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Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management

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Abstract

Pancreatic cancer is one of the dreaded malignancies for both the patient and the clinician. The five-year survival rate of pancreatic adenocarcinoma (PDA) is as low as 2% despite multimodality treatment even in the best hands. As per the Global Cancer Observatory of the International Agency for Research in Cancer estimates of pancreatic cancer, by 2040, a 61.7% increase is expected in the total number of cases globally. With the widespread availability of next-generation sequencing, the entire genome of the tumors is being sequenced regularly, providing insight into their pathogenesis. As invasive PDA arises from pancreatic intraepithelial neoplasia and mucinous neoplasm and intraductal papillary neoplasm, screening for them can be beneficial as the disease is curable with resection at an early stage. Routine preoperative biliary drainage has no role in patients suffering from PDA with obstructive jaundice. If performed, metallic stents are preferred over plastic ones. Minimally invasive procedures are preferred to open procedures as they have less morbidity. The duct-to-mucosa technique for pancreaticojejunostomy is presently widely practiced. The role of intraperitoneal drains after surgery for PDA is controversial. Neoadjuvant chemoradiotherapy has been proven to have a significant role both in locally advanced as well as in resectable PDA. Many new regimens and drugs have been added in the arsenal of chemoradiotherapy for metastatic disease. The roles of immunotherapy and gene therapy in PDA are being investigated. This review article is intended to improve the understanding of the readers with respect to the latest updates of PDA, which may help to trigger new research ideas and make better management decisions.

Key Words: Pancreatic adenocarcinoma; Pancreatic cancer; Chemotherapy; Chemoradiotherapy; Pancreaticoduodenectomy; Distal pancreatectomy

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Core Tip: Pancreatic cancer is one of the dreaded malignancies for both patients and clinicians. This narrative review highlights the newer trends and achievements in the epidemiology, etiopathogenesis, screening, diagnosis and management of pancreatic adenocarcinoma (PDA). It is intended to improve the readers' understanding of the latest updates of PDA, which may help to trigger new research ideas and make better management decisions. Newer screening and diagnostic techniques will help in diagnosing the patients in early stages and prognosticate them better. The newer discoveries in drugs and management protocols will help increase the survival and quality of life of the patients.

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INTRODUCTION

Pancreatic cancer is one of the dreaded malignancies for both patients and clinicians. For patients, it is associated with a poor survival rate and decreased quality of life due to local invasion and complications, and for the clinician, it is challenging to diagnose at an early stage and treat.

Pancreatic cancer is the third leading cause of cancer deaths in the United States of America and the seventh leading cause worldwide as *per* the 2018 GLOBACON data[1, 2]. It may arise from either the exocrine or the endocrine pancreas with the former being far more common than the latter. Pancreatic adenocarcinoma (PDA) and its subtypes constitute more than 90% of pancreatic tumors[3]. Most patients with PDA present at an advanced stage, which makes curative treatment virtually impossible[4]. The five-year survival rate of PDA is as low as 2% despite multimodality treatment even in the best hands[5]. The high mortality and morbidity associated with PDA have stimulated researchers all over the world to intensify the search for better diagnostic and treatment protocols.

Clinically, patients with PDA present to the healthcare facility with symptoms only in the advanced stage[6]. Early lesions have a good prognosis but are clinically silent. Diagnosis of an early-stage PDA is rare as there are no effective and reliable screening tools or investigations at present[7]. Surgery is the mainstay of treatment if therapy is planned with curative intention in PDA patients[8]. Patients with PDA from the surgical point of view are classified into resectable, borderline resectable, unresectable and metastatic disease categories at diagnosis. Chemotherapy and radiotherapy remain the backbone of the treatment for PDA with almost all patients requiring some form of chemoradiotherapy for curative or palliative purposes[9-11].

In view of the above facts, in the present narrative review, the authors have reviewed the latest trends in the epidemiology, diagnosis and management of PDA based on the published English literature so far. We have searched the literature using the keyword "PDA". This review article is intended to improve the understanding of the readers regarding the latest updates of PDA, which may help to trigger new research ideas and promote better management decisions.

PARADIGMS IN EPIDEMIOLOGY

In the last decade, there has been a steady increase in the incidence and mortality of PDA across the globe for both males and females (Figure 1)[12,13]. Its incidence was higher among males when compared to females and continues to be so[1,12-14]. PDA constitutes about 2.5% of the total cancers diagnosed worldwide. The 2020 estimated crude incidence rate and age-standardized rate (ASR) of pancreatic cancer are 6.4% and 4.9%, respectively[1]. The ASR of pancreatic cancer is the highest in North America (8%) and Europe (7.8%) and lowest in Africa (2.3%)[1]. The incidence rate is also very high in countries with a high human development index (HDI) when

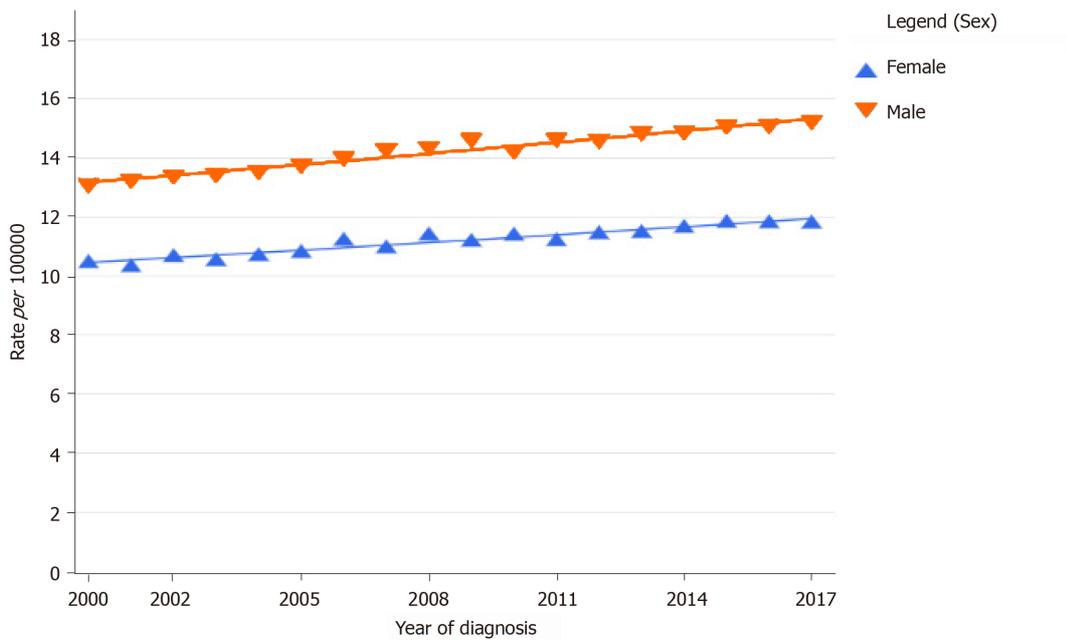


Figure 1 Pancreas cancer-recent trends in surveillance, epidemiology, and end results age-adjusted incidence rates, 2000-2017[12]. Used with permission from National Cancer Institute.

compared to countries with low HDI (Figure 2)[1]. This difference can be attributed to the variation in the tobacco smoking, alcohol consumption and obesity rates among different countries[15-18].

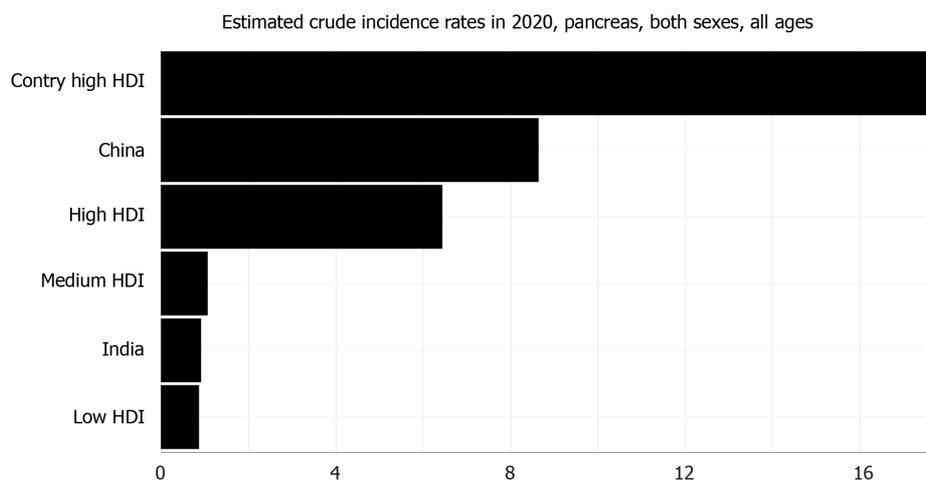
The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute reveals an age-specific trend in the increase of the incidence rate of pancreatic cancer in the age groups of 20-29 years and > 80 years in the United States[19]. The increase also varied with the stage of the disease at diagnosis. The last decade has shown a higher increase in the age-adjusted incidence rates of early and localized pancreatic cancer when compared to advanced disease. The age-adjusted incidence rate of metastatic disease has declined[12] (Figure 3). When the American Joint Committee on Cancer Tumor-Node-Metastasis staging was compared with the age-adjusted incidence rate, there was an increase in the stage I and II patients and a simultaneous decline in the stage III and IV patients at diagnosis, indicating that the evolving techniques of screening and diagnosis of pancreatic cancer are showing some result[14].

As per the Global Cancer Observatory of the International Agency for Research in Cancer estimates of pancreatic cancer, by 2040, a 61.7% increase is expected in the total number of cases globally. The most notable trend expected is the rapid increase in the number of cases from Africa (an increase of 100.1%) followed by Asia (81.5%). The expected increase from Europe and North America is less (Table 1)[1]. The mortality rates also follow the incidence rates with the expected increase in the mortality due to pancreatic cancer highest in Africa (Figure 4). There is an expected regional variation in the incidence among male and female sex in various continents[1,13]. The temporal trends of incidence and mortality of pancreatic cancer in various continents could be attributed to the temporal trends in tobacco smoking[15,20,21]. Anti-tobacco measures, which are being strongly advocated in developed countries, could be one of the main reasons for declining incidence rates[22]. On the other hand, the rise in the incidence and mortality rates in the developing and under-developed countries is a cause of concern and may be attributed to the lifestyle changes adopted as well as the impact of socioeconomic conditions.

Based on the present and expected trends of pancreatic cancer, there must be a widespread endorsement of healthy lifestyle practices and strong anti-tobacco laws. If not, the developing countries will have to bear the major brunt of the disease in the near future as the diagnostic and treatment services are still under-developed in these countries.

Table 1 The expected increase in the number of new cases among various continents by 2040[1]

Population	2020	2040	Change in number of cases	Change in number of cases due to population
Africa	17070	34165	+ 100.1%	+ 100.1%
Asia	233701	424138	+ 81.5%	+ 81.5%
Europe	140116	178438	+ 27.4%	+ 27.4%
Latin America and Caribbean	37352	67836	+ 81.6%	+ 81.6%
Northern America	62643	89124	+ 42.3%	+ 42.3%
Oceania	4891	7933	+ 62.2%	+ 62.2%
Totals	495773	801634	+ 61.7%	+ 61.7%

**Figure 2** Estimated crude incidence rates in 2020, pancreas, both sexes, all ages as per human development index[1]. Used with permission from International Agency for Research on Cancer. HDI: Human development index.

NEWER CONCEPTS IN ETIOPATHOGENESIS

PDA is recently being called a genetic disease. With the widespread availability of next-generation sequencing, the entire genome of the tumors is being sequenced regularly, providing insight into its pathogenesis. PDA has about 60 genetic alterations *per* tumor. The most important finding differentiating PDA from other cancers is the heterogeneity of the genome of each patient, meaning that each patient has a tumor with a specific genomic signature[23,24]. Four predominant genes have been identified in PDA. They are *K-ras*, *CDKN2A*, *TP53* and *SMAD4*. There are many other genes identified, but they are mutated at a lower frequency (less than 10%)[23].

The *K-ras* oncogene is the most common gene mutation in PDA with an incidence of more than 90%[25]. Due to its high frequency of mutation, it is believed that the tumor pathogenesis revolves predominantly around the molecular pathways regulated by this gene and forms the basis for research on *K-ras* inhibitors. However, *K-ras* inhibitors were associated with high in-vivo toxicity[26]. *CDKN2A* gene is involved in the regulation of *RB1* and plays an important role in the G1/S checkpoint inhibition of the cell cycle[27]. *TP53* is the predominant DNA repair pathway gene and induces cell cycle arrest at G1 or G2 checkpoint[28]. *SMAD4* gene is a part of the transforming growth factor β pathway and regulates the G1/S checkpoint of cell cycle[28]. The group of genes involved in the genome maintenance DNA repair pathway (*BRCA2*, *PALB2*, *FANCC*, *FANCG*) constitute less than 10% of the mutated genes in PDA but are important as tumors deficient in these genes can be targeted with DNA damaging agents and poly ADP-ribose pathway inhibitor therapy[23,24,29]. Other gene mutations are involved in the regulation of pathways such as *Ras*, cell cycle regulators, WNT pathway and NOTCH pathway[23,24].

Invasive PDA arises from pancreatic intraepithelial neoplasia (PanIN). The lesions of PanIN progress from PanIN1 to PanIN3 by acquiring progressive mutations as

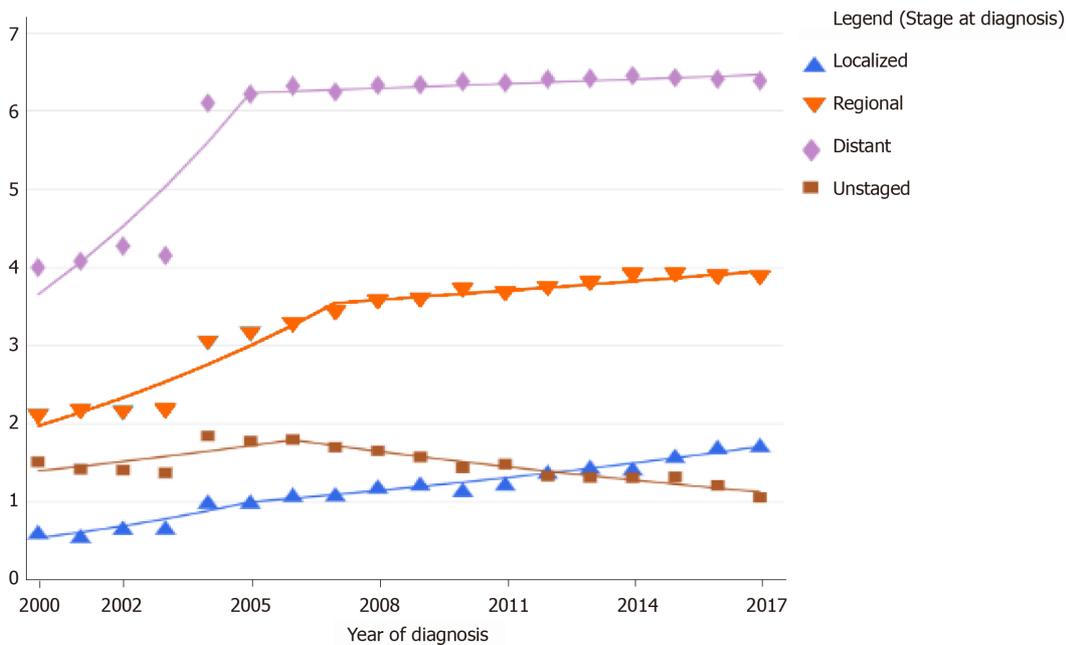


Figure 3 Pancreas cancer-recent trends in surveillance, epidemiology, and end results age-adjusted incidence rates as per stage at diagnosis, 2000-2017[12]. Used with permission from National Cancer Institute.

shown in Table 2[30]. PanINs are also associated with lobulocentric acinar atrophy and local pancreatic inflammation secondary to obstruction of small duct secretions[31]. The time required from the onset of PanIN till progression to invasive carcinoma is about 10 years suggesting a significant lead time if PanIN are screened and detected early. The proteins expressed by PanIN and invasive carcinoma are similar, which can be used for screening these lesions[32-35]. The high-grade PanINs express mucins such as MUC1, MUC4, MUC5AC, and MUC6[36-38]. These can be used for screening and in the treatment of PanIN[39,40].

Based on the transcriptome analysis, PDA is divided into molecular subtypes[41]. The three subtypes named initially were classical, quasimesenchymal and exocrine-like, which have been modified as progenitor, squamous and aberrantly differentiated endocrine exocrine types, respectively, by the International Cancer Genome Consortium study[41]. An immunogenic subtype was also identified. The squamous subtype was associated with a poor prognosis similar to the basal subtype carcinomas of other organs and has a poor response to chemoradiotherapy and also exhibits *TP53* mutations more frequently[41]. Recently, RNA-based sequencing of PDA revealed the heterogeneity of the tumor at the molecular level[42]. RNA-based subgrouping may add further insights into the pathogenesis and tumor progression. The desmoplastic stroma is the predominant component of the PDA. Recent transcriptome analysis of the stromal cells revealed two subtypes similar to PDA cells—normal subtype and activated subtype[43]. The normal subtype resembles pancreatic stellate cells, and the inflammatory subtype has immunogenic signatures. The gene expression is also different for the two subtypes leading to the inference of the role of stromal and neoplastic cell interaction in determining the tumor heterogeneity[44].

The neoplastic cells of PDA are acclimatized to survive in a microenvironment of depleted oxygen and nutrients due to the poor vascularity and intense desmoplastic stroma of the tumor. The *K-ras* mutation up-regulates several metabolic pathways such as glucose uptake and glycolysis[23]. Apart from the metabolic adaptations, cells survive by autophagy, mitophagy and macropinocytosis stimulated by the *K-ras* gene [24]. Genetic or pharmacological inhibition of autophagy leads to decreased tumor growth as seen in mouse models. Co-targeting with mitogen-activated protein kinase kinase/extracellular signal-regulated kinase inhibitors is an area of intense research in the treatment of pancreatic cancer[45,46]. Furthermore, the deregulation of these metabolic pathways is one of the reasons for resistance to chemotherapy in PDA[47-49].

Table 2 The histological features and genetic alterations in pancreatic intraepithelial neoplasia

	PanIN-1	PanIN-2	PanIN-3
Histology	Columnar epithelial cells with basally oriented uniform and round nuclei	More nuclear changes such as loss of nuclear polarity, pleomorphism, hyperchromasia and nuclear pseudostratification	Cribriform pattern, budding cells into lumen and nuclear changes
Genetic changes	<i>K-Ras</i> mutations Telomere shortening	<i>CDKN2A</i> mutations	<i>TP53</i> loss <i>SMAD4</i> loss <i>BRCA2</i> loss

PanIN: Pancreatic intraepithelial neoplasia.

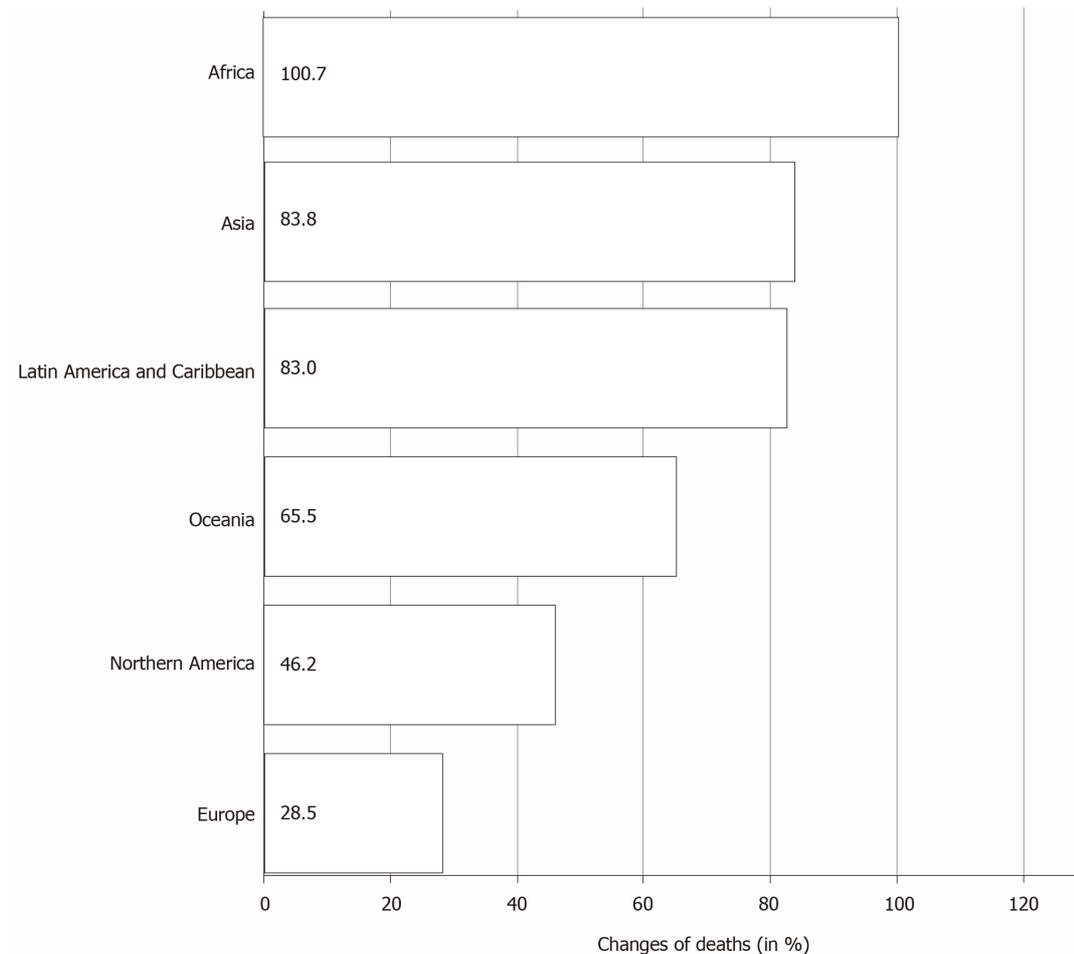


Figure 4 Projected Changes of deaths due to pancreatic cancer from 2020 to 2040, both sexes, age (0-85+)[1]. Used with permission from International Agency for Research on Cancer.

RISK FACTORS

Risk factors for PDA can be divided into modifiable and non-modifiable. Smoking has been proven beyond doubt to be the main modifiable risk factor. The risk is approximately twice in smokers, and they are at risk even after smoking cessation for about 20 years[50,51]. Alcohol is an additional risk factor in smokers but not in non-smokers [52]. Obesity is clearly associated with an increased risk of PDA as well as mortality [53]. Dietary factors such as consumption of red meat and processed foods are associated with an increased risk of PDA while consumption of fresh fruits and folate is protective[54,55]. Occupational exposure to nickel, cadmium and chlorinated biphenyls is associated with an increased risk[56].

Among the nonmodifiable risk factors, male sex, increasing age and African-American ethnicity are associated with an increased risk[13]. Genetic factors play an important role as 10% of the PDAs have a family history[57,58]. Mutations in the genes such as *BRCA2*, *PALB2*, *STK11*, *CDKN2A*, *APC*, Lynch syndrome genes, *ATM*, *FANCC* and *FANCG* are responsible for the familial causes of PDA[59]. Chronic pancreatitis is a risk factor for PDA, particularly chronic pancreatitis due to hereditary pancreatitis (*PRSS1/SPINK1* gene mutation)[60]. Diabetes type 1 and 2, particularly recent-onset diabetes, are associated with an increased risk of PDA. However, the causal association was not proved and is a matter of debate as diabetes may be a manifestation of PDA[61]. The risk of PDA decreases with an increased duration of diabetes [62]. The association of *Helicobacter pylori* infection and PDA was proved in a meta-analysis[63]. There is also growing evidence of association of PDA with chronic diseases such as hepatitis B and C[64]. Recent studies have also proved the association between non-O blood group and PDA[64,65].

RECENT ADVANCES IN SCREENING AND DIAGNOSIS

As invasive PDA arises from PanIN and from mucinous neoplasm and intraductal papillary neoplasm (IPMN) screening for these lesions can be beneficial as the disease can be cured with resection at an early stage. However, till now there is no approved and reliable screening test for PDA[66,67]. PDA is a cancer of comparatively low prevalence but with high mortality. Due to the non-availability of any standard, economical and reliable screening test, screening the entire general population for PDA is not possible. However, patients with a family history of pancreatic cancer have an increased risk of PDA and benefit from screening[66]. Screening is particularly recommended for those with at least two first-degree relatives with PDA or in patients with known familial syndromes. Even though IPMNs are visible on conventional imaging, PanIN are very small lesions of size less than 5 mm and are not identified on routine imaging studies[66]. Hence, we need to rely on biomarkers alone or in combination with imaging studies for screening.

The most commonly used biomarker is carbohydrate antigen (CA) 19-9, which is sialylated Lewis blood group antigen on MUC1 expressed by neoplastic cells of PDA and also by the normal cells of the pancreaticobiliary system, stomach, colon, endometrium and salivary glands[68]. It is elevated in only 65% of resectable pancreatic cancers and hence of low sensitivity[69]. It is also elevated in benign diseases of the biliary tract, biliary obstruction and also in malignancies arising from other organs, and hence it is also less specific[69,70]. CA19-9 cannot be used as a tumor marker in populations who do not express Lewis antigen (4%-15%)[66,69,70]. Therefore, it is primarily used to assess the response to treatment and in the follow-up of patients diagnosed with PDA[69,70]. Carcinoembryonic antigen (CEA) in the pancreatic juice can also be used to screen pancreatic cancer with reasonable accuracy [71,72]. However, the main limiting factor of CEA is the low sensitivity although specificity is high[71,72].

PAM4 is an anti MUC1 antibody, which is directed specifically against an epitope of MUC1 secreted by the pancreatic cancer cells absent in normal pancreas and other tissues and therefore found to be more specific and sensitive than CA19-9 in differentiating pancreatitis and pancreatic cancer[73]. Patients with advanced disease had higher values of PAM4 compared to early stages[74]. PAM4 can also be used to screen early lesions of PDA such as PanINs and IPMNs as the expression begins at an early stage of the disease and continues throughout[75]. The role of several new biomarkers such as CA494, CA50, CA242, CEA -related cell adhesion molecule 1, CAM 17.1-Ab, parathyroid hormone-related oncoprotein and serum beta-human chorionic gonadotropin in diagnosing early pancreatic lesions is growingly evident[70,76-80]. In a meta-analysis of seven studies evaluating the role of tumor M2-pyruvate kinase in screening pancreatic cancer, the conclusion was that the efficacy of tumor M2-pyruvate kinase was similar to CA19-9[81]. SPan-1 is also one of the markers studied for the diagnosis of exocrine pancreatic cancer, but it did not improve the rates when combined with CA19-9[82].

Various genetic and epigenetic mutations can be detected in the pancreatic juice obtained by endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography[83]. *K-ras* mutations and *TP53* mutations identified in the pancreatic juice are associated with low specificity and sensitivity even though they are mutated in most of the PDAs[84,85]. DNA methylation abnormalities of a panel of genes were associated with a sensitivity of 82% and a specificity of 100% in identifying pancreatic

cancer in a study[86]. Identification of mitochondrial mutations in the pancreatic juice is also being studied in diagnosing pancreatic cancer[87]. The main drawback of the above-mentioned tests is the requirement of invasive intervention to obtain the sample. Micro-RNAs are being intensely investigated in diagnosing various human cancers including pancreatic cancer[88]. Circulating tumor cells are also present in 47% of patients with PDA and are also associated with early lesions.

Multi-detector computerized tomography (MDCT) is presently the gold standard for the diagnosis of pancreatic lesions[89,90]. It is the virtual eye of a surgeon to assess the resectability of the tumor and also to accurately stage the disease[91,92]. The major drawback is the low sensitivity of MDCT in identifying lesions less than 2 cm and negligible sensitivity for identifying the pre-invasive lesions. Also, the routine use of MDCT for screening purposes in high-risk patients may increase the risk of radiation-induced secondary tumors. Hence, MDCT is preferably not used for the purpose of screening high-risk individuals and is comparatively inferior to EUS for the same[93]. Magnetic resonance imaging (MRI) is a non-ionizing investigation, which can image the entire abdomen as opposed to EUS. MRCP can provide very accurate details of the biliary and pancreatic ductal system and can identify small cystic lesions such as IPMNs. In fact, MRCP is proven to be superior to MDCT in detecting these lesions[93, 94]. In a prospective study evaluating the role of MRI in the screening of patients with *PI6* mutations, MRI was able to identify early lesions[95].

EUS plays an important role in the screening and diagnosis of PDA. EUS was shown to be superior to MDCT, MRI and positron emission tomography (PET) in detecting small lesions and lymph node involvement[96]. It was able to detect twice the number of lesions compared to MDCT and MRI when used for screening[94]. It can also be used for biopsying a suspected lesion. The major drawback is the invasiveness of the procedure and its operator dependence. It may also be associated with rare but severe complications such as iatrogenic gastrointestinal perforation. EUS is usually performed in sequence with biomarker tests (in those with elevated CA19-9) or after a basic imaging test rather than as a first option[66,97].

PET scan is one of the valuable investigations in PDA with good sensitivity but an average specificity. In two meta-analyses from Tang *et al*[98] and Wu *et al*[99], the pooled sensitivities were 90.1% and 87%, respectively, and pooled specificities were 80.1% and 83%, respectively[98,99]. The low specificity is because of the inability of the PET scan to differentiate between inflammatory lesions and neoplastic lesions[100]. The role of the PET scan in determining the T stage is limited and is surpassed by MDCT[101]. Even though the PET scan was able to pick up positive lymph nodes in other malignancies, the sensitivity of PET in accurately determining the N stage of PDA is limited[100,102]. However, a PET scan is invaluable in diagnosing metastatic PDA, which can alter the management of the patient[103].

ADVANCES IN SURGICAL MANAGEMENT OF PDA

Preoperative preparation

Surgical resection of PDA either pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) with splenectomy is associated with high morbidity and mortality. Hence, thorough preoperative preparation is essential to avoid complications. The preoperative preparation is similar to any other major surgery except for two unique complications encountered in PDA: Obstructive jaundice and nutritional deficiencies. Obstructive jaundice is common in patients with carcinoma involving the head of the pancreas.

There were many studies evaluating the role of preoperative biliary drainage (PBD) *vs* surgery alone. Preoperative drainage is associated with improvement in the general condition of the patient and liver function. However, it is associated with significant side effects such as the introduction of infection into the biliary tree[104]. Furthermore, preoperative drainage will make the surgery challenging due to inflammation and fibrosis induced by the common bile duct (CBD) stents and decreased diameter of the CBD making anastomosis difficult. In a meta-analysis by Sewnath *et al*[105], the lack of benefit of PBD over direct surgery in patients of perianillary carcinoma with obstructive jaundice was proven[105], further confirmed by a Cochrane review and in a meta-analysis by Wang *et al*[106] and Fang *et al*[107]. It was proven in various studies that PBD and delayed surgery to improve the general condition were not associated with any improvement in survival[108]. The only indications accepted for PBD before surgery at present include patients with cholangitis, poor general condition and poor performance status precluding surgery and in whom neoadjuvant treatment is

planned. PBD can be undertaken with the help of CBD stents or percutaneous transhepatic biliary drainage. Among the CBD stents, metallic or plastic ones can be selected. In a meta-analysis of five studies by Crippa *et al*[109], the rate of re-intervention and post-operative biliary fistula was shown to be lower in the case of metallic stents compared to plastic stents[109]. Hence, at present, the available evidence supports the use of metallic stents over plastic stents, in both unresectable PDA and for PBD.

Surgery

With the mortality and morbidity rates of pancreatic surgery improving over several decades, focus has been shifted to performing the surgeries using minimally invasive techniques. In a meta-analysis by Venkat *et al*[110] evaluating laparoscopic DP with open technique, they inferred that the laparoscopic technique was associated with lower blood loss, shorter hospital stay and lower overall postoperative complications compared to the open technique with no difference in the margin status and operating time[110]. Similar results were obtained in the meta-analysis by Jin *et al*[111].

The results from studies comparing laparoscopic PD (LPD) and open PD (OPD) are also encouraging. A summary of the outcomes of few recent studies in this regard is presented in Table 3. LPD was associated with lower intra-operative blood loss, faster recovery and shorter hospital stay with similar rate of post-operative complications and oncological outcomes[112-118]. However, in most of the studies, LPD was associated with greater operating times compared to OPD[112-118]. Robotic surgery has the added advantage of increased degrees of freedom and better images without motion artifacts compared to conventional laparoscopic surgery. In a retrospective study by Nassour *et al*[119], 428 minimally invasive PD surgeries were analyzed, and the 30-d complication rate was found to be the same between robotic and laparoscopic groups[119]. In a meta-analysis of 44 studies by Kamarajah *et al*[120] comparing robotic and conventional laparoscopic PD, the conclusion was that the robotic group was associated with lower conversion rates compared to the laparoscopic group[120]. No significant difference was noted in the operating times and blood loss between the two groups. The robotic surgery group had a shorter hospital stay compared to the laparoscopic group.

With the expertise of vascular reconstructions, venous involvement is no longer an absolute contraindication for resection of PDA with the criteria for resectability being updated regularly[121]. Venous reconstructions are widely practiced, and the present limiting factor seems to be arterial involvement. Hence, the approach has been shifted to the artery-first approach to determine the resectability of the tumor at the initial phase of the surgery itself. These include the posterior approach, medial uncinate approach, inferior infracolic approach, left posterior approach, inferior supracolic approach and superior approaches, which have become popular[122]. In a meta-analysis of 22 studies by Yu *et al*[123], PD combined with portal-superior mesenteric vein synchronous resection (PSMVR) was found to be associated with similar post-operative morbidity and mortality compared to the group without resection[123]. However, only the group with R0 resection had a significant improvement in survival [123]. In a similar meta-analysis by Bell *et al*[124], it was concluded that PSMVR was associated with a higher R1 rate, poor 5-year survival rate and was not cost effective [124]. In a meta-analysis of 26 studies by Mollberg *et al*[125] comparing pancreatectomy with arterial resection (AR) and without AR, pancreatectomy with AR was associated with an increased peri-operative mortality and poor 1-year and 2-year survival[125].

Post-operative pancreatic fistula (POPF) is one of the most dreaded complications of PD[126]. Many methods have been advocated to reduce its incidence, beginning with the type of pancreaticoenteric anastomosis. Several randomized control trial (RCTs) and meta-analysis have shown that pancreaticogastrostomy was associated with less incidence of POPF[127-129]. However, pancreatojejunostomy (PJ) is the mostly widely practiced technique because it is more physiological and is associated with lower long-term complications than pancreaticogastrostomy[130]. Several techniques of PJ have been compared in trials for the incidence of POPF. Among the duct-to-mucosa anastomoses, the Blumgart technique was found to be better compared to the Cattell-Warren technique[131]. Both the Blumgart and Kakita techniques were associated with similar results in many studies[132,133].

The continuous suturing technique was associated with a lower incidence of POPF compared to the interrupted suturing technique in several studies[134,135]. It is hypothesized that continuous sutures lead to a uniform distribution of tension along the suture line compared to intermittent sutures. A brief interest was sparked in the invagination techniques after the introduction of the jejunal eversion with binding PJ

Table 3 The outcomes of various latest studies comparing laparoscopic pancreaticoduodenectomy with open procedure

Ref.	Study	Comparison	Outcome
Nickel <i>et al</i> [112], 2020	Meta-analysis of 3 RCTs	LPD and OPD	90-d mortality, post-operative complications and oncological outcomes were similar in both groups Blood loss was less for LPD Operating time was more for LPD
Yoo <i>et al</i> [113], 2020	Retrospective cohort study of 359 patients	LPD and OPD	Post-operative complications and hospital stay were shorter for LPD Operative time was longer for LPD Recurrence free outcomes and overall survival rates were similar
Chen <i>et al</i> [114], 2020	Meta-analysis of 6 cohort studies	LPD and OPD for PDA	Number of lymph nodes harvested, number of positive lymph nodes, rate of adjuvant therapy, time to adjuvant therapy, 1 yr survival and 2 yr survival are same for both the groups
Zhou <i>et al</i> [115], 2019	Retrospective cohort study	LPD and OPD	Overall complications and survival were similar between the two groups
Chen <i>et al</i> [116], 2018	Retrospective cohort study of 102 patients	LPD and OPD	Intra-operative blood loss, post-operative recovery and hospital stay were shorter for LPD Operative time was longer for LPD Post operative complications were similar in both the groups
Dang <i>et al</i> [117], 2020	Retrospective cohort study	LPD and OPD	Intra-operative blood loss, operating time and hospital stay for shorter for LPD 30 d and 90 d mortality rates were better for LPD Long term survival rates were similar
Palanivelu <i>et al</i> [118], 2017	RCT of 68 patients with periampullary carcinoma	LPD and OPD	Intra-operative blood loss and hospital stay for shorter for LPD Operative time was longer for LPD Post-operative complications were similar in both the groups

RCT: Randomized control trial; LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy.

technique by Peng *et al*[136] and the end-to-side invagination technique by Berger *et al* [137], which showed better results with respect to POPF compared to the duct-to-mucosa technique[136,137]. However, the results were not reproduced in other trials [138]. In a study by Kojima *et al*[139], it was concluded that the Blumgart technique of PJ when combined with the tight dressings of the wound and drain sites (complete packing method) was associated with less incidence of POPF[139].

In a move to reduce the incidence of POPF, stenting of the PJ was evaluated in various trials. Stenting is hypothesized to prevent the pancreatic enzymes from coming in contact with the anastomosis, thereby promoting healing of the anastomosis. Studies comparing internal stents and no stents revealed no significant difference in the rate of POPF[140-142]. In trials comparing external stenting and no stenting, few trials have demonstrated the benefit of external stenting[142-145]. However, these stents are associated with complications such as tube-related complications, digestive enzyme loss and possible peritonitis during tube removal[141]. Moreover, no difference was observed between the internal and external stents in preventing the POPF[146]. Most of the high-volume centers do not stent the PJ at present.

In the case of DP, stump closure using hand-sewn or stapler techniques was evaluated with respect to POPF. There was no significant difference in the POPF rates between the two techniques, and the stapler technique is commonly used by most surgeons[147,148]. In a meta-analysis evaluating bare metallic staplers and reinforced staplers using bioabsorbable materials, the superiority of the reinforced staplers was not proven even though the rate of POPF was less in reinforced staplers[149]. Pancreaticoenteric anastomosis of the distal stump has been shown to reduce the rate of POPF but increased the rate of post-operative hemorrhage[150,151].

Topical application of fibrin sealants over pancreatic anastomosis has no effect on POPF incidence in various studies[152,153]. Similarly, omental wrapping around the pancreatic anastomosis has no effect on the POPF or post-operative hemorrhage[154]. Covering the distal pancreatic stump with a teres ligament patch has shown to reduce

the rate of reoperations and readmissions compared to simple closure even though the rate of POPF was not significantly different between the two groups in a randomized control trial[155].

The role of prophylactic intraperitoneal drains following pancreatectomy is controversial. In case of DP, there is no role of prophylactic intraperitoneal drains as concluded in various studies[156,157]. Moreover, prophylactic drain placement increases hospital stay. The PANDRA trial randomized 395 patients with PD with or without drains and concluded that there was no need for routine prophylactic intraperitoneal drainage[158]. However, other studies have reported increased mortality in patients who underwent PD without drains[159,160]. However, in low-risk patients, drains can be safely avoided[160]. If drains are placed, they must be removed as early as possible once their purpose is served as their prolonged placement may lead to intra-abdominal infections and increase the risk of POPF[161].

The role of somatostatin analogues in preventing POPF is unclear. Earlier RCTs revealed the efficacy of octreotide in preventing POPF. However, newer RCTs proved that there is no role of octreotide in preventing POPF[162-164]. Pasireotide was found to reduce the rate of POPF in one RCT by Allen *et al*[165], but not in other RCTs[165-167]. At present, the use of somatostatin analogues cannot be recommended due to inconsistent results in clinical trials.

ADVANCES IN SYSTEMIC THERAPY

Neoadjuvant therapy

Borderline and locally advanced lesions are started on chemotherapy ± chemoradiation as *per* the present guidelines[168,169]. The current preferred regimen is 5-Fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) ± chemoradiation, if the patient has good performance status[169-172]. Alternatively, gemcitabine and nab-paclitaxel ± chemoradiation can also be used[170-172]. In patients with known mutations in the *BRCA* gene, substituting paclitaxel with cisplatin may provide added benefit[170]. Patients with poor performance status can be started on single-agent chemotherapy or provided with palliative care. The likelihood of resection depends upon the response to neoadjuvant therapy. As *per* the latest studies, the response should be measured by falling CA19-9 Levels and absence of disease progression while on neoadjuvant therapy rather than by assessing the radiological regression[173-176].

Most of the patients with PDA in the long term, even after complete resection, develop distant metastasis. This points to the notion of micrometastasis even in a resectable localized cancer at the time of presentation. Also, due to the morbidity associated with surgery, a significant proportion of patients are unable to receive adjuvant therapy or have a delay. The encouraging results of neoadjuvant and perioperative chemoradiation therapies in esophageal, gastric and rectal carcinoma have stimulated research on the role of neoadjuvant therapy in resectable lesions of PDA. It also improves the rate of R0 resections. Multiple trials have been conducted to assess the role of neoadjuvant chemotherapy and chemoradiation in resectable PDA (Table 4). The results of many of the latest trials support neoadjuvant chemotherapy therapy in resectable PDA[177,178]. The results of ongoing trials such as NEPAFOX, NorPACT-1, NEOPAC and NCT02562716 are eagerly awaited[179-183]. The role of neoadjuvant chemoradiotherapy in resectable PDA is proved in several trials[184-186].

Adjuvant therapy

The trials of GITSG and EORTC 40891 have clearly proven the role of adjuvant chemoradiotherapy in PDA[187,188]. The ESPAC-1 trial has shown the beneficial effects of chemotherapy over chemoradiotherapy[189]. Even though the opinion on the role of adjuvant chemoradiotherapy is different among practitioners in Europe and the United States of America, most of them have a common opinion on the role of adjuvant chemotherapy. The CONKO-1 trial after showcasing the efficacy of gemcitabine in adjuvant chemotherapy has shifted the adjuvant chemotherapy regimens from 5-fluorouracil (5-FU) to gemcitabine-based regimens[190]. The ESPAC-3 trial has shown no significant difference between the 5-FU and gemcitabine regimen [191]. The ESPAC-4 trial has proved the increased efficacy of the gemcitabine and capecitabine combination over gemcitabine alone and is now the recommended regimen for adjuvant therapy[192]. The success of the FOLFIRINOX regimen in the metastatic setting has led to the evaluation of its role in the adjuvant setting. The PRODIGE 24 trial has proven the efficacy of FOLFIRINOX over gemcitabine, but its use is limited to patients with a good performance status[193]. In the Japanese trial

Table 4 Studies showing the role of neoadjuvant chemotherapy and chemoradiotherapy in resectable pancreatic adenocarcinoma

Ref.	Type of study	Type of neoadjuvant therapy	Drugs	Results
Tajima <i>et al</i> [177], 2012	Retrospective pilot study	Chemotherapy	Gemcitabine and S1	The 3 yr survival rates of NACT group (55.6%) was higher than control group (29.6%)
O'Reilly <i>et al</i> [178], 2014	Phase II trial non randomized	Chemotherapy	Gemcitabine and oxalipatin	Resectability was 71% Overall survival was 21.7 mo
Motoi <i>et al</i> [179], 2013	RCT- NACT vs direct surgery	Chemotherapy	Gemcitabine and S1	Results awaited
Scott <i>et al</i> [180], 2017	RCT- NACT vs direct surgery	Chemotherapy	FOLFIRINOX	Results awaited
Labori <i>et al</i> [181], 2017	RCT- NACT vs direct surgery	Chemotherapy	FOLFIRINOX	Results awaited
Heinrich <i>et al</i> [182], 2011	RCT- NACT vs direct surgery	Chemotherapy	Gemcitabine and oxalipatin	Results awaited
Sohal <i>et al</i> [183], 2017	RCT-FOLFIRINOX vs GnP	Chemotherapy	FOLFIRINOX vs Gemcitabine and nab paclitaxel	Results awaited
Turrini <i>et al</i> [184], 2009	Prospective study	Chemoradiotherapy	5-Flurouracil and cisplatin with radiotherapy	Resectability rate is 82.6% Median overall survival for resected patients is 23 mo
Golcher <i>et al</i> [185], 2015	RCT- NACT vs direct surgery	Chemoradiotherapy	Gemcitabine and Cisplatin with radiotherapy	R0 resection rate (52%) and median overall survival after tumor resection (27 mo) was greater NACT arm
Okano <i>et al</i> [186], 2017	Prospective study	Chemoradiotherapy	S-1 with radiotherapy	1-yr and 2-yr survival rates are 91% and 83% in resectable group

RCT: Randomized control trial; NACT: Neoadjuvant chemotherapy; NACT: Neoadjuvant chemoradiotherapy; FOLFIRINOX: 5-Flurouracil, irinotecan and oxalipatin.

JASPAC-01, S1 was proven superior to gemcitabine, but it is still not widely used outside Japan[194]. The CONKO-05 and CONKO-06 trials did not prove the efficacy of gemcitabine + erlotinib and gemcitabine +sorafenib, respectively, over gemcitabine alone[195,196].

Systemic therapy for metastatic disease

Combination chemotherapy regimens are now being recommended over single agent gemcitabine for patients with metastatic disease with good performance status. The ACCORD trial has laid the ground for the FOLFIRINOX regimen as the preferred regimen over gemcitabine[197]. Several new second-line regimens were added to the arsenal after the success of the MPACT and NAPOLI-1 trials[198,199]. The trial comparing extracellular matrix degrader pegvorhialuronidase alfa (PEGPH20) was stopped as its primary end-point was not met[200]. The results of the clinical trial AVENGER 50 comparing modified FOLFIRINOX with or without CPI-613 are awaited [201].

Studies on the role of immunotherapy in cancers are encouraging, but that is not the case with PDA[202]. The highly desmoplastic stroma and absence of any effector cells in the tumor microenvironment seem to be the predominant reason for the failure of immunotherapy[203]. Even though pembrolizumab is approved in patients with microsatellite instability, the latest results from the KEYNOTE-158 study are disappointing[204]. Two new targeted therapy drugs have been approved. Larotrectinib was approved in patients with tropomyosin receptor kinase (TRK) fusion-positive tumors[205]. Entrectinib, a multiple tyrosine kinase inhibitor, was also approved in patients with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions[206]. Cisplatin-based regimens are recommended in patients with germline mutations in *BRAC2* [207]. Based on the results of the POLO trial, olaparib is approved as maintenance therapy in patients with metastatic PDA and *BRCA2* mutation and with a good performance status[208].

Gene therapy for pancreatic cancer is being widely studied. A number of clinical trials and ongoing studies have been conducted in this regard[209]. Even though the results of gene therapy in phase 1 trials are encouraging, the same is not being

replicated in the phase 2 studies in comparison with standardized treatment. The role of miRNAs such as *miR-4516* is being studied, which may be the future target for therapies[210]. The role of intra-operative chemotherapy in PDA is being studied in the combiCaRe trial[211].

CONCLUSION

This narrative review highlights the newer trends and achievements in the epidemiology, etiopathogenesis, screening, diagnosis and management of PDA. The newer trends in epidemiology will help us to predict the population and countries at risk in the near future. The newer concepts in the field of etiopathogenesis will help us to understand this stubborn disease better. Newer screening and diagnostic techniques will help in diagnosing the patients at an early stage and prognosticate better. The newer discoveries in drugs and management protocols will help the physicians and surgeons increase the survival and quality of life of the patients.

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