The pancreas is a critical organ for both the digestive and endocrine systems of the body. It is approximately 6 inches long and sits across the back of the abdomen, behind the stomach. The head of the pancreas is on the right side of the abdomen and is connected to the duodenum (the first section of the small intestine) through a small tube called the pancreatic duct. The narrow end of the pancreas, called the tail, extends to the left side of the body. The pancreas is also nestled up against several major arteries and veins. The pancreas has both endocrine and exocrine glandular qualities. The exocrine portion secretes enzymes into the digestive tract that aid in the absorption of nutrients and digestion. The neuroendocrine secretions affect several different hormones including insulin levels. Pancreatic cancer is divided into two types: exocrine and endocrine. Pancreatic ductal adenocarcinoma is from the exocrine cells and makes up about 85-90% of all pancreatic cancers. Pancreatic neuroendocrine tumors make up about 5% of pancreatic cancers and emerge from the endocrine cells in the gland. The majority of this write-up discusses the most common, exocrine pancreatic cancer.

The pancreas is divided into three major sections, the head, the neck/body and the tail. Pancreatic ductal adenocarcinoma, the most common pancreatic cancer, occurs 60-70% of the time in the head of the pancreas, approximately 10-15% occur in the tail and about 5-10% in the neck/body. About 20% of the time there is a more diffuse presentation of the tumor that goes through the entire gland.

Pancreatic cancer causes approximately 39,590 deaths in the United States accounting for approximately 7% of all cancer deaths. The incidence and mortality are on the rise. There has been considerably less improvement in the outcomes or pancreatic cancer therapy than in other common diseases including breast and lung cancer which survival rates have been on the rise. Pancreatic cancer has been hard to treat because it is usually quite advanced by the time it is diagnosed. The biology of the tumor is often quite aggressive and, overall, there has been a poorer response to available therapies if the disease is not surgically resectable. The survival rates go up substantially when it is diagnosed early and is resectable.

**Diagnosis**

There are no special screening tests that can identify early stage pancreatic cancer. The symptoms of pancreatic cancer often depend on the location of the tumor. For patients whose tumor is in the head/neck of the pancreas, the common symptoms include weight loss, jaundice, itchiness, clay-colored stools, diarrhea and fatty stools. If the tumor is in the body/tail of the pancreas, weight loss and pain are common symptoms; the pain is often due to the tumor putting pressure on the many nerves that run through the pancreas and behind it.
When pancreatic cancer is suspected, one of the best tools for diagnosing pancreatic cancer is a helical (spiral) CT scan. When someone presents with symptoms, they may receive a CT scan, but that will only show a mass. A helical or spiral CT scan, however, displays more detail of the pancreas, other organs and the relationship of the tumor to the local arteries and veins, all of which is crucial in determining if it is resectable. The pancreas has veins and arteries running in close proximity, and if the tumor is affecting these, the patient may not be a candidate for surgery. Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) are also important in the initial work-up. An MRI/MRCP is a magnetic resonance cholangiopancreatography which allows the biliary and pancreatic ducts to be imaged. Having an MRI/MRCP helps determine the exact location of the tumor and how it might be interfering with the ducts. A PET scan identifies the metabolism of tumor cells and is occasionally obtained for staging before surgery; however, it is not required. Sometimes an FNA (Fine Needle Aspiration) is done using endoscopic ultrasound to obtain cells to review in pathology. Your doctor will also check your blood tumor markers for CA 19-9; if these markers are elevated at diagnosis, they can be a good way to follow the tumor as well.

**Risk Factors**

There are several known risk factors for pancreatic cancer and some debated issues. Hereditary factors account for a small number of patients with pancreatic cancer. However, patients with a family history of breast and ovarian cancer who have the BRCA1 and BRCA2 genetic mutation are at an increased risk for pancreatic cancer. Patients with family histories of breast cancer, ovarian cancer, and pancreatic cancer may need to see a genetic counselor and receive appropriate counseling and testing if indicated. Patients who have one of the genetic mutations that cause colon cancer such as APC (adenomatous polyposis coli) and HNPCC (hereditary nonpolyposis colorectal cancer) are also at an increased risk for pancreatic cancer. Finally, patients who have hereditary pancreatitis have 40 times the risk of developing pancreatic cancer than someone without this known hereditary risk. Most pancreatic cancer, however, is idiopathic—meaning there are no hereditary factors.

Chronic pancreatitis increases the likelihood of developing pancreatic cancer because it can cause chronic damage to the organ over time. Environmental factors include both cigarette smoking, alcohol, obesity and a high-fat diet.

Pancreatic cancer appears to take a long time to develop into advanced cancer; it has been estimated that a pancreatic tumor has been developing for over 10 years by the time it is often diagnosed. Research has identified how different pancreas cancers can be, thus making single treatment approaches for all patients less likely to be successful. Rather, more individualized and personal care based on the genetic makeup of an individual’s tumor are the focus of research. Several mutations have been identified (which have also been identified in other tumors) including KRAS, BRCA, and P53 gene mutations.

**Pre-operative Staging and Treatment**

The American Joint Commission on Cancer has evolved an elaborate staging system for cancers that take into consideration the tumor size, the number of lymph nodes and whether the disease has spread to
other organs. While it is important to do a proper staging, full staging may not occur until after surgery and in some cases, surgery now comes after significant treatment with chemotherapy. For the purpose of determining treatment and the order of treatment, the categories are divided into potentially resectable, borderline resectable, locally advanced and metastatic.

The involvement of the tumor around or into the veins/arteries is a crucial issue because removing and reconstructing the veins requires a more complex procedure and some of the arteries cannot be removed. Surgery has shown to be effective only if the tumor is removed to negative margins. If the veins and arteries are not involved, and the patient is deemed “potentially resectable” they go to surgery usually followed by adjuvant chemotherapy treatment. The patients in the “borderline resectable” and “locally advanced” stages receive chemotherapy and sometimes radiation treatment to attempt to reduce their disease and to make it operable or ensure that it is just a local process, without distant spread, and surgery will be helpful. Patients with metastatic disease receive chemotherapy only.

Having a team experienced in making pancreatic cancer diagnoses is essential. It increases your probability of having a successful surgery, whether as the first treatment or after chemotherapy and reduces the possibility of putting someone through an invasive surgery when the disease is too extensive to be resolved with surgery. It is also critical not to delay treating someone with chemotherapy because of lengthy healing times after surgery.

**Surgical Treatment of Local Disease**

The best candidates for surgery first are patients whose disease is confined to the pancreas with no distant metastasis to other organs and no vascular involvement. Your surgeon will also need to consider other medical conditions to make sure it is safe to perform the surgery.

If the disease is in the body/tail of the pancreas, a distal pancreatectomy is performed. In this procedure, the body and tail of the pancreas are removed, and the cut line of the pancreas is sewn together to prevent pancreatic fluids from leaking. Sometimes, but not always, this involves removing the spleen as well. If the disease is in multiple areas of the pancreas, the whole pancreas can be removed, called a total pancreatectomy.

If the tumor is in the head/neck of the pancreas, your surgeon will perform a pancreaticoduodenectomy—a procedure in which the pancreatic head is removed, leaving clear tissue (margins) around the edges. This procedure is called a Whipple procedure, named after the doctor who began performing this procedure in 1935 in the United States. In the standard Whipple procedure, the distal stomach, intestine, gallbladder, bile duct and head of the pancreas are removed. Once they are removed, the surgeon reconnects the remaining pancreas to the jejunum along with the liver and the intestine. More recently this procedure has been revised to ensure the pylorus, the juncture at the duodenum which permits normal emptying of the stomach, is preserved. This procedure has better recovery and prevents weight loss and is often referred to as a pylorus-preserving Whipple. Today the mortality rate for the Whipple is less than 1% of experienced physicians who perform a high volume of cases per year (e.g., at UCLA our surgeons perform 150 cases per year). Complications can be well managed with interventional radiology. The quality of life after surgery is good, and there is a 25-30% five-year survival rate. A cure is not possible without it.

The best survival outcomes are for patients who have resectable disease, no lymph nodes involvement, a small tumor size (<3 cm), clear margins (meaning a margin of healthy tissue around the removed diseased tissue), and well-differentiated cells (which indicates a low-grade tumor).

**Medical Treatment – Chemotherapy and Other Systemic Approaches**
Only 15 -20% of pancreatic cancers are resectable. Only 25-30% of node-negative patients and 10% of node-positive resected patients are alive at five years. Chemotherapy is the only treatment to reduce the risk of recurrence in patients with resectable disease. Before 2016, patients received gemcitabine or 5-FU as the adjuvant treatment. As of 2016, the new standard of care is gemcitabine and capecitabine.

We use the same drug regimen for patients with Stage II or locally advanced disease as well as patients with metastatic disease. The three most common protocols are (1) gemcitabine with or without erlotinib, (2) a regimen called FOLFIRINOX comprised of four drugs - fluorouracil also known as 5-FU, leucovorin, irinotecan, and oxaliplatin, and (3) the dual combination of nab-paclitaxel and gemcitabine. Two others are gemcitabine with capecitabine or gemcitabine, docetaxel, and fluorouracil (5FU). Of course, there are clinical trials as well. Your oncologist will decide which protocol is best based on the individual patients, including their ability to tolerate the side effects as some regimens have more side effects than others.

There are many challenges in clinical research. One of the most difficult is the subjectivity that affects decisions on what constitutes locally advanced or resectable disease. There is no consensus about the response criteria for chemotherapy to proceed with surgery. Researchers are doing a lot in the realms of chemotherapy, molecular therapy, radiation therapy and immunotherapy. Recently, researchers have come to understand that pancreatic cancer is desmoplastic, which means the tumor itself has a pervasive growth of dense fibrous tissue or stroma surrounding and possibly protecting it. The tumor stroma may play a role in preventing the anti-cancer drugs from penetrating the tumor, thereby making the drugs less effective. Some of our new approaches are looking at the tumor microenvironment to evaluate ways to better alter the impact of drugs. For pancreatic cancers that are familial and have the BRCA mutations that also occur in breast and ovarian cancers, we are conducting trials using PARP inhibitors. We are investigating the EGF-KRAS pathway as it may be an important line of attack; we now know that 90% of the patients with pancreatic cancer have the KRAS mutation. Drug development is oriented to blocking these genes, but KRAS has not been shown to be a drug target. Additionally, vaccine and immunotherapies are also being tried; however, this is completely experimental at this moment in time for pancreatic cancer.

**Neuroendocrine Pancreatic Tumors**

Endocrine or pancreatic neuroendocrine tumors are a very different disease and are less common than exocrine pancreatic cancers. They form in the islet cells of the pancreas. There are many different kinds of these tumors. They can affect different hormones and, as a result, the symptoms that patients experience can be very different. Sometimes these tumors create hormones that cause disruption in systems; sometimes they do not, and the tumor grows undetected until it causes pain or discomfort. These kinds of tumors tend to be more indolent (slow growing). They are “better acting” tumors than the exocrine pancreatic tumors, and tend to have a better prognosis. We use some of the same diagnostic techniques, but there is often other blood work and imaging that is needed. The types of treatments vary, too; we use different drugs for neuroendocrine tumors. Also, some patients may be able to have a liver transplant.

**Advantages of a Team**

It is very important to have an experienced team in treating pancreatic cancer. There is significantly lower mortality in pancreatic resection when it is done by experienced surgeons who have performed many surgeries. The UCLA Center for Pancreatic Diseases provides a strong multi-disciplinary team approach to this disease. We call this kind of approach an *Integrative Practice Unit* to describe the dedicated team of clinical and non-clinical personnel who work together to provide efficient and comprehensive care. Team members frequently meet to review their performance, see themselves as a
Cohesive unit and are located in the same multi-disciplinary clinic. At UCLA our team is composed of pancreatic surgeons, medical oncologists, radiation oncologists, gastroenterologists, radiologists, pathologists, cardiologists, diabetes nurses, genetics and the integrative psychosocial care team of the Simms/Mann – UCLA Center for Integrative Oncology.

Our team works cohesively to provide efficient value-based care and performs a rigorous evaluation of outcomes. One of our goals is to expand patient enrollment in clinical trials and increase the number of patients referred to UCLA. This approach leads to a continuous dialogue between specialists and aids decision-making around treatment before surgery and when to go to surgery. This approach allows for more tailored individual planning. UCLA has been very effective in “downstaging” pancreatic cancer patients by making them able to receive surgery through this integrated approach and following their outcomes. Preliminary data in patients that are “borderline resectable” after six months of pre-surgical chemotherapy shows a higher median survival compared to other locations. Patients who are locally advanced show median survivals similar to patients who have early stage disease.

Conclusion

Pancreatic cancer is a large disease burden in the United States. Despite the fact that we know patients have better outcomes when they are treated by high-volume surgeons, 50% of pancreatic surgeries are performed at hospitals that tend to do less than five per year compared to UCLA which does 150 per year at this moment in time. There are new therapies on the horizon. The UCLA Integrated Practice Unit in the UCLA Agi Hirshberg Center for Pancreatic Disease offers an efficient and state-of-the-art complement of patient care services and continuous evaluation of outcomes. Our patients leave with a comprehensive plan after one visit and in one place.