EPIDEMIOLOGY OF PANCREATIC CANCER AT NATIONAL CANCER INSTITUTE, CAIRO UNIVERSITY, 2006 - 2010

Thesis

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ABSTRACT

Purpose: To evaluate epidemiologic and demographic characteristics of pancreatic cancer patients managed at the National Cancer Institute (NCI), Cairo University (CU) over the period from January 2006 till December 2010, focusing on the relation of these factors with the prognosis.

Material and Methods: This is a retrospective cohort study. Between January 2006 and December 2010, 902 cases were diagnosed with pancreatic cancer at the NCI. The medical records of 336 patients were available to review. Patients' demographics and clinical characteristics were included and overall survival (OS) was calculated from the time of diagnosis to death or last follow up.

Results: The mean age of the patients was 56.4 years with a standard deviation of 12 years, 64.9% were males, 39.5% were routine and manual workers, 54.8% were from urban areas, 55.1% reside in the Cairo Metropolitan area and the Delta, 52.4% experienced abdominal pain referred to the back and 36.3% experienced jaundice. About 30.7% were diagnosed by histopathology, cytology or endoscopy while radiological diagnosis represented 31.3%. Adenocarcinoma was the predominant pathological type (66.0%) and the pancreatic head was the main site (70.0%). Resectable cases represented 13.7 %, unresectable (i.e. locally advanced and metastatic) 63.2% and 23.1% had unknown tumor stage. Sixty-two patients were metastatic at initial presentation. Studying prognosis of cases revealed that proportion surviving at 1, 2 years were 46% and 33%, respectively with the median survival time of 9.1 months.

Conclusions: The mean age of pancreatic cancer patients at the NCI, Egypt is lower than that reported in international statistics. Patients' presentation is mainly metastatic initially, overall survival is poor. The study highlights the urgent need of an effective follow up system for the patients and also further investigations are needed to explore the possible factors that may contribute to the observed epidemiological patterns.

Key words: Pancreatic cancer, prognosis, survival.

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LIST OF ABBREVIATIONS

ACS	:	American Cancer Society
AFP	:	Alpha fetoprotein
AJCC	:	American joint committee on cancer
ALPHA4GNT	:	Alpha 14 n acetylglucosaminyl transeferase
ASR	:	Age-standardized rate
BRCA2	:	Breast cancer type 2 susceptibility protein
CA125	:	Cancer antigen 125
CA15.3	:	Cancer Antigen 15-3
CA19-9	:	Carbohydrate antigen19-9
CDKN	:	Cyclin-Dependent Kinase inhibitor
CEA	:	Carcino-embryonic antigen
CEACAM-1	:	CEA-related cell adhesion molecule-1
CI	:	Confidence interval
CT	:	Computed tomography
CU	:	Cairo University
DLBCL	:	Diffuse large Bcell lymphoma
DNA	:	Deoxyribonucleic acid
EC	:	Enterochromaphin cell
EGER	:	Epidermal growth factor receptor
ERCP	:	Endoscopic Retrograde Cholangiopancreatography
FAMMM	:	Familial Atypical Multiple Mole Melanoma
FDA	:	Food and Drug Administration
HNPCC	:	Hereditary Non-Polyposis Colorectal Cancer
IPMN	:	Intraductal Papillary Mucinous Carcinoma
IQR	:	Inter quartile range
K-RAS	:	Kristen rat sarcoma
MCN	:	Mucinous Cystic Neoplasm
MECC	:	Middle East Cancer Consortium
MEN1	:	Multiple endocrine neoplasia, type 1

MIC-1	:	Macrophage inhibitory cytokine 1
MLH1	:	MutL homolog 1
MRI	:	Magnetic resonance imaging
MSH2	:	MutS protein homolog 2
NCCN	:	National comprehensive cancer network
NCI	:	National Cancer Institute
NETG1	:	Neuroendocrine tumor G1
NETG2	:	Neuroendocrine tumor G2
NF1	:	Neurofibromatosis type 1
NOS	:	Not Otherwise Specified
NS-SEC	:	National Statistics Socioeconomic classification
OS	:	Overall survival
P53	:	Phosphoprotein p53, tumor suppressor gene
PET	:	Positron emission tomography
PJS	:	Peutz-Jeghers Syndrome
PRSS	:	Protease, serine, 1 (trypsin 1)
PTC	:	Parametric Technology Corporation
RR	:	Relative risk
SD	:	Standard deviation
SEER	:	Surveillance, Epidemiology, and End Results
SPAN-1	:	Monoclonal antibody
STK	:	Serine/threonine kinase 11
US	:	United States of America
VIP	:	Vasoactive Intestinal Peptide
WHO	:	World Health Organization

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INTRODUCTION

Pancreatic cancer is considered an ‘orphan’ cancer because of its relative low incidence. Unfortunately even with early diagnosis, mortality rates are high, explaining why, despite the low incidence, it ranks eighth in a world listing of cancer mortality. International incidence rates vary in different countries, implying that environmental factors are important. Of these factors, smoking is the most well documented etiologic agent, explaining about 25% of all cases. Dietary factors may be important, but it has been difficult to define specific items which either increase or decrease the risk of pancreatic cancer ***(Best Practice & Research Clinical Gastroenterology, 2012).***

In general, pancreatic cancer affects more individuals inhabiting the Western/industrialized parts of the world; the highest incidence is reported among Maoris in New Zealand, native Hawaiians, and Black American populations, while people living in India and Nigeria have the lowest reported incidence ***(Hariharan et al., 2008).***

In the United States, approximately 45,220 patients are diagnosed with cancer of the exocrine pancreas annually (2.7% of cancer cases in both sexes), and almost all are expected to die from the disease ***(Siegel et al., 2013).***

Soliman et al. (2006) used Egypt's mortality data to estimate pancreatic cancer mortality in 2765 deaths from 2000 to 2004, and to gain insights into the disease incidence. The data were obtained from the electronic national mortality records of the Ministry of Health. They calculated

population-based age-specific and age-standardized pancreatic cancer mortality rates for Egypt, and compared them with the Surveillance, Epidemiology, and End Results (SEER) mortality data of the United States. Comparisons of age-specific mortality demonstrated higher rates in Egypt compared to the United States for subjects under age 20 years. The relative risks (RR) were 7.7 and 4.2, for the age groups 0-15 and 15-20, respectively. Significantly higher rates in the United States compared to Egypt were seen in subjects 40 years and older (RR 1.8-80.5 for the age groups of 40-45 to 75+). For the majority of age groups in Egypt and the United States, mortality in males was higher than in females. Analysis of regional distribution of pancreatic cancer mortality in Egypt showed significant variations in rates among Provinces ($p<0.001$) with Northern Provinces having average rate that is 2.85 times the rate of Southern Provinces. The highest mortality rates were observed in the Nile Delta compared to Southern Egypt and the Oasis.

To our knowledge the epidemiologic and demographic characteristics of pancreatic cancer patients at the National cancer institute and the relations of these characteristics with the prognosis and survival of the patients weren't well studied before so this is an attempt to identify the characteristics and the prognostic factors affecting the survival of Egyptian pancreatic cancer patients through the National Cancer Institute (NCI), Cairo University (CU) database.

AIM OF WORK

The overall goal of our study is to improve the diagnostic and therapeutic results of pancreatic cancer patients at the National Cancer Institute (NCI), Cairo University (CU); this can be done through the following:

1. Retrospectively evaluating the epidemiologic and demographic characteristics of pancreatic cancer patients over the period from January 2006 till December 2010.
2. Estimating the overall survival of the patients and examining the effect of patients' characteristics on their survival.

EPIDEMIOLOGY OF PANCREATIC CANCER

Incidence and mortality worldwide:

Pancreatic cancer ranked 12th in both men and women and the estimated age-standardized rate (ASR) and mortality rates are 4.2 and 4.1 for both sexes (4.9 and 4.8 in men and 3.6 and 3.4 in women), respectively ***(Globocan, 2012).***

This cancer is almost always fatal and is the 8th most common cause of cancer death, accounting for over 3% of all cancer deaths. About 60% of pancreatic cancer cases occur in more developed countries. Its highest incidence is in Northern America, Western, Central and Eastern Europe and the lowest incidence is in Eastern, Western Africa and South-Central Asia ***(Ferlay et al., 2010).***

In the United States of America, pancreatic cancer is the 10th most common diagnosed cancer among men and the 9th most common among women. It accounts for about 7% of all cancer deaths and ranks 4th as a cause of cancer death among both men and women with higher rates among African-American people than in white people ***(Cancer facts and figures, 2013)***.It is estimated that about 48,960 people (24,840 men and 24,120 women) will be diagnosed with pancreatic cancer and about 40,560 people (20,710 men and 19,850 women) will die of that cancer in 2015 ***(ACS, 2015).***

In the Middle East pancreatic cancer represented 2%, 1.9%, 2.5%, 1.9% and 1.1% of total cancer cases detected in Egypt (1999-2001), Cyprus

(1998-2001), Israel-Jews (1996-2001), Israel-Arabs (1996-2001) and Jordan (1996-2001), respectively ***(MECC, 2006).***

Pancreatic cancer in Egypt:

According to the National Population-Based Registry Program of Egypt (2008–2011), the age standardized rate (ASR) for males was 4.2 but for females it was 2.6. Lower Egypt (2009-2011) had ASR 4.4 for males and 3.2 for females. Middle Egypt (2009) had ASR 3.5 for males and 1.4 for females while Upper Egypt (2008) had 5.4 for males and 2.3 for females ***(Ibrahim et al., 2014).***

According to the ***NCI hospital based registry (2002-2010),*** pancreatic cancer represented about 2% of the diagnosed cancers (1.4% and 2.6% in females and males, respectively).

PATHOLOGY OF PANCREATIC CANCER

The pancreas has 2 parts, each perform very different functions. The exocrine part produces enzymes that help digestion of food and the endocrine one produces important hormones such as insulin, which regulate blood sugar levels. Each part forms completely different types of tumors with distinct risk factors, symptoms, diagnostic tests, treatment, and survival rates. Exocrine tumors are the most common type of pancreatic cancer, representing about 95% of cases ***(Cancer facts and figures, 2013)***

Malignant pancreatic tumors can be classified as following ***(WHO, 2010):***

1. Epithelial tumors (malignant epithelial and neuroendocrine).
2. Mesenchymal tumors.
3. Lymphomas.
4. Secondary tumors.

***Malignant epithelial tumors*:**

Ductal adenocarcinoma
Adenosquamous carcinoma
Mucinous adenocarcinoma
Hepatoid carcinoma
Medullary carcinoma, NOS
Signet ring cell carcinoma
Undifferentiated carcinoma
Undifferentiated carcinoma with osteoclast-like cells
Acinar cell carcinoma
Acinar cell cystadenocarcinoma
Intraductal papillary mucinous carcinoma (IPMN) with an associated invasive carcinoma
Mixed acinar-ductal carcinoma
Mixed acinar-neuroendocrine carcinoma
Mixed acinar-neuroendocrine-ductal carcinoma

Mixed ductal-neuroendocrine carcinoma
Mucinous cystic neoplasm (MCN) with an associated invasive carcinoma
Pancreatoblastoma
Serous cystadenocarcinoma, NOS
Solid-pseudopapillary neoplasm

***Neuroendocrine tumors*:**

Neuroendocrine tumor G1 (NET G1) / Carcinoid
Neuroendocrine tumor G2 (NET G2)
Neuroendocrine carcinoma, NOS
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Enterochromaffin cell (EC),serotonin-producing neuroendocrine tumor (NET)
Gastrinoma, malignant
Glucagonoma, malignant
Insulin producing carcinoma (insulinoma)
Somatostatinoma, malignant
Vipoma, malignant

Mesenchymal tumors:

Ewing sarcoma
Desmoplastic small round cell tumor

Lymphomas

Diffuse large B-cell lymphoma (DLBCL), NOS

STAGING OF PANCREATIC CANCER

The stage is the most important factor in choosing treatment options and predicting a patient's outcome.

TNM staging system for exocrine and endocrine tumors of pancreas:

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

(AJCC, 2010)

Anatomic stage/ prognostic groups:

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

(AJCC, 2010)

According to ***ACS (2015*)**, there are other factors which are also important in determining prognosis:

- ***Tumor grade*:** sometimes it is listed on a scale from G1 to G4, with G1 cancers looking the most like normal cells and having the best outlook. The details of grading are a little different for exocrine cancers and NETs. For NETs, measures of how many of the cells seem to be dividing is an important part of grading. This can be determined by counting mitoses under a microscope or with a Ki-67 test that recognizes cells that are almost ready to start splitting.
- ***Extent of resection*:**
    - **R0:** when all visible and microscopic tumor was removed
    - **R1:** when all visible tumor was removed, but investigation of the removed specimen show that some small areas of cancer were probably left behind.
    - **R2:** when some visible tumor could not be removed.

For treatment purposes, physicians use a simpler staging system, which divides cancers into groups based on whether or not they can likely be removed with surgery. These groups are called resectable, borderline resectable and unresectable (either locally advanced or metastatic) and these terms are used more often to describe exocrine pancreatic cancers than pancreatic neuroendocrine tumors.

- ***Resectable:*** When the cancer is only in the pancreas (or has spread just beyond it) and the surgeon believes the entire tumor can be removed.

- ***Borderline resectable:*** For some cancers that might have just reached nearby blood vessels, but which the doctors feel might still be removed completely with surgery. This would include some stage III cancers in the TNM system.
- ***Locally advanced:*** If the cancer has not yet spread to distant organs but it still can't be completely removed with surgery. Often the reason the cancer can't be removed is because too much of it is present in nearby blood vessels. Surgery to try to remove these tumors would be very unlikely to be helpful and could still have major side effects. Some type of surgery might still be done, but it would be a less involved operation with the goal of relieving symptoms or problems like a blocked bile duct or intestinal tract, not of curing the cancer.
- ***Metastatic:*** When the cancer has spread to distant organs. Surgery may still be done, but the goal would be to relieve symptoms, not to cure the cancer.

RISK FACTORS OF PANCREATIC CANCER

Consistently reported risk factors of exocrine tumors - representing about 95% of cases - are **older age and cigarette smoking.** However, **family history, diabetes and chronic pancreatitis** are also associated with a higher risk of pancreatic cancer. In some studies, **alcohol consumption, obesity and the western diet** have been proposed as additional risk factors. The risk for pancreatic cancer is very rare in people younger than age 30 but increases sharply with passing years. Peak years of incidence are between ages 70 and 80 ***(Li et al., 2004).***

Tobacco use is the most important known risk factor for pancreatic cancer; approximately 20% of pancreatic cancers are attributable to cigarette smoking ***(Iodice et al., 2008)***.The risk of developing pancreatic cancer is about twice as high among smokers as among non smokers ***(Anderson et al., 2006)***. Risk increases with greater tobacco use and longer duration of smoking ***(Lynch et al., 2009; Bosetti et al., 2012).*** Cigar and pipe smoking also increase risk ***(Henley et al., 2004; Bertuccio et al., 2011)***. Quitting smoking lowers the risk of pancreatic cancer; 5-10 years after quitting, former smokers have the same risk as those who never smoked ***(Vrieling et al., 2010).***

Men are 30% more likely to develop pancreatic cancer than women. This may be due, at least in part, to increased tobacco use in men. The difference in the risk was more pronounced in the past (when tobacco use was much more common among men than women), but the gap has closed in recent years ***(ACS, 2015).***

A number of studies have linked family history to an increased risk of pancreatic cancer. Individuals with a family history of pancreatic cancer have a nearly 2-fold increased risk for developing the disease compared to those without such a history ***(Permuth-Wey and Egan, 2009)***. The risk increases to 7- to 9-fold for individuals with at least 1 first-degree relative (a parent or sibling) with pancreatic cancer and 17- to 32-fold for individuals with 3 or more first-degree relatives with this cancer ***(Klein et al., 2004)***. Risk is also increased if a first-degree relative was diagnosed with pancreatic cancer before age of 50 years ***(Brune et al., 2010).***

Genetic factors account for approximately 5% to 10% of all pancreatic cancer cases ***(Petersen et al., 2006; Shi et al., 2009)***. There are several gene mutations that are associated with an increased risk of pancreatic cancer, though these are extremely rare in the general population ***(Vincent et al., 2011).*** Mutations in the BRCA2 gene are associated with a 3- to 10-fold increased risk of pancreatic cancer and account for the highest proportion (5% to 17%) of known causes of inherited pancreatic cancer ***(Couch et al., 2007).*** Mutations in the Cyclin-Dependent Kinase inhibitor 2A (CDKN2A) gene, which are linked to the Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome, are associated with an approximately 13 to 22 fold increased risk of pancreatic cancer ***(Lynch et al., 2008)***. Patients with Peutz-Jeghers Syndrome (PJS), which is usually caused by STK11 mutations, have an 11% to 36% risk of developing pancreatic cancer during their lifetime ***(van Lier et al., 2010)***. The risk among people with hereditary pancreatitis linked to PRSS1 mutations is approximately 70 times greater than that expected in the normal population,

with lifetime risk of developing pancreatic cancer approximately 40% to 55% ***(Raimondi et al., 2010)***.

Patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch syndrome), which is most often caused by MLH1 or MSH2 mutations, have about a 9-fold increased risk of developing pancreatic cancer ***(Kastrinos et al., 2009).***

Soliman et al. (2007) studied the molecular pathology of 54 pancreatic adenocarcinomas from Egyptian patients residing in a heavily polluted region of the eastern Nile River delta and compared the findings with 45 tumors from patients residing in low-pollution regions. They concluded that: rates of *K-ras mutation* in codon 12 and of *p53* mutation in exons 5-8 were higher in tumors of patients from the high-pollution region as compared with the low-pollution regions. Also there were distinct differences in the specific types of *K-ras* and *p53* mutations between the two regions. The ratio of G-to-T *k-ras* transversion mutation (codon 12) relative to wild-type was significantly higher in tumors from the high-pollution region (0.90) than tumors from the non-pollution site (0.28). Relative to tumors with wild-type, the ratio of *p53* mutations in exons 5, 7 or 8 to wild-type in tumors from the high-pollution region was significantly higher than the ratio from the non-pollution site (0.28 versus 0.03).

Recent studies have found that people with non-O blood groups have a slightly increased risk of pancreatic cancer, though the mechanisms of this association are still unclear ***(Amundadottir et al., 2009; Wolpin et al., 2010).***

About 25% of patients with pancreatic cancer have diabetes mellitus at diagnosis, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels) ***(Pannala et al., 2008)***. Pancreatic cancer can cause diabetes, and sometimes diabetes is an early sign of the tumor ***(Chari et al., 2008)***. Some reports also suggest that hyperglycemia, abnormal glucose metabolism and insulin resistance are associated with increased risk of pancreatic cancer ***(Stocks et al., 2009)***.

A retrospective study of 540 pancreatic cancer patients showed that the prevalence of diabetes in different stages of pancreatic cancer was 45%, of which more than half were less than 2 years in duration ***(Mizuno et al., 2013).***

Accumulating evidence suggests that long-standing chronic pancreatitis is a strong risk factor for pancreatic cancer, though pancreatitis may also be an early indicator of pancreatic cancer. After excluding the pancreatic cancer cases diagnosed within 2 years from chronic pancreatitis diagnosis, a review study reported a 6-fold increased risk of pancreatic cancer among patients with chronic pancreatitis ***(Raimondi et al., 2010).***

A positive association between alcohol use and pancreatic cancer was found in several but not all studies ***(Genkinger et al., 2009)***. A recent meta-analysis showed that consumption of three or more drinks of alcohol per day is associated with a 20% to 30% increased risk of pancreatic cancer ***(Tramacere et al., 2010).*** However, due to the strong relationship between alcohol consumption and tobacco use, it is difficult to eliminate the effect of smoking when studying the association between alcohol drinking and pancreatic cancer risk ***(Cancer facts and figures, 2013)***.

Obesity has also been consistently linked to increased risk of pancreatic cancer. Obese individuals have a 20% higher risk of developing pancreatic cancer than those who have normal weight ***(Arslan et al., 2010)***. Being obese during early adulthood may be associated with an even greater risk of pancreatic cancer and a younger age of disease onset ***(Li et al., 2009).*** Abdominal obesity may increase risk independent of general obesity, especially in women ***(Larsson et al., 2005).***

A number of dietary factors have been assessed regarding their association with pancreatic cancer risk. There is some evidence that the consumption of red and processed meat may slightly increase risk [Relative risk (RR) of 1.13; 95% confidence interval (CI) = 0.93-1.39]. Red meat consumption was positively associated with pancreatic cancer risk in men (RR=1.29; 95% CI=1.08-1.53); but not in women (RR=0.93; 95% CI=0.74-1.16). The RR of pancreatic cancer for a 50 gm per day increase in processed meat consumption was 1.19 (95% CI=1.04-1.36) ***(Larsson et al., 2012)***. Investigators have also found some evidence for increased risk among those who consume meat that has been cooked at very high temperatures ***(Anderson et al., 2012)***.

A protective effect of folate intake on pancreatic cancer risk has been reported in several studies ***(Larsson et al., 2006).*** However, a recent large analysis found no association ***(Bao et al., 2011)***. There is limited evidence supporting a protective effect of fruit and vegetable consumption on the risk of pancreatic cancer ***(Chan et al., 2005; Jansen et al., 2011)***. No association between coffee consumption and pancreatic cancer was found in a recent analysis that combined many studies ***(Turati et al., 2012).***

Several studies have detected an increased risk of pancreatic cancer among people with chronic infections with hepatitis B virus, hepatitis C virus ***(Hassan et al., 2008; El-Serag et al., 2009)*** and helicobacter pylori ***(Risch et al., 2010)***. Individuals with a history of Cholecystectomy ***(Lin et al., 2012)*** or partial gastrectomy ***(Gong et al., 2012)*** have also been found to be at increased risk of developing pancreatic cancer. Other medical conditions that may increase risk include: cystic fibrosis ***(Maisonneuve et al., 2007)*** and periodontal disease ***(Fitzpatrick et al., 2010).***

A slightly decreased risk of pancreatic cancer was linked to total and occupational physical activity in a recent literature review ***(O'Rorke et al., 2010)*** but not in a previous one ***(Bao et al., 2008).***

Heavy exposure at work to certain pesticides, dyes, and chemicals used in metal refining may increase the risk of developing pancreatic cancer ***(ACS, 2015).***

Studies are conflicting about the relationship between sunlight, vitamin D and pancreatic cancer. Some studies have found that sun exposure is associated with lower pancreatic cancer death rates, suggesting that vitamin D, acquired primarily through sun exposure to the skin, may be protective against pancreatic cancer ***(Grant, 2007)***. However, results from epidemiological studies that assessed individual-level vitamin D intake and pancreatic cancer risk have been inconsistent ***(Bao et al., 2010).***

Pancreatic neuroendocrine cancers can be caused by genetic syndromes such as Neurofibromatosis type 1 which is caused by mutations in the gene NF1. This syndrome leads to an increased risk of many tumors, including somatostatinomas. Also, multiple endocrine neoplasia, type 1 (MEN1), caused by mutations in the gene MEN1 was associated with

neuroendocrine cancers. This syndrome leads to an increased risk of tumors of the parathyroid gland, the pituitary gland, and the islet cells of the pancreas ***(ACS, 2015).***

DIAGNOSIS OF PANCREATIC CANCER

Early stage pancreatic cancer usually has no symptoms. When symptoms do occur, the tumor has usually spread to surrounding tissues or distant organs. In the US, only about 15-20% of pancreatic cancer cases are diagnosed early enough to be eligible for surgery ***(Cancer facts and figures, 2013)***.

Pancreatic cancer pain is usually insidious in onset, and has been present for one to two months at the time of presentation. It has a typical gnawing visceral quality, and is generally epigastric, radiating to the sides and/or straight through to the back. It may be intermittent and made worse by eating or lying supine. It is frequently worse at night. Lying in a curled or fetal position may improve the pain. Severe back pain should raise suspicion for a tumor arising in the body and tail of the pancreas ***(Mujica et al., 2000).***

Most people with pancreatic cancer will have jaundice as one of their first symptoms. Cancers that start in the head of the pancreas are near the common bile duct. These cancers can press on the duct and cause jaundice while they are still fairly small, which may allow these tumors to be found at an early stage. But cancers that start in the body or tail of the pancreas don't press on the duct until they have spread through the pancreas, often to the liver and this can lead to jaundice. Weight loss, poor appetite, nausea, vomiting, blood clots, fatty tissue abnormalities and diabetes can also be signs and symptoms of exocrine pancreatic cancer ***(ACS, 2015).***

Endocrine pancreatic tumors (< 5% of all pancreatic cancers) are divided into functioning and non-functioning tumors, depending on whether or not they overproduce hormones and cause a chemical syndrome:

- ***Gastrinomas*** overproduce gastrin, which causes peptic ulcers in the stomach or duodenum. Symptoms include severe pain, black tarry stools and diarrhoea.
- ***Glucagonomas*** overproduce glucagon. People with these tumors often have problems with diarrhea, weight loss, and malnutrition. The nutrition problems can lead to symptoms like irritation of the tongue (*glossitis*) and the corners of the mouth (*angular cheilosis*). The symptom that brings most people with glucagonomas to their doctor is a rash called *necrolytic migratory erythema.* It is a red rash with swelling and blisters that often travels place to place on the skin. It is the most distinctive feature of a glucagonoma.
- ***Insulinomas*** overproduce insulin leading to hypoglycemia. Symptoms may include weakness, drowsiness, dizziness or lack of energy.
- ***Somatostatinomas*** overproduce somatostatin, which causes gall bladder problems, diabetes and diarrhoea.
- ***VIPomas*** overproduce a hormone called Vasoactive Intestinal Peptide (VIP) leading to severe, watery diarrhea, with many bowel movements each day. People with these tumors also tend to have low levels of acid in their stomachs, leading to problems digesting food ***(ACS, 2015).***

To date, there is no single reliable test for the early detection of pancreatic cancer; therefore, screening the general population is not recommended by any health agency ***(Greenhalf et al., 2009)***. Existing screening programs have been limited to research settings with a focus on detecting precancerous lesions among high-risk individuals although it remains unclear whether this screening is effective in reducing pancreatic cancer mortality or not ***(Shin and Canto, 2012)***.

Pancreatic cancer is typically diagnosed with the use of an imaging test, usually a CT scan, often with a contrast dye, given by mouth or through injection, to better outline abnormal areas ***(Hidalgo, 2010; Vincent et al., 2011).*** This procedure is also often used to stage the tumor, with 70% to 85% accuracy for predicting whether or not the tumor can be surgically removed.

If pancreatic cancer is highly suspected but a CT scan appears normal, additional diagnostic tests, such as endoscopic ultrasound or ERCP, may be performed. The ERCP technique is especially useful in patients with bile duct tumors ***(Dumonceau and Vonlaufen, 2007)***. Other methods can be used for diagnosis as MRI, PET scan, PTC and laparoscopy.

Cancer diagnosis is typically confirmed with a biopsy. The most common type of biopsy to confirm pancreatic cancer is called a fine needle aspiration biopsy. The needle is inserted into the pancreas guided by an endoscopic ultrasound or CT scan images to obtain tissues for evaluation. However, a tissue diagnosis is not needed for patients who are scheduled for surgery. Due to the deep location of the pancreas and the medical

complications of biopsy, pancreatic cancer is the least likely of all major cancers to be microscopically confirmed ***(Cancer facts and figures, 2013)***.

Multiple tumor markers have been described for detecting pancreatic cancer. They are carcinoembryonic (CEA), CEA-related cell adhesion molecule-1 (CEACAM-1), CA19-9, SPan-1, DUPAN 2, macrophage inhibitory cytokine 1 (MIC-1), alpha4GnT, PAM4, pancreatic juice DNA methylation, and fecal K-*ras*; however none of them has proved superior enough to be used as a widespread screening test ***(Bussom and Saif, 2010).***

MANAGEMENT OF PANCREATIC CANCER

Patients with pancreatic cancer are best managed by a multidisciplinary team including surgeons, medical and radiation oncologists, pain management experts and nutritionists. Surgery remains the only treatment that offers a chance of cure for pancreatic cancer patients ***(Shaib et al., 2007)***.

The operative approaches include:

- Cephalic pancreatoduodenectomy (Whipple procedure): It is the removal of the head of the pancreas, the gallbladder, part of the stomach, part of the small intestine and the bile duct, retaining enough of the pancreas to produce digestive juices and insulin.
- Distal pancreatectomy: It is the removal of the body and the tail of the pancreas as well as the spleen.
- Total pancreatectomy: It is the removal of the whole pancreas, part of the stomach, part of the small intestine, the common bile duct, the gallbladder, the spleen and nearby lymph nodes ***(Cancer facts and figures, 2013)***.

Postoperative (adjuvant) chemotherapy either alone or in combination with radiation has been proven to improve progression-free and overall survival in both randomized controlled trials and observational studies ***(O'Reilly, 2010; Neoptolemos, 2011)***. Gemcitabine is usually the recommended first-line drug which is given alone or in combination with other drugs such as erlotinib (Tarceva), or fluoropyrimidine ***(Cancer facts and figures, 2013)***

Radiation can be delivered by a machine outside the body (external beam radiation) or can come from a radioactive substance implanted in or near the cancer (internal radiation or brachytherapy). Brachytherapy is rarely used in treating pancreatic cancer ***(Cancer facts and figures, 2013)***.

Targeted therapy is the use of drugs or other substances to inhibit the growth of cancer cells by interfering with specific molecules involved in tumor progression. Erlotinib, which targets the epidermal growth factor receptor (EGER), may be used with gemcitabine among pancreatic cancer patients with advanced disease ***(Cancer facts and figures, 2013)***.

There is no evidence that neoadjuvant therapy (chemotherapy or chemo radiotherapy prior to surgery) is superior to adjuvant therapy, especially among those patients who clearly have resectable disease so neoadjuvant treatment is considered more relevant for patients with locally advanced or borderline resectable disease ***(Gillen et al., 2010).***

Palliative care should be offered at the initiation of any treatment regimen in order to relieve symptoms and side effects, it includes the following:

- Pain control: using opioid analgesics (morphine and similar drugs). Another approach is nerve block (a pain specialist injects either an anesthetic or a medication to block or destroy the nerves). For example, abdominal pain can sometimes be treated effectively by endoscopic ultrasound or CT guided celiac plexus block. Radiation can be given to help relieve pain from locally advanced disease.
- Biliary decompression: by placing a stent (a thin tube) using nonsurgical approaches such as ERCP and (PTC).

- Relief of gastric outlet obstruction: by placing duodenal wall stents or PEG (percutaneous endoscopic gastrostomy). Sometimes, a patient may need surgery to create a bypass (biliary bypass or gastric bypass) to manage obstructive jaundice and gastric outlet obstruction.
- Psychological support: to relieve patients' stresses associated with pancreatic cancer diagnosis and treatment ***(Cancer facts and figures, 2013)***.

PROGNOSIS AND SURVIVAL

According to ***Bilimoria et al. (2007*)**, the median survival of stage IA pancreatic cancer was 24.1 months but it was only 4.5 months for stage IV.

At present, surgery is the only chance of prolonged survival for pancreatic cancer patients. The 5-year survival for patients with a tumor that has been surgically removed (generally stages I or II) is only about 20% to 25%. Poor survival outcome indicators include positive resection margins, poor tumor differentiation, a large tumor size, lymph node involvement, high preoperative Cancer Antigen 19-9 (CA19-9), and persistently elevated levels of postoperative CA19-9 ***(Berger et al., 2008; Maithel et al., 2008; Vincent et al., 2011).***

Measuring CA 19-9 levels prior to therapy with neoadjuvant or adjuvant chemotherapy and demonstrating a treatment related decline in its levels post-chemotherapy is associated with prolonged survival and is an independent predictor of overall survival as it has been evidenced in multiple studies that have assessed response to chemotherapy ***(Ballehaninna et al., 2012).***

A recent study showed patients with post resection CA 19-9 levels less than 90 U/ml appeared to benefit from adjuvant chemotherapy and normalization of CA 19-9 levels maybe associated with an excellent outcome. They recommended checking CA 19-9 levels at multiple time points pre-operatively, post-operatively, preadjuvant, during chemotherapy and post adjuvant therapy ***(Humphris et al., 2012)***.

PATIENTS AND METHODS

Study setting:

This study consisted of 2 parts. The first part is a retrospective cohort study conducted by reviewing the medical records of all primary pancreatic cancer patients managed at National Cancer Institute (NCI), Cairo University (CU) between January 2006 and December 2010. The second part is a prospective cohort study in which a follow up of the patients was conducted by telephone questionnaires.

Sources of data:

- Based on the automated hospital information network; lists of 902 patients were generated, duplication was checked by using names and hospital numbers and no duplicates were identified.

Data abstraction

Prepared data abstraction sheet was used (Appendix A) included

Patients' demographics and clinicolaboratory characteristics:

- Age (years)
- Gender
- Marital status
- Number of children
- Occupation
- Residence
- Clinical picture; symptoms and signs
- Investigations performed
- Tumor site
- Tumor stage {resectable – unresectable (locally advanced & metastatic) –unknown}

- Pathologic types
- Management of cases and different treatment modalities.

Follow up methods:

Patients follow up was done through telephone calls till the end of March 2015.

Data management:

All patients attended to NCI, CU from January 2006 to December 2010 were included in this study. Patients' files were retrieved from Biostatistics and Cancer Epidemiology department. The total number of files generated by the system was 902. Only 341 files were found. After data abstraction and entry 3 files were of incorrectly diagnosed as pancreatic cancer and 2 had no mentioned diagnosis. These patients were excluded. The number available was reduced to 336 cases. A comparison between those with available files and those without regarding the following characteristics:

Year of diagnosis-age groups - sex- marital status-children number-governorates - investigations- Cytopathologic type – stage was performed.

The survival analysis was done based on data retrieved from the available 336 files as well as after adjusting for censored data. A sensitivity analysis was performed. The 1st analysis was executed on the 300 patients. Thirty six patients' files had missing follow up or status information. These patients were excluded from the survival analysis **(Figure 1).**

Before the second analysis, the 36 files were rechecked and classified according to their stage into resectable, unresectable and unknown stage.

The tumor of 22 patients were unresectable. The median survival of the dead group, approximately 2 months, was substituted for the missing

information of 22 of the 36 patients. After this time, these patients were considered dead. The remaining, 14 patients, still lacking any information were excluded. The 186 patients who were, according the medical records, still alive, were categorized according the stage of the disease. The survival time of those with unresectable tumor, 136 patients, was increased by the median survival time of the dead group, 2 months, after which they were considered dead **(Figure 2).**

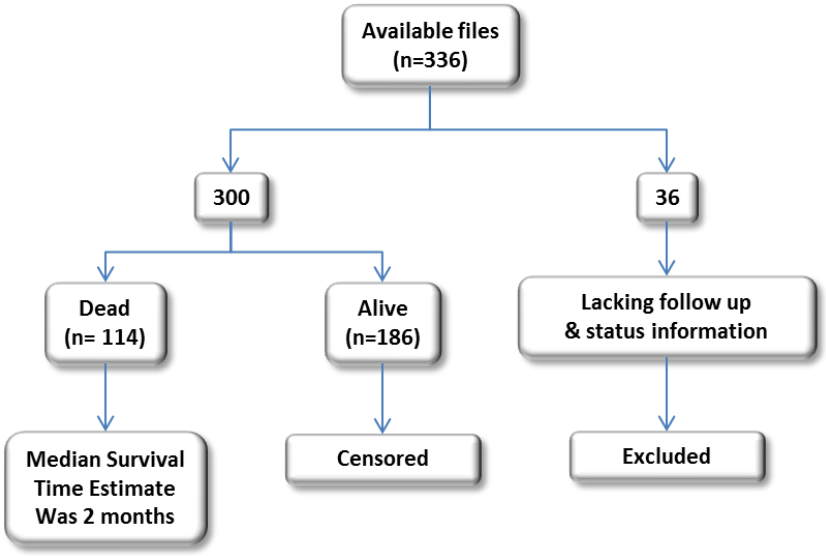

Figure (1): Flow chart showing the 1st analysis

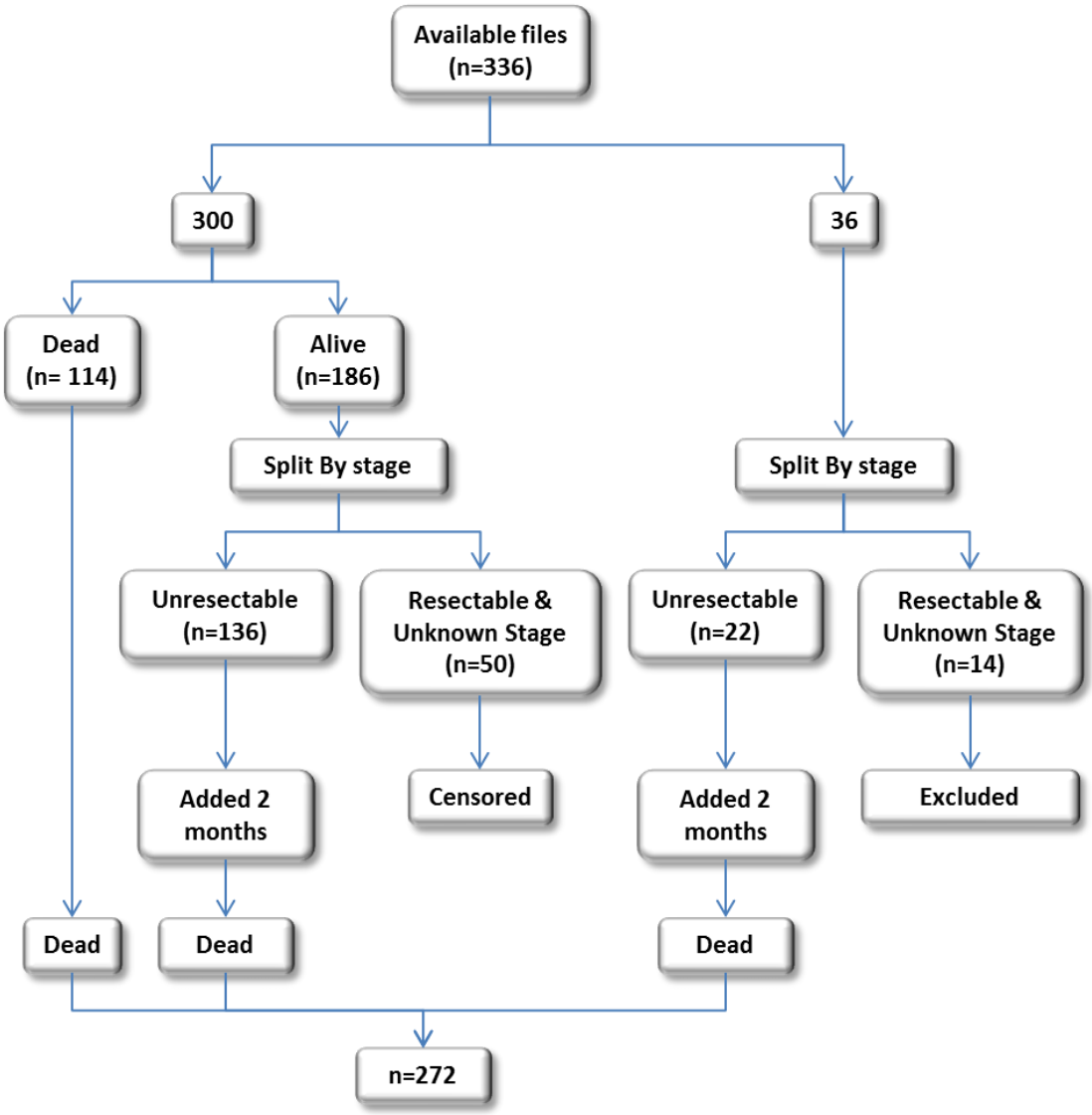

Figure (2): Flow chart showing the 2nd analysis

Ethical issues

- **IRB approval and Consent:**

Approval of Institutional Review Board (IRB) was required before start of the study.

- **Protection of privacy and confidentiality:**

The data of the patients was presented anonymously with protection of privacy and confidentiality.

Statistical methods:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21. Numerical data were summarized as means and standard deviations (SD) or medians and ranges as appropriate. While qualitative data were described as frequencies and percentages. Numeric variables were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Normally distributed variables were compared using student's t-test. The Chi square test was used for comparisons of the categorical variables. Overall survival estimates were calculated using Kaplan-Meier method. Survival curves were compared against explanatory variables using the log rank test. All tests were two-tailed. P-values ≤ 0.05 was considered significant. Overall Survival (OS) was calculated from the time of diagnosis to date of death or last follow up.

RESULTS

Pancreatic cancer patients at National Cancer Institute (NCI), Cairo University (CU), 2006-2010

In the period from January 2006 to December 2010, 902 pancreatic cancer patients attended the NCI. Those with available medical records were 336 so they were analyzed in detail.

The results will be presented in 3 parts:

1) **The first** will include description of the demographic and clinical characteristics of all patients (n=902).
2) **The second** will compare the characteristics of the patients with available records with those without.
3) **The third** will contain detailed analysis of the patients to available records (n=336).

Demographic and clinical characteristics of all pancreatic cancer patients, NCI, CU, 2006-2010 (N=902)

The distribution of the patients during the different years was similar with the highest number seen in 2009 and the lowest in 2010 **(Table 1 and Figure 3).**

The mean age of the patients was 56.4 years with standard deviation 12 and ranged from 3-92 years. More than 1/3 of the patients (35.8%) aged 50-59, about 1/4 (25.3%) were 60-69, 17.5% in their 40-49, 11.5% in their 70-79 years and minority in other age groups **(Table 1 and Figure 4).**

Male to female ratio was 1.87 (**Figure 5)** and the majority of the patients were married about 95.7%. Forty five percent of our patients had 4-6

children. The highest percent of the patients about (40.0%) were residents of Upper and Middle Egypt governorates, 30.0% were from Cairo Metropolitan, 29% were residents of Lower Egypt governorates and minority from other Egyptian governorates and countries other than Egypt (1.0% & 0.9%), respectively **(Table 2 and Figure 6).**

About 31% of the patients were diagnosed by either pathology, cytology or endoscopy, 29.2% by radiology, 3.3% by laboratory or clinical diagnosis and more than one third of the patients (36.6%) hadn't any investigations done **(Table 3).**

Two hundred and seventy four patients had mentioned pathological types; adenocarcinoma represented about 2/3 of the cases (65.0%) and the rest were of other pathological types.

At time of presentation, only 11.0% of the patients had localized tumor (resectable), about 1/4 (26.6%) had locally advanced (regional), about 1/3 (33.1%) were metastatic, for 8.4% staging was not applicable and 1/5 (20.9%) had unknown stage **(Table 3).**

Table (1): Distribution of pancreatic cancer patients at NCI 2006-2010 by year and age groups (N= 902)

Characteristic	Number	Percent
Year		
2006	196	21.7
2007	199	22.1
2008	169	18.7
2009	205	22.7
2010	133	14.7
Age category		
<10	1	0.1
10-19	4	0.4
20-29	18	2.0
30-39	45	5.0
40-49	158	17.5
50-59	323	35.8
60-69	228	25.3
70-79	104	11.5
≥80	21	2.3
Mean ±SD	56.4±12.0	
Range	3-92	

Table (2): Demographic characteristics of pancreatic cancer patients at NCI, 2006-2010 (N=902)

Characteristic	Number	Percent
Sex		
Male	588	65.2
Female	314	34.8
Marital status (n=507)		
Single	14	2.8
Married	485	95.7
Widowed	8	1.6
Children number (n=744)		
1-3	279	37.5
4-6	335	45.0
7-9	115	15.5
≥10	15	2.0
Governorate		
Cairo Metropolitan	270	29.9
Lower Egypt	258	28.6
Upper Egypt & Middle	357	39.6
Other governorates	9	1.0
Other countries	8	0.9

Table (3): Investigations and cytopathology of pancreatic cancer patients at NCI, 2006-2010 (N=902)

Characteristic	Number	Percent
Methods of diagnosis		
Laboratory or Clinical diagnosis	30	3.3
Pathology or Cytology or Endoscopy	279	30.9
Radiology	263	29.2
No investigations done	330	36.6
Pathologic type (n=274)		
Malignant neoplasm	96	35.0
Adenocarcinoma	178	65.0
Stage (n=489)		
Resectable	54	11.0
Regional	130	26.6
Distant & metastatic	162	33.1
Not applicable	41	8.4
Unknown	102	20.9

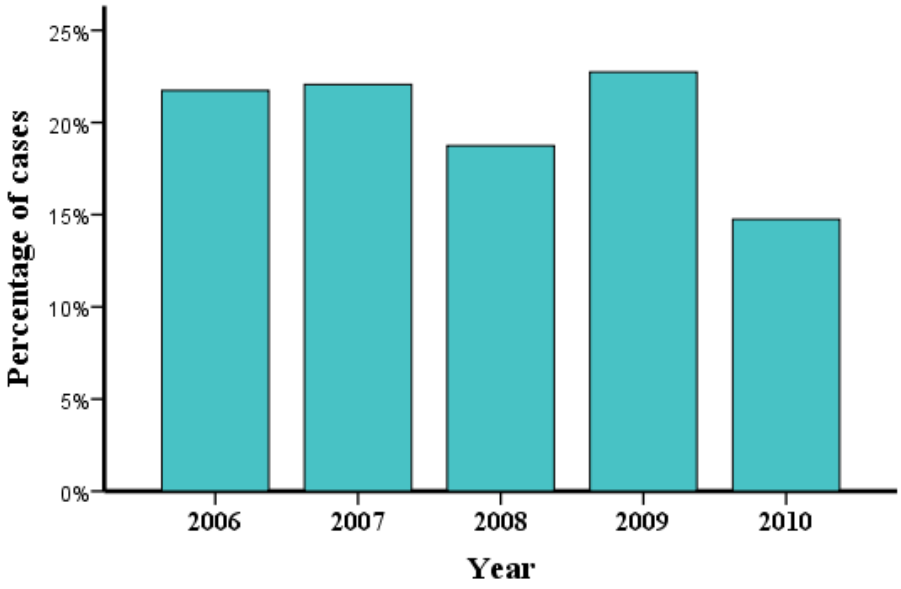

Figure (3): Distribution of 902 pancreatic cancer patients at NCI, 2006-2010 by year

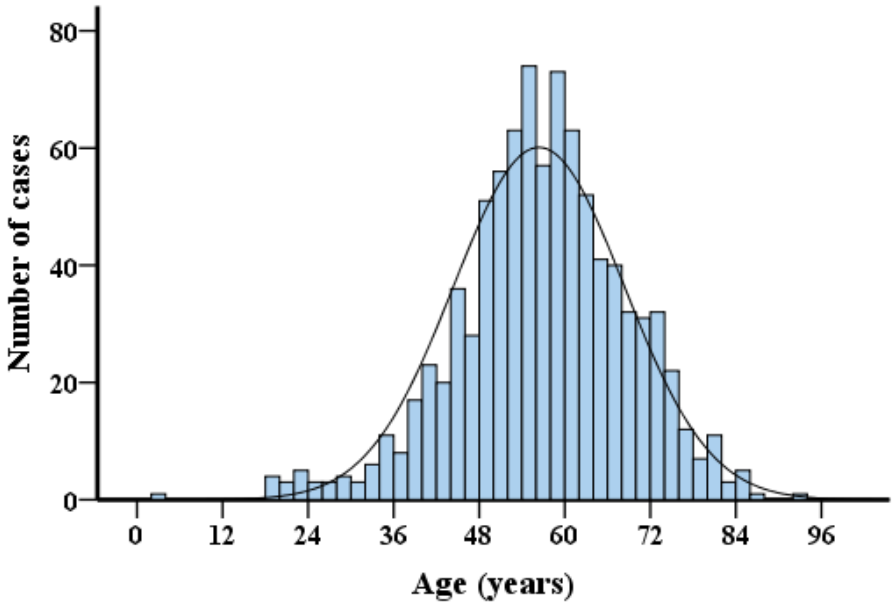

Figure (4): Age at diagnosis of 902 pancreatic cancer patients at NCI, 2006-2010

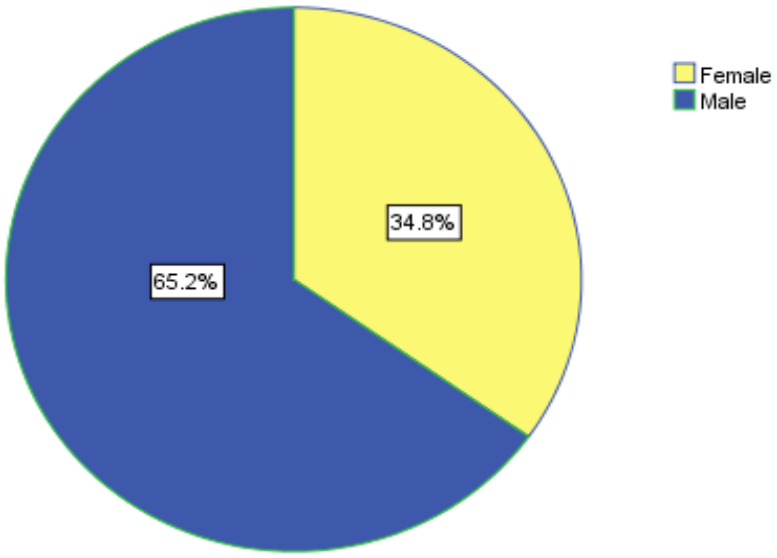

Figure (5): Distribution of 902 pancreatic cancer patients at NCI, 2006-2010 by sex

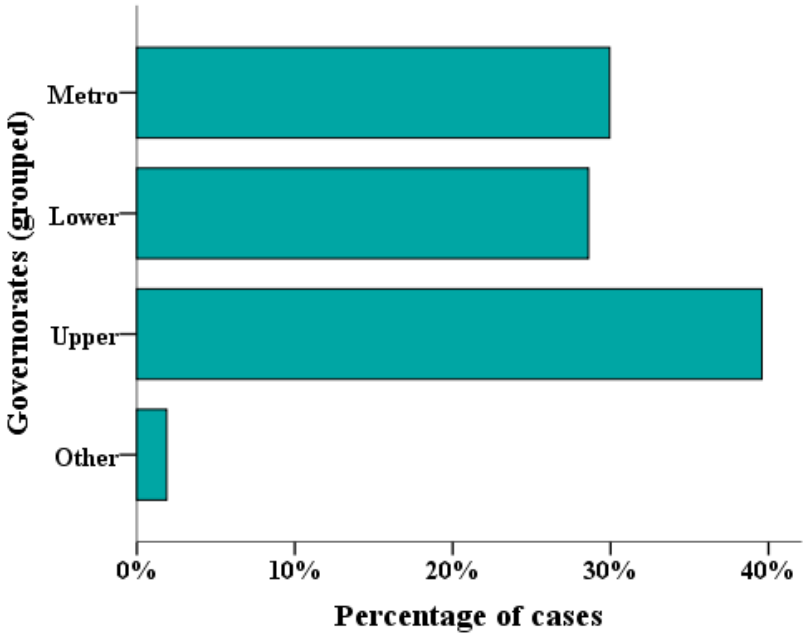

Figure (6): Distribution of 902 pancreatic cancer patients at NCI, 2006-2010 by governorate groups

Pancreatic patients with available medical records in comparison with those with missing medical data, NCI, CU, 2006-2010

Medical records were available for 336 (37.3%), more than half of them (55.6%) in the year 2010, 44.9% in 2009, 38.7% in 2007, 35.5% in 2008 and 16.8% in 2006. There was a statistically significant difference of the availability of records among years. It's observed that the availability of records increased in the recent years **(Table 4).**

Regarding the age, the available records were 35.3%, 37.8%, 37% and 33.3% in those less than 40 years old, (40 to 59), (60 to 79) and in those who were 80 or older, respectively. There was no statistically significant difference of the availability of records among age categories **(Table 4).**

Available records represented 37.6% of all females' records and about 37% of all males' records, respectively. There was no statistically significant difference of the availability of records between males and females.

Regarding marital status, available records represented 42.9%, 44.7% and 37.5% of single, married and widow patients, respectively. There was no relation between availability of records and marital status **(Table 4).**

Available records were 31.2%, 41.2% and 36.9% of patients with 1-3, 4-6 and 7 or more children, respectively. There was a statistically significant difference of availability of records among groups of children number **(Table 4).**

Regarding residence, available records were about 38.0%, 32.2%, 40.1% and 47.1% of residents of Lower Egypt, Cairo metropolitan, Upper Egypt & Middle and other regions, respectively. There was no statistically significant difference of availability of records among governorate groups **(Table 4).**

There was a statistically significant difference of the availability of records among different methods of diagnosis; those diagnosed by radiology represented 39.9% while pathological, cytological or endoscopic diagnoses represented about 37.0%. However none of them were laboratory or clinically diagnosed. No investigations were done for about 39.0% of those with available records **(Table 5).**

There was no statistically significant difference of the availability of records among the different pathological types or different stages **(Table 5).**

Table (4): Demographic characteristics for pancreatic cancer patients with available medical records and those without, at NCI, 2006-2010 (N=902)

Characteristics	Availability of records Available (n=336) n (%)	 Unavailable (n=566) n (%)	Total	P-value
Year				
2006	33 (16.8)	163 (83.2)	196	
2007	77 (38.7)	122 (61.3)	199	
2008	60 (35.5)	109 (64.5)	169	0.001
2009	92 (44.9)	113 (55.1)	205	
2010	74 (55.6)	59 (44.4)	133	
Age				
<40	24 (35.3)	44 (64.7)	68	
40 - 59	182 (37.8)	299 (62.2)	481	0.955
60 - 79	123 (37.0)	209 (63.0)	332	
80+	7 (33.3)	14 (66.7)	21	
Sex				
Female	118 (37.6)	196 (62.4)	314	0.885
Male	218 (37.1)	370 (62.9)	588	
Marital status (n=507)				
Single	6 (42.9)	8 (57.1)	14	
Married	217 (44.7)	268 (55.3)	485	0.912
Window	3 (37.5)	5 (62.5)	8	
Children number (n=744)				
1-3	87 (31.2)	192 (68.8)	279	
4-6	138 (41.2)	197 (58.8)	335	0.037
≥7	48 (36.9)	82 (63.1)	130	
Governorates				
Lower governorates	98 (38.0)	160 (62.0)	258	
Cairo metropolitan	87 (32.2)	183 (67.8)	270	0.181
Upper governorates	143 (40.1)	214 (59.9)	357	
Others	8 (47.1)	9 (52.9)	17	

Table (5): Investigations done, pathologic types and stages among pancreatic cancer patients with available medical records and those without, at NCI, CU, 2006-2010 (n=902)

Characteristics	Availability of records		Total	P-value
	Available (n=336) n (%)	Unavailable (n=566) n (%)		
Methods of diagnosis				
Laboratory or Clinical diagnosis	0 (0)	30 (100)	30	
Pathological , Cytological or Endoscopic diagnosis	103 (36.9)	176 (63.1)	279	0.001
No investigations done	128 (38.8)	202 (61.2)	330	
Radiology	105 (39.9)	158 (60.1)	263	
Pathologic types (n=274)				
Malignant neoplasm	35 (36.5)	61 (63.5)	96	0.776
Adenocarcinoma	68 (38.2)	110 (61.8)	178	
Stage (n=489)				
Resectable	28 (51.9)	26 (48.1)	54	
Regional	67 (51.5)	63 (48.5)	130	
Distant & metastatic	62 (38.3)	100 (61.7)	162	0.084
Not applicable	14 (34.1)	27 (65.9)	41	
Unknown	47 (46.1)	55 (53.9)	102	

Detailed analysis of the patients with available medical records, (2006-2010) (n=336)

Over the period from January 2006 till December 2010, 336 pancreatic cancer patients' medical records were available to be analyzed.

Patients' demographics:

Only 195 patients (58.0%) mentioned their occupation, about 40.0% of them had routine and manual work, those with intermediate occupations were about 9.2% and high managerial and administrative occupations represented 6.2%. Those who never worked represented 36.9% and only 8.2% were retired. More than half of the patients (54.8%) were residents of urban areas **(Table 6).**

More than half of the patients (55.1%) were residents of the Cairo Metropolitan area and the Delta. Those who were from Middle and Upper Egypt governorates represented about 42.6%. Those form Suez Canal cities were about 0.9%. Few patients were from other governorates while those from other countries were mainly from Sudan and Yemen **(Table 7).**

Table (6): Characteristics of pancreatic cancer patients at NCI, CU 2006-2010 (n=195)

Patient characteristics	Number	Percent
Occupational Category (195)		
High managerial and administrative	12	6.2
Intermediate	18	9.2
Routine and manual	77	39.5
Never worked	72	36.9
Retired	16	8.2
Residence		
Urban	184	54.8
Rural	152	45.2

Table (7): Distribution of pancreatic cancer patients at NCI, CU 2006-2010 by residence (n=336)

Governorates	Number	Percent
Cairo Metropolitan		
Cairo	40	11.9
Giza	32	9.5
Qualiobia	15	4.5
Lower Egypt (Delta)		
Monofeia	14	4.2
Kafr El-Sheikh	12	3.6
Behira	15	4.5
Gharbia	16	4.8
Damietta	13	3.9
Dakahlia	8	2.4
Sharkia	20	6.0
Middle Egypt		
Banisuif	30	8.9
Fayoum	35	10.4
Minia	17	5.1
Upper Egypt		
Kena	21	6.3
Aswan	13	3.9
Assuit	11	3.3
Sohag	16	4.8
Suez Canal cities		
Port Said	1	0.3
Ismailia	1	0.3
Suez	1	0.3
Other governorates		
Alexandria	2	0.6
Sinai	1	0.3
Other countries		
Yemen	1	0.3
Sudan	1	0.3

Clinical and pathological characteristics:

About 52.4% of the patients experienced abdominal pain referred to the back and 36.3% experienced jaundice. About 5% had vomiting and 3.6% presented with weight loss. Those who suffered from dyspepsia were 2.4% and 1.8% presented with ascites. Those who had diarrhoea were 0.9%. Only one case experienced bleeding per rectum and one had nausea **(Table 8 and Figure 7).**

Fifty five percent of the patients were investigated for at least one of these tumor markers: CA19.9, CEA, AFP, CA15.3 and CA125. One hundred seventy three (51.5%) patients were investigated for CA19.9; the median was 382U/ml and the interquartile range (IQR) was (20.9-2631.5)U/ml. Those who were investigated for CEA were 122 (36.3%) patients; the median was 4ng/ml and IQR (1.9-21.9) ng/ml. Fifty eight (17.3%) patients were examined for AFP; the median was 2.56ng/ml and IQR (1.8-5.3) ng/ml. Only 7 patients (2.1%) were investigated for CA15.3; the median was 28 and IQR (16.8-40.6) U/ml. Those who were investigated for CA125 were 12 (3.6%) patients; the median was 27.9 and IQR (16.8-141.8) U/ml **(Table 9).**

Regarding the tumor site, 70% of the patients had the tumor in the pancreatic head and or uncinate process while the remaining 30% had it in the other parts of the pancreas (body, tail or overlapping lesions in the body and tail). At the time of diagnosis, the majority of the patients (63.2%) had unresectable tumors (i.e. locally advanced and metastatic), only 13.7% of the patients had resectable ones and 23.1% had unknown tumor stage **(Table 10).**

Sixty-two patients had metastatic tumors, more than 1/2 (60.0%) of them metastasized in the liver, 22.6% in lymph nodes, 9.7%, 3.2% in bone and lung, respectively. Only 4.8% had metastases in spleen and adrenal gland **(Table 10).**

Only 4 patients were known to have developed recurrence; 2 distant and 2 local recurrences. Two patients had pancreatic cancer with another primary cancer as hepatocellular carcinoma and granulose cell tumor of the ovary.

Management

About 83% of the patients had mentioned treatment modalities. Surgery was done for only (9.6%) of the patients, the majority (92.6%) had Whipple's procedure. Ninety four patients (33.6%) received palliative therapy; 78.7% chemotherapy, 5.3% radiotherapy and 16.0% concomitant chemoradiotherapy. More than half (56.8%) of the patients received the best supportive care only, i.e. to ameliorate suffering from biliary obstruction, gastric outlet obstruction and tumor associated abdominal pain **(Table 11).**

The majority of the patients who had surgical treatment (81.5%) didn't receive adjuvant treatment while 11.1% had adjuvant chemotherapy, 3.7% had adjuvant radiotherapy and the same percentage had adjuvant concomitant chemoradiotherapy **(Table 12 and Figure 8).**

Table (8): Symptoms & signs of pancreatic cancer patients at NCI, CU, 2006-2010 (n=269)

Symptoms & Signs*	Number	Percent
Abdominal pain	176	52.4
Jaundice	122	36.3
Vomiting	17	5.1
Weight loss	12	3.6
Dyspepsia	8	2.4
Ascites	6	1.8
Diarrhoea	3	0.9
Bleeding per rectum	1	0.3
Nausea	1	0.3

*Some patients experienced more than one symptom and sign.

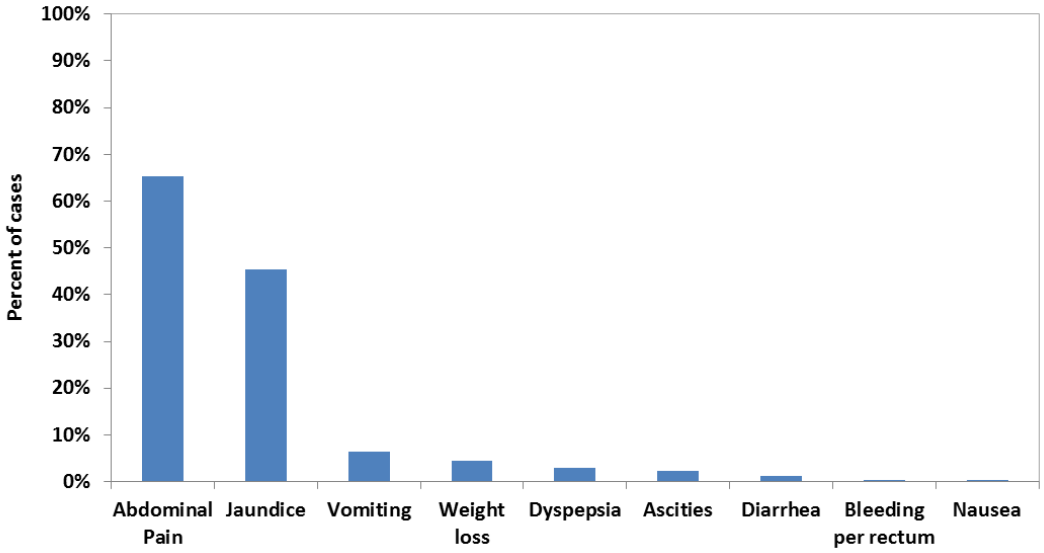

Figure (7): Symptoms & signs of pancreatic cancer patients at NCI, CU, 2006-2010 (n=269)

Table (9): Tumor marker for pancreatic cancer patients at NCI, CU 2006-2010 (n=336)

Tumor* markers	**CA19.9** (U/ml)	**CEA** (ng/ml)	**AFP** (ng/ml)	**CA15.3** (U/ml)	**CA125** (U/ml)
n (%)	173 (51.5)	122 (36.3)	58 (17.3)	7 (2.1)	12 (3.6)
Median	382	4	2.6	28	27.9
IQR**	(20.9-2631.5)	(1.9-21.9)	(1.8-5.3)	(16.8-40.6)	(16.8-141.8)

*Some patients were investigated for more than one tumor marker.

*IQR: inter quartile range.

Table (10): Tumor sites, stages and metastatic sites of pancreatic cancer patients at NCI, CU, 2006-2010 (n=336)

Characteristics	Number	Percent
Tumor site		
Head+ uncinate process	235	69.9
Any other part	101	30.1
Tumor stage (n= 204)		
Resectable	28	13.7
Unresectable	129	63.2
Unknown	47	23.1
Metastatic site (n=62)		
Lymph nodes	14	22.6
Liver	37	59.7
Bone	6	9.7
Lung	2	3.2
Others (spleen & adrenal gland)	3	4.8

Table (11): Treatment modalities of pancreatic cancer patients at NCI, CU, 2006-2010 (n=336)

Treatment	Number	Group percentage	Total percentage
Mentioned	280		83.3
Surgery	27		9.6
Whipple's operation	25	92.6	
Distal pancreatectomy	2	7.4	
Palliative therapy	94		33.6
Chemotherapy	74	78.7	
Radiotherapy	5	5.3	
Concomitant chemoradiotherapy	15	16	
Best Supportive Care	159		56.8
Not mentioned	56		16.7

Table (12): Surgical management of pancreatic cancer patients at NCI, CU, 2006-2010 (n=27)

Surgical management modality	Number	Percent
Surgery alone	22	81.5
Surgery + adjuvant chemotherapy	3	11.1
Surgery + adjuvant radiotherapy	1	3.7
Surgery + adjuvant concomitant chemo radiotherapy	1	3.7

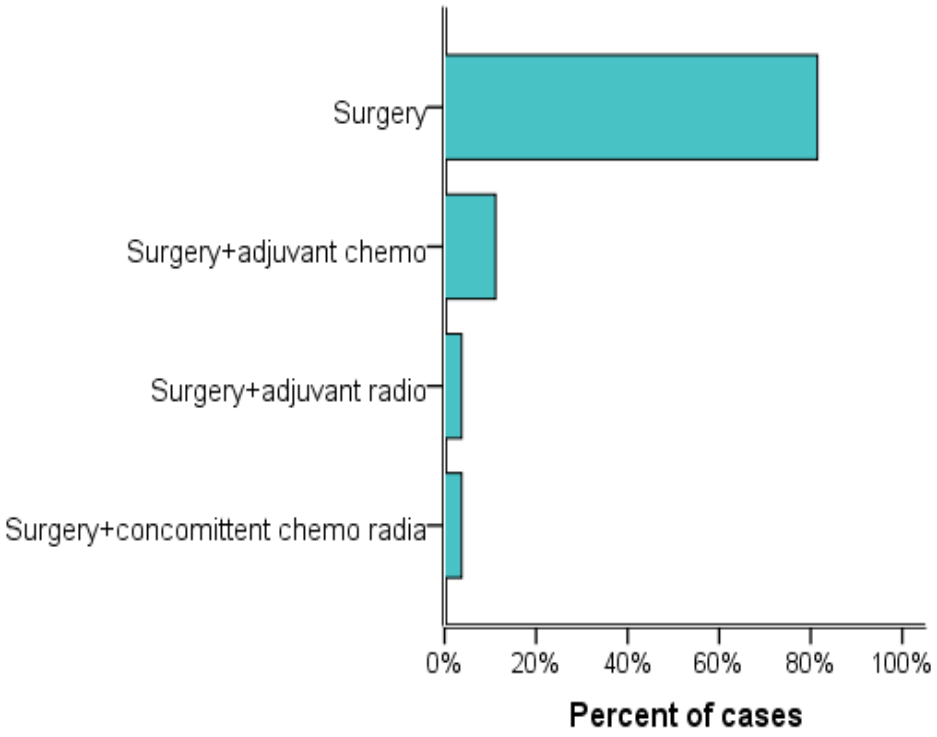

Figure (8): Surgical management of pancreatic cancer patients at NCI, CU, 2006-2010 (n=27)

Survival analysis

Survival analysis was conducted to examine the impact of: year of diagnosis, age, sex, residence, governorate, presence of pain, presence of jaundice, methods of diagnosis, tumor site, pathological types, stages and management modalities on the prognosis of pancreatic cancer patients**.** Overall survival estimates were calculated using the length of follow up as recorded in the medical records and after adjusting the length of follow up.

1. Survival analysis without adjustment (n=300)

The median follow up period was 2.1 months (range 0.03-75); survival was measured from the first day of attending NCI to the date of death from

pancreatic cancer or the date of last contact with the patient. At the time of analysis, 114 patients were dead. One year survival rate of pancreatic cancer patients was 46%, 2 years rate was 32.7% and median overall survival was 9.1 months **(Table 13 and Figure 9).**

The table also shows 1-year, 2-years survival rates and median overall survival of pancreatic cancer patients in relation to: year, age, sex, residence, governorate; the only statistically significant factor affecting survival of pancreatic cancer patients was: age (p-value=0.009) and the group of 60 or older years had better prognosis **(Figures 10, 11, 12, 13 and 14)**.

One year, 2-years and median overall survival of pancreatic cancer patients in relation to: presence of pain, presence of jaundice, methods of diagnosis, tumor site, pathological types, stage and management modalities are presented in **(Table 14 and Figures 15, 16, 17, 18, 19, 20 and 21).** There was no statistically significant effect of any of these factors on survival of pancreatic cancer patients.

Table (13): Overall survival without adjustment in relation to socio-demographic characteristics (n=300)

Characteristics	n	n of events	Overall Survival (%)		Median (months)	P-value
			1 year	2 years		
All	300	114	46	32.7	9.1	-
Year						
2006	28	11	40	26.7	11.1	
2007	69	22	54	46.4	16.7	0.164
2008	55	24	38	16.9	7.5	
2009	83	31	58.7	47.1	23.2	
2010	65	26	19.9	10.0	6.9	
Age (years)						
<=60	196	86	39	27.3	8	
>60	104	28	60	44.0	16.7	0.009
Sex						
Female	103	40	39	30.6	8.4	
Male	197	74	49.7	33.6	9.1	0.667
Residence						
Urban	163	65	46.6	31.8	11.1	
Rural	137	49	46.3	35.2	9.1	0.418
Governorates						
Cairo Metropolitan	78	32	33.2	33.2	5.1	
Lower Egypt	89	30	51.4	30.4	12.9	0.592
Upper Egypt & Middle	125	47	52.7	37.2	12.7	

Table (14): Overall survival without adjustment in relation to clinicopathological characteristics (n=300)

Characteristics	n	n of events	Overall survival (%)		Median (months)	P-value
			1 year	2 years		
Presence of pain						
No pain	142	54	44.9	27.7	11.1	0.408
Pain	158	60	47.4	37.9	9.1	
Presence of jaundice						
No jaundice	196	73	46.5	34.4	9.5	0.938
Jaundice	104	41	45.4	29.8	9.1	
Methods of diagnosis						
Pathology+ Cytology+ Endoscopy	94	30	42.2	14.1	11.1	0.812
Radiology	98	43	50.1	38.2	13.2	
Tumor site						
Head + uncinate process	214	84	40.4	24.6	7.9	0.063
Any other part	86	30	58.3	48.6	13.2	
Pathological types						
Malignant neoplasm	32	8	40.1	*	11.4	0.658
Adenocarcinoma	62	22	43.1	12.9	11.1	
Stage						
Resectable	27	12	28.2	*	2.7	
Unresectable	114	45	47.3	29.5	11.4	0.238
Unknown	42	15	38.6	28.9	8.8	
Management modalities						
Surgery	24	11	36.7	24.5	5.5	
Palliative	83	32	41.8	36.6	8.8	0.980
Supportive	146	52	48.0	26.5	11.4	

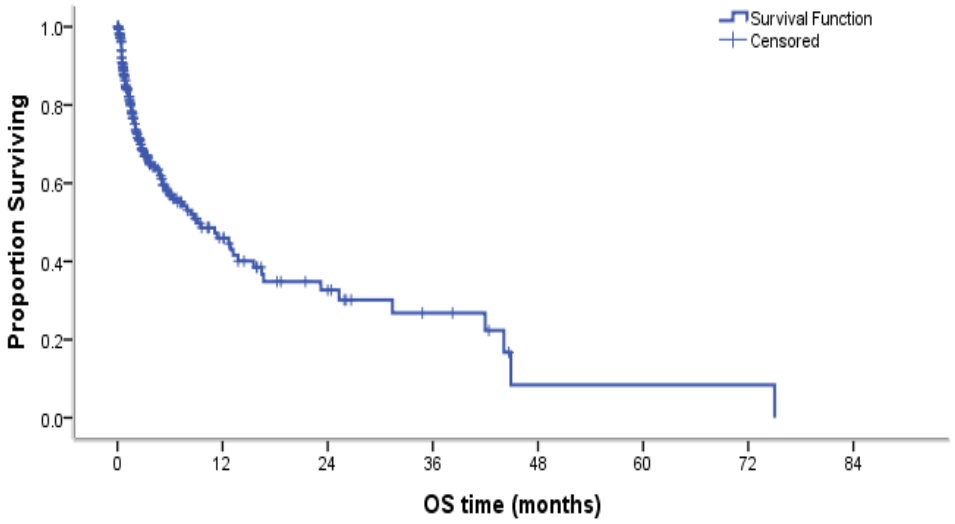

Figure (9): Overall survival without adjustment of pancreatic cancer patients at NCI, 2006-2010 (n=300)

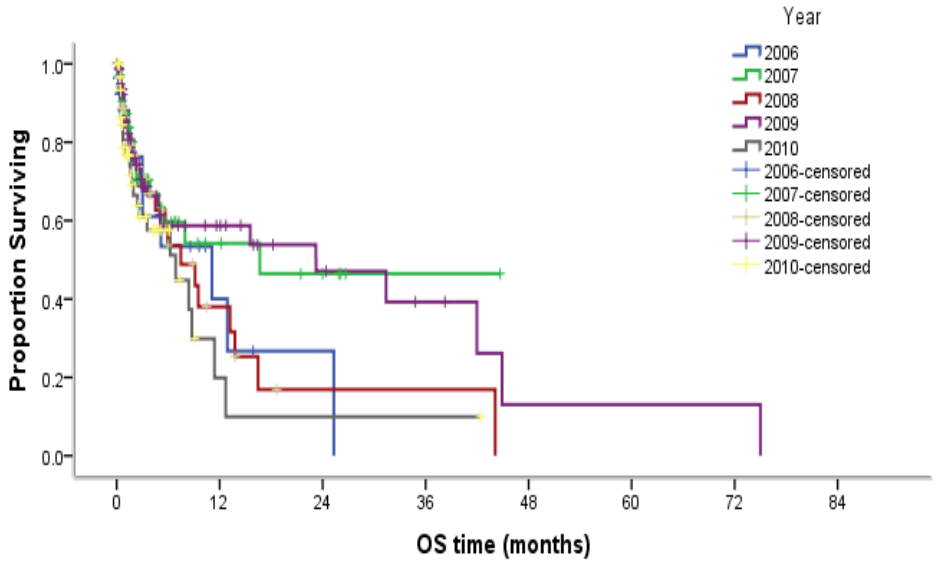

Figure (10): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to year, 2006-2010 (n=300)

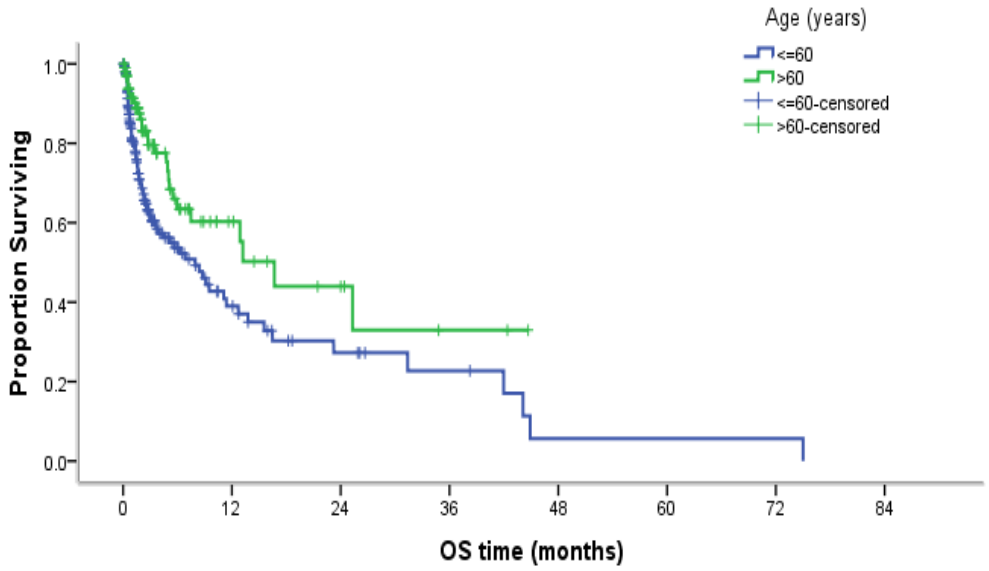

Figure (11): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to age groups, 2006-2010 (n=300)

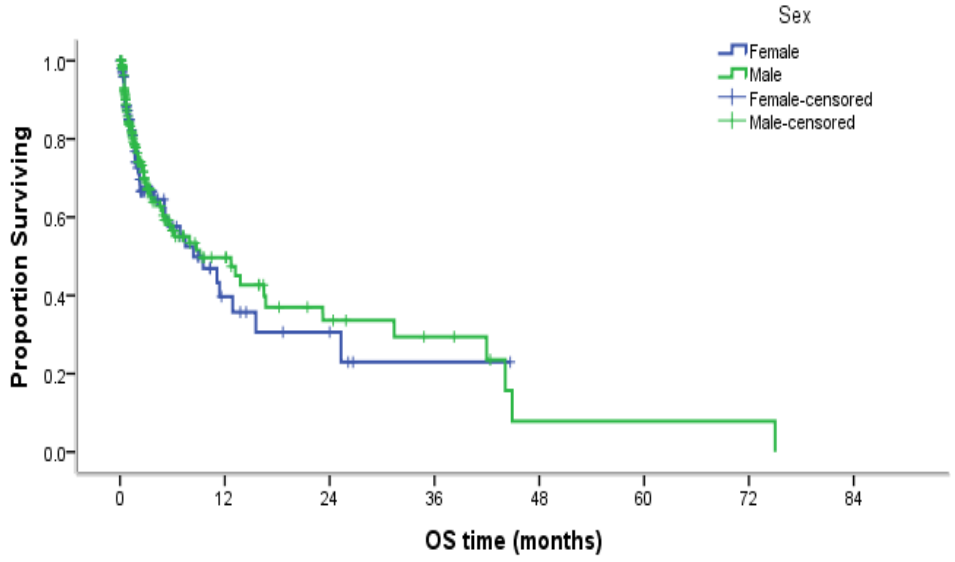

Figure (12): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to sex, 2006-2010 (n=300)

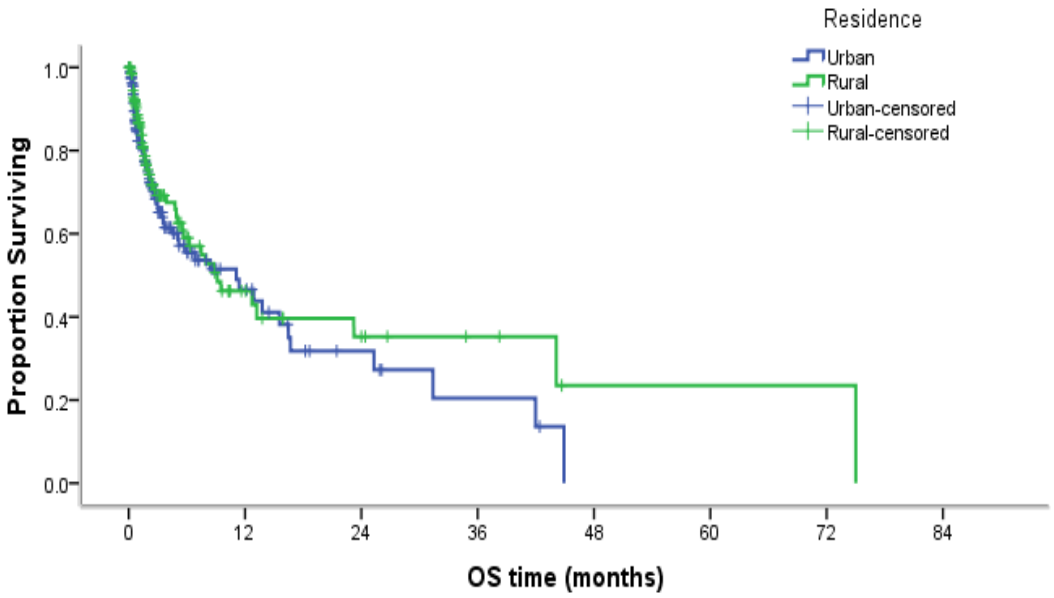

Figure (13): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to residence, 2006-2010 (n=300)

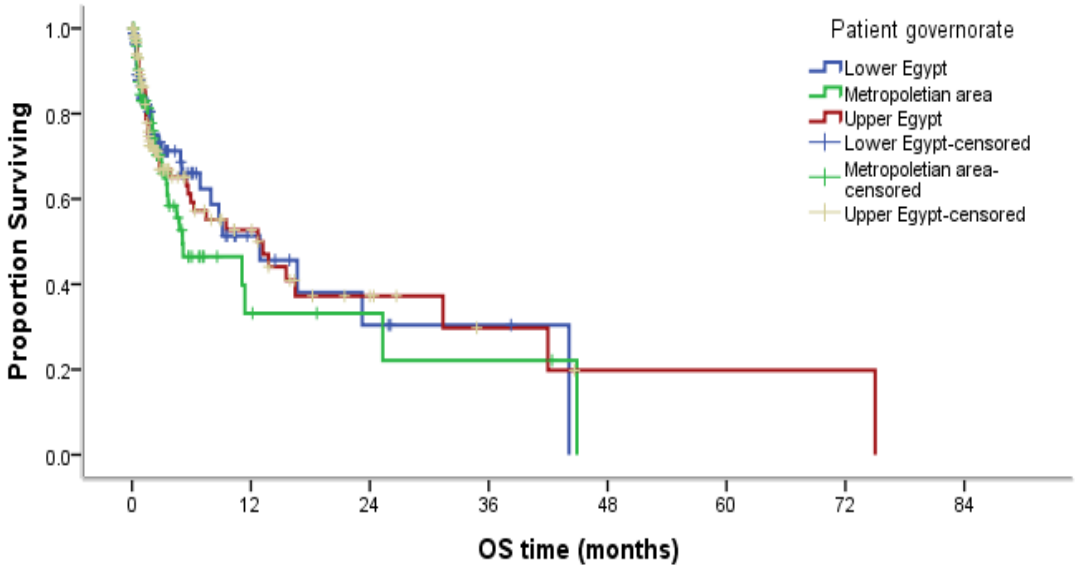

Figure (14): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to governorate groups, 2006-2010 (n=300)

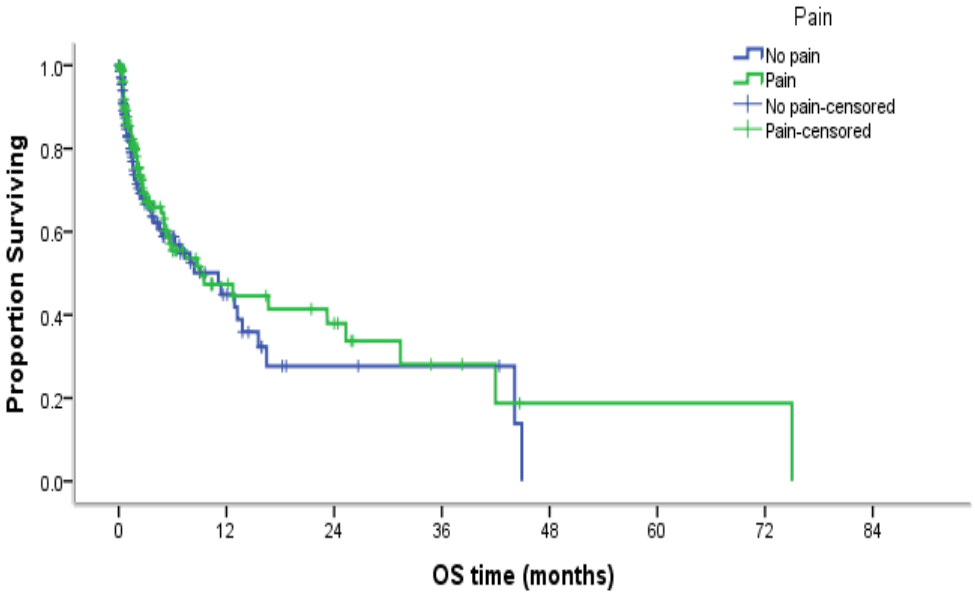

Figure (15): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to presence of pain, 2006-2010 (n=300)

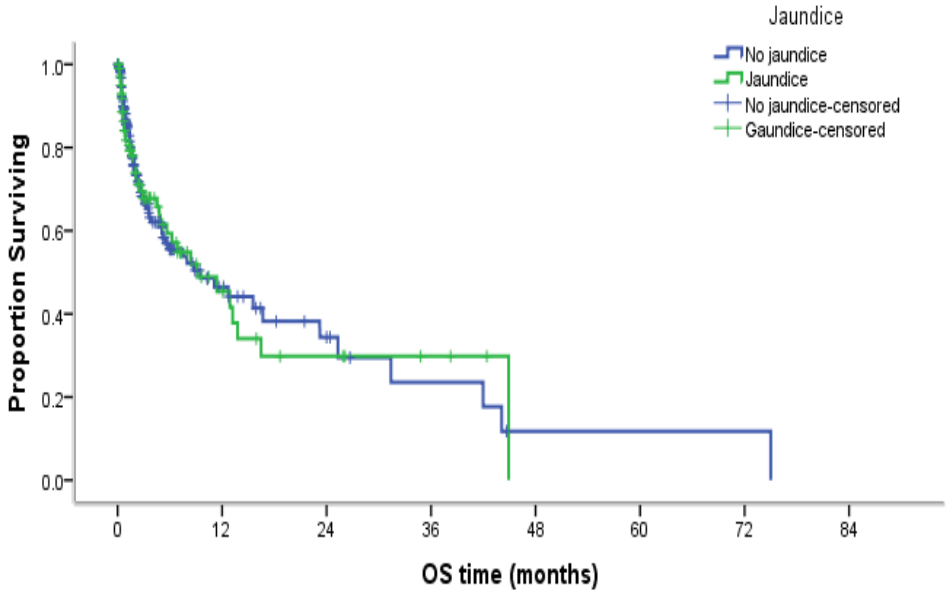

Figure (16): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to presence of jaundice, 2006-2010 (n=300)

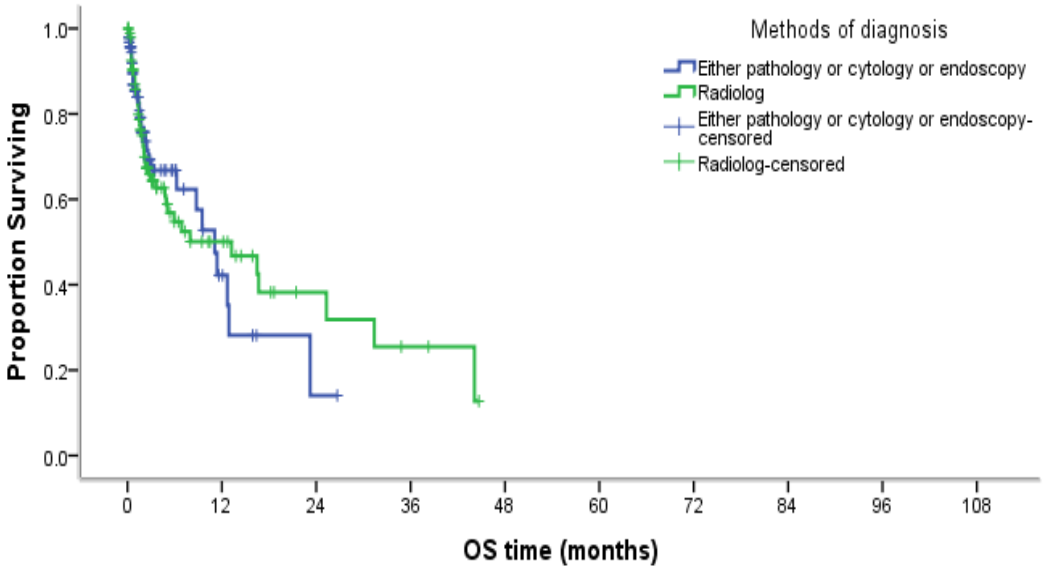

Figure (17): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to methods of diagnosis, 2006-2010 (n=300)

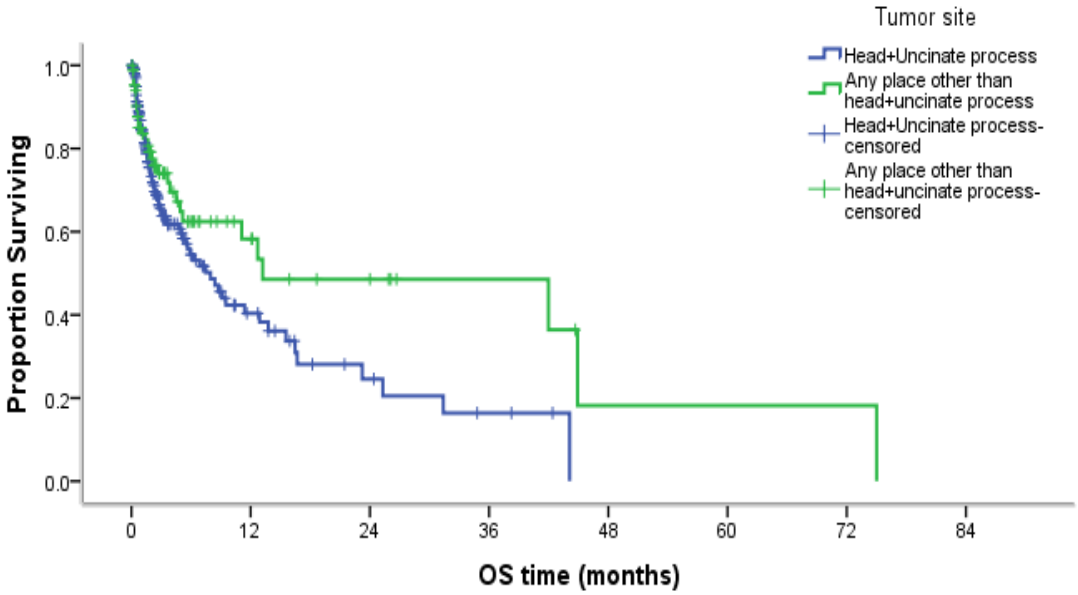

Figure (18): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to tumor site, 2006-2010 (n=300)

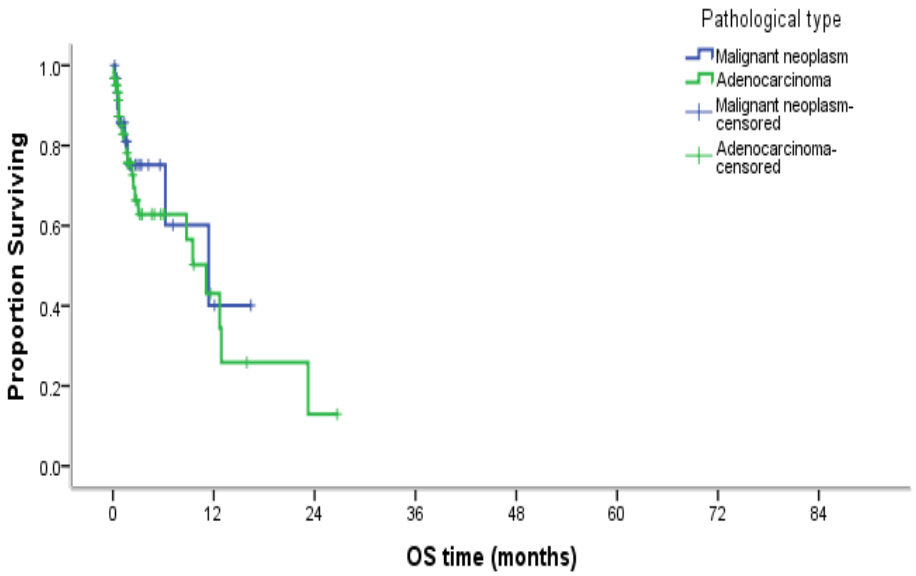

Figure (19): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to pathological types, 2006-2010 (n=300)

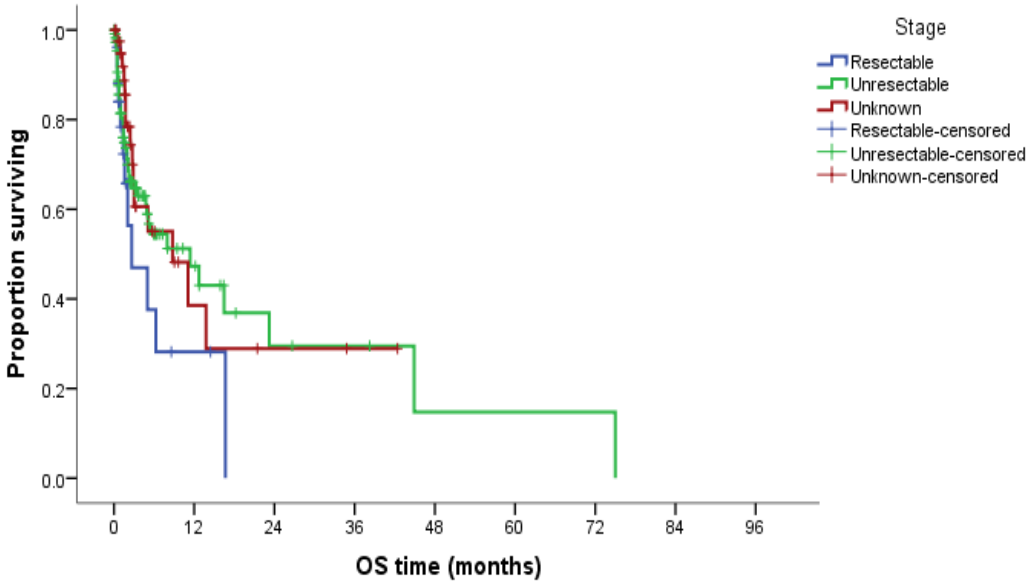

Figure (20): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to stage, 2006-2010 (n=300)

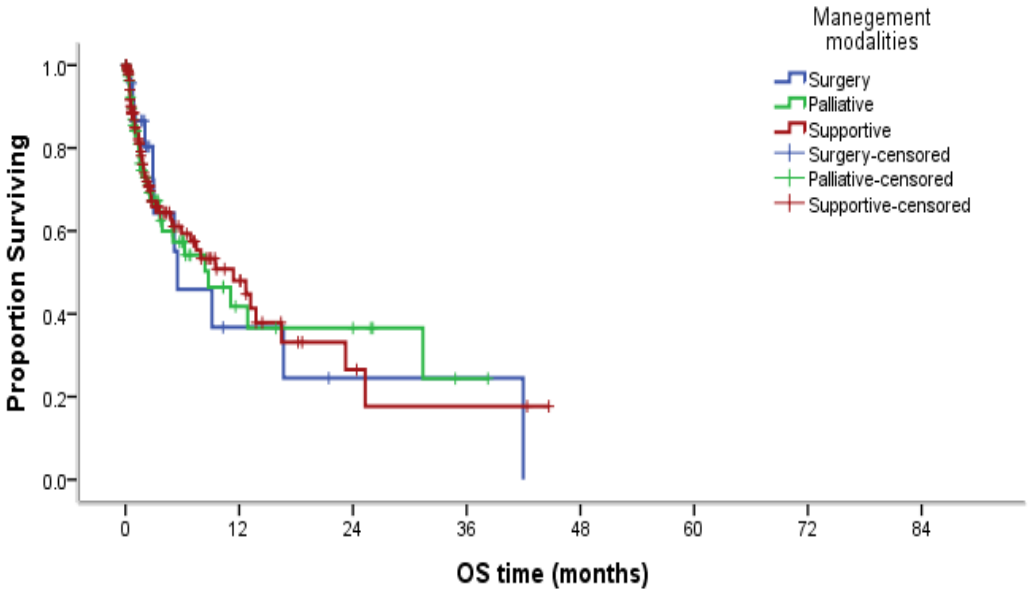

Figure (21): Overall survival without adjustment of pancreatic cancer patients at NCI in relation to presence of management modalities, 2006-2010 (n=300)

2. Uncensored versus censored pancreatic cancer patients attended NCI, CU, 2006-2010

Uncensored and censored pancreatic cancer patients were compared regarding different factors; year, age, sex, number of children-residence, presence of pain, presence of jaundice, methods of diagnosis, tumor site, pathological types, stage and management modalities as shown in **(Tables 15 and 16)**. Uncensored and censored patients weren't significantly different regarding all these factors except age; dead patients were significantly younger (mean=54.1) than censored patients (mean= 57.8), p-value=0.005.

Table (15): Demographic characteristics for uncensored and censored pancreatic cancer patients, NCI, CU, 2006-2010 (n=300)

Characteristics	Follow up status		P-value
	Uncensored n (114) n (%)	Censored n (186) n (%)	
Year			
2006	11 (39.3)	17 (60.7)	
2007	22 (31.9)	47 (68.1)	
2008	24 (43.6)	31 (56.4)	0.739
2009	31 (37.3)	52 (62.7)	
2010	26 (40.0)	39 (60.0)	
Age			
Mean (SD)	54.1(12.0)	57.8(10.5)	0.005
Sex			
Female	40 (38.8)	63 (61.2)	0.829
Male	74 (37.6)	123 (62.4)	
Number of children			
1-3	23 (30.7)	52 (69.3)	
4-6	51 (41.8)	71 (58.2)	0.265
≥7	19 (41.3)	27 (58.7)	
Residence			
Urban	65 (39.9)	98 (60.1)	0.476
Rural	49 (35.8)	88 (64.2)	
Occupation			
Routine and manual work	27 (38.6)	43 (61.4)	
Others	16 (39.0)	25 (61.0)	0.903
Never worked	27 (42.2)	37 (57.8)	

*SD: Standard deviation

Table (16): Clinical characteristics for uncensored and censored pancreatic cancer patients regarding patients' clinicopathological characteristics, NCI, CU, 2006-2010 (n=300)

Characteristics	Follow up status		P-value
	Uncensored n (114) n (%)	Censored n (186) n (%)	
Presence of pain			
No pain	54 (38.0)	88 (62.0)	0.992
Pain	60 (38.0)	98 (62.0)	
Presence of jaundice			
No jaundice	73 (37.2)	123 (62.8)	0.711
Jaundice	41 (39.4)	63 (60.6)	
Methods of diagnosis			
Pathology+ Cytology+ Endoscopy	40 (40.4)	59 (59.6)	
Radiology	29 (31.9)	62 (68.1)	0.352
No investigations done	45 (40.9)	65 (59.1)	
Tumor site			
Head+ uncinate process	84 (39.3)	130 (60.7)	0.481
Any place other than head+ uncinate process	30 (34.9)	56 (65.1)	
Pathological types (n=94)			
Malignant neoplasm	8 (25.0)	24 (75.0)	0.301
Adenocarcinoma	22 (35.5)	40 (64.5)	
Stage (n=183)			
Resectable	12 (44.4)	15 (55.6)	
Unresectable	45 (39.5)	69 (60.5)	0.768
Unknown	15 (35.7)	27 (64.3)	
Management modalities			
Surgery	11 (45.8)	13 (54.2)	
Palliative	32 (38.6)	51 (61.4)	0.615
Supportive	52 (35.6)	94 (64.4)	

3. Survival analysis after adjustment (n=322)

After adjusting the time and status for the stage, 322 patients were available for survival analysis and the impact of different factors on the prognosis of pancreatic cancer patients was re-evaluated.

Median follow up period was 2.8 months (range 0.03-75). Two hundred and seventy two patients had died. One year survival rate of pancreatic cancer patients was 15% while 2-year rate was 6.4%. The median overall survival was 3.5 months **(Table 17and Figure 22).**

The table also shows 1-year, 2-years and median overall survival of pancreatic cancer patients in relation to different prognostic factors; none of these factors significantly affected the survival of the patients.

One year, 2 years and median overall survival of pancreatic cancer patients in relation to: presence of pain, presence of jaundice, methods of diagnosis, tumor site, pathological types, stage and management modalities are presented in **(Table 18).** The only statistically significant factor affecting survival of pancreatic cancer patients was tumor site (p-value=0.034) with head and or the uncinate process had worse prognosis than any other part.

Table (17): Overall survival with adjustment in relation to socio-demographic characteristics (n=322)

Characteristics	n	n of events	Overall survival (%)		Median (months)	P-value
			1 year	2 years		
All	322	272	15	6.4	3.5	-
Year						
2006	32	25	13.7	4.6	3.0	
2007	74	60	15.5	9.7	4.3	
2008	59	49	15	2.2	3.7	0.140
2009	87	78	23	10	3.7	
2010	70	60	4.1	2.1	2.5	
Age (years)						
<=60	208	184	12.9	5.3	3.0	0.078
>60	114	88	20	8.7	4.2	
Sex						
Female	110	91	14.6	6.6	3.2	0.981
Male	212	181	15.6	6.2	3.5	
Residence						
Urban	177	160	13	4.6	3.2	0.151
Rural	145	112	19	9.1	3.7	
Governorates						
Cairo Metropolitan	82	72	7.6	4.6	3.5	
Lower Egypt	94	76	16	6.5	3.7	0.615
Upper & Middle Egypt	138	117	20	7.7	3.4	

Table (18): Overall survival with adjustment in relation to clinicopathological characteristics (n=322)

Characteristics	n	n of events	Overall survival (%) 1 year	Overall survival (%) 2 years	Median (months)	P-value
Presence of pain						
No pain	152	125	15.4	3.8	3.1	0.449
Pain	170	147	15.3	8.4	3.7	
Presence of jaundice						
No jaundice	207	177	14.8	6	3.5	0.767
Jaundice	115	95	16.3	7	3.5	
Methods of diagnosis						
Pathology+ Cytology+ Endoscopy	98	82	10.4	10.4	3.1	0.067
Radiology	102	88	23.7	7.5	4.5	
Tumor site						
Head+ uncinate process	227	195	12.9	4.3	3.1	0.034
Any other part	95	77	21.3	11.3	4.1	
Pathological types						
Malignant neoplasm	33	27	7.8	*	3.6	0.802
Adenocarcinoma	65	55	11.6	2.3	3.1	
Stage						
Resectable	28	22	9.7	*	2.6	
Unresectable	123	106	14	4.3	3.4	0.318
Unknown	45	37	11	5.7	3.6	
Management modalities						
Surgery	25	24	16.7	4.2	3.7	
Palliative	89	70	16.7	12.5	3.6	0.834
Supportive	155	131	15.3	3.4	3.0	

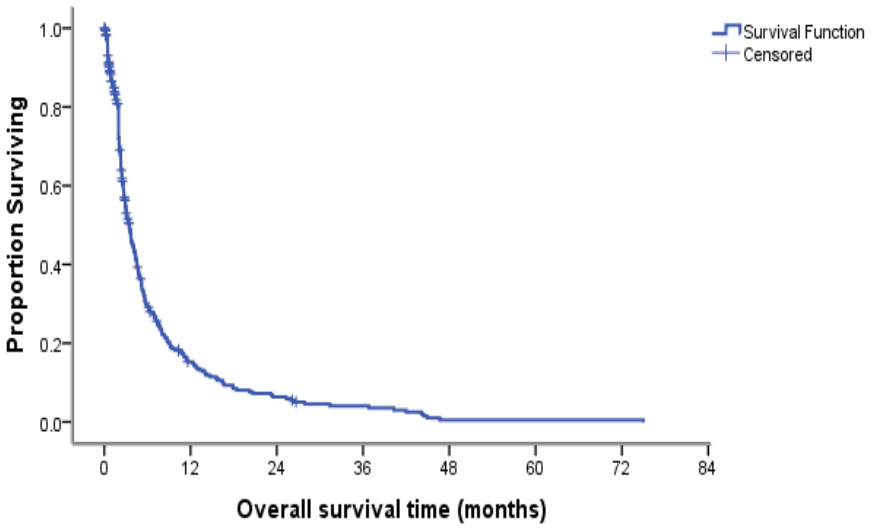

Figure (22): Overall survival with adjustment of pancreatic cancer patients at NCI, 2006-2010 (n=322)

4. Two years overall survival calculated from observed follow up time and the adjusted time for censored data

Two years overall survival was compared between observed follow up time and the adjusted time for the censored data with 95% confidence intervals. Confidence intervals overlapped regarding the following patients' characteristics: years of diagnosis 2006 and 2008, Lower Egypt governorates, pathological, cytological or endoscopic investigations, malignant neoplasm and adenocarcinoma, surgical and palliative treatments. The overlaps in the 95% confidence intervals were borderline. Confidence intervals didn't overlap for all other factors. In other words, the results show that the observed follow up time overestimated the overall survival time as compared to the estimates of overall survival after adjusting for the censored data regarding most patients' characteristics **(Table 19 and Figure 23).**

Table (19): Two years overall survival rate with 95% confidence interval for unadjusted and adjusted for censored data

Characteristics	2 years overall survival (95% CI) Observed	Adjusted
All	32.7 (22.9-42.7)	6.4 (3.8-9.9)
Year		
2006	26.7 (4.9-56.0)	4.6 (0.3-18.8)
2007	46.4 (25.8-64.8)	9.7 (3.7-19.1)
2008	16.9 (3.6-38.5)	2.2 (0.2-9.9)
2009	47.1 (28.5-63.7)	10.1 (4.5-18.3)
2010	10.0 (0.7-34.0)	2.1 (0.2-9.4)
Age (years)		
<=60	27.3 (16.6-39.1)	5.3 (2.6-9.3)
>60	44.0 (25.0-61.4)	8.7 (3.7-16.5)
Sex		
Female	30.6 (15.9-46.8)	6.6 (2.6-13.4)
Male	33.6 (21.3-46.4)	6.2 (3.2-10.6)
Governorates		
Lower Egypt	30.4 (12.1-51.2)	6.5 (2.2-14.2)
Cairo Metropolitan	33.2 (15.8-51.8)	4.6 (1.2-11.5)
Upper Egypt	37.2 (23.2-51.3)	7.7 (3.6-13.7)
Methods of diagnosis		
Pathology+ Cytology+ Endoscopy	14.1 (1.3-41.3)	10.4 (4.9-18.2)
Radiology	38.2 (23.4-52.9)	7.5 (3.1-14.5)
Tumor site		
Head+ uncinate process	24.6 (13.7-37.2)	4.3 (1.9-8.1)
Any other part	48.6 (30.9- 64.2)	11.3 (5.4-19.8)
Pathological types		
Malignant neoplasm*	40.1 (7.7-72.2)	7.8 (1.4-22.0)
Adenocarcinoma	12.9 (1.1-39.7)	2.3 (0.2-10.4)
Management modalities		
Surgery	24.5 (4.7-52.4)	4.2 (0.3-17.6)
Palliative	36.6 (20.0-53.3)	12.5 (5.7-22.1)
Supportive	26.5 (11.8- 43.9)	3.4 (1.1-7.8)

CI: confidence interval

*** One year overall survival estimate**

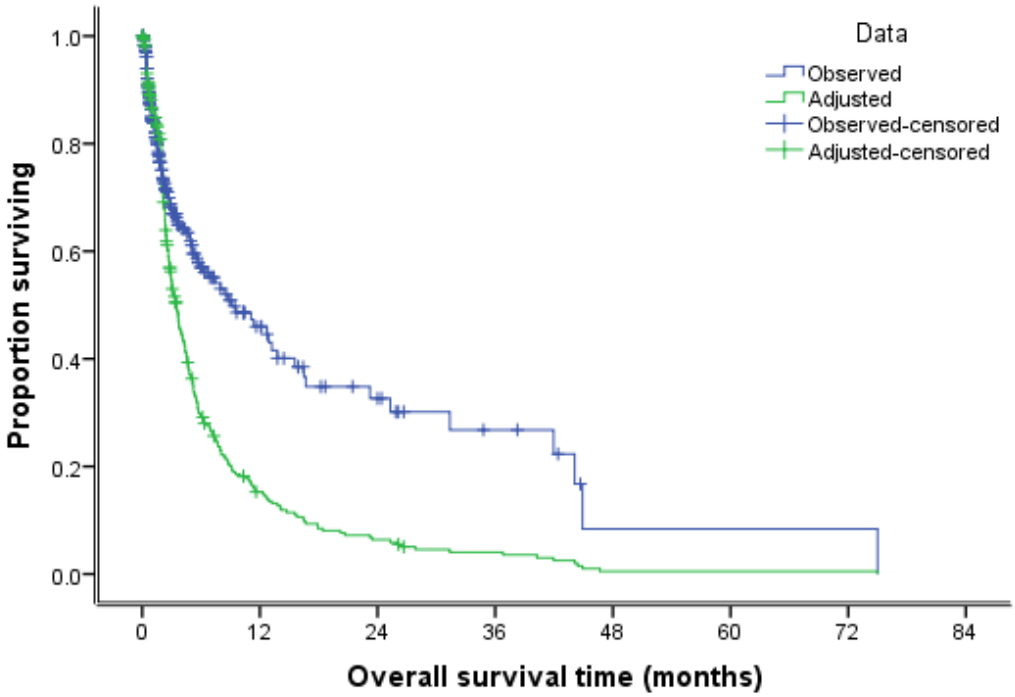

Figure (23): Overall survival rate for unadjusted and adjusted for censored data

DISCUSSION

This is a retrospective cohort study conducted by reviewing the medical records of all primary pancreatic cancer patients managed at National Cancer Institute (NCI), Cairo University (CU) between January 2006 and December 2010.Three hundred and thirty six files were analyzed in details.

Patients' demographics:

In our study the mean age of the pancreatic cancer patients attended NCI, CU (2006-2010) was 56.4 with standard deviation 12 year, this was close to that reported in a retrospective study done by ***Soliman et al. (2002)*** in which they studied 728 pancreatic cancer patients seen at the Gastrointestinal Surgery Center of Mansoura University in the East Nile Delta region of Egypt between 1995 and 2000 and divided them into 3 groups according to their primary method of treatment. They found that Approximately one-fourth of the patients were under age 50 and the mean ages of patients who had undergone Whipple's resection, other surgical procedures, and no surgical procedure were 52.9, 54.11 and 55.1,respectively with standard deviation of 11.6, 10.5 and 14.1 year, respectively. Also another study by ***Soliman et al. (2007)*** included 99 histologically confirmed pancreatic cancer patients in Egypt reported that the mean age of the patients from Mansoura governorate was 53.8 with standard deviation 10.4 year, while that of the non-Mansoura group was 55.1 with standard deviation 11.6 year. According to the ***American Cancer Society, (2015)***; the average age at the time of diagnosis was 71 years old. This can be explained by the lower life expectancy of the Egyptian

population as well as the difference in the population structure with 50% of the Egyptians below the age of 30 years ***(Mokdad et al., 2014).***

Our study revealed that males represented about 64.9%; this was close to what was reported by ***Cancer facts and figures, (2013)*** (pancreatic cancer is about 30% more common in men than in women). This may be due, at least in part, to higher tobacco use in men.

The majority of the patients were married 96.0 % and most of them had children**.** ***Beibei et al. (2014)*** concluded from their meta -analysis which involved ten cohort studies and ten case-control studies (8205 cases) that the combined RR (relative risk) of pancreatic cancer for the parous vs. nulliparous women was 0.91 (95% CI, confidence interval = 0.85–0.97) and there is an inverse association between giving birth to two children and pancreatic cancer risk with RR of 0.86 (95% CI = 0.80–0.93). They explained this finding by reporting that parous women are likely to have had longer periods of exposure to high levels of circulating estrogens and animal studies reported that the estrogen had an inhibitory effect on the growth of preneoplastic pancreatic lesions. On the contrary in our study, the majority of females were mutiparous; 57.6% had 4-6 children.

Occupation was classified according to the National Statistics Socioeconomic classification ***(NS-SEC)***. About 39.5% of the patients with mentioned occupations were with routine and manual work (all were males); this could be explained by the fact that this work may involve exposure to pesticides, dyes and chemicals which may increase the risk of developing pancreatic cancer. Thirty-seven percent of our patients were

never worked and most of them were females; this may be explained, at least in part, by obesity which is more common in females.

The study revealed that 54.8% of the patients were from urban areas and 55.1% reside in the Cairo Metropolitan area and the Delta. According to ***Alison et al. (2006)***, the northeast Nile Delta region exhibits a high incidence of early-onset pancreatic cancer. It is well documented that this region has one of the highest levels of pollution in Egypt.

Industrialization and urbanization of the Nile Valley and delta had occurred rapidly, without protective legislation, which resulted in dangerous increases in environmental carcinogens ***(Gusten et al., 1994).*** Industrial waste and by-products, agricultural wastewater, and nonrecyclable waste are increasingly dumped into the Nile, with the result that the river, especially in its lower stretch, is heavily polluted with heavy metals, pesticides, and hydrocarbons ***(Badawy et al., 1995).***

Clinical and pathological characteristics:

Results of the present study revealed that the patients who experienced abdominal pain represented about 52.4%, jaundice 36.3%, vomiting 5%, weight loss 3.6%, dyspepsia 2.4% and 1.8% presented with ascites**.** This could be explained by the fact that 63.2% of the patients in this study were unresectable (i.e. locally advanced or metastatic) so invasion of other organs and nerves may be the cause of abdominal pain so it's the main symptom. Jaundice is the second one; this may be due to the fact that 69.9% had the tumor in the pancreatic head and uncinate process which can cause obstruction of the common bile duct and also it can be secondary to a tumor in the body or tail and this may be due to liver metastases. On

contrary, ***Miquel et al. (2005)*** recorded in their study which was conducted on 185 patients with exocrine pancreatic cancer diagnosed at five general hospitals in Eastern Spain that at presentation, the most frequent symptoms were asthenia (86%), anorexia (83%), weight-loss (85%), abdominal pain (79%), and choluria (59%), this may be due to early detection of pancreatic cancer in that population.

According to ***NCCN guidelines (2015)*** imaging is the primary means through which the stage of pancreatic cancer is determined and our results are consistent with that as radiology (31.3%) was the main method of diagnosis.

In our study, 51.5% and 36.3% of the patients were investigated for CA19.9 and CEA, respectively. ***Winter et al. (2013***) reported that CA 19-9 is a unique tumor marker approved by the FDA for pancreatic adenocarcinoma and it's more sensitive and specific compared to CEA.

We found about 70.0% of the patients had the tumor in the pancreatic head and or uncinate process while the remaining 30.0% had it in the other parts of the pancreas (body, tail or overlapping lesions in the body and tail), this is consistent with that mentioned by ***Sener et al., (1999).***

Adenocarcinoma represented about 66.0% of all pathological types and this disagrees with that mentioned by ***Li and Jiao***, ***(2003)***; they reported that the majority of exocrine pancreatic cancers were adenocarcinomas which accounted for 90.0% of all pancreatic cancers. Such a disagreement between studies can be explained by the fact that only 31.0% of our patients had mentioned pathological type.

In the current study about 14 % of the patients were resectable, which is consistent with that documented by ***Cancer facts and figures, (2013)***; only about 15% to 20% of pancreatic cancer cases are diagnosed early enough to be eligible for surgery.

Survival analysis:

Survival analysis was conducted to estimate the overall survival of pancreatic cancer patients involved in the current study and to examine the effect of patient-related factors (year-age- sex- residence- governorate groups- presence of pain, presence of jaundice, investigations, tumor site, pathologic types, stage and management modalities) on the survival of pancreatic cancer patients.

In our study, the median overall and 1-year survival were 9.1 months and 46.0%, respectively and this is less than that reported in an American retrospective study conducted by ***Taylor et al., (2000)*** examining the factors influencing survival of the 616 patients***;*** the median survival was 17 months and 1-year survival rate was 63.0%***. C J et al. (1995)*** conducted a study on 201 patients at The Johns Hopkins Hospital and reported that the median survival was 15.5 months. This difference may be explained by the fact that all their cases were resectable but in our study resectable cases represented only about 14%.

Our study revealed that the only statistically significant factor affecting survival of pancreatic cancer patients was the age (p-value=0.009) with the group of 60 years or older had better prognosis. ***Emine et al. (2013)*** conducted a retrospective study to evaluate patient characteristics,

treatment modalities and prognostic factors in Turkish patients with pancreatic cancer and reported that age was found to be a prognostic factor associated with the overall survival (p=0.023) with those who were over 60 years old had the poorer prognosis. This disagreement may be attributed to the early exposure to risk factors and genetic predisposition of our younger patients so their prognosis is poorer than that of the older group and also may be due to the relatively small number of the patients in their study.

In our study, the gender wasn't a significant factor affecting the survival of the patients and this was the same reported by ***Emine et al., (2013*)**.

According to our study, tumor site wasn't a significant factor affecting the survival of pancreatic cancer patients (p=0.063) and this is in accordance with that mentioned by both ***Taylor et al., (2000)*** and ***Emine et al., (2013)***.

Emine et al. (2013) mentioned that on univariate and multivariate analysis, a statistically significant relationship was found between overall survival and the tumor stage but in our study, this relationship wasn't statistically significant. This may be explained by the fact that about 1/4 of our patients (23.0%) had missing data for stage

A comparison between the uncensored and censored pancreatic cancer patients was conducted to see if there's significant difference between them regarding: year, age, sex, number of children-residence, presence of pain, presence of jaundice, investigations done tumor site, pathological types, stage and management modalities. They weren't significantly different regarding all these factors except for age; the mean age of dead patients

was 54.1 with standard deviation 12 years while the mean age of those who were censored was 57.8 with standard deviation 10.5 years. Based on this comparison it was concluded that the dead and censored patients were more or less similar, i.e. censoring was not related to any of the risk factors. This fact made it possible to adjust the follow up time for the censored data.

After adjusting the time and status for the stage, 322 patients were available for survival analysis and the impact of different factors on the prognosis of pancreatic cancer patients was re-evaluated. The age which was a significant factor affecting the survival of the patients before adjustment was insignificant after adjustment.

The only statistically significant factor affecting the survival of pancreatic cancer patients after adjustment was: tumor site (p-value=0.034) with head and or the uncinate process had worse prognosis other than any part other than head+ uncinate process.

Two years overall survival was compared between observed follow up time and the adjusted time for the censored data with its 95% confidence intervals. These results showed that the observed overinflated the survival estimates as compared to the adjusted analysis regarding different patients' characteristics. Based on these results, it was concluded that both analyses are unreliable. The observed analysis had too many censored cases and the adjusted analysis was based on assumptions that could be true or false. This situation necessitates the need for a better follow up system to reduce the number of censored data.

STUDY LIMITATIONS

1. Patients' sheets are designed for patients care rather than for the purpose of epidemiological studies.
2. Patients' sheets were not available especially for the year 2006.
3. Incompleteness of clinical, treatment and follow up data.

CONCLUSION

The experience of the National Cancer Institute, Cairo University revealed that pancreatic cancer affects Egyptian patients at an earlier age compared to the world literature.

Abdominal pain referred to the back is the main presentation in nearly half of the patients. Late presentation is the main problem where about two-thirds of the patients presented with unresectable and metastatic tumors.

Prognostic evaluation was hindered by the incompleteness of data in patients' files. About two-thirds of the patients diagnosed with pancreatic cancer during the study period had no available records to revise. Even within the available data files, data was not complete especially the follow up data. Accordingly, we conducted survival analysis twice; first on the available data then after adjustment for the large number of censored patients.

Before adjustment, the median overall survival was 9.1 months and 1-year and 2-year survival rates were 46%, 32.7%, respectively. The only statistically significant factor affecting survival was age; 60 years old or older patients had better prognosis. After adjustment, the survival was even worse. The median overall survival was 3.5 months and 1-year and 2-year survival rates were 15%, 6.4%, respectively. Tumor site was the only factor significantly affecting survival; lesions of the head and/or uncinate process had worse prognosis than any other part.

Comparison between survival calculated from observed follow up time and the adjusted time for censored data revealed overestimation of the survival

time in observed follow up as compared to the estimates after adjusting for the censored data. Thus, both analyses are considered unreliable.

This unfortunate situation necessitates construction of a strict follow up system to reduce the number of censored data not only in cases of pancreatic cancer, but for the whole institute including all diagnoses. This is the only way to reach valid and reliable information about different cancers which hopefully improve diagnostic and therapeutic results besides improving quality of research produced in the NCI.

RECOMMENDATIONS

1. Quality of data in patient's files at the NCI has to be improved by proper and complete documentation of patients' investigations and treatments.
2. Follow-up of cancer patients should be added to the work system at the NCI to facilitate calculating survival and a specific working group can be assigned to complete follow up data for those who are lost to follow up via telephone calls.
3. CA19.9 can be used as an independent predictor of overall survival, it is therefore, recommended to check the CA 19-9 levels at multiple time points pre-operatively, post-operatively, preadjuvant, during chemotherapy and post adjuvant therapy.
4. Development of a screening program to be applied for the high risk groups to detect the disease at an earlier manageable stage.
5. Further studies are needed to explore the possible factors that may contribute to the observed epidemiological patterns.
6. Activation of rules and legislations to decrease environmental pollution.
7. Health education for the health professionals and the public for the early symptoms and signs of the disease.

SUMMARY

This study consisted of 2 parts. The first part is a retrospective cohort study conducted by reviewing the medical records of all primary pancreatic cancer patients managed at National Cancer Institute (NCI), Cairo University (CU) between January 2006 and December 2010. The second part is a prospective cohort study in which a follow up of the patients was conducted by telephone questionnaires. Based on the automated hospital information network; lists of 902 patients were generated but only 336 medical records were available for analyses.

The distribution of the 902 patients during the different years was similar with the highest number seen in 2009 and the lowest in 2010. The mean age of the patients was 56.4 years with standard deviation 12 and ranged from 3-92 years. Male to female ratio was 1.87. The highest percent of the patients (40%) were residents of Upper and Middle Egypt governorates while 30% were from Cairo Metropolitan.

About one third of the patients were diagnosed by either pathology, cytology or endoscopy. One third by radiology, laboratory or clinical diagnosis. More than one third of the patients hadn't any investigations done.

At the time of presentation, about 1/3 (33%) of the patients were metastatic. A quarter had locally advanced (regional), only 11% of the patients had localized tumor. The stage of 8.4% and 20.9% of the patients wasn't applicable and unknown, respectively.

A comparison was conducted between the patients with available medical records and those with missing medical data. It revealed that there was a

statistically significant difference between the two groups with respect to few factors. Namely, years of diagnosis, number of children, and different methods of diagnosis. The two groups were not statistically significantly different on several. Namely patients' age, gender, governorates, marital status, pathological types of tumor and stage of the disease.

A detailed analysis was conducted on 336 patients. Only 195 patients (58%) mentioned their occupation. About 40% were engaged in routine and manual work, 9.2% and 6.2% were appointed in intermediate and high managerial and administrative occupations, respectively. Those who never worked represented 36.9% of the sample and only 8.2% were retired.

More than half of the patients (55.1%) were residents of the Cairo Metropolitan area and the Delta. Those who were from Middle and Upper Egypt governorates represented about 42.6%.

About 52% of the patients experienced abdominal pain referred to the back and 36.3% experienced jaundice. Seventy percent of the patients had the tumor in the pancreatic head and or uncinate process at the time of diagnosis. The majority of the patients (63.2%) had unresectable tumors, only 13.7% of the patients had resectable ones and 23.1% had unknown tumor stage. Sixty-two patients (18%) had metastatic tumors. More than 1/2 (60%) of them metastasized in the liver, 22.6% in lymph nodes, 9.7%, 3.2% in bone and lung, respectively.

The treatment modalities of about 83% of the patients were recorded. Surgery was done for only 9.6% of the patients. The majority of those treated surgically (92.6%) had Whipple's procedure. Ninety four patients (33.6%) received palliative therapy; 78.7% chemotherapy, 5.3%

radiotherapy and 16.0% concomitant chemoradiotherapy. More than half (56.8%) of the patients received the best supportive care only.

Survival analysis was conducted to examine the impact of the following factors: year of diagnosis, age, sex, residence, governorate, presence of pain, presence of jaundice, methods of diagnosis, tumor site, pathological types, stages and management modalities on the prognosis of pancreatic cancer patients. Data was adjusted and sensitivity analysis was conducted because of the large number of censored patients.

Without adjustment, the median overall survival of pancreatic cancer patients was 9.1 months and 1-year and 2-year survival rates were 46%, 32.7%, respectively. The only statistically significant factor affecting survival of pancreatic cancer patients was: age (p-value=0.009). Those aged 60 years or older had better prognosis.

Uncensored and censored pancreatic cancer patients were compared regarding the different factors. The two groups were not significantly different regarding all factors except age. Dead patients were significantly younger (mean=54.1) than censored patients (mean=57.8), p-value=0.005. It was concluded that the dead and censored patients were more or less similar, i.e. censoring was not related to any of the risk factors. This fact made it possible to adjust the follow up time for the censored data.

After adjustment, the median overall survival was 3.5 months and 1-year and 2-year survival rates were 15%, 6.4%, respectively. The only statistically significant factor affecting survival was tumor site (p-value=0.034). The head and or the uncinate process had worse prognosis than any other part.

The 2-years overall survival calculated from observed follow up time was compared to that calculated from the adjusted time for censored data. The observed follow up time overestimated the overall survival time as compared to the estimates of the overall survival after adjusting for the censored data regarding all patients' characteristic. It was concluded that both analyses are unreliable and this situation necessitates the need for a better follow up system to reduce the number of censored data.

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Data abstraction sheet

For collecting data on pancreatic cancer, NCI

Personal data

Name**: ----------

Hospital number: ----------

Age: ----------

Gender 1- male 2- female

Residence 1-rural 2-urban

Occupation: ----------

Marital status 0- single 1- married

2-Widowed 3- divorced 4-unknown

Number of children: ----------

Telephone number: ----------

Disease data

*Date of initial diagnosis: ------/ ----- /------

*Symptoms &signs

1-Abdominal pain 2-jaundice 3-others 4-not mentioned

If others: ----------

*Investigations

1-Pathology

Type: 1-adenocarcinoma 2- others

If others: ----------

Grade ----------

2-Cytology 3-Endoscopy 4- radiology 5-others

*If cytology was done: Type ---------- Grade----------

Tumor markers: 1- Investigated 2- Not investigated

If investigated: ----------

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*Tumor site: 1- Head 2-Body 3-Tail 4- Body and tail 4-not mentioned

*Stage 1-resectable 2-unresectable 3-unknown

If metastatic, specify site of metastasis ----------

*Status 1-dead 2-alive

If dead, date of death ------/ ----- /------

*Date of last follow up ------/ ----- /------

*Recurrence 1-yes 2-no

If yes:

1-local 2- distant 3-combined 4-unknown

Site of recurrence ----------

Management data

*Surgery 1-Whipple operation 2- Distal pancreatectomy

*Chemotherapy:

1-Neoadjuvant 2- adjuvant 3- concomitant chemoradiotherapy

*Radiotherapy: 1-Neoadjuvant 2-adjuvant

*Supportive: 1- yes 0- no

**Available only for research and data will be presented anonymously.

ملخص باللغة العربية

هذه الدراسة المرجعية تمت بمراجعة الملفات الطبية الخاصة بكل مرضى سرطان البنكرياس الأولى الذين عولجوا بالمعهد القومى للأورام (جامعة القاهرة) فى الفتره ما بين يناير ٢٠٠٦ وديسمبر ٢٠١٠، ومن خلال شبكة المعلومات الآلية الخاصة بالمعهد تم تحديد قائمه تتضمن ٩٠٢ مريضاً لم يتوافر منها للدراسة سوى ٣٣٦ حالة.

كان توزيع الحالات ال٩٠٢ على السنوات متقارباً وكانت أعلى نسبة فى عام ٢٠٠٩ بينما كانت الأقل فى عام ٢٠١٠. بلغ متوسط عمر المرضى ٥٦.٤ سنه بإنحراف معيارى قدره ١٢ سنه وتراوحت أعمارهم من ٣-٩٢ سنه. بلغت نسبة الذكور إلى الإناث ١.٨٧. كانت أعلى نسبه من المرضى (٤٠%) من سكان محافظات مصر العليا والوسطى بينما بلغ عدد المرضى الذين يقطنون القاهرة الكبرى ٣٠%. حوالى ثلث المرضى تم تشخيصهم بالباثولوجى أو السيتولوجى أو المنظار وثلث تم تشخيصهم بالأشعه أو كان تشخيصهم معملياً أو إكلينيكياً بينما شكل المرضى الذين لم تجر لهم اية فحوصات أكثر من الثلث.

حوالى ثلث المرضى (٣٣%) كانت لديهم ثانويات وقت التشخيص كما شكلت الحالات المتقدمه محلياً الربع، فقط ١١% من المرضى كانت بهم أورام محلية قابلة للاستئصال. لم تكن المرحله مطبقه أو معروفه فى ٨.٤% و٢٠.٩% من المرضى على التوالى.

تم إجراء مقارنه بين المرضى الذين تتوافر ملفاتهم واولئك الذين فقدت بياناتهم الطبيه. وقد كشفت المقارنة اختلافاً ملحوظاً إحصائياً فى توافر الملفات بين سنوات التشخيص وعدد الأطفال ومختلف طرق التشخيص. لم يكن هناك إختلاف ملحوظ إحصائياً بين المجموعتين بخصوص توافر الملفات بين الفئات العمريه ومجموعات المحافظات والأنواع الباثولوجيه المختلفه والمراحل المختلفه والنوع والحاله الإجتماعيه.

تم تحليل ٣٣٦ مريضاً تفصيلياً؛ فقط ١٩٥ مريضاً (٥٨%) كانت مهنتهم مسجلة، حوالى ٤٠% كانوا مرتبطين بعمل روتينى ويدوى، ٩.٢% و٦.٢% كانوا معينين بمهن وسطى ومهن إدارية عليا

وتنظيمية على التوالى. الذين لم يمتهنوا أعمالاً مطلقاً مثلوا ٣٦.٩% من العينه كما كان ٨.٢% بالمعاش. مثل قاطنى منطقة القاهرة الكبرى والدلتا أكثر من نصف المرضى (٥٥.١%) وشكل سكان محافظات مصر العليا والوسطى حوالى ٤٢.٦%.

حوالى ٥٢% من المرضى كانوا يعانون من ألم بالبطن مرتد للخلف و٣٦.٣% كانوا يعانون من اليرقان. عند التشخيص كان الورم فى ٧٠% من المرضى فى رأس البنكرياس مع الناتئ الشصي أو فى الناتئ الشصى، معظم المرضى (٦٣.٢%) كان بهم أورام لا يمكن إستئصالها كاملة، فقط ١٣.٧% من المرضى هم من كان لهم أورام يمكن إستئصالها كما كانت مرحلة الورم غير معروفه فى ٢٣.١%. إثنان وستون مريضاً كان لديهم أورام ذات ثانويات، أكثر من نصفها بالكبد (٦٠%) و٢٢.٦% بالغدد الليمفاوية و٩.٧% و٣.٢% بالعظام والرئة، على التوالى.

سجلت الأنماط العلاجية فى حوالى ٨٣%. أجريت الجراحه فقط فى ٩.٦% من المرضى معظمهم (٩٢.٦%) خضع لإجراء ويبل. تلقى ٩٤ مريضاً (٣٣.٦%) علاجاً تلطيفياً منهم ٧٨.٧% علاجاً كيميائياً و٥.٣% علاجاً إشعاعياً و١٦% علاج كيميائى إشعاعى متزامن. وتلقى أكثر من نصف المرضى (٥٦.٨%) علاجاً داعماً فقط.

تم عمل تحليل البقاء لفحص تأثير كل من العوامل الاتيه: سنة التشخيص والسن والنوع ومحل الإقامة والمحافظة ووجود الألم واليرقان وطرق التشخيص ومكان الورم وأنواعه الباثولوجية ومراحله وأنماط العلاج على بقاء مرضى سرطان البنكرياس. تم ضبط البيانات وأجري تحليل الحساسية نظراً لوجود عدد كبير من المرضى الذين لم تكتمل متابعتهم.

بدون ضبط، بلغ متوسط المعدل الإجمالى لمدد البقاء فى مرضى سرطان البنكرياس ٩.١ شهراً كما كانت معدلات البقاء لعام واحد ولعامين ٤٦% و٣٢.٧% على التوالى. وكان السن هو العامل الذى أثر بشكل ملحوظ إحصائياً على بقاء مرضى سرطان البنكرياس (دلاله =٠.٠٠٠٩). وقد كانت النتائج أفضل فى الفئه العمريه ٦٠ عاماً فما فوقها.

تمت مقارنة مرضى سرطان البنكرياس الذين وافتهم المنيه والذين لم تكتمل متابعتهم فيما يتعلق بالعوامل المختلفة. لم تختلف المجموعتان إختلافاً ملحوظاً فيما يتعلق بجميع العوامل باستثناء السن. كان المرضى الذين وافتهم المنيه أصغر بشكل ملحوظ (المتوسط = ٥٤.١) من الذين لم تكتمل متابعتهم (المتوسط =٥٧.٨) (دلاله = ٠.٠٠٠٥). من ذلك تم استخلاص أن المرضى المتوفون وأولئك الذين لم تكتمل متابعتهم متشابهين ولاعلاقه لعدم إكتمال المتابعه بأى من عوامل الخطورة. وبذلك أصبح ممكناً ضبط وقت المتابعه لبيانات الذين لم تكتمل متابعتهم.

بعد الضبط، بلغ متوسط المعدل الإجمالى لمدد البقاء لمرضى سرطان البنكرياس ٣.٥ شهراً كما كانت معدلات البقاء لعام واحد ولعامين ١٥% و٦.٤% على التوالى. وكان مكان الورم هو العامل الذى أثر بشكل ملحوظ إحصائياً على بقاء مرضى سرطان البنكرياس (دلاله = ٠.٠٣٤). حيث كانت النتائج أسوأ فى حالات أورام رأس البنكرياس مع الناتئ الشصي أو الناتئ الشصى مقارنة بأى جزء أخر.

بمقارنة معدلات البقاء لمدة عامين المحسوبة من وقت المتابعة الملاحظ (قبل الضبط) ووقت المتابعة بعد ضبط بيانات الذين لم تكتمل متابعتهم (بعد الضبط) تبين أن وقت المتابعة الملاحظ قيم بشكل مبالغ فيه وقت البقاء الكلى مقارنة بتقييمات البقاء الكلية بعد الضبط فيما يتعلق بمعظم خصائص المرضى، تم إستنتاج أن كلا التحليلين لا يمكن الإعتماد عليهما مما يؤكد ضرورة وجود نظام متابعه أفضل للحد من البيانات الغير مكتملة المتابعه للوصول إلى نتائج دقيقة عن خصائص ونتائج علاج أورام البنكرياس وغيره من الأورام المختلفة حتى يمكن من خلال ذلك تطوير طرق علاج المرضى والوصول إلى معدلات شفاء ونوعية حياة أفضل لكل المرضى.

وبائيات سرطان البنكرياس
في المعهد القومي للأورام - جامعة القاهرة
٢٠٠٦ - ٢٠١٠

رسالة مقدمه من

الطبيبة/ أميرة إسماعيل عبد الرحمن محمد خاطر

توطئة للحصول على درجة الماجستير
فى وبائيات ومكافحة السرطان

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