Chemotherapy versus Chemo radiotherapy in Treatment of Locally Advanced Pancreatic Cancer

Thesis

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in Clinical Oncology

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List of Abbreviations

AJCCO	**:**	American Joint Committee of Cancer
BRCA 1	**:**	Breast cancer 1
BRCA 2	**:**	Breast cancer 2
CA19-9	**:**	Carbohydrate antigen
CBD	**:**	Common bile duct
CDA	**:**	Cytidine deaminase
CEA	**:**	Carcino embryonic antigen
CI	**:**	Confidence interval
CK:	**:**	Deoxycytidine kinase
CNT	**:**	Human concentrative nucleoside
CR	**:**	Complete response
CRT	**:**	Chemo radiotherapy
CT	**:**	Computed tomography
DM	**:**	Diabetes mellitus
DNA	**:**	Deoxyribonucleic acid
EBRT	**:**	External beam radiotherapy
ECOG	**:**	Eastern cooperative oncology
EGFR	**:**	Epidermal growth factor receptor
ENT	**:**	Human equilibrative nucleoside transporter
ERCP	**:**	Endoscopic retrograde cholangiopancreatography
EUS	**:**	Endoscopic ultrasonography

FDR	**:**	Fixed dose rate
FNAC	**:**	Fine needle aspiration cytology
GEM	**:**	Gemcitabine
GIT	**:**	Gastro intestinal tract
H and E	**:**	Hematoxylin and eosin
HR	**:**	Hazards ratio
IORT	**:**	Intraoperative radiotherapy
IPMN:	**:**	Intraductal papillary mucinous neoplasm
IRE	**:**	Irreversible electroporation
IV	**:**	Intravenous
KPS	**:**	Karnofsky Performance Status
LAPAC	**:**	Locally advanced pancreatic adenocarcinoma
LAPC	**:**	Locally advanced pancreatic cancer
MDCT	**:**	Multidetector computed tomography
MHz	**:**	Mega hertez
MRCP	**:**	Magnetic resonance cholangiopancreatography
MRI	**:**	Magnetic resonance imaging
MSH	**:**	Melanocyte stimulating hormone
MTD	**:**	Maximum tolerated dose
NCIC	**:**	National cancer inistitute committee
NCRP	**:**	National Cancer Registry Program
ORR	**:**	Overall response
OV	**:**	Overall response
PC	**:**	Pancreatic cancer

PD	**:**	Progressive disease
PDAC	**:**	Pancreatic duct adenocarcinoma
PET	**:**	Positron emission tomography
PFS	**:**	Progression free survival
PP	**:**	Pancreatic polypeptide
PR	**:**	Partial response
PS	**:**	Performance status
PV	**:**	Portal vein
QUL	**:**	Quality of life
RILD	**:**	Radiation induced liver disease
RNA	**:**	Ribonucleic acid
RR	**:**	Response rate
SD	**:**	Stable disease
SE	**:**	Standard error
SMV	**:**	Superior mesenteric vein
TNM	**:**	Tumor, nodes, metastasis
TUS	**:**	Transcutaneous ultrasonography
US	**:**	United states
WHO	**:**	World health organization
3D	**:**	Three dimensional
5-FU	**:**	5-flurouracil

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Abstract

Background: Pancreatic cancer is one of the most aggressive solid malignancies. It remains the fourth leading cause of cancer-related deaths in the modern world, mainly because of dismal diagnosis. In the last decades, significant improvements have been achieved in the screening and therapy of different solid cancers. However, the mortality rate has not experienced significant revision over the last few decades. The five-year survival rate remains just around 5–7% and one-year survival is achieved in less than 20% of cases. **Aim:** The study is conducted a retrospective analysis for patients with locally advanced pancreatic adenocarcinoma who were treated with chemotherapy alone or who were treated with concomitant chemo radiotherapy as regards treatment response, survival rates and toxicity. **Subjects and Methods:** This is a retrospective study that include thirty-six patients with cytological/ histological evidence of locally advanced PAC, presented to Ain Shams University hospital during the period from 1st of January 2011 till 31th of December 2016 and fulfilling the inclusion criteria, where twenty-one patients treated with chemotherapy alone compared to fifteen patients treated with concomitant chemo radiotherapy and all were treated from pancreatic cancer at Ain Shams University hospital, obtained from filing system from January of 2011 till December 2016 and had comparable characteristics. **Conclusion:** In conclusion, among patients with locally advanced pancreatic adenocarcinoma, there was no significant difference in overall survival and progression free survival with chemo radiotherapy compared with chemotherapy alone**.** **Recommendations:** In both groups of the study, the survival data and toxicity were comparable. So, addition of radiation to chemotherapy seemingly unfruitful. However, due to low number of patients with such study and treatment protocol, it is recommended to include more patients, possibly more cancer centers to reach more statistically significant number for reliable data.

Keywords: Carbohydrate antigen , Human equilibrative nucleoside transporter , Transcutaneous ultrasonography

Introduction

Pancreatic cancer is one of the most aggressive solid malignancies. It remains the fourth leading cause of cancer-related deaths in the modern world, mainly because of dismal diagnosis (**Garrido-Laguna I and Hidalgo M., 2015**). In the last decades, significant improvements have been achieved in the screening and therapy of different solid cancers. However, the mortality rate has not experienced significant revision over the last few decades. The five-year survival rate remains just around 5–7% and one-year survival is achieved in less than 20% of cases (**Vincent A et al., 2011).**

The incidence of carcinoma of the pancreas has markedly increased over the past several decades. Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood **(van den Bosch et al., 1994)**. In Egypt, cancer pancreas represents about 2.31% of all cancer cases among males and about 1.41% among females during the period from 2008-2011 according to The National Cancer Registry Program (NCRP) (**Ibrahim et al., 2014).**

Among distinct pancreatic malignancies, PDAC (whose name is derived from its histological resemblance to ductal cells), is the most common pancreatic neoplasm and accounts for more than 85% of pancreatic cancer cases (**Hezel s et al., 2006).**

There are usually no symptoms in the disease's early stages, and symptoms that are specific enough to suggest pancreatic cancer typically do not develop until the disease has reached an advanced stage **(Ryan et al., 2014)**.

Pancreatic cancer remains a highly lethal malignancy despite advances in treatment. At initial diagnosis, 50% of

patients present with metastatic disease, 30% present with a locally advanced tumor, and only 20% are resectable. Surgical resection remains the only potentially curative therapy. The large number of recurrences and/or distant failures following resection suggests that microscopic metastases continue to be an obstacle to better outcomes. Patterns of spread include direct extension, lymphatic spread to regional lymph nodes, and hematogenous spread to distant sites **(Jemal et al., 2009).**

The standard treatment for LAPC has been chemotherapy or chemo radiation therapy **(Loehrer et al., 2011, 2015).** Recently, powerful regimens, such as FOLFIRINOX or gemcitabine with nab-paclitaxel, have demonstrated a high response rate for metastatic PC **(*Ueno,* Okusaka et al., 2016, 2014).**

In particular, FOLFIRINOX has been used as a neoadjuvant treatment for LAPC, resulting in a high conversion rate to surgical resection by improving tumor shrinkage **(Nitsche et al., 2015, 2016).** Only the curative treatment for PC is surgical resection; therefore, treatment resulting for conversion surgery was an effective treatment strategy (**Satoi et al., 2013**).

Aim of the Work

The study is conducted a retrospective analysis for patients with locally advanced pancreatic adenocarcinoma who were treated with chemotherapy alone or who were treated with concomitant chemo radiotherapy as regards treatment response, survival rates and toxicity. At Ain Shams clinical oncology department during the period from 1st January 2011 to 31th December 2016.

Anatomical Considerations

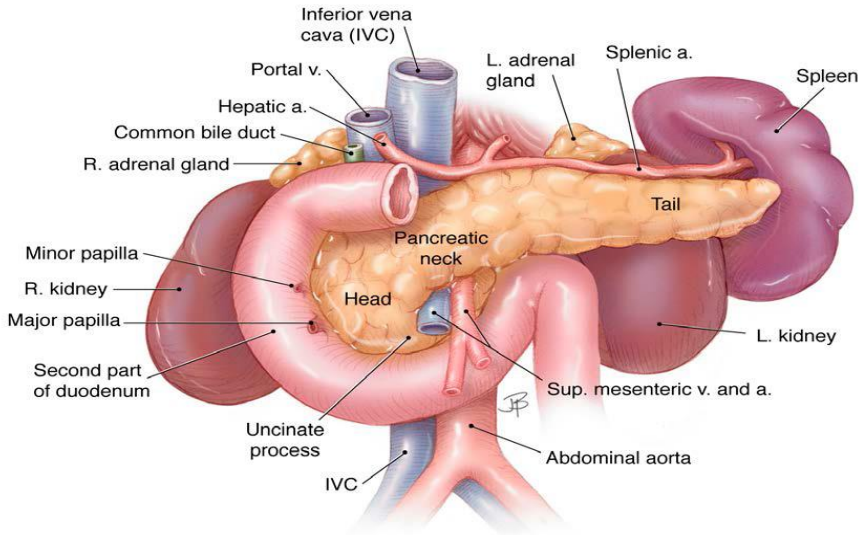

Fig. (1): Anatomic relationships of the pancreas with surrounding organs and structures **(Hruban et al., 2007)**

- The head of the pancreas lies in the loop of the duodenum as it exits the stomach.
- The tail of the pancreas lies near the hilum of the spleen.
- The body of the pancreas lies posterior to the distal portion of the stomach between the tail.
- The portion of the pancreas that lies anterior to the aorta is somewhat thinner than the adjacent portions of the head and body of the pancreas. This region is sometimes designated as the neck of the pancreas and marks the junction of the head and body.
- The close proximity of the neck of the pancreas to major blood vessels posteriorly including the superior mesenteric artery, superior mesenteric-portal vein, inferior vena cava, and aorta limits the option for a wide surgical margin when pancreatectomy (surgical removal of the pancreas) is done.
- The common bile duct passes through the head of the pancreas to join the main duct of the pancreas near the duodenum. The portion nearest the liver lies in a groove on the dorsal aspect of the head.

* The minor papilla where the accessory pancreatic duct drains into the duodenum and the major papilla (ampulla of Vater) where the main pancreatic duct enters the duodenum are depicted.

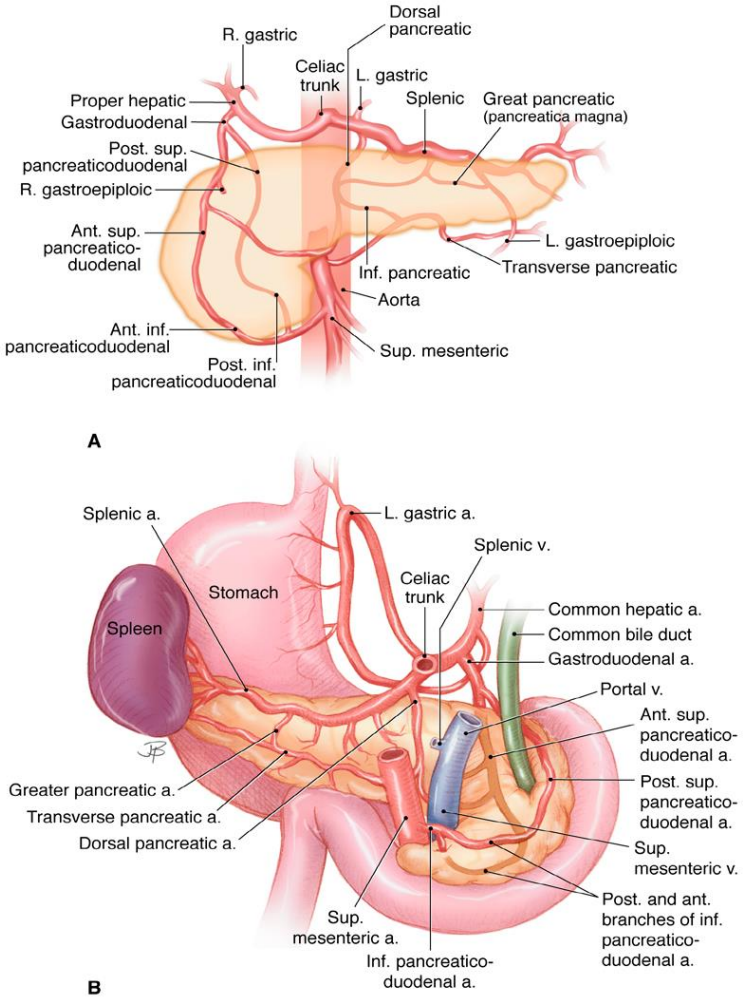

Fig (2): The arterial blood supply of the pancreas: **(Hruban et al., 2007)**

The upper panel (A) is visualized from the front, and the lower panel (B) is seen from the back. The celiac trunk and the superior mesenteric artery both arise from the abdominal aorta. Both have multiple branches that supply several organs including the pancreas. The anastomosis of their branches around the pancreas provides collateral circulation that generally assures a secure arterial supply to the pancreas. Most of the arteries are accompanied by veins (not shown) that drain into the portal and splenic veins as they pass behind the pancreas as shown in B. The superior mesenteric vein becomes the portal vein when it joins the splenic vein.