PATIENTS' CHARACTERISTICS AND PREDICTORS OF RESECTABILITY AMONG PATIENTS TREATED FOR PANCREATIC MASSES AT MUHIMBILI NATIONAL HOSPITAL

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By

Nashivai Elias Kivuyo

A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (General Surgery)

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CERTIFICATION

The undersigned certifies that, he has read and hereby recommends for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **‘‘Patients’ characteristics and predictors of resectability among patients with pancreatic masses at Muhimbili National Hospital’’** in (partial) fulfillment of the requirements for the degree of Master of Medicine (General Surgery) Muhimbili University of Health and Allied Sciences.

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Dr. Larry Akoko

(Supervisor)

_____

Date

DECLARATION AND COPYRIGHT

I, **Nashivai Elias Kivuyo**, declare that this **dissertation** is my original work it has not been presented and will not be submitted to any other university for a similar or different degree award.

Signature …….. **Date**…….

ACKNOWLEGMENT

I thank GOD, The Almighty, for his showers of blessings that enabled me to accomplish this work

I would like to express my deepest gratitude to my supervisor, Dr. Larry Akoko. His meaningful assistance, tireless supervision and exemplary patience guided me to the accomplishment of this work.

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A sense of respect to my classmates for their extraordinary motivation support as we hurdled together through the path of this Masters' degree.

I am grateful for my mother Rebeca for her faith in me, and whose constant love and support keep me motivated and confident. Deepest thanks to my siblings, Naserian and Lesian who keep me grounded, remind me of what is important in life, and are always supportive of my adventures.

DEDICATION

To my beloved Father, The Late Elias M. L. Kivuyo,

Who believed me before I believed in myself.

ABSTRACT

Background: Pancreatic masses are challenging to diagnose and treat due to their indolent course. Despite presence of both curative and palliative surgical services at MNH, there is paucity of data on how these patients are investigated, managed and what predicts a diagnosis of resectable disease. This study will enable clinicians to improve index of suspicion for pancreatic mass and improve on timely diagnosis to capture resectable disease for better outcomes. The aim of this study was to document patients' characteristics, investigations and predictors of resectability among patients with pancreatic masses at MNH.

Materials and Methods: A retrospective analytical study was conducted at MNH involving patients treated between 2018 and 2019 for pancreatic mass. Patients were identified from hospital records and their case notes extracted. Patient demographics, disease characteristics, and management was recorded and analyzed by SPSS. Association between categorical variables was tested by using chi-squared and fisher's exact tests with a p-value less than 0.005 accepted for significance.

Results: 147 patients were included in the study with a mean age of 60.1±13.6 (27 – 89) years with a male to female ratio of 1:1.16. Only 72.1% patients were diagnosed by an abdominal CT scan with only 32.7% with a histological diagnosis. Most patients presented with unresectable (20.2%) and Metastatic (57.3%) disease. The potentially resectable masses were 13.7% with a resection rate of 6%. Young age, residency within Dar es Salaam and employment were associated with diagnosis of a resectable disease.

Conclusion: Resection rates of pancreatic masses in our setting is low. Benign pancreatic masses are not uncommon Young age, urban residence and employment status were associated with resectable pancreatic masses.

Recommendations: Clinicians should attempt to capture pancreatic masses in early resectable stages so as to increase chances of curative resection.

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LIST OF ABBREVIATION

CT-Scan	Computed Tomography scan
CXR	Chest X-ray
DM	Diabetes mellitus
GOO	Gastric outlet obstruction
HIV	Human immunodeficiency virus
HTN	Hypertension
ICU	Intensive care unit
IPMN	Intraductal papillary mucinous neoplasm
MUHAS	Muhimbili University of health and allied sciences
MUHAS-IRB	Muhimbili University of Health and Allied Science Institutional Review Board
MRI	Magnetic resonance imaging
PanIN	Pancreatic intraepithelial neoplasia
OGD	Esophagogastroduodenoscopy
ORCI	Ocean road cancer institute
PTC	Percutaneous Transhepatic Cholangiography
USS	Ultrasound
FNAC	Fine Needle Aspiration Cytology

DEFINITIONS OF TERMS

Pancreatic mass is defined as a growth in the pancreas that can either be benign or malignant.

Resectable pancreatic mass - is a stage I or II disease. They have a normal tissue plane between the tumor and adjacent arterial structures (superior mesenteric artery, celiac trunk and common hepatic artery), and have a patent superior mesenteric vein-portal vein confluence, without evidence of distant metastasis.

Borderline resectable pancreatic mass - is defined as a mass that abut the superior mesenteric artery, abut or encase the common hepatic artery over a short segment, or occlude the superior mesenteric vein - portal vein confluence with suitable vein above and below such that venous reconstruction is possible and without evidence of distant metastasis.

Locally advanced and unresectable pancreatic mass – is the mass with local invasion of the superior mesenteric artery or celiac trunk more than 180^{o} or invading the superior mesenteric vein/portal vein without possibility of surgical reconstruction but without evidence of distant metastasis

Metastatic pancreatic mass - is a pancreatic mass presenting with clinical or radiological evidence of distant metastasis.

Predictors of resectability are the independent variables that when present, increase the likelihood of patients presenting with resectable disease.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Pancreatic mass is defined as a growth in the pancreas that can either be benign or malignant[1]. It can be solid (ductal adenocarcinoma, chronic pancreatitis, endocrine tumor) or a cystic lesion (cystic neoplasm, true cyst or pseudocyst). It is well known that pancreatic cancer is the most frequent cause of pancreatic mass[1]. It is the 12th most commonly occurring cancer in men and the 11th most commonly occurring cancer in women[2]. Globally, 458,918 new cases of pancreatic cancer have been reported in 2018, and 355,317 new cases are estimated to occur until 2040[2].

Pancreatic cancer is currently the fourth highest cause of cancer death in developed countries, and if outcomes are not improved, the disease is predicted to be the second leading cause of cancer-related mortality within the next decade[3]. The incidence of Pancreatic Cancer in Africa is estimated to be 2.2 per 100,000 people[4].

A study done in one hospital in Algeria reported an increasing incidence of pancreatic cancer over the recent years whereby 90 patients were diagnosed with pancreatic cancer between the years (1991-2002), and 147 patients during the second one (2003 – 2013)[5]. Another study done in Nigeria, reported the incidence of pancreatic cancer to be 238 per 100,000 hospital admissions, which also accounted for 2.1% of cancer cases[6].

Other neoplasms such as lymphoma, metastasis, cystic tumors or benign conditions as chronic pancreatitis can arise within the pancreas[1]. However, these might be under-reported due to challenges in obtaining pancreatic histology, where often time a mass in the pancreas is treated as pancreatic cancer[7]. This underestimation maybe also be due to limited knowledge among health practitioners about the disease, poor health seeking behaviors in the society, late presentation of the disease, absence of adequate diagnostic equipment and absent of clear documentations on the cases.

1.2 Literature review

Patients' demography

Pancreatic cancer is typically a disease of old age, but benign diseases can be diagnosed at any age. More than ninety of new cancers are diagnosed in patients above 55 years of age, with the majority in the 7th and 8th decade of life[8].It is extremely rare for patients to be diagnosed before the age of 30. In a study conducted in Algeria the age ranged between 16 – 96 years (median 66.2). Most of patients were in the age group of 61-80 years[5] whereas a study conducted in Zambia showed the mean age for diagnosis of pancreatic cancer to be 55.7 years[7]. There is a difference in peak ages among different countries. In India, the peak age is seen to be in the sixth decade of life but it's the 7th decade in the United States[9].

The worldwide incidence of pancreatic cancer is higher in males than females (Age-standardized rate 5.5 in males compared to 4.0 in females)[10]. A study done in Algeria also showed Male predominance with a female to male ratio of 1.46[5]. Within the United States, African-Americans are at higher risk (50%- 90% increased risk) to develop pancreatic cancer compared to Caucasians, and the incidence rates are lowest in Pacific Islanders and Asian-Americans[8]. This high incidence in the African-American population might be linked to a greater exposure to cigarette smoking, obesity, alcohol consumption and diabetes which are some risk factors for developing pancreatic cancer[11].

Risk factors

For a pancreatic mass to be called familial, two or more first degree relatives should have previously been diagnosed with the disease. This accounts for 5%-10% of Pancreatic cancer cases[11]. In a meta-analysis of nine studies individuals who have one first degree relative diagnosed with pancreatic cancer, have an 80% increased risk of developing pancreatic adenocarcinoma compared with individuals with no reported family history[12], however, in a study done in Nigeria none of the patients had family history of pancreatic cancer[6]. This difference could be attributed to poor documentation and small sample size which were limitations mentioned in the later study.

Diabetes is another risk factor for pancreatic cancer. Stevens et al performed a study which showed that the risk of pancreatic cancer to be twice as much that in patients with type one diabetes compared to those without the given condition[13]. A comprehensive meta-analysis also showed an increased risk of pancreatic cancer among patients with type-2 diabetes. The risk is almost twice as much that present in non-diabetic patients[14]. A study done in Nigeria showed that only eleven (11.5%) patients with pancreatic cancer had previous history of diabetes mellitus before the onset of the symptoms and in 8 out of the 11 patients (72.7%) the diagnosis of diabetes Mellitus was made within one year prior to the commencement of the symptoms[6].

Another study in Algeria noticed that the majority of the patients with pancreatic cancer (25.8%) suffered from diabetes mellitus; 16.5% had type1 diabetes and 9.3% had type 2 diabetes. 18.6% were those who suffered from high blood pressure[5], however, in this study, it was not clear, especially for those with type 2 diabetes, which came first between the diagnosis of diabetes and that of pancreatic cancer.

The non-modifiable risks include cigarette smoking, alcohol intake, chronic pancreatitis, high fatty diet and obesity. A meta-analysis of 82 studies reported current cigarette smokers have a 74% increased risk of pancreatic cancer compared to non-smokers whereas those who are former smokers have a 20% increased risk in developing pancreatic cancer compared to non-smokers[15]. The same study also found out that following smoking cessation the risk remains for at least 10 years while other studies have showed that it may take up to 20 years following smoking cessation for the risk to return to baseline as that of non-smokers[8].

Low and moderate alcohol consumption was not associated with pancreatic cancer risk, however, in those with a high alcohol consumption there is a 15% increased risk of pancreatic cancer[16]. This increased risk is strongest in heavy male drinkers and heavy drinkers of spirits. Excessive alcoholism as a risk factor for pancreatic cancer may also be attributed to the fact that alcohol consumption is one of the main cause of chronic pancreatitis, which is a well-established risk factor for pancreatic cancer[17].

Chronic pancreatitis is a progressive inflammatory condition of the pancreas leading to fibrosis and loss of acinar and islet cells[18]. It is documented that approximately 5% of patients with chronic pancreatitis will develop pancreatic cancer during their lifetime[18].

Diet can increase or reduce the risk of pancreatic cancer. The results of a meta-analysis that included 11 case- control studies showed that high intake of high fat diet increased the risk of developing pancreatic cancer by about 48% whereas On the other hand, increased intake of vegetables and fruits, especially those rich in citrus and antioxidants, is protective and contributes to risk reduction by 38%[19].

In a meta-analysis done by The World Cancer Research Fund in the pancreatic cancer, there were 23 studies which assessed for an association between a raised body mass index (BMI) and pancreatic cancer. Out of the 23 studies, 19 of them reported an increased risk of pancreatic cancer among individuals who have a high Body Mass Index. The same meta-analysis also showed that there is a 10% increased risk of pancreatic cancer for every increase in 5 BMI units[2].

Presenting symptoms

Unfortunately, most pancreatic masses present nonspecifically and are not diagnosed until late in the course of the disease, after the cancer has already spread to other organs[27]. Common symptoms include pain, particularly epigastric pain that radiates to the back, unexplained weight loss, jaundice, clay-colored stools and nausea[28].

A study done in Zambia showed that the most common clinical presentation was pain (52.6%), followed by Jaundice[7]. Another study in Nigeria portrayed the duration of symptoms ranged from 4 weeks to 109 weeks with a median of 8 weeks[6].

In the study done in Zambia, the most common anatomic location of the lesion was head of the pancreas (85%) followed by the body of pancreas (22%)[7]. Whereas a similar study done in Algeria (92%) were located at the head; 4.2% at the body and 4.06% at the tail of the pancreas[5].

Diagnosis

Pancreatic masses are very challenging to diagnose. Computed tomography (CT) with three-dimensional (3-D) reconstruction is currently the most preferred method to diagnose and stage pancreatic cancer[32]. This will enable discrimination of pancreatic masses into resectable, borderline resectable, locally advanced unresectable and metastatic disease which is the recommended staging system for initial evaluation and plan for management[33].

Although malignant disease can be strongly suspected when imaging reveals a pancreatic mass invading surrounding organ, tissue diagnosis is recommended to confirm the finding and to rule out benign disorders that present with pancreatic enlargement and obstructive jaundice, such as autoimmune pancreatitis[9]. However, when the suspicion for cancer is very high and when resection will provide significant therapeutic advantage, a biopsy specimen is usually not needed to confirm the diagnosis[29]. One study involving two consecutive decades in Algeria reported as well that during both periods adenocarcinoma to be the most predominant histological type; it represented 78.8% of the whole histological cases during the first decade and 80% during the second one[5].

Another staging system is the 8th AJCC system, which uses the Tumor, Node and Metastasis Classification[9]. This system separates the exocrine from endocrine tumors[27]. However, this is mainly prognostic, rather than diagnostic for it doesn't give account on resectability[9]. Another setback of this staging criteria is it includes information that can be determined only through postsurgical pathologic evaluation of resected tumor such as pathological lymph node status[27].

Potentially resectable stages include AJCC Stages I and II, and the subset of Stage III that is defined as borderline resectable. The unresectable categories include the subset of Stage III that is defined as locally advanced (unresectable), and Stage IV (metastatic). A study done in Nigeria indicated there was Liver Metastasis in 20.8% of patients at time of diagnsis[6]. Another study in Zambia showed that 100% were stage 4 at time of diagnosis[7].

The serum carbohydrate antigen 19-9 (CA 19-9) is the only marker approved for use in the routine management of pancreatic cancer[34] but unfortunately, it lacks sufficient sensitivity and/or specificity to be useful for early pancreatic cancer diagnosis, but it is routinely useful in monitoring disease progression, recurrence and/or therapy response[35]. The low positive predictive value of CA19-9 means it has no role in mass screening of asymptomatic patients and is only appropriate to monitor response to treatment and as a marker of recurrent disease[36].

Treatment

Although the management of pancreatic masses is evolving over the years, with the introduction of new surgical techniques such as laparoscopic techniques and medical therapies like neo-adjuvant chemoradiotherapy, there hasn't been a modest improvement in the outcomes[9]. Pancreatic cancer has a poor prognosis attributed to the late presentation, with overall 5 year survival of 4-6% and 17% in localized resectable disease[37].

The only hope for potential cure of pancreatic cancer is surgical resection, the addition of adjuvant chemotherapy has also shown to improve survival rates[9]. However, due to its indolent course, most patients present late with unresectable tumors. In a study done in Nigeria, only 3% had resectable tumors[6]. Pancreatico-duodenectomy (Whipple's procedure), distal or total pancreatectomy are the surgical options for the resection of pancreatic cancer depending on the anatomical location of the tumor or tumours[9]. However, even in patients with unresectable disease, there is still a role of surgery to palliate jaundice and gastric outlet obstruction caused by the tumor.

In a study done in Nigeria, fifty-five (57.3%) patients had surgery. Out of the 96 patients in that study, two patients (2%) with localized tumor of the head had pancreaticoduodenectomy and 1 patient (1%) with a tumor at the pancreatic tail had resection of the tumor and splenectomy. Most of patients who underwent surgery (81.8%) already had locally advanced pancreatic mass. The procedure done was mainly triple bypass to relieve the obstructive jaundice. Triple bypass was achieved either through isolated bowel segment (Roux-en-Y) while in the others bowel loops were used (Braun).[27] Seven patients had biopsy alone of the

pancreatic mass or the lymph node because of the widespread metastasis to the bowel, liver and other organ in the peritoneal cavity[6].

In patients with advanced disease, there is a role of palliative chemotherapy with the preferred chemotherapy regime FOLFIRONOX (mFOLFIRINOX with 5-fluorouracil). In the study done in Nigeria, 14.6% had palliative chemotherapy. Agents used include 5-fluorouracil and Adramycin[6].

1.3 Problem Statement

Although pancreatic masses are common in developed countries more than developing countries, there is an expected increase in incidence and mortality rate in Africa in the coming years. Moreover, a large disparity in pancreatic mass incidence between different countries has been observed which suggests that environmental factors play a significant role in the disease[9]. It is predicted that from 2018 to 2040, the highest mortality rate for pancreatic masses is estimated to be in Africa (+114.8%), followed by Latin America and the Caribbean (+101%), while the lowest incidence will be registered in Europe (+31.6%)[4]. Despite this threat, little is known about the patients' characteristics and their clinical presentation in Tanzania.

For any pancreatic mass, the keystone to assigning the appropriate management is adequate investigations to properly stage the patients[14]. However, the diagnostic investigations and treatment modalities offered to these patients in our setting remain unknown. Moreso, despite surgery being the main hope for cure of pancreatic masses[9], the resection rate and the factors determining resectability of pancreatic masses at MNH are still not known.

1.4 Rationale

Pancreatic mass is an important cause of morbidity and mortality worldwide. It is usually associated with late diagnosis, limited management options hence poor outcomes. This study will give an insight of the burden of pancreatic masses in Tanzania. It will also enumerate the profile and presentations of these patients in the country. It will also shed light on the management options provided to pancreatic mass patients. It will highlight areas for improvement so as to maximize standard of care to these patients.

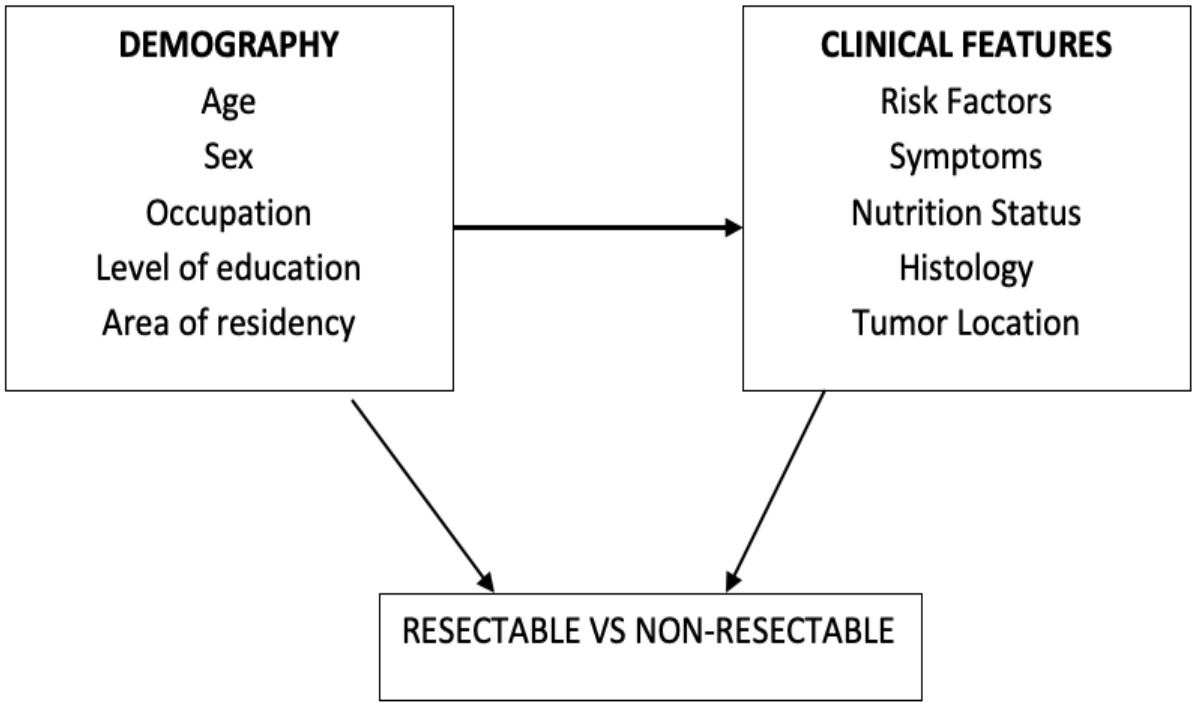
Since not much is documented about pancreatic masses in MNH and Tanzania at large, this study will serve baseline data to surgical gastroenterologists, others surgeons and researchers. It will highlight more questions and stimulate further research on this broad topic.

1.5 Research question

What are the demographic and clinical characteristics of pancreatic mass patients at MNH?

What are the predictors of resectability among patients presenting with pancreatic masses at MNH?

1.6 Conceptual framework



1.7 Objectives

1.7.1 Broad objective

To asses patients' characteristics, diagnostic investigations, treatment and predictors of resectable disease among patients with pancreatic masses at MNH between January 2018 and December 2019.

1.7.2 Specific objectives

i. To describe the demographic and clinical characteristics of patients who were attended for a pancreatic mass diagnosis at MNH between January 2018 and December 2019

ii. To identify the diagnostic investigations that were performed among patients with pancreatic masses at MNH between January 2018 and December 2019

iii. To describe the various treatment modalities offered to patients with pancreatic masses at MNH between January 2018 and December 2019

iv. To determine the predictors of resectability of pancreatic masses.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design and duration

This was a retrospective cross-sectional hospital-based analytical study conducted at MNH from March 2020 to May 2021.

2.2 Study area

The study was conducted in the department of surgery of Muhimbili National Hospital, in Dar es Salaam city, Tanzania. The city population is approximately of about 5 million people. MNH is a national referral hospital receiving patients from districts and regional referral hospitals within the country but in addition serving as city hospital by receiving more patients from the five municipalities in the city and nearby district hospitals of Coast Region due its geographical location. This hospital is a teaching hospital for both undergraduates and postgraduates MUHAS medical students.

The MNH has bed capacity of 1600, in which surgical wards have 240 beds are dedicated to the department of general surgery. The hospital contains more than 15 general surgeons, 6 surgical gastroenterologists and about 30 residents who operate 5 days a week (average 3 operating rooms per day). The Hospital is well equipped with operating theatres, Histopathology laboratory and a radiology unit capable of performing CT- scans. In a pilot study, we noted that MNH received 183 patients with a pancreatic mass over the last two years.

2.3 Study population and study sample

The study population was patients with intraabdominal masses with or without obstructive jaundice. The study sample included patients diagnosed of pancreatic mass in the head or body or tail or any of the combination of involvement. All patients who met the inclusion criteria were enrolled in the study.

2.4 Inclusion and Exclusion criteria

Patients with pancreatic masses attend at MNH between January 2018-December 2019 diagnosed either by: -

- Radiological Diagnosis from either CT-scan or abdominal ultrasonography
- Intraoperative Diagnosis/finding as is in the surgical case notes

2.5 Sample size

The sample size required was calculated by using a single standard proportion formula (Kirk wood, 2003)

The formula for minimum sample size calculation will be as follows:

$N = (Z^2 P (1-P))/E^2$

Where N=Estimated sample size

Z=is the percentage point of the normal distribution corresponding to the level of significance. For level of significance <5%Z=1.96

P=proportional of Pancreatic resection among pancreatic mass patients from a study done in Nigeria = 10.3% [6].

E-Standard error=0.05

$N=1.96^2 \times 0.103(1-0.103) /0.05^2= 142$

A sample size of 142 was considered to have 80% power at type 1 error of 5% to detect a resectability rate of 10.3% at 95% confidence level among patients with pancreatic masses at Muhimbili National Hospital for the two years under review. But during data review, we encountered 147 patients who were diagnosed with pancreatic mass and these were analyzed for study variables.

2.6 Variables

2.6.1 Dependent

WHO clinical stage grouped as resectable, borderline resectable, unresectable and Metastatic.

2.6.2 Independent

Socio-demography to include: Age of the patients, Sex, Occupation, Level of Education and Area of Residency.

Clinical variables included: Symptoms, Diagnostic investigations, Histology type, Tumor location, Treatment modalities.

2.7 Measurements

Patients demography included age as provided from year of birth documented on the case notes and was calculated in years. Sex of the participants was as documented in the case notes as either male or female. Area of residence was the administrative region within Tanzania of original domicile of the patient before coming for medical care. Clinical stage was obtained by reviewing abdominal CT scan basing on resectability and will be categorized as resectable, borderline resectable, unresectable or metastatic. Histology was obtained from Histology report signed by a pathologist. The clinical symptoms, and treatment offered were extracted from the case notes as documented by the treating physicians at the time of original treatment.

2.8 Data collection methods

Data was collected in October- November 2020. Data collection took place in 4 stages. In the first stage, a search was done in the hospital electronic medical records system to identify all patients with intraabdominal masses and obstructive jaundice, from this list, those with pancreatic masses were identified and their file numbers where extracted. Another search was done in the surgical wards' admission books and patients with admission diagnosis of intraabdominal masses and obstructive jaundice were also identified. Those with pancreatic masses were identified and their file numbers were again extracted and then matched with the numbers extracted from the electronic medical records to obtain a final list of patients with pancreatic masses. Thereafter, case notes of these patients were obtained from the hospital medical records.

Two trained research assistants were used to extract patient information independently from the retrieved case notes. A structured data collection tool was used to record relevant information for the study. Demographic information, clinical assessment of the patient including clinical stage was obtained from patients' case notes, also radiological information and pathologist report were obtained from case notes and the computer electronic system. The information obtained from the two research assistants was compared and when the information didn't match, the investigator went back to the case notes to verify the information.

2.9 Data analysis

Collected data was checked for completeness, coded and entered into SPSS software version 22 for storage and subsequent analysis. Categorical variables were summarized in proportions while continuous variables were summarized into means and standard deviations. Association between categorical dependent and independent variables was tested by using Pearson's chi-squared test and fisher's exact test to obtain p-values. A p-value less than 0.005 was considered statistically significant.

2.10 Ethical Consideration

Ethical clearance for the study was sought from MUHAS Institutional Review Board (IRB). Permission to conduct the study was requested from the MNH research and consultancy unit. In order to identify patients with pancreatic masses, names and registration numbers of patients were collected by the investigator and entered in data collection sheet. Deidentification was done by deleting the names and registration numbers before data analysis stages. The collected information shall only be used for scientific research purposes only. We were granted MUHAS IRB for waiver of consent by the patients since the data was collected retrospectively.

CHAPTER THREE

3.0 RESULTS

Description of study participants

In this study, 147 case notes of patients with pancreatic masses were reviewed and their characteristics are depicted in Table 1 below. The mean age of patients was 60.1±13.6 (27 – 89) years with a male to female ratio of 1:1.16. Majority of patients (55.1%) were educated to primary level and most of the patients were either peasants (29.9%) or retired (26.5%). The average duration of symptoms before diagnosis was 4 months with the most common symptom being abdominal pain which was reported by 72.1% of the patients, followed by Jaundice, weight loss and gastric outlet obstruction respectively.

Table 1: Characteristics of study participants, n=147

Variable	Frequency (%)	Mean + SD(Range)
Age (years)		60.1 ± 13.6 (27 – 89)
<40	16(10.9)	
40-59	41 (27.8)	
60-69	51 (34.6)	
70-79	32 (21.8)	
>79	7 (4.8)	
Sex		
Male	79 (53.7)	
Female	68 (46.3)	
Level of education		
No formal education	17 (11.6)	
Primary level	81 (55.1)	
Secondary level	38 (25.9)	
Tertiary level	11 (7.5)	
Occupation		
Peasant	44 (29.9)	
Employed	36 (24.5)	
Unemployed	28 (19.0)	
Retired	39 (26.5)	
Presenting symptoms		
Abdominal pain	106 (72.1)	
Jaundice	100 (68)	
Weight loss	82 (56)	
Gastric outlet obstruction	55 (37.4)	
Duration of symptoms (months)		4.72±5.9 (1 - 36)

Risk Factors

In **figure 1** below, we present the findings of risk factors collected from patients as documented on their case notes. Cigarette smoking was assessed in all the patients from which 43(29.3%) were smokers all of them being male patients. Alcohol intake was assessed in 141 of the patients and 60(42.6%) of them were taking alcohol for which men contributed 83.3%. Family history of pancreatic mases was available for 77 of the patients and only three (3.9%) reported to have had a family member with pancreatic mass diagnosis: 2 of them were male. Of 131 patients with diabetic information recorded, 58(44.3%) had a diagnosis of diabetes mellitus with 55% being male patients.

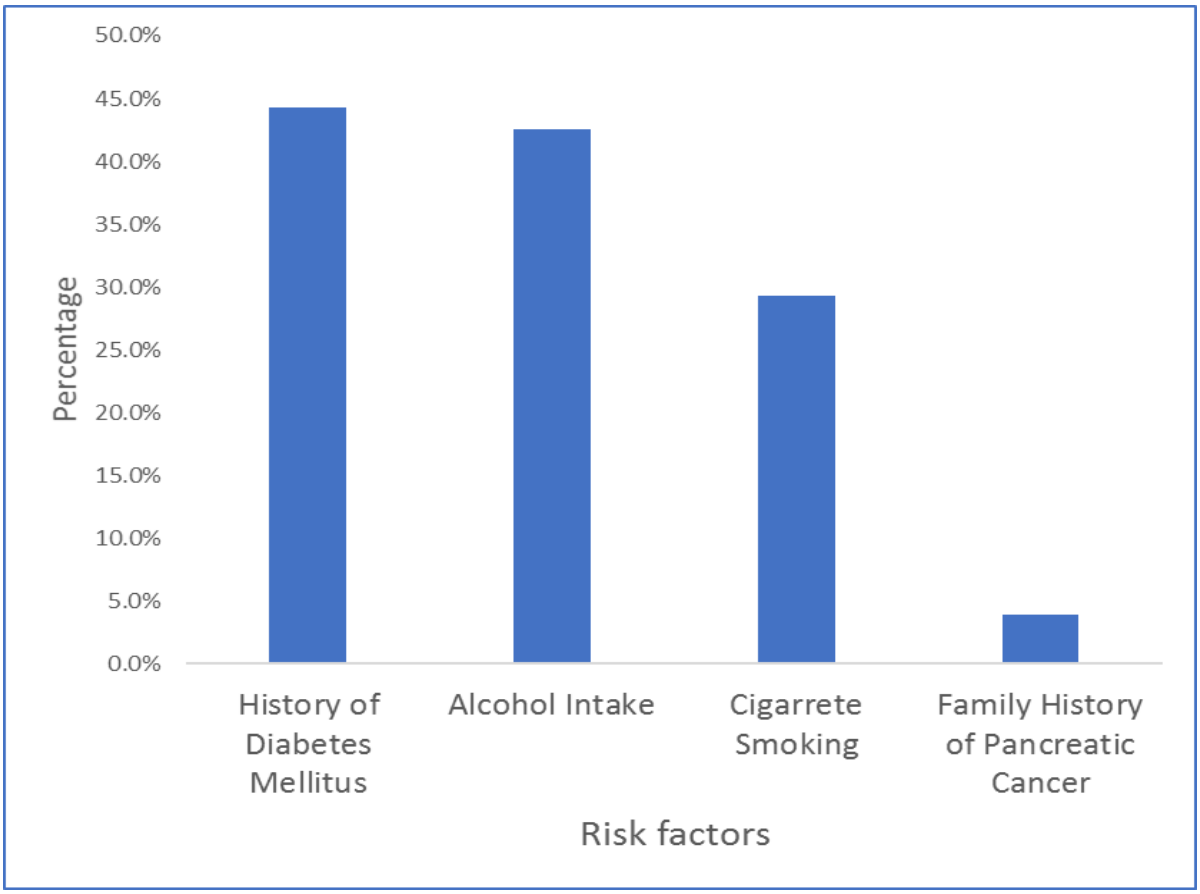


Figure 1: Showing distribution of risk factors assessed for patients with pancreatic masses at MNH between 2018 and 2019

Figure 2 below shows the timing of diagnosing DM to the occurrence or detection of pancreatic mass. It was noted that all patients developed DM in their adult life. In 51.7% of the patients, DM was diagnosed before Pancreatic Mass, while in 19% it was diagnosed after the detection of the pancreatic mass and in 29.3% the two diseases were diagnosed concurrently.

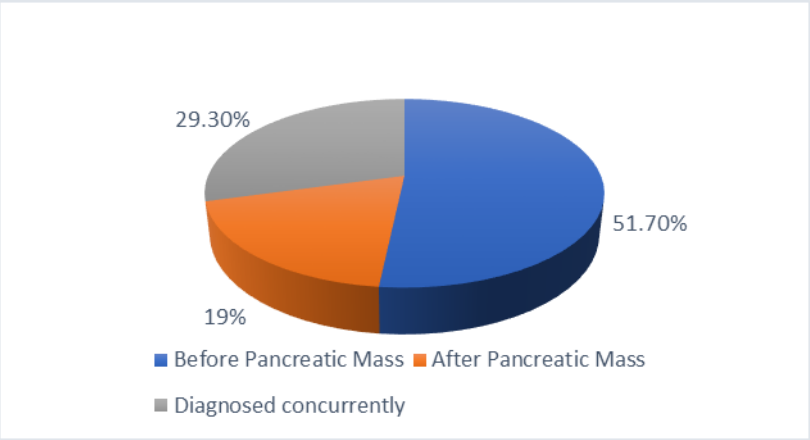


Figure 2: The Pie chart shows approximate timing of a diagnosis of Diabetes Mellitus in relation to the detection of the pancreatic mass

Investigations

Figure 3 below shows investigations that were done on patients to make diagnosis, and stage the patients. Eight investigations were done in varied proportions for these patients with abdominal CT being the most commonly done as was in 72.1% of the patients followed by chest x-ray in 69.4% and the rest as shown. Of significant to note was that only 32.7% had a histological diagnosis and 40.8% CA19.9.

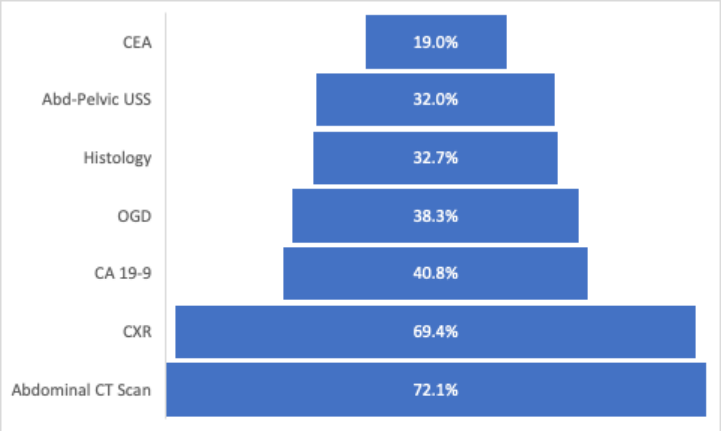


Figure 3: showing investigations done to patients with pancreatic masses at MNH in 2018/2019

Histology results, Location of the mass and WHO Staging

Table 2 below shows the histology results, the mass location on the pancreas and WHO staging. Among the 48 patients with histological diagnosis, Adenocarcinoma was the most common histology (68.8%), followed by Inflammation in (27.1%), and the rest had papillary cyst. Most pancreatic masses were located at the head of the pancreas (81.1%) and the least being masses involving the whole pancreas (4.5%). In the WHO Staging, it was revealed that only 13.7% of the masses were resectable whereas majority (57.3%) presented as metastatic disease at time of admission. 23 (15.6%) patients, were not staged due to absence of sufficient investigations. Regarding treatment modalities, only 9 patients underwent curative resections. Majority of the patients had palliative treatment which included palliative surgeries and chemotherapy. Almost a quarter of patients died before they could receive either palliative or curative treatment.

Table 2: Shows patients' histology results, location of the mass on the pancreas and the WHO stage assigned and the various treatments offered for each patient managed for pancreatic mass at MNH between 2018/2019.

	Frequency (%)
WORK UP	
Histology, N=48	
Adenocarcinoma	33 (68.8)
Inflammation	13 (27.1)
Papillary cyst	2 (4.2)
Location of the mass, N=111	
Head	90(81.1)
Body	9 (8.1)
Tail	7 (6.3)
Whole Pancreas	5 (4.5)
WHO Staging, N=124	
Resectable	17 (13.7)
Borderline Resectable	11 (8.9)
Locally advanced unresectable	25 (20.2)
Metastatic	71 (57.3)
TREATMENT	
Curative Surgery	9 (6.1)
Pancreaticoduodenectomy	5 (55.6)
Distal Pancreatectomy	4 (44.4)
Palliative Surgery	83(56.5)
CJ	30 (36.1)
GJ	23 (27.8)
CJ and GJ	29 (34.9)
Only Biopsy taken	1 (1.2)
Palliative Chemotherapy	23 (15.6)
Died before treatment	32 (21.8)

Note: CJ – Cholecystojejunostomy, GJ – Gastrojejunostomy

Association between patients' characteristics and resectability of the pancreatic mass

Table 3 below shows the association between various patients' characteristics and the resectability of the pancreatic mass depicted by the WHO clinical stage. About 66.7% of patients with young age below 40 years had resectable disease whereas majority of those with age above 40 years were associated with Metastatic disease and this difference was statistically significant. Only 9.1%of patients residing outside Dar es salaam presented with resectable disease while out of those residing in Dar es salaam 19.1% presented with resectable disease. This was also statistically significant with a P-value of 0.004.

Table 3: Shows the association between patients' characteristics and the WHO staging for resectability of pancreatic mass at MNH between 2018/2019.

	WHO Staging (N=124)				
Variable	Resectable	Borderline resectable	Locally advanced unresectable	Metastatic	P value
Age (years)					
<40	8(66.7)	-	2(16.7)	2(16.7)	
40−49	2(11.1)	3(16.7)	1(5.6)	12(66.7)	
50−59	3(14.3)	-	7(33.3)	11(52.4)	0.001
60-69	2(5.1)	3(7.7)	7(17.9)	27(69.2)	
70-79	2(6.9)	2(6.9)	8(27.6)	17(58.6)	
>79	-	3(60)	-	2(40)	
Sex					
Male	8(12.7)	2(3.2)	16(25.4)	37(58.7)	0.088
Female	9(14.8)	9(14.8)	9(14.8)	34(55.7)	
Place of Residence					
Dar es Salaam	11(19.0)	11(19.0)	12(20.7)	24(41.4)	0.004
Outside Dar es Salaam	6(9.1)	-	13(19.7)	47(71.2)	
Level of Education					
No formal education	4(14.8)	3(11.1)	-	20(74.1)	
Primary Level	11(17.7)	5(8.1)	17(27.4)	29(46.8)	0.001
Secondary Level	-	-	6(25)	18(75)	
College/University	17(13.7)	3(27.3)	2(18.2)	4(36.4)	
Employment status					
Employed	7(23.3)	-	8(26.7)	15(50)	
Retired	-	8(27.6)	8(27.6)	13(44.8)	0.024
Unemployed	10(15.4)	3(4.6)	9(13.8)	43(66.2)	
Tumor Location					
Head	9(10.5)	8(9.3)	20(23.3)	49(57)	
Body	2(22.2)	-	-	7(77.8)	0.038
Tail	4(57.1)	-	-	3(42.9)	
Whole Pancreas	2(50)	-	-	2(50)	

CHAPTER FOUR

4.0 DISCUSSION

This is the first study in Tanzania that we know of to describe pancreatic masses. A total of 147 patients were managed at MNH during the period of 2 years under review. Only 9 (6.1%) patients underwent curative resection, this is lower than global estimates[23]. In this study, only a third of patients had histology done, thus discrimination of benign from malignant masses was not feasible. Hence some parameters maybe under/overexpressed due to the differences in presentation and management of these two entities. The findings of this study can be used to make inference on the situation of pancreatic masses in the country since it was done in the National Hospital which receives patients from all regions of the country.

With several authors showing that less than 10 percent of patients are diagnosed below the age of 55 years and most of them are diagnosed in their 7^{th} and 8^{th} decades of life[9], it is clear that we see a lot of younger patients in our setting. Almost a third of patients were below the age of 55. The reason for this is yet to be studied. Likewise, there was a slight gender predilection showing a male predominance. The male to female ratio was 1.16:1, in line with international and regional studies[5,10]. The reason for this might be a greater exposure of some risk factors such as smoking and alcohol which are expected to be more common among males.

Delay in developing symptoms is a common observation among patients with pancreatic masses, with symptoms developing late in the course of the illness. It is expected that patients will show up for medical consultation right after developing symptoms. In our study, patients took over 4 months since initial presentation to time of diagnosis. This is longer time compared to that seen in the western countries where patients are usually diagnosed within the first month of symptoms presentation[35]. Another study in Nigeria showed that most patients presented within the first 2 months[6]. The reason for delay might be multifactorial, with low socio-economic status being one of them. Most of our patients had low education level and were unemployed which are surrogate markers of low socio-economic status.

Studies have shown cigarette smoking and alcohol intake to be risk factors for pancreatic masses[15-17]. The same is depicted in our study were a third of patients were cigarette smokers and almost half consumed alcohol. A similar picture is depicted in other African countries like Algeria[5]. Regarding family history of pancreatic cancer, only 3.9% of patients were picked in this study, a number very low compared to findings from other studies[40]. Similarly, a study done in Nigeria showed none of the patients had family history of pancreatic cancer[6]. This difference could be attributed to poor documentation and small sample size which were limitations mentioned in the later study and may also apply in our study.

It has been shown that DM is a common presentation among patients with pancreatic masses[14]. Our study showed that about half of patients had DM, with more than half having the diagnosis before the Pancreatic mass. With lack of insulin level measurements, it was difficult to distinguish type 1 from type 2 DM in our cohort, however, all of our patients were diagnosed in adulthood, making type 2 DM more likely. The relationship between pancreatic mass and DM as it's risk factor or a complication needs to be established. This should enlighten clinicians to have a high index of suspicion of pancreatic mass in elderly patients who are newly diagnosed to have DM.

Despite the importance of abdominal ultrasound as an initial investigation in patients with clinical features suspicious of pancreatic mass[9], it was only done in one third of our patients. We therefore emphasize clinicians to adapt this practice in all suspicious patients as some might be missed if this important step is skipped. We also noted that almost one out three of patients did not have an abdominal CT scan which is very crucial in diagnosis and staging of pancreatic mass[9]. Even though CT scan services are readily available in our center, it is not known why only a fraction of patients had this investigation. During the review of abdominal CT scan, it was observed that all of them where abdominal scans lacking the pancreatic protocol. Failure to do pancreatic protocol could partially explain the low resection rates seen in this study.

Although chest CT scan is the most preferred imaging to asses for lung and/or pleural metastasis, chest Xray is also an alternative[37] but it was done only in two third of our patients. Despite the usefulness of the marker CA 19-9 in the diagnosis and follow up of patients with pancreatic masses[37] less than half of our patients had it done, emphasizing still on how our patients are under investigated. The implication of under-investigation is assigning the wrong stage to the patient and hence the wrong management. Regarding tumor location, our study shows that 8 in 10 of the pancreatic masses were in the head. This is also shown in other studies where masses in the head where more common followed by the body and tail respectively[5,9,39].

The NCCN guidelines recommend that for patients with potentially resectable pancreatic mass, surgery should be done without prior histology, however, patients with metastatic or locally advanced unresectable disease, biopsy is required before initiation of chemotherapy treatment[37]. However, since pancreas biopsy in non-operated patients, can only be obtained by CT or USS guided percutaneous FNAC or by endoscopic USS[32], this explains why a very small proportion of our patients had histology results. We expect the number to increase in the near future due to a recent established section of interventional radiology in our center that will enable us to perform more percutaneous pancreatic biopsies. With several authors supporting the use of EUS-FNAB over percutaneous approach due to decreased safety and risk of seeding associated with the later[41,42], the need of establishing EUS-services in our center cannot be over emphasized.

This study also identified missed opportunities for establishing histological diagnosis among patients with pancreatic masses. All patients who underwent resection had reported histology. However, among the 83 patients who had palliative surgical procedures, only 39 patients, equivalent to just under half, had biopsy taken and reported. Overall, the most predominant histology was that of an adenocarcinoma, and this conquers with other literature[5]. The fact that almost one third of the reported histology was inflammation emphasizes the need of histological diagnosis to differentiate benign from malignant disease and hence offer appropriate treatment. Abandonment of care without proper histological diagnosis is

worrisome in our setting and denies patients with non-malignant diseases from receiving appropriate treatment while exposing them to unwarranted chemotherapy for palliation.

Most patients in our study had advanced disease, i.e., locally advanced unresectable and metastatic disease at time of diagnosis, with only 13.7% potentially resectable masses. We noted that young age is associated with resectable disease compared to the older group and this was statistically significant. The reason could be health seeking behavior of the former, and likelihood of benign disease in the young population. Other predictors of resectability included the area of residence, whereby majority of patients residing in the city presented with resectable disease and those who reside outside the city presented with unresectable and metastatic disease. Delays in making diagnosis in the peripheral hospitals or delays in the referral system could explain this statistically significant difference, however, further studies are needed to verify these hypotheses. On the other hand, most of our patients who had a source of income, either employed or retired, were more likely to present with a resectable disease compared to the unemployed patients.

The mainstay of treatment in unresectable disease is palliative chemotherapy and palliation of jaundice and/or gastric outlet obstruction. In absence of self-expanding metal stents in our center, biliary bypass is the alternative option for palliating jaundice hence most of our patients underwent palliative surgery the leading being cholecystojejunostomy, followed by combined cholecystojejunostomy and gastrojejunostomy then gastrojejunostomy alone. Further studies are needed to evaluate the outcomes of these procedures.

The role of neo-adjuvant chemoradiation particularly in borderline resectable pancreatic cancers is not negligible as some studies show that it improves treatment outcomes and increases survival rates[37]. However, in this study, none of the patients with borderline resectable pancreatic mass was sent for neo adjuvant chemoradiotherapy but rather they were all treated either by palliative surgery or sent for palliative chemotherapy. This denies them a chance of cure in selected patients who could benefit surgical resection following the mentioned therapy.

CHAPTER FIVE

5.0 CONCLUSION, RECOMMENDATION AND STUDY LIMITATIONS

5.1 Conclusion

Patients with pancreatic masses were found to have late presentation, had advanced disease, had DM, were under investigated and potentially assigned wrong stage, with ultimate low resection rates. Similarly, few patients had histology results with benign ones not uncommon. Young age at diagnosis, urban residency, and being employed were positive predictors of resectability due to early diagnosis.

5.2 Recommendations

All with pancreatic mass should have a pancreatic protocol CT-scan with appropriate WHO clinical staging. All patients who will not receive upfront surgery, must have histological/cytological diagnosis. All patients with borderline resectable categories must be subjected to neo-adjuvant chemo-radiotherapy if they are fit to tolerate. CA19-9 should be routinely done to all patients with pancreatic masses. A prospective study to fully understand the clinical and pathological presentation of pancreatic masses is needed.

5.3 Study Limitations

The retrospective nature of the study resulted in incomplete variables. Such missing variables were left out during the analysis part.

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APPENDICES

Appendix I: Data collection tool

A) DEMOGRAPHIC DATA

1. Name…….
2. File number……
3. Year of attendance……..
4. Firm …….
5. Age ……

6. Gender 1) Male 2) Female
7. Residence……

8. Ethnicity 1) African
   2) Asian
   3) Caucasian
   4) Others

9. Education a) no formal education
   a) Primary level
   b) Secondary level
   c) collage/university

10 . Occupation
   1) Peasant
   2) Employed
   3) Unemployed
   4) Retired

B) RISK FACTORS FOR PANCREATIC CANCER

11. Cigarrette smoking 1) Yes 2) No 3) Not documented

12. Alcohol intake 1) Yes 2) No 3) Not documented

13. Family History of pancreatic cancer 1) Yes 2) No 3) Not documented

14. History of chronic pancreatitis 1) Yes 2) No 3) Not documented

15. History of Diabetes Mellitus 1) Yes 2) No 3) Not documented If yes go to qn 16, If No or Not documented, go to qn 18.

16. Type of Diabetes Mellitus 1) Type one 2) Type two 3) Not documented

17. Which was diagnosed first 1) DM 2) Pancreatic Cancer 3) Diagnosed concurrently

C) CLINICAL PRESENTATION

18. Abdominal Pain 1) Yes 2) No

19. Obstructive Jaundice 1) Yes 2) No

20. Gastric Outlet Obstruction (Projectile Vomiting) 1) Yes 2) No

21. Weight loss. 1) Yes 2) No

22. Others …….

……

23. Duration of symptoms in months …….

D. DIAGNOSIS

24. Abdominal CT-Scan 1) Yes 2) No

25. Surgery (Intraoperatively) 1) Yes 2) No

26. Endoscopically through OGD 1) Yes 2) No

27. Histology 1) Yes 2) No, If no go to qn 29

28. Histology results

……

29. Was CA19-9 done? 1) Yes 2) No, If no, go to qn 31

30. CA19-9 level on admission ……..

31. Tumour location 1) Head 2)Body 3) Tail 4) Involving whole pancreas

E. METASTATIC WORK UP

32. CXR 1) Yes 2) No

33. CT SCAN Thorax 1) Yes 2) No

34. Abdominal - Pelvic Ultrasound 1) Yes 2) No

35. Others

……

……

36. WHO Staging 1) resectable 2) boarderline resectable 3) Unresectable 4) Metastatic

F. TREATMENT

37. Treatment Intent 1) Curative 2) Palliative, If 2 go to qn 31.

Mode of treatment

38. Type of Surgery perfomed 1) Whipple's pancreatico-duodenectomy
2) Distal Pancreatectomy
3) Total Pancreatectomy

39. Was the patient sent for adjuvant chemotherapy after the above surgery? 1) Yes 2) No

40. What palliative treatment did the patient receive? If 1) or 3), go to qn 38.

1) Palliative Surgery
2) Palliative Chemotherapy
3) Both palliative Surgery and palliative Chemotherapy
4) PTC
5) None of the above

41. Type of Surgery performed

1) Cholecystojejunostomy
2) Gastrojejunostomy plus Jejuno-jejunostomy
3) Triple bypass with Roux-en-Y reconstruction
4) Triple bypass with brauns reconstruction
5) Only biopsy taken
6) Open and close
7) Others ……