

Pancreatic Cancer: The Advanced Practitioner's Role in Early Diagnosis and Management

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Abstract

Pancreatic cancer is one of the most fatal cancers in the United States. Currently, it is the third leading cause of cancer-related deaths, and it is estimated that by 2030, it will be the second leading cause of cancer-related deaths behind lung cancer. It has poor overall survival rates, even with aggressive treatment. Quality of life is low in this patient population, due to poor prognosis at diagnosis and complex symptomatology. The purpose of this article is to explore the role of the advanced practitioner in the diagnosis, treatment, and symptom management of pancreatic cancer.

Pancreatic cancer is one of the most fatal cancers in the United States, and the incidence continues to rise due to multiple factors such as obesity, smoking, genetics, and longer lifespan. In addition, patients with pancreatic cancer experience a poor quality of life (QOL) compared with other cancers (Pihlak et al., 2023). Due to the overwhelming symptom burden and poor prognosis, it is crucial for the advanced practitioner (AP) to be educated regarding early diagnosis, treatment, and symptom management to optimize overall survival (OS) and QOL for these patients.

Pancreatic ductal adenocarcinoma (PDAC) comprises more than 90% of pancreatic cancers. These originate

in the pancreatic ductal epithelium (Jiang et al., 2022). Other, exceedingly rare, pancreatic tumors include intra-ductal papillary mucinous neoplasm, pancreatic neuroendocrine tumors, and serous cystic neoplasms (Si et al., 2021). The location and anatomy of the pancreas contribute to the complexity of this cancer and the treatment challenges it presents. Surgery remains the only curative treatment and is available to less than 20% of patients due to advanced disease at diagnosis (Jiang et al., 2022).

EPIDEMIOLOGY

In 2023, there were over 64,000 newly diagnosed pancreatic cancer cases in the United States and over 50,000 deaths (National Cancer Institute,

2024). It has recently passed breast cancer to be the third leading cause of cancer-related deaths, while only being the 11th most common cancer (Halbrook et al., 2023; Idachaba et al., 2019). Pancreatic cancer is projected to be the second leading cause of cancer-related deaths in the United States by 2030 (Chung et al., 2022; Idachaba et al., 2019). The average age at diagnosis is 65 years, but the incidence is rising in younger populations, especially in young women (Stoffel et al., 2023).

CHALLENGES

More than 80% of pancreatic cancer cases are diagnosed with advanced disease. This is largely due to the pathophysiology of pancreatic cancer and anatomy of the pancreas. Due to the location of the pancreas in the retroperitoneum, patients are often asymptomatic until they are at an advanced stage with a large tumor (Tonini & Zanni, 2022). Early symptoms tend to be vague and non-specific, such as abdominal pain and diarrhea (Idachaba et al., 2019). Furthermore, pancreatic cancer starts producing micrometastasis early in the disease process, which significantly shortens the window available to identify early stage, resectable disease. The vasculature within the pancreas also presents problems. The pancreas has a very fibrous, low-density vasculature, which makes it difficult to penetrate with chemotherapy. This ultimately leads to chemotherapy resistance (Jiang et al., 2022). Advanced disease at diagnosis correlates with the poor prognosis associated with pancreatic cancer. The average OS from diagnosis is 6 months, and the 5-year survival is only 12.5%. With early diagnosis, survival drastically increases. Patients with localized disease, which has not spread outside the pancreas, have a 44.3% 5-year survival rate (Pihlak et al., 2023; National Cancer Institute, 2024; Stoffel et al., 2023).

Pancreatic cancer is also associated with a significant symptom burden (Pihlak et al., 2023). With advanced disease, patients must contend with an aggressive, multisystem symptom profile, which can include pain, fatigue, cachexia, anorexia, diarrhea, and depression (Tang et al., 2018).

RISK FACTORS

Modifiable risk factors associated with pancreatic cancer are largely related to lifestyle and are linked

to its rising incidence. Binge drinking, smoking, obesity, high cholesterol, and hypertension are all associated with an increased risk of pancreatic cancer (Huang et al., 2021; Stoffel et al., 2023). Of note, 85% of individuals diagnosed with pancreatic cancer have elevated fasting blood sugars. It has been observed that the risk for pancreatic cancer is significantly higher within the first 3 years after a diabetes diagnosis. Research is now starting to focus on the relationship between new-onset diabetes (NOD) and pancreatic cancer (Stoffel et al., 2023).

Pancreatic cancer has numerous non-modifiable risk factors. Black Americans have the highest incidence in the United States, followed by Caucasians. Approximately 10% of pancreatic cancer cases can have a familial and/or genetic link. Familial pancreatic cancer (FPC) is seen in individuals with two first-degree relatives affected (Tonini & Zanni, 2022). Germline mutations can affect 5% to 20% of patients with pancreatic cancer. The most common germline cases arise from pathologic variants in the *BRCA1*, *BRCA2*, or *PALB2* pathways. Other variants that can increase the risk of pancreatic cancer in relation to the general population include Lynch syndrome, *CDKN2A*, *STK11*, *TP53*, *PRSS1*, *KRAS*, and *ATM* genes (Idachaba et al., 2019; Lucas & Kastrinos, 2019; Stoffel et al., 2023). These variants can also be seen somatically in approximately 8% of patients. Acute, chronic, and hereditary pancreatitis are also risk factors (Stoffel et al., 2023). While pancreatic cancer has numerous risk factors, unfortunately, there is no single risk factor that overwhelmingly causes pancreatic cancer for most patients (Halbrook et al., 2023).

There is a growing body of research and knowledge surrounding pancreatic cancer. Numerous risk factors have been identified (Huang et al., 2021). High-risk groups, such as patients with germline mutations or FPC, have been identified in which screening is recommended (Raufi et al., 2023).

PREVENTION

Huang and colleagues (2021) performed a meta-analysis of the World Health Organization Global Health Observatory database, GLOBOCAN, to analyze the worldwide burden, risk factors, and trends in pancreatic cancer. GLOBOCAN has country- and age-specific rates of incidence and

mortality for different cancers. GLOBOCAN also provides information allowing for analysis of risk factors, regional burden, and epidemiologic trends regarding different cancers. This study specifically analyzed the correlation between pancreatic cancer and lifestyle, metabolic risk factors, incidence, and other trends across 184 countries worldwide. The highest incidence and mortality of pancreatic cancer were seen in countries with high human development indexes (HDI). Education, income, and life expectancy comprise the HDI. Countries with high HDIs had higher rates of many of the modifiable risk factors, including smoking, obesity, alcohol use, inactivity, high cholesterol, and hypertension. Thus, it can be postulated that employing preventative measures towards these modifiable risk factors can help mitigate the incidence of pancreatic cancer (Huang et al., 2021).

SURVEILLANCE AND SCREENING

Currently, only high-risk individuals are advised to be screened for pancreatic cancer, as screening the general population is both ineffective, impractical, and potentially harmful (Lucas & Kastrinos, 2019; Raufi et al., 2023). These populations include those with FPC, germline mutations, and NOD. The screening modalities typically utilized are MRI and endoscopic ultrasound, although specific recommendations regarding the frequency and timing of screening are still largely undetermined (Raufi et al., 2023).

It is currently recommended to do genetic testing on all individuals with pancreatic cancer. If found to have a germline mutation, it is then recommended for first-degree relatives to also undergo genetic testing and start screening (Lucas & Kastrinos, 2019). The use of pancreatic biomarkers as a tool in surveillance is currently a promising area of research. In conjunction with imaging, biomarkers help differentiate high malignant potential cystic lesions from those with low malignant potential. Next-generation sequencing performed on fluid from various pancreatic cysts can help determine malignant potential (Stoffel et al., 2023).

TREATMENT

Patients presenting with early stage disease are candidates for surgery. The Whipple procedure is the surgery typically performed. In a Whipple,

the proximal pancreas, parts of the duodenum and jejunum, common bile duct, part of the stomach, and gallbladder are resected. Due to the high rate of complications associated with a Whipple procedure, minimally invasive and robotic surgeries are starting to be utilized with increasing frequency by surgeons, but do not yet exhibit any significant improvements in postoperative morbidity and mortality (Schepis et al., 2023). Brachytherapy is another treatment option where radioactive seeds are placed directly in the tumor. Chemotherapy is routinely used in the treatment of pancreatic cancer, especially in unresectable patients. FOLFIRINOX (leucovorin, fluorouracil, oxaliplatin, and irinotecan) or gemcitabine and abraxane or cisplatin are common chemotherapy regimens used. Studies have also shown the benefit of neoadjuvant chemotherapy and radiation followed by surgery and adjuvant treatment for patients with borderline resectable and locally advanced disease (Kolbeinsson et al., 2023; Schepis et al., 2023). Adjuvant and neoadjuvant radiation therapy are also used in the treatment of pancreatic cancer. Ultimately, treatment options are often dictated by the extent of the disease at diagnosis and performance status of the patient. Pancreatic cancer remains a disease best treated with a multidisciplinary approach (Kolbeinsson et al., 2023).

SYMPTOM MANAGEMENT

Pain, digestive symptoms (nausea, vomiting, indigestion, flatulence, altered bowel habits, and anorexia), depression, anxiety, and fatigue are some of the most common symptoms associated with pancreatic cancer (Tang et al., 2018). Moderate to severe pain is a presenting symptom in 75% of patients with pancreatic cancer. The location is primarily abdominal but varies based on the location of the tumor and extent of disease. Pain can be neuropathic, visceral, somatic, or treatment related. The severity of pain strongly correlates with prognosis in pancreatic cancer patients. First-line treatment for pancreatic cancer pain is typically opioids. Neurolytic celiac plexus block is also utilized in the management of visceral pain associated with pancreatic cancer and is shown to provide relief in 74% of patients. Neurolytic celiac plexus block also decreases the need of opioids. Steroids, antidepressants, anti-

convulsants, and cannabinoids can supplement opioid regimens as needed. Complementary and integrative medicine such as electroacupuncture and hypnosis have been shown to have potential benefit, although results are not conclusive (Lohse & Brothers, 2020).

Abdominal side effects significantly impact QOL in patients with pancreatic cancer by impacting nutritional and functional status. The pathophysiology of pancreatic cancer impairs the absorption of nutrients while also accelerating metabolism, which results in a negative energy balance resulting in anorexia, weight loss, cachexia, and fatigue. The average weight loss of pancreatic patients is more than 8% of their body weight at 3 months, and over 12% of their total body weight 6 months after diagnosis. Nutritional counseling can help minimize weight loss and muscle mass in this patient population and improve QOL (Poulia et al., 2022). Inadequate digestion stems from pancreatic exocrine insufficiency. Pancreatic enzyme replacement therapy (PERT) provides oral pancreatic enzymes to help minimize the effects of this insufficiency, although providers often are not educated regarding dosing. Ideally, PERT would be managed by a multidisciplinary team, but it remains an unmet need, which significantly impacts QOL (Scott & Jewell, 2019). It should be noted that loss of appetite is one of the most distressing symptoms experienced by patients and caregivers but is often overlooked and not prioritized (Tang et al., 2018).

Out of all patients with digestive system tumors, patients with pancreatic cancer have the highest rates of depression (Michoglou et al., 2023). This is likely linked to poor prognosis and significant symptomatology. Michoglou and colleagues (2023) advise controlling pain before evaluating a patient's depression and anxiety. Selective serotonin reuptake inhibitors (SSRIs) and psychotherapy are first-line for the treatment of depression. Tricyclic antidepressants are also commonly used in pancreatic patients for their dual antidepressant and analgesic effects. Stimulants can be used to improve appetite and energy, while benzodiazepines can be employed to help manage anxiety. Psychological symptoms should not be neglected in this patient population, as unmet needs can exacerbate other symptoms (Michoglou et al., 2023).

Fatigue is found in most patients with pancreatic cancer. This is often a sequela of prognosis, treatment, disease, poor nutrition, and depression. It is also associated with lower OS and progression-free survival (Poulia et al., 2022). Management of comorbid conditions is one step in managing fatigue. The benefits of exercise have also been demonstrated in numerous studies to improve fatigue associated with pancreatic cancer. Aerobic exercise and resistance training have been shown to increase muscle mass, balance, and performance status and have psychological benefits, such as increased feelings of well-being and QOL. Exercise programs have proven especially beneficial in treating cachexia, a significant contributor to fatigue, associated with pancreatic cancer (Luo et al., 2021).

ROLE OF THE AP IN PANCREATIC CANCER SCREENING, DIAGNOSIS, AND MANAGEMENT

The advanced practitioner has an important role in the management of patients with pancreatic cancer across specialties. In the case of advanced practice registered nurses (APRNs), primary care APRNs are on the frontline and will likely be the first to know about presenting symptoms and family history. The oncology APRN has the responsibility of treating and managing symptoms. APRNs in other settings such as surgery and radiation will also help manage these patients.

Primary Care APRN

The primary care APRN has an important role in the management and identification of patients with pancreatic cancer. Primary care APRNs should be cognizant of which patients are at high risk for pancreatic cancer by obtaining a thorough history and physical. Modifiable risk factors should be identified, and interventions implemented to minimize these. Pancreatic cancer should be in the differential for vague and worsening gastrointestinal (GI) symptoms and patients with NOD. When pancreatic cancer is a concern, prompt referrals should be made for appropriate workup, which can include bloodwork, imaging and/or biopsy. Referrals to other specialties, such as a gastrointestinal (GI) clinician, may be warranted to rule out other etiologies. Genetic testing should be performed when

appropriate and screening initiated if advised. If a pancreatic cancer diagnosis is confirmed, the primary care APRN should be in communication with other members of the patient's treatment team, and knowledgeable of resources that the patient and family may need for support.

Oncology APRN

The oncology APRN will likely see patients after they are diagnosed, although they should also be aware of who the high-risk patients are and which patients and family members need genetic testing. Symptom burden is a huge factor impacting QOL in patients with pancreatic cancer, and the oncology APRN should be knowledgeable in symptom management. Initiating palliative care early in the pancreatic patient has been correlated with increased QOL, improvements with psychological distress, and better symptom management (Chung et al., 2022; Scott & Jewell, 2019). Overall survival has been shown to improve with proper symptom management, likely related to the patient being able to tolerate treatment longer (Pouliou et al., 2022). It is also imperative that the oncology APRN be versed on current treatments for pancreatic cancer, as well as clinical trials and emerging therapies. Patients with pancreatic cancer often require multiple treatment modalities, and treatment regimens need to be tailored to each patient's individual needs.

Patients with pancreatic cancer and their caregivers identify communication as an unmet need, especially surrounding diagnosis (Chong et al., 2023; Chung et al., 2022). All advanced practitioners should be empathetic regarding this disease course and prognosis. Teaching and communication should be done with patients and caregivers at every visit, as patients are often overloaded with information when diagnosed. Patients and caregivers should also be given support to navigate the health-care system. This disease is associated with multiple tests, imaging studies, and appointments with managing doctors and support clinicians, which can prove overwhelming (Chong et al., 2023). A study by Pihlak and colleagues (2023) demonstrated a disconnect between providers and patients regarding treatment goals and expectations. The patient's main priority was OS, whereas the provider's main priority was balancing treatment with side ef-

fects. This study illustrates that patients had higher hopes for OS than their providers (Pihlak et al., 2023). Open communication, emotional support, and continuous education regarding treatment, disease course, and prognosis have been shown to have positive impacts on the pancreatic cancer patient experience (Chung et al., 2022).

FUTURE RESEARCH

In cancer research, the primary endpoint is often OS. This is particularly important for pancreatic cancer, given its low survival rates. In pancreatic cancer, there are many ways to achieve increased OS. Preventative strategies have the potential to decrease the incidence of pancreatic cancer, and new screening techniques and guidelines could improve OS. New treatments and targeted therapies have the potential to impact OS. Improved symptom management has also been shown to be correlated with OS in pancreatic cancer (Pouliou et al., 2022).

Screening and Prevention

Future research should be focused on screening modalities to help identify patients at an earlier stage of disease. It should also involve specific recommendations regarding screening modalities and frequency. Liquid biopsy is an emerging technology that shows promise in being utilized as a screening, diagnostic, and treatment guiding tool in pancreatic cancer. This analyzes circulating tumor cell DNA, exomes, microRNA, and cell-free DNA and RNA, which can be collected from a variety of bodily fluids, including blood, saliva, urine, and pancreatic secretions. Circulating tumor DNA (ctDNA) has a low sensitivity (30.8%) and specificity (57.9%) in early stage disease. Circulating exosomes appear more promising than ctDNA in PDAC. Many pancreatic cells release exosomes into the blood since they are exocrine cells. *KRAS* mutations, which are found in 90% of pancreatic tumors, were detected more using exosome analysis compared to ctDNA (Idachaba et al., 2019; Raufi et al., 2023). It has been demonstrated that combining flow cytometry with liquid biopsy exosome analysis could potentially have a screening sensitivity and specificity of 100% and 80%, although larger studies will be required before this is put into practice (Raufi et al., 2023). Prevention of pancreatic cancer linked to

modifiable risk factors is also a great opportunity for research.

Immunotherapy and Targeted Therapy

Given pancreatic cancer's proclivity to chemotherapy resistance and multiple somatic mutations, immunotherapy and targeted therapies should be a significant area of research, especially given the advent of next-generation sequencing (Jiang et al., 2022). This would provide tumor-specific treatment with fewer side effects than systemic chemotherapy.

Current research is focused on targeted therapies, especially targeting the *KRAS* mutation, which is found in 90% of pancreatic tumors (Idachaba et al., 2019; Kolbeinsson et al., 2023). *KRAS* mutations are seen early in the pancreatic cancer disease process, and work to drive tumorigenesis. *KRAS* is a complex oncogene causing mutations in numerous codons (Jiang et al., 2022). Alterations to *KRAS* codon 12 is the most common mutation in pancreatic cancer, found in over 70% of pancreatic cancer tumors. Within *KRAS* mutations on codon 12, there are multiple alterations that can be targeted. G12D is found in over 40% of codon 12 mutations and is an area of research for targetable therapy (Kolbeinsson et al., 2023). Poly(ADP-ribose) polymerase (PARP) inhibitors are also an important area of study for patients with germline or somatic *BRCA* mutations (Kolbeinsson et al., 2023; Schepis et al., 2023). Immunotherapy is an area of research that shows promise but proves to be complex. Pancreatic cells are good at evading the immune system, making them hard to target with immunotherapy. Thus far, there has been minimal success with immunotherapy in patients with pancreatic cancer (Jiang et al., 2022). One exception is tumors that exhibit high microsatellite instability (MSI-H). These tumors, which only comprise about 2% of pancreatic cancers, have been shown to respond to pembrolizumab (Keytruda). The use of T cells to produce an inflammatory response within pancreatic tumors, thus making them detectable by the immune system, is a current area of research that shows promise (Kolbeinsson et al., 2023). Understanding the complex pathophysiology of pancreatic cancer is crucial to developing new therapies and thus an area for continuing research.

Quality of Life and Symptom Management

It is also crucial to research ways to improve the QOL of patients with pancreatic cancer. Qualitative research regarding the pancreatic cancer patient and caregiver needs and experiences is one way to identify strategies to improve QOL. The patient perspective needs to be heard and understood to best develop treatment plans. Symptom management is also an important area of research. This is a fatal disease with complex symptomatology. Research focused on improving QOL through exercise, nutrition, and pain management can potentially change the course of this disease for many patients.

CONCLUSION

It is the responsibility of the advanced practitioner to keep abreast of the latest research regarding prevention, screening, treatment, and symptom management of the patient with pancreatic cancer. Advanced practitioners play a vital role in the management of this patient population. Through good communication and continued education, the advanced practitioner can help optimize care and outcomes for patients with this serious disease. ●

Disclosure

The author has no conflicts of interest to disclose.

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