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Clinical profile and treatment outcomes of patients with pancreatic cancer at ocean road cancer institute, tanzania.

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Abstract

Background Information: *Pancreatic cancer is one of the most challenging tumor entities worldwide, characterized as a highly aggressive disease with a dismal overall prognosis and an incidence rate equaling mortality. Its incidence is reported to be increasing yearly among the developing and developed countries. In Africa, the incidence of pancreatic cancer has been reported to rise at a rate of 1.4%. PC is associated with several risk factors including cigarette smoking, family history of PC as well as early-onset Diabetes Mellitus (DM), and alcohol consumption. It is diagnosed at late stages because signs and symptoms are non-specific, which cut across many other medical conditions. The majority of PC are pancreatic adenocarcinoma (PDAC), with over 85% of cases. Unfortunately, there is a scarcity of data on the burden of this form of cancer in Tanzania. Therefore, this study will describe risk factors and associated clinicopathological features with one-year overall survival.*

The objective of the study: *This study aimed to determine the clinic-histopathological characteristics of pancreatic cancer, treatment modalities as well as assess the one-year overall survival rate of PC with associated factors.*

Methodology: *This was a single center-based retrospective study conducted among 106 patients treated at ORCI from 2006-2018. The study used patient records systems to pull information such as demographics, risk factors, presentation, pathological features, treatment modalities, and survival outcome which was put on prepared data extraction form. The analysis was done using SPSS version 23 whereby proportion was used to summarize categorical data. Measures of central tendencies were used to summarize continuous variables. Kaplan Meir survival analysis was used to study the 1-year survival rates. The one-year overall survival was chosen not only due to the current median survival of 5months among PC patients (1), but also that in Africa, patients are diagnosed in advanced stages leading to failure to receive definitive treatment with curative intent, and succumb to death in less than 6 months (2).*

Association between dependent and independent factors was compared using the log-rank method while Cox regression was used to assess cumulative influence independent variables.

P-value <0.05 was considered statistically significant.

Results: *This study recruited 106 patients. Most of the study participants were male, 66(62.3%). The patients mean age (SD) was (50.44±17.87). Majority of these participants engaged with small-scale farming and business. Few, 20(18.9) had a history of smoking and 25(23.6%) had a history of alcohol consumptions. The 1-year mean overall survival rate was 43%. Clinical examination showed 63(59.4%) found with jaundice. Essentially, ductal carcinoma was prevalent with the majority of the tumor initiated in the head section of the pancreases. The majority of the patients were treated with palliative intent. Chemotherapy was given among many patients. The one-year survival rate with no history of alcohol consumption, smoking, and no family history of cancer was 40.79%(P- value=0.946), 39.74%(P-value=0.232), and 38.96%(P-value=373) respectively. The survival distribution of histologies, tumor size, and different treatments were statistically significant predictors of survival with P-value of P<0.0001, P=0.017, and P=0.001 respectively.*

Conclusion: *This is the first survey in Tanzania. It has managed to disclose similar factors related to pancreatic cancer. Pancreatic cancer is not uncommon. The majority of patients present with an advanced disease which limits the best treatment modalities with curative intent. Patients who received multiple treatment modalities i.e surgery and chemotherapy have shown to have better outcomes. The tumor size was strongly related to treatment outcomes with tumors less than 4cm had a better prognosis. Proper documentation is key to enable follow-up of patient care and aid in the continuum of research. It is non-trivial to consider an additional diagnostic Endoscopic retrograde cholangiopancreatography (ERCP) in patients above 40years suspected of GastroIntestinal conditions such as stomach cancer. With the advent of radiation therapy in the management of pancreatic cancer, a prospective study would have generated adequate information with regards to treatment outcome, and/or quality of care.*

List of Abbreviations

AHPBA American Hepato-Pancreatic-Biliary Association

AJCC American Joint Committee on Cancer.

ASR Age-standardized rate

CA Celiac axis

CT Computed tomography

DM Diabetes Mellitus

ECOG Eastern Cooperation Oncology Group

ESMO European Society of Medical Oncology

ESPAC European Study Group for Pancreatic cancer

EUS Endoscopic Ultrasound

GIT Gastrointestinal Tract

GLOBOCAN Global Cancer Incidence, Mortality and Prevalence

GUT Genito-urinary Tract

KPS Karnofsky's performance status

MNH Muhimbili National Hospital

MUHAS Muhimbili University of Health and Allied Sciences

NCCN National Comprehensive Cancer Network

ORCI Ocean Road Cancer Institute

OS Overall survival

PC Pancreatic cancer

PDAC Pancreatic Duct Adenocarcinoma

PNETS	Pancreatic Neuroendocrine Tumours
PFS	Progression-free survival
PV	Portal vein
RT	Radiotherapy
SEER	Surveillance, Epidemiology and End Results
SN	Sensitivity
SP	Specificity
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein

Introduction and Literature Review

Background information.

Pancreatic cancer is a global indisposition with increasing morbidity and mortality. Initially, it was uncommon until recent data from the GLOBOCAN 2018 that show its rising incidence by 2.5% (1). In the world, incidence rates differ from each continent and from country to country. It is highest in American and Europe but lowest in Southern Asian and Africa. PC is projected to be the second commonest cancer in the United States of America in the year 2030(3). The prognosis of this cancer has not shown any sign of improvement for over 20years.

Pancreatic cancers arise from both the exocrine parenchyma of the gland and endocrine islets cells. The majority occurs within the exocrine portion in over 90%; usually arise from the ductal epithelium, acinar cells, or connective tissue(4). Less than 2 % of the tumors of the exocrine pancreas are benign. The most common pancreatic cancer is a ductal adenocarcinoma, which accounts for 80% of all pancreatic cancers(4). Neuroendocrine tumors of the pancreas are the second most frequent pancreatic cancers.

Since the cause of pancreatic cancer remains unknown, several studies have shown relationships of factors that predispose to the development of pancreatic cancer. Cigarette smoking has been widely studied and

is commonly associated with pancreatic cancer. About 5-10% is familial (4). Diabetes Mellitus, Helicobacter pylori, Human Immunodeficiency Virus (HIV), and hepatitis B virus are other factors that have been reported to be associated with the relative risk of developing pancreatic cancer.

The mean age at diagnosis is 70years with male predominance, however, this disease is not limited to age below 50years(5). Symptoms of pancreatic cancer are non-specific, nevertheless, Obstructive jaundice is the commonest and suggestive for diagnosis of pancreatic cancer especially in the African setting, this could be because of late presentation at an older age and the fact that most tumors are located at the head of the pancreas(5,6). Other symptoms include; abdominal pain, weight loss, vomiting, pruritus, and anemia.

The biopsy is the confirmatory test for the diagnosis of pancreatic cancer. It is obtained through endoscopy ultrasound-guided fine-needle aspiration (EUS-FNA) which has a high diagnostic accuracy of about 95% (7). CA 19-9 is not a useful diagnostic marker. It's detected in patients who have Lewis enzyme, which is found in 7-10% of the population (4). Serum levels are seen to be high in advanced PC. CT scan and MRI have been shown to provide equal benefit in assessing vessel involvement. Other supportive investigations that help in assessing patients' general health include complete blood count (CBC), liver function tests (LFT), and renal function tests (RFT).

Before treatment, staging according to AJCC and classifying pancreatic cancer using the resectability criterion is important. 5-year overall survival for the combined stages is about 9% (8). Surgical resection remains the potential cure for the treatment of pancreatic cancer; however, only 20% have a resectable disease (4). Locally advanced and metastatic pancreatic cancer is treated by chemotherapy. Chemo-radiotherapy has not been recommended due to controversies from various studies, and toxicity(9).

There is a dearth of data regarding pancreatic cancer within the African continent, particularly Tanzania. For this reason, this study aims to determine the clinical characteristics (socio-demographics -age, risk factors, and clinical presentation), pathological characteristics of patients with pancreatic cancer (histological types, grade, and stage), treatment modalities, and outcome for patients attending at ORCI, Tanzania.

Problem Statement and Rationale of the Study.

Pancreatic cancer presents clinically with jaundice owing to the destruction of the bile duct by the malignant lesion, abdominal pain, or weight loss. It has a poor prognosis accredited by late diagnosis. It is ranked as the 13th most common cancer in the world, 16th in Africa but 28th in Tanzania. It is so difficult to diagnose in the early stages of pancreatic cancer because the signs or symptoms are silent and 80-90% of patients have unresectable tumors at the time of diagnosis.

Treatment of pancreatic cancer depends on the criteria for resectability and other factors mentioned. However, surgery remains the only potentially curative treatment for pancreatic cancer. Apparently, due to the advanced stage of the disease at presentation, approximately, 15%-20% of patients have resectable disease. Even so, the majority of them, actually have a borderline resectable and therefore poor prognosis. Other treatment modalities for pancreatic cancer are chemotherapy, radiation therapy, and palliation therapy. According to the European Society of Medical Oncology (ESMO), and the National Comprehensive Cancer, the roles of chemotherapy, radiation therapy, and palliative care are to alleviate symptoms. According to the Surveillance, Epidemiology and End Results Program, (SEER 18,2009-2015), the percentage of patients with pancreatic cancer that survived 5 years was 9.3%, and the relative survival rates by stage 37.4%, 12.4%, 2.9%, and 5.6% for localized, regional, distant and unknown, respectively(10).

At Ocean Road Cancer Institute (ORCI), only 91 cases were reported in 9 years, (2006- 2014). ORCI cancer protocol provides chemotherapy to patients suffering from locally advanced and metastatic pancreatic cancer, which is similar to other centers in Africa. Unfortunately, due to a lack of data, it is essential to the current clinicopathological characteristics, demographic information, treatment modalities, and overall survival predictors of pancreatic cancer patients in Tanzania. Therefore, this study aims at describing the clinical profile and one-year overall survival of patients with pancreatic cancer at ocean road cancer institute Dar es Salaam, Tanzania.

Conceptual framework

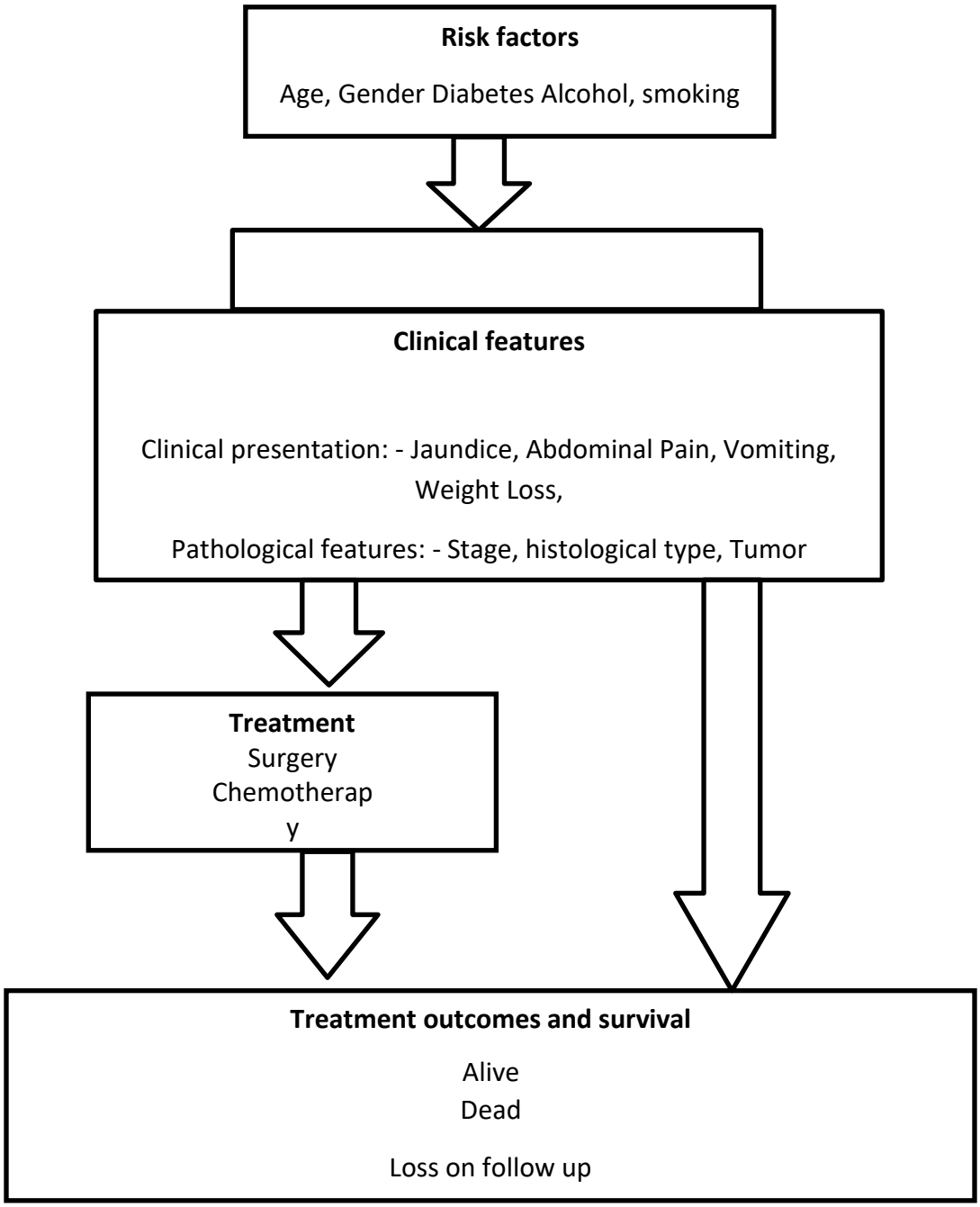

Figure 1: Conceptual framework.

The figure above shows the relationships of various factors in the study on pancreatic cancer at ORCI, Tanzania. The social-demographic factors, e.g. Age, have been associated with the development of pancreatic cancer. It's more common among the elderly. Clinical features have been shown to have a reciprocal relationship with the pathological types, stages, and location of the disease. The tumor characteristics mentioned have a significant role in the choice of treatment. The treatment outcomes will be evaluated in terms of 1- year overall survival (whether dead or alive), and any response to therapy documented from the patients' clinical records.

Research Questions:

1. What are the clinical characteristics of patients with pancreatic cancer who attended at ORCI from 2006 to 2018?
2. What are the associated risk factors of pancreatic cancer at ORCI?
3. What are the treatment modalities employed among patients with pancreatic cancer at ORCI?
4. What are the 1-year overall survival rates and associated factors among patients with pancreatic cancer at ORCI?

Objectives

Broad Objectives

1. To determine the clinical and pathological characteristics, treatment modalities, and treatment outcomes of patients with cancer of the pancreas at ORCI, Tanzania, from 2006 to 2018.

Specific Objectives

1. To identify risk factors associated with pancreatic cancer treated ORCI from 2006 to 2018.
2. To determine the clinical characteristics of patients with pancreatic cancer treated at ORCI from 2006 to 2018.
3. To determine the various treatment modalities applied for patients with pancreatic cancer treated at ORCI from 2006 to 2018.
4. To determine 1-year overall survival and associated factors among PC treated at ORCI from 2006 to 2018.

Literature Review

Risk factors of PC.

The Surveillance, Epidemiology, and End Result Program noted that the median age for the development of pancreatic cancer is around 70 years of age with a slight male to female predominance (10). On the contrary, according to the medical journal of Zambia, the median age at diagnosis was noted to be 54years (6). In Tanzania, no known study has demonstrated the median age at presentation. The risk of developing pancreatic cancer increases with age (1,2,4,11). Pancreatic cancers develop between the ages of 60 and 80 years. Pancreatic cancer rarely occurs before the age of 40 (4), and more than half of cases of pancreatic adenocarcinoma occur in those over 70 (4). A Meta-analyses demonstrated associations between both type 1 and type 2 diabetes mellitus and pancreatic cancer, with odds ratios of 2.0 and 1.8, respectively (12). The most common cause of chronic pancreatitis is excess alcohol consumption(4,13,14). However, the causal pathway is not well understood. Alcohol consumption by itself is related to an increased risk of pancreatic cancer (4). Several studies have shown that Body mass index (BMI) has a significant association with PC development, but this remains controversial (16),. A study done by Gustav Anderson found that BMI has no significant association with PC (16).

Clinical characteristics of patients with pancreatic

Clinical manifestation.

Pancreatic cancer, PC, is one of the most lethal malignancies that is diagnosed in advanced stages because the symptoms are not classical hence treatment resistance and poor overall survival (4,15). Common presenting symptoms of pancreatic cancers include jaundice (for tumors of the head), abdominal pain, weight loss, steatorrhea, and new-onset diabetes. These symptoms and signs depend on the type of pancreatic cancer and the location within the pancreatic structure as well as usually quite vague. Approximately 60% -70% of pancreatic cancer is located in the head of the pancreas, 20%–25% in the body and the tail, and the remaining 10%–20% diffusely involve the pancreas(4,16). Tumors located in the body and the tail are likely to be diagnosed at a more advanced stage than tumors located in the head, as these can develop symptoms related to obstruction of the common bile duct and/or the pancreatic duct(4,6,17).

Tumors can grow locally into the duodenum (proximal for tumor of the head and distal for tumor of the body and tail) and result in an upper gastroduodenal obstruction (5,13). In a study by Chara Ntala et al, it was found that obstructive jaundice was the most frequent presenting symptom, followed by anorexia, abdominal pain, nausea, and vomiting (5). PC was once a rare disease but the trend shows the is a gradual increase in this form of cancer whose most predictive diagnosis base on the clinical presentation, however, there is insufficient data on the most commonly reported symptoms, therefore this study will identify the sign and symptoms of PC among previously treated patients at ORCI from 2006 to 2018.

Pathological features.

The American Joint Committee on Cancer (AJCC) on the TNM system is the most used staging system for pancreatic which is based on the 3 key pieces of information: T for the extent of Tumor, N=spread to nearby lymph Node, M= spread to distant sites, Metastases (7). Appendix II shows the tumor, node, metastasis (TNM) staging, and classification criteria for resectability.

Pancreatic cancers involve either the exocrine parenchyma or the endocrine islet cells. PC is classified by histology as adenocarcinoma, neuroendocrine tumor, squamous cell carcinoma, ampullary carcinoma, intraductal papillary mucinous neoplasm, solid pseudopapillary tumor, mucinous cystic neoplasm, mucinous cystadenocarcinoma, and serous microcystic adenoma. About 98% of pancreatic cancers arise from the exocrine pancreas and the vast majority are Pancreatic cancer Ductal adenocarcinoma (PDAC), which makes up 85% to 90% of malignant pancreatic neoplasms (18). 60%-70% occur in the head of the pancreatic gland, 9% in the body, 8% in the tail, 6% in overlapping sites, and 20% in unknown anatomic subsites (4). Uncommon variants of pancreatic cancer include adenosquamous, oncocytic, clear cell, giant cell, signet ring, mucinous, and anaplastic carcinoma. According to the Ocean Road Cancer Institute, (ORCI), the total number of cases of pancreatic cancer reported was 91 between 2006 and 2014, with 45% involving the head of the pancreas (19). This, perhaps, may illustrate how rare this form of cancer is in Tanzania.

With regards to the American Hepato-Pancreato-Biliary Association (AHPBA) consensus report, pancreatic ductal adenocarcinoma especially when metastases are absent is classified as resectable, borderline resectable, or unresectable. At the time of diagnosis, pancreatic ductal adenocarcinoma is resectable in 15%–20% of patients. According to the degree of contact between the tumor and the vessels (Portal Vein(PV) or Superior Mesenteric Vein(SMV), Superior Mesenteric Artery(SMA), coeliac trunk,

and common hepatic artery), tumors are classified as resectable, borderline resectable or locally advanced. The National Comprehensive Cancer Network (NCCN) guidelines adopted the consensus report, that patients with locally advanced or metastatic disease are considered as having unresectable tumors (7).

Notably, the kind of treatment applied is profoundly influenced by the pathological feature, in Tanzania, due to the rarity of the disease, though gaining pace, the distribution of the pathological features is almost unknown. Therefore, this study will map the distribution of pathological features of these PC tumors.

Treatment of PC cancer.

According to Ocean Road Cancer Institute, (ORCI) guidelines, options for chemotherapy include; Gemcitabine alone therapy, which is given as 1000mg/m2 IV on day 1, day 8, and day 15, every 4 weeks for 6 cycles, or as a combination with Oxaliplatin, and Gemcitabine

+ Capecitabine: Gemcitabine 1000 mg/m2 iv day 1 and Capecitabine 650 mg/m2 per oral (PO) day1 to day 14 Every 3 weeks. However, ORCI guideline does not include radiation therapy as part of the treatment of pancreatic cancer.

The ESMO and the NCCN, provided profound guidelines based on whether the disease is localized, non-resectable borderline, non-resectable locally advanced, or metastatic disease(4). PC that is localized, ESMO recommends that a multidisciplinary team is necessary, the tumor clearance should be given for all seven margins identified by the surgeon, standard lymphadenectomy should involve the removal of at least 15 lymph nodes to allow adequate pathologic staging of the disease, adjuvant treatment is done with either gemcitabine or 5-FU folinic acid(4). No chemoradiation should be given to patients after surgery except in clinical trials. Treatment of non-resectable disease/borderline resectable lesions; patients in this category should be included in clinical trials wherever possible, however, in routine practice, if the patient is not included in a trial, a period of chemotherapy followed by chemoradiation and then surgery appears to be the best option(4). For non-resectable disease/locally advanced disease, the standard of care is 6 months of gemcitabine. Treatment of metastatic disease, majorly palliative and supportive care: duodenal obstruction is preferably managed by endoscopic placement of an expandable metal stent when possible, and is favored over surgery. Biliary stenting (the endoscopic method is safer than percutaneous insertion and is as successful as surgical hepaticojejunostomy). This study, therefore, aims at describing the treatment offered to PC patients at ORCI.

Treatment outcomes and survival rates

According to the Surveillance, Epidemiology and End Results Program, (SEER 18,2009- 2015), the percentage of patients with pancreatic cancer that survived 5 years was 9.3%, and the relative survival rates by stage 37.4%, 12.4%, 2.9%, and 5.6% for localized, regional, distant and unknown, respectively (10).

In a Romanian study by Timofte et al, the overall survival predicted for postoperative patients with pancreatic cancer was 41.7%, at 1year, 8.7%at 3years, and 1.9% at 5years on 188 patients. In the Nigerian study by O. I. Alatise et al, the Median survival for patients that had triple bypass using a bowel loop was 3 months, while the median survival for a patient that had triple bypass using an isolated bowel segment was 5 months(2).

From the National Comprehensive Cancer Network, (NCCN) data, chemotherapy has been shown to provide significant survival benefits to all patients with resectable, borderline resectable, and unresectable pancreatic cancer. CONKO-001 trial, compared to gemcitabine was given postoperatively (post-op), with surgery alone. Comparing the treatment group to the observation group, the median disease-free survival rate was 13.4 months in the treatment group. The patients that were randomized to post-op gemcitabine had twice the 5-year overall survival advantage compared with those in the observation group (20.7% vs 10.4% respectively)(20).

Gemcitabine based combination remedies have shown impressive survival advantages. In the European Study Group for Pancreatic Cancer,(ESPAC),4 trials; showed that adjuvant combination of gemcitabine and Capecitabine had better 5-year OS and PFS in resectable PDAC patients (21). Other multidrug regimens, for example, FOLFIRINOX, have demonstrated improved survival benefits despite its toxicity profile in comparison to gemcitabine alone regimen as adjuvant therapy in pancreatic cancer(4,22,23). For the treatment of locally advanced pancreatic cancer, the role of radiation therapy has been controversial in many studies. Based on the European Study Group for Pancreatic cancer (ESPAC-1) Trial, the study showed no survival benefit between receiving chemo- radiotherapy and those who did not (15.5 vs 16.1 months) (18). Chemotherapy remains the recommended standard of care for locally advanced and metastatic pancreatic cancer (4,24,25).

At ORCI, patients receive gemcitabine alone therapy or FOLFOX (5-fluorouracil and Oxaliplatin) as a palliative or adjuvant chemotherapy respectively. Unfortunately, no data on treatment outcome and the overall survival of patients with pancreatic cancer has been reported at ORCI, Tanzania.

Material and Methods

Study design

This was a retrospective hospital-based descriptive study, one that depended upon the records of patients who had confirmed the histopathological diagnosis of pancreatic cancer.

Study setting.

The study was conducted at the Ocean Road Cancer Institute (ORCI), Tanzania.

ORCI is a cancer treatment, research, and academic facility in Tanzania. The institute is affiliated with the Muhimbili University of Health and Allied Sciences (MUHAS), and Muhimbili National Hospital (MNH). ORCI offers both inpatient and outpatient services, including chemotherapy, radiation therapy, imaging and laboratory services, palliative care, and cancer screening services. It plays a major role in the country's National Cancer Registry and the National Cancer Control Strategy. It receives patients with a histologically confirmed diagnosis from MNH through tumor board meetings, as well as from other hospitals from within and outside the country. The majority of pancreatic cancer patients at ORCI have had a bypass surgery from the affiliated hospital,(MNH), thus receive either adjuvant or palliative chemotherapy. ORCI offers the following chemotherapy regimen for pancreatic cancer: Gemcitabine alone therapy, which is given as 1000mg/m2 IV on day 1, day 8, and day 15, every 4 weeks for 6 cycles, or as a combination with Oxaliplatin, and Gemcitabine + Capecitabine: Gemcitabine 1000 mg/m2 iv day 1 and Capecitabine 650 mg/m2 per oral (PO) day1 to day 14 Every 3 weeks. However, ORCI guideline does not include radiation therapy as part of the treatment of pancreatic cancer.

Study population

This study involved all patients with a confirmed diagnosis of pancreatic cancer attended at ORCI. It also included all patients referred from Muhimbili National Hospital, regional hospitals, and peripheral hospitals with a confirmed diagnosis of pancreatic cancer.

Target population

All patients attended at ORCI between 2006-2018

Eligibility Criteria

Inclusion criteria

1. All patients who had been referred to the Ocean Road Cancer Institute with a histologically confirmed diagnosis of pancreatic cancer from January 2006 to December 2018
2. All patients with a confirmed diagnosis of pancreatic cancer above 18 years of age.

Exclusion criteria

All patients who meet minimum inclusion criteria, whose records had missing histopathology results, missing follow up notes in the files, or imaging investigations).

Sample size estimation

According to the recent statistics by the GLOBOCAN 2018, the 5-year overall survival of pancreatic cancer between 2014 and 2018, had risen from 6% to 9% (14)

The sample size was calculated using a single proportion formula.

$$n= \frac{Z^2P(1-P)}{\varepsilon^2}$$

Where: n= minimum sample size designed. Z= Z value of 1.96 for 95% confidence level = confidence interval taken as ±5%.

P= the proportion of 5-year overall survival PC patients from previous studies is 9%(14).

$$n= \frac{1.96^2*0.09(1-0.09)}{0.05^2}$$

From the formula, the minimum number of patients with PC that was required in the study was 125 patients. We managed to collect 106 patients' medical records confirmed with histological diagnosis of pancreatic cancers. 19 files did not meet the minimum inclusion criteria.

The average number of pancreatic cancer seen, annually at ORCI is 11.4. Therefore this sample size will be achieved retrospectively by tracking patient's files for twelve consecutive years, from 2006 through 2018.

Study variables

Independent variables

The risk factors such as age, gender, BMI, diabetes, alcoholism, and smoking were included in the study.

Clinical presentation: - jaundice, abdominal pain, vomiting, weight loss, pruritus. Pathological features: - stage, histological type, grade/risks tumor location. Treatment:- surgery and chemotherapy.

Dependent variables

1-year overall survival. The one-year overall survival was chosen not only due to the current median survival of 5months among PC patients(1), but also that in Africa, patients are diagnosed in advanced stages leading to failure to receive definitive treatment with curative intent, and succumb to death in less than 6 months(2).

Data collection

This study used the researcher's self-administered questionnaire to collect data. The questionnaire had four sections. The first section covered the social demographics and baseline laboratory and imaging information, the second section involved tumor characteristics such as stage and grade, the third section consisted of treatment received, and the last part, the survival status of the patient.

The research assistant assisted the principal investigator during data collections. Before the commencement of the data collections, the principal investigator had trained two research assistants on how to collect data, what to collect while maintaining the confidentiality of the patients' medical records.

All patients who attended the ORCI from January 2006 to December 2018 with a diagnosis of pancreatic cancer were traced from the hospital medical records and registry.

After the research assistant retrieved the information and filled in the questionnaire, the principal investigator cross-checked for completeness and accuracy daily during data collection.

Validity and reliability of the questionnaire

The questionnaire was made by the principal investigator and reviewed by the panel of three senior consultants at the department of clinical and radiation oncology for assuring that the questionnaire covered the scope of the study.

After being reviewed by the panelist, a pilot of 13 patients was conducted to check for the reliability of the questionnaire.

Data Analysis

The data extraction forms were conscientiously reviewed for completeness and consistency. Raw data were entered into SPSS (IBM) version 23. To demystify the analysis, all string variables such as gender and clinical features variable were assigned a number code that was entered into SPSS whereas the numerical variable was entered as they are.

Continuous variables were summarized by means, medians, standard deviation, and range while categorical variables, by frequencies and percentages. These data were then presented using tables, figures, and text.

Kaplan Meier curves were used to study survival and the Log-rank test was used to compare different survival curves. Cox regression analysis was used to identify possible predictors. Significance was defined as the P-value of less than 0.05.

Specific objective	Analysis plan
1. To determine the risk factors of PC of patients with pancreatic cancer at ORCI	Frequency and percentage for categorical variable and parametric/non-parametric test for continuous variable
2. To determine the clinical characteristics of patients with pancreatic cancer at ORCI	Frequency and percentage
3. To determine the various treatment modalities applied for patients with pancreatic cancer	Frequency and percentage
4. To determine 1-year overall survival and associated factors among PC treated at ORCI from 2006 to 2018.	The log-rank test was used to test the difference in survival times between different groups, which was statistically different or not. Cox regression was used to test the effects of other independent variables on survival times of different groups of patients.

Table 1: Study analysis plan.

Ethical Considerations.

Ethical clearance

Ethical clearance to carry out this study was obtained from the Muhimbili University of Health and allied sciences (MUHAS) Research Ethics and Publication Committee and from the Ocean Road Cancer Institute (ORCI) to permit access to the patient's medical information from the ORCI medical registry.

To reduce the potential risks of disclosure of protected patient medical information, efforts were made to ensure and assure patient's confidentiality was preserved by ensuring that the patient's identity was not to be revealed and that the waiver requested will not cause any adverse effects to the rights and welfares of the patient, for example; any treatment modality employed to the patient, and the laboratory and imaging investigations which are clinically indicated would be done regardless of the study research, hence no study results will affect the clinical decisions about the patient's care.

Consent Process

A waiver of informed consent for the confidentiality of patients medical records were obtained from the MUHAS Research Ethics and Publication Committee since this study was a retrospective hospital-based study review of available patient's medical records from the hospital setting, and that some of the patients may have died by the time of data collection causing challenges to obtain consent from individual participants.

Publication and dissemination of study results

This study is part of, partial fulfillment of Master of Medicine in Clinical Oncology, therefore the research findings will be disseminated to various institutions, including, Muhimbili University of Healthy and Allied Science (MUHAS), ORCI, and MNH. It will be submitted to recognized local and international journals for possible publication as well as presented in various conferences.

Results

This study recruited 106 patients. Most of the study participants were male, 66(62.3%). The patients' mean age (±SD) was (50.44±17.87) whereby the majority of the participants were over sixty years old, 32 (30.2%). Majority of these participants engaged with small- scale farming and business. Few, 20(18.9) had a history of smoking and 25(23.6%) had a history of alcohol consumptions. Very few of these participants 5/106 were diabetic. Majority presented with abdominal pain, vomiting, and weight loss while on 4/106 had a family history of cancer. Clinical examination showed 63(59.4%) found with jaundice.

Essentially, ductal carcinoma was prevalent with the majority of the tumor initiated in the head section of the pancreases. Also, the majority of the participants were on late-stage (stage III and IV) at the time of diagnosis as well as the majority had tumor size >2 cm.

The majority of the patients were treated palliatively. Chemotherapy was given among many patients. The overall mean survival rate was 43%.

Variable		Frequency	Percent
Gender	Male	66	62.3
	Female	40	37.7
Age	<20	2	1.9
	21-40	28	26.4
	41-60	44	41.5
	61+	32	30.2
Occupation	Peasants	38	35.8
	Petty business	36	34.0
	Civil worker	27	25.5
	Housewife	3	2.8
	Students	2	1.9
Smoking status	Yes	20	18.9
	No	86	81.1
Alcohol consumption	Yes	25	23.6
	No	81	76.4
Diabetes	Yes	5	4.7
	No	101	95.3
Family History of cancer	Yes	4	3.8
	No	102	96.2

Table 2: Study participant's social demographic information, N=106

The mean age was 50.4±18. Very few participants were taking alcohol and smoking cigarettes as well as a diabetic.

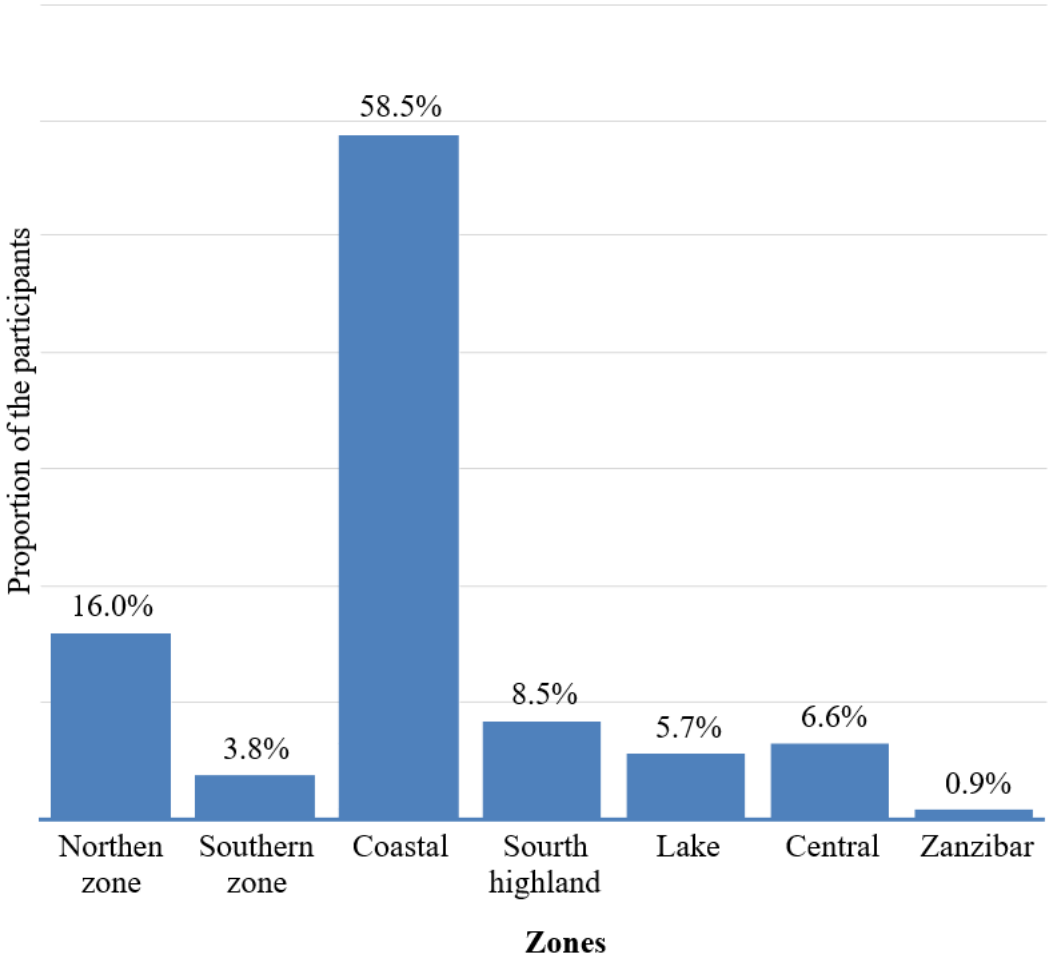

Figure 2: Zone wise geographical distribution of the study participants, N=106.

Key

Coast zone	Dar es Salaam, coast and Morogoro
Northern zone	Kilimanjaro, Arusha, Manyara and Tanga
Central zone	Dodoma and Singida.
Southern Highland zone	Mbeya, Rukwa, Iringa, and Njombe.
Southern zone	Lindi, Mtwara and Ruvuma
Lake zone	Mwanza, Simiyu, Shinyanga and Mara

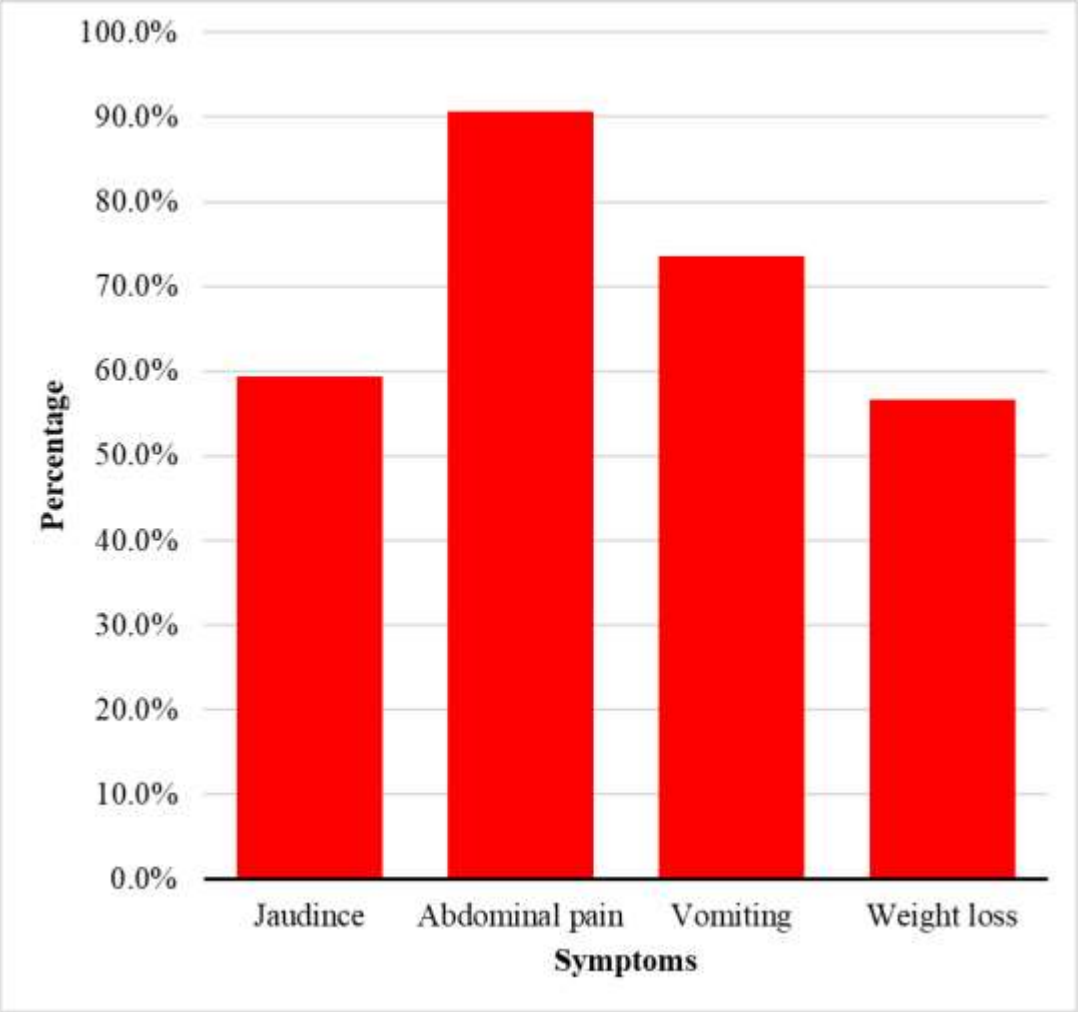

Figure 3: Patients' symptoms reported before diagnosis, N=106.

The most common symptoms were abdominal pain and vomiting while the most frequent was abdominal pain.

Characteristic		Frequency	Percent
Tumor location	Head	64	60.4
	Body	15	14.2
	Tail	11	10.4
	Not documented	16	15.0
Histology	Adenocarcinoma	55	51.9
	Solid papillary tumor	8	7.5
	pseudopapillary tumor	10	9.4
	Neuroendocrine	17	16.1
	Not stated	16	15.1
Stage group	T2	4	3.7
	T3	22	20.8
	T4	36	34.0
	N1	18	17.0
	M1	26	24.5
Tumor size	2-4	48	45.3
	>4	58	54.7

Table 3: Patients' histological Characteristics, N=106.

Most of the tumor started in the head of the pancreases. Adenocarcinoma most occurred. The majority had stage T4 and M1 disease. At least 50% of patients had a tumor size of more than 4cm.

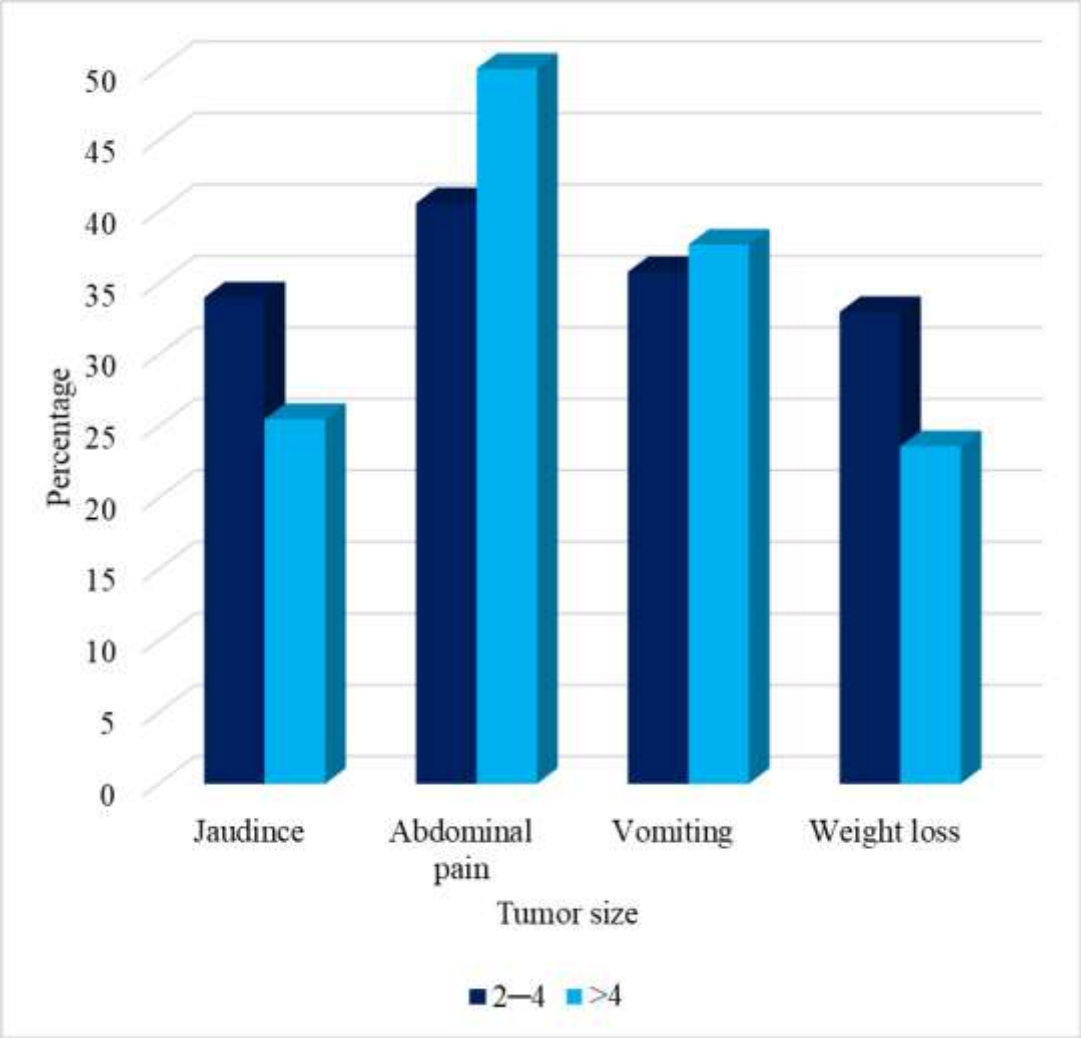

Figure 4: Distribution of PC clinical symptoms with tumor size, N=106

Jaundice and weight symptom presented by the patients were correlating with tumor size with a statistically significant p-value of 0.003 and 0.002 respectively. Despite the majority of the patients in both tumor categories presented abdominal pain but were not found statistically significant, p=0.09 while the p-value for vomiting was 0.236.

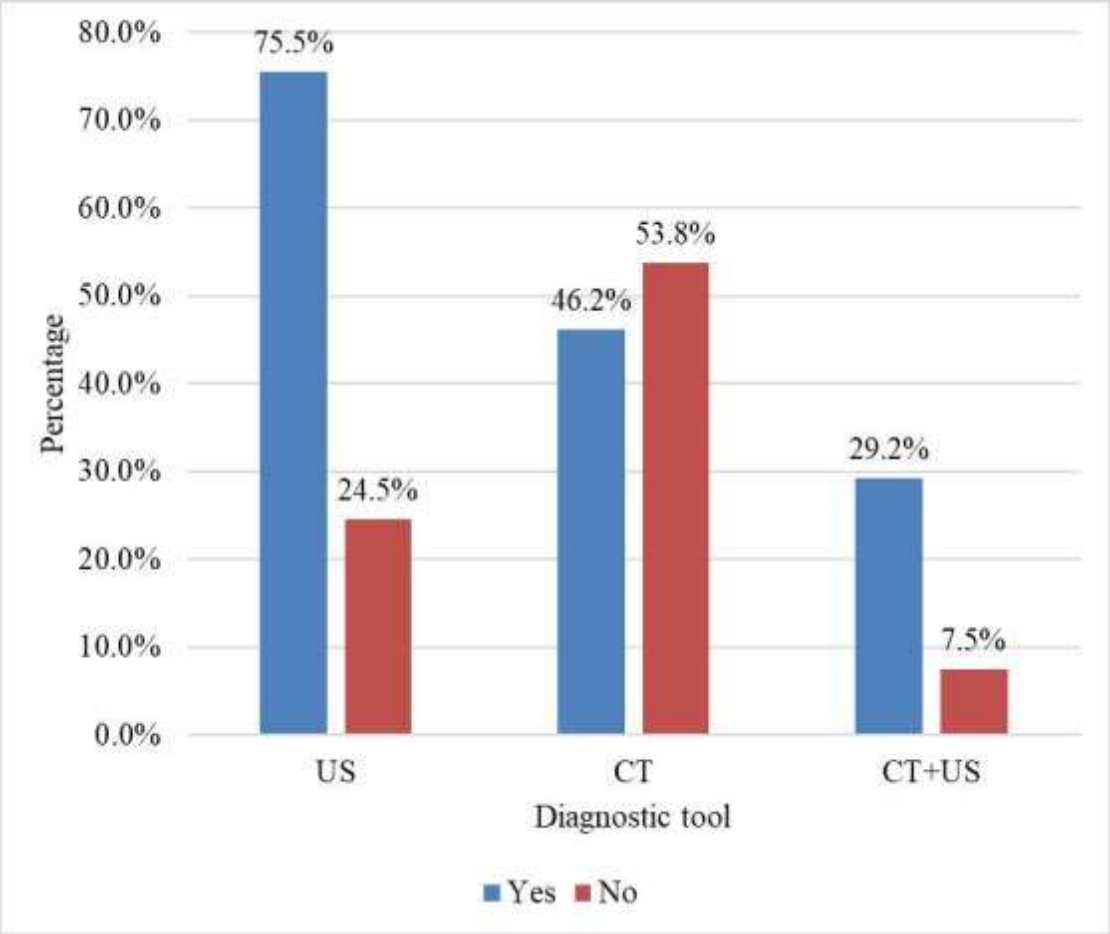

Figure 5: Diagnostic tools used in the examination of pancreatic cancer, N=106

Only one patient had undergone MRI but the MRI report could not available. Enlargement of the liver, presence of multiple lesions, hepatobiliary cirrhosis with parietal fibrosis, urinary bladder cystitis, dilation of the common bile duct, and pancreatic bile duct was the major US report among the majority of the participants. Enlarged liver with multiple hypodense areas of different sizes, mild splenomegaly, hepatomegaly, multiple lesion of different dimensions were the most common CT reports.

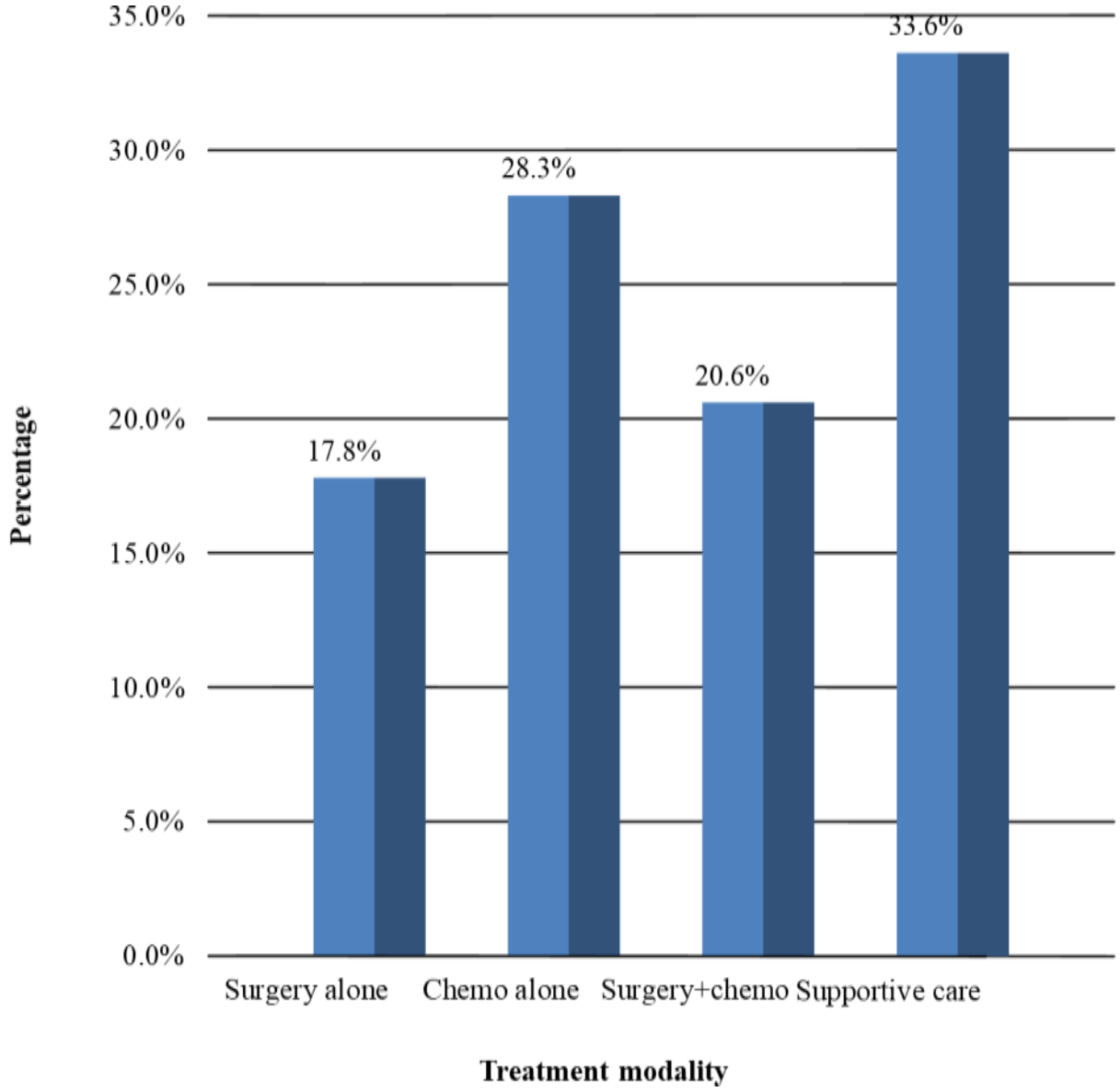

Figure 6: Distribution of Pancreatic cancer treatment among participants, N=106.

None of the patients were treated with radiotherapy. Only four patients were treated with neoadjuvant chemotherapy while the rest of the chemo was neoadjuvant. The neoadjuvant drug used was gemcitabine in 6 mean cycles.

Treatment mode		Frequency	percentage
Surgery procedure	Bypass surgery	20	66.7
	Exploratory laparotomy	10	33.3
Adjuvant regime	Epirubicin	7	11.1
	Adriamycin+ Prednisolone	28	44.5
	Gemcitabine	7	11.1
	Gemcitabine + Cisplatin	11	17.5
	Capecitabine	2	3.2
	Doxorubicin	5	7.9
	Gemcitabin+Carboplatin	2	3.2
	Gemacitabin+5FU	1	1.6

Table 4: Description of the kind of Surgery and adjuvant chemotherapy prescribed, N=106.

No patient was treated with curative resection of the tumor, rather received salvage surgery. The majority, 74.6% of patients who were given chemotherapy were given in 6 cycles. However, the mean cycles of chemo administration 6±1.1. Only 30 patients went through exploratory laparotomy, out of which only 20 patients did a bypass surgery.

		Tumor size ≤4cm		Tumor size >4cm		
		n	%	n	%	P-value
Histology	Adenocarcinoma	23	(21.7)	32	(30.2)	0.015
	Solid papillary tumor	2	(1.9)	6	(5.7)	
	Solid pseudopapillary tumor	3	(2.8)	7	(6.6)	
	Neuroendocrine	14	(13.2)	3	(2.8)	
	Not stated	6	(5.7)	10	(9.4)	
Tumor location	Head	30	(28.3)	34	(32.1)	0.391
	Body	9	(8.5)	6	(5.7)	
	Tail	4	(3.8)	7	(6.6)	
	Not documented	5	(4.7)	11	(10.4)	
Treatment	Surgery alone	12	(11.3)	7	(6.6)	<0.0001
	Chemo alone	10	(9.4)	20	(18.9)	
	Surgery+chemo	18	(17.0)	4	(3.8)	
	Supportive care	8	(7.5)	27	(25.5)	

Table 5: PC tumor size distribution about histopathological information and treatment modalities. N=106.

There was a statistically significant association between tumor size and treatment. The Majority of patients who had a tumor size less than 4cm received dual therapy, i.e both bypass surgery and adjuvant chemotherapy. The P-value was less than 0.0001.

		Treatment				
		Surgery alone	Chemo alone	Surgery+ chemo	Supportive	
		N (%)	N (%)	N (%)	N (%)	P-value
Histology	Adenocarcinoma	10(9.4)	22(20.8)	4(3.8)	19(17.9)	0.0001
	Solid papillary tumor	4(3.8)	1(9)	0(.0)	3(2.8)	
	Solid pseudo papillary tumor	2(1.9)	3(2.8)	0(0)	5(4.7)	
	Neuroendocrine	1(.9)	0(.0)	16(15)	0(.0)	
	Not stated	2(1.9)	4(3.8)	2(1.9)	8(7.5)	
Stage	T2	0(.0)	0(.0)	3(13.6)	1(2.9)	0.004
	T3	5(26.3)	3(10.0)	10(45.5)	5(14.3)	
	T4	8(42.1)	12(40.0)	7(31.8)	8(22.9)	
	N1	2(10.5)	(16.7)	2(9.1)	9(25.7)	
	M1	4(21.1)	10(33.3)	0(.0)	12(34.3)	
Tumor location	Head	13(12.3)	19(17.9)	14(13.2)	18(17.0)	0.85
	Body	4(3.8)	4(3.8)	2(1.9)	5(4.7)	
	Tail	1(.9)	3(2.8)	2(1.9)	5(4.7)	
	Not documented	1(.9)	4(3.8)	4(3.8)	7(6.6)	

Table 6: PC treatment distribution about histopathological information, N=106

Histology and disease stage were found statistically significant with treatment.

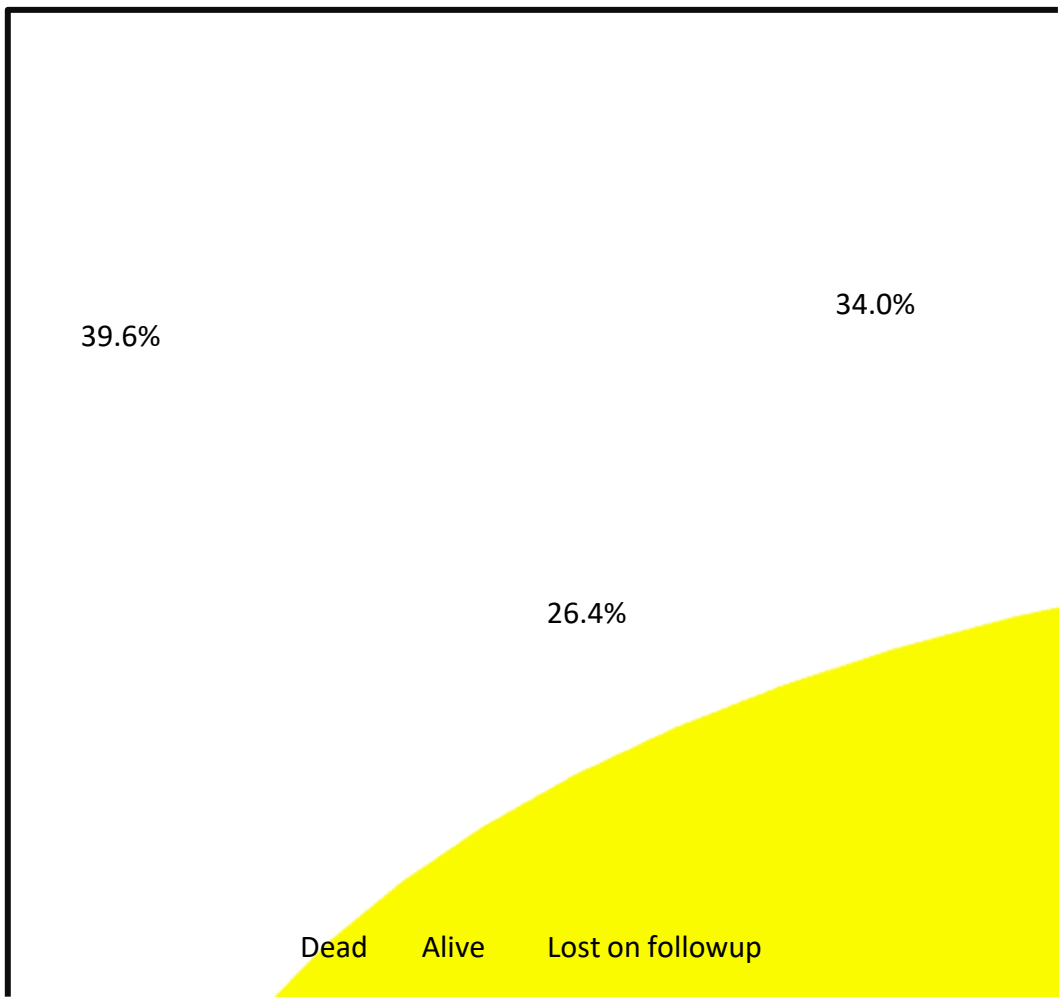

Figure 7: Summary of the survival status of pancreatic cancer patients.

The majority of the participants were tentatively lost on follow up. Lost to follow up cases preceded certain missing information such as treatment modalities, and whether alive or dead and that clarifications were required. Unfortunately, the patients' contacts documented from their records were unreachable and unreliable. All patients recruited had progressive disease. The sample median survival time was three months, and a range of 1-15 months.

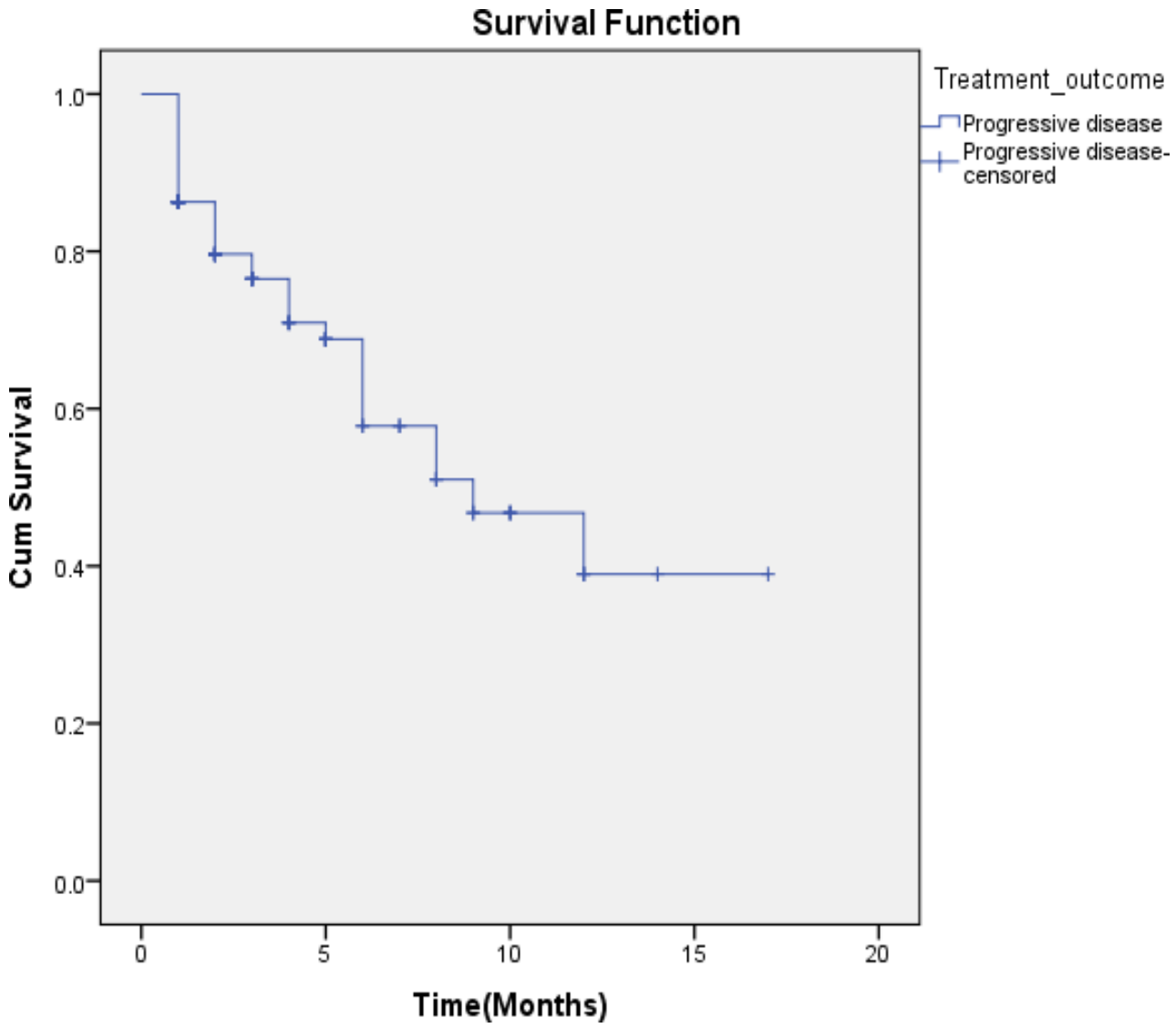

Figure 8: Disease progression survival curve, N=106.

The overall one-year survival rate was 38.97%.

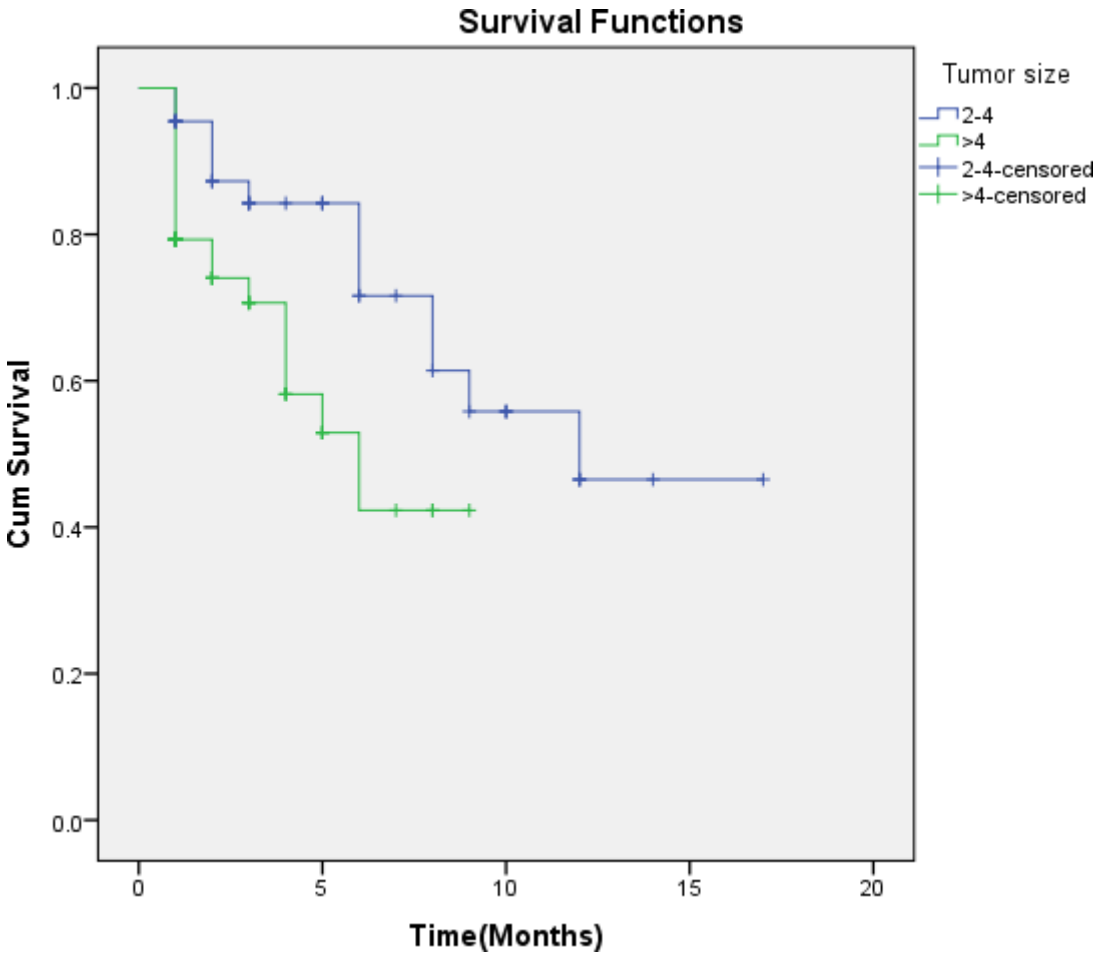

Figure 9: Survival curve of different tumor size at the time of diagnosis

A log-rank test was run to determine if there were differences in the survival distribution for the different tumor size categories: 2-4 and >4cm. The survival distributions for the size were statistically significantly different, $\chi 2$ (1) = 5.697, p = 0.017. The 1-year survival for 2-4 cm and >4 cm were 46.51% and 42.32% respectively.

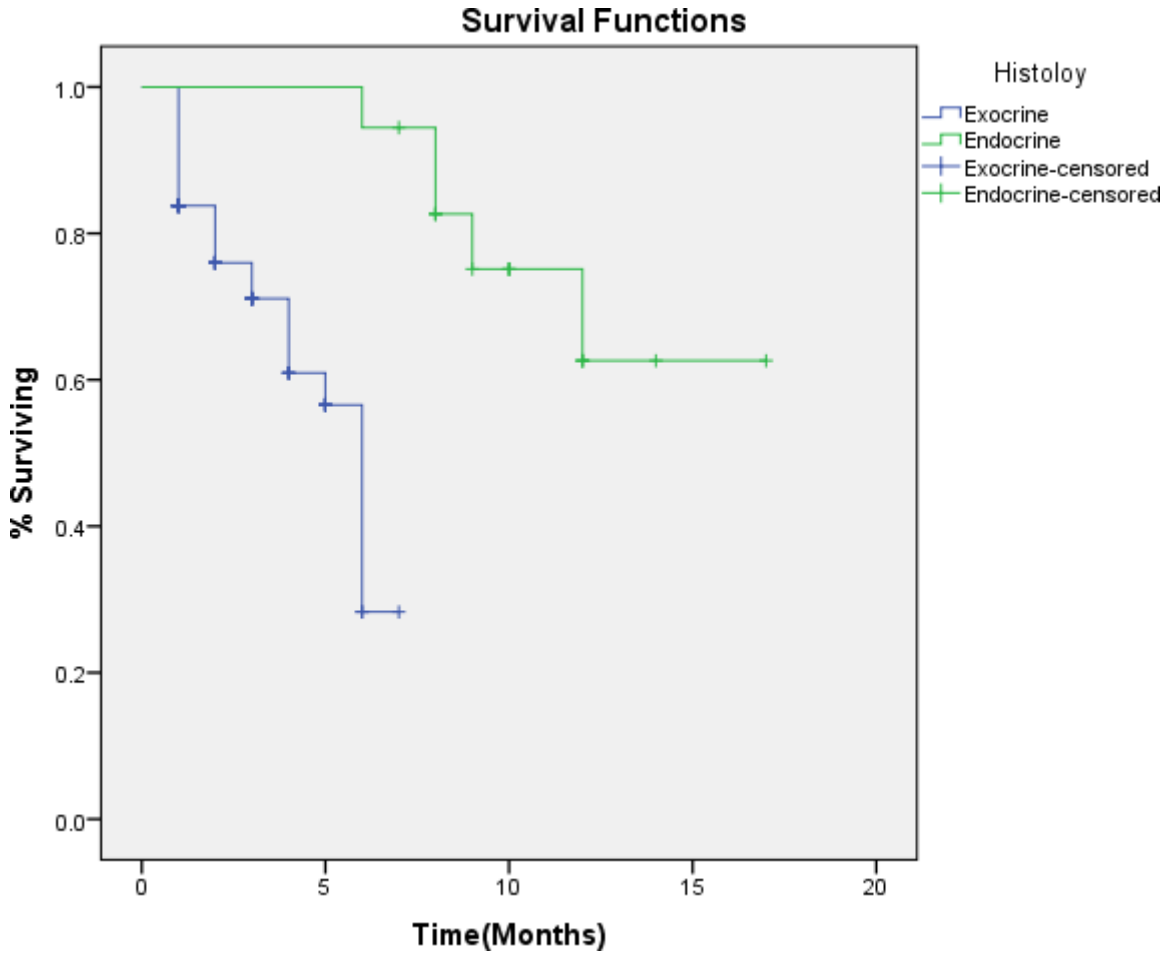

Figure 10: Survival curve of histology

A log-rank test was run to determine if there were differences in the survival distribution for the different histological type: Endocrine and exocrine, the survival distributions for the two histological types were statistically significantly different, $\chi 2\ (1) = 14.944$, $p < 0.0001$. Patients with endocrine survived to 62.61% while those with exocrine tumors survived less than one year.

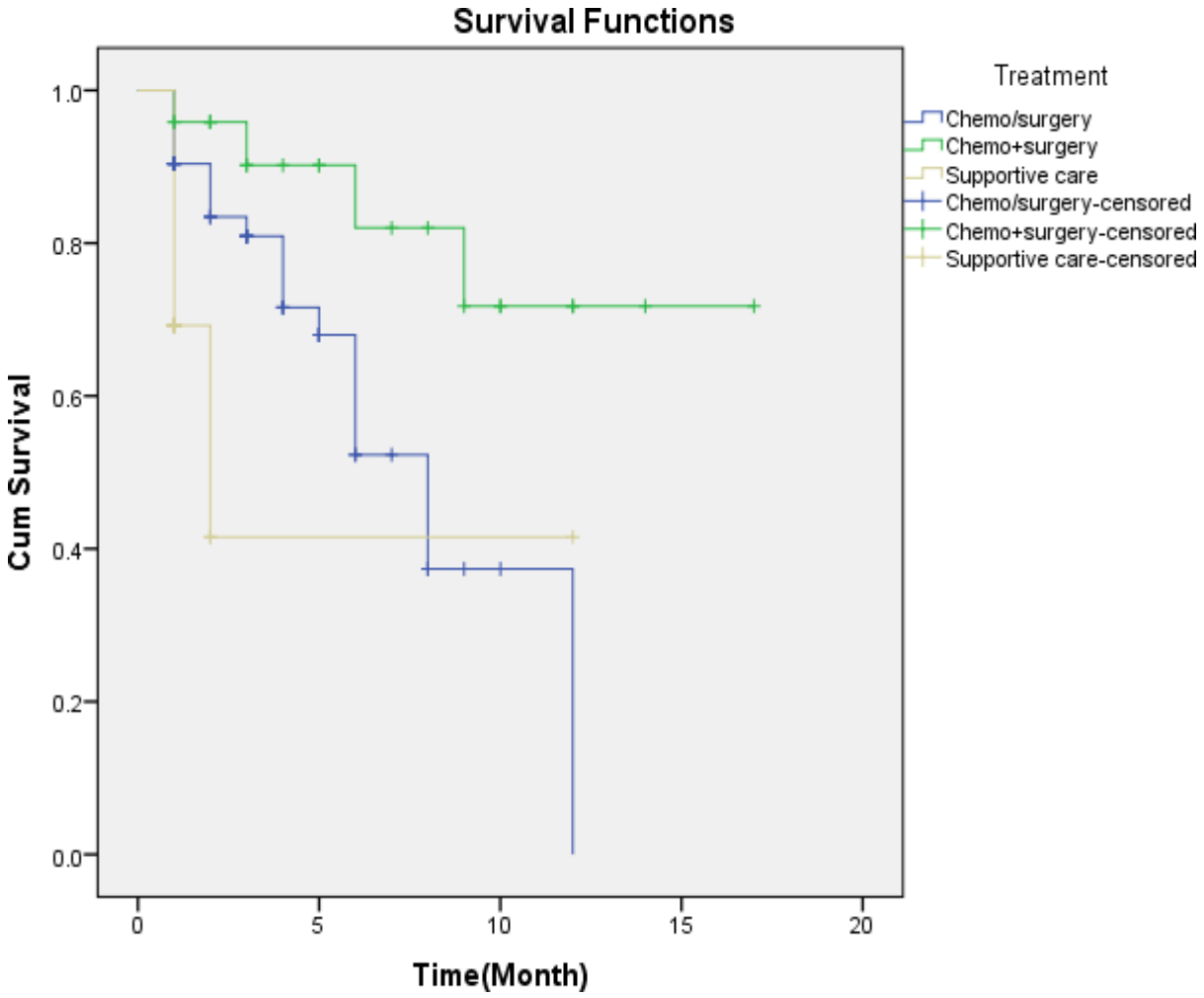

Figure 11: Survival curve of different treatments.

A log-rank test was run to determine if there were differences in the survival distribution for the different treatment, the survival distributions were statistically significantly different, $\chi 2$ (3) = 40.292, p =0.001

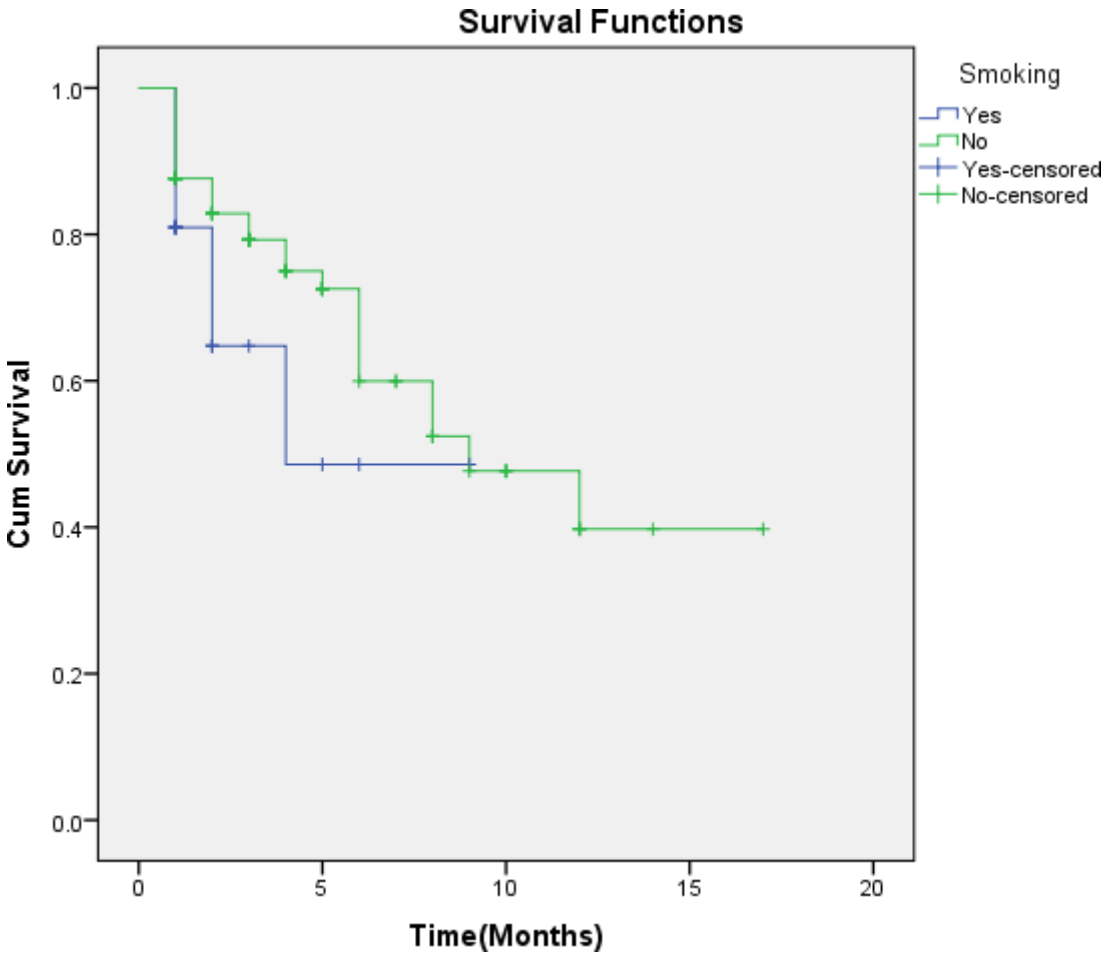

Figure 12: Survival curve for smoking status

A log-rank test was run to determine if there were differences in the survival distribution for the smoking status, the survival distributions were not statistically significantly different, $\chi 2$ (1) = 1.428, p =0.232.

Those who had no history of smoking had an overall one-year survival of 9.74% while those who had a history of smoking had an overall survival of less than one year.

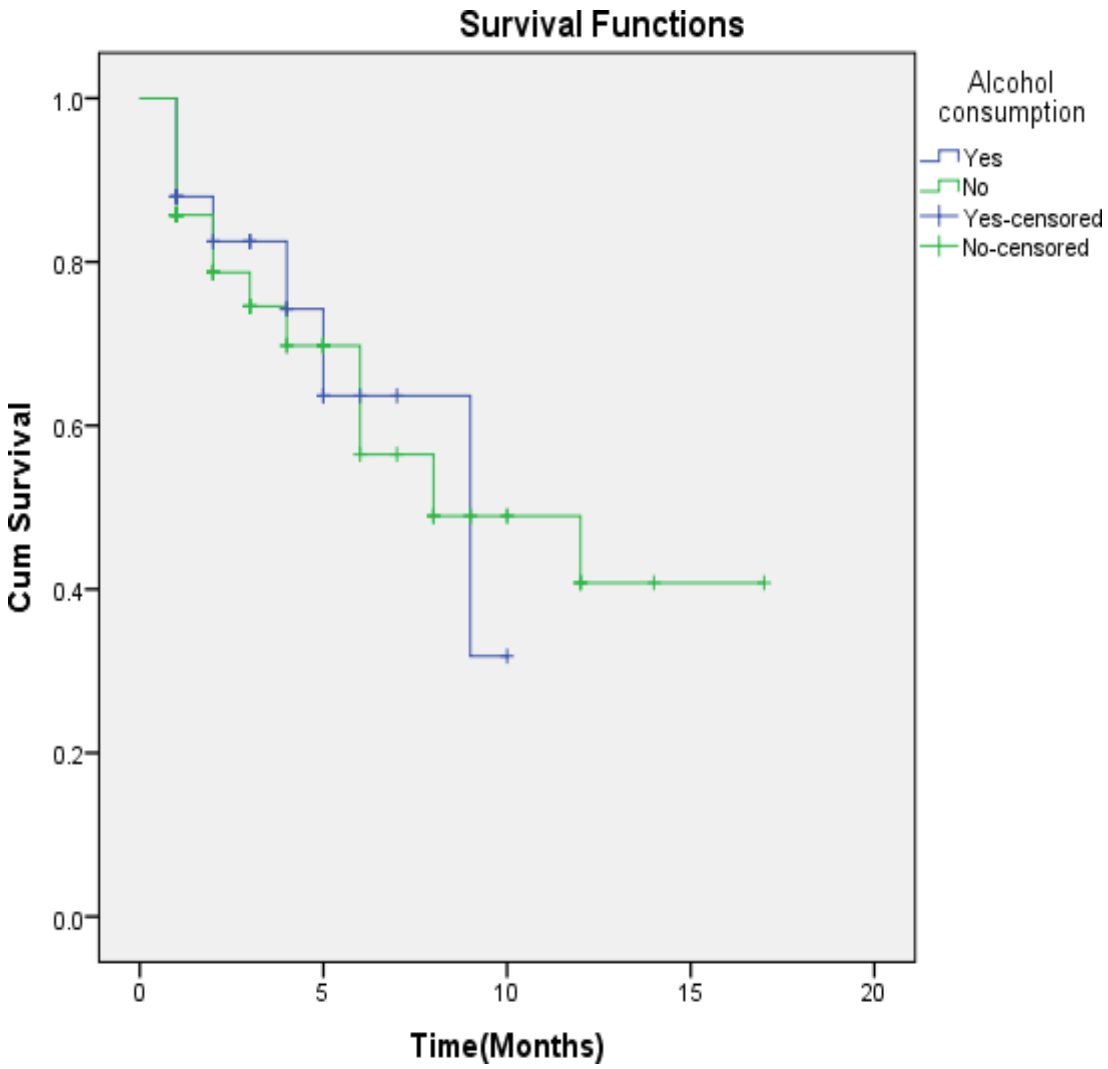

Figure 13: Survival curve for alcohol consumption status.

A log-rank test was run to determine if there were differences in the survival distribution for the drinking alcohol status, the survival distributions were not statistically significantly different, $\chi 2$ (1) =0.005, p-value =0.946

Those who had no history of drinking alcohol had a one-year overall survival of 40.79% while those who had a history of drinking alcohol had an overall survival of less than one year.

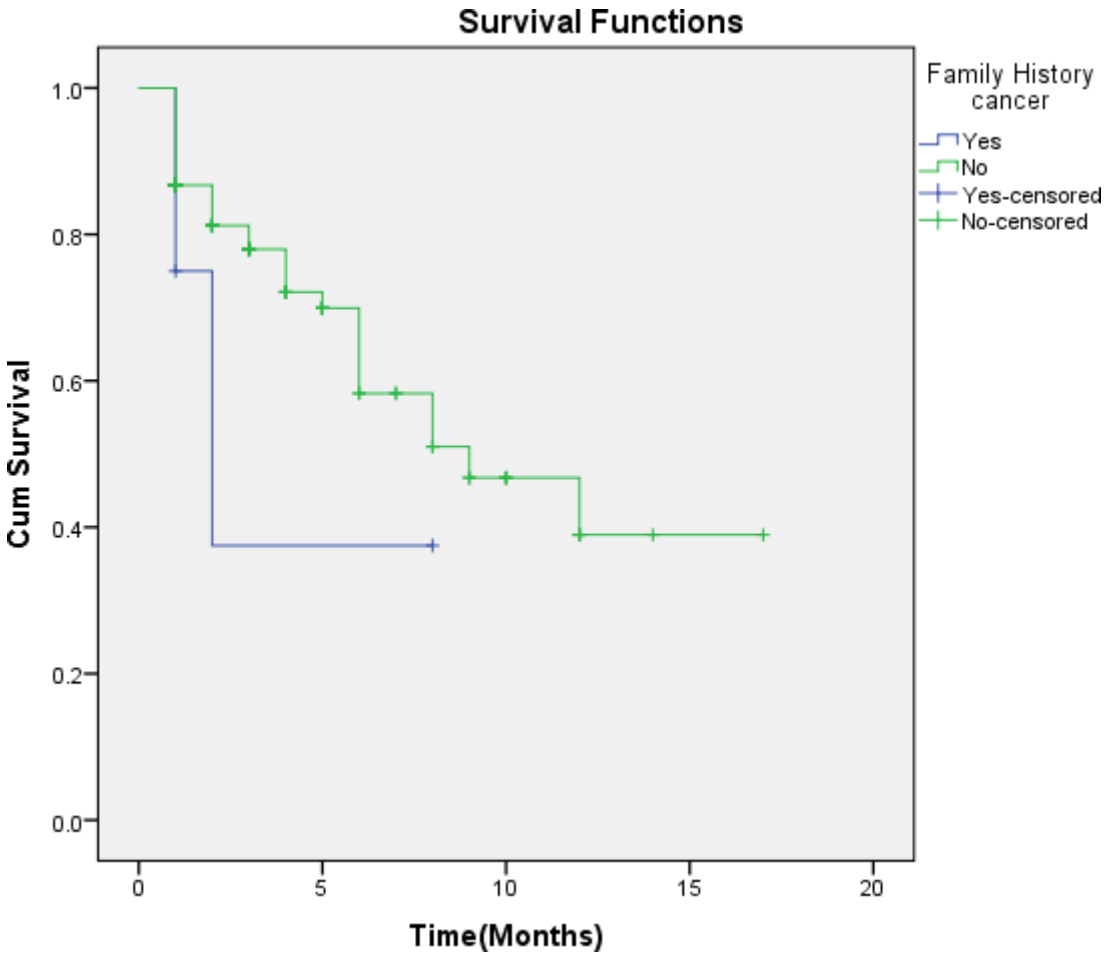

Figure 14: Survival curve for family history of cancer

A log-rank test was run to determine if there were differences in the survival distribution for the prior family history of cancer, the survival distributions were not statistically significantly different, $\chi 2$ (1) =0.793, p value=0.373

Those who had no family history of cancer had a one-year overall survival of 38.96% while those who had a family history of cancer overall survival of less than one year.

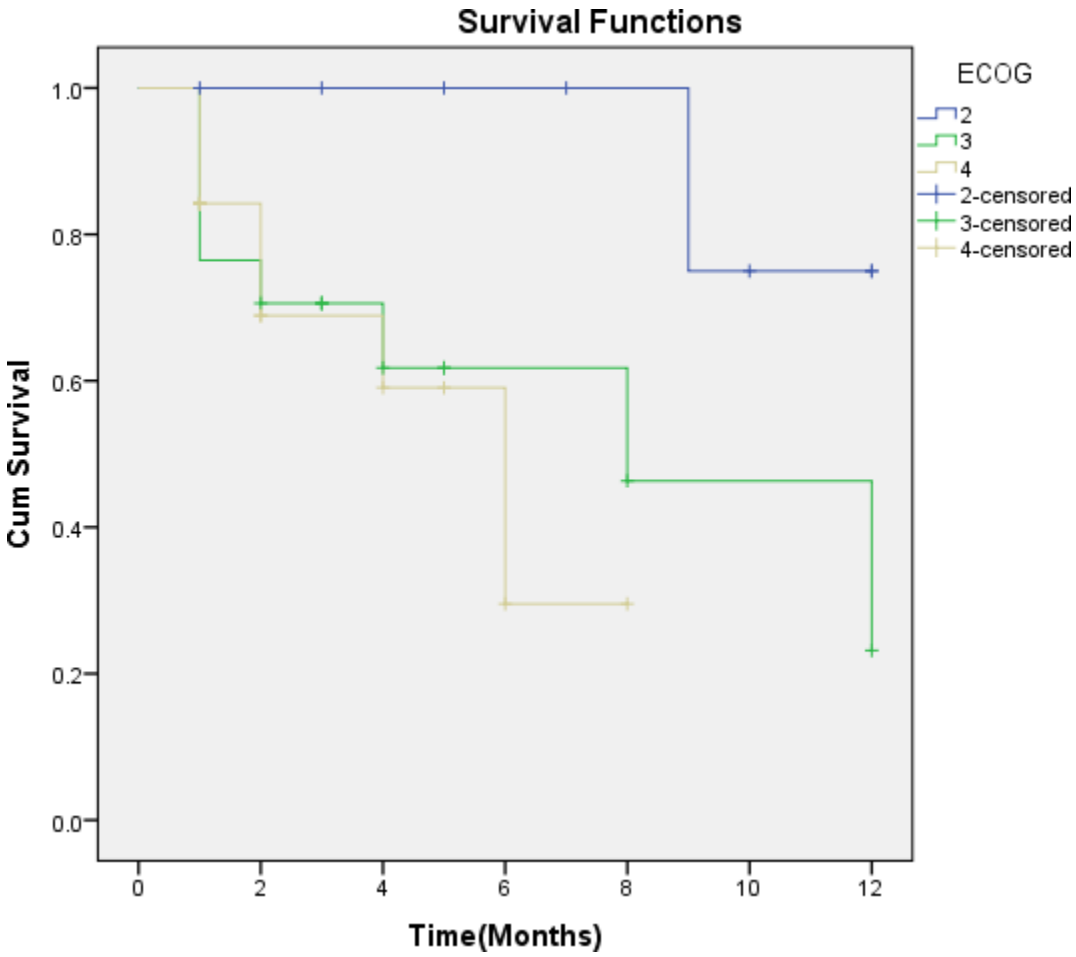

Figure 15: Survival curve for different ECOG at the time of diagnosis.

A log-rank test was run to determine if there were differences in the survival distribution for the ECOG at the first time presentation to the hospital, the survival distributions were not statistically significantly different, $\chi 2$ (2) =5.585, and p value=0.061.

Those who had no family history of cancer had a one-year overall survival of 38.96% while those who had a family history of cancer overall survival of less than one year.

Variable	Category	Total N (%)	Dead N (%)	X2	P-value
Gender	Male	66(62.3)	25(69.4)		
	Female	40(37.7)	11(30.6)	0.558	0.455
Age	<20	2(1.9)	0(.0)		
	21-40	28(26.4)	12(33.3)		
	41-60	44(41.5)	15(41.7)		
	61+	32(30.2)	9(25.0)	2.74	0.434
Family History cancer	Yes	4(3.8)	2(5.6)		
	No	102(96.2)	34(94.4)	0.793	0.373
Smoking status	Yes	20(18.9)	4(11.1)	1.428	0.232
	No	86(81.1)	32(88.9)		
Alcohol consumption	Yes	25(23.6)	7(19.4)	0.005	0.946
	No	81(76.4)	29(80.6)		
Tumor size at the time of diagnosis	2-4	48(45.3)	16(44.4)	5.697	0.017
	≥4	58(54.7)	20(55.6)		
Histology	Exocrine	74(80.4)	25(83.3)	14.944	<0.0001
	Endocrine	18(19.6)	5(16.7)		.
Stage	I	9(8.5)	0(.0)		
	II	25(23.6)	11(30.6)		
	III	22(20.8)	8(22.2)		
	IV	47(44.3)	15(41.7)		
	Unknown	3(2.8)	2(5.6)		
Treatment	Surgery alone	19(17.9)	7(19.4)	40.292	0.001
	Chemo alone	30(28.3)	11(30.6)		
	Surgery+chemo	22(20.8)	5(13.9)		
	Palliative	35(33.0)	13(36.1)		

Table 7: Tabular summary of overall survival

Tumor size at the time of diagnosis, histology, stage, and treatment offered was found statistically significant with a log-rank test p-value <0.05.

Variable	HR	95.0% CI for HR		P-value
		Lower	Upper	
Tumor size	1.149	0.458	2.879	0.768
Histology	1.239	0.140	10.961	0.847
Supportive care				0.014
Chemo and surgery	0.008	0.000	0.149	0.001
Chemo/surgery	0.094	0.012	0.734	0.024

Table 8: Cox regression for multivariate analysis

The kind of treatment given to pancreatic cancer was an independent risk factor of mortality among pancreatic cancer patients. Patients who were on supportive treatment were 0.8% more likely to die than those treated with a combination of surgery and chemo at any point HR= 0.008, 95% CI=0.0001-0.149, P=0.001. Furthermore, those who received chemotherapy alone or surgery alone were 9.4% more likely to die than those treated with chemo or surgery alone.

Discussion

This study is the first retrospective study in Eastern Africa that describes the clinical profile and treatment outcomes of pancreatic cancer patients between the years 2006 and 2018 conducted at a single center in Tanzania.

We observed the incidence of pancreatic cancer and various factors attributable to the development of pancreatic cancer at Ocean Road Cancer Institute, Tanzania. Those identifiable factors include socio-demographics (age, gender, location/zones, and occupation), smoking, alcohol consumption as well as tumor characteristics.

Despite several contemptuous treatments available in the world, there have been minimal effects on the natural history of pancreatic cancer. Still, remains a very difficult cancer to cure(4).

A total of 106 patients with pancreatic cancer were seen in the study period of 13years, (Jan2006-Dec2018). The incidence rate corresponds to the Globocan 2018 observatory report in Tanzania with only 0.36%.

Our survey revealed an increasing frequency of pancreatic cancer with advanced age and male predominance. The patients' mean age was 50.44+/- 17.87 where the majority of them belonging to the age group 41-60years. This corresponded to the findings of A.W. Asombang et al, that the incidence of pancreatic cancer at diagnosis was 54 years and that the disease can occur even before 40years(6). On the contrary, the Surveillance, Epidemiology, and End Results (SEER) reported that the development of PC was around 70years but, with a slight male to female predominance(10). The sex ratio finding in our survey was higher compared to many studies, perhaps due to the identifiable factors such as smoking and alcohol consumption that contribute to the development of PC, were commonly reported among men. Aside from the fact that most of our patients were from low socioeconomic status, the majority of them had very few histories of these factors.

With regards to the symptomatology, according to Chara Ntala et al findings, they reported that obstructive jaundice was the most common presentation at diagnosis followed by anorexia and abdominal pain(5). Our findings noted that abdominal pain was the most common symptom at presentation followed by vomiting and jaundice. This can be explained by the fact that clinical features of PC are non-specific and usually presentations depend on the tumor location in the pancreas and the histological type of cancer. It’s known that tumors located in the head of the pancreas present with symptoms related to obstructive jaundice.

According to Ducreux M et al(4), the most common site of PC is the head of the pancreas in approximately 60-70%. This corresponded to our findings with the highest proportion rate of 66% occurring at the Head of the pancreas.

Among the histological types, Ryan et al found that the vast majority of PC was ductal adenocarcinoma, which makes up 85-90% of malignant pancreatic neoplasms(18). This was per our survey which found that adenocarcinoma was the most predominant type with an average of 54% for the 12year study period whereas neuroendocrine with only 16%. Very few cases had a pseudopapillary type.

According to the American Hepato-Pancreato-Biliary Association (AHPBA), a consensus report, pancreatic cancer in the absence of metastases is classified as resectable, borderline, and unresectable(18). This classification is based on the tumor-vessel interface. Determining this interface requires a good

imaging tool. John Dewitt et al study found that endoscopic ultrasound was superior to CT scans for tumor detection and tumor staging with 98% sensitivity but the equivalent for nodal staging and resectability of preoperatively suspected PC(26). However, due to the unavailability of the CT scan in the period of 2006-2012 at the center, 75.5% were being diagnosed using an ultrasound scan. Even with availability thereafter, the cost of a CT scan is prohibitive to most of our patients who are poor. This may need an urgent formal social support strategy or structure in our setting.

Concerning histology in this study, patients with neuroendocrine histology had better 1- year overall survival rates compared to those with adenocarcinoma, 62.61% ($p<0.0001$). This could be explained by the fact that adenocarcinoma is known to be very aggressive and even progress despite initial chemotherapy(16). From our survey, we noted that histology was not only a statistically significant predictor of survival but also can influence the choice of treatment modality. Patients who had advanced adenocarcinoma of tumor size more than 4cm received either chemotherapy alone or best supportive care. This can be explained by its aggressive behavior and its late presentation at diagnosis(27).

Most clinicians have now adopted the consensus report as it can guide treatment options. The patients with locally advanced or metastatic disease are considered unresectable but can benefit from other treatment modalities. Since the majority of our patients present in the advanced or metastatic stage, 52%, the best supportive care was the main therapy offered at ORCI. 28.3% of patients only received chemotherapy and at least 20% with both bypass surgery and adjuvant chemotherapy.

For nonresectable disease, the standard of care is 6 months of a single-agent or combined chemotherapy(4). The majority, 74% of patients who were given chemotherapy received 6 cycles. Gemcitabine-based remedies have been shown to improve survival. According to the CONKO-001 trial, adjuvant Gemcitabine had twice a 5-year overall survival advantage compared to those who received surgery alone (20.7% vs 10.4% respectively(25)). From our survey, Adriamycin has commonly prescribed chemotherapy in the study period between 2006 and 2012, (44%). Only 11.1% received single-agent gemcitabine and about 21% had combined gemcitabine-based regimens. Perhaps this could be attributed to either rare availability or high cost of gemcitabine during that period. None of our patients received radiotherapy, this s because of their poor performance status as well as the advanced stage at presentation. The role of radiotherapy remains controversial in locally advanced PC. The European Study Group for Pancreatic Cancer (ESPAC-1trial) showed no survival benefit between receiving chemo-radiotherapy and those who did not (15.5mos vs 16.1mos)(28).

One-year overall survival was found to be 38.97% whereas treatment given after diagnosis was revealed to be a statistically significant predictor of pancreatic ca survival rate. Although this 1-year survival obtained is low but this result is higher compared to a study in the UK by Rawla P, Sunkara et al which reported 22%(14), further confirmed that, among other factors, treatment modality affects the 1-year overall survival among PC patients(14).

Limitation, Conclusion And Recommendation

Limitations study.

First and foremost, this was a retrospective study. Challenges precede missing information thus may have contributed to the sample size. A prospective study would have been appropriate to alleviate this challenge.

This study was conducted in a single center. Despite the rarity of the disease, a multicenter would have been significant to find adequate analysis.

The majority of patients were lost to follow 39%, leading to a small sample size. This may have affected the overall survival outcome.

Conclusion

This is the first survey in Tanzania. It has managed to disclose similar factors related to pancreatic cancer. However, risk factors such as smoking, and alcohol consumption were relatively not significantly associated with pancreatic cancer. Pancreatic cancer is not uncommon. The majority of patients present with an advanced disease which limits the best treatment modalities with curative intent. . Patients who received multiple treatment modalities i.e surgery and chemotherapy have shown to have better outcomes. The tumor size was strongly related to treatment outcomes with tumors less than 4cm had a better prognosis. Proper documentation is key to enable follow-up of patient care and aid in the continuum of research. With the advent of radiation therapy in the management of pancreatic cancer, a prospective study would generate adequate information with regards to treatment outcome, and/or quality of care.

Recommendations

Since there are challenges with the diagnosis, treatment, and research, it's important to create awareness about pancreatic cancer among the medical professionals and the community at large, and the need to explore the best and affordable diagnostic tools and treatment modalities.

Of note, the Tanzania National Treatment Guidelines should include pancreatic cancer in the guidelines as one of the ways of creating awareness for all medical practitioners.

It is non-trivial to consider an additional diagnostic Endoscopic retrograde cholangiopancreatography (ERCP) in patients above 40years suspected of GI conditions such as stomach cancer.

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