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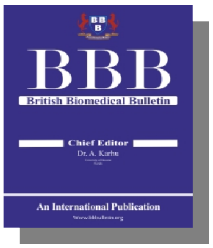

Review

Interpretation and Management of Pancreatic Cancer

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A R T I C L E I N F O

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A B S T R A C T

The uncontrolled division and growth of pancreatic cell results in abnormal physiological and anatomical modifications of the pancreas, subsequently pancreatic carcinoma, which is a major cause of death in humans among other cancers worldwide, which often has a poor prognosis, even when diagnosed early, and also referred as “silent” disease, because symptoms are rarely present in its early stages. Although; most pancreatic cancer is exocrine, but may be endocrine also. The present review aims to compile data on all the aspects of pancreatic cancer, including its pathogenesis, diagnosis, symptoms and treatment. The attention has also been made towards the recent approaches used in all these procedures.

Introduction

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell[1].

Cancer can be induced by other factors such as; nuclear radiation, electromagnetic radiation (microwaves, X-rays, Gamma-rays, Ultraviolet-rays, etc.), viruses, bacteria and fungi, parasites (due to tissue inflammation / irritation, heat, chemicals in the air, water and food, mechanical cell-level injury, free radicals, and ageing of DNA and RNA, etc. All these can produce mutations that may start cancer[2].

In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called metastasis. It happens when the cancer cells get into the bloodstream or lymph vessels of our body. Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer. Not all tumors are cancerous. Tumors that aren't cancer are called benign. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize)[3].

Usually, cancer is named after the body part in which it originated; thus pancreatic cancer refers to the erratic growth and proliferation of cells that originate in the pancreatic tissue[4]. Pancreatic cancer is the fourth most common cause of cancer-related deaths in the United States and the eighth worldwide. Pancreatic cancer has an extremely poor prognosis for all stages[5]. Pancreatic cancer is a malignant neoplasm originating from transformed cells arising in tissues forming the pancreas. The most common type of pancreatic cancer, accounting for 95% of these tumors, is adenocarcinoma[6].

The pancreas is prismoid in shape and appears triangular in cut section with superior, inferior, and anterior borders as well as anterosuperior, anteroinferior, and posterior surfaces (Figure1). The head of the pancreas lies in the duodenal C loop in front of the inferior vena cava (IVC) and the left renal vein (see the following images). The uncinate process is an extension of the lower (inferior) half of the head toward the left; it is of varying size and is wedged between the superior mesenteric vessels (vein on the right, and artery on left) in front and aorta behind it. The body and tail of the pancreas run obliquely upward to the left in front of the aorta and left kidney[7].

The body and tail of the pancreas lie in the lesser sac (omental bursa) behind the stomach. The main pancreatic duct (of Wirsung) runs from the tail through the body to the head of the pancreas where it descends into the lower (inferior) part of the head. There, it joins the duct of the uncinate process coming from the left and then the lower part of the common bile duct to form a common channel (called the hepatopancreatic ampulla, when dilated), which runs through the medial duodenal wall and opens on the dome of the major duodenal papilla (a nipple like projection on

the medial wall of the middle segment of the second part [C loop] of the duodenum) [8].

Epidemiology of pancreatic cancer

Pancreatic cancer is currently the fourth leading cause of cancer death in the western countries, claiming 32,000 lives annually. The rate of incidence seems to be increasing; not only is the disease becoming more common, but it is also extremely difficult to treat: signs and symptoms of the disease seldom show until more advanced stages of cancer. By the time symptoms do show up, cancer cells are likely to have metastasized to other parts of the body, often rendering surgical removal of tumors impossible. While there is currently no treatment for pancreatic cancer, medical research is advancing rapidly[9].

Types of pancreatic cancer

It may be further categorized as; exocrine pancreatic cancer and endocrine pancreatic cancer.

1. **Exocrine pancreatic cancer[10]:** This type of cancer is further sub categorized as**;**

- **Acinar cell carcinoma:** It is a very rare form of pancreatic cancer, which leads excessive production of pancreatic lipase, a fat digesting enzyme, and is an indication of acinar cell carcinoma.
- **Adenocarcinoma:** it accounts about 90% of all pancreatic cancer, which begins in the cell lining of the pancreatic duct. It may form glands, or a collection of cells surrounding an empty space.
- **Adenosquamous carcinoma:** Similar to adenocarcinoma, but the glands becomes flattened as it grows.
- **Giant cell tumor:** They are extremely rare and may not be as aggressive as adenocarcinoma. They contain larger cells.
- **Intraductal papillary - mucinous neoplasm (IPMN):** An IPMN grows from the main pancreatic duct or from side branches of the duct. The tumor may appear as a finger-like, or papillary, a projection into the duct. However, it has a high risk of progressing to malignancy. An IPMN may therefore be a precursor for adenocarcinoma.
- **Mucinous cystadenocarcinoma:** It is rare, malignant, spongy, cystic tumor. The cyst is filled with a thick fluid called mucin. It is similar to an IPMN, but occurs in just one area of the pancreas.
- **Pancreatoblastoma:** The rare form of pancreatic cancer found primarily in children under the age of 10, and also called as pancreatic cancer of infancy.

2. **Endocrine pancreatic cancer[11]:**

- **Gastrinoma (Zollinger - Ellison syndrome):** Associated with over production of gastrin, and is malignant or have the ability to become malignant. The genetic basis of the same is Multiple Endocrine Neoplasia Type 1 (MEN1).
- **Glucagonoma**: it has over production of glucagon, and are large, often metastasize and about 70% are malignant. Commonly found in the body and tail of the pancreas.
- **Insulinoma:** It induces over production of insulin, and are most common & benign.
- **Nonfunctional islet cell tumor**: This is usually malignant and hard to detect.
- **Somatostatinoma:** It includes over production of somatostatin. They vary in their potential to become malignant.
- **Vasoactive intestinal peptide-releasing tumor (VIPoma or Verner-Morrison syndrome):** These tumors are usually located in the body and tail of the pancreas. Two-thirds of VIPomas are found in women. The syndrome is also known as Watery Diarrhea and

Hypokalemia Achlorhydria (WDHA) Syndrome.

Pathophysiology

A number of risk factors and basis for pancreatic cancer have been reported viz. age, gender[12], cigarette smoking[13], obesity and physical activity[14], diabetes[15], chronic pancreatitis[16], cirrhosis of the liver[17], genetic causes[18], stomach problems, diet, alcohol[19] etc.

Pancreatic cancer probably arises through a stepwise progression of cellular changes, just as colon cancer progresses by stages from hyperplastic polyp to invasive cancer. Systematic histologic evaluation of areas surrounding pancreatic cancers has revealed the presence of precursor lesions that have been named pancreatic intraepithelial neoplasia Three stages of pancreatic intraepithelial neoplasia have been defined. These lesions demonstrate the same oncogene mutations and loss of tumor-suppressor genes found in invasive cancers, the frequency of these abnormalities increasing with progressive cellular atypical and architectural disarray. Any change in sequence leads to pancreatic cancer[20,21].

The ability to detect these precursor lesions in humans at a stage where the cancer can still be prevented or cured is an important goal of current pancreatic cancer research. About two thirds of pancreatic adenocarcinoma arise within the head or uncinate process of the pancreas; 15% are in the body, and 10% in the tail, with the remaining tumors demonstrating diffuse involvement of the gland. Tumors in the pancreatic body and tail were generally larger at the time of diagnosis, and therefore, less commonly respectable. Tumors in the head of the pancreas are typically diagnosed earlier because they cause obstructive jaundice. Ampullary carcinomas, carcinomas of the distal bile duct, and periampullary duodenal adenocarcinoma present in a similar fashion to pancreatic head cancer, but have a slightly better prognosis, probably because early obstruction of the bile duct and jaundice leads to the diagnosis. In addition to ductal adenocarcinoma, which makes up about 75% of nonendocrine cancers of the pancreas, there are a variety of less common types of pancreatic cancer. The figure 2 shows the growth of pancreatic intra neoepithelial cells along with activation of tumor inducing genes such as K-ras, DPC4 and others.

Interpretation of pancreatic cancer

There are several stages involved in pancreatic cancer, and two models for accurately describing them.

1. **Tumor node metastasis (TNM) model:** In this system, tumor size, lymph node health and metastasis activity are measured separately, each with its own number scale. For tumors, T1 means that a tumor is less than 2cm across in any direction; T2 means that the tumor is larger than 2cm across; T3 means that the tumor has started to grow into the tissues, duodenum and bile ducts that surround the pancreas; finally, T4 means that the tumor has grown into the spleen, large intestines and major blood vessels. For lymph nodes, N0 means that there are no lymph nodes containing cancer; N1 means that there are lymph nodes containing cancer, and so the tumor has likely metastasized beyond the pancreas. Finally, for metastasis (tumor migration), M0 means the tumor has not spread, and M1 means that it has.

2. **Stage Model:** The second model for pancreatic cancer involves 4 numbered stages, as follows:

- **Stage 1:** The tumor has not progressed outside of the pancreas. The TNM

equivalent would be T1 or 2; N0; M0, meaning that there has been no spread and that the tumor is relatively small.

- **Stage 2:** The tumor has grown into nearby tissues and perhaps the duodenum. Lymph nodes are not affected. The TNM equivalent would be T3; N0; M0.
- **Stage 3:** The tumor may be quite large and has spread to the lymph node system, and thus is capable of spread to other organs. The TNM equivalent would be T1, 2 or 3; N1; M0.
- **Stage 4:** This stage is often divided into two sub-stages. 4A describe a situation in which cancer has grown into nearby organs, including the spleen and/or stomach, as well as large blood vessels. The TNM equivalent of this stage would be T4; N1 or 2; M0. Stage 4B describes a situation in which cancer has spread to other organs such as the liver or lungs, and has a TNM equivalent of T1, 2, 3, or 4; N0 or 1; M1[22].

Signs and symptoms

Upper abdominal pain that may extend to middle or upper back, weight loss due to malignant cancer cells tendency to deprive healthy cells of nutrients. Jaundice leads to yellowing of the skin and whites of the eyes. This condition is fairly common among pancreatic cancer patients, and develops when blood cells become worn out and break down into bilirubin. Normally, bilirubin is eliminated in the bile, which is a fluid produced by the liver. However, if a pancreatic tumor blocks the flow of bile, jaundice may occur. Nausea and vomiting can occur during later stages, if a pancreatic tumor has grown sufficiently large to block a portion of the digestive tract (usually the duodenum) Digestive problems may occur, as the pancreas is an integral part of the digestive system. Due to Zollinger Ellison syndrome, stomach ulcers can also happen[23].

Common diagnostic approaches

- **Ultrasound of the abdomen**: An ultrasound can identify a tumor or mass in the pancreas or the bile duct system that may be causing a blockage and jaundice[24].
- **Endoscopic ultrasonography (EUS)**: The EUS test is done with a lighted tube that is inserted through the mouth and placed into the stomach. Ultrasound images of the pancreas are obtained through the stomach wall. It is highly sensitive for diagnosing pancreatic cancer. EUS is particularly useful for detecting small (<2 cm) pancreatic tumors, which may not be well visualized by CT. It can also identify tumors that may involve important blood vessels. The procedure can provide details about the arteries and veins next to the pancreas. A biopsy with a small or fine needle aspiration (FNA) of the tumor may also be performed during EUS for diagnosis pancreatic cancer. Intravenous sedation is used for this procedure[25].
- **Endoscopic retrograde cholangio-pancreatography (ERCP)**: An ERCP is done with a lighted tube called an endoscope to look at the bile ducts. It can also be used to place a stent or tube to open a blocked bile duct for drainage. Intravenous sedation is most commonly used for this procedure[26].
- **Computed tomography (CT)**: The CT scan can show small tumors as well as important blood vessels that the tumor might be growing in or around. A CT scan can also look at surrounding organs for spread (metastasis) of the cancer into lymph nodes, liver and other areas[27].

Recent advancement in diagnosis of pancreatic cancer

Andraka's diagnostic tool which is dipped in a solution of carbon nanotubes

(Figure 3), having hollow cylinders with walls the thickness of a single atom, coated with a specific antibody designed to bind with the virus or protein one is looking for. Andraka's key insight is that there are noticeable changes in the electrical conductivity of the nanotubes when the distances between them changes. When the antibodies on the surface of the nanotubes come in contact with a target protein, the proteins bind to the tubes and spread them apart a tiny bit. That shift in the spaces between tubes can be detected by an electrical meter[28].

A nanotube sensor with a targeted antibody is extremely sensitive. In a single-blinded test of 100 patient samples, Andraka's sensor spotted the presence of mesothelin, a protein commonly used as a biomarker for pancreatic cancer, at a limit of 0.156 nano grams per milliliter, well below the 10 ng/mL considered an over expression of mesothelin consistent with pancreatic cancer. It's also 100 times more selective than existing diagnostic tests, which means no false positives or false negatives[29].

Management of pancreatic cancer

The following approaches are to be made for the management of breast cancer. They are as follows;

- **Surgery:** Approximately 20% of the tumors are found to be operable or resectable. The location of the pancreas adds to the technical difficulties of a surgical operation. Ideally, surgery would remove the tumor with a wide band of surrounding normal tissue. However, important veins and arteries are located near the pancreas and it may not be possible to do surgery.

Diagnostic tests give information about the size, location and involvement of other surrounding tissues and vessels. These tests help the surgeon determine whether a cancer is operable or resectable. If the tumor is found to be at the head of the pancreas and is operable, the surgical procedure performed is a pancreaticoduodenectomy, also called a Whipple procedure (Figure 4). This surgery involves removing the head of the pancreas, the gallbladder, part of the bile duct, and part of the stomach. Surgery includes re-connecting the remainder of the bile duct, pancreas and stomach to bowel so that these structures can drain properly[30].

- **Radiation therapy:** Radiation therapy (also called radiotherapy, x-ray therapy, or irradiation) is the use of a beam of energy to kill cancer cells and shrink tumors. Radiation therapy injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly[31].
- **Chemotherapy:** Chemotherapy may be used at any stage of pancreatic cancer and is commonly used when the cancer is advanced and can't be removed completely with surgery. It may also be used as adjuvant treatment after the cancer has been removed with surgery to try to kill any cancer cells that have been left behind. It can also be used as neoadjuvant to surgery to try to shrink the tumor. Gemcitabine, 5-fluorouracil (5-FU), Cisplatin, Irinotecan, Paclitaxel, Docetaxel, Capecitae, or Oxaliplatin are prescribed as single or in combination with each other. The adverse reactions are there, which depend on the type of drugs, the amount taken, and the length of treatment. Many of the chemo drugs used for pancreatic cancer can cause diarrhoea. For example; cisplatin can cause nephropathy, and in combination with oxaliplatin may produce

neuropathy. Now days, targeted therapy (for certain gene) have also been being employed to achieve better therapeutic effects and to minimize adverse drug reactions. The drug Sunitinib (approved by FDA) attacks both blood vessel growth and other targets that stimulate cancer cell growth. Everolimus works by blocking cell protein (mTOR), which normally promotes cell growth and division. Somatostatin analogs: Octreotide, lanreotide and Pasireotide are very helpful as they can stop the tumor from releasing its hormone into the bloodstream. This reduces symptoms and helps patients feel better. Diazoxide block insulin release, which can be used to prevent hypoglycemia in patients with Insulinomas. Beside these; proton pump is being used to inhibit gastrinomas[32].

Gemcitabine (2', 2'-difluorudeoxy-cytidine, dFdC) is a nucleoside cytidine analogue that exhibits antitumor activity. This drug exhibits cell phase specificity by primarily inhibiting cell proliferation in DNA synthesis (S-phase) and on the G1/S-phase boundary. Gemcitabine is intracellularly metabolized to the active diphosphate and triphosphate nucleosides by nucleoside kinases. The mechanisms of action of gemcitabine involve competition for incorporation into DNA, thereby inhibiting the synthesis of DNA; preventing DNA repair by masked termination; and undergoes self-potentiation. Gemcitabine undergoes phosphorylation by deoxycytidine kinase to gemicitabine di- and then triphosphate. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is the primary enzyme involved in the formation of deoxycytidine triphosphate (dCTP) that is a natural substrate in DNA replication, thus allowing the incorporation of gemcitabine triphosphate nucleotides into the DNA chain during replication[33].

Recent approaches in management of pancreatic cancer

Although a number of approaches have been made for the rectification of the problem, still work is going on. Recently, attention has been made on other targets.

- **Gene therapy:** Pancreatic adenocarcinoma, is an area where gene transfer and immunotherapy have a maximal opportunity to demonstrate efficacy. These therapies, which do not require efficient gene transfer, generally lead to systemic biological effects and therefore the effects of limited gene transfer are biologically "amplified." The second category of gene transfer strategies requires the delivery of therapeutic genetic material to all or most tumor cells[34].
- **Oncogenes inactivation:** The KRAS oncogene is frequently mutated in human malignancies such as colon, lung, and ovarian cancer. In pancreatic cancer, mutations in KRAS are found in more than 90% of patient samples. The most frequent mutation is the constitutively active $KRAS^{G12D}$ allele Interestingly, KRAS mutations are frequently detected in the most common precursor lesion to pancreatic cancer, pancreatic intraepithelial neoplasia (PanIN), indicating a potential role early in the disease[35].
- **Immune enhancement:** Autologous natural killer (NK) cell and activated T-lymphocyte based immunotherapy termed as autologous immune enhancement therapy (AIET) can be used to enhance immunity[36].
- **Enzyme therapy:** Pancreatic enzyme administration serves to reverse the effects of pancreatic exocrine insufficiency and may reduce or alleviate the pain experienced by patients. Conventional enzyme preparations are partially degraded by

gastric acid, but are available within the duodenal and jejunal regions to bind to CCK-releasing peptide, and down regulate the release of CCK[37].

Conclusion

Pancreatic cancer is the major cause of death around the world. Due to its poor prognosis, the mortality rate with pancreatic cancer is high, so that newly developed cheaper and sensitive diagnostic tools are required to create a breakthrough to determine it. Although a number of approaches have been made to identify the disease, and its management, still a lot of work is required to minimize mortality rate and to minimize adverse reactions of the synthetic drugs.

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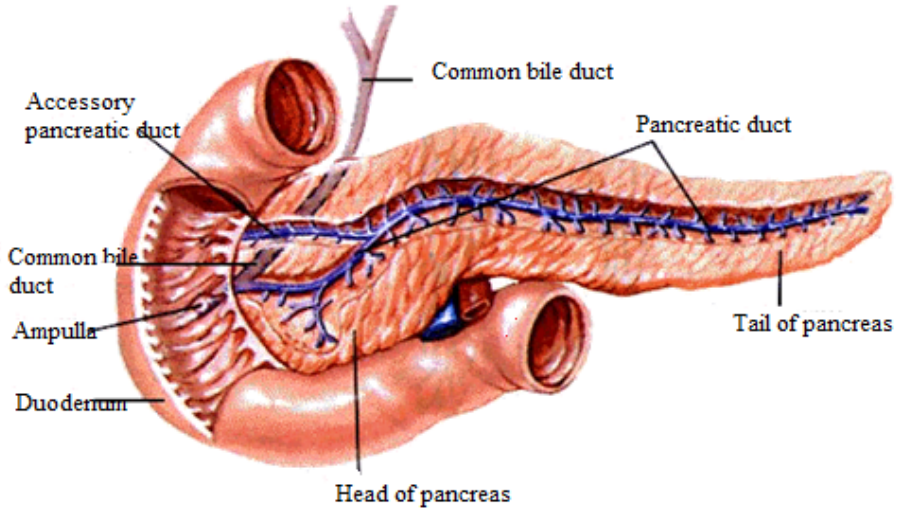

Figure 1. Human pancreas

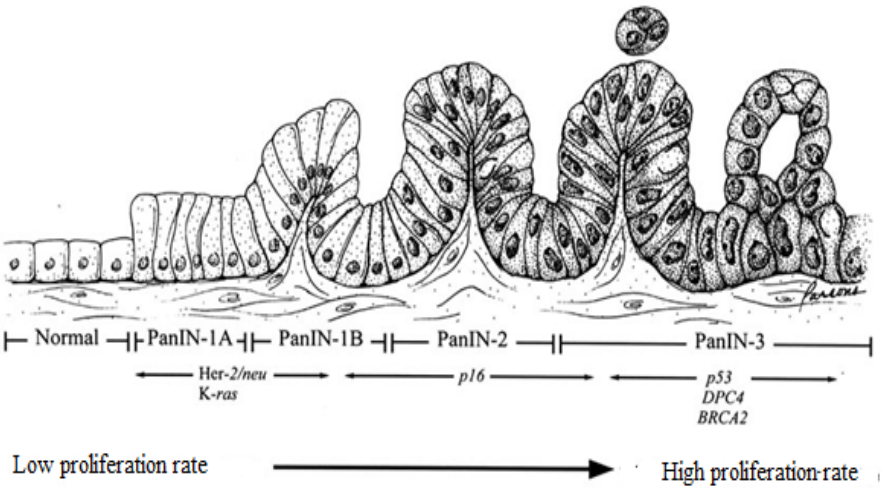

Figure 2. Progression of pancreatic cancer

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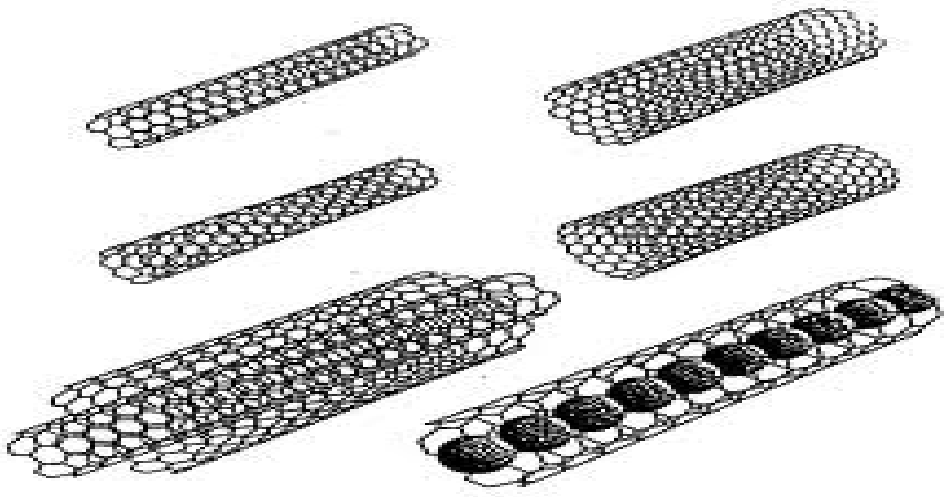

Figure 3. Carbon nanotubes

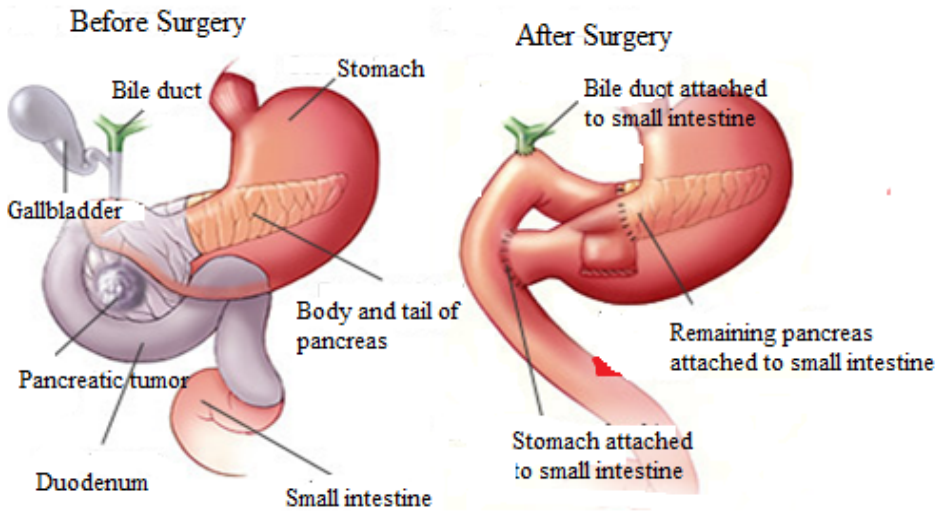

Figure 4. Whipple procedure for pancreatic cancer surgery