Percutaneous hepatic perfusion in unresectable liver metastases: focus on ocular melanoma

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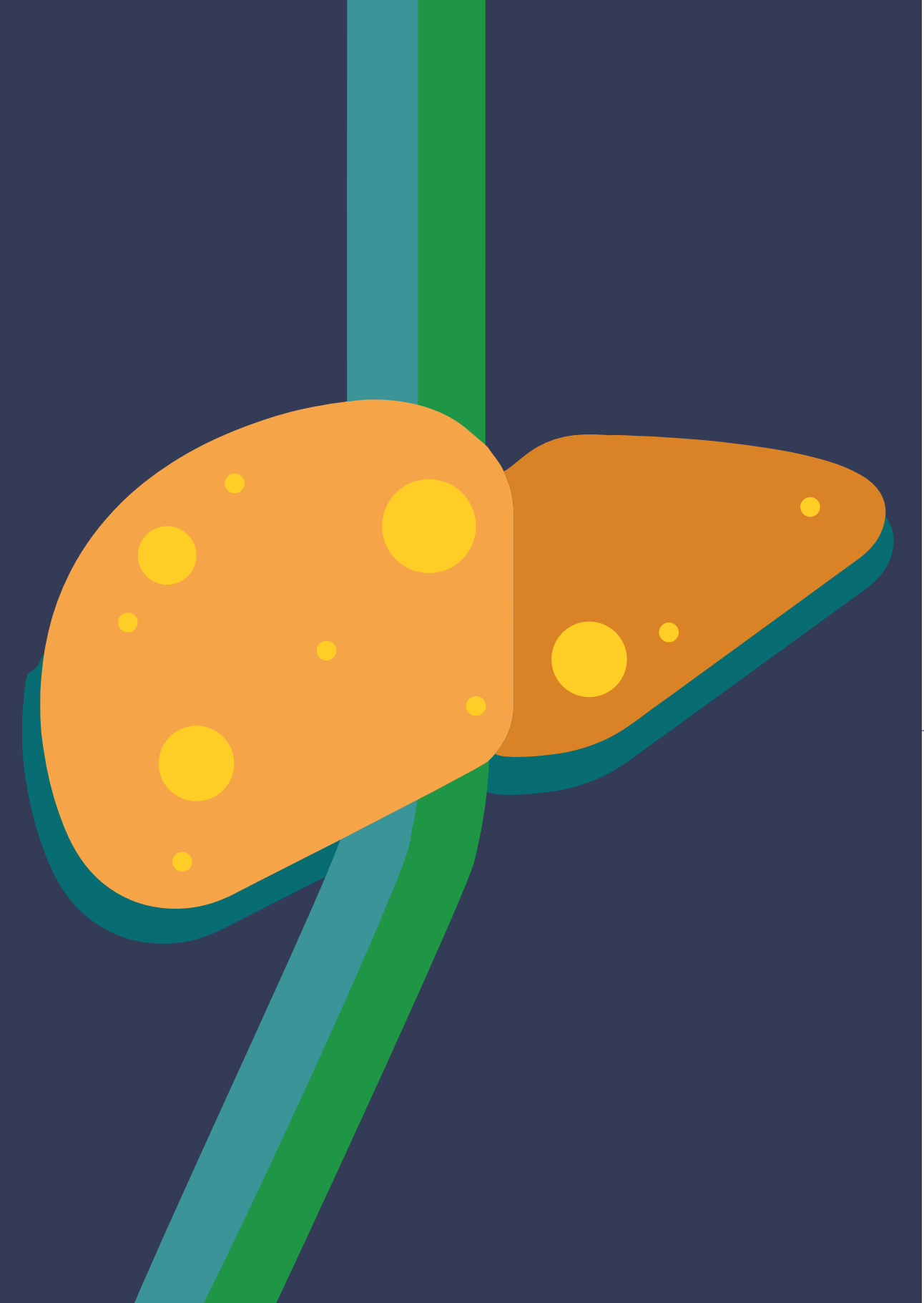

CHAPTER 1

General introduction

INTRODUCTION

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Ocular melanoma and colorectal cancer

Ocular melanoma is a rare malignancy with an overall annual incidence rate of up to 11.6 per million in Europe.[1] Most patients with ocular melanoma in the Netherlands are seen in the Leiden University Medical Center (LUMC) as it is the national referral center for the diagnosis and treatment of ocular tumors. As in most cases ocular melanoma arises from melanocytes located in the uveal tract of the eye which is composed of the iris, ciliary body, and choroid, it is also referred to as uveal melanoma.

Unlike ocular melanoma, colorectal cancer is a very common cancer type. In 2018, approximately 1.8 million new cases of colon cancer were diagnosed worldwide, which accounted for 9.2% (880.000) of all cancer-related deaths.[2]

Liver metastases from ocular melanoma and colorectal carcinoma

In solid malignancies, not the primary tumor but the metastatic spread and systemic disease account for the majority of cancer-related deaths.[3,4] The most common site of distant metastases in solid tumors is the liver (59%), followed by non-regional lymph nodes (53%), lungs (44%), bones (38%), and pleura (38%).[4]

Ocular melanoma and colorectal carcinoma are two malignancies with a predilection for metastasizing to the liver. Although local disease control of the primary tumor with enucleation or radiotherapy is high, up to 50% of patients with ocular melanoma will eventually develop metastatic disease with predominant liver involvement.[5-7] Similarly, approximately 50% of patients with colorectal carcinoma will develop liver metastases at some point in the course of their disease.[8,9] Whereas the close proximity and direct communication between colon and liver via the mesenteric veins that drain into the portal vein might partly explain the high hepatic metastatic rate for colorectal carcinoma, it does not explain the high hepatic metastatic rate for ocular melanoma.[10] Though we know that ocular melanoma spreads purely hematogenously as the eye has no lymphatic vessels, the liver tropism of ocular melanoma metastases is currently not fully understood.[11]

Liver-directed therapies

Patients with liver-only or liver-dominant metastatic disease might be eligible for locoregional or so-called liver-directed therapy. Liver-directed therapies include surgery and thermal ablation, both considered potentially curative, as well as various arterial therapies such as hepatic arterial infusion, transarterial chemoembolization, transarterial radioembolization and percutaneous hepatic perfusion with melphalan (M-PHP). The rationale behind all arterial therapies is the dual blood supply of the liver, with hepatic tumors deriving blood almost exclusively from the hepatic artery, while the normal liver parenchyma is primarily (70-80%) perfused by the portal vein. All arterial therapies share the common advantage of treating both radiologically visible and occult tumors (micrometastases), while normal

hepatocytes are relatively spared and systemic toxicity is limited.

Percutaneous hepatic perfusion with melphalan

M-PHP is a minimally invasive, repeatable technique in which the liver vasculature is isolated from the systemic circulation allowing the administration of a high dose of melphalan to the liver through a catheter that is placed in the proper hepatic artery. The chemosaturated blood returning via the hepatic veins is aspirated through fenestrations in a double balloon catheter in the inferior vena cava, and then pumped through an extracorporeal hemofilter. After filtration, the blood is returned to the patient by a vascular sheath in the internal jugular vein.

Although M-PHP is well-tolerated by most patients, hematologic events due to bone marrow suppression were quite common in M-PHP using the first-generation filter.[12-16] In an attempt to reduce bone marrow suppression by increasing the filter extraction rate, a new second-generation filter (GEN 2 filter) was developed by Delcath Systems Inc. (New York, NY, USA) and became commercially available in 2012.

OUTLINE OF THIS THESIS

The primary objective of this thesis is to evaluate the safety and efficacy of M-PHP using the GEN 2 filter in patients with unresectable liver metastases from ocular melanoma and colorectal carcinoma.

Chapter 2 is a review of current literature on liver-directed therapies that are used in the treatment of hepatic metastases from cutaneous and ocular melanoma.

As ocular melanoma has a high tendency to metastasize to the liver, patients in the Netherlands, as in most other European countries, are offered bi-annual screening with ultrasonography (US) for the detection of liver metastases. With the introduction of promising liver-directed therapies such as M-PHP, the relevance of early detection of liver metastases has increased. Although it is generally accepted that the sensitivity of magnetic resonance imaging (MRI) in detecting liver metastases is superior to US, it is unclear whether earlier detection would increase the chance of patients being eligible for M-PHP or other locoregional therapies and if so, whether this would increase survival. In **Chapter 3**, we represent the results of a cost-effectiveness study examining whether bi-annual screening of ocular melanoma patients for liver metastases with MRI is cost-effective compared with US.

In 2014, a single-arm, prospective phase II study was initiated to investigate M-PHP using the GEN 2 filter in patients with unresectable liver metastases from ocular melanoma. During the process of recruitment, we demonstrated that the extraction rate of the GEN 2 filter decreases over time, most likely as a result of saturation of the filter.[17] This suggested that patients with a prolonged extracorporeal filtration time are at risk of increased systemic exposure to melphalan. This, together with the knowledge that a longer extracorporeal filtration time results in a prolonged cardiac strain, an increased risk of hemolysis and

hypothermia, prompted us to limit the extracorporeal filtration time when possible. The presence of variant hepatic arteries in patients undergoing M-PHP may require catheter repositioning in order to deliver chemotherapy to all liver metastases and thus prolong extracorporeal filtration time. We addressed this problem by using so-called 'redistribution of flow' in which variant hepatic arteries are embolized with coils, after which perfusion of liver segments is taken over by preexisting intrahepatic arterial collaterals originating from an adjacent segment. In **Chapter 4**, we present a retrospective study, evaluating whether redistribution of flow has any negative effect on therapeutic response in ocular melanoma patients undergoing M-PHP.

Results of our single-arm, prospective phase II study investigating M-PHP using the GEN 2 filter in patients with unresectable liver metastases from ocular melanoma are reported in **Chapter 5 and 6. Chapter 5** reports on the safety and toxicity of the procedure and the outcomes are compared with historical data from studies using the first-generation filter. **Chapter 6** reports on the efficacy of the procedure and comments on the effect it has on quality of life.

M-PHP was developed as a minimally invasive, repeatable alternative to isolated hepatic perfusion which is a complex surgical procedure that was shown to be effective in patients with colorectal liver metastases (CRLM). The results of a single-arm, prospective phase II study evaluating the safety and efficacy of M-PHP using the GEN 2 filter in patients with unresectable CRLM are presented in **Chapter 7**.

Chapter 8 and 9 provide a summary, general discussion and future perspectives in English and Dutch.

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