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Welcome letter from Editor-in-Chief



Welcome to the Int J Cancer and Biomedical Research (IJCBR)!

It is with great pleasure that I write this editorial to welcome you to the IJCBR. This journal provides a platform for publication of original and reviews research articles, short communications, letter to editor, thesis abstract, conference report, and case studies. These types of publication are directed at the interface of the fields of cancer and biomedical research.

The IJCBR relies on a distinguished expert of the Advisory and Editorial Board Members from the top international league covering in depth the related topics. They timely review all manuscripts and maintain highest standards of quality and scientific methodology and ethical concepts. Meanwhile, we take all possible means to keep the time of the publication process as short as possible.

I take this chance to welcome your contributions to the IJCBR and have every expectation that it will soon become one of the most respected journals in both the fields of cancer and biomedical research.

A handwritten signature in blue ink that reads "Mohamed L. Salem". The signature is fluid and cursive.

Mohamed L. Salem,

Editor in Chief

Management of locally advanced periampullary tumor: Multicenter study

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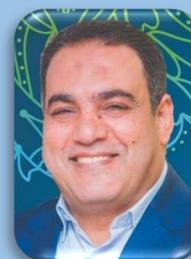
ABSTRACT

Background: pancreas may be either benign or malignant tumors. Pancreatic cancer(PC) is one of the most lethal solid tumors which ranking as the fourth cause of death related cancers in the United States. **Aim of work:** Is to establish the results of the treatment of locally advanced pancreatic cancer. **Patients and Methods:** 136 patients retrospectively evaluated with periampullary carcinoma where 40 patients diagnosed as locally advanced periampullary carcinoma, from January 2010 to January 2018 in multicenter. **Results:** Patients diagnosed as pancreatic head carcinoma in 20/40 and periampullary carcinoma in 20/40 of patients, all patients were diagnosed as locally advanced pancreatic cancer by radiological imaging, 28/40 (70%) was males and 12/40(30%) females with male: female ratio 2.3:1, the age of patients at diagnosis was 39-62 years with median age 51 years, with all patients evaluated and followed up for 24 months with Multislice CT, PET-CT and markers with some of them underwent neoadjuvant treatment for down staging then surgery done for all 25/40 cases with Whipple's operation without VR in 17/25 and VR done in 8/25 cases where 6/40 cases died during chemotherapy and 9/40 unfit for surgery due to disseminated disease and complications of chemotherapy. **Conclusion:** Patients diagnosed as locally advanced or metastatic with pancreatic cancer and the need for MDT to decide for treatment with the use of different modes of treatment to obtain good results.

Keywords: chemotherapy; locally advanced pancreatic carcinoma; pancreatic carcinoma; vascular resection.

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INTRODUCTION

Periampullary adenocarcinoma including adenocarcinoma of the pancreatic head, the distal common bile duct (CBD), the second portion of the duodenum, and the ampulla of Vater, and accounts for approximately 0.2% of all gastrointestinal tract tumors, (Yeo et al., 1998) Pancreatic cancer (PC) is one of the most lethal solid tumors which ranking as the fourth cause of death related cancers in the United States with the 5years survival rates about 5% (Sahmoun et al., 2003; Jemal et al., 2006). The majority of pancreatic adenocarcinoma

presented in an advanced stage or metastatic without possibilities of cure, but in last year's, there is a hope to improve the results and prognosis for few months with the use of new trends in chemotherapy regimens with the prognosis remain dismal, pancreatic adenocarcinoma affecting the head in 60% of cases, body in 5% of cases and affecting the tail of pancreas in 5% and 20% are diffuse within the pancreas, (Zamboni et al., 2000). Tumors located in the head are smaller(2.5-3cm) as compared to those located in the body and tail of the pancreas(5-7cm) that are also more metastatic with an earlier presentation due to

close relationships with the bile ducts. The prognosis is very poor with 1year survival rate 20% while the 5years survival rate is 5% and the complete resection of the tumor may lead to good survival of approximately 25%, while there is about 15% presented as unresectable from the start, so the main aim of pre-operative imaging evaluation is to evaluate the cases resectable to avoid unnecessary exploration and risk for the patients. (Torre et al., 2012).

Patients with borderline resectable PDAC were primarily described by (Katz et al., 2008), as those with the localized disease with tumor or patient characteristics precluding immediate surgery. The outcome in periampullary and pancreatic cancer resectable tumors is an area of intense scrutiny. Neoadjuvant treatment, also in patients with resectable tumors, is widely accepted in the United States (Malafa, 2015; Roland et al., 2015), whereas upfront surgery is still considered the standard of care in influential European centers (Roland et al., 2015). Clinical and preclinical data support the concept that PDAC metastases appear early in the pathogenesis, even before the tumor can be identified (Werner et al., 2013), favoring neoadjuvant chemotherapy. A meta-analysis focusing on outcome in patients with resectable and unresectable tumors (Yachida et al., 2010), found that resection frequencies and survival after neoadjuvant therapy in resectable patients were similar to patients undergoing upfront surgery and adjuvant chemotherapy. In patients with unresectable tumors, approximately one third became resectable after restaging. In another meta-analysis of neoadjuvant chemotherapy in patients with borderline resectable PDAC, primary outcome measures were proportion of complete or partial response, stable or progressive disease as well as percentages of exploration and resection, and these results were also similar (Gillen et al., 2010; Tang et al., 2016). This study highlights the management of locally advanced periampullary tumor and the result of each line of treatment (resection versus chemotherapy or both).

PATIENTS AND METHODS

From January 2010 to January 2018, 136 patients, with periampullary tumors were

retrospectively evaluated in Hepato-Pancreatico-Biliary Surgery and Liver Transplantation Department, National Liver Institute, Menoufia University and surgical oncology department, Tanta cancer center, 96 patients (group A) were operated upon for PD, by a team of surgeons specialized in hepatopancreatic-biliary (HPB) surgery. According to CT criteria 40 (29.4%) patients (group B) were locally advanced periampullary tumor including (mass more than 5cm with vascular invasion or abutting more than 180 degrees to PV, SMV HA, SMA, or locally metastases liver) with no resectability at this staging of the disease. And our plan for these patients was downstaging of the tumor by using chemotherapy or radiotherapy or both for six months then reevaluating for surgery.

Group B data on preoperative, intraoperative and postoperative care were collected and maintained on a secure database. Preoperative parameters included demographics, clinical presentation, preoperative risk factors, laboratory testing, and preoperative imaging modalities such as ultrasound, multi-detector abdominal CT with three-dimensional reconstructions and magnetic resonance cholangiopancreatography is used to evaluate the periampullary tumors and their relation to vascular structures. CT accurately diagnoses mesenteric vein involvement, aiding in operative planning, endoscopic retrograde cholangiopancreatography (ERCP) with or without endoscopic stent drainage and endoscopic ultrasound Intraoperative details such as operative time, total blood loss, transfusion needs and the type of surgical reconstruction were recorded. Postoperative events, complications, mortality, pathological data were also collected.

According to the AHPBA/SSAT/SSO/NCCN definition, borderline resectable PDAC includes tumors (Figure1) that display; (1) venous involvement of the SMV/PV demonstrating tumor abutment, encasement, or short segment venous occlusion, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; (2) gastroduodenal artery encasement up to the hepatic artery and short segment encasement/direct tumor abutment of

the hepatic artery with no extension to the celiac axis; or (3) tumor-SMA involvement < 180° (Callery et al., 2009). The Postoperative pancreatic fistula was defined as drainage of >50 mL per 24 h of fluid, with amylase content >3 times serum amylase activity for >10 d after the operation, (Strasberg et al., 2007). Perioperative mortality was defined as death in the hospital or within 30 d (Mortensen, 1989). Delayed gastric emptying (DGE) was defined to be present when nasogastric intubation was maintained for P10 d, combined with at least one of the following: vomiting after removal of the nasogastric tube, reinsertion of a nasogastric tube, or failure to restore oral feeding (Yeo et al., 1993). The regimen of chemotherapy in the form of protocol FOLFIRINOX: triple combination chemotherapy (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², and 5-fluorouracil (400 mg/m²) given as a bolus followed by 2,400 mg/m² administered as a 46h continuous infusion q 2 weeks), the dose adjusts individually and during this course, the patient followed by Multislide CT abdomen and PET. Serum level of markers CA19.9 and CEA before treatment and every 3 months after treatment either chemoradiation or surgery.

Patients characteristics and presentations

All patients diagnosed with Jaundice, advanced cancer head of the pancreas or periampullary cancer with encased or infiltrated superior mesenteric vessels or associated with significant coeliac Lymph nodes and all patients received Neoadjuvant chemotherapy or radiotherapy or both and subjected to surgery.

RESULTS

40 patients as a group B that were diagnosed as locally advanced periampullary tumor included in this study, as pancreatic head carcinoma in 20/40 (50%) and periampullary carcinoma in 20/40 (50%) of patients, all patients were diagnosed as locally advanced pancreatic cancer by radiological imaging as ultrasound and multi-sliced CT scan presented 28/40 (70%) as males and 12/40(30%)as females with male: female ratio 2.3:1, the age of patients at diagnosis was 39-62 years with median age 51 years (Figure 2). Risk factors including smoking detected in 24/40 patients (60%) while 16/40

(40%) nonsmokers, Diabetes Mellitus in 12/40 (30%) and hypertension detected in 12/40 patients (30%) while all patients screened for HBV and HCV and found as negative for both (Table 1).

Table 1. Risk factors

Risk factor	Yes	No
Smoking	24	16
DM	12	28
Hypertension	12	28

Patients were diagnosed radiologically as pancreatic head cancer in 20/40 (50%) of cases and periampullary carcinoma in 20/40(50%) of cases with 8/40 (20%) had a decrease in prothrombin time and concentration (hypoprothrombonaemia) less than 70% and treated medically to correct the coagulation profile (Figure 3). Most of the patients presented with jaundice and high level of bilirubin mainly direct bilirubin with a high level reaching in some cases above 20 with a slight increase in indirect bilirubin, Patients presented with jaundice only in 28/40 cases (70%), obstructive jaundice with weight loss in 4/40 cases (10%), obstructed jaundice with hematemesis in 4/40 (10%) cases and presented with melena in 4/40(10%) of cases and all cases are provisionally diagnosed as cancer head and periampullary pancreatic carcinoma before any interference (Figure 4). All patients had full laboratory investigations for detection of serum bilirubin both total, direct and indirect bilirubin together with kidney function tests, liver profile and coagulation profile and serum tumor markers to detect the prognosis and follow up the stage and found a high increase of serum CA19.9 that ranges between 180-2734 with the majority of patients ranging between 600-1000 and 8/40 (20%) had more than 2000 in the estimation (Table 2).

All patients had different imaging models to confirm the diagnosis and facilitate the decision making for approach starting with the ultrasound of the abdomen and pelvis with dilated common bile duct(CBD) in 16/40 (40%) of cases, obstructed distal part of CBD in 20/40(50%) of cases while liver cirrhosis was detected in 4/40(10%) of cases by U/S with the measurement of the size of tumor that detects



Figure 1. CT scans: Tumour infiltration of the PV confluence (white circle). SMV (black arrow), PV (broken black arrow), and SPV (white arrow) without thrombosis.

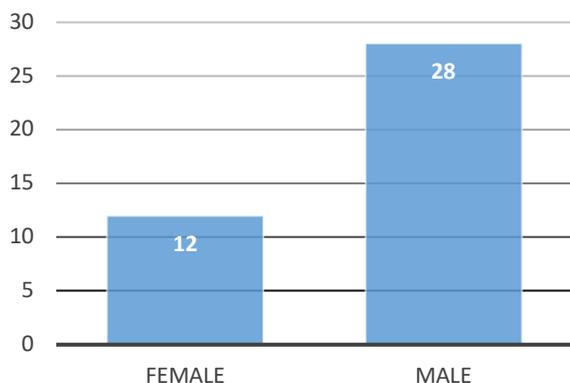


Figure 2. Patient type

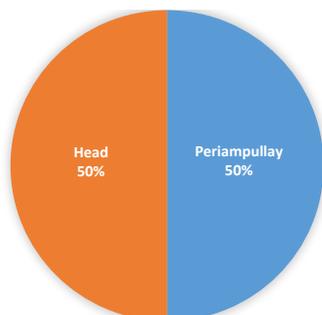


Figure 3. Tumor location

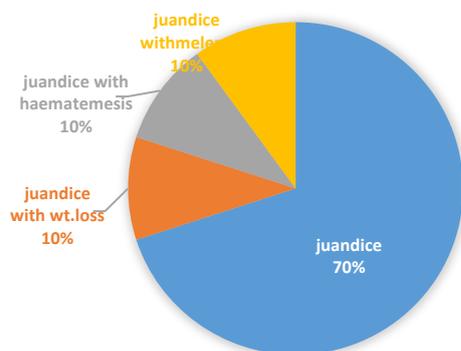


Figure 4. Patient presentation

Table 2. laboratory investigations

Lab indicator	Number of patients (40)
Total bilirubin	
1-10	8
10.1-20	28
>20	4
Direct	
1-10	8
10.1-20	28
>20	4
Indirect	
1-10	40
10.1-20	0
>20	0
Albumin	
<4	16
>4	24
Prothrombin concentration (PT)	
<70%	12
>70%	28
CA19.9	
0-300	8
300-600	8
600-1000	16
>1000	8
CEA	
0-10	36
>10	4

8/40 (20%) of patients <3cm in dimensions and 12/40(30%) of them had 3-4 cm in tumor size while cases diagnosed more than 4cm was 20/40 (50%) of cases.

Multislice computerized tomography (MC-CT) with the pancreatic protocol used for all patients to detect the radiological staging of the tumor with vascular status either invaded or abutted with measurement of the degree of invasion, looking for the superior mesenteric artery (SMA), superior mesenteric vein(SMV) affection, also the hepatic artery(HA), coeliac artery(CA), inferior vena cava (IVC), coeliac Lymph nodes and para-aortic lymph nodes status and infiltration and the presence of liver metastasis, all these points were detected by multi sliced CT scan for all patients then all patients had MRCP(magnetic resonant cholecys to pancreaticography) to comment on the site of the mass and CBD status together with the intrahepatic pancreatic duct dilatation and its level.

All patients then evaluated by PET-CT scan to confirm the accurate diagnosis and staging with the vascular status and detection of any hidden

Table 3. Preoperative radiological diagnosis

Radiological imaging	Number of patients (%)
Ultrasound (US)	
Dilated CBD	16(40%)
Obstructed lower CBD	20(50%)
Cirrhotic liver	4(10%)
Size of tumor:	
<3cm	8(20%)
3-4cm	12(30%)
>4cm	20(50%)
Computerized tomography (CT)	
Portal vein:	28(70%)
Encasement	12(30%)
No encasement	8(20%)
Superior mesenteric artery(SMA)	
Abutting	0(0%)
Infiltration	32(80%)
No	
Superior mesenteric vein:	
Infiltration	4(10%)
abutting	16(40%)
No	20(50%)
inferior vena cava (IVC):	
abutting	4(10%)
No	36(90%)
hepatic artery:	
main HA	
encasement>180	4(10%)
No	36(90%)
RHA:	
Encasement	4(10%)
No	36(90%)
coeliac and Para aortic LNS	
coeliac infiltration	4(10%)
both	32(80%)
No	4(10%)
Liver metastasis:	
Yes	4(10%)
No	36(90%)
MRCP:	
Mass at the head and uncinat process	24(60%)
Dilated IHBD and proximal CBD	8(20%)
Dilated CBD and pancreatic duct	8(20%)
PET-CT scan	
Size of tumor:	
<3cm	8(20%)
3.1-4cm	28(70%)
>4cm	4(10%)
Vascular invasion:	
Portal vein and SMV Encasing	20(50%)
Portal vein and SMV Abutting	8(20%)
IVC abutting	4(10%)
Hepatic artery	4(10%)
PV&SMV&RHA	4(10%)
LNs	40(100%)
Liver metastases	4(10%)
Distant metastases	0(0%)
Biliary drainage	
ERCP stenting	24(60%)
PTD	16(40%)

lesions or metastasis together with the Lymph nodes status and affection in both the coeliac group and par aortic group and also used as a routine in the follow up of all patients.

Biliary drainage done before the start of neoadjuvant treatment, 24/40 (60%) of patients undergone ERCP with plastic stents to drain bilirubin while 16/40(40%) need the insertion of PTD to drain bilirubin and improve the general condition of patients and state of the liver (Table 3).

After a full evaluation, all 40 patients with locally advanced tumor-directed to neoadjuvant chemotherapy and radiotherapy (not palliative radiotherapy due to good performance status that can afford chemotherapy effect and complications) after MDT discussion in the protocol of Chemotherapy given for all patients for 6months as the protocol FOLFIRINOX: triple combination chemotherapy (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2, and 5-fluorouracil (400 mg/m2) given as a bolus followed by 2,400 mg/m2 administered as a 46h continuous infusion q 2 weeks), with only 4/40 cases had radiotherapy (the dose of radiotherapy is changeable according to the patient’s performance and status). Then patients evaluated again after chemotherapy with multislice CT, PET-CT with follow up by tumor markers serum levels and found to have marked regression of the size of the tumor to be less than 3cm in dimensions in all cases with the improvement of the degree of infiltration of vascular supply and status of lymph nodes either the coeliac or para-aortic, with marked regression of tumor size noted in all cases, the degree of invasion of the IVC, Coeliac artery(CA) and SM vessels was decreased to a great level with the disappearance of liver metastasis noted pre-chemotherapy and also marked regression of the level of markers noted to reach between 5-423 and lymph node infiltration noted in only 4/40 cases (Table 4).

Surgical interference and approach

After neoadjuvant chemotherapy for 6 months, (mostly for 6 months for the effect of the neoadjuvant treatment as this is the exact time for patients to have at least 3 courses of

Table 4. Radiological diagnosis after chemotherapy

Imaging	Number of cases (%)
CT scan:	
Size:	
<3cm	40(100%)
>3cm	0(0%)
Portal vein (PV):	
Encased	4(10%)
Abutted	12(30%)
No	24(60%)
SMA (superior mesenteric artery):	
Abutted <90	4(10%)
No	36(90%)
SMV (superior mesenteric vein):	
Infiltrated	4(10%)
Abutted	16(40%)
No	20(50%)
IVC (inferior vena cava):	
Infiltrated	0
No	40(100%)
HA (hepatic artery):	
Encased	4(10%)
Abutted	4(10%)
No	32(80%)
CA (Coeliac artery):	
Infiltrated	0
No	40(100%)
LN (lymph nodes)	
Infiltrated	4(10%)
No	36(90%)
LM (liver metastasis):	
Yes	0
No	40(100%)
PET-CT:	
Size:	
<2cm	28(70%)
>2cm	12(30%)
PV	
Abutted	24(60%)
No	16(40%)
SMA	
Abutted	24(60%)
no	16(40%)
SMV	
Abutted	24(60%)
No	16(40%)
HA	
Abutted	8(20%)
No	32(80%)
CA	
Abutted	4(10%)
No	36(90%)
LN	
Infiltrated	4(10%)
No	36(90%)
Tumor markers:	
CA19.9:	
<50	16(40%)
50-200	12(30%)
200-500	12(30%)
>500	0
CEA:	
<2	0
2-4	40(100%)
>4	0

chemotherapy to evaluate the effect) Surgery in the form of Whipple's operation done for 25/40 patients resecting distal stomach, duodenum head of the pancreas and proximal jejunum together with distal CBD, 8/25 patients had a vascular resection and 17/25 patients without vascular resection and 15/40(30%) of cases found as advanced from which 6/15 died during the course of chemotherapy due to various causes as(IHD, liver failure and brain stroke) with 9/15 found to be advanced and unfit for surgery due to variable causes (local as a spread of the disease and general causes as complications of chemotherapy). Complications recorded in the form of hematomas in 4/40(10%) cases, 24/40 (60%) had postoperative wound infection, 4/40 (10%) cases had wound dehiscence in the next two weeks after surgery and 8/40(20%) had no complications post-operatively with all the cases treated conservatively.

Morbidity in the form of chest infection and complications noticed in 12/40 (30%) of cases, with 4/40(10%) patients developed minimal ascites post-operative and only 4/40(10%) had wound dehiscence during the next 2 weeks while no morbidity at all recorded in this study in next 3 months following surgery and follow up and all patients was subjected to have chemotherapy for 3 months' post-operative (Table 5).

Tumor pathology: Periampullary including (pancreas, duodenum and ampulla)

Pathological examination of the specimens after surgery showed that all cases were adenocarcinoma of periampullary with 24/40(60%) was diagnosed as grade III and 16/40(40%) grade II in the examination and all cases had free surgical margins both proximal and distal, and the regional lymph nodes harvested ranged between 0-13 nodes and the infiltrated lymph nodes also between 0-13 nodes with all harvested nodes was 190 nodes in all cases at which 26 nodes only found to be infiltrated by the tumor (Figures 6 and 7).

Follow up of patients at 3,6,12,18 and 24 months

After 3 months: Follow up by CT after 6 months showed that 25/40 had surgery with no recurrence either regional or nodal recurrence

Table 5. Surgery procedures and complication

Procedure	Number of patients
Surgery:	
Whipple's operation:	
With vascular resection:	8
Without vascular resection	17
Complications:	
Leakage	0
Wound infection	24
Dehiscence	4
Hematoma	4
No	8
Morbidity:	
Chest infection	12
Ascites	4
Wound dehiscence	4
No	20
Mortality:	
Yes	6
No	34

detected by multi-slice CT that was confirmed by examination by PET-CT to be the same with the majority of patients had CA19.9 level below 20 while small number ranged between 40-60 and all patients had chemotherapy as an adjuvant treatment, also 6/40 patients died during chemotherapy while 9/40 cases had disseminated disease with local and systemic complications during neoadjuvant in the form of vomiting, recurrent mucositis, chest infections, loss of hair and abdominal pain with immunosuppression, hepatic failure, cardiac toxicity and intolerance to doses, So not fit for surgery. During the first 3 months of follow up, ascites developed in 16/40(40%) of cases while incisional hernia at the site of incision for surgery detected in 12/40(30%) of cases and also chest infections and complications in 4/40(10%) of patients.

After 6 months: All patients had the same examination by CT., PET-CT and markers and no recurrence detected by CT or PET-CT and no ascites present with CA19.9 level estimation still majority of patients under 20 with no continuation of chemotherapy at any of the patients who had surgery before but still advanced cases having chemotherapy (9/34) and ascites detected in 6/34 patients and incisional hernia in 9/34 of patients with no mortality recorded in this series of patients.

After 12 months: Local recurrence at the operative bed confirmed by both CT and PET-CT in 6/34 (17.65%) of patients while still had a normal level of CA19.9 markers and 6/34 were returned to have chemotherapy for treatment of recurrence, incisional hernia detected in 6/34cases and chest problems in 3/34 cases while 3/34 developed diabetes mellitus (DM) with no mortality detected.

After 18 months: CT and PET-CT that confirmed the diagnosis of local recurrence in 4/34 cases and development of new liver distant metastasis in another 4/34 cases with the level of the marker as CA19.9 start to increase gradually in some cases up to 200 with 50% of cases 17/34 had to have chemotherapy again for treatment of metastasis and recurrence or increased level of serum tumor marker and also 7/34 (20%) had cardiac problems in the form of heart failure and 7/34 (20%) also had diagnosed as pneumonia but after 18 months 7 patients out of 30 died from heart failure.

After 24 months: Two years follow up for 27 patients, examined by CT and PET-CT with no detected recurrence or ascites and the level of CA19.9 was within the normal range in the majority of cases but 6/27 patients undergone chemotherapy again due to gradual increase in serum marker level with 3/27 (12.5%) of cases had chest problems in the form of severing pneumonia and died within this period due to pneumonia (Table 6).

DISCUSSION

Pancreatic cancer is an aggressive type of cancer and is usually presented as an advanced and inoperable with-late stage, so the prognosis is poor, it is listed as the fourth leading cause of cancer-related death. periampullary cancers that account for pancreatic, ampullary, biliary and duodenal carcinomas (He et al., 2014; Chen et al., 2010). To patients, the diagnosis is a life-changing disaster; however, to maximally extend the pancreatic cancer patients' life is the most important task after diagnosis, Pancreatic cancer is a common and highly aggressive type of malignancy, for which the 5-year overall survival (OS) rate is <6%. In recent years, the incidence of pancreatic cancer has continuously increased (Lin et al., 2015; Yu X and Lu, Y2014).

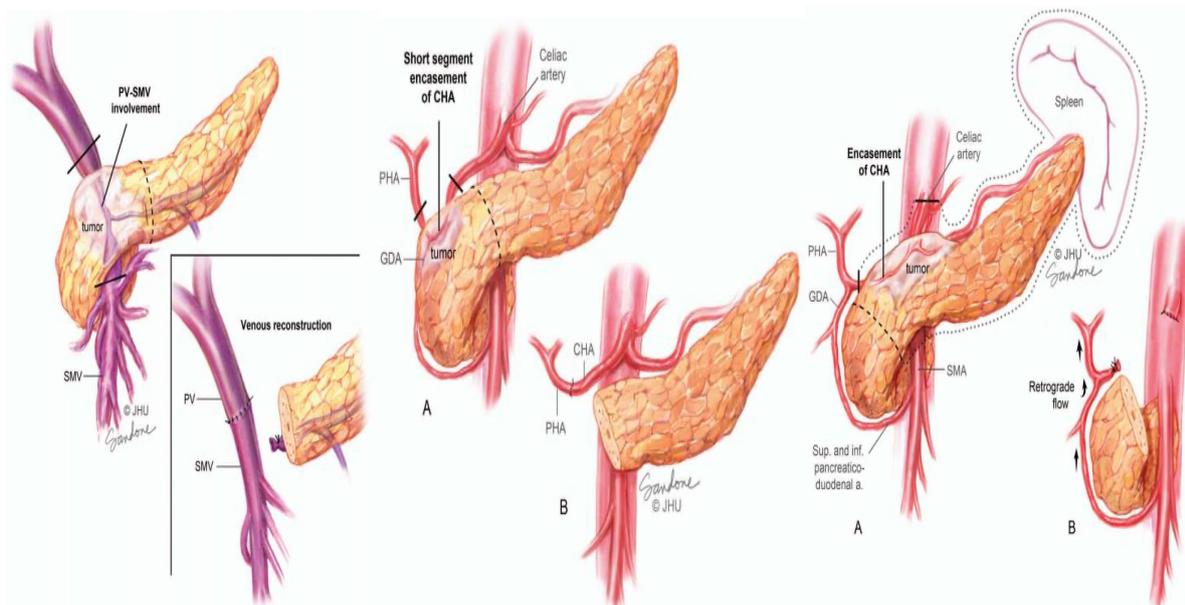


Figure 5. Infiltration of the portal vein and SMV confluence // encasement of common hepatic artery //tumor encasing coeliac, CHA and splenic artery.

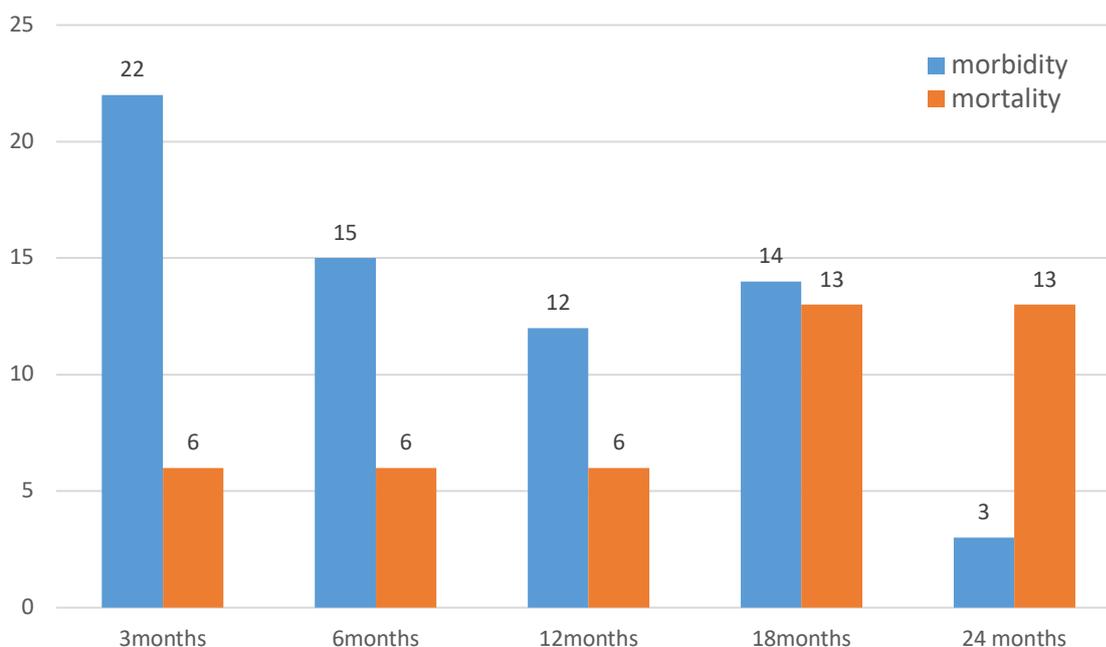


Figure 6. Mortality and Morbidity

Locally advanced pancreatic cancer is usually defined as patients with American Joint Committee on Cancer (6th edition) T4 lesions, where the primary tumor involves branches of the celiac axis or the superior mesenteric artery, indicating an unresectable primary tumor and representing stage III disease. These patients often require operative or non-operative palliation of disease-related processes such as obstructive jaundice, gastroduodenal

obstruction, or abdominal pain. Anticancer treatment for such locally advanced pancreatic adenocarcinoma can involve chemoradiation approaches, chemotherapy alone, or locally directed therapy. Jaundice is present in the majority of patients with pancreatic adenocarcinoma. If untreated, obstructive jaundice can result in progressive liver dysfunction, hepatic failure and early death (Roland et al., 2015).

Table 6. Follow up of patients for 2years

Item	No of patients				
	3 months	6 months	12 months	18 months	24 months
CT					
Recurrence					
Yes				4	
No	0			30	
Ascites	40	0	6		0
Yes	16	34	28		27
No	24			4	
Liver Mets.					
PET-CT					
Recurrence					
Yes				4	
No	0	0	6	30	0
Liver Mets.	40	34	28	4	27
CA19.9					
0-20	15	18	12	9	12
20-40	14	8	8	6	6
40-60	11	8	5	4	3
60-200	0	0	9	15	6
Chemotherapy					
Yes	40	9	15	17	6
no	0	25	19	17	21
Morbidity					
Incisional Hernia	12	9	6		
Ascites	3	6			
Chest problems	4	0			
Cardiac problems	0	0	3	7	3
DM	3			7	
No	0	0	3		
	18	19	22	18	21
Mortality					
Yes	0	0	6	13	0
No	34	30	34	27	27

In our study, we start to evaluate the patient 1st with drainage of jaundice either by stenting the CBD or PTD (percutaneous transhepatic drainage) to improve the liver functions and prevent the development of hepatic failure and enable patients to accommodate for neoadjuvant or adjuvant treatment.

The nonoperative palliative management of patients with pancreatic cancer can be applied to patients with unresectable locally advanced disease, or less frequently to patients with distant metastases. This is also the approach of choice for patients with unresectable disease with acute or chronic debilitating diseases that make anesthesia and surgery difficult or risky, one of the exceptions for this type is the presence of obstruction by the tumor that need to bypass by gastrojejunostomy to relieve that obstruction and improve the quality of life for patients (PA Philip et al., 2007).

Although the best chance of long-term survival for patients with localized pancreatic cancer is through complete resection of the primary lesion and the systemic nature of pancreatic cancer at diagnosis, the impact of pancreatectomy on quality of life and the relatively low chance of long-term survival must all be taken into consideration when selecting patients who benefit from surgery. As most patients have a locally invasive and micrometastatic disease at the time of surgery, the risk of both local and systemic recurrence following a potentially curative operation is high. Several factors, in addition to the stage, need to be considered in the selection of patients who will benefit from pancreatectomy, (Hsu et al., 2012). These include the patient's overall health, their tumor biology and the use of neoadjuvant therapy.

The operations necessary to resect pancreatic cancer are associated with significant morbidity in 40–60% of patients and mortality in the 2–3% range, (Sohn et al., 2000, Winter et al., 2006). Moreover, complete recovery to a normal quality of life can take 2–3 months even in the absence of complications. In addition, long-term survival is uncommon. The median survival reported for resected pancreatic cancer ranges from 17–27 months and the 5-year survival is approximately 20%, (Winter et al., 2006).

In this study, the patients were selected depending on the imaging preoperatively and during follow up with complete evaluation to select the patients who will benefit from surgery to improve the outcome, with the protocol of neoadjuvant chemotherapy needed after MDT discussion, and showed that the morbidity is so high with different conditions including chest infections and pneumonia, wound infection, development of ascites or incisional hernia while the mortality was low with 32.5% (13/40) patients mortality after 2 years of follow up.

Neoadjuvant therapy remains controversial in the treatment of pancreatic cancer. It has the advantage of down-staging of some locally advanced patients and sterilizing the margin of borderline resectable patients allowing them to undergo a surgery with a higher likelihood of an R0 resection, (Evans et al., 2008; Gillen et al., 2010), 15–40% of patients with initially borderline or unresectable tumors can eventually undergo surgery. Neoadjuvant therapy also has the advantage that will spare the 15–35% of patients who develop the metastatic disease the risks and stress of a major operation; as metastases develop they would no longer be considered for surgery, (Katz et al., 2008; Laurence et al., 2011; White et al., 2001). Neoadjuvant therapy also guarantees that almost all patients will receive some form of chemotherapy or radiation because they do not have any post-operative complications and recovery to overcome before starting therapy.

There is a group of pancreatic cancer called "borderline resectable." Diagnosed and staged radiologically These are pancreatic cancers

considered unresectable by standard treatment guidelines because of vascular involvement or encasement, but there have been recent studies performed showing benefit in median survival for patients undergoing neoadjuvant chemoradiation trial and then reevaluation using traditional staging techniques, (Katz et al., 2008). Those patients showing tumor response, which is measured by shrinkage of tumor size, will then undergo surgical resection with some success with venous resection (VR), which is necessary when there is a locally advanced disease in the superior mesenteric vessels, portal vein, or IVC.

Many studies were reviewed for the effect of neoadjuvant therapy on the effect of vascular resection and mortality and morbidity with the median overall survival, the analysis of two studies comparing FOLFIRINOX versus gemcitabine demonstrated an improvement in OS ($P < 0.001$), PFS ($P < 0.001$) and response rate (RR 3.38; $P < 0.001$) but also significantly more neutropenia and thrombocytopenia (Conroy et al., 2011) and (Singhal et al., 2014). There was an improved quality of life (QOL). These results suggest that FOLFIRINOX reduces the risk of death by 49%, reduces the risk of progression by 54% and triples the rate of response compared with gemcitabine. The absolute survival gains are still modest, with OS in the gemcitabine alone arm ranging from 6.8 months to 7.4 months and in the FOLFIRINOX arms between 10.8 months to 11.1 months.

Miiller et al. (2009) investigates the morbidity, mortality, and survival in patients with advanced pancreatic adenocarcinoma (PAC) whom have had PD (pancreaticoduodenectomy) with VR (venous resection) with study of 488 cases at Germany between October 2001 and December 2007 with 100 cases had VR, The authors found that the median survival for patients undergoing PD with VR was 14.5 months, with 1 and 3 year survival rates of 55% and 14% respectively and 15 /110 under gone mortality, In Kaneoka et al. (2009) investigated the operative outcomes of portal vein resection (PVR) for portal vein (PV) or superior mesenteric vein (SMV) involvement in patients with PAC and had median survival of 12 months in patients had vascular resection, Wang et al.

(2008) studied 61 patients in china with locally advanced pancreatic carcinoma with vascular resection done with PD and had median survival of 13 months and 13% 5 years survival, and Martin et al. (2009) studied 36 patients, had PD and VR with median survival of 18 months.

In our study, the results were similar with a study done at 40 patients undergone neoadjuvant chemotherapy for all patient according to MDT decision aiming to downstaging and make the resectability more applicable and obtaining R0 resection with the feasibility of vascular resection, 25/40 patients subjected to pancreaticoduodenectomy with or without vascular resection with the good outcome as regards the safety margins and the regional Lymph nodes dissection to improve the quality of life for the patients with benefits and 6/40 died during chemotherapy while 9/40 was unfit for surgery due to either disseminated disease or the complications of chemotherapy, then all living patients had adjuvant chemotherapy protocol to prevent recurrence or metastasis. PD done after 6 months of chemotherapy in a protocol of FOLFIRINOX: The new triplet combination chemotherapy (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², and 5-fluorouracil (400 mg/m²) given as a bolus followed by 2,400 mg/m² administered as a 46-h continuous infusion q 2 weeks). Then reevaluation by the use of CT and PET-CT and serum level of CA19.9 and CEA level then all patients had pancreaticoduodenectomy with vascular resection in 8/40 (20%) of cases while PD without vascular resection done in 17/40 (42.5%) of patients with mortality in 13/40 by the end of 24 months follow up due to effect of chemotherapy and dissemination of the disease with also the aggressive local recurrence with the median survival rate of 22.7 months in average.

CONCLUSION

Pancreatic cancer is a complex and highly lethal disease in most cases diagnosed in an advanced stage with vascular invasion or abutting but and is best treated in the multidisciplinary setting. Although the survival statics are currently bleak, there are several bright spots on the horizon including individualized therapies and new

trends in neoadjuvant chemotherapy, the stage can be changed with the possibility of PD and vascular resection with good prognosis and results and improved overall survival and decreased mortality.

Abbreviations

- BMI= Body mass index
- OR=odds ratio
- PC=pancreatic carcinoma
- SMA=superior mesenteric artery
- SMV=superior mesenteric vein
- PV=portal vein
- HA=hepatic artery
- VR=venous resection
- PD=pancreaticoduodenectomy
- MDT=multidisciplinary team
- APC=advanced pancreatic carcinoma
- QOL=quality of life
- PVR=portal vein resection
- IVC=inferior vena cava
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CONFLICTS OF INTEREST

All authors have approved this article and declare no conflicts of interest.

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