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DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

CLINICOPATHOLOGIC CHARACTERISTICS AND SURVIVAL OUTCOMES OF PATIENTS WITH PANCREATIC CANCER AT KENYATTA NATIONAL HOSPITAL

BY

SHEILA WANJIRU MUCHIRI

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STUDENT'S DECLARATION

This dissertation is my original work and has not been presented for a degree in any other University.

Signature.....**Date**.....22ND NOV 2023.....

Dr. Sheila Wanjiru Muchiri

Resident, Internal Medicine

Department of Clinical Medicine and Therapeutics

Faculty of Health Sciences

University of Nairobi

Registration number: H58/40206/2021

APPROVAL OF SUPERVISORS

This dissertation has been submitted with the approval of my supervisors:

Prof. Elly Otieno Ogutu

Professor, Consultant Physician and Gastroenterologist, Department of Clinical Medicine and Therapeutics, University of Nairobi

Signature.....**Date**21/11/23.....

Prof. Lars Aabakken

Professor of Medicine and Chief of Gastrointestinal Endoscopy

Oslo University Hospital-Rikshospitalet

Signature... ...**Date**...21/11/23.....

Dr. Peter Oyiro

Consultant Physician and Medical Oncologist, Department of Clinical Medicine and Therapeutics,

University of Nairobi

Signature.....**Date**21/11/23.....

CHAIRMAN OF THE DEPARTMENT APPROVAL

Prof. E. O. Amayo

Chairman of the Department of Clinical Medicine and Therapeutics

Professor, consultant Physician and Nephrologist, Department of Clinical Medicine, and Therapeutics

Signature.....**Date**24/11/2022.....

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LIST OF ABBREVIATIONS AND ACRONYMS

AJCC/UICC:	American Joint Committee on Cancer/Union for International Cancer Control
CA:	Celiac axis
CHA:	Common hepatic artery
CT:	Computed tomography
DM:	Diabetes mellitus
ECOG:	Eastern Cooperative Oncology Group
EUS:	Endoscopic ultrasound
KNH:	Kenyatta National Hospital
MDCT:	Multidetector-row computed tomography.
MRCP:	Magnetic resonance cholangiopancreatography
MRI:	Magnetic resonance imaging
NCCN:	National Comprehensive Cancer Network
PC:	Pancreatic cancer
PDAC:	Pancreatic ductal adenocarcinoma
PET:	Positron emission tomography
PNET:	Pancreatic neuroendocrine tumour
PS:	Performance status
PV:	Portal vein
SMA:	Superior mesenteric artery
SMV:	Superior mesenteric vein

OPERATIONAL DEFINITIONS

Resectable pancreatic cancer: No arterial tumour contact (celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA). No contact with the superior mesenteric vein (SMV) or portal vein (PV), or ≤180° contact without vein contour irregularity.

Borderline resectable pancreatic cancer: Pancreatic head/uncinate process solid tumour contact with the CHA without extension to the CA or hepatic artery bifurcation; contact with SMA of ≤180°; or contact with variant arterial anatomy. Pancreatic body/tail solid tumour contact with the CA of ≤180°. Venous contact with the SMV or PV of >180°, or vein contact ≤180° with vein contour irregularity or thrombosis but allowing for vein reconstruction.

Locally advanced pancreatic cancer: Pancreatic head/uncinate process solid tumour contact >180° with SMA or CA. Body/tail contact >180° with SMA or CA or contact with the CA and aortic involvement. Unreconstructible SMV/PV due to tumour involvement or occlusion (by tumour or bland thrombus).

ABSTRACT

Background: Pancreatic cancer (PC) has the poorest prognosis of any common solid tumour. Previous studies have suggested worse outcomes among individuals of African descent. The characteristics of patients with PC in Kenya, their contemporary management and survival outcomes are unknown.

Objective: To determine the clinicopathologic characteristics, management, and survival outcomes of patients with pancreatic cancer at Kenyatta National Hospital (KNH).

Methodology: Records of 242 patients diagnosed with pancreatic cancer at KNH between 1st January 2014 and 31st September 2021 were assessed in this retrospective cohort study. Data on sociodemographic, clinical, histopathologic and treatment characteristics was presented as mean (± standard deviation) and/or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Kaplan-Meier and Cox proportional hazard ratios were used for survival analysis.

Results: Pancreatic cancer occurred in a relatively young population, the median age being 58.5 years. The majority, 131 (54%), had metastatic disease at diagnosis, while 67 (28%) and 34 (14%) had stage III and stage I/II disease respectively. Surgical resections were performed in 15 (44%) of stage I/II cases. Patients were more likely to have resection or chemotherapy if they had good performance status and insurance coverage. Patients who underwent surgical resection (HR for mortality 0.20, 95% CI 0.05-0.83) and chemotherapy (HR for mortality 0.15, 95% CI 0.08-0.29) had significantly improved survival, reflecting a more favourable stage of the disease more amenable to aggressive therapies. Median survival time was 3 months and the one-year survival rate was 32%.

Conclusion: Pancreatic cancer occurred at a young age in this population. The majority presented with advanced disease, precluding curative treatment. Good performance status was the most important determinant of survival, reflecting earlier stage of disease and better tolerance for aggressive treatment. Survival at one year was poor.

CHAPTER ONE: INTRODUCTION

Despite its relatively low incidence, pancreatic cancer (PC) is one of the leading causes of cancer-related mortality worldwide (1). Several studies conducted in mixed-race populations including America have suggested that individuals of African descent not only have a considerably higher risk of PC than other racial groups but also have a younger age of disease onset, more advanced disease at diagnosis and a higher mortality rate (2,3). Up to 95% of these tumours arise from the exocrine pancreas, the vast majority (90%) being pancreatic ductal adenocarcinoma (PDAC) (4). Prognosis of PDAC remains very poor despite advances in therapy, reflected by an average survival of 5-8 months and an overall 5-year survival rate of less than 10%, owing largely to advanced stage at diagnosis (5,6). Surgery is the only potentially curative treatment, but only 10%-20% of patients are eligible for curative resection (6). The majority (50%-60%) present with metastatic disease, leaving palliative chemotherapy as the only option for these patients (5). Whereas historically there was little variability in survival outcomes, there is a widening gap in survival between patients with resectable PC and those with unresectable disease (7,8) . This is due to significant therapeutic advancements in the last three decades. These include improved peri-operative outcomes of patients with resected tumours due to advances in surgical capabilities and the development of vascular reconstruction techniques which have expanded the indications for surgical resection (8,9). Neoadjuvant chemotherapy has been proven to significantly improve survival, particularly for patients with borderline resectable disease and selected patients with locally advanced disease (6). Combination chemotherapy in the adjuvant setting demonstrated significantly longer survival than traditional monotherapy in clinical trials (10). For patients with metastatic disease, it was not until the introduction of combination chemotherapy that we started to see survival of patients with metastatic PC approach one year (11). The uptake of these treatment modalities and the survival outcomes of patients with PC remain unknown in the local setting. This study aims to characterise the clinical and tumour features, management and survival outcomes of patients diagnosed with PC in a Kenyan population.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology

Pancreatic cancer is a disease associated with an increasing impact on cancer-related mortality worldwide. The global incidence and mortality rates have more than doubled since 1990 (12). It is currently the fourth most common cause of cancer-related mortality in the economically developed world where it is set to be the second leading cause by 2030 (7,13). The greatest rise in incidence is projected to occur in Africa (5). This trend is due to an increase in the ageing population as well as the rising prevalence of diabetes and obesity, important risk factors for pancreatic cancer (14). On the other hand, the case fatality rate has changed little over the past decades (5).

Pancreatic cancer is predominantly a disease of the older population with 90% of patients being over the age of 50 (15). Data from the Global Burden of Disease Study shows that incident cases peak at 65 to 69 years for men and at 75 to 79 years for women (12). A young age of onset among Africans has been documented by several studies. A study conducted in Zambia found the mean age of diagnosis was 55.7 years (16). In Malawi, a similar study recorded a mean age of 52.1 years (17). In Kenya, a peak incidence in the 51- 60 year age group has been documented (18,19). It is generally more common in males, with a male-to-female ratio of 1.3:1 thought to be due to differing exposures to environmental factors (15).

Incidence and mortality rates also vary with race. Several US-based studies have demonstrated that not only are African-Americans at considerably higher risk of PC than any other racial group, but they also have a poorer prognosis from the disease (2,3,20). These racial disparities are attributed, at least in part, to greater environmental exposure to cigarette smoking and obesity, as well as a higher prevalence of diabetes, but there is possibly a contribution from underlying genetic or gene-environment interactions (3). Additionally, their low socio-economic status may limit access to healthcare (21). Studies describing patterns of PC in Africans are limited, necessitating further research to better understand the disease in this population.

2.2 Burden of Pancreatic Cancer in Kenya

According to a dissertation study by Ongile in 2005, 42 patients with PC were seen at Kenyatta National Hospital (KNH) over one year between 2003 and 2004 (18). The peak was in the 51-to-60-year age group, with a range of 25 to 87 years. Out of 42 patients, only one had radical resection surgery while the remainder either had palliative bypass surgery or exploratory laparotomy only. Two patients received adjuvant chemotherapy while one received adjuvant radiotherapy (18). An earlier retrospective study by Kanyi in 1985 found that between 1977 and 1985, 49 patients had a diagnosis of PC at KNH, with age ranging from 21 to 80 years (19). Only one patient had a partial resection while the remaining patients had either palliative bypass or exploratory laparotomy only due to inoperability of the tumour (19). During the period of these studies, nearly all the interventions were palliative. To date, there is very limited data on the survival outcomes of patients with PC in the Kenyan population.

2.3 Clinicopathologic Characteristics of Prognostic Significance

Up to 95% of malignant tumours of the pancreas arise from the exocrine pancreas, 90% of cases comprising pancreatic ductal adenocarcinoma (PDAC) and its subtypes (4). Hence, the terms "pancreatic cancer" and "pancreatic ductal adenocarcinoma" are often used interchangeably (4). Pancreatic neuroendocrine tumours are far less common than PDAC, accounting for less than 5% of cases (5). They are generally more indolent tumours with a more favourable prognosis (22).

The signs and symptoms associated with PC are non-specific, giving a broad differential diagnosis and leading to delayed diagnosis, with a median time of more than 2 months from initial presentation (23). The initial signs and symptoms vary with tumour location (24). About 60 to 70% of PCs arise from the head of the pancreas, while approximately 15% each arise from the body and tail (25). In general, tumours of the pancreatic head tend to be diagnosed earlier than those in the body and tail because even small tumours near the common bile duct or ampulla of Vater can cause biliary obstruction and jaundice (25). Jaundice secondary to a tumour arising from the body or tail typically occurs later in the course of the disease and is more likely due to liver metastases (26). Tumours arising from the body of the pancreas tend to invade local vascular structures and are more like to present with back pain (24). Pancreatic tail tumours, due to fewer surrounding anatomical structures, have unrestrained growth, often presenting at an advanced stage (26).

An important contributor to the poor survival rate is the difficulty with early diagnosis of PC, owing to the vagueness of symptoms and the lack of specific diagnostic tests (27). As a result, the majority of patients present with advanced disease. The overall survival rate of PC is 24% at 1 year and 4% to 9% at 5 years (5). Current data from the US shows that the 5-year survival rate by stage is 40% for localized disease, 14% for regional disease and 3% for distant metastasis (7).

On account of significant advances in multimodality therapy over the last three decades, treatment of PC has had significant bearing on its prognosis (8,28). Advances in surgical techniques have resulted in dramatically reduced peri-operative morbidity and mortality from surgical resection as well as expansion of the indications for surgery due to increasing capabilities in vascular reconstruction (8,9).

Neoadjuvant therapy has been demonstrated to convert a significant proportion of initially staged non-resectable (borderline and locally advanced) tumours to resectable tumours, with survival comparable to initially resectable tumour patients (6). Several studies have suggested that total neoadjuvant therapy (chemotherapy plus chemoradiotherapy) is more likely to achieve complete pathologic response than chemotherapy or chemoradiation alone, resulting in improved overall survival outcomes (29,30).

Adjuvant chemotherapy is the standard of care for patients with resected pancreatic adenocarcinoma. Several randomised controlled trials have demonstrated significantly greater long-term survival rates from adjuvant chemotherapy. Notably, in the ESPAC-1 trial, both the two-year (40% versus 30%) and the five-year (21% versus 8%) survival rates were significantly greater among patients randomized to adjuvant chemotherapy consisting of leucovorin-modulated 5-fluorouracil compared to those who did not receive it (31). Similarly, the CONKO-001 trial demonstrated that the survival advantage from adjuvant gemcitabine chemotherapy persisted long-term (five-year OS 20.7% versus 10.4%; 10-year OS 12.2% versus 7.7%) (32). The high rate of local and systemic recurrence after surgery alone, even with negative resection margins, necessitates additional therapy (33). Current National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines recommend that patients with resected PC receive adjuvant therapy . Based on evidence that multiagent chemotherapy combinations such as FOLFIRINOX as shown in the PRODIGE-24 trial produce better outcomes than gemcitabine monotherapy, they are the preferred choice in the adjuvant setting for patients with good performance status who are able to tolerate them (37,38). For less fit patients, options include gemcitabine plus capecitabine or gemcitabine plus nab-paclitaxel, with gemcitabine monotherapy reserved for patients whose performance status or comorbidity index preclude multiagent therapy (34).

Current guidelines recommend that for patients with locoregionally advanced and metastatic pancreatic cancer, the goals of care are palliation and lengthening of survival, with selection of patients for systemic chemotherapy based on performance status (34). Palliative chemotherapy using either FOLFIRINOX or gemcitabine alone or combined with nab-paclitaxel has been demonstrated to prolong survival (11,39). Severely disabled patients with a poor PS are offered chemotherapy only on a case-by-case basis, with emphasis placed on best supportive care (34).

Survival decreases with advancing age; however, for the subgroup of patients post-pancreatectomy, survival may be similar across all age groups (8). Performance status at diagnosis and the comorbidity burden significantly affect survival outcome (8,40). They also weigh into the into consideration of the benefits versus potentially harmful effects of treatment, hence influencing choice of therapies (8,40).

2.4 Problem Statement and Study Justification

The prognosis of pancreatic cancer has remained dismal with a mortality rate almost equal to its incidence despite developments in diagnostic and therapeutic strategies. Individuals of African descent are disproportionately affected, with higher incidence and mortality rates than any other racial group. Previous local studies were done prior to availability of several therapeutic modalities hence little is known about current management and trends in survival outcomes of PC in the Kenyan population.

The need to generate local data becomes imperative in the face of projections that the highest increase in incidence and mortality of PC will be registered in Africa in the next decade. This study provides data on uptake of available therapies and survival outcomes of patients with PC at KNH.

2.5 Research Question

What are the clinicopathologic characteristics and survival outcomes of patients with pancreatic cancer in Kenyatta National Hospital?

2.6 Study Objectives

2.6.1 Broad Objective

To determine the clinicopathologic characteristics and survival outcomes of patients with pancreatic cancer at Kenyatta National Hospital.

2.6.2 Specific Objectives

2.6.2.1 Primary objectives

1. To describe the clinical, tumour and treatment characteristics of patients with pancreatic cancer at Kenyatta National hospital between 2014 and 2021.
2. To determine the survival outcomes at one year of patients with pancreatic cancer at Kenyatta National Hospital between 2014 and 2021.

2.6.2.2 Secondary Objective

1. To determine association between the clinical, tumour and treatment characteristics and the one-year survival outcomes of patients with pancreatic cancer at Kenyatta National Hospital between 2014 and 2021.

CHAPTER THREE: METHODOLOGY

This was a retrospective cohort study conducted at the Kenyatta National Hospital (KNH), a tertiary referral institution offering comprehensive cancer services including surgical oncology, medical oncology, radiotherapy, and palliative care. The study setting was the main KNH Health Information department, which stores files from medical and surgical wards and clinics as well as the records departments of the cancer treatment centre and the radiotherapy unit. The International Classification of Diseases for Oncology-10th edition (ICD-10) code: C25 was used to identify and retrieve records of patients with a diagnosis of pancreatic cancer (PC). All files of patients with a diagnosis of PC, made between January 1, 2014, and September 30, 2021, were reviewed. All those which met the case definition were enrolled in the study, forming the final sample size.

Minimum sample size calculation:

Cochran's formula for categorical data[16]

$$n_0 = \frac{(t)^2 * (p)(q)}{d^2}$$

- t = value for selected alpha level (1.96)
- p =expected true proportion, based on prior study on PC patterns and survival which estimated proportion of patients alive at 1 year at 17%.[17]
- q= 1-p
- d = desired precision (0.05)
- **n= 216**

Data was collected in October 2022. A data collection form was used for the abstraction of all the relevant information from each file by the principal investigator and qualified medical personnel.

The case definition of pancreatic cancer was based on a diagnosis made using computed tomography and/or magnetic resonance imaging, positron emission tomography, endoscopic ultrasonography, with or without cytological or histological confirmation of ductal adenocarcinoma of the pancreas. Those with benign and premalignant tumours, neuroendocrine tumours, acinar cell tumours, periampullary tumours and non-pancreatic neoplasms metastatic to the pancreas were excluded from the analysis. Cases without a record of cross-sectional imaging

to make the diagnosis of pancreatic cancer were also excluded from the study. Microscopic diagnosis was not required since there is consensus that in the presence of a solid mass suspicious for malignancy, biopsy proof is not required before resection (34,35).

The study was approved by the institutional review board of the Kenyatta National Hospital/University of Nairobi (P436/05/2022). Confidentiality and data protection were maintained throughout the duration of the study.

Data on age, sex, county of residence, education, insurance status, risk factors including alcohol and cigarette use, family history of cancer, history of chronic pancreatitis, comorbidities, clinical presentation, tumour characteristics, cancer staging and treatment were collected.
For the survival analysis, data on date of PC diagnosis, documented date of last contact and vital status at last contact were collected from the files. Based on the radiological and clinical information documented in the files, patients were categorised into three stages, defined according to the AJCC/UIC TNM staging system, 8th edition (Appendix A) (41). Charlson comorbidity index (CCI) was calculated based on the comorbidities documented prior to or at the time of diagnosis of pancreatic cancer. ECOG performance score and Charlson comorbidity index were categorised into the following groups "0-1", "2' and "3+".

Surgery was defined as surgical resection of the primary tumour with curative intent. Post-operative mortality was calculated at 30 days and 90 days following surgery. The assignment of oncologic treatment categories as neoadjuvant, adjuvant or palliative was based on clinicians' notes and the timelines with respect to surgery. In patients who had an operation, neoadjuvant therapy was defined as chemotherapy or chemoradiation given prior to surgery and adjuvant therapy was that given within six months of radical surgery. Chemotherapy and/or radiotherapy were considered palliative if no resection was done. Patients who received neither surgical resection nor chemotherapy were classified as having received best supportive care only.

Survival time was defined as the time from the date of diagnosis to the date of death or last follow up. Patients' vital status was recorded as documented in their files on the date last contact. In cases

where the vital status at one-year post-diagnosis was not known, they were recorded as "lost to follow-up". The data collection tool is illustrated in Appendix B.

Data on sociodemographic, clinical, tumour and treatment characteristics was presented as mean (± standard deviation) and/or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. The Kaplan-Meier method was used to analyse survival probabilities for various groups, and the differences were compared using the log-rank test. Cox proportional hazards regression was used to assess the strength of association between the various covariates and survival, with the hazard ratio and the corresponding confidence intervals reported.

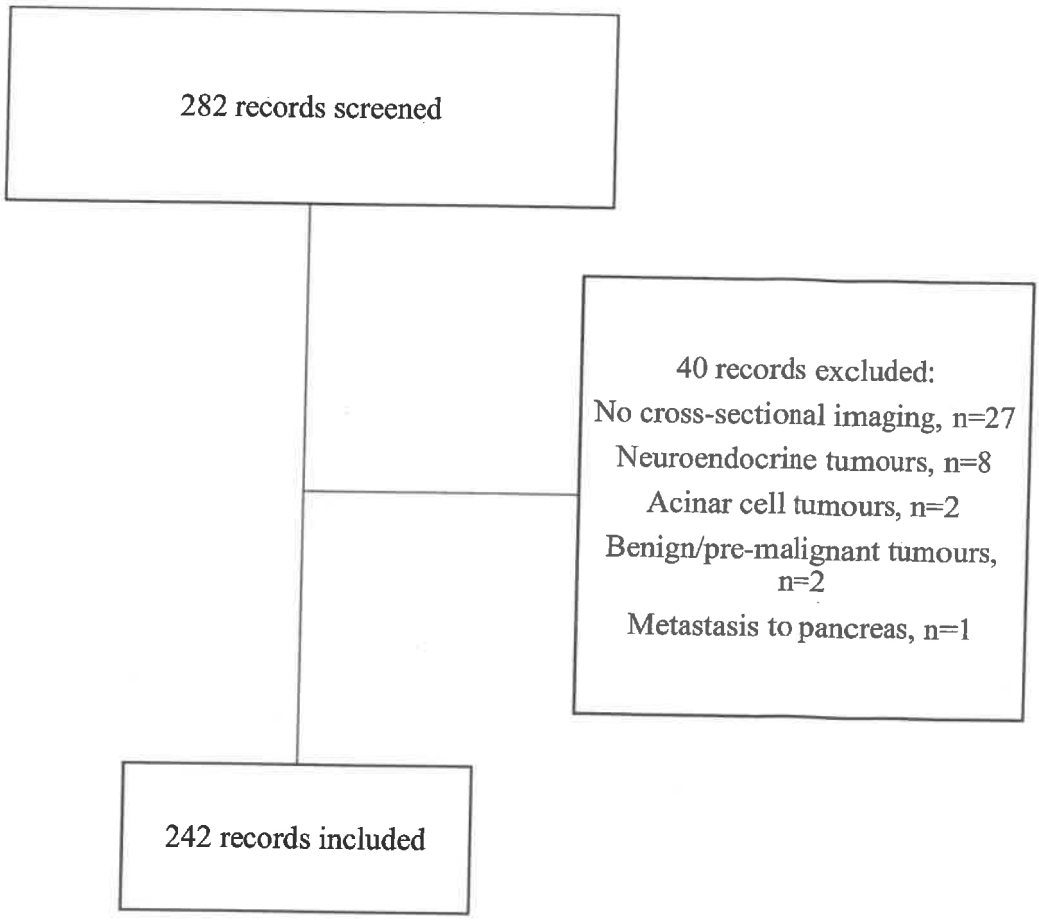
Patient demographics, tumour characteristics and treatment modalities were compared among the stage categories using Fisher's Exact or Pearson Chi-square test for categorical variables and analysis of variance or Kruskal-Wallis equality-of-populations rank test for continuous variables. Logistic regression was used to determine the associations of chemotherapy with age, sex, performance status, comorbidity index and cancer stage.

In the post-hoc analysis, clinical, tumour and treatment characteristics were compared among the stage categories using Fisher's Exact or Pearson Chi-square test for categorical variables. Logistic regression was used to determine associations of various covariates with chemotherapy.

The follow-up time was restricted to one year for the cox regression analysis. Statistical analysis was performed using STATA. Statistical significance was defined by two-sided $p < 0.05$.

CHAPTER FOUR: RESULTS

3.1 Recruitment of Study Participants



3.2 Sociodemographic Characteristics

A total of 242 patient files were recruited, the majority of whom 129 (53%) were female and 113 (47%) were male. The median age was 58.5 years (IQR 35-88; range 32-92). The counties of residence with the highest numbers were Murang'a, Kiambu and Nyeri counties with 37 (15%), 30 (12%), 21 (8%) patients respectively, likely representing their close proximity to KNH. Most were farmers, 70 (36%), and had some formal education, 186 (77.4%). About 75% paid their treatment costs by insurance. These characteristics were generally equally distributed between males and females. Table 1 illustrates the sociodemographic characteristics of this population.

Table 1: Sociodemographic characteristics of patients with PC at KNH 2014-2021.

Sociodemographic characteristics	Male (n=113)	Female (n=129)	Overall (n=242)
	n (%)	n (%)	n (%)
Age (years)			
<50	22 (19.5)	33 (25.6)	55 (22.7)
50–64	44 (38.9)	57 (44.2)	101 (41.7)
65–74	32 (28.3)	29 (22.5)	61 (25.2)
≥75	15 (13.3)	10 (7.7)	25 (10.3)
Residence			
Murang'a	17 (15.0)	20 (15.5)	37 (15.2)
Kiambu	13 (11.5)	17 (13.2)	30 (12.4)
Nyeri	10 (8.9)	11 (8.5)	21 (8.7)
Meru	8 (7.1)	8 (6.2)	16 (6.6)
Kirinyaga	6 (5.3)	9 (6.9)	15 (6.2)
Nakuru	9 (7.9)	6 (4.6)	15 (6.2)
Machakos	10 (8.8)	4 (3.1)	14 (5.8)
Nairobi	5 (4.4)	6 (4.7)	11 (4.6)
Others	35	48	83 (34.3
Level of education			
Primary	43 (47.2)	55 (50.5)	98 (49.0)
Secondary	26 (28.6)	29 (26.6)	55 (27.5)
Tertiary	16 (17.6)	17 (15.6)	33 (16.5)
No formal education	6 (6.6)	8 (7.3)	14 (7.0)
Occupation			
Farmer	34 (36.6)	36 (35.6)	70 (36.1)
Formal employment	26 (27.9)	30 (29.7)	56 (28.9)
Business	11 (11.8)	20 (19.8)	31 (15.9)
Metal work	5 (5.3	0 (0)	5 (2.5)
Chemical industries	3 (3.2)	0 (0)	3 (1.6)
Unemployed	14 (15.1)	15 (14.8)	29 (14.9)
Insurance			
Insured	80 (70.8)	103 (79.8)	183 (75.6)
Uninsured	33 (29.2)	26 (20.2)	59 (24.4)

3.3 Clinicopathologic Characteristics

Table 2: Clinicopathologic characteristics of patients with PC at KNH 2014-2021.

Variable	Overall (n=242)
Clinical presentation	**n (%)**
Abdominal pain	176 (72.7)
Jaundice	165 (68.2)
Pruritus, pale stools, dark urine	92 (38.0)
Weight loss	74 (30.6)
Loss of appetite	64 (26.5)
Back pain	21 (8.7)
Symptom duration, mean (± SD) months	4.1 (3.9)
Risk factor	
Alcohol consumption	58 (23.9)
Smoking	57 (23.6)
Diabetes	45 (18.6)
Family history of cancer	14 (5.8)
Obesity (BMI ≥30kg/m^2)	6 (2.5)
Chronic pancreatitis	4 (1.7)
CA 19-9 at diagnosis	
<37 U/mL	26 (10.7)
≥37U/mL	68 (27.9)
ECOG performance score	
0–1	73 (46.2)
2	37 (23.4)
3-4	48 (30.4)
Charlson comorbidity index	
0–1	92 (38.0)
2	60 (24.8)
3+	90 (37.2)
Location	
Head	196 (80.9)
Body and tail	46 (19.0)
Diagnosis	
Histology/cytology	146 (60.3)
Radiology	96 (39.7)

Table 2 continued

Cancer stage	
Stage I/II	34 (14.1)
Stage III	67 (27.7)
Stage IV	131 (54.1)
Not documented	10 (4.1)

Table 2 illustrates the clinicopathologic characteristics of this population. The most common presenting features were abdominal pain, present in 73%, jaundice in 68%, features of cholestasis-pruritus, pale stools, dark urine in 38% and weight loss in 30% of cases. Other clinical features at presentation were loss of appetite (26.5%), and back pain (8.7%). The median duration of symptoms was 3 months (IQR 1-18; range 0.5-24 months).

Family history of cancer was present in 14 (5.8%) of patients, none of whom had a documented family history of pancreatic cancer. Of those whose records included this information, history of alcohol use was positive in 58 (24%) of cases whereas 57 (24%) had a documented history of smoking. History of chronic pancreatitis was present in 4 patients (1.7%). Forty-five patients (18.6%) were known to have diabetes mellitus, and of the 38 patients with documented duration since diagnosis of diabetes, 24 (36%) were diagnosed within 12 months of diagnosis of pancreatic cancer.

Thirty-four (14%) patients had stage I/II disease, 67 (28%) had stage III disease and 131 (54%), had stage IV disease at diagnosis. For patients with stage III/unresectable disease, the reason for unresectability was arterial and/or venous invasion in 32 (48%) of cases, extra-pancreatic local extension in 21 (31%) and regional lymph node extension in 9 (13%). There was no staging information for 10 (4%) patients.

The majority of patients, 196 (81%) had tumour involving the head of pancreas, whereas 46 (19%) had tumour involving the body and/or tail of the pancreas. Tumours involving the pancreatic head were dominant in stage I/II disease (97.1%) compared to stage III disease (80.6%) and stage IV disease (76.3%) whereas the occurrence of tumours in the body or tail of the pancreas was higher in advanced disease; 2.9% of stage I/II vs 19.4% of stage III and 23.7% of stage IV (All p=0.013).

A total of 94 (38.8%) had their CA 19-9 documented at diagnosis. There was no difference among the stages in the distribution of age, sex, duration of symptoms or serum levels of CA 19-9. Pre-treatment CA 19-9 levels were normal (<37U/mL) in 26 (10.7%) cases out of the entire population and in 14 (11.4%) cases with histologically confirmed PDAC.

Of those who had their performance status documented, the majority had relatively good performance scores: ECOG 0-1in 73 (46.2%), 2 in 37 (23.4%) whereas 48 had poor performance scores, ECOG 3-4 in 48 (30.4%).

Patients were significantly more likely to present with jaundice if they had tumour located in the head of the pancreas (76%) compared to the body or tail (35%) ($p<0.001$). Similarly, presentation with features of cholestasis- pruritus, pale stools, and dark urine- were significantly associated with tumour location in the head (43%) versus the body or tail of the pancreas (15%) ($p<0.001$). There was no significant association between CA 19-9 level at diagnosis and tumour location. The distribution of clinical presentation and CA 19-9 by tumour location is illustrated in Appendix C.

The most common site of metastasis was the liver, found in 28% of cases, followed by the peritoneum at 22% and distant lymph nodes and lungs at 13.6% and 10% respectively. Factors associated with metastases at diagnosis included presentation with abdominal pain and tumour located in the body or tail of the pancreas.

Of the 242 patients, 146 (60%) had a histologic or cytologic diagnosis, of which 123 (84%) confirmed PDAC. Five (29%) of the 17 patients who underwent pancreatoduodenectomies had pre-operative histologic confirmation of PDAC. Of the patients with histologically-confirmed PDAC, 16 (13%) had well differentiated tumours whereas 62 (50%) had moderately or poorly differentiated tumours.

3.4 Treatment

3.4.1 Surgery

A total of 70 patients underwent surgery, of whom 40, representing the majority at 57% had palliative procedures whereas 13 patients (19%) had exploratory surgery only. Seventeen patients, (7%) of whose who had surgery, underwent radical resection. These included 15 of the 34 (44%) patients who presented initially with stage I-II tumours and 2 of the 67 (3%) patients with stage III tumours at diagnosis who underwent resection after having been down-staged to resectable disease with neoadjuvant chemotherapy. All resected tumours involved the head of the pancreas and all resections were pancreaticoduodenectomies, with no distal or total pancreatectomies. There was no documentation of vascular resection. Of the remaining patients initially diagnosed with stage I/II disease, 9 were found to have unresectable disease intraoperatively, whereas 5 declined surgery and 5 were lost to follow-up after their initial diagnosis. Older patients were less likely to undergo radical resections given that 6 (10.9%) of patients aged <50 years underwent resection compared to 9 (8.9%) of those aged 50-64 years, 2 (3.3%) of those aged 65-74 years and none of those aged ≥75 years. However, this did not meet the threshold of statistical significance ($p = 0.176$), likely due to small numbers.

Among the 17 patients who underwent pancreatoduodenectomies, there was 1 mortality (5.8%) in the 30-day post-operative period and none recorded in the 90-day post-operative period.

Analysis of the temporal trend in surgical resection over the 8-year period of this study revealed an increase in the number of pancreatoduodenectomies conducted between 2014-2015, 2016-2017 and 2018-2019 with 2,4 and 7 cases for each of these respective periods. This likely reflects an increase in the number of patients diagnosed with PC over this period of time. There was subsequently a decrease during the 2020-2021 interval to 4 cases. This trend is illustrated in figure 1.

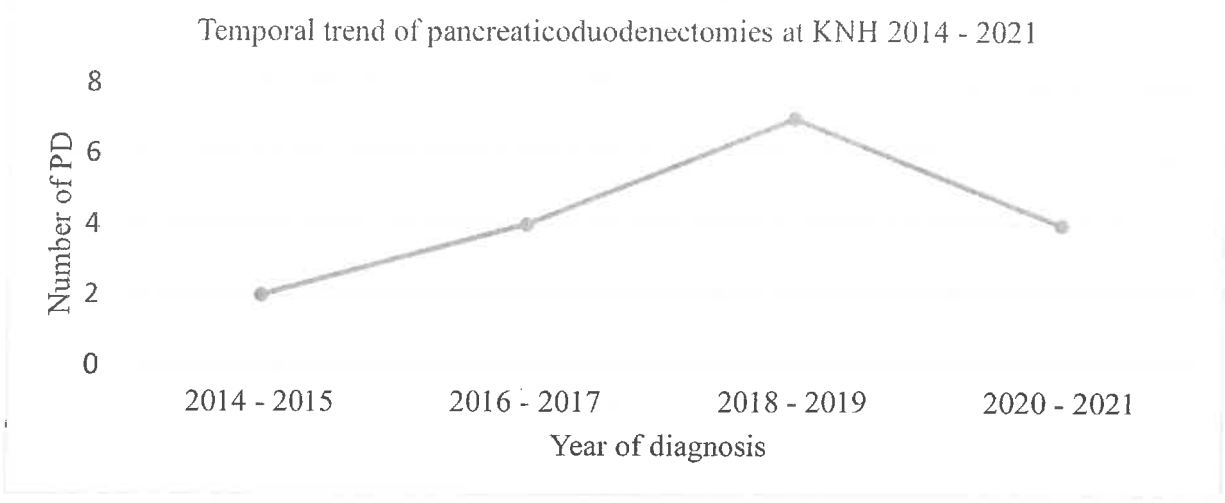


Figure 1: Temporal trend of pancreaticoduodenectomies at KNH 2014 - 2021

PD, pancreatoduodenectomies.

3.4.2 Chemotherapy and Chemoradiation

Of the 242 patients, 88 (37%) received at least one cycle of chemotherapy. Assessed by stage, 18 (52.9%) patients with stage I/II disease received chemotherapy, as did 24 (35.8%) of patients with stage III disease and 46 (35.1%) of patients with metastatic disease.

Among the 101 patients with non-metastatic disease, a total of 12 patients were offered neoadjuvant chemotherapy with the intention to subsequently undergo surgery. The most common regimen was FOLFIRINOX, given in 6 (50%) of cases, followed by gemcitabine plus oxaliplatin in 3 (25%), gemcitabine in 2 (17%) and FOLFOX in 1 (8%) case. The median number of cycles was 5 (IQR 3-6). Of these patients, 9 had stage I/II disease whereas 3 had stage III disease at diagnosis. Subsequently, only 5 of these patients went on to have surgery; 2 patients underwent pancreatoduodenectomy whereas 3 were found to be inoperable. The remaining 7 did not undergo surgery, either because they declined operative management or because they were lost to follow-up. Pre-operative chemotherapy was therefore in effect administered to 5 (4.9%) of patients with non-metastatic disease.

Nine patients (53%) out of 17 who had a surgical resection received adjuvant chemotherapy, for a median of 6 cycles, (IQR 4-8). Out of these, one had also received pre-operative chemotherapy while the rest received adjuvant chemotherapy alone. Four patients (44%) received adjuvant FOLFIRINOX whereas 3 (33%) received gemcitabine plus cisplatin and 2 (22%) gemcitabine plus oxaliplatin. No patients received adjuvant chemoradiation.

Palliative chemotherapy was administered to 70 (29%) patients, for a median of 3 cycles, (IQR 1-11; range 1-20). The most common chemotherapy regimen, administered in 47 (40.5%) cases was FOLFIRINOX. Gemcitabine in combination with capecitabine, cisplatin or oxaliplatin was given in 42 (36%) cases whereas in 6 (5%) cases gemcitabine was given alone. In 18 (16%) cases patients received capecitabine either alone or in combination with oxaliplatin. FOLFOX was administered in 3 (2.5%) cases. One patient with stage III disease received concurrent chemoradiation with capecitabine.

Overall, 154 (63.6%) patients did not receive chemotherapy. For 27.6% of these patients, this was due to loss to follow-up, with no repeat visit following their first admission to KNH. 20% of patients with multiple repeat visits had no documented reason for non-administration of chemotherapy. Among patients with documented reasons for not offering chemotherapy, in 24% of cases, it was related to early death; in 23% it was due to poor performance status and/or old age. In 4% of cases, patients refused chemotherapy whereas 1.3% had a contraindication.

A post-hoc analysis of factors associated with chemotherapy was conducted, the results of which are illustrated in appendix E. Factors significantly associated with failing to receive chemotherapy in the bivariable analysis were ECOG performance score ≥3, Charlson comorbidity index ≥3 and lack of NHIF insurance. In the multivariate analysis, performance score ≥3 (AOR 0.07, 95% CI 0.02-0.24, p=<0.001) and lacking NHIF insurance (AOR 7.18, 95% CI 1.43-36.19, p=0.017 remained significantly associated with not receiving chemotherapy.

3.4.3. Supportive Care

Table 3: Best Supportive Care Interventions for Patients with Pancreatic Cancer at KNH 2014-2021

Indication for palliative intervention	Number	Percent
Pain		
Opioid analgesia	84	25
Palliative radiotherapy	3	1
Obstructive jaundice		
Endoscopic biliary stent	71	22
Open biliary-enteric by-pass	42	13
Percutaneous transhepatic cholangiography	28	9
Gastric outlet obstruction		
Open gastrojejunostomy	28	8
Endoscopic enteral stent	1	0.4
Others		
Nutritional support	45	14
Palliative medicine review	28	8

Overall, 146 (60%) patients received best supportive care only. There was a significant difference among the three clinical stages, with higher rates among those with advanced disease. Nine (26.5%) of patients with stage I/II disease, 42 (62.7%) of those with stage III and 85 (64.9%) of patients with stage IV disease at diagnosis received best supportive care only (p=<0.001).

For the palliation of obstructive jaundice, 71 (29.3%) patients underwent endoscopic biliary stenting, whereas 42 (17.3%) and 28 (11.6%) underwent open biliary-enteric bypass and percutaneous transhepatic cholangiography respectively. The majority of patients with gastric outlet obstruction underwent open gastrojejunostomy, performed on 28 (11.5%) patients whereas only 1 (0.4%) had an enteral stent placed endoscopically. Three (1.2%) patients with metastatic disease received palliative radiotherapy. Other supportive measures included analgesia including opioids, given to 84 (34.7%) and nutritional support, given in 45 (18.6%) cases. Of note, only 28 (11.5%) patients had a documented formal palliative care team review.

3.5 Survival

The median survival time was 3 months. The one-year survival rate was 32%. Survival time is illustrated in Figures 2 and 3, stratified by surgery and chemotherapy respectively. Patients who underwent surgical resection with curative intent had significantly better survival than those who did not (p=0.021), and this benefit persisted for the duration of 105 months until close of the study. Patients who received chemotherapy were also found to have significantly improved survival compared to those who did not (p<0.001), although this difference was diminished after about 20 months.

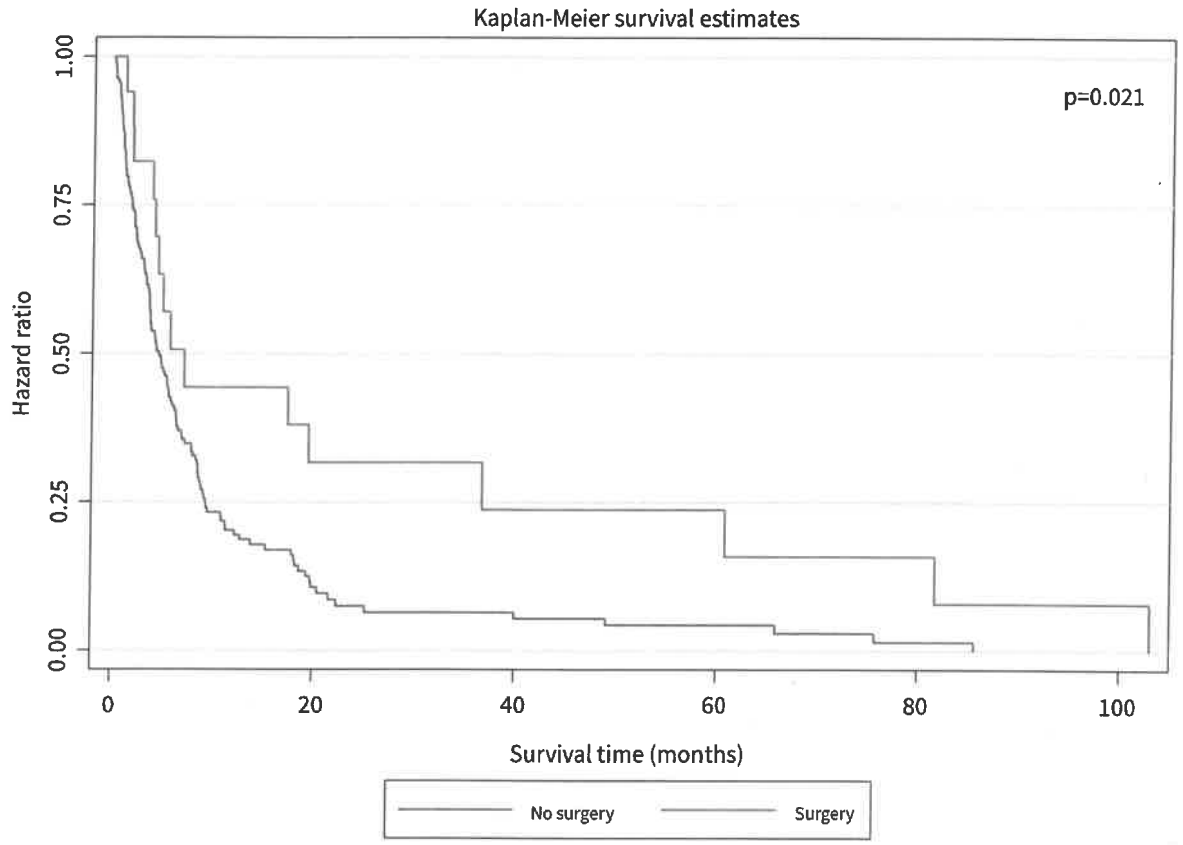


Figure 2: Kaplan-Meier survival curve of overall survival (in months) among pancreatic cancer patients diagnosed between 2014-2021 stratified by surgical treatment.

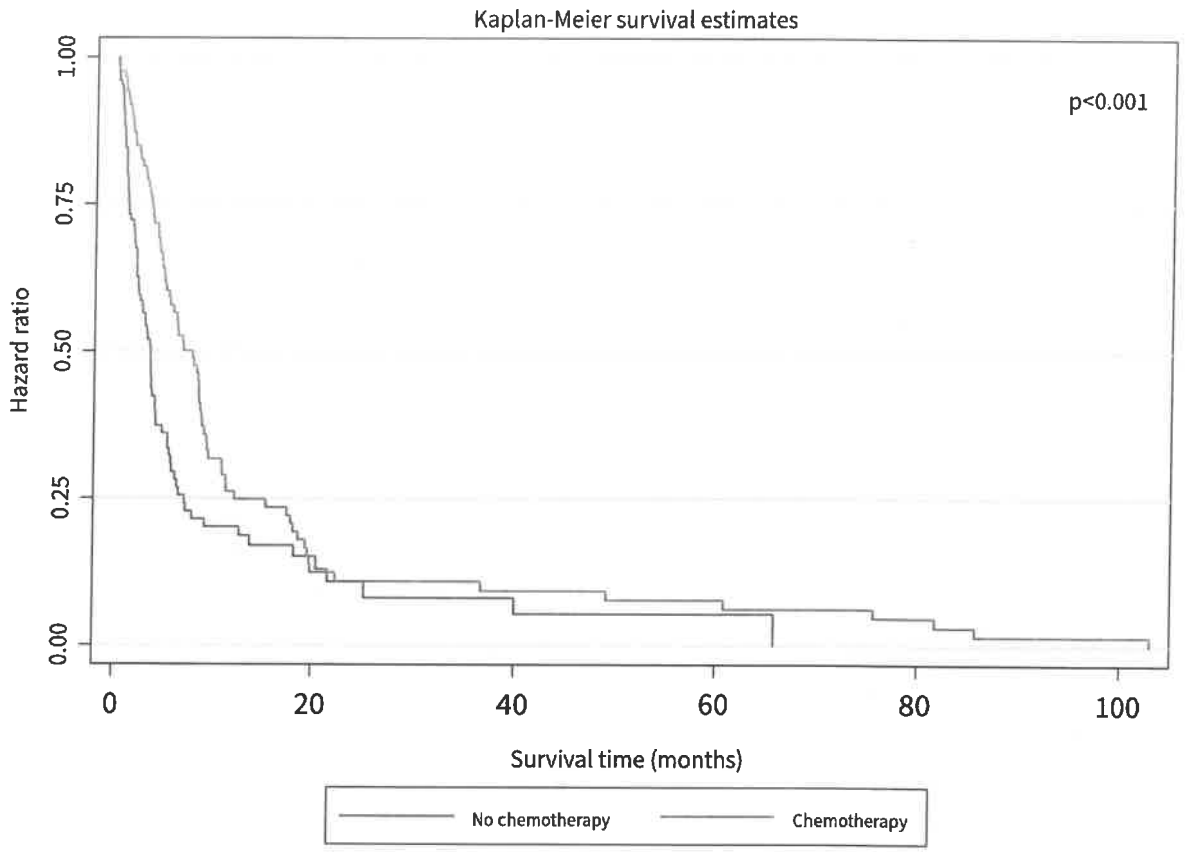


Figure 3: Kaplan-Meier survival curve of overall survival (in months) among pancreatic cancer patients diagnosed between 2014-2021 stratified by chemotherapy use.

Table 4: Bivariable and Multivariable Cox regression Analysis of One-year Overall Survival in Patients with PC at KNH 2014-2021.

Clinical characteristics	Cohort n (%)	Bivariable analysis		Multivariable analysis	
		HR (95% CI)	p value	AHR (95% CI)	p value
Age					
<50y	26 (26.0%)	Ref		Ref	
50–64y	39 (39.0%)	0.71 (0.39-1.31)	0.281	1.52 (0.23-10.37)	0.665
≥65y	35 (35.0%)	0.92 (0.49-1.70)	0.781	0.34 (0.02-5.73)	0.459
Sex					
Male	46 (46.0%)	Ref		Ref	
Female	54 (54.0%)	1.09 (0.67-1.76)	0.739	0.73 (0.13-4.12)	0.725
ECOG PS					
0–1	19 (28.4%)	Ref		Ref	
2	15 (22.4%)	30.61 (3.97-235.76)	**0.001**	1.90 (0.12-29.34)	0.645
3–4	33 (49.2%)	94.26 (12.78-695.35)	**0.000**	25.25 (2.80-227.47)	**0.004**
CCI					
0–1	37 (37.0%)	Ref		Ref	
2	26 (26.0%)	1.29 (0.70-2.41)	0.408	2.29 (0.78-6.72)	0.132
3+	37 (37.0%)	1.39 (0.79-2.44)	0.250	2.45 (0.87-6.90)	0.089
Tumour location					
Head	89 (89.0%)	Ref		Ref	
Body and tail	11 (11.0%)	1.82 (0.83-3.98)	0.134	5.20 (0.49-55.45)	0.172
Baseline CA 19-9					
< 37 U/mL	9 (25.7%)	Ref			
≥37 U/mL	26 (74.3%)	1.57 (0.59-4.22)	0.369	1.98 (0.49-8.02)	0.336
Cancer staging					
Stage I/II	12 (12.6%)	Ref		Ref	
Stage III	25 (26.3%)	2.36 (0.67-8.27)	0.181	0.81 (0.16-4.04)	0.793
Stage IV	58 (61.1%)	5.53 (1.72-17.79)	**0.004**	1.93 (0.41-9.00)	0.402

Table 4 illustrates the bivariable and multivariable cox regression analysis of factors associated with 1-year survival. ECOG PS of ≥2 and cancer stage IV were negatively associated with survival. In the unadjusted Cox proportional-hazards regression model, compared to patients with ECOG PS 0-1, survival outcomes were significantly worse among those with ECOG PS 2 (HR 30.61, 95% CI 3.97-235.76, p=0.001) and 3-4 (HR 94.26, 95% CI 12.78-695.35, p<0.001). Patients with stage IV cancer had worse survival than those with stage I /II cancer (HR 5.53 95% CI 1.72-17.79, p=0.004). However, in the adjusted multi-variate model, only ECOG PS remained a strong predictor of overall survival (HR 33.65, 95% CI 4.23-267.44, p=0.001; HR 81.17, 95% CI 10.74-613.58, p<0.001) for ECOG PS 2 and 3-4 respectively, compared to ECOG PS 0-1. Patients who underwent surgical resection had improved survival rates compared to those who did not (HR 0.20, 95% CI 0.05-0.83, p=0.021). Similarly, patients who received chemotherapy had improved survival rates (HR 0.15, 95% CI 0.08-0.29, p<0.001) compared to those who did not. Age, gender, the comorbidity burden, and tumour characteristics including tumour location and baseline CA 19-9 levels did not show significant association with 1-year survival.

CHAPTER FIVE: DISCUSSION

This retrospective study aimed to evaluate the baseline characteristics, management, and outcomes of patients with pancreatic cancer in the setting of a national referral hospital with specialist oncology services in Kenya. The results indicate that pancreatic cancer occurred at a relatively young age in this cohort of patients, with a median age of 58.5 years (IQR 35-88; range 32-92) and the majority (64%) being younger than 65 years. This is similar to the findings of other studies conducted in African populations including Zambia (mean 55.7 years) (16) and Malawi (mean 52.1 years) (17) and in African American populations, where it has been found that the age of onset is significantly younger compared to Caucasians (63.3 vs 67.1 years, $p<0.001$) (3). The majority of patients (54%) had metastatic disease at diagnosis, as is reported in other studies (5). A post-hoc analysis showed that, as has been found in other studies (24,26), patients were more likely to present with abdominal pain if they had stage IV disease than if they had stage I/II or stage III disease. Conversely, patients were more likely to present with features of cholestasis if they had stage I/II disease, compared to stage III disease or stage IV disease. The distribution of clinicopathologic characteristics by stage is illustrated in appendix D.

The prevalence of alcohol use in the current population (24%) was higher than that of the general Kenyan population, reported as 19%, as was that of cigarette smoking, at 24% compared to the national average of 13% (42). Alcohol and cigarette consumption were not quantified in this retrospective study hence the association with excessive use could not be analysed. Diabetes mellitus was more prevalent, at 18%, compared to 4% in the general Kenyan population (43). In US studies, the higher prevalence of cigarette smoking, alcohol use, diabetes and obesity has been suggested as a possible contributor, at least in part, to the disproportionately higher incidence of PC among African Americans compared to Caucasians as well as its occurrence at a younger age (3). It is however understood that there are likely multiple reasons for the racial differences in PC incidence and mortality including socio-economic discrepancies limiting access to care; further, the possibility of an underlying genetic aetiology which is then exacerbated by social and environmental risk factors is being explored (3).

The majority of patients received palliative and best supportive care. Patients were more likely to undergo surgical resection and to receive chemotherapy if they had better performance scores, whereas those with poorer performance scores were more likely to receive palliative and best supportive care only.

The rate of surgical resection among patients with resectable disease (stage I/II) was 44%. This represents an increase compared to historical data from the same institution. A retrospective study of pancreatic cancer at KNH during the 8-year period spanning 1977 to 1985 found that out of 49 patients, none had a pancreatectomy while the majority (75.5%) had palliative bypass procedures (19). A later prospective study conducted over one year between 2003 and 2004 found that out of 42 patients, 1 (2.4%) had a pancreatoduodenectomy whereas 62% had palliative surgery (18). During the 8-year period of the current study, there was an initial steady increase in the number of pancreatoduodenectomies, with a decrease in 2020-2021 which may be explained by the limitations in healthcare access and the constraints on non-emergent operations occasioned by the outbreak of the COVID-19 pandemic as has been widely reported (44,45).

Low rates of overall resection have been reported in other African studies including a single-centre study in Nigeria which reported a rate of 3% (46), and in Malawi, where a similar study found that 94% of pancreatic resections were palliative (17). An international study of population-based cancer registries in Europe and the USA reported variable resection rates across countries, ranging from 13.2% to 21.2% overall and 34.8% to 68.7% for stage I–II tumours (47). In advanced, high-volume centres, the application of vascular resection and the administration of neoadjuvant chemotherapy to render locally advanced tumours more amenable to surgical resection have been used to achieve resectability rates of up to 60% of previously unresectable tumours (48,49). Such advances in systemic chemotherapy and surgery have expanded the guideline-based indications for surgical resection of pancreatic cancer from stage I and II cancer to locally advanced, previously unresectable disease (34).

About half of the patients with resected tumours received adjuvant chemotherapy, the standard of care for this category of patients. The most common adjuvant chemotherapy regimen was FOLFIRINOX, given to 4 (44%) whereas the combination of gemcitabine with cisplatin or with

oxaliplatin was given to 3 (33%) and 2 (22%) patients respectively. Most patients received at least six cycles, likely reflecting the selection of medically fit patients.

Half of the post-resection patients were not offered chemotherapy. In the majority of cases, these patients had no documented review by a medical oncologist and no documented reason for failing to offer chemotherapy. This may be related at least in part to lack of insurance given that having insurance significantly increased the odds of receiving chemotherapy. The multivariable analysis of factors associated with chemotherapy administration revealed that poor performance status (ECOG $\geq$3) was significantly associated with decreased odds of receiving any chemotherapy. Comparable rates of adjuvant chemotherapy have been reported in settings such as Europe, where they range from 31% to 52% (50). An American study based on a national cancer database reported a rate of initiation and completion of adjuvant chemotherapy of 35% and 7% respectively (51). Treatment at a high-volume cancer centre has been associated with greater compliance with guideline-complaint care including the utilisation of adjuvant chemotherapy (52). In the current context, increased multi-disciplinary collaboration with the involvement of medical oncologists to formulate care plans may help to improve chemotherapy rates.

Neoadjuvant chemotherapy was infrequently administered, offered to 12 patients (12%) of those with non-metastatic disease, of whom 5 went on to have surgery, with 2 undergoing pancreatoduodenectomies whereas the rest were subsequently found inoperable. Similarly low rates of neoadjuvant chemotherapy are reported in other settings. A large international population-based study assessing management of PC between 2003 and 2014 found that the rate ranged from 0.3% of patients in Slovenia to 2.2% in the Netherlands and 3.1% in Belgium (50). Current NCCN guidelines recommend that patients with borderline resectable disease, who are at high risk of positive surgical margins, should be considered for neoadjuvant chemotherapy followed by restaging and resection for those without disease progression precluding surgery (34). It is worth noting that the term 'borderline resectable', which was recently developed, was not uniformly applied in this patient cohort, making it difficult to assess the suitability for pre-operative chemotherapy by this criterion. Of the 12 patients who were offered neoadjuvant chemotherapy, nine were classified as having stage I/II disease whereas three had stage III disease. Appropriate staging according to resectability criteria may help to increase the proportion of patients selected for neoadjuvant chemotherapy.

The majority of patients with stage III and IV disease received palliative and best supportive care only (63% and 65% respectively). Of the patients with stage III disease, 39% received chemotherapy as did 35% of those with metastatic disease. These results are comparable to those in other populations such as the USA and Europe, where a study showed that the majority of unresected patients did not receive any non-surgical treatment (50). The selection of patients with good performance status for palliative chemotherapy is reflected in the distribution of palliative chemotherapy regimens, where the most commonly administered were combination therapies with FOLFIRINOX (40.5%) and gemcitabine with capecitabine or cisplatin or oxaliplatin (36%), whereas only a minority of patients received monotherapy. Current guidelines recommend that for patients with locoregionally advanced and metastatic pancreatic cancer, the goals of care are palliation and lengthening of survival, with selection of patients for systemic chemotherapy based on performance status (34). Interestingly, unlike in other studies, the odds of chemotherapy administration did not vary with advancing patient age in the multivariable analysis, possibly due to the small population. Older age has severally been found to be associated with decreased likelihood of chemotherapy application, due to the presence of more frequent serious comorbidities, poorer performance status and higher likelihood of toxicities in this population (50,53). In addition, elderly patients have been found to be more likely to refuse chemotherapy (54). While it has been shown that elderly patients derive similar survival benefits from chemotherapy compared to those who are younger, their performance status must be taken into consideration when deciding on aggressive treatment (53,55).

Radiotherapy was rarely used, given to only 4 patients (1.6%) across the study population. One patient with stage III disease received capecitabine-based chemoradiation while 3 patients with metastatic disease received palliative radiotherapy. No resected patient received neoadjuvant or adjuvant chemoradiation. Other studies have reported similarly low uptake of radiotherapy (50). The role of radiotherapy in resectable pancreatic cancer remains controversial, having been shown by some trials to improve local control when added to chemotherapy whereas other trials have shown no benefit, and potentially worse survival, from adjuvant chemoradiation compared to chemotherapy alone (31,56,57). Whereas American guidelines suggest the addition of chemoradiation to adjuvant chemotherapy (34), European guidelines recommend chemotherapy alone (35). Likewise, the role of chemoradiation in neoadjuvant PC remains uncertain (58).

There is limited evidence for the use of chemoradiation in the setting of locally advanced disease, having failed to consistently demonstrate survival benefit and potentially having greater toxicity compared to chemotherapy alone (59). The low uptake of radiotherapy for treatment of non-metastatic PC likely reflects this lack of consistent evidence in its favour.

The majority of patients received palliative care interventions for the relief of symptoms, the most common indications being biliary, duodenal, and gastric outlet obstruction, and tumour-related pain. A large proportion of patients had open surgical procedures despite the availability of endoscopic alternatives. With the widespread availability of endoscopic biliary and duodenal stents, the treatment paradigm has shifted away from traditional surgical management (60). That said, in the case of gastric outlet obstruction, surgical gastrojejunostomy may be the best option for patients with good performance status and a life expectancy of greater than 2 months while endoscopic stenting, associated with significantly more re-intervention, is preferred in patients with shorter life expectancy and who are poor surgical candidates (34,61). A large proportion of patients did not receive a formal palliative medicine review, yet the PC patient is the stereotypical patient who would benefit from these services. Early referral and initiation of palliative care services improves clinical and quality of life outcomes (62,63). It also helps to avoid non-beneficial treatment and inappropriate care towards the end of life (64).

The one-year survival rate was 32%. In comparison, the global, the overall survival rate of PC is 24% at 1 year (5). This being a single-centre retrospective study with a relatively small sample size, it may be difficult to compare the survival rate of the current population to the findings of population-based studies that are able to assess survival prospectively. It is difficult to exclude the possibility of a confounding effect from patients who underwent surgical resection or medically fit patients who continued to receive their chemotherapy at KNH and were followed up for considerably longer than those who did not receive such interventions and were more likely to be discharged earlier and lost to follow-up at KNH. A previous retrospective cohort study on the survival outcomes of patients with PC at KNH between 2015 and 2019 based on data from the hospital medical records reported a one-year survival rate of 81.3%, a finding, as highlighted by the authors, at great variance with other studies in this population (65). One possible explanation for the difference between these findings and those of the current study is the lack of a clear case

definition for PC, making it possible that some patients in the previous study had a diagnosis of PC made presumptively based on their clinical presentation, without confirmatory diagnosis using imaging or biopsy. Few studies on survival outcomes have been conducted in Africa. A retrospective study conducted in Algeria that evaluated 160 patients diagnosed with PC between 2006 and 2013 reported an overall 1-year survival rate of 20% and a 5-year survival rate of less than 5% (66). In a single-centre retrospective study conducted in Nigeria analysing outcomes of patients treated for PC between 1999 and 2013, the 1-year survival rate was 20% (67).

The most important factor associated with survival was performance status (PS). This is in keeping with the findings that good PS was significantly associated with both earlier stage of disease and with higher likelihood of receiving aggressive therapy. Both surgery and chemotherapy significantly improved survival, reflecting earlier stage of disease amenable to aggressive treatment.

CONCLUSION

In conclusion, the results of this study indicate that pancreatic cancer occurred at a relatively young age, supporting other studies in African populations. The majority of patients presented at advanced stages. Patients selected for curative-intent surgery and for chemotherapy comprised individuals with good performance status. Compared to previous studies in the same institution, there was an increase in the number of patients who underwent curative intent surgery, including patients initially diagnosed with stage III disease who were down-staged with neoadjuvant chemotherapy. Half of those who underwent surgical resection with curative intent were not offered adjuvant chemotherapy, which is the standard of care, despite having no documented contraindication. Survival outcomes were poor with a median survival time of 3 months and a 1-year survival rate of 32%. Surgical resection and chemotherapy were associated with significantly improved survival rates, reflecting earlier stage disease and better tolerance of aggressive therapies. Finally, the lack of insurance coverage presented a significant barrier to receiving treatment.

STRENGTHS AND LIMITATIONS

This study has a number of strengths, including being the first to evaluate both the surgical and oncologic therapies for pancreatic cancer in the Kenyan setting. It was conducted in the largest regional referral hospital, encompassing the breadth of cancer care services. Having been conducted following several advances in treatment, it offers perspective into the incorporation of various diagnostic and therapeutic modalities into the management of pancreatic cancer.

This being a retrospective study, it is subject to the limitations of missing or incomplete data. For example, it was not possible to assess remission status as most patients did not have documented restaging information. Secondly, due to the relatively small sample size, some groups were too small for detailed analyses. It is possible that some differences may become significant with a larger number of patients. Third, there was wide variability in some analyses, particularly survival analysis, due to relatively small numbers, compounded by high rate of loss to follow-up. Fourth, whereas in current clinical practice PC is assessed according to resectability criteria, these criteria were not consistently applied in the population studied, therefore tumour staging was assessed using the conventional TNM stages. Lastly, the high rate of loss to follow up limits our ability to conduct a comprehensive survival analysis, given that less than half the population was on follow-up one year after their diagnosis. That said, it is worth noting that this study was conducted at a national referral hospital, and we cannot exclude the possibility that many of the patients lost to follow up subsequently received their care at other facilities, and given the survival data, that many of them died.

RECOMMENDATIONS

There is need to have a high index of suspicion in younger patients presenting with features suggestive of pancreatic cancer in our setting, as this may aid earlier diagnosis. We recommend advocacy by healthcare workers as well as policy-makers to control risk factors such as cigarette smoking, alcohol use and diabetes. Enhanced use of systemic chemotherapy for appropriately selected patients will allow the accrual of maximal survival benefit from the application of multimodal therapy. This is especially important for patients with resectable disease. Vascular resection should be considered for appropriately selected patients to expand resectability criteria. Finally, a prospective study is needed to evaluate treatment outcomes.

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APPENDIX

Appendix A: Exocrine pancreatic cancer TNM staging AJCC UICC 8th edition.

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*. This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1 to 2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Prognostic stage groups	
0	Tis N0 M0
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T3 N0 M0
IIB	T1, T2, T3 N1 M0
III	T1, T2, T3 N2 M0 T4 any N M0
IV	Any T any N M1

Appendix B: Data collection tool- Clinicopathologic characteristics and survival outcomes of patients with pancreatic cancer at KNH 2014-2021.

Sociodemographic characteristics	
Patient number	
Age	
Sex	
Residence	
Occupation	
Education	
Insurance	
Clinicopathologic characteristics	
Alcohol	
Smoking	
Weight	
Height	
Family history of cancer	
History of chronic pancreatitis	
Co-morbidity	
Diabetes duration	
Symptom duration	
CA 19-9 at diagnosis	
ECOG score	
Imaging mod	
Date of diagnosis	
Tumour location	
TNM stage	
Resectability status	

Tumour size	
N stage	
Metastasis site	
Biopsy method	
Histology	
Grade	
Treatment	
Neoadjuvant chemotherapy regimen/cycles	
Surgery date	
Surgery type	
Adjuvant chemotherapy regimen/cycles	
Palliative chemotherapy regimen/cycles	
Best supportive care interventions	
Radiotherapy	
Treatment response	
Resection margin	
Radiologic restaging	
CA 19-9 post Rx	
Operative complications	
Recurrence date/pattern	
Survival data	
Date of last contact	
Vital status at last contact	
Date of death	
Cause of mortality	

Appendix C: Distribution of clinical characteristics by tumour location of patients with pancreatic cancer at KNH 2014-2021.

Characteristics	Tumour location		P value
	Head n (%)	Body/tail n (%)	
Clinical presentation			
Abdominal pain	139 (70.9)	37 (80.4)	0.192†
Jaundice	149 (76.0)	16 (34.8)	**<0.001†**
Weight loss	59 (30.1)	15 (32.6)	0.740†
Back pain	17 (8.7)	4 (8.7)	0.996∞
Loss of appetite	53 (27.0)	11 (23.9)	0.665†
Pruritus, pale stools, dark urine	85 (43.4)	7 (15.2)	**<0.001†**
CA 19-9, median (range) U/mL	288.0 (36.5 - 1000)	167.0 (9.7 - 1000)	0.667¶

† Pearson Chi-square; ∞ Fisher's exact; ¶ Kruskal-Wallis equality-of-populations rank test.

Appendix D: Clinicopathologic characteristics by stage of patients with PC at KNH 2014-2021.

Characteristics	Stage I/II	Stage III	Stage IV	P value
	n (%)	n (%)	n (%)	
Age, mean (±SD), years	55.8 (11.7)	61.7 (11.2)	58.7 (12.3)	0.0509*
Gender				
Male	17 (50.0)	30 (44.8)	60 (45.8)	0.879†
Female	17 (50.0)	37 (55.2)	71 (54.2)	
Lifestyle factor				
Alcohol consumption	8 (23.5)	14 (20.9)	33 (25.2)	0.797†
Smoking	7 (20.6)	7 (10.5)	24 (18.3)	0.286∞
Body mass index Mean (± SD), kg/m^2	23.7 (3.0)	21.3 (5.4)	21.7 (6.1)	0.3772*
Diabetes	9 (26.5)	13 (19.4)	22 (16.8)	0.437†
Family history of cancer	3 (8.8)	1 (1.5)	10 (7.6)	0.123∞
History of chronic pancreatitis	2 (5.9)	0 (0.0)	2 (1.5)	0.082∞
Clinical presentation				
Abdominal pain	18 (52.9)	49 (73.1)	106 (80.9)	0.004†
Jaundice	28 (82.4)	47 (70.2)	82 (62.6)	0.079†
Weight loss	14 (41.2)	22 (32.8)	35 (26.7)	0.237†
Back pain	0 (0.0)	6 (9.0)	15 (11.5)	0.096∞
Loss of appetite	5 (14.7)	21 (31.3)	31 (23.7)	0.174†
Pruritus, pale stools, dark urine	22 (64.7)	27 (40.3)	35 (26.7)	0.000†
Duration of symptoms, mean (± SD) months	3.9 (4.3)	4.8 (4.7)	3.8 (3.2)	0.2213*

Appendix D continued

CA 19-9, median (range) U/mL	135 (13–371)	245 (59.3–1000)	438 (36.5–1000)	0.2962¶
ECOG performance score				
0–1	18 (81.8)	26 (53.1)	29 (34.9)	0.003∞
2	2 (9.1)	11 (22.5)	23 (27.7)	
3-4	2 (9.1)	12 (24.5)	31 (37.4)	
Charlson comorbidity index				
0–1	19 (55.9)	21 (31.3)	48 (36.6)	0.164†
2	7 (20.6)	17 (25.4)	35 (26.7)	
3+	8 (23.5)	29 (43.3)	48 (36.6)	
Location				
Head	33 (97.1)	54 (80.6)	100 (76.3)	0.013∞
Body and tail	1 (2.9)	13 (19.4)	31 (23.7)	
Treatment				
Surgical resection	15 (44.1)	2 (3.0)	0 (0.0)	0.000∞
Chemotherapy	18 (52.9)	24 (35.8)	46 (35.1)	0.162∞
Best supportive care only	9 (26.5)	42 (62.7)	85 (64.9)	0.000∞

*Anova; † Pearson Chi-square; ∞ Fisher's exact; ¶ Kruskal-Wallis equality-of-populations rank test.

Appendix E: Factors associated with administration of chemotherapy in patients with pancreatic cancer at KNH 2014-2021.

Variable	Chemotherapy	Bivariable analysis		Multivariable analysis	
	n (%)	OR (95% CI)	p value	AOR (95% CI)	p value
Age					
<50y	18 (32.7)	Ref		Ref	
50–64y	47 (46.5)	1.79 (0.90-3.55)	0.096	2.47 (0.81-7.51)	0.110
≥65y	23 (26.7%)	0.75 (0.36-1.57)	0.446	1.51 (0.35-6.59)	0.577
Sex					
Male	37 (32.7)	Ref		Ref	
Female	51 (39.5)	1.34 (0.79-2.28)	0.274	1.66 (0.74-3.70)	0.217
ECOG PS					
0–1	48 (65.8)	Ref		Ref	
2	19 (51.3)	0.55 (0.25-1.23)	0.146	0.41 (0.16-1.07)	0.069
3–4	5 (10.4)	0.06 (0.02-0.17)	**0.000**	0.07 (0.02-0.24)	**0.000**
CCI					
0–1	39 (42.4)	Ref		Ref	
2	28 (46.7)	1.19 (0.62-2.29)	0.604	1.08 (0.35-3.38)	0.894
3+	21 (23.3)	0.41 (0.22-0.78)	**0.007**	0.50 (0.14-1.74)	0.278
Cancer staging					
Stage I/II	18 (52.9)	Ref		Ref	
Stage III	24 (35.8)	0.49 (0.21-1.15)	0.101	0.77 (0.22-2.65)	0.677
Stage IV	46 (35.1)	0.48 (0.22-1.03)	0.060	1.29 (0.39-4.27)	0.677
NHIF status					
Uninsured	4 (6.7)	Ref		Ref	
Insured	84 (45.9)	16.19 (4.89-53.61)	**0.000**	7.18 (1.43-36.19)	**0.017**

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LEAD SUPERVISOR AND CHAIRMAN OF DEPARTMENT APPROVAL

This dissertation has been submitted with the approval of my lead supervisor and the chairman of the department of Clinical Medicine and Therapeutics.

Lead Supervisor:

Prof. Elly Otieno Ogutu

Professor, Consultant Physician and Gastroenterologist, Department of Clinical Medicine and Therapeutics, University of Nairobi

Signature.....**Date**21/11/2023.....

Chairman of the department:

Prof. E. O. Amayo

Chairman of the Department of Clinical Medicine and Therapeutics

Professor, consultant Physician and Nephrologist, Department of Clinical Medicine, and Therapeutics

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF CLINICAL MEDICINE & THERAPEUTICS
P.O. Box 19676-00202 NAIROBI

Signature.....**Date**24/11/2023.....