

## Challenges of Pancreatic Cancer Management in a Resource Scarce Setting

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**Backgrounds:** Of all forms of gastrointestinal malignancy, adenocarcinoma of the pancreas is associated with the worst survival. Management of pancreatic cancer is associated with some challenges. This study is aimed at determining the hospital incidence, sociodemographic characteristics, managements and management's outcome of carcinoma of pancreas at our hospital. We also discuss the management challenges encountered with these patients.

**Material and methods:** We reviewed 96 pancreatic cancer patients seen at Awolowo University Teaching Hospital Complex, Ile –Ife, Nigeria, from July 1989 to July 2007.

**Results:** There were ninety six patients diagnosed with cancer of the pancreas but only 80 patients had histological proof of pancreatic cancer. This account for 2.1% of all malignancies seen and 238/100000 total admissions during the study period. The median age is 55.0. There were 62 (64.6%) male and 34 (35.4%) female with male to female ratio been 2:1. Duration of symptoms in the patients ranges from 4 weeks to 109 weeks. Only three (3.1%) patients has tumor located in a particular anatomical sub site: two head of pancreas and one tail of the pancreas. Other patients had extensive tumor involving the head and body of the pancreas. Two patients had pancreaticoduodenectomy, one had resection of the tumor at the tail of pancreas and 45 patients had triple bypass. Patients with low serum albumin and serum sodium and elevated transaminases at presentation, had poorer prognosis than other patients.

**Conclusion:** Pancreatic cancer is not uncommon in our center with male preponderance. Most patients present with advanced condition only amenable to palliative measures. There are significant challenges in the area of diagnosis, screening, treatment and research.

### Introduction

Pancreatic cancer is one of the most lethal human cancers and continues to be a major unsolved health problem at the start of the 21st century. Similarly, of all forms of gastrointestinal malignancy, adenocarcinoma of the pancreas is associated with the worst survival<sup>1</sup>. Most patients die within a year after establishment of the diagnosis<sup>2</sup>. It is the fourth leading cause of death in both men and women in United State of America and it has been estimated that in 2007 about 37,170 people in the United States will be diagnosed with pancreatic cancer and about 33,370 will die of the disease<sup>3-4</sup>.

The peak incidence of pancreatic carcinoma occurs in the seventh decade with a slight male to female predominance<sup>5</sup>. There are variations in incidence in different populations ranging from 2.2 new cases per 100,000 population in India, Kuwait, and Singapore to 12.5/100,000 in Sweden<sup>5,6</sup>. The incidence in most developed countries is similar to that of the United States<sup>6</sup>.

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<sup>7-8</sup>. The environmental factors include cigarette smoking, alcohol consumption, high meat intake and occupational exposure to carcinogen like 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<sup>9-10</sup>. However, few works have been done on this area of interest in Nigeria. 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<sup>3-7</sup>.

This retrospective study was aimed at highlighting the hospital incidence, sociodemographic characteristics, managements and management's outcome of carcinoma of pancreas at Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Nigeria. We also discuss the challenges associated with management of the disease in resource-scarce settings that are typical of the health sector in the sub-Saharan African region.

### Patients and Methods

The study was conducted at Obafemi Awolowo University Teaching Hospital Complex, Ile –Ife, Nigeria, from July 1989 to June 2007. The hospital services the rural and semi-urban agrarian communities in the southwestern Nigeria. The hospital serves as the referral tertiary hospital for an estimated population of approximately 7.7 million persons in the southwestern states of Nigeria.

#### Data Collection.

This was a retrospective cohort study. Admission and discharge diagnosis and procedure codes as well as the cancer registry database were obtained from the Corporate Data Store 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 Institutional Ethical Committee approved the study. The data collected include the sociodemographic, 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 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 (16.7%) 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) version 11.0. 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 were 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

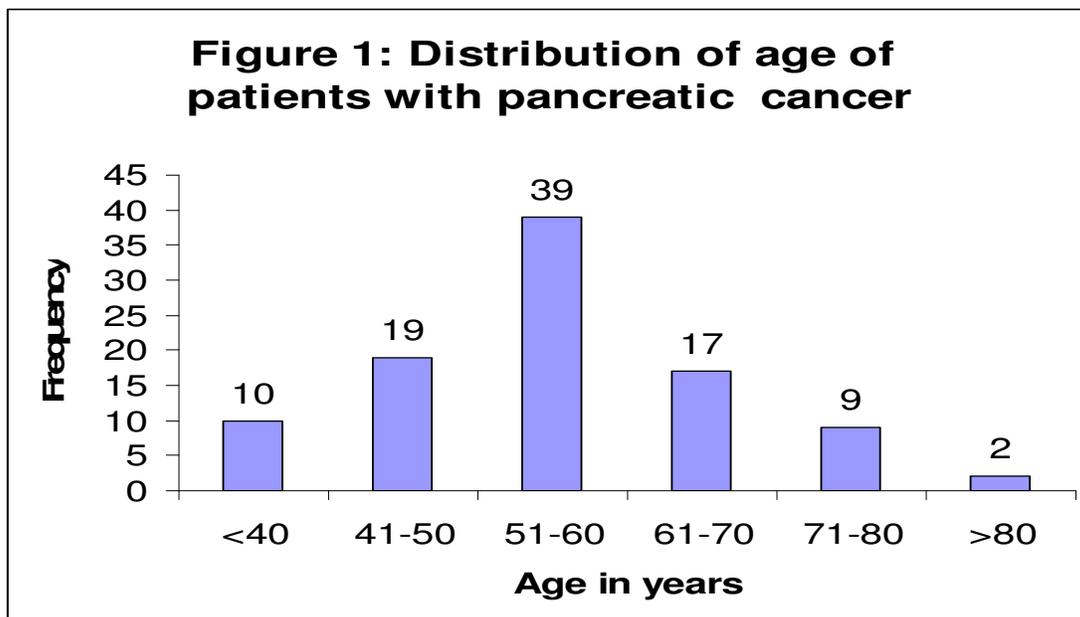
There were ninety six patients diagnosed with cancer of the pancreas but only 80 patients had histological proof of pancreatic cancer. This account for 2.1% of all malignancies seen and 238/100000 total admissions during the study period. The age of the patients ranges from 32 to 90 years. The median of the age is 55.0. As shown in figure 1, the most common age group affected with pancreatic cancer is age group 51-60. There were 62 (64.6%) male and 34 (35.4%) female with male to female ratio been 2:1. Majority of the patients were farmers (39.8%) and traders (26.4%). Other patients were either artisan or work in Government establishment.

Duration of symptoms ranged from 4 weeks to 109 weeks with a median of 8 weeks. None of our patients have family history of pancreatic cancer. Only eleven (11.5%) 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 8 of the 11 patients. Seven and ten patients had significant history of cigarette smoking and alcohol intake respectively. On investigation, 98% of the patients had elevation of alkaline phosphatase, 20% had elevated Aspartate transaminase, 98% had elevated bilirubin and 62.5% had packed cell volume of less than 25 at presentation.

Only 3 (3.1%) patients has tumor located in a specified anatomical sub site: 2 in head of pancreas and one in tail of the pancreas. Other patients had extensive tumor involving the head and body of the pancreas. There were liver metastases in 20(20.8%) patients at presentation.

**Table 1.** Factors Affecting the Outcome of Managements of Patients with Pancreatic Cancer.

| Factors                                  | Degree of Freedom | P-value | 95% Confident Interval |
|--|-------------------|---------|------------------------|
| Age                                      | 94                | 0.354   | 2.535 – 7.012          |
| Sex                                      | 1                 | 0.036   |                        |
| Duration of symptoms before presentation | 94                | 0.427   | -11.439 – 4.886        |
| Serum bilirubin                          | 94                | 0.292   | -28.488 – 93.678       |
| SGOT                                     | 94                | 0.001   | 13.285 – 51.161        |
| SGPT                                     | 93                | 0.00001 | 9.370 – 29.352         |
| Alkaline phosphatase                     | 94                | 0.798   | - 354.731- 272.684     |
| Total serum protein                      | 94                | 0.031   | - 10.231 - -493        |
| Serum Potassium                          | 94                | 0.782   | - 2834 – 2140          |
| Serum Sodium                             | 94                | 0.024   | 5.4893 - -3977         |
| Serum cretinine                          | 94                | 0.402   | -18.6939 – 46.1860     |
| Serum bicarbonate                        | 94                | 0.014   | - 3.4820 - -4085       |
| PT                                       | 94                | 0.078   | - 2.981 – 52.8287      |
| INR                                      | 28                | 0.193   | - 3566 – 1.852         |



**Table 2.** Complication Associated with Methods of Triple Bypass

| Complications      | Braun Method | Roux-en-Y method |
|--------------------|--------------|------------------|
| Bile leak          | 3            | 1                |
| Recurrent vomiting | 2            | 0                |
| Prolonged ileus    | 2            | 1                |
| Wound infection    | 2            | 0                |
| <b>Total</b>       | <b>9</b>     | <b>2</b>         |

Fifty five (57.3%) patients had surgery. Two patients with localized tumor of the head had pancreaticoduodenectomy. A patient with tumor at the pancreatic tail had resection of the tumor and splenectomy. Forty-five (81.8%) of the operated patients had locally advanced pancreatic mass. These patients had triple bypass to relieve the obstructive jaundice. Eleven of the 45 triple bypasses were done with isolated bowel segment (Roux-en-Y) while in the others bowel loops were used (Braun). Seven 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. Fourteen patients had adjuvant chemotherapy. Agents used include 5-fluorouracil and Adramycin.

One of the patients that had pancreaticoduodenectomy presented three month later with metastasis to the spine. He died five month after surgery. The other patient 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 using a bowel loop was 3 months, while the median survival for patients that had triple bypass using an isolated bowel segment was 5 months. This was statistically significant ( $p=0.02$ ). One of the patients that had pancreaticoduodenectomy had bile leak which was managed conservatively. Within one month of presentation, 46 (47.9%) patients with pancreatic cancer died. As shown in table 1, the factors that were found to be significant in patients that died within one month of presentation include elevated transaminases, low sodium, serum protein and bicarbonate. Table 2 shows the various complications from bypass surgery. The most common complication of triple bypass is bile leak which was seen in 4 patients.

### Discussion

Despite past efforts, conventional treatment approaches, such as surgery, radiation, chemotherapy, or combinations of these, have had little impact on the course of pancreatic cancer. The tumor is rarely curable<sup>2,3</sup>. In this study, we found that the hospital incidence of pancreatic cancer is 238 per 100, 000 hospital admission. It also accounts for 2.1% of 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<sup>8,11-12</sup>. From 1995 to 1999, the average annual age-adjusted incidence rates were 16.6/100,000 for blacks and 10.7/100,000 for whites<sup>12</sup>. The incidence of pancreatic cancer is higher in black patients owing to several factors attributable to genetic mutations, socioeconomic status, smoking, long-term diabetes, and alcohol use<sup>11-12</sup>. However in our series, aside from the fact that most of our patients belong to low socioeconomic class, few of our patients have history suggestive of these identified risk factors. Majority of our patients are farmers. Occupational exposure to carcinogen may play a major role in the occurrence of pancreatic cancer in our environment as stated in previous work from Africa<sup>9-10</sup>. Further studies will be necessary to identify the particular carcinogen that our patients are exposed to. One interesting finding of this study is that the peak age of occurrence of pancreatic cancer is 6<sup>th</sup> decade. Generally, cancers tend to occur in earlier age in the country; and pancreatic cancer is not an exception<sup>13</sup>. Our study concurred with finding in other studies that showed male preponderance in pancreatic cancer<sup>6,13-14</sup>.

Pancreatic cancer can mimic other benign conditions like chronic pancreatitis and biliary tree stone. Several modalities are used in developed centres before primary therapy is initiated. These modalities include endoscopic retrograde cholangiopancreatography, laparoscopy, endoscopic ultrasound, helical computerized tomography (CT), Magnetic resonance imaging and the use of tumor markers<sup>7,15-16</sup>. Most of these facilities are not readily available in most centers in the developing countries. Though CT scan is available, the cost of the procedure is prohibitive to most of our patients who are poor. This suggests an urgent need for formal social support structure in our environment. Most developing centers like ours depend on clinical presentations and few radiological investigations while confirmation of the diagnosis is done at laparotomy or at autopsy. Previous study has shown that pancreatic cancer is the most common cause of obstructive jaundice in our environment<sup>13</sup>. Hence, all patients with features of obstructive jaundice are painstakingly screened for pancreatic cancer and subsequently, offered surgery after stabilization. The need to undertake definitive treatment without prior tissue diagnosis had been substantiated by previous study<sup>16-17</sup>.

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<sup>7</sup>. Stage of the tumor has been found to be an important predictor of resectability and death in patients with pancreatic tumor<sup>18</sup>. Because of 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 behaviour of our patients<sup>19-20</sup>. 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 lead to early dissemination of the tumor<sup>7,21</sup>. Various efforts had been made on how to diagnose pancreatic cancer early with little success<sup>16,22</sup>. 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 been 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<sup>22-23</sup>.

Most of our patients had diversion of bile and the gastric contents to ameliorate the jaundice and the possible gastric outlet obstruction. We found that patients that had triple bypass using Roux -en- Y live longer than when a loop of bowel was used for the bypass. A randomized control trial will be needed to substantiate this finding. However, a diversion using Roux en Y is said to be associated with less complication<sup>21</sup>. There are debates about the rational for triple bypass since the procedure is essentially palliative<sup>21-22</sup>. The rate of gastric outlet obstruction is said to be about 20% and the rate may be on the increase the longer the patient live<sup>3,23</sup>. Most of our patients are poor and may not be able to afford a repeat surgery hence the need to do a more encompassing surgery like triple bypass when indicated. Endoscopy bypass was not done for any of our patient because the facility was not available. These may not be a disadvantage because it has been found that surgical bypass are more durable than endoscopic stents which is prone to recurrent obstruction and cholangitis<sup>24</sup>. It worth noting however, that the minimally invasive approach is associated with considerable less initial morbidity and mortality than surgical bypass<sup>24-26</sup>.

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<sup>27-29</sup>. Several studies had shown that outcome of patients are improved when placed on adjuvant chemotherapy, radiotherapy or combination of both<sup>7,28-29</sup>. Pancreatic cancer is moderately sensitive to few agents like gemcitabine, capecitabine, cisplatin, bevacizumab and cetuximab<sup>8,30</sup>. 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.

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 long time, pancreatic cancer has been regarded as terminal disease; hence little attention is given to the research on the disease. Report on pancreatic cancer is extremely scarce in Nigeria or Africa. If it is true that blacks have higher risk to develop pancreatic cancer, concerted effort must be put to characterize pancreatic cancer in Nigeria, the largest black nation in the world.

### Conclusion

- Pancreatic cancer is not uncommon in our center with a male preponderance.
- Most patients present with advanced condition only amenable to palliative measures.
- There are significant challenges in the area of diagnosis, screening, treatment and research.

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