ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE DEPARTMENT OF SURGERY

MAGNITUDE AND PREDICTORS OF UNRESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA AT TIKUR ANBESA SPECIALIZED HOSPITAL IN ETHIOPIA 2024.

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JULY, 2024

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Magnitude and predictors of unresectable Pancreatic Ductal Adenocarcinoma at Tikur Anbesa Specialized Hospital in Ethiopia 2024.

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A research thesis submitted to the department of surgery, school of medicine, collage of health sciences for the partial fulfillment of the requirements for subspecialty training in Hepatopancreaticobiliary surgery.

JULY, 2024

ADDIS ABABA, ETHIOPIA

ACKNOWLEDGMENTS

My appreciation goes to Addis Ababa University, College of Health sciences, department of surgery, for giving me the chance to conduct this study as a partial fulfillment for my subspecialty certificate in Hepatopancreaticobiliary surgery. Great gratitude to my advisor,Dr. Abebe Alemayehu, for his continuous mentorship in preparation of this thesis starting form proposal development. I thank department of oncology head and outpatient clinic nurses for their permission in gathering pancreas cancer patients list from their side. I thank the data collectors and supervisor of this project.

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ABBREVIATIONS

BMI	Body Mass Index
CA	Celiac Artery
CA 19-9	Carbohydrate Antigen 19-9
CHA	Common Hepatic Artery
CP	Chronic pancreatitis
DM	Diabetes Mellitus
ECOG	Eastern Cooperative Oncology Group
FNAC	Fine needle Aspiration Cytology
GLOBOCAN	Global Cancer Observatory
GOO	Gastric outlet obstruction
IQR	Inter Quartile Range
LAPC	Locally Advanced Pancreatic Cancer
NCCN	National Comprehensive Cancer Network
MR	Mortality Rate
OJ	Obstructive Jaundice
PDAC	Pancreatic Ductal Adenocarcinoma
PV	Portal Vein
RVI	Retroviral Infection
SD	Standard Deviation
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
TASH	Tikur Anbesa Specialized Hospital
TNM	Tumor Node Metastasis
USA	United States of America

ABSTRACT

Background: *Pancreas ductal adenocarcinoma is the most common type of pancreas cancer with a dismal prognosis. Over the previous 50 years, it has increased in incidence and fatality rate, and for the next three decades, it will continue to rise.*

Objectives: *The objective of this study was to assess the magnitude and predictors of unresectable pancreatic ductal adenocarcinoma at a tertiary hospital in Ethiopian.*

Method*: Institution based cross sectional study was conducted on 173 consequently selected patients. Data was collected from patients' medical records, entered in to Epi data version 3.1 and transported to SPSS version 23 for analysis. Variable with P-value less than 0.05 in multi variable logistic regression was used to declare the level of significance at 95% confidence interval.*

Result: *Males account for 53.8% (93 patients) of cases. The average age of participants was 55.77 years. The common clinical presentations were abdominal pain 89.0%, jaundice 82.2%, anorexia in 80%, weight loss 73.3% and pruritus 42.2%. In 65.3% of patients the tumor was located on pancreas head. Ninety three (53.8%) of patients had unresctable pancreatic cancer. In 39 (22.5%) of patients the tumor was resectable. LAPDAC and borderline resectable pancreas cancer accounts for 14.5% and 9.2% respectively. Patients who had pancreas cancer confined to the pancreas had lower risk of unresctability by 63% (COR = 0.37, CI: 0.18, 0.80) compared to pancreas cancer with local direct invasion. The risk of developing unresctable pancreas cancer reduced by 50% (COR =0.50, 95% CI: 0.27, 0.93) in patients who had jaundice than non-jaundiced patients.*

Conclusion: *About 53.8% of PDAC patients were unresctable. Local direct tumor invasion and presentation without jaundice were found to be predictors of unresctability. Detecting pancreas cancer as it is confined to the pancreas is the only chance for cure by surgery.*

Keywords: *Pancreas cancer, unresectability, Ethiopia*

1. INTRODUCTION

1.1. Background

Pancreas ductal adenocarcinoma is the most common type of pancreas cancer accounting for 90% of all pancreas cancers(1). Although there is a regional variation in incidence Pancreas ductal adenocarcinoma (PDAC), it is a rare cancer accounting for about 3% of all cancers in Europe. Its incidence and Mortality Rate (MR) increases over the past 50 years and will continue to increase for the next three decades as the longevity and diagnosis ability is increasing (2).

PDAC is one of the fatal cancers with great challenge in diagnosis and treatment(3). Most patients die within 4 to 6 months following diagnosis, however, after curative resection 30-58% five year survival reported. The five year over all survival slightly increased from 1970s to 2010s(4).

Hereditary factors accounts for about 5- 10% of PADC (1, 2, 5). The rest are sporadic. BRCA 1 and 2 were the commonly identified genetic mutations(6).

The main preoperative modality of diagnosis for PDAC is triphasic abdominal computed tomography scan. Cancer antigen 19-9 is not specific for preoperative diagnosis rather used for post operative follow up (5). Diagnosis in early stage is difficult because it remains silent and its retroperitoneal location(2, 3) but early diagnosis and treatment is the way to increase survival(7).

Although the acceptable test is yet to be defined, screening high risk groups is required and found to increase five year survival by early detection of cancer (5, 8, 9). USA Prevention and Screening Task Force recommends screening efforts be focused on well-defined high-risk cohorts but against mass screening as no acceptable testing tool is identified (10-12). Tumor markers and ultrasound have limited value in early detection of the tumor and effective method is not available. Surgical resection, which is the only chance of cure, cannot be an option for unresectable PDAC. Despite increase in incidence and mortality rate therapy remains low and PDAC will be a major health problem in the near future (13).

1.2. Statement of the Problem

According to GLOBOCAN 2020, pancreas cancer accounts for about 495,773, (2.6%) of new cancer cases and 4.7% of cancer deaths ranking the 7th cause of cancer death worldwide (14). PDAC has variation in incidence partly due to variation in risk factors and partly due to diagnosis tool variation. In Europe, PDAC accounts for the 7th common cancer and 4th common cause of cancer related death (2). It is the 6th most common cause of cancer death in china (3). According to the cancer statistical estimate of USA in 2023 there were about 64, 050 PDAC of which 79% expected to be died the same year (15). At the time of diagnosis, about 34% of pancreas cancers were unresectable because of liver metastasis in USA (16). According to GLOBOCAN 2020, 878 pancreas cancer cases were expected in Ethiopia ranking for 18th among all cancer types and 833 deaths the same year ranking 17th of all cancer deaths.

Incidence and mortality is increasing over the past two decades but with variation in demography and geography (17-20). In the next three decades, both incidence and mortality rate is predicted to increase partly due to increasing in longevity, increasing population growth, increasing of risk factors, improved diagnosis and registry of cancer (2, 5, 14). According to GLOBOCAN 2020 PC will be the third leading cancer death in 2025 at least in Europe (14). In china the mortality rate increased since 1991 (7). In Ethiopia both the prevalence and the incidence are being increasing in the past one decade (21).

PDAC is generally a disease of old age occurring in high incidence after the age of 55 (5). Smoking and obesity are the two most important risk factors identified (2). The other incriminated risk factors are gender, asthma, habitual heavy alcohol consumption of more than three drinks per day for decades, Diabetes Mellitus (DM), family history, chronic pancreatitis (CP)(5, 8, 16, 22).

Despite significant variation in incidence and MR, PDAC it remains the most fatal cancer with little geographic variation in survival rate (5). The median survival time was nine months from large USA study (16). The survival of patients with PDAC depends on multiple factors including duration of presentation of patients, age at diagnosis, comorbidity, quality of health care and life style habits, location on pancreas, stage of disease and histologic grade of the tumor (9).

Advanced stage presentation with symptom is due to its anatomical position in retroperitonium (23).

Most patients die within the same year of diagnosis. In USA, 50,550 patients died the same year of diagnosis out of 64, 050 (15). Globally in 2020, 466, 000 patients died among 496,000 new cases (14). The overall five year survival of PDAC is less than 10% (3, 5, 9). Kenner .et al reported 3% over all five year survival for metastatic PDAC (10). From China 10 - 25% five year survival reported (13).

Malnutrition is the other impact of pancreas cancer, which can affect the curative treatment. About 45% of operated patients were found to have lower albumin level (24).

If the stage distribution of pancreas cancer can be reversed by early detection of PDAC, the survival could have increased by double without improving the existing therapy (10). By reducing modifiable risk factors, mainly smoking, pancreas cancer risk can be reduced up to 27% (25). Active smoking reduces survival in pancreas cancer (26).

Little is known about the burdens, risk factors and epidemiologic trends in pancreatic cancer among African populations (27, 28). Among the few reports from Africa more than 50% were from Egypt and Nigeria(28). In Ethiopia, from five year retrospective review for operated PDAC patients, about 19% were operated for curative intent while the remaining operated for palliation. But this study included only surgically fit patients (24). In this study all potential socio demographic variables, clinical, laboratory and radiologic variables were included using cross sectional study design. Hence the aim of the study is to assess the magnitude of unresectable PDAC and is contributing factors in TASH, Ethiopia where there is little prior evidence on the problem.

1.3. Significance of the Study

- High risk groups of populations can use the evidence to avoid risk factors as a primary prevention and seek medical service visit soon after developing symptoms.
- Surgeons, hepatopancreaticobiliary surgeons in particular, may use the result of this study as a reference to their work measure and improve outcome in subsequent practices.

- Hospitals may use it to fulfill necessary diagnostic and therapeutic methods which are currently not widely available for early detection of the disease.
- Primary physicians, gastroenterologists and radiologists can use the result as an input to give an attention for the early diagnosis of PDAC at a resectable stage and advise their patients for further work up and evaluation.
- Healthcare professionals and policy makers could make more efforts to control the associated risk factors that may range from advocating for lifestyle changes, awareness campaigns and to imposing more strict laws.
- The study may be used as reference for subsequent studies.

2. LITERATURE REVIEW

2.1. Magnitude of unresectable PDAC

Globally the 80 - 90% of PDAC are unresectable (5, 13). From a retrospective review of 84, 275 PDAC in USA from 1975 to 2011, 81% were found to be non resectable (4). Blackford et al from USA reported 20% of pancreas cancers were resectable from retrospective study (29). Coa and colleagues reported 28% resctability, the others being non resectable. Most of unresectability was due to liver metastasis which remains the major cause of cancer related death in PDAC (16). From five year retrospective review of operated pancreas cancer patients in Ethiopia, about 19% were operated for curative intent while the rest operated for palliation(24).

2.2. Associated factors for unresectable PDAC

About 70% of cases were above the age of 60 years (30). Sellam et al from Algeria reported median age of 66 years (range 16 – 96 years) (31). A study from Norway showed median age of 69 years (32) while a case control study from China showed median age of pancreas cancer patients 64 years, and 30% were older than 70 years (33). Molina et al reported mean age of 65 years in Europe (22). Gad, M, M et al from USA reported 78% of cases were older than 60 years of age (34). On the same year mean age of 68 and 67.5 years were reported by Bengtssone and Blackford respectively from USA (4, 29). A median age of 46 years from another study in USA (6). Mean age of 56 years was reported from Zambia among 27 patient of PDAC (27). The median age at diagnosis was 67 years and 38% of patients were older than 70 years. From systematic review of African articles the mean age was found to be 57 years (28). Age less than 70 years was more likely to be unresectable due to liver metastasis likely due to due to higher and more aggressive histopathology (16). Aga and Abdurehman from Ethiopia reported median age of 55 years from 52 operated pancreas cancer cases (24).

The majority of PDAC occur in males. Males contributed for 51-59 % of cases (4, 6, 16, 29, 30). Pearlstein et al review from Africa showed 59% male contribution (28). Study from Ethiopia showed 52% contribution from males (24). Males account for 57% form Europe study (22). Among 264 pancreas cancer cases from China 57% were males (33). A study from Zambia

showed 63% male contribution (27). Equal gender distribution was reported from USA by Gad, M.M et al (19, 34) and from Norway study (32).

Twenty two percent of patients were found to be obese, BMI > 30kg/m^2, however, it was not associated with increased risk for PC(22). A study from USA showed median BMI of 25.2 kg/m^2 (6).

Shaib et al from Zambia reported abdominal pain as the most common clinical presentation accounting for 53% (27). Aga and Abdurehman from Ethiopia reported mean duration of presentation 32 weeks. In this study the commonly reported symptoms were abdominal pain (89%), anorexia (81%) significant weight loss (79%) and yellowish eye discoloration (71%). Only 40% of PDAC patients were found to have elevated CA19-9 more than 130mg/dl (24).

About 14 % of PC patients had DM (30). Xu Li et al from China reported 23% prevalence of DM in pancreas cancer patients and the risk of PDAC increased by 1.5 times (33). At diagnosis, 25% of patients were found to have DM and this increase the risk of PC by 1.24 times (22). Study from USA by Setiawan et al showed DM increase PDAC by two times (35). Another study from USA showed at initial diagnosis 17% of patients had DM (6). A study from Europe showed bronchial asthma in 7% and DM in 25% of patients (22). Hypertension and DM were the commonly identified comorbidities from study in Ethiopia each occurred in 12% of PDAC patients (24).

From a study in, USA Sanfransisco, 69% of patients were found to be smokers (30). Forty percent of patients were smokers and smoking was found to increase risk of PADC by 3.2 times (22). Smoking was reported in 19% of pancreas cancer patients from China study and it was not associated with increased risk for PDAC (33). Study from South Africa showed 44% of PDAC patients were found to be smokers and smoking is found to increase risk of PDAC in female patients (18). Fifty one percent of PDAC never smoke and about 91% of patients present at ECOG 1 or 2 physical statuses (6). Alcohol drinking was reported in 13% of cases but was not found to increase risk for PDAC (33). A study form Ethiopia showed smoking in 6% of patients and heavy alcohol consumption in 2% (24).

Chronic pancreatitis increase risk of PC by 11 times (33). Chronic pancreatitis was found in 0.7 % of patients (22).Family history of PDAC increase the risk by 2.7 times, and if there are ≥ 2

first degree relatives the risk increases by 3.9 times. Cancers other than PC were not found to be risks (22). A study from China among 264 patients only one pat (0.4%) was found to have positive family history for PADC (33). Two percent of patients had family history of pancreatic cancer from a study in Ethiopia (24).

Lymph node metastasis and poor grade of differentiation are predictors of unresctability and distant metastasis. Cancer with un/ poorly differentiated histology had 2.3 times more likely to have liver metastasis and unresectable (16).

Yuan et al reported 65.3% distant metastasis, 19.4% localized and 15.3% locally advancer PDAC from 1,039 patients (26). A study from USA on Asian- American patients showed 9% of PDAC were localized, 30% locally advanced and 56% distant metastasis (34). Another retrospective study from USA showed 7% localized, 31% regional, 56% distant metastasis and 6% unstaged disease (4). At diagnosis, 48% were stage IV, 27% LAPC, 23% resectable and the remaining unstaged (6). Abidoye et al in 2023 from USA reported 42% metastasis disease, 24% regional disease, 10% localized and 10% unstaged disease (19). A study from Ethiopia showed 29% stage I & II, 71% locally advanced and metastasis disease (Stage III & IV) after patients were operated for curative or palliative intent among operated cases only (24).

Regarding location of tumor in the pancreas, 48% on head, 15% on tail, 13% on body and 24% other location from study in USA (29). Another study from USA showed 47% of PDAC location on head of pancreas, 14% on tail, 12% on body and the others either overlapping/ unspecified (34). A study by Shaib and et al from Zambia in 2020 showed 83% of location on pancreas head (27). About 61% of cancer occur at head, 20% at body and 19% at tail (6). Abidoye et al in 2023 from USA reported 42% metastasis disease, 24% regional disease, 10% localized and 10% unstaged disease (19). Another study from USA showed 54% in head, 30% body & tail and 16% on other location. Larger and more advanced tumors were located on body & tail of pancreas probably due to lack of OJ. Location on body and tail of pancreas were 2.3 times more likely to have liver metastasis and unresectable. Location in body and tail of pancreas is predictor of unresctability and distant metastasis (16). About 77% of pancreas cancers were located at pancreas head (24).

The median tumor size was 3.9 cm from study in USA (29). From 33, 459 PDAC patients in USA study, 55% of cases hade size less than 4cm resectable. Size more than 4 cm were 2 times

more likely to be non resectable (16). A study from Algeria showed 92% of tumors located on head of pancreas and on body and tail each 4% (31). The mean diameter was reported to be 5.5 centimeters but tumors from body and tail had larger size compared with head cancers (24).

2.3. Conceptual framework

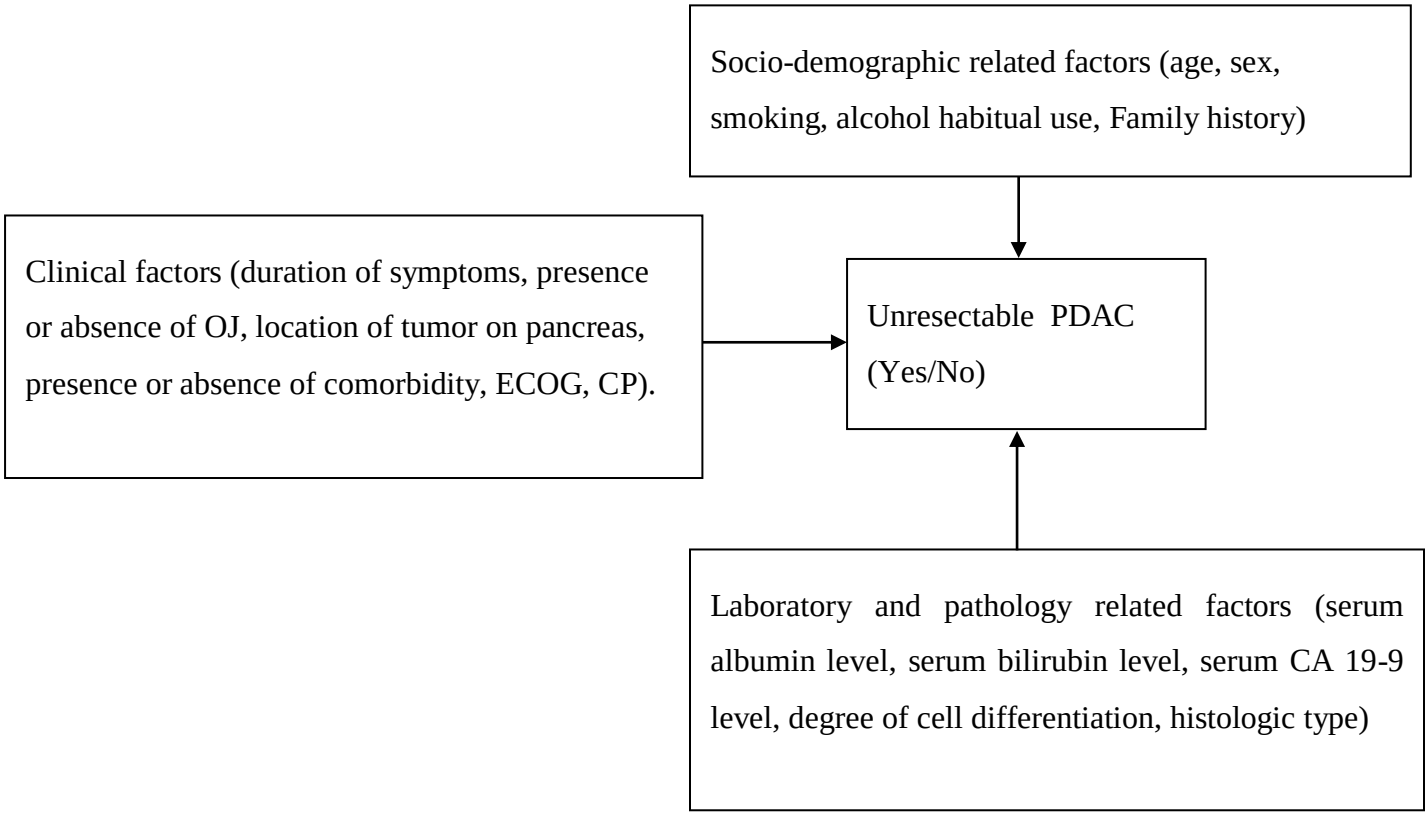


Figure 1: Conceptual framework adapted from literatures

3. OBJECTIVE

3.1. General objective

- To assess the magnitude of unresectable PDAC and associated factors among patients who attended surgical referral and oncology outpatient department of TASH, Addis Ababa Ethiopia, 2023/24.

3.2. Specific objective

- To determine the magnitude of unresectable PDAC in the study period.
- To assess sociodemographic profile of PDAC.
- To assess clinicopathological profile of PDAC.
- To assess factors contributing for unresectable PDAC.

4. METHODS AND MATERIALS

4.1. Study area and period

The study was conducted at Tikur Anbesa Specialized Hospital. TASH is located in Addis Ababa, the capital city of Ethiopia, with a projected population size of more than 3,945,000 according to Ethiopian Statistical service 2023. It is the country's biggest tertiary hospital serving as referral center from all over the country with estimated population number of 107,334,000 according to Ethiopian Statistical service 2023. The hospital provides necessary diagnostic and therapeutic services for pancreas cancer cases by subspecialty and specialty experts. The study period was from January 1, 2023 to June 30, 2024.

4.2. Study design

Institution based retrospective cross sectional study was conducted.

4.3. Source population

All patients with PDAC who attended surgical referral and oncology outpatient clinics of TASH.

4.4. Study population

All patients with PDAC who attended surgical referral and oncology outpatient clinics of TASH during the study period.

4.5. Study variables

4.5.1. Dependent variables

- Is PDAC unresectable or not.

4.5.2. Independent variables

- Socio-demographic related factors (age, sex, smoking, alcohol habitual use, Family history)
- Clinical Factors (duration of symptoms, presence or absence of OJ, location of tumor on pancreas, presence or absence of comorbidity, ECOG, CP).
- Laboratory and pathology related factors (serum albumin level, serum bilirubin level, serum CEA level, degree of cell differentiation, histologic type)

4.6. Sample size and sampling technique

4.6.1. Sample size

The assumptions of single population formula was used for sample size calculation at 95% confidence interval (two sided), 5% margin of error. Considering 81% prevalence of non resectable PDAC among operated patients in Ethiopia (24). So sample size was calculated as follows:-

$$\boldsymbol{n_o = \frac{(Z\alpha/2)^2 p\,(1-p)}{d^2}}$$

$$\boldsymbol{n_o = \frac{(1.96)^2 0.81\,(1-0.81)}{0.05^2} = 236}(aproximated\boldsymbol{)}$$

Where: n_o is the maximum possible sample size

$Z_{\alpha/2}$ is standard score value for 95 % confidence level for two sides normal distribution

p = is the proportion of population (the magnitude of unresectable PDAC). p = 0.81)

d = is margin of error tolerated, 5%

Za/2 = the standard and normal variable at (1-a) % with 95% (1.96) confidence level

Baseline data collected from TASH surgical referral and oncology outpatient registry books showed that there were around 182 patients. As the source population is less than the calculated sample size, all cases were taken without use of correction formula. After excluding participants with missed variable, the final sample size determined to be 173 patients.

4.6.2. Sampling technique /procedure

The medical record of all PDAC patients above the age of 14 years in the study period were reviewed in order of hospital visit from January 1, 2023 to June 30, 2024. Total enumerative/ consecutive sampling used.

4.7. Inclusion and exclusion criteria

4.7.1. Inclusion criteria

All patients with PDAC above the age of 14 years visiting the surgical referral clinic and oncology outpatient department in the study period were included.

4.7.2. Exclusion criteria

Nine patients whom clinical data, imaging, laboratory and FNAC/biopsy results incomplete were excluded from the study.

4.8. Data collection procedure

Data was collected by a trained general practitioner from patients medical record data. All necessary socio demographic and clinicopathological data were filled.

4.9. Quality control

The questionnaire was written in English language and checked consistency. Pretest was conducted at Minilik II comprehensive specialized hospital, in 5% of samples to check the completeness and consistency of the questionnaire. The data was collected by using a structure and pre tested paper based questionnaire in close supervision by the PI. The filled data were checked by PI for completeness and consistency visually. Data was entered to Epi data version 3.1.

4.10. Data analysis

Data cleaning was conducted to check for accuracy, consistency and missing values. The cleaned data was entered to EPI Data version 3.1 and was exported to SPSS version 23 for analysis. Descriptive statistics in terms of frequency tables and percentages was used to describe the study variable in relation to other variables. Bi-variable logistic regression analysis was conducted to assess independent variable association with the dependent variable. Variables with P-value of $\leq$ 0.3 was candidate for multivariable logistic regression analysis. The degree of association between the dependent and independent variables was assessed by crude and adjusted Odds

ratios along with 95% CI to measure the strength of the association. Adequacy of the model was assessed using Omnibus Tests of Model Coefficients and standard error to test whether the required assumptions for the application of multivariable logistic regression was fulfilled. Level of statistical significance was declared at P-value less than 0.05.

4.11. Result dissemination

The result of the study will be disseminated to concerned bodies of Addis Ababa University, TASH, MOH and other concerned bodies. Hard copy will be left to university library periodical. It can be presented on seminars and national research conferences, published in to peer reviewed local or international journal.

4.12. Operational definition

- **PDAC** = A pancreas malignant mass as described by typical triphasic CT scan features with or without pathologic diagnosis
- Resectable PDAC border line resectable, locally advanced and unresectable defined according to NCCN 2022 guideline during initial patient presentation to TASH.
- **Resectable PDAC**
    - PDAC no contact with Celiac artery (CA), Superior Mesenteric Artery (SMA) or Common Hepatic Artery (CHA).
    - PDAC no tumor contact with Superior mesenteric vein (SMV) / Portal Vein (PV) or ≤ 180° contact without vein contour irregularity.
- **Borderline resectable PDAC artery**
- Pancreatic head/ uncinate process
    - Contact with CHA without extension to CA or HA bifurcation allowing safe & complete resection and reconstruction.
    - Contact with SMA of ≤ 180°.
    - Contact with variant arterial anatomy.
- Pancreatic body/tail
    - Tumor contact with the CA of ≤ 180º

- Borderline resectable Venous
    - Contact with the SMV or PV of >180° or
    - Contact ≤ 180° with contour irregularity of the vein / thrombosis, but with suitable vessel proximal & distal to the site of involvement for safe & complete resection and vein reconstruction.
    - Contact with IVC.
- **Locally Advanced PDAC**
    - Head/ uncinate process
        - Contact >180° with the SMA / CA.
    - Pancreatic body/tail
        - Contact of >180° with the SMA / CA.
        - Contact with aortic involvement.
    - Venous – unreconstructable SMV/PV due to tumor involvement or occlusion or thrombus
- **Unresectable PDAC** = Tumor that cannot be removed due to growth to the surrounding tissue or spread to distant organs at time of diagnosis.
- **Local invasion** = means pancreas cancer invading surrounding structures by direct invasion (T4) and/ or peri pancreatic regional lymph node involvement (N1).

4.13. Ethical considerations

Ethical clearance was obtained from research ethics committee of college of health sciences, Addis Ababa University. Then formal letter of cooperation was obtained from departments of surgery and oncology. The collected data will be kept anonymous and maintained confidentiality.

5. RESULTS

5.1. Socio-demographic characteristics of study participants

One hundred seventy three patients were analyzed. Males account for 53.8% (93 patients) of cases. The average age of participants was 55.77(SD=13.86) years ranging from 19 to 83 years. Sixteen (9.2%) of patients were younger than 40 years old. The peak age was 60 years. Regular alcohol abuse and smoking was found in 14(8.1 %) and 8(4.6%) of patients respectively. Comorbidity was found in 50 (28.9%) patients. Thirty one patients (17.9%) had diabetes mellitus of which 27 (84.4%) were on treatment before pancreas cancer diagnosis. Nineteen patients (10.9%) found to have hypertension of these 8 patients also had DM (Table 1). RVI and cardiac disease (Valvular, degenerative and hypertensive heart disease) found in 2(2.3%), and 3(1.7%) of patients respectively. In two patients (1.2%) pancreas cancer was diagnosed incidentally.

Table 1:- Socio demographic characteristics.

Variable	Category	Number	Percent
Gender	Male	93	53.8
	Female	80	46.2
Age	<40	16	9.2
	≥40	157	90.8
Regular alcohol consumption	Yes	14	8.1
	No	159	91.9
Recent / active Smocking	Yes	8	4.6
	No	165	95.4
Comorbidity	Yes	50	28.9
	No	123	71.1
DM	Yes	31	17.9
	No	142	82.1
HTN	Yes	19	10.9
	No	154	90.1

5.2. Clinical characteristics

The common clinical presentations were abdominal pain in 154 patients (89.0%), weight loss in 124 (71.7%) anorexia in 117 (67.6%) and jaundice in 76 (43.9%). The median duration of abdominal pain was 157(IQR=120) days among 144(83.2%) patients. The median duration of jaundice was 60(IQR=105) days among 139 (80%) patients. Four (2.3%) patients had confirmed episodes of acute cholangitis at presentation. Chronic and acute pancreatitis was found in 2(1.2%) and 1(0.6%) of patients respectively. Ascites was found in 31(17.9%) of patients. Gastric outlet obstruction was reported in 10(5.8%) of patients (Table 2).

Table 2: Clinical characteristics

Variable	Category	Number	Percent
Abdominal pain	Yes	154	89.0
	No	19	11.0
Weight loss	Yes	124	71.7
	No	49	28.3
Anorexia	Yes	117	67.6
	No	56	32.4
Jaundice	Yes	76	43.9
	No	97	56.1
Confirmed acute cholangitis	Yes	4	2.3
	No	169	97.7
Confirmed acute pancreatitis	Yes	1	0.6
	No	172	99.4
Chronic pancreatitis	Yes	2	1.2
	No	171	98.8
Incidentally diagnosed	Yes	2	1.2
	No	171	98.8
Ascites(clinical & radiological)	Yes	31	17.9
	No	142	82.1
GOO	Yes	10	5.8
	No	163	94.2

5.3. Radiologic characteristics

In 113(65.3%) of patients the tumor was located on pancreas head followed by 26(15%) on body of pancreas. In 6 patients (3.5%) the tumor located in more than one pancreas parts. Tumor size was reported in 92 patients (53.25%) and the mean diameter was 4.9 (SD = 2) centimeters. In 43(24.9%) of patients the tumor involved surrounding structures by direct invasion the

commonest being duodenum 15(34.9%) and stomach 12(27.9%). Other involved organs in decreasing frequency are, transvers mesocolon 3(7%), spleen 2(4.6%) Jejunum 2(4.6%), right kidney 2(4.6%), left adrenal gland with stomach 2(4.6%), isolated left adrenal gland 1(2.3%), colon 1(2.3%), diaphragm 1(2.3%), left adrenal gland with diaphragm crura 1(2.3%), combined stomach, spleen & left adrenal gland (2.3%).

Hematogenous distant metastasis reported in 89(51.4) of patients. Among the metastasis (51.4%) isolated liver, liver with lung, and peritoneum metastasis was found in 62.9%, 12.4% and 7.9% of patients. Metastasis to omentum (5 patients), isolated lung (4 patients), abdominal wall, pleura and vertebral bone in each one patient found. Intra-abdominal lymph node involvement was found in 37(21.4%) of patients.

Major vascular invasion found in 101(58.4%) of patients. Combined artery and vein invasion was found in 38(37.6%) of patients (Table 3). Isolated major artery and vein invasion detected in 32 (31.7%) and 31 (30.7%) of patients respectively. SMA and CA were the most common involved arteries in 25 (35.7%) and 10 (14.3%) of patients. PV involved in 24(33.3%) and SMV in 20(27.8%) of cases among major vein involvement.

5.4. Laboratory characteristics

The mean serum albumin was 3.32 (SD= 0.82) g/dL ranging from 1.38 to 4.9g/dL among 71 patinets. The median total bilirubin is 2.62 (IQR=16.76) mg/dL ranging from 0.3- 44.30 mg/dL among 114 patients. The mean hemoglobin was 12.42mg/dL (SD= 2.3) among 144 patients. The median serum CA 19-9 level was 61.73 (IQR = 706) ranging from 0.01 to 50,000 units/mL among 122 patients. The median serum CEA level was 6.11(IQR=15.06) ranges from 0.2 to 215ng/mL among 42 patients.

Table 3: Radiologic characteristics

Variable	Category	Number	Percent
Location on pancreas	Head	113	65.3
	Neck	11	6.4
	Body	26	15.0
	Tail	17	9.8
	Combined	6	3.5
Local direct tumor invasion	Yes	43	24.9
	No	130	75.1
Hematogenous distant organ metastasis	Yes	89*	51.4
	No	84	48.6
Major vessel invasion	Yes	101	58.4
	No	72	41.6
Lymph node involvement	Yes	37	21.4
	No	136	78.6

Hematogenous distant organ metastasis = 89. Totally distant metastasis is 93 patients. The other four distant metastasis were via lymphatic system.

5.5. Tumor resectability and staging

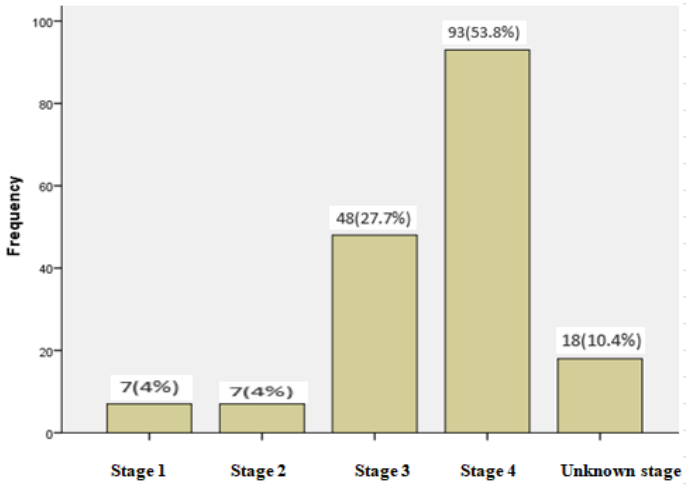
Ninety three (53.8%) of patients had unresctable pancreatic cancer due to distant hematogenous and lymphatic metastasis metastasis. In 39 (22.5%) of patients the tumor was resectable. LAPDAC and borderline resectable pancreas cancer accounts for 14.5% and 9.2% respectively (Table 4).

Regarding TNM staging, stage I PDAC accounts for 7(4%), of this 5(2.9%) are stage IB. Stage II PDAC accounts for 7(4%). Stage III and IV accounts for 48(27.7%) and 93 (53.8%) of cases. TNM unknown stated for those tumors size was not mentioned but the tumor did not invade surrounding organs, vessels, lymph nodes or no distant metastasis (difficult to categorize to T1, T2 , T3)(Figure 2).

Table 4: Tumor staging and resectability

Variable	Category	Number	Percent
Tumor unresectability	Yes	93	53.8
	No	80	46.2
Resectability status according to NCCN 2022	Resectable	39	22.5
	Borderline	16	9.2
	Locally advanced	25	14.5
	Metastasis	93	53.8
Extent of tumor	Localized to the pancreas	32	18.5
	Local invasion*	48	27.7
	Distant metastasis	93	53.8

Local invasion* = T4 and N1 pancreas cancer



- All stage II cases were stage IIA classes

Figure 2: TNM staging of PDAC

5.6. Factors determining unresectablility

5.6.1 Results of bivariable logistic regression analysis

Independent variables relation with dependent variable was tested in binary logistic regression.

Participants of age more than 40 years of age were 2.8 times more likely (COR = 2.81, 95% CI: 0.93, 8.46) to develop metastasis pancreas cancer than age less than 40 years. However this was not statistically significant (p-value = 0.067). Patients who does not have comorbidity had reduced risk of developing unresectable pancreas cancer by 49% (1-0.51) (COR = 0.51, 95% CI: 0.26, 0.10) compared to patients with any of the comorbid illness (p-value= 0.05). In patients who had pancreas cancer confined to the pancreas, the risk of unresctability decrease by 65% (1-0. 35) (COR= 0.35, CI: 0.17, 0.75) compared to pancreas cancer with local direct invasion (p-value = 0.006). The risk of developing unresctable pancreas cancer reduced by 53% (1-0.47), (COR= 0.47, 95%CI: 0.26, 0.87) in patients who had jaundice than non-jaundiced patients (p-value= 0.016) (Table 5).

5.6.2. Results of multivariable logistic regression analysis

After controlling confounders on multivariable logistic regression, local tumor invasion and clinical presentation without jaundice were found to be factors associated with unresctable pancreas cancer. The finding revealed that patients who had pancreas cancer confined to the pancreas had lower risk of unresctability by 63% (COR = 0.37, CI: 0.18, 0.80) compared to pancreas cancer with local direct invasion (P-value =0.011). The risk of developing unresctable pancreas cancer reduced by 50% (COR =0.50, 95% CI: 0.27, 0.93) in patients who had jaundice than non-jaundiced patients (P-value =0.03) (Table 6).

Table 5: Results of bivariable logistic regression analysis

Variable	**Unresectable PDAC**			
	Yes, n (%)	No, n (%)	COR (95% CI)	P-value
Age at presentation				
<40	5 (31.3)	11 (68.7)	1.0	
≥40	88 (56.1)	69 (43.9)	2.81(0.93,8.46)	**0.067**
Gender				
Male	52(55.9)	41(44.1)	0.83(0.46,1.51)	0.54
Female	41(51.3)	39(48.7)	1.0	
Weight loss				
No	28(57.1)	21(42.9)	1.0	
Yes	65(52.4)	59(47.6)	0.83(0.42,1.61)	0.575
Diabetes mellitus				
No	80(56.3)	62(43.7)	0.56(0.26,1.23)	**0.148**
Yes	13(41.9)	18(58.1)	1.0	
Comorbidity				
No	72(58.5)	51(41.5)	0.51(0.26,0.10	**0.05**
Yes	21(42)	29(58)	1.0	
Tumor location				**0.277**
Head	55(48.75)	58(51.3)	2.11(0.37,11.98)	0.400
Neck	5(45.5)	6(54.5)	2.04(0.30,19.04)	0.407
Body	17(65.4)	9(34.6)	1.06(0.16,6.94)	0.952
Tail	12(70.6)	5(29.4)	0.83(0.11,6.11)	0.858
Combined *	4 (66.7)	2 (33.3)	1.0	
Local tumor invasion				
No	62 (47.7)	68 (52)	0.35 (0.17,0.75)	**0.006**
Yes	31 (72.1)	12 (27.9)	1.0	
Vascular invasion				
No	41 (56.9)	31 (43.1)	1.0	
Yes	52 (51.5)	49 (48.5)	0.80 (0.44,1.47)	0.49
GOO				
No	89 (54.6)	74 (45.4)	0.55 (0.15,2.04)	0.374
Yes	4 (40)	6 (60)	1.0	
OJ				
No	60 (61.9)	37 (38.1)	1.0	
Yes	33 (43.4)	43 (56.6)	0.47 (0.26,0.87)	**0.016**

Combined * = Pancreas cancer involving more than 1 pancreas parts

COR = Crude Odds ratio

Table 6: Results of multivariable logistic regression analysis

Variable	**Unresectable PDAC**				
	Yes, n (%)	No, n (%)	COR (95% CI)	AOR (95% CI)	P-value
Local tumor invasion					
No	62(47.7)	68(52)	0.35(0.17,0.75)	0.37(0.18, 0.80)	0.011
Yes	31(72.1)	12(27.9)	1.0	1.0	
OJ					
No	60(61.9)	37(38.1)	1.0	1.0	
Yes	33(43.4)	43(56.6)	0.47(0.26,0.87)	0.50 (0.27, 0.93)	0.03

6. DISCUSSION

The main aim of this study was to assess the magnitude of unresectable PDAC and associated factors contributing to it. About 54% (93 patients) had unresectable pancreas cancer as explained by distant metastasis either through hematogenous or lymphatic spread outside the rescetability area. This result is consistence with other studies in USA (4, 34). On the other hand the result in this study is higher than (42- 48%) other studies from USA (6, 19). The possible explanation may be in these USA studies the sample size was very large from data base review for longer period of years as compared to this study. The unresctability of pancreas cancer in this study is lower than another study (65%) from study from USA (26) partly explained by old evidence the study was completed in 2013. A study done in the same hospital, Ethiopia, reported 25% distant metastasis (24) which is lower than the current study. This may be explained by that study was on only 52 surgically treated patients for curative and palliative intents unlike the current study which includes all pancreas cancer patients in outpatient department of oncology and surgery.

In this study 18.5% of pancreas cancer is found to be confined to the pancreas which is similar to results from one study in USA (26) but higher than reports from other studies (7-10%) (4, 19, 34). On the other side this study result is lower than report from same hospital (44%) (24) explained by study population difference as that study included only surgically treated patients.

Regarding factors predicting unresectability local tumor invasion and clinical presentation without jaundice were found to be unresctable pancreas cancer. This finding revealed that patients who had pancreas cancer confined to the pancreas had lower risk of unresctability by 63% compared to pancreas cancer with local direct invasion. The risk of developing unresctable pancreas cancer reduced by 50% in patients who had jaundice than nonjaundiced patients. The possible explanation is patients with jaundice will seek medical attention early at resectable stage of disease.

Regarding gender, males contributed for 53.8% of pancreas cancer patients. This result is supported by other studies (4, 6, 16, 22, 24, 28-30, 33) but lower than (63%) report from Zambia (27).

The average age in this study result was 56 years, which is similar from other study results (24, 27, 28), but lower than(65-67years) from studies in USA(4, 29). From other study age less than

70 years were more likely to be unresectable due to liver metastasis likely due to due to higher and more aggressive histopathology (16), however in this study different age categories were tested in binary logistic regression and not found to be associated.

Comorbidity was found in 28.9% patients. The common comorbidities were DM and HTN as supported by study from the same hospital, Ethiopia (24) and USA study (6). DM was found in 18% of PDAC patients of which 84.4% were on treatment before pancreas cancer diagnosis. On the other hand the magnitude of DM in this study was lower than (23-25%) other studies (22, 33) that reported DM was found to increase risk of PDAC by 1.24 to 1.5 times, however in the current study no association was found for possible explanation of lower magnitude in this study.

Majority (65.3%) of the cancer was located on pancreas head in consistent with other study (6), however lower than reports from Zambia(27), Algeria(31) and Ethiopia prior study(24) 83%,77% and 92% respectively. On the other hand this study result is higher than (47-54) study from USA (16, 29) partly explained by geographic and genetic differences. Location in body and tail of pancreas was reported to be predictor of unresctability and distant metastasis from USA study (16), however in this study there was no association both in binary and multivariable logistic regression.

The mean diameter of the tumor was 4.9 centimeters as calculated only from 53% of patients. This result was smaller than study from the same hospital(24) (mean diameter 5.5 centimeters). The possible explanation for this difference may be, in the current study, all pancreas cancer patients were studied unlike the other study which includes on surgical patients and partly in the current study only half of the participants cancer size was calculated.

Regarding smocking, contradicting reports published. In two studies smoking was found to increase risk of PADC(18, 22) while in one other study it was not associated with increased risk for PDAC (33). In the current study association of smoking with PDAC risk was not done as 4.6% were found to be smokers which do not fulfill association test assumption.

Chronic pancreatitis was associated with increased risk of PDAC (33). In this study only 1.2% of patients had a documented chronic pancreatitis for which association test cannot be done.

7. CONCLUSION AND RECOMMENDATION

Conclusion:

From this retrospective single institution cross sectional study, about 54% of PDAC patients were unresctable. Local tumor invasion and presentation without jaundice were found to be predictors of unreachability.

Strength of the study

This study includes wide spectrum of clinical variables. The study is pioneer in this study area.

Limitation of the study

It was a retrospective cross sectional study done in a tertiary specialized hospital, so generalizability may be limited.

Laboratory variable such as serum albumin, CA 19-9 and CEA were not available for all patients to be analyzed in logistic regression.

Recommendation:

- Primary physicians and radiologists who evaluate older patients with abdominal pain, weight loss and anorexia has to seriously look for the pancreas cancer and diagnose in the early stage of the disease
- Surgeons shall work to improve pancreas cancer patients survival by extending indication of resection for borderline and LAPDAC patients.
- DM patients have to have concern of PDAC and get physician evaluation. Physicians who care for diabetic patients has to investigate for pancreas cancer.
- Researches can further study on this problem including multiple centers and using different study design using this study as baseline reference.

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9. APPENDEX

ANNEX I: Approval Sheet

I the undersigned agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the research and publications office of Addis Ababa University.

PI:

Dr. Hailemaryam Shiferaw (MD, General surgeon, HPB surgery fellow)

Signature _____Date _____

Advisor:

Dr. Abebe Alemayehu (MD, Assistant professor of General surgery, consultant HPB surgeon)

Signature _____ Date_____

Annex II: Questionnaire

Questionnaire for research on magnitude and predictors of unresectable PDAC at TASH, Ethiopia 2023/24.

Part 1. Socio demographic data

S. No	Socio-demographic factors		Remark
1	Age in complete years	_____	
2	Sex	1. Male 2. Female	
3	Address, district	1. Urban 2. Rural	
3.1	Name of district	_____	
3.2	Distance from Addis Ababa in Km	_____	
4	BMI in kg/m^2 (if possible)	----------	
5	MUAC in cm (if possible)	_____	
6	Occupation	_____	
7	Self history of other organ cancer	1. Yes 2. No	
7.1	If yes which organ cancer?	----------	
8	Family history of similar illness	1. Yes 2. No	
8.1	If yes, which family member?	1. Mother 2. Father 3. Sister 4. Brother 5. Others,----------	

Part 2. Questions related to symptom, sign

S. No	Symptom, sign and treatment		Remark
1	Abdominal pain	1. Yes 2. No	
1.1	If yes, duration in days	----------	
2	Weight loss	1. Yes 2. No	
2.1	If yes, duration in days	----------	
2.2	If yes, how much ?	1. ----- Kg over---- month 2. -------% weight loss/ --- months	
3	Anorexia	1. Yes 2. No	
4	Vomiting	1. Yes 2. No	
5	Nausea	1. Yes 2. No	
6	Yellowish eye discoloration	1. Yes 2. No	
6.1	If yes, duration in days	----------	
7	Clay Colored stool	1. Yes 2. No	
8	Dark urine color	1. Yes 2. No	
9	Abdominal swelling	1. Yes 2. No	
9.1	If yes, duration in days	----------	

9.2	If yes location of the swelling	……..	
10	Other symptoms	————————,————————,—————	
11	Physical status of patient (ECOG)	----------	
12	History of habitual excess alcohol abuse?	1. Yes 2. No	
13	History of smoking?	1. Yes 2. No	
14	Other known medical illness	1. DM 2. Hypertension 3. Other_____	
14.1	If yes for DM, which diagnosed/comes first?	1. DM 2. PDAC	
15	Proven episode of acute pancreatitis	1. Yes 2. No	
16	Proven episode of cholangitis	1. Yes 2. No	

Part 3. Radiologic features of PDAC (CT scan or MRI)

1	Location of tumor	1. Head 2. Neck 3. Body 4. Tail If combination, mention--------	
2	The largest size of the tumor in cm	----------	
3	Vascularity of the tumor	Pre contrast---------- Arterial phase---------- PVP/delayed phase---------	Summary ……
4	Main pancreatic duct size	------mm at ------ part of pancreas	

5	Is there gross report of pancreas atrophy	1. Yes 2. No	
6	Is there direct invasion of extra pancreatic organs	2. Yes 2. No	
6.1	If yes, Which organ	1. Stomach 2. Colon 3. Spleen 4. Others, --------	
7	Involvement of distal organ by metastasis	1. Yes 2. No	
7.1	If yes, which organ ? mention	----------	
8	Is there involvement of major vascular structure	1. Yes 2. No	
8.1	If yes, which vessel? (please mention the involvement extent)	1. -------- artery/s,,, $\leq 180^{o}$/ > 180^{o} 2. ---------vein/s,,,, $\leq 180^{o}$/ > 180^{o} 3. If combination, mention all	
9	Is there involvement of intra abdominal lymph nodes ?	1. Yes 2. No	
9.1	If yes, which area of LN	1. Peri pancreatic 2. Celiac 2. Aortico caval 3. Others,------ 4. If combination , mention it…….	
10	Is there clinical / radiological evidence of ascites?	1. Yes 2. No	
12	Is there evidence of GOO?	1. Yes 2 . No	
11	Is there evidence (clinical or biochemical) of OJ	1. Yes 2. No	
11.1	How much is the largest diameter of CBD in mm	----------	

Part 4. Laboratory and pathology results

S. No	Laboratory (the most recent value) and pathology reports		Remark
1	Serum Albumin	_____g/L	
2	Bilirubin Total/direct	----------/----------mg/dl	
3	INR		
4	WBC count		
5	Hgb in mg/dl		
6	ALP		
7	Creatinine		
8	CA 19-9	----------	
9	CEA level		
10	Is there FNAC / Biopsy result	1. Yes 2. No	
10.1	If yes, how was the specimen taken?	1) Image guided (U/S or CT) 2) Direct from palpable masses 3) By endoscopy (ERCP,…) 4) By needle aspiration of metastasis sites 5) Others,--------	
11	Is imaging & CA19-9 (> 37 iu/L) results correlated in confirming PDAC	1. Yes 2. No	
12	Is CA19-9 (> 37iu/L) level and biopsy/ FNAC correlated	1. Yes 2. No	

13	Imaging category of resectability according to NCCN 2020 guideline	1. Resectable 2. Borderline resectable 3. Locally advanced 4. Distant metastasis	
14	**Is the tumor unresectable at 1st presentation at TASH**	**1. Yes 2. No**	
15	What could be the possible explanation for un resectability?	1. Delayed presentation of patient 2. Delayed diagnosis by clinicians	
15.1	Why patient present late after onset of symptoms?	----------	
15.2	Why delayed diagnosis by clinicians?	1. Diagnostic investigations were not requested 2. Patient was unable to afford for CT-scan of abdomen 3. Initial presentation was attributed for other diagnosis/ misdiagnosis	

Thank you.

Magnitude and predictors of unresectable Pancreatic Ductal Adenocarcinoma at Tikur Anbesa Specialized Hospital, Ethiopia 2024.

ORIGINALITY REPORT

18%	17%	10%	7%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS