CLINICAL, IMAGING AND PATHOLOGICAL CHARACTERISTICS OF PANCREATIC TUMORS AMONG ADULT PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL IN ELDORET, KENYA

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MASTERS OF MEDICINE DEGREE IN GENERAL SURGERY

of

MOI UNIVERSITY

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Dissertation submitted in partial fulfillment of the requirements for the award of the degree of

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DECLARATION

I declare that this research is my original work and to the best of my knowledge has not been presented at any other university/institution for examination.

Sign_____ Date_____

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DECLARATION BY SUPERVISORS

This thesis has been submitted to Moi University with our approval as University supervisors.

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DEDICATION

To my mother Patricia Akinyi, for her continuous prayers for the success of her children.

To my father Joseph Akello, for motivating me to pursue a career in the sciences.

To my dear wife Hilda and son Justin, you have endured my absence through the many years I have had to be away.

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ABSTRACT

Background: Pancreatic cancer is a leading cause of cancer-related death globally. Kenya reports a uniquely high incidence of pancreatic cancer in the East-African region. Increased recognition of mass forming chronic and autoimmune pancreatitis in surgical specimens in other populations has led to increased uptake of preoperative pancreatic biopsy. Pancreatic tumors have hitherto not been studied to guide approach to patient management in our setting.

Objective: To describe the clinical, imaging and pathological characteristics of pancreatic tumors among adult patients at Moi Teaching and Referral Hospital.

Methods: This was a cross sectional study conducted among 39 adult patients who presented with pancreatic tumors at Moi Teaching and Referral Hospital (MTRH) between August 2018 and July 2019. All study participants underwent imaging guided pancreatic biopsy except one who underwent pancreatic resection. Demographics, clinical signs and symptoms, preoperative imaging and histological findings for all participants were collected for description, analysis and discussion. Mean, median, frequencies and percentages were used to describe the clinical, imaging and laboratory characteristics of pancreatic tumors.

Results: Twenty-one (54 %) of the participants were male and eighteen (46 %) were female. The mean age was 55.8±13.5 years and median age was 58 years (IQR 49 -67 years). There was a low incidence of smoking, alcohol use, family history of cancer, individual history of cancer and pancreatitis. The most common symptoms were abdominal pain at 89.5 % (n = 35), mostly in the epigastrium and right upper quadrant, and yellowness of eyes at 79.5 % (31). The mean duration of symptoms was 3.5 months with a median duration of 2 months. About 71 % (n = 28) of all tumors were of the head and 87 % (n = 34) were solid. Seventy-four percent (74 %, n = 29) of tumors were more than 4 cm. Seventy-nine percent (79.5 %, n = 31) of tumors were pancreatic cancer, 8.6 % (n=3) were metastases to the pancreas and 10.3 % (n = 4) were benign conditions. Among the subgroup with pancreatic cancer, 19 % were below the age of 50 years.

Conclusions: Majority of the patients presented with advanced pancreatic cancer at a younger age than the global average. Large pancreatic head masses comprised the vast majority of tumors. Despite the bulk of tumors being primary pancreatic cancers, there was a significant proportion of metastatic cancers and benign conditions.

Recommendations: Further studies to look at why patients with pancreatic cancer are presenting at a younger age and with advanced disease. Tissue diagnosis should be sought for all patients with pancreatic tumors to enable individualized patient care.

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LIST OF ABBREVIATIONS

ACCs	Acinar Cell Carcinomas
AFP	Alpha Fetoprotein
AIP	Autoimmune pancreatitis
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CA19-9	carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CT	Computer Tomography, imaging modality
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
EUS FNA	Endoscopic ultrasound guided Fine Needle Aspiration
H&E	Hematoxylin-Eosin
ICD	International Coding of Diseases
IPMN	intraductal papillary mucinous neoplasm
MCN	mucinous cystic neoplasms
MDCT	Multi-Detector-row Computed Tomography
MRCP	MRI cholangiopancreatography

MRI	Magnetic Resonance imaging
MTRH	Moi Teaching and Referral Hospital
PaniN	pancreatic intraepithelial neoplasia
PanNEC	Pancreatic neuroendocrine carcinoma
PDAC	Pancreatic adenocarcinoma
PET	Positron Emission Tomography
PNETs	Pancreatic neuroendocrine tumors
SCAs	Solid Cystadenoma(s)
SPENs	Solid pseudopapillary epithelial neoplasms
TBil	Total Bilirubin
US	Ultrasound scanning, imaging modality
VIP	Vasoactive intestinal peptide
WHO	IARC
WHO	IARC - World Health Organisation-International Agency for Research in Cancer
Y-GT	Gamma-Glutamyl Transferase

CHAPTER ONE: INTRODUCTION

1.1 Background

Tumors of the pancreas carry a wide spectrum of pathology, with varying prognoses and in some cases, different therapies (Kamisawa et al., 2008). The most lethal of these tumors is pancreatic cancer which is a leading cause of cancer death and has been on the rise over the years (GLOBOCAN, 2020; Wong et al., 2017). Non-neoplastic tumor-like pathologies have been shown to mimic pancreatic neoplasms in their presentation and often modern imaging and available tumor markers are unable to distinguish them. However, with a mortality rate close to its incidence, Pancreatic cancer (PC) remains the most important pathology to rule out in pancreatic tumors.

The age-standardized incidence rates for PC per 100 000 have increased globally for both sexes by 9% (5.31 to 5.78) with a larger relative increase in developing (29% from 2.84 to 3.66) compared with developed countries (10% from 8.6 to 9.54) (*The Global Burden of Cancer 2013*, 2015). In East Africa, Kenya has the highest incidence and mortality rates (GLOBOCAN, 2020; Korir et al., 2015). Variable incidence across continents and regions, has been attributed to the environmental factor in its etiology as well as differences in demographics (Wong et al., 2017). Several environmental risk factors have been implicated in the risk of pancreatic cancer, including tobacco use which has been attributed the highest risk, diet, alcohol and high caloric intake.

Surgery is curative for benign and some malignant pancreatic neoplasms and confers improved survival in advanced pancreatic cancer (Lopez et al., 2014; Mohammed et al., 2014). Therefore most guidelines have recommended upfront surgery for tumors that can be resected (Tempero et al., 2019). Conversely, surgical resection for a non-neoplastic tumor of autoimmune pancreatitis is not first line management and may be

undesirable (Al-hawary et al., 2013; Kamisawa et al., 2016). Notably, increased recognition of mass forming chronic or autoimmune pancreatitis which closely mimic pancreatic cancer, has caused a shift from this practice in certain populations. This has led to more uptake of pre-operative pancreatic biopsy which has proved to be safe (Terracciano et al., 2021).

A look at the local practice shows a grim picture whose hallmark is inadequate patient evaluation. Most diagnosis of PC was based on CA 19-9 in presence of a mass, as is captured by data at the Eldoret cancer registry. Most of the patients then undergo interventions without a definitive diagnosis. Despite the availability of both expertise and equipment at MTRH, uptake of pancreatic biopsy had remained low. If the situation remained, all patients presenting with pancreatic masses would likely be managed for PC. The biggest challenge to pancreatic biopsy being the fear of complications following biopsy. The data at the Eldoret cancer registry had only the anatomical location of tumor without histopathogy. This situation leads to stagnation in care and even research in the care of patients with pancreatic tumors.

Locally, there has been very little surgical intervention other than for palliation due to late presentation by patients coupled with limited human resource and capacity for comprehensive work-up. However, the increased accessibility to CT scans and availability of interventional radiologists in Kenya has opened opportunities for comprehensive evaluation of these patients to adequately characterize these tumors to guide management. Further, proper description of the behavior of these tumors will guide early detection of malignant tumors (Porta et al., 2005).

This study describes the clinical, imaging and pathological features of pancreatic tumors among patients seen at Moi Teaching and Referral Hospital (MTRH).

1.2 Problem Statement

Tumors of the pancreas carry a wide spectrum of potential pathology, with very different prognoses and in some cases, different therapies. There is increased recognition of benign conditions mimicking pancreatic cancer, which do not require surgery primarily, a finding that has led to increased uptake of pre-operative pancreatic biopsy in other regions of the world. Despite these findings, local patient evaluation practices remain incomplete with most diagnosis being based on presence of a pancreatic mass and an elevated CA 19-9. It is likely that the prevailing circumstances lead to suboptimal care and stagnation.

Despite Kenya reporting a uniquely high incidence and mortality rate of pancreatic cancer in the region, these tumors remain unstudied locally.

1.3 Justification

There is a lack of data on the characteristics of pancreatic tumors in our region to back the entrenchment of a management protocol that promotes adequate patient evaluation.

1.4 Research Questions

1. What are the clinical manifestations of pancreatic tumors in patients at MTRH?
2. What are the CT scan features of pancreatic tumors in MTRH?
3. What are the laboratory, cytological and histopathological characteristics of pancreatic tumors in MTRH?

1.5 Research Objectives

1.5.1 Broad Objectives

To describe the clinical, pathological and imaging characteristics of pancreatic tumors in MTRH

1.5.2 Specific Objectives

1. To describe the clinical presentation of pancreatic tumors in MTRH.
2. To describe the CT scan features of pancreatic tumors in MTRH.
3. To describe the laboratory, cytological and histopathological characteristics of pancreatic tumors in MTRH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Tumors of the pancreas carry a wide spectrum of pathology, with different prognoses and therapies (Kamisawa et al., 2008). At the histologic level, neoplasms of the pancreas can arise from ductal cells, acinar cells, or islet cells. Some pancreatic neoplasms appear to arise from primitive cells that have the potential to differentiate along several lines, giving rise to complex tumors with mixed cell types. Some pancreatic tumors are highly lethal making them one of the leading causes of cancer related deaths globally (Siegel et al., 2017). In contrast other types are completely curable or have good long-term prognosis (Norton, 1999; Norton et al., 2006).

A patient who presents with signs and symptoms suggesting a pancreatic tumor typically undergoes initial imaging with abdominal ultrasound or CT scanning. When a pancreatic mass is identified, it may represent an inflammatory mass, benign process or malignancy (Kamisawa et al., 2008). For example, mass forming autoimmune pancreatitis and pancreatic cancer have many common clinical features, such as tendency to occur in older people (aged ≥60 years) painless jaundice, development of new-onset diabetes mellitus, and raised levels of serum tumor markers (Al-hawary et al., 2013; Kamisawa et al., 2008). Often, modern imaging is not able to distinguish these lesions. When determined to be resectable, current guidelines recommend upfront surgery whereas unresectable tumors are recommended to undergo pancreatic biopsy.

Often within a setting of limited resources, patients presenting with suspected pancreatic tumors risk being labeled pancreatic cancer particularly if they fit the clinical picture. This denies patients the chance for a definitive diagnosis and the benefit of a less serious diagnosis.

The identification of benign and malignant conditions of the pancreas that are favorable surgical challenges with excellent long-term outcomes has brought in new interest in the diagnosis and management of tumors of the pancreas (Fritz et al., 2012). Elsewhere in the world, in-depth description of pancreatic cancer has specifically led to improvement in the care and survival.

Pancreatic tumors remain uncharacterized in Kenya and the wider region. This is despite Kenya having the highest reported incidence and mortality rates of pancreatic cancer in the East African region. The age standardized incidence and mortality rates for Kenya stand at 2.9 and 2.8 respectively in sharp contrast to Tanzania with rates averaging 0.2 (WHO-IARC, 2012). This glaring difference in rates may partly be explained by distribution of environmental factors among them tobacco use, alcohol and dietary habits. However it is also important to note that due to a paucity of studies in the region, these are estimates generated from weighted averages across countries (WHO-IARC, n.d.). Even so, these findings raise important questions on the epidemiology of pancreatic cancer in the region.

2.2 Anatomy and Physiology of the pancreas

The pancreas is retroperitoneal mixed exocrine and endocrine gland lying transversely across the posterior abdominal wall lying behind the stomach from the curve of the duodenum to the splenic hilum. It can be divided into parts; head, neck, body and tail. In an adult, the pancreas weighs 75 to 100 g and is about 15 to 20 cm long. The fact that the pancreas is situated so deeply in the abdomen and is sealed in the retroperitoneum explains the poorly localized and sometimes ill-defined nature with which pancreatic pathology presents. Patients with pancreatic cancer without bile duct obstruction usually present after months of vague upper abdominal discomfort, or no

antecedent symptoms at all. Due to its retroperitoneal location, pain associated with pancreatitis often is characterized as penetrating through to the back.

2.3 Surface anatomy

The head lies within the curve of the duodenum, the neck along the transpyloric plane behind the pylorus. The body is represented by a line from the neck behind the pylorus, which extends 10 cm to the left slightly above the transpyloric plane and the tail lies above the meeting of the transpyloric and the left lateral planes.

2.4 Relations of the pancreas

The head of the pancreas lies in the C-loop of the duodenum lying behind the transverse colon and mesocolon and coils of jejunum. Posterior to the head are the inferior vena cava, terminal parts of the renal veins, the right renal vessels, the right crus of the diaphragm, the common bile duct which may be embedded in its substance. The uncinate process is a prolongation from the lower and left parts of the head anterior to it are the superior mesenteric vessels and posterior is the abdominal aorta. The neck is related anteriorly to the lesser sac which separates the neck from the pylorus and the first inch of the first part of the duodenum. Posterior to the neck is the union of the splenic and superior mesenteric veins to form the portal vein in front of the inferior vena cava.

The body and tail of the pancreas lie just anterior to the splenic artery and vein. The vein runs in a groove on the back of the pancreas and is fed by multiple fragile venous branches from the pancreatic parenchyma. These branches must be ligated to perform a spleen-sparing distal pancreatectomy. The splenic artery runs parallel and just superior to the vein along the posterior superior edge of the body and tail of the pancreas. The splenic artery often is tortuous. The body of the pancreas overlies the

aorta at the origin of the superior mesenteric artery. The anterior surface of the body of the pancreas is covered by peritoneum. Once the gastrocolic omentum is divided, the body and tail of the pancreas can be seen along the floor of the lesser sac, just posterior to the stomach. Advanced cancers of the pancreas invade the vessels in close relation to it. This complicates and determines the resectability of such tumors.

2.5 Pancreatic duct anatomy

The pancreas is formed by the fusion of a ventral and dorsal bud. The duct from the smaller ventral bud, which arises from the hepatic diverticulum, connects directly to the common bile duct. The duct from the larger dorsal bud, which arises from the duodenum, drains directly into the duodenum. The duct of the ventral anlage becomes the duct of Wirsung, and the duct from the dorsal anlage becomes the duct of Santorini.

In about one third of patients, the bile duct and pancreatic duct remain distinct to the end of the papilla, the two ducts merge at the end of the papilla in another one third, and in the remaining one third, a true common channel is present for a distance of several millimeters. Commonly, the duct from the dorsal anlage, the duct of Santorini, persists as the lesser pancreatic duct, and sometimes drains directly into the duodenum through the lesser papilla just proximal to the major papilla. In approximately 30% of patients, the duct of Santorini ends as a blind accessory duct and does not empty into the duodenum. In 10% of patients, the ducts of Wirsung and Santorini fail to fuse. This results in the majority of the pancreas draining through the duct of Santorini and the lesser papilla, while the inferior portion of the pancreatic head and uncinate process drains through the duct of Wirsung and major papilla.

The main pancreatic duct is usually only 2 to 3 mm in diameter and runs midway between the superior and inferior borders of the pancreas, usually closer to the posterior than to the anterior surface. Pressure inside the pancreatic duct is about twice that in the common bile duct, which is thought to prevent reflux of bile into the pancreatic duct. The main pancreatic duct joins with the common bile duct and empties at the ampulla of Vater or major papilla, which is located on the medial aspect of the second portion of the duodenum. The muscle fibers around the ampulla form the sphincter of Oddi, which controls the flow of pancreatic and biliary secretions into the duodenum. Contraction and relaxation of the sphincter is regulated by complex neural and hormonal factors. When the accessory pancreatic duct or lesser duct drains into the duodenum, a lesser papilla can be identified approximately 2 cm proximal to the ampulla of Vater.

2.6 Vascular and lymphatic supply

The blood supply to the pancreas comes from multiple branches from the celiac and superior mesenteric arteries. The common hepatic artery gives rise to the gastroduodenal artery before continuing toward the porta hepatis as the proper hepatic artery. The gastroduodenal artery becomes the superior pancreaticoduodenal artery as it passes behind the first portion of the duodenum and branches into the anterior and posterior superior pancreaticoduodenal arteries. As the superior mesenteric artery passes behind the neck of the pancreas, it gives off the inferior pancreaticoduodenal artery at the inferior margin of the neck of the pancreas. This vessel quickly divides into the anterior and posterior inferior pancreaticoduodenal arteries. The superior and inferior pancreaticoduodenal arteries join together within the parenchyma of the anterior and posterior sides of the head of the pancreas along the medial aspect of the C-loop of the duodenum to form arcades that give off numerous branches to the

duodenum and head of the pancreas. Therefore, it is impossible to resect the head of the pancreas without devascularizing the duodenum, unless a rim of pancreas containing the pancreaticoduodenal arcade is preserved. Variations in the arterial anatomy occur in one out of five patients.

2.7 Venous drainage from the pancreas

The venous drainage of the pancreas follows a pattern similar to the arterial supply, with the veins usually superficial to the arteries. Anterior traction on the transverse colon can tear fragile branches along the inferior border of the pancreas, which then retract into the parenchyma of the pancreas. Venous branches draining the pancreatic head and uncinate process enter along the right lateral and posterior sides of the portal vein. There are usually no anterior venous tributaries, and a plane can usually be developed between the neck of the pancreas and the portal and superior mesenteric veins.

The lymphatic drainage from the pancreas is diffuse and widespread. The profuse network of lymphatic vessels and lymph nodes draining the pancreas provides egress to tumor cells arising from the pancreas. This diffuse lymphatic drainage contributes to the fact that pancreatic cancer often presents with positive lymph nodes and a high incidence of local recurrence after resection. Lymph nodes can be palpated along the posterior aspect of the head of the pancreas in the pancreaticoduodenal groove, where the mesenteric vein passes under the neck of the pancreas, along the inferior border of the body, along the hepatic artery ascending into the porta hepatis, and along the splenic artery and vein. The pancreatic lymphatics also communicate with lymph nodes in the transverse mesocolon and mesentery of the proximal jejunum. Tumors in the body and tail of the pancreas often metastasize to these nodes and lymph nodes along the splenic vein and in the hilum of the spleen.

2.8 Nerve supply

The pancreas is innervated by the sympathetic and parasympathetic nervous systems. The acinar cells responsible for exocrine secretion, the islet cells responsible for endocrine secretion, and the islet vasculature are innervated by both systems. The parasympathetic system stimulates endocrine and exocrine secretion and the sympathetic system inhibits secretion.2 The pancreas is also innervated by neurons that secrete amines and peptides, such as somatostatin, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and galanin. The exact role of these neurons in pancreatic physiology is uncertain, but they do appear to affect both exocrine and endocrine function. The pancreas also has a rich supply of afferent sensory fibers, which are responsible for the intense pain associated with advanced pancreatic cancer, as well as acute and chronic pancreatitis.

2.9 Histology and physiology

The exocrine pancreas accounts for about 85% of the pancreatic mass; 10% of the gland is accounted for by extracellular matrix, and 4% by blood vessels and the major ducts, whereas only 2% of the gland is comprised of endocrine tissue. The endocrine and exocrine pancreas are sometimes thought of as functionally separate, but these different components of the organ are coordinated to allow an elegant regulatory feedback system for digestive enzyme and hormone secretion. This complex system regulates the type of digestion, its rate, and the processing and distribution of absorbed nutrients. This coordination is facilitated by the physical approximation of the islets and the exocrine pancreas, the presence of specific islet hormone receptors on the plasma membranes of pancreatic acinar cells, and the existence of an islet-acinar portal blood system.

Although patients can live without a pancreas when insulin and digestive enzyme replacement are administered, the loss of this islet-acinar coordination leads to impairments in digestive function. Although only approximately 20% of the normal pancreas is required to prevent insufficiency, in many patients undergoing pancreatic resection, the remaining pancreas is not normal, and pancreatic endocrine and exocrine insufficiency can develop with removal of smaller portions of the gland.

2.10 Exocrine Pancreas

The pancreas secretes approximately 500 to 800 mL per day of colorless, odorless, alkaline, isosmotic pancreatic juice. Pancreatic juice is a combination of acinar cell and duct cell secretions. The acinar cells secrete amylase, proteases, and lipases, enzymes responsible for the digestion of all three food types: carbohydrate, protein, and fat. The acinar cells are pyramid-shaped, with their apices facing the lumen of the acinus. Near the apex of each cell are numerous enzyme-containing zymogen granules that fuse with the apical cell membrane. Unlike the endocrine pancreas, where islet cells specialize in the secretion of one hormone type, individual acinar cells secrete all types of enzymes. However, the ratio of the different enzymes released is adjusted to the composition of digested food through nonparallel regulation of secretion.

Pancreatic amylase is secreted in its active form and completes the digestive process already begun by salivary amylase. The proteolytic enzymes are secreted as proenzymes that require activation. Trypsinogen is converted to its active form, trypsin, by another enzyme, enterokinase, which is produced by the duodenal mucosal cells. Trypsin, in turn, activates the other proteolytic enzymes such as chymotrypsinogen, elastase, carboxypeptidase A and B, and phospholipase. Trypsinogen activation within the pancreas is prevented by the presence of inhibitors that are also secreted by the acinar cells. Deficiency of these enzymes in pancreatic

pathology results in characteristic symptomatology of exocrine pancreatic insufficiency.

The acinar cells release pancreatic enzymes from their zymogen granules into the lumen of the acinus, and these proteins combine with the water and bicarbonate secretions of the centroacinar cells. The pancreatic juice then travels into small intercalated ducts. Several small intercalated ducts join to form an interlobular duct. Cells in the interlobular ducts continue to contribute fluid and electrolytes to adjust the final concentrations of the pancreatic fluid. Interlobular ducts then join to form about 20 secondary ducts that empty into the main pancreatic duct. Destruction of the branching ductal tree from recurrent inflammation, scarring, and deposition of stones eventually contributes to destruction of the exocrine pancreas and exocrine pancreatic insufficiency. Various pathologies produce characteristic dilation of the ductal tree.

2.11 Endocrine Pancreas

There are nearly 1 million islets of Langerhans in the normal adult pancreas. They vary greatly in size from 40 to 900 m. Larger islets are located closer to the major arterioles and smaller islets are embedded more deeply in the parenchyma of the pancreas. Most islets contain 3000 to 4000 cells of five major types: alpha cells that secrete glucagon, -cells that secrete insulin, delta cells that secrete somatostatin, epsilon cells that secrete ghrelin, and PP cells that secrete pancreatic polypeptide. Plasma levels of these hormones are used in assessment of pancreatic disease and pancreatic neuroendocrine tumors. Insulin and glucagon have well established roles in regulation of blood glucose and energy metabolism. Any of the islet cells can give rise to PanNETs. Diseases affecting pancreas often affect endocrine function resulting in impaired glucose tolerance and diabetes mellitus secondary to insufficient insulin production.

2.12 Histology

A thin capsule of connective tissue covers the pancreas and sends septa into it, separating the pancreatic lobules. The secretory acini are surrounded by a basal lamina that is supported by a delicate sheath of reticular fibers and a rich capillary network. Each exocrine acinus of the pancreas is composed of several serous cells surrounding a very small lumen (figure 1). The acinar cells are highly polarized, with a spherical nucleus, and are typical protein-secreting cells. The number of zymogen granules present in each cell varies and is maximal in animals that have fasted.

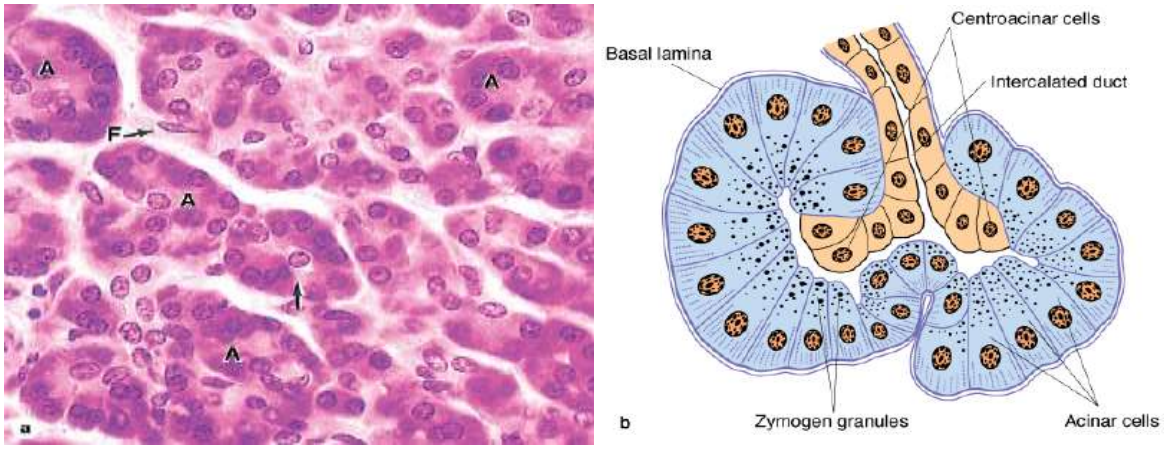

Figure 1: Micrograph of exocrine pancreas

(a): Micrograph of exocrine pancreas shows the serous, enzyme-producing cells arranged in small acini (A) with very small lumens. Acini are surrounded by small amounts of connective tissue with fibroblasts (F). Each acinus is drained by an intercalated duct with its initial cells, the centroacinar cells (arrow), inserted into the acinar lumen. X200. H&E. (b): The diagram shows the arrangement of cells more clearly. Under the influence of secretin, the centroacinar and other cells of these small ducts secrete a copious HCO3– - rich fluid that hydrates and alkalinizes the enzymatic secretions of the acinar cells. Pancreatic acini lack myoepithelial cells and their intercalated ducts lack striations.

2.2 Classification of Pancreatic Tumors

Tumors within the pancreas are classified as neoplastic (benign, pre-malignant or malignant) and benign non-neoplastic conditions (Al-hawary et al., 2013).

2.2.1 Pancreatic exocrine neoplasms

Benign neoplasms

These include serous cystadenoma and acinar cell cystadenoma. They remain asymptomatic until their size causes pressure on the surrounding structures. They are more common in females. These benign tumors are reliably cured by surgical resection alone.

Premalignant lesions

These include grade 3 pancreatic intraepithelial neoplasia (PaniN-3), mucinous cystic neoplasms (MCN) with low-, intermediate-, and high-grade dysplasia, and intraductal papillary mucinous neoplasm (IPMN) with low-, intermediate-, or high-grade dysplasia. Their incidence increases with age mostly occurring in those over 50 years of age. Patients with these neoplasms are considered to be at risk for progression to invasive malignancy because of the presence of cellular dysplasia of any grade in the neoplasm. The risk for progression to an invasive malignancy is considered to increase with the degree of dysplasia (Fritz et al., 2012).

Malignant neoplasms

"Pancreatic cancer" usually refers to a ductal adenocarcinoma of the pancreas (including its subtypes), which represents about 85 percent of all pancreatic neoplasms (Al-Majed et al., 2013). The other types of tumors are: adenosquamous carcinoma which accounts for 4 percent of all pancreatic malignancies, acinar cell carcinoma – <1 percent, undifferentiated (anaplastic) carcinoma, mucinous non-cystic

(colloid) carcinoma (2 percent), intraductal papillary mucinous neoplasm with an associated invasive carcinoma – 2 to 3 percent, mucinous cystic neoplasms with an associated invasive carcinoma – 1 percent, solid-pseudopapillary neoplasm – <1 percent, pancreatoblastoma – <1 percent, signet ring cell carcinoma, serous cystadenocarcinoma – <1 percent. Adenocarcinoma has the poorest prognosis.

2.2.2 Pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors is second most common of all primary pancreatic malignancies, occurring in just about 5 % of the cases (Al-hawary et al., 2013; O'Grady & Conlon, 2008). Included in this group are insulinomas, gastrinomas, glucagonoma and somatostatinomas.

2.2.3 Metastatic Tumors

Metastatic tumors to the pancreas are rare, representing less than 2% of all pancreatic malignancies. Tumors associated with pancreatic metastases include; renal cell carcinoma, colorectal cancer, gall bladder cancer, gastric cancer, gastrointestinal stromal tumors, melanoma, sarcoma, lung cancer, breast cancer and ovarian cancer.

2.2.4 Non-neoplastic pancreatic masses

These include tumor-forming autoimmune pancreatitis (AIP), chronic pancreatitis, and pancreatic pseudocyst among other types of pancreatitis.

2.3 Clinical and pathological features of exocrine Pancreatic Tumors

The most common presenting symptoms in patients with exocrine pancreatic cancer are abdominal pain, epigastric pain, back pain, jaundice, weight loss, dark urine and nausea which occur in more than half patients with exocrine pancreatic tumors. Vomiting and diarrhea are less common occurring in one quarter to a third of patients.

Thrombophlebitis is rare. The most frequent signs are jaundice in over half of the patients and less commonly occurring are hepatomegaly, right upper quadrant mass, cachexia, Courvoisier's sign, epigastric mass and ascites.

The initial presentation of pancreatic cancer varies according to tumor location. Approximately 60 to 70 percent of exocrine pancreatic cancers are localized to the head of the pancreas, while 20 to 25 percent are in the body/tail and the remainder involves the whole organ. Compared to tumors in the body and tail of the gland, pancreatic head tumors more often present with jaundice, steatorrhea, and weight loss. Steatorrhea is attributable to loss of the pancreas' ability to secrete fat-digesting enzymes or to blockage of the main pancreatic duct.

Pain is one of the most frequently reported symptoms, even with small (<2 cm) pancreatic cancers. The pain associated with pancreatic cancer is usually insidious in onset, and has been present for one to two months at the time of presentation. It has a typical gnawing visceral quality, and is generally epigastric, radiating to the sides and/or straight through to the back. It may be intermittent and made worse by eating or lying supine. It is frequently worse at night. Lying in a curled or fetal position may improve the pain. Severe back pain should raise suspicion for a tumor arising in the body and tail of the pancreas. Rarely, pain develops very acutely, as a result of an episode of acute pancreatitis due to tumoral occlusion of the main pancreatic duct.

Jaundice, which is usually progressive, is most often due to obstruction of the common bile duct by a mass in the head of the pancreas, causing hyperbilirubinemia. Jaundice may be accompanied by pruritus, darkening of the urine, and pale stools. Hyperbilirubinemia is characteristically of the cholestatic type, with a predominant increase in the conjugated fraction of bilirubin.

Jaundice is a relatively early sign in tumors arising from the pancreatic head, and pancreatic tumors that present with painless jaundice have been ascribed a relatively more favorable prognosis compared to those that present with pain and obstructive jaundice. Jaundice secondary to a tumor in the body or tail typically occurs later in the course of the disease, and may be secondary to liver metastases.

A recent onset of atypical diabetes mellitus may be noted. Unexplained superficial thrombophlebitis, which may be migratory (classic Trousseau's syndrome), is sometimes present and reflects the hypercoagulable state that frequently accompanies pancreatic cancer. There is a particularly high incidence of thromboembolic (both venous and arterial) events, particularly in the setting of advanced disease. Thromboembolic complications occur more commonly in patients with tumors arising in the tail or body of the pancreas.

Skin manifestations occur as paraneoplastic phenomena in some patients. As an example, both cicatricial and bullous pemphigoid are described, even as a first sign of disease. Rarely, erythematous subcutaneous areas of nodular fat necrosis, typically located on the legs (pancreatic panniculitis), may be evident, particularly in patients with the acinar cell variant of pancreatic cancer. It is hypothesized that the condition is initiated by autodigestion of subcutaneous fat secondary to systemic spillage of excess digestive pancreatic enzymes.

Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone. Signs of advanced, incurable disease include: an abdominal mass or ascites, Virchow's node, Sister Mary Joseph's node or a palpable rectal shelf. Pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7 to 9 percent of cases.

2.3.1 Pancreatic ductal adenocarcinoma

Ductal adenocarcinomas are the most common type of exocrine pancreatic neoplasm, estimated at over 80 percent. The majority of ductal adenocarcinomas are gritty, hard, scirrhous, gray-white masses that are poorly circumscribed due to invasion of the adjacent pancreas or nearby tissues. PDAC shows haphazardly arranged infiltrating glandular and ductal structures typically surrounded by abundant desmoplastic stroma. The cells have eosinophilic to clear cytoplasm and usually enlarged pleomorphic nuclei. Poorly differentiated ductal adenocarcinomas have more irregular and smaller glands and significant pleomorphism. Perineural, lymphatic and blood vessel invasion are frequently present. These tumors most commonly arise in the head of the pancreas (the ratio of head to body/tail lesions is 3:1).

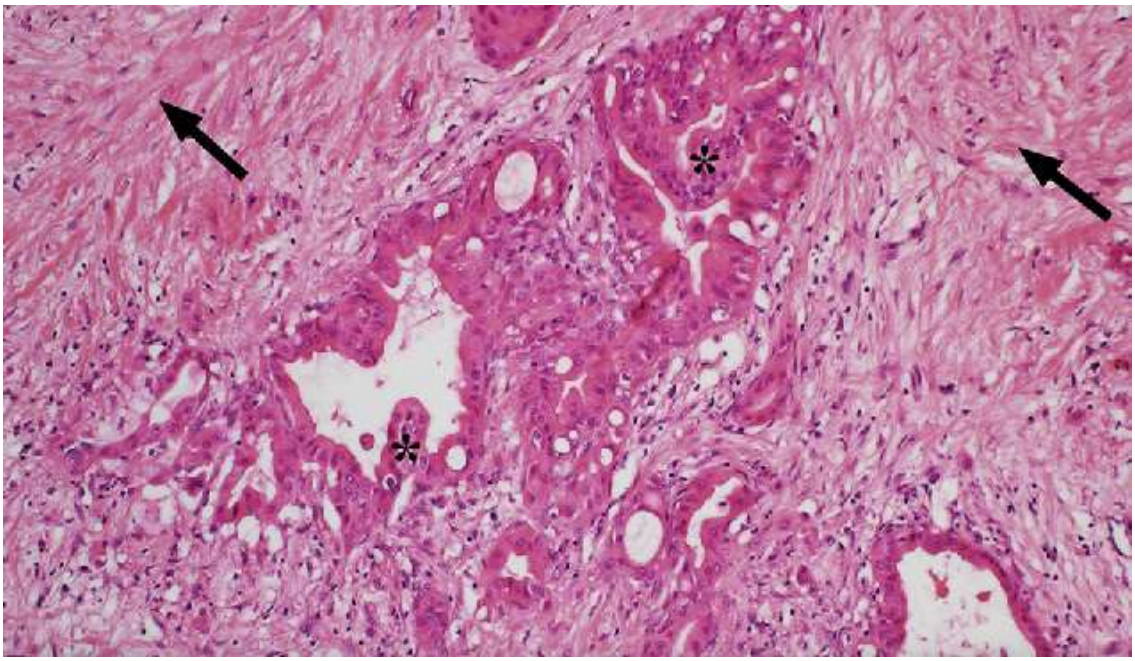

Figure 2: Photomicrograph of pancreatic adenocarcinoma, arrows show intense desmoplastic reaction, asterixes show malignant cells.

Most pancreatic ductal adenocarcinomas are moderately to poorly differentiated, with varying degrees of duct-like structures and mucin production. Dense stromal fibrosis

is characteristic of ductal adenocarcinomas, and is the reason that they are referred to as "scirrhous" or "desmoplastic" carcinomas (Figure 1).

Local extension typically involves adjacent structures such as the duodenum, the portal vein, or superior mesenteric vessels. Occasionally there may be local extension to the spleen, adrenal glands, vertebral column, transverse colon, and/or stomach. Regional peripancreatic lymph nodes frequently harbor metastatic deposits. More distant lymph node groups that are less often involved include the perigastric, mesenteric, omental, and portahepatic nodes.

2.3.2 Adenosquamous carcinoma

Adenosquamous carcinoma of the pancreas is a rare aggressive histologic type of pancreatic carcinoma that constitutes 1% to 4% of all pancreatic exocrine malignancies. It has a clinical presentation similar to that of adenocarcinoma of the pancreas, but with a worse overall prognosis, with most patients surviving for less than 2 years. It demonstrates both malignant squamous cell and glandular differentiation.

2.3.3 Solid pseudo-papillary neoplasm

These neoplasms occur predominantly in females (90 percent) and at a younger age (mean age in the 20s) than other pancreatic neoplasms except pancreatoblastoma (Hackeng et al., 2016). Solid pseudopapillary neoplasms are equally distributed throughout the pancreas. They begin as solid neoplasms that often become cystic as they grow large and the cells become so far removed their blood supply that they undergo apoptosis or necrosis. Most of these neoplasms are cured by resection, but malignant progression with metastasis is reported in 8 to 15 percent (Hackeng et al., 2016).

2.3.4 Acinar cell carcinoma

Acinar cell carcinomas are rare malignant neoplasms that are usually solid, but are sometimes cystic. They occur throughout the pancreas, at any age but predominantly arise in adults and more often in males than in females (Hackeng et al., 2016). Some acinar cell carcinomas give rise to a clinical syndrome related to lipase hypersecretion with distant manifestations, subcutaneous fat necrosis (pancreatic panniculitis), and polyarthralgia. This syndrome is associated with poor prognosis. Most acinar cell neoplasms, even those that are highly differentiated, are malignant, although a few benign acinar cell neoplasms have been described. The overall prognosis for patients with acinar cell carcinoma is better than for ductal adenocarcinomas, but worse than typical pancreatic neuroendocrine tumors.

2.3.5 Pancreatoblastoma

Pancreatoblastomas are malignant neoplasms that arise from primitive cells that have the potential to differentiate along several lines. These tumors most often occur in infants and children. They may develop in the head, body or tail of the pancreas, usually as solid masses (Hackeng et al., 2016). The clinical presentation is that of a large retroperitoneal mass. About 30 percent of pancreatoblastomas secrete alpha-fetoprotein.

Histologically, pancreatoblastoma is composed of primitive small polygonal or spindle-shaped cells that may be mixed with acinar, ductal or islet cells. They are less aggressive than ductal adenocarcinoma and have a higher cure rate after surgical resection. The prognosis is better in children than in adults.

2.4 Clinical and pathological features of pancreatic neuroendocrine tumors (PNETs)

Collectively these neoplasms are classified as functional PNETs. Where a PNET is not associated with a clinical syndrome due to hormone over secretion, it is referred to as a non-functioning PNET.

Non-functioning tumors are slow growing and occur most commonly in the head of the pancreas. However, they secrete a number of substances such as chromogranins, neuron-specific enolase, pancreatic polypeptide, and ghrelin. As a result, they often present later in the course of the disease with symptoms of local compression or metastatic disease. When symptomatic, the most common presenting symptoms of a nonfunctioning PNET are abdominal pain (35 to 78 percent), weight loss (20 to 35 percent), and anorexia and nausea (45 percent). Less frequent signs include obstructive jaundice (17 to 50 percent), intraabdominal hemorrhage (4 to 20 percent), or a palpable mass (7 to 40 percent). Symptoms may also be attributable to metastatic disease. At the time of diagnoses, excluding insulinoma, 50 to 60% of PET's have metastasized.

Treatment is surgical excision with chemotherapy. For functioning PNETs, surgery remains the optimal therapy; however, long-term survival can be expected even in the presence of metastases. With advances in medical management, radiolabelled somatostatin therapy, hepatic arterial chemoembolisation and radiofrequency ablation, symptoms may be controlled to optimize quality of life.

2.4.1 Insulinomas

Insulinomas arise from islet B cells, and are the commonest type of PNET. Majority of insulinomas are benign (90%). They are generally found within the pancreatic parenchyma equally distributed throughout the gland, with only 3% being found in ectopic locations. The duodenal mucosa is the commonest location for ectopic

insulinomas. Presentation of insulinomas is with symptoms of hypoglycemia due to uncontrolled insulin production, confusion, behavioral changes, blurred vision, fatigue, seizures, coma and even death. Measurement of C-peptide levels excludes factitious hypoglycemia. Malignant insulinomas invade locally and metastasize to regional lymph node and the liver. Treatment is by enucleation. Outcome depends on the stage of the disease. Malignant insulinomas are generally solitary and larger than their benign counterparts; 4 cm or more on average.

2.4.2 Gastrinoma

Gastrinomas are the second commonest PET, occurring only half as often as insulinomas. They are most frequently diagnosed in the 5th and 6th decades of life with a slight female preponderance. At the time of diagnosis 50 to 60% of patients will have evidence of metastases. Patients typically present with symptoms of peptic ulcer disease in 90% of cases, and a small ulcer is found in 75% of patients in the 1st part of the duodenum. Diarrhea occurs in approximately 40% of patients as a result of gastric acid hypersecretion. As many gastrinomas will have metastasized at the time of diagnosis, imaging modalities should be directed at the liver as well as the pancreas and duodenum. Norton et al have reported a significant increased survival (98% fifteen year survival) following gastrinoma resection (Norton et al., 2006).

2.4.3 Glucagonoma

The classical presentation is with the ‘‘4D’s’’ of diabetes, dermatitis, deep vein thrombosis and depression. The pathognomonic rash is known as necrolytic migratory erythema and may appear before other symptoms of hyperglucagonemia. It is the presenting feature in 70% of patients with glucagonoma. Following treatment and normalization of glucagon levels, this rash generally resolves. At the time of presentation, the tumors are generally quite large (>4 cm) and up to 50% of patients

with a glucagonoma will have evidence of distant disease most commonly the liver. Even in the presence of metastases, prolonged survival may be expected and treatment with somatostatin analogues may benefit symptoms.

2.4.4 VIPoma

Vasoactive intestinal peptide (VIP) acts on the intestinal lumen to stimulate the secretion of fluids and electrolytes into the intestine. This combines to result in a profuse watery diarrhea with loss of water, sodium, chloride and potassium from the body. As with other PNETs, complete resection is the only chance for complete cure. Even in the presence of metastatic disease, debulking may assist in the postoperative management of VIP hypersecretion.

2.4.5 Somatostatinoma

Hypersecretion of somatostatin presents with diabetes, malabsorption, steatorrhoea, and cholelithiasis due to reduced gallbladder contractility. These symptoms are relatively non-specific and thus the majority of somatostatinomas are diagnosed incidentally and confirmed with a fasting somatostatin level >14 mol/L. Metastases are frequently found at presentation.

2.5 Metastatic Tumors

Metastatic tumors to the pancreas are rare, representing less than 2% of all pancreatic malignancies. Isolated metastatic disease to the pancreas is unusual in that most patients present with diffuse metastatic disease without the option for operative therapy. Because of the relatively favorable biology and prognosis of many tumors that metastasize to the pancreas, for example, renal cell carcinoma and colorectal cancer, pancreatic resection of isolated pancreatic metastasis should be considered. Other tumors that metastasize to the pancreas with resection reported include

melanoma, sarcoma, lung cancer, gastric cancer, gallbladder cancer, breast cancer and others.

These tumors are best distinguished from primary pancreatic malignancy by immunohistochemistry. However, where a patient has an active cancer with suspicion of a pancreatic secondary, careful scrutiny of H &E stain can help to rule out pancreatic cancer which has a typical desmoplastic reaction.

2.6 Non-neoplastic pancreatic masses

Autoimmune pancreatitis (AIP) is a type of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. Between 10 and 13 % of suspected pancreatic carcinomas have been found to be cases of pseudo tumors with half of them being AIP (Kajiwara et al., 2008; Kennedy et al., 2006). A focal type of AIP, which affects a localized area of the pancreas often exhibits mass formation. Autoimmune pancreatitis responds dramatically to steroid therapy; therefore, to avoid unnecessary surgery, an accurate diagnosis of AIP is required. The most important disease that should be differentiated from AIP is pancreatic cancer (Kamisawa et al., 2008). Because it is usually difficult to take adequate specimens from the pancreas, AIP is currently diagnosed based on a combination of clinical, laboratory, and imaging studies. In 2006, the Japan Pancreas Society proposed the Clinical Diagnostic Criteria for Autoimmune Pancreatitis. It contained 3 items: (1) radiological imaging showing diffuse or localized enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct; (2) laboratory data showing abnormally elevated levels of serum gamma-globulin, IgG, or IgG4, or the presence of autoantibodies; and (3) histological findings showing marked interlobular fibrosis and prominent lymphoplasmacytic infiltration in the pancreas. To

make the diagnosis of AIP, criterion 1 is mandatory, and either criterion 2 or criterion 3 must be present.

However, in particular, AIP forming a mass like lesion on pancreas head may be difficult to differentiate from locally advanced pancreatic head cancer. Histologically, most cases of pancreatic head mass are pancreatic cancer, and a few of them are AIP (Kamisawa et al., 2008).

Chronic pancreatitis is a progressive fibroinflammatory process of the pancreas that results in permanent structural damage, which leads to impairment of exocrine and endocrine function. Chronic pancreatitis may be asymptomatic over long periods of time, can present with a fibrotic mass, or there may be symptoms of pancreatic insufficiency without pain (Kajiwara et al., 2008).

Pancreatic pseudocyst is a collection of inflammatory exudate and pancreatic secretions encased in a wall of fibrous or granulation tissue. They occur following an episode of acute pancreatitis and persist for 4 or more weeks. About 10% persist causing complications; abdominal discomfort, hyperamylasaemia, vomiting and obstructive jaundice.

2.7 Imaging of the Pancreas

Ultrasound (US), computed tomography (CT) and Magnetic Resonance imaging (MRI) represent the mainstay in the evaluation of pancreatic solid and cystic tumors affecting pancreas in 80-85% and 10-15% of the cases respectively (Balachandran et al., 2014). Integration of transabdominal US, EUS, CT or MR imaging is essential for an accurate assessment of pancreatic parenchyma, ducts and adjacent soft tissues in order to detect and to stage the tumor, to differentiate solid from cystic lesions and to establish an appropriate treatment. Other imaging modalities that can be utilized in the

evaluation of patients with pancreatic tumors include Endoscopic Retrograde Cholangiopancreatography (ERCP) and PET/CT. The role of ultrasound and CT which were utilized during this study are further discussed below.

2.7.1 Ultrasound

In patients presenting with nonspecific abdominal pain, weight loss, or jaundice, the initial imaging modality often used for evaluation is ultrasound (US). The reported sensitivity for ultrasound in diagnosing pancreatic cancer is 95 percent for tumors >3 cm, it is much lower for smaller-sized tumors. Sensitivity is also dependent upon the expertise of the sonographer and the presence or absence of bile duct obstruction.

Transabdominal US is particularly helpful for minimally invasive procedures such as percutaneous approach, as it guarantees a real-time imaging that allows to precisely evaluate each step of the procedure. It is also cheap, widely available and can be used under local anesthesia. As such transabdominal ultrasound is safely used to guide pancreatic biopsies in many centres without endoscopic ultrasound.

2.7.2 Multi-Detector-row Computed Tomography (MDCT)

This most widely used imaging modality for pancreatic tumors evaluation with sensitivity between 76%-92% for diagnosing pancreatic cancer. CT has an accuracy of 85%–95% for tumor detection, a positive predictive value of 89%–100% for unresectability and a negative predictive value of 45%–79% for resectability. MDCT allows to accurately assess tumor morphology, ductal anatomy, and its relationship to surrounding organs and vascular structures, permitting a surgical planning(Balachandran et al., 2014; Lee & Lee, 2014). Multidetector row computed tomography is perhaps the most widely used modality in the staging of pancreatic neoplasms.

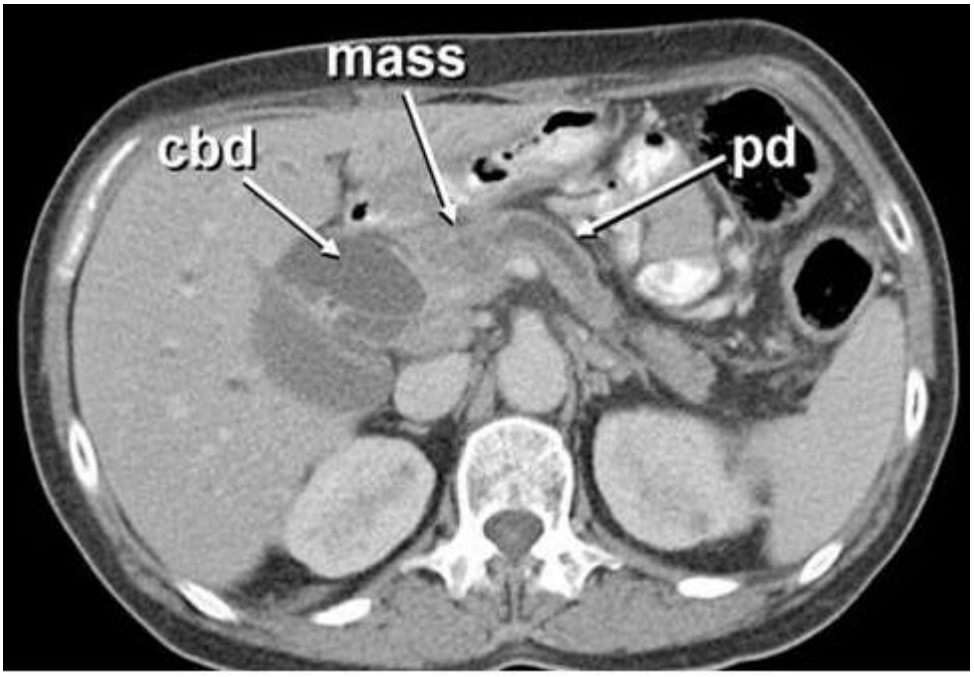

Figure 3: An abdominal CT scan shows a small hypodense, pancreatic mass causing obstruction of both the common bile duct (cbd) and pancreatic duct (pd). Source:https://images.medicinenet.com/images/slideshow/pancreatic_cancer_s6_mass.jpg

PDAC has an ill-defined low-attenuation appearance on CT (Figure 2). The margins of the tumor are often difficult to perceive. There is periarterial extension seen. The primary tumor is best seen on the pancreatic phase of imaging because of the increased enhancement of surrounding normal pancreatic parenchyma and the primary tumor being highlighted because of its low-attenuation appearance. The primary tumor can also occlude veins from mass effect with adjacent venous collaterals. Metastases to the nodes, liver, and peritoneum are the most common sites of spread.

Small PDAC can be isoattenuating; in these instances, evaluation for secondary signs, such as duct dilatation, abrupt duct obstruction, venous obstruction, or contour abnormality, should be made. The incidence of isoattenuating tumors varies, ranging from 11% to 27% based on the size of the PDAC. The sensitivities of MDCT in the detection of PDAC vary based on the size of PDAC and typically range from 72% to

97% for all tumors. CT has a sensitivity of 94% for the assessment of vascular involvement. Vascular involvement of less than or equal to 180^{o} of the circumference of the vessel is called abutment. Vascular involvement of greater than 180^{o} of the circumference of the vessel is called encasement.

SCAs are lobulated and cystic tumors on the non-contrast CT. They can demonstrate intense enhancement on the pancreatic parenchymal phase because of enhancement of the septations and appear as hypervascular masses, especially when the cystic areas are small. When a definitive diagnosis cannot be made by CT, MRI may be of help in these patients. A central scar can be seen in up to 30% of patients. Coarse calcifications can be seen in the region of the central scar.

SPENs are typically mixed solid and cystic neoplasms with calcifications. Irregular peripheral calcifications can be seen in more than 65% of patients. They demonstrate slow enhancement of the solid portions of the neoplasm. When they are small, they are ill defined and more homogeneously solid with gradual enhancement. Calcifications are also less common in smaller lesions. Metastases have been reported in 5% to 15% of patients, with the most common sites being the liver, peritoneum, and nodes.

Primary insulinomas are best seen on the pancreatic phase of enhancement as homogeneously enhancing nodules within the pancreas. Insulinomas are small, well defined, and typically hypervascular tumors. Additional sites of insulinomas within the pancreas may be found on CT, especially in patients with MEN I syndrome. The sensitivity of CT depends on the size of the insulinoma. As the size increases, there is increased sensitivity. Recent papers with the use of thin-section MDCT report higher

sensitivities. One of the papers reports a sensitivity of 63.0% prospectively, and another has sensitivity as high as 94.4%.

In gastrinoma, because of the larger size of the tumor, there is higher sensitivity seen. The approximate sensitivity for PNET with MDCT is reported to be between 63% and 94%. The consensus statement states that the overall sensitivity of CT is approximately 82%, with a specificity of 92% in the detection of liver metastases. Gastrinomas are typically hypervascular tumors. They may be homogeneous when small and heterogeneously enhancing when larger. It is thought that the enhancement is related to microvascular density. They can show calcifications and central necrosis. Occasionally, PNETs may be isoattenuating or hypoattenuating to the rest of the pancreas; it is thought that this is related to poorer prognosis.

Non-functional PNETs are typically heterogeneous tumors. They demonstrate heterogeneous enhancement. They can show calcifications (20%–50%) and central necrosis. NF PNETs may be isoattenuating or hypoattenuating to the rest of the pancreas, and this is thought to be related to poorer prognosis. Lymph node metastases are typically hypervascular with the short axis diameter of greater than 1 cm. Liver metastases can be homogeneously hypervascular or heterogeneously hypervascular in the early phase of enhancement and may demonstrate washout on the portal venous phase.

Pseudocysts are well-defined low-attenuation (cystic) lesions within or adjacent to the pancreas. Their walls may initially appear irregular but become smooth and well defined over time. Their walls are usually thin but may be thickened initially. There can be a communication to the main pancreatic duct. If there is hemorrhage in a pseudocyst, this will be of high attenuation on the non-contrast CT. Pseudocysts can

be locally aggressive with erosion of adjacent vessels and formation of pseudoaneurysms. The most commonly involved arteries are the superior mesenteric, pacreaticoduodenal, gastroduodenal and splenic arteries.

Chronic Pancreatitis on CT and ultrasound will show calcifications, ductal dilatation, enlargement of the pancreas, and fluid collections (eg, pseudocysts) adjacent to the gland.

On CT, a mass caused by AIP shows delayed enhancement, unlike in PC, and substantial parenchymal atrophy is lacking. A capsule-like low-density rim surrounds the pancreas, which may correspond to peripancreatic inflammation.

2.8 Laboratory Investigations of pancreatic tumors

2.8.1 Tumor markers

With regard to blood-based biomarkers, carbohydrate antigen 19-9 (CA19-9) remains the most commonly used tumor biomarker for following the therapeutic outcomes of pancreatic cancer (Hanada et al., 2014). However, only 50 % of cases of pancreatic cancer with tumors smaller than 20 mm are associated with a rise in CA19-9 levels. In addition, its levels are also increased in other gastrointestinal malignancies and benign pancreatic diseases. The combination of serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) has been reported to decrease sensitivity to 37%, but increase specificity to 84% compared with CA19-9 alone, for diagnosis of pancreatic cancer (Kamisawa et al., 2016).

The tumor markers CA19-9 and CEA will be considered increased when there were more than 37 units/mL and 5 mg/L, respectively. About 5-10% of patients lack the enzyme necessary to produce CA 19-9; in these patients with low or absent titer of CA 19-9, monitoring disease with this tumor marker will not be possible. Patients

with increased serum bilirubin levels will be excluded from the analysis of tumor markers to avoid any confounding effect of hyperbilirubinemia. Other carbohydrate markers that have recently been evaluated, include CA 50 and CA 242, and the mucins MUC1, MUC2 and MUC5AC.

Chromogranin A is a secretory protein, composed of 439 amino acids, found in the large dense-core vesicles of the neuroendocrine cells. Chromogranin A can be either measured in the serum or detected by immunohistochemistry in a tissue specimen.Gastro-entero-pancreatic neuroendocrine tumors that stain positive for chromogranin A are as follows: Carcinoid tumor, Gastrinoma, Insulinoma, Glucagonoma, VIPoma, Somatostatinoma. However, it is thought to be unreliable in insulinomas. Chromogranin A can be used to rule out PNETs.

2.8.2 Liver Function Tests

Patients presenting with obstructive jaundice show significant elevations in bilirubin (conjugated and total), alkaline phosphatase, gamma-glutamyl transpeptidase, and to a lesser extent, aspartate aminotransferase and alanine aminotransferase. These are however non-specific.

2.8.3 Pancreatic Function Tests

Serum amylase and/or lipase levels are elevated in less than half of patients with resectable pancreatic cancers and are elevated in only one quarter of patients with unresectable tumors. However, about 5% of patients with pancreatic cancer present initially with acute pancreatitis, in which case amylase and lipase would be uniformly elevated. Thus, pancreatic cancer should be in the differential diagnosis of an elderly patient presenting for the first time with acute pancreatitis without any known precipitating factors.

2.9 Biopsy and histology

Histology is the gold-standard for diagnosis of pancreatic cancer. According to latest guidelines, once pancreatic cancer is suspected on initial imaging studies, the next step in the workup is generally a staging evaluation to establish disease extent and resectability rather than biopsy. Patients fit for major surgery with potentially resectable pancreatic cancer after the staging evaluation is complete need not a preoperative biopsy confirming the diagnosis. However, the increased recognition of chronic or autoimmune pancreatitis, which can closely mimic pancreatic cancer, has altered this paradigm in certain populations. A preoperative biopsy may be recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected on the basis of history (e.g., extreme young age, prolonged ethanol abuse, history of other autoimmune diseases) or chronic pancreatitis. Biopsy is not possible for small tumors and instead fine needle aspiration for cytology (FNAC) is an alternative.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study design

This was a descriptive prospective cross-sectional study.

3.2 Study setting

The study was conducted at the Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya. MTRH is a level 6 public hospital which serves as a referral hospital for counties in western Kenya and the wider northern and mid-Rift counties. It therefore serves nearly half of Kenya's population. It is also the undergraduate and specialist training hospital for Moi University School of Medicine. There are specialists in Imaging and radiology, surgery and pathology.

3.3 Study population, recruitment procedures

All adult patients with pancreatic tumors confirmed through CT scan imaging at MTRH constituted the study population. Initial contact and recruitment of patients occurred at the adult general surgical wards and at the Department of Imaging-Interventional Radiology unit.

3.4 Sampling

A census study was conducted.

3.5 Procedures

The flow diagram below summarizes the activities of this study (Figure 3).

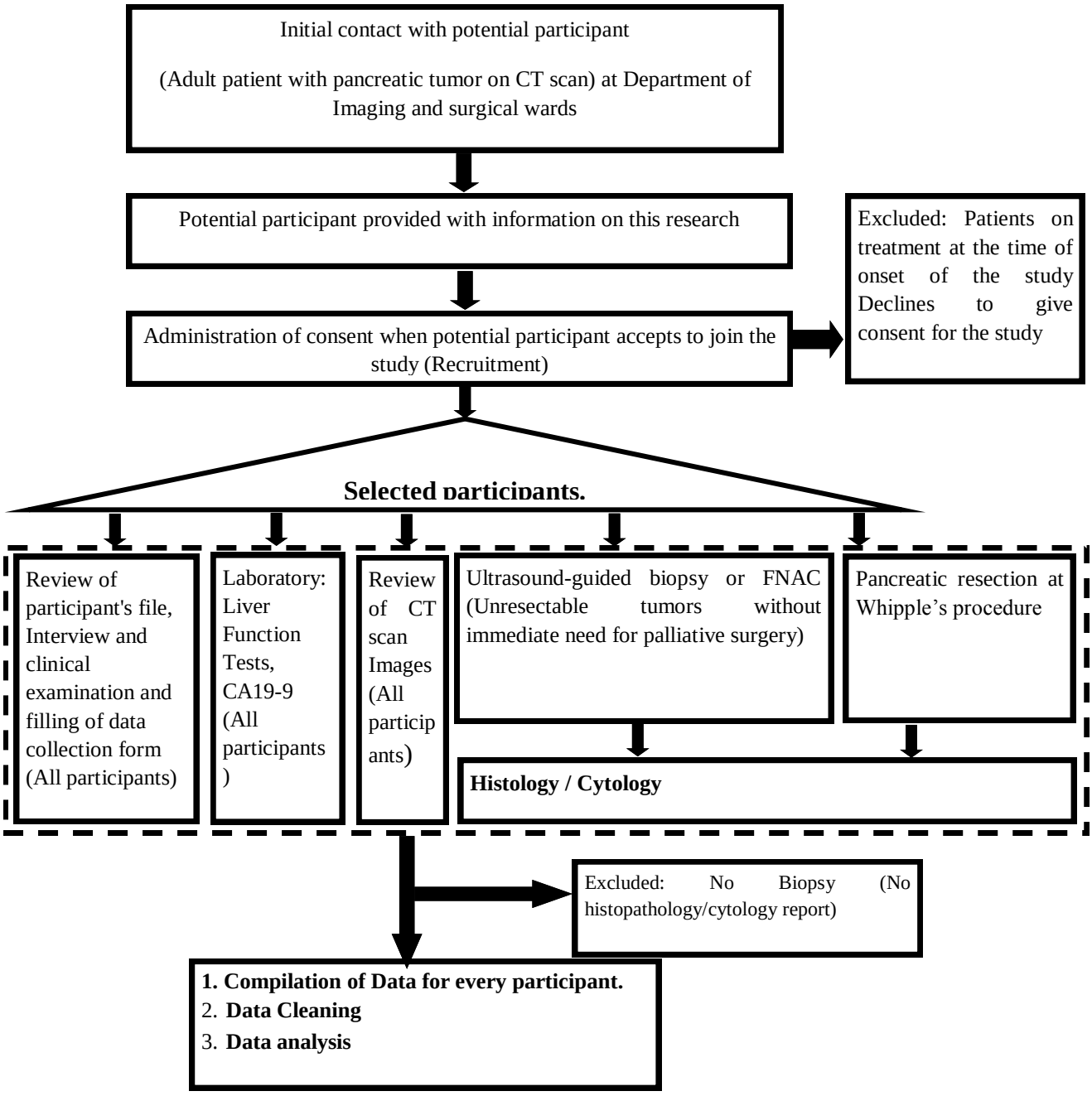

Figure 4: Flow diagram of study processes.

Data was captured using a data collection form (Appendix I) consisting of a questionnaire section for demographics and medical history, a checklist section for clinical findings, and a structured sheet for CT scan and pathological findings.

3.5.1 Demographics

Demographic data was collected by questionnaire and included; patient age, sex, family history of cancer, smoking, alcohol intake, occupation, permanent and current residence, history of chronic illness and history of cancer.

3.5.2 Clinical Manifestations

A focused history taking and physical examination and systemic review was conducted and data captured in a questionnaire. Focused clinical evaluation sought to identify the common signs and symptoms associated with pancreatic tumors such as: Asthenia, weight loss, anorexia, abdominal pain, epigastric pain, dark urine, jaundice, nausea, back pain, diarrhea, vomiting, steatorrhea, thrombophlebitis, jaundice, hepatomegaly, right upper quadrant mass, cachexia, courvoisier's sign (non-tender but palpable distended gallbladder at the right costal margin), epigastric mass and ascites. Systemic review and whole body examination and was carried out for other findings.

3.5.3 Laboratory investigations

Laboratory investigations were done at the Moi Teaching and Referral hospital laboratories using the laboratory's standard operating protocol (SOPs) and reference ranges. The laboratory has internal and external quality control systems. External quality control is by American Professional Institute quality assurance systems and Human Quality Assessment Systems (HuQAS). These tests are as follows:

1. Liver Function Tests: This panel of tests will include bilirubin (conjugated and total), alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate aminotransferase and alanine aminotransferase.
2. The tumor marker carbohydrate antigen (CA19-9).

The Automated chemical analyser model COBAS Integra 400 plus was used for pancreatic and liver function tests. COBAS E411- Hitachi was used for tumor marker assays. Reference ranges for adults are shown in the table below:

Table 1: Laboratory reference ranges for adult males and females

Test	**Male**	**Female**
AST	0 – 38 U/L	0 – 31 U/L
ALT	0 – 41 U/L	0 – 32 U/L
GGT	9 – 48 U/L	9 – 32 U/L
ALP	40 – 129 U/L	35 – 104 U/L
TBil	0 – 17 mMol/L	0 – 17 mMol/L
DBil	0.3 – 4.0 mMol/L	0.3 – 4.0 mMol/L
CEA	0 – 4.7 ng/mL	0 – 4.7 ng/mL
CA19-9	0 – 39 U/mL	0 – 39 U/mL

Specimen collection and handling

Blood samples were collected using aseptic technique as follows:

1. Clean the area of skin around a vein of the cubital fossa or on the forearm with an antiseptic.
2. An elastic band around upper arm to apply pressure and allow blood to fill the vein.
3. A needle inserted into the vein.
4. Blood removed and put into an appropriate vacutainer.
5. The elastic band removed.
6. The blood sent to a laboratory for analysis within two hours.

Samples for pancreatic function tests: Non-hemolyzed serum, heparinized plasma.

Samples for tumor markers and liver function tests: Non-hemolyzed serum, heparinized plasma.

Lab processing for Liver Function Tests

1. Serum separated immediately as soon as possible after collection by centrifugation at 3000 rpm for 2 minutes.
2. Calibration of the machine was done every Monday or when reagent lot was changed or when internal quality controls were repeatedly out of range values.
3. Test the controls in parallel with old controls if the control was new.
4. Samples were run within two hours of collection as described in the SOP for the COBAS INTEGRA 400 PLUS Analyser. The controls from COBAS (Precinorm U and Precipath U) are run in each assay run for internal quality control.
5. Sign off results if the control passes.

Lab processing for CA19-9

1. Serum separated immediately as soon as possible after collection by centrifugation at 3000 rpm for 2 minutes.
2. Calibration of the machine is done as per COBAS E411 SOPs.
3. Samples were run within two hours of collection as described in the SOP for the COBAS E411- Hitachi.

3.5.4 CT scan Imaging

The machine used was a 32-slice Siemens Multi-Detector CT scanner. All images and reports were reviewed alongside a Consultant radiologist.

Technique:(Balachandran et al., 2014).

The evaluation was done using a pancreas protocol technique. This involves pre-contrast imaging from the dome of the liver to cover the entire liver reconstructed to 0.75 mm slice thickness images for review. Following this, a total of 125 mL of

iodinated contrast is administered at a rate of 3 to 5 mL/s. With bolus tracking, imaging is performed 10 seconds after a Hounsfield unit value of 100 is reached in the aorta at the level of the celiac axis. Scanning is performed from the dome of the liver to the iliac crests. This post-contrast sequence is referred to as the pancreatic phase or late arterial phase of imaging. Portal venous phase imaging is performed at a delay of 20 seconds from the pancreatic phase. Delayed images are obtained at a 15-second delay after the portal venous phase. Water is used as negative oral contrast.

3.5.5 Biopsy, Histology and Cytology

Percutaneous ultrasound guided biopsy of the mass was obtained for histology. Surgical specimen was used for histology for the patient who underwent Whipple's procedure. Open biopsy was done for one patient who underwent bypass surgery. Procedures for processing specimens for histology and Fine needle aspiration cytology (FNAC) are described later in this section.

Biopsy Technique

Ultrasound-guided biopsy was performed percutaneously with electronically focused transducers with a laterally mounted guide kit. All biopsies were undertaken by a single team consisting of two Interventional Radiologists at the Department of Diagnostics and Imaging of MTRH. Before sampling, the pancreatic lesion was routinely studied with conventional ultrasound and doppler ultrasound. The content and organization of the lesion (solid or fluid content, intra-lesional necrotic areas, calcifications, and perilesional capsule) were evaluated for the best site for sampling. Color Doppler images were used for identifying major blood vessels.

All biopsies were taken with core biopsy needles of an 18 or 20gauge needle. All biopsies were performed through an anterior abdominal approach with the patient in

the supine position to avoid traversing the colon. Local anesthesia (lidocaine) was administered to the abdominal wall at the chosen entry point. Samples were immediately placed in formalin.

Histology

All specimens and histological reports were analyzed alongside the MTRH/Moi university pathologist. Tissue processing was as follows:

1. Fix the pancreas in freshly prepared 10% buffered neutral formalin for 24 hr.
2. Followed by washing under running tap water for 24 hrs.
3. Routine dehydration process in graded alcoholic series with two changes in absolute alcohol each of 15 minutes duration, then wash in benzene.
4. Then keep the tissue in methyl benzoate overnight.
5. Thereafter go for paraffin embedding. Allow it to float in water for a while till the wax freezes completely.
6. Cut paraffin sections at 5 mU.
7. Stain in Hematoxylin-Eosin (H&E). Hereafter, the process will move to microscopy.

Fine needle aspiration cytology (FNAC)

All specimens and histological reports were analyzed alongside the MTRH/Moi university pathologist. Ultrasound-guided Fine needle aspiration (FNA) technique was used to obtain samples for cytology where tumors are too small for biopsy. Processing of smears was as follows:

1. Express the aspirate onto the slides immediately after withdrawing the needle.
2. Prepare the smears. Gently apply firm flat pressure to crush large fragments.
3. Rapid fixation by with 95% ethyl alcohol.
4. Nuclear staining with Haematoxylin stain.

5. Cytoplasmic staining with OG-6 and EA-36.
6. Dehydration; Rinse the smears in absolute alcohol for two or three changes for the removal of water.
7. Clearing which is done with xylene.
8. Mounting of the slide done with xylene using a clean cover slip.
9. Microscopy.

3.6 Data Management

3.6.1 Data Collection, Cleaning and Entry

All data was collected using data collection sheet and subsequently entered on SPSS datasheet. Data was checked for completeness and consistency. Double data entry into SPSS and comparison was subsequently done.

3.6.2 Data Protection and Security

All paper records are securely kept in a locked cabinet. The computer used for data entry and analysis are password protected.

3.7 Data analysis

Descriptive statistics, such as frequencies, means, medians and percentages for categorical data were calculated and compared between subgroups of age, sex, family medical history, alcohol and smoking history and type of tumor.

3.7.1 To describe the demographics of patients presenting with pancreatic neoplasms in MTRH.

Mean age and median age for participants and by class of tumors was calculated. Percentage distribution of participants' residence, occupation, educational, family, medical, smoking, and alcohol history was calculated. Data is presented in text, tables and graphs.

3.7.2 To describe the clinical presentation of pancreatic tumors in MTRH.

For every type of neoplasm percentage distribution of signs and symptoms was calculated.

3.7.3 To describe the Imaging features of pancreatic tumors in MTRH.

Tumors were characterized in terms of size, location, solid or cystic nature, density, vascularity, vascular invasion and calcification.

3.7.4 To describe the laboratory, cytological and histopathological characteristics of pancreatic tumors in MTRH.

Tumors were classified as benign or malignant. They were further summarized by specific histological types. Malignant tumors were classified as primary or secondary. Primary tumors were classified as exocrine, endocrine or other types. Further summary was done by specific histological types.

CHAPTER FOUR: RESULTS

4.1 Demographics

A total of 51 patients were seen out of whom 1 declined to join the study while 11 had inconclusive pathology or did not get pancreatic biopsy. Thirty-nine (39) participants were recruited into the study with 54% being male over a period of one year. Majority of the participants were drawn from Uasin-Gishu and the neighboring counties with contribution from other counties of the wider western region and North-rift. The mean age was 55.8±13.5 years with the range 28 years– 78 years, and median age was 58 years (IQR 49 – 67 years). The mean age among males was 57.6 years and 54.2 years for females with median ages of 61 years and 55 years respectively. Among the 31 patients with a pathological diagnosis of pancreatic cancer, the mean and median age was 57.81 and 58 years respectively and 19 % of participants were below the age of 50 years falling under the category of early onset pancreatic cancer (Figure 4). Overall, the male to female ratio was 1.17: 1, and 1.2:1 for the pancreatic cancer subgroup.

About 20 % of the participants had no formal education, 48.7 % had primary level, 15.4 % had secondary level and 15.4 % had college education. Farmers constituted 56.4 % of participants, small scale traders 17.9 %, different professionals 10.3 %, and service careers like hairdressers and barbers 5.1 % construction workers, 5.1 % support staff 2.6 % and there was 1 driver (2.6 %).

About 26 % of all participants and 19.4 % of those diagnosed with pancreatic adenocarcinoma had used alcohol at some point in their lifetime. About 7.7 % of participants and 6.5 % of those diagnosed with pancreatic adenocarcinoma had smoked at some point in their lifetime.

Past medical history of any cancer was reported in 5.1 % of participants, 2.6 % of pancreatitis and 10.3 % of diabetes mellitus. All the participants with diabetes mellitus were diagnosed with pancreatic cancer constituting about 12.9 percent of patients with pancreatic adenocarcinoma. One participant had a past medical history of pancreatitis constituting 3.2 % of this subgroup of participants.

Table 2: Demographic characteristics of all participants.

Variable	**n (%) or Mean ± SD**
Age (Years) Mean ± SD **Median + IQR**	55.8 ± 13.5 years 58 + (49 -67) years
<50 years	10 (25.6 %)
Gender Male Female Male: Female ratio	 21 (54 %) 18 (46 %) 1.17: 1
Level of Education No formal Education Primary Secondary Tertiary	 8 (20.5 %) 19 (48.7 %) 6 (15.4 %) 6 (15.4 %)
Occupation Farmers Small scale traders Professionals Service: beauticians, barbers Construction industry Drivers/mechanics Office support staff	 22 (56.4 %) 7 (17.9 %) 4 (10.3 %) 2 (5.1 %) 2 (5.1 %) 1 (2.6 %) 1 (2.6 %)
Medical and Social History Smoking Alcohol use History of cancer History of pancreatitis History of diabetes mellitus	 3 (7.7 %) 10 (26 %) 2 (5.1 %) 1 (2.6 %) 4 (10.3 %)

Table 3: Distribution of participants by county of residence

Country of Residence	**n (%)**
Uasin Gishu	9 (23 %)
Nandi	5 (12.8 %)
Kericho	5 (12.8 %)
Elgeiyo-Marakwet	4 (10.3 %)
Trans-Nzoia	3 (7.7 %)
Narok	3 (7.7 %)
Kisumu	2 (5.1 %)
Nakuru	2 (5.1 %)
Kakamega	2 (5.1 %)
Vihiga	2 (5.1 %)
Kisii	2 (5.1 %)
Total	**39 (100 %)**

Table 4: Demographics for pancreatic cancer subgroup

Variable	**n (%) or Mean ± SD**
Age (Years) Mean ± SD	57.8 ± 11.3 years
Median + IQR	58 years (52 - 67) years
<50 years	6 (19.4 %)
Gender	
Male	17 (54.8 %)
Female	14 (45.2 %)
Male: Female ratio	1.2: 1
Occupation	
Farmers	18 (58.1 %)
Small scale traders	7 (22.6 %)
Professionals	2 (6.5 %)
Service: beauticians, barbers	1 (3.2 %)
Construction industry	2 (6.5 %)
Drivers/mechanics	0
Office support staff	1 (3.2 %)

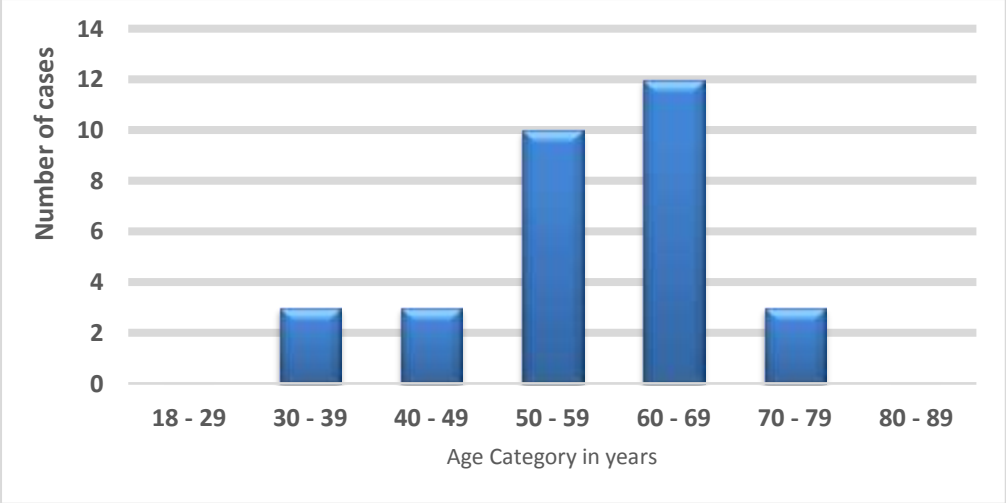

Figure 5: Bar graph showing age distribution among the pancreatic cancer subgroup.

4.2 Clinical Presentation

Abdominal pain was the most common first symptom among all participants and among the pancreatic cancer subgroup at 56.4 % and 51.6 % respectively. Yellowness of eyes was the second most common first symptom occurring in about 30 % of all participants. The other less common first symptoms were nausea and vomiting, weight loss and generalized body malaise.

Duration of symptoms

The mean duration of symptoms was 107.3 days, median duration 60 days, the shortest duration being 4 days with a maximum of 365 days.

Symptoms and signs at presentation

The occurrence of symptoms among participants was as follows: abdominal pain 89.5 %, yellowness of eyes 79.5 %, itching 71.8 %, weight loss 79.5 %, anorexia 76.9 %, fatigue 74.4 %, nausea and vomiting 79.5 %, dark urine 60.5 %, abdominal swelling 44.7 %, diarrhea 34.2 %, back pain 15.8 %.

It is notable that 89.5 % of all patients had abdominal pain at the time of presentation irrespective of the pathological diagnosis. Abdominal pain was the leading first symptom in 56 % of the participants. Among patients with pancreatic cancer the occurrence of symptoms was as follows; abdominal pain 90 %, yellowness of eyes 90.3 %, itching 80.6 %, weight loss 77.4 %, anorexia 74.2 %, fatigue 74.2 %, nausea

and vomiting 74.2 %, dark urine 66.7 %, abdominal swelling 46.7 %, diarrhea 40 %, back pain 13.3 %.

Epigastric pain was reported by 54 % of participants, right upper quadrant pain in 18 % of the participants, and non-specific abdominal pain in 27 % of participants. Two of the three cases of metastatic disease had right upper quadrant pain. All patients with pain in the epigastrium reported prior treatments for peptic ulcer disease without improvement.

At presentation, the prevalence of various signs among all participants was as follows; jaundice 79.5 %, pruritus 66.7 %, wasting 64.1 %, abdominal mass 41.0 %, ascites 12.8 %, pallor 10.3 %, lymphadenopathy 2.6 %.

The prevalence of signs in the subgroup of participants with pancreatic cancer was as follows; jaundice 90.3 %, pruritus 74.2 %, wasting 58.1 %, abdominal mass 45.2 %, ascites 12.9 %, pallor 12.9 %, lymphadenopathy 3.2 %.

Table 5: Frequency of first symptoms reported by participants

Symptom	**All participants - n (%)**	**Pancreatic cancer, n (%)**
Abdominal Pain	22 (56.4)	17 (51.6)
Jaundice	11 (28.2)	9 (32.3)
Nausea and vomiting	3 (7.7)	3 (9.7)
Fatigue and general malaise	1 (2.6)	1 (3.2)
Abdominal swelling	1 (2.6)	0
Weight loss	1 (2.6)	1 (3.2)
Total	**n = 39**	**n = 31**

Table 6: Symptoms reported by participants at presentation.

Symptom	All participants n=39	Pancreatic Cancer n=31	Pancreatitis n=3	Metastatic Cancer n=3	PNET n=1	Pseudocyst n = 1
Abdominal Pain	89.5 %	90.0%	100 %	100 %	100 %	100 %
Yellowness of Eyes	79.5 %	90.3 %	33.3 %	33.3%	100 %	0.0%
Itching	71.8 %	80.6 %	67.7 %	33.3%	0.0%	0.0%
Weightloss	79.5 %	77.4 %	100 %	66.7 %	100 %	100 %
Anorexia	76.9 %	74.2%	100 %	66.7 %	100 %	100 %
Fatigue	74.4 %	74.2 %	100 %	66.7 %	100 %	100%
Nausea & Vomiting	79.5 %	74.2 %	100 %	100 %	100 %	100 %
Dark Urine	60.5 %	66.7 %	33.3%	33.3 %	100 %	0 %
Abdominal swelling	44.7 %	46.7 %	66.7 %	100 %	0 %	0 %
Diarrhoea	34.2 %	40.0 %	66.7 %	33.3 %	0 %	0 %
Back pain	15.8 %	13.3 %	0.0 %	33.3 %	100%	0.0 %

Table 7: Physical findings of participants at presentation.

Sign	All participants n=39	Pancreatic Cancer n=31	Pancreatitis n=3	Metastatic Cancer n=3	PNET n=1	Pseudocyst n = 1
Jaundice	79.5 %	90.3 %	33.3 %	33.3 %	100 %	0.0 %
Pruritus	66.7 %	74.2 %	33.3 %	33.3 %	100 %	0.0 %
Wasting	64.1 %	58.1 %	100 %	66.7 %	100 %	100 %
Abdominal Mass	41.0 %	45.2 %	0.0 %	66.7 %	0.0 %	0.0 %
Ascites	12.8 %	12.9 %	0.0 %	0.0 %	0.0 %	0.0 %
Pallor	10.3 %	12.9 %	0.0 %	0.0 %	0.0 %	0.0 %
Lymphadenopathy	2.6 %	3.2 %	0.0 %	0.0 %	0.0 %	0.0 %

4.3 CT scan characteristics of pancreatic tumors

77.4 % of pancreatic cancers occurred in the head of pancreas with 9.7 %, 6.5 % in the body and tail respectively as shown in

Table 8: CT scan findings of participants. Each of the other two cancers involved contiguous areas of the pancreas. Two of the three cases of pancreatitis involved the head as with metastatic cancer in the pancreas. The third case of pancreatitis had diffuse involvement of the gland without a well-defined tumor. The only case of PNET occurred in the body of the pancreas as with the pseudocyst.93.5 % of pancreatic cancers were solid with the rest (two cases) being cystic. The only other cystic tumor was a pseudocyst. About 74 % of the tumors with pancreatic cancer were more than 4 cm, 19 % between 2 – 4 cm and over 6 % were under 2 cm in the greatest dimension.

All the hypodense tumors except one (a pseudocyst) were pancreatic adenocarcinomas. 19.4 % of pancreatic cancers were of mixed intensity and another 12.9 % were isodense. All the cases of pancreatitis were of mixed intensity. The one case of PNET was hyperdense.

77 % of all the tumors showed ductal dilation which occurred in over 82 % of the pancreatic cancer subgroup. Duct dilation occurred in 2 of the 3 cases each of pancreatitis and metastatic cancer. There was no duct dilation in the cases of pseudocyst and PNET.

Vessel invasion and involvement of other structures occurred in 20 % and 33.3 % of pancreatic cancer subgroup and was not observed in other conditions. 71.4 % of all pancreatic cancers were non-vascular with the rest only mildly -moderately vascular. Calcification was only demonstrated in 5.1 % of pancreatic cancers.

Table 8: CT scan findings of participants.

Tumor Location						
Location	**All participants n=39**	**Pancreatic Cancer n=31**	**Pancreatitis n=3**	**Metastatic Cancer n=3**	**PNET n=1**	**Pseudocyst n = 1**
Head	28(71.8%)	24 (77.4%)	2 (66.7%)	2 (66.7%)	0	0
Body	5 12.8%	3 9.7%	0	0	100 %	100 %
Tail	2 5.1%	2 6.5%	0	0	0	0
Body and Tail	2 5.1%	1 3.2%	0.0 %	1 33.3%	0	0
Head and Body	1 2.6%	1 3.2%	0 0	0	0	0
Diffuse	1 2.6%	0	1 33.3%	0	0	0
Tumor Consistency						
Solid	34 87.2%	29 93.5%	2 66.7%	2 66.7%	1 100.0%	0
Cystic	3 7.7%	2 6.5%	0	0	0	1 100.0%
Diffuese enlargement	2 5.1%	0	1 33.3%	1 33.3%	0	0
Tumor Intensity						
Hypodense	21 53.8%	20 64.5%	0	0	0	1 100.0%
isodense	5 12.8%	4 12.9%	0	1 33.3%	0	0
Hyperdense	3 7.7%	1 3.2%	0	1 33.3%	1 100.0%	0
Mixed intensity	10 25.6%	6 19.4%	3 100.0%	1 33.3%	0	0
Duct Dilation						
Duct Dilation	77.1%	82.1%	66.7%	66.7%	0.0%	0.0%
Calcification						
Calcification	5.1%	6.5%	0	0	0	0
Vessel involvement						
Vessel involvement	16.0%	20.0%	0	0	0	0
Invasion of other structures						
Invasion of other structures	26.9%	33.3%	0	0	0	0
Tumor size						
Size	**All tumors**	**Pancreatic cancer**				
< 2 cm	6 %	9.6 %				
2 – 4 cm	19 %	22.5 %				
> 4 cm	74 %	67.7 %				

4.4 Pathological characteristics of pancreatic tumors

89.3% (n = 35) of all tumors were neoplastic and 10.3 % (n= 4) were non-neoplastic. 91.4 % of the neoplastic tumors were primary to the pancreas, while 8.6 % of the neoplastic tumors were metastatic (Table 10: Findings in pathology specimens of pancreatic tumors). 8.6 % of the neoplastic tumors were metastatic from the breast (n = 1); which underwent immunohistochemistry, ampullary carcinoma (n = 1); where endoscopy was used to biopsy an ampullary/duodenal extension of the mass, and an adenocarcinoma of unknown primary (n = 1) where H & E staining was relied upon to exclude primary pancreatic adenocarcinoma. Non-neoplastic tumors included 3 cases of pancreatitis and one case of a pseudocyst.

Table 9: Finding in pathology specimens of pancreatic tumors.

Pathology	**N**	**(%)**
Pancreatic cancer Adenocarcinoma Acinar cell carcinoma	31 30 1	79.5
Metastatic cancer	3	7.7
PNET	1	2.55
Pseudocyst	1	2.55
Pancreatitis	3	7.7
Total	**39**	**100**

79.5 % of all the pancreatic tumors were pancreatic cancers consisting of one case of acinar cell carcinoma and the rest being adenocarcinomas. Overall, pancreatic cancer constituted 88.6 % of all neoplasms and 96.9 % of all primary pancreatic neoplasms. 50 % of the pancreatic cancers were poorly differentiated, 33 % were moderately differentiated while only 17 % were well differentiated (Table 10).

Table 10: Histologic grade for cases of pancreatic cancer.

Histologic Grade	**N**	**Percent (%)**
Poorly differentiated (G3)	16	52
Moderately differentiated (G2)	10	32
Well differentiated (G1)	5	16
Total	**31**	**100**

The laboratory values for all parameters of liver function showed wide variations within subgroups of pathologies and across subgroups as shown with high values of standard deviations. About 79 % of cases had laboratory findings consistent with obstructive jaundice, (

4.3 CT scan characteristics of pancreatic tumors

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Vessel invasion and involvement of other structures occurred in 20 % and 33.3 % of pancreatic cancer subgroup and was not observed in other conditions. 71.4 % of all pancreatic cancers were non-vascular with the rest only mildly -moderately vascular. Calcification was only demonstrated in 5.1 % of pancreatic cancers.

Table 8: CT scan findings of participants. Over 80 % of those with pancreatic cancer had elevated liver enzymes and bilirubin.

CA-19-9 levels were elevated in 76.9 % of the 26 participants who took the test. 85 % of cases of elevated tumor marker consisted of pancreatic adenocarcinomas. One case of pancreatitis had CA-91-9 over 1000 ng/mL and the only case of PNET had normal levels. 19.2 % of all participants who had normal levels of CA-19-9 had pancreatic adenocarcinoma.

Table 11: Laboratory findings of participants.

Laboratory tests						
	All	Pancreatic cancer n=31	Pancreatitis n=3	Metastatic n=3	PNET n=1	Pseudocyst n=1
TBil	Mean±SD Median	199±33 203	128±119 13	78±64 15	14	4.5
ALP	Mean±SD Median	532±74 534	1101±656 904	230±83 249	78	52
GGT	Mean±SD Median	407±83 283	586±288 829	251±107 219	18	11.5
AST	Mean±SD Median	102±16 99	102±54 85	85±26 104	21	52
ALT	Mean±SD Median	106±22 80	103±54 91	18±7 22	13	36
CA19-9	Mean±SD Median	665±121 1000	1000(1)	390±306 147	1000	-
Elevated lab values						
		Pancreatic cancer	Pancreatitis	Metastatic	PNET	Pseudocyst
TBil		26 (83.8%)	1	1	0	0
ALP		27 (87.0%)	2	2	0	0
GGT		28 (90.3%)	2	3	0	0
AST		25 (80.6%)	2	2	0	1
ALT		25 (80.6%)	2	0	0	0
CA19-9 > 37 IU		17/22 (77.27%)	1	2	1	0

CHAPTER FIVE: DISCUSSION

5.0 Introduction

Thirty-nine participants were recruited into the study 54 % of whom were male, with a male to female ratio of 1.17: 1. The mean age of the participants was 55.8 years and the median age was 58 years with range of 28 years to 78 years. The age parameters are similar to those of a KNH study in the 1980s. However, the KNH study had a male to female ratio of 1.7 : 1 (Samuel, 1988).

The most common pathology in pancreatic tumors was pancreatic cancer at 79.5 %. Neoplasms constituted 89.3% (n = 35) of all tumors while 10.3 % (n= 4) were benign conditions (Figure 6). A similar rate was reported by Tiago et al. in their Brazilian study looking at ultrasound/CT guided pancreatic biopsies among 47 patients where the PC rate was 77 %. Of the neoplasms, 91.4 % were primary to the pancreas while 8.6 % of the neoplastic tumors were metastatic from the breast (n = 1), ampullary carcinoma (n = 1) and an adenocarcinoma of unknown primary (n = 1). Non-neoplastic benign tumors included 3 cases of pancreatitis and one case of a pseudocyst. Pancreatic cancer constituted 96.9 % of all primary pancreatic neoplasms. All the cases of pancreatic cancer were adenocarcinomas except the only case of acinar cell carcinoma.

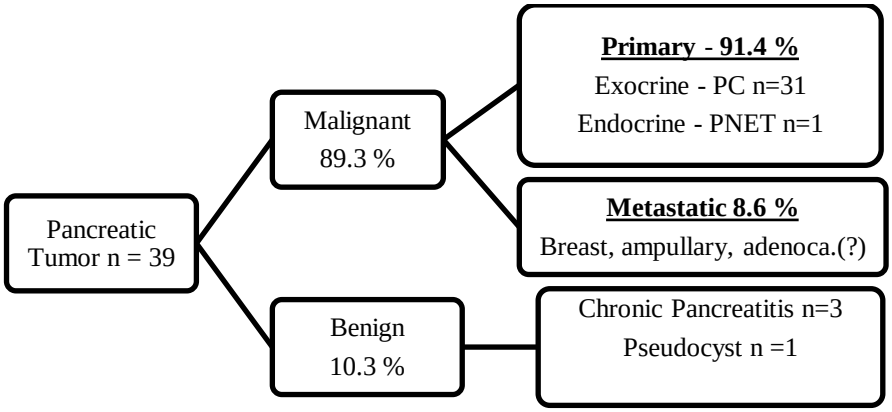

Figure 6: Distribution of pathologies demonstrated in pancreatic masses among adult patients in MTRH.

The rate of benign tumors compares with previous studies in various populations where the rate of benign conditions in pancreatic tumors was found to be 5 %– 15 % mostly consisting of mass forming pancreatitis (Abraham et al., 2003; Frampas et al., 2013; Kennedy et al., 2006; Nakazawa et al., 2007). Yarandi et al showed increased incidence (10.86 %) of benign pancreatic pathology following pancreaticoduodenectomy for presumed malignancy in their retrospective 10-year series of 878 patients despite increased use of imaging at the Emory University hospital in Atlanta (Yarandi et al., 2014). In their study, patients undergoing Whipple's procedure for relief of symptoms of chronic pancreatitis were excluded.

The clinical manifestation of pancreatic tumors and pancreatic cancer in this study was similar to findings of previous studies (Porta et al., 2005; Samuel, 1988). A majority of the tumors were solid and involved the head of the pancreas with attendant clinical manifestations of obstructive jaundice. The incidence of known modifiable risk factors for pancreatic cancer deductible from medical history was low. Most of the participants were drawn from Uasin Gishu county and the bordering counties. A majority of these participants were subsistence farmers.

5.1 Clinical, Imaging and Pathological characteristics of tumors bearing pancreatic cancer

Demographics

The mean and median age for this group was 57.81 and 58 years respectively, very close to findings of a similar study in KNH in the 1980s but considerably younger than the global median age at about 72 years (Pandol et al., 2013; Porta et al., 2005; Samuel, 1988). Age is a key risk factor for pancreatic cancer, with the median age at diagnosis of pancreatic cancer at 72 years, and less than 10% of patients develop pancreatic cancer before the age of 50 (Pandol et al., 2013). The difference in

prevalence between countries with high prevalence has been thought to be due to a difference in life expectancy and possibly environmental factors. In our study and the KNH study, nearly 20 % and over 30 % of participants were below 50 years, a subgroup referred to as early onset pancreatic cancer. The median age in this study is over a decade younger than that reported globally. It has been shown that the younger group is likely to include a higher proportion of patients with underlying predisposing genetic disorders who tend to present with aggressive and advanced disease (Pandol et al., 2013).

The male: female ratio was 1.2:1, similar to global figures and local studies (Ongile, 2005; Samuel, 1988). Ongile in a thesis dissertation conducted in KNH had a male: female ratio of 1.2:1 (Ongile, 2005). Male preponderance of the disease has been explained by the higher smoking rates among men (Kuzmickiene et al., 2013; Raimondi et al., 2007; Sharp et al., 2020). We also find a slight male preponderance although we had a low prevalence of smoking of 6.5 % compared to other studies which could attribute differences to smoking trends. Kenya's smoking prevalence among persons over 15 years is estimated at 26 % and 2.4 % among males and females respectively (WHO, 2010). This is compared to 39 % and 19 % in Europe which reports highest incidence of pancreatic cancer (WHO, 2012). Similar rates were reported in the KNH study where alcohol and smoking rates were 24 % (Ongile, 2005). Smoking may therefore not be a major factor in the incidence of pancreatic cancer in this setting.

About 20 % of participants with pancreatic cancer reported alcohol use which is close to the global average but considerably low compared to Europe or the Americas. Alcohol has recently been shown in a study to increase the incidence of pancreatic cancer in a dose-dependent manner (McWilliams et al., 2016).

A recent onset of atypical diabetes mellitus is noted to precede a diagnosis of pancreatic cancer. About 10.3 % of the participants were diabetics and all had pancreatic cancer on histology. About 7.7 % had family history of DM and 2.6 % of pancreatitis.

About 20 % of the participants had no formal education while 48.7 % had primary level, another 15.4 % secondary level and 15.4 % had tertiary or college level education. Subsistence farmers constituted 56.4 % of participants, small scale traders 17.9 %, different professionals 10.3 %, service careers like hairdressers and barbers 5.1 % construction workers 5.1 %, support staff 2.6 %, and drivers 2.6 %. Higher prevalence and risk of pancreatic cancer has been shown to occur among those of lower socioeconomic status which constituted a majority in the study group (Mihor et al., 2020; Wong et al., 2017). Socioeconomic status may have an indirect link with an environmental factor be it occupational exposure, environmental exposure or diet.

Clinical presentation

The clinical presentation of pancreatic cancer varies according to tumor location. A majority of tumors in this study involved the pancreatic head and therefore most presented with jaundice and attendant signs and symptoms. The constellation of signs and symptoms are very similar to those established for malignant obstructive jaundice and pancreatic tumors (Porta et al., 2005; Samuel, 1988). The most common presentation in patients with pancreatic cancer were abdominal pain, yellowness of eyes, weight loss, dark urine, and nausea which occur in more than half patients with exocrine pancreatic tumors. Diarrhea, abdominal swelling and back pain were less common, occurring in under half of patients. The most frequent signs are jaundice in over half of the patients and less commonly occurring are hepatomegaly, right upper quadrant mass, cachexia, courvoisier's sign, epigastric mass and ascites. However,

higher prevalence of these symptoms and signs were reported in this study, a finding that reflects advanced disease.

The participants with tumors of the tail did not have manifestations of obstructive jaundice and had presented primarily with abdominal mass and pain, typical of tumors of the tail. The two cases had the longest duration of symptoms of about 1 year with large tumors of 5 cm and 6 cm. As in this study, tumors of the tail are rarer, present late and at advanced stages.

Pain has been shown to be one of the most frequently reported symptoms, even with small (<2 cm) pancreatic cancers. In this study, a majority of abdominal pain was in the epigastrium and right upper quadrant with about 13 % having radiation to the back. A number of these patients were treated for peptic ulcer disease in the periods leading to the overt features of obstructive jaundice. New onset upper abdominal pain in adults may be a harbinger of pancreatic malignancy, and prolonged acid suppression should be avoided without further investigation. Presence of pain signifies advanced disease with likely perineural infiltration, retroperitoneal spread and tumors causing pressure effects.

Jaundice, which is usually progressive, is most often due to obstruction of the common bile duct by a mass in the head of the pancreas, causing hyperbilirubinemia. Jaundice is a relatively early sign in tumors arising from the pancreatic head, and pancreatic tumors that present with painless jaundice have been ascribed a relatively more favorable prognosis compared to those that present with pain and obstructive jaundice. Jaundice secondary to a tumor in the body or tail typically occurs later in the course of the disease, and may be secondary to liver metastases. Participants in this study reported a high rate of jaundice but with large tumors mostly over 4 cm.

Skin manifestations occur as paraneoplastic phenomena in some patients although pruritus is a direct consequence of biliary obstruction. As an example, both cicatricial and bullous pemphigoid are described, even as a first sign of disease. Rarely, erythematous subcutaneous areas of nodular fat necrosis, typically located on the legs (pancreatic panniculitis), may be evident, particularly in patients with the acinar cell variant of pancreatic cancer. It is hypothesized that the condition is initiated by autodigestion of subcutaneous fat secondary to systemic spillage of excess digestive pancreatic enzymes. The presence of this condition is not pathognomonic for an exocrine pancreatic cancer, as it has been described with pancreatic neuroendocrine tumors, intraductal papillary mucinous neoplasms, and in chronic pancreatitis. Besides pruritus, skin manifestations were not reported in this study perhaps because of the low rate of PNETs which are associated with them.

Unexplained superficial thrombophlebitis, which may be migratory (classic Trousseau's syndrome), is sometimes present and reflects the hypercoagulable state that frequently accompanies pancreatic cancer. There is a particularly high incidence of thromboembolic (both venous and arterial) events, particularly in the setting of advanced disease. Thromboembolic complications occur more commonly in patients with tumors arising in the tail or body of the pancreas. None of the participants was diagnosed with thromboembolism.

The mean duration of symptoms was 107.3 days, median duration 60 days, the shortest duration being 4 days with a maximum of 365 days. The duration of symptoms does not seem to show a lot of variation in time in our setting. Kanyi et al in 1985 showed a symptom duration of about 1 – 3 months for most patients in Kenyatta National Hospital where a majority of patients were drawn from the neighboring Kiambu area (Samuel, 1988). Miquel Porta in Eastern Spain reported a

median symptom duration of 2 months and a mean of 3.5 months (Porta et al., 2005). That the vast majority of patients are diagnosed with advanced disease characterizes the aggressive nature of the disease.

About 13 % of the participants had overt signs of metastatic disease including ascites, supraclavicular lymphadenopathy and abdominal mass. Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone. Signs of advanced, incurable disease include: An abdominal mass or ascites, left supraclavicular lymphadenopathy (Virchow's node). A palpable periumbilical mass (Sister Mary Joseph's node) or a palpable rectal shelf are present in some patients with widespread disease. Pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7 to 9 percent of cases.

Imaging (CT scan) characteristics

77.4 % of pancreatic cancers occurred in the head of pancreas with 9.7 %, 6.5 % in the body and tail respectively. In this study the proportion of head tumors is slightly higher than that reported in literature where approximately 60 to 70 percent of exocrine pancreatic cancers are localized to the head of the pancreas, while 20 to 25 percent are in the body/tail and the remainder involved the whole organ. Tumors with pancreatic cancers were mostly solid tumors, hypodense, and exhibited non-vascularity to moderate vascularity. These tumors were associated with vascular invasion and infiltration of surrounding structures. Compared to tumors in the body and tail of the gland, tumors of the head are more likely to present early compared to those of the body. In this study, tumors of the body and tail were larger and had longer duration of symptoms. Certain patterns in tumor characteristics may predict pancreatic cancer, in the absence of risk for a secondary malignancy and without

characteristics suggestive of pancreatitis. The use of IgG serology to rule out autoimmune pancreatitis may assist in decision making.

About 74 % of the tumors with pancreatic cancer were more than 4 cm, 19 % between 2 – 4 cm and just over 6 % were under 2 cm in the greatest dimension. Agarwal et al showed that tumor size not only affected median survival but also resectability with only about 7 % of tumors greater than 3 cm being resectable as opposed to 83 % of those less than 2 cm (Agarwal, Correa, & Ho, 2008). As such, our findings represent a group of patients with advanced disease and dismal median survival. However, the low rate of resectable tumors is seen globally as these cancers clinically manifest late and there aren't established screening methods (Jellas et al., 2017). Haeno et al in a mathematical model showed that the chances of harboring a metastatic disease are 23%, 78% and 94 % when the tumor is 1 cm, 2 cm or 3 cm, respectively (Haeno et al., 2012).

There was local spread beyond the pancreas in 33 % of the cases and vascular invasion in 20 % of cases, all indicators of unresectability. Local extension typically involves adjacent structures such as the duodenum, the portal vein, or superior mesenteric vessels. Pancreatic ductal adenocarcinomas also show a striking tendency for perineural invasion both within and beyond the pancreas (e.g., the retro-peritoneum). Occasionally there may be local extension to the spleen, adrenal glands, vertebral column, transverse colon, and/or stomach. In most cases, tumors with this degree of local invasion are not resectable for cure. Regional peri-pancreatic lymph nodes frequently harbor metastatic deposits. More distant lymph node groups that are less often involved include the perigastric, mesenteric, omental, and porta-hepatis nodes. Porta-hepatis nodes may be the cause biliary obstruction in tumors of the body or tail.

An individual patient's prognosis depends to some extent upon the histologic grade of the tumor, but more importantly on the extent of spread (TNM stage). However, even in the setting of completely resected, node-negative pancreatic cancer, the majority of patients with ductal adenocarcinoma die of their disease. For patients with unresected pancreatic adenocarcinoma, prognosis is uniformly dismal, regardless of stage.

Laboratory findings

Carbohydrate antigen 19-9 (CA19-9) levels were elevated in both benign and malignant conditions. About one fifth of those with normal CA 19-9 levels were diagnosed with pancreatic cancer. Carbohydrate antigen 19-9 (CA19-9) remains the most commonly used tumor biomarker for following the therapeutic outcomes of pancreatic cancer (Hanada et al., 2014). However, only 50 % of cases of pancreatic cancer with tumors smaller than 20 mm are associated with a rise in CA19-9 levels. In addition, its levels are also increased in other gastrointestinal malignancies and benign pancreatic diseases (Lachter et al., 2012; Wu et al., 2013). The combination of serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) has been reported to decrease sensitivity to 37%, but increase specificity to 84% compared with CA19-9 alone, for diagnosis of pancreatic cancer (Kamisawa et al., 2016). CA 19-9 therefore cannot distinguish exocrine pancreatic disease from other pathology.

Liver function parameters showed wide variations within subgroups of pathologies and across subgroups as shown with high values of standard deviations. About 79 % of cases had laboratory findings consistent with obstructive jaundice. Liver function tests are important adjuncts in diagnosis and preparation of patients for interventions.

Pathological characteristics

Pancreatic cancer was the most common pathology in pancreatic tumors at 79.5 % with all cases being adenocarcinoma except one case of acinar cell carcinoma. Over 80 % of the cases consisted of moderate and high grade characteristics. A majority presented with features of advanced pancreatic cancer. Most pancreatic ductal adenocarcinomas are moderately to poorly differentiated, with varying degrees of duct-like structures and mucin production (Kamisawa et al., 2016). Acinar cell carcinomas though a rare variant has a better prognosis than pancreatic ductal adenocarcinoma (Duffy & Reber, 2003). In this study there was one case of acinar cell carcinoma with the rest of the cases being PDAC. The other variants which are equally rare did not occur in this study. Most pancreatic cancers are solid tumors however, the cystic variants merit comment because of their special characteristics. Cystic neoplasms must be distinguished from non-neoplastic cystic pancreatic masses, such as pseudocysts and developmental cysts. Cystic neoplasms comprise approximately 5 percent of exocrine pancreatic neoplasms. In this study there were three cases of cystic tumors two of which were pancreatic cancers (6.5 %) and one a pseudocyst.

An individual patient's prognosis depends to some extent upon the histologic grade of the tumor, but more importantly on the extent of spread (TNM stage). However, even in the setting of completely resected, node-negative pancreatic cancer, the majority of patients with ductal adenocarcinoma die of their disease. For patients with unresected pancreatic adenocarcinoma, prognosis is uniformly dismal, regardless of stage.

Like most other cancers, pancreatic cancer is thought to follow a multi-step carcinogenesis process progressing from premalignant lesions like MCNs, PanINs and IPMNs to invasive cancer over about a decade. Their incidence increases with age

mostly occurring in those over 50 years of age. Patients with these neoplasms are considered to be at risk for progression to invasive malignancy because of the presence of cellular dysplasia of any grade in the neoplasm. The risk for progression to an invasive malignancy is considered to increase with the degree of dysplasia (Fritz et al., 2012).

Smoking, obesity, alcohol abuse and exposure to toxic substances are potentially all suitable for primary prevention in our setting even though their incidence was relatively low. Other non-genetic conditions associated with an increased risk of PC are diabetes type 1 and 2, chronic pancreatitis and a history of peptic ulcer. Only the risk associated with chronic pancreatitis seems to be sufficiently high to justify screening of affected individuals. Non-modifiable risk factors include increasing age, familial cancer syndromes, Afro-American race, hereditary pancreatitis, and non-O blood group in addition to diabetes and chronic pancreatitis earlier mentioned (Midha et al., 2016). Screening in individuals with genetic syndromes associated with high risk of PC was shown to result in detection of early tumors with resultant higher resectability and survival rates (Canto et al., 2018).

5.2 Clinical, Imaging and Pathological characteristics of tumors with Pancreatic Neuroendocrine tumor

This study reported one case of non-functional PNET in a 61-year-old female, constituting 3.2 % of primary malignancies. The tumor was 5 cm on the longest dimension, solid and hyperdense on imaging and occurred in the body of the pancreas. The patient presented with abdominal pain and weightloss without a clinical syndrome. There was no obstruction of biliary flow and the liver function tests were normal. CA19-9 was however elevated above 1000 units. PNETs comprise 2% to 4%

of all pancreatic neoplasms, are the second most common primary pancreatic malignancy, and peak incidence is found between the sixth to the eighth decades (Al-hawary et al., 2013; Chiruvella, 2016; O'Grady & Conlon, 2008). These include insulinomas, gastrinomas, glucagonoma and somatostatinomas. Collectively these neoplasms are classified as functional PNETs. Where a PNET is not associated with a clinical syndrome due to hormone over secretion, it is referred to as a non-functioning PNET. Non-functioning PNETs are pancreatic tumors with endocrine differentiation but lack a clinical syndrome of hormone hypersecretion. Non-functioning tumors are slow growing and occur most commonly in the head of the pancreas.

Non-functioning PNETs secrete a number of substances such as chromogranins, neuron-specific enolase, pancreatic polypeptide, and ghrelin, but do not present clinically with a hormonal syndrome. As a result, they often present later in the course of the disease with symptoms of local compression or metastatic disease. When symptomatic, the most common presenting symptoms of a nonfunctioning pancreatic NET are abdominal pain (35 to 78 percent), weight loss (20 to 35 percent), and anorexia and nausea (45 percent). Less frequent signs include obstructive jaundice (17 to 50 percent), intraabdominal hemorrhage (4 to 20 percent), or a palpable mass (7 to 40 percent). Symptoms may also be attributable to metastatic disease. At the time of diagnoses, excluding insulinoma, 50 to 60% of PNET's have metastasized.

Life expectancies of patients with PNETs may be markedly reduced from normal, but even in the worst cases their prognoses remain significantly better than that of patients with the more common pancreatic adenocarcinomas (Brooks et al., 2019). In some very favorable cases, the life expectancy is near-normal, especially amongst 1- and 5-year survivors (Brooks et al., 2019).

5.3 Clinical, Imaging and Pathological characteristics of tumors bearing metastatic cancers to the pancreas

Secondary metastases to the pancreas account for about 5 % to 11 % of pancreatic malignancies and as high as 15 % reported in an autopsy study (Adsay et al., 2004; Chhieng & Stelow, 2007; Nakamura et al., 2001; Pan et al., 2012). We report a slightly higher occurrence of these tumors at 8.6 % which were metastatic from the breast, ampullary carcinoma and an adenocarcinoma of unknown primary. The diagnosis of cancer metastatic to the pancreas should be suspected when patients have a history of malignancy, especially of kidney, skin, lung, colon, and breast cancer and tumors will reflect characteristics of the primary tissue. These tumors can occur in any part of the pancreas and about half the time may be multiple lesions (Pan et al., 2012). One of the cases had multiple lesions with diffuse enlargement. One of the tumors was hypodense, another isodense and one with multiple lesions showed mixed intensity. Nakamura et al in their autopsy series of 103 patients found that the stomach was the most common primary tumor site (20%), followed by the lung (18%) and extrahepatic bile duct (13%). Isolated metastases to the pancreas can be resected with favorable prognosis but overall survival is dependent on the primary cancer (Dar et al., 2008).

5.4 Clinical, Imaging and Pathological characteristics of tumors with Benign conditions in pancreatic masses

The rate of benign disease in this study was just over 10 % consisting of 3 cases of pancreatitis and a pseudocyst. Between 10 % and 15 % of suspected pancreatic carcinomas have been found to be cases of pseudo tumors with half of them being AIP (Abraham et al., 2003; Kajiwara et al., 2008; Kennedy et al., 2006; Yarandi et al.,

2014). Chronic pancreatitis may be asymptomatic over long periods of time, there may be symptoms of pancreatic insufficiency without pain, or can present with a fibrotic mass (Kajiwara et al., 2008). A focal type of AIP which affects a localized area of the pancreas, often exhibits mass formation.

Kennedy et al evaluated 162 patients who underwent pancreaticoduodenectomy for suspected periampullary cancer and had a 12.9 % occurrence of chronic inflammatory pancreatic disease (Kennedy et al., 2006). In their study, they noted that chronic inflammatory disease was associated with higher incidence of smoking (75 %) and chronic alcohol use (66.7 %). In our case however, the incidence of smoking and alcohol use was significantly low at 7.7 % and 25 % among all 39 participants.

Pancreaticoduodenectomy is a highly morbid condition and inasmuch as it may improve symptoms of pancreatitis, it is not recommended first line management for this condition. Furthermore, when it is done for focal mass forming pancreatitis causing biliary obstruction, it is likely to be limited pancreatic head resection. As such it becomes important that patients in our setting with pancreatic masses should be evaluated for variants of mass forming pancreatitis. Autoimmune pancreatitis responds to steroid therapy; therefore, to avoid unnecessary surgery, an accurate diagnosis of AIP is required. The most important disease that should be differentiated from AIP is pancreatic cancer (Kamisawa et al., 2008).

It is important to note that pancreatic ductal neoplasms can cause obstruction of the pancreatic duct, leading to chronic pancreatitis in the obstructed segment of the pancreas. However, because the accessory duct of Santorini can allow bypass of the main pancreatic duct, steatorrhea and malabsorption are usually not a clinical problem. Inasmuch as rate of cancer in chronic pancreatitis is low, it is important to

maintain a high index of suspicion for cancer. It is estimated that less than 5 % of cases of chronic pancreatitis will harbor cancer or develop cancer in over a 20 year period (Dhar et al., 2015; Wu et al., 2013). Overlap of acute pancreatitis and cancer is unusual. Pancreatic cancer represents 1—2% of acute pancreatitis etiologies and only 3% of cancers manifest as acute pancreatitis.

AIP has commonly been reported in other studies as a cause of pancreatic mass (Estrada & Pfau, 2020). It is currently diagnosed based on a combination of clinical, laboratory, and imaging studies. In 2006, the Japan Pancreas Society proposed the Clinical Diagnostic Criteria for Autoimmune Pancreatitis. It contained 3 items: (1) radiological imaging showing diffuse or localized enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct; (2) laboratory data showing abnormally elevated levels of serum gamma-globulin, IgG, or IgG4, or the presence of autoantibodies; and (3) histological findings showing marked interlobular fibrosis and prominent lymphoplasmacytic infiltration in the pancreas. To make the diagnosis of AIP, criterion 1 is mandatory, and either criterion 2 or criterion 3 must be present.

The single case of a pseudocyst presented with abdominal swelling and a mass without features of biliary obstruction. The participant was a young male in his 4^{th} decade with a history of alcohol use. The cyst of the body of pancreas did not have a solid component on imaging and histology revealed a simple inflammatory cyst. Pancreatic pseudocyst is a collection of inflammatory exudate and pancreatic secretions encased in a wall of fibrous or granulation tissue. They occur following an episode of acute pancreatitis and persist for 4 or more weeks. About 10% persist causing complications; abdominal discomfort, hyperamylasaemia, vomiting and obstructive jaundice.

5.5 Tissue diagnosis in the evaluation of pancreatic masses

Histologic confirmation is required to establish a diagnosis of pancreatic cancer. Specimen for histopathology may be obtained through CT or ultrasound-guided percutaneous biopsy, or endoscopic ultrasound FNA or biopsy or through washings obtained at ERCP. Immunohistochemistry is ideal to distinguish between pancreatic cancer and other pathologies such as lymphomas and pancreatic secondaries. However, where a patient has an active disseminated malignancy, careful scrutiny of H & E stain may distinguish primary pancreatic adenocarcinoma from secondaries by its characteristic desmoplastic reaction.

As per current guidelines, patients who are fit for major surgery and who appear to have potentially resectable pancreatic cancer after the staging evaluation is complete do not necessarily need a preoperative biopsy confirming the diagnosis of a pancreatic cancer before proceeding directly to surgery. The subgroup of patients with resectable disease is low leaving a vast majority who then need histopathology prior to initiation of definitive treatment.

In Kenya, pancreatic biopsy is yet to take root due to a lack of expertise, interventional radiology units and acceptability of the procedure among surgeons. A theoretical concern is that percutaneous FNA or biopsy of the pancreas may disseminate tumor cells intraperitoneally or along the needle path in patients who are believed to be candidates for potentially curative resection. However, the risk appears to be quite low or absent. In one study of 41 patients undergoing resection for primary pancreatic adenocarcinoma, 21 of 32 patients without preoperative open biopsies had undergone preoperative CT or fluoroscopically guided FNA (Johnson et al., 1997). There was no increase in positive peritoneal washings, peritoneal failure rate, or median survival in these patients (Johnson et al., 1997).

Lately, increased recognition of chronic or autoimmune pancreatitis, which can closely mimic pancreatic cancer, has led to increased uptake of preoperative biopsy which is remains recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected on the basis of history (e.g., extreme young age, prolonged ethanol abuse, history of other autoimmune diseases), particularly if imaging studies (EUS, ERCP, or MRCP) reveal multifocal biliary strictures (suggestive of autoimmune pancreatitis) or diffuse pancreatic ductal changes (suggestive of chronic pancreatitis).

Survival among pancreatic cancer has been dismal but has shown improvement over the last twenty years. With advancement in cancer treatment and improved survival, pancreatic biopsy is likely to become routine for patients with pancreatic masses even where resectable. This will be bolstered not only by the improved pancreatic cancer treatment but also by the increased finding of conditions with well-established treatments such as lymphoma and benign conditions such as autoimmune pancreatitis. Most recent expert recommendations include addition of serology in suspected AIP in patients with resectable tumors including a trial of steroids prior to biopsy (Asbun et al., 2014). Where AIP remains a concern, biopsy is recommended (Asbun et al., 2014).

In this study, only one patient met the criteria for resectability and underwent a Whipple's procedure. Nearly all patients in our setting have unresectable disease and should get biopsies for confirmation of diagnosis and initiation of therapy. In the past the treatment options for these patients would be empirical and limited due to the lack of histopathological diagnosis. The treatment plan has been based on imaging finding of a pancreatic mass and elevated CA19-9 levels. The recent introduction of percutaneous pancreatic biopsy in the public service at MTRH offers scientists the opportunity to study these tumors and enables patients to get targeted care and in

some cases the benefits of a more favorable diagnosis. Many more patients go into surgery in other centres. Often these are patients on surveillance programs at high-volume centers. It is clear that percutaneous pancreatic biopsy is safe and its uptake will promote the advancement of care for patients with pancreatic tumors in this setting (Johnson et al., 1997; Terracciano et al., 2021).

5.5 Treatment options for pancreatic cancer

Patients with confirmed pancreatic cancer or with tumors highly suspicious for malignancy for which benign conditions have been considerably ruled out should foremost be evaluated for pancreatic resection which is the only treatment that is potentially curative (Tempero et al., 2019). However, over 80 % of patients diagnosed with pancreatic cancer have unresectable tumors and nearly half of resectable tumors on initial evaluation are found to be unresectable at surgery due to peritoneal and omental spread or vascular involvement. Surgical options include the classical Whipple's procedure, pylorus-sparing pancreaticoduodenectomy, and gastric sparing pancreaticoduodenectomy for tumors of the head of the head and neck. Distal pancreatectomy is appropriate for other tumors.

Neoadjuvant chemotherapy has been shown to have a survival benefit and may have some benefit in increasing resectability (Hackert et al., 2016; Michelakos et al., 2019). Single agent and multiple agent adjuvant chemotherapy has shown improved survival post resection. Palliative procedures available for inoperable disease include single, double and triple bypass surgeries. Stenting at ERCP is a low risk procedure for relieving biliary obstruction.

5.6 Study Limitations

Immunohistochemistry was not done in two of three cases of cancers classified as metastatic in this study, where H & E scrutiny was relied upon to distinguish the pancreatic metastases.

Recall bias with regard to description of early symptoms by participants since most of them presented following overt abdominal symptoms and features of obstructive jaundice.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Majority of the patients presented with advanced pancreatic cancer at a younger age than the global average age. The prevalence of known risk factors for pancreatic cancer was relatively low. Large pancreatic head masses comprised the vast majority of tumors. Despite the bulk of tumors being primary pancreatic cancers, there was a significant proportion of metastatic cancers and benign conditions. As has been shown in many studies, case reports and in this study, CA19-9 is elevated in both benign and malignant pancreatic conditions and may not distinguish pancreatic cancer from other conditions.

6.2 Recommendations

1. Further studies to look at why patients with pancreatic cancer are presenting at a younger age and with advanced disease.
2. Further studies to identify the risk factors for pancreatic cancers in this population.
3. Tissue diagnosis should be sought for all patients with pancreatic tumors to enable individualized patient care.
4. CA 19-9 may not distinguish pancreatic cancer from benign pancreatic disease and should not be used to diagnose pancreatic cancer.

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APPENDICES

Appendix 1: Data Collection Form

Participant No: _____

Date: dd/mm/yy _____

1. Demographic Variables
    a. Unique anonymous identification number _____
    b. Date of birth dd/mm/yy _____ Sex _____
    c. Race (black, Asian, white or other); _____Ethnicity _____
    d. Education- completed level (No school, primary, secondary, Tertiary, University)
    e. Permanent residence (Province/county) _____/_____
    f. Current Residence (for how many years?) _____/_____
2. Occupation
    a. Management and Business Occupations
    b. Health care professionals, scientists, engineers
    c. Lawyers and education professional
    d. Office support, sales personnel, communications personnel
    e. Construction work, farming, fishing, forestry, installation, production, transportation
    f. Service workers (barbers, beauticians, housekeepers, cooks, clothes designers)
    g. Government workers, military, law enforcement
    h. Computer technicians, production and support personnel

Notes_____
_____
_____

3. Past Medical History
    a. Personal history of pancreatitis (yes, no) _____
    b. Personal history of cancer (yes, no) _____
    c. Personal history of diabetes (yes, no) _____
4. Family Medical History
    a. First-degree family history of cancer (mother, sister, daughter) and age: <50, >50
    b. First-degree family history of pancreatic cancer (mother, sister, daughter) and age: <50, >50
    c. First-degree family history of pancreatitis
    d. First-degree family history of diabetes mellitus
5. Smoking history
    a. If you currently smoke or if you have ever smoked cigarettes:
        a. How many cigarettes do (did) you usually smoke each day? _____
        b. How old were you when you first started smoking cigarettes regularly? _____ years old
    b. If you do not smoke cigarettes now, how old were you when you stopped smoking? _____ years old
    c. Have you regularly spent 1 hour or more per day in a room (at home or work) where someone other than you was smoking?
6. Alcohol history

    If you currently drink or if you have ever taken alcohol:

        i. Drinking pattern: Every day? / Weekends?/ Occasionally?
        ii. Time of day – mornings / evenings / all day
        iii. How much (units = % abv x vol (L)----------), type of alcohol ----------
        iv. Times, days of week----------continuous/binge----------?

HISTORY AND PHYSICAL EXAM

FOCUSSED HISTORY AND EXAMINATION Checklist

At the beginning or in the course of your illness have you had any of the following problems?

General-

a. □ Weight loss
b. □ Anorexia
c. □ Fatigue
d. □ Fever or chills
e. □ Weakness

Skin-

a. □ Rashes
b. □ Lumps
c. □ Itching
d. □ Dryness
e. □ Color changes
f. □ Hair and nail changes

Gastrointestinal system

a. □ Swallowing difficulties
b. □ Change in appetite
c. □ Indigestion
d. □ Heartburn
e. □ Nausea
f. □ Vomiting
g. □ Change in bowel habits
h. □ Abdominal pain
i. □ Abdominal swelling
j. □ Constipation
k. □ Diarrhea
l. □Yellow eyes or skin (jaundice)

On a focused examination, does the patient exhibit any of the following signs?

General-

a. □ Wasting
b. □ Pallor
c. □ Edema
d. □ Weakness
e. □ Lymphadenopathy
f. □ Jaundice

Abdomen

a. □ Epigastric mass
b. □ RUQ mass
c. □ Hepatomegally
d. □ Ascites
e. □ Courvoisier's sign
f. □ Murphy's sign

Skin-

a. □ Rashes
b. □ Lumps
c. □ Itching
d. □ Dryness
e. □ Color changes
f. □ Hair and nail changes
g. □ Thrombophlebitis
h. □ Spider nevi

Other findings

Investigations

1. CT Scan Findings
    a. Solid / Cystic _____
    b. Size _____
    c. Nodes _____
    d. Vascularity _____
    e. Intensity _____
    f. Loculations _____
    g. Duct dilation : Diffuse/Local_____
    h. Calcifications: Yes/No _____
    i. Local spread
        i. SMV invasion
        ii. SMA invasion
        iii. Portal Vein invasion
        iv. Duodenum invasion
        v. spleen, adrenal glands, vertebral column, transverse colon, stomach
        vi. Other _____
    j. Notes

        _____

        _____

        _____

        _____

2. Histopathology
    a. Classification
        i. Non-Neoplastic _____
        ii. Benign neoplasm _____
        iii. Malignant: Primary Exocrine _____
        iv. Malignant: Primary Endocrine _____
        v. Malignant Primary, other _____
        vi. Malignant Secondary _____
    b. Notes:
        _____
        _____
        _____
        _____
        ____
3. Laboratory -Biochemistry
    a. TBil _____
    b. ALP _____
    c. AST _____
    d. ALT _____
    e. Y-GT _____
    f. CA-19 9_____
4. Other comorbidities

    _____
    _____
    _____
    ___

Appendix 2: Consent form

Barua Ya Utangulizi

Mimi ni daktari Walter Akello. Nimehitimu kama daktari na nimesajiliwa na Bodi ya Madaktari ya Kenya. Kwa sasa, ninasomea shahada ya juu (masters) ya udaktari wa upasuaji katika Chuo Kikuu cha Moi. Ninafanya utafiti kuhusu asili ya uvimbe na saratani za kongosho (pancreas) miongoni mwa wagonjwa wanaopata matibabu MTRH.

Ninaomba ujiunge na utafiti huu. Maelezo yafuatayo yanahusu utafiti wangu. Ningependa usomee na iwapo unamaswali yoyote kwa sasa ua baadaye kuwa huru kuuliza.

Kujiunga kwako ni kwa hiari. Kutojiunga hakutaathiri matibabu yako. Una huru wa kujiondoa kutoka kwa utafiti huu wakati wowote. Iwapo kutatokea maelezo zaidi kuhusu utafiti huu tutakueleza na utapata fursa ya kuamua iwapo ungependa kuendelea na kujihusisha na utafiti huu.

Kuhusishwa kwako, utakuwa kwa kupimwa na daktari, kupigwa picha na kiwango kidogo (mililita 6) cha damu utatolewa kutoka kwa mshipa wa mkono na ufanyiwe uchunguzi kwenye maabara. Vile vile kipande kidogo cha kongosho kilicho na uvimbe itachukuliwa na kuchunguzwa kwenye maabara.

Uchunguzi huu inaambatana na namna ya kawaida ya matibabu kwa wagonjwa walio na uvimbe kwenye kongosho. Kwa hivyo uchunguzi hautachangia kuwepo kwa madhara yoyote inayokuja kuambatana na kushiriki kwako katika uchunguzi huu.

Maelezo yote utakayotoa yatahifadhiwa vyema na kwa njia ya siri. Pia, hatutatumia maelezo yoyote ambayo yanawezesha kukufahamisha.

Iwapo utahitaji maelezo zaidi, waweza kuwasiliana na kikundi kinachoangazia utafiti na usawa wake wa IREC katika nambari ya rununu 053 – 33471 (ext 3008)

_____

Dr. Walter Akello

P.O Box 442, Siaya, Kenya,

Simu ya Rununu: 0724240840

FOMU YA KIBALI

MADA YA UTAFITI: Clinicopathologic and Imaging characteristics of Pancreatic Tumors in Moi Teaching and Referral Hospital.

MTAFITI - Dr. Walter Akello

P.O Box 442, Siaya, Kenya,

Simu ya Rununu: 0724240840

Mimi _____ wa Sanduku la Posta _____, Nambari ya Simu_____ najitolea kwa hiari yangu mwenyewe kutoa kibali cha kujihusisha katika utafiti uliotajwa hapo juu unaendelezwa katika MTRH. Nimepokea maelezo ya tafsili kuhusu utafiti huu kutoka kwa Daktari Walter Akello(au watafiti msaidizi wake) katika lugha, kanuni na masharti ninayoelewa vyema. Nimehakikishiwa kuwa, sitadhurika kutokana na kujihusisha kwangu katika utafiti huu. Ilibainishwa kuwa kujihusisha katika utafiti huu ni kwa hiari na nina uhuru wa kujiondoa wakati wowote ule bila ya kuhujumiwa hasa kuhusu haki yangu ya kupokea matibabu katika MTRH. Zaidi ya hayo, nilihakikishiwa kuwa, kanununi zote za maadili ya utabibu,uhuru, haki, na manufaa zitazingatiwa katika utafiti huu.

Jina la Mhojiwa_____Sahihi _____Tarehe _____

Jina la Shahidi_____Sahihi _____Tarehe _____

Jina la Karani_____Sahihi _____Tarehe _____

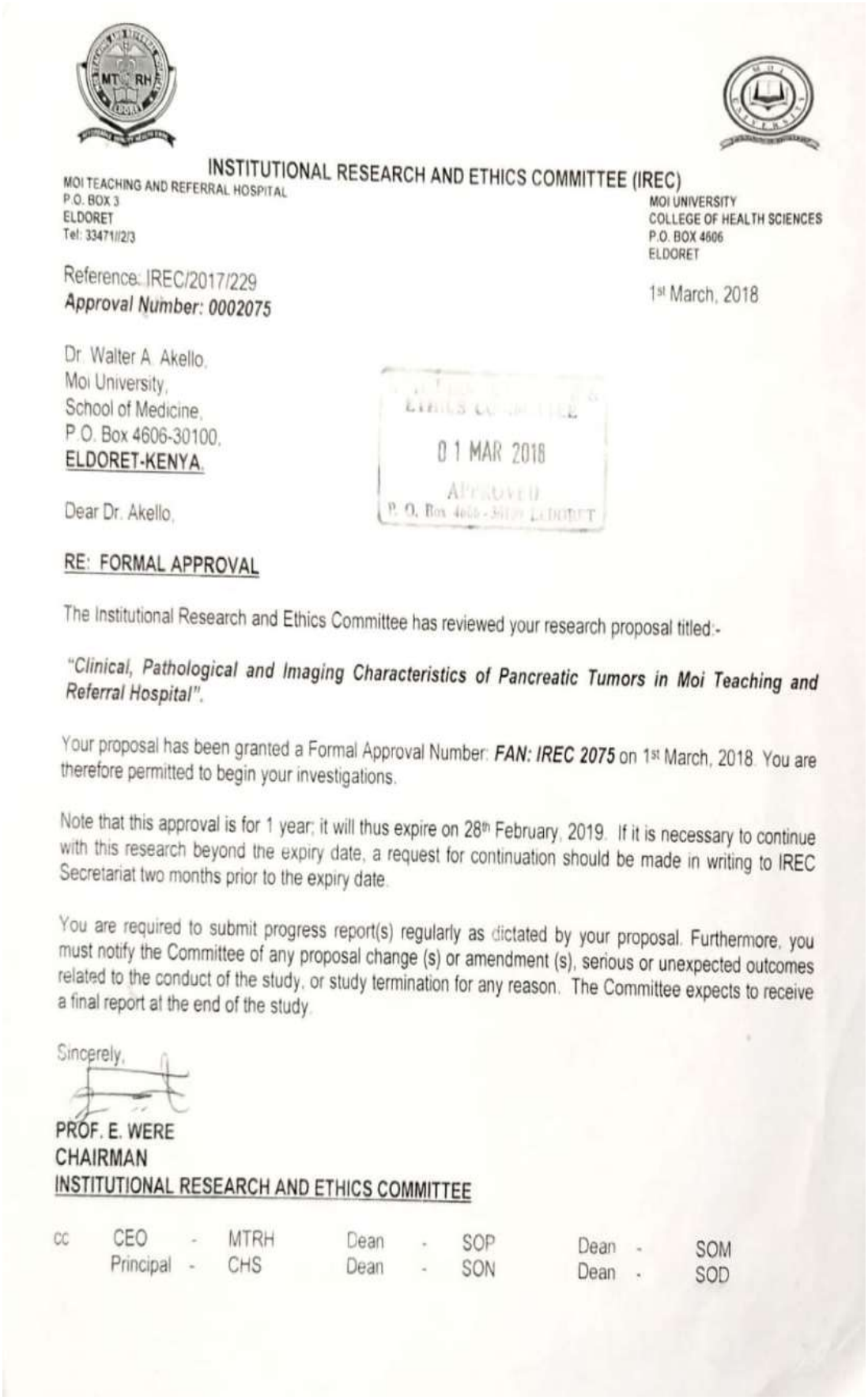
Jina la Mtafiti_____Sahihi _____Tarehe _____

Part II: Consent of Participant:

I have read or have had read to me the description of the research study. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts and side effects as well as the possible benefits (if any) of the study. I freely volunteer to take part in this study.

_____	_____	_____
Name of Participant	Signature of subject/thumbprint	Date & Time
_____	_____	_____
Name of Representative/Witness	Relationship to Subject	Date & Time
_____	_____	_____
Name of person Obtaining Consent	Signature of person Obtaining Consent	Date
_____	_____	_____
Dr. Walter Akello	Signature of Investigator	Date

Appendix 3: Institutional Research and Ethics Committee Approval



INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/229
Approval Number: 0002075

1st March, 2018

Dr. Walter A. Akello,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

01 MAR 2018
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Akello,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Clinical, Pathological and Imaging Characteristics of Pancreatic Tumors in Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 2075*** on 1st March, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 28th February, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD