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Other non-surgical treatments for liver cancer

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ABSTRACT

Interventional radiology plays a major role in the modern management of liver cancers, in primary hepatic malignancies or metastases and in palliative or curative situations. Radiological treatments are divided in two categories based on their approach: endovascular treatment and direct transcapsular access.

Endovascular treatments include mainly three applications: transarterial chemoembolization (TACE), transarterial radioembolization (TARE) and portal vein embolization (PVE). TACE and TARE share an endovascular arterial approach, consisting of a selective catheterization of the hepatic artery or its branches. Subsequently, either a chemotherapy (TACE) or radioembolic (TARE) agent is injected in the target vessel to act on the tumor. PVE raises the volume of the future liver remnant in extended hepatectomy by embolizing a portal vein territory which results in hepatic regeneration.

Direct transcapsular access treatments involve mainly three techniques: radiofrequency thermal ablation (RFA), microwave thermal ablation (MWA) and percutaneous ethanol injection (PEI). RFA and MWA procedures are almost identical, their clinical applications are similar. A probe is deployed directly into the tumor to generate heat and coagulation necrosis. PEI has known implications based on the chemical toxicity of intra-tumoral injection with highly concentrated alcohol by a thin needle.

1. Background

Interventional radiology became a central element in the treatment of liver cancer, providing multiple possibilities for the management of primary hepatic malignancies or metastases. Technological advances of the two past decades have metamorphosed the prognosis of a number of patients, turning palliative situations into curative hopes. Radiological means are attractive through their potential efficiency, their minimally invasive nature and even more by the fact that they can be used in combined treatment strategies, like granting

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in situ pathways to heighten chemotherapy effect or allowing a surgical resection by increasing the size of the future liver remnant.

The common characteristic of radiological methods is the organ approach which consists of arterial or venous endovascular access, or a direct transcapsular approach either in a percutaneous way or concurrently with a surgical procedure.

In the following sections, we offer an overview of some radiological methods that can be integrated into liver malignancy therapeutic projects, broaching technical principles and leading applications.

Stereotactic body radiation therapy can also be part of this multidisciplinary approach while it has shown to provide promising results in the treatment of hepatocellular carcinoma and liver metastases.[1,2]

2. Endovascular treatments

2.1. *Transarterial chemoembolization (TACE)*

This treatment is based on the following vascular features: the non-tumor liver parenchyma receives two-third of its blood supply from the portal vein and only one-third from the hepatic artery, whereas hepatic tumors are mainly vascularized by branches of the hepatic artery. Through a peripheral arterial access, a selective catheterization of the targeted arterial branch is performed, allowing the injection of a chemotherapeutic molecule combined with an embolic agent. Beside the hepatic artery, it is crucial to search and to treat extrahepatic arterial supplies of the tumor, such as the right inferior phrenic artery, to ensure an optimal effectiveness. Two types of procedures have been described.

2.1.1. *Transarterial oily-chemoembolization*

This procedure employs a mixture of highly concentrated chemotherapy agent with ethiodized oil, marketed as Lipiodol®. The latter combines substantial inherent benefits beyond its carrier nature. Its high iodine concentration makes it opaque to X-ray, which is helpful to adapt flow delivery during the injection to prevent the reflux issue and to control the captation rate of the tumor on CT. Indeed, the degree of Lipiodol® uptake appears to be an independent prognosis factor (Fig. 1).[3,4] Furthermore, it has tumor-seeking properties, its viscosity slows down the washout of the chemotherapy agent, and its oily nature provides tropism to small tumor vessels.[5,6] The most widely used chemotherapy agent is doxorubicin but no scientific proof of its superiority has been established, and cisplatin or epirubicin might be as effective.

Afterwards, an embolic agent is injected causing ischemia and necrosis of the tumor and delaying the drug washout. Multiple embolic agents can be employed, the most widely used is gelatin sponge made of purified porcine-derived gelatin which facilitates repetitive procedures by its resorbability.

In patients with hepatocellular carcinoma (HCC), the frequently underlying cirrhosis narrows therapeutic options since TACE can lead to liver decompensation. Thus, functional hepatic reserve becomes a prerequisite for TACE treatment.[7] Consequently, patients need to be rigorously selected: a panel of experts has determined contraindications including biliary obstruction, decompensated cirrhosis (Child-Pugh B8 or higher), hepatofugal portal flow or portal vein thrombosis, extensive tumor with replacement of both lobes and severe renal insufficiency.[8]

Other complications of TACE include non-target embolization, hepatic abscess and bilioma, facilitated by biliary obstruction, renal failure or variceal bleeding.

The post-embolization syndrome, which is a combination of pain, fever, nausea and vomiting lasts a few hours to a few days and is more of an expected consequence than a complication.

2.1.2. *TACE with drug-eluting beads*

More recently, drug-eluting beads have been developed. These are non-resorbable agents, their chemical structure combines polymeric microspheres doped with sulfonyl groups that provide a reversible ionic binding with polar molecules such as doxorubicin. Benefits reside in a reduced systemic passage of the cytotoxic substances employed, with comparable outcomes to lipiodol (Fig. 2).[9–11] Indeed, the PRECISION V study compared, for a 6 months follow-up, oily-TACE and TACE with DC Beads. The DC Bead group showed non-significantly higher rates of complete response, objective response, and disease control compared with the oily-TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively), $P = 0.11$.[11] Nevertheless, the DC Bead group showed improved tolerability, with a reduction in liver toxicity ($P < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($P = 0.0001$).[11]

2.2. *Transarterial radioembolization (TARE)*

This treatment is based on similar principles to TACE, applied to nuclear medicine. TARE selectively delivers high radiations doses to hepatic tumors and minimizes as much as possible the radiation dose received by the non-tumor liver parenchyma and other organs, especially the lungs, stomach and bowel.[12]

For this purpose, quite a few combinations of vectors and radionuclides have been proposed.

2.2.1. *^{131}I-Lipiodol®*

The first example of this strategy is the use of radiopharmaceutical ^{131}I-Lipiodol®. This combination takes advantages of Lipiodol® properties discussed previously and of the gamma rays emitted by this radioisotope. The therapeutic dose is estimated not to exceed the threshold of 30 Gy to the lungs and to the non-tumor liver.

The preliminary step to perform this technique consists of a procedure achieved with a low radiation dose. The aim of this procedure is to quantify the shunting of microparticles to the lungs or the gastrointestinal tract. It is helpful for patient selection because risks of radiation gastritis, enteritis or pneumonia are supposed to be dose-dependent effects. This first phase also allows the evaluation of the dose necessary for treatment.

Subsequently, the treatment is performed via radiologic techniques comparable to TACE (Fig. 3).

Main benefits of this method are: a real-time control of the injection allowed by the radio-opacity of the drug and a simplified evaluation of the efficiency which is correlated to

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