Review

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Pancreatic cancer: from early detection to personalized treatment approaches

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Abstract

Pancreatic cancer is notorious for its persistently poor prognosis and health outcomes, so some of the questions that may be begged are "Why is it mostly diagnosed at end stage?", "What could we possibly do with the advancing technology in today's world to detect early pancreatic cancer and intervene?", and "Are there any implementation of the existing novel imaging technologies?". Well, to start with, this is in part because the majority of patients presented would already have reached a locally advanced or metastatic stage at the time of diagnosis due to its highly aggressive characteristics and lack of symptoms. Due to this striking disparity in survival, advancements in early detection and intervention are likely to significantly increase patients' survival. Presently, screening is frequently used in high-risk individuals in order to obtain an early pancreatic cancer diagnosis. Having a thorough understanding of the pathogenesis and risk factors of pancreatic cancer may enable us to identify individuals at high risk, diagnose the disease early, and begin treatment promptly. In this review, the authors outline the clinical hurdles to early pancreatic cancer detection, describe high-risk populations, and discuss current screening initiatives for high-risk individuals. The ultimate goal of this current review is to study the roles of both traditional and novel imaging modalities for early pancreatic cancer detection. A lot of the novel imaging techniques mentioned seem promising, but they need to be put to the test on a large scale and may need to be combined with other non-invasive biomarkers before they can be widely used.

Keywords: diagnosis, early screening, high-risk groups, imaging, pancreatic cancer, risk factor

Introduction

Globally, pancreatic cancer ranks seventh among the leading causes of cancer-related mortality, predominantly affecting high-income regions[1–3]. In Europe, it stands as the fourth deadliest cancer for both sexes, and in Northern America, it claims the third spot[4]. It is estimated that in 2023, there will be 1 958 310 new cases of cancer and 609 820 deaths from cancer in the United States[5].

Pancreatic cancer confines a group of malignancies originating from either the exocrine or endocrine tissue of the pancreas. The predominant form is pancreatic ductal adenocarcinoma (PDAC), accounting for about 85% of cases[6]. While 90% of PDAC cases occur sporadically, about 10% are linked to hereditary and familial predisposition syndromes. Smoking, alcohol use, and chronic pancreatitis are established risk factors, and the likelihood of PDAC rises with age, particularly between 60 and 80 years[7].

Unfortunately, PDAC is projected to become the second leading cause of cancer-related deaths by 2030[8]. The majority of patients present with metastatic or locally advanced disease, and

HIGHLIGHTS

- Globally, pancreatic cancer ranks seventh among the leading causes of cancer-related mortality, predominantly affecting high-income regions. In Europe, it stands as the fourth deadliest cancer for both sexes, and in Northern America, it claims the third spot. Pancreatic cancer comprises a group of malignancies originating from either the exocrine or endocrine tissue of the pancreas. The predominant form is pancreatic adenocarcinoma (PDAC), accounting for about 85% of cases.
- Early detection and staging are essential for the proper management of pancreatic malignancy, including surgical planning and better prognosis. Nevertheless, the prognosis is poor due to aggressiveness, hidden growth, fluctuating signs till late stages, and mostly the lack of reliable early detection methods.
- The multimodality approach has led to recent significant advancements in pancreatic imaging; however, each modality has specific roles, benefits, and drawbacks for pancreatic cancer.

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surgical resection is viable for only 10–20% of individuals[9]. The prognosis for pancreatic cancer remains grim, with a 5-year survival rate of 8–10%[10]. Given late-stage diagnoses and the correlation between prognosis and disease stage, there is a crucial need for early detection methods. Despite the commendable goal of early PDAC detection, general population screening for asymptomatic individuals is discouraged[11]. However, screening high-risk individuals can be advantageous, enabling earlier diagnosis and potentially life-saving surgical intervention, which remains the most effective curative approach[12]. The identification of optimal imaging modalities for early PDAC detection is still an ongoing challenge.

High-risk groups

- Pancreatitis:
  - Acute and chronic pancreatitis have been associated with the risk of pancreatic cancer.
  - Ongoing tissue injury, inflammation, fibrosis, and damage to cellular DNA promote neoplastic development and progression in chronic pancreatitis, especially in hereditary, recurrent, acute pancreatitis.
  - Tissue damage is sustained over a period of decades in chronic pancreatitis.
  - Estimates associated with hereditary pancreatitis and pancreatic cancer were high up to 70%[13].
- Smoking:
  - Numerous epidemiological studies have shown that chronic cigarette smoking is linked with an average two-fold increase in its risk, with the population-attributable risk of pancreatic cancer due to smoking ranging from 11 to 32%[14].
- Obesity:
  - It has been hypothesized that increased obesity in the population contributes to the global increase in pancreatic cancer.
  - Several epidemiological studies have shown a correlation between increasing body mass index and the risk of pancreatic cancer[15].
- Diabetes:
  - The risk of pancreatic cancer in people with type 2 diabetes is about twice that of the general population.
  - However, the risk of pancreatic cancer is significantly higher within 1–3 years of diabetes onset, especially within the first 6 months (referred to as new-onset diabetes [NOD]).
  - A cohort study conducted through the Mayo Clinic found that half of PDAC patients met clinical criteria for diabetes, and 85 percent had raised fasting blood glucose, supporting the hypothesis that the cause of diabetes in this environment is a tumour.
  - Experiments with cell lines and animal models suggest that pancreatic cancer cells themselves produce factors that impair glucose metabolism, inducing β-cell dysfunction and insulin resistance[16,17].
- Hereditary:
  - Pancreatic cancer related to innate disorders or familial pancreatic cancer happens in around 10% of cases[18].
  - A family history of pancreatic cancer has been related to an expanded chance of pancreatic cancer compared to cancer-free families, and the hazard is higher on the off chance that greater than or equal to 2 first-degree relatives have had pancreatic cancer and are current smokers[19].
- Genetic mutations:
  - Genetic mutations associated with an increased risk of pancreatic cancer include STK11/LKB1, CDKN2A (p16), BRCA1/2, PRSS1/SPINK1/CFTR, mismatch repair genes (MLH1/MSH6/MSH2/PMS2), ATM, and PALB2 (new pancreatic cancer) susceptibility gene.
  - Pancreatic cancer has also been found to be associated with familial cancer syndromes corresponding to genetic mutations, such as Peutz-Jeghers syndrome (STK11/LKB1), familial atypical multipolar melanoma (CDKN2A), hereditary breast cancer ovarian cancer syndrome (BRCA1/) and hereditary nonpolyposis colorectal carcinoma syndrome (MLH1/MSH6/MSH2/PMS2)[20,21].
- Age:
  - In the United States, 89.4% of new pancreatic cancer cases and 92.6% of deaths occur in patients over 55 years of age.
  - New cases are typically diagnosed in people between 65 and 74 years old, with the average age of diagnosis being 70 years old, and the mortality rate is also highest among people in the same age group with an average age of death of 72 years[22](Table 1).

Odds ratio[23,24].-

Role of screening and target population

Evaluating the advantages of cancer screening

There has been disagreement over the value of early detection and screening for many different types of cancer, but it is important to consider the supporting data[25]. The death rates from colorectal, breast, and prostate cancers have significantly decreased in the United States over the past ten years[26]. The decline in death rates can be partially attributed to increased and widespread screening for these three cancers. The noted decrease in mortality has been attributed in part to the identification of localized tumours that can be successfully treated through early detection through screening. It has been demonstrated that colorectal cancer screening increases survival[27]. Techniques such as colonoscopy provide benefits for treatment and lower mortality. Different recommendations are produced as a result of conflicting evidence regarding the reduction of mortality in breast cancer screening (mammography) and prostate-specific antigen (PSA) testing for prostate cancer[28–33].

Pancreatic cancer screening is a complex task, and the techniques used today frequently have safety and accuracy issues.

Table 1

Risk Factors.

Risk factor	Adjusted odds ratio (95% CI)
Pancreatic cancer family history	1.23 (1.11–3.70)
Obesity	1.77 (1.22–2.57)
Diabetes	2.96 (1.48–5.92)
Smoking	1.78 (1.02–3.10)
Age (<60 vs. > 60)	4.830 (1.556–14.99)
Acute exacerbation of pancreatitis	2.566 (0.955–6.896)

Even though early detection is crucial, current methods such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) can cause discomfort and unfavourable reactions that can range from psychological distress to acute pancreatitis. This dilemma highlights the urgent need for novel screening methodologies. We have the potential to revolutionize early detection, minimize invasiveness, and maximize accuracy by utilizing cutting-edge technologies like liquid biopsy and artificial intelligence. Furthermore, putting patient-centred design first guarantees that safety is the top priority and that negative effects are kept to a minimum, which encourages at-risk populations to participate and build trust. By taking on these obstacles head-on, we can change the paradigm of pancreatic cancer screening and save lives while putting the needs of patients first.

Programs for screening people may be biased by nature, which could inflate the intervention's advantages[34]. The perceived efficacy of screening initiatives may be impacted by these biases, which include lead-time and length bias. Lead-time bias occurs when patients who have undergone screening appear to have a longer survival time without the screening having an impact on the disease's natural progression[35]. It results from identifying tumours earlier in their progression without altering the ultimate time of death. Length bias is observed when screening programs tend to detect tumours with a longer natural history, contributing to debates in breast and prostate cancer screening about whether identifying and treating such cancers truly affects overall outcomes[34]. In screening validation studies for pancreatic cancer, it is essential to contemplate strategies aimed at mitigating the impact of lead-time and length biases.

For whom is screening recommended?

In line with their 2004 recommendation, the United States Preventive Services Task Force (UPSTF) recommended against screening for pancreatic cancer in adults who do not exhibit any symptoms in 2019. Interestingly, evaluation for high-risk individuals with particular genetic syndromes or familial pancreatic cancer is not included in this guidance. However, this recommendation also took into account people with other pancreatic risk factors, such as older age, obesity, smoking, diabetes, or a history of chronic pancreatitis. The evidence review conducted by UPSTF highlighted the dangers of overdiagnosis and overtreatment and found no evidence of a benefit for the general public in having pancreatic cancer screenings[36].

Our understanding of pancreatic cancer risk factors is incomplete, but certain groups with heightened risks have been identified based on clinical and genetic features[37]. Clinical risk factors include age, obesity, smoking, diabetes, and chronic pancreatitis. Pancreatic cancer risk increases with age, primarily occurring in individuals over 45. Body habitus, particularly in overweight or obese individuals, is associated with an elevated risk, as well as an earlier onset of the disease. Smoking, especially current and recent past use, raises the risk, with smokeless tobacco also implicated. Diabetes is linked to a higher risk, and new-onset diabetes may signal early pancreatic cancer. Patients with chronic pancreatitis face a significantly higher incidence of pancreatic cancer compared to the general population[25].

Contrastingly, various societies, including the American College of Gastroenterology (2015), International Cancer of the Pancreas Screening Consortium (2020), and the American Gastroenterology Association (2020), have published guidelines endorsing pancreatic cancer screening for high-risk individuals[38–40]. These guidelines recommend screening for conditions like Peutz-Jeghers syndrome, CDKN2A gene mutation, hereditary pancreatitis, Lynch syndrome, and mutations in BRCA1, BRCA2, PALB2, and ATM genes. The International Cancer of the Pancreas Screening Consortium extends screening recommendations to individuals with specific familial patterns of pancreatic cancer.

The American Gastroenterology Association (AGA) suggests that screening for pancreatic cancer in high-risk individuals should commence at the age of 50 or 10 years earlier than the familial onset age[39]. Given the potential for earlier onset in genetic syndromes, screening is advised to begin at 40 for CKDN2A and PRSS1 mutation carriers with hereditary pancreatitis and at 35 for individuals with Peutz-Jeghers syndrome. In line with this, the International Cancer of the Pancreas Screening Consortium recommends initiating screening at age 50 for those with familial risk and no genetic syndromes[38].

The AGA also suggests that if a high-risk individual has other significant comorbidities, is not eligible for pancreatic resection, or is more likely to die from non-pancreatic causes, screening should be stopped. This highlights how crucial personalized factors are when deciding whether to continue or stop pancreatic cancer screening in high-risk individuals[39]. The study from a Danish national screening program found that screening for pancreatic cancer in high-risk groups, such as those with familial pancreatic cancer (FPC) and hereditary pancreatitis (HP), yielded incremental cost-utility ratios (ICERs) ranging from $35 493 to $58 647 per life-year and $47 867 to $58 647 per quality-adjusted life-year (QALY). Despite variations, the screening program was deemed cost-effective, particularly for FPC patients, with an estimated ICER of $28 834 per life-year and $38 785 per QALY[41].

Traditional modalities used for detection and screening of pancreatic cancer

Early detection and staging are essential for the proper management of pancreatic malignancy, including surgical planning and better prognosis. Nevertheless, the prognosis is poor due to aggressiveness, hidden growth, fluctuating signs till late stages, and mostly the lack of reliable early detection methods[25,26]. The conventional imaging techniques to detect and stage pancreatic cancer include the following: transabdominal ultrasonography (TAUS): This is the first imaging technique used for individuals with jaundice or gastrointestinal discomfort. It is a non-invasive and cost-effective method that detects tumours and reveals whether the pancreatic or bile duct is obstructed[27]. It offers less information for pancreatic cancer diagnosis and staging, as compared to the computed tomography (CT) scan and MRI described below.

From the recent studies, TAUS has an overall diagnostic accuracy of 67.5% with a sensitivity and specificity range from 75% to 89% and 90% to 99% for the diagnosis of pancreatic cancer, respectively. Its primary limitation is the dependence on the patient's condition and the operator's skill[28,34].

Computed tomography

Often referred to as a CT scan, this is a less-invasive procedure commonly used for the initial assessment of pancreatic

malignancies. Because it provides detailed cross-sectional images of the pancreas and surrounding organs, it aids in the more accurate diagnosis of tumour unresectability[31,33]. According to Kato, S., & Honda, K. (2020), the CT scan-based detection of PDAC has 90% sensitivity, 87% specificity, and an accuracy of 89%[28,30]. While the CT scan is more efficient and accessible than an MRI, it is unlikely to identify small pancreatic tumours or iso-attenuating PDACs with indistinct borders. Nonetheless, in clinical practice, CT scans such as the multidetector CT model are still the approach of choice most widely available for detecting and staging pancreatic cancer[33,34]. Furthermore, even though CT scans are less invasive since they require radiation, they become more invasive when contrast agents are used, which may be harmful to the patients[35].

MRI

Although this approach is non-invasive, it costs more than a CT scan. Due to its comprehensive pictures, it may help in the detection and accurate staging of pancreatic tumours and aid in assessing the local dissemination through possible venous and arterial vascular invasion. It can also be used to detect metastases, particularly hepatic and peritoneal metastases that are not detectable with a CT scan. Therefore, MRI is more accurate than CT to detect pancreatic lesions[27,30,33]. Additionally, MRI can use a variety of imaging techniques to measure tissue microstructures and view the internal structure of the pancreatic ducts, which may help identify indirect hallmarks of pancreatic cancer as duct dilatation[28,31].

The reported sensitivity of MRI for the detection of PDAC is at 93%, whereas the specificity and accuracy were 89% and 90%, respectively, which is relatively high compared to the CT scan and the EUS. However, people who have implants and claustrophobia may find the MRI challenging[28,33]. As one of its limitations, even at a higher resolution, MRI cannot depict small PDAC tumours[42].

In addition to the above, Nakahiro and colleagues have reported that cross-sectional imaging modalities, including CT scans and MRI, are not effective in detecting high-grade pancreatic intraepithelial neoplasia (PanIN) without invasive carcinoma, also referred to as carcinoma *in situ* (CIS) at in the early stages which is the primary precursor of PDAC[42].

Endoscopic ultrasonography

This method involves placing an ultrasonic probe through an endoscope to take precise pictures of the pancreas. Therefore, in addition to using EUS for pathological tissue acquisitions through fine-needle aspiration (FNA) for patients suspected of having a primary pancreatic tumour, it is categorized as an invasive technique and not appropriate for routine follow-up. Its main advantage is the ability to detect small pancreatic tumours (high resolution for small lesions of less than 2 cm at 95.2% compared to TAUS and CT at 52.4% and 42.8%, respectively). However, like the conventional ultrasound, the EUS performance depends on the operator's skills and cannot help to evaluate solid pancreatic lesions. Its sensitivity and specificity for pancreatic cancer are 72% and 90%, respectively[29,33,34].

In contrast to CT scan and MRI (except magnetic resonance cholangiopancreatography, or MRCP), the EUS can identify abnormalities driven on by CIS, such as focal pancreatic parenchymal atrophy and dilation of the main pancreatic duct (MPD), as part of the early diagnosis of pancreatic cancer[42]. Endoscopic ultrasound (EUS), for instance, is essential in identifying unusual image findings like branch duct dilatation, calibre MPD changes, small cystic lesions, and local irregular MPD stenosis. In certain patients with High-grade PanIN, it may additionally detect hypoechoic areas surrounding the MPD[42,43].

Positron emission tomography (not readily accessible for routine use) and endoscopic retrograde cholangiopancreatography (which helps diagnose pancreatic head cancer), are additional modalities that could be used to detect and stage pancreatic tumours[29,31–33](Table 2).

To conclude, even though those traditional imaging methods have been used widely in clinical settings, histopathological confirmation, which is an invasive approach, is often required to confirm the disease. As a result, cutting-edge modalities like liquid biopsy and molecular imaging techniques present an opportunity to overcome some of the previously mentioned limitations and enhance early detection capacity.

Novel imaging techniques for early detection and staging of pancreatic cancer

Diffusion weighted imaging (DWI) is a relatively recent MRI technique that provides unique insights into tissue characteristics by measuring changes in water mobility influenced by cellular structures and microenvironment alterations. DWI, with its quantitative measurement of the apparent diffusion coefficient (ADC), aids in assessing microcirculation and has demonstrated its utility in differentiating pancreatic cancer (PDAC) from pancreatitis[45]. Studies, such as one by Kamisawa *et al*[46], highlighted the significantly lower ADC values in pancreatitis compared to PDAC and normal pancreas, establishing DWI's potential as a diagnostic tool. Its high accuracy in identifying pancreatic lesions, with reported sensitivity and specificity of 96% and 99%, respectively, underscores its value in clinical applications[47].

Intravoxel incoherent motion (IVIM) extends DWI capabilities by separating microcirculation effects from molecular diffusion, offering additional insights into pancreatic lesions[48]. Although DWI faces technical challenges like respiratory motion and field inhomogeneity, its role in improving staging and aiding in the evaluation of pancreatic ductal adenocarcinoma is increasingly recognized[49].

Dynamic contrast-enhanced MRI (DCE-MRI) can also provide other advanced techniques such as dynamic contrast-enhanced MRI (DCE-MRI) for evaluation of perfusion. The potential major interest of functional imaging is to show early fibrotic and metabolic changes in pancreatic parenchyma despite the absence of morphological changes. It is another advanced technique that is typically utilized to assess morphology and contrast agent (CA) kinetics in the tissue of interest and provide functional insights into pancreatic perfusion[48]. It has shown promise in characterizing solid pancreatic diseases, with potential applications in assessing tumour hypoxia—a crucial factor in cancer progression[50,51]. However, the overall accuracy of DCE-MRI in evaluating pancreatic cancer remains uncertain, and further research is needed[52,53].

Hyperpolarized MRI, utilizing agents like [1-13C] pyruvate, enables the detection of metabolic aberrations indicating preneoplastic changes[54]. Hyperpolarized MRI can identify

Table 2

Imaging modalities characteristic for early detection and screening pancreatic cancer[25,27,30,41,42,44].

Imaging modalities	Diagnostic accuracy	Sensitivity	Specificity	Advantages	Limitations
TAUS	67.5%	75–89%	90%	Non-invasive, cost-effective, able for early detection of bile/pancreatic duct obstruction	Provide less information on PDAC diagnosis and staging, rely on patients' conditions and operator technical skills
CT scan	89%	90%	87%	Less invasive, greater availability, cost-effective,	Radiation exposures, unable to detect iso-attenuating PDACs with indistinct borders and small pancreatic tumours, the use of contrast agents sometimes leads to allergic reactions for the patients.
MRI	90%	93%	89%	No radiation exposure, improved soft tissue resolution, better to determine the metastasis, increased accuracy for assessing local involvement of pancreatic lesion, precise result for diagnosis and staging PDACs	Costly, difficult to use in patients with claustrophobia, and implants like metal devices, inability to detect the small PDAC tumours
EUS	75%	72%	90%	Effective in detecting the indirect clinical features (MPD dilatation for instance) associated with CIS; help tissue acquisition (FNA; or fine-needle biopsy) for definitive diagnoses; highest sensitivity among all imaging modalities for detecting tiny pancreatic tumours	Harmful and invasive for the patient, Relying solely on the operator's skills, difficulties in routine follow-up, and failure to assist in the evaluation of solid pancreatic tumours.

CIS, carcinoma *in situ*; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; TAUS, transabdominal ultrasound.

metabolic aberrations in the pancreas that indicate preneoplasia. Metabolic MRI imaging with hyperpolarized agents enables the detection and monitoring of the progression of precursor lesions towards invasive PDAC. Clinical studies have successfully differentiated pancreatic tumour tissue using hyperpolarized [1-13C] MRI, emphasizing its potential for monitoring disease progression[55].

MR elastography (MRE), a phase contrast-based MRI technique that can measure displacement due to propagating mechanical waves, from which material properties such as shear modulus can be calculated, is emerging as a method to detect fibrosis in pancreatic tissue[56,57]. Studies have demonstrated its ability to differentiate PDAC from pancreatitis with high accuracy, utilizing stiffness and fluidity measurements. Incorporating MRE into the characterization of solid pancreatic lesions has shown promising results in clinical trials[58].

Dual-energy contrast-enhanced CT, with its ability to simultaneously image the patient with two X-ray energies, is gaining traction for its improved contrast-to-noise ratio. This technique enhances the detection of pancreatic tumours, especially those with low vascularity[59,60].

Nanomaterials and molecular imaging offer exciting prospects for advancing pancreatic cancer imaging. Molecular imaging has emerged as a potential way to identify smaller lesions, translating into the potential to diagnose at a much earlier stage than is available. Molecular imaging has the benefit of being able to identify differences between tumour and normal tissue on a molecular level, not based on morphological differences.

Nanotechnology has the potential to non-invasively differentiate between tumour and stromal elements in pancreatic cancer, thus, nanoparticles could be used to target tumour elements and stromal elements of pancreatic cancer. Nanotechnology is defined as the manipulation of organic or inorganic materials to form structures on the scale of nanometres. Nanoparticles have the potential to target tumour and stromal elements, improving imaging contrast[61]. Molecular imaging, coupled with conventional techniques, holds promise for early lesion identification[62–65].

Radiomics is a quantitative analysis of medical image data, and the extraction of imaging features, also called 'radiomics', represents an emerging approach in personalized medicine and advanced diagnostics, especially for disease characterization or outcome prediction. It is a quantitative analysis of medical image data, and artificial intelligence-assisted methods represent a growing field in personalized medicine. Despite challenges like protocol variability, radiomics shows promise in risk stratification, surgical decision-making, treatment response prediction, and differential diagnosis for PDAC. Deep learning in radiomics could pave the way for objective evaluations of medical images, providing accurate predictions of pancreatic cancer in pre-diagnostic stages[66].

Conclusion

While the exact benefit of pancreatic cancer screening remains unclear, screening of the general population is not recommended due to the low disease incidence and high costs. The main goal, therefore, is the early detection of asymptomatic high-grade precursor lesions and non-invasive PDAC through targeted screening of high-risk populations to enable the detection of

resectable lesions. In effect, the task remains to identify the most at-risk within this high-risk population. Due to the relatively low incidence of PDAC, pooling of data from individual screening trials is needed to accumulate sufficient evidence of a clinical benefit. The multimodality approach has led to recent significant advancements in pancreatic imaging; however, each modality has specific roles, benefits, and drawbacks for pancreatic cancer diagnosis, treatment, and follow-up. It is important for radiologists and clinicians to be aware of these features of imaging modalities and to use them whenever appropriate. In the near future, it is anticipated that cutting-edge imaging techniques that are developing quickly, such as DWI, DCE-MRI, hyperpolarized MRI, MRE, Dual-energy contrast-enhanced CT, Nanomaterials and molecular imaging will be widely employed and perform exceptionally well for pancreatic cancer imaging. As our understanding of this disease improves through future research, we can expect better panels of markers combined with these novel imaging modalities to improve detection such that screening becomes the norm to eventually guide therapy by revealing the tumour microenvironment and the class of driver mutations. Therefore, we highly encourage the publication of evidence-based articles to expand and implement the initiative of early screening in high-risk individuals, as well as address any challenges that may come ahead.

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References

[1] Pancreas - International Agency for research on cancer. (n.d.) https://gco.iarc.fr/today/data/factsheets/cancers/13-Pancreas-fact-sheet.pdf
[2] Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
[3] U.S. National Library of Medicine. (n.d.-b). The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: A systematic analysis for the global burden of disease study 2017. The lancet. Gastroenterology & hepatology. https://pubmed.ncbi.nlm.nih.gov/31648972/
[4] J F, M E, F L, *et al*. (n.d.). Cancer today (powered by Globocan 2018). IARC Publications Website https://publications.iarc.fr/Databases/Iarc-Cancerbases/Cancer-Today-Powered-By-GLOBOCAN-2018--2018.
[5] Siegel RL, Miller KD, Wagle NS, *et al*. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.
[6] I H L. (n.d.). Pathology of pancreatic cancer. Translational gastroenterology and hepatology. https://pubmed.ncbi.nlm.nih.gov/31304427/
[7] R B. (2001). The diagnosis of pancreatic cancer. Cancer journal (Sudbury, Mass.). https://pubmed.ncbi.nlm.nih.gov/11561605/
[8] Bray F; Ferlay J; Soerjomataram I;, *et al*; (n.d.). Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. https://pubmed.ncbi.nlm.nih.gov/30207593/
[9] Strobel O, Neoptolemos J, Jäger D, *et al*. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol 2018;16:11–26.
[10] Ferlay J, Colombet M, Soerjomataram I, *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356–87.
[11] F L A. Screening for pancreatic cancer. JAMA 2019. https://pubmed.ncbi.nlm.nih.gov/31386115/
[12] L A, K D. Familial pancreatic ductal adenocarcinoma. Am J Pathol 2019a. https://pubmed.ncbi.nlm.nih.gov/30558720/
[13] Greenhalf W, Levy P, Gress T, *et al*. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology 2020;20:910–8.
[14] Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol 2021;18:493–502.
[15] Farias AJ, Streicher SA, Stram DO, *et al*. Racial/ethnic disparities in weight or BMI change in adulthood and pancreatic cancer incidence: the multiethnic cohort. Cancer Med 2021;10:4097–106.
[16] Pannala R, Leirness JB, Bamlet WR, *et al*. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134:981–7.
[17] Singhi AD, Koay EJ, Chari ST, *et al*. Early detection of pancreatic cancer: opportunities and challenges. Gastroenterology 2019;156:2024–204.
[18] Ohmoto A, Yachida S, Morizane C. Genomic features and clinical management of patients with hereditary pancreatic cancer syndromes and familial pancreatic cancer. Int J Mol Sci 2019;20:561.
[19] Molina-Montes E, Gomez-Rubio P, Márquez M, *et al*. PanGenEU Study Investigators. Risk of pancreatic cancer associated with family history of cancer and other medical conditions by accounting for smoking among relatives. Int J Epidemiol 2018;47:473–83.
[20] Ghiorzo P. Genetic predisposition to pancreatic cancer. World J Gastroenterol 2014;20:10778–89.
[21] Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol 2019;10:10–27.
[22] Surveillance , Epidemiology , and End Results Program. Cancer Stat Facts: Pancreatic Cancer. In: National Cancer Institute [Internet] Accessed 20 January 2021. https://seer.cancer.gov/statfacts/html/pancreas.html
[23] Zheng Z, Zheng R, He Y, *et al*. Risk Factors for Pancreatic Cancer in China: A Multicenter Case-Control Study. J Epidemiol. 2016;26:64–70.

[24] Kim HS, Gweon TG, Park SH, *et al*. Incidence and risk of pancreatic cancer in patients with chronic pancreatitis: defining the optimal subgroup for surveillance. Sci Rep 2023;13:106.
[25] Poruk KE, Firpo MA, Adler DG, *et al*. Screening for pancreatic cancer: why, how, and who? Ann Surg 2013;257:17–26.
[26] Siegel R, Ward E, Brawley O, *et al*. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
[27] Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7.
[28] Berry DA, Cronin KA, Plevritis SK, *et al*. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784–92.
[29] Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2009:CD001877; Published 2009 Oct 7.
[30] Hankey BF, Feuer EJ, Clegg LX, *et al*. Cancer surveillance series: interpreting trends in prostate cancer--part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst 1999;91:1017–24.
[31] Loeb S, Vonesh EF, Metter EJ, *et al*. What is the true number needed to screen and treat to save a life with prostate-specific antigen testing? J Clin Oncol 2011;29:464–7.
[32] Carroll PR, Whitson JM, Cooperberg MR. Serum prostate-specific antigen for the early detection of prostate cancer: always, never, or only sometimes? J Clin Oncol 2011;29:345–7.
[33] Shen Y, Yang Y, Inoue LY, *et al*. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 2005;97:1195–203.
[34] Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302:1685–92.
[35] Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. Semin Oncol 2010;37:202–15.
[36] Preventive Services Task Force US, Owens DK, Davidson KW, *et al*. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA 2019;322:438–44.
[37] Waleleng BJ, Adiwinata R, Wenas NT, *et al*. Screening of pancreatic cancer: target population, optimal timing and how? Ann Med Surg (Lond) 2022;84:104814.
[38] Goggins M, Overbeek KA, Brand R, *et al*. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium[published correction appears in Gut. 2020 Jun;69(6):e3]. Gut 2020;69:7–17.
[39] Aslanian HR, Lee JH, Canto MI. AGA clinical practice update on pancreas cancer screening in high-risk individuals: expert review. Gastroenterology 2020;159:358–62.
[40] Syngal S, Brand RE, Church JM, *et al*. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223–63.
[41] Joergensen MT, Gerdes AM, Sorensen J, *et al*. Is screening for pancreatic cancer in high-risk groups cost-effective?–Experience from a Danish national screening program. Pancreatology 2016;16:584–92.
[42] Nakahodo J, Kikuyama M, Nojiri S, *et al*. Focal parenchymal atrophy of pancreas: an important sign of underlying high-grade pancreatic intraepithelial neoplasia without invasive carcinoma, i.e., carcinoma in situ. Pancreatology 2020;20:1689–97. https://doi.org/10.1016/j.pan.2020.09.020
[43] Hanada K, Shimizu A, Kurihara K, *et al*. Endoscopic approach in the diagnosis of high-grade pancreatic intraepithelial neoplasia. Digest Endosc 2022;34:927–37.
[44] Chatterjee A, Shah J. Role of endoscopic ultrasound in diagnosis of pancreatic ductal adenocarcinoma. Diagnostics (Basel, Switzerland) 2023;14:78.
[45] Kamisawa T, Takuma K, Anjiki H, *et al*. Differentiation of autoimmune pancreatitis from pancreatic cancer by diffusion-weighted MRI. Am J Gastroenterol 2010;105:1870–5.
[46] Kamisawa T, Chen P-Y, Tu Y, *et al*. MRCP and MRI findings in 9 patients with autoimmune pancreatitis. World J Gastroenterol 2006;12:2919–22.
[47] Messina C, Bignone R, Bruno A, *et al*. Diffusion-weighted imaging in oncology: an update. Cancers 2020;12:1493.
[48] Granata V, Fusco R, Sansone M, *et al*. Magnetic resonance imaging in the assessment of pancreatic cancer with quantitative parameter extraction by means of dynamic contrast-enhanced magnetic resonance imaging, diffusion kurtosis imaging and intravoxel incoherent motion diffusion-weighted imaging. Ther Adv Gastroenterol 2020;13:1756284819885052.
[49] De Robertis R, Cardobi N, Ortolani S, *et al*. Intravoxelincoherent motion diffusion-weighted MR imaging of solid pancreatic masses: reliability and usefulness for characterization. Abdom Radiol 2018;44:131–9.
[50] Muz B, de la Puente P, Azab F, *et al*. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia 2015;3:83–92.
[51] Petrova V, Annicchiarico-Petruzzelli M, Melino G, *et al*. The hypoxic tumour microenvironment. Oncogenesis 2018;7:10.
[52] Gaustad JV, Hauge A, Wegner CS, *et al*. DCE-MRI of tumor hypoxia and hypoxia-associated aggressiveness. Cancers 2020;12:1979.
[53] Wegner CS, Hauge A, Gaustad J-V, *et al*. Dynamic contrast-enhanced MRI of the microenvironment of pancreatic adenocarcinoma xenografts. Acta Oncol 2017;56:1754–62.
[54] Serrao EM, Kettunen MI, Rodrigues TB, *et al*. MRI with hyperpolarised [1-13C] pyruvate detects advanced pancreatic preneoplasia prior to invasive disease in a mouse model. Gut 2016;65:465–75.
[55] Jørgensen SH, Hyperpolarized MRI—. An update and future perspectives. Semin Nucl Med 2022;52:374–81.
[56] 1Streitberger KJ, Lilaj L, Schrank F, *et al*. How tissue fluidity influences brain tumor progression. Proc Natl Aca Sci USA 2019;117:128–34.
[57] Shahryari M, Tzschätzsch H, Guo J, *et al*. Tomoelastography distinguishes noninvasively between benign and malignant liver lesions. Cancer Res 2019;79:5704–10.
[58] Zhu L, Guo J, Jin Z, *et al*. Distinguishing pancreatic cancer and autoimmune pancreatitis with in vivo tomoelastography. Eur Radiol 2020;31:3366–74.
[59] Heye T, Nelson RC, Ho LM, *et al*. Dual-energy CT applications in the abdomen. Am J Roentgenol 2012;199:S64–70.
[60] Graser A, Johnson TRC, Chandarana H, *et al*. Dual energy CT: preliminary observations and potential clinical applications in the abdomen. Eur Radiol 2008;19:13–23.
[61] Anselmo AC, Mitragotri S. Nanoparticles in the clinic. Bioeng Transl Med 2016;1:10–29.
[62] McCarroll J, Teo J, Boyer C, *et al*. Potential applications of nanotechnology for the diagnosis and treatment of pancreatic cancer. Front Physiol 2014;5:2.
[63] Marchegiani G, Andrianello S, Malleo G, *et al*. Does size matter in pancreatic cancer? Reappraisal of tumour dimension as a predictor of outcome beyond the TNM. Ann Surg 2017;266:142–8.
[64] Marchegiani G, Ballarin R, Malleo G, *et al*. Quantitative assessment of pancreatic texture using a durometer: a new tool to predict the risk of developing a postoperative fistula. World J Surg 2017;41:2876–83.
[65] Kokkinos J, Jensen A, Sharbeen G, *et al*. Does the microenvironment hold the hidden key for functional precision medicine in pancreatic cancer? Cancers 2021;13:2427.
[66] Casà C, Piras A, D'Aviero A, *et al*. The impact of radiomics in diagnosis and staging of pancreatic cancer. Ther Adv Gastrointest Endosc 2022;15:26317745221081596.