MAGIPAC trial: Magnetic Resonance Imaging for Improved Detection of Liver Metastases in Pancreatic Cancer Patients

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INTRODUCTION

Pancreatic cancer has a dismal prognosis with a 5-year survival of only 8% [1]. Despite surgery being the only chance for cure, only 20% of the patients are eligible for surgical treatment, as most have metastatic disease at diagnosis [2]. Furthermore, pancreatic cancer surgery is a major procedure with a 30-50% risk of complications and 2-3% risk of fatal outcome [3]. It is therefore important to avoid futile resections that will delay initiation of life-prolonging chemotherapy in patients who will not benefit from surgery.

Eligibility for surgical treatment depends on tumor involvement of major vessels around the pancreas and the presence of liver or lung metastases, which are contraindications to surgery [4-6]. Computed tomography (CT) is the state-of-the-art imaging modality for assessing pancreatic cancer resectability [7], but it has some shortcomings. Although CT performs well in assessing the local extent of the tumor [8], it has a sensitivity of only 75% to detect liver metastases from pancreatic cancers [9]. Thus, relying solely on CT imaging will inevitably lead to futile resections in patients with undetected liver metastases. This likely impairs survival, as patients will need to recover from surgery, before they can begin life-prolonging chemotherapy.

These shortcomings of CT may be overcome by using magnetic resonance imaging (MRI) instead. MRI seems to be superior to CT for detection of liver metastases in pancreatic cancer [10]. As liver metastases from resectable pancreatic cancer tend to be small [11], for which MRI with use of diffusion-weighted imaging and liver-specific contrast has a sensitivity of around 90% [12], routine use of preoperative MRI could be beneficial.

However, the feasibility of using MRI in pancreatic cancer patients has been sparsely investigated. One prospective study of 69 pancreatic cancer patients found that almost 25% had liver metastases on MRI that were not visible on CT [13], whereas a retrospective study of 216 patients found that MRI identified liver metastases in only 5% of patients with CT-assessed non-metastatic pancreatic cancer [14]. They study also found a longer time to recurrence after surgery in patients undergoing preoperative MRI, suggesting that MRI may be beneficial in selection of pancreatic cancer patients for surgical treatment. However, they did not provide information on why MRI was performed, and findings are unlikely to be generalizable. Another prospective study of 116 patients found liver metastases in 10% of patients with resectable tumors, but they did not use a liver-specific contrast, which likely contributed to underestimation of the true incidence [15].

Thus, adding routine MRI to the diagnostic workup in pancreatic cancer patients may lead to more precise treatment allocation and improved survival, but this requires further investigation.

OVERALL AIM OF THE PROJECT

The overall aim of this project is to increase pancreatic cancer survival through improved selection of patients for surgical treatment. We will conduct a nationwide, prospective clinical trial to examine the incremental value of using MRI for identification of liver metastases in pancreatic cancer patients.

RESEARCH PLAN

Study design and population

We will include 200 patients with CT-assessed resectable or borderline resectable pancreatic cancer allocated to surgery by the local multidisciplinary tumor board (MDT); Figure 1.

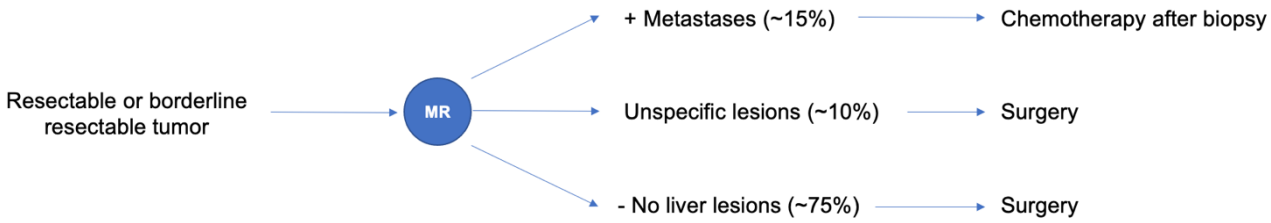

Figure 1. Study design.

Patient flow

Patients will be offered inclusion after informed consent for surgical treatment. After consent to participate in the study, an MRI will be performed. If the interval from CT to MRI is >14 days, a new CT will be performed to assure a valid comparator. The MRI will be read by an experienced gastro-radiologist. Based on the MRI, the treatment decision will be made (Figure 1):

1) **No liver metastases on MRI** (expected ~75%): Surgery as planned.
2) **Unspecific liver lesions on MRI, not seen on CT** (expected ~10%): Surgery as planned.
3) **Liver metastases on MRI** (expected ~15%): Referral to liver biopsy and oncological treatment if malignancy is verified. If biopsy is inconclusive, repeated assessment at the local MDT.

Follow-up

Patients will be followed for up to three years for information on vital status, recurrence, and treatment. Patients will adhere to the standard follow-up regimens at the participating centres (usually clinical examinations and potentially CA19-9 measurements).

Outcomes

Primary outcome:

- Change in treatment strategy from intended curative resection.

Secondary outcomes:

- Proportion of patients with MRI-detected liver metastases.
- Proportion of patients undergoing resection or surgical exploration.
- Proportion of patients with intraoperatively detected liver metastases not seen on **either** CT or MRI.
- One-year overall survival according to final treatment strategy.
- Three-year overall survival according to final treatment strategy.
- Recurrence-free survival according to final treatment strategy.
- Healthcare costs in patients with change of treatment.

Inclusion and exclusion criteria

Inclusion criteria:

- Pancreatic cancer patients considered to have a locally resectable or borderline resectable tumor by the local hepato-pancreato-biliary MDT board
- No liver metastases on CT
- At least 18 years old and able to provide informed consent
- Expected pancreatic ductal adenocarcinoma based on CT scan

Exclusion criteria:

- Metastatic disease
- Prior receipt of neoadjuvant chemotherapy or downstaging/-sizing treatment
- Comorbidity rendering major surgery unfeasible (inoperable)
- No informed consent

- Unable to undergo MRI (Kidney insufficiency (eGFR < 60 ml/min/1.73 m2 body surface area); Claustrophobia; Cardiac pacemaker)
- Postoperative histology other than adenocarcinoma of pancreato-biliary origin.
- MR performed during standard workup.

Statistical analysis plan

In the manuscript, we will present descriptive characteristics at baseline. Continuous variables will be presented as medians or means with appropriate measures of variation (interquartile ranges or standard deviations). Categorical variables will be presented as counts and percentages. For our outcome analyses, there are two different types of outcomes defined below.

- Survival: We will estimate overall survival in the entire cohort, following patients from the date of inclusion to end of follow-up (study end, emigration, dropout, or death). In sensitivity analyses, we will start follow-up on the date of surgery, including only patients who underwent operation. We will assess one- and three-year survival and median survival using the *Kaplan-Meier estimator*.
- Proportions: We will estimate proportions of patients for each outcome specified above including 95% confidence intervals.

Power calculations

Below, we provide the precision of the confidence intervals for different proportions of patients with MRI-detected liver metastases according to potential sample sizes.

Liver metastases	**N=100**	**N=200**	**N=300**
5%	1.6%-11.3%	2.4%-9.0%	2.8%-8.1%
10%	4.9%-17.6%	6.2%-15.0%	6.8%-14.0%
15%	8.6%-23.5%	10.4%-20.7%	11.1%-20.0%
20%	12.7%-29.2%	14.7%-26.2%	15.6%-25.0%

Evidently, very little statistical power is gained by increasing the study population from 200 to 300 patients, but this would be infeasible for practical purposes. Thus, we aim to include 200 patients. We aim to finalize patient enrolment during the first 18 months of the study period. During this

period, ~300 resections at the participating sites will be performed. It is considered realistic to include two-thirds of these patients.

PRACTICAL EXECUTION

CT imaging protocol

As a part of the routinely workup for staging pancreatic cancer, all patients referred to the local hepato-pancreato-biliary MDT board undergo a pancreas-specific CT scan. All CT scans include a portal venous phase (PVP) of the liver. CT scanners from different vendors will be used to acquire the images. The PVP will routinely obtained by 120 KV and mAs range from 150 to 290 depending of the body mass of the patient and the scan system. Contrast medium will be administered intravenously as a bolus injection by weight bases contrast Iodine concentration of 500 – 750 mg I/kg and a rate of 3-5 ml/s, followed by a saline flush of 20–40 ml. The scan delay for the PVP will be 50 sec (post-threshold, bolus tracking). Axial slice thickness of 2 mm slices will be reconstructed with 1 mm increments.

MR imaging protocol

The MRI will be performed using 1.5 or 3.0 T MR scanners of different vendors. The liver will be scanned using axial and coronal T2W single shot (SS) TSE, axial DWI (minimum b-values of 50 and 800) and axial T1W 3D spoiled gradient echo for gadoxetic acid (Primovist, Bayer Pharma, Berlin, Germany) contrast scans. Both a dynamic contrast scan consisted of; pre-contrast phase, arterial phase (timed using bolus tracking) followed immediately by porto-venous phase; late phase at 2 min and hepato-biliary phase 15 min after contrast injection. The gadoxetic acid contrast will be injected at 1 or 2 mL/s depending of using a dilution 1:1 of gadoxetic acid and saline 9mg/ml or not. The dose will be 0.025 mmol/kg body weight with a maximum of 2.5 mmol using a power injector.

Liver biopsies

Liver biopsies are standard procedure when malignancy is suspected on a scan. Therefore, all patients with suspected malignancy either on CT- or MR scan will have liver biopsies taken. The biopsies are performed percutaneous and under ultrasound guidance. Through a thin needle (diameter of 0,2 mm), a small piece of liver tissue is collected. The harvested liver tissue is destructed immediately after examination unless additional biological diagnostics toward targeted (individualized)

oncological treatment is needed. If so, the liver tissue will be destructed hereafter. No biological material will be stored in a biobank.

Analysis for metastatic lesions

Both CT and MR images will be read independently by experienced gastro-radiologists. The CT scan will be performed as the first examination followed by MR scan within 14 days after the CT scanning. For all focal hepatic lesions confidence of malignancy will be categorized via a 5-point scale, 1: definitely benign, 2: likely benign, 3: indeterminate, 4: likely malignant, 5: definite malignant.

Inclusion of patients

Potential patients will be identified at our MDT meetings when they are judged to have resectable disease. Patients will be informed of the possibility to participate in this study by the surgeon informing the patient about the operative procedure and associated risk of complications. They will receive oral and written information. This consultation will take place at an undisturbed consultation room in the outpatient clinic. Patients are allowed a companion for this interview, and consent can be withdrawn without any consequences for their subsequent treatment.

After the oral information has been given, the patients are offered at least 24 hours to consider their decision to participate, before providing written informed consent form. Informed consent is obtained prior to any study-related procedures. The signed and dated consent forms are stored in a locked room at the trial office and are available for audit and inspection at any time.

The written participant information contains contact information to the person being primary responsible for the project, and to the persons being responsible at the participating departments. The information clearly states that these people can be contacted in case of further questions.

It also mentions that the participant at any time may withdraw his or her consent, causing immediate destruction of all their individual data collected for the project. The consent withdrawal has no influence on their relationship to the department or their current/future treatment.

The patient information states that when the patient gives consent to participate, he or she also accept that the PI, and representative of the PI, have direct access to collect the necessary information regarding treatment and clinical outcome from medical records and health registries to complete the study. This information is required to conduct the study, to use in the statistical analyses, and for

monitoring and quality control of the study. All clinical information will be obtained and processed in compliance with data protection laws.

RISK AND POTENTIAL HARM

Assessment of risks and potential harm

There will be no radiation associated with the MR scans and no expected harm associated with this. The CT scan is a part of the standard diagnostic workup and would have been performed regardless of this study. Some patients will have liver biopsies taken to verify malignancy found on MR scans. Liver biopsy is a safe procedure that causes few adverse effects and can be performed in an outpatient setting. Risks includes infection and bleeding (1-2% [16]), as well as local tumor seeding (<1% [17]). Tumor seeding is only found in patients with disseminated disease. Therefore, it is not considered to influence the patient's prognosis. The potential benefit associated with preoperative MRI substantially outweigh any potential harm to the patients.

PROJECT PLAN

Time schedule

The project will commence on 1 September 2022. The study duration is expected to be 24 months for subject recruitment, and additional 3 years of follow-up. Interim analyses will be performed after 12 and 24 months. We expect to finalize the data analysis and present our findings during 2027.

Scientific and non-scientific personnel

At each institution, one research nurse will be responsible for identification of potential study subjects and, in collaboration with the surgeon, perform the practical work on obtaining informed consent. The research nurse will also be responsible for each patient's path through the project, *e.g.* schedule the imaging and collect data, and to coordinate the project with the research nurses at the other participating sites.

The PI is **MD, PhD, Associate Professor Jakob Kirkegård** who will be responsible for the project. **Professor, DMSc, Chief Surgeon Frank Viborg Mortensen** will assist the PI. Having published over 130 scientific papers, Frank has a strong track-record with clinical, experimental, and epidemiological research. Specifically, he has participated in several clinical studies [18-24] and has led epidemiological pancreatic cancer projects [25-37].

Collaborations

The study will be conducted in collaboration with the Department of Radiology, Aarhus University Hospital, represented by **MD, PhD, Consultant Radiologist Kim Sivesgaard** and **MD, Associate professor, Consultant Radiologist Lars Peter Larsen**. Both are experts in imaging of gastrointestinal cancers and have published a substantial number of papers within this field. At our institutions, we have a strong experience in clinical research [18-24]. Furthermore, we are currently conducting another trial in liver surgery (ARAPS Study, currently enrolling; ClinicalTrials.gov ID: NCT04107324) and participate in the ASAC trial (EudraCT: 2014-003601-15). We thus possess all intellectual expertise and infrastructure needed to conduct this study.

This project will be anchored at the Department of Surgery at Aarhus University Hospital and be conducted in collaboration between all four centers performing pancreatic cancer surgery in Denmark (Rigshospitalet, Aarhus, Odense, and Aalborg). All participating sites are represented in the steering committee of the Danish Pancreatic Cancer Group, who has endorsed the project. Aarhus will analyze data and draft the scientific papers originating from this study and thus have 1st, 2nd, and last authorship. Each of the remaining three centers will each have two authors. Ordering will be determined the number of included patients (the more patients, the higher order).

FINANCIAL ASPECTS

The study is investigator-initiated and independent of any commercial interests. The study is funded by the Danish Cancer Society (DKK 1.725.000), Novo Nordisk Fonden (DKK 1.471.950), Spogards Fond (DKK 350,000), Neye Fonden (DKK 270.000), Thora og Viggo Groves Mindelegat (DKK 20.000), Frimodt Fonden (DKK 30.000) and Korning Fonden (DKK 15.000). The funders do not have any role in the designing of the study or data analyses. Participants will not receive any financial compensation.

FUTURE DIRECTIONS

We expect this project to substantially improve our ability to tailor the optimal treatment for each individual with pancreatic cancer. Underdiagnosis of liver metastases delays the initiation of life-prolonging chemotherapy. Thus, with proper preoperative detection of liver metastases, our project will improve both survival and quality-of-life, as patients will be spared from unnecessary major

surgery. Thus, findings from our project are expected to have an immediate clinical impact. Furthermore, if MRI is non-inferior to CT with respect to tumor staging, it may replace CT in the diagnostic workup of pancreatic cancer patients.

ETCHICAL CONSIDERATIONS

This project is registered at the internal list of research projects in the Central Denmark Region (1-16-02-151-19). We will obtain approval from the local scientific ethics committee prior to inclusion of the first patient. We will adhere to the Helsinki declaration, and all data will be handled in accordance with Danish legislation ("Databeskyttelsesforordningen" and "Databeskyttelsesloven"). All findings, whether positive, negative, or inconclusive will be published in international peer-reviewed scientific journals and at national and international scientific meetings. The project is registered at www.clinicaltrials.gov (*NCT05428358*).

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