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Identification of New Biomarkers in Patients with Pancreatic Cancer (BIOPAC): A Study Protocol of an Open Cohort Study

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Abstract

Background: The overall survival of patients with pancreatic cancer (PC) is dismal and has improved only slightly during the last decades. Early detection of PC is difficult, and less than 25% of all patients with PC are eligible for surgery. No validated biomarkers exist that identify PC at an early stage and predict treatment outcomes in the individual patient. The objective of the present study is to find diagnostic, prognostic and predictive biomarkers that can be used (1) to diagnose PC with high specificity and sensitivity early in the course of the disease, (2) to improve prognostication, and/or (3) to predict and monitor treatment effectiveness and tolerability for the individual patient.

Methods and analysis: Observational and translational open cohort study with prospective collection of biological materials and clinical data during all stages of the routine care of patients with PC and including patients with suspected pancreatic malignancy disproved after surgery. Blood samples are collected sequentially during the course of a patient's treatment: before surgery, at start of adjuvant or palliative chemotherapy as well as during treatment until disease progression. The patients are followed until death. Demographics, disease characteristics, comorbidities and lifestyle factors are registered at inclusion and weight and performance status in association with each treatment cycle. Routine blood tests (i.e., haematology, creatinine, liver enzymes, bilirubin, carbohydrate antigen 19-9, C-reactive protein) are collected at regular intervals, and type of operation, chemotherapy and number of cycles given, date of disease recurrence in patients subjected to surgery, date of disease progression for each line of chemotherapy and date of death are recorded. Currently in July 7, 2019 a total of 5156 samples from 2141 patients have been collected.

Discussion: Biomarker analyses include a range of molecules such as deoxyribonucleic acid (DNA), single nucleotide polymorphism (SNPs), ribonucleic acid (RNA), microRNA, proteins and metabolites. Data will be analysed using appropriate methods and statistical analyses.

Conclusion: It is our hope that this ongoing study will provide new information on biomarkers and will contribute to precise treatment options for patients with PC in order to improve outcomes.

Trial Registration: ClinicalTrials.gov ID: NCT03311776. The trial was registered retrospectively; registration date 10/06/2017.

Keywords: Biobank; Biomarkers; Diagnostic biomarkers; Pancreatic cancer; Predictive biomarkers; Prognostic biomarkers

Abbreviations: BIOPAC- Biomarkers in patients with pancreatic cancer; BMI- Body mass index; CA 19-9: Carbohydrate antigen 19-9; CPR- Central personal registry; CNVs- Copy number variations; CT- Computed tomography; DNA- Deoxyribonucleic acid; DPCD- Danish pancreatic cancer database; EDTA- Ethylenediaminetetraacetic acid; ELISA- Enzyme linked immunosorbent assay; EMT- Epithelial mesenchymal transition; FOLFIRINOX- 5-FU leucovorin, irinotecan and oxaliplatin; KRAS- Kirsten rat sarcoma viral oncogene homolog; mRNA- Messenger RNA; NGS- Next generation sequencing; PC- Pancreatic cancer; PET/CT- Positron emission tomography and computed tomography; RNA- Ribonucleic acid; SNPs-Single nucleotide polymorphism; SOPs- Standard Operating Procedures; T2DM- Type 2 diabetes mellitus; TNM- Tumor, node, and metastases; VEK- Danish ethics committee; WGS-Whole genome sequencing

Background

Pancreatic cancer (PC) has one of the highest mortality rates of all cancers [1,2]. By 2030, PC will be the second most common cancer-related death after lung cancer [3], and today PC is the third leading

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cause of cancer death, surpassing breast cancer. The incidence of PC increases with age, and half of the patients are older than 65 years at time of diagnosis [4,5]. Worldwide 458,918 people were registered with PC in 2018 [1]. An estimated 56,770 new cases of PC will be diagnosed in the United States in 2019 [2], and 45,750 patients will die [2]. In Denmark, there were 957 new cases of PC and 982 deaths in 2016 [6].

The most common type of PC is ductal adenocarcinoma (90–95%) [4,5], characterised by disperse tumour cells in a dense desmoplastic stroma [4,5], resulting in a hypoxic and avascular environment. Inflammation is one of the hallmarks of cancer [7-9] and contributes to PC initiation, promotes cell survival, inhibits apoptosis, induces epithelial-mesenchymal transition (EMT), and plays an important role in chemoresistance and enhanced invasiveness and metastasis of PC [10-12].

The prognosis of many cancer patients has significantly improved during the last decade, whereas the prognosis of patients with PC is still dismal, and only 8–9% of the all patients are alive after 5 years [4,5]. Due to the aggressive tumour biology and paucity of clinical signs, the patient often presents with locally advanced or metastatic PC. Thus, only 15–20% of patients are suitable for surgical resection [4,5], which is the only curative treatment of PC. However, the majority of patients relapse within 2 years after pancreatic resection followed by adjuvant treatment with gemcitabine either in combination with capecitabine or nab-paclitaxel or as monotherapy [13-15]. Adjuvant treatment with modified FOLFIRINOX (5-fluorouracil [5-FU], leucovorin, irinotecan, oxaliplatin) for patients having performance status ≤1, results in the longest overall survival yet reported after resection, with 63% being alive after three years [16]. In patients with locally advanced or metastatic disease, chemotherapy is the only treatment option to palliate symptoms and prolong life. Only a few types of chemotherapy have clinical effect: monotherapy with gemcitabine, FOLFIRINOX and nab-paclitaxel in combination with gemcitabine [4,5,17,18]. Unfortunately, current treatments have moderate or no effect in many patients, and only 20% of the patients with locally advanced or metastatic PC are alive after 1 year, and the 5-year survival is only 4–7% [13]. Furthermore, it is a clinical challenge to identify older patients who will benefit from combination chemotherapy [19].

Although the aetiology of PC is not fully elucidated, several non-genetic risk factors including older age, smoking, high body mass index (BMI), heavy alcohol use, chronic pancreatitis, inflammatory bowel disease and long-standing diabetes mellitus are associated with PC [4,5]. It has recently been concluded that chronic stimulation and proliferation of the pancreatic duct gland compartment in response to islet inflammation in type 2 diabetes mellitus (T2DM) are potentially novel mechanisms that serve as a link to the increased risk of pancreatitis in T2DM [20]. About 5 to 10% of PC occurs due to genetic predisposition [21]. Furthermore, pancreatic intraepithelial neoplasia in association with intraductal papillary mucinous and mucinous cystic neoplasms is a putative histologic precursor of PC [22].

In 1998, the National Institutes of Health Biomarker Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" [23]. Biomarkers are divided into three categories: diagnostic biomarkers (ideally, diagnostic biomarker should establish the correct diagnosis with high sensitivity and specificity) which may be used for early diagnosis of a given disease [23-24]; prognostic biomarkers which correlate with specific clinical outcomes and thus progression of disease regardless of any treatment [23-25]; and predictive biomarkers which may be used to predict whether a given patient may benefit from a given treatment [23-26]. Hence, biomarkers may be promising tools to personalise the treatment of patients with PC. Potential biomarkers include a wide spectrum of genes, deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNAs), microRNAs, proteins and metabolites [27-29]. Genetic variation can be caused by single nucleotide polymorphism (SNPs) and copy number variations (CNVs), among which, the SNP is the most common type of genetic variation. In patients with PC, these biomarkers may be related to the disease itself, the associated inflammation or treatment-related pharmacokinetics. Biomarkers can be detected in peripheral blood, circulating cells or cell-free DNA in plasma [30,31], or in cancer tissue. Biomarkers in blood have the potential of being a more feasible, specific and reproducible tool for both diagnostic and prognostic purposes and for the monitoring of treatment and disease progression.

Currently, the concentration of Carbohydrate antigen (CA) 19-9 in serum is the most widely used biomarker for assessing disease burden and monitoring disease recurrence and prognosis of patients with PC [32]. However, CA 19-9 is not a specific biomarker for PC. Elevated CA 19-9 is also seen in pancreatitis, obstructive jaundice, cirrhosis and other gastrointestinal cancer. Moreover, CA 19-9 is not expressed in patients who lack Lewis antigen [33].

In line with increasing demand for precision medicine, the need to bridge patients and high-quality clinical data to molecular and genetic research is self-evident. New biomarkers for early diagnosis, prediction of treatment effects and better evaluation of prognosis and monitoring of patients with PC, including older (> 70 years) patients and patients with risk factors for PC, among others diabetes mellitus, pancreatitis, pancreatic intraepithelial neoplasia as well as genetic predisposition, are urgently needed to reduce mortality from PC. The focuses of our study, the BIOPAC "Biomarkers in patients with Pancreatic Cancer" study, are the identification of a panel of biomarkers in blood and tissue for early detection of PC, selection of patients who may benefit from neoadjuvant chemotherapy, prognostication and prediction of effect of different types of systemic therapies. Furthermore, the role of genetic factors and lifestyle in PC will be investigated. The present protocol is an observational, prospective, translational research study of patients with PC included in the nationwide Danish BIOPAC Biobank. It will include many translational biomarker studies of gene profiles, DNA, RNAs, microRNAs, SNPs, proteins and metabolites in patients of all ages and stages of PC. We will test the following hypothesis: "New circulating biomarkers and tissue biomarkers from patients with PC, including older patients and patients with comorbidity (e.g. T2DM), are useful for early diagnosis and valuable for better prediction of prognosis and selection of treatment".

This protocol has been prepared and implemented according to the REMARK guidelines [34,35]. To increase awareness of the BIOPAC study and facilitate dissemination of methods to the scientific community, the standard operating procedures used, current progress as well as completed and ongoing studies, are constantly updated on the BIOPAC Biobank website (www.herlevhospital.dk/BIOPAC). In this paper, we describe the study design and specify methods for sample collection, processing and archiving of data in the BIOPAC Biobank.

Objectives

The translational goal of the BIOPAC study is to improve outcomes and quality of life for patients with PC by improving personalised cancer treatment. The aims are to:

- identify patients with PC at an early stage and thereby increase the number of patients who can be radically resected.
- predict treatment response and prognosis of patients with PC to optimise treatment selection, i.e. to select patients who will benefit or not benefit from different types of therapy.
- identify tumour progression before computed tomography (CT) scans during treatment and follow-up to save patients with PC from unnecessary toxic therapies which are ineffective and compromise quality of life.
- include real-life, unselected patients including older patients (>70 years) and patients with comorbidities such as T2DM.

Materials and Methods

Study design and setting

In July 2008, the Danish BIOPAC Study "Biomarkers in patients with Pancreatic Cancer (BIOPAC) – can they provide new information of the disease and improve diagnosis and prognosis of the patients?" was initiated with the aim of conduction translational research. It is a prospective multicentre biomarker study in which biological samples (blood and cancer tissue), and clinical data are collected prospectively in Danish patients with localised, locally advanced or metastatic PC treated at seven oncological expert centres in Denmark as well as patients subjected to surgery in whom PC was suspected but not histologically confirmed. All patients included in the study are >18 years of age, have histologically verified PC or ampullary adenocarcinoma in a resected specimen, or histopathological confirmation of carcinoma if surgery has not been performed, and have signed an informed consent form. The patients are treated with different types of chemotherapy according to national guidelines www.gicancer.dk. One group consists of patients that have undergone surgery for PC, and a subgroup of patients consists of patients who have undergone surgery due to suspected PC but in whom no cancer was found on histologic examination after resection. Clinical data and outcomes are registered in the BIOPAC database, and biological samples are collected via the Danish nationwide BIOPAC biobank. Patient inclusion started in July 2008 and will continue until July 2028, with follow-up until July 2035. The inclusion period can be extended if deemed advisable after assessment by the investigators.

The patients included in the BIOPAC study are followed from time of diagnosis and during treatment and follow-up until death. Relevant clinical characteristics of the patients are included in the BIOPAC database and include a large number of parameters.

The BIOPAC study is a nationwide collaboration between Departments of Oncology, Clinical Biochemistry and Pathology in Denmark. As of July 7, 2019, seven hospitals from all parts of Denmark (Rigshospitalet, North Denmark Regional Hospital, Copenhagen University Hospital in Herlev, Zealand University Hospital in Roskilde and Næstved, Odense University Hospital, Aalborg University Hospital, and Hospital Lillebaelt in Vejle) have agreed to participate in the BIOPAC study. The BIOPAC biobank is housed at the Copenhagen University Hospital in Herlev and represents the first comprehensive PC biobank in Denmark.

Inclusion of patients is ongoing and will continue until 5000 patients are included. As of 7 July 2019, 5156 blood samples from 2141 patients have been collected. The number of patients included each year in the BIOPAC Study is approximately 200. Different types of biological material, e.g. blood and cancer tissue, are collected, handled and stored according to nationally approved Standard Operating Procedures (SOPs), see section "Biological Material".

Participants

The BIOPAC study is an open cohort study. Patients are eligible for inclusion if they are in routine clinical follow-up after a diagnosis of PC. A subgroup of patients operated on due to suspicion but without evidence of PC is also included since blood samples were taken before surgery. Patient inclusion and follow-up are carried out by nurses and physicians when the patients meet for scheduled routine clinical visits. The numbers of potentially eligible patients for the study are shown in Figure 1.

Clinical data

At the time of inclusion, the following clinical data are collected in the BIOPAC database:

1. Patient demographics: e.g. age, gender, diagnosis, weight and weight loss, height, BMI, performance status, family history of PC, medications, histological/cytological characteristics, TNM stage, site of metastasis, as well as lifestyle factors like smoking status and alcohol intake.
2. Comorbidities including Charlson comorbidity index: e.g. other types of cancer, diabetes, hypertension and hypercholesterolemia.
3. Paraclinical information: e.g. routine blood tests (haematology, liver enzymes, bilirubin, creatinine) including CA 19-9 and C-reactive protein and information on CT and/or positron emission tomography and computed tomography (PET/CT).
4. Exposures: e.g. date of operation and treatment with one or more of the following types of chemotherapy: gemcitabine, *nab*-paclitaxel + gemcitabine, FOLFIRINOX, capecitabine + gemcitabine, or oxaliplatin + capecitabine. Start and stop date and reason for treatment withdrawal as well as number of cycles in each line of treatment and adverse events.
5. Outcomes: e.g. respectability status and date of disease recurrence (in patients operated on), date of disease progression after each line of treatment and date of death.

Any oncological, surgical and/or medical treatment undertaken, and the monitoring of disease status (CT, PET/CT) are done as part of routine care according to international and national guidelines.

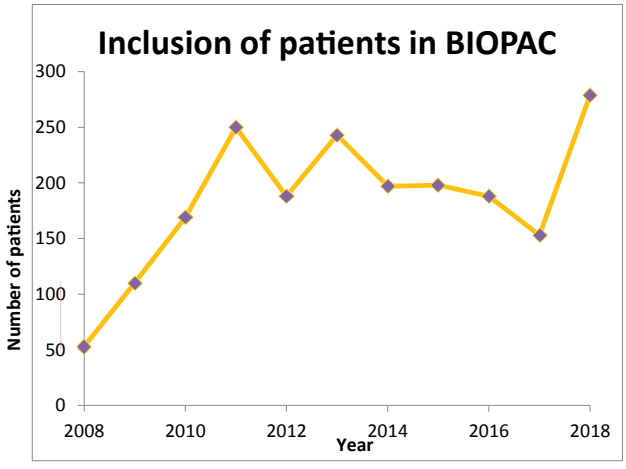

Figure 1: Inclusion of patients in the BIOPAC study per year.

Biological samples

The collected biological materials include blood samples and tissue from the primary tumour and/or metastasis. Blood collection timepoints for patients operated on and patients with unresectable PC are shown in Figure 2. Blood sampling continues until patient's withdrawal of the informed consent at his/her own request and until the study is closed or terminated.

Peripheral blood is collected in four EDTA tubes (4 x 9 ml), two serum tubes (2 x 9 ml) and two PAX gene blood RNA tubes (2 x 2.5 ml, Becton & Dickinson, Lyngby, Denmark). Samples are processed according to the nationally approved SOP for blood (Figure 3). Within 2 hours, tubes are centrifuged at 2300xg at 4˚C for 10 min. After centrifugation, plasma, buffy coat and serum are aliquoted into 10 tubes with 1.5 ml plasma EDTA, 3 tubes with buffy coat (from the EDTA tubes) and 5 tubes with 1.5 ml serum. The 2.5 ml whole blood in 2 PAX gene blood RNA tubes is collected and handled according to the manufacturer's instructions. PAX gene blood RNA tubes are kept at room temperature for 2-72 hours, then frozen at -20˚C for 24-48 hours and finally stored at -80˚C. Buffy coat, EDTA plasma and serum are stored at -80˚C.

Pre-analytical factors such as date of sampling, handling and storage, and the exact handling procedure are registered in the nationwide BIOPAC registry. Tissue samples collected at time of surgery are handled according to the SOP used in the nationwide Bio- and Genome Bank Denmark registry (http://www.cancerbiobank.dk).

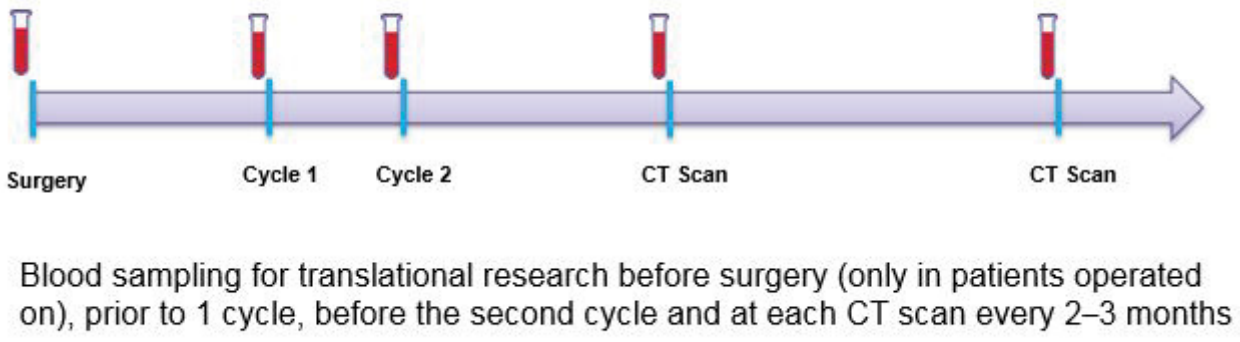

Figure 2: Schematic presentation of blood sampling strategies. Any patient followed in the BIOPAC study may participate at time of diagnosis and before surgery or at start of adjuvant or palliative chemotherapy.

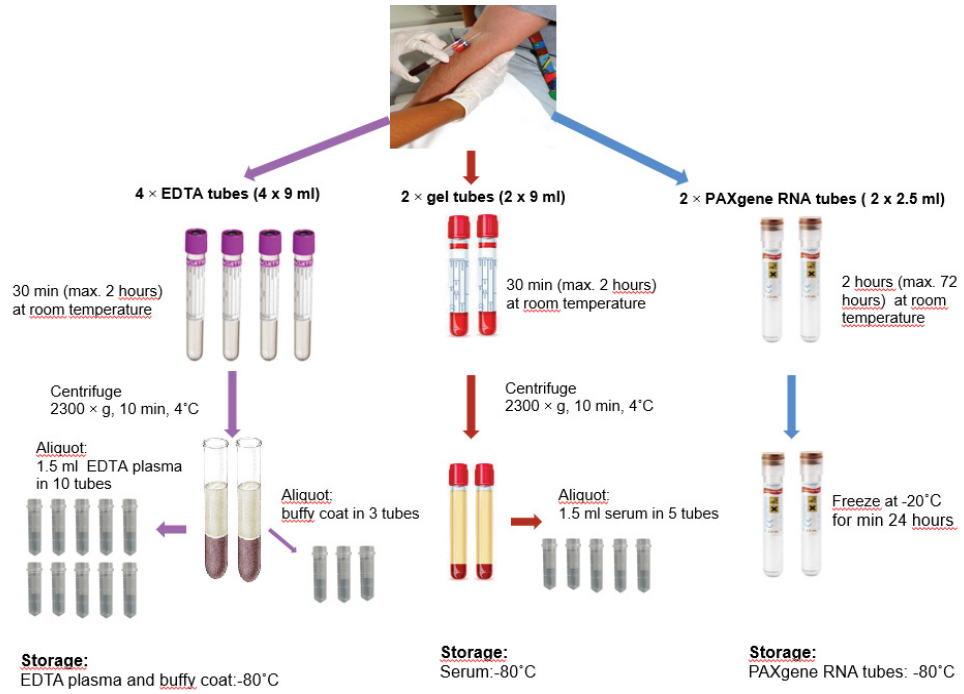

Figure 3: Standard Operating Procedure (SOP) for blood handling in the BIOPAC study. Peripheral blood is collected in four EDTA tubes (each with 9 ml blood), two serum gel tubes (each with 9 ml blood) and two PAXgene blood RNA tubes (each with 2.5 ml blood). Serum tubes coagulate at room temperature for 30 min to 2 hours. EDTA and serum tubes are centrifuged at 2300 × g at 4°C for 10 min. EDTA plasma (10 × 1.5 ml) and serum (5 × 1.5 ml) are isolated. From the EDTA tubes, buffy coat is isolated after removal of EDTA plasma (in three tubes). Plasma and serum samples are stored at ≤ -80°C. PAXgene blood RNA tubes are kept at room temperature for 2–72 hours, then frozen at -20°C for 24–48 hours and stored at -80°C.

Assay methods

The BIOPAC study aims to investigate the following biomarkers in blood and tissue:

1) Genetic variation using next generation sequencing (NGS) and whole genome sequencing (WGS), Kirsten rat sarcoma viral oncogene homolog (*KRAS)* mutations, specific mutations, and RNA and microRNA expression profiles.

2) Protein biomarker profiles of cancer, angiogenesis and inflammation using enzyme-linked immunosorbent assay (ELISA) and the Proseek Multiplex protein arrays (panels of 92 proteins) (Olink Proteomics, Uppsala, Sweden, www.olink.com), or proteomics platforms, such as mass spectrometry, protein-array or multiplexed ELISA.

3) Cell-free DNA in plasma or serum.

4) Metabolites using nuclear magnetic resonance spectroscopy.

All samples will be analysed in pseudo or anonymised form to ensure blinded testing by the laboratory personnel.

The list of specific diagnostic, prognostic and predictive biomarkers will be updated continuously according to new discoveries. The methods of biomarker analysis are rapidly expanding and improving; the best method will be used at time of analysis.

Statistical methods

For the longitudinal samples, it is expected that the numbers collected during a 20-year period will provide sufficient statistical power to identify diagnostic, prognostic and predictive biomarkers. Knowledge within the field is still insufficient; thus, it is not possible to perform a comprehensive power calculation. This will, however, be performed before any biomarker analysis is done.

In general, statistical analyses are carried out according to available data. Comparison of group demographics will be performed with Student's *t*-test, Pearson's chi-square test or Mann-Whitney U-test according to the distribution of data. Treatment duration and time to event will be explored with Kaplan-Meier curves, log-rank statistics and Cox regression analyses. Treatment outcomes across groups or according to specific biomarkers are analysed with logistic regression analyses. Multivariable analyses will be performed to study the impact of potential confounders. These confounders may be identified in the BIOPAC registry (gender, age, smoking status, or other baseline characteristics).

All included patients are recruited and treated in routine care across Denmark, and this will inevitably lead to missing data (missing sampling of biological material, missing registration of corresponding clinical data whenever biological material is collected). However, due to the unique Danish Central Personal Registry (CPR) there will be a 100% follow-up regarding date of death and patients are only lost to follow-up if they emigrate from Denmark. For sensitivity, various statistical methods may be applied to test the robustness of the results. Statisticians are involved if necessary.

Ethics and Dissemination

The BIOPAC study protocol has been approved by the Danish Ethics Committee (VEK, j.nr. KA-20060113) and the Danish Data Protection Agency (j.nr. 2012-58-0004; HGH-2015-027; I-Suite j.nr. 03960). All patients receive verbal and written information before enrolment and give written consent at baseline according to the guidelines of the Danish Ethics Committee. All patients are informed that they can withdraw from the study at any time without any consequences for their treatment. If a patient withdraws, all blood and tissue samples are discarded, and all patient-related information is deleted from the BIOPAC study.

The sampled volume of blood for the study is 59ml per patient visit and a maximum of 767 ml per year. The sampling of blood for the study is performed simultaneously with scheduled routine blood sampling, thus minimising the discomfort for the patient. Tissue samples are collected at time of operation and at time of diagnosis (core needle and/or fine-needle aspiration biopsies from metastases or primary tumour) in patients with locally advanced or metastatic PC.

The results of the studies are expected to be valid on a group level but not on an individual level, and the individual patient is, therefore, not expected to benefit from knowledge of individual measurements. Patients will be given the option to be contacted with information about overall study results and whether these have any significance for them. Direct feedback to the patient may be relevant if mutations in known disease-linked genes are discovered, and it will be provided according to the guidelines directed by the Danish Ethics Committee (document no. 1293688, October 2013). The physician in charge of the project at each participating department is responsible for conducting the study in accordance with the Helsinki declaration. Study participation does not affect the treatment course of individual patients, and the patients will be treated according to normal clinical practice.

Due to the large number of patients included in the study, it will be possible to perform exploratory/discovery biomarker studies as well as validation biomarker studies. All biomarkers will be evaluated and published according to the REMARK [34,35] guidelines. Results will be published in international peer-reviewed scientific journals and presented at international conferences. Negative, positive as well as inconclusive results will be published. If relevant, collaboration with international researchers will be established to facilitate the right expertise for biomarker analyses. Several biomarker studies that include patients from the BIOPAC study have already been published [36-46] and others are in preparation.

Study Status

Recruitment started 3 July 2008 and is expected to continue until 1 July 2028, with follow-up until 2 July 2035. Currently (7 July 2019) 2141 patients (out of planned 5000) have been enrolled in the study and 5156 blood samples have been collected.

Strengths and limitations of this study

- Nation-wide collection of biological materials and corresponding extensive clinical data provide the opportunity to discover and/or validate a wide range of diagnostic, prognostic and predictive biomarkers in patients with suspected or confirmed PC.
- Recruitment of patients with PC treated in routine care is expected to provide valuable data on "real-life patients" (e.g. older patients with comorbidities), which are different from the more homogeneous patient population in randomised controlled trials.
- Standardised collection of samples and quality control ensure comparability between samples from different departments and enable research in a large group of patients.

- Limitations may be encountered regarding patient recruitment and in the collection of clinical and biological data in patients with PC during follow-up in routine care and across several types of treatment.
- The non-randomised study design inherits the risk of confounding, and thorough statistical analysis and confounder adjustment are therefore important.

Discussion

In this observational, prospective, translational research, biomarker study of patients with PC, blood and tissue samples are collected in routine care. Each blood and tissue sample are closely linked to extensive clinical data regarding PC, medical treatment, treatment efficacy, adverse events and comorbidities. The BIOPAC study protocol allows for a large-scale collection of blood and tissue samples with the aim to identify new biomarkers that can be used for improved personalised treatment of patients with PC.

Apart from serum CA 19-9, no biomarkers are used in routine evaluation of patients with PC, and serum CA 19-9 is non-specific as a diagnostic, predictive or prognostic marker.

Due to the generally poor outcome in these patients, it would be useful to identify clinical predictors to avoid over-treatment. The identification of patients with resettable tumours on imaging modalities but with micro-metastases would also be of great clinical value. These patients should be treated with chemotherapy upfront without the waste of time and potential harm associated with unnecessary surgery. In some cases, patients are exposed to explorative surgery without confirmation of cancer; thus, differentiation between benign pancreatic conditions and PC is another but no less important issue.

Future treatments stress the importance of an improved ability to select the most effective treatment in the individual patient with PC. Development of diagnostic, prognostic and predictive biomarkers is expected to facilitate personalised medicine in the future.

Since it is mandatory in Denmark to register all newly diagnosed cases of cancer (Danish Cancer Registry) as well as patients diagnosed with PC (Danish Pancreatic Cancer Database (DPCD)) [47], we can estimate that the completeness of inclusion of patients in the BIOPAC study is ≈20%. One of the reasons for this low degree of coverage is that some patients are not referred to oncological or surgical treatments due to their poor performance status. In addition, implementation of new IT systems (EPIC) or local reorganisation in the hospitals involved clearly affects BIOPAC enrolment. Two oncological departments (out of nine departments in Denmark treating patients with PC) did not have the capacity to participate in the BIOPAC study.

Since patients are recruited across several types of treatment, patient inclusion may take some time in order to obtain enough samples for a specific research question. The non-randomised study design inherits the risks of confounding. On the other hand, the wide recruitment of patients treated in routine care may provide valuable data in a broad spectrum of patients such as older patients with comorbidities and patients with T2DM. This may be a supplement to data generated in randomised trials.

Hopefully, the BIOPAC study will lead to biomarkers that improve our ability to diagnose PC more accurately and at an earlier stage, improve prognostication of patients with PC, and predict treatment effectiveness in the individual patient (tailored treatment).

Conclusion

The BIOPAC study is the first comprehensive study with prospective collection of biological materials and clinical data for researchers and clinicians wishing to conduct basic, clinical and translational research in PC in and outside Denmark. Since its initiation, the BIOPAC study has undertaken several projects in a multidisciplinary setting and constantly promotes the advance of translational research and precision medicine within the PC landscape.

Researchers who are interested in collaboration regarding samples and/or clinical data from the BIOPAC study should contact the BIOPAC team.

Ethics approval and consent to participate

The study protocol is approved by the Regional Ethics Committee for the Capital Region of Denmark (j.nr. KA-20060113). Any changes in the protocol are to be reported to the Regional Ethics Committee. The last study protocol, version 3 from February 16th, 2016, is approved by the Regional Ethics Committee for the Capital Region of Denmark. Informed verbal and written consent is to be obtained for all participants before inclusion in the study.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

None

Funding

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Authors' contributions

JSJ and BVJ wrote the protocol for the Research Ethics Committee. All authors contributed to study conception and design and to inclusion of patients in the BIOPAC study. All authors are involved in acquisition of data, analysis and interpretation of data. IC, AZJ, JB, LSR and JSJ included the clinical data in the database. IC and JSJ drafted and wrote the manuscript and revised the manuscript after feedback from all authors. All authors contributed to review of the present manuscript and approved the final version of the manuscript.

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Provenance and peer review

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