Advancements in minimally invasive image-guided liver therapies

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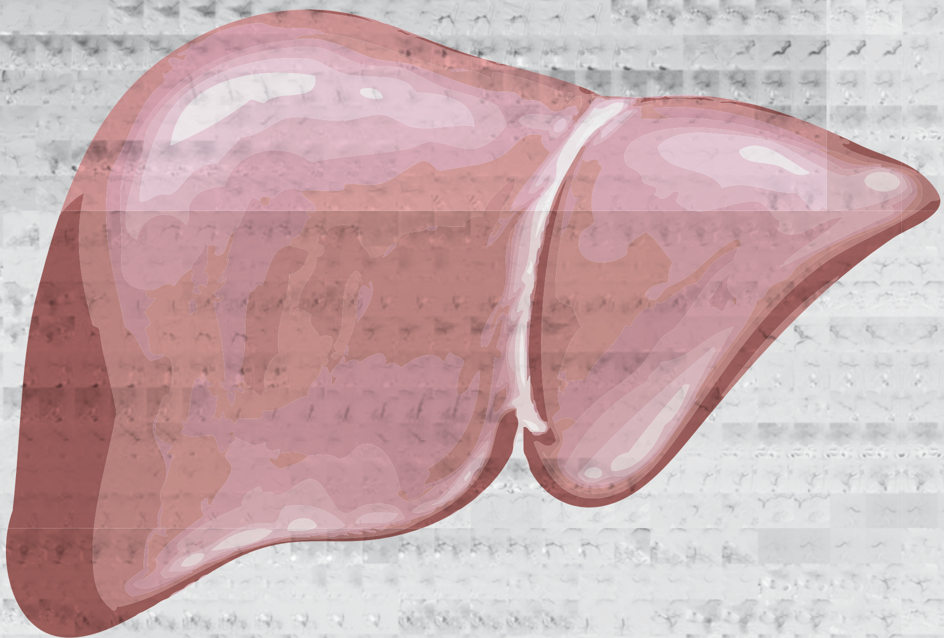
Chapter 1

General introduction



INTRODUCTION

Interventional oncology

Interventional oncology (IO) is a rapidly evolving sub-specialty of interventional radiology with increasing importance in the management of cancer patients. Over the past two decades interventional radiologists together with scientists have ridding the tidal wave of technological innovation to introduce multiple novel cancer treatments. Therapies such as percutaneous ablation, drug-eluting bead trans-arterial chemo-embolization and radioembolization have found their way to clinical practice and are now considered standard of care for various indications. As interventional radiology procedures are targeted minimally invasive therapies, complication rates are generally low and hospital admissions short. This offers clear advantages over surgical procedures and intense chemotherapeutic regimes that put a larger burden on both the health care budget and patients.

IO is a relatively new medical specialty compared to other specialties involved in cancer care, such as surgery, radiotherapy and medical oncology. Whereas many surgical procedures and chemotherapeutic therapies have gone through decades of improvements and evaluation in clinical research and trials, some of the IO procedures have only been introduced in clinical practice over recent years. There is a need for further research to optimize novel minimally invasive therapies and to determine the role in the treatment algorithms for various cancer types.

LIVER MALIGNANCIES

Liver malignancies have been at the center of attention of interventional oncologists. The liver has several unique features that can be utilized when performing minimally invasive image-guided therapies. It is the largest solid organ in the human body and occupies much of the right hypochondrial region of the upper abdomen. The location, size and texture of the liver allow excellent visualization with ultrasonography. Furthermore, the liver has a unique dual blood supply. Most of the blood supply to the hepatocytes is derived from the portal vein (70-80%) and the hepatic arteries supply the remaining 20-30%. In contrast, most hepatic malignancies have a dominant or exclusive vascular supply from the hepatic artery. The difference in vascularization between non-tumorous liver parenchyma and liver malignancies is utilized in transarterial therapies, such as transarterial (chemo)embolization, radioembolization and percutaneous hepatic perfusion.

Primary liver malignancies

Most patients in this thesis are patients with hepatocellular carcinoma (HCC). Primary liver cancer is a rare disease in the Netherlands, but the third most common cause of cancer-related death in the world (1). HCC represents more than 90% of primary liver tumors and the incidence of HCC in Europe is estimated to increase from 21.000 cases in 2008 to 78.000 cases in 2020 (1). Approximately 90% of HCC are associated with an underlying liver disease (1). At the time of diagnosis, the majority of patients with HCC are not surgical candidates. Surgical resection may not be feasible as a result of tumor location, advanced stage of disease or contra-indications such as liver cirrhosis with portal hypertension, deranged liver function or co-morbidity.

For patients who are not surgical candidates, minimally invasive image-guided therapies are often the treatment of choice. In patients with very early stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system (HCC <2cm), percutaneous ablation is the treatment of choice for patients who are not a candidate for liver transplantation. Ablation is the first-line therapy for patients with BCLC early stage (≤3 HCC of ≤3cm each), if surgical resection or transplantation is contra-indicated (2). In patients with BCLC intermediate stage, the superiority of transarterial chemo-embolization (TACE) over best-alternative care has been demonstrated in two randomized controlled trials (3,4). The efficacy of transarterial radioembolization has been proven in several phase II and retrospective studies in patients with either intermediate or advanced BCLC stage (5,6).

Secondary liver malignancies

The liver is a predilection site for metastases from various malignancies. The high incidence of liver metastases may be attributed to several factors. First, the likelihood of metastatic deposits is increased as a high volume of blood perfuses the liver. The liver has an extensive capillary network and therefore blood flow in the liver is relatively slow, increasing the likelihood that tumor cells nestle in the liver (7). Second, several organs with a high incidence of malignancies, such as the colon and pancreas, drain into the portal vein through the splanchnic veins and subsequently into the capillary bed of the liver. Finally, the endothelium of the liver sinusoids lacks a basal lamina and endothelial fenestration may allow tumor cells to exit the bloodstream more easily (7).

MINIMALLY INVASIVE, IMAGE-GUIDED LIVER INTERVENTIONS

Radiofrequency ablation

Radiofrequency ablation (RFA) is the most commonly used ablation technique used for the treatment of liver tumors. After placement of a RFA probe into a tumor using a percutaneous or open approach, an alternating electrical current can be delivered through the RFA probe. This causes ionic cell agitation that results in heat generation. The heat is generated in an active zone around the tip of the RFA probe and more peripheral areas receive heat through thermal conduction. RFA is most suitable for tumors smaller than 3cm as larger tumors are associated with higher local tumor recurrence rates (8-10).

Much of the research on ablation focuses on ways to reduce recurrence rates. More accurate tumor targeting and improved response assessment is essential in achieving better outcomes after RFA. Also, on-going trials are analyzing the efficacy of combination treatment of RFA with either other locoregional therapies or systemic therapy. Furthermore, new RFA systems and alternative ablation techniques, such as microwave ablation (MWA) and irreversible electroporation (IRE), have been introduced over recent years.

Transarterial chemoembolization

Transarterial chemoembolization (TACE) was accepted as the first line treatment in patients with intermediate stage HCC after two randomized trials showed the superiority of TACE over best alternative care (3,4). TACE has not been widely adopted in the Netherlands as a treatment for secondary tumors, but there is growing scientific evidence that TACE offers symptomatic relieve and/or survival benefit in patients with liver metastases from various histologic origins (11,12). Over the past decade, there has been an increased use of TACE with drug-eluting beads. These embolic beads can be preloaded with a chemotherapeutic agent and allow a sustained, local drug release with lower systemic toxicity (13). The availability of smaller micro-catheters, allowing more selective hepatic artery catheterization, and better imaging techniques, such as cone-beam computed tomography (CBCT) and computed tomography hepatic arteriography (CTHA), has led to more accurate tumor targeting. Nevertheless, recurrence rates after TACE are high and the long-term prognosis remains poor. There is an on-going demand for improvements in patient selection, tumor targeting and response assessment.

Radioembolization

The liver has low tolerance to external radiation therapy, and cirrhosis further decreases this tolerance. External beam radiation may cause radiation-induced liver disease at a whole liver dose exceeding 40 Gray (Gy), but such a dose is generally insufficient to cause necrosis in liver tumors (14). Radioembolization enables delivery of a high radiation dose to a liver tumor with limited radiation injury to the non-tumorous liver tissue. Radioembolization is a form of brachytherapy, in which microspheres loaded with a radionuclide are delivered to the hepatic tumors by selective hepatic arterial infusion. Currently, microspheres loaded with either yttrium-90 (SIR-spheres or Theraspheres) or Holmium-166 (QuiremSpheres) are commercially available. The infused microspheres lodge permanently within the vascular bed of the tumor to deliver high-energy ß-radiation. Each microsphere has a limited therapeutic range (mean tissue range 2.5-3.2mm; maximum 9-11mm), but radiation of the entire tumorous region can be achieved by infusion of large numbers of spheres. Radioembolization has been proven to be an effective treatment for patients with irresectable HCC and is used in clinical practice to treat intermediate and advanced stages of this disease (6,15). Also, radioembolization has gained acceptance as an effective treatment in patients with liver metastases from colorectal carcinoma and other tumors (16).

Percutaneous hepatic perfusion

The unique hepatic anatomy allows vascular isolation of the liver from the systemic blood circulation Percutaneous hepatic perfusion (PHP) is a novel minimally invasive technique that enables vascular isolation and perfusion of the liver with the use of endovascular techniques (17). This technique allows administration of a very high dose of chemotherapy to the liver with limited systemic side effects. This innovative therapy has been shown to be effective, especially in patients with hepatic metastases from ocular melanoma (17).

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to evaluate and advance minimally invasive image-guided liver therapies. Current practices and therapies are evaluated and new imaging techniques and treatment strategies are analyzed. PART I focuses on image-guided percutaneous RFA. In chapter 2, the results are presented of a retrospective study of 279 HCC patients treated with percutaneous RFA in either a tertiary referral center in Northern-Europa or South-East Asia. The study investigates how differences in base-line patient characteristics may vary per geographical region and influence long-term outcome. Chapter 3 is a phantom study that investigates the accuracy of electromagnetic fusion of volumetric computed tomography (CT) with real-time ultrasonography (US). Such fusion imaging may enable US-guided targeting of tumors, even if lesions are inconspicuous on US. In the phantom study, manual fusion of images is compared with automatic and semi-automatic fusion and the accuracy and errors of fusion imaging are investigated. In chapter

4, the efficacy of RFA with adjuvant drug-eluting bead TACE is evaluated in patients with HCC >3cm. PART II discusses transarterial liver therapies. The subject of chapter 5 is a prospective study comparing catheter-directed contrast-enhanced ultrasound (CCEUS) and catheter-directed computed tomography hepatic arteriography (CTHA) as adjuncts to digital subtraction angiography (DSA) to guide TACE. Chapter 6 describes the feasibility and safety of yttrium-90 (Y90) infusion into the right inferior phrenic artery in large HCC tumors with extra-hepatic vascular supply, using CTHA in addition to DSA to plan and execute therapy.. The superior imaging capabilities of CTHA are also demonstrated in Chapter 7. As shown in this chapter, CTHA enables better detection of the falciform artery compared to DSA and Tc99m-macroaggregated albumin single photon emission computed tomography with integrated computed tomography (Tc99m-MAA SPECT/CT). The value of CTHA is further illustrated in Chapter 8 that discusses the development of personalized predictive dosimetry in radioembolization with the use of artery-specific SPECT/CT partition modeling. Chapter 9 is a review of the current literature on PHP. The results of a prospective pharmacological study investigating the efficacy and safety of the Delcath GEN2 filter are reported in Chapter 10. PART III is a short but indispensible part of this thesis. In Chapter 11, a prospective study is presented that evaluates the impact of an outpatient interventional radiology clinic on patient safety and satisfaction. Finally, the main conclusions of this thesis are summarized and discussed in Chapter 12.

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