1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas. PDAC is an aggressive and difficult malignancy to treat. Complete surgical removal of the tumor remains the only chance for cure, however 80-90% of patients have disease that is surgically incurable at the time of clinical presentation (15). Despite our advancing knowledge of the tumor biology of PDAC, improvement in diagnosis and management, and the rise of centers specialized in the care of patients with PDAC, the prognosis remains strikingly poor (4,17). The following overview will discuss the epidemiology and tumor biology of PDAC, as well as important information for patients and family including diagnosis, treatment, and prognosis. This overview will not discuss cancer that arises in cystic lesions of the pancreas, nor will it discuss pancreatic neuroendocrine tumors, as these variants have a different biology and prognosis.

2. Epidemiology and Demographics

It was estimated that 46,420 new cases and 39,590 deaths were attributable to pancreatic cancer in the United States in 2014, of which PDAC represents the vast majority. That the number of deaths per year nearly equals the number of new cases per year highlights the lethality of this disease. Pancreatic cancer was the 12th most common type of cancer in the US in 2014, representing just 2.8% of all new cancer cases. Despite this, pancreatic cancer was the 4th most common cause of cancer-related death (15). Furthermore, the incidence of pancreatic cancer is rising. It is estimated that in 2015 the above figures will rise to 48,960 new cases and 40,560 deaths attributable to pancreatic cancer. Approximately 96% of these cases will be PDAC (16). By 2030, researchers project that pancreatic cancer will become the 2nd leading cause of cancer related death in the US after lung cancer, surpassing colorectal, breast, and prostate cancer (14).

The median age for diagnosis of pancreatic cancer is 71, with 75% of cases diagnosed between the ages of 55 and 84. The median age for death as a result of pancreatic cancer is 73 years of age (4). Pancreatic cancer is slightly more common in men than women, but this gap has narrowed in recent years. Risk factors for pancreatic cancer are identifiable in approximately 40% of cases, and include (but are not limited to) the following:

- **Race/Ethnicity:** Black, Ashkenazi-Jewish descent.
- **Medical Conditions:** Chronic pancreatitis, acute pancreatitis, diabetes (long-term and new-onset), cirrhosis, *Helicobacter pylori* infection, human immunodeficiency virus (HIV) infection, hepatitis B, cystic fibrosis, obesity.
**Hereditary**: Family history of pancreatic cancer, Lynch syndrome, Li-Fraumeni syndrome multiple endocrine neoplasia 1, hereditary breast and ovarian cancer, Familial atypical multiple mole melanoma syndrome, von-Hippel Lindau syndrome, Peutz-Jegher syndrome.

**Lifestyle**: tobacco use, heavy (not mild or moderate); alcohol use, high fat/cholesterol diet (11, 23).

### 3. Tumor Biology

PDAC is an epithelial tumor that arises from the cells of the pancreatic duct or ductules, for which it is named. In health, the pancreatic duct(s) serve as the conduit through which digestive enzymes and bicarbonate ion produced in acinar cells reach the small intestine. Ductal cells and acinar cells together represent the “exocrine” pancreas, from which the vast majority of pancreatic neoplasms arise.

It is now believed that the development of PDAC occurs over an extended period of time, and likely follows a stepwise progression similar to other carcinomas (colorectal carcinoma, in particular). This progression is characterized by the transition of a normal pancreatic duct to a pre-invasive precursor lesion known as pancreatic intraepithelial neoplasia (PanIN), which can ultimately develop into an invasive PDAC (5). This progression is spurred on by the gradual accumulation of genetic mutations (Figure 1). A mutation in the *K-ras* oncogene is one of the most common and earliest found in PDAC, occurring in 90% of cases. Other common genetic mutations commonly found in PDAC include activation of oncogenic Her-2/neu, and loss of function in tumor suppressor genes such as *p16*, *p53*, and SMAD4 (5, 6). Advanced PanIN lesions develop increasing genetic variability, proliferate, and eventually acquire the means to invade and metastasize.

![Figure 1: The “Progression Model” for Pancreatic Cancer. From Hruban et al, reused with permission (5). Progression is divided into morphological stages which are usually associated with mutation in the genes showed below.](image-url)
4. Clinical Presentation - Signs and Symptoms

The most common symptoms of PDAC are pain and weight loss, and the most common clinical sign is jaundice. More specifically, one study has reported the following frequency of sign and symptoms in patients with PDAC, in descending order (13):

- Weakness/fatigue (asthenia)—86%
- Loss of appetite (anorexia)—85%
- Weight loss—85%
- Abdominal pain—79%
- Dark urine—59%
- Jaundice—56%
- Nausea—51%
- Back pain—49%
- Diarrhea—44%
- Vomiting—33%

It is important to understand that the presenting signs and symptoms are often related to the location of the tumor. Grossly, the pancreas is divided into the following anatomic regions: the uncinate process, the head, the body, and the tail. In the context of PDAC, the anatomy may be simplified into two groups, namely the head of the pancreas (including the uncinate process) and the body/tail. Approximately 60-70% of PDAC arise from the head of the pancreas, whereas 20-25% arise from the body/tail (9). In general, tumors arising from the head of the pancreas come to clinical attention earlier than tumors arising from the body and tail, as the head of the pancreas contains the common bile duct. A tumor that obstructs the common bile duct leads to the phenomenon known as “painless jaundice” as bile constituents accumulate in the blood, often prompting an imaging study that will reveal the underlying tumor. In contrast, tumors of the body and tail do not produce jaundice, and therefore most often come to clinical attention later once weight loss and/or pain become apparent.

PDAC may occasionally be the cause of acute pancreatitis (caused by obstruction of the pancreatic duct), and come to clinical attention in that manner. New onset diabetes in an adult patient that is otherwise healthy is also an uncommon presentation of PDAC, and one that carries a poor prognosis. Finally, PDAC may be identified incidentally abdominal imaging for an unrelated issue, but this is exceedingly rare.

5. Diagnosis

The presenting symptoms and signs discussed above are not specific for the diagnosis of PDAC, and therefore a diagnosis of PDAC can only be made after further investigation. Laboratory investigation—particularly liver function tests—should be performed in all patients suspected to have a pancreatic malignancy, and especially if there are signs of jaundice on physical exam. The tumor marker carbohydrate antigen 19-9 (CA 19-9) may be increased in 75-85% of patients with PDAC. It is non-specific and may be elevated in benign biliary or pancreatic disease, nor is it perfectly sensitive. Therefore while an elevated CA 19-9 in a patient with a pancreatic mass is highly suspicious for PDAC, it does not make the diagnosis. Rather, the role of CA 19-9 is predominantly one to assess for recurrence after surgery (21).

Because laboratory tests are not specific for PDAC, dedicated imaging studies are indicated. Abdominal computed tomography (CT) is the most common initial test performed to identify a pancreatic mass (Figure 2), but other imaging studies include abdominal magnetic resonance imaging (MRI) with or without cholangiopancreatography (MRCP), abdominal ultrasonography (US), and endoscopic ultrasound (EUS) with or without endoscopic cholangiopancreatography (ERCP). EUS and ERCP are the most invasive of the above-mentioned tests, but are the only studies among those listed that allow for a biopsy that may provide the exact diagnosis.
Figure 2: Typical CT appearance of PDAC. (A) An axial CT scan demonstrating a “hypoattenuating” mass (yellow arrow) in the head of the pancreas with proximity to the superior mesenteric vein. (B) A coronal CT scan of same “hypoattenuating” mass (yellow arrow) in the head of the pancreas. Please note there is abnormal dilatation of the pancreatic duct (red arrow), indicating that the mass is obstructing the outflow of the pancreas.

Unless there are specific contraindications or extenuating clinical circumstances that favor performing an alternative test, abdominal CT is the recommended initial test of choice. CT is widely available and has a high degree of accuracy in identifying most tumors, and can determine whether a tumor is resectable in 90% of cases (10).

Unlike in most other solid malignancies, it remains controversial whether a biopsy should be attempted if PDAC is suspected, except in two particular situations. The majority of surgeons recommend proceeding directly to surgery when a mass suspected to be PDAC is causing obstructive jaundice—in this case surgery will be required to alleviate the obstruction regardless of the tissue diagnosis. On the other hand, in cases where PDAC is suspected but there is evidence of metastasis or locally advanced disease that precludes an attempt at curative resection, tissue biopsy is universally required in order to guide chemotherapy. In the remainder of clinical situations, a multidisciplinary team may be necessary to determine whether a biopsy should be performed prior to surgery (19).

6. Staging

Once a diagnosis of PDAC is confirmed or highly suspected, an attempt to stage the tumor is made. This is achieved primarily through triphasic CT scan of the abdomen (19). Rarely, an investigation outside of the abdomen is performed to identify distant metastasis, usually with CT scan of the chest or whole body positron emission tomography (PET). The 7th edition of the American Joint Committee on Cancer (AJCC) Pancreas Cancer Staging follows the standard “TNM” (Tumor size, lymph Node status, Metastasis) format and is shown in Table 1 and Table 2 (1). The AJCC staging system is most commonly used to determine prognosis (see “Prognosis” section). Further information regarding staging is publically available through the website of the National Cancer Institute (http://www.cancer.gov/cancertopics/pdq/treatment/pancreatic/Patient/page2).

Preoperative surgical staging refers to the determination of whether a suspected PDAC is amenable for surgery. A tumor is considered potentially resectable, borderline resectable, or unresectable (7).
Although the criteria for calling a tumor resectable versus borderline resectable may change somewhat depending on the institution and the comfort level of the surgeon, in general, PDAC is considered resectable when the following criteria are met: (1) there is no evidence of distant metastasis, (2) there is a lack of tumor involvement of the major arteries, and (3) if there is venous invasion then it must be suitable for venous reconstruction (22). If patients are considered borderline resectable, it is generally related to questionable involvement of the arteries and/or veins that cannot be fully assessed preoperatively.

In these patients, preoperative chemotherapy and possibly radiation therapy may be beneficial (see above).
7. Treatment

Surgery
Surgical resection remains the only definitive treatment for PDAC, and the only treatment that offers a chance for cure. Unfortunately, only approximately 10-20% of patients will have tumors that are amenable to surgical resection. In order to be eligible for surgery with curative intent, a tumor must be considered resectable (see above) by the operating surgeon. If that criterion is met, then the location of the tumor determines the type of operation that will be performed. Regardless of location, the goal of surgery is to achieve a complete removal of the tumor with negative margins—both macroscopically and microscopically (known as R0 resection). Less adequate resections leave tumor behind, whether it is microscopic (an R1 resection) or macroscopic (R2 resection).

For PDAC located in the head of the pancreas, a pancreaticoduodenectomy (also known as a “Whipple” procedure) is the only surgery of choice (Figure 3). Although historically plagued by high operative mortality, the Whipple procedure is now performed safely with perioperative mortality around 2% when performed by a surgeon in a high-volume center. However, between 30-40% of patients will endure a major complication, most commonly pancreatic fistula or delayed gastric emptying (2).

For tumors of the body and tail, a distal pancreatectomy and splenectomy is performed. This has also become a safe procedure over the past three decades, with low operative mortality in high-volume centers. The complication rate also approaches 35%, with a leak from the transected pancreas being the most common (12).

Chemotherapy
Currently, chemotherapy is indicated in the treatment of PDAC in all cases, although the duration and type of chemotherapy depends on the goals of therapy. For patients that have undergone surgery, adjuvant chemotherapy is given postoperatively and has been shown to impart a survival advantage when compared to surgery alone. The current agents that are the standard of care in this setting are gemcitabine, or...
a combination of 5-flurouracil plus leucovorin. For patients with advanced PDAC—metastatic or unresectable—a survival benefit has been demonstrated with the administration of FOLFIRINOX (5-flurouracil, leucovorin, irinotecan, oxaliplatin) as induction chemotherapy, indicating that it is the primary treatment of the disease (8). Finally, a recent development in the treatment of PDAC has been the increasing use of neoadjuvant chemotherapy for borderline resectable or locally advanced disease, meaning that chemotherapy is given prior to surgery. The rationale for giving chemotherapy in borderline resectable PDAC is that the tumor becomes resectable as a result of treatment. Studies are ongoing to determine the ideal combination of agents with or without radiation therapy (20).

Radiation
The use of radiation in PDAC is somewhat controversial. Some studies have failed to show a significant survival benefit when radiation is added to chemotherapy in the adjuvant setting. There have even been some data to suggest that adding radiation may have a negative overall effect when used in the adjuvant or neoadjuvant setting. However, there is also data that demonstrates radiation therapy imparts a significant advantage when used in the neoadjuvant setting, allowing for improved local control of the tumor and an increased chance of an R0 resection in tumors that are initially considered borderline resectable (3).

Palliation
A number of complications of PDAC may arise that require intervention, even in patients that are not candidates for surgery with curative intent. These include: malignant biliary obstruction, malignant gastric outlet obstruction, and intractable tumor-associated pain. Malignant biliary obstruction occurs as a result of tumor compression of the common bile duct, leading to severe jaundice. Malignant gastric outlet obstruction refers to tumor blockage of the outlet of the stomach, prohibiting the passage of food from the stomach into the small intestine, and causes severe nausea and vomiting, in addition to malnutrition. Both biliary and gastric outlet obstruction may be treated initially via endoscopy, but may require surgical bypass. Severe pain related to PDAC that is refractory to oral pain medications is often related associated pain is often the result of local extension of the tumor into the nerves of the celiac plexus. Targeted therapies including ethanol ablation or anesthetic injection into the celiac plexus have been shown to reduce tumor-associated pain (18).

8. Prognosis
Currently, overall 5-year survival is 7.2% for patients with PDAC, meaning that 7.2% of all patients diagnosed with PDAC are expected to be alive 5 years after diagnosis. The subset of patients that have “localized” disease (and therefore are surgical candidates) may expect a 27.1% 5-year survival. This discrepancy is a testament to the fact that surgery remains the only truly effective treatment modality. The prognosis by stage is summarized in Table 3, and is based on data from the National Cancer Data Base for patients diagnosed between 1992 and 1998.
9. References

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Table 3: PDAC Prognosis by Stage

| Stage | 5 year observed survival rate |
|-------|------------------------------|
| IA    | 14%                          |
| IB    | 12%                          |
| IIA   | 7%                           |
| IIB   | 5%                           |
| III   | 3%                           |
| IV    | 1%                           |
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