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

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Voor alle patiënten die participeerden in en hoop haalden uit de klinische studies die beschreven staan in dit proefschrift, en voor hen die zij achterlieten.

Dedicated to all the patients participating in and gaining hope from the clinical trials presented in this thesis, and to those they left behind.

CONTENTS

['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

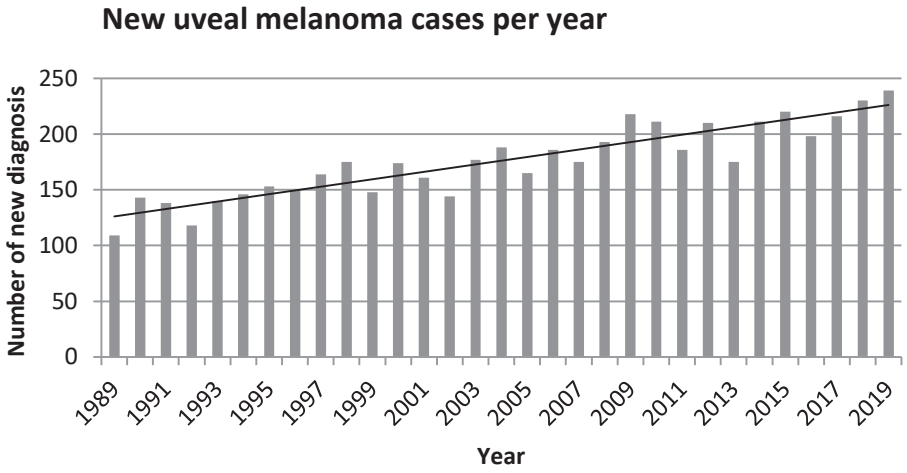

FIGURE 1. **Incidence of uveal melanoma**
Data from Netherlands Cancer Registry (www.cijfersoverkanker.nl)

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

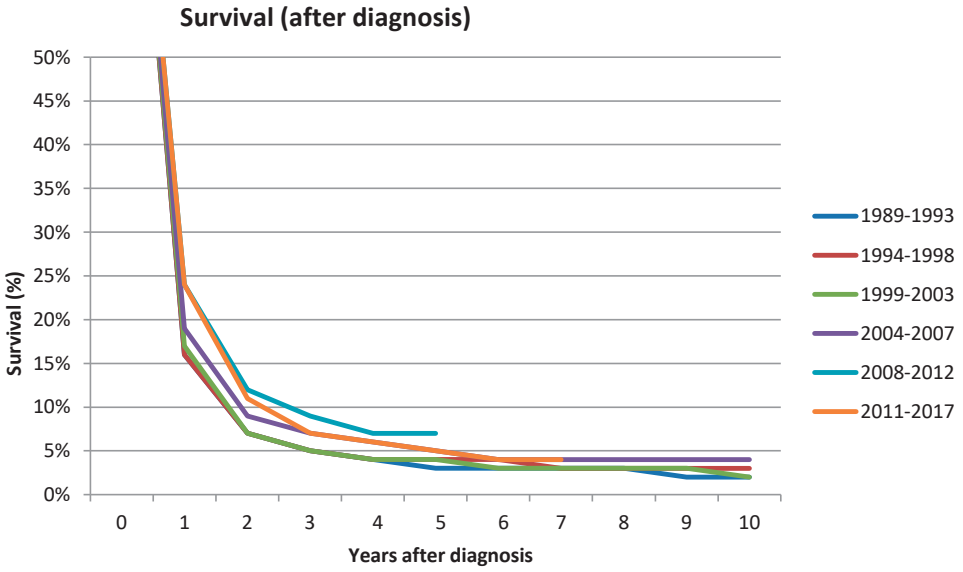

FIGURE 2. **Survival of patients after diagnosis Pancreatic cancer.**
Data from Netherlands Cancer Registry (www.cijfersoverkanker.nl)

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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I

[‘Patiënten met metastasen hebben vaak nog mogelijkheden,
maar dan moet je buiten de richtlijn durven te gaan.’
Professor Bob Pinedo, Arts&Auto Februari 2015]

PART I

Hepatic perfusion for the treatment of unresectable liver metastases

CHAPTER 2

Isolated hepatic perfusion with oxaliplatin combined with 100 mg melphalan in patients with metastases confined to the liver: a phase I study

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ABSTRACT

Aim

To improve isolated hepatic perfusion (IHP), we performed a phase I dose-escalation study to determine the optimal oxaliplatin dose in combination with a fixed melphalan dose.

Methods

Between June 2007 and July 2008, 11 patients, comprising of 8 colorectal cancer and 3 uveal melanoma patients and all with isolated liver metastases, were treated with a one hour IHP with escalating doses of oxaliplatin combined with 100mg melphalan. Samples of blood and perfusate were taken during IHP treatment for pharmacokinetic analysis of both drugs and patients were monitored for toxicity, response and survival.

Results

Dose limiting sinusoidal obstruction syndrome (SOS) occurred at 150mg oxaliplatin. The areas under the concentration-time curves (AUC) of oxaliplatin at the maximal tolerated dose (MTD) of 100mg oxaliplatin ranged from 11.9 mg/L x h to 16.5 mg/L x h. All 4 patients treated at the MTD showed progressive disease 3 months after IHP.

Conclusions

In view of similar and even higher doses of oxaliplatin applied in both systemic treatment and hepatic artery infusion (HAI), applying this dose in IHP is not expected to improve treatment results in patients with isolated hepatic metastases.

INTRODUCTION

Liver metastases are diagnosed in 10-25% of colorectal cancer patients at the time of primary tumour resection, while up to 70 % of patients with colorectal cancer will at some stage of their disease develop liver metastases [1-3]. Surgical resection is considered the golden standard for isolated hepatic metastases, with 10-year survival rates as high as 17% [4]. Recently, the number of patients suitable for resection has increased to up to 60% with the introduction of new neoadjuvant systemic treatment regimens [5-9]. Nonetheless, a significant number of patients still remain unsuitable for resection. For patients with uveal melanoma, 70-90% will eventually develop metastases confined to the liver. Because disease is often multifocal, surgical resection is not an option in the majority of patients. Median survival in this group is less than 1 year and currently there is no standard systemic therapy. [25]

Isolated hepatic perfusion (IHP) is a possible therapeutic option for unresectable liver metastases, but recent developments in systemic treatment in colorectal cancer have limited the role of IHP [10]. For IHP to remain a treatment option, response rates and overall survival need to increase, by improving both the procedure and drugs applied in IHP. Several drugs have been applied in IHP including 5-FU [11, 12], mitomycin C [13, 14], cisplatin [11] and melphalan [11, 14-16], but in the past 10 years melphalan has been the main drug used in clinical trials [16, 17]. To improve the current standard of IHP, we considered some of the newly developed drugs for systemic treatment of colorectal cancer for application in IHP. As IHP is a regional treatment, the drug should be in the active form or easily transformed to its active agent in the liver. Preferably, this drug shows a steep dose-response curve. Moreover, IHP is a short treatment of usually 1 hour, therefore the drug should cause rapid irreversible tumor cell cytotoxicity. Finally, liver toxicity should be minimal. We evaluated all registered drugs for colorectal cancer, taking into account the considerations above. Irinotecan is not an ideal candidate for IHP, since it is a pro-drug and the bioactivation to its active metabolite SN-38 is slow[18]. The monoclonal antibodies bevacizumab, cetuximab and panitumumab may not be suitable either, because they are not directly cytotoxic. Therefore oxaliplatin was selected as the most promising new candidate for IHP. Phase III trials have shown the superiority of oxaliplatin combination therapy versus oxaliplatin monotherapy [19, 20], suggesting a role for the possible application of a combination of oxaliplatin and melphalan in IHP. *In vitro* results showed a synergistic schedule dependent interaction between melphalan and oxaliplatin [21].

In this report we present the results of a phase I trial with IHP with escalating doses of oxaliplatin combined with a fixed dose of 100mg melphalan.

PATIENTS AND METHODS

Patient Eligibility

All patients had measurable, unresectable metastases confined to the liver. Unresectability was based on the decision made by the HPB multidisciplinary team. Often this was because the tumour is multifocal, too large or positioned close to central vascular structures. Standard staging studies were performed including CT scan of the chest and abdomen. Additional MRI or PET scans were performed if clinically indicated. Eligibility criteria included a WHO performance status of 0 or 1, leukocyte count ≥ 3.0 × 10^9/L, platelet count ≥ 100 × 10^9/L, minimum creatinine clearance level of 40 ml/min and maximum bilirubin level 17 µmol/L. Exclusion criteria were age over 65 years, more than 60% hepatic replacement by tumour tissue as estimated from the preoperative abdominal CT scan, evidence of extrahepatic metastatic disease or coagulation disorders (disorders affecting APTT, PT and/or INR). The interval between resection of the primary colorectal tumour and perfusion had to be at least 6 weeks.

Study design

This study is a prospective cohort study, including 11 patients with isolated liver metastases that were treated between June 2007 and July 2008. Patients were treated with IHP with escalating doses of oxaliplatin combined with 100mg melphalan. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center, was registered in the EudraCT database: number 2006-005088-25 and written informed consent was obtained from all patients.

IHP technique

All patients were treated with IHP, consisting of an extracorporeal veno-venous bypass, as described previously [15].

Leakage Detection

Leakage of perfusate into the systemic circuit was monitored by adding 10 MBq ^{99m}Tc-pertechnetate to the isolated circuit with subsequent measurement of the level of radioactivity in both the systemic and isolated circuit, as described previously [22, 23]. If no leakage was detected, oxaliplatin was administered. During the one hour treatment leakage was constantly monitored, if leakage exceeded 10% during the perfusion period, the procedure was immediately aborted and the liver flushed.

Postoperative Care

All patients received a daily subcutaneous dose of 480 µg granulocyte colony-stimulating factor (G-CSF) (Filgrastim/Neupogen®; Amgen, Breda, The Netherlands) starting the day after the operation until the nadir in leukocyte count was reached and the count had risen to more than 1.0 × 10^9/L. Patients were monitored in the intensive care unit for at least 1 day after IHP. Liver and renal function tests and full blood counts were carried out daily in the first week and henceforth as indicated by their respective levels. Antibiotics in a combination of cefuroxim and metronidazol were given to all patients for 5 days after IHP.

Oxaliplatin and melphalan

Oxaliplatin (Sanofi-Aventis, Gouda, The Netherlands) was obtained as a ready-made solution and administered as a bolus in the isolated hepatic circuit. Melphalan 100mg (Alkeran®, GlaxoSmithKline, Zeist, The Netherlands) was dissolved in 40 mL Wellcome Diluent (a 60/40 (v/v) mixture of propylene glycol containing 5.2% (v/v) ethanol and 0·068 mol/l sodium citrate), which was subsequently diluted with 60 mL sterile saline. The melphalan was administered as a bolus in the isolated hepatic circuit 30 minutes after the oxaliplatin was administered.

Dose escalation

Dose escalation depended on toxicities at the prior dose level. At least 3 patients were treated at each dose level. If 1of 3 patients experienced dose limiting toxicity (DLT), 3 additional patients were entered at that dose level. DLT was defined as grade 4 thrombopenia or neutropenia for more than 7 days or febrile neutropenia or irreversible grade 3/4 liver toxicity or other grade 3/4 non-hematological toxicity other than nausea and vomiting without adequate treatment. The maximal tolerated dose (MTD) was defined as the dose level below that, which induced DLT in at least one-third of the patients. (i.e., ≥ 2 of 3 or 6 patients). Melphalan was kept at a fixed dose of 100 mg, because this was considered standard treatment in several phase II trials [24-26]. Oxaliplatin was escalated with 50mg at a time. Oxaliplatin was administered 30 minutes prior to melphalan based on *in vitro* findings, suggesting a schedule dependent interaction between melphalan and oxaliplatin [21].

Toxicity

Systemic and regional toxicity were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Hepatic toxicities were considered melphalan-related if elevations in liver function persisted beyond 7 days after perfusion, as previously suggested [16]. Non-hepatic toxicities were defined as all toxicities that were not reversed within 24 hours after perfusion.

Melphalan and oxaliplatin pharmacokinetics

Heparinized samples of all patients were taken from the perfusion medium at hepatic inflow and outflow tracts and from the systemic circulation, at 15 different time points (t=0, 1, 5, 10, 15, 20, 25, 30, 31, 33, 35, 40, 45, 50, 60 minutes). Samples were stored at -80° C until analysis. All samples were analysed for melphalan by a HPLC assay as previously described [27]. Oxaliplatin concentrations were determined by ICP-MS (Inductively Coupled Plasma- Massa Spectrometry). The areas under the concentration-time curves (AUC) were calculated with the trapezoidal rule.

Response evaluation

Objective tumour response measurements were obtained by follow up CT scans of the liver and remaining abdomen at 3-month intervals after treatment and at 6-month interval after 1 year. Additional imaging was performed if clinically indicated. RECIST criteria were used to determine response rates. For the RECIST criteria lesions were only considered measurable if ≥10mm. Complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of maximal diameters of ≥30%, stable disease as a reduction of <30% or an increase of <20% and progressive disease as an increase of ≥20% or the appearance of new intra- or extrahepatic lesions [28]. Metastases were localized according to the Bismuth classification [29].

Serum carcinoembryonic antigen (CEA) levels were determined in colorectal cancer patients prior to treatment and at all follow-up visits.

Statistics

All data were analyzed using SPSS (version 12.0) software and presented as mean +/- SD or median followed by the range. All survival and disease progression analysis were performed using Kaplan-Meier statistics.

RESULTS

Patient characteristics

Demographics and tumour characteristics of the patient population are listed in Table 1. In total 11 ASA 1-2 patients were treated with escalating doses of oxaliplatin. Three women were treated and eight men with a mean age of 57.9 years (range 40-64 years). The liver metastases originated from uveal melanoma in three patients and from colorectal cancer in the other eight patients. In all patients there was more than 75% healthy liver tissue. One of the included patients (patient no. 5) in retrospect showed extrahepatic disease prior to IHP. Therefore one extra

TABLE 1. **Characteristics of 11 patients treated with IHP with oxaliplatin and melphalan**

Patient No.	Sex	ASA-score	Age (Y)	Primary tumour	Number of metastases in liver	Size largest tumour (mm)	Healthy liver tissue	Previous systemic treatment	Dose Melphalan (mg)	Dose Oxaliplatin (mg)	AUC Hepatic inflow Melphalan (mg/L x h)	AUC Hepatic inflow Oxaliplatin (mg/L x h)	Response	Duration response (months)	Overall survival (months)
1	F	2	51	Uveal melanoma	throughout liver	43	>80%	none	100	50	9.6	4.1	partial	7.6	30.7
2	M	2	64	Colorectal cancer	>10	30	80%	RT rectum	100	50	2.8	6.2	progressive	-	26.8
3	M	2	54	Uveal melanoma	throughout liver	11	>90%	CT (DTIC)	100	50	7.3	6.9	progressive	-	18.7
4	M	2	59	Colorectal cancer	5	68	90%	CT	100	100	6.4	12.6	progressive	-	4.9
5+	F	1	40	Colorectal cancer	>20		75%	CT	100	100	15.4	16.5	-	-	5.5
6	F	2	61	Uveal melanoma	4	34	>80%	none	100	100	10.3	16.5	progressive	-	7.8
7	M	2	63	Colorectal cancer	multiple	23	>90%	CT	100	100	2.8	11.9	progressive	-	22.0
8	M	2	63	Colorectal cancer	5	50	>90%	CT	100	150	6.7	19.6	partial	6.5	27.3
9¤	M	2	63	Colorectal cancer	10	30	>90%	RT rectum	100	150	4.8	16.7	partial	11.1	71.3¤
10*	M	2	57	Colorectal cancer	throughout liver	9	90%	CT	100	150	9.9	20.6	-	-	0.5
11*	M	2	62	Colorectal cancer	throughout liver	25	90%	RT rectum	100	150	6.5	18.2	-	-	1.0

+ In retrospect patient showed extrahepatic metastases prior to IHP, which were immediately progressive after IHP.
* Both patients died perioperatively. Patient no. 10 due to excessive bleeding and patient no. 11 due to hepatotoxicity.
¤ Patient still alive.
CT = chemotherapy RT= radiotherapy (5x5 Gy)

patient was included at this dose-level. Some of the patients have been treated with chemotherapy after resection of the primary tumour. One uveal melanoma patient with DTIC (Dacarbazine) and most colorectal patients with combinations of oxaliplatin and capecitabine (Xeloda).

Treatment characteristics

Treatment characteristics are shown in Table 2. In 10 patients the perfusion took place for the intended 60 minutes. None of the patients showed more than one percent leakage during the entire procedure. Patients were admitted in the hospital for 16.8 days (mean ± 10.5). Time of surgery, blood loss, hospital stay and hepatic artery and portal vein flow rates and pressures are similar as previously reported in 73 and 105 treated patients. [17, 30].

Pharmacokinetics

Samples for pharmacokinetic analysis were collected from all patients. Individual data of the AUC of both melphalan and oxaliplatin are shown in Table 1. Escalating doses of oxaliplatin corresponded to an increasing AUC, with the maximum of 20.6 mg/L x h achieved at the highest dose level of 150 mg oxaliplatin. The maximum peak concentration of oxaliplatin was 40.8 mg/L and was achieved in patient no 9, also at the highest dose level. Little difference was observed between the oxaliplatin concentrations in the hepatic inflow and outflow tract, suggesting only limited hepatic extraction of oxaliplatin. This is shown in Figure 1, for different dose levels of oxaliplatin in different patients. An increasing dose-level shows an increasing peak in concentration within five minutes. All curves show a decline over time.

Toxicity and complications

Major complications occurred in four patients of which two patients died perioperatively. One perioperative death was due to massive blood loss, due to damage to the hepatic artery, which was repaired with a venous interponate. This perioperative death was attributed to the procedure and not toxicity. Therefore another patient was included at this dose-level. The other perioperative death was due to hepatotoxicity as a result of sinusoidal obstruction syndrome (SOS). Toxicity levels according to dose-level are shown in Table 3. Reversible grade 3-4 hepatoxicity occurred in seven patients. DLT consisted of irreversible grade 4 hepatotoxicity requiring hepatic-replacement therapy due to SOS and was reached at 150mg oxaliplatin combined with 100mg melphalan.

Tumour response and patient survival

Of the five patients with colorectal cancer with an elevated CEA prior to IHP, three showed 50% or more reduction in CEA after IHP. Only eight patients were

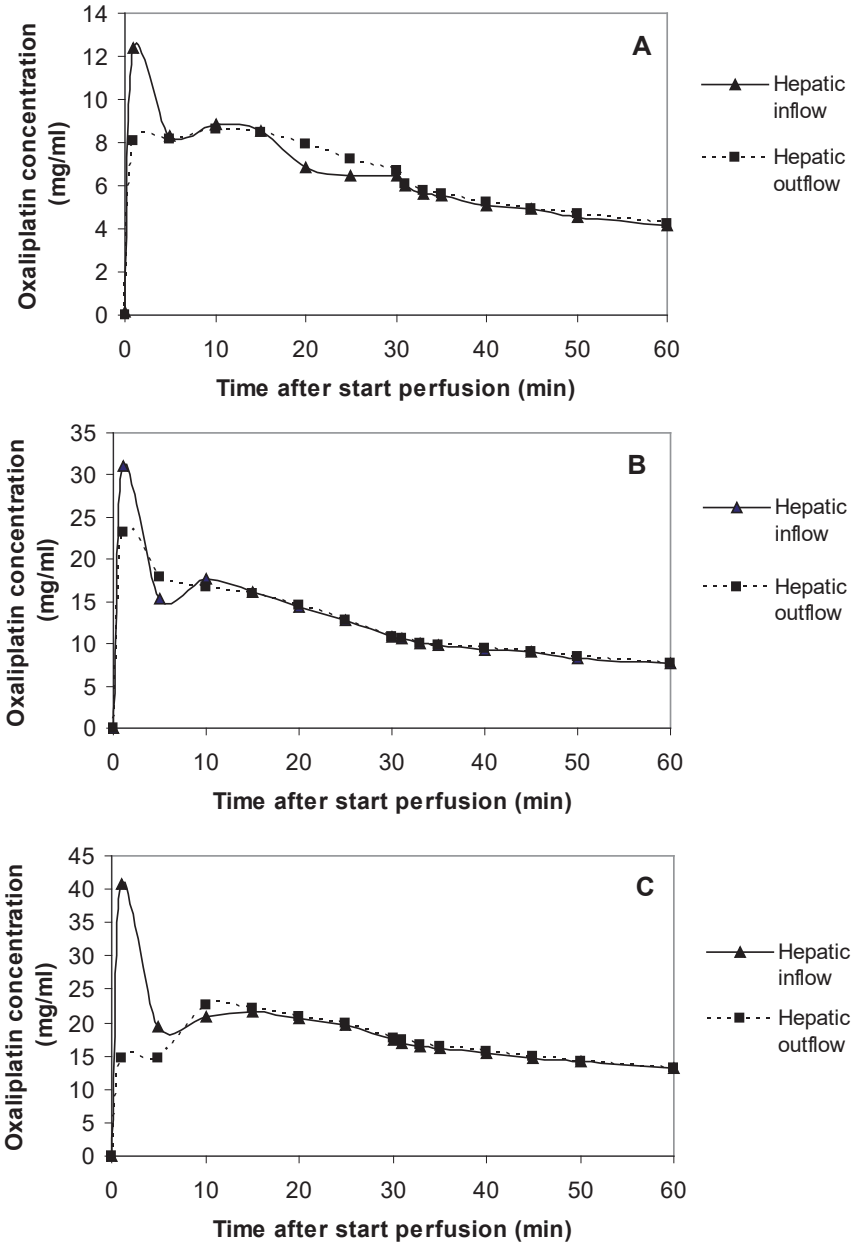

FIGURE 1 **Typical examples of concentration time curves of oxaliplatin for each dose-level (A = 50 mg oxaliplatin, B = 100 mg oxaliplatin, C = 150 mg oxaliplatin). Increasing dose-levels show increasing peak concentrations of oxaliplatin. All concentration curves show a gradual decline over time.**

TABLE 2. **IHP Treatment parameters**

Parameter	*Mean ± SD*	*n*
Flow rate hepatic artery (mL/min)	293.9 ± 68.1	
Flow rate portal vein (mL/min)	312.8 ± 31.3	
Pressure hepatic artery (mm/Hg)	129.4 ± 20.0	
Pressure portal vein (mm/Hg)	49.1 ± 4.0	
Percentage leakage during perfusion (%)	0.4 ± 0.5	
Blood loss (L)	5.5 ± 5.8	
Operative time (h)	8.4 ± 1.6	
Hospital stay (days)	16.8 ± 10.5	
Perioperative mortality		2
Major complications		4
Sinusoidal obstruction syndrome		1
Hepatic artery obstruction		1
Wound infection		1
Re-operation due to bleeding		1

available for response evaluation of which three patients showed a partial response according to the RECIST criteria, with a duration of response of 6.5 – 11.1 months. After a follow up of 71 months, one patient is still alive. This was measured from the day of treatment until the last appointment in the hospital. The median overall survival was 18,7 months (SD 20,44) including three uveal melanoma patients, as displayed in Table 1.

DISCUSSION

In this study we evaluated escalating doses of oxaliplatin combined with a fixed dose of 100mg melphalan in an isolated hepatic perfusion setting for patients with metastatic disease confined to the liver. Dose limiting toxicity (DLT), consisting of sinusoidal obstruction syndrome (SOS), occurred at a relatively low dose level of 150mg oxaliplatin.

In previous IHP studies DLT also consisted of SOS as one of the main limitations of IHP with melphalan [15, 16]. Nonetheless, we did not expect DLT to occur at such a low dose of oxaliplatin, especially considering the 50% reduction in melphalan dose compared to our previous IHP trials[17, 31]. At the time of development of this study protocol, oxaliplatin was considered a non-hepatotoxic drug, with only limited hepatoxicity reported in both systemic and hepatic arterial infusion (HAI)

TABLE 3. **Toxicity according to National Cancer Institute Common Toxicity Criteria version 3.0 (*n=11*)**

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte nadir					
- Dose level I	3	0	0	0	0
- Dose level II	4	0	0	0	0
- Dose level III	4	0	0	0	0
Bilirubin					
- Dose level I	2	1	0	0	0
- Dose level II	2	0	0	1	1
- Dose level III	0	0	0	2	2
Alkaline phosphatase					
- Dose level I	1	2	0	0	0
- Dose level II	0	1	2	0	1
- Dose level III	0	2	2	0	0
Alanine aminotransferase (ALAT)					
- Dose level I	2	0	0	1	0
- Dose level II	1	1	1	0	1
- Dose level III	0	1	2	0	1
Asparate aminotransferase (ASAT)					
- Dose level I	0	1	2	0	0
- Dose level II	0	2	0	2	0
- Dose level III	0	1	1	1	1

trials [32-36]. These findings combined with the synergistic interaction between melphalan and oxaliplatin, as demonstrated by our previously published *in vitro* data, supported the development of this study protocol [37]. However, more recently, after development of our study protocol, an increasing number of studies reported on the hepatotoxicity, especially the risk of SOS, after treatment with oxaliplatin prior to hepatectomy of colorectal liver metastases. Incidence rates of SOS have been reported of up to 59% and oxaliplatin-based chemotherapy has been shown an independent risk factor for complications associated with hepatectomy with conflicting data concerning impact on both morbidity and mortality [38-42]. In view of the above, the addition of a cytostatic agent with a high incidence of SOS to a procedure with already a high risk of SOS, can explain the occurrence of DLT at only 150mg of oxaliplatin.

Similarly to our study, Zeh *et a.* published a phase I study of IHP with oxaliplatin, but instead of oxaliplatin combination therapy, the perfusate consisted of oxaliplatin alone [43]. Dose-limiting toxicity, also consisting of SOS, was observed at only 60 mg/m2, again indicating the high potential of inducing SOS if oxaliplatin is applied in isolated hepatic perfusion circuit, irrespective of combination with other agents. This study reported an overall response rate of 66%, but IHP was performed under hyperthermic conditions and combined with HAI, complicating the interpretation of both toxicity and response rates.

Recently Zeh *et al* published another study combining oxaliplatin with a fixed dose of 40mg/m2 with escalating doses of 5-FU. Dose limiting toxicity occurred at the second dose (300 mg/m2) and consisted of hyperbilirubinemia and ascites because of hepatic failure [44]. In our study meaningful interpretation of the response rate is complicated because of the phase I design and the inclusion of both uveal melanoma and colorectal cancer patients. Of the 8 colorectal cancer patients included, only two patients showed a partial response, both were treated at the highest dose level of 150mg oxaliplatin. All patients treated at the MTD of 100mg oxaliplatin showed progressive disease 3 months after IHP. Considering the dose of oxaliplatin used in regular systemic combination treatment in colorectal cancer patients of over 100mg/m2 per treatment cycle, conducting a phase II IHP trial based on the MTD dose of 100mg oxaliplatin seems hardly beneficial.

Although the Cmax in our study was higher than the Cmax reported after a 2-hour infusion of oxaliplatin at 130mg/m2 in systemic trials, the AUC of oxaliplatin at the MTD in our study ranged from 11.9 mg/L x h to 16.5 mg/L x h and was similar to the AUC reported in systemic trials[45]. A possible survival benefit for IHP over systemic treatment can only be achieved at this dose if response to oxaliplatin therapy is concentration- rather than dose-dependent. Our previous experience with melphalan showed that an increase in melphalan concentration in the perfusate did not increase response rates, but did increase toxicity [31]. Moreover, current HAI study protocols already apply a dose of oxaliplatin of up to 150mg/m2 [32-36]. Similarly to IHP, HAI offers the advantage of high concentrations of the cytostatic agent in the liver metastases, but contrary to IHP, HAI is a minimally invasive procedure and is suitable for repetitive treatment, further limiting the possible role of oxaliplatin in IHP.

For IHP to remain a treatment option for isolated liver metastases, perioperative morbidity and mortality needed to be reduced, most likely by adapting the procedure. Recently, percutaneous hepatic perfusion (PHP) was developed. This percutaneous approach to treat liver metastases with melphalan aims to decrease

morbidity compared to the open procedure. Another aim i to increase the response rate, since the procedure can be performed more than once and a selection of patients can undergo a curative resection after tumour response to the perfusion. [46-49]. Our team is currently investigating this new technique in a phase I/II trial aiming to include 34 patients.

In conclusion, we have established the MTD of oxaliplatin in combination with 100mg melphalan in IHP at 100mg. Further escalation is limited by the occurrence of SOS. In view of similar and even higher doses of oxaliplatin applied in both systemic treatment and HAI, applying this dose in IHP will not result in a further improvement of the treatment of patients with isolated hepatic metastases. Improvement of the treatment must be sought in improving the perfusion system, such as a percutaneous procedure.

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CHAPTER 3

Perfusion with high dose chemotherapy in patients with unresectable liver metastases of uveal melanoma: results from two experienced centers

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ABSTRACT

Objective

Uveal melanoma patients have a poor survival after diagnosis of metastatic disease. Isolated hepatic perfusion (IHP) was developed to treat patients with unresectable metastases confined to the liver. This retrospective analysis focusses on treatment characteristics, complications, toxicity and survival after IHP.

Methods

Patients with uveal melanoma metastases confined to the liver treated with IHP in two experienced hepato-pancreatic-biliary surgery centers (EMC and LUMC) were included.

Results

Between March 1999 and April 2009, 30 patients were treated with IHP. The duration of surgery was 3.7 hours (EMC) versus 8.7 hours (LUMC) and also the dosage of melphalan differed; 1 mg/kg body weight (n=12) versus a dose of 170-200 mg (n= 18) or melphalan (100 mg) combined with oxaliplatin (50 or 100 mg) (n=3). The length of hospital stay was 10 days. Two patients developed occlusion of the hepatic artery, and died respectively 3 days and 1.5 month after surgery. Progression free survival was 6 (1-16) months and recurrences occurred mainly in the liver. Median overall survival was 10 (3-50) months.

Conclusions

IHP is a potentially beneficial treatment modality resulting in a reasonable overall survival for uveal melanoma patients. Because of substantial morbidity related to the open procedure, a percutaneous system has been developed and is currently being investigated.

INTRODUCTION

Uveal melanoma arises from melanocytes in the ocular chorioid, ciliary body or iris of the eye. It is the most common primary intraocular malignant tumour in adults and the age at diagnosis is most often between 55 and 65 years. [1] Intraocular tumours are detected incidentally or present with visual symptoms and are diagnosed using fundoscopic and ultrasound examination by an ophthalmologist. The treatment of the primary tumour consists of local radiotherapy (brachytherapy, proton beam irradiation or stereotactic radiotherapy) or enucleation of the eye. After treatment of the primary tumour with no synchronous metastases, patients are kept under surveillance often with half-yearly liver function tests and hepatic ultrasound. Up to 62% of the patients may develop metastases, most commonly or solely in the liver [2, 3, 4]Liver metastases are the life-limiting risk factor for these patients. [5] The median survival after diagnosis of metastatic disease in the liver is poor: 2-12 months without treatment and 10-12 months after loco-regional chemotherapy-based treatments. [4, 5, 6, 7, 8, 9] The survival time after detection of metastatic disease is significantly associated with several factors such as tumour burden, symptoms of the metastases, length of interval between treatment of primary tumour and detection of metastases, liver function and patients performance score. [8 10]

Currently, surgical resection of liver metastases is the gold standard for any patient with 'liver only' disease. However, most uveal melanoma patients do not meet the criteria for resection because the metastases are spread diffusely throughout the liver or because of excessive (miliary) tumour burden. Besides surgery, treatment options are limited and currently there is no standard treatment available for patient with uveal melanoma metastases. Systemic therapy, such as dacarbazine (DTIC), is used to treat patients with metastatic disease, but results have been disappointing. [11] Singh *et al.* reported that the 5-year relative survival in the United States did not improve over time from 1973-2008 despite the development of new agents. [12] New treatment options like targeted therapy and immunotherapy are widely investigated in clinical trials, but effectiveness in uveal melanoma is as yet unclear. [13] Besides systemic therapy and surgery, locoregional treatments are being investigated, such as radiofrequency ablation (RFA), microwave ablation, isolated hepatic perfusion (IHP), selective internal radiation therapy with Yttrium-90 microspheres and trans-arterial chemoembolization (TACE). These locoregional modalities could be implemented in the treatment plan of patients with uveal melanoma metastases, since the metastases are often confined to the liver. Furthermore, the rare complete responses that have been reported, were achieved with local therapies, indicating the value of these modalities.[8]

IHP was developed about thirty years ago to treat patients with unresectable metastases from various origin confined to the liver.[14] The principle of IHP is to isolate the liver from the systemic circulation and perfuse it with high dose chemotherapy. Systemically administered this high dose chemotherapy could potentially cause fatal complications.[15] The advantage of IHP as a whole liver treatment is the fact that all (micro) metastases are being treated whereas other local treatment modalities often only target detectable tumours. Many patients with unresectable uveal melanoma and especially colorectal cancer liver metastases have been treated with IHP with radiological response rates ranging from 50 to 62%. [16, 17, 18, 19, 20, 21]

Two University Medical Centers in the Netherlands have an IHP program since the early nineties and gained experience with this procedure; IHP has been performed during laparotomy in over 130 patients with liver metastases (colorectal cancer, uveal melanoma, neuroendocrine tumours, GIST, HCC etc.)[16, 17, 21, 22]. The aim of the study was to investigate the efficacy of this treatment for patients with uveal melanoma metastases confined to the liver. In this paper, we describe the results of treating 30 patients with uveal melanoma liver metastases with IHP in two centers using melphalan (in some cases combined with oxaliplatin) as chemotherapeutic agent.

METHODS

Patient selection criteria

All patients with uveal melanoma metastases who were treated with IHP in either the Erasmus MC Cancer Institute (EMC) or the Leiden University Medical Center (LUMC) were selected for this retrospective analysis. Treatment of the primary tumour (enucleation or radiotherapy) had been performed prior to entering the study protocol. The liver metastases had to be unresectable and were considered so on the basis of multiple lesions (>10) in multiple segments and/or a location near vascular structures, making an oncological resection impossible, as seen on imaging (CT or MRI). Moreover, all patients were discussed in a multidisciplinary meeting (radiologist, medical oncologist, surgeon, pathologist).

Tumour involvement had to be less than 50% of liver tissue, determined by volumetric measurements by the radiologist, to prevent massive necrosis and subsequent organ failure in case of a good response. All patients had to be above 18 years of age and have a World Health Organization (WHO) performance status of 0 or 1, liver enzymes (ALAT, ASAT and alkaline phosphatase) less than five times the upper limit of normal (ULN) and bilirubin not higher than twice the ULN. In case a patient did not meet one of the criteria, he or she was not included in the

trial. Exclusion criteria were age over 70 years, evidence of extrahepatic disease on CT scan of thorax and abdomen, and administration of chemotherapy within four weeks prior to the IHP treatment. Routinely, angiography was performed prior to IHP to exclude aberrant hepatic arteries or to visualize other anatomic anomalies, as well as to screen for secondary signs of portal hypertension, such as hepatofugal flow. The study protocol was approved by the Medical Ethical Committee of both centers and informed consent was obtained from all patients.

Chemotherapeutic agents

A dosage of 1 mg/kg melphalan was used in the EMC, based on a study by Verhoef. [22] Doses of 170-200 mg were given to the LUMC patients (Alkeran, Wellcome Pharmaceuticals B.V., Utrecht, The Netherlands), based on an earlier phase I study of IHP with melphalan, where a total dose of 200 mg appeared to be the maximally tolerated dose. [23] Also, in the LUMC patients have been treated in a dose-escalation trial; 50 or 100 mg of oxaliplatin (Sanofi-Aventis, Gouda, The Netherlands) was added to a fixed dose of 100 mg melphalan. In all cases melphalan was infused into the perfusion circuit through a side-line. In case of patients treated in the dose escalation study, the oxaliplatin was administered as a bolus before melphalan infusion.

Surgical procedure

The patients were treated with a single IHP procedure as described previously: in the EMC as described by Verhoef *et al*. in 2008 [22] *(Figure 1)* and in the LUMC as described by Rothbarth *et al.* in 2003 [16] and Vahrmeijer *et al*. in 2000 [23] *(Figure 2)*. After laparotomy, the portal vein (PV) and proper hepatic artery (HA) were dissected and the HA artery was cannulated via the gastroduodenal artery followed by heparinization of the blood. The inferior caval vein (ICV) was isolated and clamped above the renal veins and below the diaphragm to prevent venous leakage. Tourniquets/clamps were also secured around the HA and PV to isolate the hepatic circuit. The HA and PV catheters were connected to the perfusion circuit.

Melphalan was infused into the perfusion circuit using an infusion pump and IHP was performed under mild hyperthermic conditions (39°C). After one hour period of perfusion a wash-out procedure was performed. Finally, all cannulas and clamps were removed and normal circulation was restored and all incisions were closed. In the EMC the portal vein was cannulated for outflow; resulting in a hypoxic technique, with retrograde outflow, hence isolated hypoxic hepatic perfusion (IHHP). An aortic clamp was placed for controlling systemic blood pressure. A constant flow perfusion (of approximately 350 ml/min, mean) under pressure monitoring was established.

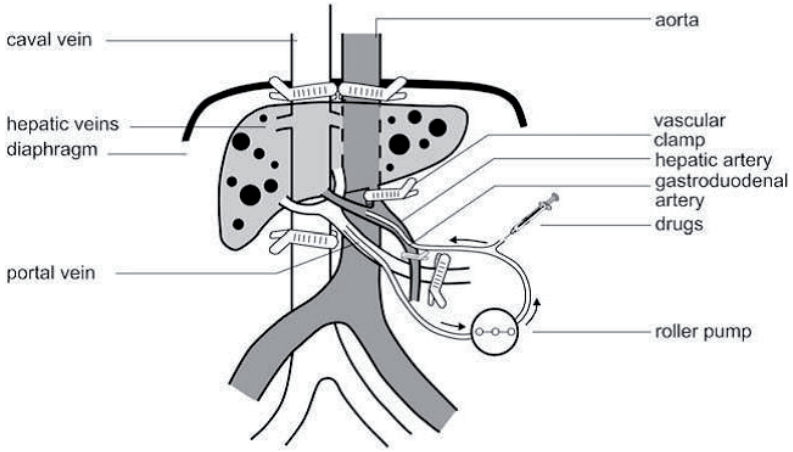

FIGURE 1. **The retrograde perfusion setup, as used in the Erasmus University Medical Center**

During the procedure at the LUMC the perfusate was oxygenated using a heart–lung machine. An extracorporeal veno-venous bypass was used to maintain circulation in the abdomen and the lower extremities. To achieve this, the right femoral vein and the PV were cannulated proximal to a tourniquet and connected to the right axillary vein. To prevent possible post-operative cholecystitis, a cholecystectomy was performed routinely.

Leakage detection

Leakage of perfusate into the systemic circuit was monitored using a radioactive tracer (10 MBq 99mTc-pertechnetate, 99mTc). This was injected into the isolated circuit with subsequent measurement of the radioactivity levels in both the systemic and isolated circuit as previously described [24, 25]. Systemic leakage was continuously monitored with a scintillation counter and was expressed quantitatively as a percentage. If no leakage was detected, the chemotherapeutic agent(s) were administered. Leakage during perfusion was allowed to be 10%. If this level was reached, perfusion was immediately stopped.

Postoperative care and follow-up

Patients were monitored in the intensive care unit for at least one day after IHP. Liver and kidney function tests, such as ALAT, ASAT, bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, creatinine, urea, number of platelets and white blood cell count were measured frequently. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Criteria (CTCAE

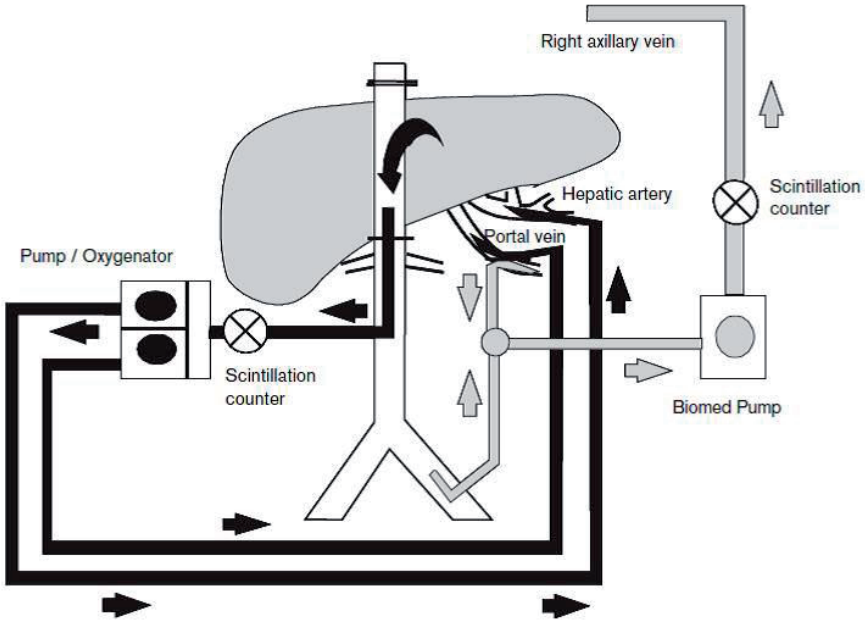

FIGURE 2. **Isolated hepatic perfusion with extracorporeal veno-venous bypass, as used in the Leiden University Medical Center.**

v4.0). Granulocyte colony-stimulating factor (G-CSF, Filgrastim/Neupogen®, Amgen B.V., Breda, The Netherlands) was administered, however not routinely.

Response evaluation

Tumour response was evaluated by comparing post-procedural abdominal contrast-enhanced CT and/or MRI scans at three month intervals with pre-perfusion scans. Progressive disease was defined an increase in size of ≥25% or the appearance of new intra- or extrahepatic lesions.

Statistical Analysis

All data were analysed using SPSS software for Windows version 20 (SPSS, Chicago, Illinois, USA).

RESULTS

Patient characteristics *(Table 1)*

Between March 1999 and April 2009, 31 patients with histologically proven uveal melanoma with metastases confined to the liver underwent surgery for isolated hepatic perfusion in either the EMC or LUMC. Biopsies of the liver lesion(s) were

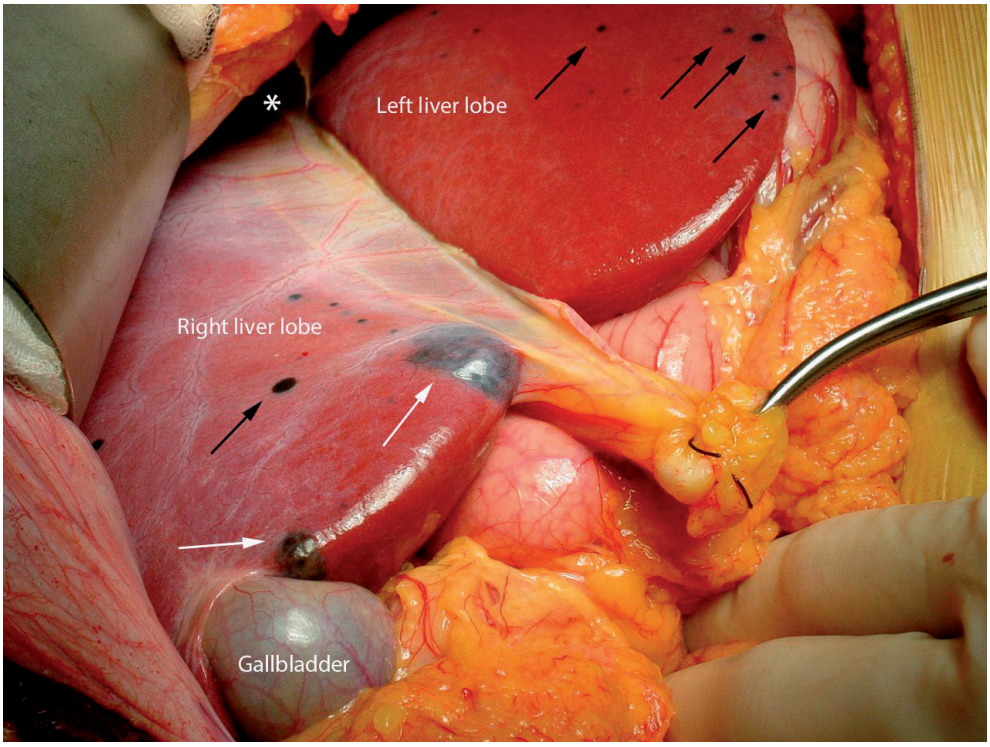

FIGURE 3. **Per-operative photograph of the liver. Black spots (pointed by arrows) are uveal melanoma metastases; black arrows indicate small lesions, most likely not seen on CT-scan, white arrows indicate larger metastases. Picture was taken in a cranial direction from the right side of the patient (asterix in direction of head of the patient).**

obtained to proof that the suspected hepatic lesions seen on imaging or during surgery were indeed melanoma metastases. The median age at the time of treatment was 57 years. Treatment of the primary tumour was mostly enucleation and most patients developed liver metastases metachronously. Most patients had multiple metastases (over 10) and/or metastases diffusely spread throughout the liver (see Figure 3). Four patients received previous treatment of the liver metastases: one patient received dacarbazine and three patients trial-related immunotherapy (consisting of GM-CSF, IL-2 and IFNalpha). The time interval between the primary diagnosis of uveal melanoma and the clinical diagnosis of liver metastases ranged from synchronous liver metastases at time of diagnosis of the primary tumour up to eleven years (range 0-133 months). Metastases were detected during routine 3 or 6 monthly follow-up visits including liver enzyme blood tests and ultrasound of the abdomen.

TABLE I. **Patient characteristics and history.**

No. of patients included	**31**
Male : female	**12:19**
Median age at time of primary diagnosis , years, range) Median age at time of treatment, years, range)	**53 (27-68)** **57 (28-70)**
Treatment of primary tumour (number of patients) Enucleation Local stereotactic irradiation Local Ruthenium plaque Proton beam treatment	 **18** **4** **8** **1**
Liver metastases (number of patients) Metachronous Synchronous	 **29** **2**
Median time from primary diagnosis to metastases, months (range)	**27 (0-133)**
Previous treatment of liver metastases (number of patients) Dacarbazine° Immunotherapy/trial	 **1** **3**
Median time from diagnosis of liver metastases to IHP, weeks (range)	**10 (4-58)**

(°DTIC – dacarbazine, an alkylating oncolyticum)

Surgical characteristics *(Table 2)*

One procedure in the LUMC was aborted before melphalan infusion because of systemic leakage of the radioactive tracer; this patient did not receive chemotherapy and was therefore excluded from further survival analysis. The dosage of melphalan differed between the two centers. The 12 patients in the EMC received a dose of 1mg/kg body weight (dose 60 – 95 mg). In the LUMC 15 patients were treated with 170-200 mg of melphalan, and 3 patients in a combined melphalan–oxaliplatin dose-escalation study: 2 patients with a combination of 100 mg melphalan and 50 mg of oxaliplatin, and 1 patient with 100 mg melphalan and 100 mg of oxaliplatin. [26] Median time of surgery was 3.7 hours (2.6 – 4.8) in the EMC and 8.4 hours (6.2 – 10.2) in the LUMC. At the EMC, the IHHP procedure was performed without a veno-venous bypass and a heart-lung machine. Consequently an extracorporeal perfusionist is not needed and operation time and blood loss are reduced using this method.

Complications and toxicity

One patient died three days postoperatively because of liver failure caused by occlusion of the hepatic artery leading to multi-organ failure. One patient was discharged with impaired liver functions because of an occluded hepatic artery and died 1.5 months after surgery. Veno-occlusive disease (VOD) occurred in two patients who both had a 7 months survival after surgery. One patient developed

TABLE 2. **Treatment characteristics and survival (n=30 patients)**

	Total (n=30)	**EMC (n=12)**	**LUMC (n= 18[‡])**
Dose chemotherapeutic agent : melphalan (mg) (O.: Oxaliplatin)		65-95 mg	170-200 mg (n=13) 100 mg & O. 50 mg (n=2) 100 mg & O. 100 mg (n=1)
Leakage (median)		n.r.	0.5%
Operation time (median, hours)		3.7 hours	8.4 hours
Perioperative blood loss (median, ml)		700[*] ml	3500 ml
Hospital stay (median)	**10 days**		
Postoperative treatment (no. of patients) Systemic therapy Ablation	**8** **2**		
Progression-free survival (median, (range))	**6 months (1-16)**		
Localisation of progression (no. of patients) Hepatic Extrahepatic Both hepatic and extrahepatic	**14** **4** **10**		
Overall survival (median, months (range)) IHP until death Diagnosis of liver metastasis until death Diagnosis of primary tumour until death	**10 months (0-50)** **13.5 months (2-53)** **39 months (11-149)**		

(n.r.=not reported of most patients, [‡] One procedure aborted in LUMC; no further analysis, [*]missing of four patients)

non-infectious fever postoperatively that resolved within a few days. Hepatic toxicity consisted of a transient rise of liver enzymes. Systemic toxicity was mainly leukopenia, with CTCAE grade 0-1 and grade 4 in one patient.

Progression-free and overall survival

Results of progression-free survival and overall survival of the 30 treated patients are shown in Table 2. Median progression-free survival after IHP was 6 months (range 1-16) and progression was hepatic (14/30), both hepatic and extrahepatic (10/30) or extrahepatic (4/30). Extra-hepatic progression consisted of lung and bone metastasis and skin metastasis in 14 patients. Median overall survival after IHP treatment was 10 months (range 0-50 months). Median overall survival from diagnosis of liver metastasis was 13.5 (range 2-53) months. Besides the two patients that died postoperatively of liver failure, all patients died because of progression of metastatic disease. The 1-year survival for this cohort was 41.9% and the 2-year

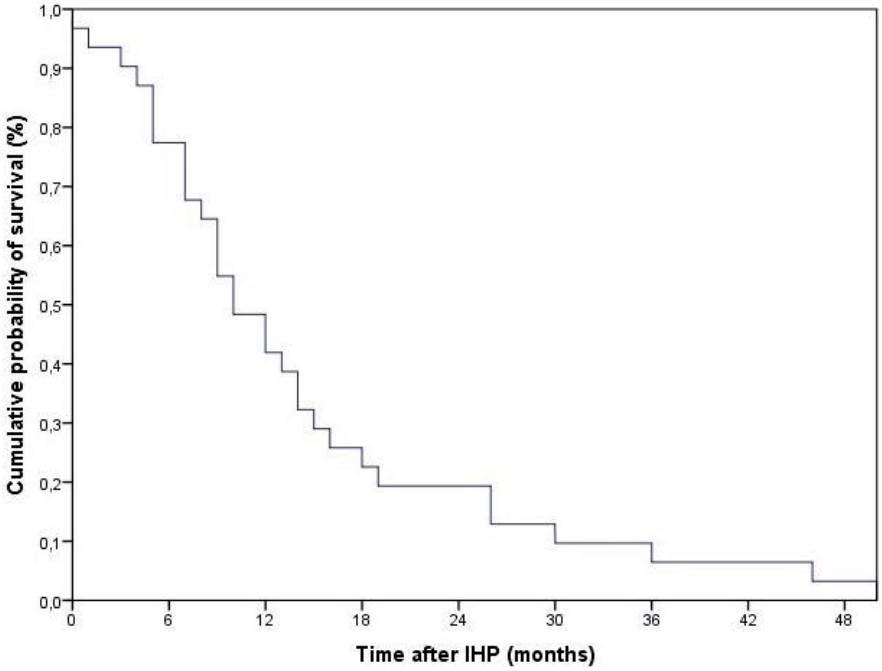

FIGURE 4. **Kaplan-Meier curve for overall survival after isolated hepatic perfusion with melphalan. All patients combined. (n=*31*) *One patient died 1.5 days after the procedure and therefor at time point 0.**

survival was 19.4% as shown in the Kaplan-Meier curve in figure 4. Median overall survival from primary tumour diagnosis was 39 months (range 11-149). Ten patients received postoperative (systemic) treatment after diagnosis of disease progression. The other patients did not receive systemic therapy often at their own wish or due to rapidly progressive disease. Since no standard treatment modality was (and still is) available, the only option for treatment was to participate in phase I/II trial protocols.

DISCUSSION

This study presents the results of 30 patients with unresectable liver metastases of uveal melanoma treated with isolated hepatic perfusion with melphalan in two experienced centers. For this selected group of patients, the median overall survival was 13.5 months after diagnosis of liver metastases and the 1-year survival was 41.9%.

Augsburger *et al. (2009)* listed 20 prospective studies with several treatment modalities (chemotherapy; systemic and applied locally to the liver, and

chemoembolization) for patients with metastatic uveal melanoma. The study groups were of comparable size to our study and the median overall survival was 5.0- 24 months (for prospective studies). Our study with 30 patients treated with I(H)HP fits in the middle of these listed studies with a median overall survival of 13.5 months. The median survival for unselected case series was even worse; 3.6-15 months. However, this might be a better representation of reality, since the prospective studies describe the results in a study population. [6] Previously reported median overall survival after diagnosis of metastatic disease in the liver was 4.2-12.5 months if untreated, with a 1-year survival of 13-20%. [8, 10, 27, 28, 29] For patients that received treatment, mostly in phase I/II study protocols, the median overall survival increased to 5.2-27 months. Most of these studies contain selected patient groups. [28, 29]

Compared to several other treatment modalities, intrahepatic treatment was associated with prolonged survival. [30 31] Current literature reports on new treatment modalities, such as dendritic cell vaccination and new (application of excisting) chemotherapy, however the results of research on these new modalities have not been confirmed in large trials yet. [32, 33] Based on the above mentioned data we conclude that patients might benefit from I(H)HP compared to untreated patients and possibly have a longer overall survival compared to other treatment modalities. These data should be judged with caution as case selection could have influenced the results: the median age at the time of diagnosis (53 years) of the primary tumour in our series was lower than in most reported series of uveal melanoma. The average age of uveal melanoma patients reported in previous studies is 61 years old, and in high risk cases 59. [1 34] Also, the group consisted mostly of women, although uveal melanoma does not show a sex preponderance.

In order for isolated perfusion of the liver to become an acknowledged treatment option for liver only metastases, peri-operative morbidity needs to be reduced, most likely by adapting the procedure. Firstly, the I(H)HP procedure performed during laparotomy, is associated with morbidity due to the 'open' approach and the invasive manner of clamping and cannulating various blood vessels. In the current analysis, four patients experienced a thromboembolic adverse event or veno-occlusive disease and two patients died from the consequences of hepatic artery occlusion. By creating a different approach, the laparotomy-associated morbidity could be prevented. A second adjustment to the procedure should concern 'repeatability', because the predominant site of progression or recurrence is the liver. Indeed, a possible way to achieve longer progression free survival is repeating the IHP treatment. In case of an 'open' IHP procedure, adhesions and effects on the vascular anatomy of the cannulation and clamping impede repetition. Already in 1994 Ravikumar *et al.* investigated a percutaneous in-human approach for isolated liver

perfusion. [35] Several studies report on a less invasive, percutaneous approach, but had disappointing results, for instance because the occlusion balloon methodology failed to obtain leakage control.[36] Due to lack of evidence of efficacy, the technique was largely abandoned until the early 2000's when it was re-evaluated by the National Cancer Institute (NCI) in the United States.[37] A renewed method of isolated hepatic perfusion was developed recently, which isolates the liver from the systemic circulation using a new system of percutaneous placed catheters. Percutaneous hepatic perfusion (PHP) with chemosaturation is minimally invasive, has limited systemic toxicity combined with high local drug exposure like IHP and has been performed up to 8 times. [38, 39] This new approach meets the two improvements needed as mentioned above: (1) change to a minimally invasive procedure and (2) repeatability. Recent studies using PHP for uveal melanoma report a 50% complete and partial response rate, and improved hepatic progression free survival (7 versus 1.6 months) after percutaneous hepatic perfusion compared to best alternative care. [40 41] Our centers are currently investigating this new technique in a two-center phase II trial aiming to treat uveal melanoma patients with unresectable liver metastases

CONCLUSION

We have analysed the results of isolated (hypoxic) hepatic perfusion in treating 30 patients with unresectable liver metastases of uveal melanoma treated from 1999-2009. Patients treated with IHP seem to benefit from IHP compared to no treatment and equally compared to other treatment modalities. Because of substantial morbidity related to the open procedure, a percutaneous method has been developed and is currently being investigated.

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CHAPTER 4

Percutaneous Hepatic Perfusion (PHP) with melphalan as a treatment for unresectable metastases confined to the liver

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ABSTRACT

Unresectable liver metastases of colorectal cancer can be treated with systemic chemotherapy, aiming to limit the disease, extend survival or turn unresectable metastases into resectable ones. Some patients however, suffer from side effects or progression under systemic treatment. For patients with metastasized uveal melanoma there are no standard systemic therapy options. For patients without extrahepatic disease, isolated liver perfusion (IHP) may enable local disease control with limited systemic side effects. Previously, this was performed during open surgery with satisfying results, but morbidity and mortality related to the open procedure, prohibited a widespread application. Therefore, percutaneous hepatic perfusion (PHP) with simultaneous chemofiltration was developed. Besides decreasing morbidity and mortality, this procedure can be repeated, hopefully leading to a higher response rate and improved survival (by local control of disease). During PHP, catheters are placed in the proper hepatic artery, to infuse the chemotherapeutic agent, and in the inferior caval vein to aspirate the chemosaturated blood returning through the hepatic veins. The caval vein catheter is a double balloon catheter that prohibits leakage into the systemic circulation. The blood returning from the hepatic veins is aspirated through the catheter fenestrations and then perfused through an extra-corporeal filtration system. After filtration, the blood is returned to the patient by a third catheter in the right internal jugular vein. During PHP a high dose of melphalan is infused into the liver, which is toxic and would lead to life threatening complications when administered systemically. Because of the significant hemodynamic instability resulting from the combination of caval vein occlusion and chemofiltration, hemodynamic monitoring and hemodynamic support is of paramount importance during this complex procedure.

INTRODUCTION

Resection of malignant liver tumours is the first choice of treatment for both primary and secondary hepatic malignancies. However, a large proportion of patients are no candidates for surgery because of extended disease or location of the metastases. For patients with unresectable metastases from colorectal carcinoma, systemic therapy is often the preferred treatment. Hepatic metastases from uveal melanoma are often small and diffusely spread throughout the liver. No standard systemic therapy is available for this group of patients. Local therapy can be an alternative to systemic treatment, in case the metastases are confined to the liver.

Because of the specific vascular anatomy of the liver, this organ can be isolated from the systemic circulation. This allows perfusion of the liver with high dose chemotherapy (IHP, isolated hepatic perfusion). Besides, liver malignancies have a dominant or exclusive vascular supply from the hepatic artery, whereas 70-80% of the supply of the non-tumorous liver parenchyma is derived from the portal vein. [1,2] This technique was developed over twenty years ago, to treat patients with unresectable metastases from various primary origins.[3,4] Especially, uveal melanoma patients with metastases in the liver may be candidates for IHP because the metastases are often small and spread throughout the entire liver, and at present no standard systemic therapy is available. [5, 6]

The principle of IHP is to temporarily isolate the liver from the systemic circulation and perfuse the organ with a high dose of chemotherapy, leading to high local drug exposure with limited systemic side effects.[7] This high dose of chemotherapy would be toxic and lead to complications when administered systemically. The majority of IHP studies were performed with melphalan, and have investigated treatment of hepatic metastasis from colorectal cancer patients, as well as patients with uveal melanoma metastases [8,9] Several studies of IHP during open surgery suggest that this treatment might be effective: 50%-59 % tumour response rates (partial and complete response) for the treatment of colorectal cancer and a 68% tumour response rate for patients with metastatic uveal melanoma have been reported.[8,10,11,12] Despite these treatment results, this procedure never gained wide acceptance, because of the complexity of the procedure, the duration of hospital stay and the associated morbidity and mortality.

Percutaneous hepatic perfusion (PHP) offers a minimal invasive alternative to IHP and was first demonstrated in a porcine model in 1993 using doxorubicin[13] and the first in human trial was performed by Ravikumar *et al* in 1994.[14] Due to lack of evidence of efficacy, the technique was largely abandoned until the early 2000's

when it was re-evaluated in National Cancer Institute (NCI) in the United States.[15] During PHP, a catheter is placed percutaneous into the proper hepatic artery via the femoral artery to infuse the chemotherapeutic agent. A second catheter is placed in the inferior caval vein via the femoral vein to aspirate the hepatic chemosaturated outflow (see the PHP circuit in Figure 1). The isolation aspiration catheter placed in the caval vein is a double balloon catheter, prohibiting leakage into the systemic circulation. (See Figure 2) The aspirated chemosaturated blood is filtered by a double charcoal filter and returned to the patient by a third catheter placed in the internal jugular vein. The patient is admitted in the hospital with a length of stay of approximately 3 days. The PHP procedure is performed in an angiography room under general anaesthesia by a well-trained multidisciplinary team consisting of a dedicated interventional radiologist, anaesthesiologist and an extracorporeal perfusionist. A surgical oncologist and medical oncologist are also members of this multidisciplinary team, and especially focus on informing the patient, patient selection and post-operative care.

This minimal invasive procedure is associated with less operative morbidity and can be repeated several times (at least up to four times). Besides, it only takes

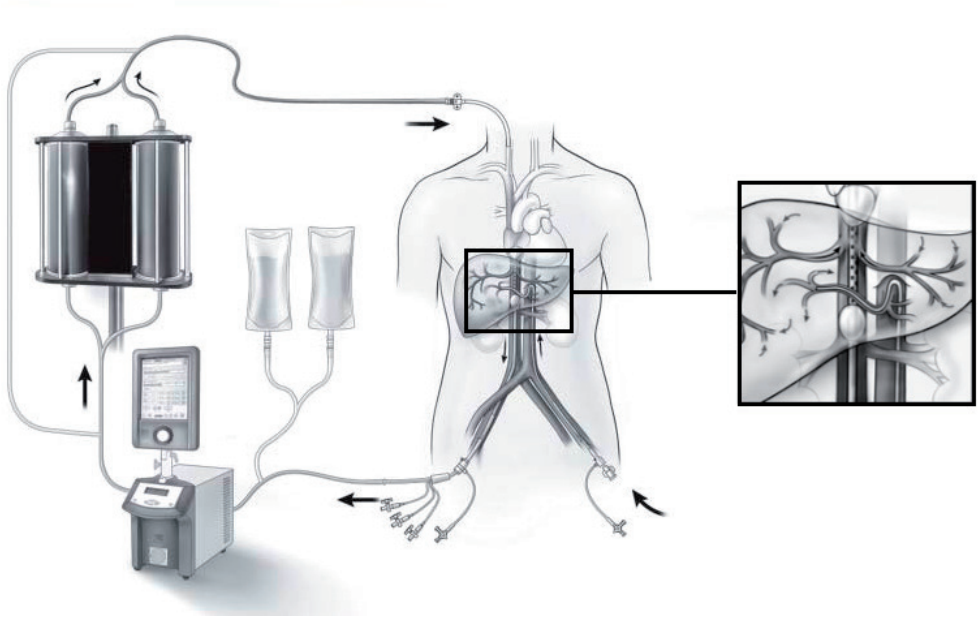

FIGURE 1: **Schematic image of the PHP circuit.**
This figure displays the set-up of the PHP circuit. It shows an isolated hepatic perfusion circuit with extra-corporeal bypass line.

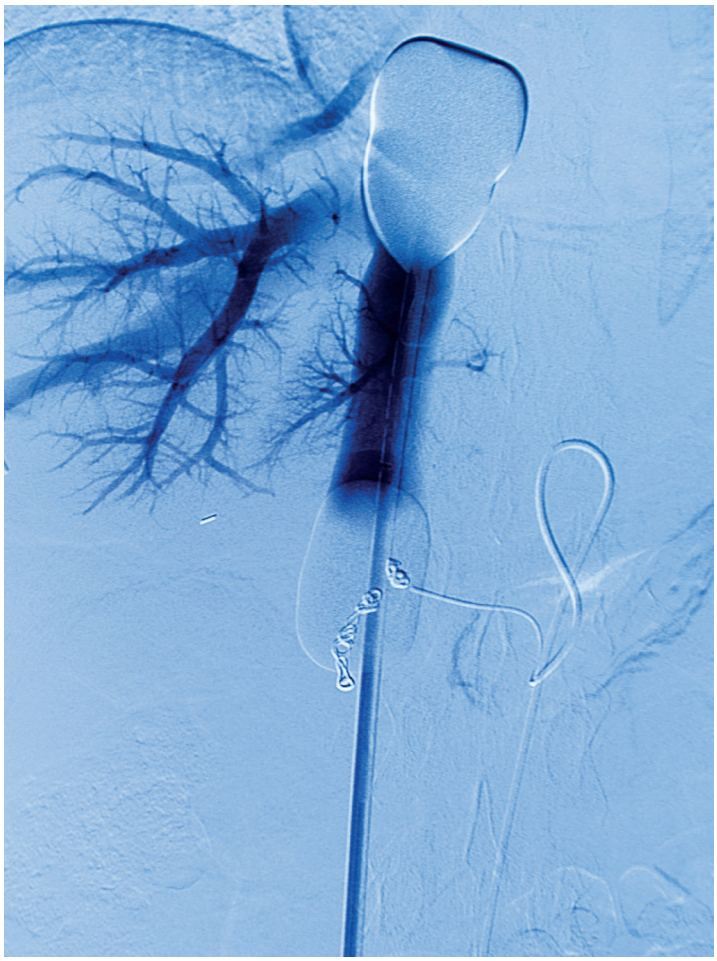

FIGURE 2: **Per-procedural angiogram**
Venous double balloon catheter in the inferior caval vein and arterial infusion catheter in the proper hepatic artery. Retrograde contrast is injected via the venous catheter. Coils from the pre-procedural angiography and embolization are in place.

approximately 3 to 4 hours and patient recovery is fast. The advantage of PHP is the fact that all sizes of metastases can be treated, and micro metastases are being treated as well. Also the location of the metastases, close to vascular structures and bile ducts, is not a contraindication for PHP. Initial studies were performed with the 1st generation filter, with a 77% (mean) filter extraction efficiency. [16]

Recently, the results of a phase III trial were published by Hughes et al. showing a significant improvement of hepatic progression free survival in uveal melanoma

patients with hepatic metastases treated with PHP compared to best alternative care. [17]

Since April 2012 a 2nd generation filter is available. In pre-clinical studies the 2nd generation filter is extracting 98% of melphalan. Several studies and case series investigating PHP for multiple indications have been published, but apart from the recent published phase III trial, survival has not extensively been analysed. [16,18,19,20] In the present video paper, we focus on the interventional radiology procedure, as well as the anaesthetic management and the extra corporeal circulation that is used during this procedure in order to facilitate the use of this treatment in other medical centers.

PROTOCOL

After a patient met all inclusion criteria and was carefully evaluated by a medical oncologist, surgeon and anaesthesiologist, a patient was included in the study. All patients provided written informed consent. Both clinical studies were approved by the Local Medical Ethics Committee of the Leiden University Medical Centre and are performed in accordance with the ethical standards of the Helsinki Declaration.

For an extensive description of the protocol, see chapter

REPRESENTATIVE RESULTS

Knowledge about PHP is based on small phase I and II trials and case series and a recent larger phase III trial; an overview of published results is shown in Table 1. · One paper discusses the anaesthesiology procedure, hemodynamic and metabolic aspects of the treatment. Three larger trials that were reported, included metastatic liver disease from different primary tumours and the results are therefore difficult to interpret [16,22]. The first manuscript was published in 1994 and 5-FU and doxorubin were used. [20,23]. Published overall response rates vary between 30 and 90% and limited data on survival data are reported.

A recent phase III trial, comparing PHP to best alternative care (BAC) for patients with hepatic metastases of uveal melanoma, reports improved hepatic progression free survival of 7 months compared to 1.6 months for the group that received BAC ($p< 0.0001$). [17] In the PHP group 36% of patients had a partial response and another 52% had a stable disease. No significant difference in median overall survival was

TABLE I: **Published results of percutaneous hepatic perfusion**

Author	Year	n	Tumor	Chemotherapeutic agent	ORR	CR	PR	SD	Median hPFS	Median survival	Mortality
Hofmann	2014	1	pseudopapillary pancreatic tumor	melphalan			1			n.a.	n.a.
Vogl	2014	14	Metastatic hepatic disease	melphalan	86%	1/14 (7%)	6/14 (43%)	5/14 (36%)	240 days	n.a.	1
			(melanoma, carcinoma)				11/14 (78%)				
Fitzpatrick	2014	5	Melanoma	melphalan	n.a.					n.a.	n.a.
Forster	2013	10	Melanoma/Sarcoma	melphalan	90%		9/10 (90%)			n.a.	0
Deneve	2012	1	Sarcoma	melphalan					16 months	n.a.	n.a.
Miao	2008	51	Metastatic hepatic disease	melphalan	n.a.					n.a.	n.a.
			(NET, melanoma, carcinoma)								
Pingpank	2005	28	Primary and metastatic hepatic tumors	melphalan	30%	2	6			n.a.	n.a.
		(10)	(Ocular melanoma–subgroup)		50%	2	3				
Savier	2003	4	Primary and metastatic hepatic tumors	melphalan	n.a.					n.a.	
Ravikumar	1994	21	Primary and metastatic hepatic tumors	5-FU, doxorubin	n.a.		2	2		n.a.	0
							4 (19%)				

Publications with clinical outcomes reported for patients with metastases confined to the liver treated with PHP.
ORR=overall response rate; CR=complete response; PR = partial response; SD= stabile disease. hPFS= hepatic progression free survival; n.a.=not available

observed (10 months), probably because patients in the BAC group could crossover to the PHP treatment. [17]

Reported peri-procedural events (during the procedure up to 72hours after the procedure) included thrombocytopenia (74%) and anemia (60%), often treated with transfusion. Also procedure-related hypotension and hepatic artery spasm were observed, which could be treated with vasopressors and nitroglycerin respectively. Four deaths (4% mortality rate) were reported; two bone-marrow suppression associated(neutropenia and streptococcal sepsis) , one because of progressive hepatic failure and one from gastric perforation. [17]

Initial studies where performed with the 1st generation filter, with a 77% (mean) filter extraction efficiency.[16] The filter set and the associated protocols were adjusted in response to occurring complications. Studies using the first generation filter also report grade 3 and 4 coagulopathy, possibly related to consumption of clotting factors by the filters. [22] [17] Based on these findings, a 2nd generation filter was developed, and is available since April 2012.In pre-clinical studies the filter efficacy was improved (98%).

The chemotherapeutic agent of choice for the PHP procedure is melphalan, because it has previously shown to be effective in the treatment of different kinds of liver metastases, without being hepatotoxic, even when administered in myeloablative dosages. [7,22] Melphalan is an alkylating agent of the nitrogen mustard group. It adds an alkyl group to DNA, interfering normal mitosis in rapidly dividing cells by damaging the original structure.[24] Adding other chemotherapeutic agents such as 5-fluorouracil (5-FU) and leucovorin [25], oxaliplatin[26] or TNF [11] did not improve response rate and an increase in hepatotoxicity was observed in most studies [27]

To investigate the efficacy and safety of this procedure with the 2nd generation filter in patients with unresectable liver metastases of uveal melanoma or colorectal cancer, two phase II trials have been initiated at the Leiden University Medical Center and Erasmus MC Cancer Institute (NTR4112 respectively NTR4050). Primary endpoint is the response rate according to RECIST 1.1 criteria on CT / MRI-scans. Secondary endpoints are safety, toxicity according to CTCAE 4.0, (overall) survival and (hepatic) progression free survival and duration of response. Up to now, 27 patients have been treated and there has been no PHP related mortality.

DISCUSSION

Patients with unresectable liver metastases can be treated with systemic therapy. However, for patients with metastatic uveal melanoma, no standard systemic therapy is available and immunotherapy or targeted therapy have not yet been able to show improved survival. Isolated hepatic perfusion has been shown to be an effective treatment for patients with unresectabel uveal melanoma metastases confined to the liver. [9] [28]

For colorectal cancer metastases more therapeutic systemic options are available, but some patients progress under these regimens or do not tolerate this treatment because of toxicity. In 2009, Van Iersel and colleagues reported a median overall survival of 25.0 months for patients treated with one IHP procedure versus 21.7 months after treatment with systemic therapy. Although not significant, it shows a trend towards benefit from one IHP procedure versus the CAIRO-1 cycles of systemic chemotherapy.[29]

IHP is a complex surgical intervention and because of the complexity, duration of hospital stay and associated morbidity and mortality never gained wide acceptance. Because of the promising results, a less invasive percutaneous system was developed. Because of hemodynamic perturbations during the procedure and post-procedural haematological toxicity, patient selection is of great importance. Patients with WHO status 0 and 1, no or limited cardiopulmonary risk factors and preserved liver functions can be selected for PHP treatment.

Due to the high dose chemotherapy, there is a risk of hepatic failure and therefore no more than 60% of liver volume should be replaced by tumour.

Another crucial aspect of the PHP procedure is the anaesthetic management of the patient and especially the control of blood pressure.[30] During the procedure, transient hypotension occurs due to the reduction in preload due to caval vein occlusion and peripheral vasodilation from passage of blood through the chemofilters (hemofiltration) and removal of vasoactive agents (e.g. norepinephrine and phenylephrine) by the chemofilters. Ravikumar *et al.* first described percutaneous hepatic vein isolation and infusion of chemotherapy and the consequent transient hypotension after balloon inflation in 79% of the procedures and the importance to anticipate this.[14] A second period of hypotension occurs after the flow is diverted through the charcoal-activated filters.[22] [17]This hypotension is of short duration and responds well to administration of fluids and sympatico-mimetics.

Although a filter extraction rate of 77% (generation 1 filter) has been observed, still small systemic leakage of melphalan occurs, leading to myelosuppression. This has been reported in the majority of cases in literature, is of transient nature and well manageable with GCSF growth factor and/or blood products, mostly on an outpatient basis. [16,19] [17] The nadir of cytopenia is generally reached 10-14 days after PHP. Therefore, regular blood tests in the first two weeks after PHP are mandatory. The 2nd generation filter that is currently being used, hopefully reduces toxicity by an increased filter extraction.

During the procedure, teamwork and clear communication is of utmost importance. The procedure is best performed by a dedicated team with well-trained members. During the PHP procedures in our hospital, the interventional radiologist acts as team leader.

The current status of PHP in treating hepatic malignancies is not yet settled. Future trials will have to prove whether PHP can be integrated in treatment strategy for other types of malignancies. The short hospital stay after the procedure, indicating the tolerability of this procedure, and the manageable complications supports ongoing research of PHP in the treatment of cancer confined to the liver.

In summary, PHP is a well-tolerated local therapy for patients with unresectable liver metastases. Survival and duration of response are investigated in various trials.

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CHAPTER 5

Prospective clinical and pharmacological evaluation of the Delcath System's second generation (GEN2) hemofiltration system in patients undergoing percutaneous hepatic perfusion with melphalan

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ABSTRACT

Introduction

Percutaneous hepatic perfusion (PHP) with melphalan is an effective treatment for patients with hepatic metastases, but associated with high rates of bone marrow depression. To reduce systemic toxicity, improvements have been made to the filtration system. In pre-clinical studies, the Delcath System's GEN2 filter was superior to the first generation filters. In this clinical study, we analysed the pharmacokinetics and toxicity of PHP using the new GEN2 filter.

Methods and Materials

Starting February 2014, two prospective phase II studies were initiated in patients with hepatic metastases from ocular melanoma or colorectal cancer. In 10 PHP procedures performed in the first 7 enrolled patients, blood samples were obtained to determine filter efficiency and systemic drug exposure. PHP was performed with melphalan 3mg/kg with a maximum of 220 mg. Complications were assessed according to CTCAE v4.03. Response was assessed according to RECIST 1.1.

Results

Pharmacokinetic analysis of blood samples showed an overall filter efficiency of 86% (range 71.1–95.5%). The mean filter efficiency decreased from 95.4% ten minutes after the start of melphalan infusion to 77.5% at the end of the procedure (p=0.051). Bone marrow depression was seen after up to 80.0% of 10 procedures, but was self-limiting and mostly asymptomatic. No hypotension-related complications or procedure related mortality occurred.

Conclusion

The GEN2 filter has a higher melphalan filter efficiency compared to the first generation filters and a more consistent performance. PHP with the GEN2 filter appears to have an acceptable safety profile, but this needs further validation in larger studies.

INTRODUCTION

Percutaneous hepatic perfusion (PHP) is an innovative, minimally invasive procedure that is gaining interest as a therapeutic option for patients with hepatic malignancies. A recently published randomized controlled trial (RCT) has shown superiority of PHP over best alternative care in patients with hepatic metastases from ocular and cutaneous melanoma[1]. Furthermore, small prospective cohort studies have shown promising results in patients with secondary liver tumours as well as primary liver tumours [2-7]. Wide acceptance of PHP in clinical practice has been halted due to concerns about the safety profile of PHP. The most notable complication of PHP is bone marrow depression resulting in anaemia, neutropenia and/or thrombocytopenia. Reported rates of complications related to bone marrow depression vary from 43.7% to 85.7% [8]. In PHP, the liver vasculature is isolated from the systemic circulation using percutaneously inserted catheters. A micro-catheter is placed in the hepatic artery to deliver a high dose of the chemotherapeutic agent melphalan. Prior to the start of infusion of the chemotherapeutic drug, a double-balloon catheter is placed in the inferior caval vein (ICV). The balloons prevent leakage of chemotherapeutics to the systemic circulation by occluding the ICV at the level of the atrio-caval junction and infra-hepatic ICV. Through catheter side-holes located in between the two balloons, the chemosaturated blood returning through the hepatic veins is aspirated and the blood is then pumped through an extra-corporeal filtration system. After filtration, the blood is returned to the patient through a catheter in the internal jugular vein [8]. The high rate of bone marrow depression associated with PHP indicates that systemic exposure to chemotherapeutic drugs does occur. This may result from failure to achieve complete isolation of the liver vasculature or from incomplete extraction of chemotherapeutics by the hemofiltration system. In a phase I trial including 28 patients treated with PHP, pharmacological analyses of blood samples demonstrated a mean filter extraction rate of 77% (range 58.2% - 94.7%) [9]. In this study, and most of the other published studies, PHP was performed using a first generation hemofiltration system. In 2012, a second generation detoxification cartridge (GEN 2 filter; Delcath Systems, New York, NY, USA) was made commercially available. Compared to the first generation hemofiltration system, the GEN 2 filter has been modified in several ways to improve the filter extraction rate. The activated carbon particles have been changed in shape (from granular to spherical), density (from 0.600 – 0.560g/ml to 0.195–0.185 g/mL), size (mean ± standard deviation from 1363 ± 457 µm to 720 ±102 µm) and volume per cartridge (from 500ml to 550ml). In a porcine study, the extraction rate of the GEN 2 filter was 99 ± 0.4%[10]. Initial clinical experiences seem to indicate that the use of the GEN 2 filter may indeed reduce systemic toxicity[7]. In 2014, we initiated two phase II trials investigating PHP with the GEN 2 filter in patients with hepatic metastases

from either ocular melanoma or colorectal carcinoma. As part of these trials, we obtained blood samples in a subset of patients to investigate the pharmacokinetics of PHP with the GEN 2 filter. Our hypothesis was that the use of the GEN 2 filter would result in a higher filter extraction rate and lower incidence of bone marrow depression compared to those reported after PHP with the first generation filter. The primary objective of this pharmacological study was to determine the melphalan filter efficiency of the GEN 2 filter. The objective of the phase II studies was to analyse the safety and efficacy of PHP with melphalan.

MATERIAL AND METHODS

Study design and patients

Patients were included in one of two prospective phase II studies on PHP with melphalan, starting February 2014. In this pharmacological study the first consecutive seven patients treated with PHP were included as part of the aforementioned phase II studies. In the first three patients, pharmacological samples were also obtained during the second PHP procedure. Thus, pharmacological data of 10 PHP procedures in 7 patients was analysed. The phase II studies and the presented pharmacological study were approved by the Local Medical Ethics Committee of the Leiden University Medical Centre. Patients were potential candidates for one of the two phase II studies, if they had histologically proven, unresectable metastases confound to the liver from either ocular melanoma or colorectal carcinoma. Patients were ineligible for surgical resection because of diffusely spread of liver disease or a metastasis not accessible for surgical resection or radiofrequency ablation, as evaluated by a multidisciplinary liver team of hepatic surgeons, medical oncologists and interventional radiologists. Both phase II studies had similar inclusion criteria: life expectancy > 4 months, resection of the primary tumour >4 weeks prior to PHP, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤ 5 times upper limit of normal, leucocyte count ≥ 3,0 $\times 10^9$/l, platelet count ≥ 100 $\times 10^9$/l and estimated GFR ≥ 40 ml/min. Exclusion criteria were a World Health Organization (WHO) performance status of ≥ 2, age <18 and > 65 years, less than 40% healthy liver tissue based on computed tomography (CT) or magnetic resonance imaging (MRI), evidence of extrahepatic disease or coagulation disorders: activated partial thromboplastin time (APTT) > 32,5 seconds and prothrombin time (PT) > 13,7 seconds. Contrast-enhanced CT of chest, abdomen (arterial and venous phase) and brain were performed to exclude extra-hepatic disease and detect vascular variants precluding PHP. All patients underwent pre-procedural angiography with cone-beam CT. The later was used to exclude extrahepatic enhancement and vascular tumor supply from extrahepatic collaterals. All patients provided written informed consent for the study.

Patients were routinely scheduled to undergo two PHP procedures with a six-week interval, in case there was no progression of disease after the first PHP.

PHP Procedure

Details of the PHP procedure have been described previously (Chapter 4) [8]. The following description is a summary of the most relevant parts of the procedure. Procedures were performed under general anesthesia in the angiography room by a dedicated team of an interventional radiologist, anesthesiologist and perfusionist. After creation of vascular accesses to both internal jugular veins, the right common femoral vein and left hepatic artery, heparin was administrated to achieve an activated clotting time (ACT) of > 400 sec. A 2.7F microcatheter (Progreat, Terumo, Tokyo, Japan) was placed in the hepatic artery to deliver melphalan. A double balloon catheter (Isofuse Isolation Aspiration catheter, Delcath Systems Inc., New York, USA) was positioned in the ICV and the balloons were inflated to prevent the flow of chemosaturated blood to the systemic circulation (See Figure 1). During set-up and initiation of the extracorporeal filtration circuit, sufficient blood

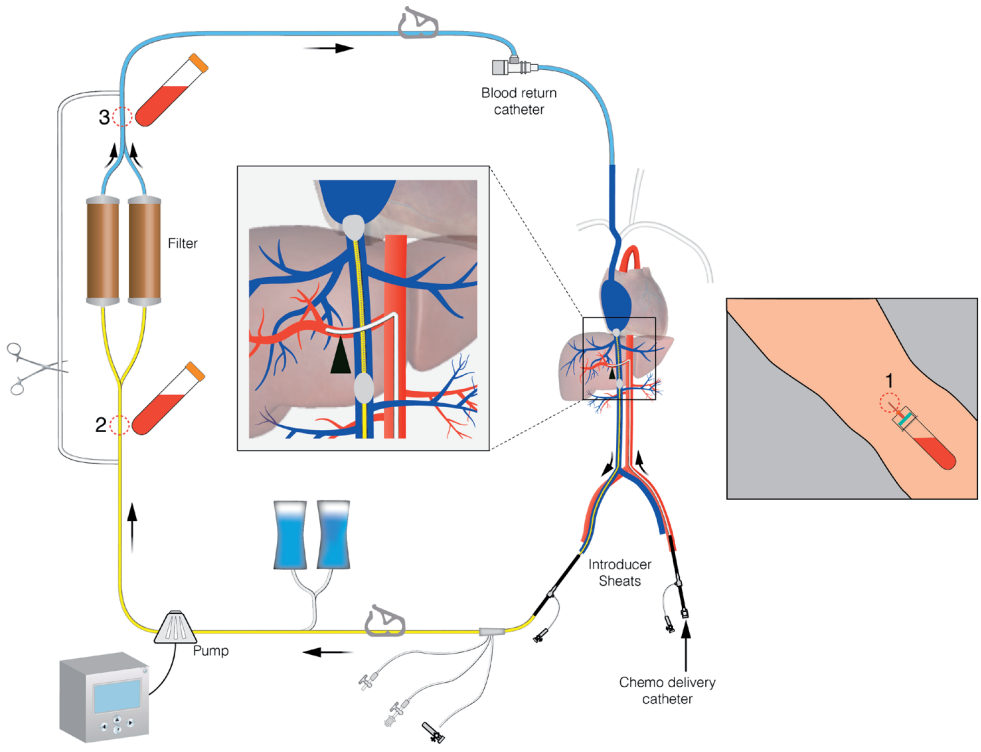

FIGURE 1 **Schematic overview of PHP circuit. Indicated are the pharmacokinetic sampling points**

pressure was maintained by the anesthesiologist by administration of fluids and intravenous infusion of norepinephrine and/or phenylephrine. All PHP procedures were performed with the GEN 2 filtration system. Melphalan (Alkeran, Aspen, Dublin, Ireland) was infused at a dose of 3mg/kg (with a maximum of 220mg) at a rate of 0.4 ml/sec in about 30 minutes. After melphalan infusion, extracorporeal circulation of blood returning through the hepatic veins was maintained for an additional 30 minutes ('wash-out' period). At the end of the procedure, protamine sulphate was administrated to reverse the effects of heparin. Patients were monitored in a medium or intensive care unit 12-24 hours after the procedure. Patients were discharged from the hospital at day 3 after PHP.

Pharmacokinetic sampling

Blood samples were taken simultaneously from the median cubital vein as well as of the tubing before and after the filter of the extracorporeal system starting 10 minutes after commencement of melphalan infusion (T_{10}), at the end of melphalan infusion ($T_{end\ infusion}$) and at the end of the wash-out period ($T_{end\ wash\text{-}out}$) (see Figure 2). In addition to this, venous (systemic) blood samples were obtained 10 and 20 minutes after the start of the wash-out period, at the end of the wash-out period and 5, 30, 60 and 120 minutes after the end of the wash-out period. Blood was drawn in 10 mL sodium heparin tubes and placed in ice immediately after collection. Directly after the PHP procedure, the blood samples were centrifuged for 10 minutes at 1000G at room temperature. After centrifugation, the plasma was split into two aliquots and stored in cryovials at -70°C until analysis. All samples were analysed for melphalan by a high-performance liquid chromatographic analysis with ultraviolet detection as previously described[11]. The detection limit of melphalan in plasma was 0.5 µg/ml. The intra-assay coefficients of variation were 2,5% for melphalan in plasma in the concentration range of 0.5 -5.0 µg/ml and the inter-assay coefficients of variation were 12.4% for melphalan in plasma in the concentration range of 0.5 µg/ml, and 3.6% for melphalan in plasma in the concentration range of 5.0 µg/ml.

Safety and efficacy of PHP

Blood tests were performed on each patient prior to treatment, on day 1, 2, 3, 9, 12, 15 and 18 after PHP and then weekly, until both blood cell count and liver function tests were normalized or reduced to grade I-II toxicity according to the common terminology criteria for adverse events v4.03 (CTCAE v4.03). Routine study blood tests included: full blood count, APTT, PT, international normalized ratio (INR), glucose, creatinine, sodium, potassium, bilirubin, amylase, alkaline phosphatase, ALT, AST, lactate dehydrogenase (LDH), γ-glutamyl transferase, protein, albumin, bicarbonate. Routine follow-up included visits to the outpatient clinic at 1 and 6 weeks and then every three months as well as telephonic consultation at day 9, 12,

15 and 18. Patients underwent CECT of the abdomen and chest (including arterial phase of the liver) 4 and 12 weeks after the first PHP procedure and every 3 months thereafter. In patients with poor visibility of metastases on CT, multiphase MRI of the liver was performed instead of CECT of the abdomen. If the CECT at 4 weeks post-PHP did not demonstrate disease progression and no complications occurred during the first PHP that contra-indicated repeated treatment, patients underwent a second PHP procedure as per protocol.

Outcome assessment

Technical success was defined as the successful delivery of the prescribed dose of melphalan.

The mean filter efficiency of the GEN 2 filters was determined by calculation of the difference between the areas under the plasma melphalan concentration-time curves (AUC) before and after the filter. The AUCs were calculated with the trapezoidal rule. The overall mean filter efficiency was calculated as follows: [(prefilter AUC) – (postfilter AUC)/(prefilter AUC)] x100. For the filter efficiency at a specific time point, the filter efficiency was calculated using the pre- and postfilter concentrations [(prefilter concentration T_x) – (postfilter concentration T_x)/(prefilter concentration T_x)] x100. The maximum concentration (Cmax) was defined as the peak systemic concentration of melphalan during a PHP procedure. Post-procedural blood test abnormalities, toxicity and adverse events were assessed according to CTCAE v4.03. Haematological laboratory disorders occurring within 3 days after PHP were categorized as 'early' and those occurring more than 3 days after PHP as 'late'. Early haematological complications were considered to be related to the procedure itself, i.e. to the dilution of blood as a result of fluid administration and/or to haemolysis by the hemofiltration system. Late haematological complications were most likely attributable to bone marrow depression as a result of melphalan toxicity. CT and MRI scans were assessed by an independent abdominal radiologist according to Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1). Time to progression and overall survival were assessed.

Statistical Analysis

The filter extraction rates for all perfusions at different time points are expressed as mean ± standard deviation (SD). The mean filter efficiency rates and mean melphalan plasma concentration were compared using a paired t-test. Time-to-progression and overall survival was expressed in months as mean and median ± SD. All data were analysed using SPSS software for Windows version 20 (SPSS, Chicago, Illinois, USA). Graphs were created using GraphPad Prism 6 Software for Windows (GraphPad Software, La Jolla California USA). A difference was considered significant when $p<0.05$.

TABLE 1. **Characteristics of 7 patients with unresectable liver metastases treated with percutaneous hepatic perfusion.**

PT	Sexe/ Age	Type of cancer	Time between first diagnosis and PHP (months)	Time between diagnosis liver metastases and PHP (months)	No. PHP's	Best response	Time to progr. (months)	Location of progression	Status	Follow up after first perfusion (months)
1	M, 57	UM	105	34	2	PR	28	Liver	Alive	28†
2	F, 62	UM	36	6	1	PR	9	Liver	Dead	11
3	M, 42	UM	36	3	1	PR	11	Bone, liver	Alive	26
4	M, 58	CRC	34	34	1	SD	1	Lymph node, LTR	Dead	7
5	M, 46	CRC	28	27	2	PR	5	Lung	Alive	27
6	F, 43	UM	40	16	2	PR	14	Liver	Alive	25‡
7	M, 64	CRC	30	30	2	SD	5	Lung	Alive	24

Abbreviations: PT = patient; PHP = percutaneous hepatic perfusion; UM = uveal melanoma; CRC = colorectal cancer; LTR = local tumor recurrence at colonic anastomosis

† 2nd perfusion was followed by radiofrequency ablation (RFA) of 6 small residual tumors.

‡2nd perfusion was followed by RFA of 3 small residual tumors. Because of hepatic progression another 2 perfusions were performed.

TABLE 2. **Treatment parameters for the ten procedures**

Procedure	Dose melphalan (mg)	Duration PHP procedure (hours)	Duration of melphalan infusion (min)	Duration of filtration (min)	Location of infusion
1	220	3:58	NR	75	PHA
2	180	3:26	51	88	RHA (144mg) and LHA (36mg)
3	220	3:05	50	85	PHA
4	220	3:28	40	81	LHA (180mg) and RHA (40mg)
5	165	3:54	40	82	PHA
6	210	3:59	39	98	PHA
7	220	4:44	43	79	RHA (110 mg) and LHA (110 mg)
8	220	4:45	45	80	PHA (110 mg) and RHA (110mg)
9	210	3:55	40	95	CHA
10	220	4:15	55	84	PHA (110 mg) and replaced RHA(110mg)

NR = not recorded. PHA = proper hepatic artery. RHA = right hepatic artery.
LHA = left hepatic artery. CHA = common hepatic artery.

RESULTS

Patients and procedure

Patients and tumour characteristics of the 7 patients are listed in Table 1. Median age at time of treatment was 57 years (range 42-64 years); 5 patients were males. All patients received previous treatment for their hepatic metastases, such as systemic chemotherapy, radiofrequency ablation (RFA) or immunotherapy in a clinical trial. Four out of the seven patients underwent two technically successful PHP procedures as per protocol, however not all these procedures were included in this pharmacological study. Three patients underwent only one PHP procedure. One patient was reluctant to undergo a second PHP as the first procedure was complicated by pancytopenia with severe bacterial pharyngitis. In another patient, the CT 6 weeks after the first procedure showed progression of colorectal hepatic metastases and this patient did therefore not undergo a second PHP procedure. The third patient developed a pulmonary embolus three weeks after the procedure and was reluctant to undergo a second PHP. All ten PHP procedures were technically successful. Median duration of infusion for all procedures was 45 minutes (range 39 – 55 minutes). The overall mean duration of the entire PHP procedure was 4:02

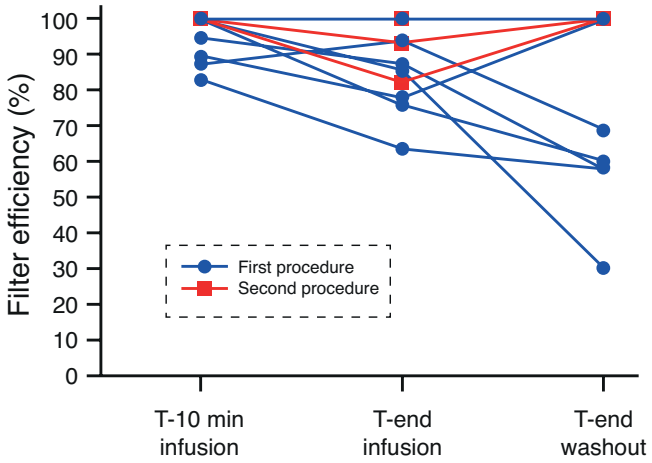

FIGURE 2. **Filter efficiency per patient at different time-points during the procedure**
The mean filter efficiency was calculated at three time points during the 10 procedures. First at ten minutes after the start of the melphalan infusion, than at the end of the melphalan infusion and at the end of the wash-out period.

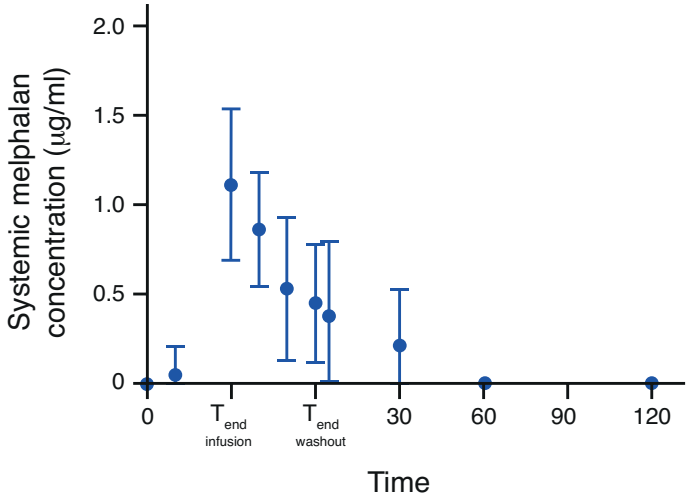

FIGURE 3. **Mean systemic concentration of melphalan of all patients over time.**
A mean concentration of systemic melphalan was calculated at different time points, for all ten procedures, the bars indicate the standard deviation (SD). The horizontal dotted line at 0.5 µg/ml indicates the detection limit of melphalan in plasma.

TABLE 3. **Outcomes of filter efficiency in 10 procedures**

Parameter (n=10)	Cmax (µg/ml)	AUC (h.mg/L)		Filter efficiency*	Filter efficiency at time T_x (%) ±			
		Pre-filter	Post-filter	Overall	T_{10} $	$T_{end\ infusion}$ $	$T_{end\ washout}$ $	Mean
Mean	1,13	4,29	0,57	86,0	95,4	85,9	77,5	86,3
SEM	0,13	0,28	0,0	2,5	2.1	3.6	8.1	3,7
Median	1,15	4,55	0,49	87,2	100	86,3	84.4	86,2
Minimum	0,50	2,20	0,23	71,1	82.7	63,6	30,0	68.2
Maximum	1,80	5,20	1,30	95,5	100	100	100	100
Range	1,30	3,00	1,07	24,4	17.2	36.4	70	31.8

SEM = standard error of the mean

*$[(AUC_{prefilter} - AUC_{postfilter})/AUC_{prefilter}] \times 100$

±[(prefilter concentration) – (postfilter concentration)/(prefilter concentration)] at time T_x

hours (range 3:26 – 4:45h). The perfusion parameters are listed in Table 2. All patients were successfully treated with the planned dose of 3 mg/kg body weight, with a maximum dose of 220 mg of melphalan. The median follow-up was 24 months (interquartile range 9.0-26.5 months).

Pharmacokinetic analysis

Heparinized blood samples were successfully obtained during all ten PHP procedures as per protocol. A summary of the Cmax, Area Under the Curve (AUC) and filter efficiency is shown in Table 3. The overall mean filter efficiency during 10 PHP procedures was 86.0% (range 71.1 %–95.5%). No significant differences were observed in filter efficiency and systemic concentrations between the first and second procedure in the patients that underwent two procedures. Figure 2 illustrates the changes in filter efficiency during the 10 PHP procedures. The mean filter efficiency at specific time points decreased from 95.4% (range 82.7-100%) at T_{10} to 77.5% (range 30-100%) at $T_{end\ washout}$ (p=0.051). Figure 3 displays the mean plasma concentration of melphalan of all patients during the PHP procedure. The systemic concentration increases rapidly during the infusion period. The mean peak melphalan plasma (Cmax) was 1.1 µg/ml (range 0,5-1,8 µg/ml). In the majority of the procedures (67%), Cmax occurred at $T_{end\ infusion}$. The melphalan plasma concentration decreased rapidly after cessation of infusion and was undetectable in the blood samples in all patients 2 hours after the start of the infusion.

TABLE 4. **Main procedure-related adverse events by severity in all perfusions (n=10), categorized as early phase (day 0-3) and late phase (day 4-6 weeks after perfusion).**

CTCAE*		All grades (n)	Grade 3 (n)	Grade 4 (n)
Hematologic events				
Anemia	*Early*	9	1	-
	Late	9	1	-
Thrombocytopenia	*Early*	9	1	-
	Late	9	-	4
Leukopenia	*Early*	3	-	-
	Late	8	1	7
Neutropenia	*Early*	-	-	-
	Late†	8	-	8
Lymphocytopenia	*Early*	8	4	1
	Late†	9	6	1
Hepatic events				
Elevated AST level	*Early*	5	-	-
	Late†	3	-	-
Elevated ALT level	*Early*	3	-	-
	Late†	2	-	-
Elevated serum bilirubine level	*Early*	1	-	-
	Late†	2	-	-
Other				
Fever		2	-	-
Thromboembolic event‡		1	1	-
Post-procedural hemorrhage±		2	-	-
Pharyngitis≠		1	1	-
Alopecia		1	-	-
Nausea		2	-	-
Edema limbs€		1	-	-

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
* Grades of adverse events were defined according to CTCAE (version 4.0).
† Not determined in 1 perfusion.
‡ Pulmonary emboli (PE) was diagnosed in one patient 17 days after PHP. Symptoms resolved in after treatment with low-molecular weight heparin.
± Bleeding from puncture site groin, managed conservatively.
≠ Sepsis based on bacterial pharyngitis for which intravenous antibiotics and immunoglobulins were given, followed by aspiration of retropharyngeal abscess.
€ As a result of administration of intravenous fluid during procedure.

Safety of PHP

Procedure-related adverse events in all 10 PHP procedures are summarized in Table 4. This excludes peri-procedural transient hypotension, which was seen and managed successfully by the anesthesiologist in all patients and did not result in any hypotension-related complications. Haematological laboratory disorders were the most common post-procedural complication. Early (<3 days) anaemia and thrombocytopenia grade III occurred after 10% of the procedures. No early grade III or IV leukopenia or neutropenia were observed, but asymptomatic early grade III (40%) or IV (10%) lymphocytopenia occurred after half of the perfusions. Late haematological complications, indicative of bone marrow depression, were observed in the majority of patients in our study. Late grade III/IV leukopenia, neutropenia and thrombocytopenia were observed after 80.0%, 80.0% and 40.0% of perfusions respectively. After the first two procedures, pancytopenia occurred: the first patient was asymptomatic, but the second patient was admitted to the IC because of a bacterial pharyngitis. After this, the protocol was amended; during subsequent procedures 6 mg of granulocyte colony-stimulating factor (GCSF) was administered 48 hours after the treatment. Four patients received blood transfusion to correct post-procedural blood cell abnormalities. No relation was found between the occurrence of grade 3/4 haematological complications and the administered melphalan dose. In all patients haematological laboratory values had returned to baseline within 3 weeks. Mean time for blood cell count to return to normal was 8.3 days (range 1-20 days) for thrombocytes (normal lab value 150-400 $\cdot 10^9$/L) and 13 days (range 4-20 days) for leukocytes (normal lab value 40-10 $\cdot 10^9$/L).

Efficacy of PHP

Although response and survival rates were not the primary endpoints of this pharmacological study, all patients were assessable for response evaluation. The results are displayed in Table 1. A partial response was achieved in all patients with ocular melanoma liver metastases (n=4). The mean TTP in these patients was 15.5 months (range: 9-28 months). In the patients with CRC metastases (n=3), partial response was achieved in one patient (33.3%) and the mean TTP of this patient was 4.3 months (range: 1-5 months).

DISCUSSION

In our study, we demonstrated an overall mean filter efficiency of 86.0% in patients undergoing PHP with the GEN 2 filter. The efficacy of this filter compares favourably to that of first generation PHP-filters. As mentioned in the introduction, the mean filter extraction rate of the first generation filter (Hemosorba; Asahi Medical, Tokyo,

Japan) was found to be 77% in a phase I study. [9] Apart from a better filter efficiency, also a more consistent performance of the GEN 2 filter was observed. The filter extraction rate varied from 71.1% to 95.5%, whereas a considerably wider range has been reported with the Hemosorba filter (range 58.2% - 94.7%). The mean filtration rate in our study was lower than that obtained in in-vivo, pre-clinical studies. In a study including 6 pigs treated with PHP with the first generation filter, the filter extraction rate was 99% [10]. In our study the mean efficiency dropped from 95.4% at T_{10} to 77.5% at $T_{end\ infusion}$, although the difference did not reach statistical significance. Pre-clinical studies have also shown that the filter efficiency decreases during the perfusion [10]. We hypothesize that the filter is more saturated at the end of the procedure. Based on this study finding, we recommend shortening the time that a patient is on the extracorporeal filtration system. This requires optimal coordination between members of the team performing the procedure and timely ordering of melphalan, as the short half-life of the drug mandates preparation shortly before the start of infusion. Furthermore, infusion time can be shortened by coil-embolization of variant hepatic arteries during the pre-procedural angiography. By this so-called consolidation of hepatic arterial inflow, the locations of infusion can be reduced and thus the need for repositioning of the catheter during the procedure. This strategy has been well established in the treatment of liver tumors with radioembolization [12 13]. The low percentage of early grade III/IV anaemia, leukopenia, neutropenia and thrombocytopenia indicates that the modified activated carbon of the GEN 2 filter does not cause significant haemolysis. After half of the perfusions early grade III / IV lymphocytopenia occurred. As decreases in number were much less frequent for other blood cells, the observed early lymphocytopenia may also be related to causes other than haemolysis by the filter. Factors such as pre-procedural fasting, peri-procedural stress or administration of corticosteroids and fluids may play in role in causing lymphocytopenia. Late haematological complications, indicative of bone marrow depression related to systemic exposure to melphalan, were observed in the majority of patients in our study. The rates of bone marrow depression in our study are comparable to those reported after PHP with the first generation filter [8]. Our study findings thus indicate that the improved filtration rate of the GEN 2 filter does not translate to lower rates of grade III/IV haematological complications. It is important to note though, that grading of leukopenia, neutropenia and thrombocytopenia according to CTCAE v4.03 is based on laboratory investigations, not on symptoms. Furthermore, in all patients haematological disorders were transient. There has been some speculation over the cause of systemic exposure to melphalan in patients undergoing PHP. It has been suggested that systemic toxicity may be related to causes other than incomplete filtration by the hemofiltration system [8]. In a small prospective study by Savier et al, 4 patients underwent surgical isolated liver perfusion followed by one or two consecutive percutaneous liver

perfusions [2]. For the percutaneous procedures, a closed circuit was created using thread-occlusion of the hepatic artery and portal vein occlusion with a transhepatic occlusion-balloon. Blood returning from the hepatic veins was pumped into the hepatic artery and no hemofiltration system was used. In all percutaneous liver perfusions, leakage of melphalan was seen and grade 3 or 4 neutropenia occurred after two-thirds of the procedures. In the surgical procedures, systemic levels of melphalan were almost undetectable and no grade 3/4 hematological complications occurred. The authors postulated that leakage may occur alongside the balloons or though veins around the common bile duct or the diaphragmatic veins. In our study, systemic exposure to melphalan may have been a caused by either incomplete filtration and/or leakage due to incomplete isolation of the hepatic circulation. Unfortunately, we were unable to differentiate between these two different causes of systemic exposure to melphalan.

Clearly, the toxicity of PHP with melphalan has to be balanced against the potential benefits. To date, there are limited treatment options for patients with metastatic ocular melanoma.

No standard systemic therapy is available and chemotherapy, immunotherapy or targeted therapies have not yet been able to show improved survival [15]. Radioembolisation and transarterial chemoembolisation are effective locoregional therapies for patients with primary and secondary liver tumors, but the results in patients with liver metastases from ocular melanoma has only been described in retrospective, small cohort studies [16 17]. The superiority of PHP with melphalan over best alternative care (BAC) has been demonstrated in a multi-center RCT including 93 patients with unresectable hepatic metastases from either ocular (n = 83) or cutaneous (n = 10) melanoma [1]. The hepatic progression-free survival (hPFS) and overall progression-free survival (oPFS) in the PHP group were 7.0 and 5.4 months respectively, compared to 1.6 and 1.6 months respectively for the BAC group ($p < 0.0001$). Given the potential benefit, we consider the safety profile of PHP to be acceptable in patients with hepatic metastases from ocular melanoma and PHP should therefore be considered as a first line therapy for these patients. For patients with colorectal cancer metastases several other treatment options are available, such as chemotherapy, radio-embolisation or targeted therapy. Therefor the place of PHP as treatment option for these patients has yet to be determined.

The small sample size is the most important limitation of our study. Another limitation is related to the difficulties of melphalan analysis, which precluded immediate assessment of melphalan levels during the procedure and only allowed detection of melphalan above a threshold of 0.5 µg/ml. The inability to detect

melphalan levels below 0.5 µg/ml may have led to overestimation of the filter efficiency at the different time-points. Yet, this limitation had little influence on determination of the overall filter efficiency as this was measured as area under the curve using the trapezoid method.

In conclusion, our study demonstrates that the filtration rate of the GEN 2 hemofiltration system performs better than the first generation filtration system. The filter efficiency decreases during the PHP procedure. Despite the improved filtration rate, haematological laboratory disorders grade III/IV are common, but these are transient and usually asymptomatic.

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5

CHAPTER 6

Percutaneous hepatic perfusion as treatment for patients with liver metastases of uveal melanoma

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To be submitted

ABSTRACT

Introduction

For patients with metastases of uveal melanoma, at present no effective treatment is available. Liver-directed therapies seem to be most effective since the disease is often limited to the liver. Therefore, percutaneous hepatic perfusion (PHP) is investigated in a prospective clinical trial.

Methods

Twenty patients (>18 years of age) with unresectable liver metastases from uveal melanoma were included in the study. Patients underwent two PHP-procedures with the GEN 2 filter and all procedures were performed. The melphalan dose was fixed at 3 mg/kg body weight. Study endpoints were response according to RECIST 1.1, one-year survival, overall survival (OS), progression-free survival (PFS) after PHP and safety according to CTCAE 4.03.

Results

Between February 2014 and May 2016, 20 patients were included in this prospective clinical trial (10male, 10 female) and 38 procedures were performed. The side-effects were as expected and were transient and well manageable. One-year overall survival was 70%. Median overall survival was 18.5 months and median progression free survival was 10 months. No treatment related deaths occurred.

Conclusion

The results of this prospective clinical trial indicate that the median survival after PHP exceeds survival data mentioned in literature using alternative strategies.

INTRODUCTION

Uveal melanoma (UM) is (although rare) the most common primary intraocular malignancy in adults. It arises from the melanocytes in the uveal tract. The incidence is highest in Caucasians (fair skin and light eye colour). (1-3). The age at diagnosis of UM is most often 65-75 years. (2-4) Despite successful treatment of the primary tumour, up to 62% of patients will eventually develop metastatic disease, predominantly in the liver (95%). (3, 5-7) Because no effective systemic treatment is available, metastatic ocular melanoma has a poor prognosis. (8-11) Reported median overall survival after diagnosis of metastatic disease in the liver is 2-12 months without treatment and 4 – 13 months after systemic therapy (including immunotherapy). Several liver-directed therapies have been investigated to treat UM liver metastases: chemo- and radioembolization, isolated hepatic perfusion (IHP) and percutaneous hepatic perfusion. Patients treated with liver directed therapies or successful surgical resection had longer overall survival, of up to 14 months. (7, 12-19) Percutaneous Hepatic Perfusion (PHP) was introduced as a minimal invasive and repeatable alternative to IHP, as described in the previous chapters (4 and 5). During PHP the liver is isolated from the systemic circulation by a double balloon catheter in the caval vein. After placing a catheter in the proper hepatic artery, the liver is subsequently infused with high-dose chemotherapy. In the double balloon catheter, a separate lumen is used to aspirate the chemosaturated blood returning through the hepatic veins. This chemosaturated blood is then passed through an extra-corporeal filtration system. After filtration, the blood is returned to the patient by a third catheter in the right internal jugular vein (See Figure 1 in chapter 5). It is the only liver-directed therapy that has been investigated in a multicentre, randomized controlled trial by Hughes et al (2016). In this trial, PHP was compared to best alternative care (BAC) in 93 patients with uveal and skin melanoma metastases. (20) A significant improvement in hepatic progression free survival (hPFS) was demonstrated in the PHP group compared to BAC; 7 months versus 1.6 months, respectively. Median overall survival was 10.6 months in the PHP group compared to 10.0 months in the BAC group. However, extrahepatic metastases were present in 40% of all patients in both groups at baseline. Due to the fact that crossover was allowed from the BAC group to the PHP group results of overall survival were comparable in both groups. Patients were included in this RCT between February 2006 and July of 2009. In 2012 the modified activated carbon GEN 2 filter became commercially available which was designed to improve the results of the hemofiltration and consequently decrease the haematological adverse events by lowering systemic drug exposure. (21) (22) This current prospective clinical trial reports the outcome of treating 20 patients with solely hepatic metastases of uveal melanoma. All 38 procedures were performed per protocol at LUMC, by the

same dedicated team, using the GEN 2 filter. In this trial patients underwent two PHP procedures provided that there was no progression of disease after the first procedure.

METHODS

This prospective, single-arm, single-center, phase II study was conducted in accordance with the 1964 Helsinki Declaration. The clinical trial was approved by the Local Medical Ethics Committee of the Leiden University Medical Centre and was performed in accordance. It was registered in the Netherlands Trial Register (NTR4112). Before inclusion, all patients had to provide written informed consent.

Patient selection

Patients with unresectable metastases in the liver of histologically confirmed uveal melanoma were eligible. All patients were discussed in a multidisciplinary meeting containing at least a radiologist, medical oncologist and surgeon. Inclusion and exclusion criteria are displayed in Table 1.

Study protocol

In advance of the PHP treatment an angiography was routinely performed one week prior to PHP in order to evaluate hepatic arterial vasculature. If necessary, hepatico-enteric shunts (eg, right gastric and gastroduodenal artery) were embolized to prevent leakage of melphalan during PHP. Treatment consisted of two PHP procedures with hepatic artery infusion of melphalan dosed at 3 mg/kg with a 6-to-8-week interval between the procedures. Percutaneous hepatic perfusion was performed using the GEN2 filter chemosaturation system (Chemosaturation Hepatic Delivery System, Delcath Systems Inc, New York, USA) as described before. (23) The used chemotherapeutic agent is Melphalan (Alkeran, Aspen, Dublin, Ireland), an alkylating agent of the nitrogen mustard group. It adds an alkyl group to DNA, interfering normal mitosis in rapidly dividing cells by damaging the original structure. At baseline a CT and/or MRI was performed. Six weeks after the first PHP procedure, the imaging was repeated to verify the response after the first procedure. If this follow-up CT/MRI did not demonstrate progressive disease (PD) and no complications occurred during the first PHP that contra-indicated repeated treatment, patients underwent a second PHP procedure 6-8 weeks after PHP. In case of a grade 3/4 hematologic toxicity, the melphalan dose was reduced by 20-25%. Patients routinely received a subcutaneous injection of granulocyte-colony stimulating factor (pegfilgastrim) within 72h after each PHP. All adverse events

TABLE I. **In- and exclusion criteria**

Inclusion	Exclusion
Informed consent Liver metastases of histologically confirmed primary uveal melanoma Resection of primary tumour > 1 month before PHP, full recovery from surgery Unresectable metastases confined to the liver based on CT-Thorax/abdomen and PET imaging Metastases measurable on CT-scan / MRI Life expectancy > 4 months APTT < 32.5 sec (≤ 1.5 times ULN if considered due to tumour) PT < 13.7 sec (≤ 1.5 times ULN if considered due to tumour) Leukocytes ≥ 3.0 X 10^9/L Thrombocytes ≥ 100 X 10^9/L Creatinine Clearance ≥ 40 ml/min AST and ALT ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumour) Serum bilirubin ≤ 1.5 times ULN ALP ≤ 2.5 times ULN. (≤ 5 times ULN if considered due to tumour)	Biological age <18 and >75 years . In case of a fit elderly patient, an age >75 is allowed. In addition to the normal pre-operative screening, the patient is also screened by a cardiologist and if necessary a cardiac ultrasound is performed. WHO performance status ≥ 2 (Appendix A) < 40% healthy liver tissue Aberrant vascular anatomy or vascular abnormalities (e.g. severe atherosclerosis, vascular dissections), which impede PHP Severe comorbidity (e.g. cardiovascular and pulmonary disease precluding general anaesthesia, diabetes with nephropathy, active infections, other liver disease) Incompetent / Mentally disabled Pregnancy, inadequate contraception Intracranial lesions with a propensity to bleed (on Brain CT or MRI)

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *APTT* activated partial thromboplastin time, *AST* aspartateaminotransferase, , *FDG-PET/CT* positron emission tomography with integrated non-contrast enhanced CT and 18F-2-fluoro-2-deoxy-D-glucose as radiotracer, *LDH* lactate dehydrogenase, *MRI I* Magnetic Resonance Imaging, *PHP* percutaneous hepatic perfusion with melphalan, *PT* prothrombin time, *ULN* upper limit of normal

were monitored continuously and reported according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

PHP procedure

The PHP procedure was performed under general anesthesia, monitoring central venous and arterial pressure by a dedicated anaesthesiologist. Besides catheters in the right internal jugular vein, the right common femoral vein and the left common femoral artery, a double-balloon catheter (Isofuse Isolation Aspiration Catheter, Delcath Systems Inc, New York, NY, USA) was placed in the inferior caval vein. The cranial and caudal balloons were inflated at the atriocaval junction and infrahepatic IVC, respectively, to prohibit leakage of melphalan into the systemic circulation. The melphalan was infused through a microcatheter in the proper hepatic artery. Melphalan-rich blood was aspirated through catheter fenestrations in a segment between the two balloons and pumped through an extracorporeal hemofiltration system before being returned to the patient via the sheath in the right internal jugular vein. Once all melphalan was administered, filtration was continued for 30 minutes to allow complete clearance of melphalan from the liver. The anticoagulant

effects of heparin were reversed by protamine sulphate 3 mg/kg, the arterial sheath was removed and hemostasis was achieved using a closure device. The procedure is more extensively described in Chapter 4.

Outcomes

The primary endpoint was to determine the response on imaging after two percutaneous hepatic perfusions with the Delcath GEN2 system and melphalan. CT and MRI scans were assessed by an independent radiologist according to Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1). Primary endpoints were overall response rate (ORR) and best response rate (BRR). Secondary endpoints were best hepatic response according to RECIST 1.1, one-year survival, overall survival (OS), (hepatic) progression-free survival (PFS). Overall survival was defined as time from the first PHP to last follow-up or death in months. PFS was defined as time from the first PHP to documentation of progression in the follow-up imaging report, or death.

Statistical Methods

Time-to-progression and overall survival was expressed in months as mean and median ± SD. The analyses of overall and progression-free survival were performed using the Kaplan-Meier estimations. Survival data were censored at the data of last follow-up if patients were still alive. The log-rank test was used to compare curves. The Wilcoxon signed rank-test was used to compare scores from questionnaires filled in at baseline and after treatment. P-values <0.05 were considered statistically significant. All data were analysed using SPSS software for Windows version 25 (SPSS, Chicago, Illinois, USA). Graphs were created using GraphPad Prism 6 Software for Windows (GraphPad Software, La Jolla California USA).

RESULTS

Patients characteristics

Between February 2014 and May 2016, 20 patients were included in this clinical trial (10 male, 10 female) and 38 procedures were performed. Patients' characteristics are displayed in Table 2. Mean age at the first PHP procedure was 57.5 years (range 41-70). Patients presented at a median of 5 months (range 1-34 months) after the diagnosis of liver metastases and 90% of these were metachronous metastases. Eleven patients received prior (systemic) therapy in clinical trials or radiofrequency ablation (RFA). Thirteen patients (65%) underwent two procedures as per protocol. Median time between the first and the second PHP was 47 days (28-63). This deviates from the 42 days (6 weeks) as described in the protocol because of logistic reasons and availability of the dedicated team. Four patients underwent only one

PHP procedure; one patient was reluctant to undergo a second PHP after the first procedure being complicated by pancytopenia with severe bacterial pharyngitis and admission to the ICU. A second patient developed a pulmonary embolus three weeks after the first procedure and therefor did not wish a second PHP. The third developed bone metastases before being able to undergo a second PHP procedure. The fourth patient did not want to undergo a second procedure because shortly after the first procedure pulmonal difficulties occurred. Further evaluation did not reveal an underlying problem. Two patients completed a third PHP and one patient even a fourth PHP, because of recurrent hepatic disease after one respectively four years.

Response and survival analysis

All 20 patients were included in the response analysis. Best responses according to RECIST 1.1 were partial response in 15 patients (75%) and stable disease in 4 patients (20%). One-year overall survival was 70%. Median overall survival was 18.5 months (SE4.6, 7-79), see also Figure 2. One patient is still alive after the first PHP procedure (83 months). Median overall progression-free survival was 7 months (SE 1.1, range 1-29) and median hepatic progression-free survival 10 months (SE 1.5, range 2-29).

Safety

No procedure-related deaths occurred. Two severe adverse events were reported. One patient was admitted to the IC because of a bacterial pharyngitis and pancytopenia and this was successfully treated with intravenous administration of antibiotics and immunoglobulins, followed by percutaneous abscess aspiration (grade 4, non-hematological event). A second patient developed a pulmonary embolus (grade 4, vascular event).

Adverse events were reported for two other patients: one patient developed a heparin-induced thrombocytopenia and thrombosis (HITT) during the PHP procedure. The procedure was then aborted. During one other procedure the proximal balloon of the double-balloon catheter ruptured while positioning. No melphalan was yet administered and the catheter could be replaced, and the procedure was continued. The majority of patients developed asymptomatic grade 3/4 hematologic events, mostly leukopenia (60% grade 3 – without complaints) and thrombocytopenia (10% grade 3 – the first two patients). In all patients, haematological laboratory values had returned to baseline within 2-3 weeks. After the first two patients were treated pancytopenia occurred. Consequently, the protocol was amended; during subsequent procedures 6 mg of granulocyte colony-stimulating factor (GCSF) was administered routinely within 48 hours after the treatment. Hair loss was reported as grade 1/2 adverse event. Peri-procedural transient hypotension, which occurs due

TABLE 2. **Patients characteristics**

Parameters	
Gender (*n*)	
Male	10
Female	10
Age (years)*	58 (41-70)
BMI (kg/m^2)*	24.7 (20.4-32.5)
WHO status (*n*)	
WHO 0	19
WHO 1	1
Therapy primary tumor	
Enucleation	15
Brachytherapy	2
Stereotactic radiotherapy	1
Brachytherapy followed by enucleation	2**
Proton beam therapy	0
Type of liver metastases (*n*)	
Synchronous	2
Metachronous	18
Time between diagnosis of primary tumor and metachronous liver metastases (months)*	30 (13-71)
No. of metastases (*n*)	
1 metastasis	0
2-5 metastases	7
6-10 metastases	3
> 10 metastases	10
Prior therapy for liver metastases (*n*)	
SUMIT trial	3
Ipilimumab	1
Ipilimumab + RFA	1
AEB071 trial	5
Dendritic cell therapy	3
RFA	1
Metastasectomy	3
No prior therapy	9

* Data are median (range)
** In one patient additional enucleation was performed after 2 cycles of PHP
Abbreviations: *BMI* Body Mass Index; *No* number; *RFA* radiofrequency ablation. SUMIT: clinical trial investigating Selumetinib in Metastatic Uveal Melanoma. Ipilimumab: human anti-CTLA-4 monoclonal antibody (IgG1κ).
AEB071: Protein Kinase C inhibitor.

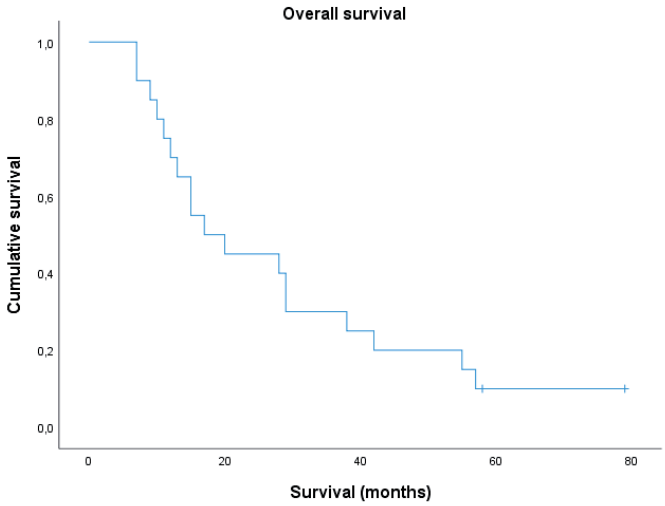

FIGURE 2 **Kaplan Meier curve showing cumulative survival of 20 patients treated wit PHP.**

to the reduction in preload due to caval vein occlusion and peripheral vasodilation from passage of blood through the chemofilters (hemofiltration) and removal of vasoactive agents (e.g. norepinephrine and phenylephrine) by the chemofilters. A second period of hypotension occurs after the flow is diverted through the charcoal-activated filters. Both periods of hypotension are of short duration and respond well to administration of fluids and sympatico-mimetics and were therefore managed successfully by the anaesthesiologists in all patients and did not result in any hypotension-related complications.

DISCUSSION

In the current study, the clinical response, survival and safety of percutaneous hepatic perfusion of 20 patients with liver metastases of uveal melanoma were assessed. No standard treatment for patients with metastasized uveal melanoma is available yet, therefore several treatment options have been investigated in the last decade. A meta-analysis including 29 prospective trials investigating patients with metastatic ocular melanoma who were treated with immunotherapy, kinase inhibitors, chemotherapy, or liver-directed therapy, reported a median OS of 10.2 months, one-year OS of 43%, and median PFS of 3.3 months. Patients treated with liver directed treatments had statistically significant longer PFS and OS. (24)

The median overall survival in our current clinical study is 18.5 months and one-year overall survival is 70%. In 75% of the patients a partial response was observed. These results clearly exceed previously reported survival data after liver directed therapy. Prior to PHP, 55% of the patients received other types of therapy, such as checkpoint inhibitors, RFA or dendritic cell therapy. However, it is unlikely that subsequent systemic therapies would have a large impact on OS as the efficacy of systemic treatments has been limited so far. The combination of several therapies was not further investigated but might need extra attention in future studies.

In our study, the majority of patients (74%) developed extrahepatic metastatic disease during follow-up. These may have been new metastases that developed after PHP or metastases that were radiologically occult at baseline. This indicates that many patients with ocular melanoma would benefit from systemic treatment besides liver-directed therapy. We noticed that overall survival was related to hepatic progression free survival This suggests that controlling liver disease with PHP in patients with liver-only disease improves OS. We hope that in the future PHP can be combined with an effective systemic therapy, to offer ultimate treatment for patients with metastasized UM. Recently, the phase I/II CHOPIN trial started, investigating combination therapy of PHP with ipilimumab/nivolumab in order to better control both hepatic and extrahepatic disease (NCT04283890).

Haematological complications, fatigue and hair loss were reported by our group as adverse events. (22) It is important to note though, that grading of leukopenia, neutropenia and thrombocytopenia according to CTCAE v4.03 is based on laboratory investigations, not on symptoms. Furthermore, in all patients, haematological disorders were transient. (23) (25)

A Quality-of-Life substudy by Vogl *et al* (26) showed the tolerability of the procedure; both overall health and QOL were slightly improved after PHP. Patients were very satisfied with the PHP treatment. Similar results were found by our group; PHP is well-tolerated with maintenance of QoL . (27)

Our study had several limitations. First, this was a single-arm study with a relatively small sample size. Second, we studied a selected group of patients by applying multiple exclusion criteria such as the absence of extrahepatic disease, and some with prior therapies as reported in Table 1. The relatively high median OS could therefore partly be attributed to selection bias.

Concluding, the results of this prospective clinical trial indicate that PHP is a relatively safe, minimal invasive and repeatable therapy resulting in a median overall

survival of 18.5 months, exceeding other survival data mentioned in literature. These procedures were all performed by the same dedicated team, with the GEN2 filter. The side-effects were as expected and were transient and well manageable. To improve our results, a phase I/II trial started investigating combination therapy of PHP with ipilimumab/nivolumab in order to better control both hepatic and extrahepatic disease.

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[‘Baat het niet, dan schaadt het wel.’
Professor Emile Voest, NRC januari 2015]

PART II

Tailored care for patients with pancreatic cancer

CHAPTER 7

Common variables in European pancreatic cancer registries: The introduction of the EURECCA pancreatic cancer project

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ABSTRACT

Background

Quality assurance of cancer care is of utmost importance to detect and avoid under and over treatment. Most cancer data are collected by different procedures between different countries, and are poorly comparable at an international level. EURECCA, acronym for European Registration of Cancer Care, is a platform aiming to harmonize cancer data collection and improve cancer care by feedback. After the prior launch of the projects on colorectal, breast and upper GI cancer, EURECCA's newest project is collecting data on pancreatic cancer in several European countries.

Methods

National cancer registries, as well as specific pancreatic cancer audits/registries, were invited to participate in EURECCA Pancreas. Participating countries were requested to share an overview of their collected data items. Of the received data sets, a shared items list (core data set) was made of items that are present in 7 out of 11 datasets. This common item list, creates insight in similarities between different national registries and will enable data comparison on a larger scale.

Results

Over 24 countries have been approached and up till now 11 confirmed participation: Austria, Belgium, Bulgaria, Denmark, Germany, The Netherlands, Slovenia, Spain, Sweden, Ukraine and United Kingdom. The number of collected data items varied between 29 and 130. This led to a shared items list of 25 variables divided into five categories: patient characteristics, preoperative diagnostics, treatment, staging and survival.

Conclusions

A list of 25 shared items on pancreatic cancer coming from eleven participating registries was created, providing a basis for future prospective data collection in pancreatic cancer treatment internationally.

INTRODUCTION

Pancreatic cancer is associated with a poor prognosis for most patients. In trial populations a median survival of 23 months for initially resectable tumours in combination with neoadjuvant therapies was reached.[1] Over time, a clear increase of prescribed chemotherapy was observed in the Netherlands for patients with and without metastatic pancreatic cancer without any benefit of survival.[2] Capturing data on cancer outcome is crucial to detect over and under treatment in pancreatic cancer. Variations in incidence and mortality between European countries have been described previously.[3,4] Because survival might, besides lifestyle habits (such as smoking) and genetic differences, also be influenced by variances in treatment, structural international comparison would increase insight in 'best practices' in pancreatic cancer. Auditing cancer care with adequate case-mix adjustments is a very effective instrument to impact on outcome. For example, in rectal cancer, national audits were able to implement total mesorectal excision, (TME), reducing local recurrence and variation in other outcome parameters within countries.[5,6] Patterns of care can be identified and communicated to hospitals or physicians.[5,7,8] Feedback generates optimization of treatment standards and (neo)adjuvant therapy and avoidance of over and under treatment. Moreover, an important advantage of registries over clinical trials is that audit registries include the entire patient population which offers the opportunity to study patient groups that are usually excluded from clinical trials (e.g. elderly, high comorbidity).[5] However, registries across Europa differ and can therefore not easily be compared.[9] A 2013 EUROCHIP survey (European Cancer Health Indicators Project) showed that cancer registry data are a reliable source for evaluation and strategy planning, but not all data is available in every registry, impeding a complete comparison.[9] To create uniformity in the collected data and to enable a robust international comparison and report on outcomes, the European Society of Surgical Oncology (ESSO) and the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The EURECCA projects collaborates with existing national audits and cancer registries. [10,11,12] Following EURECCA Colorectal, Breast and Upper Gastro-Intestinal (GI), EURECCA Pancreas focusses on pancreatic cancer and is following the roadmap of the previous projects. The first step in the EURECCA Pancreas project is to describe a common data item list among the responding European countries. The data items will be the basis to design the future prospective international comparison EURECCA Pancreas project.

METHODS

From the start of EURECCA Pancreas, 36 (pancreatic) cancer registries have been approached and invited to join the EURECCA Pancreas platform and 44% responded (n=16). Reasons for not collaborating were the absence of a well-functioning cancer registry or no available data because the registry started recently. Eleven European countries agreed to participate in this comparison. An overview of variables that are collected on each patient, was requested. All recorded data items compared in a database and matching items were scored. If items were present in the database or could be calculated using other items in the database, they were marked 'present' in the shared items comparison. If an item was present in 7 or more datasets, it was marked as a 'shared item'. After all the items were entered in the database, a report was sent back to the national data managers to check for errors or incompleteness. The corrected lists were returned and processed in the database. Most audit registries described in this article have given their full commitment to participate in the EURECCA framework by approval of the Call For Agreement.

RESULTS

Eleven complete lists of items were received from the collaborators; Austria, Belgium, Bulgaria, Denmark, Germany, The Netherlands, Slovenia, Spain, Sweden, Ukraine and the United Kingdom. Besides national or regional cancer registries (n=5), several pancreatic cancer specific cancer audits (n=6) in Europe supplied lists with recorded data items. Table 1 presents the eleven participating registries in this study. The number of collected items differs between the different countries, from 16-285. This is also depending on whether the registry is a national cancer registry or a specific registry on pancreatic cancer. Only four registries contain data on palliative treatment, the other seven registries are general cancer registries or surgical registries. Therefor it was decided that only data concerning surgically treated patients could be used.

A total of 25 items was marked present in seven out of eleven datasets, and thus form the common items data set, displayed in Table 2. These items were divided into five subcategories: patient characteristics, diagnostics, treatment, staging and survival.

TABLE I. *Characteristics of the participating registries; the EURECCA consortium*

Country	Audit	Since	Type of registry	National/ regional data	Numbers of items
Austria	ABCSG registry for pancreatic cancer[13]	2010	Pancreatic Cancer	National*	37
Belgium	National Cancer Registry	2005	Cancer	National	51
Bulgaria	National Cancer Registry	1952	Cancer	National	76
Denmark	Danish Pancreatic Cancer Database	2007	Pancreatic cancer	National	36
Germany	Halle/Magdeburg	2010	Pancreatic cancer	Regional	128
Netherlands	Dutch Pancreatic Cancer Audit	2013	Pancreatic cancer	National**	130
	Netherlands Cancer Registry	1989	Cancer	National	
Slovenia	Cancer Registry of Republic of Slovenia	1950	Cancer	National	50
Spain	Catalonian Pancreatic Cancer Audit	2013	Pancreatic cancer	Regional***	82
Sweden	National Quality Register for Pancreatic cancer	2010	Pancreatic cancer	National	285
Ukraine	National Cancer Registry Ukraine	1996	Cancer	National	16
United Kingdom	AUGIS HPB cancer registry	2009	Pancreatic cancer	National	54

*6 centres operating on pancreatic cancer **National audit, data from one high volume centre *** 6 parallel pancreatic cancer audits

DISCUSSION

Audit and registry structures have led to greater improvements in cancer care outcome than trial and drug development. EURECCA, the European cancer audit, is a valuable collaborative platform to increase our insights on performances in cancer care. Especially for pancreatic cancer with its aggressive biological behaviour it is crucial to collaborate on collecting data, from treatment to outcome. Capturing clinical relevant international benchmarks is not challenged before and would provide tools for feedback. Combining forces and population-based data will represent the actual patterns of care, more than results from clinical trials. International comparisons are the superlative measure to effectively benefit patients with pancreatic cancer.

Experience gained by all participants during years of setting-up (pancreatic) cancer registries and collecting data of patients, is combined in this new EURECCA project.

TABLE 2. *Shared items in eleven participating registries of the EURECCA Pancreas consortium*

Category	Data item
Patient demographics	Gender
	Patient number
	Patient name
	Age / Date of Birth
	ASA or ECOG or WHO performance status
Diagnostics	CT
	ERCP
	Date of diagnosis / Date of incidence
	Localization (Caput, Corpus, Cauda, etc.)
	Diagnosis cytology or histology (ICD-morfology) (Adenocarcinoma, Neuroendocrine, IPMN, etc.)
Treatment	Type of neoadjuvant therapy
	Date of surgery
	Type of surgery (PPPD, Whipple, distal/total, etc.)
	Vascular resection/reconstruction
	Complications Date of discharge / Duration of stay
	Postoperative radiotherapy
	Postoperative chemotherapy
	Postoperative radio-chemotherapy
	Date of start adjuvant therapy
Staging	pT
	pN
	pM
	Resection margin: R0/ R1/ R2
Survival	Date of death

A common dataset that covers all shared aspects concerning pancreatic cancer and its treatment is identified. A core dataset formation is the next step. For instance optimisation of the data set by adding 'date of diagnose', 'clinical TNM stage' and 'CA19.9' would form the template of future comparisons. Important information about the current common data set and the planned core dataset is that no individual physician or hospital data will be incorporated during future analysis; in no way it will be a name and shame report.

Not all audits or registries are population-based, containing data on all consecutive pancreatic cancer patients; 3 registries only collect data on surgically treated patients. In other registries, data from patients treated in a group of collaborating centers is collected. The coverage of the patients included in these audits might not be as complete as a national cancer registry, although several of them cover a majority of hospitals in a specific territory.

In EURECCA colorectal and EURECCA upper GI, common data items were included if present in 6 out of 7 respectively 8 out of 9 participating registries.[10,14] In EURECCA Pancreas presence in 7 out of 11 datasets was set as a limit, to achieve a more complete data set. A limitation of this dataset is that in contains no information on non-surgically treated patients. Often the data collections are surgical driven and no data on solely palliative treated patients is registered.

In the near future a retrospective analysis is planned with merged data from the collaborating registries. Differences in age, gender, incidence, tumour stage and differences in treatment can be identified. Also elderly patients are included in the EURECCA projects and consequently care patterns for the elderly pancreatic cancer patients can be analysed. The aggressive tumor biology and the late onset of complaints and consequently the late presentation of patients, results in high percentages of advanced stage disease and less therapeutic options. Only (borderline) resectable patients, the smallest group, are expected to be discussed in the tumour boards. Locally advanced pancreatic cancer patients, as well as metastasized patients are often directed to the medical oncologist. In future registry or audit structures of all stages should be combined to have a clear view of the medical decision making, clinical care pathways and treatment strategies in the different collaborating countries. By calculating with the date of diagnosis and date of surgery, waiting times for surgery or start of neoadjuvant treatment can be calculated. If patients are treated, neoadjuvant therapies impact on pathological responses, so it is very important to stratify for clinical stage before therapy starts. Pre-treatment TNM stages can then be compared to post-operative pathology reports on TNM stage, to unravel information about medical decision making in pancreatic cancer.

In conclusion, a common data set is identified for this new EURECCA Pancreas project. Establishing a core data set is the next step, and invitations for collection are planned in the near future. Among our future perspectives, a prospective international auditing of pancreatic cancer will be designed in a collaborative way respecting high data security and ethical analysis.

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CHAPTER 8

An international comparison of treatment and short-term survival for elderly patients with pancreatic cancer

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ABSTRACT

Background

A significant proportion of pancreatic cancer patients is over the age of 70 years. International comparisons could provide evidence for the optimal treatment strategy. The aim of this study was to compare treatment and survival for pancreatic cancer patients ≥70 years treated throughout the Netherlands or at Moffitt Cancer Center, a US-NIH designed comprehensive cancer and research center in Tampa, Florida.

Methods

All age-eligible patients with pancreatic adenocarcinoma (2008 – 2012) were identified. Results were stratified by stage. Treatment (neo-adjuvant, surgery, adjuvant and palliative treatment) and short-term survival at 1 and 3 years were compared, and where appropriate adjusted (sex, age, grade, year) or stratified according to age or type of hospital (Netherlands–academic, teaching, non-teaching).

Results

In total, 2728 patients were included. After stratification for stage, there were no marked differences in age, sex or grade. Neo-adjuvant chemoradiation was more often administered at Moffitt (non-metastatic stages), as was adjuvant chemoradiation and chemotherapy ($p<0.001$). However, the proportion surgery was not significantly different. In patients with advanced disease, more patients at Moffitt underwent palliative chemotherapy (64.5% versus 17.4%; $p<0.001$). Short-term 1-year survival rate was statistically significantly better among Moffitt patients (HR 0.30 (95%CI 0.11-0.82), HR 0.56 (0.41-0.72), HR 0.43 (0.36-0.52) for early, locally advanced and advanced, respectively). In subgroup analyses, differences were less pronounced comparing Dutch academic hospitals to Moffitt.

Conclusions

In the present comparison, a treatment regimen as delivered at Moffitt was associated with prolonged short-term survival. Further detailed analyses of selection criteria for systemic treatment could lead to tailored treatment and improved outcomes in older patients with pancreatic cancer.

INTRODUCTION

Due to the aging of Western populations, the number of older patients with cancer is expected to increase at an accelerating rate in coming years. For pancreatic cancer, more than half of patients is over the age of 70 years at diagnosis. Despite developments in treatment modalities, overall and cancer specific survival are however still poor for most pancreatic cancer patients. [1] A multidisciplinary approach including radical surgical resection and systemic therapy is the only potentially curative option for selected patients. [2] This is however associated with a high risk of perioperative morbidity and mortality, especially in older patients. [3, 4] Moreover, most patients present at an advanced stage, where surgery is not an option, thereby largely precluding long-term survival. [5]

Studies concerning the outcome of complex major surgery in older patients are most crucial, as the proportion of older cancer patients increases, and concerns are expressed as to whether these surgical endeavors are justified. [6] Surgical treatment of pancreatic cancer presents distinctive challenges due to a high perioperative morbidity in patients with a dismal prognosis. [6] Previous studies have shown conflicting results with respect to pancreatoduodenectomy in older patients. Some studies show a comparable complication rate and survival as compared to younger patients; [7]others have shown that older patients present more often with postoperative cardiac events, stay longer in the intensive care unit, experience more nutritional and functional difficulties, and are more often readmitted than younger patients. [8, 9] [10] Therefore, as mentioned by Turrini et al [11], two questions are pertinent in the selection of older patients for surgery: is the older patient able to overcome the complex pancreatic surgery and secondly, will the older patient benefit from surgery considering the reduced life expectancy? Van der Geest et al [12] showed that over time resection rates increased in older patients, and that despite higher short-term mortality, octogenarians who underwent pancreatic resection showed long-term survival similar to younger patients.

Beyond surgery, the appropriate use of adjuvant chemoradiation in older patients is controversial [13]; a prospective randomized study conducted by the Gastrointestinal Tumor Study Group (GITSG) showed a significant longer median survival in patients who received radiation and chemotherapy. [14] However, two RCTs from the European Study Group for Pancreatic Cancer (ESPAC) showed no survival benefit. (Neoptolemos *et al.*, 2001;Neoptolemos *et al.*, 2004) On the other hand, studies have clearly shown the benefit of adjuvant chemotherapy and adjuvant Gemcitabine has become the standard of care in many centres . [15] [16] [17] [18]. Nonetheless, population-based studies show that a lower proportion of older patients receive chemotherapy

and due to the inclusion criteria in the RCTs, leaving older patients out, its efficacy in (frail) older patients is still unclear.

A large proportion of the pancreatic cancer patients will present with metastatic (unresectable) disease; Gemcitabine is widely used in the treatment of unresectable pancreatic cancer. [19] [20] More recently, trials have shown an improvement in efficacy with combination chemotherapies such as FOLFIRINOX or combinations of gemcitabine over gemcitabine alone. [21] However, there are only a few studies evaluating the efficacy and safety of these treatments for older patients. [19]

Beyond RCTs, observational studies offer an important alternative source of evidence; in particular, comparisons of treatment and survival using the instrumental variable assumptions could provide clues to optimize the treatment strategy for older patients. Country may be a suitable instrumental variable as place of residence determines a patient allocation to one of the cohorts, assuming that there are differences in treatment between the countries to study and that patient and tumor characteristics are equally distributed and that, in general, health systems are similar in both countries. The aim of the present study was to compare treatment and survival for pancreatic cancer patients aged 70 years and older in the Netherlands or treated at Moffitt Cancer Center, Tampa (Florida, US) which offers specialized care tailored to geriatric cancer patients.

METHODS

All age-eligible patients with histologically confirmed pancreatic adenocarcinoma (ICD-O morphology codes 8140 and 8500, where known) diagnosed between 2008 and 2012 were identified. At Moffitt Cancer Center, patients were identified through the Moffitt Cancer Registry and the Total Cancer Care™ program and details were retrieved from medical records. Only patients who had their first treatment at Moffitt (and not in another hospital) were included in the cohort. For the Netherlands, treatment and survival data was retrieved from the Netherlands Cancer Registry for all hospitals in the Netherlands; this population-based registry contains data from all cancer patients in the Netherlands.

For the present comparison, the instrumental variable methodology was followed, and the 'three assumptions' to use country as a valid instrument were assessed. In short, the three assumptions are that (1) "country" (cohort from a specific country) should be related to the chance of receiving a specific treatment strategy, (2) that the instrument should not be related to the prognosis of the patients and (3) that

country should not have an effect on the outcome other than through the chance of receiving a certain treatment strategy. Baseline patient and tumor characteristics were compared between the two cohorts; as stage was differentially distributed between the cohorts (p<0.001) and associated with survival, analyses were stratified for stage (early stage T1-2, N0,M0 (UICC stage IA and IB); locally advanced T3, N0, M0 or T1-3, N1, M0 (UICC stage IIA and IIB) or advanced disease (T4, N0-1, M0 or metastatic disease M1). Baseline patient and tumor characteristics were compared between the two cohorts. Neo-adjuvant treatment (none, chemo-radiation, chemotherapy), surgery (yes or no), adjuvant treatment (none, chemo-radiation, chemotherapy) and non-surgical treatment (no treatment, chemo-radiation, chemotherapy) were compared. For advanced stage, palliative treatment by type (no treatment, chemo-radiation, chemotherapy or radiotherapy) was compared.

Overall Survival (OS) and 95% Confidence Intervals (95%CI) at 1 and 3 years after diagnosis were calculated with death due to any cause as event with time from diagnosis to death, stratified by stage. Cause of death was not recorded for the Netherlands cohort, we used Overall Survival; this seems justified as cause of death was known for the Moffitt cohort and 92.8% died as a result of pancreatic cancer. Besides, a Dutch study showed that 94.7% of the deaths was attributable to pancreatic cancer. [22] Cox proportional hazards models were used to compare the short-term survival with the Netherlands cohort as reference. Two adjusted models were constructed; one with adjustment for age, sex, grade and year of incidence and one model with an additional adjustment for treatment. Kaplan-Meier survival curves for both cohorts were generated according to stage at diagnosis. Finally, stratified survival analyses (adjusted for sex, grade, year and age (where appropriate), with the Netherlands as reference cohort) were performed according to age (70-74, 75-79 and 80 years and older) and type of hospital in the Netherlands (academic, teaching or non-teaching) as pancreatic (surgical) cancer care is mostly centralized in specialized hospitals.

RESULTS

Overall, 2837 patients of 70 years and older were included: 2523 from the Netherlands (early stage 179; locally advanced 603; advanced 1639 and unknown stage 102 patients) and 314 from Moffitt Cancer Center (early stage 15, locally advanced 124, advanced 168 and unknown stage 7 patients). Table 1 shows the characteristics of the patients, according to stage at diagnosis. Age, sex and grade were not differentially distributed between the cohorts, with the exception of age in patients with locally advanced disease (median age Netherlands 75.0 and Moffitt 77.0 years; p=0.02).

TABLE 1 **Characteristics of patients, according to stage at diagnosis**

		Netherlands	Moffitt	p-value
Early stage T1-2, N0, M0 (UICC stage IA & IB)		**N=179**	**N=15**	
Age	Median (range)	77.0 (70.0-93.0)	78.0 (71.0-85.0)	0.8
Sex	Male Female	83 (46.4) 96 (53.6)	11 (73.3) 4 (26.7)	0.1
Differentiation grade	I II III Unknown	22 (12.3) 34 (19.0) 17 (9.5) 106 (59.2)	1 (6.7) 5 (33.3) 0 (0.0) 9 (60.0)	0.4
Locally advanced T3, N0, M0 or T1-3, N1, M0 (UICC stage IIA & IIB)		**N=603**	**N=124**	
Age	Median (range)	75.0 (70.0-98.0)	77.0 (70.0-90.0)	0.02
Sex	Male Female	285 (47.3) 318 (52.7)	71 (57.3) 53 (42.7)	0.1
Differentiation grade	I II III Unknown	32 (5.3) 188 (31.2) 136 (22.6) 247 (40.9)	3 (2.4) 45 (36.3) 23 (18.6) 53 (42.7)	0.3
T4, N0-1, M0 or metastatic (UICC stage III & IV)		**N=1639**	**N=168**	
Age	Median (range)	75.0 (70.0-99.0)	74.0 (70.0-90.0)	0.2
Sex	Male Female	802 (48.9) 837 (51.1)	79 (47.0) 89 (53.0)	0.6
Differentiation grade	I II III Unknown	31 (1.9) 105 (6.4) 176 (10.7) 1327 (81.0)	5 (3.0) 10 (6.0) 15 (8.9) 138 (82.1)	0.7

Treatment

Table 2 shows the treatment strategy in both cohorts according to stage. Most early stage pancreatic cancer patients received no neo-adjuvant treatment, both in the Netherlands (97.2%) and at Moffitt (88.9%). Surgical resection was more often performed at Moffitt though the difference was not significant (60.0% versus 39.7%; p=0.1). Adjuvant treatment was initiated more frequently at Moffitt (66.7% versus 18.3%; p<0.001). For early stage patients who had no surgery, chemo-radiation (33.3% versus 0%) or chemotherapy (16.7% versus 3.7%) was more often part of the treatment strategy at Moffitt than in the Netherlands (p<0.001).

In patients with locally advanced disease, neo-adjuvant chemo-radiation was more often part of the treatment strategy at Moffitt (16.7% versus 0.3%; p<0.001). The proportion of patients who received surgery was higher in the Netherlands (63.3%

TABLE 2: **Treatment strategies in both cohorts, according to stage**

Treatment		Netherlands	Moffitt	p-value
Early stage T1-2, N0, M0				
Neo-adjuvant treatment#	None	69 (97.2)	8 (88.9)	0.3
	Chemo-radiation	1 (1.4)	1 (11.1)	
	Chemotherapy	1 (1.4)	0 (0.0)	
Surgery	No	108 (60.3)	6 (40.0)	0.1
	Yes	71 (39.7)	9 (60.0)	
Adjuvant treatment#	None	58 (81.7)	3 (33.3)	<0.001
	Chemo-radiation	0 (0.0)	1 (11.1)	
	Chemotherapy	13 (18.3)	5 (55.6)	
Non-surgical treatment	No treatment	104 (96.3)	3 (50.0)	<0.001
	Chemo-radiation	0 (0.0)	2 (33.3)	
	Chemotherapy	4 (3.7)	1 (16.7)	
Locally advanced T3, N0, M0 or T1-3, N1, M0				
Neo-adjuvant treatment#	None	380 (99.5)	54 (81.8)	<0.001
	Chemo-radiation	1 (0.3)	11 (16.7)	
	Chemotherapy	1 (0.3)	1 (1.5)	
Surgery	No	221 (36.7)	58 (46.8)	0.04
	Yes	382 (63.3)	66 (53.2)	
Adjuvant treatment#	None	266 (69.6)	17 (25.8)	<0.001
	Chemo-radiation	0 (0.0)	21 (31.8)	
	Chemotherapy	116 (30.4)	28 (42.4)	
Non-surgical treatment	No treatment	192 (86.9)	14 (24.1)	<0.001
	Chemo-radiation**	6 (2.7)	28 (48.3)	
	Chemotherapy	21 (9.5)	16 (27.6)	
	Radiotherapy	2 (0.9)	0 (0.0)	
T4, N0-1, M0 or metastatic				
Palliative treatment$	No treatment	1284 (79.5)	25 (15.1)	<0.001
	Chemo-radiation	23 (1.4)	34 (20.5)	
	Chemotherapy	281 (17.4)	107 (64.5)	
	Radiotherapy	27 (1.7)	0 (0.0)	

#Proportion calculated for the operated patients. $Selection of patients who received no surgery, **Typically initiated as neo-adjuvant treatment, however detection of liver metastases resulted in cancellation of the surgery.

versus 53.2%; p=0.04). In patients that underwent surgery, adjuvant therapy was more often administrated at Moffitt (74.2% versus 30.4%; p<0.001). In patients who received no surgery, treatment strategies were different with a higher proportion of no treatment in the Netherlands and a higher proportion of systemic treatment at Moffitt (p<0.001).

With respect to palliative treatment for patients with advanced pancreatic cancer, treatment strategies were also different (p<0.001); in particular, the proportion of

TABLE 3. **Short-term survival for older pancreatic cancer patients, according to stage**

	OS NL (%)	OS Moffitt (%)	Comparison	HR (95%CI)*	p-value
1-year Overall Survival					
T1-2,N0,M0	40.7 (33.2-48.0)	72.0 (41.2-88.6)	Comparison cohort Adjusted* Adjusted model 2**	0.35 (0.13-0.95) 0.30 (0.11-0.82) 0.61 (0.07-5.19)	0.04 0.02 0.65
T3, N0, M0 or T1-3, N1, M0	43.0 (38.7-47.3)	57.4 (48.1-65.6)	Comparison cohort Adjusted* Adjusted model 2**	0.63 (0.47-0.84) 0.56 (0.41-0.75) 0.68 (0.34-1.33)	0.002 <0.001 0.26
T4, N0-1, M0 or metastatic	8.2 (6.9-9.8)	27.7 (21.1-34.6)	Comparison cohort Adjusted* Adjusted model 2**	0.45 (0.37-0.54) 0.43 (0.36-0.52) 0.84 (0.68-1.03)	<0.001 <0.001 0.10
3-years Overall Survival					
T1-2,N0,M0	21.5 (14.9-28.9)	32.0 (8.2-59.5)	Comparison cohort Adjusted* Adjusted model 2**	0.52 (0.25-1.06) 0.39 (0.19-0.81) 0.33 (0.04-2.50)	0.07 0.01 0.28
T3, N0, M0 or T1-3, N1, M0	11.4 (8.0-15.3)	12.9 (6.9-20.9)	Comparison cohort Adjusted* Adjusted model 2**	0.74 (0.59-0.92) 0.66 (0.52-0.83) 0.64 (0.40-1.04)	0.007 <0.001 0.07
T4, N0-1, M0 or metastatic	0.9 (0.4-1.7)	1.0 (0.1-4.7)	Comparison cohort Adjusted* Adjusted model 2**	0.51 (0.43-0.60) 0.49 (0.42-0.58) 0.90 (0.74-1.09)	<0.001 <0.001 0.27

Netherlands as reference cohort, *adjusted for age, sex, grade and year, **additionally adjusted for treatment.

patients receiving chemotherapy was higher at Moffitt (17.4% in the Netherlands versus 64.5% at Moffitt).

Survival

Table 3 shows the 1-year and 3-years OS rate; overall, survival was higher for patients from Moffitt. The adjusted (age, sex, grade and year) Hazard Ratio (HR) for early stage patients was 0.30 (95%CI 0.11-0.82; p=0.02) at 1 year and 0.39 (95%CI 0.19-0.81; p=0.01) at 3 years, respectively. Further adjustment for treatment partly explained the association; the HR was attenuated and no longer significant with treatment included in the regression (HR 0.61 (95%CI 0.07-5.19; p=0.65) at 1 year and HR 0.33 (95%CI 0.04-2.50; p=0.28) at 3 years.

For patients with locally advanced disease, survival rate was higher for patients at Moffitt (HR 0.56 (95%CI 0.41-0.75; p<0.001) at 1 year and HR 0.66 (95%CI 0.52-0.83; p<0.001) at 3 years. Further adjustment for treatment explained part of the association, although the survival rate seems to be higher at Moffitt at 3 years (HR 0.64 (95%CI 0.40-1.04; p=0.07)).

Pancreatic cancer patients with advanced disease showed a higher survival rate in the Moffitt cohort, adjusted HR at 1 year was 0.43 (95%CI 0.36-0.52; p<0.001), and at 3 years (HR 0.49 (95%CI 0.42-0.58; p<0.001). Further adjustment for treatment again explained part of the association, especially at three years OS (HR 0.90 (95%CI 0.74-1.09; p=0.27). Figure 1 shows the corresponding survival curves according to stage.

Table 4 shows the differences in survival stratified by age and stratified by type of hospital in the Netherlands. A significantly improved survival rate at Moffitt was more pronounced for patients over the age of 75 years with early stage or locally advanced disease; for patients with advanced disease the survival rate was better at Moffitt in all age groups. Comparing survival between academic hospitals in the Netherlands and Moffitt showed no statistically significant difference in survival for patients with early stage (adjusted HR 0.42 (95%CI 0.16-1.07; p=0.07)) and locally advanced stage (adjusted HR 0.81 (95%CI 0.61-1.08; p=0.15)).

TABLE 4 **Adjusted HR (with Netherlands as reference category), stratified for stage, age and type of hospital in the Netherlands**

Stage	3-years survival	Adjusted HR (95%CI)	p-value
Stratified according to age			
T1-2,N0,M0	70-74	1.26 (0.26-6.07)	0.77
	75-79	0.22 (0.05-1.00)	0.05
	80+	0.32 (0.11-0.98)	0.05
T3, N0, M0 or T1-3, N1, M0	70-74	0.82 (0.56-1.19)	0.30
	75-79	0.60 (0.39-0.92)	0.02
	80+	0.57 (0.37-0.86)	0.009
T4, N0-1, M0 or metastatic	70-74	0.54 (0.43-0.68)	<0.001
	75-79	0.51 (0.36-0.73)	<0.001
	80+	0.39 (0.28-0.53)	<0.001
Stratified according to type of hospital			
T1-2,N0,M0	Academic	0.42 (0.16-1.07)	0.07
	Teaching	0.40 (0.19-0.84)	0.02
	Non-teaching / other	0.30 (0.09-0.99)	0.05
T3, N0, M0 or T1-3, N1, M0	Academic	0.81 (0.61-1.08)	0.15
	Teaching	0.60 (0.47-0.77)	<0.001
	Non-teaching / other	0.43 (0.29-0.64)	<0.001
T4, N0-1, M0 or metastatic	Academic	0.66 (0.54-0.81)	<0.001
	Teaching	0.46 (0.38-0.54)	<0.001
	Non-teaching / other	0.41 (0.33-0.50)	<0.001

Adjusted for sex, grade, year and age

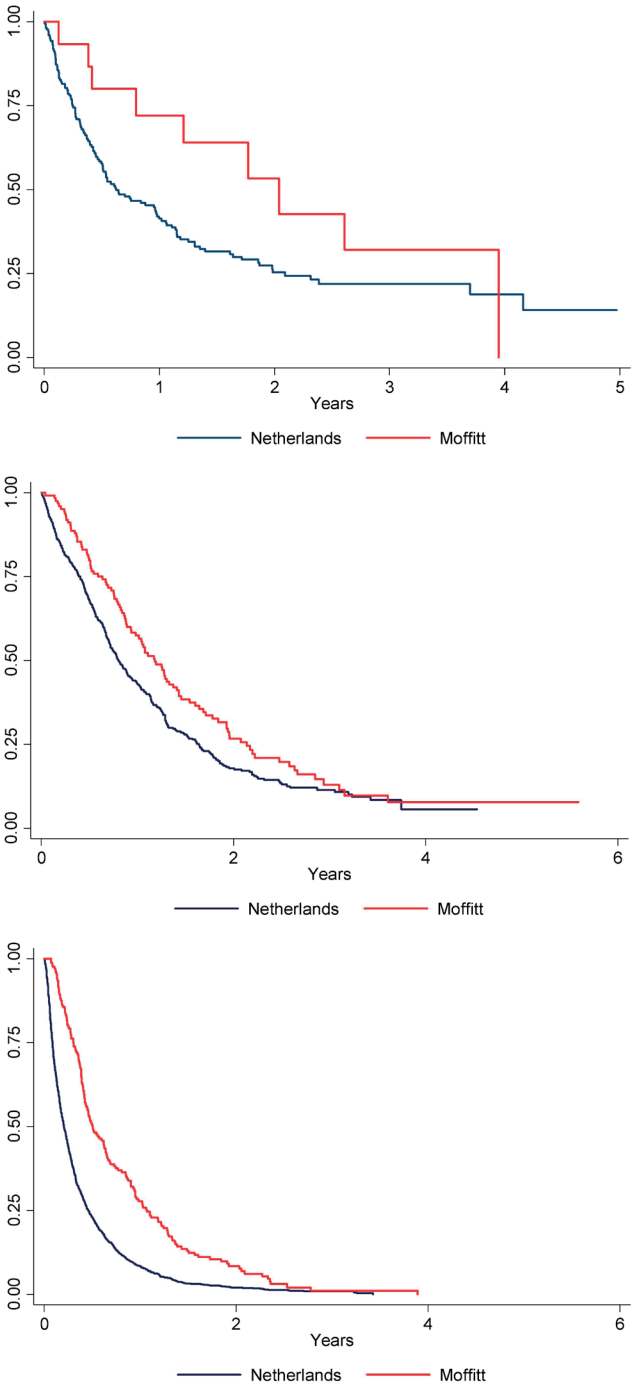

FIGURE 1. **Survival curves according to stage at diagnosis, (A) T1-2,N0,M0; (B) T3, N0, M0 or T1-3, N1, M0; (C) T4, N0-1, M0 or metastatic**

DISCUSSION

This international comparison of older pancreatic cancer patients treated at Moffitt Cancer Center and the Netherlands shows differences in treatment strategies, especially in systemic treatment administration with a higher proportion at Moffitt. Overall Survival rates were higher for patients treated at Moffitt, and were in a large part explained by the differences in treatment. The survival difference was less pronounced when compared with patients with locally advanced disease treated at an academic hospital in the Netherlands.

For locally advanced disease, earlier data from the US (Duke University Medical Center) showed that the proportion of older patients receiving neoadjuvant therapy was similar to younger patients, but a smaller proportion of older patients received adjuvant therapy. [23] In the present study, the proportion of patients who received neoadjuvant chemoradiation was higher for patients at Moffitt (16.7% versus 0.3% for patients with locally advanced disease). One possible explanation is a difference in the approach to borderline resectable disease, where a neoadjuvant chemotherapy with or without radiation is often used in the US to attempt to improve resectability, and is described as an option in the NCCN guidelines but not yet in the Dutch guidelines (2011). Currently the benefit of neoadjuvant chemoradiation is being investigated in a multicenter clinical trial in the Netherlands. Furthermore, a geriatric oncologist is included in the multidisciplinary tumor board at Moffitt and might provide a more accurate evaluation and management plan for older patients. In addition, a more favorable health status of elderly patients at Moffitt compared with the nationwide Dutch cohort cannot be ruled out.

Differences in the administration of adjuvant chemoradiation and chemotherapy were also observed in the present study, with a larger proportion of patients receiving adjuvant therapy for Moffitt in both early stage and locally advanced patients. Decision-making in choosing adjuvant chemotherapy or chemoradiation is complex; some RCTs show an improved overall survival with the use of adjuvant chemoradiation followed by adjuvant chemotherapy [14] or adjuvant chemoradiation versus surgical resection alone [24]; while others did not confirm a survival benefit with chemoradiation [25] or even found a detrimental effect of chemoradiation compared with chemotherapy or surgery alone . The survival benefit of adjuvant chemotherapy after surgical resection was however clearly demonstrated in two RCTs. [26] [15] [18] . Whereas few older patients were included in RCTs, a recent retrospective series demonstrated a longer survival in patients 75 and older from adjuvant chemoradiation. [27] However others have also shown that older patients less often receive adjuvant chemotherapy. Many factors contribute to this difference, some

are patient driven and some physician driven; factors that are mentioned in studies are the observation that older patients are more often discharged to a rehabilitation facility, and have a longer recovery period after surgery and consequently are less likely to pursue further therapy. [23] Besides, older patients who undergo surgical resection with the intention of receiving adjuvant therapy might never receive it because of complications. Studies in older patients are however scarce and more evidence is needed regarding the efficacy and safety of chemotherapy for older patients and for appropriate patient selection. [19]

The difference in receipt of systemic treatment is particularly striking for advanced disease: 85% of Moffitt patients received chemotherapy and /or radiation therapy, versus only 20% of the Dutch patients. A significant difference in 1 year overall survival was observed for these patients: 27.7% (21.1-34.6) for patients at Moffitt versus 8.2% (6.9-9.8). This might be due to various factors; one hypothesis might be the differences in cultural perception of the benefit of giving palliative chemotherapy to pancreatic cancer patients. Transcultural perceptions were explored in detail between French and American patients. [28] Interestingly enough, whereas older non-cancer patients were less interested in moderate chemotherapy on the European side, nearly all older cancer patients were interested in the option on either side of the Atlantic Ocean. Given the associated survival benefit, this indicates that there might be a need for a reconsideration of the general avoidance of chemotherapy observed in our cohort of Dutch patients. Although one might hypothesize some referral bias at Moffitt, it should be noted that even in Dutch academic centers, only 54% of patients with advanced disease did receive systemic treatment. Therefore in our opinion, this would only explain a small proportion of the inter-country variance. The Moffitt practice appears representative of the practice at other American Comprehensive Cancer Centers with geriatric oncologists. A recent series in pancreatic cancer patients with metastatic disease showed that 65% of patients above age 65 did receive chemotherapy, compared with 75% of younger ones. [29] In that series, receipt of chemotherapy, preferably with two agents, was also associated with a survival benefit at all ages.

Whereas survival is improved with palliative systemic treatment, this benefit might be counterbalanced by quality of life concerns. The commonly used regimens for advanced pancreatic cancer are: FOLFIRINOX, gemcitabine doublets (nab-paclitaxel, erlotinib, or capecitabine) or, when tolerance is a concern, gemcitabine single agent. FOLFIRINOX was studied in patients below the age of 76 with ECOG 0-1(median 61) and has significant side effects. However, a recent series showed that with a reduced-dose of FOLFIRINOX in patients aged 70 and older a median overall survival of 11 months could be achieved, comparable to that obtained in younger patients.

However this comes at the cost of a greater impact on quality of life [30], and most older patients are treated with gemcitabine or a gemcitabine doublet. Studies for older patients are also scarce in this area. One retrospective study compared older and younger patients who received gemcitabine and patients under best supportive care. The response rate, disease stabilization, improvement of tumor makers and median survival time were similar in young and older patients, although bone marrow suppression and hematological toxicity of grade 3 or more was seen more frequently in older patients and older patients tended to need dose reduction of gemcitabine in the first cycle .[19]. The benefits of chemotherapy are clearly linked to baseline performance status, and there is no evidence of a benefit for patients with poor ECOG performance status. On the other hand, with proper supportive care such as e.g. provided with a geriatric oncology program, older patients maintain quite well their functional status despite side effects of chemotherapy. [31] Yamagishi et al mentioned several reasons for the tendency to avoid chemotherapy in older pancreatic cancer patients with advanced disease: the fact that unresectable pancreatic cancer is not curable by chemotherapy alone (possibly resulting in patient distress), the higher susceptibility of older patients for severe toxicity and the presence of comorbidities which may lead to contraindications for chemotherapy.

An accurate estimation of the expected perioperative morbidity and mortality is based on thorough preoperative (geriatric) patient assessment and is central to surgical decision-making with respect to the risks and benefits for an individual patient. [23] As a Whipple resection is a major surgery, treating physicians may hesitate to refer elderly patients for surgery, concerned with the risk of poor post-operative quality of life. [32] There is however a lack of evidence with respect to quality of life studies for older patients with pancreatic cancer, although it is known from the literature that older patients have a higher complication rate and a significant proportion will be admitted to a chronic care facility after surgery. Studies from Khan et al [6] and Hardacre et al [33] showed that one out of five patients (21%) over the age of 80 years in the first study and 59% in the second were discharged to an outside health care facility and that 51% of the patients developed complications. Comorbidities and functional reserve might have a key role in the postoperative morbidity (and mortality); the presence of comorbidities such as hyperlipidemia, diabetes and coronary artery disease were shown to be possible risk factors for major complications. [34] [4] Despite this, one of the few quality of life studies in older patients who underwent pancreatoduodenectomy in a high-volume referral center showed that within 3 months after surgery, quality of life scores were lower yet comparable to their matched controls undergoing laparoscopic cholecystectomy. A gradual rather than a rapid recovery process was observed for the older patients, and fatigue was common, lasting for 3 to 6 months after surgery. [32] Other studies

have shown a higher prevalence of postoperative depression in the older population , which was confirmed in this study; a longer emotional recovery in older patients.

A large number of studies compared younger and older patients who received surgery, however the results with respect to survival are difficult to interpret due to selection bias. Nonetheless these studies show that pancreatoduodenectomy can be safely performed in selected older patients, [11] [35] although some series show that age is one of the determinants for postoperative mortality. [8] Recently there have been unquestioned advancements in patient selection, techniques, perioperative care and management of complications, which resulted in better outcomes for patients who underwent pancreatic resection. [36] In the present study, the proportion of patients who underwent surgery in each country was not significantly different between the two cohorts for early stage patients, although this might be due to a low number of patients in this group. For patients with locally advanced disease, there was a 10% difference in surgery rate with a higher proportion in the Netherlands. This higher proportion of surgery was especially marked for academic hospitals in the Netherlands (80.9% versus 53.2%, p<0.001), and less pronounced in the teaching (54.2% versus 53.2%; p=0.8) and non-teaching/other hospitals (50.0% versus 53.2%; p=0.7). This can be explained by centralization of pancreatic cancer care in academic hospitals in the Netherlands. Chronological age is a poor predictor for functional status (physically, mentally and medical) and selecting appropriate therapy for older patients remains challenging because of concerns with respect to the patients comorbidities, their functional and nutritional status, cognitive function, social support and their expected survival. [6] [37]

The present study showed a higher survival rate for patients treated at Moffitt; these differences seem to be largely explained by differences in treatment strategy between the Netherlands and Moffitt. The assumptions for the instrumental variable methodology were assessed: country was indeed related to the chance of a certain treatment strategy and there were large differences between both countries; second, there were no differences in known patient and tumor characteristics between the countries that are associated with the outcome, apart from age for locally advanced stage. Stratification for age showed that the survival difference was more pronounced for the patients above the age of 75 years. The third assumption, that country should not influence outcome other than through the chance to receive a certain treatment strategy, is difficult to assess with the data. Although differences in health care systems do exist between the Netherlands and Moffitt, patients included in this cohort were of Medicare age. Besides, a previous study comparing both countries, showed that there are no marked differences between patients who resided inside or outside the catchment area of Moffitt Cancer Center.

(38) As pancreatic surgical care is centralized in the larger hospitals in the Netherlands, we performed a sensitivity analysis to compare the survival stratified by type of hospital. This showed smaller survival differences for patients treated at an academic hospital in the Netherlands compared to Moffitt, especially for patients with locally advanced disease. Another drawback in the present comparison is related to the administration of neo-adjuvant treatment, which is not part of the Dutch guidelines. Some patients treated at Moffitt with locally advanced disease progressed during neo-adjuvant chemoradiation and thus became not surgical candidates. Last/ Finally, for older patients with pancreatic cancer, it is essential to balance quality of life and expected survival. Unfortunately, we had no quality of life information for the patients in these cohorts. In summary, patients treated at Moffitt were more often treated with systemic treatment and had a higher survival rate. Differences in survival were largely explained by differences in treatment and less pronounced in comparison with academic hospitals in the Netherlands. Further detailed analyses of selection criteria for systemic treatment and assessment of quality of life could lead to tailored treatment and improved outcomes in older patients with pancreatic cancer.

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8

PART III

General discussion

[Failure is a much more faithful teacher than immediate success.
David DuChemin, world & humanitarian photographer]

CHAPTER 9

General discussion and Future perspectives

Summary

General Discussion and Future Perspectives

Part I–Hepatic perfusion for the treatment of unresectable liver metastases

In a recent report of the Dutch Melanoma Treatment Registry (DMTR) on metastasized uveal melanoma patients, who received all kinds of treatments, one-year survival is reported to be 47.8%. The authors state that the best results in terms of survival are among patients in whom surgery or locoregional procedures can be performed and among patients with solitary hepatic metastases. [1] Currently, no systemic therapy has shown to improve survival for patients with metastatic uveal melanoma (UM) and there is no specific standard of care. Therefore patients should be treated in clinical trials. [1] This underlines the urge for development of successful (locoregional) therapy, like described in this thesis. The results of percutaneous hepatic perfusion (PHP) are promising as described in Chapter 6; one-year overall survival was 80%. Median overall survival was 29 months. PHP is amongst the few treatment options for UM that seems to really increase survival time and holds promise for further investigations.

Combination of systemic and locoregional therapy

Research on systemic therapy agents for UM is ongoing. Several authors suggest that combined treatment could be considered as part of a multimodal treatment approach combined with locoregional interventions. [2-4] A significant part of the patients treated with PHP, developed extrahepatic disease in the follow-up, whereas the liver metastases were mainly stable. Effective systemic treatments for extrahepatic metastases are urgently needed to further improve survival.

Targeted therapy

Uveal melanoma differs significantly from cutaneous melanoma at biological level. Unlike cutaneous melanoma (characterized by BRAF or NRAS mutations), mutations in GNAQ or GNA11 are present in about 80% of primary uveal melanomas. Consequently, advances in targeted therapy for cutaneous melanoma are not applicable to metastatic uveal melanoma; treatment with BRAF inhibitors (such as vemurafenib or dabrafenib) are not effective. [5-7] MEK-inhibitors (like selumetinib) achieved tumour regression, but the effects were not clinically relevant.[8, 9] A phase II study (2014) comparing selumitinib (a MEK inhibitor) to chemotherapy (temozolomide or dacarbazine) led to a median overall survival of 11.8 months in the

selumitinib group (versus 9.1) and a median progression-free survival of 16 weeks (versus 7 weeks). [9] The randomized placebo-controlled SUMIT trial, investigated adding a MEK-inhibitor (selumetinib) to chemotherapy in metastatic UM patients without an effect on progression free survival (2.8 versus 1.8 months).[10, 11] Other targeted therapy trials (such as AEB071) were preliminary closed due to toxicity.

Checkpoint inhibitors

Checkpoint inhibition, also called immunotherapy, was investigated as treatment for UM after ipilimumab (anti-CTLA-4), pembrolizumab (anti-PD-1) and nivolumab (anti-PD-1) had shown strong survival benefits for cutaneous melanoma patients. [12-14] Limited clinical activity was reported in several phase I/II trials investigating monotherapy in UM patients; overall survival data of 3-7 months were reported. [2-4, 15-17] The limited efficacy of checkpoint inhibitors in uveal melanoma has led to the agreement among members of the 'Dutch Working Group on immunotherapy and oncology' (WIN-O) not to treat patients with immune checkpoint inhibitors outside a clinical trial. [1] Currently, a phase II randomized multicenter study is recruiting patients with metastasized UM investigating the safety and efficacy of a specific antibody acting on T-cells (IMCgp100) compared to either dacarbazine, ipilimumab or pembrolizumab. An interim analysis of 19 patients showed a prolonged response to treatment and longer survival times. (EudraCT 2016-002236-32)

Dendritic cell therapy

Pre-clinical work on the combination of radiofrequency ablation (RFA) and a checkpoint inhibitor showed enhanced antigen-loading of natural present dendritic cells (DCs), and induced long-lasting anti-tumour immune responses in a murine melanoma model. Dendritic cells are antigen-presenting cells that can activate antigen-specific T-cells with anti-tumour immune activity. This principle was used in the development of dendritic cells loaded with tumour-antigens based on the patient's primary tumour genetics, as adjuvant treatment for patients with stage-IV melanoma after resection. Transient flu-like symptoms were reported as adverse effects. Currently, randomized phase III trials are recruiting to determine whether dendritic cell vaccination can prevent or delay progression of disease for uveal melanoma patients. (NCT01983748). [18] To further investigate this combination a phase I/II study was conducted to investigate the safety and efficacy of the combination of RFA and ipilimumab in UM patients with liver metastases. In one evaluable patient, a significant broadening of the melanoma-associated antigens T cells was observed. Also clinical and biological activity was observed. [19]

In future trials, combinations of locoregional and (yet to be defined) systemic therapy could be investigated. During PHP tumour cells are damaged by the alkylating

agent melphalan. Concurrent administration of currently investigated systemic therapy could be investigated, to determine whether this enhances anti-tumour efficacy. The combination of ipilimumab and nivolumab has achieved improved response rates in several clinical studies. [20] [21]. Interestingly, the majority of responders underwent liver-directed therapy (TACE, surgery or PHP) prior to systemic therapy. In the current CHOPIN trial a combination therapy with immunotherapy (ipilimumab with nivolumab) and PHP with chemotherapy (melphalan) is assessed for the treatment of disseminated uveal melanoma. (NCT04283890).

Besides combinations of therapies, different ways of administration are being studied. Recently, a randomized controlled trial was initiated investigating adjuvant hepatic arterial infusion pump (HAIP) chemotherapy for patients with resectabel colorectal liver metastases. In this PUMP trial (NTR7493) intra-arterial floxuridine is delivered in the hepatic artery via a surgically implanted pump with a catheter in the gastroduodenal artery. Like PHP, the biological rationale for HAIP is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumours. This HAIP technique has been previously investigated for unresectable cholangiocarcinoma (combined with systemic therapy) and appeared to be active and tolerable [22]. It has not been investigated for uveal melanoma liver metastases.

In the meanwhile, genetic investigations are ongoing. It is known that gene expression profiling is very accurate in predicting metastatic risk, more than clinical stage [23]. Monosomy 3 is a common chromosomal abnormality in uveal melanoma and is associated with metastatic disease. Simultaneous monosomy 3 and chromosome 8 alterations, are associated with a worse prognosis. [15] The previously mentioned mutations in GNAQ or GNA11 (which upregulate hepatocyte growth factor) led to the development of specific inhibitors (currently being investigated preclinical trials). [24, 25]This profiling could be used for patient-tailored treatment selection; if the genetic profile predicts that the patient will not benefit from the treatment, the adverse events can also be prevented. [15] This will help clinicians to select the best treatment option for patients with uveal melanoma, maybe even in a very early stage.

Part II–Tailored care for patients with pancreatic cancer

The importance of auditing and data registries

A significant number (>34%) of pancreatic cancer (PC) patients is over the age of 70 years at diagnosis. [26] In clinical trials, elderly patients are often not included, consequently the efficacy of (chemo-)therapy in older patients remains unclear. There are only few studies evaluating the efficacy and safety of chemotherapeutic

treatment for older PC patients. [27] Audits and registry structures cover the entire population, including elderly patients. Therefore, auditing cancer care with adequate case-mix adjustments is a very effective instrument to gain insight in care patterns, determine best practices and have a possible impact on outcome, also for specific groups such as elderly patients. Latter form the basis of the foundation of Eurecca (European REgistration of Cancer Care). Following the roadmap of previous projects on colorectal, breast and upper gastrointestinal cancer, Eurecca Pancreas was initiated (Chapter 7). In 2018, the results of a first comparison of data from the Eurecca Pancreas Consortium were reported providing an insight in clinical practices in several countries in Europa as well as regional registries. Variations in treatment and outcomes of patients who underwent tumour resection for stage I and II pancreatic adenocarcinoma illustrate the difference in implementation of universally accepted guidelines. It also provides a basis for further investigation of the best practices and indicates the need of uniform registration in order to perform international comparisons. [28] This will hopefully lead to a population-based audit structure that covers all pancreatic cancer patients across the participating countries (and eventually across Europe). The aim is to eventually monitor the quality of care of European pancreatic cancer patients, as well as perform analysis on patient groups that deviate from guidelines such as the elderly. These data should be studied with great care, considering that differences in survival and other outcomes are not only based on treatment strategies, but differ between countries, regions and centres based on other factors. Lifestyle factors, but also stage of disease at time of presentation and genetics (e.g. ethnicity and ABO blood group). [27] [28]

Adjust treatment to age

Following determination of best practices in the treatment of elderly pancreatic cancer patients, they have to be implemented in clinical practice. A collaborative geriatric and oncology management can optimize care in elderly patients. [29] It leads to greater attention being paid to existing comorbidity and geriatric issues, which may result in better selection of adequate treatment (or no treatment), prevention of complications, and lower the risk of patient deconditioning. Integrated geriatric care for (the recognition of frail) elderly has proven to increase efficiency of healthcare, leading to retaining independence and an optimal quality of life. [30] [31] At Moffit Cancer Center, Tampa (Florida, US) specialized care tailored to geriatric cancer patients is offered. A comparison was made between collected patient data from Moffit and the Dutch Cancer Registry, as described in this thesis (Chapter 8). Whereas survival seems to improve with palliative systemic treatment, this benefit might be counterbalanced by toxicity and quality of life concerns; an important consideration for elderly patients. Unfortunately, no quality of data was available for these cohorts. For young patients, prolongation of life might be the most important end point;

however, elderly patients may prefer quality of life (their cognitive function, their social situation/capability to stay at home) above quantity of life. There is a need for delineation of relevant clinical endpoints for older individuals, which can then be uniformly incorporated into future clinical trials. [32]

For patients presenting with resectable pancreatic cancer, it is important to question the patient's condition and whether the patient will benefit from the treatment, taking life expectancy into account. Surgical resection with or without systemic therapy is associated with a high risk of perioperative morbidity and mortality, especially in older patients. [26] Apparently contradictory conclusions are reported concerning surgical treatment of elderly patients with pancreatic cancer; patients over 65 years of age would suffer more from side effects and post-treatment morbidity, and mortality would be higher amongst patients older than 70 years. [33] [34] On the other hand it is stated that pancreatico-duodenectomy can be performed safely in carefully selected patients of 75 years and older and that age does not influence the postoperative outcome. [35] [36] A recent trial comparing time to functional recovery after minimal invasive- versus open distal pancreatectomy for left-sided pancreatic tumours favoured minimal invasive surgery and was associated with less delayed gastric emptying and better quality of life without increasing costs. [37] Age specific analysis of these data will have to indicate whether there is also a difference for elderly patients.

Decision aid tools

For breast cancer, research on elderly patients is ongoing. [38] Trials are especially designed and population-based studies are used to develop prediction models. [39]The Dutch Pancreatic Cancer Group (DPCG) developed several decision aid tools for physicians to help gain insight in survival after surgery of pancreatic cancer which may be useful for counselling patients during follow-up [Pancreascalculator, found on DPCG website]. Elderly patients however might benefit from decision aid tools incorporating quality of life, instead of only survival data. Decision aid tools indicating the benefit of a specific treatment, such as Predict for breast cancer patients, could be of help in clinical practice and shared-decision making with elderly pancreatic cancer patients. Recently, a 'consultation card' was developed for patients with pancreatic cancer, as an initiative of a patient federation (Living With Hope) and the Dutch Society of Surgery (NVVH). At this card information about different treatment options after surgery are displayed in a scheme. These valuable tools can be used as supportive measure in shared decision making. [consultkaart NL].

Systemic therapy for patients with pancreatic cancer

Neoadjuvant chemotherapy with gemcitabine in The Netherlands was only administered in a clinical trial setting: the national randomized controlled Preopanc-1 trial. Preliminary outcomes, as presented by Van Tienhoven et al. at the 2018 ASCO Annual Meeting show that neoadjuvant chemotherapy increases median overall survival (17.1 months after neo-adjuvant therapy, compared to 13.7 after immediate surgery). For patients with a successful surgical resection this difference was even greater; 42.1 versus 16.8 months. [40] In the phase III PRODIGE 24 study, Folfirinox (modified scheme) was compared to gemcitabin in fit patients with pancreatic ductal adenocarcinoma (18-79 years of age) after resection. Median overall survival (OS) was 54.4 months in the mFolirinox group compared with 35.0 months for standard gemcitabine. [41] Also for metastatic PC patients (age 25-76 years) folfirinox improved overall survival compared to gemcitabine (11.1 months versus 6.8 months). [42] In continuation of Preopanc-1, knowing the results of folfirinox schemes, Preopanc-2 (NTR7292) is an RCT currently investigating the (cost-) effectiveness of neoadjuvant folfirinox versus neoadjuvant gemcitabine, and adjuvant gemcitabine for (borderline) resectable pancreatic cancer. The results have to be awaited. In 2017 a retrospective analysis reported on survival data of fit patients over 70 years old with inoperable pancreatic cancer treated with folfirinox: median OS in elderly was similar to that reported in younger patients (ACCORD 11 trial (11.7 months vs 16.6 months, p=0.69)), although 57% of patients needed a dose reduction because of toxicity. [43] This indicates that elderly patients might benefit from treatment with an adjusted treatment scheme. Age specific analysis of recent clinical trial data could help to define recommendations in Dutch /European Guidelines for the treatment of elderly patients with pancreatic cancer.

The importance of medical care with a special focus on elderly patients, is also described in the Dutch Residents education Plan, called the CanBetter themes: one of the key items is care for elderly patients. [44] The new generation of medical specialists is trained in the treatment of this specific group of patients since there will be a growing number of elderly patients in need of (cancer) care.

In conclusion, population-based data, as well as specific trial data on subgroups of patients could be helpful in answering the question: what is the best available care for pancreatic cancer patients in a different stage of the disease or at a different age?

Summary

Part I–Hepatic perfusion for the treatment of unresectable liver metastases
Because the majority of metastasized uveal melanoma (UM) patients have unresectable liver only metastases, locoregional therapy was developed. In this thesis percutaneous hepatic perfusion (PHP) is described as a treatment for these patients. Previous to PHP, patients were treated with isolated hepatic perfusion (IHP) during an open surgical procedure (***Chapter 1***). To determine the most effective therapeutic agent used in IHP, several drugs have been investigated. It was hypothesised that IHP treatment with a combination of drugs would improve the treatment effect and hopefully improve survival of patients with liver metastases of colorectal cancer or uveal melanoma. Contrary to the hypothesis it did not, because of hepatotoxicity and therefore, the combination of two chemotherapeutic agents has not been investigated further (***Chapter 2***). In more recent trials, melphalan alone was used in IHP. After successful in vivo studies, clinical trials for UM patients were initiated (***Chapter 3***). In two centers, 30 patients with UM liver only metastases were treated with IHP using melphalan in a clinical trial setting. Progression-free survival was 6 months (1–16) and median overall survival was 10 months (3–50). Compared to survival with no treatment (2-6 months [45]) or best supportive care treatment (OS 5.2 months) [46] this seems to be quite an improvement. Because of the considerable peri-operative morbidity, the complexity and duration of the procedure, IHP did not become standard of care. First, the procedure had to be adjusted and simplified. With advances in surgical techniques, imaging modalities and the emergence of interventional-radiology, percutaneous hepatic perfusion (PHP) was developed, as described in this thesis. During the 3-4 hours PHP procedure, the chemotherapeutic agent is infused in the hepatic artery and thereby delivered to the liver and metastases directly. Via a veno-venous filtration system, the chemotherapeutic agent is filtered before it reaches the systemic circulation. (***Chapter 4***) As described in ***Chapter 5*** a clinical study was conducted treating 20 UM patients with metastases confined to the liver with repeated PHP procedures (up to four procedures, 38 in total). In this study, pharmacokinetic analysis showed an overall filter efficiency of 86% (range 71.1–95.5%) with the Delcath Second Generation hemofiltration system, which is higher compared to earlier generation filters. Median overall survival was 29 months (range 7-40). Partial responses were achieved in 75% of patients and one-year overall survival was 80%. Median hepatic progression-free survival was 10 months (range 2-29). The side-effects were as expected, transient and well manageable. It was concluded that the results PHP outbalanced the (minimal) toxicity for patients with uveal melanoma metastases. (***Chapter 6***)

Part II - Tailored care for patients with pancreatic cancer

The poor prognosis of pancreatic cancer did not change much over the last decades, despite the improvements in treatment modalities. Previous studies have reported variations in incidence and mortality in pancreatic cancer between countries worldwide and European countries. [45, 46] A 2013 EUROCHIP survey (European Cancer Health Indicators Project) showed that cancer registry data are a reliable source for evaluation and strategy planning, but not all data is available in every registry, impeding a complete comparison. EURECCA aims to augment quality assurance by investigating differences in data registry, sharing knowledge in treatment strategies and science and thus improve cancer care throughout Europe. (***Chapter 7***) Previously, these international comparisons were performed for colon cancer, upper GI cancer, breast cancer and rectal cancer. [47-50] This data was collected by audit and registry structures, based on the assumption that an international comparison of population-based data will represent the actual patterns of care. Based on the experience gained by the researchers of this previous consortia, a collaboration was initiated across Europe to compare patterns of care and identify best practices for pancreatic cancer care. A core dataset was identified to identificate differences in age, gender, incidence, tumour stage and differences in treatment strategies.

At Moffitt Cancer Centre (Tampa, U.S.A.) a 'Senior Adult Oncology Program' was specially designed. [51] It was developed for patients aged 70 and older with all types and stages of cancer and offers a complete range of diagnostic, educational, therapeutic and preventative services, all tailored to meet the needs of the elderly population. For instance, a geriatric oncologist is included in the multidisciplinary tumour board. To identify any differences in treatment and/or survival a comparison was performed of data on geriatric pancreatic cancer care and survival at Moffitt and elderly patients in The Netherlands. (***Chapter 8***). We reported that patients treated at Moffitt more often received chemotherapy, also without surgery or as palliative treatment. For patients with locally advanced pancreatic cancer, a higher percentage underwent surgery in The Netherlands. One- and three-year overall survival was higher for patients treated at Moffitt, this difference seems to be largely explained by differences in treatment strategy. Given the associated survival benefit, this indicates that there might be a need for a reconsideration of the used therapies for elderly Dutch patients.

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[Work expands so as to fill the time available for its completion
Parkinson’s Law]

Summary (in Dutch) / Samenvatting

Dankwoord / Acknowledgements

Curriculum Vitae

List of publications

Summary (in Dutch) / Samenvatting

Voor zowel patiënten met alvleesklierkanker, als patiënten met levermetastasen van oogmelanoom geldt dat ze een slechte prognose hebben. In dit proefschrift worden beide ziekten besproken. In deel 1 wordt de ontwikkeling van percutane geïsoleerde leverperfusie beschreven, alsmede de behandeling van gemetastaseerde oogmelanoom patiënten met deze techniek. De behandeling van alvleesklierkanker en hoe deze internationaal soms verschilt, wordt beschreven in deel 2.

Deel I: Leverperfusie voor patiënten met irresectabele levermetastasen

Jarenlang was chirurgie de gouden standaard in de behandeling voor levermetastasen omdat er geen systemische behandeling was. Echter zijn niet alle tumoren geschikt voor chirurgie en met dat gegeven werden locoregionale therapieën ontwikkeld. De vasculaire anatomie van de lever maakt dat deze geschikt is voor isolatie van de systemische circulatie. Dit vormt het basisprincipe voor geïsoleerde leverperfusie (isolated hepatic perfusion, IHP). In deel 1 van dit proefschrift werd de ontwikkeling en introductie van IHP als behandeling van irresectabele levertumoren beschreven. IHP werd rond 1986 *in vivo* ontwikkeld en in 1998 werden de eerste patiënten behandeld in het Leids Universitair Medisch Centrum (LUMC, toen nog Academisch Ziekenhuis Leiden). Om de resultaten te verbeteren, werden combinaties van diverse chemotherapeutica onderzocht. In **Hoofdstuk 2** werd een combinatie van melphalan en oxaliplatin beschreven als behandeling voor patiënten met oogmelanoom en colorectale levermetastasen. Omdat patienten met levermetastasen van oogmelanoom meer baat bleken te hebben bij de behandeling, worden in **hoofdstuk 3** de resultaten van alle IHP behandelingen in het Erasmus Medisch Centrum in Rotterdam en het LUMC gebundeld beschreven. De resultaten zijn veelbelovend, maar gezien de morbiditeit als gevolg van de laparotomische langdurige behandeling, wordt IHP geen standaard behandeling. Daarom is er een minimaal invasieve variant op de procedure ontwikkeld, percutane geïsoleerde perfusie (percutaneous hepatic perfusion, PHP). Dit wordt in detail beschreven in **hoofdstuk 4**. In **hoofdstuk 5** is de veiligheid en toxiciteit van PHP onderzocht in een klinisch en pharmacologische studie. Ten slotte beschrijft **hoofdstuk 6** de behandeling van 20 patiënten met levermetastasen van oogmelanoom met PHP. Oogmelanoom verschilt genetisch van cutaan melanoom. Bij cutaan melanoom spelen mutaties in BRAF en NRAS een grote rol. Echter bij oogmelanoom zijn dit mutaties in GNAQ en GNA11 (in 80% van de patiënten). Het gevolg hiervan is dat

targeted therapy, gericht op BRAF bijvoorbeeld (zoals vemurafenib or dabrafenib), geen effect hebben op oogmelanoom. MEK inhibitors (zoals selumetinib) zorgden in studies voor tumor regressie, maar de effecten waren niet klinisch relevant. Omdat er voor patiënten met oogmelanoom dus nog geen standaard (systemische) behandeling is, werden deze patiënten in studieverband met PHP behandeld.

Deel II: Zorg op maat voor patiënten met alvleesklierkanker

In deel 2 van dit proefschrift wordt ingegaan op alvleesklierkanker, en met name op uitkomsten van de diverse behandelstrategieën in Europa en wereldwijd. Door behandelingen en uitkomsten daarvan te vergelijken, kunnen we leren of specifieke behandelkeuzes geassocieerd zijn met verschillen in overleving. In **hoofdstuk 7** wordt de ontwikkeling van de eerste internationale Europese alvleesklierkanker database beschreven. Deze database is een samenwerking tussen bestaande nationale audits en (lokale) kankerdatabases, onder leiding van European Cancer Audit (EURECCA). In **hoofdstuk 8** wordt een internationale vergelijking gemaakt tussen de behandeling van oudere patiënten met alvleesklierkanker in een speciaal programma voor ouderen-oncologie in de Verenigde staten, met Nederlandse data. Is het mogelijk om een optimaal behandelregime voor oudere patiënten met alvleesklierkanker vast te stellen? Tenslotte bevat **hoofdstuk 9** de discussie en een blik op de toekomst. In dit hoofdstuk wordt met name ingegaan op een combinatie van systemische therapie met PHP voor patiënten met gemetastaseerd oogmelanoom. Met de toegenomen lever-ziektevrije overleving na PHP, zou een combinatie van deze behandeling met een effectief middel voor extrahepatische metastasen een volgende stap zijn om de gehele overleving verder te verbeteren. Wat betreft de (oudere) patiënten met alvleesklierkanker wordt in hoofdstuk 9 een pleidooi gehouden voor meer zorg op maat en afgestemd op de wensen van de patiënt.

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Curriculum Vitae

Noor de Leede werd in 1986 geboren in Gouda als oudste in een gezin met vier dochters. Na de basisschool ging ze naar het Driestar College, waar ze in 2004 haar VWO diploma haalde. Toen ze in hetzelfde jaar werd uitgeloot voor geneeskunde, besloot Noor een jaar HBO verpleegkunde te gaan doen, om alvast iets te leren over de gezondheidszorg. Toen ze het jaar erop opnieuw werd uitgeloot, startte ze de studie Biomedische Wetenschappen aan de Katholieke Universiteit in Leuven, waar ze toen ook ging wonen. In 2006 mocht ze dan toch Geneeskunde gaan studeren aan de Universiteit Leiden. Tijdens haar studie werkte ze bij het Centre for Human Drug Research (CHDR) als meet-assistent en recruiter. Haar reislust wist ze te combineren met haar studie; in 2009 reisde ze naar Ghana voor een klinische stage op de afdeling chirurgie in het Komfo Anokye Teaching Hospital in Kumasi. In 2011 deed ze haar co-schappen gynaecologie en sociale geneeskunde in Paramaribo, Suriname.

Toen ze tijdens haar wetenschapsstage betrokken raakte bij de Kauwgomstudie, werd haar enthousiasme voor de wetenschap geboren. In 2013 ontving ze haar artsendiploma en startte daarna bij het Dutch Institute for Clinical Auditing (DICA) waar ze ervaring opdeed in statistische programma's om vervolgens te beginnen aan haar promotietraject op de afdeling Heelkunde van het Leids Universitair Medisch Centrum (LUMC) onder begeleiding van professor Cock van de Velde, dr. Bert Bonsing en dr. Alexander Vahrmeijer, hetgeen resulteerde in dit proefschrift. Onderdeel van haar onderzoekswerk was ook het meewerken aan de opzet van een zorgpad voor patiënten met alvleesklierkanker in het LUMC. In het kader daarvan bezocht ze samen met dr. Lieke Welling drie grote ziekenhuizen in de Verenigde Staten waar grote aantallen patiënten met alvleesklierkanker worden behandeld. De zorg voor goede informatie voor patiënten met alvleesklierkanker en hun naasten zette ze voort door zich in te zetten in de medische commissie van de Living With Hope Foundation (voorheen Lisa Waller Hayes Foundation).

In 2015 begon ze als ANIOS chirurgie in het Groene Hart Ziekenhuis (GHZ) in Gouda, waar ze klinische ervaring opdeed. In januari 2017 startte ze met de opleiding Heelkunde in regio drie, met dr. Roderick Schmitz en dr. Abbey Schepers als haar opleiders. In haar vrije tijd houdt ze van reizen, lezen, documentaires kijken, muziek en skiën.

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