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Minimal invasive treatments for liver malignancies

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ABSTRACT

Minimal invasive therapies have proved useful in the management of primary and secondary hepatic malignancies. The most relevant aspects of all these therapies are their minimal toxicity profiles and highly effective tumor responses without affecting the normal hepatic parenchyma. These unique characteristics coupled with their minimally invasive nature provide an attractive therapeutic option for patients who previously may have had few alternatives. Combination of these therapies might extend indications to bring curative treatment to a wider selected population. The results of various ongoing combination trials of intraarterial therapies with targeted therapies are awaited to further improve survival in this patient group. This review focuses on the application of ablative and intra-arterial therapies in the management of hepatocellular carcinoma and hepatic colorectal metastasis.

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1. Introduction

Liver involvement in neoplastic pathologies represents a main clinical issue in oncology, both for primary and secondary tumors. When the liver is affected, it "overrules" the patient's prognosis, presenting a main clinical issue for the patient. In the majority of patients affected by hepatocellular carcinoma (HCC), the simultaneous presence of liver cirrhosis and tumor nodules limits the indications for an aggressive local approach, such as resection, due to the high risk of post-treatment liver failure. Moreover, the high rate of developing new nodules after any local treatment (>80% after 4 years) plays a key role in the decision making on treatment strategies. Hepatic resection (HR) has generally been accepted as the first choice for the treatment of HCC in many medical centers. Nevertheless, the cirrhosis that accompanies HCC limits the extent of surgery and thus increases the risk of postoperative liver failure [1]. Taken cirrhosis into consideration, several classification systems have been developed in recent years to combine tumor stage and the grade of cirrhosis for determining treatment strategies. Among these, the Barcelona Clinic Liver Cancer (BCLC) classification has emerged as the standard classification, allocating the standard of care for each tumor stage [2]. In liver metastases, specifically in colorectal liver spread, it's clinically proven that local treatments, such as resection, in combination with perioperative systemic chemotherapy yield better outcomes with respect to survival than chemotherapy alone. The same holds for the innovative targeted therapies. While surgical hepatic excision has been recognized as the treatment of choice for patients with hepatic metastasis derived from colorectal cancer, it can be performed only in approximately 10–20% of patients [3]. Surgical exclusion, in most cases, is limited by the insufficient remnant hepatic parenchyma after a radical resection.

Thus, on-surgical metastatic patients have to rely on new and effective systemic therapies (new drugs, biological, etc.) to achieve prolonged survival. Even greater local control and longer survival can be obtained if systemic therapies can be combined with minimally invasive local treatments that inflict less harm to patients. In addition, minimally invasive local techniques can compliment surgical resection to achieve better clinical results. According to the level of liver involvement with respect to the number, site and size of hepatic malignancies, different minimally invasive approaches can be used. Currently available minimally invasive therapies can be divided into two categories: ablative therapies and intra-arterial therapies. We will focus this review on the application of ablative and intra-arterial therapies in the management of hepatocellular carcinoma and hepatic colorectal metastasis.

2. Local ablative therapies

This broad category includes those modalities that employ different forms of energy, delivered "in situ", with the common goal of targeted tissue destruction. Chemical, thermal and electrical energy sources have been vigorously used, researched, developed, improved and clinically deployed in the last several years. Chemical ablation is the oldest percutaneous technique that has been broadly performed using agents such as ethanol or acetic acid (percutaneous ethanol injection, PEI), which destroys tumor cells within the targeted tissue by induction of coagulative necrosis. However, such chemical substances, when injected percutaneously

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through thin needles, can diffuse into nearby tissues, which may increase the risk of drug diffusion into the arterial system and cause harmful complications. Neverthless, this technique has had low procedural complication rate and very promising results in terms of local control for treating capsulated HCC nodules that are less than 5 cm. 5-year overall survical (OS) is at 47% and 29% respectively, for Child A and B cirrhotic patients. In the treatment of single infiltrating or multiple encapsulated tumors, the injection of chemical substances has shown least efficacy, mainly due to the absence of a peripheral capsule which can retain the chemical agents within tumor tissues [4]. The same issue could probably account for the unsatisfactory results when this technique is employed for treating liver metastases.

Chemical ablation has been replaced by newer technologies, based on induction of temperature variations: both increase and decrease, until the desired cytotoxic level is achieved within the targeted tissues. When heat is applied and maintained for sufficient time, over a target temperature, tissue ablation is achieved. Usually, a temperature less than −40 °C or higher than 60 °C, the onset of cell destruction is almost instantaneously via the induction of proteins denaturation or plasma membrane collapse due to ice crystal formation. Complete necrosis can be induced in almost all tissue types at such extreme temperatures. When reaching a temperature near to 50 °C, cell death related to microvascular thrombosis, ischemia, and hypoxia may occur [5]. At temperatures slightly more than −40 °C cells cool off slower and are susceptible to cell death from osmotic shock. Ice formation outside the cells, induces a hyperosmotic extracellular space with cell dehydration and, upon thawing, a reversal flux inward the cell, inducing cell swelling and membrane rupture [6].

3. Radiofrequency ablation

Radiofrequency energy represents the most well studied technology and the main reference for the evaluation of other more recently developed ablative techniques. When RF energy is applied, an oscillating electrical current flows through the body between electrodes in a simple circuit in which tissues, being weak electrical conductors, represent the resistive element. Thus, ionic agitation is induced in tissues around interstitial electrode and resistive heating is produced in the areas closest to the interstitial probe. As a result, tissues in proximity to the electrode are subjected to the highest current and thus a greater rise in temperature than tissues further away from the probe that are heated mostly via thermal conduction [7]. Radiofrequency ablation has emerged as the standard technique for local tumor treatment and has demonstrated better survival than PEI. Cho et al. in a recent meta-analysis of RCTs on small HCC treatment reported better local control and significant improvement in 3-year survival with RFA when compared to PEI (odds ratio 0.477, 95% confidence interval 0.340–0.670; $P < 0.001$) [8]. The main limitations of RFA are the dimension of lesions to be treated, the "heat sink effect" produced by main vessels close to the tumor and the possibility of high major complication rate when used for sub-capsular lesions and when bile duct is in the proximity. Livraghi et al. [9] reported the safety of RFA in liver malignancies in a multicenter study involving 3500 patients: low mortality (0.3%) and low morbidity rate with major and minor complications were observed in 2.2% and less than 5% of patients, respectively. This large cohort study has established percutaneous RFA as a safe and relatively low-risk procedure.

3.1. RFA for HCC

According to the BCLC staging system, image-guided tumor ablation is the first-line option for the very early-stage HCC, in cases where transplant is not available. Local control of this condition by radiofrequency ablation is nearly 100% with survival almost identical to surgical anatomical resection [10,11]. Rate of complete response using RF ablation in this stage has been reported to be nearly 97% with a 5 year survival rate of 68% [12]. Subcapsular, gallbladder or bile duct proximity as well as patient characteristics (overweight, portal hypertension) may influence treatment, increasing incidence of major complication and incomplete treatment with worst results than the average [13,14].

In BCLC early-stage, while the reciprocal roles and the indications of hepatic resection and percutaneous thermal ablation were the main objectives analyzed in several retrospective studies and randomized controlled trials, they remain to be clarified. Hepatic resection (HR) appears superior to RFA in terms of survival and recurrence-free interval.

Three published RCTs comparing RF and HR for Child Pugh A and B patients, reported a 3-year overall survival (OS) and 3-year recurrence free survival (RFS) at 67–71% and 46–64%, respectively. Two retrospective studies [15,16] reporting long-term follow-up results in a large cohort undergoing RFA for early stage HCC (met Milan criteria). The two studies also have observed an 8-year survival rate of 43.2% and 32.3%, and a 10-year survival rate of 45.1% and 27.3%, respectively which are roughly comparable with those reported for hepatic resection (10-year survival: 20–28.7%) [17,18]. Although hepatic resection shows a better local tumor control than RF, it has not translated into survival benefit. An aggressive management of local recurrence is effective in improving OS outcome [15,19].

A single session of RFA may achieve a necrotic area up to 5 cm thus covering a 3 cm tumor with at least 1 cm of safe margin [20]. Several authors have described combined therapy in order to achieve larger ablation volumes. The aim of combining trans-catheter arterial embolization, by microparticles or other embolizing agents, is to reduce hepatic parenchymal flow and thus the impact of "heat-sink effect" on heat passive diffusion. Bonomo et al. retrospectively evaluated the feasibility, efficacy, and safety of combining in the same session bland 100 μm microparticles embolization and RFA in unresectable malignancies. Liver lesions had a maximum axial diameter ranging 16–59 mm. Postintervention unenhanced ablated areas ranged 28–104 mm in maximum axial diameter with safe margins ranging from 1 to 30.5 mm. No tumor local relapse was observed up to 12 months. Other RCTs are ongoing and will clarify the role of RFA and other ablative therapies for the management of in this type of HCC patients.

3.2. RFA for colorectal liver metastases (CRLM)

The 5-year survival rate of CRC is reportedly at 61% [21]. Hepatic metastasis, present in up to 50% of the CRLM patients [24], represents the leading cause of cancer-related morbidity and mortality [22,23]. Surgical hepatic excision has been the choice of treatment for CRLM patients, which can achieve an R0 resection, offering long-term survival between 25% and 50% at 5-year depending on the series [25,26]. However, surgical resection can be performed only in approximately 10–20% of CRLM patients [26–29].

Several trials have analyzed the role of RFA in the two main scenarios of CRLM: the resectable and the unresectable disease. To date, therapeutic equivalence to surgery for RFA have not been established [30]. For RFA, the overall 5-year survival rate is between 27% and 50% and recurrence-free survival rate from 0% to 34%, with the local recurrence rate of 11–37%. However, in most cases, patients who underwent RFA had a poorer prognosis compared to patients who underwent hepatic resection [30]. Two studies showed a progression free survival of 10% and 27.6% respectively in the RFA arm versus 10.6% in the chemotherapy-alone arm

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