

Rare cancers of pancreas: information for patients

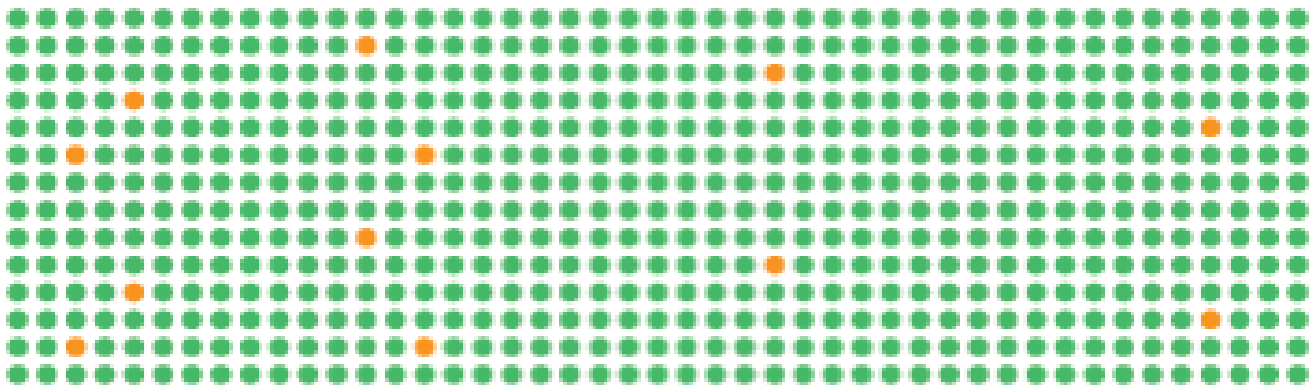


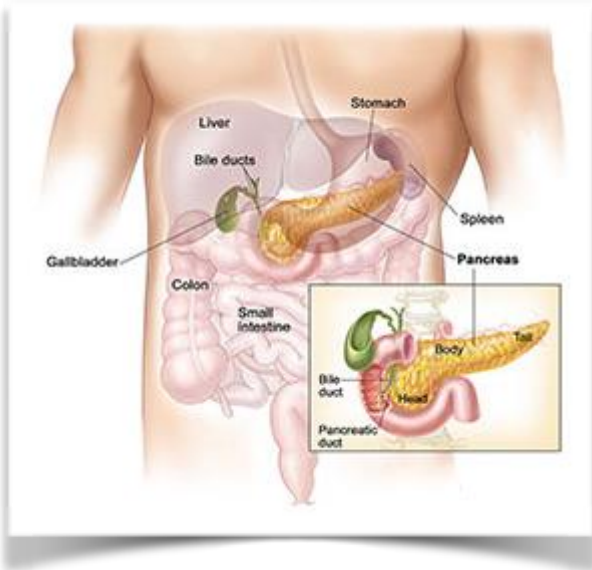
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1. Rare cancer of pancreas: definition

Pancreatic cancer begins in the tissues of pancreas, a gland placed in abdomen that lies horizontally behind the lower part of the stomach. The pancreatic gland secretes enzymes that aid digestion and hormones that help regulate the metabolism of sugars.



Pancreatic cancer often has a poor prognosis, even when diagnosed early. Pancreatic cancer typically spreads rapidly and is seldom detected in its early stages, which is a major reason why it's a leading cause of cancer death [1]. Signs and symptoms may not appear until pancreatic cancer is quite advanced and complete surgical removal isn't possible.

Ductal adenocarcinoma (PDAC) is the most frequent type. However, other types of adenocarcinoma might arise in the pancreas such as squamous cell carcinoma (SCC), acinar cell carcinoma (ACC), mucinous cystadenocarcinoma (MCAC), intraductal papillary mucinous carcinoma (IPMC), serous cystadenocarcinoma (SCAC), carcinoma with osteoclastic-like giant cells (OGCP), solid pseudopapillary carcinoma (SPC).

The rare cancers of the pancreas with their incidence rate (IR) provided by RARECAREnet follow:

- the squamous cell carcinoma (SCC) with variants of pancreas (IR=0.02/100,000);
- the acinar cell carcinoma (ACC) (IR=0.03/100,000);
- the mucinous cystadenocarcinoma (MCAC) (IR=0.01/100,000);
- the intraductal papillary mucinous carcinoma invasive (IPMC) (IR=0.01/100,000)
- the solid pseudopapillary carcinoma (SPC) (IR=0.003/100,000)
- the serous cystadenocarcinoma (SCAC) (IR=0,0003/100,00) and
- the carcinoma with osteoclast-like giant cells (OGCP) (IR=0,0012/100,000)

In the following paragraphs we briefly report relevant information on pancreatic cancer highlighting differences and similarities between rare and common cancers of pancreas.

Rare cancers of pancreas

Squamous cell carcinoma (SCC)

The incidence is approximately 0,5-2% of all malignant pancreatic carcinomas. The squamous cell epithelium is not present in heath pancreas tissue and several theories have been proposed to explain the development of squamous cell carcinoma of pancreas.

- ✓ The disease may result from the malignant transformation of squamous metaplasia secondary to chronic inflammation as the chronic pancreatitis

- ✓ The lesion may originate from mixed adenosquamous carcinoma in which the glandular components have disappeared
- ✓ The tumour may drift from an unscheduled differentiation of a malignant pancreatic cancer stem cell [2].

Acinar cell carcinoma (ACC)

The acinar cell carcinoma of the pancreas is a rare aggressive neoplasm constituting 1–2% of pancreatic cancers. The pancreas is primarily composed of acinar cells that produce pancreatic enzymes. The molecular mechanisms involved in ACC pathogenesis and progression are largely unknown. The average age of adult patients is approximately 59 years old. Males are more commonly affected with a male/female ratio of 2:1 [3].

Mucinous cystadenocarcinoma (MCAC)

The incidence of mucinous cystadenocarcinomas is 1% of pancreatic neoplasms. It is a rare type of pancreatic cancer that develops from a fluid-filled noncancerous (benign) tumor called a cystadenoma and it is a type of pancreatic mucinous tumour. Like the more benign mucinous cystadenomas, these are found almost exclusively in females and occur in the distal part of pancreas

Intraductal papillary mucinous carcinoma, invasive (IPMC)

The invasive Intraductal papillary mucinous carcinoma arise from Intraductal papillary mucinous neoplasia (IPMN), a lesion potentially malignant of pancreas. The prevalence of IPMN is equal in men and women; the majority of patients are diagnosed around 60 years of age [4].

When invasive carcinomas arise from IPMN, overall they are associated with better prognosis and patient survival as compared to adenocarcinomas not associated with IPMN. In addition, adequate comparisons of malignant IPMN and classic malignant PDAC, controlling for stage, have not yet been done and the rarity of this histology could depend on a bad coding by pathologists that encode only the PDAC rather than opens IPMC invasive.

Solid pseudopapillary carcinoma (SPC)

Solid pseudopapillary carcinoma of pancreas derived from solid-pseudopapillary neoplasm, uncommon but has been recognized with increasing frequency in recent years; it's characterized by tumor recurrence and/or metastasis [5-6]. It accounts for approximately 1-2% of all exocrine pancreatic tumours and it occurs predominantly in adolescent girls and young women and it is rare in men.

Serous cystadenocarcinoma (SCAC)

Serous cystadenocarcinoma of pancreas is a malignant cystic tumours of the pancreas and it is very rare, accounting for about 1% of all pancreatic malignancies [5]. According to the literature most cases of serous cystadenocarcinoma show synchronous or metachronous liver metastases [7].

Carcinoma with osteoclast-like giant cells of pancreas (OGCP)

Carcinoma with osteoclast-like giant cells of pancreas (OGCP) is an extraskeletal tumours containing multinucleated osteoclastlike giant cells (OGCs), which morphologically resemble those found in giant cell tumours of the bone, are uncommon and they are most frequently found in the pancreas. This rare tumour currently accounts for <1% of all pancreatic malignancies [5]. Over the last decade, the number of reports of UCOGCP has increased. However, the clinical features of OGCP remain obscure as many cases are already advanced when detected [8]. For patients with unresectable OGCP, the overall median survival period is 6.5 mo [9].

Common cancers of pancreas

Ductal adenocarcinoma (PDCA) is the most common type representing 85-90% of all pancreatic neoplasms and clinically the most relevant malignant tumour [5], in fact it is a difficult malignancy to treat. Complete surgical removal of the tumour remains the only chance for cure, however 80-90% of patients have disease that is surgically incurable at the time of clinical presentation. Furthermore, the prognosis of pancreatic cancer is poor even in those with potentially resectable disease. The five-year survival following pancreaticoduodenectomy is only about 25- 30% for node-negative and 10% for node-positive tumours.

Despite our advancing knowledge of the tumour biology of PDAC, improvement in diagnosis and management, and the rise of specialized center in the care of patients with PDAC, the prognosis remains strikingly poor.

1. What cause pancreatic cancer?

Factors that may increase the risk of pancreatic cancer include:

- ✓ **Age:** the risk of developing pancreatic cancer increases with age. Over 80% of pancreatic cancers develop between the ages of 60 and 80 years.
- ✓ **Smoking:** cigarette smoking doubles the risk of pancreatic cancer. In fact, some scientists have estimated that one in four, or one in five cases of pancreatic cancer are caused by smoking cigarettes. Smoking is also associated with early age at diagnosis. Very importantly, the risk of pancreatic cancer drops close to normal in people who quit smoking. Simply put, cigarette smoking is the leading preventable cause of pancreatic cancer.
- ✓ **Obesity:** significantly it increases the risk of pancreatic cancer. Believe it or not, it has been estimated that 8% of cancers are related to obesity.
- ✓ **Diet:** certain published medical articles have associated diets rich in fat, with a high level of meat, and/or with processed meat and nitrosamines may increase risk of pancreatic cancer. Coffee is currently thought not to be a risk factor. Moderate intake of alcohol appears relatively safe, but in recent studies the excessive and prolonged drinking of alcohol has been linked to an increased likelihood of pancreatic cancer. While diets high in fruits and vegetables reduce risk. The vitamin folate may be protective.
- ✓ **Diabetes mellitus:** also known as sugar diabetes can be a symptom of pancreatic cancer, and long-standing adult-onset diabetes also increases the risk of pancreatic cancer. It is not entirely clear if diabetes is a cause or a result. However, it is important to remember that not all people who have diabetes or who develop diabetes as adults develop pancreatic cancer.
- ✓ **Chronic inflammation of the pancreas (pancreatitis):** long-term (chronic) inflammation of the pancreas has been linked to cancer of the pancreas.
- ✓ **Genetic syndromes:** a number of inherited cancer syndromes increase the risk of pancreatic cancer, these include the breast cancer syndrome (BRCA2 and PALB2), familial atypical multiple mole melanoma syndrome (FAMMM), Lynch syndrome (also known as hereditary non-polyposis colorectal cancer syndrome), and the Peutz-Jeghers syndrome.

- ✓ **Personal or family history of pancreatic cancer:** pancreatic cancer may run in the family, called familial pancreatic cancer, if two or more first-degree relatives such as parents, brothers, sisters, or children are diagnosed with pancreatic cancer. Families with three or more close relatives such as grandparents, aunts, uncles, nieces, nephews, grandchildren, or cousins who are diagnosed with pancreatic cancer and with one relative diagnosed before age 50 are also considered to have familial pancreatic cancer. The National Institutes of Health (NIH) estimates that the risk of developing pancreatic cancer is increased four to five times for a person with one first-degree relative with this disease, six to seven times for a person with two first-degree relatives, and 32 times for a person with three first-degree relatives with the disease.

What about rare cancers of pancreas?

Because of the small number of cases and the paucity of data, not yet been made specific studies on risk factors of rare cancer of pancreas

2. How is pancreatic cancer diagnosed?

A combination of biochemical tests, radiological imaging, endoscopic ultrasound fine needle aspiration (EUS-FNA) and discussion at a pancreas multidisciplinary team meeting is necessary for diagnosis and staging of the disease and for an appropriate management plan to be put in place. Despite earlier detection and surgical and oncological improvements, the outcome has not greatly changed over the last few decades and research strives to find targets for successful therapeutic agents [5].

About the biochemical tests for the pancreatic cancer diagnosis, the blood tests more used are CA19.9, blood glucose level, blood bilirubin level, but the blood test isn't always reliable, and it isn't clear how best to use the CA19-9 test results.

Among the radiological imaging are included computed tomography (CT) scanning, magnetic resonance imaging (MRI) and positron emission tomography (PET).

The endoscopic ultrasound (EUS) device is a thin, lighted tube that is passed through the patient's mouth and stomach and down into the small intestine to take a picture of the pancreas. This procedure is very specialized and requires a gastroenterologist who has special training in this area. EUS is generally done under sedation, so the patient sleeps while the procedure is performed.

A biopsy is a procedure to remove a small sample of tissue or of cells for examination under a microscope. The sample of tissue or of cells be obtained by inserting a needle through your skin and into your pancreas (fine-needle aspiration or so called FNA). Or it can be done using endoscopic ultrasound to guide special tools into your pancreas where a sample of cells can be obtained for testing; so the FNA and the EUS may also be done at the same time.

4.Symptoms

Pancreatic cancer is a silent disease because there are not many noticeable symptoms early on; in fact, signs and symptoms of pancreatic cancer often don't occur until the disease is advanced. When signs and symptoms do appear, they may include:

- ✓ Upper abdominal pain that may radiate to your back: about 7 out of 10 people with pancreatic cancer first go to their doctors because they have pain. Pain is more common in cancers of the body and tail of the pancreas. People describe it as a dull pain that feels as if it is boring into you. It can begin in the stomach area and spread around to the back.
- ✓ Jaundice: it is yellowing of your skin and the whites of your eyes. Jaundice is more common with cancer of the head of the pancreas because the tumour blocks the bile duct that carries bile into the duodenum. around 1 in 10 people will have painless jaundice.
- ✓ Loss of appetite and/or Weight loss: they are the common to almost all types of cancer. The cancer cells compete with normal cells for nutrients; also, tumours of the pancreas often interfere with digestion which further contributes to weight loss. The people diagnosed with pancreatic cancer may have recently lost a lot of weight (at least 10% of their total body weight) for no apparent reason. This symptom is more common in cancers of the head of the pancreas.
- ✓ Depression: most common, it is related both to the emotional reaction to the diagnosis and to direct effects of the cancer.

Rare cancers of pancreas: symptoms

The clinical presentation of rare cancers of the pancreas is similar to that of adenocarcinoma and, in general, the difference depend only on the sub site and the stage of the pancreatic cancer.

But small differences can be found in some cases as the acinar cell carcinoma (ACC) of pancreas. In fact, there are also significant differences in the clinical presentation of ACCs compared to pancreatic adenocarcinoma. Contrary to pancreatic adenocarcinoma cases, patients with early stage ACC frequently present with abdominal pain and bloating as the dominant symptom. Occasionally, ACCs produce excessive lipase causing systemic fat necrosis whose clinical manifestation can include panniculitis, discrete skin lesions and subcutaneous nodules [10].

5.What are the treatment options?

About the rare pancreatic cancer there is a paucity of data and even less evidence to guide their treatment respect the adenocarcinoma. To date there are not specific treatment for a rare cancer of pancreas, in fact these are treated as the adenocarcinoma.

In general, the treatment for pancreatic cancer depends on the stage and location of the cancer as well as on your age, overall health and personal preferences. The first goal of pancreatic cancer treatment is to eliminate the cancer, when possible. By the time a patient is diagnosed with pancreatic cancer, the disease is often already in an advanced stage. For this reason, a large majority of patients are not candidates for surgical treatment. When the surgery isn't an option, the focus may be on preventing the pancreatic cancer from growing. When pancreatic cancer is advanced and treatments aren't likely to offer a benefit, the only medical strategy will be to relieve the symptoms and improve the quality of life of the patient.

Surgery

Surgery remains the corner stone of treatment but unfortunately is not curative with the clinical course complicated by local and/or distant relapses [11]. One of the following types of surgery can be used:

- ✓ Whipple procedure: a surgical procedure in which the head of the pancreas, the gallbladder, part of the stomach, part of the small intestine and the bile duct are removed. Enough of the pancreas is left to produce digestive juice and insulin.
- ✓ Total pancreatectomy: this operation removes the whole pancreas, part of the stomach, part of the small intestine, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes.
- ✓ Distal pancreatectomy: the body and the tail of the pancreas and usually the spleen are removed.

These kind of surgery carries a risk of bleeding and infection.

If a surgical resection is not possible because the cancer has spread and cannot be removed, the following types of palliative surgery may be done to relieve symptoms and improve quality of life:

- ✓ Surgical biliary bypass: if cancer is blocking the small intestine and bile is building up in the gallbladder, a biliary bypass may be done.
- ✓ Endoscopic stent placement: if the tumour is blocking the bile duct, surgery may be done to put in a stent (a thin tube) to drain bile that has built up in the area.
- ✓ Gastric bypass: if the tumour is blocking the flow of food from the stomach, the stomach may be sewn directly to the small intestine so the patient can continue to eat normally.

Research shows pancreatic cancer surgery tends to cause fewer complications when done by experienced surgeons.

Radiation therapy

Radiation therapy uses high-energy beams, such as X-rays, to destroy cancer cells or keep them from growing. It is possible receive radiation treatments before or after cancer surgery, often in combination with chemotherapy (chemoradiation) specially when the cancer can't be treated surgically. Chemoradiation is typically used to treat cancer that has spread beyond the pancreas, but only to nearby organs and to distant regions of the body. This combination may also be used after surgery to reduce the risk that pancreatic cancer may recur.

Only a limited number of studies have regarded the value of radiochemotherapy in MCACs [12,13], and most of them only investigated the effect of adjuvant or neoadjuvant radiochemotherapy. There is thus currently a lack of guidelines for treatment of patients with MCACs.

Chemotherapy

There are no universally agreed upon firm guidelines for medical treatment for those patients with pancreatic cancer who are not candidates for surgery or who have a recurrence of the cancer after surgical resection. In part, this is because there is no one great treatment option – there are a number of medical treatment approaches for cancer of the pancreas which may be more or less appropriate, given certain variables. Also, medical treatment offerings in pancreatic cancer are often highly tailored to patient circumstance and wishes, which can be exceptionally individual. Chemotherapy uses drugs to help kill cancer cells or stop the growth of cancer cells, either by killing the

cells or by stopping them from dividing [14]. Chemotherapy can be injected into a vein or taken orally. You may receive only one chemotherapy drug, or you may receive a combination of chemotherapy drugs.

In people with advanced pancreatic cancer, chemotherapy may be used alone or it may be combined with targeted drug therapy.

Because of the rarity of this disease, normally the drugs used for the pancreatic adenocarcinomas are few, but about the rare pancreatic cancer as ACC no chemotherapeutic regimens have been established [10,15].

About the UCOGCP, the roles of chemotherapy and radiotherapy either as adjuvant or neoadjuvant agents have not been clearly established. Long term follow-up of patients with these rare tumours is essential in order to compile a body of literature to help guide treatment, since the rarity of this tumour renders prospective studies unlikely [16].

Targeted therapy

Targeted therapy is a treatment that targets the cancer's specific genes, proteins or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells while limiting damage to healthy cells.

Recent studies show that not all tumours have the same targets. To find the most effective treatment, it's possible may run tests to identify the genes, proteins, and other factors in tumour. About the pancreatic cancer, not always is possible use the target therapy.

The targeted drug erlotinib (Tarceva) blocks chemicals that signal cancer cells to grow and divide. Erlotinib is usually combined with chemotherapy for use in people with advanced pancreatic cancer.

6.Prognosis

In general, pancreatic cancer prognosis is poor and attributable to the fact that pancreatic cancer is often diagnosed at a late stage and the cancer has progressed to a point where surgical removal is impossible.

Rare cancers of pancreas

Squamous cell carcinoma (SCC) of pancreas has a poor prognosis as other pancreatic carcinomas [11].

Acinar cell carcinoma (ACC) of pancreas although this is regarded to be equally aggressive as pancreatic adenocarcinomas in the past, it has been recently elucidated that ACCs show lower malignant potential and significantly better survival than pancreatic adenocarcinomas [15].

Mucinous cystadenocarcinoma (MCAC) of pancreas, as well as for other types of pancreatic cancer, the correct and early characterization of a premalignant mucinous cystic neoplasm and subsequent adequate surgical resection, if it is possible, offers a comparably favourable prognosis. However, once invasive or metastasized, the outcome of a cystic pancreatic carcinoma is merely as poor as for ductal adenocarcinomas of pancreas [17].

Intraductal papillary mucinous carcinoma (IPMC) of pancreas show the rate survival higher than for patients with typical ductal adenocarcinomas [18].

Serous cystadenocarcinoma (SCAC) of pancreas is slowly growing neoplasm and palliative resection may be helpful even in advanced stage and its prognosis depends upon many factors including the stage of the tumour and overall health of the individual.

Carcinoma with osteoclastic-like giant cells (OGCP) of pancreas presents a favourable prognosis; it is predicted for her long-term follow-up [8].

Solid pseudopapillary carcinoma (SPC) of pancreas presents a favourable prognosis even in the presence of distant metastasis. Although surgical resection is generally curative, a close follow-up is advised in order to diagnose a local recurrence or distant metastasis and choose the proper therapeutic option for the patient [19].

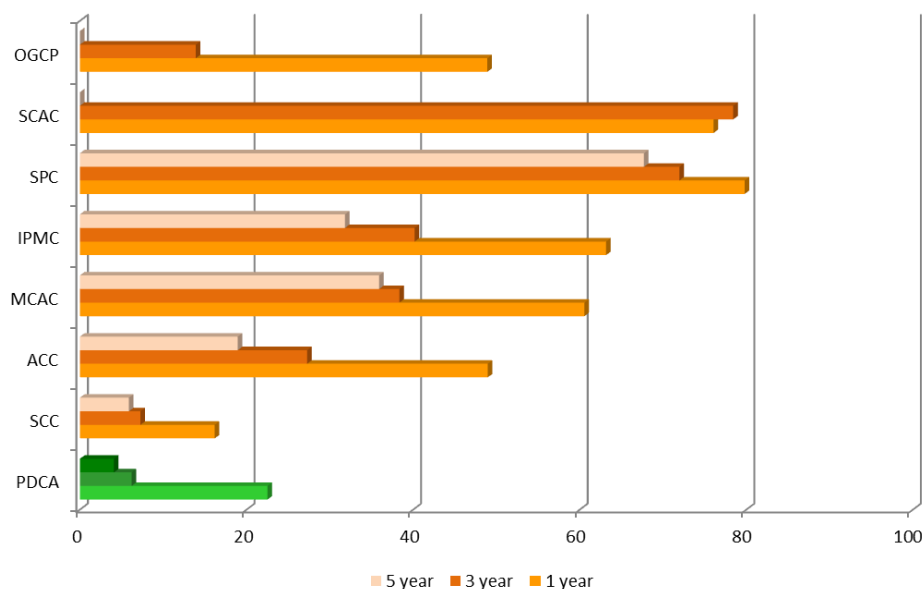


Figure 1. 1-3-5-year relative survival (%) of pancreas cancers (source: RARECAREnet analyses)

7. Where should I go to get the appropriate treatment?

Pancreatic cancer is a complex disease, and patients with pancreatic cancer are best treated by a multi-disciplinary team. A multidisciplinary team is necessary for accurate diagnosis, staging and for the definition of appropriate management plan. Although the radical surgery is the only treatment method resulting in “long-term survival” in pancreatic cancer, centers that display a high surgical volume of pancreatic cancer cases treated and that provide multidisciplinary team in the decisional process should be contacted for primary care or at least for second opinion prior to start a treatment.

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