UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Klinik und Poliklinik für Allgemein-, Viszeral- und Thoraxchirurgie

Direktor: Prof. Dr. med. Prof. h.c. Dr. h.c. Jakob R. Izbicki

Overall survival after pancreatectomy with en bloc portal vein resection for macroscopically infiltrating pancreatic cancer

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
an der Medizinischen Fakultät der Universität Hamburg.

vorgelegt von:

Ramez Wahib
aus Kairo, Ägypten

Hamburg 2019

Angenommen von der Medizinischen Fakultät am: 13.09.2019

Veröffentlicht mit Genehmigung der Medizinischen Fakultät der Universität Hamburg.

Prüfungsausschuss, der Vorsitzender: **PD Dr. Dean Bogoevski**

Prüfungsausschuss, zweiter Gutachter: **Prof. Dr. Guido Sauter**

Table of contents:

1.Introduction:

1.1 Embryological and anatomical background of the Foregut and Pancreas:

The foregut gives rise to the esophagus, stomach, liver, gallbladder, pancreas and the caudal portion of the duodenum. Pancreas development begins during the 4th-5th weeks of gestation as distinct dorsal and ventral buds arising from the endoderm of the caudal foregut, the proximal duodenum. The dorsal bud is larger than and slightly more cranial to the ventral bud. Each bud communicates with the foregut through a duct. Rotation of the duodenum causes the ventral pancreatic bud to rotate clockwise to the left of the duodenum and brings it posterior and inferior to the dorsal pancreatic bud.

The two buds fuse to form the pancreas during the 7^{th} week of gestation. The ventral bud forms the inferior part of the head of the pancreas and the uncinate process and the dorsal bud forms the superior part of the head, the body, and the tail of the pancreas. The ductal systems of the two buds fuse in the 8^{th} week. The main pancreatic duct (duct of Wirsung) which enters the duodenum at the major duodenal papilla (ampulla of Vater) is formed by the longer dorsal duct draining into the proximal ventral duct to form. If the proximal portion of the dorsal duct remains, it forms an accessory duct (duct of Santorini) that opens into a minor accessory papilla located about 2 cm above the main duct. The accessory duct opens into a minor papilla in 33% of people and ends blindly in 8% of people. Fifty percent of people do not have an accessory duct. Endocrine cells (islets) are identifiable by the 8^{th} week. Exocrine pancreatic development continues after birth with maturation of specific digestive enzymes.[1,4]

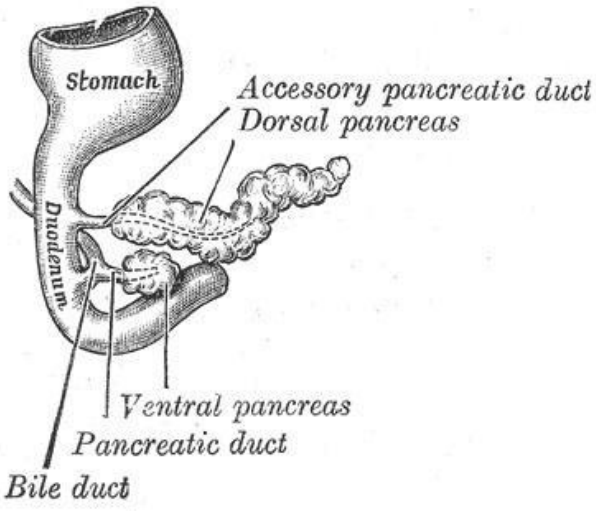


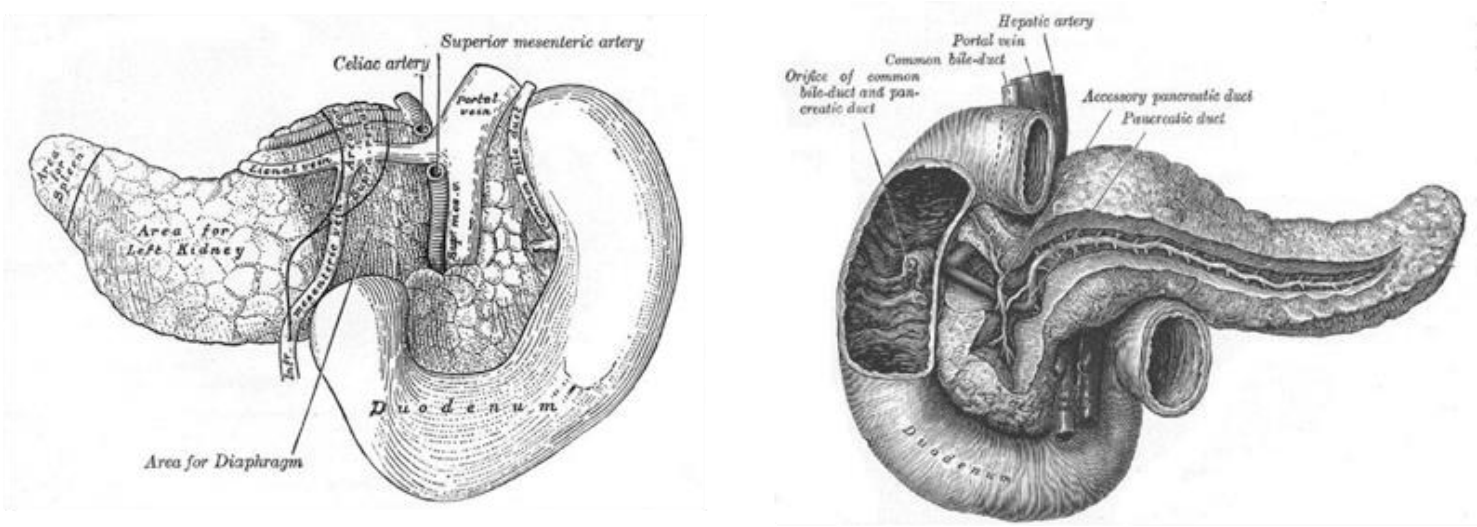
Figure1: Embrology of the pancreas:

Pancreas of a 5-week-old human embryo.(Naspghan)

The fully developed pancreas is arbitrarily divided into head, uncinate process, neck, body and tail. The pancreatic head constitutes about 50% and the body and tail the remaining 50% of the pancreatic parenchymal mass. The head of the pancreas lies in the duodenal C loop in front of the inferior vena cava and the left renal vein. The uncinate process is an extension of the lower (inferior) half of the head toward the left; it is of varying size and is wedged between the superior mesenteric vessels (vein on right, and artery on left) in front and the aorta behind it. The lower (terminal) part of the common bile duct runs behind (or sometimes through) the upper half of the head of pancreas before it joins the main pancreatic duct of Wirsung to form a common channel (ampulla), which opens at the papilla on the medial wall of the second part of the duodenum.

The neck of the pancreas lies in front of the superior mesenteric vein, splenic vein and portal vein junction. The body and tail of the pancreas run obliquely upward to the left in front of the aorta and left kidney. The pancreatic neck is the arbitrary junction between the head and body of the pancreas. Portal vein lies behind the neck of the pancreas; no tributaries drain from the posterior surface of the pancreas into the anterior surface of the portal vein; therefore, a tunnel can be easily created behind the neck of the pancreas before its division. The narrow tip of the pancreas tail reaches the splenic hilum in the splenorenal (lienorenal) ligament.[2,3,4]

Figure 2: Anatomy of the pancreas:



The pancreas and duodenum posterior view (Left), anterior view (Right). (Naspghan)

1.2. Histological build up and function of the Pancreas:

The histological build up of the pancreas includes two glandular systems:
- Exocrine pancreas:

This part arises as little grape-like cell clusters, each called an acinus located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich pancreatic juice into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct. The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine.
The pancreas produces over a liter of pancreatic juice each day. This juice contains protein-digesting enzymes in their inactive forms which are activated in the duodenum via the enteropeptidase enzyme which stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin. Amylase, Lipase and nuclease are secreted in their active forms.[5]

- Endocrine pancreas:

The islets of the endocrine pancreas each contain four varieties of cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.[5]

1.3. Pancreatic neoplasia:

1.3.1. Cellular components:

Basically, pancreatic neoplasms are classified according to their cellular linage. Every cell type that exists in the pancreas has been described to have one or more neoplastic lesions.[6,7,8,9]

Cellular components of the pancreas can be classified to six categories:

I. ***Acinar cells***

II. ***Ductal cells***

These two cell lineage constitute the exocrine pancreas.

III. ***Islets of Langerhans:*** which represents the endocrine component.

IV. ***Ambiguous cells:*** less characterized centroacinar cells.

V. ***Supportive elements:*** surrounding connective tissue, vessels, nerves…ect.

VI. ***Potenial cells:*** *no clear function in adult human pancreas. (ex: stem cells) (6,7,8,9)*

1.3.2. Overview of the various types of pancreatic neoplasms:

1. Ductal Neoplasia:

With their high regenerative capacity and secretory properties, ductal cells are more vulnerable to neoplastic transformations. Moreover, the ducts are the only component of the pancreas exposed to the outside world (mutagens). The vast majority of pancreatic neoplasms have ductal origin. Mucin related glycoproteins (MUC1) and onkoproteins such as carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) are typically detected in ductal and mucinous tumors.[6,7]

- Invasive Ductal Neoplasia:

The most common form of ductal neoplasms is the ***invasive ductal adenocarcinoma (pancreatic cancer).*** It is also the most common pancreatic tumor constituting more than 85% of all pancreatic tumors. Invasive ductal adenocarcinomas have some unique morphological characters such as rapid perineural invasion and vascular invasion. The former would be a possible cause of back pain in pancreatic cancer, while the later may explain the metastatic nature of the tumor.[6]

Some other invasive tumors from the ductal cell lineage have been reported and described. For example, a less differentiated form of ductal adenocarcinoma known as ***undifferentiated carcinoma*** which has a much more aggressive behavior.[10] Some further distinctive tumors with osteoclast like giant cell components have been reported ***(Undifferentiated carcinoma with osteoclast-like giant cells)***.[11]

A squamous differentiation can also be seen in ductal adenocarcinomas ***(adenosquamous carcinoma).***[11,12,13] Other rarer and highly aggressive forms of ductal tumors have been reported such as ***colloid carcinoma*** and ***medullary carcinoma.***[14,15,16,17]

- Noninvasive Ductal Neoplasia:

The relative recently identified ***Pancreatic intraepithelial Neoplasms (PanIN)*** represent the most common form under this category (18). These tumors can grow in a metaplastic form to resemble a carcinoma in situ. However, usually they are accidently found in morphologically normal pancreata.[19]

Some large non invasive ductal tumors which usually grow up to clinically detectable masses have been identified. These include ***mucinous cystic neoplasms, intraductal papillary mucinous neoplasms,*** and ***intraductal oncocytic papillary neoplasms***. Such tumors may show a sort of precancerous behavior similar to the adenoma-carcinoma sequence of tumors from other gastrointestinal origin.[20,21]

Furthermore, non malignant serous-cystic pancreatic tumors ***(serous adenoma)*** have been described.[6,22] These tumors lack mucinous differentiation and appear almost always in body-tail parts of the pancreas.[6,22]

2. Pancreatic Endocrine Neoplasia (PEN):

Previously known as islet cell tumors, PENs are well differentiated hormonally and clinically functional tumors. They are named upon the hormonal syndrome for example insulinoma or glucagonoma, gastrinoma …ect. Non functional PENs are detected accidentally. PENs can be part of multiple endocrine neoplasia (MEN type 1) Although they tend to follow a benign course, metastasis and recurrence are not rare. High proliferation index with high mitotic activity are signs of aggressive tumor behavior. Recently, the WHO distinguished between well differentiated pancreatic endocrine tumors and well differentiated pancreatic carcinomas.[23-29]

Other rare forms of pancreatic tumors include: (6)

3. Acinar Cell carcinoma (ACC).

4. Mixed carcinomas.

5. Solid Pseudopapillary Tumor.

6. Cystic Pancreatic Lesions: the most common forms are: ***intraductal papillary mucinous neoplasm (IPMN)*** and ***serous cystadenoma.***

7. Pseudotumors.

8. Mesenchymal Tumors.

9. Secondary Tumors.

1.4. Invasive Ductal Adenocarcinoma ,*Pancreatic Cancer'*:

1.4.1. Epidemiology and risk factors:

Pancreatic Cancer is the 14th most common cancer and the 7th common cause of cancer mortality worldwide.[30] Though, there is a remarkable variation of the incidence among different geographical regions. Developed western countries have higher incidence compared to developing African and south American countries.[30-32] This variation suggests that environmental factors play an important role as risk factors for the development of pancreatic cancer.

Figure 3: Epidemiology of pancreatic cancer:

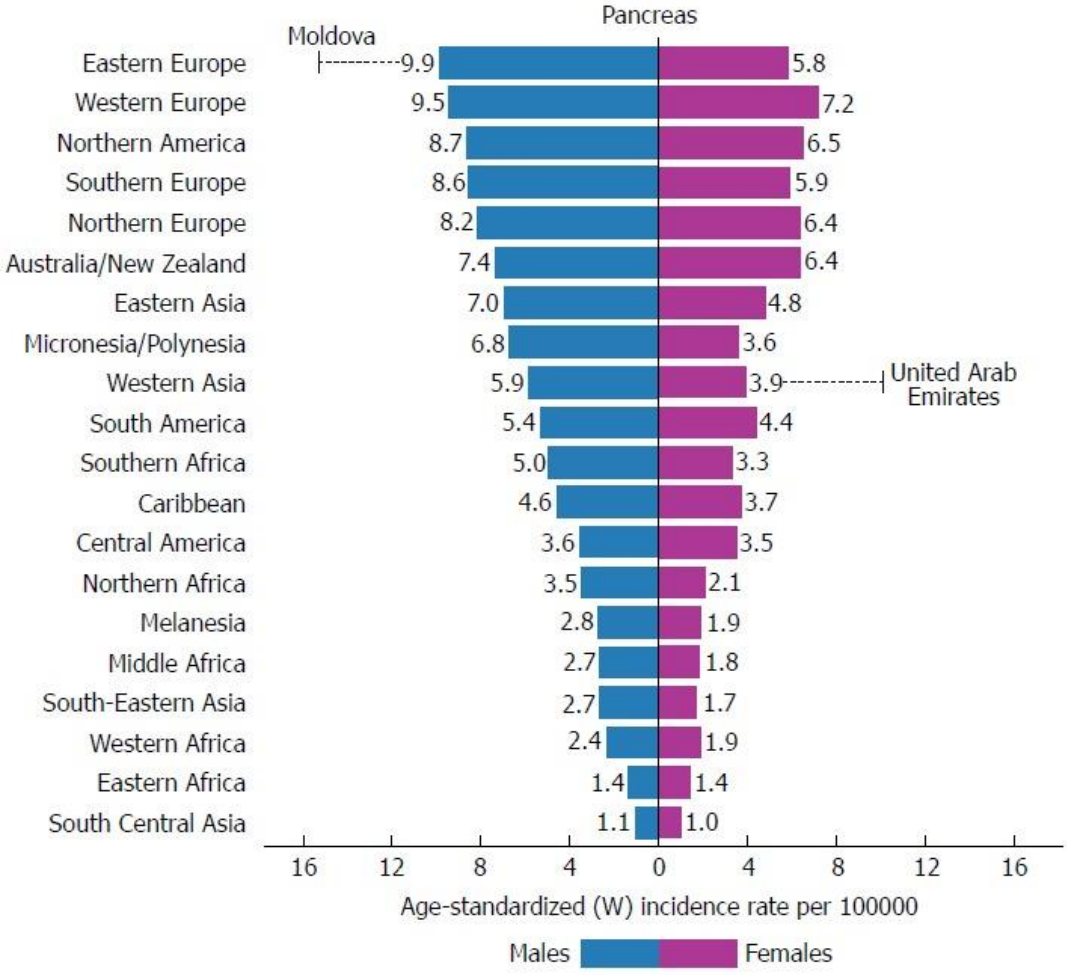


Diagram of incidence of pancreatic cancer in both sexes throughout the world Adapted from Globocan 2018. [31]

Data investigating risk factors for pancreatic cancer are still preliminary. Generally, risk factors can be divided into 2 main categories:

- Non modifiable risk factors:

Age:

Pancreatic cancer is a disease of the elderly. 90% of newly diagnoses patients are older than 55 years. Though, demographic differences have to been taken in consideration.[30]

Gender:

The incidence of pancreatic cancer tend to be slightly higher in males than females. (Age-standardised rate 5.5 in males compared to 4.0 in females).[30,31] *Wahi et al 2009* showed in his review that reproductive factors are not associated with development of pancreatic cancer in females.[33] Environmental exposure is meant to be an alternative explanation for incidence difference.

Ethnicity:

It has been postulated that the incidence of pancreatic cancers is higher in African Americans than in their fellow Caucasians.[34] This was attributed to higher nicotine and alcohol consumption and higher body mass index within African Africans.[35] Genetic predisposition has been also postulated.[36]

Microbiota:

The potential role of gut micobiota and gastrointestinal cancer has been under extensive investigation over the last decade. A recent review showed that lower levels of Neisseria elongate and Streptococcus mitis, and higher levels of Porphyromonas gingivalis and Granulicatella adiacens are associated with an increased risk of pancreatic cancer.[37]

Diabetes:

Both types of diabetes are established risk factors for pancreatic cancer.[38,39]

Genetic susceptibility:

Familial Pancreatic cancer accounts for 5 to 10% of new cases. Pancreatic cancer is considered to be for familial if two or more first degree relatives as previously being diagnosed with the disease. Patients with familial risk factors have a higher risk of developing pancreatic cancer than those with no family history. Specific syndromes such as Peutz-Jegherz syndrome and hereditary non polyposis colon cancer are also associated with an increased risk of pancreatic cancer compared to the general population.[40-44]

- Modifiable risk factors:

Chronic pancreatitis:

Chronic pancreatitis is a well established risk factor for pancreatic cancer.[52,53] Patients with chronic pancreatitis have up to 13 fold higher risk of pancreatic cancer.[52]

Smoking:

Many studies have identified the significantly increased risk to develop pancreatic cancer in smokers.[45,46] Even after smoking cessation, the risk remains high. [46,47]

Alcohol:

Alcohol consumption has been linked to pancreatic cancer since years. Several studies have investigated the role of alcohol consumption in development of pancreatic cancer.[48,49] One recent meta-analysis showed that low and moderate alcohol consumption was not associated with pancreatic cancer risk, however, in those with a high alcohol consumption there was a 15% increased risk of pancreatic cancer.[50] Excessive alcohol consumption is the leading cause of chronic pancreatitis which is per se a risk factor for pancreatic cancer.

Obesity:

Obesity is a rising problem in the modern world. Studies which investigated the association of increased body mass index (BMI) and pancreatic cancer reported an increased risk of pancreatic cancer up to 10% in obese patients with every 5 BMI units.[51] As obesity is a serious problem more in developed countries, this might explain the increased incidence of some cancers including pancreatic cancer in these countries.

Infection:

Correlation between pancreatic cancer and some infections such as H. pylori and hepatitis C. have been investigated. However, More research work is needed in this field.[30]

Diet:

There is no such a strong evidence about the impact of dietary factors on the risk of pancreatic cancers.[51]

Figure 4: Impact of modifiable factors on pancreatic cancer:

Summary of impact of dietary factors, nutrition and physical activity on pancreatic cancer risk

		Diet, nutrition, physical activity and pancreatic cancer	
		Decreases risk	**Increases risk**
Strong evidence	Convincing		Body fatness
	Probable		Adult attained height
Limited evidence	Limited - suggestive		Red meat, Processed meat; alcoholic drinks (heavier drinking); foods and beverages containing fructose; foods containing saturated fatty acids
	Limited - no conclusion	Physical activity; fruits; vegetables; folate; fish; eggs; tea; soft drinks; coffee; carbohydrates; sucrose; glycaemic index; glycaemic load; total fat; monounsaturated fat; polyunsaturated fats; dietary cholesterol; vitamin C; and multivitamin/mineral supplements	
Strong evidence	Substantial effect on risk unlikely		

World Cancer Research Fund global report 2015. [51]

1.4.2. Pathophysiology and molecular biology:

As in many other solid malignant tumors accumulation of genetic mutations triggers the development of pancreatic cancer.[64] Mutation in three different gene groups take place to start the carcinogenesis; oncogenes, tumor-suppressor genes and genomic maintenance genes.[65,66]

Genetic alteration in pancreatic cancer include numerous genes such as oncogenes *(K-ras, HER2, AKT2, and MYB)* as well as tumor suppressor genes *(TP53, P16, CDKN2, CDKNB, MADH4, FHIT, BRCA2, TGFBR2 and MLH1).*[64]

In around 80% of non familial pancreatic cancers a mutation the K-*ras* takes place.[67] P16 and TP53 are the most commonly inactivated tumor suppressor genes in pancreatic cancer.[68,69] Additionally**,** pancreatic cancer overexpresses many growth factors and their receptors, including the epidermal growth factor family, vascular endothelial growth factor, fibroblast growth factor, and many cytokines, such as transforming growth factor β, interleukins 1, 6, 8, and tumor necrosis factor α.[70-78].

1.4.3. Diagnostic tools and Screening:

The success in reducing cancer mortality in some solid tumors is not particularly related to the development of new drugs or other therapeutic agents, rather to a remarkable extent due to the advance achieved in early detection and screening programs.[56,60]

Within this strategy the concept of prophylactic therapies had been developed. Preemptive surgical interventions have been recognized as useful and effective therapeutic tools for the management of several premalignant conditions in high risk patients.

For example, prophylactic liver transplantation in patients with primary sclerosing cholangitis reduces the risk of cholangiocarcinoma.[57]
Total thyroidectomy is recommended for patients with multiple endocrine neoplasia MEN typ 2/familial medullary carcinoma.[58] prophylactic bilateral mastectomy and oophorectomy in patients with BRCA1 and BRCA2 mutations reduces the risk of breast cancer and ovarian cancer by 90%.[59]
Total proctocolectomy is recommend for patient with familial hereditary non polyposis colorectal cancer. [60]

Due to its rapid progression and aggressive nature as well as it's low incidence, pancreatic cancer was considered historically not a suitable disease for an effective preventive or early detection program. Nowadays, accumulating knowledge about the tumor biology and the continuous development in diagnostic tools changed our vision to the disease.[56]

The carcinogenesis in pancreatic cancer is indeed a multistep process which takes place over a couple of years as in other gastrointestinal tumors. Therefore, this process allows a potential window of time to detect and manage pre-invasive lesions.[61,62]

Already existing diagnostic methods can now detect some precancerous lesion such as PanINs and IPMNs.[63] However, a cost effective screening program with this relatively low incidence is still awaited. On the other hand, high risk individuals are evaluated for potential precancerous lesions.[61]

- Symptoms and clinical presentation:

Symptoms primarily are caused by mass effect rather than exocrine or endocrine insufficiency . The clinical features depend on the size and location of the tumor as well as its metastases. Jaundice, pain, and weight loss are classic symptoms of pancreatic cancer. Nonspecific early symptoms often are unrecognized; therefore, most pancreatic cancers are advanced at the diagnosis.(79)

More than two thirds of pancreatic cancers occur in the head of the pancreas and usually present as steadily increasing jaundice caused by biliary duct obstruction. Obstruction of the bile duct causes jaundice with disproportionately increased levels of conjugated bilirubin and alkaline phosphatase in the blood. Urine becomes dark because of the high level of conjugated bilirubin and the absence of urobilinogen. Stool turns pale because of the lack of stercobilinogen in the bowel.(80)

In addition to jaundice, rising bilirubin levels can cause severe pruritus. As hepatic function becomes compromised, patients experience fatigue, anorexia, and bruising caused by loss of clotting factors.

Patients with tumors in the body and tail of the pancreas generally present with nonspecific pain and weight loss. Body and tail tumors are much less likely to cause obstructive signs and symptoms. Patients may have pain in the epigastrium or the back ranging from a dull ache to a severe pain. Tumors in the body and tail usually do not cause symptoms until they are large and most present as locally advanced disease extending to the peritoneum and spleen.(80)

Unexplained weight loss may be the presenting feature of pancreatic cancer. Weight loss may be caused or exacerbated by anorexia, diarrhea, or early satiety. Obstruction of the pancreatic duct causes steatorrhea, exacerbating weight loss and malnutrition. Patients commonly become cachectic as the disease progresses.

- Physical examination:

Other than jaundice, weight loss, and bruising, physical examination findings may be normal. A distended, palpable but non tender gall- bladder in a jaundiced patient (Courvoisier's sign) is 83 to 90% specific but only 26 to 55% sensitive for malignant obstruction of the bile duct. Although Courvoisier's sign increases the likelihood of malignancy, absence of the sign does not rule it out. The liver may be tender and enlarged. In advanced disease stages, patients may present with ascites, palmar erythema, and spider angioma. Other findings associated with advanced pancreatic cancer or other abdominal malignancies include left supraclavicular lymphadenopathy (Virchow's node) and recurring superficial thrombophlebitis (Trousseau's sign).[81]

- Diagnostic Tests:

Together with patient history, physical examination, serum bilirubin and alkaline phosphatase levels can point to pancreatic cancer, but they are not diagnostic. The serum tumor marker carbohydrate antigen CA19-9 may help confirm the diagnosis in symptomatic patients and may help predict prognosis and recurrence after resection. However, CA19-9 lacks sufficient sensitivity (only 50 to 75%) and specificity (80%) to effectively screen asymptomatic patients.[82] Recent data suggested that the serum tumor markers beta subunit of human chorionic gonadotropin (beta-HCG) and CA72-4 are also strong independent prognostic factors.[83,84]

Conventional computed tomography (CT) and transabdominal ultrasonography are appropriate for initial imaging. However, dual-phase helical CT scanning is the most sensitive test, and it noninvasively identifies 98% of pancreatic cancers and distant metastases, providing diagnostic and staging information. If CT findings are not concrete or negative and clinical suspicion remains high, endoscopic ultrasonography can be performed. A fine-needle aspiration biopsy guided by endoscopic ultrasonography may provide tissue diagnosis in patients with primarily nonresectable tumors. Patients who are surgical candidates can undergo definitive surgery without preoperative histologic confirmation. Magnetic resonance imaging is less sensitive than CT and is not used in typical clinical practice.

Endoscopic retrograde cholangiopancreatography (ERCP) is used only when other modalities are inconclusive and the suspicion for malignancy is high or when delineation of the biliary tree is crucial. ERCP also is appropriate when stent placement to relieve biliary obstruction is needed.[85-87]

1.4.4. Tumor staging:

The most widely used staging system for pancreatic cancer is the one designed by the American Joint Committee on Cancer (AJCC) together with the Union for International Cancer Control (UICC). The 8th and latest edition of the AJCC staging manual was released in 2016 und have been effective since the beginning of 2018.[88]

Table 1: 8th Edition Staging Manual AJCC:

AJCC (TNM)			
Primary tumor (T)			
Tx	*Primary tumor cannot be assessed*		
T0	*No evidence of primary tumor*		
Tis	*Carcinoma in situ*		
T1	*Tumor ≤2 cm in greatest dimension*		
T2	*Tumor >2≤ 4 cm in greatest dimension.*		
T3	*Tumor >4cm without involvement of coeliac axis or superior mesenteric artery*		
T4	*Tumor involves coeliac axis or superior mesenteric artery*		
Regional Lymph Nodes (N)			
NX	*Regional lymph nodes cannot be assessed*		
N0	*No regional lymph nodes metastasis*		
N1	*Metastasis in 1-3 lymph nodes*		
N2	*Metastasis in* ≥ 4 lymph nodes		
Distant Metastasis (M)			
M0	*No distant metastasis*		
M1	*Distant metastasis*		
UICC			
Stage 0	*Tis*	*N0*	*M0*
Stage IA	*T1*	*N0*	*M0*
Stage IB	*T2*	*N0*	*M0*
Stage IIA	*T3*	*N0*	*M0*
Stage IIB	*T1*	*N1*	*M0*
	T2	*N1*	*M0*
	T3	*N1*	*M0*
Stage III	*T4*	*Any N*	*M0*
	Any T	*N2*	*M0*
Stage IV	*Any T*	*Any N*	*M1*

Patients included in this series have been treated at our institute between 2006 and 2012. Therefore, they have been staged according to the 6th and 7th editions of the AJCC staging manual released on 2002 and 2009 and effective since 2003 and 2010 respectively.

Differences between these three editions include mainly tumor size and number of lymph nodes metastases.

Table 2: 7th Edition Staging Manual AJCC:

AJCC (TNM)			
Primary tumor (T)			
Tx	*Primary tumor cannot be assessed*		
T0	*No evidence of primary tumor*		
Tis	*Carcinoma in situ*		
T1*	*Tumor limited to pancreas, ≤2 cm in greatest dimension*		
T2*	*Tumor limited to pancreas, >2 ≤ 4 cm in greatest dimension.*		
T3*	*Tumor extends beyond pancreas without involvement of coeliac axis or superior mesenteric artery*		
T4*	*Tumor involves coeliac axis or superior mesenteric artery*		
Regional Lymph Nodes (N)			
NX	*Regional lymph nodes cannot be assessed*		
N0	*No regional lymph nodes metastasis*		
N1	*Metastasis in 1-3 lymph nodes*		
N2*	-		
Distant Metastasis (M)			
M0	*No distant metastasis*		
M1	*Distant metastasis*		
UICC			
Stage 0	*Tis*	*N0*	*M0*
Stage IA	*T1*	*N0*	*M0*
Stage IB	*T2*	*N0*	*M0*
Stage IIA	*T3*	*N0*	*M0*
Stage IIB	*T1*	*N1*	*M0*
	T2	*N1*	*M0*
	T3	*N1*	*M0*
Stage III*	*T4*	*Any N*	*M0*
Stage IV	*Any T*	*Any N*	*M1*

Table 3: 6th Edition Staging Manual AJCC:

AJCC (TNM)			
Primary tumor (T)			
Tx	*Primary tumor cannot be assessed*		
T0	*No evidence of primary tumor*		
Tis	*Carcinoma in situ*		
T1*	*Tumor limited to pancreas, ≤2 cm in greatest dimension*		
T2*	*Tumor limited to pancreas, >2 cm in greatest dimension.*		
T3*	*Tumor extends beyond pancreas without involvement of coeliac axis or superior mesenteric artery*		
T4*	*Tumor involves coeliac axis or superior mesenteric artery*		
Regional Lymph Nodes (N)			
NX	*Regional lymph nodes cannot be assessed*		
N0	*No regional lymph nodes metastasis*		
N1	*Metastasis in 1-3 lymph nodes*		
N2*	-		
Distant Metastasis (M)			
M0	*No distant metastasis*		
M1	*Distant metastasis*		
UICC			
Stage 0	*Tis*	*N0*	*M0*
Stage IA	*T1*	*N0*	*M0*
Stage IB	*T2*	*N0*	*M0*
Stage IIA	*T3*	*N0*	*M0*
Stage IIB	*T1*	*N1*	*M0*
	T2	*N1*	*M0*
	T3	*N1*	*M0*
Stage III*	*T4*	*Any N*	*M0*
Stage IV	*Any T*	*Any N*	*M1*

* Variations between the 6th, 7th and the 8th edition of the AJCC staging manual.

1.4.5. Treatment:

Although many patients are not good candidates for resection at the time of presentation, surgery remains the only chance for a potentially curative treatment. Only 20% of the patients have resectable tumors at the time of diagnosis. Multimodality therapeutic strategies are carried out in most of the operated cases. This includes combinations between Surgery, Chemotherapy and Radiationtherapy on adjuvant and/or neoadjuvant basis.[89] According to the size and extention of the primary tumor and the presence of distant metastases pancreatic cancer is clinically classified into resectable, borderline resectable, locally advanced disease and metastatic disease.[89]

- Resectable pancreatic cancer:

Surgery is recommended for small organ-localized lesions without distant metastases. Tumor free resection margins (R0) should be targeted. Patients with macroscopically rest tumors (R2) will get no benefit at all from the surgery.[89] Until now there is no universally accepted standard pathological reporting for R0, which leads to relevant discrepancies regarding R0/R1 rates. The American-European AJCC/UICC staging system defines R1 resection as the presence of microscopic tumor cells on the resection tissue margin (0mm rule). While the British Royal College of Pathology considers a resection as R1 if tumor cells are present within 1mm of the resected margin.[91]

- Borderline resectable pancreatic cancer:

The definition of borderline resectable pancreatic cancer is not uniform and still under debate. Typically it is defined as the imprecise continuum between radiologically and technically resectable and nonresectable disease. Imaging criteria and clinical features are the main deciding factors.[89] As vascular reconstruction is usually the limiting factor during surgery. Therefore, vascular involvement plays the key role in deciding whether the tumor is resectable or not. Older studies have shown that pancreatic resection en bloc with resection of parts of the mesenterico portal axis did not improve outcomes.[97] This hypothesis has been challenged by later studies from single institution high volume centers.[98,99]

Data about arterial resection alongside pancreatectomy procedures for pancreatic cancers is limited. Mollberg et al showed in his meta analysis of 26 studies that patients undergoing pancreatectomy en bloc with arterial resection had significantly greater perioperative morbidity and mortality.

However, arterial resection indeed improved the survival compared to patients who did not undergo resection.[100] This conclusion was supported by other studies from high volume centers.[101]

- Locally advanced pancreatic cancer:

The term locally advanced pancreatic cancer implies the involvement of adjacent structures, especially major arteries, by the pancreas tumor that precludes surgical resection, without evidence of distant metastases.[89] Subjective clinical assessment und staging as well as variations between different institutions lead to overlap at the presentation of borderline and locally advanced tumors.[102]

- Metastatic pancreatic cancer:

Surgical resection of the primary tumor is no more of a benefit for patients with metastatic tumors. Gastric and biliary bypass procedures can be offered to control symptoms such as icterus and mechanical bowel obstruction.

Figure 5: Criteria for resectability: *(source: Anuhya Kommalapati et al 2018)*

Criteria for resectability

	NCCN	AHPBA/SSAT/SSO	MD Anderson	Intergroup (Alliance)
Celiac artery	No abutment for pancreatic head cancer. For body/tail, ≤ 180° contact	No abutment or encasement	Abutment	Tumor-vessel interface < 180° of vessel wall circumference
CHA	Solid tumor contact ≤ 180° allowing for reconstruction	Abutment or short segment encasement	Abutment or short-segment encasement	Reconstructable short-segment interface of any degree
SMA	Solid tumor contact ≤ 180°	Abutment	Abutment	Tumor-vessel wall interface < 180° of vessel wall circumference
SMV/PV	Solid tumor contact > 180° or contact of ≤ 180° with contour irregularity or thrombosis allowing for safe reconstruction	Occlusion	Occlusion	Tumor-vessel interface ≥ 180° of vessel wall circumference and/or reconstructible occlusion

CHA: Common hepatic artery; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; PV: Portal vein; NCCN: National Comprehensive Cancer Network; AHPBA/SSAT/SSO: Americas Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology.

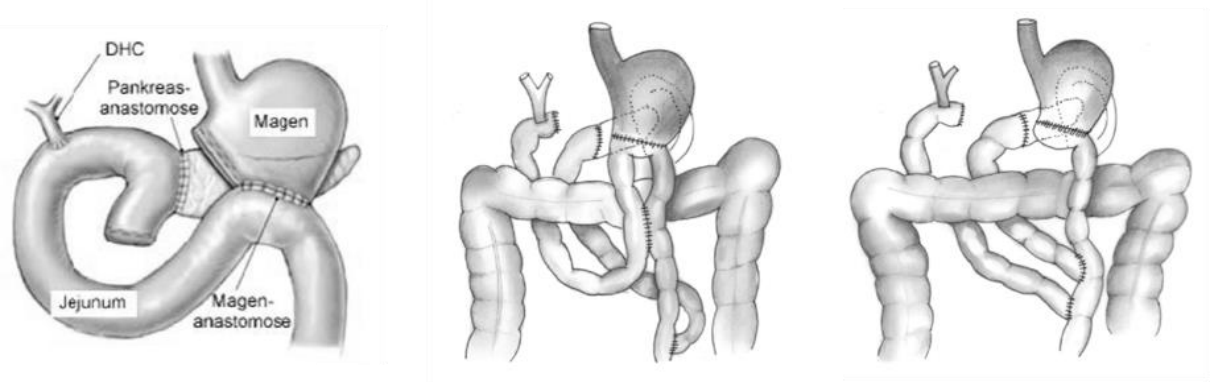
- Surgical procedures:

According to tumor location, size and invasion of adjacent structures surgical procedures vary from one patient to another. Tumors in the head part of the pancreas are resected via a partial pancreaticoduodenctomy *(Whipple procedure).*

Figure 6: Whipple procedure:
Removal of most of the duodenum, the pylorus, head of pancreas, distal part of the common bile duct, the gallbladder and regional lymph nodes. Bruns, Kleespies et al 2009[95]

Reconstruction can take place using 1, 2 or even 3 loops of small intestine. At our institution a reconstruction using 2 loops of small intestine is carried out on standard basis.[95] Independently from the type of reconstruction, three anastomoses have to be accomplished: a pancreaticojejunostomy, a gastroenterostomy and a biliary anastomosis.

Figure 7: Types of reconstruction in Whipple procedure:
one loop (left), two loops (middle) or three loops (right). Bruns, Kleespies et al 2009[95]



To avoid dumping symptoms caused by loss of regulation of stomach emptying after pyloric resection, a pylorus preserving Whipple are carried out sometimes. In tumors of the body or tail parts of the pancreas or tumors to the left from the mesenterico portal axis a distal pancreatectomy with splenectomy is carried out in most of the cases (distal splenopancreatectomy). Big pancreas body tumors can be removed using a total or subtotal pancreatoduodenectomy with or without splenectomy.

- Vascular 'venous' resection:

Irrespective of the type of procedure performed, a complete mobilization of the specimen should be done before the vascular resection resulting in an en bloc resection of the whole specimen including the affected vessel. Tangential resection of the lateral superior mesenteric vein or portal vein or segmental sleeve resection can be performed based on tumor location. Tangential resection in case of attachment of the tumor to the right-sided superior mesenteric vein or portal vein was usually reconstructed by simple venous suture. In case of resection of more than one-third of the lateral wall, autologous venous patches (internal jugular, saphenous, inferior mesenteric vein) can be performed to avoid venous narrowing. Hereby, the splenic vein can be preserved. In case of infiltration of more than half of the circumference a venous segment resection should be done. Reconstruction is carried out using an end to end anastomosis or using a venous patch. In case of confluence resection the splenic vein stump is not reinserted when adequate collateral circulation is present via the short gastric veins. [152]

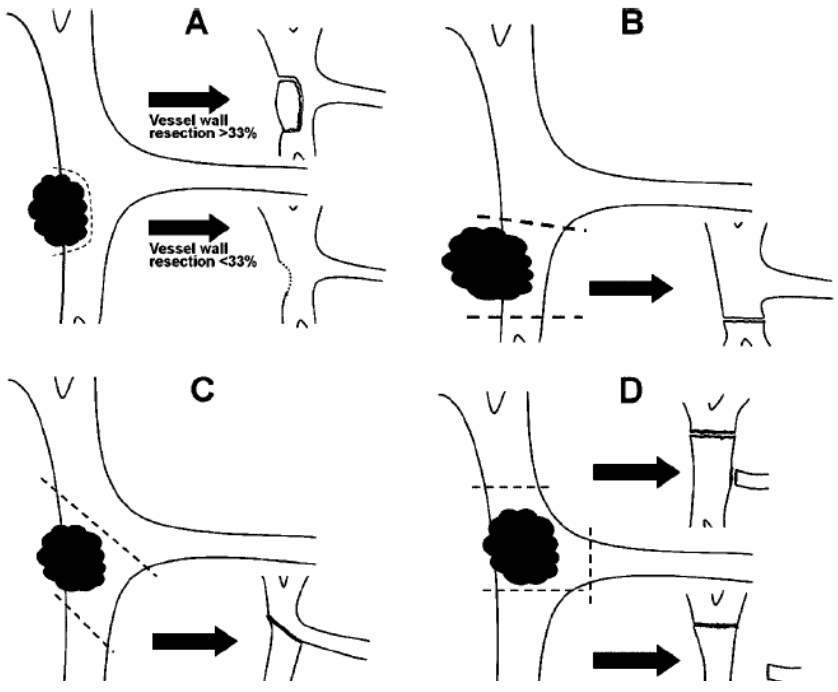


Figure 8: Types of reconstruction after resection of parts of the mesenterico portal axis:

A: tangential resection with or without vascular patch.

B: SMV segment resection.

C/D: Confluence resection.

Neoadjuvant and adjuvant therapies:

- Neoadjuvant treatment:

Over the recent years data from single institutions und some meta analyses increased focus on the neoadjuvant treatment options for early stage disease as well as locally advanced tumors.[103] Decreasing tumor size, disease downstaging, increasing the R0 resection rates, limiting surgical complexity and treating micrometastases at the time of diagnosis were the main driving forces for application of neoadjuvant treatment in pancreatic cancer. [103]

Table 4: Recent meta analyses supporting neoadjuvant treatment: *(source Raufi et al 2018)*

Study	Patient population	Data	Comment
Gillen et al. (2010) [13]	• Pooled data from 111 neoadjuvant trials conducted between 1966 and 2009 • 4,394 patients with PDAC grouped into two cohorts: resectable and nonresectable disease	• Amongst patients initially diagnosed with nonresectable disease who underwent neoadjuvant therapy: → 46.9% underwent surgical exploration → 69.9% had successful resection → 79.2% had R0 resection • Estimated mOS = 20.5 months	• Estimated mOS of 20.5 months, mirrors that of patients with resectable disease at diagnosis • Major drawback that analysis not done by ITT which would reduce potential bias in treatment effect (survival bias), since not all patients proceed to surgery
D'Angelo et al. (2017) [14]	• Pooled data from 12 prospective neoadjuvant studies published between 2008 and 2015 • 624 patients with resectable, BR, and LA PDAC	• ITT analysis • Resection rate = 65% • Similar mOS of 22.78 months	• One of the first meta-analyses to report survival using ITT analysis • Focused solely on prospective trials
Versteijne et al. (2018) [15]	• Pooled data from 38 trials • 3,484 patients with resectable or BR PDAC	• ITT analysis • Resectable disease → Similar mOS for upfront surgery (17.4 months) *v* neoadjuvant therapy (18.2 months) → R0 rates favored neoadjuvant therapy (85% *v* 71.4%) • BR disease • mOS favored neoadjuvant therapy (19.2 months) over upfront surgery, (12.8 months) • R0 rates favored neoadjuvant therapy (88.6 *v* 63.9%)	• One of the largest ITT meta-analysis performed to date
Suker et al. (2016) [16]	• Pooled data from 11 studies of neoadjuvant FOLFIRINOX • 315 patients with LA PDAC	• 25% of patients effectively downstaged and able to undergo resection • Estimated mOS = 24.2 months	• Focused on solely on LA PDAC
Mokdad et al., (2017) [17]	• Retrospective study of National Cancer Database between 2006 and 2012 • Utilized propensity score matched analysis to investigate role of neoadjuvant therapy in stage I or II PDAC who underwent surgery • 2,005 patients treated with neoadjuvant therapy followed by surgery matched with 6,015 patients with upfront resection	• Median overall survival of 26 months with neoadjuvant therapy *v* 21 months with upfront resection	• Limited by inherent selection bias, as neoadjuvant therapy group populated with those patients who tolerated neoadjuvant therapy • Demonstrates the utility of neoadjuvant therapy as a selection strategy for management of patients with early stage disease

Abbreviations: mOS, median overall survival; ITT, intention-to-treat; BR, borderline resectable; LA, locally advanced; PDAC, pancreatic ductal adenocarcinoma

The indication of neoadjuvant treatment in patients with resectable tumors was also under debate. Failure to response to the treatment or even disease progress into metastatic or locally advanced 'nonresectable' tumor have been reported up to 16% according to *Zhan et al 2017*.[104] *Golcher et al 2015* demonstrated that neoadjuvant treatment for resectable tumors could not increase the resection rates but indeed increased the median overall survival.[105]

Table 5: Studies discussing neoadjuvant treatment for resectable pancreatic cancer: *(source Raufi et al 2018)*

Trial	N	Therapy	Resection rate (%)	R(0) Resection rate (%)	Median survival
Palmer et al. (2007) [27]	50	A: Gemcitabine 1 g/m^2 every 7 days for 43 days B: Gemcitabine 1 g/m^2 + cisplatin 25 mg/m^2 every 7 days (omitting day 22 or days 15 and 36 [revised schedule])	A: 9/24 (38) B: 18/26 (70)	A: 6/9 (75) B: 12/18 (75)	A: 9.9 months B: 16.6 months
Heinrich et al. (2008) [26]	28	Gemcitabine 1 g/m^2 + cisplatin 50 mg/m^2 biweekly for 4 cycles	25/28 (89)	(20/25) 80	26.5 months
O'Reilly et al. (2014) [28]	38	Gemcitabine 1 g/m^2 + oxaliplatin 80 mg/m^2 biweekly for 4 cycles	27/38 (71)	20/27 (74)	27.2 months
Golcher et al. (2015) [29]	66	A: Surgery B: Gemcitabine 300 mg/m^2 + cisplatin 30 mg/m^2 days 1, 8, 22, 29 with RT	A: 23/33 (70) B: 19/33 (58)	A: 16/23 (70) B: 17/19 (89)	A: 14.4 months B: 17.4 months
Casadei et al. (2015) [30]	38	A: Surgery B: Gemcitabine 1 g/m^2 days 1, 8, every 21 days x 2 cycles followed by gemcitabine 50 mg/m^2 twice weekly for a total of 6 weeks + RT	A: 15/20 (75) B: 11/18 (61)	A: 5/15 (33) B: 7/11 (64)	A: 19.5 months B: 27.5 months

The role of neoadjuvant treatment in borderline resectable and locally advanced tumors has been also distinctively investigated. Furthermore, radiation therapy was included in some trials. However, most of the trials were carried out at single centers and had small sample sizes.

For example, the PREOPANC study from 2018 showed survival benefit and higher rates of R0 resection for patients with borderline resectable tumors who received neoadjuvant chemotherapy + Radiation therapy compared to patients who were directly operated. Notably, resection rates were lower in the neoadjuvant group. Trials of neoadjuvant treatment in locally advanced tumors showed some superiority in R0 resection rates but no survival benefit.[103]

Table 6: Studies discussing neoadjuvant treatment for borderline and locally advanced pancreatic cancer: *(source Raufi et al 2018)*

Neoadjuvant clinical trials for patients with borderline resectable pancreatic cancer.

Trial	N	Therapy	Resection rate (%)	R(0) Resection rate (%)	Median survival
Motoi et al. (2013) [31]	35	Gemcitabine 1,000 mg/m^2 days 1 and 8 with S-1 40 mg/m^2 BID for 14 days every 21 days x 2 cycles	30/35 (86)	26/30 (87)	19.7 months
Landry et al. (2010) [32]	21	A: Gemcitabine 500 mg/m^2 weekly for 6 weeks with RT	A: 3/10 (30)	Not reported	A: 19.4 months
		B: Gemcitabine 175 mg/m^2 on days 1, 5, 29, and 33, cisplatin 20 mg/m^2 on days 1–5 and 29–32, 5-FU 600 mg/m^2 on days 1–5 and 29–32 followed by radiation with continuous infusion 5-FU 225 mg/m^2 for 6 weeks	B: 2/11 (18)		B: 13.4 months
Kim et al. (2013) [33]	68	Gemcitabine 1 g/m^2 on days 1, 8, 15 + oxaliplatin 85 mg/m^2 on days 1, 15 every 21 days for 2 cycles with RT, 30 Gy	43/68 (63)	36/43 (84)	18.2 months
Katz et al. (2016) [34]*	22	modified FOLFIRINOX (85 mg/m^2 of oxaliplatin, 180 mg/m^2 of irinotecan hydrochloride, 400 mg/m^2 of leucovorin calcium, and 2,400 mg/m^2 of 5-FU) followed by 5.5 weeks of external-beam RT (50.4 Gy) concurrently with capecitabine 825 mg/m^2 BID	15/22 (68)	14/15 (93)	21.7 months
Murphy et al. (2018) [35]	48	FOLFIRINOX (85 mg/m^2 oxaliplatin, 400 mg/m^2 bolus 5-FU on day 1, then 2,400 mg/m^2 continuous infusion for 46 hours. Leucovorin calcium, 400 mg/m^2, and irinotecan hydrochloride, 180 mg/m^2) x8 cycles. Upon restaging, patients with resolution of vascular involvement received RT (5 Gy × 5) with capecitabine. Patients with persistent vascular involvement received RT with 5-FU or capecitabine.	32/48 (66)	31/32 (97)	37.7 months
van Tienhoven et al. (2018) [36]	246	A: Surgery	A: 91/127 (72)	A: 28/91 (31)	A: 13.5 months
		B: 15 times of 2.4 Gray (Gy) combined with gemcitabine, 1,000 mg/m^2 on days 1, 8, and 15, preceded and followed by a cycle of gemcitabine	B: 72/119 (60)	B: 45/72 (63)	B: 17.1 months

* Trial included patients with resectable disease.

Neoadjuvant clinical trials for patients with locally advanced pancreatic cancer.

Trial	N	Therapy	Resection rate (%)	R(0) Resection rate (%)	Median survival
Herman et al. (2015) [37]	49	Gemcitabine (1,000 mg/m^2) x3 doses followed by RT (33.0 Gy)	4/49 (8)	4/4 (100)	13.9 months
Ikeda et al. (2013) [39]	60	S-1 80 mg/m^2 BID with RT (50.4 Gy) in 28 fractions over 5.5 weeks	2/60 (3)	Not reported	16.2 months
Marthey et al. (2015) [43]	77	Folfirinox oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), irinotecan (180 mg/m^2), 5-FU (400 mg/m^2 bolus with a 46-hour continuous infusion of 2.4 g/m^2) every 2 weeks	28/77 (36)	25/28 (89)	22 months
Sherman et al. (2015) [38]	45	GTX capecitabine (1500 mg/m^2, days 1–14), gemcitabine (750 mg/m^2, days 4 and 11) and docetaxel (30 mg/m^2, days 4 and 11) followed by GX/RT if extensive arterial involvement	40/45 (89)	28/40 (70)	29 months

- Adjuvant Treatment:

For patients with potentially curable pancreatic tumors adjuvant chemotherapy is recommended on standard basis to prevent disease recurrence which is very common even with the earliest tumor stages. Reproducible data showed better overall survival for patients who received adjuvant chemotherapy following surgical resection.[92] Gemcitabine had been the most widely used regimen for adjuvant chemotherapy for pancreatic cancers. 5 Fluorouracil and Leucovorin have been also tried.[93] The ESPAC-4 Study *(European Study Group for Pancreatic Cancer)* showed remarkable survival benefit when combining Gemcitabine with Capecitabine compared to Gemcitabine only. This regimen is currently the standard adjuvant therapy for resected pancreatic cancer.[89,94]

Recently, and based on the experienced beneficial application of FOLFIRINOX as a palliative chemotherapy, *Conroy et al. 2018* demonstrated remarkable survival benefit for FOLFIRINOX as an adjuvant chemotherapy for resected pancreatic cancer compared to Gemcitabine. Though, this benefit is achieved at the expenses of more toxic effects.

- Palliative therapy:

Palliative therapy in nonresectable pancreatic cancer targets mainly pain and obstructive symptoms aiming to improve the quality of life. Biliary digestive and gastrojejunal anastomoses (double Bypass) can be carried out to overcome jaundice and gastric output obstruction. Stenting the bile duct using endoscopic retrograde cholangiopancreatography (ERCP) can be carried out in cases of isolated jaundice without gastric output obstruction.

1.5. Purpose of the study:

Pancreatic cancer is one of the most aggressive tumors of the gastrointestinal tract. The complex pathophysiology and molecular biology of the tumor as well as the unfavorable anatomical relations to the major visceral blood vessels add more difficulty to the management of such a malignancy. Hence, the prognosis of pancreatic cancer remains almost unchanged over years with a 5 year survival rate around 5%.

Surgical resection represents the only possible chance for a potential cure. However, only 15-20% of the patients present with small localized tumor at the time of diagnosis. Extension of the surgical procedures to include resection of neighboring organs or adjacent vital blood vessels has been a focus for clinical surgical research over the last decades. Till the 1990s, tumor infiltration of the mesenterico portal axis had been considered a contraindication for surgical resection. Nowadays, due to the increasing surgical experiences in high volume pancreas centers as well as development of the perioperative care, an en bloc pancreatectomy with vascular resection is carried out on regular basis with very promising outcomes regarding overall survival and postoperative morbidity.

On the other hand, systemic chemotherapy is an essential component of the multimodality therapy in pancreatic cancer. Chemotherapy can be applied on adjuvant or neoadjuvant basis with curative intention and also as a palliative therapy for non resectable tumors. Recent trials in chemotherapy for pancreatic cancer have shown some improvement in terms of survival.

With this improvement in chemotherapy regimens and the remaining controversy about the indication for an extended pancreatectomy with en bloc vascular resection for locally advanced tumors, two hypotheses have been suggested:

a) In terms of survival, it is still worthy to carry out an en bloc vascular resection instead of palliative chemotherapy for borderline resectable and locally advanced pancreatic cancer.

b) The survival benefit after en bloc vascular resection is NOT balanced out by the postulated higher postoperative morbidity and mortality.

2. Material and Methods:

This is a retrospective data analysis of patients with different stages of pancreatic cancer who underwent pancreatic resections at the department of General, Visceral and Thoracic Surgery at the University Medical Center Hamburg-Eppendorf.

2.1. Selection of patients:

Between 2006 and 2012 a total of 764 patients have been admitted at our department for a planned pancreatic resection by pancreatic cancer. A curative concept of therapy have been intended for all patients.
Patients who underwent a neoadjuvant chemotherapy (n=185) were excluded. Surgical exploration showed inoperable tumors in 142 patients. These patients were also excluded. The final cohort included a total of 437 patients.

2.2. Subgroups of patients:

The cohort of 437 patients was divided into two main groups: 364 patients who underwent conventional pancreatectomy procedures without vascular resections (*n*VR) and 73 patients who underwent extended pancreatectomy procedures enbloc with resection of parts of the mesenterico portal axis (VR). The later group (VR) was further divided according to microscopic proof of tumor invasion of the resected venous segment.

2.3 Perioperative management:

The preoperative tumor work up included routine laboratory tests including tumor markers (CA19-9 and CEA), abdominal ultrasound, computed tomography as well as endoscopic investigations such as endoscopic retrograde cholangiopancreatography with or without ultrasound. Distant metastases were investigated using standard imaging procedures such as x-ray and/or computed tomography.

The postoperative management included routine laboratory tests alongside with daily physical examinations with special regards for the common surgical complications such as hemorrhage, bile leak, anastomosis insufficiency and pancreatic fistula. Portal vein thrombosis was investigated via Doppler ultrasound on routine basis in patients who underwent an enbloc vascular resection. Perioperative mortality was defined as death within the first 30 days after surgery.

2.4. Follow up:

Follow up was carried out through regular patients' visits at our outpatient clinic for the first 3 months after surgery. Later on, the follow up was done through contacting the patients' family doctors or from the data collected from our regional cancer registry. In some cases the patients have been directly contacted. In this study the median follow up of the whole cohort was 22 months.

2.5. Ethical Consideration:

All the collected data was treated anonymously and was saved only by the author. The data was only generated for this study and was not shown/manipulated to/by a third party. Under this limitation and according to the law of the medical syndicate in Hamburg *(Berufung, § 9 Abs.2 Hamburgerisches Kammergesetz für Heilberufe)*, there was no need for an additional ethical approval.
The offered treatment at the time of surgery as well as all surgical decisions taken were completely independent from all research studies including this one.

2.6. Statistical analysis:

The statistical analysis was performed using SPSS software and Prism Graphpad. Survival probabilities were estimated using the Kaplan Meier curves. Differences between patient groups were assessed by Log-rank test. Differences were considered to be statistically significant at a P value of <0.05. Patients who died within 90 days after the surgery were excluded from the overall survival statistics.

3. Results:

3.1. Characteristics of patients:

The age of included patients ranged from 32 to 90 years old. The median age was 67.5 years. Among the 437 patients included there was 224 males and 213 females.
The cohort of 437 patients was divided into two main groups: 364 patients who underwent classical pancreatectomy procedures without vascular resections (*n*VR) and 73 patients who underwent extended pancreatectomy with en bloc vascular resection (VR). The later group (VR) was further divided according to the histological proof of tumor invasion of the resected vessel.
Thirty one patients had histologically tumor invasion of the resected vein (VR+), whereas in 42 patients the histology reports had shown no signs of tumor invasion of the portal vein (VR-).
Other findings such as tumor differentiation, lymph node involvement and vascular invasion were assessed at our department of histopathology at our institute.

Table 7: Characteristics of patients:

		VR		**(nVR) (n=364)**	**Total (n=437)**	***P***
	VR+ (n=31)	*VR- (n=42)*	Total (n=73)			
Gender M/F	*15/16*	*16/26*	31/42	193/171	224/213	*0.1285*
Median age	*67 (49-87)*	*66 (41-83)*	66 (41-87)	69 (32-90)	67.5 (32-87)	*0.9203*
Age groups:						
30-50 years	*5 (16.1%)*	*3 (7.2%)*	8 (11%)	37 (10.2%)	45 (10.3%)	*0.3802*
51-70 years	*23 (74.2%)*	*30 (71.4%)*	53 (72.6%)	201 (55.2%)	254 (58.1%)	*0.2059*
>71 years	*3 (9.7%)*	*9 (21.4%)*	12 (16.4%)	126 (34.6%)	138 (24.6%)	***0.0298***

VR+ = vascular infiltration. VR- = no vascular infiltration. nVR= no vascular resection.

3.2. Types of Surgery:

Based on perioperative assessment as well as intraoperative findings regarding the location of the tumor different surgical procedures had been carried out.

Partial pancreato-duodendectomy *‚Whipple'* (PPD) was the most common procedure carried out. In the VR group, 22 patients (71%) from the VR+ group and 31 patients (73.8%) from the VR- group had undergone a Whipple resection.

Total duodeno-spleno-pancreatectomy (TDSP) procedures had been carried out in 8 patients (25.8%) from the VR+ group and in 10 patients (23.8%) from the VR- group. One VR+ patient (3.2%) had undergone a pyloric preserving pancreatoduodenectomy (PPPD) and one VR- patient (2.3%) had undergone a distal spleno-pancreatectomy (DSP).

In the nVR group the procedures were divided as follows: 203 patients (55.8%) > PPD, 64 patients (17.6%) > PPPD, 34 patients (9.3%) > TDSP and 63 patients (17.3%) > DSP.

Table 8: Types of surgery:

	VR			**(nVR) (n=364)**	**Total (n=437)**	***P***
	VR+ (n=31)	*VR- (n=42)*	Total (n=73)			
Type of surgery						
PPD	*22 (71%)*	*31 (73.8%)*	53 (72.6%)	203 (55.8%)	256 (58.6%)	*0.2238*
TDSP	*8 (25.8%)*	*10 (23.8%)*	18 (24.7%)	63 (17.3%)	81 (18.5%)	*0.2987*
PPPD	*1 (3.2%)*	*0*	1 (1.4%)	64 (17.6%)	65 (14.9%)	***0.0024***
DSP	*0*	*1 (2.3%)*	1 (1.4%)	34 (9.3%)	35 (8%)	*0.0541*

VR+ = vascular infiltration. VR- = no vascular infiltration. nVR= no vascular resection. PPPD = Pylorus preserving pancreatoduodenectomy. TDSP = total duodeno-splenopancreatectomy. PPD = partial pancreatoduodenectomy (whipple). DSP = distal splenopancreatectomy

3.3. Tumor classification:

In the nVR group 334 patients had T3 or T4 tumors and only 30 patients had T1 or T2 tumors. Whereas all 73 patients in the VR group had T3 or T4 tumors *(P= 0.698)*. Nodal involvement was present in 60 and 280 patients in the VR and nVR groups respectively. *(P=0.402)* Resection margins were free (R0) in 69.9% of the VR patients and in 55.2% of the nVR patients *(P= 0.029).* From the 22 patients with R1 resection margins in the VR group, the R1 situation was on the venous resection site only in one patient. In the other 21 patients the R1 situation was at the dorsal resection margin. Within the 163 patients with R1 resection margins in the nVR group, only 41 patients had had microscopically tumor cells the at the dorsal or the intrapancreatic resection sites. In the other 122 patients, tumor cells were present at the SMV groove.

Table 9: Tumor classification:

	VR			**(nVR) (n=364)**	**Total (n=437)**	***P***
	VR+ (n=31)	*VR- (n=42)*	Total (n=73)			
Tumor						
T1	*0*	*0*	0	8 (2.2%)	8 (1.9%)	
T2	*0*	*0*	0	22 (6%)	22 (5%)	
T3	*25 (80.6%)*	*39 (92.9%)*	64 (87.7%)	320 (87.9%)	385 (88.1%)	*0.887*
T4	*6 (19.4%)*	*2 (4.8%)*	8 (10.9%)	14 (3.9%)	22 (5%)	*0.024*
Nodal involvement						
N0	*4 (12.9%)*	*9 (21.4%)*	13 (17.8%)	84 (23.1%)	97 (22.2%)	
N1	*27 (87.1%)*	*33 (78.6%)*	60 (82.2%)	280 (76.9%)	340 (77.8%)	*0.402*
Resection margins						
R0	*18 (58.1%)*	*33 (78.6%)*	51 (69.9%)	201 (55.2%)	252 (57.7%)	
R1	*13 (41.9%)*	*9 (21.4%)*	22 (30.1%)	163 (44.8%)*	185 (42.3%)	***0.029***

VR+ = vascular infiltration. VR- = no vascular infiltration. nVR= no vascular resection.
* R1 at the SMV groove in 122 patients.

3.4. Perioperative morbidity and mortality:

Anastomosis insufficiency (AI) was the most common complication reported. A total of 74 patients (16.9%) had at least one anastomosis which was insufficient. With respect to the type of surgery and the carried out anastomoses the pancreaticojejunostomy was the most vulnerable anastomoses with leakage rates of 20.2% and 3.7% in the nVR and the VR groups respectively *(P=0.010).* An insufficiency of the biliary anastomoses was seen in 3 VR patients (4.2%) and in 11 nVR patients (3.3%) *(P= 0.740).* Two nVR patients (0.6%) had an insufficient gastroenterostomy. Two more nVR patients had insufficient panreaticojejunostomy and biliary anastomosis.

From the whole cohort 58 patients (15.9%) suffered a pancreatic fistula: 3 (5.5%) from the VR group and 55 (18.2%) from the nVR group *(P=0.036).* Grade C pancreatic fistula had been only reported in 14 patients (4.7%) from the nVR group.

One VR Patient (1.4%) had a postoperative hemorrhage compared to 35 patients (9.6%) from the nVR group *(P= 0.027).* Nine nVR patients (2.5%) had a postoperative portal vein thrombosis compared to only one VR patient (1.4%) *(P=0.571).* Intraabdominal infections have been also reported in comparable rates in both VR (9.6%) and nVR (5.2%) groups *(P=0.180).*

In-hospital mortality (30 days mortality) was slightly higher in the VR group (12.3%) than in the nVR group (5.8%) *(P=0.064).*

Table 10: Perioperative morbidity and mortality:

	VR			(nVR) (n=364)	Total (n=437)	*P*
	VR+ (n=31)	*VR- (n=42)*	Total (n=73)			
Pancreatic fistula						
Grade A	*1(4.3%)*	*1 (3.1%)*	2(3.6%) ⊠	9 (3%) ⊠	11(3%) ⊠	
Grade B	*0*	*1 (3.1%)*	1(1.8%) ⊠	32 (10.6%) ⊠	33 (9%) ⊠	
Grade C	*0*	*0*		14 (4.7%) ⊠	14 (3.8%) ⊠	
total			3 (5.5%) ⊠	55 (18.2%)⊠	58 (15.9%) ⊠	***0.036***
Anastomoses insufficiency						
GE	*0*	*0*	0	2 (0.6%)*	2 (0.5%)*	
PJ	*1(4.3%)***	*1 (3.2%)***	2 (3.7%)**	54 (20.2%)**	56 (16.5%)**	***0.010***
Biliary	*2 (6.5%)****	*1 (2.4%)****	3 (4.2%)***	11 (3.3%)***	14 (3.5%)***	*0.740*
PJ+ biliary	*0*	*0*	0	2 (0.7%)**	2 (0.6%)**	
total			5 (6.8%)	69 (18.9%)	74 (16.9%)	***0.027***
Hemorrhage	*1(3.2%)*	*0*	1 (1.4%)	35 (9.6%)	36 (8.2%)	***0.027***
Portal vein thrombosis	*1(3.2%)*	*0*	1 (1.4%)	9 (2.5%)	10 (2.3%)	*0.571*
Intraabdominal infections	*4 (12.9%)*	*3 (7.1%)*	7 (9.6%)	19 (5.2%)	26 (5.9%)	*0.180*
30 days mortality	*6 (19.3%)*	*3 (7.1%)*	9 (12.3%)	21 (5.8%)	30 (6.9%)	*0.064*

GE: Gastroenterostomy. PJ: Pancreaticojejeunostomy.

⊠ Patients who underwent a total duodenosplenopancreatectomy (n= 18 VR, 63 nVR) are excluded as they could not develop a pancreas fistula.

* Patients who underwent a distal splenopancreatectomy (n=34) are excluded as they lack a gastroenterostomy.

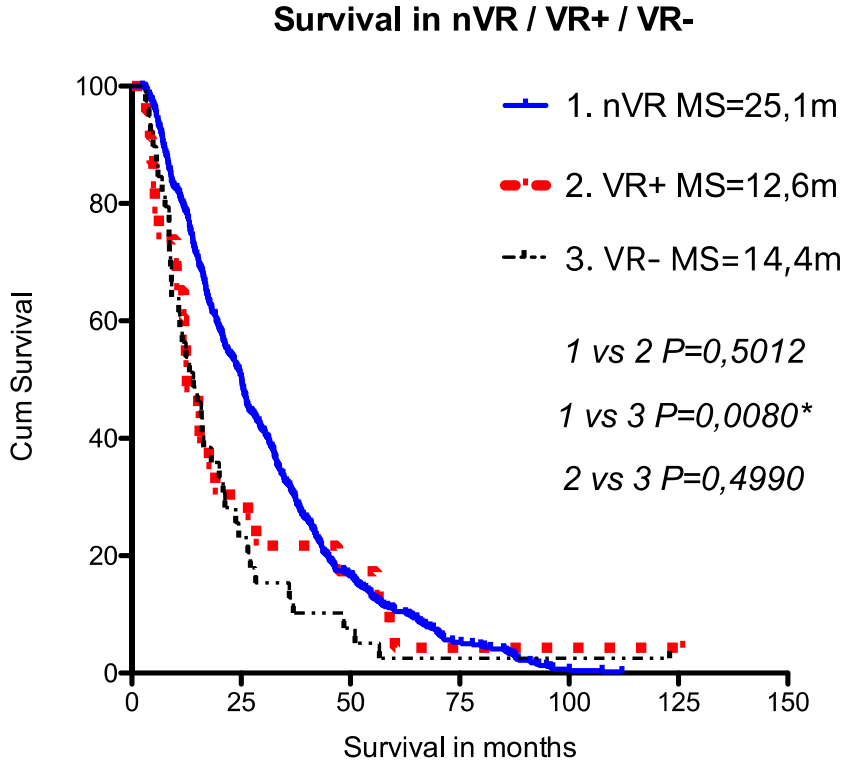
** Patients who underwent a total duodenosplenopancreatectomy (n= 63) or a distal splenopancreatectomy (n=34) are excluded as they lack a pancreaticojejunostomy.

*** Patients who underwent a distal spelnopancreatectomy (n=34) are excluded from the statistik as they lack a biliary anastomosis.

3.5. Survival:

The median survival (MS) was 25.1 months in the nVR group compared to 14.1 months in the VR group *(P=0.0158).* Patients with histological proof of tumor invasion (VR+) had a MS of 12.6 months, while those without tumor invasion (VR-) had a MS of 14.4 months. Two patients (2.7%) from VR group and 16 patients (4.4%) from the nVR group survived for more than 10 years. The MS in the whole VR group was 14.1 months.

Figure 9: Survival in nVR, VR+ and VR- groups

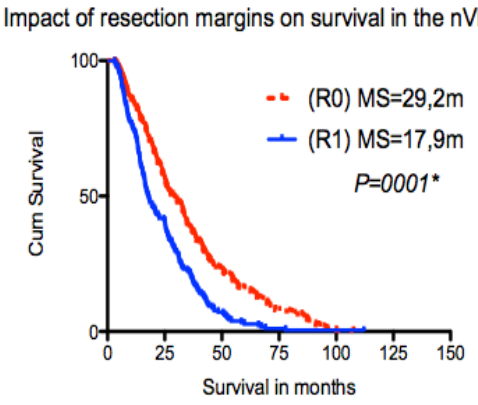


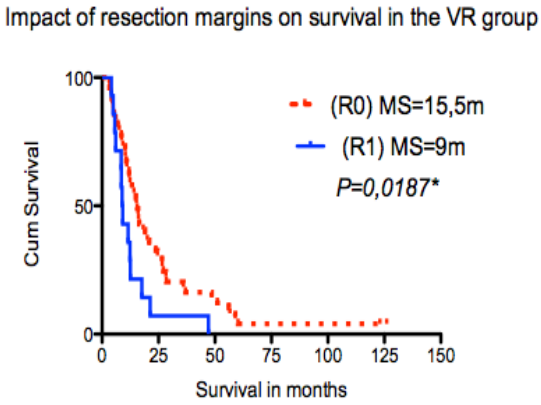
The following graphs show the differences in MS between the nVR and VR groups and between the VR+ and VR- subgroups regarding vascular infiltration, nodal involvement, resection margins, tumor size, and age.

- Resection margin:

Regardless of the vascular resection, patients with tumor free resection margins had significantly better MS.

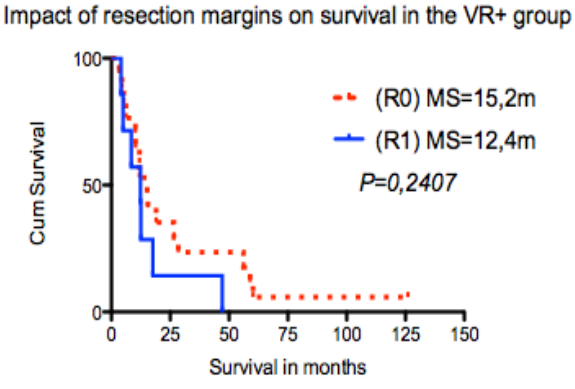
Figure 10: Impact of resection margins on survival in nVR and VR groups:

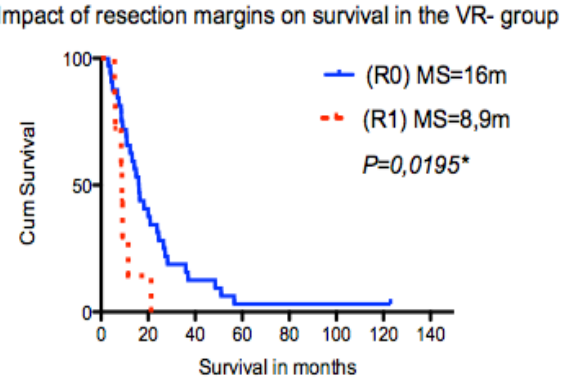




Independant of vascular tumor invasion patients with tumor free resection margins had also better but statistically non significant MS.

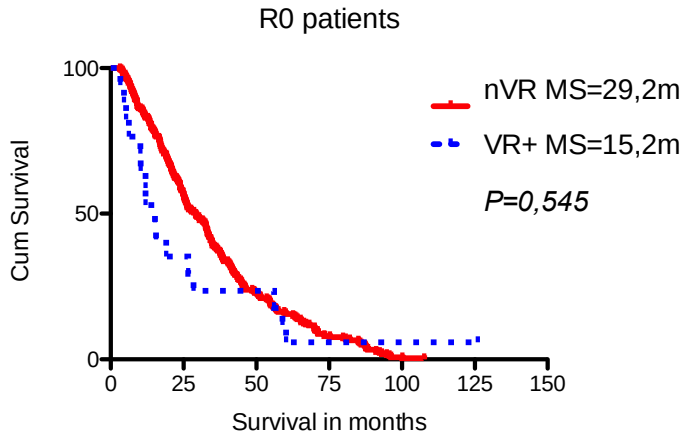
Figure 11: Impact of resection margins on survival in VR+ and VR- groups:





Moreover, there was no significant difference in survival between only R0 patients from the nVR (29,2m) and VR+ (15,2m) groups. (*P=0,545)*

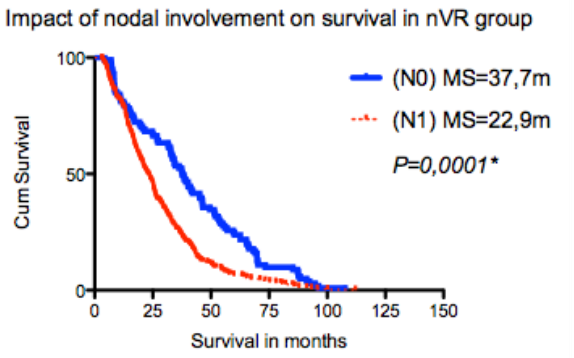
Figure 12: Impact of resection margins on survival in nVR and VR+ groups:

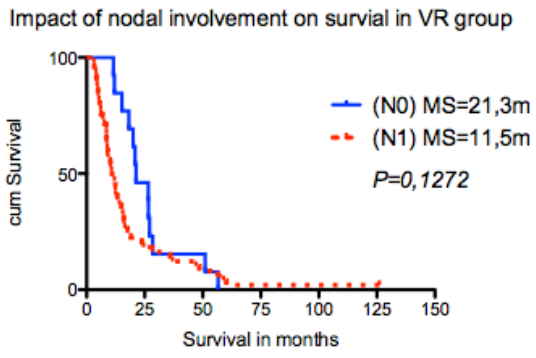


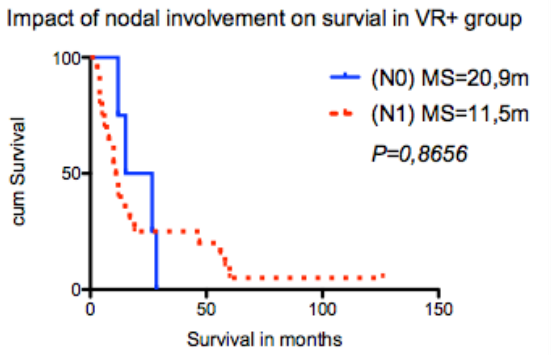
- Nodal involvement:

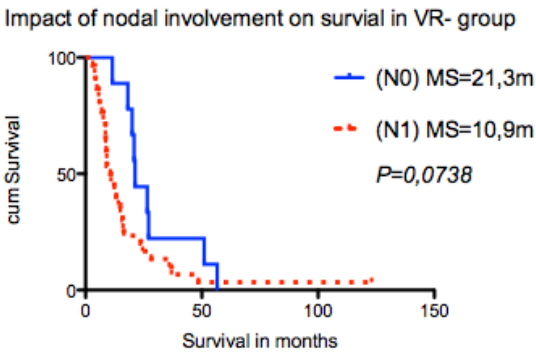
The impact of nodal involvement on survival was similar to that of the resection margin. Patients without lymph node metastasis had a better survival than those with lymph node metastases. Neither vascular resection nor vascular invasion changed the better survival trends of N0 patients.

Figure 13: Impact of nodal involvement on survival in all groups:





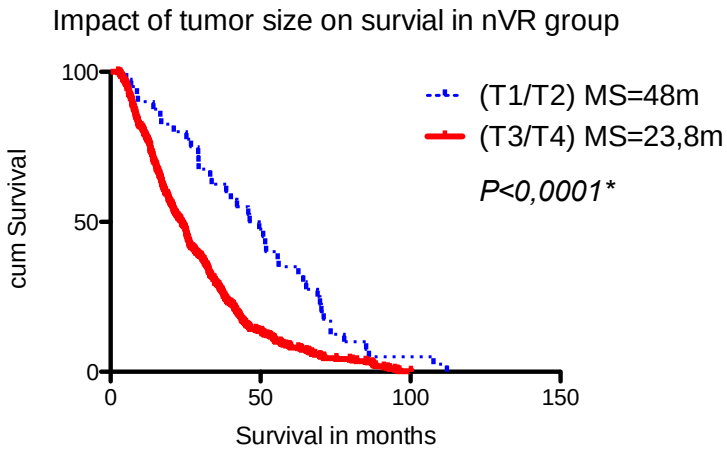




- Tumor size:

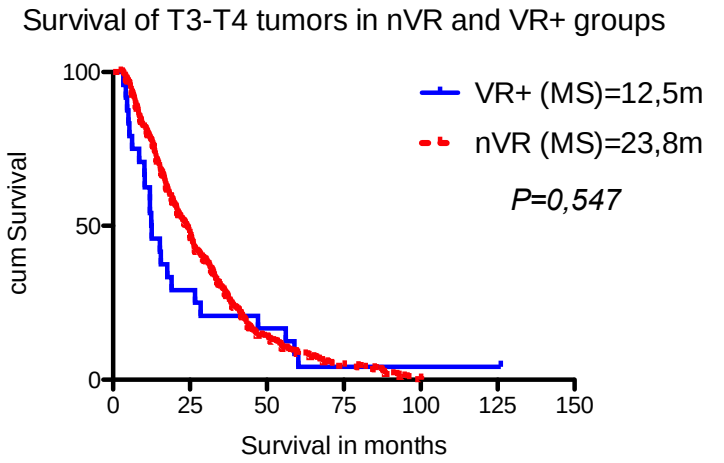
As mentioned before, T1-T2 tumors were present only in the nVR group. Patients with T1-T2 tumors had a remarkably better MS than patients with T3-T4 tumors (48m Vs 23.8m respectively, *P<0.0001*).

Figure 14: Impact of tumor size on survival in nVR group:



That statistically non significant trend seen in MS between nVR and VR+ patients shrunk when patients with T1-T2 tumors from the nVR group were excluded.

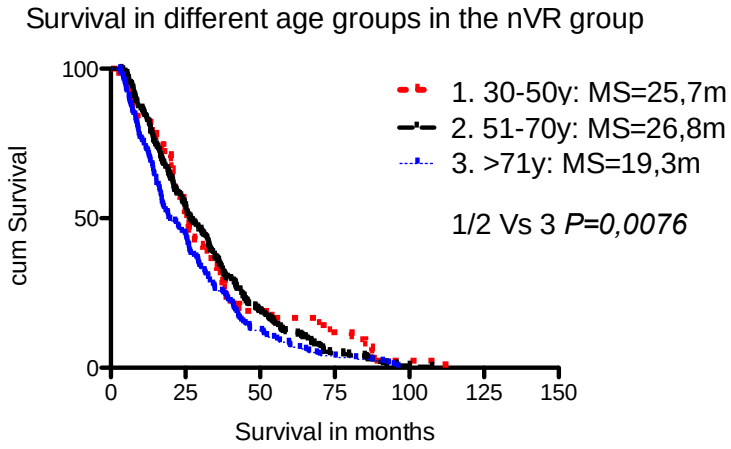
Figure 15: Survival in T3-T4 tumors between nVR and VR groups:



- Age:

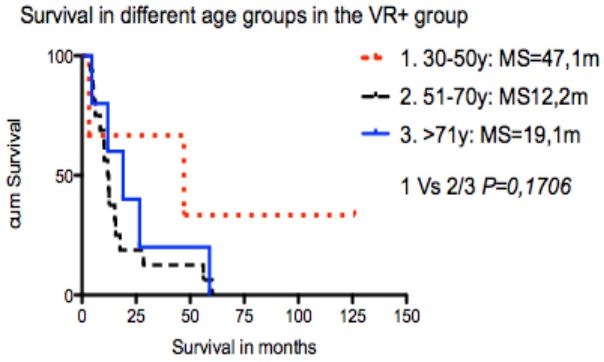
Survival data was diverse throughout different age groups in all groups of patients. In the nVR group age groups (30-50y) (51-70y) had better MS of 25.7 months and 26.8 months respectively compared to 19.3 months in elderly patients (>71y) *(P=0.007)*.

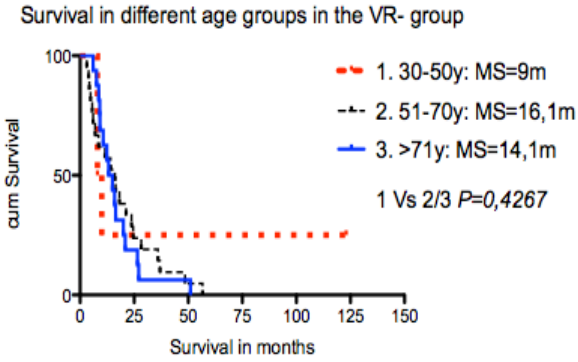
Figure 16: Impact of age on survival in the nVR group:



In the VR+ group although the MS was obviously higher with 47.1 months in age group (31-50y) compared to 12.2 months in age group (51-70y) and 19,1 months in elderly patients >71y, this was not statistically significant *(P=0.1706)* due to the very few number of patients in age group (31-50) (n=3). Adversely, the same age group in the VR- group had the lowest MS (9months) compared to 16.1 and 14.1 months in patients between 51-70y and >71 respectively. (*P=0.462*)

Figure 17: Impact of age on survival in the VR groups:





4. Discussion:

Pancreatic cancer is the 4th most common cause of cancer death in the Western world.[32] Till now the surgical resection is considered the only chance for a definitive cure. However, only one quarter of the patients have resectable tumors without distant metastasis or infiltration of adjacent structures at the time of presentation.

Historically, patients with locally advanced tumors involving infiltration of segments of the mesenterico portal axis have been considered primarly inoperable. According to the current literature, vascular (venous) resection had been carried out in up to 20% of pancreatic resections.[89] Resection and reconstruction of parts of the portal venous system have been the challenging procedure even for experienced surgeons. Advances in perioperative care and surgical techniques alongside with increasing experience at tertiary high volume pancreatic centers countered the challenge of borderline resectable and locally advanced tumors especially in tumors invading the mesenterico portal axis. This in turn increased the rates of resectability and improved the perioperative outcomes.

Several studies over the last two decades have shown that extended enbloc vascular resection had comparable mortality rates and median survival rates. Enbloc vascular resection should be targeted only when an R0 resection can be achieved in patients without distant metastasis.[148-152]

The exclusion of the surgical option for those patients with borderline resectable or locally advanced tumos directs therapeutical efforts into palliative procedures. Till now, systemic chemotherapy is the only feasable accepted form of palliative treatment.[89]

However, recent improvement in chemotherapies invigorated some old discussions which question the benefit of surgical resection of borderline resectable and local advanced tumors.

Therefore, published data on survival after palliative chemotherapy have been revised and compared to survival data presented in this series.

4.1. Survival:

Gemcitabine has been considered for long years as the only releable effective monotherapy. Patients with locally advanced or metastatic tumors treated palliatively with Gemcitabine as a monotherapy had a median survival of 6.8 months.[113] Recently *Gargiulo et. al 2019* published the results of the phase III multicenter clinical trial (APC-SAKK) using palliative Gemcitabine based chemotherapy. The study showed a median survial of 7.9 months.[110]

It was not untill 2011 when *Conroy et. al* introduced his polychemotherapy with the FOLFIRINOX protocol (Oxaliplatin, Leucovorin, Irinotecan, Fuorouracil) which showed a significant improvement in terms of survival. Under FOLFIRINOX survival rates rose up to 11.1 months.[111-113]
In 2013 a large prospective clinical multicenter clinical trial showed some improvement of survival rates when Gemcitabine was combined with the albumin-bound nanoformulation of paclitaxel (Nab-paclitaxel). *Von Hoff et. al* showed survival rates up to 8.5 months under Gemcitabine + Nab-paclitaxel compared to 6.7 months under Gemcitabine only.[112]

Prospective studies directly comparing Gemcitabine based chemotherapy and FOLFIRINOX still don't exist. A most recent Meta-Analysis from *Pusceddu et al. 2019* investigated 16 retrospective studies including over 3000 patients, who have been treated with Gemcitabine + Nab-Paclitaxel or FOLFIRINOX. The Meta-Analysis concluded that despite the reproducible better survival rates under FOLFIRINOX, the overall risk of disease progression and death was not favoring one protocol over the other.[114]

Toxicity of the different chemotherapy regimens has been also a matter of debate in pancreatic cancer research field. Nevertheless, FOLFIRINOX since its introduction as one of the reliable options as a first line of treatment is known to be much more aggressive than other regimens of chemotherapy. Its adverse effect include hematological suppression, gastrointestinal distress as well as neurotoxicity.[111-113] These toxic side effects raised interests for further modification to be applied to the dose or the drug combination of the FOLFIRINOX protocol. For example, *Kang H et al. 2018* showed that modified dose of FOLFIRINOX would have comparable efficacy but lower toxicity than the initially introduced standard dose.[115]

Hence, the application of FOLFIRINOX has been restricted to fit patients (ECOG 0-1).[109-112] Alternatively, the application of FOLFIRINOX on an adjuvant or neoadjuvant setting has emerged as an option under trial.[116-118]

In this series, the median survival in the VR group as a whole was 14.1 months regardless of the microscopic tumor infiltration of the resected venous segment. Interestingly, in more than half of the patients presented (42/73), it was peritumoral inflammation rather than true cancer tissue which adhered to the resected segments of the mesenterico portal axis. Within the VR group, the MS was 12.6 and 14.4 months in the VR+ and VR- groups respectively *(p=0.499).*

Hence, the main issue about borderline resectable and to lesser extent local advanced tumors is that the preoperative staging does not match the real situation. Nevertheless, the decision to carry out an en bloc vascular resection or not is usually based on macroscopic intraopertive findings and supported by personal experience as well as institutional standards. Macroscopic infiltration of the mesenterico portal axis should not be considered a contraindication for surgical resection.

For a better understanding of the survival data presented in this series, the impact of the different prognostic factors had been reviewed separately.

- Resection margin:

The American-European AJCC/UICC staging system defines R1 resection as the presence of microscopic tumor cells on the resection tissue margin (0mm rule). While the British Royal College of Pathology considers a resection as R1 if tumor cells are present within 1mm of the resected margin.

The role of microscopic tumor infiltration of resection margins (R1) on the overall survival has been intensivly discussed in the literature. *Ravikumar et al. 2014* and *Tseng et al. 2004* have shown no adverse effect of R1 resection on the overall survival.[119,120]

Some other authors suggested that differences of handling the histological samples - especially from the circumferential resection margins – in different institutes might lead to the variation R1 rates and consequently on the relevance of resection margins on the overall survival.[120-122] On the contrary, some studies such as the ESPAC-1 study showed a negative prognostic role of the R1 status.[123]
Despite the existing discrepencies in the litertaure about the prognostic value of the R status, curative surgical intention should always target an R0 resection.

In the presented series patients with tumor free resection margins indeed enjoyed better MS. This finding had been observed in all patients groups . In R0 patients MS was 15.2 months, 16 months and 29.2 months in the VR+, VR- and nVR groups respectively. Whereas R1 patients had MS of 12.4 months, 8.9 months and 17.9 months in the VR+, VR- and nVR groups respectively. *(see tables 10-11-12)*

- Nodal involvment:

Lymph node status is considered one of the most important postoperative prognostic factors for pancreatic cancer.[124,125] For long years the N status of the AJCC classification has been used as the standard lymph nodal staging system.[125]

Unlike the R status, the literature has been quite homogenous upon describing the adverse relationship between lymph nodes metastasis and survival.[124-128]

The presented data are consistent with the data shown in the literature. Patients without lymph nodes metastasis (N0) had better survival rates in all groups. In the nVR group N0 patients had a median survival of 36.3 months comapred to a median survival of 22.1 months in N1 patients *(p: <0.0001).* Correspondingly, in the VR group, N0 patients had also a better median survival than N1 patients: 21.3 months compared to 11 months respectively. Though statistically not significant *(p value: 0.1272)*

Recently, there have been some helpful studies trying to stratify or subgroup Patients in each N status-group. Hereby, a more specific prognostic role of nodal involvment was targeted. Statistics such as number of lymph nodes, nodal ratio (NR) as well as log odds of positive lymph nodes (LODDS) have been introduced as additional staging systems.

Ramacciato et al. 2017 investiged the prognostic role of NR and LODDS in patients who underwent an enbloc vascular resection. Further prognostic stratification could be achieved for N1 patients using the mentioned staging systems. No statistical superiority was observed for one staging system over the others. Application of these staging systems in N0 was ruled out.[124]

La Torre et al. 2014 also investigated the prognostic values of N status, NR and LODDS. This study showed better prognostic stratification when the

LODDS staging system was applied compared to NR in node negative patients.[129]

- Tumor size:

Tumor size has been notabely considered as an influencing prognostic factor in pancreatic cancer.[130,131]
All patients who underwent an enbloc vascular resection (VR) and the majority of patients who had underwent a classical pancreatectomy (nVR) had T3 or T4 tumors. Whereas, Patients with T1 or T2 tumors were only existent in the nVR group.

The presented data reproduced the findings in the literature. Patients with T1 or T2 tumors had significantly better survival rates (48m) compared to (23.8m) for patients with T3 or T4 tumors. *(p <0.0001)*
This adverse relationship between tumor size and survival would explain the significant difference in survival rates when the nVR group as a whole (25.1m) was compared to the VR (14.6m) or VR+ (12.2m) groups *(p=0.0158, p=0.5517* respectively*).*

Interestingly, this statistical significance in survival rates was lost when only patients with T3/T4 tumors from the nVR group (23.8m) were compared to patients from the VR+ (12.6m) *(p=0.5470).*

- Age/Gender:

With a median age at the diagnosis of around 70 years pancreatic cancer is not a disease of young patients. Only 11% of the diagnoses are occur the age of 54 or younger.[133,135]

Famous trials such as the ACCORD-11 excluded patients older than 75 years to avoid possible bias caused by lower survival rates expected from older patients. Furthermore, the Toxicity of FOLFIRINOX would have been very risky for those low-reserve patients.[111,133]

Although a direct relationship between age and increasing morbidity and mortality ratios would be, postulated. Several studies have shown that even elderly patients would benefit from a surgical resection in terms of survival with increased risk for postoperative mortality to be taken in consideration.[136-138]

Sugiura et al. 2014 investigated the impact of age on survival. In this the 3 age groups were: >70y, 70-80y and >81y. Here younger patients had significantly better survival rates than elderly and the very elderly *(p = 0.007 and p < 0.001).*[139] Demographic aspects of the study population have to be taken in consideration.

Khan et al. 2010 arguably investigated the indication for surgical resection in very elderly patients. As the options for systemic therapies decline with the decreasing age, the surgical resection stays a viable option for this group of patients. The payoff would be increased morbidity and short term mortality.[140]

In this series, patients were subdivided into 3 age groups: 30y-50y, 51y-70y and >71y. Patients from the first group (30-50y) had better median survival than the other two groups. This trend was independent from the procedure. Vascular resection did not alter the survival compass between different age groups.
Moreover, the two patients from the VR group who survived more than 10 years were both from the younger group aging 41 and 49 years old.

Gender did not establish itself as a deciding factor in pancreatic cancer.

Thus, if the targeted R0 resection can be achieved via an en bloc vascular resection the overall median survival is expectedly better than the best possible survival attained by applying a palliative chemotherapy.

4.2. Perioperative Morbidity and mortality:

Does the extended en bloc vascular resection increase the perioperative morbidity and short term mortality?!
This assumption has been previously discussed in the literature.

The argument that morbidity and mortality is substantially elevated,[141-148] has been disproved by several surgical series that evidenced comparable in-hospital morbidity and mortality rates after VR.[149-152] Nonetheless, the belief in the usefulness of VR is still controversial. In the present series, vascular reconstruction was not associated with increased prevalence of specific vascular complications, such as hemorrhage or thrombosis. Overall, the analysis of in-hospital morbidity and mortality rates of VR patients were nearly identical compared with patients without vascular resections.

- Pancreatic fistula and anastomosis insufficiency:

Postoperative pancreatic fistula [POPF] is one of the most common complications after pancreatic surgeries. It is one of the main causes of postoperative morbidity.[141-144,149] In 2005 the International study group of pancreatic fistula[ISGPF] set up the first definition and clinical staging of POPF. According to the ISGPF the incidence POPF can reach up to 29%.[108]

Independent of the severity of the POPF, the demonstrated data in the present series showed that POPF was even more common among nVR patients (18.2%) than in VR patients (5.5%) *(p=0.036)*

Within the same context, vascular resection did not increase the incidence of anastomosis insufficiency. Five VR (6.8%) patients had been proven to have an insufficiency of at least one anastomosis. Whereas anastomosis insufficiency had been reported in 69 (18.9%) nVR patients *(p=0.027).*

These data were similar to data published in other series. For example *Bachellier P et al 2001* showed rates of POPF of 6.7% and 13.9% in VR and nVR groups respectively.[152]

- Vascular complications:

Vascular complications such as hemorrhage and thrombosis after panceatectomy procedures are not very uncommen. It has postulated that extending the already complex pancreatectomy procedures to include vascular resection and reconstruction would increase the incidence of such complications.[147,148] Arguably, some studies had shown that a vascular resection did not necessarily increase the incidence rates of vascular complications.

For example, in his series from our institution Yekebas et al 2008 showed close rates of hemorrhage (5.6% and 4.4% in VR and nVR groups respectively) as well as portal vein thrombosis (0.7% and 1.5% in VR and nVR groups respectively). [153]

Regarding port vein thrombosis similar findings have been reproduced in the presented series. Herein, one VR patient (1.4%) and 9 nVR patients (2.5%) *(p=0.571)* suffered a postoperative thrombosis of the portal vein. Thirty five nVR patients (9.6%) had had a relevant postoperative hemorrhage compared to only VR patient (1.4%) *(p=0.027)*.

Despite statistical pairing of VR and nVR groups, the remarkable difference in sample sizes between the two groups could explain why some complications are numerically higher in the nVR group.

- Other complications:

The incidence of other complications such as intraabdominal infections showed also no significant difference between the VR and nVR groups with a slight trend to be more often in the VR group. Seven (9.6%) VR patients and 19 (5.2%) nVR patients had been reported to have intraabdominal infections *(p=0.180)*. Here again previously published data could have been reproduced.[149,153]

- Perioperative mortality:

As a matter of fact, reviewing the previous data about the perioperative morbidity would conclude that the perioperative mortality would follow the same comparable pattern in both nVR and VR groups. The 30 days mortality have been reported in 9 (12.3%) VR patients and 21 (5.8%) nVR patients *(p=0.064)*. Previously published data from other series were not different.[149,152]

Hence, accumulating data from this series and similar previuosly published series concluded that vascular resection is not likely to increase vascular related complications or other non vascular related complications which in turn leads to comparable in hospital mortality.

After analysing the data generated from this series and after reviewing the related literature, the two suggested hypotheses could be persuadively defended.

5. Summary:

Pancreatic cancer is the 4th most fatal cancer in the western world. In spite of continuous trials to improve the multimodality therapeutic approaches, the prognosis of pancreatic cancer did not remarkably improve over the years.

Although around half of the patients present with borderline resectable or local advanced tumors, surgical resection is the only definite treatment. In the last two decades, accumulating data from single center series brought strong evidence that tumors infiltrating the mesenterico portal axis can be safely resected with comparable perioperative morbidity and mortality.

Data presented in this series demonstrated the survival benefit after en bloc vascular resection for tumors macroscopically infiltrating the mesenterico portal axis. This survival benefit over palliative chemotherapy is more obvious when the targeted R0 resection is achieved. Moreover, perioperative morbidity and mortality did not significantly differ in patients who underwent en bloc vascular resections when compared to patients who underwent classical pancreatectomy procedures without vascular resection at the same period of time.

Furthermore, tumor size, nodal involvement and age have been proven to have prognostic value on the median survival independently from the surgical procedure carried out.

Recently developed and eventually more effective chemotherapy regimens such as FOLFIRINOX pose strong toxic side effects so that its application is restricted to younger and fitter patients.

Convincing data from this series consolidates previously published results. En bloc vascular resection still pays off with better median survival and comparable perioperative morbidity and mortality. Extended pancreatectomy with en bloc vascular resection pursuing tumor free resection margins remains the only realistic chance for a potential cure.

6. Zusammenfassung:

Pankreaskarzinom ist die vierthäufigste Ursache für Krebstod in der westlichen Welt. Trotz wiederholter Studien zur Verbesserung der multimodalen Therapieansätze, verbesserte sich die Prognose des Pankreaskarzinoms über die Jahre nicht wirklich.

Obwohl etwa die Hälfte der Patienten an borderline resectable oder lokal fortgeschrittenen Tumoren zur Zeit der Diagnose leidet, bleibt die chirurgische Resektion die einzig definitive Behandlung. In den letzten zwei Jahrzehnten haben akkumulierte Daten aus einzelnen Zentrumsreihen starke Beweise dafür erbracht, dass Tumoren, die in die Mesentericо-Portal-Achse eindringen, mit vergleichbarer perioperativer Morbidität und Mortalität sicher reseziert werden können.

Die in dieser Serie vorgestellten Daten zeigten den Überlebensvorteil nach en-bloc-Gefäßresektion bei Tumoren, die makroskopisch die mesentericо-Portalachse infiltrieren. Dieser Überlebensvorteil gegenüber einer palliativen Chemotherapie ist offensichtlicher, wenn die gezielte R0-Resektion erreicht wird. Darüber hinaus waren die perioperative Morbidität und Mortalität bei Patienten, bei den eine en-bloc-Gefäßresektion durchgeführt wurde, nicht signifikant unterschiedlich im Vergleich zu Patienten, bei den im gleichen Zeitraum klassischen Pankreatektomie-Verfahren ohne Gefäßresektion durchgeführt wurden.

Zusätzlich, zeigten sich Tumorgröße, Lymphknotenbefall und Alter - unabhängig vom durchgeführten chirurgischen Eingriff - einen prognostischen Einfluss auf das mediane Überleben, zu haben.

Neuerlich entwickelte und letztendlich wirksamere Chemotherapien wie FOLFIRINOX weisen starke toxische Nebenwirkungen auf, sodass ihre Anwendung auf jüngere, fitte Patienten beschränkt ist.

Überzeugende Daten aus dieser Studie konsolidieren die bereits veröffentlichten Evidenzen. En-bloc-Gefäßresektion zahlt sich immer noch mit einem besseren medianen Überleben und vergleichbarer perioperativer Morbidität und Mortalität aus. Eine erweiterte Pankreatektomie mit en-bloc-Gefäßresektion unter Erzielung tumorfreier Resektionsränder bleibt die einzige realistische Chance für eine mögliche Heilung.

7. Abbreviations:

PEN	Pancreatic Endocrine Neoplasia
IPMN	Intraductal Papillary Mucinous Neoplasm
MS	median survival
CA19-9	Carbohydrate Antigen 19-9
CEA	Carcinoembryogenic Antigen
nVR	classical pancreatectomy without vascular resection
VR	pancreatectomy with vascular resection
VR+	histological proof of tumor invasion of the resected vessel
VR-	no histological proof of tumor invasion of the resected vessel
PPD	partial pancreatoduodenectomy
TDSP	total duodenosplenopancreatectomy
DSP	distal splenopancreatectomy
PPPD	pyloric preserving pancreatoduodenectomy
POPF	postoperative pancreatic fistula
IGSPF	international study group of pancreatic fistula
LODDS	log odds of positive lymph nodes
GE	gastro-enterostomy anastomosis
PJ	pancreatico-jejunostomy anastomosis
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control

8. References:

1- NASPGHAN: Embryology and Anatomy of the Gastrointestinal Tract. https://www.naspghan.org/files/documents/pdfs/training/curriculum-resources/physiologyseries/Embryology_and_Anatomy_of_the_Gastrointestinal_Tract_NASPGHAN.pdf

2- Agur AMR, Lee MJ, Grant JCB. Grant's Atlas of Anatomy. 13th ed. London, UK: Lippincott Williams and Wilkins; 2013.

3- Gray H. Lewis WH, ed. Gray's Anatomy of the Human Body. 20th ed. New York, NY: Bartleby.com; 2000.

4- Medscape. https://emedicine.medscape.com/article/1948885-overview#showall.

5- BC Open Textbooks. https://opentextbc.ca/anatomyandphysiology/chapter/17-9-the-endocrine-pancreas/

6- Adsay, N. V., Thirabanjasak, D., & Altinel, D. (2008). Spectrum of Human Pancreatic Neoplasia. Pancreatic Cancer, 3–26. doi:10.1007/978-0-387-69252-4_1

7- Vyas P AA, Sarkar F, Leach S, et al. In search of stem cell in pancreatic ducts: the nature of round, non-ductal appearing cells in human pancreatic ducts. Mod Pathol 2003, 16(1):287A.

8- Klimstra DS, Adsay N. Benign and malignant tumors of the pancreas. In: Odze R, Goldblum JR, Crawford JM (eds.) Surgical pathology of the GI tract, liver, biliary tract and pancreas. Philadelphia, Saunders, 2004.

9- Klimstra DS. Pancreas. In: Sternberg SS (ed.) Histology for pathologists. New York, Lippincott-Raven, 1997.

10- Hoorens A, Prenzel K, Lemoine NR, et al. Undifferentiated carcinoma of the pancreas: analy- sis of intermediate filament profile and Ki-ras mutations provides evidence of a ductal origin. J Pathol 1998, 185:53–60.

11- Westra WH, Sturm P, Drillenburg P, et al. K-ras oncogene mutations in osteoclast-like giant cell tumors of the pancreas and liver: genetic evidence to support origin from the duct epithelium. Am J Surg Pathol 1998, 22:1247–1254.

12- Adsay V, Sarkar, F, Vaitkevicius V, et al. Squamous cell and adenosquamous carcinomas of the pancreas: a clinicopathologic analysis of 11 cases. Mod Pathol 2000, 13(1):179A.

13- Kardon D, Thompson LD, Przygodzki RM, et al. Adenosquamous carcinoma of the pancreas: a clinicopathologic series of 25 cases. Mod Pathol 2001, 14(5):443–451.

14- Adsay NV, Pierson C, Sarkar F, et al. Colloid (mucinous noncystic) carcinoma of the pancreas. Am J Surg Pathol 2001, 25:26–42.

15- Seidel G, Zahurak M, Iacobuzio-Donahue C, et al. Almost all infiltrating colloid carcinomas of the pancreas and periampullary region arise from in situ papillary neoplasms: a study of 39 cases. Am J Surg Pathol 2002, 26:56–63.

16- Goggins M, Offerhaus GJ, Hilgers W, et al. Pancreatic adenocarcinomas with DNA replica- tion errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER+. Am J Pathol 1998, 152:1501–1507.

17- Wilentz RE, Goggins M, Redston M, et al. Genetic, immunohistochemical, and clinical fea- tures of medullary carcinoma of the pancreas: a newly described and characterized entity. Am J Pathol 2000, 156:1641–1651.

18- Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 2001, 25:579–586.

19- Andea A, Sarkar F, Adsay VN. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. Mod Pathol 2003, 16:996–1006.

20- Adsay NV, Merati K, Andea A, et al. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. Mod Pathol 2002, 15:1087–1095.

21- Evans DB, Willet CG. Cancer of the pancreas. In: DeVita VT, Rosenberg SA (eds.) Cancer principle and practice of oncology. Philadelphia, Lippincott Williams & Wilkins, 2001, 1126–1161.

22- Christoph F Dietrich, Yi Dong, Christian Jenssen, Valentina Ciaravino, Michael Hocke, Wen-Ping Wang, Eike Burmester, Kathleen Moeller, Nathan SS Atkinson, Paola Capelli, Mirko D'Onofrio. Serous pancreatic neoplasia, data and review. World J Gastroenterol. 2017 Aug 14; 23(30): 5567–5578. Published online 2017 Aug 14. doi: 10.3748/wjg.v23.i30.5567

23- Hochwald S, Conlon K, Brenann M. Nonfunctioning pancreatic islet cell tumors. In: Doherty GM, Skogseid B (eds.) Surgical endocrinology. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 361–373.

24- La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. Virchows Arch 1996, 429(6):323–333.

25- Donow C, Pipeleers-Marichal M, Schroder S, et al. Surgical pathology of gastrinoma. Site, size, multicentricity, association with multiple endocrine neoplasia type 1, and malignancy. Cancer 1991, 68:1329–1334.

26- Bertelli E, Regoli M, Bastianini A. Endocrine tissue associated with the pancreatic ductal system: a light and electron microscopic study of the adult rat pancreas with special reference to a new endocrine arrangement. Anat Rec 1994, 239:371–378.

27- Pelosi G, Bresaola E, Bogina G, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. Hum Pathol 1996, 27:1124–1134.

28- Kloppel GHR, Longnecker DS, Adler G, et al. Tumours of exocrine pancreas. In: Hsa LA (ed.) World Health Organization classification of tumours: pathology and genetis tumours of the digestive system. Lyon, France, IARC Press 2000, pp 219–251.

29- Solcia E, Capella C, Klöppel G (eds.) Tumors of the pancreas. Washington, DC, American Registry of Pathology, 1997, pp 145–209.

30- Andrew McGuigan, Paul Kelly, Richard C Turkington, Claire Jones, Helen G Coleman, and R Stephen McCain Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018 Nov 21; 24(43): 4846–4861.

31- Ilic M, Ilic I. Epidemiology of pancreatic cancer.
World J Gastroenterol. 2016;22:9694–9705.

32- International Agency for Research on Cancer, World Health Organization. Global Cancer Observatory 2018; Available from: URL: http://gco.iarc.fr/

33- Wahi MM, Shah N, Schrock CE, Rosemurgy AS 2nd, Goldin SB. Reproductive factors and risk of pancreatic cancer in women: a review of the literature. Ann Epidemiol. 2009;19:103–111.

34- Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer Lett. 2016 Oct 10; 381(1):269-77.

35- Silverman DT, Hoover RN, Brown LM, Swanson GM, Schiffman M, Greenberg RS, Hayes RB, Lillemoe KD, Schoenberg JB, Schwartz AG, Liff J, Pottern LM, Fraumeni JF Jr. Why do Black Americans have a higher risk of pancreatic cancer than White Americans? Epidemiology. 2003 Jan; 14(1):45-54.

36- Arnold LD, Patel AV, Yan Y, Jacobs EJ, Thun MJ, Calle EE, Colditz GA. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity?
Cancer Epidemiol Biomarkers Prev. 2009 Sep; 18(9):2397-405.

37- Memba R, Duggan SN, Ni Chonchubhair HM, Griffin OM, Bashir Y, O'Connor DB, Murphy A, McMahon J, Volcov Y, Ryan BM, Conlon KC. The potential role of gut microbiota in pancreatic disease: A systematic review. Pancreatology. 2017 Nov - Dec; 17(6):867-874.

38- Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. Br J Cancer. 2007 Feb 12; 96(3):507-9.

39- Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005 Jun 6; 92(11):2076-83.

40- Hruban RH, Canto MI, Goggins M, Schulick R, Klein AP
Update on familial pancreatic cancer. Adv Surg. 2010; 44():293-311.

41- Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. World J Gastroenterol. 2014 Aug 28; 20(32):11182-98.

42- Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Fam Cancer. 2009; 8(2):109-17.

43- Chen F, Roberts NJ, Klein AP. Inherited pancreatic cancer. Chin Clin Oncol. 2017 Dec; 6(6):58.

44- Del Chiaro M, Segersvärd R, Lohr M, Verbeke C. Early detection and prevention of pancreatic cancer: is it really possible today? World J Gastroenterol. 2014 Sep 14; 20(34):12118-31.

45- Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol. 2012 Jul; 23(7):1880-8.

46- Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg. 2008 Jul; 393(4):535-45.

47- Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, Canzian F, Steplowski E, Arslan AA, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Petersen G, Zheng W, Albanes D, Amundadottir L, Bingham SA, Boffetta P, Boutron-Ruault MC, Chanock SJ, Clipp S, Hoover RN, Jacobs K, Johnson KC, Kooperberg C, Luo J, Messina C, Palli D, Patel AV, Riboli E, Shu XO, Rodriguez Suarez L, Thomas G, Tjønneland A, Tobias GS, Tong E, Trichopoulos D, Virtamo J, Ye W, Yu K, Zeleniuch-Jacquette A, Bueno-de-Mesquita HB, Stolzenberg-Solomon RZ. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009 Aug 15; 170(4):403-13.

48- Rohrmann S, Linseisen J, Vrieling A, Boffetta P, Stolzenberg-Solomon RZ, Lowenfels AB, Jensen MK, Overvad K, Olsen A, Tjonneland A, Boutron-Ruault MC, Clavel-Chapelon F, Fagherazzi G, Misirli G, Lagiou P, Trichopoulou A, Kaaks R, Bergmann MM, Boeing H, Bingham S, Khaw KT, Allen N, Roddam A, Palli D, Pala V, Panico S, Tumino R, Vineis P, Peeters PH, Hjartåker A, Lund E, Redondo Cornejo ML, Agudo A, Arriola L, Sánchez MJ, Tormo MJ, Barricarte Gurrea A, Lindkvist B, Manjer J, Johansson I, Ye W, Slimani N, Duell EJ, Jenab M, Michaud DS, Mouw T, Riboli E, Bueno-de-Mesquita HB. Ethanol intake and

the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control. 2009 Jul; 20(5):785-94.

49- Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, Kurosawa M, Ohno Y. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. Int J Cancer. 2002 Jun 10; 99(5):742-6.

50- Wang YT, Gou YW, Jin WW, Xiao M, Fang HY. Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. BMC Cancer. 2016 Mar 12; 16():212

51- 2015. WCRFI. Pancreatic cancer statistics | World Cancer Research Fund International. Available from: URL: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/pancreatic-cancer-statistics.

52- Raimondi, S., Lowenfels, A. B., Morselli-Labate, A. M., Maisonneuve, P., & Pezzilli, R. (2010). Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Practice & Research Clinical Gastroenterology, 24(3), 349–358. doi:10.1016/j.bpg.2010.02.007

53- Machicado JD, Rebours V, Yadav D. Epidemiology of chronic pancreatitis. Pancreapedia. 2016:1–15.

54- Guo Y, Liu W, Wu J. Helicobacter pylori infection and pancreatic cancer risk: A meta-analysis. J Cancer Res Ther. 2016 Dec; 12(Supplement):C229-C232.

55- El-Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, Amaratunge HC, Giordano TP. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. Hepatology. 2009 Jan; 49(1):116-23.

56- Marco Del Chiaro, Ralf Segersvärd, Matthias Lohr, and Caroline Verbeke. Early detection and prevention of pancreatic cancer: Is it really possible today? World J Gastroenterol. 2014 Sep 14; 20(34): 12118–12131.

57- Patt CH, Thuluvath PJ. Liver transplanatation for primary sclerosing cholangitis: screening for biliary malignancy and the role of preemptive transplantation. Curr Opin Organ Transplant. 2002;7:129–136

58- McAuliffe PF, Cance WG. Preemptive surgery. Surgery. 2006 Jul; 140(1):1-5.

59- Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, Evans GR, Narod SA, Isaacs C, Matloff E, Daly MB, Olopade OI, Weber BL. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004 Mar 15; 22(6):1055-62.

60- Vasen HF, van Duijvendijk P, Buskens E, Bülow C, Björk J, Järvinen HJ, Bülow S. Decision analysis in the surgical treatment of patients with familial adenomatous

polyposis: a Dutch-Scandinavian collaborative study including 659 patients. Gut. 2001 Aug; 49(2):231-5

61- Maitra A, Kern SE, Hruban RH. Molecular pathogenesis of pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006 Apr; 20(2):211-26.

62- Shin EJ, Canto MI. Pancreatic cancer screening. Gastroenterol Clin North Am. 2012 Mar; 41(1):143-57.

63- Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijt I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M, International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. International Cancer of Pancreas Screening (CAPS) Consortium. Gut. 2013 Mar; 62(3):339-47.

64- Li, D., Xie, K., Wolff, R., & Abbruzzese, J. L. (2004). Pancreatic cancer. The Lancet, 363(9414), 1049–1057.doi:10.1016/s0140-6736(04)15841-8

65- Sohn TA, Yeo CJ. The molecular genetics of pancreatic ductal carcinoma: a review. Surg Oncol, 9 (2000), pp. 95-101

66- Sakorafas GH, Tsiotos GG. Molecular biology of pancreatic cancer: potential clinical implications. BioDrugs, 15 (2001), pp. 439-452.

67- Almoguerra C, Shibata D, Forrester K, et al.Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell, 53 (1988), pp. 549-554

68- Caldas C, Hahn SA, LT da Costa, et al.Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma
Nat Genetics, 8 (1994), pp. 27-32

69- Hahn SA, Schutte M, Hoque ATMS, et al.DPC4, a candidate tumor-suppressor gene at 18q21.1. Science, 271 (1996), pp. 350-353

70- Korc M. Role of growth factors in pancreatic cancer. SurgOncolClinN Am, 7 (1998), pp. 25-41

71- Luo J, Guo P, Matsuda K, et al.Pancreatic cancer cell-derived vascular endothelial growth factor is biologically active in vitro and enhances tumorigenicity in vivo. Int J Cancer, 92 (2001), pp. 361-369.

72- Shi Q, Le X, Peng Z, et al.Constitutive Sp1 activity is essential for differential constitutive expression of vascular endothelial growth factor in human pancreatic adenocarcinoma. Cancer Res, 61 (2001), pp. 4143-4154.

73- Yamanaka Y, Friess H, Buchler M, et al.Overexpression of acidic and basic fibroblast growth factors in human pancreatic cancer correlates with advanced tumor stage. Cancer Res, 53 (1993), pp. 5289-5296.

74- Kleeff J, Ishiwata T, Friess H, et al. The TGF- signaling inhibitor Smad7 enhances tumorigenicity in pancreatic cancer. Oncogene, 18 (1999), pp. 5363-5372.

75- JA Blanchard 2nd, Barve S, Joshi-Barve S, Talwalker R, Gates LK Jr. Cytokine production by CAPAN-1 and CAPAN-2 cell lines. Dig Dis Sci, 45 (2000), pp. 927-932.

76- Saito K, Ishikura H, Kishimoto T, et al. Interleukin-6 produced by pancreatic carcinoma cells enhances humoral immune responses against tumor cells: a possible event in tumor regression. Int J Cancer, 75 (1998), pp. 284-289.

77- Watanabe N, Tsuji N, Kobayashi D, et al. Endogenous tumor necrosis factor functions as a resistant factor against hyperthermic cytotoxicity in pancreatic carcinoma cells via enhancement of the heart shock element-binding activity of heat shock factor 1. Chemotherapy, 43 (1997), pp. 406-414.

78- Shi Q, Abbruzzese J, Huang S, Fidler IJ, Xie K. Constitutive and inducible interleukin-8 expression by hypoxia and acidosis renders human pancreatic cancer cells more tumorigenic and metastatic. ClinCancer Res, 5 (1999), pp. 3711-3721

79- DiMagno EP. Cancer of the pancreas and biliary tract. In: Winawer SJ, ed. Management of gastrointestinal diseases. New York: Gower. Medical Publishing, 1992:28.1-28.37.

80- Kalser MH, Barkin J, MacIntyre JM. Pancreatic cancer. Assessment of prognosis by clinical presentation. Cancer 1985;56:397-402.

81- McGee SR. Palpation and percussion of the abdomen. In: Evidence based physical diagnosis. Philadelphia: Saunders, 2001:601-4.

82- Malesci A, Montorsi M, Mariani A, Santambrogio R, Bonato C, Bissi O, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancre- atic carcinoma in symptomatic patients: a prospective study. Pancreas.1992;7:497-502.

83- Montgomery RC, Hoffman JP, Riley LB, Rogatko A, Ridge JA, Eisenberg. BL. Prediction of recurrence and survival by post-resection CA 19-9 val- ues in patients with adenocarcinoma of the pancreas. Ann Surg Oncol 1997;4:551-6.

84- Louhimo J, Alfthan H, Stenman UH, Haglund C. Serum HCG beta and CA 72-4 are stronger prognostic factors than CEA, CA 19-9 and CA 242 in pancreatic cancer. Oncology 2004;66:126-31.

85- Diehl SJ, Lehmann KJ, Sadick M, Lachmann R, Georgi M. Pancreatic cancer: value of dual-phase helical CT in assessing resectability. Radiol- ogy 1998;206:373-8.

86- Maringhini A, Ciambra M, Raimondo M, Baccelliere P, Grasso R, Dardanoni G, et al. Clinical presentation and ultrasonography in the diagnosis of pancreatic cancer. Pancreas 1993;8:146-50.

87- Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc 1997;45:387-93.

88- American Joint Comittee on Cancer (AJCC)
http://cancerstaging.org/references-tools/deskreferences/Pages/default.aspx

89- Anuhya Kommalapati, Sri Harsha Tella, Gaurav Goyal, Wen Wee Ma, Amit Mahipal. Contemporary Management of Localized Resectable Pancreatic Cancer. Cancers (Basel) 2018 Jan; 10(1): 24. Published online 2018 Jan 20. doi: 10.3390/cancers10010024

90- Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;

91- Schlitter AM, Esposito I. Definition of microscopic tumor clearance (r0) in pancreatic cancer resections. Cancers (Basel). 2010 Nov 25; 2(4):2001-10.

92- Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial.
JAMA. 2007 Jan 17; 297(3):267-77.

93- Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW, Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. European Study Group for Pancreatic Cancer.
JAMA. 2010 Sep 8; 304(10):1073-81.

94- Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW, Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial.

95- Bruns CJ, Kleespies A, Seeliger H, Angele MK, Heinemann V, Jauch KW.
Carcinoma of head of pancreas: most common cause of obstructive jaundice
MMW Fortschr Med. 2009 Dec 3;151(49-50):37, 39. Review. German.

96- Mahipal A, Frakes J, Hoffe S, Kim R. Management of borderline resectable pancreatic cancer. World J Gastrointest Oncol. 2015 Oct 15; 7(10):241-9.

97- Siriwardana HP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. Br J Surg. 2006 Jun; 93(6):662-73.

98- Adham M, Mirza DF, Chapuis F, Mayer AD, Bramhall SR, Coldham C, Baulieux J, Buckels J Results of vascular resections during pancreatectomy from two European centres: an analysis of survival and disease-free survival explicative factors.

99- Zhou Y, Zhang Z, Liu Y, Li B, Xu D. Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis.
World J Surg. 2012 Apr; 36(4):884-91.

100- Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J
Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg. 2011 Dec; 254(6):882-93.

101- Bockhorn M, Burdelski C, Bogoevski D, Sgourakis G, Yekebas EF, Izbicki JR. Arterial en bloc resection for pancreatic carcinoma. Br J Surg. 2011 Jan; 98(1):86-92.

102- Balaban EP, Mangu PB, Khorana AA, Shah MA, Mukherjee S, Crane CH, Javle MM, Eads JR, Allen P, Ko AH, Engebretson A, Herman JM, Strickler JH, Benson AB 3rd, Urba S, Yee NS
.Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline.J Clin Oncol. 2016 Aug 1; 34(22):2654-68.

103- Raufi, A., Fojo, T., Manji, G., Chabot, J., & Bates, S. (2018). Neoadjuvant Treatment for Pancreatic Cancer. Seminars in Oncology.doi:10.1053/j.seminoncol.2018.12.002

104- Zhan HX, Xu JW, Wu D, et al. Neoadjuvant therapy in pancreatic cancer: 539 a systematic review and meta-analysis of prospective studies. Cancer Med. 540 2017;6(6):1201–19.

105- Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation ther- 551 apy with gemcitabine/cisplatin and surgery versus immediate surgery in re- 552 sectable pancreatic cancer: results of the first prospective randomized phase 553 II trial. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft 554 [et al] 2015;191(1):7–16.

106- van Tienhoven G. Journal of clinical oncology: official journal of the American society of clinical oncology. 2018;36

107- FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biagi JJ, Lecomte T, Assenat E, Faroux R, Ychou M, Volet J, Sauvanet A, Breysacher G, Di Fiore F, Cripps C, Kavan P, Texereau P, Bouhier-Leporrier K, Khemissa-Akouz F, Legoux JL, Juzyna B, Gourgou S, O'Callaghan CJ, Jouffroy-Zeller C, Rat P, Malka D, Castan F, Bachet JB, Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group.
N Engl J Med. 2018 Dec 20; 379(25):2395-2406.

108- Bassi, C., Marchegiani, G., Dervenis, C., Sarr, M., Abu Hilal, M., Adham, M., … Buchler, M. (2017). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery, 161(3), 584–591. doi:10.1016/j.surg.2016.11.014

109- Gargiulo P[1], Dietrich D[2], Herrmann R[3], Bodoky G[4], Ruhstaller T[5], Scheithauer W[6], Glimelius B[7], Berardi S[2], Pignata S[8], Brauchli P[2].Predicting mortality and adverse events in patients with advanced pancreatic cancer treated with palliative gemcitabine-based chemotherapy in a multicentre phase III randomized clinical trial: the APC-SAKK risk scores. Ther Adv Med Oncol. 2019 Jan 2;11:1758835918818351. doi: 10.1177/1758835918818351

110- Conroy T[1], Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup.
FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923.

111- Von Hoff DD[1], Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF.
Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16.

112- Bisht S. · Brossart P. · Feldmann G.
Current Therapeutic Options for Pancreatic Ductal Adenocarcinoma
Oncol Res Treat. 2018;41(10):590-594. doi: 10.1159/000493868. Epub 2018 Sep 28.

113- Pusceddu S[1], Ghidini M[2], Torchio M[3], Corti F[4], Tomasello G[5], Niger M[6], Prinzi N[7], Nichetti F[8], Coinu A[9], Di Bartolomeo M[10], Cabiddu M[11], Passalacqua R[12], de Braud F[13,14], Petrelli F[15] Comparative Effectiveness of Gemcitabine plus Nab-Paclitaxel and FOLFIRINOX in the First-Line Setting of Metastatic Pancreatic Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel). 2019 Apr 5;11(4). pii: E484. doi: 10.3390/cancers11040484.

114- Kang H[1], Jo JH[1], Lee HS[1], Chung MJ[1], Bang S[1], Park SW[1], Song SY[1], Park JY[2]. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. World J Gastrointest Oncol. 2018 Nov 15;10(11):421-430. doi: 10.4251/wjgo.v10.i11.421.

115- Seufferlein T[1], Ettrich TJ[1]. Treatment of pancreatic cancer-neoadjuvant treatment in resectable pancreatic cancer (PDAC). Transl Gastroenterol Hepatol. 2019 Mar 27;4:21. doi: 10.21037/tgh.2019.03.05. eCollection 2019.

116- Assenat E, De La Fouchardiere C, Mollevi C, et al.: Sequential treatment with nab-paclitaxel plus gemcitabine and folfirinox in metastatic pancreatic adenocarcinoma: GABRINOX phase II results. J Clin Oncol 2017;36:(suppl; abstr 4109).

117- Conroy T, Hammel P, Hebbar M, et al.: Unicancer gi prodige 24/cctg pa.6 trial: A multicenter international randomized phase III trial of adjuvant mfolfirinox versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. J Clin Oncol 2018;36 (suppl), abstr LBA4001.

118- Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, et al. Pancreaticoduodenectomy with vascular resection: margin status and sur- vival duration. J Gastrointest Surg 2004; 8: 935-50.

119- Ravikumar R, Sabin C, Hilal MA, Bramhall S, White S, Wigmore S, et al. Portal vein resection in borderline respectable pancreatic cancer: a United Kingdom multicenter study. J Am Coll Surg 2014; 218: 401-11.

120- Flis, V., Potrc, S., Kobilica, N., & Ivanecz, A. Pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head with venous resection. Radiology and Oncology, 50(3), 321–328. doi:10.1515/raon-2015-0017

121- Esposito I, Kleef J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008; 15: 1651-60.

122- Neoptolemos JP, Stocken DD, Dunn JA, Alomd J, Beger HG, Pederzoli P, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001; 234: 758-68.

123- Giovanni Ramacciato,1 Giuseppe Nigri,1 Niccolo' Petrucciani,1 Antonio Daniele Pinna,2 Matteo Ravaioli,2 Elio Jovine,3 Francesco Minni,4 Gian Luca Grazi,5 Piero Chirletti,6 Giuseppe Tisone,7 Fabio Ferla,8 Niccolo' Napoli,9 and Ugo Boggi9 Prognostic role of nodal ratio, LODDS, pN in patients with pancreatic cancer with venous involvement. BMC Surg. 2017; 17: 109. Published online 2017 Nov 23. doi: 10.1186/s12893-017-0311-1

124- Asano, D., Nara, S., Kishi, Y., Esaki, M., Hiraoka, N., Tanabe, M., & Shimada, K. (2019). A Single-Institution Validation Study of Lymph Node Staging By the AJCC 8th Edition for Patients with Pancreatic Head Cancer: A Proposal to Subdivide the N2 Category. Annals of Surgical Oncology. doi:10.1245/s10434-019-07390-z.

125- Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006;13:1189–200.

126- Ueda M, Endo I, Nakashima M, et al. Prognostic factors after resection of pancreatic cancer. World J Surg. 2009;33:104–10.

127- Tarantino I, Warschkow R, Hackert T, et al. Staging of pancreatic cancer based on the number of positive lymph nodes. Br J Surg. 2017;104:608–18.

128- La Torre M, Nigri G, Petrucciani N, et al. Prognostic assessment of different lymph node staging methods for pancreatic cancer with R0 resection: pN staging, lymph node ratio, log odds of positive lymph nodes. Pancreatology. 2014;14:289–294. doi: 10.1016/j.pan.2014.05.794.

129- Fortner JG[1], Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg. 1996 Feb;223(2):147-53.

130- Dumont R[1], Puleo F[2], Collignon J[1], Meurisse N[3], Chavez M[4], Seidel L[5], Gast P[1], Polus M[1], Loly C[1], Delvenne P[6], Meunier P[7], Hustinx R[7], Deroover A[3], Detry O[3], Louis E[1], Martinive P[8], Van Daele D[1]. A single center experience in resectable pancreatic ductal adenocarcinoma : the limitations of the surgery-first approach. Critical review of the literature and proposals for practice update. Acta Gastroenterol Belg. 2017 Oct-Dec;80(4):451-461.

131- Ogden JR, Xie H, Ma WW, Hubbard JM. The Management of Older Adults with Pancreatic Adenocarcinoma. Geriatrics (Basel). 2018;3(4):85. Published 2018 Nov 26. doi:10.3390/geriatrics3040085

132- Siegel R.L., Miller K.D., Jemal A. Cancer statistics, 2018. CA Cancer J. Clin. 2018;68:7–30. doi: 10.3322/caac.21442.

133- Cancer Facts & Figures 2018. [(accessed on 23 October 2018)]; Available online: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf.

134- Zhang Q., Zeng L., Chen Y., Lian G., Qian C., Chen S., Li J., Huang K. Pancreatic Cancer Epidemiology, Detection, and Management. Gastroenterol. Res. Pract. 2016;2016:8962321. doi: 10.1155/2016/8962321.

135- Riall T.S., Sheffield K.M., Kuo Y.-F., Townsend C.M., Goodwin J.S. Resection Benefits Older Adults with Locoregional Pancreatic Cancer Despite Greater Short-Term Morbidity and Mortality. J. Am. Geriatr. Soc. 2011;59:647–654. doi: 10.1111/j.1532-5415.2011.03353.

136- Van der Geest L.G.M., Besselink M.G.H., van Gestel Y.R.B.M., Busch O.R., de Hingh I.H., de Jong K.P., Molenaar I.Q., Lemmens V.E. Pancreatic cancer surgery in elderly patients: Balancing between short-term harm and long-term benefit. A population-based study in the Netherlands. Acta Oncol. (Madr.) 2016;55:278–285. doi: 10.3109/0284186X.2015.1105381

137- Turrini O., Paye F., Bachellier P., Sauvanet A., Sa Cunha A., Le Treut Y.P., Adham M., Mabrut J.Y., Chiche L., Delpero J.R., et al. Pancreatectomy for adenocarcinoma in elderly patients: Postoperative outcomes and long term results: A study of the French Surgical Association. Eur. J. Surg. Oncol. 2013;39:171–178. doi: 10.1016/j.ejso.2012.08.017.

138- Sugiura T., Okamura Y., Ito T., Yamamoto Y., Ashida R., Uesaka K. Impact of Patient Age on the Postoperative Survival in Pancreatic Head Cancer. Ann. Surg. Oncol. 2017;24:3220–3228. doi: 10.1245/s10434-017-5994-0.

139- Khan S, Sclabas G, Lombardo KR, et al. Pancreatoduodenectomy for ductal adenocarcinoma in the very elderly: is it safe and justified? J Gastrointest Surg. 2010;14(11):1826–31.

140- Carrère, N., Sauvanet, A., Goere, D., Kianmanesh, R., Vullierme, M.-P., Couvelard, A., … Belghiti, J. (2006). Pancreaticoduodenectomy with Mesentericoportal Vein Resection for Adenocarcinoma of the Pancreatic Head. World Journal of Surgery, 30(8), 1526–1535. doi:10.1007/s00268-005-0784-4

141- Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenec- tomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8:935–950.

142- Yoshimi F, Asato Y, Tanaka R, et al. Reconstruction of the portal vein and the splenic vein in pancreaticoduodenectomy for pancreatic cancer. Hepatogastroenterology. 2003;50:856–860.

143- Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreaticoduodenectomywith resection of the superior mesenteric-portal vein confluence for adenocarcinoma. Ann Surg. 1996;224:342–347; discussion 347–349.

144- Allema JH, Reinders ME, van Gulik TM, et al. Portal vein resection in patients undergoing pancreatoduodenectomy for carcinoma of the pancreatic head. Br J Surg. 1994;81:1642–1646.

145- Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg. 1996;223:154 –162.

146- Harrison LE, Brennan MF. Portal vein resection for pancreatic adenocarcinoma. Surg Oncol Clin N Am. 1998;7:165–181.

147- Sindelar WF. Clinical experience with regional pancreatectomy for adenocarcinoma of the pancreas. Arch Surg. 1989;124:127–132.

148- Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg. 2004;8:935–949; discussion 949–950.

149- Koniaris LG, Staveley-O'Carroll KF, Zeh HJ, et al. Pancreaticoduodenectomy in the presence of superior mesenteric venous obstruction. J Gastrointest Surg. 2005;9:915–921.

150- Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection?

151- Bachellier P, Nakano H, Oussoultzoglou PD, et al. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg. 2001;182:120 –129.

152- Yekebas, E. F., Bogoevski, D., Cataldegirmen, G., Kunze, C., Marx, A., Vashist, Y. K., … Izbicki, J. R. (2008). En Bloc Vascular Resection for Locally Advanced Pancreatic Malignancies Infiltrating Major Blood Vessels. Annals of Surgery, 247(2), 300–309.doi:10.1097/sla.0b013e31815aab22

9. Danksagung:

An diesem guten Gelingen dieser Arbeit waren jede Menge mir nahestehender Menschen beteiligt, denen ich meinen Dank schulde.

An erster Stelle möchte ich meinem Doktorvater PD Dr. Dean Bogoevski und meinem Chef Prof. Jakob Izbicki für die Bereitstellung dieses Themas sowie für die angenehme Zusammenarbeit und die aufbauende Kritik danken.

Weiterhin bedanke ich mich bei meinem Mentor Dr. Stefan Wolter, der mich in den schweren Phasen mit Rat und Tat unterstützt hat.

Für die essentielle Hilfe bei der Datensammlung und bei der statistischen Analyse möchte ich meinen Dank meinen Kollegen in der Abteilung der Allgemein-, Viszeral und Thoraxchirurgie am UKE aussprechen.

Den Beistand, den ich nie als selbstverständlich gesehen habe, habe ich in besonderem Maße von meinen Kollegen und besten Freunden Peter Felix und Samer Hefzy. Dafür, sowie für die zahlreiche Abende der Ablenkung, bedanke ich mich bei euch sehr.

Ein besonderes Dankeschön richte ich an Christine und Michael Salib für das Korrekturlesen sowie für die dauernde Unterstützung.

Schlussendlich, gilt mein größter Dank natürlich meinen Eltern, ohne die ich nie dahin gekommen wär, wo ich heute bin. Durch euch und meine beiden Schwestern Heidi und Dina wurde mir den Weg zum beruflichen Erfolg geebnet. Ihr standet mir immer bei, habt mich aufgerichtet als ich gefallen war. Ihr alle habt meine Abwesenheit sowie mein klagen jahrelang ertragen und mich doch in meinen Entscheidungen immer bestärk.

10. Lebenslauf:

Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

11. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Hamburg, den 19.07.2019

Unterschrift: .....
Ramez Wahib