REVIEW ARTICLE

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UEG position paper on pancreatic cancer. Bringing pancreatic cancer to the 21st century: Prevent, detect, and treat the disease earlier and better

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Abstract

Background: Pancreatic ductal adenocarcinoma is the deadliest cancer worldwide with a 98% loss-of-life expectancy and a 30% increase in the disability-adjusted life years during the last decade in Europe. The disease cannot be effectively prevented nor being early detected. When diagnosed, 80% of patients have tumors that are in incurable stages, while for those who undergo surgery, 80% of patients will present with local or distant metastasis. Importantly, chemotherapies are far from being effective.

Objective: Pancreatic cancer represents a great challenge and, at the same time, a huge opportunity for advancing our understanding on the basis of the disease, the molecular profiles, that would lead to develop tools for early detection and effective treatments, thus, boosting patient survival.

Results: Research on pancreatic cancer has being receiving little or minimal funds from European funding bodies. UEG is calling for public-private partnerships that would effectively fund research on pancreatic cancer.

Conclusion: This would increase our understanding of this disease and better treatment, through pan-European efforts that take advantage of the strong

academic European research landscape on pancreatic cancer, and the contribution by the industry of all sizes.

KEYWORDS
chronic pancreatitis, familial pancreatic cancer, funding, Horizon Europe, intraductal papillary mucinous neoplasm, pancreatic cancer, pancreatic ductal adenocarcinoma

INTRODUCTION

Pancreatic cancer has become an increasing health problem in the Westernized world, which is currently out of control. Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, could be considered an orphan disease, as it has not received the necessary attention from the pharmaceutical industry to date. The U.S. Congress has defined PDAC as a "recalcitrant cancer," leading to the implementation of a 5-year effective "Pancreatic Cancer Research and Education Act" involving research for bio-markers of early detection. Similarly, the European Commission-supported "Innovative Partnership for Action Against Cancer" called PDAC a "neglected cancer" due to its biological aggressiveness, late diagnosis, and lack of effective treatments and therefore prioritized all actions to control this disease.[1] Remarkably, public and private funding for PDAC research over time has been significantly less than for other cancers for which a large impact in their survival has been achieved.[2]

Facing this situation, the following position paper initiated by members of the UEG Public Affairs and Research committees and co-authored by scientists from six European countries aims to increase awareness for pancreatic cancer among European stakeholders from politics, industry, and academia by identifying areas with immediate need for joint actions.

EPIDEMIOLOGY: CURRENT SITUATION AND PERSPECTIVES FOR 2030 AND BEYOND

Incidence & mortality

Despite its relatively low population-wide incidence, PDAC remains the deadliest cancer worldwide. In 2020, the estimated number of new PDAC cases in Europe is 140,116, with a crude incidence rate of 18.7 per 100,000 men and women per year. The corresponding mortality figures are 132,134 and 17.6, respectively, almost paral-leling the incidence numbers.[3] PDAC is a deadly tumor still harboring a 98% loss-of-life expectancy and associated with a 30% increase in the disability-adjusted life years during the last decade in Europe.[4,5] Due to its aggressiveness, it has risen from the seventh position in the cancer incidence ranking to the fourth leading cause of cancer-related deaths in Europe[3] and the third leading cause in USA.[6] PDAC incidence and mortality increases with age; therefore, this tumor will become an increasing health problem in the aging

European countries. Recent publications have raised awareness of the dramatically increasing incidence of PDAC in the Western world unless urgent action is taken. In Europe, PDAC death rates are steadily rising while rates for all other cancers continue to fall.[7,8] US data suggest that PDAC will become the second-leading cause of cancer-related deaths by 2030.[9] The high mortality from PDAC is mainly due to the difficulties in early diagnosis, in particular the absence of specific symptoms and biomarkers in early stages, as well as the aggressive nature of the disease and frequent resistance to systemic therapies, which makes early detection and treatment highly challenging.

Clinical Scenarios and survival

PDAC is the only cancer entity for which there has been only mar-ginal improvement of its appalling prognosis over the last decades despite considerable efforts in tertiary prevention and novel treat-ment strategies. Overall, PDAC still has a 5-year survival of <10%.[3,10] At the time of diagnosis, 80% of patients have tumors that are in incurable stages (locally advanced or metastatic). In the remaining 20% (localized resectable disease), surgery is the only potentially curative treatment. However, even after complete surgical resection, 80% of patients will present with local or distant relapses[4] due to the existence of micrometastatic disease at the time of diagnosis. Adju-vant chemotherapy (Gemcitabine-fluoropyrimidine/mFOLFIRINOX) is commonly used to improve this scenario.[11] The impact of this strategy on the survival of PDAC is significant, but still 60%–70% of patients relapse at 3 years.[12] Unfortunately, new personalized treatment strategies, through improved multimodal approaches including surgical resection, in combination with neoadjuvant and targeted chemotherapy, have yet to prove a significant benefit for the majority of patients.

ETIOLOGY, PREVENTION, & SCREENING: CHALLENGES TO DEFINE THE POPULATION-AT-RISK

Given the rising incidence of PDAC over the past 2 decades, special efforts must be made to better understand the risk factors contrib-uting to disease development in order to promote prevention stra-tegies and define the population at risk which could benefit from a protocolized screening.[13] Currently, the known risk factors do not

fully explain the rising incidence and its dramatic projections for the future. To date, no screening protocol exists that has demonstrated a medical and socio-economic benefit for patients at high-risk or the general population.

Etiology

PDAC is a paradigm of complex disease. Known environmental risk factors explain only about 40% of the disease. Family history (population attributable fraction, PAF = 3%–10%), tobacco (PAF = 11%–32%), type-2 diabetes mellitus (T2DM) (PAF = 1%–16%), obesity (PAF = 3%–16%), chronic pancreatitis (PAF ≤ 3%), heavy alcohol intake (PAF ≤ 3%), and A/B blood group (PAF = 13%–19%) are the only firmly established environmental risk factors for PDAC, while allergy/asthma (PAF = 3%–7%) decrease the risk.[14–19]

The growing prevalence of diabetes and obesity, mainly in Westernized countries (www.who.int/diabetes/global-report), may partly account for the increased incidence of PDAC. Many meta-analyses, carried out collecting datasets from studies including >3000 PDAC patients assessed that diabetic patients showed a 1.8-fold increased risk of PC (95% CI 1.5–2.1).[14] Similarly, obesity and overweight at any age are associated with increased incidence of PDAC, with hazard ratio ranging from 1.15 to 1.53. In this context, a longer duration of BMI > 25 kg/m^2 is significantly associated with PDAC risk (HR per 10 years increment of duration: 1.06 95% CI: 1.05–1.32).[20]

Chronic inflammation is well-known to play an important role in pancreatic carcinogenesis. For chronic pancreatitis, the pooled relative risk estimates for PDAC varies from 2.7 to 13.3. The PDAC risk is especially high in hereditary pancreatitis due to PRSS1 mutations. Among all risk factors associated with PDAC, pancreatitis has the highest relative risk of greater than 2, however, the prevalence of PDAC in sporadic chronic pancreatitis is not high enough to justify screening or surveillance, except for hereditary pancreatitis.[21] In addition, recent data also suggests a contribution of the microbiome[22] which warrants further clinical validation and exploitation. Despite these accumulating data, there are still important knowledge gaps on the association between all these factors and the resulting PDAC risk. In particular, knowledge is limited on the cumulative risk of cancer in case of the presence of multiple parallel risk factors.

Epidemiological studies have classically approached the analysis of risk factors on a "one-by-one basis." However, this strategy is too simplistic when considering the reality that genetic and non-genetic exposures concur within a given individual. In most cases, a context of interactions between multiple (epi)genomic, and environmental risk factors is involved. This fact supports the use of multifactorial strategies as a must to mimic biology. The technological omics revolution provides a wealth of information that can be exploited under this concept to generate knowledge that can be applied at the population level. As the complexity of the biological mechanisms underlying disease increases, so does the need to adopt an interdisciplinary or trans-disciplinary approach in order to disentangle the intricate factors involved in disease development and progression.

A better understanding of the modifiable risk factors, the major component involved in pancreas carcinogenesis, and their interactions with (epi)genetic host profiles would allow designing appropriate primary prevention interventions with the ultimate goal of decreasing PDAC incidence and mortality in Europe. Large-scale international collaboration is essential to accelerate and strengthen discovery in PDAC etiology, as well as to speed-up translation of results into the public health domains. Primary prevention is aimed at reducing the effects of contributory risk factors of which tobacco smoking is a moderate, and obesity, excess alcohol consumption (>30 g [3.8 units] per day) and red meat consumption are low risk relative factors.[14] Thus, the top 6 of the 12 recommendations of the European Code against Cancer to prevent cancer are all directly relevant to pancreatic cancer prevention.[23] The difficulties in defining a high-risk population explain, in part, the lack of success of the screening interventions showing a large proportion of false positive findings. More multi-national large-scale studies are needed to elucidate the impact of lifestyle habits, diets and dietary constituents, physical activity, microbiota, hydrocarbon compounds, pesticides, fine particles, heavy metals, and other yet unidentified triggers of carcinogenesis.

Genetic susceptibility

PDAC, like many other complex diseases, has genetic and environmental components to its etiology. Up to 40 common genetic variants with modest effects on PDAC risk have been identified playing a role in genetic susceptibility to sporadic forms of the disease.[24] The relatively high frequency of such variants means that they could potentially explain a substantial portion of disease risk. Several

Action needs

Implementation of the following cancer-preventing guidelines into European health policies:

1. Do not smoke. Do not use any form of tobacco.
2. Make the home smoke free; smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time spent sitting.
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits.
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
   - Avoid processed meat; limit red meat and foods high in salt.
6. Limit the intake of alcohol of any type.

attempts to build polygenetic scores have not been successful in their translation into the prevention field.[25] More comprehensive approaches are needed to make progress, including global analyses of biologically relevant pathways and genome-wide association studies. In this regard, a recent multi-step GWAS strategy conducted solely in European population, combined with an in-depth in silico functional analysis, allowed to identify further low-penetrance loci.[26] A number of consortia comprising pre-existing studies have already been formed to facilitate the identification of further low-penetrance variants and gene-environment interaction through meta-GWAS strategies. However, these approaches do not substitute for the design of novel, sufficiently powered studies that apply uniform criteria to case selection, the acquisition of environmental exposure information, and to biological sample collection.[27]

Screening of individuals-at-risk (IAR)

For now, a specific screening program is proposed to individuals with a strong family history of pancreatic cancer and/or genetic susceptibility of developing PDAC, among them individuals with suspected familial pancreatic cancer (FPC). FPC is defined by occurrence of PDAC in at least two first-degree relatives and could account for up to 10% of all PDAC cases.[28] The risk increases with the number of first-degree relatives with PDAC, with a standardized incidence ratio between 17 and 32 for individuals with ≥3 first-degree relatives with PDAC. In 2020, the international CAPS consortium proposed updated recommendations for surveillance. The main objectives of this screening are to detect high-grade dysplastic precancerous lesions (including intraductal papillary mucinous neoplasm [IPMN] and PanIN) and T1N0M0 pancreatic cancer. This surveillance relies on a morphological evaluation using endoscopic ultrasound (EUS) and/or Magnetic Resonance Imaging (MRI)/magnetic retrograde cholangiopancreatography (MRCP) as preferred procedures. However, no consensus was found regarding the preferred modality. An annual surveillance was proposed with no robust data to support this recommendation. Moreover, no consensus was reached for surveillance in case of chronic pancreatitis due to genetic defects. The difficulties to reach consensus by this consortium (which combined the main experts of this field) reflects the lack of robust data in the literature. It also highlights the lack of biological tools to detect early precancerous lesions.[28]

Research & action needs

- Develop new methods to better define and validate multi-parametric risk constellations and persons-at-risk involving large-scale trials and a cross-national pan-European effort with public-private partnerships (PPP).
- Identify screening markers and algorithms with a sufficient diagnostic accuracy and cost effectiveness to detect precancerous lesions in persons-at-risk.

EARLY DIAGNOSIS: CHALLENGES TO FIND INVISIBLE PRECURSORS

Due to its location deep in the body, the pancreas is not easily accessible for screening procedures such as the breast, colon, or prostrate. When suspected, only macroscopic pancreatic cancer lesions can be detected using imaging techniques, often revealing advanced or metastatic stages. Therefore, early diagnosis has to rely on imaging and blood tests rather than direct inspection.

Given the absence of early clinical symptoms or currently available reliable clinical indicators for preneoplastic stages or early PDAC in the general population, early diagnosis is most likely to succeed in high-risk individuals described above. In this population, potential novel markers can be searched that eventually can be used for screening after clinical validation.

In this context, two groups of individuals-at-risk (IAR) stand out: (1) members from families with heredity for PDAC development, particularly in case of suspected familial pancreatic cancer (FPC) and (2) patients with preneoplastic lesions such as cystic pancreatic tumors, so-called "intraductal papillary mucinous neoplasm" (IPMN). IPMN are further divided in main-duct IPMN that represent an obligatory precancerous lesion and are generally subjected to surgery, and side-branch IPMN which represent cystic lesions with a lower potential for malignant transformation. Current recommendations and guidelines for both IAR[28] and IPMN[29] describe how to conduct surveillance but are frequently limited by lack of evidence.

State-of-the-art imaging

Modern imaging technologies, preferably with MRI and MRCP given the need for repetitive investigations in these patients groups,[30] are able to detect millimeter-size lesions. Current guidelines define "worrisome features" indicating a progress towards malignancy in IPMN.[29] All suspicious lesions IAR need to be further studied.[28] In such patients, more invasive diagnostic methods could be discussed in a multidisciplinary team[31]: EUS with fine-needle biopsy[32] being standard of care, and ERCP with direct pancreatoscopy (Spyglass),[33] eventually with confocal laser microscopy (pCLE)[34] representing appealing additional tools. While there is a definitive diagnostic gain, all these invasive methods carry a risk for complications. They should only be performed in patients in which the diagnosis is doubtful and a therapeutic consequence (e.g., surgery) is considered. While current imaging is able to detect millimeter-size lesions, the vast majority of these cystic lesions will never progress to malignancies. To date, imaging tools to reliably predict the malignant potential are lacking. In this context, PET imaging modalities have attracted increasing attention which needs to be further explored.[35] To achieve a higher diagnostic accuracy, molecular imaging, radiomics, digital pathology approaches, and refined cross-sectional and EUS-based techniques have to be developed and evaluated. In addition, blood-based liquid biopsies may be suitable to identify high-risk lesions more reliably.

Liquid biopsies

Identifying biomarkers in body fluids (liquid biopsies) for early PDAC or preinvasive precursors with potential for malignant transformation is the holy grail in pancreatic cancer research. Although the tumor marker CA 19-9 has a low sensitivity, it is the best available marker for PDAC to date.[36] Increase in CA 19-9, even if still in the normal range (<35 u/ml), is indicative of a progress in IPMN[37] and indication for surgery.[38] In contrast to other tumors, the development of liquid biopsies in PDAC is lacking behind. Circulating tumor cells are a rare event in PDAC.[39] Some reports described the presence of circulating epithelial cells in premalignant lesions such as IPMN.[40,41] Free circulating DNA (ctDNA)[42,43] and exosomes have been studied in invasive PDAC,[44] less so in premalignant conditions. Currently, extracellular vesicles (exosomes) are among the most promising candidates for early diagnosis of PDAC.[45] In these vesicles, several candidate markers for IPMN in exosomes such as KRAS mutations and glycipan have been proposed.[46] Apart from serum, several publications have proposed pancreatic juice as another promising source for molecular analysis for diagnosis of early lesions.[47] In addition to individual markers, panels of different markers are more likely to predict malignancy with sufficient diagnostic accuracy. Stemming from a study in serum protein profiling,[48] a panel of immunoregulatory marker proteins has been tested in PDAC patients.[49] A study in IAR testing this panel has finished recruiting (PANFAM, NCT03693378). Given the fact that many initially promising markers or combinations thereof have failed validation in large trials, it is evident that all of these approaches need confirmation in independent multi-center cross-national prospective trials requiring a pan-European network that utilizes all state-of-the-art methodologies including multi-omics platforms and artificial intelligence algorithms developed by academic centers and industry.

CURATIVE THERAPY: CHALLENGES TO IMPROVE SURGICAL OUTCOMES – THERAPY SEQUENCE AND MULTIMODAL THERAPY

Systemic chemotherapy is the mainstay for improving progression free and overall survival (OS) in patients with metastatic disease and/or locally advanced PDAC.[50–54] Using additional chemoradiotherapy increases toxicity without improving OS, either upfront to systemic chemotherapy or following chemotherapy without progression for locally advanced disease.[55–57]

Adjuvant therapy

In patients with locally resectable tumors but without metastatic disease, advances in surgical techniques and post-operative management combined with multimodality therapy in the form of adjuvant systemic chemotherapy has led to a dramatic improvement in outcomes (Table S1).[55–57] There has been a remarkable reduction in post-

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Research & action needs

- Develop novel imaging technologies including molecular imaging, radiomics, digital pathology approaches, and refined cross-sectional and endosonography-based techniques to detect precancerous lesions or tumors at a very early stage, with joint technology development efforts by industry and academic partners.
- Identify biomarkers or combinations of markers suitable for reliable detection of preneoplastic lesions or early tumors in liquid biopsies based on distinct genetic, epigenetic, proteomic, or immunological alterations.

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operative mortality from 30% in general surgical units to less than 5% in specialist centralized units.[58,59] The use of adjuvant systematic chemotherapy has resulted in an amazing increase in a 5-year survival from 8% with resection alone to 30%–50% when this was followed by 6 months combination chemotherapy.[11,12,60–63] The longest OS achieved with adjuvant chemotherapy is using mFOLFIRINOX (modified folinic acid, 5-fluorouracil [5-FU], irinotecan, and oxaliplatin), but this comes with added toxicity and frequent hospitalizations compared to adjuvant gemcitabine and capecitabine.[11,12,60–63] Although mFOLFIRINOX is recommended as the preferred treatment it should be borne in mind that the PRODIGE24 trial used highly selected patients with a more favorable prognosis than those in the ESPAC-4 trial and there may be differences between the two regimens in survival responses in different subgroups.[11,12,60–63]

The combination of gemcitabine and nab-paclitaxel was found to be effective in the metastatic setting, although less so than FOLFIRINOX in this same setting. In the adjuvant setting gemcitabine and nab-paclitaxel was not superior to gemcitabine for the primary endpoint of disease-free survival and is not approved for this purpose by the FDA.[64] Nab-paclitaxel was developed to target the stroma of the primary cancer and may explain the failure of the combination in this setting.[65] As in advanced PDAC the use of chemoradiotherapy in addition to chemotherapy does not improve survival whilst increasing toxicity and may even be deleterious.[11,12,60–64,66–71]

Neoadjuvant therapy

The use of neoadjuvant therapy appears to increase resectability and hence survival in patients with otherwise unresectable local disease due to local vessel encasement, even in the presence of resectable oligometastatic disease (Table S2).[72,73] An argument has also been made to extend the use of neoadjuvant therapy to patients with resectable disease because the total chemotherapy delivered might be reduced to post-operative complications but in reality, this is not achieved.[74–76] A recent trial of perioperative chemotherapy comprising 12 weeks preoperative chemotherapy, followed by surgery, and then 12 weeks postoperative chemotherapy randomized

patients to either mFOLFIRINOX or gemcitabine plus nab-paclitaxel.[74–76] The findings showed that using neoadjuvant chemotherapy, compared with adjuvant trials did not demonstrate an improved OS.[74–76]

Randomized studies using a mixture of resectable, borderline resectable, and locally advanced disease have tended to produce a confused picture.[77–79] Two recent trials focusing only on borderline resectable disease, however, have produced more consistent results.[80,81] The ESPAC-5FT trial has shown that using neoadjuvant therapy is superior to upfront surgery with little difference in OS between mFOLFIRINOX and gemcitabine/capecitabine.[80,81] Both ESPAC-5FT and the Alliance A021501 randomized trials showed that chemoradiotherapy (as in the advanced and adjuvant settings) was inferior to chemotherapy alone.[80,81] However, further evidence from other ongoing trials is awaited.

Despite marked progress achieved through the advent of potent adjuvant and neoadjuvant chemotherapy regimens, many questions on optimized treatment sequences depending on defined molecular subtypes or on the role of targeted therapies in the (neo)adjuvant setting remain to be addressed and require a concerted pan-European trial network.

Research & action needs

1. Define optimized multimodal approaches and treatment sequences for resectable and locally advanced tumors depending on molecular subtypes in order to minimize the risk of systemic spread and to maximize the chances for complete surgical resection, thereby improving long-term survival.
2. Establish an Europe-wide clinical trials infrastructure with funding made available for investigator-led clinical trials in partnership with industry.
3. Introduce centralized pancreatic cancer services across European countries to improve quality control and optimization of surgical and medical care, including mandatory reporting of clinical characteristics and survival data.
4. Establish a Europe wide experimental pancreatic cancer centre infrastructure with PPP to support the clinical trials network and develop existing and future opportunities for surgical and medical oncological therapies.

OVERCOMING RESISTANCE: CHALLENGES TO TARGETED THERAPIES

Genetically, PDAC is an extremely heterogenous disease, characterized by an abundant stroma reaction and a highly immune-evasive phenotype, contributing to the primary or secondary resistance to systemic therapies frequently observed in this tumor.

In patients with metastatic PDAC, systemic chemotherapy represents the only treatment option. During the last decade clinically relevant survival benefits could be achieved by using combination regimens such as FOLFIRINOX[52] and gemcitabine + Nab-paclitaxel.[82] However, only a fraction of patients responds to these cytotoxic drugs and current targeted options have proven largely futile.[83]

Genetic Heterogeneity

Following genomic and transcriptomic profiling results, two major transcriptomic subtypes of PDAC ("classical" and "basal-like") have been proposed,[84–86] with basal-like PDACs frequently responding poorly to conventional chemotherapy protocols.[83] Moffitt et al. further refined the transcriptional subtypes by proposing "normal" and "activated" stromal subtypes, the latter being associated with poor survival.[85] Given the fact that currently systemic therapies of PDAC still rely on conventional chemotherapy, increasing interest is focused on developing transcriptomic signatures predictive of treatment response to different agents.[87] So far, however, subtype-specific treatment strategies have not been shown to be clinically relevant.[88]

Similarly, targeting single driver mutations has proven difficult in the clinical setting, given the low frequency of individual druggable mutations.[83] Exceptions affect only small fractions of PDAC patients and include microsatellite instable tumors amenable to checkpoint inhibition,[89] tumors with germline BRCA1/2 mutations benefiting from platinum-based chemotherapies and PARP-inhibitors[90] and the rare KRAS wild-type tumors with a higher frequency of mutations such as NRG1 or NTRK fusions.[83,91,92] In contrast to other tumor entities such as melanoma, lung cancer, and breast cancer, prospective evidence for genetic testing strategies in sporadic PDAC patients is still missing and molecular characterization of PDAC in patients with advanced disease has not yet entered routine clinical practice.[83] Due to the low frequency of individual genetic alterations, clinical evaluation requires innovative trial concepts (umbrella or basket trials) involving large patient cohorts that are evaluated through a common genetic testing platform and subsequently enrolled in mutation-specific trials arm.

Complex stromal reaction

PDAC is characterized by an extensive stromal reaction with massive extracellular matrix deposition accounting for up to 90% of the tumor volume, rendering this tumor entity one of the most stroma-rich solid tumor types.[83,93] The pancreatic tumor microenvironment has attracted much interest in the past decade, particularly its role as a determinant of therapy resistance. The PDAC stroma contains a variety of cellular components, including inflammatory cells, cancer-associated fibroblasts, endothelial and nerve cells as well as numerous acellular components including collagens, fibronection and hyaluronic acid.[93] The initial enthusiasm to target the dense, hypovascular stroma was belied by the failure of all previous large trials targeting cellular or acellular stroma components as well as stromal

signaling pathways,[93] indicating that the highly complex, time- and space-dependent interactions between different stromal components and tumor cells represent an ongoing challenge for therapeutic intervention.

Immune-evasive phenotype

In contrast to numerous cancer types, most prominently malignant melanoma, PDAC is largely immune-evasive and refractory to conventional immunotherapy by checkpoint inhibitors, probably reflecting the immunosuppressive nature of the its microenvironment,[93] Mechanisms by which PDAC suppresses the immune response are currently being extensively studied, including activation of regulatory T cells (Treg cells),[94] or myeloid-derived suppressor cells (MDSCs),[95] inhibition of cytotoxic T cells, or modulation of macrophage populations within the tumor.[93,96] Numerous therapeutic combination strategies addressing various components of the adaptive and innate immune response are currently being evaluated to enhance the immunogenicity of PDAC. However, none of these strategies so far has proven to be improve patients outcome so far.

Research & action needs

- Identify novel drivers of tumor development including genetic drivers and inflammatory cues such as obesity- and diabetes-induced or microbiome-associated modifiers in order to establish novel diagnostic, prognostic and predictive biomarkers.

- Improve the understanding of complex tumor biology and decipher events driving tumor development and therapy resistance to foster the development of novel precision medicine avenues based on molecular signatures. This requires joint efforts using state-of-the-art -omics and non-omics technologies in PPP between academia and industry, integrating academia-based technologies, Europe-wide digital registries, well-annotated biobanks, research consortia and large-scale screening units in pharmaceutical industries.

- Implement Europe-wide umbrella trial platforms recruiting patients whose tumors are molecularly characterized in a comprehensive manner at a multi-omics level to test new targeted therapeutic avenues for small molecular subgroups of patients. Given the low frequency of many molecular alterations, it is essential that these efforts encompass multi-national, multi-center, public-private trial platforms allowing simultaneous access to multiple targeted agents depending on the molecular subtype, if feasible in multimodal approaches involving systemic therapies, radiotherapy and nuclear medicine-driven strategies.

A PATIENT-CENTERED VIEW OF PANCREATIC CANCER CARE

While measurement of "value of healthcare," engagement of patients and evaluation of patient-reported outcomes (PROs) are becoming essential parts of modern medicine,[97] this is particularly relevant for a disease such as PDAC, where life expectancy is often modest, quality of life (QoL) is heavily impaired and care requires specific skills and organization. However, specific performance indicators for the care of PDAC patients that take into account their view and preferences are rarely employed in clinical practice.

PROs are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[98] Accordingly, PROs should be measured by structured instruments, defined patient-reported outcome measures (PROMs) that should be developed and validated in conjunction with patients and caregivers and patients' advocacy groups. A recent systematic review on PROs and PDAC identified only 170 studies employing PROMs in PDAC patients.[99]

The more frequently employed tools to evaluate patient-reported outcome measure (PROMs) in PDAC are the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire Pancreatic Cancer Module (QLQ-PAN26).[100]

QLQ-C30 has been used more diffusely in PDAC patients with different disease stage, typically as secondary outcome in randomized controlled trials investigating treatment strategies.[11] Overall, the available data suggest that PDAC patients report a lower quality of life with more challenges for themselves and caregivers compared to other tumor types.[100]

The QLQ-PAN26, which is more specific and should possibly be used together with the QLQ-C30 to gain a global view of different aspects of QoL, has been developed taking into consideration the view of patients and patients' advocacy groups.[101] This instrument, however, needs further validation in the different disease stages and has not been translated in many languages yet. Besides PAN26, another specific instrument developed with PDAC patients, and employed in a more limited number of studies being the Functional Assessment of Cancer Therapy–Hepatobiliary.[102]

Notably, the number of studies investigating PROs in advanced disease, especially beyond 12 months of disease is extremely limited, urging more investigation in this field, as the introduction of more effective intensified chemotherapy regimens is likely to guarantee a longer life expectancy for many patients.[99]

Over the past few years, there have been other attempts to develop specific sets of PROs with the collaboration of patients' representatives, but they have not been validated yet.[103,104]

Another important aspect of patient-centered care is the need to engage the patient in the treatment process to obtain optimal compliance and better QoL and clinical results. Patient-engagement can be measured by specific validate scales, such as the PHE, that is currently being explored in PDAC patients.[105]

Finally, the experience and perception of patients during each step of the care process should be measured with questionnaires reporting patient-reported experience measures (PREMs).[106] There are no PREMs investigating PDAC patients trajectories during the different specific steps of care, such as endoscopic procedures, surgery, chemotherapy, or other clinical episodes.

Integration of PROMs and PREMs into the whole process of cure of PDAC patients is likely to improve not only the engagement of patients and their QoL, increasing the awareness of the treating medical team toward unmet needs, but eventually to result in improved survival as recently demonstrated.[107] The development of specific user-friendly mobile Applications (App) may result particularly useful in this setting as suggested by preliminary findings with an App developed for the management of PROs after pancreaticoduodenectomy.[108] The development of such integrated, digitalized systems to monitor the whole health care process, requires joint public-private efforts with technical know-how from the industry and input from academic sites and patients' advocacy groups.

Research & action needs

- Develop integrated systems to measure the quality of care from the patients' viewpoint with specific tools and their monitoring through mobile Apps, which may reduce the need for hospital stays, improve compliance with the treatment plan and ultimately prognosis.

- Digitalize the whole health care process, which may result in an optimization of costs and resources and in a reduced burden for caregivers. Integrating a "patient oriented" measure of the quality of care is likely to improve not only the quality of life but also engagement and eventually the clinical outcomes. Development of digital health care networks requires joint public-private efforts with technical know-how from the industry and input from academic sites and patients' advocacy groups.

THE URGENT NEED: A PAN-EUROPEAN CONCERTED ACTION ON PANCREATIC CANCER WITH STRONG PUBLIC-PRIVATE PARTNERSHIPS

Pancreatic cancer represents a huge challenge for researchers across Europe, spanning from understanding the fundamental basis of the disease, its peculiar molecular profiles, lack of existing tools for early detection, and effective treatments that would enhance patient survival and quality of life.

Despite its staggering growing epidemiology, research on pancreatic cancer is receiving fractions of the budgeted funds for cancer research established by European funding bodies. In order to effectively slow down the epidemiological trend and beat the disease, it is mandatory to establish quick and concerted actions to accelerate advances and reduce the high mortality burden that will need to see multiple stakeholders involved throughout the continent. Thus, co-ordinated efforts are absolutely vital in order to generate advancements that will inevitably lead to better prevention and treatment.

The new framework program, Horizon Europe, will aim at providing significant opportunities to improve European citizens' health. Within Horizon Europe, the new Innovative Health Initiative will create a European multi-sector partnership for health innovation, fostering in particular PPP, with the overall goal to "accelerate the development of safer and more effective healthcare interventions that respond to unmet public health needs, and that can be taken up by healthcare systems" (https://www.euhealthppp.org). We believe that research on pancreatic cancer fits completely within the agenda for Innovation in Healthcare that falls in the framework of the proposed PPP.

While policy makers must produce a targeted EU funding policy for pancreatic cancer, PPP are crucial to tackle the barriers that are hampering the advancement for understanding and treating this disease, boosting cross-national, pan-European efforts. This will require co-operation across sectors, that will lead to meeting the priorities set by the Europe's beating cancer plan and the Mission on Cancer. The partnerships will take advantage of the strong academic European landscape, which consists of existing centers and researchers of excellence devoted to research on pancreatic cancer.

The contribution by the industry of all sizes will be crucial for the development of new programs that would develop new technological tools (including AI), platforms for high-quality data sharing and new pharmacological strategies by taking advantage of a more synergic efforts through the sharing of big data from relevant cohorts, registries, and by federating biobanks across Europe.

While boosting the competitiveness of the industry across the continent, such partnership will lead to a more precise prevention, early diagnosis, effective treatment and personalized, patient-centered care, for a disease that up to now has not reached any of these goals.

Thus, we strongly support such partnership and the inclusion of the challenges of pancreatic cancer in the Mission on Cancer and Europe´s Beating Cancer Plan. We believe that these initiatives represent a unique opportunity for beating pancreatic cancer in Europe, with the ultimate goal of contributing to better health outcomes across the EU.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.