

Clinicopathologic Pattern and Outcome of Management of Pancreatic Carcinoma in Ibadan, Nigeria

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Abstract

Background

Pancreatic cancer is one of the most challenging tumor entities worldwide, characterized as a highly aggressive disease with dismal overall prognosis and an incidence rate equaling mortality rate.

Objective

In order to have an up to date data on pancreatic cancer incidence and trend in Nigeria, West- Africa; we conducted an epidemiological analytical review of the pattern, management and management outcome of pancreatic cancer in Ibadan, Nigeria.

Methods

We performed a retrospective hospital-based study in which we analyzed the records of 126 pancreatic cancer patients registered, evaluated and treated in the University College Hospital, Ibadan, a major referral tertiary Hospital in the South Western region of Nigeria, West African from January 1999 to January 2013. The data obtained include bio-data, clinical presentation, treatment and outcome which were analyzed with descriptive statistics using SPSS 22.

Results

During the period of study, 126 patients were diagnosed with pancreatic cancer; with a mean age of 60.2 years, and a male to female ratio of 1.52:1; other parameters such as a medical history smoking and alcoholism history, tumor site; histological type as well as the stage of diagnosis were also enrolled in the study. Our statistical analyses reported a very significant correlation between patients who belonged to the age group of 30-45 years and the advanced stage of diagnosis (based on TNM classification) with $P=0.02$.

Conclusion

Pancreatic cancer is increasingly diagnosed in young adults at an advanced stage in the West African sub-region. Most patients present with advanced condition only amenable to palliative measures. There are significant challenges in the area of diagnosis, screening, treatment and research. The role of public health campaign to educate the populace on the disease and early presentation cannot be overemphasized.

Introduction

Pancreatic cancer is one of the most challenging tumor entities worldwide, characterized as a highly aggressive disease with dismal overall prognosis and an incidence rate equaling mortality rate [1,2]. Less developed regions have low rates of pancreatic cancer (2.4%); it is relatively rare in Africa and Asia [3,4]. However, despite all medical research efforts; it ranks as the fourth deadliest cancer in the United States after cancers of the lung, colon, and breast. The Cancer Registry at the University College Hospital (UCH), Ibadan indicates that it trails behind primary carcinoma of the liver, carcinoma of the stomach and carcinoma of the colon among gastrointestinal tumors [5]. The incidence rate in UCH, Ibadan is 3.8% [5].

In 2013, an estimated 45,220 newly diagnosed of pancreatic cancer and 38,460 deaths were expected in the US [6]. The main reason could be the difficulty of its diagnosis since no specific cost-effective screening tests can easily and reliably find early-stage pancreatic cancer in people who have no symptoms of the disease. This means it is often not found until later stages when the cancer can no longer be removed with surgery and has spread from the pancreas to other parts of the body [7]. In fact, the Surveillance, Epidemiology, and End Results (SEER) database also shows that for every 12.2 patients diagnosed per 100,000, 10.9 will die from pancreatic cancer, despite the best efforts of researchers and clinicians to improve survival outcomes

in patients [8]. The overall 5-year survival rate is less than 5% [9-11]. The peak incidence of pancreatic carcinoma occurs in the seventh decade [12]. There are variations in incidence in different populations ranging from 2.2 new cases per 100,000 populations in India, Kuwait, and Singapore to 12.5/100,000 in Sweden [12,13]. The incidence in most developed countries is similar to that of the United States [13]. Most research on pancreatic cancer has come from developed countries. Some of these researches have indicted some environmental factors in the occurrence of this disease [14,15]. The environmental factors include cigarette smoking, alcohol consumption, high meat intake and occupational exposure to carcinogen like Dichlorodiphenyltrichloroethane (DDT) and other organochlorine pesticides. Most of these environmental factors are very prevalent in Africa especially Nigeria- the world largest black nation. Study from Egypt showed that the incidence of pancreatic cancer is higher in the area of the country where this environmental factor abound [16,17]. Numerous reports have been published from Western countries on this disease entity but only few works have been done on this area of interest in Nigeria and Africa in general [5,8-12,18-24]. The need to look at local data also becomes very imperative because of the finding of some study that African American and economic disadvantage population have higher incidence of pancreatic cancer [12-14,18-26].

This study aimed to bring to the fore, the hospital incidence, sociodemographic characteristics and management's outcome of carcinoma of pancreas at the University College Hospital, Ibadan, Nigeria. We also discuss the challenges associated with management of the disease in low- resource settings like ours that are typical of the health sector in the sub-Saharan African region.

Patients and Methods

The study was conducted at University College Hospital, Ibadan, Nigeria, from January 1999 to January 2013. The hospital is the largest Hospital in the South of the Sahara and provides services for both the rural and urban communities in the south western Nigeria. The hospital also serves as the referral tertiary hospital for an estimated population of approximately 20 million persons in the south western states of Nigeria and neighbouring West African countries.

Data Collection

This was a retrospective cohort study of all patients managed for pancreatic cancer in the surgical wards of the University College Hospital (UCH), Ibadan, Nigeria between January 1999 and January 2013. The admission and discharge diagnosis and procedure codes as well as the Cancer Registry database were obtained from the Central Record of the hospital. Current procedural terminology (CPT) and International Classification of Diseases Ten Revision (ICD-10) codes for "Triple bypass", "pancreaticoduodenectomy" and "pancreatic cancer" were used to identify patients with proven or suspected pancreas neoplasm undergoing surgery. Manual review of patient records was performed to obtain relevant data points. The data collected include the sociodemographics, laboratory parameters and the treatment modalities, as well as the outcome of management.

The diagnosis of pancreatic cancer was made using the combination of clinical parameters, upper gastrointestinal endoscopy and radiological findings. Clinical parameters used included jaundice, upper abdominal mass, upper abdominal pain that radiate to the back, weight loss and palpable gall bladder. Radiological parameters included ultrasound and/or Computerized Tomography (CT) scan showing pancreatic mass. Upper gastrointestinal endoscopy was done for most of the patients to rule out the possibility of gastric cancer. Endoscopic retrograde cholangiopancreatography was not done for any of the patients because the facility was not available. All the patients with conflicting findings which could not be substantiated at surgery were excluded from the study. Histopathological finding further corroborated the diagnoses for patients that had surgery or on postmortem examination. Sixteen (12.7%) patients do not have histopathology result.

All the data obtained were coded, edited appropriately and entered into personal computer. Analysis of the data was done using Statistical Packaging for Social Sciences (SPSS; IBM Corporation; Chicago, IL, USA. August 2011) version 22.0. Simple descriptive statistics were used. Median and frequencies were calculated based on the numerous data points. The *P*-values were provided to indicate statistical significance. *P*-value less than 0.05 was regarded as significant. Chi-square tests were used to compare categorical variables such as sex. Fisher exact test was used where applicable. Student *t* test was used to compare mean age between the groups.

Results

The study population was one hundred twenty-six patients diagnosed with cancer of the pancreas but only 82 patients had histological proof of pancreatic cancer. This account for 3.1% of all malignancies seen and 358/100000 total admissions during the study period. The median age is 60.2years with male to female ratio of 1.52.

Based on Table - 1, the most common age group affected with pancreatic cancer is age group 51-60. There were 76 (60%) male and 50(40%) female with male to female ratio been 1.52:1. Majority of the patients were artisans (39.8%) and farmers (26.4%). Other patients were either traders or professionals.

Table 1: *Patients Medical features*

Characteristics	No of Cases	Percentage %
Sex (N= 126)		
Male	76	60
Female	50	40
Sex ratio		1.52
Age(Years)		
< 20	1	0.8
21 - 30	12	9.2
31 - 40	30	24
41 - 50	18	14

51 - 60	25	19.8
61 - 70	31	25
>70	9	7.2
Alcohol	31	24.3
Smokers	38	30.2
Symptoms		
Jaundice	118	94
Abdominal pain	120	95
Right Hypochondrial pain	113	90
Nausea & Vomiting	111	88
Weight loss	107	85
Dark Urine	88	70
Pruritus	82	65
Tumor Site		
Head of the Pancreas	113	90
Body of the Pancreas	8	6.2
Tail of the Pancreas	5	3.8

Duration of symptoms ranged from 6 weeks to 125 weeks with a median of 25 weeks. None of our patients have family history of pancreatic cancer. Only twenty five (20%) have previous history of diabetic mellitus (DM) before the onset of the symptoms. The diagnosis of DM was made within one year prior to the commencement of the symptoms in all the 25 patients. Twelve and fifteen patients had significant history of cigarette smoking and alcohol intake respectively. On investigation, 94% of the patients had elevation of alkaline phosphatase, 40% had elevated Aspartate transaminase, 96% had elevated bilirubin and 70% had packed cell volume of less than 28 at presentation.

Only 12 (11%) patients has tumor located in a specified anatomical sub site: Ten in head of pancreas and two in tail of the pancreas. Other patients had extensive tumor involving the head and body of the pancreas. There were liver metastases in 32 (29.1%) patients at presentation.

98 (78%) patients had surgery. Seventy-one (56%) patients had triple bypass and twenty-seven (22%) patients had double bypass procedure. Two patients with localized tumor of the head of pancreas had pancreaticoduodenectomy. The two patients with tumor at the pancreatic tail had resection of the tumor and splenectomy. Eighty-six (88%) of the operated patients had locally advanced pancreatic mass. These patients had triple bypass to relieve the obstructive jaundice. Ten patients had biopsy alone of the pancreatic mass or the lymph node because of the widespread metastasis to the bowel, liver and other organ in the peritoneal cavity. Twenty-eight patients had adjuvant chemotherapy. Agents used include 5-fluorouracil and Adramycin.

The two patients who had pancreaticoduodenectomy was lost to follow-up after a year. No recurrence was recorded for the patient with tumor at the tail of pancreas after 5 years of follow up. Median survival for patients that had triple bypass was 8 months. This was statistically significant ($p=0.02$). Within three months of presentation, 42(33.3%) patients with pancreatic cancer died. As shown in Table - 2, the factors that were found to be significant in patients that died within three month of presentation include elevated transaminases, low serum protein and bicarbonate. Table 3 shows the various complications from bypass surgery. As shown also in Table 3, the most common complication of triple bypass is bile leak which was seen in 2 patients.

Table 2: Factors Affecting the Outcome of Managements of Patients with Pancreatic Cancer

Factors	Degree of Freedom	P- Value	95% Confident Interval
Age	94	0.245	3.122 - 6.880
Sex	1	0.045	
Duration of Symptoms before presentation	94	0.624	-12.431 - 5.765
Serum Bilirubin	94	0.442	-33.854 - 78.623
ALT	94	0.004	12.254 - 66.732
AST	93	0.0002	11.684 - 49.271
Alkaline Phosphate	94	0.932	-354.821- 197.472
Total Serum Protein	94	0.054	-11.641- -782
Serum Potassium	94	0.851	-3446 - -2378
Serum Sodium	94	0.444	-6.576 - -4123
Serum Creatinine	94	0.234	-22.678 - 54.544
Serum Bicarbonate	94	0.022	-5.777 - -3240
PT	94	0.044	-2.789 - 1.233
INR	32	0.232	

Table 3: Complications Associated with Methods of Triple Bypass

Complications	Braun Method	Roux -en - Y Method
Bile leak	2	1
Recurrent vomiting	3	0
Prolonged ileus	3	1
Wound infection	2	1
Total	10	3

Discussion

All around the globe significant progress are being made to better understand the molecular biology of pancreatic cancer which has not significantly impacted on the outcome of management. This is because such concerted past efforts, on the conventional treatment approaches, such as surgery, radiation, chemotherapy, or combinations have yielded very little results. Pancreatic tumors remain deadly and rarely curable [25,27-29]. In this study, we found that the hospital incidence of pancreatic cancer is 358 per 100,000 hospital admission which accounts for 3.1% of all cancer cases seen in our centre. For several decades, the incidence of pancreatic cancer has been consistently higher in blacks than in whites in the United States [27,28,30].

The present survey is one of the very few surveys that studied the profile of pancreatic cancer in West Africa in general and Nigeria in particular.

With a sex-ratio of 1.52 our investigation confirmed once more that men are more likely to develop pancreatic cancer than women. These results matched with many other previous investigations as those of Schiffman *et al* [18,19,31].

Our results showed that 28% of our patients were cigarette smokers, and 22% were alcoholics; which could represent a risk factor for developing a pancreatic cancer since several published reports showed that smokers had about a 2-fold increased risk, compared to non-smokers [32,33].

We noticed also that most of our patients complained of jaundice; right hypochondrial pain and abdominal pain; which proves that pancreatic cancer is a silent disease, as reported in many other findings which stated that pancreatic cancer symptoms do not manifest early and initial symptoms are often nonspecific [18,19,34]. Concerning tumors' location, most of them were located in the head of the pancreas (90%), followed respectively by cancer of the neck and the tail of the pancreas which represented a tiny minority. The study of Kalser *et al* demonstrated as well that more than two thirds of pancreatic cancers occur in the head of the pancreas [18,35].

Diabetes mellitus was associated and pointed in several investigations as possible risk factor for pancreatic cancer [18,33]; in concordance with our findings since 25% of our studied population presented with type 1 and type 2 of diabetes.

Our survey also demonstrated an increasing frequency of pancreatic cancer with the advanced age of patients since most of them were aged between 60 and 80 years old, these results agree with those of Shibata's *et al* who concluded that this could be due to the dietary habits of the patients [18,19,36].

In the other hand; the current investigation confirmed indeed the rarity of pancreatic cancer in young adults; since only 8% of our population suffered from it, which agrees with the results of Perez *et al* who found that the incidence of identified pancreatic carcinomas in patients under the age of 30 was only about 0.46/million [37]. Same conclusion for Lüttges *et al* who evaluated the incidence of pancreatic ductal adenocarcinomas in patients aged of 40 years old and was approximately equal to 0.3%, and the incidence in patients aged of 20 years was only about 0.1% [38].

However, despite the low rate of our patients (8%) belonging to that young age group; 35% of them were diagnosed at M1 stage which represented the majority.

Concordant with our results and those of Brand *et al* who found that pancreatic cancer is increasingly diagnosed in the younger at an advanced stage [39]. Berry *et al* stated that nearly 50% of patients aged between 16 and 54 with pancreatic cancer are more likely than those who are older to be diagnosed at a stage when the disease is incurable, because of poor awareness, misdiagnosis and care delays [18,19,40].

Some authors confirm that pancreatic cancer is frequently diagnosed at an advanced stage, possibly because of the tumor biology showing an aggressive behaviour and symptoms often being non-specific mainly in the young [41]; Gulliford *et al* reported as well that patients with some less common cancers such as pancreatic cancer were more likely to require three visits or more to their primary care physician before they were referred to a specialist [42]. What we have to emphasize as well is the status of Nigeria as a developing country, thus it's undeniable that inadequacy of healthcare facilities, high prices of drugs, lack of cancer diagnostic and therapeutic kits, insufficient medical check-ups as well as the low socioeconomic level of Nigerian citizen are all major factors which may have a direct impact on that fatal disease survival chances.

Since most of our patients had pancreatic adenocarcinomas (Table 2) presented in late stage at the time of diagnosis; their prognosis was very poor; with a 1-year survival rate of 20% and a 5-year survival rate of less than 5%: similar to the survey of Kuvshinoff *et al* [43]. The only hope of long-term survival is if curative resection can be undertaken; however, since pancreatic cancer patients seldom exhibit disease-specific symptoms until late in the course of the disease, very few patients (<15-20%) have resectable disease by the time the diagnosis is made [18,19, 44,45]. While complete surgical resection may lead to long-term survival in approximately 25% of patients, only 15% are actually resectable [43]. It is therefore essential to distinguish all kinds of tumor from other pancreatic neoplasms particularly adenocarcinoma for which the prognosis is extremely poor as stated above [46]. Surgery for pancreatic cancer is probably the most demanding and risky operative procedure in abdominal surgery [47]. Nevertheless the huge lack of diagnostic facilities and cancer research centers in Nigeria and other developing countries have a major negative impact on the precision and quality of the diagnosis.

Seelig *et al* reported that in a young patient with advanced disease, resection may give a weak but valuable increased survival. In fact, metastatic pancreatic cancer could become overt when the point of no return has already been reached as it could be the case in the presence of positive intraaortic lymph nodes, or metastatic cancer will be detected during operation despite negative imaging results preoperatively [48]. Picozzi *et al* affirmed that despite R0 resection, long-term survival does not exceed 25% even in the most experienced pancreatic centres may prove that carcinoma of the pancreas is a systemic disease [49]. At presentation, most of our patients had advanced disease. Resection rate is about 3% which was very low compared with data from developed country where resection rate of as high as 15-20% has been quoted [14]. Stage of the tumor has been found to be an important predictor of resectability and death in patients with pancreatic tumor [50]. This is because the location of pancreas, early symptoms of pancreatic cancer are so vague and are usually ignored by most patient. Presentation with advanced stage of the disease may also be due to poor health seeking behavior of our patients [18,19,51,52]. Obviously, a high index of suspicion

on the part of health workers is essential to early detection of pancreatic cancer. Another reason for late presentation in our patients may be due to aggressive growth behaviour of the pancreatic cancer which leads to early dissemination of the tumor [14,53]. Various efforts had been made on how to diagnose pancreatic cancer early with little success [54,55]. Presently, no population screening modality is available for pancreatic cancer. Moreover, targeted screening is also very difficult for pancreatic cancer because primary causal factors for this tumor are poorly understood. While effort is being made along this line, it is worthy to note that endoscopic ultrasonography has been shown to be a reliable way to detect tumor invasion of visceral vessels and thus predict unresectability and it also has the potential to be used to diagnose pancreatic cancer early [18,19,55,56].

In Solanke *et al* [20] series, pancreatoduodenectomy was performed on only three out of his 47 patients; two with carcinoma of head of pancreas and one with disease of the ampulla of Vater. One died after two months, another after five months and the third with ampullary carcinoma was alive and well after ten months. Palliative procedures were carried out on 14 patients and laparotomy alone was performed on eleven patients. The one-year survival rate of 2% was reported by Solanke *et al* which was similar to this study [20]. Only six of the 36 patients of Ajao *et al* [21] had exploratory laparotomy; none had resectable disease. In Lagos, ten of the 20 patients encountered by Olumide *et al* [22] had laparotomy; none was resectable and seven had palliative operations consisting of bypass procedures.

Further improvement of survival can only be achieved by adjuvant treatment [49].

The need for adjuvant therapy in pancreatic cancer cannot be over emphasized. Even with complete surgical resection, most patients will die of recurrent disease because of the multifocality of the disease and micrometastasis [57,58]. Several studies had shown that outcome of patients are improved when placed on adjuvant chemotherapy, radiotherapy or combination of [14,18,19,58,59]. Pancreatic cancer is moderately sensitive to few agents like gemcitabine, capecitabine, cisplatin, bevacizumab and cetuximab [15,18,19,60]. Most of these agents are more toxic, rarely available in our environment or very expensive. One important question that is yet to find an answer is the reason why pancreatic cancer is resistance to most commonly available chemotherapy. Radiotherapy facilities are extremely congested; hence, the facilities are made available to those that will benefit most from the facilities and the privileged few. These made management of patients with pancreatic cancer very difficult.

Our survey showed clearly that young adults who suffered from pancreatic cancer in general; and cancer of the head of pancreas in particular; are unfortunately diagnosed at a very late stage in South Western Nigeria; when the likelihood of recovery is poor and patients have no other choice than to accept their ongoing symptoms

Furthermore, we found that patients with elevated transaminases, low serum sodium and reduced total protein indicate that patients had very advanced disease with a much reduced life expectancy. These may be due to involvement of the liver in this condition. These simple parameters can help predict a poorer outcome at presentation. Further study will be needed to substantiate this finding. For a long time, pancreatic cancer has been regarded as terminal disease ("captain of death"); hence little attention is given to the research on

the disease. Report on pancreatic cancer is extremely scarce in Nigeria or Africa. There is a great need therefore for concerted effort to characterize pancreatic cancer in Nigeria.

Conclusion

The incidence of pancreatic cancer is relatively low in our centre. Most patients present with advanced condition only amenable to palliative measures. Young adult patients are often seen to be healthier than older ones. Lack of awareness, socio-cultural habits and carelessness could be fatal for patients who suffer from pancreatic cancer; therefore awareness should be increased among healthcare professionals and mainly among third world countries' citizen. The earlier the diagnosis is made, the better are chances for the patient's survival. There are still significant challenges in the area of diagnosis, screening, treatment and research. The role of public health campaign to educate the populace on the disease and early presentation cannot be overemphasized.

Declarations

Ethics Approval and Consent to Participate

Not Applicable/ Waived

Consent for Publication

Not Applicable/ Waived -This is a retrospective study therefore there is no direct human participant's involvement.

Availability of Data and Material

Confirmed by the Author

Funding

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Competing Interest

There is no submission of any financial and non-financial conflict of interest.

Disclosures

The authors have no disclosure.

Authors' Contributions

The Authors conceived of the study and participated in its design and coordination and helped to draft the manuscript; Also read and approved the final manuscript.

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None

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