Advancements of interventional oncology treatments for early stage hepatocellular carcinoma

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Chapter 1

General introduction and outline of thesis

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, accounting for 75-80% of all liver cancers [1]. Liver cancer is the sixth most prevalent malignancy worldwide and ranks as the fourth leading cause of cancer-related death [2]. HCC typically arises in the context of chronic liver disease, primarily caused by hepatitis B or C virus infection, alcohol-related liver disease, or metabolic dysfunction-associated liver disease (former non-alcoholic fatty liver disease). Large geographical variation in incidence is observed, with the highest rates reported in Eastern Asia and Sub-Saharan countries and viral hepatitis as the most common etiology. In the Netherlands, the number of new HCC diagnoses in 2021 reached nearly 800, having doubled since 2008 [3], mainly due to an ageing population. Early diagnosis is challenging, as patients often remain asymptomatic until the disease has progressed to an advanced stage with limited treatment options left. However, screening programs for high-risk patients have led to earlier detection and improved outcomes [4].

The staging of HCC in the background of cirrhosis follows the Barcelona Clinic for Liver Cancer (BCLC) criteria [5]. Very early stage HCC (BCLC 0) refers to solitary lesions up to 2 cm. The treatment of choice for BCLC 0 is thermal ablation (TA) with curative intent. Early stage HCC (BCLC A) includes solitary lesions larger than 2 cm or up to 3 lesions of ≤3 cm each, and surgical resection or liver transplantation are generally considered as the treatments of first choice. However, due to portal hypertension caused by cirrhosis, patients may not be eligible for surgical resection. In such cases, depending on lesion size and location, thermal ablation, trans-arterial chemoembolization (TACE), transarterial radioembolization (TARE), or a combination of these therapies can be considered. Intermediate stage patients (BCLC B) have tumor load beyond early stage HCC, remaining confined to the liver. These patients are often treated with trans-arterial or systemic therapy. Patients with extra-hepatic metastases or macrovascular invasion are considered advanced stage (BCLC C) and are, according to the BCLC criteria, eligible for systemic treatment only.

Despite effective HCC treatments, the presence of underlying cirrhosis often leads to development of new intrahepatic lesions elsewhere in the liver [4]. For BCLC A-B patients meeting specific criteria, liver transplantation may be a suitable option [5]. Regardless the risks associated with this major treatment procedure, long-term clinical outcomes are good as it addresses both the underlying liver disease as well as the liver cancer.

Thermal ablation

Over the past decades, TA techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), have emerged as effective alternatives to liver surgery. These minimally

invasive treatments are usually performed percutaneously under image guidance [6]. Both RFA and MWA induce tissue heating to at least 55-60 degrees Celsius to necrotize tumor tissue [7]. RFA uses a high-frequency monopolar alternating current leading to resistive heat propagation away from the active tip, resulting in ablation zones up to 4-5 cm. MWA, a more recent technique, employs microwaves to induce oscillation of water molecules for heat induction. Compared to RFA, it relies less on heat conduction, reaches higher temperatures, and is less susceptible to heat sinking by large blood vessels close to the ablation zone. The popularity of MWA has grown due to these advantages, although no significant difference in clinical outcome between the techniques has been reported in literature [8].

Ultrasound, CT or cone-beam CT can all be used for image guidance during needle positioning. While the patient is still under general anestheisa or conscious sedatation, a post-treatment contrast-enhanced CT scan is typically acquired to assess treatment success. In contrast to surgical treatment, technical success after thermal ablation cannot be determined by pathological assessment of the resected specimen. Therefore, a technically successful treatment has been defined as a full ablation of the entire lesion, with a 5 mm safety margin [6]. This margin assessment is usually performed by a side-to-side comparison of pre- and post-ablation cross-sectional images aided by 2D in-plane measurements. Additional ablation may be performed at the discretion of the physician if the margins are deemed insufficient. Despite these efforts the chances of developing local recurrences are generally considered to be higher when compared to surgical resection, for HCC lesions >2 cm [9].

Transarterial radioembolization

TARE is a minimally invasive treatment in which beta radiation-emitting microspheres are delivered trans-arterially to tumor bearing parts of the liver. Since TARE is administered arterially, the treatment makes use of the biological difference in tumor tissue perfusion (mostly arterial) versus parenchymal perfusion (mostly portal venous) [10]. Previous trials in which radioembolization was compared with systemic therapy in BCLC advanced stage HCC did not show overall survival benefit [11], but recent literature has shown that efficacy increases with personalized dosimetry, and beneficial use in earlier stages HCC [12].

Outline of thesis

This thesis aims to evaluate minimally invasive treatments for HCC, with a focus on ‘early stage’ HCC. Patients within this BCLC category are often not eligible for surgical treatment due to underlying liver cirrhosis with portal hypertension. Especially in tumors >3 cm precision ablation and optimized minimally invasive treatments are warranted as these tumors are prone to local recurrence after TA.

PART I of this thesis focuses on reproducibility of TA and ablation margins. *Chapter 2* compares two commercially available MWA devices at different settings in a controlled, ex-vivo environment, evaluating the size and sphericity of their ablation zones. *Chapter 3* presents a systematic review of the available evidence concerning ablation margin quantification in TA, in which recent literature regarding image processing techniques for ablation margin quantification after TA is reviewed. *Chapter 4* is a retrospective study correlating local tumor progression with quantified ablation margins after TA of HCC, using commercially available software based on a non-rigid registration algorithm. *Chapter 5* presents a prospective study evaluating the feasibility of intraprocedural ablation margin quantification using in-house developed software and an optimized pre- and post-ablation CT scanning protocol.

PART II of this thesis explores treatment combinations within early stage HCC. As local recurrence rates after TA increase with lesion size, TA is combined with a transarterial treatment in HCC lesions >3 cm to increase the treatment efficacy. *Chapter 6* evaluates a historic cohort of HCC patients treated with TA and TACE. *Chapter 7* outlines the clinical study protocol of the HORA EST HCC study, in which RFA is combined with adjuvant TARE using holmium-166 microspheres. A dose-escalation study protocol for adjuvant TARE is used to determine the administration dose of holmium-166. The results of this trial are presented in *Chapter 8*.

PART III of this thesis evaluates clinical outcomes of TARE treatment for HCC beyond early stage HCC, where TARE is mainly applied in intermediate or advanced stage HCC. A retrospective cohort of 85 patients in three hospitals was evaluated in respect of clinical outcomes and radioembolization induced liver disease in *Chapter 9*.

Finally, *Chapter 10* provides a summary, general discussion and future perspectives. In *Chapter 11* a Dutch summary can be found.

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