

# PANCREATIC CANCER

## OBJECTIVES

When the learner has completed this module, he/she will be able to:

1. Identify three commonly agreed upon risk factors for pancreatic cancer.
2. Identify the three factors used to stage pancreatic cancer
3. Identify the most effective diagnostic/detection technique for pancreatic cancer.
4. Identify two metastatic sites of pancreatic cancer.
5. Identify the serum marker that can be used as a screening test for pancreatic cancer.
6. Identify three signs/symptoms of pancreatic cancer.
7. Identify the surgical procedure most commonly performed on patients with pancreatic cancer.
8. Identify two common post-operative complications of this procedure.
9. Identify the chemotherapeutic drug that is considered most effective for pancreatic cancer.
10. Identify the therapeutic approach that is used for treating non-resectable pancreatic cancer.

## INTRODUCTION

Pancreatic cancer is a very serious neoplastic disease, because although there are far more common cancers, it is one of the most dangerous. The five year survival rate (the percentage of patients who are living five years after a diagnosis is made) is approximately 5%, although some authorities feel that the five year survival rate is as low as 1% to 2%. The median time of survival for all patients is four to five months, and if the disease is not detected very early and if it has metastasized, there is currently no cure for pancreatic cancer.

## ANATOMY AND PHYSIOLOGY OF THE PANCREAS

The pancreas is located in the retroperitoneal space, behind and inferior to the stomach on the left side of the abdomen. It is divided into a head, body, and tail, and it is between 12 and 20 inches long. The pancreatic duct anastomoses with the common bile duct in the head of the pancreas.

The pancreas is an *endocrine* gland (a gland that produces hormones that affect other organs; the hormones travel to these organs via the vascular system or lymphatic system) and an *exocrine* gland (a gland that releases its secretions onto an internal or external body surface). The endocrine cells of the pancreas are located in the islets of Langerhans. The *alpha cells* secrete *glucagon*, a hormone that increases glycogenolysis. The *beta cells* secrete *insulin*, a hormone that facilitates the transport of glucose into cells. The *delta cells* secrete *somatostatin*, a hormone that suppresses the secretion of glucagon and insulin. The exocrine cells of the pancreas secrete digestive enzymes that travel through the pancreatic duct to the duodenum, and these enzymes (e.g., lipase and amylase) aid in the breakdown of food in the gut.

## EPIDEMIOLOGY

An estimated six percent of all deaths from cancer in the United States in 2008 were from pancreatic cancer, and an estimated three percent all cancer cases in the United States in 2008 (approximately 37, 680) will be pancreatic. The lifetime risk of developing pancreatic cancer is about 1 in 76, or 1.31%. The incidence of pancreatic cancer is slightly higher for women than for men and slightly higher for African Americans. The median age of diagnosis is 72 years. Survival rates have been going up each year since 1975, albeit very, very slowly.

The majority (approximately 90%) of pancreatic tumors are adenocarcinomas (cancers that arise from glandular tissue) and are located in the head of the pancreas: a small percentage are located in the body or the tail. There are many other types of pancreatic neoplasms (e.g., cystic tumors, lymphomas or sarcomas), but they are rare.

## ETIOLOGY

Although researchers are still trying to definitively determine the causes of pancreatic cancer, it is generally accepted that certain life style and demographic factors and genetics are definitely very, very strong risk factors.<sup>1</sup>

- Cigarette smoking – Cigarette smoking is a universally accepted as a risk factor for pancreatic cancer; this is not surprising, as cigarette smoke contains 43 known carcinogens.<sup>2</sup> Smoking increases the chances of developing pancreatic cancer by approximately 60%, and the risk increases as the consumption of tobacco increases.<sup>3</sup> Women who smoke may be more at risk, and people with diabetes mellitus who smoke are also more at risk.<sup>4</sup> Also, smokeless tobacco and passive smoking (inhalation of cigarette smoke in the environment) may increase the risk.<sup>5,6</sup>

**Learning Break:** Cigarette smoking is a strong, well-established risk factor for developing pancreatic cancer, yet there are millions of people who smoke and relatively few cases of pancreatic cancer. The reason for this may be genetics. Researchers have found that there are variations in carcinogen-metabolizing genes that almost certainly are responsible for this effect. Although it is not clear why, this seems to be more the case for women than men.<sup>7</sup>

- Family history – Family history has been identified as a risk factor for pancreatic cancer.<sup>8,9</sup> A family history that includes a first degree relative with pancreatic cancer may increase the risk of developing the disease by as much as 2.5 to 5.3 times,<sup>10</sup> and the more relatives that are affected, the greater the risk.<sup>11</sup> In patients with two first-degree relatives with pancreatic cancer, the risk increases 18-fold, and the risk increases 57-fold if there are three or more affected relatives. However, as with smoking, there is a lot that is not known about family history and pancreatic cancer, because although the risk may be two-fold for someone if

he/she has a close family member with pancreatic cancer, family history may account for a little as 7% to 10% of all cases of pancreatic cancer.<sup>12</sup>

- Obesity – Although people who are obese may have a slightly increased risk of developing pancreatic cancer, it has not been definitively proven that being obese is a risk factor. If obesity is a causal factor, it may be because obese people have what is called the chronic inflammatory condition: an elevated level of inflammatory mediators, e.g., interleukin 6, tumor necrosis factor alpha, that can contribute to many of the complications of obesity such as hypertension and, perhaps, pancreatic cancer.
- Diet – There is no *definite* association, at this time, between diet and pancreatic cancer, although there is a strong suspicion that a high dietary intake of fat increases the risk. Researchers have tried to determine if consumption of fruits and vegetables,<sup>13</sup> green tea and coffee,<sup>14</sup> sugar and sugar-sweetened foods,<sup>15</sup> dietary fat,<sup>16</sup> and alcohol<sup>17</sup> increase or decrease the risk of developing pancreatic cancer and have not found a link or the evidence has been equivocal. However, studies suggest that increased consumption of meat (the types of meat and the way they are cooked),<sup>18</sup> may increase the risk, and increased consumption of whole grains<sup>19</sup> and flavonoids (e.g., vitamin E, beta-carotene) may decrease the risk.<sup>20</sup>
- Physical activity – Although several studies have found that being physically active decreases the risk of pancreatic cancer,<sup>21,22</sup> there is also strong evidence that the level of exercise does not influence this risk.<sup>23</sup>
- Disease states – It would seem intuitive that chronic pancreatitis might be a risk factor for pancreatic cancer, and some authorities feel there is a definite link,<sup>24</sup> but others disagree and this association has never been definitively proved.<sup>25</sup> Diabetes mellitus (DM) has also been linked to pancreatic cancer, and although the evidence is strong and suggestive that it increases risk,<sup>26,27</sup> it is still not *proven* that DM can cause pancreatic cancer.<sup>28</sup>

**Learning Break:** Although diet, exercise, lifestyle, concomitant medical conditions, occupational history, and a host of other factors have been examined to determine what role they may have in causing pancreatic cancer, at this point, the only definite, universally agreed upon risk factors for the disease are cigarette smoking, advanced age, and a family history of the disease.

## SCREENING FOR PANCREATIC CANCER

There is no reliable screening test for pancreatic cancer. This is especially critical because most patients are asymptomatic until the diagnosis is made and when the diagnosis *is* made, the disease is at an advanced stage, there is no effective treatment and the prognosis is poor. However, there are some screening guidelines that can be followed. People with a family history of the disease, who smoke cigarettes, and/or who have DM

should consider being screened. Also, people with Peutz-Jeghers syndrome (a genetic disorder characterized by polyps in the small intestine and excessive melanin pigmentation of the skin), familial atypical multiple mole melanoma syndrome, or BRCA2 mutations (BRCA2 is a tumor suppressor gene) should be screened. For these patients, genetic testing may be an option as there are certain mutations that may increase the risk of pancreatic cancer.<sup>29</sup> At-risk patients can be screened using imaging studies such as ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS).<sup>30</sup> Of all of these, EUS appears to be the most sensitive and specific, and once a tumor is detected, fine needle aspiration can be performed to confirm the diagnosis.

There is also a serum marker – **carbohydrate antigen 19-9** (CA 19-9) – that can be used to screen for pancreatic cancer: elevated levels may be a marker for the presence of pancreatic cancer. CA 19-9 is a carbohydrate antigen that is produced by normal pancreatic cells and by pancreatic tumor cells. The test has a sensitivity and specificity of about 80-90%,<sup>31</sup> but the level of CA 19-9 may not be elevated if a pancreatic tumor is less than centimeters and elevated levels can be seen in patients with biliary obstruction from pancreatitis and choledocholithiasis.<sup>32</sup> A level of greater than 100 IU/mL is highly suggestive for a pancreatic tumor.

**Learning Break:** Pancreatic cancer is deadly, so it would seem to make sense to screen for it. But large scale screening would be expensive, potentially hazardous for patients, and unless it was done aggressively, would not yield much.

## DIAGNOSIS/STAGING

Making a diagnosis of pancreatic cancer is very important because, as mentioned previously, the five year survival rate is 5%. Unfortunately, approximately 40% of all patients with the disease will have metastatic involvement when they are first diagnosed, 40% will have advanced disease, and of the remaining 20%, approximately half will have a tumor that is not considered resectable/operable.<sup>33</sup>

Pancreatic cancer can be diagnosed by computerized tomography (CT), positron emission tomography (PET), Magnetic resonance imaging (MRI), endoscopic ultrasound fine needle aspiration, or serologic markers (already discussed).

- CT scanning – CT scanning is widely used to make the diagnosis of pancreatic cancer, and it has been shown to be 88-97% sensitive for this purpose.<sup>34</sup> CT scanning can accurately predict which tumors cannot be resected, but it does not accurately identify which tumors can be resected.<sup>35</sup> Small areas of metastases may not be detectable with CT scanning.<sup>36</sup>
- PET scanning – PET scanning can also be useful for detecting pancreatic tumors, but as with CT scanning, area of metastases may not be detected.<sup>37</sup>
- MRI scanning – MRI scanning does not appear to superior to CT scanning for making the diagnosis of pancreatic cancer, but its use for this application has not been as well studied.

- Endoscopic ultrasonography – In this technique, an ultrasound transducer is placed on an endoscope and the endoscope is placed in the patient's stomach. It is very accurate: 99-100% of all pancreatic tumors are detectable using this method.<sup>38</sup>
- Endoscopic ultrasound fine needle aspiration – This technique (EUFNA) has been shown to be safe and accurate and is recommended for confirmation of the diagnosis.<sup>39,40</sup>

Once a tumor has been found, it is staged in order to determine how advanced the disease is and if surgical treatment is an option. The American Joint Committee on Cancer uses a staging system that evaluates the tumor (size, e.g., greater or smaller than 2 centimeters), and whether or not it has spread to the adjacent major blood vessels, the lymph nodes, or other organs.

**Learning Break:** There are several staging systems, but they all, basically, perform the same assessment: they look at the size of the tumor and the degree to which it has spread, and where it has metastasized to.

## **SIGNS AND SYMPTOMS OF PANCREATIC CANCER**

It is difficult to use patient complaints and a physical exam to make a diagnosis of pancreatic cancer. Patients frequently report malaise, nausea, anorexia, fatigue, and weight loss. Mid-epigastric pain is relatively common, and it may radiate to the back. Jaundice – due to obstruction – may be seen, along with pruritus and darkening of the urine. When the patient is examined physically, the most common findings are weight loss and abdominal pain.<sup>41</sup>

**Learning Break:** Although in some disease states there may be characteristic signs and symptoms that can be learned, pancreatic cancer only produces sign and symptoms that are vague, non-specific, and easily attributable to many other pathologies and clinical conditions.

**Learning Break:** Pancreatic cancer usually metastasizes to the lymph nodes and the liver. Less commonly, it will spread to the lungs and other visceral organs such as the duodenum, stomach, and colon. Metastatic sites in the brain and bone are possible, but are rarely seen.

## **TREATMENT: SURGERY**

### **Surgery: Whipple procedure**

Most cancers of the pancreas are not diagnosed until they are very advanced or have disseminated and the surgery is not considered to be a useful option. However, if the tumor is considered to be resectable, surgery is an option: resectable tumors are those that

have not metastasized to remote sites, have not involved the portal or superior mesenteric vein or the roots of the celiac or superior mesenteric artery.<sup>42</sup>

The most commonly performed procedure for pancreatic cancer is the **pancreaticoduodenectomy**, also known as the **Whipple** procedure, named after the American surgeon, Dr. Allen O. Whipple, who perfected the procedure in the 1930s. The Whipple procedure is a complicated operation. The head of the pancreas, the distal bile duct, and most of the duodenum and the proximal jejunum are resected, then anastomoses are formed between the pancreas, the bile duct, and the duodenum to what remains of the jejunum.<sup>43</sup> Some surgeons will also do an extended lymph node resection, but the evidence seems to suggest that this technique does not improve survival rate.<sup>44</sup>

In past years, the mortality rate for the Whipple procedure was considerable – up to 20% - but mortality rates in the present are much lower, usually below 5%. However, morbidity rates after a Whipple are high.<sup>44</sup> A common complication is a leak at one the anastomoses.

**Learning Break:** Leaks at the anastomosis of the pancreas and the jejunum occur 10% to 20% of the time after a Whipple procedure. Leaks at the other anastomoses are seen much less often.

Another common complication is delayed gastric emptying. This can cause nausea and vomiting and in some cases can persist for weeks.

The five year survival rate after a Whipple procedure, according one authority, is greater than 20%.<sup>45</sup>

### **Surgery: Other procedures**

For patients with small or low-grade cancers that are in the middle of the pancreas, a *central pancreatectomy* (removal of tumors in the neck of the pancreas) may be safe and effective, reduce the risk of diabetes, and not affect the stomach or the biliary tract.<sup>46</sup> A *distal pancreatectomy* is often done when the tumor is in the body or the neck of the pancreas; in this procedure, the duodenum and the bile duct are not removed. *Total pancreatectomy* may be performed in cases in which the cancer has spread to a degree in which a Whipple will not remove all malignant tissue. Unfortunately, removing the entire pancreas almost invariably results in diabetes that is very difficult to control, puts the patient's immune status at risk because of the splenectomy that is often performed along with the removal of the pancreas, and doesn't produce better long-term outcomes than the Whipple procedure. *Laparoscopic pancreatectomy* is also an option; studies have indicated that it may have several benefits (e.g., shorter hospital stay, reduced pain, increased long-term survival) but there is not a lot of clinical experience with the procedure.<sup>47</sup> Finally, some surgeons have advocated the pylorus-preserving pancreaticoduodenectomy. This procedure preserves the stomach and pylorus and part of the proximal duodenum, hopefully to prevent the complications of delayed gastric emptying and ulcers of the standard Whipple procedure. It is not clear that this operation offers significant benefits beyond what can be obtained with the standard pancreaticoduodenectomy.<sup>48</sup>

## **Adjuvant Therapy**

Surgery can be curative for pancreatic cancer, but the survival rates after the operation are, at best, modest. There have been many attempts to improve the survival rates after surgery by using chemotherapy and/or radiotherapy, and the results are encouraging. In several studies, the patients who had their tumors resected survived, on average, 11 months while the patients who had their tumors resected and then received chemotherapy (e.g., 5-fluoracil) and external-beam radiation therapy survived, on average, 18 months. Treatment of a small group (53 patients) with 5-fluoracil, cis-platinum, and interferon- $\alpha$  after resection improved the survival time even more; the median survival time was longer than 36 months and the five-year survival rate was approximately 50%, and clinical trials are being conducted to further investigate this promising approach.<sup>49</sup>

### **Preoperative Adjuvant Therapy**

Chemotherapy and/or radiotherapy have been used preoperatively to shrink tumors. The smaller the tumor, the easier it is, technically, to resect, and there is also hope that shrinking the tumor may decrease the rate of metastasis. However, at this time, this approach is still considered experimental.

## **TREATMENT: ADVANCED DISEASE**

Most patients with pancreatic tumors are not candidates for resection; the disease has advanced and involved the superior mesenteric vein, portal vein, superior mesenteric artery, or the celiac artery. In these cases, radiation therapy or chemotherapy can be used.

Radiation therapy appears to extend, albeit slightly, the life span of patients with advanced pancreatic cancer. However, because of where the tumors and involved lymph nodes are located, delivering effective doses of radiation is difficult: the adjoining organs, kidney, liver, bowel, and spinal cord are very sensitive to radiation, and there are other issues that limit the practicality of radiotherapy.

Chemotherapy with 5-fluoracil, or more recently, gemcitabine can also be used, and gemcitabine has been shown to definitely improve survival rate and provide better pain control and improve nutritional status.

However, a combination of radiotherapy and chemotherapy is considered the standard of care.<sup>50</sup>

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