MAGIPAC trial: Magnetic Resonance Imaging for Better Selection of Pancreatic Cancer Patients for Surgery: A Randomized Clinical Trial.

BACKGROUND AND SIGNIFICANCE

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]. Pancreatic cancer surgery is a major procedure with a substantial morbidity and mortality [3]. Therefore, it is important to avoid futile resections that will delay initiation of life-prolonging chemotherapy in patients who will not benefit from surgery. Whether the patient can be operated depends on the local extent of the tumor and the presence of distant metastases (most often in the liver), which are contraindications to surgery [4-6].

Currently, computed tomography (CT) is state-of-the-art for assessing pancreatic cancer resectability [7]. However, CT has some shortcomings. Although it performs well in assessing the local extent of the tumor, it has limited sensitivity for detecting small liver metastases in pancreatic cancer [8]. Relying solely on CT imaging therefore leads to futile resections in patients with undetected liver metastases. This will impair survival, as patients will have to recover from surgery and the associated complications before they can initiate chemotherapy. These shortcomings may be overcome by using liver and pancreatic magnetic resonance imaging (MRI) instead of CT.

MRI may be superior to CT for detection of liver metastases in pancreatic cancer [9]. As liver metastases from resectable pancreatic cancer tend to be small [10], for which MRI (with use of diffusion weighted imaging and liver-specific contrast) has a high sensitivity, routine use of preoperative MRI could be beneficial. However, the feasibility of using MRI in detection of liver metastases 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 [11], whereas a retrospective study of 216 patients found that MRI revealed liver metastases in only 5% of patients with CT-assessed non-metastatic pancreatic cancer [12]. The latter study also found a longer time to recurrence after surgery in patients undergoing preoperative MRI, suggesting that preoperative MRI may be beneficial in pancreatic cancer patients. However, they did not provide information on why MRI was performed, and findings are unlikely to be generalizable. Furthermore, only few studies have examined the use of MRI in assessing the local extent of the tumor, suggesting it is not inferior to CT [13, 14].

Thus, MRI may provide a superior alternative to conventional CT in order to improve treatment allocation for pancreatic cancer patients. However, there is a substantial need for high-

quality research to examine this. Specifically, no randomized clinical trial (RCT) has been conducted.

PURPOSE AND OVERALL AIM

We propose to conduct a nationwide RCT to examine the feasibility of using MRI for tumor staging and identification of liver metastases in pancreatic cancer patients. *The aim is to improve selection of pancreatic cancer patients for surgery in order to increase overall survival*. Within this RCT, we will conduct three studies outlined below.

STUDY POPULATION AND DESIGN

Patients

200 patients with CT-assessed resectable pancreatic cancer allocated to surgery by the local multidisciplinary tumor board (MDT) will be included. Patients will be randomized to either the intervention (preoperative MRI, n=100) or control/standard-of-care (no preoperative MRI, n=100) arm.

Study design and patient flow

An overview of the proposed study design is shown in *Figure 1*.

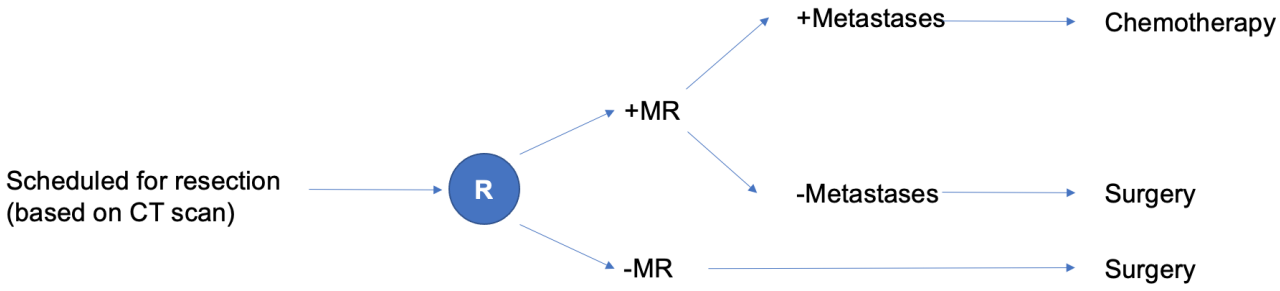

Figure 1. Study design. R: Randomization.

Upon consent, patients will be electronically randomized to one of the two treatment arms. Patients in the control arm will proceed directly to surgery. Patients in the intervention arm will have an MRI performed after randomization and before treatment. 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-radiologists blinded to the patient's identity and initial CT scan. Based on the MRI, the treatment decision will be made (*Figure 2*):

1) No liver metastases on MRI (expected ~75%): Surgery as planned.
2) Non-specific 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, repeat liver MRI after one month.

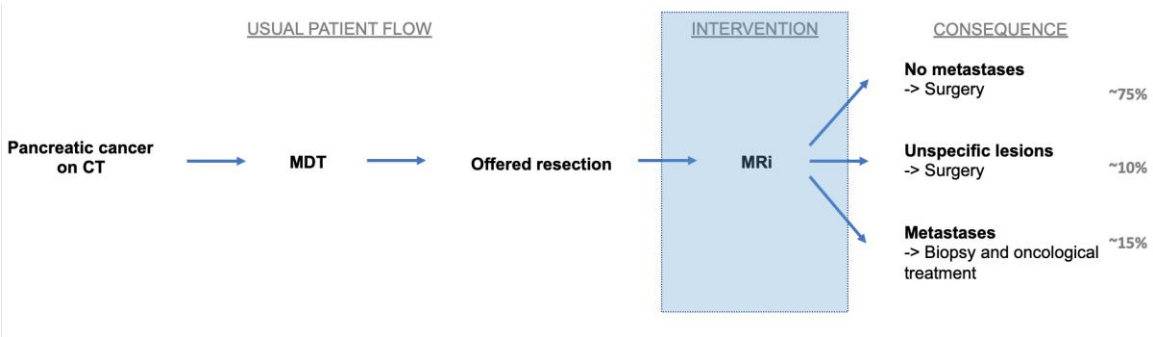

Figure 2. Patient flow in the intervention arm. MDT: Multidisciplinary team conference.

Follow-up

Patients will be followed for up to three years for information on treatment, recurrence, and vital status. We will conduct standard-of-care follow-up CT at 3, 6, 9, 12, 18, 24, 30, and 36 months postoperatively in all patients. Primary end-point for this project will be one-year survival. For subsequent studies, we will also perform analyses of three-year survival.

SPECIFIC STUDY AIMS, HYPOTHESES AND OUTCOMES

Study I: To compare tumor staging of pancreatic cancer patients assessed by MRI versus upper abdominal CT.

Study II: To assess the ability of MRI to detect liver metastases in pancreatic cancer patients with resectable tumor on CT.

Study III: To assess the impact of MRI on treatment allocation, recurrence, and survival in pancreatic cancer patients with a resectable tumor on CT.

Details of study hypotheses, population, and analytical plans are outlined in *Figure 3*.

	Study I	Study II	Study III
Aim	To compare tumor staging of pancreatic cancer patients assessed by MRI versus upper abdominal CT	To assess the ability of MRI to detect liver metastases in pancreatic cancer patients with resectable tumor on CT	To assess the impact of MRI on treatment allocation, recurrence, and survival in pancreatic cancer patients with a resectable tumor on CT
Hypothesis	MRI is non-inferior to CT with respect to tumor staging	MRI will detect liver metastases in patients with a resectable tumor on CT	Use of MRI will change treatment allocation and improve overall survival
Population	Patients in the intervention arm (N=100)	Patients in the intervention arm (N=100)	Patients in both arms (N=200)
Analysis	Agreement assessed by intraclass correlation coefficient (ICC)	Agreement assessed by intraclass correlation coefficient (ICC)	Treatment allocation and recurrence by Chi^2 test Survival analyses by Kaplan-Meier estimation

Figure 3. Outline of the three studies.

POWER CALCULATIONS AND FEASIBILITY

Assuming alpha=0.05, power of 80%, and a hazard ratio of death of 1.5, we need 191 patients in total. To guard against dropout of 5%, we aim to include 200 patients. On average, all four institutions performing pancreatic cancer surgery in Denmark (Rigshospitalet, Aarhus, Aalborg, and Odense) shall include 50 patients. We aim to finalize patient enrollment during the first 18 months of the study period, equaling to 2.8 patients monthly in each institution. In total, ~300 resections will be performed during this 18-month period. We consider it feasible and realistic to include two-thirds of these patients.

IMAGING PROTOCOLS

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.

Analysis for metastatic lesions

Each modality will be read anonymized. Both CT and MRI images will be read independently by dedicated radiologist from each participating site as part of the routine work-up in staging pancreatic cancer. The CT scan will be performed as the first examination followed by MRI scan within 14 days after the CT scanning. For all focal hepatic lesions confidence of malignancy will be categorized via a 3-point scale, 1: benign, 2: indeterminate, 3: malignant.

FEASIBILITY

Time schedule

The project will begin in January 2022 and end in December 2024. We will include the patients within the first 18 months of the project period. In the final year of the study period, we will perform data analyses and writing of scientific papers. This will allow for a sufficient follow-up period of all patients (please see *Figure 4* for detailed time schedule).

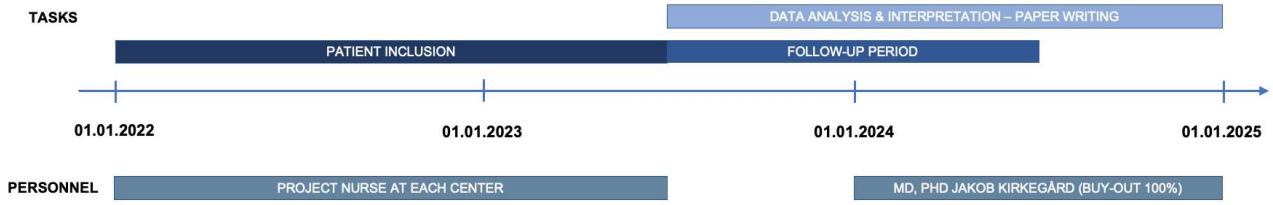

Figure 4. Time schedule.

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 and randomize the patients. 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 applicant is **Professor, DMSc, Chief Surgeon Frank Viborg Mortensen**. 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 [15-21] and has led epidemiological pancreatic cancer projects [22-34].

MD, PhD, Resident Surgeon Jakob Kirkegård will be responsible for data analyses and paper writing. For this purpose, he will be employed for one year (2024) as buyout from his position as surgical registrar. Jakob has a PhD on epidemiological studies of pancreatic cancer and has served as PI on a multicentre study on multidisciplinary team assessments of pancreatic cancer patients, coordinating the study with seven international collaborating institutions [35].

Collaborations

We will collaborate with the Department of Radiology, Aarhus University Hospital, represented by **MD, DMSc, Consultant Radiologist Erik Morre Pedersen** 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 [15-21]. Furthermore, we are currently conducting another RCT 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.

Nationwide collaboration

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

Beside the salary for Jakob Kirkegård and two research nurses mentioned above, we apply the Danish Cancer Society for expenses related to MRI scans. The departments will hold expenses for CT scans for the 50% of the patients that are expected to have more than 14 days between CT and MRI. Please see the attached budget for more details.

FUTURE PERSPECTIVES

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 is 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.

ETHICAL CONSIDERATIONS

This project will be conducted according to the Helsinki Declaration. The project needs to be registered at the Danish Data Protection Agency in accordance with the Central Denmark Region common registration system and it also requires approval from the Central Denmark Region Ethics Committee. We will ensure that all permissions are granted when study starts. All information involving patients will be handled according to national law on personal data information. Both positive, negative, and inconclusive results will be published, and presented at scientific meetings. Results will be presented at international scientific congresses, and we will aim for publications in

high-impact journals with focus on oncology, radiology, and surgery. The study will be registered at ClinicalTrials.gov and monitored by the Good Clinical Practice Unit at Aarhus University Hospital.

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