Hyperthermia European Adjuvant Trial (HEAT)

A study of the European Society for Hyperthermic Oncology (ESHO)
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CLINICAL STUDY PROTOCOL

Hyperthermia European Adjuvant Trial:

A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with

Gemcitabine alone (Arm G) vs.

Gemcitabine plus Cisplatin with regional hyperthermia (Arm GPH)

Short title: Hyperthermia European Adjuvant Trial
Study code: HEAT
EudraCTNumber: 2008-004802-14

Sponsor:

Klinikum Grosshadern Medical Centre
University of Munich
represented by the medical director
Prof. Dr. med. Burkhard Göke
D-81377 Munich

Coordinating Investigator:

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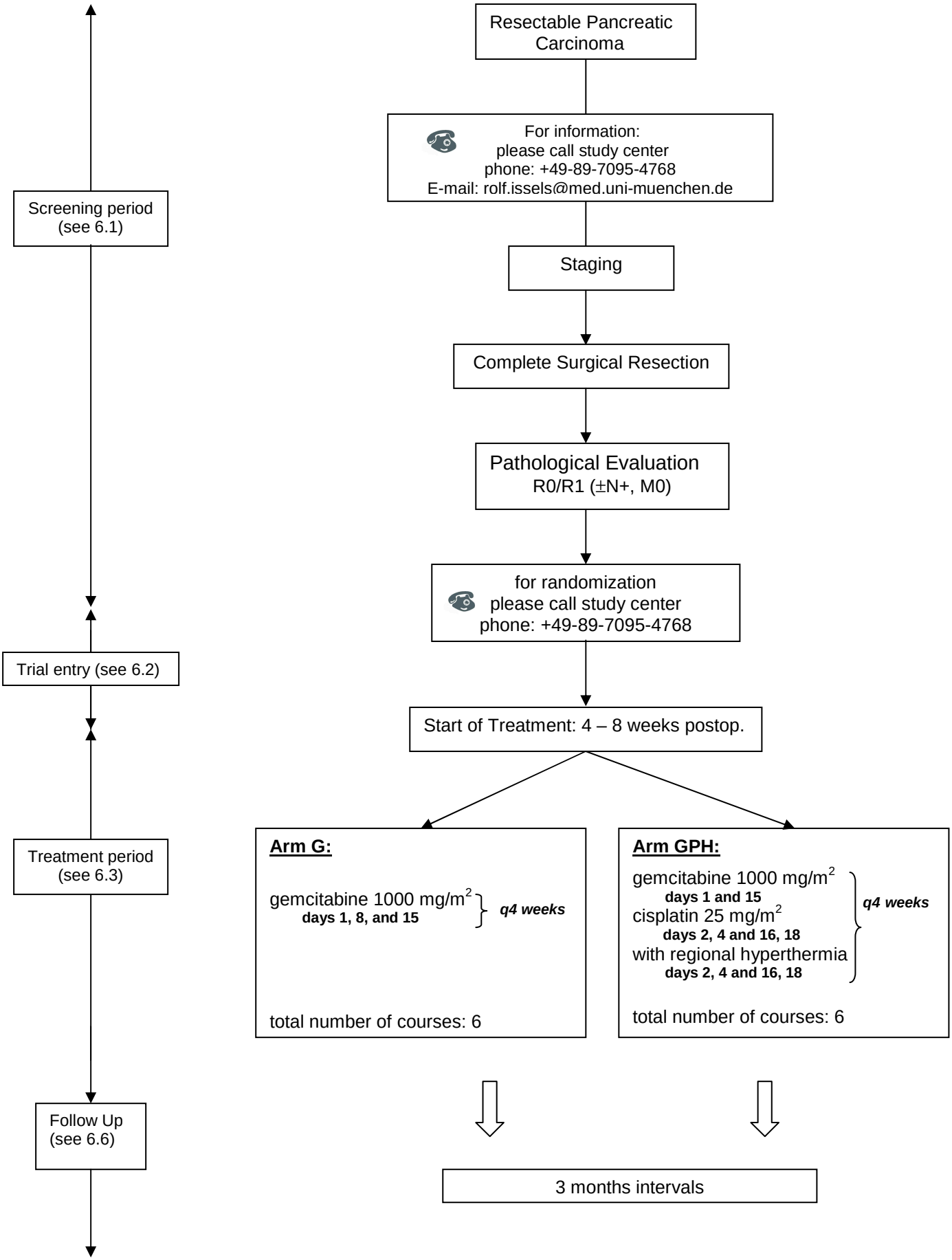
Approval by the ethics committee
of the LMU: date, 2011

TRIAL FLOW CHART:



Signature Page I

By signing this page I agree:

- to conduct the trial described in this protocol in compliance with GCP (including German GCP-V, dated 09 August 2004), with applicable regulatory requirements and with the protocol given approval by the Ethics Committee and the regulatory authority;
- to comply with procedures for data recording and reporting (including data protection);
- to permit monitoring, auditing and inspection;
- to retain the trial-related essential documents until the documents are no longer needed (at least 10 years).

Munich, 11.02.09
Place, Date

Signature
Prof. Dr. Burkhard Göke
Representative Sponsor

Munich, 11.02.09
Place, Date

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PD Dr. Christiane Bruns,
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Signature Page II

By signing this page I agree:

- to conduct the trial described in this protocol in compliance with GCP (including German GCP-V, dated 09 August 2004), with applicable regulatory requirements and with the protocol given approval by the Ethics Committee and the regulatory authority;
- to comply with procedures for data recording and reporting (including data protection);
- to permit monitoring, auditing and inspection;
- to retain the trial-related essential documents until the documents are no longer needed (at least 10 years).

Munich, 10.02.2009 — **Place, Date**

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PD Dr. med. Frank Kolligs
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München, 10.02.2009 — **Place, Date**

Signature
Prof. Dr. rer. nat. Ulrich Mansmann
Head of Dept. of Biostatistics

INVESTIGATOR SIGNATURE PAGE

Investigator:

Signature of Main Investigator at Site	Date
Printed Name of Main Investigator at Site	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Table of contents

1. SYNOPSIS **10**

1.1 STUDY FLOW CHART **15**

1.2 DOSE REGIME **16**

ARM G **16**

ARM GPH **16**

1.3 INTRODUCTION **17**

1.3.1 GEMCITABINE IN THE ADJUVANT SETTING 17

1.3.2. GEMCITABINE PLUS CISPLATIN 17

1.3.3 CHEMOTHERAPY IN COMBINATION WITH REGIONAL HYPERTHERMIA 18

2. STUDY RATIONALE **20**

3. OBJECTIVES OF THE STUDY **20**

3.1 PRIMARY OBJECTIVE 20

3.2 SECONDARY OBJECTIVES 20

4. STUDY DESIGN **21**

5. STUDY POPULATION **21**

5.1 INCLUSION CRITERIA 21

5.2 EXCLUSION CRITERIA 22

5.3 NUMBER OF PATIENTS 22

6. OUTLINE OF THE STUDY **22**

6.1 SCREENING PERIOD 22

6.2 STUDY ENTRY - RANDOMIZATION 23

6.3 EVALUATION DURING THE TREATMENT PERIOD 24

6.4 END OF STUDY 25

6.5 PREMATURE DISCONTINUATION 25

6.5.1 Premature discontinuation from the study 25

6.5.2 Patient withdrawal 26

6.5.3 Early stopping rules 26

6.5.4 Adjustment of standard treatment arm 26

6.6 FOLLOW-UP PERIOD ASSESSMENTS 26

7. TREATMENT ADMINISTRATION **27**

7.1 GEMCITABINE ADMINISTRATION (ARM G) 27

7.2 GEMCITABINE ADMINISTRATION (ARM GPH ONLY) 27

7.3 CISPLATIN ADMINISTRATION (ARM GPH ONLY) 28

7.4 REGIONAL HYPERTHERMIA (ARM GPH ONLY) 28

7.5 DURATION OF TREATMENT 28

7.6 GUIDELINES FOR TREATMENT MODIFICATIONS 28

7.6.1 Gemcitabine and Cisplatin 28

7.6.2 Regional hyperthermia 28

7.7 STEPS FOR DOSE REDUCTION 29

8. CONCOMITANT MEDICATIONS **31**

8.1 SUPPORTIVE CARE 31

8.2 HAEMATOPOIETIC GROWTH FACTORS 31

8.3 USE OF OPIATES 31

8.4 OTHER ANTI-NEOPLASTIC AGENTS 31

9. MEASUREMENTS AND EVALUATION 31
9.1 EFFICACY ASSESSMENT 31
9.2 QUALITY OF LIFE 31
9.3 SAFETY ASSESSMENT 32
9.4 TRANSLATIONAL RESEARCH PROGRAM 32

10. RELAPSE STRATEGY 32

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 33
11.1 ADVERSE EVENTS (AE) 33
11.1.1 Definition of an AE 33
11.1.2 Grading of adverse events 33
11.1.3 Reporting of Adverse Events 33
11.2 SERIOUS ADVERSE EVENTS (SAE) 33
11.2.1 Definition of a SAE 33
11.2.2 Reporting of SAE 34
11.2.3 Follow-up of SAE/AE 34
11.2.4 SAE occurring after the trial 34

12. STATISTICAL ANALYSIS 35
12.1 POPULATIONS ANALYSED 35
12.1.1 Intent-to-treat analysis 35
12.1.2 Per-protocol analysis 35
12.1.3 Safety analysis 35
12.2 DEFINITIONS 35
12.3 STATISTICAL ANALYSIS 35
12.4 SAMPLE SIZE 37

13. STUDY MONITORING AND DATA COLLECTION 38
13.1 CASE REPORT FORM 38
13.2 SOURCE DOCUMENTS 38
13.3 TRIAL MONITORING 38

14. DATA MANAGEMENT 39
14.1 DATA ENTRY 39
14.2 DATA REVIEW 39
14.3 DATA FREEZING 39

15. ETHICAL CONSIDERATIONS 40
15.1 ETHICAL CONDITIONS 40
15.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL ARRANGEMENTS 40
15.3 PATIENT INFORMATION AND CONSENT 40

16. CONFIDENTIALITY 40
16.1 DATA PROTECTION 40

17. ADMINISTRATIVE CONSIDERATIONS 40
17.1 PROTOCOL AMENDMENT 40
17.2 SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE 41
17.3 TRIAL TERMINATION 41
17.4 AUDIT/INSPECTION 41
17.5 INSURANCE POLICY 41
17.6 PUBLICATIONS 41

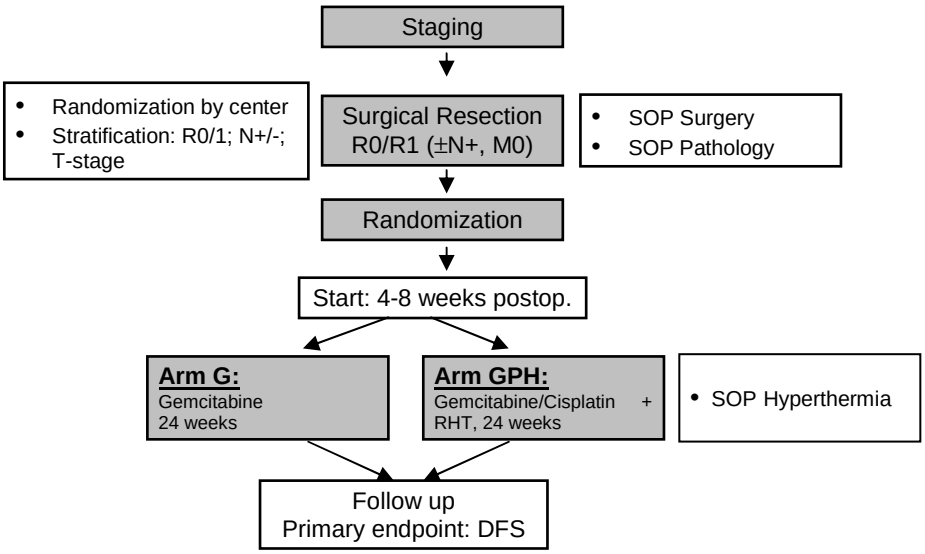
18. REFERENCES 42

19. APPENDICES 45
19.1 SOP SURGERY (GERMAN VERSION) 45
19.2 SOP REGIONAL HYPERTHERMIA (ENGLISH VERSION) 48
19.2.1 Treatment planning 48
19.2.2 Standard set-up for sigma Eye, sigma-60 or elliptical sigma-60 applicators: 49
19.2.3 Temperature and E-Field measurements: 50
19.2.4 Standard parameters of the applicator 50
19.2.5 Treatment procedure 50
19.2.6 Treatment documentation 51
19.2.7 Safety aspects 51
19.3 SOP PATHOLOGY 52
19.4 SHIPPING OF PRIMARY TISSUE AND SERUM PROBES 55
19.5 WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI 56
19.6 INFORMED CONSENT 60
19.7 KARNOFSKY AND WHO PERFORMANCE STATUS SCALE 61
19.8 COMMON NCI TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 62
19.9.1 INFORMATION ABOUT GEMCITABINE (GEMZAR®) 63
19.9.2 INFORMATION ABOUT CISPLATIN 64

Tables

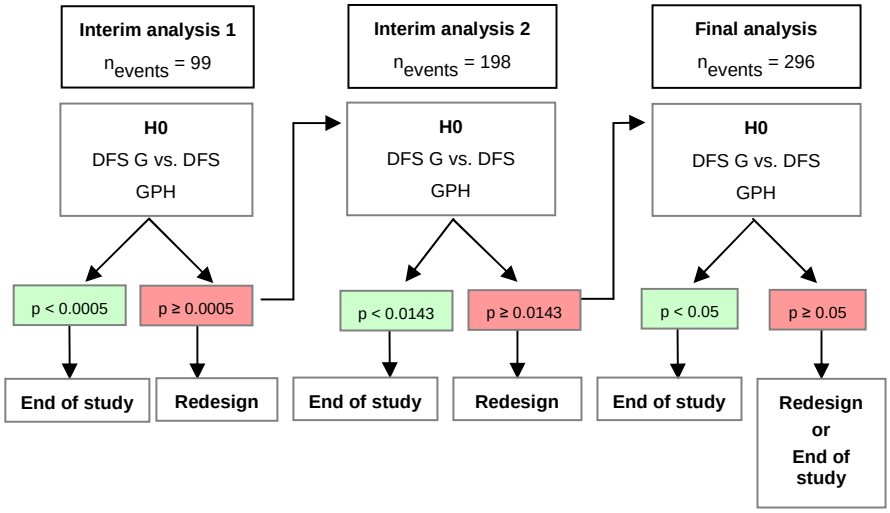
Table 1: Study Flow Chart 15
Table 2: Dose regime 16
Table 3: Treatment modifications for hematological toxicities 29
Table 4: Treatment modifications for hepatic toxicities 29
Table 5: Treatment modifications for renal toxicities 30
Table 6: Treatment modifications for other non-haematological toxicities 30

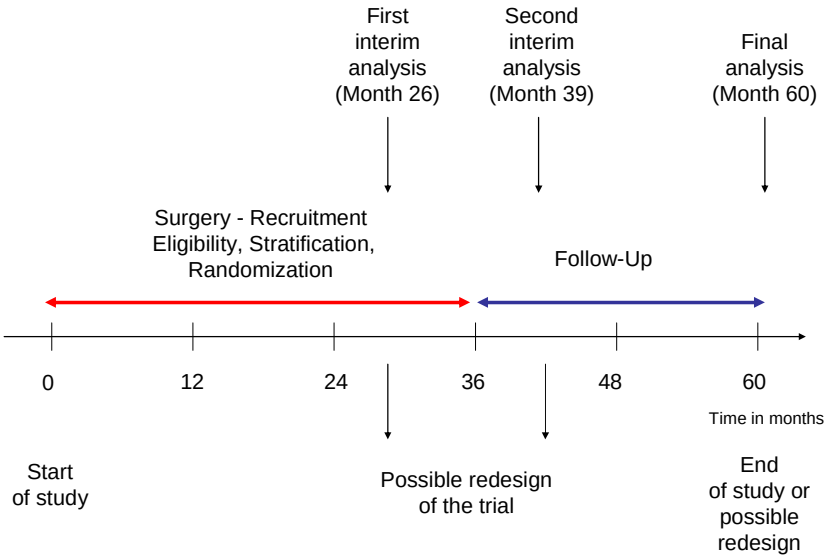
SYNOPSIS

SPONSOR	*Klinikum Grosshadern Medical Center* *University of Munich* *represented by the medical director* *D-81377 Munich*
COORDINATING-INVESTIGATOR	*Prof. Dr. Rolf Issels* and *Helmholz Zentrum münchen* *Dept. Internal Medicine III* *- German Research Center for* *Klinikum Grosshadern Medical Center* *Environmental Health* *University of Munich* *Ingolstädter Landstr. 1* *D-81377 Munich* *D-85764 Neuherberg*
STEERING COMMITTEE	*Surgery: Prof. Dr. Christiane Bruns* *Prof. Dr. Karl-Walter Jauch* *Medical Oncology/Gastroenterology:* *Prof. Dr. Volker Heinemann (Hematology/Oncology)* *PD Dr. Frank Kolligs (Gastroenterology)* *Dr. Eike Gallmeier* *Hyperthermia/Medical Oncology:* *Dr. Katharina Tschoep-Lechner* *PD Dr. Lars Lindner* *Prof. Dr. Rolf Issels* *Klinikum Grosshadern Medical Center* *University of Munich* *D-81377 Munich*
SITES	*Adequately qualified and experienced sites were invited to participate in this trial. The decision about participation of sites has been taken by the steering committee in cooperation with the sponsor. It is planned that 14 randomizing surgical departments and 9 centers for hyperthermia will be participating.*
TITLE OF STUDY	*A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with Gemcitabine alone (Arm G) vs. Gemcitabine plus Cisplatin with regional hyperthermia (Arm GPH)*
CONDITION	*R0/R1 resected ductal pancreatic adenocarcinoma*
STUDY TYPE	*Multicenter, national, randomized (stratification: R0/1; N+/-; T-stage)* **H**yperthermia **E**uropean **A**djuvant **T**rial (HEAT) Resectable Pancreatic Cancer 

OBJECTIVES	*(1) To prove that regional hyperthermia therapy (RHT) as an additional component to an adjuvant chemotherapy (Gemcitabine + Cisplatin) is superior to the adjuvant chemotherapy with Gemcitabine alone.*
INTERVENTIONS	***Course:*** *A course is defined as a period of 28 days.* ***Intervention 1 (G):*** *Gemcitabine* ***Gemcitabine:*** *1000 mg/m² as iv-infusion on days 1, 8 and 15 of each course (Total dose: 18 g/m²)* ***Intervention 2 (GPH):*** *Gemcitabine + Cisplatin + regional hyperthermia* ***Gemcitabine:*** *1000 mg/m² as iv-infusion on days 1 and 15 of each course (Total dose: 12 g/m²)* ***Cisplatin:*** *25 mg/m² as iv-infusion on days 2, 4 and 16, 18 of each course (Total dose: 600 mg/m²)* ***Regional hyperthermia:*** *60 minutes on days 2, 4 and 16 ,18 of each course* ***Duration of treatment:*** *It is planned to administer 6 courses. Treatment will be stopped in case of a recurrence of pancreatic carcinoma (local recurrence or distant metastases), unacceptable toxicity, patient's wish or other conditions under which continuation of treatment would not be in the best interest of the patient according to the investigator's opinion.*
KEY INCLUSION AND EXCLUSION CRITERIA	***Inclusion criteria:*** 1. *any ductal adenocarcinoma of the pancreas confirmed by histology* 2. *previous R0 or R1 resection of pancreatic tumor with a standardized procedure* 3. *willingness to participate in translational research program* 4. *no other previous or concomitant treatment of pancreatic carcinoma like radiation, neoadjuvant therapy or immunotherapy* 5. *no macroscopic manifestation of pancreatic cancer detectable by CT/MRT after surgery* 6. *postoperative tumor marker (CEA/CA19-9) ≤2.5 x upper limit of normal (ULN) to be documented within 1 week prior to randomization* 7. *performance status ECOG 0-2* 8. *adequate bone marrow function defined as* *- leucocytes ≥ 3.5 x 10^9/L and* *- thrombocytes ≥150 x 10^9/L and* *- hemoglobin ≥9 g/dl* *documented within 1 week prior to randomization* 9. *adequate renal function defined as* *- serum creatinine ≤1.2 mg/dL and* *- calculated GFR ≥60 ml/min* *documented within 1 week prior to randomization* 10. *adequate coagulatory function defined as* *- Quick-value ≥70% and* *- aPTT ≤1.5 x ULN* *documented within 1 week prior to randomization* 11. *transaminases (AST, ALT) ≤ 3 x ULN and bilirubin ≤ 2 x ULN* 12. *at least 18 years of age* 13. *women with childbearing potential and fertile men must use adequate contraceptive measures during and for at least 3 months after completion of study therapy (Adequate methods for women are oral contraceptives with estrogen and progesterone, vaginal rings, contraceptive patches, estrogen-free ovulation inhibitors, intrauterine devices with progesterone, 3-month injections with depot progesterone, implants setting free progesterone, abstinence or sterilization (vasectomy) of the male partner. Men must use condoms.)* 14. *women with childbearing potential must have a negative pregnancy test within 1 week prior to randomization (postmenopausal women with amenorrhea for more than 1 year are regarded as having no childbearing potential)* 15. *written informed consent* ***Exclusion criteria:*** 1. *cystic carcinoma of the pancreas* 2. *periampullary cancer*

	3. *presence of an active infection grade 3 or higher* 4. *other severe disease which could impair the patient's ability to participate in the study according to the investigator's opinion* 5. *pregnant or breastfeeding women* 6. *known allergies or contraindications with regard to substances or procedures of study therapy* 7. *severe, non-healing wounds, ulcers or bone fractures* 8. *participation in another clinical trial during this study or within 4 weeks prior to randomization* 9. *past or current abuse of illegal or legal drugs or alcohol* 10. *other primary malignant diseases in the medical history* during the last 5 years *(exceptions: carcinoma in situ of the cervix or adequately treated basal cell carcinoma of the skin).* 11. *permanent cardiac pacemaker* 12. *gross adiposity defined as BMI > 40 kg/m²* 13. *treatment with regional hyperthermia not possible for technical reasons (e.g. metal implant)*
CRITERIA FOR EVALUATION	*Primary efficacy criterion: Disease free survival (DFS)* *Secondary efficacy criterion: Overall Survival (OS)* *Safety: Adverse events (including abnormal laboratory values) scored according to CTCAE (version 4.0)* *Quality of Life: EORTC QLQ C30* *Assessment for efficacy is scheduled every 12 weeks, quality of life is assessed every two weeks adverse events are recorded on an ongoing basis. Full safety laboratory tests are required prior to the start of each course and after the end of complete study treatment. Other required laboratory tests will be performed as indicated in the study flow chart page 15.*
SAMPLE SIZE	*For sample size calculation we use a group-sequential design with two interim analyses and the following assumptions:* *Median DFS with treatment group 1 (G): 14 months ($\lambda_G = 0.05$)* *Median DFS with treatment group 2 (GPH): 19 months ($\lambda_{GPH} = 0.036$)* *For specified alpha = 0.05, hazards $\lambda_G = 0.05$, $\lambda_{GPH} = 0.036$ (hazard ratio = 0.72) and power of 80.0% the design would require a maximum of 366 patients to be recruited. Hence, a total number of 183 patients per arm is recruited. Interim analyses are planned after occurring of 99, 198 and 296 events on an appropriate significance levels using the stratified Cox proportional hazards model. Assuming a recruitment rate of 122 patients per year and a follow-up of two years the duration of the trial will be a maximum of five years.*

STATISTICAL ANALYSIS	Primary efficacy criterion: We test the following null-hypothesis (H0): DFS under treatment group 1 (G) == to DFS under treatment group 2 (GPH) In order to test this null hypothesis a stratified Cox proportional hazards model is used to trial the differential effect between the treatment group 2 (GPH) and treatment group 1 (G) with respect to DFS. The proportional hazards model will be stratified by the factors R0/1, N+/- and T-stage. Each trial center will be represented by a gamma-distributed frailty effect. The p-value for the treatment effect will be calculated by a likelihood ratio test between this model and a model which is reduced by the treatment covariate. The analysis is performed on all randomized patients (ITT). We use a group-sequential design according to O'Brien and Fleming with a maximum of three stages. Therefore, two interim analyses and one final analysis are planned as displayed below.  Secondary efficacy criterion: For overall survival (OS) we follow the same procedures as described for the primary endpoint DFS. Prespecified subgroup analyses: Analysis (DFS and OS) of patients who received at least 4 cycles of standard gemcitabine (12 x G) vs at least 4 cycles of standard gemcitabine (12 x G) + Cisplatin (24 x P) plus RHT (24 x H); patients with early progression or death will be included. The comparison is based upon a thermal dose concept according to the number of RHT treatments. Prespecified analysis using hsp27 as predictive factor. Sensitivity analyses: Sensitivity analyses are performed to test the stability of the efficacy finding (adjustment for relevant prognostic factors, per-protocol analysis, and further exploratory analyses, if applicable). Details of the analyses will be provided in a statistical analysis plan (SAP) which is determined prior to each analysis. Safety: The incidences of adverse events in the treatment arms will be presented by type and severity. At each interim analysis there is a chance for redesigning the group sequential trial as a consequence of deviations from the trial plan: decreased recruitment, loss or gain of centers, etc. The reanalysis will be based on the proposal of Müller & Schäfer (SIM, 2004).

TRIAL DURATION	*First patient in to last patient in: 3 years* *Duration of the entire trial: 5 years* *Flow for stage I of trial* 
RANDOMIZATION	*Randomization to the two treatment groups in the ratio of 1:1 will be performed by the Institute of Medical Informatics, Biometry, and Epidemiology (IBE) at the University of Munich. Randomization is stratified by N+/-, R0/R1 and stage T. The IBE conduct the randomization providing an internet based randomization tool (Randoulette).*
MONITORING	*The trial will be monitored by the contract research organization ClinAssess, Leverkusen, according to the monitoring Standard Operation Procedures (SOPs) of ClinAssess which are based on ICH guidelines for Good Clinical Practice. Monitoring will be performed to verify that the rights and well-being of human subjects are protected, the documented trial data are accurate, complete and verifiable from source documents, and the conduct of the trial is in accordance with the currently approved protocol / amendment(s), with GCP and with local regulatory requirements.* *Monitoring will be done by personal visits of a representative of the CRO ClinAssess, who will check the CRFs and source documents. Source data verification of all study data will be performed for all randomized subjects. All study sites will be visited by the monitor in regular intervals depending on the recruitment rate. By frequent communication (letter, telephone, fax, email) the monitor will check the current state and the progress of the trial.*
DATA MANAGEMENT	*The central data processing services (CDPS) will be provided by the Institute of Medical Informatics, Biometry, and Epidemiology (IBE) at the University of Munich. It is responsible for the CDPS, including central server, data banks, data exchange, and data security. It will provide safe and secure data transfer according to the security laws between the partners and protect their privacy rights as well as the privacy rights of the patients.*

STUDY FLOW CHART

Table 1: Study Flow Chart

REQUIRED ASSESSMENTS	SCREENING			RANDOMIZ.	TREATMENT PERIOD 6 courses (1 course = 28 days)										FOLLOW-UP
TIMING	pre OP	OP (4-8 weeks before. rand.)	week before rand.		Day of treatment course								After course 2 & 4	End of the study[1]	3-month intervals
					1	2	4	8	15	16	18	22			
Signed Informed Consent	X														
Med. History	X														
Physical Examination	X		X		X[5]									X	X
Resection		X													
Laboratory 1	X[3]		X[3]												
CEA, CA19-9	X		X		X									X	X
10 ml Serum and 30 ml heparinized blood for translational research program (s. page 34)			X		X									X	
Shipping of primary tumor (s. page 57)		X													
Abdominal CT or MRT[7]	X		X[8]										X	X	X[1]
Chest CT[2]	X[2]		X[2]										X[2]	X[2]	X[2]
Concomitant Medication			X		X	X	X	X	X	X	X	X		X	
EORTC QLQ C30					X				X					X	X
Adverse Events					X	X	X	X	X	X	X	X		X	
Survival Status															X
x-ray chest	X														
Arm G															
Gem. (1000 mg/m² iv)					X			X	X						
Laboratory 2/3					X[4]			X[6]	X[4]			X[6]		X[4]	X[4]
Arm GPH															
Gem. (1000 mg/m² iv)					X				X						
Cisplatin (25 mg/m²)						X	X			X	X				
Regional Hyperthermia						X	X			X	X				
x-ray abdomen			X[9]												
Laboratory 2/3					X[4]			X[6]	X[4]			X[6]		X[4]	X[4]
Audiogram					X									X	

1 4 weeks after the final dose (Treatment will be continued for 6 courses *or* until one of the following occurs: recurrence of pancreatic carcinoma (local recurrence or distant metastases), unacceptable toxicity, patient's wish or other conditions under which continuation of treatment would not be in the best interest of the patient according to the investigator's opinion).

2 Investigations to exclude or confirm tumor manifestations must be performed if tumor manifestations are suspected and if the investigations are clinically indicated.

3 Laboratory 1: erythrocytes, haemoglobin, leucocytes, neutrophils, platelets, serum creatinine, creatinine clearance, urea, electrolytes (sodium, potassium, calcium, magnesium), ALT, AST, alkaline phosphatase, total bilirubin, total protein, Quick, aPTT, and (only in women with childbearing potential) pregnancy test.

4 Laboratory 2: haemoglobin, leucocytes, neutrophils, platelets, serum creatinine, creatinine clearance, ALT, AST, total bilirubin, Quick, aPTT)

5 May be omitted on day 1 of the first course if treatment is started within one week after randomization.

6 Laboratory 3: erythrocytes, haemoglobin, leucocytes, neutrophils, platelets, serum creatinine, electrolytes (sodium, potassium).

7 CT during screening requires CTs during trial. MRT during screening requires MRT during trial.

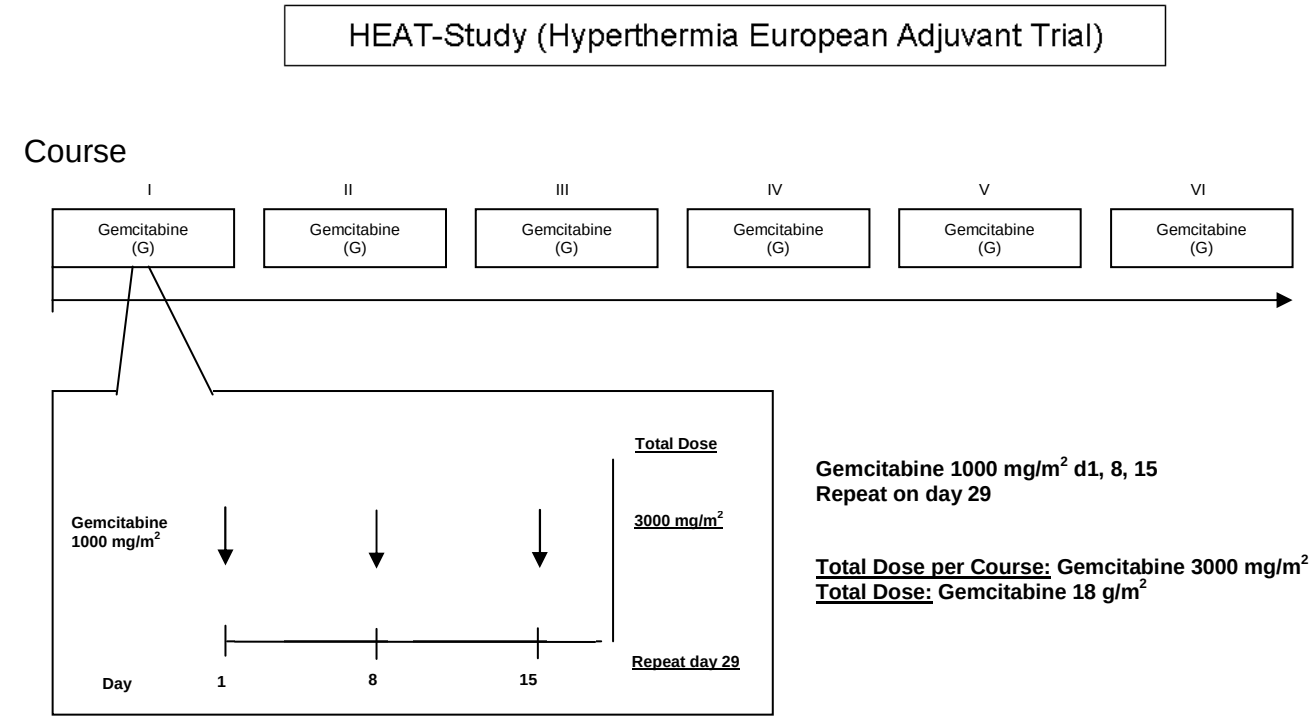
8 CT or MRT has to be taken within 4 weeks before randomization.

9 X-ray abdomen must only be performed if there is no postoperative CT-scan of the abdomen, excluding metal implants.

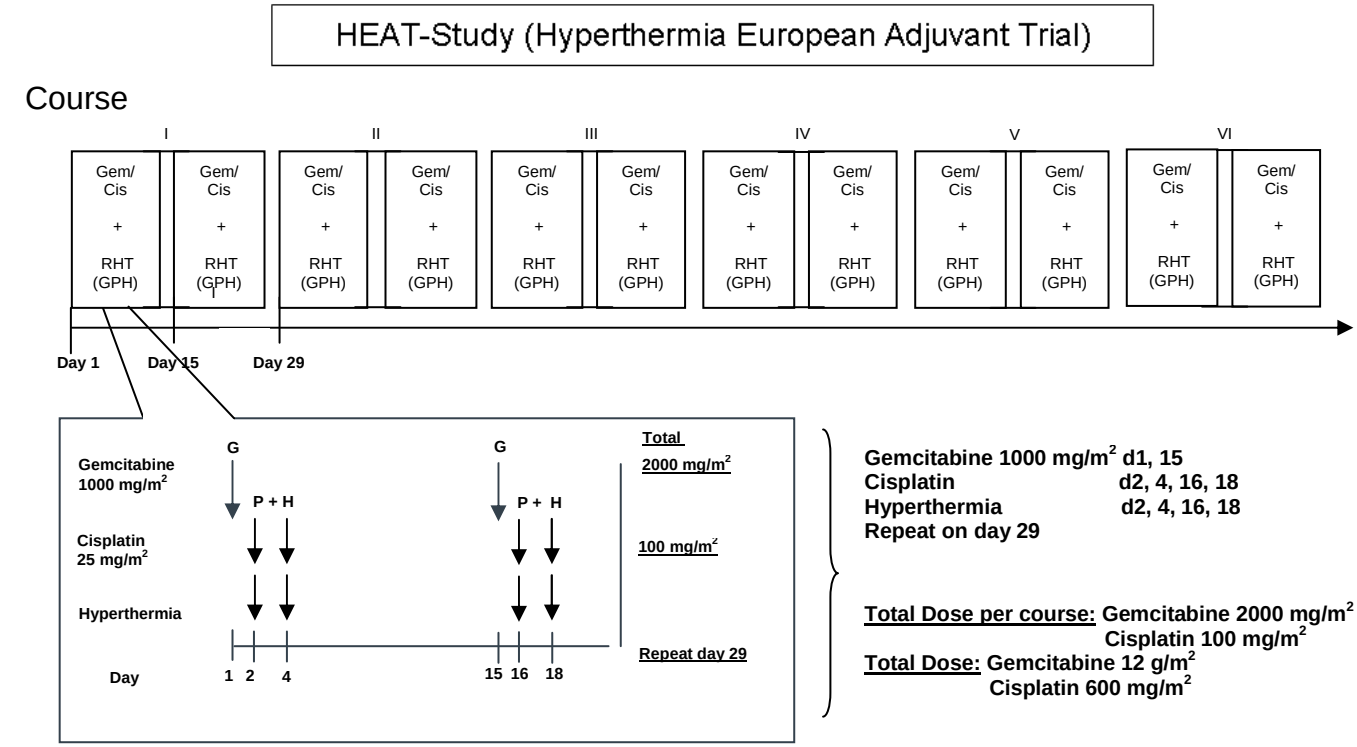
1.2 DOSE REGIME

Table 2: Dose regime

ARM G



ARM GPH



1.3. INTRODUCTION

1.3.1 Gemcitabine in the adjuvant setting

The minority of pancreatic cancer patients present with resectable disease at first diagnosis. Approximately 10%-15% of patients undergo partial or complete pancreaticoduodenectomy as the established standard of care. Despite the curative intent of surgery and optimized application of supportive therapy, median survival after resection of pancreatic cancer remains in the range of 11-20 months and is associated with a 5-year-survival of 7%-25%. As the poor prognosis of patients with pancreatic cancer is primarily determined by systemic and not local failure, it becomes self-evident that adjuvant treatment strategies should predominantly focus on an improvement of systemic treatment.

Gemcitabine is still regarded as one standard of care in the adjuvant treatment of patients. Within the CONKO-001 study adjuvant chemotherapy with gemcitabine (for a duration of 6 months) was compared with observation only after R0/R1 resection of pancreatic cancer [1]. The final results of this multicenter study (n=368) presented at the ASCO 2008 meeting showed a significant increased DFS in all subgroups of stratification (stratified for R0/R1) and an improved OS with 22,8 months in the gemcitabine group versus 20,2 months [2].

The results of the ESPAC-1 trial also support the use of adjuvant chemotherapy (e. g. 5-FU/FA for 6 months) after curative intent resection of pancreatic cancer. This study used a 2 x 2 factorial design to compare adjuvant chemotherapy vs. no chemotherapy and adjuvant chemoradiotherapy (CRT) vs. no CRT [3]. The median survival for the chemotherapy group was estimated with 20.1 months compared to 15.5 months for the no-chemotherapy group (HR=0.71, 95% CI 0.55-0.92; p=0.009). The ESPAC-1 study furthermore could not show a survival benefit for adjuvant CRT: median survival was even inferior in the CRT group (15.9 months vs. 17.9 months) as was 5-year survival (10% vs. 20%, p=0.05). The ESPAC-3 trial did not confirm the superiority of gemcitabine vover 5-FU if combined with radiation in the adjuvant setting and moreover the study left the role of radiation inconclusive [4]. But, the hematological toxicity was less in the gemcitabine group.

In contrast, results of the randomized phase III trial by the Radiation Therapy Oncology Group (RTOG) [5] indicate that gemcitabine applied before and after adjuvant 5-FU-based CRT is associated with a survival benefit as compared to fluorouracil-based chemoradiation alone. Though statistically not significant, patients reached a median survival of 20,5 months and 3-year survival of 33% versus 16,9 months an 22% (p=0,9).

Altogether these data generally support the role of an adjuvant treatment in patients suffering from curatively resectable pancreatic cancer and they strengthen the role of a gemcitabine-based therapy.

1.3.2. Gemcitabine plus cisplatin

Several randomized phase III trials investigated the role of gemcitabine-based combination chemotherapy in advanced pancreatic cancer. Most promising results were obtained, if gemcitabine was combined with a platinum analog or the oral fluoropyrimidine capecitabine [6-9]. In a German multicenter phase III trial (n=195), the gemcitabine plus cisplatin combination induced a prolongation of progression-free survival (5.3 vs. 3.1 months, p=0.053) and also an increase in overall survival (7.5 vs. 6.0 months, p=0.15) compared to single-agent gemcitabine in patients with advanced pancreatic cancer [6]. These differences did not reach a level of statistical significance. However, a pooled analysis of two European phase III trials (n=503) -

both comparing gemcitabine vs. gemcitabine + platinum analog (cisplatin and oxaliplatin, respectively) - indicated a significant survival benefit (HR 0.81, 95% CI 0.67-0.98; p=0.031) for platinum-based combination chemotherapy in patients with advanced pancreatic cancer [10]. This benefit was pronounced in patients with a good performance status at treatment initiation [11].

Moreover a meta-analysis of 16 randomized controlled trials investigating the role of gemcitabine-containing combination chemotherapy showed a significant survival benefit (HR 0.85, 95% CI 0.76-0.96; p=0.01) for the use of a gemcitabine + platinum combination compared with gemcitabine alone in patients with advanced pancreatic cancer [11].

However, the GIP-1 trial by Colucci et al. showed no benefit regarding PFS or objective response rate for patients with gemcitabine plus cisplatin versus gemcitabine alone as firstline treatment in advanced or metastatic disease [12]. In this trial 150 mg/m^2 cisplatin was given in the first six weeks with 75 mg/m^2 following during one 29 day cycle. Gemcitabine was also given in a higher total dose with initially 7 g/m^2 in six weeks and then 3 g/m^2 during the 29-day cycle.

Whereas, the most recent randomized phase III trial in 360 patients with metastatic pancreatic cancer comparing the platinum-based therapy folfirinox with gemcitabine as firstline treatment could show a significant increase in median survival from 7 to 10 months [13].

Taken together, currently there are conflicting data regarding the impact of gemcitabine and cisplatin, whereas the data of Conroy and colleagues clearly argue for a platinum-based intensified treatment schedule. Therefore we will assess the combination of gemcitabine and cisplatin mit the “intensification”/additive effect of regional hyperthermia.

In addition after a R0/R1-resection of pancreatic cancer, most patients receiving adjuvant therapy can be attributed to the good performance group (Karnofsky performance status ≥ 80%). Given, that specifically this group of patients might benefit most from gemcitabine combined chemotherapy [14] or a more aggressive regimen (FOLFIRINOX) [13], we hypothesize that the efficacy of adjuvant treatment can further be improved by the addition of cisplatin and hyperthermia to the present standard of gemcitabine.

1.3.3 Chemotherapy in combination with regional hyperthermia

Regional hyperthermia is a therapeutic procedure used to raise the temperature of a region of the body affected by cancer and it is administered together with other cancer modalities such as systemic chemotherapy [15]. Today the quality assurance guidelines for regional hyperthermia in combination with chemotherapeutics or radiotherapy have been defined under the guidance of the European Society of Hyperthermic Oncology (ESHO) [16]. The temperature increase is achieved applying electromagnetic waves in a power-density specific absorption rate (SAR). Regional hyperthermia of deep-seated upper-abdominal tumor areas after surgical resection - as planned in the HEAT study protocol - requires exact treatment planning of the heating field and quality assurance for the applicator position.

Based upon preclinical and clinical studies several mechanisms suggest synergism between cytostatic drugs and hyperthermia in malignant tumor cells [17]. These include stronger inflow of the cytostatic drug, thermal enhancement of cytotoxicity of chemotherapeutics, inhibition of repair of drug-induced damage and almost selective destruction of tumor cells in hypoxic areas. It is generally accepted that platinum compounds and most alkylating agents (i.e. ifosfamide) are linearly enhanced in their cytotoxic effect if temperatures are raised from 37℃ to over 40℃ [18]. For gemcitabine it has been shown in vitro and in vivo that the treatment with gemcitabine

20 to 48 hours before hyperthermia results in potentiation of the cytotoxic effect of the drug, whereas its application simultaneously with hyperthermia reduces gemcitabine-induced cytotoxicity [19, 20]. In contrast, platin compounds exhibit maximal efficacy if applied during hyperthermia treatment. As far as the underlying effect is understood, it is a combination of drug accumulation, enhanced DNA adduct formation and reduced DNA repair [21]. Applying heat and cisplatin, even a re-sensitization of formerly cisplatin resistant cells can be achieved [22]. Heat could theoretically enhance both the cytotoxic and oncogenic potential of the drugs. The examination of transformation incidences showed that for a given level of cell killing the combination of heat and e.g. cisplatin resulted in fewer transformants per surviving cell than for cisplatin alone [23].

Besides experimental data on the synergistic effects of gemcitabine and cisplatin under heat conditions two phase II clinical trial comparing cisplatin (50 mg/m²) and regional hyperthermia in patients with recurrent cervical cancer have been performed. The results of both trials showed high efficacy (objective response rates > 50%) but also the proof of feasibility and low toxicity (no grade 3/4 renal toxicity) for this regimen [24, 25].

We analysed data of 84 patients who received up to eight biweekly cycles of gemcitabine (1000 mg/m²) on day 1 followed by cisplatin (25 mg/m²) simultaneously with regional hyperthermia on day 2 and day 4. In this retrospective data analysis there was no grade 4 hematological toxicity besides two patients with a thrombocytopenia below 25 G/l during one cycle. Nine out of 84 patients showed once a maximum of a grade 3 leucopenia (>1-2 G/l). Altogether, even though this is a small patient group with retrospective data, there was no hint for an additional hematological toxicity caused by the addition of hyperthermia.
The hyperthermia associated toxicity mainly consisted of discomfort (22 out of 84 patients) and position-related pain (54 out of 84 patients) associated with lying on the treatment bed for 90 minutes with the water filled silicon cushion placed around the abdomen of the patient. This was manageable in any case with either repositioning of the patient or singular administration of pain reliever. A power-related pain occurred solely during the first hyperthermia treatment in 40 patients and dissolved completely after power-reduction. Dermal burn grade 1 occurred in only one patient once during first treatment, as the patient suffered hypoesthesia post surgery.

In a subgroup of patients, who received thermochemotherapy after gemcitabine-mono failure (23 patients), time to progression was 4.3 months (95% CI 1.2; 7.4) with an overall survival of 12.9 months (95% CI 9.9; 15.9). This compares very well with published clinical trials on secondline treatment of patients after gemcitabine failure [26-29].

Most recently we completed a large randomized EORTC/ESHO multicenter intergroup phase III trial evaluating the impact of hyperthermia if combined with chemotherapy in patients with locally advanced, high-risk soft tissue sarcomas. Intention-to-treat analysis of 341 randomized patients showed a significantly superior local disease-free survival (31,7 months versus 16,2 months; p<0,01) for patients who received chemotherapy *and* hyperthermia. Median disease-free survival and objective response rate were also significantly increased [30, 31]. Most important the subgroup of patients receiving the thermochemotherapy after abdominal surgery did not show any increased toxicity or post-surgery complication [30].

Based upon these data and current recommendations for chemotherapy after gemcitabine failure [32] a phase II clinical trial has been initiated using gemcitabine and cisplatin with regional hyperthermia as secondline treatment in firstline gemcitabine-resistant or –refractory patients (EudraCT Number 2005-003855-11; [33]).

2. STUDY RATIONALE

The only curative option for patients suffering pancreatic cancer is surgery. At least 80% of patients relapse after R0/R1 resection and die of pancreatic cancer [34], emphasizing the need of an adjuvant therapy. Although numerous trials have been conducted so far, there is not yet a general consensus on the most effective regimen. Data on the use of systemic 5-FU with or without radiation are conflicting [35, 36, 3]. The superiority of gemcitabine in the palliative setting prompted the RTOG-9704 trial evaluating the benefit of adjuvant gemcitabine [5]. The results confirmed the advantage of gemcitabine versus 5-FU with no conclusive data on the impact of radiation.
The CONKO-1 trial compared adjuvant gemcitabine versus best supportive care and could show the great tolerability of gemcitabine. Though there was significant increase in disease free survival, the advantage in overall survival was not significant [1]. Though the recently published ESPAC-3 trial could not confirm the advantage of gemcitabine against 5-FU, patients had less adverse events if treated with gemcitabine [4].

As shown most recently at the ASCO meeting this year for firstline treatment of pancreatic cancer, prolonged disease free survival and improved overall survival might be achievable using an intensified combination therapy containing platinum [13].

Adjuvant treatment should be offered to all curatively resected patients. Whereas there are no conclusive data regarding radiation, gemcitabine, platin and 5-FU are the most active chemotherapeutics. In our study we expect an additive effect using gemcitabine, cisplatin and hyperthermia, focused on the pancreatic tumor bed, with no additional *systemic* toxicity.

The present trial is performed in order to confirm the hypothesis that gemcitabine and cisplatin combined with regional hyperthermia (GPH) for pancreatic cancer patients is superior to gemcitabine alone (G) as current standard therapy.

3. OBJECTIVES OF THE STUDY

3.1 PRIMARY OBJECTIVE

- Comparison of disease free survival (DSF) in both treatment arms (GPH and G)

3.2 SECONDARY OBJECTIVES

Comparison of the both treatment arms with regard to

- overall survival (OS)
- subgroup analysis (DFS/OS)
- quality of life
- toxicity profile
- use of CA19-9 for monitoring tumor recurrence
- prespecified analysis using hsp27 as predictive factor

4. STUDY DESIGN

- This is a randomized, parallel-group, open-label, phase III study that will be conducted in 14 surgical departments and 9 regional hyperthermia centers.
- Patients eligible for participation in this study will have a diagnosis of pancreatic adenocarcinoma and a previous R0 or R1 resection with no tumor manifestation after surgery confirmed by CT or MRT.
- Study accrual is expected to take about 36 months and it is planned to randomize 366 patients (183 patients for each treatment arm).
- Randomization will be performed 4 to 8 weeks after tumor resection
- Six 4-week treatment courses will be administered to all patients unless treatment has to be stopped due to recurrence of pancreatic cancer (local recurrence or distant metastases), unacceptable toxicity, patient's wish or other conditions under which continuation of treatment would not be in the best interest of the patient according to the investigator's opinion.
- Patients will be followed for 24 months after randomization of the last patient.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

1. any ductal adenocarcinoma of the pancreas confirmed by histology
2. previous R0 or R1 resection of pancreatic tumor with surgery according to the standard operating procedure (see Appendix 19.1)
3. willingness to participate in translational research program
4. no other previous or concomitant treatment of pancreatic cancer like irradiation, chemotherapy, any neoadjuvant therapy or immunotherapy
5. no manifestation of pancreatic cancer detectable by CT or MRT after surgery
6. postoperative tumor marker (CEA/CA19-9) $\leq$ 2.5 x upper limit of normal (ULN) to be documented within 1 week prior to randomization
7. performance status ECOG 0-2
8. adequate bone marrow function defined as
   - leucocytes $\geq 3.5 \times 10^9$/L and
   - thrombocytes $\geq 150 \times 10^9$/L and
   - hemoglobin $\geq$ 9 g/dl
   documented within 1 week prior to randomization
9. adequate renal function defined as
   - serum creatinine $\leq$ 1.2 mg/dl and
   - calculated GFR $\geq$ 60 ml/min
   documented within 1 week prior to randomization
10. adequate coagulatory function defined as
    - Quick-value $\geq$ 70% and
    - aPTT $\leq$ 1.5 x ULN
    documented within 1 week prior to randomization
11. transaminases (AST and ALT) $\leq$ 3 x ULN and bilirubin $\leq$ 2 x ULN documented within 1 week prior to randomization
12. at least 18 years of age
13. women with childbearing potential and fertile men must use adequate contraceptive measures during and for at least 3 months after completion of study therapy

(Adequate methods for women are oral contraceptives with estrogen and progesterone, vaginal rings, contraceptive patches, estrogen-free ovulation inhibitors, intrauterine devices with progesterone, 3-month injections with depot progesterone, implants setting free progesterone, abstinence or sterilization (vasectomy) of the male partner. Men must use condoms.)

14. women with childbearing potential must have a negative pregnancy test within 1 week prior to randomization (postmenopausal women with amenorrhea for more than 1 year are regarded as having no childbearing potential)
15. written informed consent

5.2 EXCLUSION CRITERIA

1. cystic carcinoma of the pancreas
2. periampullary cancer
3. presence of an active infection grade 3 or higher
4. other severe disease which could impair the patient's ability to participate in the study according to the investigator's opinion
5. pregnant or breastfeeding women
6. known allergies or contraindications with regard to substances or procedures of study therapy
7. severe, non-healing wounds, ulcers or bone fractures
8. participation in another clinical trial during this study or within 4 weeks prior to randomization
9. past or current abuse of illegal or legal drugs or alcohol
10. other primary malignant diseases in the medical history during the last 5 years (exceptions: carcinoma in situ of the cervix or adequately treated basal cell carcinoma of the skin).
11. permanent cardiac pacemaker
12. gross adiposity defined as BMI > 40 kg/m²
13. treatment with regional hyperthermia not possible for technical reasons (e.g. metal implant)

5.3 NUMBER OF PATIENTS

It is planned to randomize 366 patients, 183 per treatment arm.

6. OUTLINE OF THE STUDY

6.1 SCREENING PERIOD

The screening period is the time preceding randomization and includes staging, surgery, and assessment of eligibility. Patients can also be eligible for the trial after R0/R1 resection. In this case, the "screening data" are documented retrospectively. The informed consent will be signed after surgery, before randomization.

Patients will be informed about the study, both verbally and by reviewing the patient information sheet and consent form. The patient must be given the opportunity to ask questions and given time to consider his participation. The investigator and the patient will both sign and personally date the consent form (see: Appendix 19.4) as confirmation of consent.

The following procedures and assessments will be completed during the screening period (see Table 1):

Prior to surgical resection of pancreatic tumor:

- Signed informed consent
- Medical history
- Physical examination including vital signs, height, weight, and ECOG performance status to confirm operability
- Laboratory 1: erythrocytes, haemoglobin, leucocytes, neutrophils, platelets, serum creatinine, creatinine clearance, urea, electrolytes (sodium, potassium, calcium, magnesium), ALT, AST, alkaline phosphatase, total bilirubin, total protein, Quick, aPTT, and (only in women with childbearing potential) pregnancy test.
- Tumor marker (CEA, CA19-9)
- Abdominal CT or MRT to document extent of disease (method chosen for screening has to be used continuously). Evaluation has to be done within 4 weeks before randomization. Documentation on CD-Rom has to be done at coordinating investigators disposal.
- Chest-X-ray to confirm operability and to exclude pulmonary metastases, only if clinical indicated. Evaluation has to be done within 4 weeks before randomization.
- Other investigations to exclude tumor manifestations if they are clinically indicated
- ECG to confirm operability

Surgical resection of pancreatic tumor:

Surgical resection of the tumor and histological examination of the resected material will be performed according to standardized procedures (see: Appendix 19.1 SOP Surgery (German Version)). It should be noted that randomization must be performed within 4 to 8 weeks after surgery. Shipping of primary tumor tissue to the Medical Clinic III, Ludwig-Maximilans-University, Munich. Phone +49-89-7095-4768 (see: Appendix 19.4).

Within one week prior to randomization:

- Documentation of concomitant medication to document baseline status
- Physical examination including vital signs, weight, and ECOG performance status to confirm eligibility
- Laboratory 1 (see Table 1) to confirm eligibility Tumor marker (CEA, CA19-9)
- 10 ml serum and 30 ml heparinized blood for translational research program
- Abdominal CT or MRT. Documentation on CD-Rom has to be done at coordinating investigators disposal.
- X-ray abdomen only if there is no CT-scan, to exclude metal implants
- Chest-CT*
- Other investigations*
- ECG
- Echocardiography to document baseline status

* These investigations will only be performed if tumor manifestations are suspected and if the investigations are clinically indicated.

6.2 STUDY ENTRY - RANDOMIZATION

All inclusion/exclusion criteria must be checked prior to randomization. As soon as patient eligibility is verified the patient is randomized. Randomization stratified by N+/-, R0/R1 and T stage to the treatment groups in the ratio of 1:1 will be performed by the Institute of Medical

Informatics, Biometry, and Epidemiology (IBE) at the University of Munich. The IBE will conduct the randomization using an internet-based tool (Randoulette). This application enables the investigators to randomize their patient in a secure way. Randoulette works according to GCP and a special SOP is available at IBE.

The randomization is the reference point of the trial. Trial treatment (first administration of gemcitabine or gemcitabine+cisplatin with the addition of regional hyperthermia) should be started within four to eight weeks after randomization. In any case, all events occurring after randomization must be recorded in the CRF and will be taken into account in the analysis, whether the patient received the trial treatment or not.

Patients who comply with all selection criteria and who have given written informed consent will be given a patient number. The patient number is the identifier of the subject throughout the study. It must be reported on all CRF pages and in any study document.

6.3 EVALUATION DURING THE TREATMENT PERIOD

The treatment period starts with the day of randomization and continues until 30 days after the last study treatment administration.

The following assessments need to be completed throughout the treatment period (see Table 1):

- Physical examination at the beginning (day 1) of each course (This examination includes weight, vital signs, performance status, any changes in ongoing symptoms, and new symptoms. It may be omitted on day 1 of the first course if treatment is started within one week after randomization.)
- Laboratory 2 (see Table 1) at the beginning (day 1) of each course (It may be omitted on day 1 of the first course if treatment is started within one week after randomization.)
- 10 ml serum and 30 ml heparinized blood for translational research program
- Concomitant medication must be recorded
- EORTC QLQ-C30 at day 1 and 15 of every course
- All adverse events which occurred during the treatment period must be assessed and documented.

For patients in Arm GPH:

- Audiogram at the beginning and at the end of study (except in case of pathological findings)

After course 2, 4 and 6 or if disease recurrence is suspected the following assessments must be performed:

- CEA, CA19-9 has to be taken before chemotherapy and following every 4 weeks (always before application of chemotherapy)
- Abdominal CT or MRT* Documentation on CD-Rom has to be done at coordinating investigators disposal.
- Other investigations (i.e. including chest CT)*

* These investigations will only be performed if tumor manifestations are suspected and if the investigations are clinically indicated.

6.4 END OF STUDY

Six treatment courses will be administered unless one of the following occurs:

- disease recurrence,
- unacceptable toxicity,
- patient's wish,
- other conditions under which continuation of treatment is not in the patient's best interest according to the investigator's opinion.

A final evaluation has to be performed within 30 days after the patient's discontinuation of study treatment and includes the following assessments (see Table 1):

- Physical examination (This examination includes weight, vital signs, performance status, any changes in ongoing symptoms, and new symptoms.)
- All adverse events which occurred during the treatment period must be assessed and documented
- Concomitant medication must be recorded
- EORTC QLQ-C30
- Laboratory 2 (see Table 1)
- 10 ml serum and 30 ml heparinized blood for translational research program
- CEA, CA19-9
- **Audiogram in patients in Arm GPH**
- ECG
- Echocardiography
- Abdominal CT or MRT*. Documentation on CD-Rom has to be done at coordinating investigators disposal
- Chest-CT
- Other investigations*

* These investigations will only be performed if tumor manifestations are suspected and if the investigations are clinically indicated.

6.5 PREMATURE DISCONTINUATION

6.5.1 Premature discontinuation from the study

A patient may voluntarily discontinue his or her participation in this study at any time. The investigator may also, at his or her discretion, discontinue the patient from participating in this study at any time. If a patient is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the assessments as outlined in Section "end of study". These data should be recorded, as they comprise an essential evaluation that should be done prior to discharging any patient from the study.

If a patient is prematurely discontinued from the study at any time due to an AE (as defined in section "definition of an AE") or SAE (as defined in section "definition of an SAE"), the procedures stated in section "AEs and SAEs" must be followed.

All patients who have received at least one dose of a study drug will be evaluable for safety analysis.

6.5.2 Patient withdrawal

Patients may voluntarily withdraw from the study at any time.

Patients will be withdrawn from the study for the following administrative and/or medical reasons:

- Disease recurrence = any patient who experiences disease recurrence. The patient will be withdrawn from the study and reported as patient with disease recurrence for the final evaluation.
- Patient refusal of further treatment = reason for refusal (if known) must be clearly documented in the patient's medical records.
- Patient lost to follow-up = the date of the last contact should be reported. The investigator must make every effort to determine and document the state of health of the patients lost to follow-up.
- Adverse events/toxicity = a patient may be removed from the study following a severe or life-threatening adverse experience at the discretion of the treating physician. The study monitor must be notified immediately.
- Patient compliance = any significant non-medical deviation from the protocol without prior agreement of the coordinating investigator and the sponsor.
- Investigator non-compliance = any significant medical or non-medical deviation from the protocol
- Other reason to be documented.

The primary reason for withdrawal will be clearly documented in the subject's medical record and recorded in the CRF. A final evaluation will be completed at the time of discontinuation of the study.

6.5.3 Early stopping rules

The study will be stopped if the following circumstances occur:

- Emerging adverse events are of such a serious nature that continuation of the study becomes unacceptable.
- The recruitment rate is too low to expect completion of the study in its present form within an acceptable period of time.
- Evidence from other studies answering the main study question.
- The result of an interim analysis is in favor to stop the trial.

6.5.4 Adjustment of standard treatment arm

The standard treatment arm G will be adjusted, if a new comparable standard treatment would be defined according to the German AWMF treatment guidelines. This will be subject to a substantial amendment. The GPH arm will not be changed in any case.

6.6 FOLLOW-UP PERIOD ASSESSMENTS

The follow-up period is the time from 30 days after the last study treatment administration until death. Survival information will be collected regularly (every 3 months) until death.

The following data will be recorded (see Table 1):

- Date of disease recurrence (unless disease recurrence has been documented before)
  The following examinations are performed to exclude disease recurrence:
  - Physical examination
  - CEA, CA19-9
  - Abdominal CT or MRT*
  - Other investigations*
- Survival status (date last known to be alive, if deceased, date of death)

* These investigations will only be performed if tumor manifestations are suspected and if the investigations are clinically indicated.

7. TREATMENT ADMINISTRATION

For a detailed view see **1.2** Dose regimen.

7.1 GEMCITABINE ADMINISTRATION (ARM G)

For Patients between 18 years and 64 years of age and patients ≥ 65 years of age without signs of renal impairment:
Gemcitabine will be administered as an intravenous infusion once a day at **days 1, 8 and 15** of each course followed by a 1-week pause. A dose of **1000 mg/m² per day** will be applied over a period of 30 minutes (**3000 mg/m² per course**). A course is defined as a period of 28 days.

For Patients ≥ 65 years of age with signs of renal impairment:
Similar to administration scheme above, but dose of gemcitabine will be reduced according to table 3.

Despite the described age adjustment, it is the investigator's responsibility to take into account the patient's individual clinical condition. For further details see Appendix Summary of Product Characteristics (SmPC) gemcitabine.

7.2 GEMCITABINE ADMINISTRATION (ARM GPH ONLY)

For Patients between 18 years and 64 years of age and patients ≥ 65 years of age without signs of renal impairment:
Gemcitabine will be administered as an intravenous infusion once a day at **days 1 and 15** of each course. A dose of **1000 mg/m² per day** will be applied over a period of 30 minutes (**2000 mg/m² per course**). A course is defined as a period of 28 days.

For Patients ≥ 65 years of age with signs of renal impairment:
Similar to administration scheme above, but dose of gemcitabine will be reduced according to table 3.

Despite the described age adjustment, it is the investigator's responsibility to take into account the patient's individual clinical condition. For further details see Appendix Summary of Product Characteristics (SmPC) gemcitabine.

7.3 CISPLATIN ADMINISTRATION (ARM GPH ONLY)

For Patients between 18 years and 64 years of age and patients ≥ 65 years of age without signs of renal impairment:
Cisplatin will be administered as an intravenous infusion once a days at **days 2, 4 and 16, 18** of each course. A dose of **25 mg/m² per day** will be applied over a period of 30 minutes (**100 mg/m² per course**). A course is defined as a period of 28 days. A pre- and post-hydration should be given according to manufacturer`s instructions (see: Appendix 19.9.2).

For Patients ≥ 65 years of age with signs of renal impairment:
Similar to administration scheme above, but dose of cisplatin will be reduced according to table 3.

Despite the described age adjustment, it is the investigator's responsibility to take into account the patient's individual clinical condition. For further details see Appendix Summary of Product Characteristics (SmPC) cisplatin.

7.4 REGIONAL HYPERTHERMIA (ARM GPH ONLY)

In Arm GPH regional hyperthermia will be applied once daily on days 2, 4 and 16, 18 of each course followed by a 1-week pause. A course is defined as a period of 28 days.
For a detailed procedure see Appendix SOP regional hyperthermia (English version).

7.5 DURATION OF TREATMENT

Six treatment courses will be administered unless early discontinuation in case of a recurrence of pancreatic carcinoma (local recurrence or distant metastases), unacceptable toxicity, patient's wish or other conditions under which continuation of treatment would not be in the patient`s best interest according to the investigator's opinion.

7.6 GUIDELINES FOR TREATMENT MODIFICATIONS

7.6.1 Gemcitabine and Cisplatin

The treatment schedule may be modified in case of treatment associated toxicity as described in the following tables.
Gemcitabine/Cisplatin associated toxicities will be graded according to CTCAE (see: Appendix CTCAE**, v4.0**). The following guidelines outline dose adjustments in case of toxicity. However, it is the investigator's responsibility to take into account the patient's individual clinical condition and the recommendations for use of the preparations as outlined in the SmPCs.

If administration of Gemcitabine has to be delayed, the 28-day period should be maintained with the next trial medication if possible.
Application of RHT alone is not allowed.

7.6.2 Regional Hyperthermia

In case of ulceration/infection of skin or in case of redness/edema of skin due to regional hyperthermia treatment modification has to be done according to guidelines for regional hyperthermia (see 19.2: Appendix SOP regional hyperthermia (English version)).

7.7 STEPS FOR DOSE REDUCTION:

Table 3: Treatment modifications for hematological toxicities

Leucocytes	> 3,0 G/l *(= grade 1)* 2,5-3,0 G/l *(= grade 2)* < 2,0 G/l *(= grade ≥3)*	100 % Chemotherapy 75 % Chemotherapy dose Delay treatment and reassess weekly
Platelets	100 G/l <100 G/l *(= grade ≥ 1)*	100 % Chemotherapy Delay treatment and reassess weekly
Febrile neutropenia	≥ grade 3 (ANC < 1,0 G/l and fever > 38,5℃)	• Delay treatment till patient´s complete recovery • Apply G-CSF in the following cycle • Reduce chemotherapy dose to 75% if FN occurs

Table 4: Treatment modifications for hepatic toxicities

Toxicity type	Grade	Treatment modification
AP, ALT, AST (with no sign of cholestasis)	2-3 *(= 2.5-20 X ULN)*	• Delay treatment for up to 2 weeks and reassess in weekly intervals • If recovered (grade < 2) within 2 weeks: continue treatment as planned • If there is no improvement: discuss individually treatment procedure
AP, ALT, AST (with no sign of cholestasis)	4 *(> 20 X ULN)*	Terminate trial
Bilirubin (with no sign of cholestasis)	2-3 *(= 1,5-10 X ULN)*	• Delay treatment for up to 2 weeks and reassess in weekly intervals • If recovered (grade < 2) within 1 week: continue treatment as planned • If not recovered after 2 weeks: discuss individually stent implantation/dose reduction to 75%
Bilirubin (with no sign of cholestasis)	4 *(> 10 X ULN)*	Terminate trial

Table 5: Treatment modifications for renal toxicities

Toxicity type	Grade	Treatment modification
Determine creatinine clearance in case of borderline creatinine values	1 **or** GFR 40-60ml/min	• Delay treatment for up to 2 weeks and reassess in weekly intervals • Cisplatin: Individual decision: cisplatin may be reduced dose to 50% with monitoring of renal function • Gemcitabine: dose reduction depends on individual tolerance
	>1 **or** GFR< 40ml/min	Terminate trial

If a dose reduction is required the following applications are given with the same reduced dose. Increase of dosage is only allowed in the following cycle if any toxicity is resolved.

Table 6: Treatment modifications for other non-haematological toxicities

Toxicity type	Grade	Treatment modification
Neuropathy	2 *(= sens. alteration or paresthesia not interfering with ADL- activity of daily life)*	Individual decision: dose reduction of cisplatin to 50 to 75% If after 2 cycles of reduction no improvement occurs, treatment will be discontinued
Neuropathy	≥ 3 *(= sens. alteration or paresthesia interfering with ADL)*	Terminate trial
Hearing	≥ 2 *(= threshold shift or loss of ≥ 25 dB)*	Terminate trial
Other major organ toxicity (excluding nausea/vomiting and any toxicity that is related to other causes than treatment, e.g. caused by tumor and/or concomitant diseases)	≥ 3	• Delay treatment for up to 2 weeks and reassess in weekly intervals • If recovered (grade < 2) within 2 weeks: continue treatment as planned • If not recovered after 2 weeks: terminate trial

8. CONCOMITANT MEDICATIONS

Before start of treatment it is the investigator's responsibility to assess patient's current therapies and to inform the patient about any other putative contraindication, warnings or possible drug-trial treatment interactions as indicated in the SmPCs of gemcitabine and cisplatin (see Appendices for details).

Systematic antiemetic treatment is strongly recommended for all patients. Preventive medication with i.v. neurokinine-1 receptor antagonist (i.e. aprepitant) in combination with 5-HT_3 antagonist is recommended.
All treatments given in addition to the study treatment at study entry (within one week before randomization) or at any time during the trial are considered as concomitant treatments and **must be reported in the Case Report Form (CRF)**.

8.1 SUPPORTIVE CARE

Patients should receive full supportive care including antibiotics, antidiarrheals, analgesics, transfusion of blood products, when appropriate.

8.2 HAEMATOPOIETIC GROWTH FACTORS

The **prophylactic use** of Granulocytic Colony Stimulating Factor (G-CSF) is not allowed prior to the first administration of study medication. Growth factors may be given to patients who experience hematological toxicity according to institutional rules. The use of G-CSF should be correctly documented in patient's medical file and in the CRF.

8.3 USE OF OPIATES

Patients receiving opiates must receive preventive treatment for constipation and should be followed carefully (to be reported in the CRF).

8.4 OTHER ANTI-NEOPLASTIC AGENTS

Treatment with other anti-neoplastic agents is not allowed and will result in patient's withdrawal.

9. MEASUREMENTS AND EVALUATION

9.1 EFFICACY ASSESSMENT

The observation starts at the date of randomization. Additionally, date of recurrence and / or date of death will be used to assess efficacy. For further details see chapter 12.

9.2 QUALITY OF LIFE

The EORTC QLQ-C30 will be used to assess quality of life.

9.3 SAFETY ASSESSMENT

Adverse events as reported by the patients or detected during the physical examination or on the basis of laboratory tests, ECG, echocardiography, audiogram, or any other investigations. This will be used to assess safety.

9.4 TRANSLATIONAL RESEARCH PROGRAM

The translational program will be coordinated by the Clinical Cooperation Group Hyperthermia (Head: Prof. R. D. Issels, Medical Clinic III and Helmholtz Zentrum münchen-HGF).
The program implies the following 6 different topics and cooperating institutions:

1) Prof. Dr. Th. Kirchner (Head of the Pathological Institute of the LMU Munich): Histopathomorphological analysis of paraffin-embedded tissue
2) Prof. Dr. Ch. Bruns (Department of surgery and Head of the laboratory for neoangiogenesis): Analysis of neoangiogenetic targets in patient´s whole blood samples before and during study treatment.
3) PD Dr. E. Noessner (Institute of Molecular Immunology, HGF) and Dr. K. Lechner (Medical Clinic III):
    - Analysis of stress response markers before and during study treatment in whole blood samples and paraffin-embedded tissue.
    - Characterzation of tumor microenvironment using paraffin-embedded tissue and its correlation with clinical outcome
4) Prof. V. Heinemann (Medical Clinic III): Pharmacodynamic studies using expression analysis of targets such as hENT1, hCNT3, ... as far as gemcitabine is concerned and ERCC1 and XPD regarding cisplatin.
5) Dr. E. Gallmaier (Medical Clinic II): The prognostic role of hsp27 expression and its predictive potential for hyperthermia induced chemotherapy sensibilization.
6) Roche Diagnostics: Gene expression profiling using i.e. the RAS RT-PCR-Panel.

With signing the informed consent form and entering the clinical trial, each patient agrees to the 10 ml serum and 30 ml whole blood drawn for the translational program as indicated in table 1 and the scientific use of remaining primary and paraffin-embedded tissue. This program does not require an additional visit of the patient.

10. RELAPSE STRATEGY

For patients with disease progression after adjuvant gemcitabine based therapy of the HEAT protocol several salvage or second-line treatment protocols can be offered.
For further information on relapse strategy please contact the HEAT study coordinator or trial office: Phone: +49-89-7095-4768 / -4769

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 ADVERSE EVENTS (AE)

11.1.1 Definition of an AE

Not any expected, known and common side effect of therapy has to be documented as adverse event. Expected side effects have to be documented on the corresponding page of the treatment cycle of the CRF, but not as AE. This includes: nausea, vomiting, pancytopenia up to grade 1 (for dose reduction please see chapter 7.7) and all other toxicities ≤ grade 1 as described in CTCAE v4.0 (see: Appendix 19.8).
An adverse event is any adverse change from the patient's baseline condition, i.e. any subjective signs and symptoms, or worsening of a concomitant disease present at baseline, that is not expected. This includes intercurrent signs, symptoms, illness and significant deviations from baseline laboratory values, which may occur during the course of the clinical trial, whether considered related to treatment or not.
All laboratory tests for which abnormal results are collected after trial treatment initiation should be repeated until the values return to normal or to stable status. Abnormal results are defined as those falling out of the laboratory normal range with clinical significance. The frequency with which such checks should be made will be defined at the investigator's opinion depending on the degree of abnormality.
In all cases, the etiology should, as far as possible, be identified and the sponsor notified.
Patients are asked to specifically describe any adverse event (regardless of relationship to drug) that they have noticed.

11.1.2 Grading of adverse events

The severity of adverse events should be determined using CTCAE (see: Appendix 19.8).

11.1.3 Reporting of Adverse Events

Any adverse or intercurrent event occurring during the trial period, spontaneously reported by the patient or observed by others, will be recorded in the Case Report Form (CRF). The records will describe the nature (diagnosis, signs and symptoms), severity, date/time of onset, date/time of end, outcome and actions taken, and relationship to trial treatment (according to the investigator's opinion).
It will be specified whether the event is serious or not.
Adverse events already recorded and designated as "continuing", should be reviewed at each subsequent assessment. If resolved, the details in the CRF are to be completed. If any adverse event changes to the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e. distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

11.2 SERIOUS ADVERSE EVENTS (SAE)

11.2.1 Definition of a SAE

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- results in death (whatever the cause)
- is life-threatening
- results in persistent or significant disability/incapacity
- requires patient hospitalization or prolongation of existing hospitalization
- is a congenital abnormality or birth defect
- other events such as cancer, over dosage, and any additional adverse experience or abnormal laboratory values occurring during the trial period which the investigator considers significant enough or that suggest a significant hazard, contraindication, side effect or precaution will be handled as a serious adverse event.

All deaths occurring while the patient is on trial including deaths due to disease progression and deaths within 30 days after last administration of trial drug should be notified as SAE.

Unexpected adverse event is defined as:
An experience not previously reported (in nature, severity or incidence) in the SmPCs of gemcitabine and cisplatin, the protocol or elsewhere (Good Clinical Practice for trials on medicinal products in the European Community - 1990).

11.2.2 Reporting of SAE

All serious adverse events, according to the above-mentioned definitions, regardless of its relationship to trial drug, must be recorded by the investigator as soon as he/she is informed of the event.

The investigator must notify the CRO by sending within 24 hours the “Notification of serious adverse event” form with all the available information concerning the event to the CRO:

ClinAssess GmbH, Birkenbergstr. 82, 51379 Leverkusen, Fax: 02171/ 36 336 55

11.2.3 Follow-up of SAE/AE

All adverse events should be medically well documented and the information should be reported as described above as soon as possible.
In all cases, the investigator must ensure the patient receives medical follow-up as necessary until the condition has stabilized or returned to normal state, even if the period of the trial is over.
The investigator should be able to supply copies of all relevant results of examination/treatments, etc., relating to such medical follow-up of the AE.

11.2.4 SAE occurring after the trial

Any SAE occurring during the **30 days following last trial drug administration** for the subject should be notified as described above to the CRO.
The investigator should be able to supply copies of all relevant results of examination/treatments, etc., relating to such medical follow-up of the SAE.
Any event occurring at any time after the end of the trial for the subject that may be related to the trial treatment according to the investigator’s opinion should be reported as described above to the CRO.

12. STATISTICAL ANALYSIS

12.1 POPULATIONS ANALYSED

The classification of individual patients to each of the trial populations will be performed before closure of the data base in a patient review meeting.

12.1.1 Intent-to-treat analysis

All randomized patients having received at least one dose of trial medication will be analysed unless the patient was lost to follow-up immediately after the start of treatment (no follow-up visit, in particular no information about adverse events). Randomized patients who are excluded from the intent-to-treat (ITT) analysis will be described individually.

12.1.2 Per-protocol analysis

Subsets of the ITT-analysis may be analysed after exclusion of patients with relevant deviations from the trial protocol. Whether one or several per-protocol (PP) analyses will be performed or not, will be outlined in a statistical analysis plan (SAP). If a PP-analysis is performed, the criteria for the exclusion of patients from the PP-analysis will also be documented in the SAP.

12.1.3 Safety analysis set

Each patient who received one dose of trial treatment will belong to the safety analysis set.

12.2 DEFINITIONS

Disease-free survival (DFS)

DFS is measured from the day of randomization until date of disease recurrence or death, whichever occurs first. If neither recurrence nor death has been observed (no event), then the patient will be censored at the date of the patient's last follow-up examination without disease recurrence. Disease recurrence should be suspected when a patient complains of pain, anorexia, nausea, vomiting, jaundice, weight loss, or other symptoms that might indicate disease recurrence, if tumor markers increase or if physical examination or abdominal ultrasound indicates disease recurrence. Disease recurrence must be confirmed by appropriate imaging procedures. Ascites as such is not by definition a sign of peritoneal metastases unless malignant cells have been detected in the peritoneal fluid. An isolated increase in serum levels of CA19-9 cannot be considered as a proof of recurrence.

Survival time (OS)

The OS comprises the time from the day of randomization until death. Patients who are alive or lost to follow-up will be censored with the last date they were known to be alive.

12.3 STATISTICAL ANALYSIS

Details of the statistical analyses will be outlined in a statistical analysis plan (SAP) prior to performing the analyses. The SAP must be authorized by the coordinating investigator. The database will be closed when all outstanding issues concerning the data have been resolved. The main features of the intended statistical analyses are:

Descriptive analyses

Standard descriptive methods will be used to present all relevant data.

Continuous data will be summarized with the following items: median, quartiles, range and mean and standard deviation if relevant.
Categorical data will be presented in contingency tables with frequencies and percentages of each modalities (including missing data modality).

Baseline characteristics

All baseline data will be tabulated overall and sorted by both treatment groups for the patients in the respective analysis set:

- Demographic data
- Characteristics of the disease at diagnosis
- Characteristics of the disease at inclusion
- Clinical and hematological parameters

Efficacy:

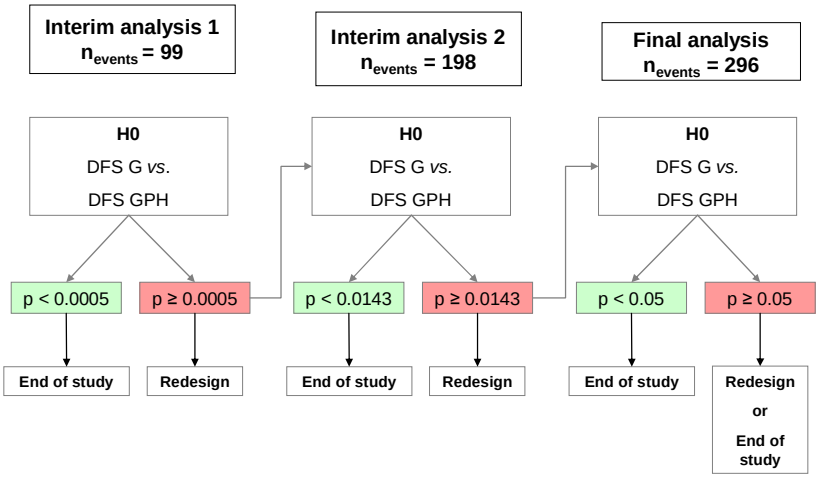
Primary efficacy criterion:

We test the following null-hypothesis (H0):

DFS under treatment group 1 (G) == to DFS under treatment group 2 (GPH)

In order to test this null hypothesis a stratified Cox proportional hazards model is used to trial the differential effect between the treatment group 2 (GPH) and treatment group 1 (G) with respect to DFS. The proportional hazards model will be stratified by the nodal status N+/-, R0/R1, and T stage. Each trial center will be represented by a frailty effect. The p-value for the treatment effect will be calculated by a likelihood ratio test between this model and a model which is reduced by the treatment covariate. The analysis is performed on all randomized patients (ITT).

We use a group-sequential design according to O'Brien and Fleming with a maximum of three stages. Therefore, two interim analyses and one final analysis are planned as displayed below.



Secondary efficacy criterion:
For overall survival (OS) we follow the same procedures as described for the primary endpoint DFS.

Sensitivity analyses:
Sensitivity analyses are performed to trial the stability of the efficacy finding (adjustment for relevant prognostic factors, per-protocol analysis, and further exploratory analyses, if applicable). Details of the analyses will be provided in a statistical analysis plan (SAP) which is written prior to each analysis.

Safety: The incidences of adverse events in the treatment arms will be presented by type and severity.

12.4 SAMPLE SIZE

As outlined above the following null-hypothesis with regard to the primary endpoint will be tested:

DFS under treatment group 1 (G) == to DFS under treatment group 2 (GPH)

The trial design is as follows. We use the group sequential design according to O'Brien and Fleming with two arms and a maximum of three stages. We calculated the critical values and test characteristics for this design using the formula of Schoenfeld according to the sample size calculation software 'ADDPLAN' (version 4.2).

For sample size calculation we use the following assumptions:

Median DFS with treatment group 1 (G): 13.86294 months ($\lambda_G = 0.05$)
Median DFS with treatment group 2 (GPH): 19.25409 months ($\lambda_{GPH} = 0.036$)

For specified alpha = 0.05, hazards $\lambda_G = 0.05$, $\lambda_{GPH} = 0.036$ (hazard ratio = 0.72) and power of 80.0% the design would require a maximum of 366 patients to be recruited. Hence, a total number of 183 patients per arm is recruited. Interim analyses are planned after occurring of 99, 198 and 296 events on the following significance levels: interim analysis 1 α_1=0.0005, interim analysis 2 α_2=0.0143, and final analysis α_3=0.05. The patients will be randomized equally into the two treatment groups, i.e. the allocation ratio equals to one leading to 183 patients per arm. A recruitment rate of 122 patients per year is seen as a realistic upper bound for the recruitment capacities. Patients will be recruited during three years and will be followed another two years. Therefore, the duration of the trial is expected to be maximum five years.

The trial will be stopped if a statistically significant difference between treatment group 2 (GPH) and treatment group 1 (G) is established at any of the two interim analysis.

It should be annotated that it is possible to redesign the group sequential design based on the procedure of Müller and Schäfer at any time during the course of the trial [37]. This option will be considered in the case of divergent results between the parameters used for calculating the sample size and the observed parameters when the trail will run. If necessary, any redesign will be laid down in an amendment of this trial protocol.

In case of a change in the baseline therapy, a new strata will be opened: Study under initial standard, study under new standard.

13. STUDY MONITORING AND DATA COLLECTION

13.1 CASE REPORT FORM

All data obtained in the study described in this protocol will be recorded on CRFs. The CRF for each subject will be presented in a folder. The CRF will be completed chronologically and updated regularly in order to reflect the most recent data on the patient included in the study.
Prior to the start of the study, the investigator will complete a form, showing the signatures and initials of all those who are authorized to make or change entries on the CRFs.
Each CRF must be neatly filled in with a black-inked pen. For each page on which information is entered, the subject number must be recorded. The Randomization Form, the Case Report Form, the Follow-up Forms and the SAE Forms must be dated and signed by an authorized investigator.
Errors must be corrected by drawing a single line through the incorrect entry and by writing the new value as close as possible to the original. The correction must then be initiated and dated by an authorized person.
Although subjects may be interviewed by a research nurse or a trained equivalent (e.g. medical student, physician's assistant), the investigator must verify that all data entries are accurate and correct, including verification that the subject fulfils the criteria for entrance into the study before study medication is dispensed. Physical examinations have to be performed by a registered medical practitioner.
The End of Treatment Form must be completed for each patient either finishing the study or dropping out of it.
The investigator will add to the subject trial file, after completion of the study, any relevant post-trial information brought to his attention.
The data may have to be used to support efficacy and/or safety claims, and therefore may have to be submitted for inspection to Health Authorities. If the investigator moves, the subject files will be kept in the hospital archives.

13.2 SOURCE DOCUMENTS

Definition:
Source Data: all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source Documents: original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
The patient must have consented to their medical records being viewed by medical personnel and by local and possibly foreign regulatory authorities. This information is included in the informed consent.

13.3 TRIAL MONITORING

A qualified monitor will be appointed by the sponsor to monitor this study and periodically contact the sites, including conducting on-site visits.

Monitor activities will include:

- Site initiation to collect and distribute essential pre-study documents; to instruct the investigator and site personnel about the protocol, study procedures and expectations; to obtain investigator's assurance to comply with study requirements and GCP guidelines and to inform the investigator and appropriate study staff about study materials.
- Monitoring visits: according to Good Clinical Practices, the study monitors involved in the present study are fully instructed concerning confidentiality and able to perform any necessary control on informed consent and CRFs, including cross-checking clinical and laboratory data with the patient's file. All observations and findings should be verifiable. During monitoring visits, they will:
  - check and assess the progress of the study;
  - review study data collected;
  - conduct Source Document Verification (hospital files);
  - identify any issue and address its resolution;

This will be done in order to verify that the:

- data are authentic, accurate, and complete;
- safety and rights of subjects are being protected;
- study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Termination visit: at study closure.

14. DATA MANAGEMENT

The processes of data management will be performed at the IBE (LMU, Munich).

14.1 DATA ENTRY

The trial data will be performed and the entries will be compared in order to identify and resolve any data entry errors.

14.2 DATA REVIEW

Consistency checks will be performed on the data. The resulting edit queries will be transmitted to the monitoring team. Answers to these queries will be integrated into the database.

14.3 DATA FREEZING

After corrections and modifications will have been performed, the database will be locked.
The data will be extracted from the database into the data files for statistical analysis.

15. ETHICAL CONSIDERATIONS

15.1 ETHICAL CONDITIONS

This trial will be performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline.

15.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL ARRANGEMENTS

All the documents required by the national law and any other informative documents that may be requested will be submitted for review to an independent Ethics Committee whose procedures and operations meet the national legal requirements.
Selection of the patients will not start before approval of the Ethics Committee has been obtained.

15.3 PATIENT INFORMATION AND CONSENT

An information must be given to the patients themselves providing the common features of the research. Restraints and risks must be explained, as well as the right to refuse or discontinue participation in the trial at any stage, without further affecting the relationship to the investigator and/or their future care.
These written information and consent form will be submitted to the patient with an orally explanation before the patient enters the trial and it will be agreed and signed by the patient and the responsible investigator.

16. CONFIDENTIALITY

All information from this study (excluding data from informed consent) will be entered into a computer in accordance with the German law (Datenschutzgesetz BGBl. I Nr. 1999/165).

16.1 DATA PROTECTION

Clinical and demographic data about trial patients is always submitted and stored in a pseudonymized manner.
Each trial patient is identified by a pseudonym. The pseudonym is called the patient number or patient identificator. The pseudonym is a combination of the recruiting site code and a consecutive number starting at 1 for the first patient at each site. The format of the pseudonym is xxx-yyy containing the site code xxx and the consecutive number yyy.
The identifying personal information about a patient is retained at the recruiting medical site. Only the local medical or administrative staff at a site is able to reveal a pseudonym. In accordance to the guidelines of the national ethics committees initials are considered as personal information, are never transmitted and remain at the medical site.

17. ADMINISTRATIVE CONSIDERATIONS

17.1 PROTOCOL AMENDMENT

All changes to the protocol will be subject to an amendment which must be dated and signed by the Coordinating Investigator and must appear as an addendum to the protocol.

Depending on the importance of the change in the conditions of the trial, the amendment will be sent to the Ethics Committee for prior approval or for information.

17.2 SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

All trial-related documents must be kept by the investigator in appropriate file folders. Records of subjects, original informed consents forms, source documents, case report forms, and Ethics Committee correspondence to the trial must be kept on file.
The investigator authorizes direct access to source documents for monitoring, audits and inspections.
GCP-V requires these documents to be retained at the investigator's site for at least 10 years after the completion or discontinuation of the trial.

17.3 TRIAL TERMINATION

The trial will be stopped if the following circumstances occur:

- emerging adverse drug events are of such a serious nature that continuation of the trial becomes unacceptable,
- recruitment rate is too low to except completion of the trial in its present form within the period foreseen for inclusions.
-

17.4 AUDIT/INSPECTION

The main investigator at the site is responsible for assuring that all personnel involved in the trial (for example: doctors, medical students, nurses, trial nurse) fulfill their requirements as specified by the GCP guidelines. The investigator will provide direct access to source documents.

17.5 INSURANCE POLICY

In accordance with the provisions of the law and the GCP, the sponsor has an insurance policy intended at HDI Gerling to guarantee against possible damages caused by treatment.
The studies performed on behalf of the sponsor are specifically and expressly guaranteed. It is advisable to underline that non-compliance with the research legal conditions are causes of guarantee exclusion.

17.6 PUBLICATIONS

The results will be published at the end of the trial according to the publication policy consent determining the authors` order. A trial report containing the relevant information on all trial aspects and following the CONSORT Statement will be published in any case.

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19. APPENDICES

19.1 SOP SURGERY (GERMAN VERSION)

1. Operation eines Pankreaskopfkarzinoms

Nach der Laparotomie und der abdominellen Exploration (Suche nach Lebermetastasen und Peritonealkarzinose) sollten folgende Schritte bei der Pankreaskopfresektion durchgeführt und dokumentiert werden:

1. Eröffnung der Bursa omentalis nach Durchtrennung des Lig. gastrocolicum.

2. Kocher-Manöver zur Mobilisierung des Pankreaskopfes.

3. Postpylorische Präparation des Duodenums sowie Durchtrennung des Duodenums.

4. Klärung der lokalen Resektabilität und danach Untertunnelung des Pankreaskopf/-korpusüberganges auf der Ebene der V. mesenterica superior und dem venösen Konfluens.

5. Die Lymphadenektomie sollte folgende Lymphknotengruppen beinhalten:
   rechtsseitige Lymphknoten des hepatoduodenalen Ligamentes (12 B1, 12 B2, 12 C), anteriore pankreatoduodenale Lymphknoten (17 A, 17 B), posteriore pankreatoduodenale Lymphknoten (13 A, 13 B), rechtsseitig der A. mesenterica superior gelegene Lympknoten von der Aorta bis zum Abgang der inferioren pankreatikoduodenalen Arterie (14 A, 14 B).

6. Präparation des Treitz'schen Ligamentes, Durchtrennen der 1. Jejunalschlinge, Mitentfernung des Mesenteriums der 1. Jejunalschlinge bis links an die A. mesenterica superior.

7. Präparation der Gallenblase zum D. choledochus hin und Durchtrennen des D. hepaticus communis oberhalb der Mündung des D. cysticus.

9. Durchtrennung des Pankreas über oder linksseitig des mesenterikoportalen Venenstammes.

10. Die Tumorfreiheit der Resektionsebene ist durch eine Schnellschnittuntersuchung zu sichern. Eine Fotodokumentation des operativen Situs nach Resektion ist wünschenswert.

11. Alle gängigen Rekonstruktionsverfahren und Anastomosenformen wie z. B. die E/S- oder die E/E-Pankreatojejunostomie und Choledochojejunostomie in eine Schlinge oder in zwei separate Dünndarmschlingen sowie die Pankreatogastrostomie mit separater Drainage des Gallengangs durch eine Hepatikojejunostomie sind zugelassen. Technische Varianten und die Verwendung von Hilfsmitteln wie Drainagen, Fibrinkleber o.ä. sollen dokumentiert werden.

12. Der Einsatz sowohl von Magen- als auch Ernährungssonden sowie die verwendete Ernährung sollte dokumentiert werden.

13. Eine Dokumentation über die Entfernung von Drainagen, Sonden, Kostaufbau sowie postoperative Interventionen/Diagnostik soll erfolgen.

2. Operation eines Pankreaskorpus-/schwanzkarzinoms

Nach der Laparotomie und der abdominellen Exploration (Suche nach Lebermetastasen und Peritonealkarzinose) sollten folgende Schritte bei der Resektion eines Pankreaskorpus-/-schwanzkarzinoms durchgeführt und dokumentiert werden:

1. Eröffnung der Bursa omentalis nach Durchtrennung des Lig. gastrocolicum. Inspektion der Bursa omentalis bzgl. Peritonealkarzinose.

2. Inzision des Peritoneums vor der V. mesenterica superior am Pankreasunterrand bis hin zum Pankreasschwanz.

3. Präparation der A. hepatica communis, gastroduodenalis und hepatic propria am Pankreasoberrand. Klärung der Resektabilität. Entfernung der umgebenden Lymphknoten.

4. Untertunnelung des Pankreaskopf/-korpusüberganges auf der Ebene der V. mesenterica superior und dem venösen Konfluens bzw. rechts davon.

5. Mobilisieren der Milz, Lösen derselben sowie des Pankreasschwanzbereiches von links her unter Inzision des Retroperitoneums, Durchtrennung der kurzen Magenvenen und Vorluxieren der Milz mit Pankreasschwanz.

6. Weiteres Ablösen des Pankreasorgans von Niere und Nebenniere bis paraaortal links.

7. Präparation der A. und V. lienalis im Abgangsbereich und Durchtrennung zwischen Durchstechungsligaturen.

8. Darstellen von Tr. coeliacus und A. mesenterica superior von links und Entfernen der Lymphknoten links-paraaortal vom Tr. coeliacus bis zur linken Nierenarterie, entlang des Tr. coeliacus und der A. mesenterica superior analog zur Pankreaskopfresektion in 180° Ausdehnung.

9. Absetzen des Pankreas vor der V. mesenterica superior unter Erhaltung der A. gastroduodenalis. Übernähung des Pankreasgangs und Übernähung der Pankreasresektionsfläche (auch Stapler für die Resektion erlaubt).

10. Die Tumorfreiheit der Resektionsebene ist durch eine Schnellschnittuntersuchung zu sichern. Eine Fotodokumentation des operativen Situs nach Resektion ist wünschenswert.

11. Technische Hilfsmittel – Drainagen, Fibrinkleber usw. sowie die Verwendung von Stapler und Nahtmaterial – müssen im OP-Bericht genannt werden.

12. Der Einsatz sowohl von Magen- als auch Ernährungssonden sowie die verwendete Ernährung sollte dokumentiert werden.

13. Eine Dokumentation über die Entfernung von Drainagen, Sonden, Kostaufbau sowie postoperative Interventionen/Diagnostik soll erfolgen.

14. Die Lymphknoten sollen nach der Klassifizierung der Japanischen Pankreasgesellschaft bezeichnet werden (Japanese Pancreas Society 1993).

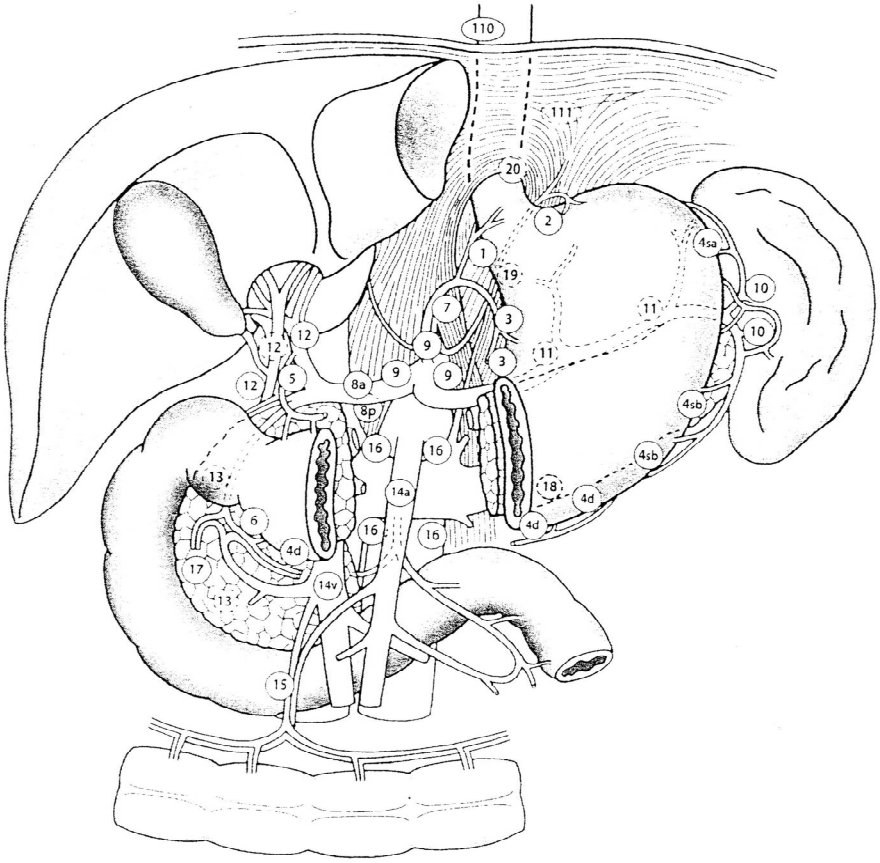


Abb.: Klassifikation und Nummerierung der LK-Stationen gemäß der japanischen Klassifikation

19.2 SOP REGIONAL HYPERTHERMIA (ENGLISH VERSION)

The standard operating procedures for the application of hyperthermia are defined upon the ESHO quality assurance guidelines for regional hyperthermia [11]. Additional general information for treatment planning within the context for the HEAT protocol derived from our own experience in the treatment of pancreatic cancer (phase II Trial) [33] and of soft tissue sarcoma patients with tumors of the upper abdomen (phase III clinical trials: ESHO-95 and EORTC 62961) [30, 38]. The primary objective of the quality assurance for regional hyperthermia in the HEAT protocol is the adequate positioning of the hyperthermia applicator to generate the heating field in the area of resected pancreatic tumor and immediate surrounding tissue and organs of interest (e.g. liver). A secondary objective is the improvement of the patient's compliance.

19.2.1 Treatment planning

Pancreatic cancer tumors are deep-seated and their location in the upper abdomen renders them difficult to position the applicator correctly at least in small patients. Modern applicators (e.g. sigma Eye applicator which contains 24 adjustable antennas) provide 3 dimensional steering in radial and longitudinal direction. The multi-antenna arrangement in three dimensions enables even a larger treatment volume (e.g. the upper abdomen including the liver). The elliptical shape of the sigma Eye applicator turns the treatment for the patient into a more comfortable procedure (i.e. lower bolus pressure).

The rate of energy which is absorbed by the body when exposed to radio frequency is the specific absorption rate (SAR), which is quantified by W/kg. The SAR is predictable for temperature distribution in the treatment area.

The patient-specific treatment planning system "HyperPlan" calculates the specific absorption rate (SAR) and temperature distribution in the treatment area based on the CT-images of the patient. Like this the optimal technical parameters for achieving a therapeutic temperature in the region of interest can be displayed before start of hyperthermia treatment.

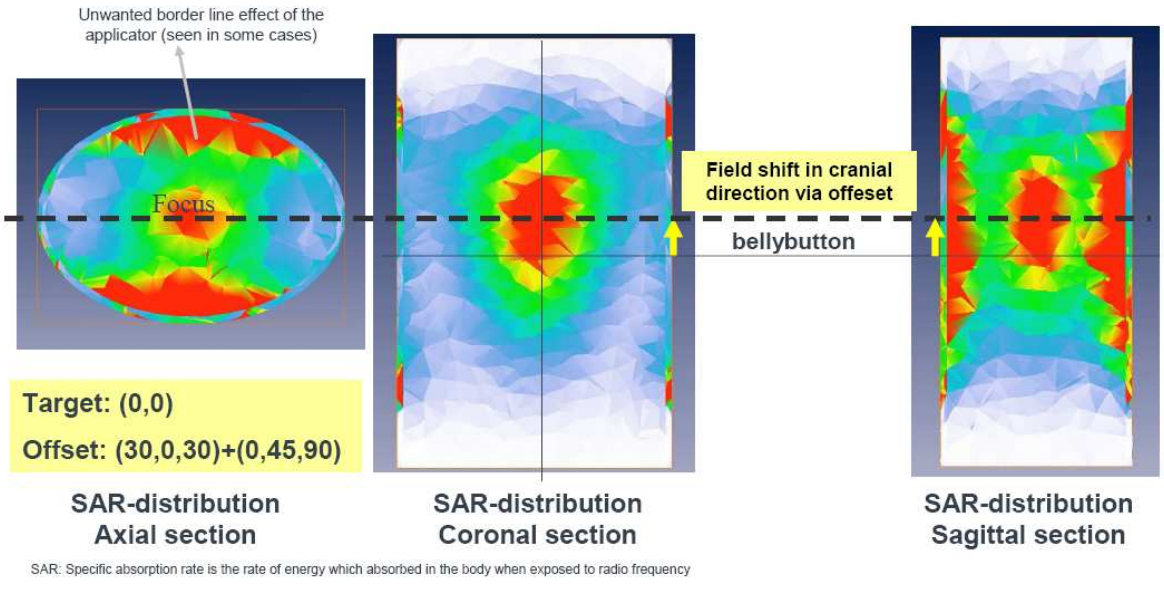


Figure: SAR distribution distribution in sigma Eye applicators

The treatment planning system "HyperPlan" illustrates the SAR-distribution in different sections of the treatment area (see Figure) using the sigma Eye applicator.

Because invasive temperature measurement with thermal sensors kept for a longer period of time in such deep-seated areas of the upper abdomen are of potential risk, patients can be treated without implanted thermal probes. Previous extensive work with the Sigma-60 Applicator using invasive thermometry in patients of the upper abdomen demonstrated a T_{max} between 40,9℃ and 43,5℃ (median: 42,1℃). Some of these patients were treated with regional hyperthermia after tumor resection and the heating field was focused on the resection area, showing no additional side effects as compared to patients without previous surgery.
In conclusion, regional hyperthermia can be applied without thermal sensors in the target area, if technical standard parameters for the defined heating field are used. These technical parameters of treatment planning depend also on the patient's weight and height and can be defined as followed:

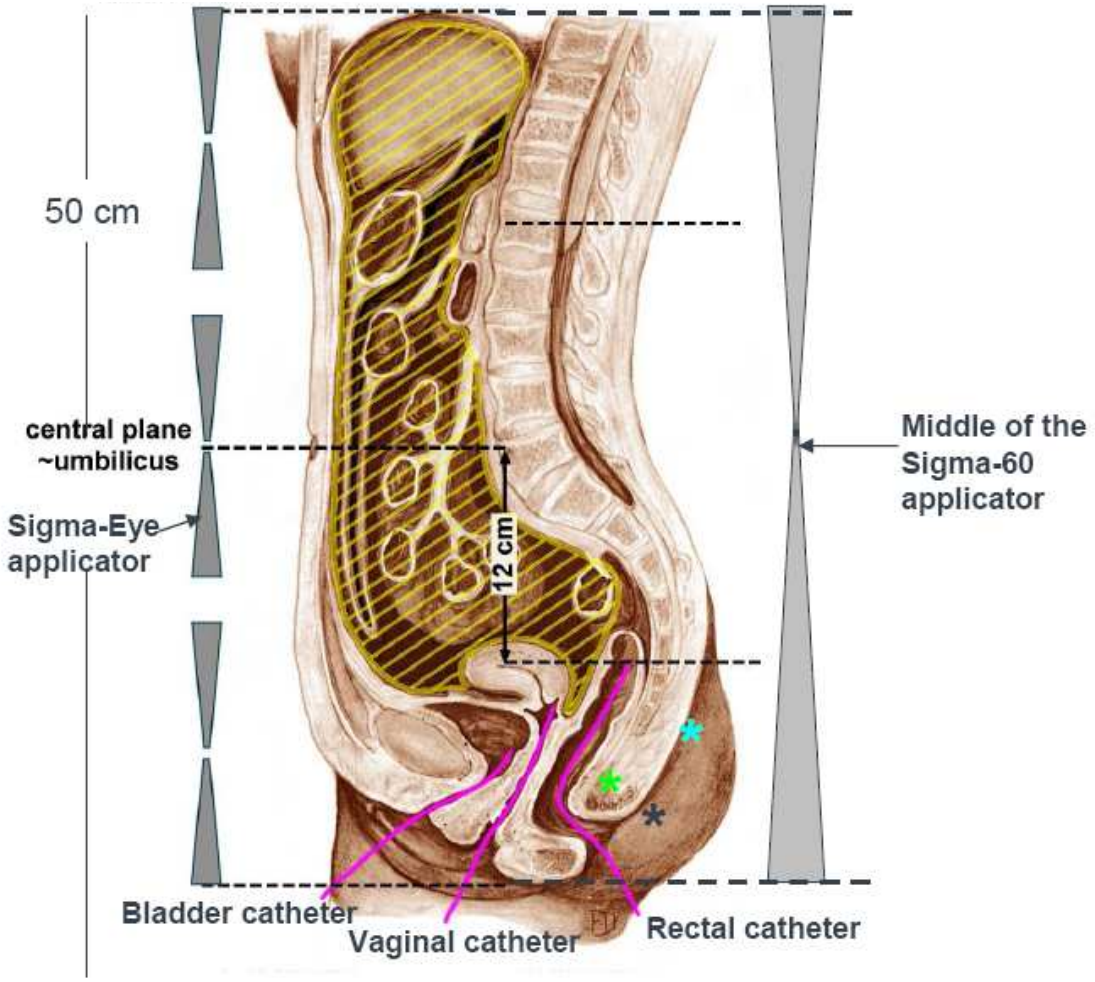
19.2.2 Standard set-up for sigma Eye, sigma-60 or elliptical sigma-60 applicators:

If different regional hyperthermia applicators are available the assignment of a treatment applicator depends on the maximum anterior posterior (a.p.) extension of the patient to reach maximum patients comfort concerning water bolus pressure.
At least 5 cm of the bolus water profile must be measurable from both applicator sides (upper and lower) to avoid undesirable hot spots.

For patients with an a.p. extension < 25 cm:	the use of the sigma Eye or elliptical sigma 60 applicator is recommended.
For patients with an a.p. extension ≥ 25 cm:	the use of the sigma 60 applicator is recommended.

If these applicators are not available patients can be treated with the standard sigma 60 applicator

Positioning of the applicators:
Independently of the type of applicator used the middle point of the applicator must be positioned at the bellybutton.



Examples for the position of applicators for a treatment of abdominal fields (left: sigma Eye; right: sigma 60)

19.2.3 Temperature and E-Field measurements:

All temperatures will be measured by sensors calibrated with a traceable standard. High resistant lead or fiber optic type sensors are permitted if calibration determines their inaccuracy to be < 0,2℃.

1. Invasive Thermometry should be aimed at if possible. Therefore the implementation of thermal catheters will be planned during surgery of pancreatic cancer. Catheters will be left till first two hyperthermia treatments of first cycle are performed. If the patient is assigned to standard treatment arm (Gemcitabine alone) thermal catheters are removed after randomization.
2. Due to far distance between pancreas and pelvis, endoluminal temperature measurement during hyperthermia treatment will not give adequate information about the temperature elevation of the pancreatic area itself. Nevertheless thermometry sensors should be positioned endoluminal in the bladder, rectum (if applicable in the vagina) to control unwanted hot spots at the edge of the applicator. 1-2 Thermal sensors must be applied on the skin surface of the upper abdomen, especially on the scar of surgery.
3. A mapping system for a thermometric scan should be performed every 5 to 10 minutes.

4. Specific absorption rate (SAR) measurements during treatment, using E-Field probes and/or thermal pulse techniques are recommended but not mandatory.

19.2.4 Standard parameters of the applicator

Standard Sigma 60 or elliptical sigma 60 applicator:
Forward power: 500 W – 700 W, depending on the patient´s weight (in general 600 W)
Frequency: 70 MHz for obese patients, 90 MHz for slim patients
Focus:

- If the tumor was located in the head of the pancreas and Whipple surgery has been performed: (0,0)
- If the tumor was located in the corpus or tail of the pancreas and surgery of the left part of the pancreas has been performed: (0,1)

Sigma Eye applicator:
Forward power by standard applicator: 700 W – 900 W (in general 700 W)

Forward power by MRI compatible applicators: 900 W – 1100 W. *Here we presume that about 200 W are absorbed by the Magnet of the MRI System. In case of deviation of this assumption, please take into account the actual amount of power, which is absorbed through the magnet of your MRI system.*

Focus:

- If the tumor was located in the head of the pancreas and Whipple surgery has been performed: (0,0)
- If the tumor was located in the corpus or tail of the pancreas and surgery of the left part of the pancreas has been performed: (0,1)

Off sets (food, middle, head): (30,0,30)
Frequency: 100 MHz.

19.2.5 Treatment procedure

Start:
For the start of the 1st treatment it is recommended to begin with about 1/3 to 2/3 of the required power needed for the specific patient`s weight. From 2nd treatment onward, data for positioning and power set are adapted from the settings used during the prior treatment.

Heat up phase:
Minute 10 - 30: Stepwise increase of the forward power depending on the patient's comfort until the recommended maximum forward power is reached. A temperature increase of 1 °C in 5 minutes is optimal. In case o f a temperature increase of less than 0.6 °C, power should be increased (until max. power) is reached.
If invasive temperature measurement is done, the heat up phase ends when 42°C in the pancreatic area are achieved (even before the 30th minute).

Treatment time:
Regional hyperthermia treatment is performed over 60 minutes after finishing the heat up phase.

These standard technical parameters represent the **minimal requirements** for all patients enrolling the HEAT protocol.

In case of pain or signs of patient's discomfort:

1. Set power off to evaluate whether the pain is power-related. If symptoms are power-related change the technical parameter (e.g. frequency, focus) or reduce the forward power.
2. In case of bolus pressure causing discomfort the water of the bolus system should be released and adjusted so that it is possible for the patient to find a comfortable position.
3. Bolus extension (additional water bags) must be applied if the patient suffers from localized pain at the edges of the bolus caused by borderline effects of the applicator.
4. Additional cooling to improve patient comfort.
5. Depending on the cause of pain (i.e. if tumor- or position-related) and if it is not power related, analgesic or sedative drugs can be given under medical supervision.

The heat help program
The regional hyperthermia centers participating in the HEAT protocol should contact the coordinating center in Munich, Klinikum Grosshadern, for technical advice or planning support (Phone number: +49-89-70954768, Herr Rahman and colleagues).

19.2.6. Treatment documentation

Treatment duration:
In the protocols the start, heat up time and duration of treatment time must be documented (see 18.2.5).

The following details must be recorded on the patient's treatment record form:

- Patient's and tumor characteristics
- System used, mechanical set-up, patient's position, bolus configuration, additional boluses, etc.,
- System settings: frequency, phase, amplitude, power (forward and reflected) and any changes during treatment in these settings
- Endoluminal temperatures, normal tissue temperatures, systemic temperature, bolus temperature
- Paratumoral temperature, in case of implanted thermal catheters into the tumor bed or surrounding tissue
- Hemodynamic parameters (heart rate, blood pressure)
- Acute toxicities: the occurrence, nature, cause and duration of any discomfort and pain
- The occurrence of treatment limiting factors, discontinuation of treatment and its causes

19.2.7. Safety aspects

A good contact with the patient must exist. The patient provides essential information with regard to power control and his/her general condition. Any information about pain sensation, discomfort or other feelings related to the hyperthermia treatment must be immediately forwarded to the responsible physician and to the treatment team.

Metal implants:
Presence of surgical clips is a reason to omit hyperthermia treatment, but only if they are clustered densely (Lee et al. 1992). According to our experience several, distributed smaller clips (max. 1 cm long) are no problem for the performance of deep hyperthermia. Patients with surgical clips lined up to 5 cm and more do not qualify for hyperthermia treatment. MR compatibility must be ascertained for treatment in a hybrid system (hyperthermia system combined with MRT).

Pacemaker:
Patients with implanted pacemaker do not qualify for hyperthermia treatment.

Ascites:
The presence of larger ascites in the treatment area can be an exclusion criteria for hyperthermic treatment. Therefore in case of ascites peritoneal puncture must be performed before starting hyperthermia treatment.

19.3 SOP PATHOLOGY

Resektionsverfahren

● Duodenopankreatektomie nach Kausch-Whipple mit Entfernung des Pankreaskopfes, Duodenum, distalen Gallenganges, der Gallenblase und eines Drittel des Magens, sowie regionaler und (bei radikaler Resektion) juxtaregionaler Lymphknotendissektion
● Pylorus-erhaltende Duodenopankreatektomie (wie Whipple aber ohne Entfernung des Magens) mit Lymphknotendissektion
● Totale Pankreatektomie mit Lymphknotendissektion
● Pankreaslinksresektion mit Entfernung von Pankreaskörper- und –schwanz sowie meistens mit Splenektomie

Präparation des Resektionspräparates

Das Präparat sollte im frischen Zustand beurteilt werden. Als erstes erfolgt die Tuschemarkierung der retroperitonealen Seite des Pankreas. Danach wird das Duodenum und der Magen eröffnet. Für die weitere Beurteilung ist von großer Bedeutung, den Duktus choledochus und/oder den Pankreasgang von den Absetzungsrändern her bis in das Duodenum hinein zu sondieren. Bei richtiger Sondierung ist es möglich, das Pankreas entlang der Sonde(n) horizontal vom pankreatischen Absetzungsrand zum Duodenum hin aufzuschneiden. Diese Präparation ermöglicht eine schnelle Identifizierung von tumorösen Prozessen im Pankreas, da zur Lokalisation und damit Erkennung des Tumors die meist vorliegende Stenose im pankreatischen Teil des Duktus choledochus sehr hilfreich ist. Nach dieser ersten Beurteilung des Pankreasgewebes sind die Ausmaße der resezierten Organe, insbesondere des Pankreas zu bestimmen. Nach evtl. Entnahme von Frischgewebe wird das Präparat dann zur adäquaten Fixierung in anatomisch korrekter Lage auf eine Korkplatte für 12 bis 24 Stunden aufgespannt. Anschließend erfolgt die Gewebsentnahme für die Histologie. Aus dem retroperitonealen Fettgewebe sollten mindestens 4 Gewebeproben entnommen werden.

Makroskopische Beurteilung

Bei Tumoren muss eine dreidimensionale Größenangabe erfolgen, zumindestens aber ein maximaler Durchmesser bestimmt werden. Alle Veränderungen sind hinsichtlich ihrer Lage und Ausdehnung im Pankreas möglichst genau anzugeben. Die Lokalisation der Befunde im Pankreas beziehen sich dabei auf folgende anatomischen Orientierungspunkte, die, da nur selten im Resektionspräparat anwesend (z. B. Mitresektion mesenterialer Gefäße), virtuell verstanden werden müssen. Die A. mesenterica superior, die hinter dem Pankreas verläuft, bildet die Grenzlinie zwischen Pankreaskopf und Pankreaskörper. Der Pankreaskörper liegt zwischen der A. mesenterica superior und dem linken Rand der Aorta. Der Pankreasschwanz schließlich liegt zwischen linkem Rand der Aorta und dem Milzhilus.

Resektionsränder

Die Resektionsränder umfassen den pankreatischen Resektionsrand (in dessen Mitte der Pankreasgang liegt), den retroperitonealen Resektionsrand (definiert als das retroperitoneale an das Pankreasgewebe angrenzende peripankreatische Fettgewebe) und der Absetzungsrand des Gallenganges. Die Entfernung zum pankreatischen Resektionsrand kann makroskopisch bestimmt werden, die Entfernung zur retroperitonealen Resektionsfläche ist dagegen erst histologisch festzulegen. Gewebe zur Beurteilung des pankreatischen und biliären Resektionsrandes wird zumeist vom Chirurgen separat eingeschickt.

Gewebsentnahme zur histologischen Beurteilung
Generell wird Gewebe vom Tumor, von nicht-tumorösem Gewebe, von den Resektionsrändern (zusätzlich zum Schnellschnittgewebe), und, wenn mitreseziert, von den mesenterialen Gefäßen entnommen. Alle präparierten Lymphknoten werden eingeblockt.

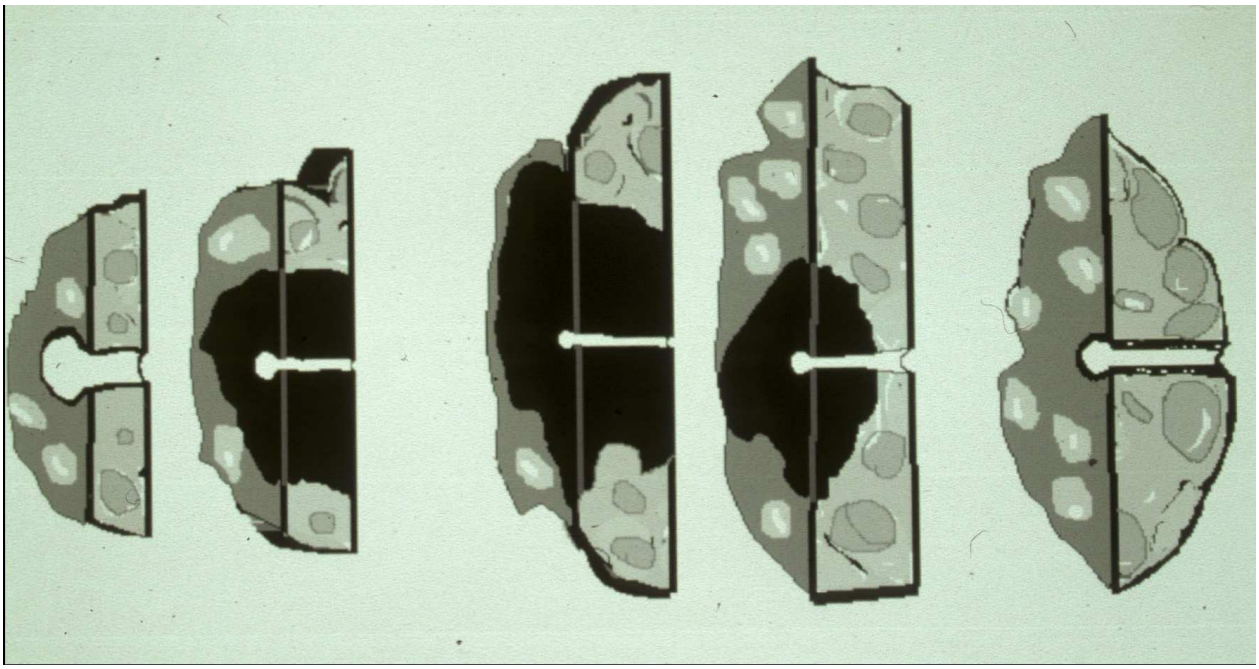
Pankreatektomiepräparat nach Whipple:
Zur Beurteilung des Tumors muss die Gewebsentnahme so erfolgen, dass die Beziehungen zum intrapankreatischen Teil des Gallengangs, zum Pankreasgang und zur Papilla vateri zu beurteilen sind. Dies bedeutet, dass das Tumor enthaltende Gewebe senkrecht zum Gallengang und Pankreasgang nach retroperitoneal lamelliert und dann entnommen wird (Abb. 1). Dabei wird auch der retroperitoneale Resektionsrand (oder besser die retroperitoneale Resektionsfläche) erfasst und kann somit beurteilt werden. Bei einer Tumorausbreitung in die Wand eines mitresezierten mesenterialen Gefäßes, müssen die Gefäße bei der Gewebsentnahme mit einbezogen werden. Lymphknoten, die am Pankreasgewebe hängen, können separat oder anhängend an das Pankreasgewebe entnommen werden. Es sollten bis zu zehn Lymphknotenpräpariert werden. Bei einer radikalen Lymphadenektomie werden die juxtaregionalen Lymphknoten durch den Chirurgen isoliert und unter Angabe der Lokalisation entfernt und zur Untersuchung gegeben.

Pankreaslinksresektat: Nach Lamellierung (maximale Dicke 0,5 cm) des Pankreasgewebes senkrecht zum Pankreasgang erfolgt die Entnahme von Pankreasquerschnitten. Dabei muss der Resektionsrand sowie die Anwesenheit von peripankreatischen Lymphknoten beachtet werden.

Mikroskopische Beurteilung
Bei neoplastischen Veränderungen muss die mikroskopische Beurteilung zu folgenden Aussagen führen:

- Typisierung und Klassifizierung des Tumors nach WHO2000, bzw. TNM
- Einschätzung der Differenzierung und mitotischen Aktivität
- WHO Grading
- Ausdehnung intra- und extrapankreatisch unter Berücksichtigung der makroskropischen Beurteilung
- Resektionsränder
- Lymphknotenbefall sowie vaskuläre und perineurale Invasion.

Abbildung 1: Schematische Darstellung des dorsalen Segmentes des Pankreas für die orientierte Gewebsentnahme



Konsilliardienst

Pathologisches Institut der LMU
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Telefax +49 (0)89 2180-73604

19.4 SHIPPING OF PRIMARY TUMOR TISSUE AND SERUM PROBES

Hyperthermia European Adjuvant Trial:

A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with

Gemcitabine alone (Arm G) vs.

Gemcitabine plus Cisplatin with regional hyperthermia (Arm GPH)

Short title: Hyperthermia European Adjuvant Trial
Study code: HEAT
EudraCTNumber: 2008-004802-14

Please send paraffin-embedded primary pancreatic tissue and serum probes (see table 1) to the Coordinating Investigator:

Prof. Dr. Rolf Issels/ Dr. K. Lechner
Medical Clinic III
Department of Hyperthermia
Klinikum Grosshadern Medical Center,
University of Munich
Marchioninistr. 15
D-81377 Munich

Tel.: +49-89-7095-4768, -4769
E-mail: rolf.issels@med.uni-muenchen.de

PLEASE ALWAYS GIVE THE EUDRACT-NUMBER AND PATIENT CODE!

19.5 WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their

research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

19.6 INFORMED CONSENT

see separate File

19.7 KARNOFSKY AND WHO PERFORMANCE STATUS SCALE

KARNOFSKY (%)		WHO PS = ECOG	
100	Normal, no complaints, no evidence of disease	0	Able to carry out all normal activity without restriction
90	Able to carry on normal activity, minor signs or symptoms of disease		
80	Normal activity with effort, some signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
70	Cares for self, unable to carry on normal activity or to do active works		Ambulatory and capable of all self-care but unable to carry out any work; up about more than 50% of waking hours
60	Requires occasional assistance but is able to care for most needs.	2	Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance	3	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.
30	Severely disabled, hospitalization is indicated although death not imminent		
20	Very sick, hospitalization necessary, active supportive treatment necessary	4	
10	Moribund, fatal processes progressing rapidly		
0	Dead	5	

Consideration of the following information (in addition to information in the scale itself) in determining the Karnofsky Performance Status score will add consistency to the rating across centres and studies. Please try to obtain this information in a consistent manner in determining the Karnofsky Performance Status.

1. Weight loss or gain
2. Reduction in energy, increase in fatigue
3. Difficulty in bathing or grooming
4. Difficulty in walking or moving around
5. Difficulty in driving
6. Difficulty in working full or part time

19.8 COMMON NCI TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0

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see separate File or
http://129.43.7.106/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

19.9.1 INFORMATION ABOUT GEMCITABINE (GEMZAR®)

See separate file or:
http://www.fachinfo.de/data/fi/jsearch?praep

19.9.2 INFORMATION ABOUT CISPLATIN

See separate file or:
http://www.fachinfo.de/data/fi/jsearch?praep