A multidisciplinary approach to improve treatment strategies for patients with hepatic or pancreatic cancer

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['Teach thy tongue to say 'I do not know,' and thou shalt progress.'
Maimonides, 12th Century (ook bekend als de Rambam)]

CHAPTER 1

General Introduction and Outline of this thesis

GENERAL INTRODUCTION

In this thesis two types of cancer are described with limited effective treatment options and poor survival: uveal melanoma and pancreatic cancer.

Uveal melanoma

Uveal melanoma (UM) is an ocular tumour with 200 new cases per year in the Netherlands. The incidence is slightly rising (Figure 1). Despite radical primary treatment (enucleation), nearly 50% of patients develop metastases, predominantly in the liver. [1] In 2005 the Collaborate Ocular Melanoma Study (COMS) trial reported a mean survival of less than six months from time of diagnosis of metastasis, and only 20% survival after one year.[2, 3]

From 1980 multiple phase I-II studies with systemic treatment regimens were conducted. Treatment agents that were found to be effective for cutaneous melanoma were investigated for UM patients. Neither chemotherapy nor targeted therapy (MEK inhibitors such as seluminitib, or immunotherapy like ipilimumab) have shown to be clinically effective with regard to tumour regression or survival benefit (Table 1). [3-13] This is most likely explained by the different molecular biology of cutaneous and uveal melanoma.[14, 15] Clinical data showed that UM patients with liver metastasis had poorer prognosis than patients with extrahepatic metastasis. Therefore locoregional treatment was thought to be an important alternative for

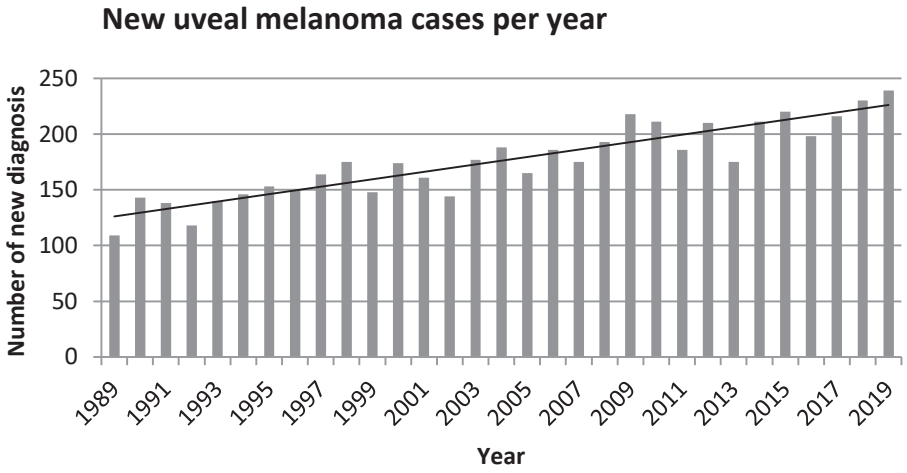

FIGURE 1. **Incidence of uveal melanoma**
Data from Netherlands Cancer Registry (www.cijfersoverkanker.nl)

TABLE 1. **Published studies on treatment of metastasized uveal melanoma patients**

Year	Author	Study	Groups / Agents	No patients	ORR (%) (PD+CR)	hPFS	OS months
1991	Gragoudas [8]	Evaluation of 145 patients	No treatment	44	n.r.	n.r.	2.0
			Any treatment	98	n.r.	n.r.	5.2
2013	Luke et al. [9]	Retrospective	Ipilimumab	39	5.1	n.r.	9.6
2013	Maio et al. [10]	Prospective; failed systemic therapy	Ipilimumab	82	5	3.6 months (PFS)	6.0
2014	Carvajal et al. [14]	Phase II, randomized	Selumitinib	50	14	16 weeks (PFS)	11.8
			Chemotherapy (temozolomide/DTIC)	51	0	7 week (PFS)	9.1
2015	Zimmer et al. [9]	Phase II, single arm: DeCOG-study	Ipilimumab	53	0	2.8 months (PFS)	6.8
2016	Algazi et al. [11]	Retrospective	PD-1 or PD-L1 antibody	56	3.6	2.6 months (PFS)	7.7
2018	Carvajal et al. [7]	RCT: SUMIT trial	Selumetinib + dacarbazine	97	3	2.8 months (PFS)	awaited
			Placebo + dacarbazine	32	0	1.8 months (PFS)	awaited
2019	Xu [12]	Retrospective	Systemic therapy (carboplatin, dacarabazine, etc)	14	n.r.	2 months (PFS)	10.3
			Checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab)	18	n.r.	3 months (PFS)	15.8
			Local therapy (resection, RFA, IHP)	30	n.r.	4.6 months (PFS)	18.7
			No treatment	11	n.r.		4.9
2019	Luke et al. [13]	Phase II, randomized	cabozantinib	31	n.r.	60 days	6.4
			chemotherapy: dacarbazine	15	n.r.	59 days	7.3

patients with liver-only metastases. The results of transarterial chemoembolization (TACE) and radio-frequent ablation (RFA) were not convincing and often not applicable because of the miliary spread of these liver metastases. [16, 17]

The unique hepatic anatomy allows vascular isolation of the liver to deliver high doses of cytotoxic agents with minimal systemic toxicity. This principle provided

the basis of isolated hepatic perfusion (IHP) which was first described in 1961 and investigated in porcine and canine models. [18, 19] Several small, single institution series were published in the 80's and one decade later, study protocols were designed to evaluate safety and efficacy.[20-24] Median time to progression was 6.7 – 8 months and median overall survival was 9.9 – 24 months, compared to an overall survival of 10 months at the most after systemic therapy (see again Table 1). [25-29] The IHP procedure however was complex and long, and associated with considerable morbidity which inhibited wide acceptance. With advances in imaging modalities and interventional-radiology, a less invasive endovascular and percutaneous alternative of IHP was developed in a porcine model: percutaneous hepatic perfusion (PHP). [30-32] Several clinical safety and feasibility studies on PHP were performed using doxorubicin and later also melphalan.[33, 34] Study populations were heterogeneous considering origin of metastases, treatment schedule and study design and therefore no definitive conclusions could be drawn. The majority of studies however included metastasized UM patients. Survival data was sparsely reported, but response rates were promising, compared to systemic therapy (Table 2). PHP seemed feasible and safe: reported complications were mostly asymptomatic effects of bone marrow suppression. These results are the

TABLE 2. **Studies on PHP with survival data available**

Author	Year	Study	No patients	Endpoint	ORR (%) (PR+CR)	hPFS	OS
Pingpank	2005	Phase I PHP Melphalan	28	MTD, toxicity, pharmacokinetics	50	n.r.	n.r.
Miao et al.	2008	Prospective PHP melphalan	51	Hemodynamics and metabolic changes	n.r.	n.r.	n.r.
Forster et al	2013	Retrospective study PHP melphalan	10	Response and toxicity	49	240 days	n.r.
Fitzpatrick et al.	2014	Case series PHP melphalan	5	Feasibility and toxicity	n.r.	n.r.	n.r.
Vogl et al.	2014	Retrospective study PHP melphalan	14	Response and toxicity	75% for UM	n.r.	n.r.
Hughes et al.	2015	RCT PHP melphalan vs. BAC	93	Response (primary hPFS)	27,3 (vs 4,1)	7.0 months (vs 1.6 months)	10.6 months (vs 10.0 months)
Karydis	2018	Retrospective, PHP with melphalan	51	Response and toxicity	49	9.1	15.3
Artzner et al.	2019	Retrospective, PHP with melphalan	16	Safety, response(PFS, OS)	60	11.1 months PFS	35.4 months (liver only disease)

basis for this thesis: a prospective *per protocol* clinical study investigating the use of percutaneous hepatic perfusion for patients with metastasized uveal melanoma.

Pancreatic cancer

The incidence of pancreatic cancer in The Netherlands is increasing and counted 2500 patients in 2019. Despite improvements in systemic and surgical therapies in the last decades, survival of patients with pancreatic cancer (PC) did barely improve (Figure 2). [35, 36] Radical surgery is the aim of the operative treatment since R0 resection (pathologically negative margin) results in prolonged survival.[37] However, the vast majority of patients (80-85%) present with advanced disease, and upfront surgery is not an option.[36]

Data from clinical trials suggest that neoadjuvant chemotherapy (with or without radiation) can increase resectability of borderline resectable and locally advanced pancreatic cancer and improve overall survival (Table 3). [36, 38, 39] Especially Folfirinox treatment schemes (chemotherapy regimen consisting of folinic acid, fluorouracil, irinotecan and oxaliplatin) seem to be effective. Adjuvant treatment with Folfirinox for patients with resectable PC increased survival up to 54 months. In the Netherlands patients are treated with neo-adjuvant therapy in clinical trial

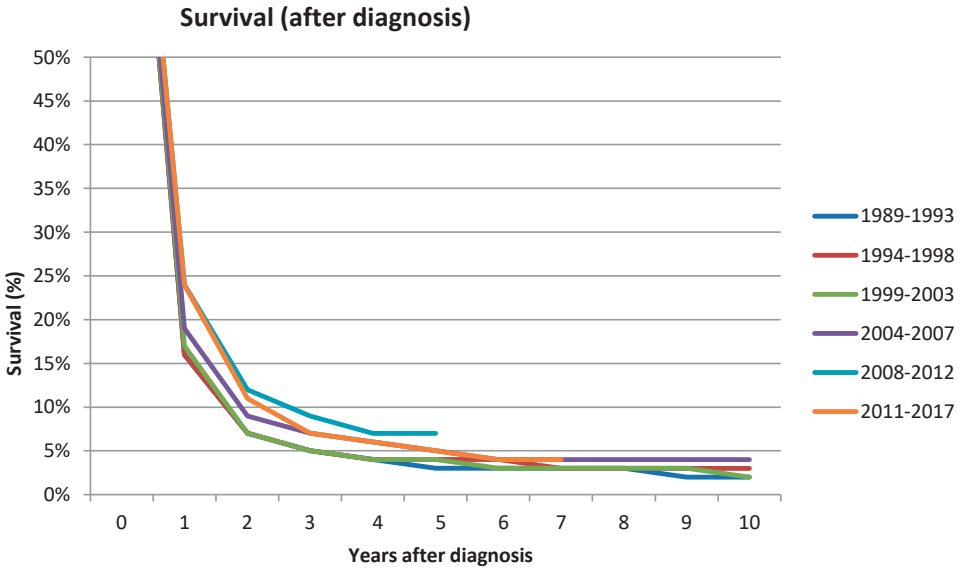

FIGURE 2. **Survival of patients after diagnosis Pancreatic cancer.**
Data from Netherlands Cancer Registry (www.cijfersoverkanker.nl)

TABLE 3. **Clinical trials investigating (neo-) adjuvant chemo(radio)therapy for patients with pancreatic cancer**

Pancreatic cancer type	Author	Year	Study		No patients	PFS/DFS (months)	mean OS (months)
Resectable	Conroy et al.	2018	Prodige trial	Adjuvant FOLFIRINOX	247	21.6 (DFS)	54.4
			Phase III trial adjuvant therapy	Adjuvant gemcitabin	246	12.8 (DFS)	35.0
	van Tienhoven et al.	2018	Preliminary data Preopanc-1 trial	A: immediate surgery	127		13.5
			(Borderline) resectable PC	B: preoperative chemoradiotherapy	119		17.1
	Gillen et al.	2009	Systematic review and meta-analysis	Neoadjuvant therapy (various)	27		23.2
Borderline resectable	Versteijne et al.	2018	Meta-analysis	Neoadjuvant therapy (gemcitabine)	1738		18.8
			Neoadjuvant therapy , (borderline) resectabel PC	Upfront surgery	1746		14.8
	Jang et al.	2018	RCT	Neoadjuvant CRT (gemcitabine)	27		21
			Neoadjuvant CRT vs upfront surgery voor BRPC	Upfront surgery	23		12
	Janssen et al.	2019	Systematic review and meta-analysis	Neoadjuvant FOLFIRINOX	313		22.2
			Neoadjuvant FOLFIRINOX in patients with BRPC				
Locally advanced	Suker et al.	2016	Systematic review and meta-analysis		315	15.0 (PFS)	24.2
			FOLFIRINOX for LAPC				
	Suker et al.	2018	Cohort study		44	11 (PFS)	15.4
			FOLFIRINOX and radiotherapy for LAPC				
Advanced/	Burris et al.	1997	RCT	Gemcitabine	63		5.65
Metastasized			Palliative chemotherapy	5-FU	63		4.41
	Conroy et al.	2011	RCT	FOLFIRINOX	171	6.4 (PFS)	11.1
			Palliative chemotherapy	Gemcitabine	171	3.3 (PFS)	6.8
	Kamath et al.	2019	Phase 1b study		21	2.78 (PFS)	6.90
			Ipilimumab and gemcitabine				

setting, according to the ESMO (European Society for Medical Oncology) guidelines. Ongoing randomized trials will have to determine the effect of neoadjuvant therapy on resectability and long term survival.[40] Patients with metastasized pancreatic cancer have very limited survival, even after treatment (in trials).

Alongside improving treatment regimens, centralization of surgical pancreatic cancer care in high volume centres led to an increase in resection rates, decreased postoperative mortality and prolonged survival.[41-44] More patients with advanced tumours underwent resection; R0 resection rates were doubled and 1- and 2 – year survival rates after resection improved in high volume hospitals.[45] High volumes of patients also enable initiation of clinical trials to investigate new therapeutic agents or diagnostic strategies. To further investigate the effects of centralization and adjustments of treatment regimens, (nationwide) clinical databases and cancer registries are used to audit and improve the outcomes of pancreatic cancer treatment, not only in the Netherlands (Netherlands Cancer Registry, Dutch Pancreatic Cancer Audit), but across the world. It is known that variations in incidence exist between regions and countries, treatment, mortality and survival of patients with pancreatic cancer. The European REgistration of Cancer Care (EURECCA) consortium, which was established by European Society of Surgical Oncology (ESSO) and funded by the European CanCer Organisation (ECCO), aims to investigate these variations in order to improve the quality of cancer care throughout Europe. Breast cancer, colorectal cancer, gastric cancer and pancreatic cancer collaborations have yet been initiated.[46-49] An important advantage of registries over clinical trials is the inclusion of the entire patient population, including elderly and patients with serious comorbidity, which offers the opportunity to study patient groups that are usually excluded from clinical trials.[50, 51]

Besides the oncological outcomes of the treatment, patient's perception should be considered crucial in treatment selection. For some patients, and especially elderly, quality of life (cognitive function, capability to stay at home) is more important than prolonged survival.[51] This aspect of cancer care is often not taken into account in clinical trials. Cancer-related endpoints might not fit the needs and desires of elderly patients. Side effects of therapy might outweigh the potential benefit and this can lead to different treatment decisions and ask for patient tailored care. Comparing data on patient selection, treatment and outcomes across Europe or even worldwide could be helpful in answering the question: what is the best available care for this specific patient in this stage of the disease and at this age?

OUTLINE

Patients with pancreatic cancer as well as patients with uveal melanoma liver metastases, have a poor prognosis. This thesis consists of three parts. In part I the development of percutaneous hepatic perfusion and treatment of patients with uveal melanoma liver metastases is described. The treatment of pancreatic cancer and how international data can be used to compare outcomes of different existing treatment regimens is described in part II. Part III contains the general discussion.

For years, surgery has been the gold standard for the treatment of liver metastases in the absence of effective systemic therapy. However not all tumours are eligible for surgery and therefore locoregional therapies have been developed. Because of the vascular anatomy of the liver, the organ can be isolated from the systemic circulation and that is the basic principle of isolated hepatic perfusion (IHP). Part I focusses on the development and introduction of hepatic perfusion for the treatment of unresectable liver metastases. IHP was developed around 1986 *in vivo* and in 1998 the first patients were treated at the Leiden University Medical Centre. To improve the results of the treatment, combinations of chemotherapeutic drugs were investigated. In **Chapter 2** isolated hepatic perfusion with a combination of melphalan and oxaliplatin in different doses was investigated in patients with metastases of uveal melanoma and colorectal cancer metastases. Because uveal melanoma patients seem to benefit more from the IHP treatment, in **Chapter 3** the results of all IHP procedures in patients with uveal melanoma liver metastases from both the Erasmus Medical Centre in Rotterdam and the Leiden University Medical Centre are reported. The results of the treatment of patients with IHP are promising, but because of the morbidity that came along with the laparotomy and duration of the procedure, IHP never gained wide acceptance. Therefore, a minimal invasive and repeatable procedure, Percutaneous Hepatic Perfusion (PHP) was developed and in the following chapters PHP is described in detail and investigated. **Chapter 4** provides an overview of the development and first use of PHP. In **Chapter 5** the safety and toxicity of the PHP procedure is investigated in a clinical and pharmacological evaluation. In **Chapter 6** the treatment of 20 patients with uveal melanoma liver metastases with PHP is described.

Part II of this thesis focusses on pancreatic cancer and especially on capturing outcome data to study variation in treatment strategies between countries to eventually assess whether country specific strategies are associated with variations in survival. In **Chapter 7** the initiation of the first international European pancreatic cancer database is described, consisting of national audits and (local) cancer registries on pancreatic cancer under the auspices of EURECCA. In **Chapter 8**

Dutch data on pancreatic cancer treatment in elderly patients are compared to the treatment results of a Senior Adult Oncology Program in the United States, to investigate a possible difference in treatment and outcome. Is it possible to distil an optimized treatment regimen for elderly patients? Finally, **Chapter 9** contains the general discussion and future perspectives.

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