at an intermediate or advanced stage, thereby missing the window for surgical intervention.[3] Liver transplantation (LT) is the most effective treatment for liver cancer. Unfortunately, a substantial number of patients do not meet the Milan criteria, rendering them ineligible for transplantation. Radiotherapy, aimed at downsizing the tumor, plays a crucial role in enabling subsequent liver resection or transplantation. The advent of novel technologies and materials has given rise to ^{90}Y selective internal irradiation as a new approach for treating advanced hepatocellular carcinoma, and this article provides an overview of recent advancements in this technique.

Reasons for Transarterial Internal Radiotherapy

Studies have demonstrated the radiosensitivity of hepatocellular carcinoma cell lines in vitro.[4] However, due to the radiosensitivity of normal liver tissue, exposing the entire liver to an average radiation dose exceeding 43 Gy results in liver dysfunction in more than 50% of patients.[5] Consequently, the utilization of external radiation therapy has historically been limited, with conventional fractionated therapy restricted to doses below 40 Gy for most normal livers, proving ineffective for treating hepatic malignancies.[6] T This limitation stems from the potential occurrence of Radiation-induced Liver Damage (RILD) due to irradiation of a significant portion of the normal liver.

Received: 6 November 2023
Accepted: 17 February 2024
Published: 23 February 2024

The concept of intrahepatic transcatheter arterial-directed therapy originated from groundbreaking research by pathologists at the University of Pennsylvania. They demonstrated that the portal vein is the primary source of blood to the normal hepatic parenchyma, while hepatic tumors, highly vascular structures, are predominantly supplied by the hepatic artery and its branches. Notably, hepatic tumors lack the dual parenchymal blood supply provided by both hepatic arteries and the portal vein.[7,8] Additionally, the blood supply to these tumors may also be parasitic from extrahepatic sites. The celiac trunk branches into the common hepatic artery, which further divides into the right and left lobar hepatic arteries, supplying blood to the respective liver lobes. This unique anatomical structure allows for the transarterial delivery of therapeutic substances like radioactive microspheres.[9,10] Consequently, transarterial internal radiation therapy has emerged as a novel treatment for advanced hepatocellular carcinoma.[5]

^{90}Y Selective Internal Radiation Therapy (SIRT) is a therapeutic procedure administered through the hepatic artery, allowing targeted delivery of high radiation doses to liver tumors. The concept behind SIRT involves transferring intra-arterial brachytherapy to the targeted tumor via a branch of the hepatic artery.[11] This treatment is typically delivered via trans-arterial intervention of ^{90}Y microspheres in excess of 600 Gy into the blood supply within liver tumors for a localized radiation therapy effect. The radiation exposure to the normal liver parenchyma is maintained within tolerable limits, minimizing damage to surrounding healthy tissue.[12] In contrast to conventional TACE, transarterial internal radiation therapy primarily leverages ^{90}Y microsphere radiation for its anti-tumor effect, rather than relying on hypoxia induced by microembolization or the chemotherapeutic effects of agents. Based on this principle, patients with advanced hepatocellular carcinoma associated with portal vein thrombosis can also be effectively treated using this method.

Advantages and Physical Properties of ^{90}Y

^{90}Y is produced in a nuclear reactor by bombarding yttrium-89 with neutrons, possessing a physical half-life of 64.2 hours (2.67 days), after which it decays to stable zirconium-90. ^{90}Y emits pure, high-energy β-rays (maximum energy of 2.27 MeV; average energy of 0.9367 MeV), with an average penetration range of 2.5 mm and a maximum of 11 mm. A dose of 1 Gigabecquerel (27 mCi) of ^{90}Y provides a total absorbed radiation dose of 50 Gy/kg. In therapeutic applications, where the isotope decays to infinity, 94% of the radiation is delivered within 11 days.[13] Unlike external beam radiation sources,^{90}Y microspheres act as point sources of radiation, preferentially targeting the peri-tumor and intra-tumor arterial vascular systems.[14] This property enables them to selectively deliver high doses of radiation to the tumor, localizing radiotherapy within the tumor without affecting the surrounding normal tissue. The small size of the drug-carrying microspheres, coupled with the transient penetration of radiation into the tissue, enhances tumor targeting while preserving liver parenchyma.[15] Additionally, these microspheres, made of glass, are non-biodegradable and do not redistribute to other organs in the body.

Currently, two commercially available devices incorporate ^{90}Y microspheres: one made of resin (SIR-Spheres; Sirtex Medical, Sydney, Australia) and the other made of glass (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada). The resin microspheres have a diameter of 35 (±10) μm and an activity of 50 Bq per sphere, while the glass microspheres have a diameter of 25 (±10) μm and carry 2500 Bq of radioactivity per sphere. A notable difference is the relative activity in individual spheres, with resin microspheres requiring a larger injection volume than glass microspheres. Given the physical distinctions between the two types of spheres, specific training and learning curves need to be established for each. However, to date, no discernible differences have been identified in their clinical applications, necessitating further research for definitive conclusions.[16]

Indications and Contraindications for Yttrium-90

Indications

Collating multiple literatures, indications for selective internal irradiation with ^{90}Y encompass:[17] (1) Patients with intermediate and advanced hepatocellular carcinoma, where the tumor size or number precludes treatment with TACE.[18,19] (2) Patients with lobar-level portal vein thrombosis in middle- and advanced-stage hepatocellular carcinoma.[20] (3) Patients with poor or failed TACE, targeted therapy, and similar interventions.(4) For patients with unresectable overt liver disease, SIRT with ^{90}Y serves as an effective option for translational therapy before liver transplantation or surgical resection.[21](5) Follow-up treatment for

post-surgical recurrence of hepatocellular carcinoma.(6) Patients more likely to benefit from SIRT with ^{90}Y may include those with fewer than six intrahepatic lesions, no extrahepatic disease, and a tumor-to-liver ratio of less than 25%. SIRT with ^{90}Y has shown promise in operable disease as a supportive modality for multidisciplinary treatment of low-volume disease before definitive resection or ablation.[22] Recently, the LEGACY multicenter study reported the ablative intent of TARE in isolated, unresectable ≤8cm HCC. The best objective remission rate was 88.3%, with 76.1% of remissions lasting 6 months, and the 3-year overall survival rate was 86%.[23]

Contraindications

Contraindications for ^{90}Y SIRT encompass[24,25]: (1) Patients with poor hepatic function, as indicated by aminotransferase levels exceeding baseline by more than five times, Child-Pugh scores > 7, and bilirubin levels > 3.0 mg/dL. (2) Patients with poor renal function, with creatinine levels exceeding 188 μmol/L. (3) Pregnant and breastfeeding patients. (4) Patients with pulmonary shunts treated with TheraSphere, where the cumulative dose exceeds 30 Gy for a single treatment or the cumulative radiation dose for multiple treatments exceeds 50 Gy. This also applies if the lung shunting fraction (LSF) exceeds 20% when SIR-Sphere microspheres are employed, posing a risk of radiation pneumonitis. (5) Patients with platelet counts lower than 50×109 /L or those with concomitant blood system disorders. (6) Patients with platelet counts lower than 50×109 /L or those with concomitant blood system disorders.(7) Patients in poor general condition unable to tolerate interventional surgery.[26]

Dose Selection and Therapeutic Approach

Dose Selection

The dose of ^{90}Y microspheres is calculated differently depending on the nature of the microspheres. The most widely used algorithm for calculating the dose of ^{90}Y glass microspheres is the medical internal radiation dose (MIRD); D=A·M/50. D: radiation dose expected to be received by the treated segment or lobe of the liver in Gy; A: radiation activity required to be received by the treated segment or lobe in GBq; M: represents the mass of the treated segment or lobe in kg; M=volume in mL·1.03 mg/mL, volume in GBq. A: Activity to be received by the treated segment or lobe, in GBq; M: represents the mass of the treated segment or lobe, in kg, M=volume (mL)·1.03 mg/mL, volume can be measured by imaging. Methods for calculating ^{90}Y resin microspheres include: body surface area and partition modeling. The body surface area method is more widely used. The formula is: (1) Whole liver treatment: IA = (BSA-0.2) + tumor volume as a percentage of liver volume. (2) Liver lobe treatment alone: IA = [(BSA-0.2) + tumor volume as a proportion of liver volume] ·treated liver lobe as a proportion of the whole liver. IA: the radiation activity of ^{90}Y received by the treated liver lobe, unit: GBq; BSA: the body surface area, unit: m2.

Therapeutic Approach

Bridging Therapy for Liver Transplantation

In 2016, Mohamed et al retrospectively evaluated four treatment modalities as bridging therapy for liver transplantation: stereotactic body radiation therapy (SBRT, n=24), ^{90}Y microspheres (n=9), radiofrequency ablation (RFA) (n=9), and TACE (n=34). (n=34) as a bridging therapy for liver transplantation showed that patients treated with ^{90}Y radioactive microspheres had the highest rate of complete pathological remission (^{90}Y /TACE/RFA/SBRT: 75%/41%/60%/28.5%) and had good outcomes after liver transplantation. Therefore, as a bridging therapy for liver transplantation, ^{90}Y radioactive microspheres may be an alternative to other therapeutic modalities.

Radioactive Segmental Hepatectomy

Radioactive segmental hepatectomy can be performed in patients with poorly located liver tumors ≤3 cm (near the biliary system and vital vascular system) that are not amenable to surgery and ablation and are confined to 2 liver segments. The safety and efficacy of segmental hepatectomy was investigated in a study by Riaz et al, which enrolled 84 patients, each of whom underwent an individualized dose of segmental hepatectomy. In this study, 84 patients were enrolled and each patient was treated with an individualized dose of segmental hepatectomy, and all patients received glass microspheres infused with an average dose of 512 Gy and 210 Gy. The results of the study showed a tumor response rate of 59%

[World Health Organization (WHO) criteria] and 81% [European Association For the Study of the Liver (EASL) criteria], confirming the efficacy of segmental hepatectomy for early-stage tumors. The effectiveness of radiologic segmental hepatectomy for early-stage tumors has been confirmed.

Radioactive Lobectomy

This treatment modality involves the use of internal radiation therapy to the focal liver lobe to atrophy the treated lobe and increase the volume of the contralateral normal liver lobe, in keeping with the fact that the remaining liver volume after tumor resection can maintain body function. This application is similar to portal vein embolization (PVE) in surgical bridging with the goal of increasing the remaining liver volume to improve surgical success and patient survival. In addition radioactive hepatic lobectomy can inhibit tumor growth while not affecting the portal vein system, avoiding tumor progression and metastasis while the patient is waiting for surgery. Therefore, radioactive lobectomy may replace PVE as a bridging treatment for liver cancer surgery.

Efficacy and Prognostic Evaluation of Yttrium-90

With the development of glass and resin ^{90}Y microspheres in the early 1990s, numerous studies have commenced examining the long-term outcomes of different treatment stages. For instance, Salem et al conducted the first long-term outcome analysis of 291 hepatocellular carcinoma patients treated with glass microspheres for ^{90}Y selective internal irradiation, assessing efficiency and time to progression (TTP).[27] According to World Health Organization (WHO) and European Association For the Study of the Liver (EASL) criteria, the Objective Response Rate (ORR) was 42% and 57%, respectively. The median TTP for the entire patient cohort was 7.9 months. Survival outcomes varied according to Child-Pugh stage, with patients in Child-Pugh class A surviving significantly longer (17.2 months) than those in Child-Pugh class B (7.7 months).[28] In a similar European study of 108 patients with moderately advanced hepatocellular carcinoma who underwent glass microsphere radioembolization, the TTP for the entire cohort was 10 months, and the mean OS was 16.4 months,[29] In 2013, Mazzaferro et al conducted a Phase 2 study investigating the efficacy and long-term outcomes of ^{90}Y selective internal irradiation for treating Barcelona Clinic Liver Cancer (BCLC) stage intermediate- to advanced-stage HCC. Among 52 patients with a median follow-up of 36 months, the median TTP was 11 months, with no significant difference observed between patients with and without portal vein thrombosis. The median OS was 15 months, with an objective response noted in 40.4% of patients.[30]

ALBI classification was proposed in 2014 by JOHNSON et al. Regarding the calculation of the ALBI score, two clinically measured laboratory markers - albumin and bilirubin - need to be used, after which the score can be calculated according to the formula - ALBI score = (log10 bilirubin μmol/L × 0.66) + (−0.085 × albumin g/L), the score can be calculated. The score is then calculated according to the formula - ALBI score = (log10 bilirubin μmol/L × 0.66 + (−0.085 × albumin g/L). The score is then graded according to the calculated value - ALBI grade 1: score ≤ −2.60; ALBI grade 2: −2.60 < score ≤ −1.39; ALBI grade 3: score > 1.39.

LO et al found that the ALBI classification was a predictor of survival and hepatotoxicity, and that the combination of the Child-Pugh classification and the ALBI classification could more accurately predict the risk of hepatotoxicity after radiotherapy. LOUISE et al studied the role of ALBI classification in Western patients with Child A HCC treated with radiotherapy. They found that the ALBI classification was a better predictor of OS and incidence of radiotherapy-induced hepatotoxicity in Child A patients than the C-P score, and that the ALBI classification could be a more detailed classification for Child A patients and a more accurate predictor of prognosis for HCC patients treated with radiotherapy. Whether the ALBI classification can predict the prognosis of HCC patients treated with radiotherapy for portal vein embolization needs to be further investigated by clinicians.

Alkaline phosphatase (ALP) is mainly used in the clinic for the diagnosis of primary liver cancer, secondary liver cancer, hepatitis, obstructive jaundice and other diseases. In the presence of these diseases in the organism, hepatocytes can overproduce ALP, which then passes through the lymphatic channels and hepatic sinusoids into the bloodstream, while impaired bile excretion from the intrahepatic biliary tracts leads to reflux into the bloodstream, thus causing a significant increase in ALP expression. Previous studies have shown that the level of ALP is significantly elevated in

patients with hepatocellular carcinoma and is higher than that of hepatitis diseases and healthy people, and the rate of abnormally elevated ALP in patients with hepatocellular carcinoma is as high as 80%.

ALR is an indicator consisting of the ratio of AST to lymphocytes, ALRI = aspartate aminotransferase/lymphocytes. AST is a sensitive indicator of hepatocellular injury, and intracellular AST release is increased when hepatic parenchymal cells are damaged; therefore, elevated serum AST is a consequence of liver disease progression. Studies have shown that higher AST levels are associated with increased replication of hepatitis B virus, which correlates with lower overall survival in patients with HCC. In contrast, the immune response to tumors is determined by the presence of lymphocytes, which mediate cytotoxic responses and release cytokines that inhibit tumor proliferation and metastasis. Primary tumor-infiltrating lymphocytosis is a good prognosis for tumor regression. Some studies have shown that absolute lymphocyte count is a strong predictor of HCC recurrence. However, few studies have examined the relationship between ALRI and the prognosis of radiation therapy in patients with hepatocellular carcinoma. Therefore, prospective studies with large samples are still needed to demonstrate our findings on the prognostic value of ALRI in primary liver cancer and to further determine its optimal critical value for clinical application, which will bring a promising prospect for improving the prognosis of patients with hepatocellular carcinoma.

Advantages and Safety of Yttrium-90

Comparison of the Efficacy of Yttrium-90 and TACE

Recent years have witnessed numerous studies comparing the efficacy of ^{90}Y selective internal irradiation therapy with TACE and other local therapies concerning definitive treatment and staging as a bridge to transplantation.[31] In 2016, Laila Lobo et al conducted a systematic review and meta-analysis of five studies encompassing 553 patients with unresectable hepatocellular carcinoma treated with TACE or ^{90}Y. The meta-analysis results indicated no significant differences in survival up to 4 years between the two groups. Moreover, despite increased post-treatment pain in TACE-treated patients, partial and complete remission rates were similar, as were the complication profiles between the two treatments.[32] In 2016, results were released from a landmark Phase 2 study, the PREMIERE trial, which compared the TTP of 45 patients with BCLC Class A or B randomised to receive either TACE or ^{90}Y selective internal irradiation. The researchers found that patients treated with ^{90}Y had a significantly longer median TTP compared to TACE (26 months vs 6.8 months), although no significant difference in survival was found, which on the face of the data may "suggest that local control is not sufficient to improve survival in cirrhotic patients at risk of death"[33] but it should be noted that the trial ended prematurely due to slow gains. While the trial results lacked a survival benefit, the researchers did note that increased TTP and improved local control in ^{90}Y-treated patients increased the likelihood of liver transplantation in patients with advanced disease. Conventional transarterial chemoembolisation (TACE) is the most commonly used treatment in this setting, but this phase 2 randomised controlled trial [TTP (>26 months) was significantly longer in the ^{90}Y group than in the TACE group (6.8 months) (p=0.0012)] was the first level I evidence of improved TTP with ^{90}Y over TACE, which led to the adoption of ^{90}Y as the standard arterial treatment for liver cancer[34]. In addition, the lower incidence of diarrhoea and hypoproteinaemia, and improved quality of life compared to TACE may make ^{90}Y a more attractive alternative for transplant-eligible HCC patients[35].

Efficacy of Yttrium-90 versus Sorafenib

The SARAH trial in 25 centres specialising in liver disease in France assessed the relative efficacy of ^{90}Y selective internal irradiation therapy versus sorafenib in patients with advanced hepatocellular carcinoma. This was a Phase 3, randomised, controlled, open-label, multicentre trial including 459 patients with locally advanced hepatocellular carcinoma (BCLC C) or patients who had failed two previous rounds of TACE. Patients were randomised to receive sorafenib or ^{90}Y selective internal irradiation with the primary endpoint of Overall Survival (OS) and secondary endpoints of Progression-free Survival (PFS), TTP, Efficacy, Adverse Events and Quality of Life. There was no significant difference in mean OS between the two treatment groups, with patients surviving for 8.0 and 9.9 months in the ^{90}Y and sorafenib groups, respectively. The median PFS was similar between the two groups in the Intention To Treat (ITT) population and the per-protocol population.^{90}Y The objective rate of effectiveness (ORR) was significantly higher in the intention-to-

treat (ITT) population. In addition, the sorafenib group had a higher incidence of treatment group-related adverse events, including fatigue, haematological abnormalities, diarrhoea, abdominal pain and dermatological reactions[15,34]. Thus, the earlier ^{90}Y selective internal irradiation therapy is introduced in non-operable settings, the more likely the less damaged liver is to tolerate the toxicity and potentially better control local disease[22].

With greater understanding of the safety and efficacy of ^{90}Y,^{90}Y selective internal irradiation therapy has been shown to be a safe and effective treatment for patients with HCC spanning the Barcelona Clinical Liver Cancer (BCLC) stage. Compared with alternative therapies such as transarterial chemoembolisation (TACE) and sorafenib,^{90}Y selective internal irradiation therapy is increasingly used in the treatment of hepatocellular carcinoma because of its durable local control, good long-term efficacy, and equivalent tumour responsiveness and tolerability.[36] In addition, SIRT with ^{90}Y remains an effective option for patients with unresectable overt liver disease who have failed chemotherapy or require a chemotherapy holiday while maintaining a progression-free grace period[37–39].

Adverse Effects and Prevention

^{90}Y-selective internal irradiation therapy is relatively safe in general, with a lower incidence and milder manifestation of postoperative adverse effects compared to conventional TACE, in three main ways:

Liver Parenchymal Complications

Radioembolisation-induced liver disease (RILD):RILD is a syndrome characterised by jaundice, ascites and elevated bilirubin.Initial treatment of RILD consists of diuretic administration.More severe cases may require intravenous fibrin-lowering peptides, steroids, or even transjugular intrahepatic portosystemic shunt.

Post-radioembolization syndrome (PRS): Post-radioembolization syndrome is characterized by fever, fatigue, nausea, vomiting and anorexia.PRS is a self-limiting condition and many centres prescribe a course of steroids and an antiemetic regimen to minimize the symptoms of PRS.

Biliary tract injury: the most common biliary adverse effects include biliary necrosis and biliary stricture formation. Patients requiring further intervention require drainage of cholangiomas and abscesses and cholecystectomy for radiation cholecystitis.

Complications of Non-Targeted Delivery of Radioembolisation

Radiation gastritis: The clinical manifestations of radiation gastrointestinal ulcers include abdominal pain, anorexia, nausea and vomiting, which appear on average after 5 weeks of treatment. Although most patients make a full recovery, symptoms may persist for up to 1 year, and some may require surgical intervention, which also carries a risk of fatality[40].

Radiation pneumonitis: Radiation pneumonitis (a restrictive lung dysfunction) can be seen when the LSF is greater than 13%. Radiation pneumonitis can be diagnosed clinically and solid lung lesions can also be found on imaging[41]. Treatment of radiation pneumonitis is not widely supported by evidence, but usually includes oxygen supplementation and intravenous steroids[40].

Radiation cholecystitis: The mechanism of radiation cholecystitis after selective internal irradiation is not fully understood, but may include direct mucosal injury secondary to radiation and ischaemia associated with microsphere embolism. Patients who develop radiation cholecystitis will develop signs and symptoms of acute cholecystitis, including right upper abdominal pain, nausea, vomiting, and fever, over a period of weeks to months. Most patients can be treated conservatively with supportive care (hydration, pain control, and antibiotics). Cholecystectomy is an option for patients with refractory symptoms.

Vascular Complications

Performing selective endo-irradiation creates the same risks of arterial access and vascular injury as other intra-arterial treatments, such as puncture site haematomas, pseudoaneurysms, and arterial clips. When vascular injury is encountered, angioplasty, stenting, and subsequent pharmacological treatment may be required[40].

In the case of ^{90}Y selective internal irradiation therapy, the correct identification and differentiation of adverse reactions and complications is an important part of guiding the subsequent management; most of the adverse reactions

are non-specific symptoms that require only symptomatic treatment; whereas complications require early identification and active management.[42] Complications, on the other hand, require early identification and active management.

In addition, in the 2014 Korean Practice Guidelines, it is recommended that if a patient has preserved liver function (ie, Child-Pugh class A or superb B), is not eligible for primary treatment, has an incomplete response to TACE, or has portal vein invasion when the percentage of the total liver volume irradiated with ≥30 Gy is ≤60%, and has a need to alleviate the symptoms caused by primary HCC or its metastases, then external beam radiation therapy (EBRT) may be considered. Modern EBRT approaches include three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic ablative body radiation therapy (SBRT), and image-guided radiation therapy. Targeted therapy + immunosuppressant therapy, such as Sorafenib or Lenvatinib in combination with a PD-1 inhibitor, can also be considered for HCC when the patient does not tolerate radiation therapy.

Conclusion

^{90}Y Selective internal irradiation therapy has become a localised treatment with good efficacy, safety and quality of life in the past decade. Since 2017,^{90}Y selective internal irradiation therapy has been included in the primary liver cancer treatment guidelines; the Primary Liver Cancer Treatment Guidelines (2022 Edition) even states that:^{90}Y selective internal irradiation therapy can be used for palliative (bridging or downstaging) treatment of liver cancer as well as explicitly stating that ^{90}Y microsphere therapy is a localised treatment for liver cancer. In the future,^{90}Y will also occupy a more important position in the treatment of liver cancer. Clinical experience with ^{90}Y for the treatment of HCC began with advanced HCC and then gradually expanded to intermediate and early stages. Clinical trials to date have yielded promising results in early-stage patients, using tailored dosimetric and super-selective approaches that allow selective delivery of high doses of radiation to the tumor, yielding high radiological responses and long-term survival rates comparable to other options for therapeutic purposes (eg, surgery and ablation). As a result, ^{90}Y is emerging as an early treatment for HCC.

Although ^{90}Y has excellent efficacy in primary liver cancer, there is no clear evidence that ^{90}Y has the same effect in other related cancers. For example, Intrahepatic Cholangiocarcinoma (ICC) is a primary liver tumour with a lower incidence than hepatocellular carcinoma. Resection moderately improves survival and is only one option for patients with resectable ICC. Chemoembolisation has a limited role in cholangiocarcinoma and may improve survival, but is highly toxic. Although radioembolisation has been shown to be effective in the treatment of hepatocellular carcinoma, its role in the management of ICC has not been studied in detail[43].

An important area of research in the coming years will be the possible combination of ^{90}Y radioembolisation with other treatments. Indeed, since ^{90}Y selective internal irradiation therapy may have the same indications as TACE or sorafenib, questions will arise as to whether these treatments can be used in combination or sequentially[44,45]. In addition, the appropriate timing of combination therapy may be of concern, as combination therapy may be more effective but more toxic[5].

Many advances have been made in the field of therapeutic nuclear medicine. Iodine oil is a radio-opaque agent that serves as a suitable carrier for therapeutic radionuclides. It has a direct uptake affinity for cancer cells in the liver. Beta-emitting iodine-131 (Iodine-131, ^{131}I) conjugated to this drug shows higher tumour radiation doses compared to ^{90}Y microspheres. Targeted alpha-particle therapy (TAT) has emerged as a potential treatment for metastatic disease using alpha-emitting particles such as actinium-225 (Actinium-225, ^{225}Ac), astatine-211 (astatine-211, ^{211}At) and lead-212 (Lead- 212, ^{212}Pb)[46,47]. They provide short-range, highly linear energy delivery to cancer cells with minimal toxicity to surrounding tissues. Using radioimmunotherapy, these particles attach to monoclonal antibodies or peptides, which attract tumour antigens or receptors[48]. These promising targeted therapies with better energy delivery are the future of precision medicine.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Inner Mongolia Medical University Postgraduate Talent Excellence Program (NO. YKD2023ZY001).

Disclosure

The authors report no conflicts of interest in this work.

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