International University of Africa

Deanship of Graduate Studies

Faculty of Medicine

Department of Biochemistry

Biochemical Assessment of Bilirubin Level in Pancreatic Adenocarcinoma Patients in Khartoum State

A thesis Submitted in partial fulfillment of the requirement for the degree of Master's of Science in Biochemistry

By:

Fauzia Ali Elzain Abdelrahman

Omdurman Islamic University

Faculty of science and technology

B.Sc Biotechnology

October 2013

Supervisor:

Dr. Fatima Elsammani Alsheikh

International University of Africa

Sudan

November-2018

بسم الله الرحمن الرحيم

International University of Africa

Deanship of Graduate Studies

Faculty of Medicine

Department of Biochemistry

Biochemical Assessment of Bilirubin Level in Pancreatic Adenocarcinoma Patients In Khartoum State

A thesis Submitted in partial fulfillment of the requirement for the degree of Master's of Science in Biochemistry

By:

Fauzia Ali Elzain Abdelrahman

Omdurman Islamic University

Faculty of science and technology

B.Sc Biotechnology

October 2013

Supervisor:

Dr. Fatima Elsammani Alsheikh

International University of Africa

November-2018

بسم الله الرحمن الرحيم

قال تعالى:

(قل إنما أنا بشر مثلكم يوحى إلي أنما إلهكم إله واحد فمن كان يرجو لقاء ربه فليعمل عملا صالحا ولا يشرك بعبادة ربه احدا)

صدق الله العظيم

سورة الكهف الاية(110)

Dedication

To

My parents

For making everything worthwhile

My brothers and sister

For giving me love and inspiration

My grandfather

For pushing me forward

My blue heart my comrade Alanood

For her abundant support and her love

My faithful friend Fatima

for their support and encouragement

My friends

For their support

Fauzia 2018

Acknowledgment

I would like to thank Allah who give me strength, health and patients to complete my study.

I would like to thank Dr. Fatima Elsammani Alsheikh for supervising and guiding my work, and for her support throughout my dissertation.

I would like to thanks prof. Oshman Mohmmed for guiding my work.

My special thanks to department of biochemistry International University of Africa for their unlimited support.

Special thanks to my family who supported and helped me to complete this study.

I would like to express my gratitude to Mr. MohmmedI brahim Algasim for his help with statistical analysis by SPSS.

List of abbreviation:

Term	Abbreviation
AJCC	American joint committee on cancer
BRCA2	Breast cancer gene and colon
CT	Computed tomography
CA19.9	Carbohydrate antigen 19.9
CDKN2A	Cyclin-dependent kinase inhibition 2A
D.bil	Direct bilirubin
EUS	Endoscopic ultrasound
ERCP	Cholangiopancreatography
FDA	Food and drug administration
FAMMM.PC	Familial atypical multiple mole and melanoma syndrome-pancreatic cancer
GNAS	Guanine nucleotide binding protein
In.bil	Indirect bilirubin
IPMNs	Intra ductal papillary mucinous neoplasms
INR	International normalized ratio(for prothrombin time)
KRAS	Ki-rasscaroma 2 viral encogene
MCNs	Mucinous cystic neoplasms
NETs	Neuroendocrine tumors
Nab-paclitaxel	Protein-bound paclitaxel
PDAC	Pancreatic ductal adenocarcinoma
PAL	Patterns in antirrhinum
PTCD	Precutaneous trans hepatic biliary drainage
PanNets	Pancreatic neuroendocrine tumors
RNFL31	Ring finger protein 43
RIC	Radiation and isotopes center of

	Khartoum
STK11	Serine threonine kinase11
SWI/SNF	Switch/source non-fermentable
SMAD	Small mother against decapenntaplegic
TP53	Tumor protein 53
T.bil	Total bilirubin
TNM	T=Tumor, N= Lymph Node, M=Metastasis
UICC	Union for international cancer control
ULN	Upper limits of normal
Wnt	Wingless/integrated signaling pathway

Abstract

Background: The most common type of cancer is an adenocarcinoma of the pancreas, 95% of all cancerous tumors is adenocarcinoma. Pancreatic adenocarcinoma is the 4th leading cause of cancer death.

The objective of this study is to assess serum bilirubin in relation to pancreatic cancer before and after treatment according to age and gender.

The study was conducted in Radiation and Isotopes center Khartoum state during the period from December 2017 to September 2018.

84 patients with pancreatic cancer were included in the study (50 males and 34 females). Their ages range from 20 to 70 years. The normal range of total bilirubin (up to 1.2 mg/dl), direct bilirubin (up to 0.25mg/dl) and indirect bilirubin(up to 0.95mg/dl) was used as a control for the cases.

The study was a survey for 3 years ago.

The serum values of total bilirubin (T.Bil) in primary stage before treatment, after surgery and after chemo-radio therapy were (9.56±1.48, 2.01±0.77, and 1.48±0.49)mg/dl respectively.

Direct bilirubin (D.Bil) values before treatment, after surgery and after chemo-radio therapy were (5.56±1.40, 0.80±0.60, and 0.45±,0.38)mg/dl respectively.

Indirect bilirubin (ID.Bil) values before treatment, after surgery and after chemo-radio therapy were (3.96±1.26, 1.19±0.46 and1.02±0.37)mg/dl respectively.

The results showed that the effective treatment that lower bilirubin level in the primary stage was chemo-radio therapy in all 3 years cases.

Effect of chemo-radio therapy was highly significant difference (P≤0.000), (P≤0.007) respectively in (T.bil) and (D.bil) than surgery. But there was no significant difference between chemo-radio therapy and surgery in (ID.bil).

The serum values of total bilirubin (T.Bil) in advanced stage before treatment, after chemo-radio therapy and after surgery were (14.16±2.40, 2.70±1.42 and3.75±1.23)mg/dl respectively.

Direct bilirubin (D.Bil) values before treatment, after chemo-radio therapy and after surgery were (9.42±1.99, 1.22±0.93and1.47±0.79)mg/dl respectively.

Indirect bilirubin (ID.Bil) values before treatment, after chemo- radio therapy and after surgery were (4.52±1.86, 1.44±0.76and2.28±0.83)mg/dl respectively.

The results showed that the effective treatment that lower bilirubin level in the advanced stage was surgery in all 3 years cases.

Effect of surgery was highly significant difference (P≤0.000) in (T.bil) and (ID.bil) than chemo-radio therapy. But there was no significant difference between surgery and chemo-radio therapy in (D.bil).

The serum values of total bilirubin (T.Bil) in more advanced stage before treatment and after chemotherapy were (22.70±5.46 and 15.74±6.21)mg/dl respectively, direct bilirubin (D.Bil) values before treatment and after chemotherapy were (17.66±5.59 and 11.14±5.72)mg/dl respectively, and indirect bilirubin (ID.Bil) values before treatment and after chemotherapy were (4.90±2.42 and4.60±1.84)mg/dl respectively.

The results showed that treatment with chemotherapy lower bilirubin level in more advanced stage in all 3 years cases.

There was significant difference (P≤0.000) before and after treatment with chemo therapy in more advanced stage in (T.bil) and (D.bil). But there was

no significant difference before and after treatment with chemotherapy in (ID.bil).

The results showed that there was no significant difference between serum values of bilirubin in pancreatic cancer patients before and after treatment according to age, gender and years in all studies.

المستخلص

الخلفية :اكثر الانواع المنتشره لمرض البنكرياس هو(مرض خبيث ينشأ في الغده) 95% منه عباره عن سرطان البنكرياس يوجد في رأس البنكرياس وهو المسبب الرابع من أسباب الوفاة في العالم.

الهدف من الدراسه قياس معدل الماده الصفراويه لمريض سرطان البنكرياس قبل وبعد العلاج وفقا للعمر والجنس.

اجريت الدراسه في مركز الخرطوم للعلاج بالأشعه والطب النووي في الفتره ديسمبر 2017 الى سبتمبر 2018.

تضمنت الدراسه اربعه وثمانون مريضا (50رجلا و 34امراه) تتراوح اعمارهم بين ال 20سنه الي 70سنه . المعدل الطبيعي للماده الصفراويه الكليه (الى 1.2 مل/دسم) ,الماده الصفراويه المباشره(الى 0.25مل/دسم) والماده الصفراويه الغير مباشره(الى0.95مل/دسم).

اجريت الدراسه لثلاث سنوات سابقه.

أظهرت الدراسه أن معدل الماده الصفراويه الكلي في المرحله الأولى قبل العلاج وبعد الجراحه وبعد العلاج الكيماوي الاشعاعي كان(1.48±0.49 and 2.01±0.77, 9.56±1.48)ملغم/دسم على التوالي.

ومعدل الماده الصفراويه المباشره قبل العلاج وبعد الجراحه وبعد العلاج الكيماوي الاشعاعي كان(0.38±, 0.45 ,0.80±0.60 ,5.56±1.40) ملغم/دسم على التوالي.

معدل الماده الصفراويه الغير مباشره قبل العلاج وبعد الجراحه وبعد العلاج الكيماوي الاشعاعي كان(1.02±0.37 ,0,46±1.19,,3.96±1.26)ملغم /دسم على التوالي.

أظهرت الدراسه ان العلاج الأفضل لخفض نسبة الماده الصفراويه كان العلاج الكيماوي الاشعاعي في المرحله الأوليه في كل الثلاث سنوات للمصابين.

كان تاثير العلاج الكيماوي الاشعاعي عالي المعنويه(P≤0.007),(P≤0.000)على التوالي للماده الصفراويه الكليه والمباشره اكثر من الجراحه. ولكن لايوجد اختلاف معنوي بين العلاج الاشعاعي الكيماوي والجراحه في معدل الماده الصفراويه الغير مباشره.

كما أن معدل الماده الصفراويه الكلي في المرحله المتقدمه قبل العلاج وبعد الجراحه وبعد العلاج الكيماوي الإشعاعي كانت(14.16±2.40, 2.70±1.42 and 3.75±1.23)ملغم/دسم على التوالي.
ومعدل الماده الصفراويه المباشره قبل العلاج وبعد الجراحه وبعد العلاج الكيماوي الإشعاعي (9.42±1.99, 1.22±0.93 and1.47±0.79)ملغم/دسم على التوالي.
ومعدل الماده الصفراويه الغير مباشره قبل العلاج وبعد الجراحه العلاج الكيماوي الإشعاعي (4.52±1.86, 1.44±0.76 and 2.28± 0.83)ملغم/دسم على التوالي.
أظهرت الدراسه أن العلاج الأفضل لخفض الماده الصفراويه في المرحله المتقدمه كانت الجراحه في كل الثلاث سنوات للمصابين.
كان تاثير الجراحه عالي المعنويه(P≤0.000) على الماده الصفراويه الكليه والغير مباشره اكثر من العلاج الاشعاعي الكيماوي. ولكنه لايوجد اختلاف معنوي بين الجراحه والعلاج الاشعاعي الكيماوي على معدل الماده الصفراويه المباشره.
وأيضا أظهرت الدراسات أن معدل الماده الصفراويه الكلي ه في المرحله المتقدمه جدا قبل العلاج وبعد العلاج الكيماوي كان (22.70±5.46, 15.74±6.21) ملغم/دسم على التوالي ومعدل الماده الصفراويه المباشره قبل العلاج وبعد العلاج الكيماوي كان (17.66±5.59,11.14±5.59) ملغم/دسم على التوالي ومعدل الماده الصفراويه الغير مباشره قبل العلاج وبعد العلاج الكيماوي كانت(4.90±2.42, 4.60±1.84) ملغم/دسم على التوالي.
أظهرت الدراسه أن معدل الماده الصفراويه في المرحله المتقدمه جدا انخفض بعد العلاج الكيماوي في كل الثلاث سنوات للمصابين.
هناك علاقه معنويه(P≤0.000) قبل وبعد العلاج الكيميائي في المرحله المتقدمه جدا على الماده الصفراويه الكليه والمباشره. ولكنه لايوجد اختلاف معنوي بين قبل وبعد العلاج الكيميائي على الماده الصفراويه الغير مباشره.

أظهرت الدراس ه انه ليس هناك علاقه معنويه بين معدل الماده الصفراويه لمريض سرطان البنكرياس قبل وبعد العلاج بالجنس والعمر والسنوات في كل الدراسات .

List of Contents

Chapter one

1.1. Introduction:

Definition of cancer: Cancers are a largefamily of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body [1] [2] .They form a subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely[3] [4].All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor. They include: [5]

- Cell growth and division absent the proper signals
- Continuous growth and division even given contrary signals
- Avoidance of programmed cell death
- Limitless number of cell divisions
- Promoting blood vessel construction
- Invasion of tissue and formation of metastases [6]. The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.[5] [6] .

Pancreas: Pancreas is an endocrine and digestive organ that, in humans, lies in the upper left part of the abdomen. It is found behind the stomach.[7] The pancreas is about 15 cm (6 in) long.[8]

Anatomically, the pancreas is divided into the head of pancreas, the neck of pancreas, the body of pancreas, and the tail of pancreas.[9] The head is surrounded by the duodenum in its concavity. The head surrounds two blood vessels, the superior mesenteric artery and vein. From the back of the head emerges a small unicinate process, which extends to the back of the superior mesenteric vein and ends at the superior mesenteric artery.[10] The neck is about 2.5 cm (1 in) long and lies between the head and the body and in front of the superior mesenteric artery and vein. Its front upper surface supports the pylorus (the base) of the stomach. The body is the largest part of the pancreas and lies behind the pylorus, at the same level as the transpyloric plane.[11] The tail ends by abutting the spleen.

The pancreas is a secretory structure with an internal hormonal role (endocrine) and an external digestive role (exocrine). The endocrine part is composed of hormonal tissue distributed along the pancreas in discrete units called islets of Langerhans.[9] Islets of Langerhans have a well-established structure and form density routes through the exocrine tissue.[9] The exocrine part has two main ducts, the main pancreatic duct and the accessory pancreatic duct. These drain enzymes through the ampulla of Vater into the duodenum.[12]

Pancreatic cancer: pancreatic cancer arises when cells in the pancreas, a glandular organ behind the stomach, begins to multiply out of control and form a mass. These cancerous cells have the ability to invade other parts of the body.[13] There are a number of types of pancreatic cancer.[10] The most common, pancreatic adenocarcinoma, accounts for about 85% of cases, and the term "pancreatic cancer" is sometimes used to refer only to that type.[6] These adenocarcinomas start within the part of the pancreas which makes digestive enzymes [10]. One to two percent of cases of pancreatic cancer are neuroendocrine tumors, which arise from the hormone-producing cells of the pancreas.[10] These are generally less aggressive than pancreatic adenocarcinoma.[10]

Most pancreatic cancers are exocrine cancers, the head of pancreas located close to the common bile duct and duodenum (small bowel), so tumors located in the pancreas may grow and block these structures. Bile duct blockage can lead to jaundice in 70-85% of patients with tumors in the head of the pancreas [14].

Jaundice it is a clinical condition characterized by yellow discoloration of skin, sclera and mucus membrane. It is due to increase plasma bilirubin above 3 mg/dl. At this level, bilirubin diffuses into tissues giving yellow color.

Bilirubin is a yellow compound that occurs in the normal catabolic pathway that breaks down heme in vertebrates [15].

Formation of Bilirubin:

The heme ring is catabolizied by the microsomal heme oxygenase enzymes of the endoplasmic reticulum cells.

In this reaction (which needs, heme oxygenase enzyme, O_2 and NADPH), iron (fe^{++}) is removed for re-use. The remaining of heme ring is cleaved between pyrrole rings number I and II to form biliverdin (green pigment) and carbon monoxide (Co).

Biliverdin is then reduced into bilirubin (golden yellow) in a reaction requires biliverdin reductase enzyme [16].

Transport of bilirubin in the plasma:

Bilirubin is non polar, and is insoluble in plasma. Therefore it binds noncovalentling bonds to plasma albumin. This form is called: unconjugated or indirect bilirubin[16].

Uptake of bilirubin by the liver:

Bilirubin dissociates from the carrier albumin molecule and enters hepatocytes.

Bilirubin is conjugated with one or two molecules of glucuronic acid (the acid form of glucose) to form bilirubin monoglucuronide and bilirubin diglucuronide. This reaction needs UDP-glucuronyltransferase enzyme:

Bilirubin +UDP –Glucuronate ----------transferase-------- bilirubin glucuronide (s) +UDP [16].

Secretion of bilirubin into bile:

Bilirubin diglucuronide is actively transported against concentration gradient into the bile canalciuli and then into the bile [16].

Formation of urobilin in the intestine:

Intestinal bacteria acts on bilirubin diglucuronide leading to:

removal of glucuronides (by B- glucuroidase enzymes).

Reduction of bilirubin to colorless compounds called: urobilinogens(=stercobilinogen)[16].

A small fraction of urobilinogens are reabsorbed from intestine to the liver again and re-excreted in the bile, forming the entrohepatic urobilinogens cycle [16].

Excretion of urobilinogens in stool and urine:

Most of the colorless urobilinogens are oxidized to the colored urobilin (stercobilin), which excreted in the stool giving its brown color.

Part of urobilinogens are reabsorbed to the liver, then to the blood to be excreted by the kidney in urine and coverted into urobilin.

Urobilin – together with urochrome give the characteristic yellow color of urine [16].

1.2. Justification

- Pancreatic cancer associated with jaundice is the fourth leading cause of cancer death in the world.
- Around 70-85% of patients with tumor in the head of pancreas cause obstructive jaundice (Diane 2012).

1. 3. Objective

1.3.1. General objective:

To assess the level of serum bilirubin in pancreatic cancer patients attended at Radiation and Isotopes Center Khartoum.

1.3.2. Specific objective:

- To estimate the total serum bilirubin (T.Bil) concentration (mg/dl) before and after treatment according to age and gender.
- To estimate the direct serum bilirubin (D.Bi) concentration (mg/dl) before and after treatment according to age and gender.
- To estimate the indirect serum bilirubin (ID.Bil) concentration (mg/dl) before and after treatment according to age and gender.

Chapter two

Literature review

2.1. Types of pancreatic cancer:

2.1.1. Exocrine cancer: Nearly all these start in the ducts of the pancreas, as pancreatic ductal adenocarcinoma (PDAC).[19] This cancer originates in the ducts that carry secretions (such as enzymes and bicarbonate) away from the pancreas. About 60–70% of adenocarcinomas occur in the head of the pancreas [9].The pancreas makes pancreatic juices. These pancreatic juices are produced by the exocrine glands and contain enzymes that help digest food. When food enters the stomach, the pancreas releases these enzymes into a system of ducts. The main pancreatic duct joins the common bile duct, which originates from the liver and gallbladder. The common bile duct carries bile, a fluid that helps in digestion of fat, and it empties into the duodenum, the first part of the small intestine [20].

2.1.2. Neuroendocrine: The small minority of tumors that arise elsewhere in the pancreas are mainly pancreatic neuroendocrine tumors (PanNETs).[21]Neuroendocrine tumors (NETs) are a diverse group of benign or malignant tumors that arise from the body's neuroendocrine cells, which are responsible for integrating the nervous and endocrine systems.

2.2. Signs and symptoms:

Pain in the upper abdomen or back, often spreading from around the stomach to the back [23].

Jaundice, a yellow tint to the whites of the eyes or skin, with or without pain ,and possibly in combination with darkened urine. This results when a cancer in the head of the pancreas obstructs the common bile duct as it runs through the pancreas [24] .Weight loss, either from loss of appetite, or loss of exocrine function [25]. The tumor may compress neighboring organs, disrupting digestive processes and making it difficult for the stomach to empty, which may cause nauseaand a feeling of fullness [25].Constipation is common[26]. At least 50% of people with pancreatic adenocarcinoma have diabetes at the time of diagnosis.[9]

2.3. Risk factors:

The strongest risk factor for pancreatic cancer is increasing age. In the USA, the median age at diagnosis is 72 [9] [27] [25]. Risk is low (10.4 per 100,000) in those aged 50–54, increasing sharply to 73.5 per 100,000 in those aged 75–79 [27] [12] [15]and continuing to increase in older individuals. Gender: risk is higher in men than in women [28] [20] [29]. In 2015, pancreatic cancers of all types resulted in 411,600 deaths globally [30]. The disease is more common in men than women [10] [9] .

2.4.Pathophysiology:

Exocrine cancers are thought to arise from several types of precancerouslesions within the pancreas. But these lesions do not always progress to cancer, and the increased numbers detected as a by-product of the increasing use of CT scans for other reasons are not all treated.[27] Apart from pancreatic serous cystadenomas (SCNs), which are almost always benign, four types of precancerous lesion are recognized. The first is pancreatic intraepithelial neoplasia. These lesions are microscopic abnormalities in the pancreas and are often found in autopsies of people with no diagnosed cancer. These lesions may progress from low to high grade and then to a tumor. More than 90% of cases at all grades carry a faulty KRAS gene, while in grades 2 and 3 damage to three further genes – CDKN2A (p16), p53 and SMAD4 – are increasingly often found.[9] A second type are the intraductal papillary mucinous neoplasms (IPMNs). These are macroscopic lesions, which are found in about 2% of all adults. This rate rises to ~10% by age 70. These lesions have about a 25% risk of developing into invasive cancer. They may have KRAS gene mutations (~40–65% of cases) and in the GNAS Gs alpha subunit and RNF43, affecting the Wnt

signaling pathway [9]. Even if removed surgically, there remains a considerably increased risk of pancreatic cancer developing subsequently.[27] The third type, pancreatic mucinous cystic neoplasms (MCNs) mainly occur in women, and may remain benign or progress to cancer.[33] If these lesions become large, cause symptoms, or have suspicious features, they can usually be successfully removed by surgery [27]. A fourth type of cancer that arises in the pancreas is the intraductaltubulopapillary neoplasm. This type was recognised by the WHO in 2010 and constitutes about 1–3% of all pancreatic neoplasms. Mean age at diagnosis is 61 years (range 35–78 years). About 50% of these lesions become invasive. Diagnosis depends on histology as these lesions are very difficult to differentiate from other lesions on either clinical or radiological grounds.[34] Invasive cancer: the genetic events found in ductal adenocarcinoma have been well characterized , and complete exome sequencing has been done for the common types of tumor. Four genes have each been found to be mutated in the majority of adenocarcinomas: KRAS (in 95% of cases), CDKN2A (also in 95%), TP53 (75%), and SMAD4 (55%). The last of these are especially associated with a poor prognosis.[27] SWI/SNF mutations/deletions occur in about 10–15% of the adenocarcinomas.[9] The genetic alterations in several other types of pancreatic cancer and precancerous lesions have also been researched [27].Transcriptomics analyses and mRNA sequencing for the common forms of pancreatic cancer have found that 75% of human genes are expressed in the tumors, with some 200 genes more specifically expressed in pancreatic cancer as compared to other tumor types.[35]

2.5. Staging:

Exocrine cancers: Pancreatic cancer is usually staged following a CT scan.[36] The most widely used cancer staging system for pancreatic cancer is the one formulated by the American Joint Committee on Cancer (AJCC) together with the Union for International Cancer Control (UICC). The AJCC-UICC staging system designates four main overall stages, ranging from early to advanced disease, based on TNM classification of tumor size, spread to lymph nodes, and metastasis.[37]

To help decide treatment, the tumors are also divided into three broader categories based on whether surgical removal seems possible: in this way, tumors are judged to be "resectable", "borderline resectable", or "unresectable".[38] When the disease is still in an early stage (AJCC-UICC stages I and II), without spread to large blood vessels or distant organs such as the liver or lungs, surgical resection of the tumor can normally be performed, if the patient is willing to undergo this major operation and is thought to be sufficiently fit.[25] The AJCC-UICC staging system allows distinction between stage III tumors that are judged to be "borderline resectable" (where surgery is technically feasible because the celiac axis and superior mesenteric artery are still free) and those that are "unresectable" (due to more locally advanced disease); in terms of the more detailed TNM classification, these two groups correspond to T3 and T4 respectively.[27] Locally advanced adenocarcinomas have spread into neighboring organs, which may be any of the following (in roughly decreasing order of frequency): the duodenum, stomach, transverse colon, spleen, adrenal gland, or kidney. Very often they also spread to the important blood or lymphatic

vessels and nerves that run close to the pancreas, making surgery far more difficult. Typical sites for metastatic spread (stage IV disease) are the liver, peritoneal cavity and lungs, all of which occur in 50% or more of fully advanced cases.[40]

2.6. Management:

2.6.1. Surgery:

There are some studies indicating that Since pancreatic cancer was first described by Montiere in 1836, the apparent global incidence of the disease has increased three or four times[41-42] . In the United States in 1990, about 27,000 new cases will be diagnosed. Approximately the same number of patients will die of the disease during that period [43] [44]. Only 10% to 15% of patients with pancreatic cancer are suitable for possible curative resection [45] [46]. The symptoms that most commonly require relief in patients with pancreatic cancer are jaundice, gastric outlet obstruction, and pain. Opinions vary concerning the best approach to the treatment of these problems, as well as their efficacy. To shed some light on these issues, They reviewed retrospectively a 16-year experience (1973 to 1988) with the palliation of pancreatic cancer at the University of California, Los Angeles (UCLA). Pancreatic cancer is considered resectable if the tumor appears to be localized to the pancreas without invasion into important surrounding structures such as the mesenteric blood vessels (that supply blood to the intestines) which are located adjacent to the head portion of the pancreas. Furthermore there should be no evidence of metastatic spread to liver or lining of the intestines surgical removal of the tumor is a treatment of choice for patients with resectable pancreatic cancer. The surgery involves removal

of all tumors that is visible at the time of surgery [43]. For cancers involving the head of the pancreas, the Whipple procedure is the most commonly attempted curative surgical treatment. This is a major operation which involves removing the pancreatic head and the curve of the duodenum together ("pancreato-duodenectomy"), making a bypass for food from the stomach to the jejunum ("gastro-jejunostomy") and attaching a loop of jejunum to the cystic duct to drain bile ("cholecysto-jejunostomy"). It can be performed only if the person is likely to survive major surgery and if the cancer is localized without invading local structures or metastasizing [9] [79] [7].

A whipple operation involves removal of the head (first part) of the pancreas and usually about 20% of the pancreas is removed. The bottom half of the bile duct and the first portion of the intestine called the duodenum is also removed and the stomach is preserved. This procedure called the pylorus preserving whippleoperation .occasionally part of stomach may be removed and this operation is called the standard operation [47].This operation will lowering the bilirubin concentration to normal range. Although curative surgery no longer entails the very high death rates that occurred until the 1980s, a high proportion of people (about 30–45%) still have to be treated for a post-operative sickness that is not caused by the cancer itself. The most common complication of surgery is difficulty in emptying the stomach.[27] [79] Certain more limited surgical procedures may also be used to ease symptoms: for instance, if the cancer is invading or compressing the duodenum or colon. In such cases, bypass surgery might overcome the obstruction and improve quality of life but is not intended as a cure.[25] Obstructive jaundice is the most common symptom in patients with advanced cancer (borderline resectable) of the pancreatic head. For patients

with a resectable tumor who have no radiologic evidence of metastasis, surgical resection is the only option for cure [48] [49] Since surgery in patients with jaundice is thought to increase the risk of postoperative complications, preoperative biliary drainage was introduced to improve the postoperative outcome [50]. In several experimental studies and retrospective case series, preoperative biliary drainage reduced morbidity and mortality after surgery [50] [51].patients with pancreatic cancers located in the head of the gland present with biliary obstruction. A decision regarding preoperative biliary decompression must then be made, and a number of different bilirubin threshold levels and approaches have been described [52].Reported results from a multicenter, randomized trial of 202 patients with elevated bilirubin levels (2.3 to 14.6 mg/dl) who were assigned to undergo immediate surgery or preoperative endoscopic biliary drainage. The authors found that the biliary drainage group had significantly higher endoscopic and stent-related complications ($P< 0.001$) without an improvement in the rate of perioperative complications ($P = 0.14$). Similarly.from Memorial Hospital in New York also found that the preoperative endoscopic placement of biliary stents resulted in a two-fold increase in postpancreatectomy infectious complications. These two studies suggest that preoperative biliary stenting should be used selectively in patients with biliary obstruction prior to pancreaticoduodenectomy. They have taken a similar approach and have arranged for patients with bilirubin levels of greater than 25 mg/dl or those with evidence of synthetic liver dysfunction, as assessed by an elevated serum INR level, to undergo preoperative stenting. Surgery is delayed until the bilirubin level is less than 20 mg/dl and the INR is within a normal range [53] [80].

Around 60-70% of pancreatic cancers are located in the pancreatic head [53], leading to hyperbilirubinaemia caused by obstruction of the central bile duct in 70-80% of these patients [54]. Biliary obstruction and the resulting hyperbilirubinaemia usually complicate the management of patients by increasing the risk of cholangitis and causing frequent hospitalizations [55]; hyperbilirubinaemia has been associated with shorter overall survival in patients with pancreatic cancer [56] [57]. Biliary decompression in patients with obstructive hyperbilirubinaemia is commonly performed using endoscopic stent placement[58], which not only reduces morbidity but also facilitates treatment with chemotherapy by allowing total bilirubin levels to drop to ≤ 1.5-2 times the upper limit of normal (≤ 1.5-2 × ULN). Other possible causes of hyperbilirubinaemia in patients with pancreatic cancer are obstruction of the peripheral intrahepatic bile ducts due to tumour metastases, without major impairment of other aspects of liver function, or massive infiltration of the liver by tumour metastases resulting in non-cirrhotic liver failure[59][79][77]. The rationale for biliary decompression in patients with resectable pancreatic cancer and obstructive cholestasis is the normalisation of the bilirubin levels to allow palliative chemotherapy, and the prevention of other adverse outcomes such as cholangitis and frequent hospitalizations [55]According to the current German, European and American treatment guidelines, stent placement via endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for biliary decompression in these patients[54][58][60].In case ERCP is not possible, percutaneous transhepatic biliary drainage (PTCD) is recommended[54] [58] [60].

.Endoscopic ultrasound-guided transoesophageal or transduodenal biliary drainage represents a treatment alternative in selected patients not suitable for conventional ERCP and PTCD [61] [62].

2.6.2. Chemotherapy:

After surgery, neo adjuvant chemotherapy with gemcitabine or 5-FU and radition has been effective than surgery in lowering bilirubin levelin pancreas cancer in attempt to improve out come and can be offered if the person is sufficiently fit for those with resectable tumors[63] [64] [65][72] [74] , Before surgery , neo adjuvant chemotherapy or chemo-radiotherapy may be used in cases that are considered to be "borderline resectable" in order to reduce the cancer to a level where surgery could be beneficial ,the surgery more effective in this cases than chemo-radio therapy[27] [7] [75], but in other hands the chemo-radio therapy is more effective in lowering bilirubin level to normal range[73] [72] [75] . In other cases neoadjuvant therapy remains controversial, because it delays surgery. After a recovery period of one to two months [7] [67]. In people not suitable unresectable for curative surgery, chemotherapy may be used to extend life or improve its quality on hyperbilirubineama [27] [76] [78]. Gemcitabine was approved by the United States Food and Drug Administration (FDA) in 1997, after a clinical trial reported improvements in quality of life and a 5-week improvement in median survival duration in people with advanced pancreatic cancer[68] .This was the first chemotherapy drug approved by the FDA primarily for a nonsurvival clinical trial endpoint.[69] Chemotherapy using gemcitabine alone was the standard for about a decade, as a number of trials testing it in combination with other drugs failed to demonstrate significantly better outcomes. However, the combination of gemcitabine with erlotinib was found to increase survival modestly, and erlotinib was licensed by the FDA for use in pancreatic cancer in 2005[70].

The FOLFIRINOXchemotherap regimen using four drugs was found more effective than gemcitabine, but with substantial side effects, and is thus only suitable for people with good performance status. This is also true of protein-bound paclitaxel (nab-paclitaxel), which was licensed by the FDA in 2013 for use with gemcitabine in pancreas cancer [71]. By the end of 2013, both FOLFIRINOX and nab-paclitaxel with gemcitabine were regarded as good choices for those able to tolerate the side-effects, and gemcitabine remained an effective option for those who were not. A head-to-head trial between the two new options is awaited, and trials investigating other variations continue. However, the changes of the last few years have only increased survival times by a few months.[68] Clinical trials are often conducted for novel adjuvant therapies [7].

2.6.3. Radiotherapy:

The role of radiotherapy as an auxiliary (adjuvant) treatment after potentially curative surgery has been controversial since the 1980[27]. Radiotherapy may form part of treatment to attempt to shrink a tumor to a resectable state, but its use on unresectable tumors remains controversial as there are conflicting results from clinical trials. The preliminary results of one trial, presented in 2013, "markedly reduced enthusiasm" for its use on locally advanced tumors , concurrent external-beam radiotherapy delivered in daily fractions over a six week period to total dose of approximately 5000 rads [9].

Chapter three

Material and Methods

3. Material

3.1. Study design:

Retrospective prospective study was done in pancreatic cancer patients.

3.2. Study area and period:

This study was conducted in Radiation and Isotopes Centre Khartoum during the period from December 2017 to September2018.

3.3. Study subjects:

Pancreatic cancer patients who have the disease at any age and gender.

3.4. Sample size:

84 Pancreatic cancer patients before treatment (control group) and pancreatic cancer patients after treatment with surgery and chemotherapy or radiation in this study(test group) .

3.5. Exclusion criteria:

- Any patients with one of the following conditions was excluded:
- Other type of cancer.
- Gall stones.

3.6. Ethical consideration:

- Written consent was obtained from Ethical Committee- Ministry of Health_ statewide of Khartoum.

3.7. Data collection and clinical assessment:

Data were collected from records survey for 3 years ago.

3.8. Biochemical measurements:

Serum samples were analyzed for total bilirubin (T.BIL) and direct bilirubin (D.BIL) by photometric (instrument limited model BS-200 Germany) using commercial kits (Mindary chemical, china).

3.8.1. Estimation of total bilirubin:

3.8.1.1. Principle of the method:

By the action of vanadic acid ion at PH 3.0, bilirubin is oxidized to dehydrobilirubin, and the absorbency decreases at 450 nm is directly proportional to the concentration of total bilirubin.

3.8.1.2. Reagents:

- R1 Citrate buffer surfactant, 100mmol/L <1%.
- R2 phosphate buffer vanadiate 10mmol/L, 4mmol/L.

3.8.1.3. Method:

Into a measuring cuvette 2800µl of working reagent (1) were mixed with 100 µl of sample , and incubated for 3 minutes at 37 c^o then700 µl of reagent (2) were mixed thoroughly then incubated at 37c^o for 5 minutes and then read the absorbance:

(T.BIL)=Absorbance of sample- Absorbance of blank

A= {Δ A sample} – {Δ A blank}

3.8.2. Estimation of direct bilirubin:

3.8.2.1. Principle of method:

By the action of inhibitor and vandic acid ion at PH 3.0, direct bilirubin is specially oxidized to dehydrobilirubin, and the absorbency decreases at 450 nm is directly proportional to the concentration of direct bilirubin.

3.8.2.2. Reagents:

- R1 Tartrate buffer 100mmol/L.
- R2 Phosphate buffer vanadiate 10mmol/L, 4mmol/L.

3.8.2.3. Method:

Into a measuring cuvette 2800 µl of working reagent(1) were mixed with 100 µl of sample, and incubated for 3 minutes at 37 c^o then700 µl reagent (2) were mixed thoroughly and incubated at 37c^o for 5 minutes and then read the absorbance :

(D.BIL)=Absorbance of sample- Absorbance of blank

A={Δ A sample} – {Δ A blank}

3.8.3. Estimation of indirect bilirubin:

Was measured from the following equation :

(ID.BIL)=(T-BIL) - (D-BIL)

3.9. Data analysis:

Data were managed and analyzed using statistical package for the social sciences (SPSS) program.

Chapter four
4. Results

Primary stage:

Table (1) :Relationship between total bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer.

	Mean±SD Mg/dl	P-value
A	9.56±1.48	0.000
B	2.01±0.77	
A	9.56±1.48	0.000
C	1.48±0.49	
B	2.01±0.77	0.000
C	1.48±0.49	

A: bilirubin level before treatment
B: bilirubin level after surgery
C: bilirubin level after chemo_radio therapy

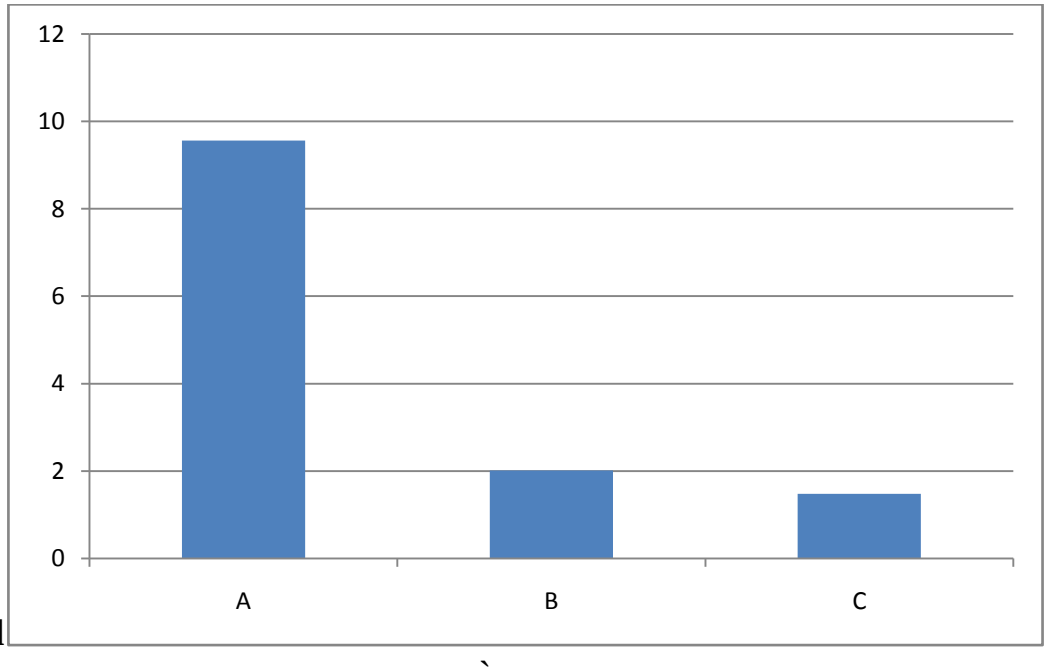


Fig (1): Relationship between total bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer

Results presented in table and fig (1) indicated that there was significant difference ($P \leq 0.000$) between total bilirubin level before treatment, after surgery and chemo-radiotherapy. Before treatment total bilirubin level was 9.56 mg/dl , after surgery was 2.01 mg/dl and after chemo radio therapy was 1.48 mg/dl. Also the results showed that there was significant difference ($P \leq 0.000$) between total bilirubin level after surgery and chemo-radiotherapy.

Table (2): Relationship between direct bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	5.56±1.40	0.000
B	0.80±0.60	
A	5.56±1.40	0.000
C	0.45±0.38	
B	0.80±0.60	0.007
C	0.45±0.38	

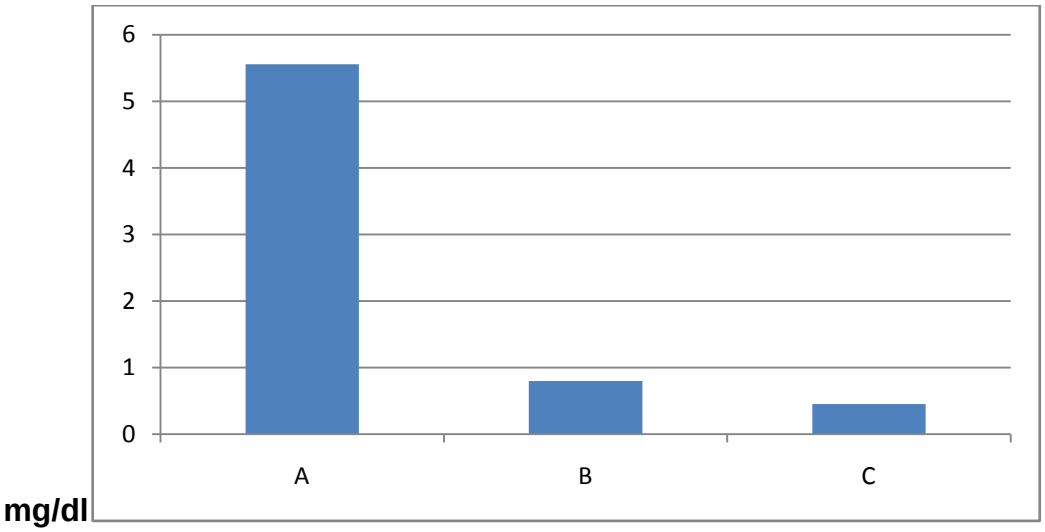


Fig (2): Relationship between direct bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer

Results presented in table and fig (2) indicated that there was significant difference (P≤0.000) between direct bilirubin level before treatment, after surgery and after chemo-radiotherapy. Before treatment direct bilirubin level was 5.56 mg/dl after surgery was 0.80 mg/dl and after chemo-radio therapy was 0.45 mg/dl .The results showed that there was significant difference (P≤0.007) between direct bilirubin levels after surgery and chemo-radio therapy.

Table (3): Relationship between indirect bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	3.96±1.26	0.000
B	1.19±0.46	
A	3.96±1.26	0.000
C	1.02± 0.37	
B	1.19±0.46	0.118
C	1.02± 0.37	

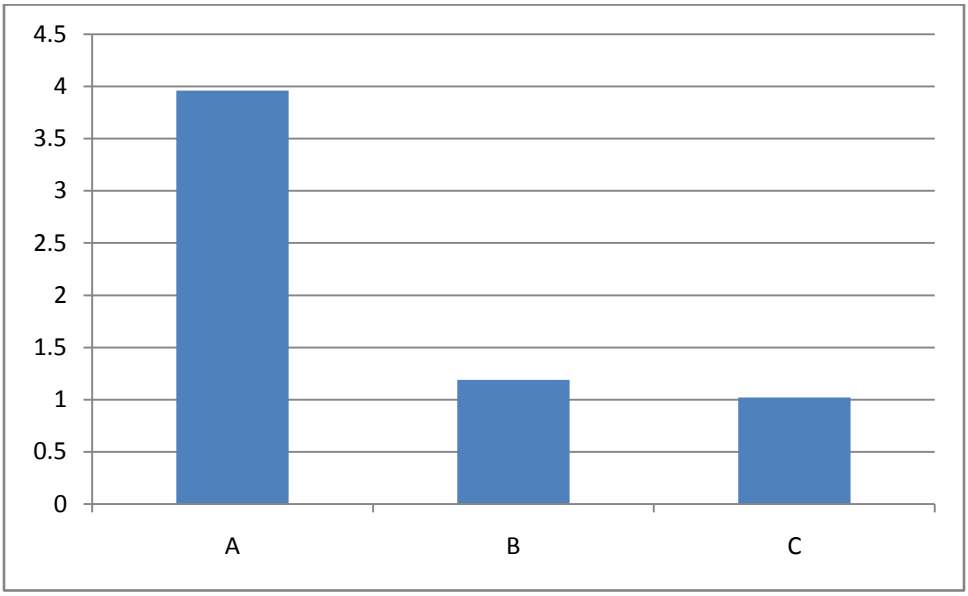


Fig (3): Relationship between indirect bilirubin level before treatment, after surgery and chemo- radio therapy in primary stage of pancreatic cancer

Results presented in table and fig (3) indicated that there was significant difference (P≤0.000) between indirect bilirubin level before treatment, after surgery and chemo- radio therapy .Before treatment indirect bilirubin was 3.96mg/dl after surgery was 1.19mg/dl and after chemo-radio therapy was 1.02mg/dl. The results showed that there was no significant difference between indirect bilirubin level after surgery and chemo-radio therapy.

Advance stage:

Table (4): Relationship between total bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	14.16±2.40	0.000
B	2.70±1.42	
A	14.16±2.40	0.000
C	3.75±1.230	
B	2.70±1.42	0.000
C	3.75±1.23	

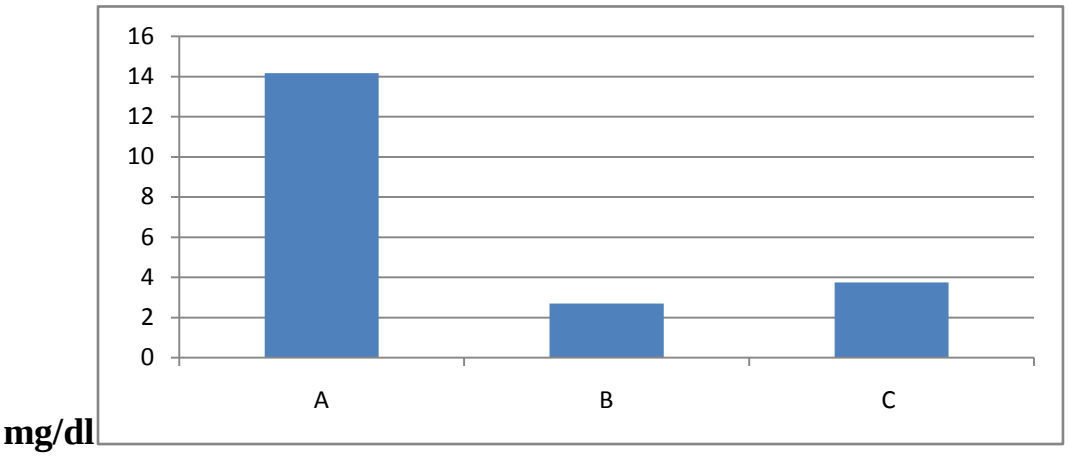
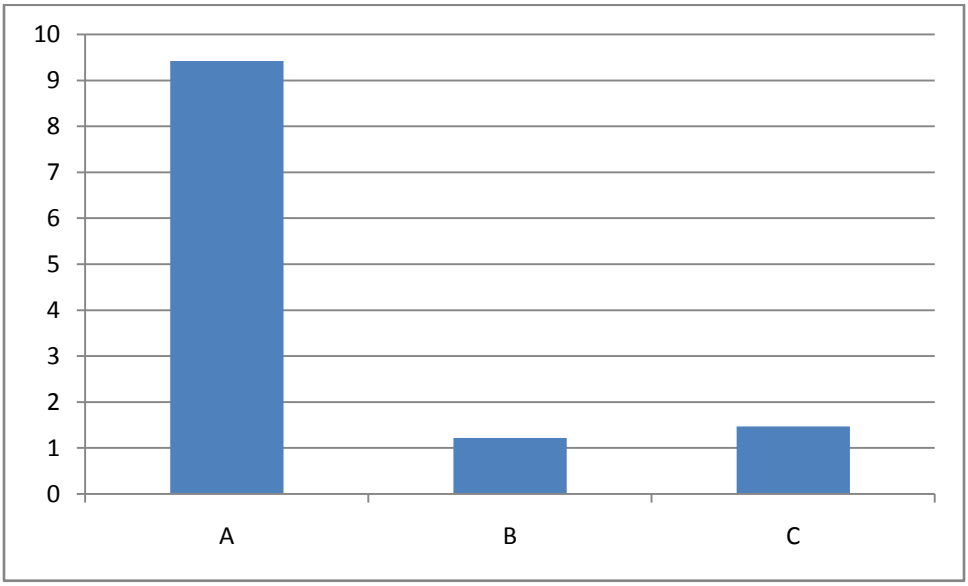


Fig (4) :Relationship between total bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

Results presented in table and fig (4) indicated that there was significant difference (P<0.000) between total bilirubin level before treatment, after surgery and chemo-radio therapy. Before treatment total bilirubin level was 14.16 mg/dl after surgery was 2.70 mg/dl and after chemo-radio therapy was 3.75 mg/dl. The results showed that there was significant difference (P≤0.000) between total bilirubin level after surgery and chemo-radio therapy.

Table (5): Relationship between direct bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	9.42±1.99	0.000
B	1.22±0.93	
A	9.42±1.99	0,000
C	1.47±0.79	
B	1.22±0.93	0.141
C	1.47±0.79	



mg/dl

Fig (5): Relationship between direct bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

Results presented in table and fig (5) indicated that there was significant difference (P≤0.000) between direct bilirubin level before treatment and after surgery and chemo-radio therapy. Before treatment direct bilirubin level was 9.42 mg/dl, after surgery was 1.22 mg/dl and after chemo-radio therapy was 1.47 mg/dl. The results showed that there was no significant difference between direct bilirubin level after surgery and chemo-radio therapy.

Table (6): Relationship between indirect bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	4.52±1.86	0.000
B	1.44±0.76	
A	4.52±1.86	0.000
C	2.28±0.83	
B	1.44±0.76	0.000
C	2.28±0.83	

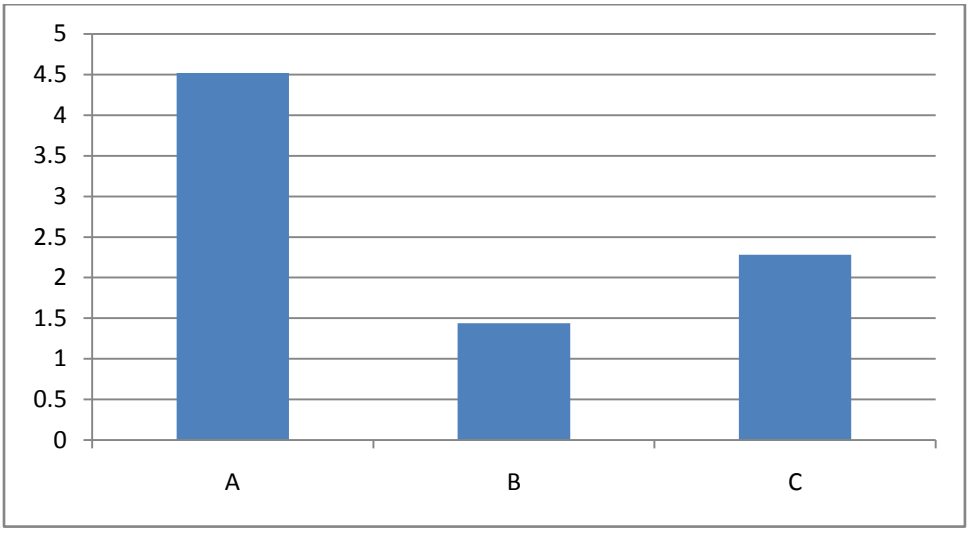


Fig (6): Relationship between indirect bilirubin level before treatment, after surgery and after chemo-radio therapy in advance stage of pancreatic cancer

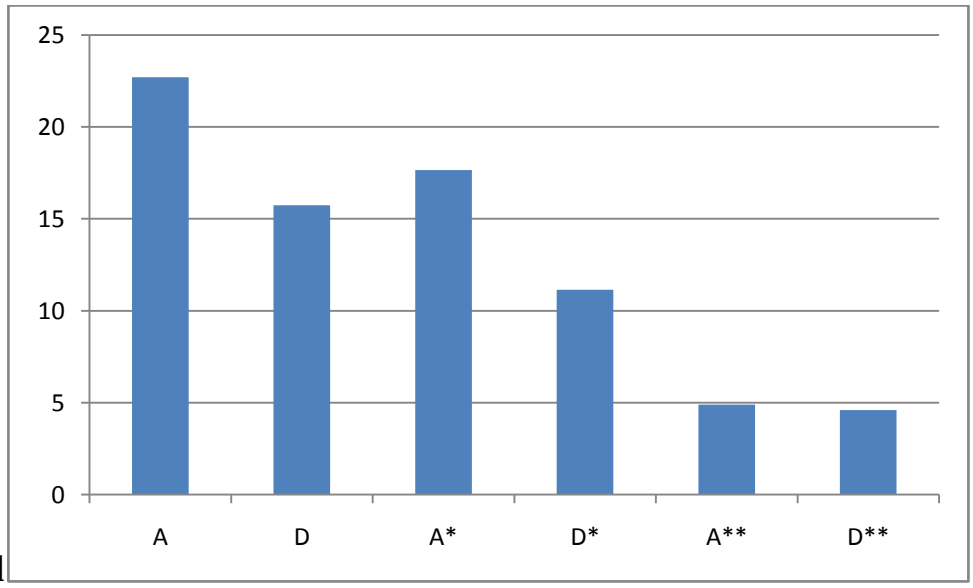
Results presented in table and fig (6) indicated that there was significant difference (P<0.000) between indirect level before treatment, after surgery and after chemo-radio therapy. Before treatment indirect bilirubin was 4.52 mg/dl after surgery was 1.44 mg/dl and after chemo-radio therapy was 2.28 mg/dl. The results showed that there was significant difference (P≤0.000) between indirect bilirubin level after surgery and chemo-radio therapy.

More advance:

Table (7): Relationship between bilirubin level before treatment and after chemotherapy in more advance stage of pancreatic cancer

	Mean±SD Mg/dl	P-value
A	22.70±5.46	0.000
D	15.74±6.21	
A*	17.66±5.59	0.000
D*	11.14±5.72	
A**	4.90±2.42	0.614
D**	4.60±1.84	

A=Total bilirubin before treatment
D=Total bilirubin after chemotherapy
A*=Direct bilirubin before treatment
D*= Direct bilirubin after chemotherapy
A**=Indirect bilirubin before treatment
D**= Indirect bilirubin after chemotherapy



Mg/dl

Fig (7): Relationship between bilirubin level before treatment and after chemotherapy in more advance of pancreatic cancer

Results presented in table and fig (7)indicated that there was significant difference (P<0.000) between total bilirubin level before treatment and after chemo therapy the total bilirubin level before treatment was 22.70 mg/dl and

after chemo therapy was 15.74 mg/dl, there was significant difference($P<0.000$) between direct bilirubin level before treatment and after chemo therapy the direct bilirubin before treatment was 17.66 mg/dl and after chemotherapy was 11.14 mg/dl, and there was no significant difference between indirect bilirubin level before treatment and after chemo therapy ,indirect bilirubin level before treatment was (4.9) mg/dl and after chemo therapy was (4.6)mg/dl.

Chapter five

5.1. Discussion:

Pancreatic cancer is the fourth leading cause of cancer death in the world.

The aim of this study is to see level of serum bilirubin in relation to pancreatic cancer before and after treatment according to age and gender.

Results presented in table and fig (1, 2, 3) indicated that there was highly significant difference between bilirubin level before treatment and after surgery and chemo-radio therapy in primary stage of pancreatic cancer. This indicated that the different methods of treatment lead to decrease bilirubin level. But the most effective treatment was after chemo-radio therapy. This result was in agreement with the study of [63],[64], [65] who found that after surgery, neo adjuvant chemotherapy and radiation have been effective than surgery in lowering bilirubin level in pancreatic cancer.

Result presented in table and fig (4, 5, 6) indicated that there was highly significant difference between bilirubin level before treatment and after surgery and chemo-radio therapy in advance stage of pancreatic cancer. This indicated that the different methods of treatment lead to decrease bilirubin level .But the most effective treatment was after surgery. This result was in agreement with the study of [27], [7], [47], ,[58], [59], [60] who said that before surgery ,neo adjuvant chemo-radio therapy may used in cases are considered to be borderline resectable in order to reduce the cancer to a level where surgery could be beneficial, the surgery more effective in this cases than chemo-radio therapy. The rationale for biliary decompression in patients with unresectable pancreatic cancer and obstructive cholestasis is

the normalisation of the bilirubin levels to allow palliative chemotherapy, and the prevention of other adverse outcomes such as cholangitis and frequent hospitalization According to the current German, European and American treatment guidelines, stent placement via endoscopic retrograde cholangiopancreatography (ERCP) is the preferred method for biliary decompression in these patients.In case ERCP is not possible, percutaneous transhepatic biliary drainage (PTCD) is recommended ,But disagreement with the study of [73] who found that the chemo-radio therapy is more effective in borderline resectable in lowering bilirubin level.

Results presented in table (7) indicated that there was significant difference between bilirubin level before treatment and after chemotherapy in more advance stage of pancreatic cancer. This result was in agreement with [27], [68] who said that in patients not suitable un resectable for curative surgery chemotherapy may be used to extend life or improve its quality on hyperbilirubineama . Gemcitabine was approved by the United States Food and Drug Administration (FDA) in 1997, after a clinical trial reported improvements in quality of life and a 5-week improvement in median survival duration in people with advanced pancreatic cancer.

Results presented in table (8, 9, 10, 11) in appendix indicated that there was no significant difference between bilirubin level before and after treatment in pancreatic cancer according to age and gender that mean bilirubin level was not affected by gender and age. There was no previous study concerning the affect of gender and age on bilirubin level in patients with pancreatic cancer which need further conformations. This result was in agreement with[9],[27],[25],[12],[15],[28],[20],[29],[30] who found that there were many studies related the pancreatic cancer to gender and age and with high

incidence of the cancer in male than female, and there was great relation related the bilirubin level to the patients age which appears in average over 60.

Result presented in table (12) in appendix indicated that was no significant difference between bilirubin level before treatment, after chemo-radio therapy and years (2015, 2016, 2017).But there was significant difference after surgery, after chemo therapy and years.

Conclusions

1- Elevated level of serum bilirubin in pancreatic cancer patients (ductal adenocarcinoma) due to blockage of common bile duct by tumor in the head of pancreas.
2- Effective treatment that lower bilirubin level in pancreatic cancer patients was after chemo-radio therapy in primary stage, after surgery in advance stage and after chemo therapy in more advance stage studied in(2015,2016,2017).
3- level of serum bilirubin in pancreatic cancer was not affected by gender and age in all 3 years.

Recommendations

1. Elevated level of bilirubin may related to pancreatic cancer so can used serum bilirubin as marker for detection pancreatic cancer.

2. The strongest risk factor for pancreatic cancer is increasing age. Risk is low in those aged between50-54 increasing sharply in those aged 75-79.

3. The disease slightly more common in men than women.

References

1. Warren KW, Braasch JW, Thum CW. Carcinoma of the pancreas. Surg Clin North Am 1968; 48:601-618.

2 .Steele GD Jr, Osteen RT, Winchester DP, et al. Clinical highlights from the National Cancer Data Base: 1994. Ca Cancer J Clin 1994: 44:71-80.

3. American Cancer Society. Cancer facts and figures. New York, 1987.

4. Hanahan D, Weinberg RA "The hallmarks of cancer",(January 2000). Cell.**100** (1): 57–70. PMID 10647931.

5.Hanahan D, Weinberg RA "The hallmarks of cancer"(January 2000),Cell.**100**(1)*57–70*.doi:10.1016/S0092-8674(00)816 PMID 10647931.

6.Hanahan D, Weinberg RA "Hallmarks of cancer: the next generation". Cell(March 2011),**144** (5): 646–74. doi*:*10.1016/j.cell.2011.02.013. PMID 21376230.

7.Vincent A, Herman J, Schulick R, Hruban RH, Goggins M (August 2011). "Pancreatic cancer" (PDF).Lancet.**378** (9791): 607–20. doi:10.1016/S0140-6736(10)62307-0. PMID 21620466. Archived from the original (PDF) on 12 January 2015.

8."Can pancreatic cancer be prevented?". American Cancer Society. 11 June 2014. Archived from the original on 13 November 2014.Retrieved 13 November 2014

9.Ryan DP, Hong TS, Bardeesy N (September 2014). "Pancreatic adenocarcinoma" (PDF). N. Engl. J. Med. **371** (11): 1039–49. doi:10.1056/NEJMra1404198. PMID 25207767. Archived from the original (PDF) on 26 December 2014.

10 World Cancer Report. World Health Organization. 2014. Chapter 5.7. ISBN 92-832-0429-8.

11.Cancer Facts & Figures (PDF). American Cancer Society. 2010. Archived from the original (PDF) on 14 January 2015. Retrieved 5

December 2014. See p. 4 for incidence estimates, and p. 19 for survival percentages.

12. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators. (8 October 2016). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet.**388** (10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6. PMC 5055577.PMID 27733282

13.Bridenbaugh LD, Moore DC, Campbell DD, et al. Management of upper abdominal cancer pain: treatment with celiac plexus block with alcohol. JAMA 1964; 190:99-102.

14.Staff of the Comprehensive Cancer Center's Multidisciplinary PancreaticCancer Program provided information for this handbookGI Oncology Program, Patient Education Program, Gastrointestinal Surgery Department,Medical Oncology, Radiation Oncology and Surgical Oncology, ©2012 The Regents of the University of Michigan Document #0231/Revised 11/2012

15."Bilirubin blood test", U.S. National Library of Medicine

16.Orabys Illustrated Reviews of Biochemistry By Said Oraby (III)

17. Harris, RE (2013). "Epidemiology of pancreatic cancer".Epidemiology of Chronic Disease.Jones & Bartlett. pp. 181–190. ISBN 978-0-7637-8047-0.Archived from the original on 24 June 2016.

18.Öberg K, Knigge U, Kwekkeboom D, Perren A (October 2012). "Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Annals of Oncology. 23 Suppl 7: vii124–30. doi:10.1093/annonc/mds295. PMID 22997445.Archived from the original on 11 October 2013.

19.Handbook of Pancreatic Cancer. New York: Springer. 2009. p. 288. ISBN 978-0-387-77497-8.Archived from the original on 10 September 2017.Retrieved 12 June 2016.

20. Ferrucci L, Giallauria F, Guralnik JM. Epidemiology of aging. Radiol Clin North Am. 2008;46(4):643–52. [PMC free article] [PubMed]

21.Strasberg, S.M.; Drebin, J.A., Linehan, D. Radical antegrade modular pancreatosplenectomy. Surgery. **2003**, 133, 521-527.

22.Burns WR, Edil BH "Neuroendocrine pancreatic tumors: guidelines for management and update". Current treatment options in oncology. (March 2012), **13** (1): 24–34. doi:10.1007/s11864-011-0172-2. PMID 22198808.

23. Copping J, Willix R, Kraft R. Palliative chemicalsplanchnicectomy.Arch Surg 1969; 98:418-420.
24 De La Cruz MS, Young AP, Ruffin MT ."Diagnosis and management of pancreatic cancer"(April 2014),**89** (8): 626–32. PMID 24784121

25.Bond-Smith G, Banga N, Hammond TM, Imber CJ. "Pancreatic adenocarcinoma". BMJ (Clinical research ed.) (2012),**344**: e2476. doi:10.1136/bmj.e2476. PMID 22592847.

26. Alberts, SR; Goldberg, RM "Chapter 9: Gastrointestinal tract cancers". In Casciato, DA; Territo, MC. Manual of clinical oncology.Lippincott Williams & Wilkins. ISBN 978-0-7817-6884-9(2009),pp. 188–236

27.Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH ."Recent progress in pancreatic cancer". CA: A Cancer Journal for Clinicians. (September 2013),**63** (5): 318–48. doi:10.3322/caac.21190. PMC 3769458 .PMID 23856911.

28. Zhan HX, Xu JW, Wu D, Zhang TP, Hu SY. "Pancreatic cancer stem cells: New insight into a stubborn disease". (2015), Cancer Lett.**357** (2): 429–37. doi:10.1016/j.canlet.2014.12.004. PMID 25499079.

29. Stoita A, Penman ID, Williams DB ."Review of screening for pancreatic cancer in high risk individuals".(May 2011), World J. Gastroenterol.**17** (19): 2365–71. doi:10.3748/wjg.v17.i19.2365. PMC 3103788 .PMID 21633635.

30.GBD 2015 Mortality and Causes of Death, Collaborators. "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015".(8 October 2016),Lancet.**388** (10053): 1459–1544. doi:10.1016/s0140-6736(16)31012-1. PMC 5388903 .PMID 27733281.

31.Bussom S, Saif MW (5 March 2010). "Methods and rationale for the early detection of pancreatic cancer.Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22–24, 2010".Journal of the Pancreas.**11** (2): 128–30. PMID 20208319.Archived from the original on 8 December 2014.

32. Reber HA. Palliative operations for pancreatic cancer. In Howard JM, Jordan GL Jr, Reber HA, eds. Surgical Diseases of the Pancreas. Philadelphia: Lea & Febiger, 1987.

33.Delpu Y, Hanoun N, Lulka H, Sicard F, Selves J, Buscail L, Torrisani J, Cordelier P (2011). "Genetic and epigenetic alterations in pancreatic carcinogenesis".CurrGenomics.**12**(1):15–24. doi:10.2174/138920211794520132. PMC 3129039 .PMID 21886451.

34.Rooney, SL; Shi, J."IntraductalTubulopapillary Neoplasm of the Pancreas: An Update From a Pathologist's Perspective". Archives of pathology & laboratory medicine. (October 2016), **140** (10): 1068–73. doi:10.5858/arpa.2016-0207-RA. PMID 27684978.

35. Malangoni MA, McCoy DM, Richardson JD, Flint LM. Effective palliation of malignant biliary obstruction. Ann Surg 1985; 201: 554-557.

36. De La Cruz MS, Young AP, Ruffin MT. "Diagnosis and management of pancreatic cancer".(April 2014), **89** (8): 626–32. PMID 24784121.

37.Cascinu S, Falconi M, Valentini V, Jelic S. "Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Annals of Oncology. (May 2010), 21 Suppl 5: v55–8. doi:10.1093/annonc/mdq165. PMID 20555103.Archived from the original on 17 August 2011.

38."Staging of pancreatic cancer". American Cancer Society. 11 June 2014. Retrieved 29 September 2014.

39."Neuroendocrine tumors, NCCN Guidelines Version 1.2015". NCCN Guidelines. National Comprehensive Cancer Network, Inc. 11 November 2014. Retrieved 25 December 2014.

40.Zyromski, Nicholas J.; Nakeeb, Attila; Lillemoe, Keith D. (2010).Silberman, Howard; Silberman, Allan W., eds. Principles and practice of surgical oncology : multidisciplinary approach to difficult

problems Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. Chapter 35.ISBN 978-0-7817-6546-6.Archived from the original on 6 February 2015.Retrieved 3 November 2014.

41.Warren KW, Braasch JW, Thum CW. Carcinoma of the pancreasSurgClin North Am 1968; 48:601-618.

42.Krain LS. The rising incidence of cancer of the pancreas-furtherepidemiological studies.J Chronic Dis 1971; 23:685-690.

43.American Cancer Society. Cancer facts and figures. New York, 1987. 5. Singh SM, Reber HA. Surgical palliation for pancreatic cancer. InReber HA, ed. Surgery Clinics of North America: The Pancreas.Philadelphia: WB Saunders, 1989, pp. 599-61 1.

44.Singh SM, Reber HA. Surgical palliation for pancreatic cancer. InReber HA, ed. Surgery Clinics of North America: The PancreasPhiladelphia: WB Saunders, 1989, pp. 599-61 1.

45. Aston SJ, Longmire WP Jr. Pancreatico-duodenal resection. ArchSurg

1973; 106:813-817.

46.Tanaka T, Kodama M, Seikoh R, et al. Surgical treatment for periampullarycarcinoma: a study of 129 patients. Hiroshima J MedSci 1984; 33:179-182.

47. Sun, J; Yang, Y; Wang, X; Yu, Z; Zhang, T; Song, J; Zhao, H; Wen, J; Du, Y; Lau, WY; Zhang, Y. "Meta-analysis of the efficacies of extended and standard pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas"(October 2014).**38** (10): 2708–15. doi:10.1007/s00268-014-2633-9. PMID 24912627.

48. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut2005;54:Suppl 5:v1-v16

49. Phoa SS, Reeders JW, Rauws EA, De Wit L, Gouma DJ, Lameris JS. Spiral computed tomography for preoperative staging of potentially resectable carcinoma of the pancreatic head. Br J Surg1999;86:789-794

50. van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. J GastrointestSurg2009;13:814-820

51. Kimmings AN, van Deventer SJ, Obertop H, Rauws EA, Huibregtse K, Gouma DJ. Endotoxin, cytokines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage.Gut2000;46:725-731

52.Pannala R, Basu A, Petersen GM, Chari ST (January 2009). "New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer". Lancet Oncol.**10** (1): 88–95. doi:10.1016/S1470-2045(08)70337-1. PMC 2795483 .PMID 19111249

53.Ryan DP, Hong TS, Bardeesy N: Pancreatic adenocarcinoma. N Engl J Med 2014;371:1039-1049

54.Seufferlein T, Bachet JB, Van Cutsem E, Rougier P; ESMO Guidelines Working Group: Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(suppl 7):vii33-vii40.

55. Boulay BR, Parepally M: Managing malignant biliary obstruction in pancreas cancer: choosing the appropriate strategy. World J Gastroenterol 2014;20:9345-9353.

56.Strasberg SM, Gao F, Sanford D, Linehan DC, Hawkins WG, Fields R, Carpenter DH, Brunt EM, Phillips C: Jaundice: an important, poorly recognized risk factor for diminished survival in patients with adenocarcinoma of the head of the pancreas. HPB (Oxford) 2014;16:150-156.

57.Nakata B, Amano R, Kimura K, Hirakawa K: Comparison of prognosis between patients of pancreatic head cancer with and without obstructive jaundice at diagnosis. Int J Surg 2013;11:344-349.

58.National Comprehensive Cancer Network (NCCN): Clinical practice guidelines

59.Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P: Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut 1989;30:1132-1135.

60.Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O'Beirne J, Fox R, Skowronska A, Palmer D, Yeo W, Mo F, Lai P, Inarrairaegui M, Chan SL, Sangro B, Miksad R, Tada T, Kumada T, Toyoda

H: Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach - the ALBI grade. J ClinOncol 2015;33:550-558.

61. Satake K, Nishiwaki H, Yokomatsu H, et al. Surgical curability and prognosis for standard versiss extended resections for T, carcinoma of the pancreas. Surg Gynecol Obstet 1992; 175:259-265.

62.Will U, Meyer F: [Endoscopic ultrasonography (EUS)-guided transluminalcholangiodrainage (EUCD) - a novel option of interventional endoscopy in the interdisciplinary management of obstructive jaundice]. ZentralblChir 2012;137:2031.

63. Evans, D.B., T.A. Rich, D.R. Byrd, et al. Preoperativechemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg, 1992. 127(11): 1335-1339.

64. Evans, D.B., G.R. Varadhachary, C.H. Crane, et al. Preoperativegemcitabine-based chemoradiation for patients with resectableadenocarcinoma of the pancreatic head .J ClinOncol, 2008. 26(21):3496-3502.

65.Varadhachary,G.R.,R.A.Wolff,C.H.Crane,etal. Preoperativegemcitabine and cisplatin followed by gemcitabine-basedchemoradiationfor resectable

66. Staff of the Comprehensive Cancer Center's Multidisciplinary PancreaticCancer Program provided information for this handbookGI Oncology Program, Patient Education Program, Gastrointestinal Surgery Department,Medical Oncology, Radiation Oncology and Surgical Oncology, ©2012 The Regents of the University of Michigan Document #0231/Revised 11/2012.

67.Seufferlein T, Bachet JB, Van Cutsem E, Rougier P (October 2012). "Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Annals of Oncology. 23 Suppl 7: vii33–40. doi:10.1093/annonc/mds224. PMID 22997452.

68.Thota R, Pauff JM, Berlin JD (January 2014). "Treatment of metastatic pancreatic adenocarcinoma: a review". Oncology (Williston Park, N.Y.).**28** (1): 70–4. PMID 24683721.

69. Ryan, DP "Chemotherapy for advanced exocrine pancreatic cancer: (8 July 2014). Topic 2475, Version 46.0"

70."Cancer Drug Information: FDA Approval for Erlotinib Hydrochloride". National Cancer Institute. National Institutes of Health. 3 July 2013. Archived from the original on 29 November 2014.Retrieved 5 December 2014.

71 Borazanci E, Von Hoff DD; Von Hoff, DD (September 2014). "Nab-paclitaxel and gemcitabine for the treatment of people with metastatic pancreatic cancer". Expert Rev GastroenterolHepatol. **8** (7): 739–47. doi:10.1586/17474124.2014.925799. PMID 24882381.

Appendix

Table(8): Effect of gender on total bilirubin (T.bil) level on pancreatic cancer patients:

		Mean±SD	P-value
A	Male	12.59±3.17	0.414
	Female	11.85±2.82	
B	Male	2.32±0.88	0.285
	Female	2.72±1.90	
C	Male	2.99±1.48	0.352
	Female	2.58±1.54	

Result presented in table (8) there was no significant difference before and after treatment in on (T.bil) according to gender.

Table(9) : Effect of gender on direct bilirubin (D.bil) level on pancreatic cancer patients:

		Mean±SD	P-value
A	Male	8.04±2.71	0.625
	Female	7.66±2.31	
B	Male	1.01±0.55	0.455
	Female	1.20±1.33	
C	Male	1.06±0.79	0.858
	Female	1.11±0.93	

Result presented in table (9) there was no significant difference before and after treatment in on (D.bil) according to gender.

Table(10) : Effect of gender on indirect bilrubin(ID.bil) level on pancreatic cancer patients:

		Mean±SD	P-value
A	Male	4.37±1.73	0.642
	Female	4.14±1.54	
B	Male	1.30±0.60	0.434
	Female	1.46±0.83	
C	Male	1.92±0.99	0.093
	Female	1.46±0.65	

Result presented in table (10) there was no significant difference before and after treatment in on (ID.bil) according to gender.

Table(11): Effect of age on bilirubin (bil) level on pancreatic cancer patients

Bilirubin mg/dl		Age group (year) Mean±SD			P. value
		Less than 40	40-60	More than 60	
A	Total	16.76±1.79	14.64±0.97	15.99±1.09	0.491
	Direct	11.98±1.67	10.38±0.93	11.08±1.05	0.677
	Indirect	4.80±0.37	3.99±0.33	4.82±0.36	0.171
B	Total	2.11±0.18	2.84±0.34	2.17±0.17	0.121
	Direct	0.66±0.11	1.24±0.22	1.06±0.14	0.192
	Indirect	1.45±0.13	2.03±0.43	1.09±0.13	0.084
C	Total	2.26±0.35	3.27±0.31	2.75±0.33	0.178
	Direct	0.80±0.19	1.21±0.18	1.07±0.18	0.422
	Indirect	1.46±0.18	2.05±0.20	1.68±0.20	0.175
D	Total	18.09±1.96	13.28±1.51	16.20±1.55	0.172
	Direct	12.95±1.54	8.91±1.65	11.76±1.42	0.208
	Indirect	5.14±0.71	4.37±0.39	4.44±0.42	0.529

Result presented in table (11) there was no significant difference before and after treatment in bilirubin level and age.

Table 12. Bilirubin parameters of the pancreatic patients among the study period

Bilirubin parameters		Study period (year)			Overall	P. value
		2015	2016	2017		
A	Total	16.12±1.51	14.55±1.11	15.91±0.98	15.62±0.68	0.679
	Direct	11.18±1.53	10.05±0.98	11.31±0.93	10.98±0.65	0.719
	Indirect	4.94±0.42	4.40±0.59	4.41±0.25	4.50±0.21	0.648
B	Total	3.53±0.74	2.69±0.36	2.10±0.12	2.44±0.17	0.005
	Direct	1.70±0.52	0.91±0.15	0.96±0.10	1.06±0.11	0.044
	Indirect	2.98±1.07	1.78±0.23	1.13±0.07	1.55±0.19	0.002
C	Total	3.22±0.46	2.89±0.43	2.79±0.26	2.88±0.20	0.752
	Direct	1.50±0.29	0.83±0.16	1.05±0.14	1.08±0.11	0.187
	Indirect	1.72±0.20	2.06±0.34	1.74±0.15	1.80±0.12	0.585
D	Total	10.08±1.45	13.59±1.32	19.38±1.31	15.90±0.99	0.001
	Direct	5.50±1.26	8.98±1.40	14.73±0.96	11.28±0.90	0.000
	Indirect	4.58±0.36	4.61±0.43	4.65±0.50	4.62±0.29	0.997

Result presented in table (12) showed that there was no significant difference between level of bilirubin before treatment and years . But there was significant difference (P≤0.005),(P≤0.044)and(P≤0.002)respectively after surgery between (T.bil) in 2015,2016 and 2017 ,in 2015 (T.bil) was3.53mg/dl ,in was 2016 2.69mg/dl and in 2017 was 2.10mg/dl (D.bil) in 2015 was 1.70mg/dl ,In

2016 was (0.91)mg/dl and in 2017 was(0.96)mg/dl,(In.bil) in 2015 was (2.98)mg/dl, in 2016 was(1.78)mg/dl and in 2017 was(1.13)mg/dl . But there was no significant difference between level of bilirubin and years after chemo-radio .But there was significant difference (P≤0.001),(P≤0.000) respectively after chemo therapy therapy between (T.bil) in 2015,2016 and 2017, In 2015(T.bil) was 10.08mg/dl,In 2016was 13.59 in 2017 was 19.38mg/dl .(D.bil)was in2015 5.50 mg/dl ,in 2016 was 8.98mg/dl and in 2017 was 14.73 mg/dl but there is no significant difference between level of indirect bilirubin after chemo therapy and years.