Diplomarbeit

Incidences, prediction and outcome of venous and arterial thromboembolism in patients with advanced pancreatic cancer treated with palliative first line chemotherapy of Gemcitabine/nab-Paclitaxel or FOLFIRINOX

eingereicht von

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Graz, am 07.06.2021 *Schwarzenbacher Esther eh*

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Abbreviations

ADP – Adenosinephosphate

AIO – Arbeitsgemeinschaft internistische Onkologie

AP – Alkaline Phosphatase

aPC – advanced pancreatic cancer

ATE – arterial thromboembolism

BMI – Body Mass Index

BSC – best supportive care

CA-19 – Carboanhydrase 19

CAVK – cranielle arterielle Verschlusskrankheit

CEA – carcinoembryonal antigen

ChT – Chemotherpy

CR – Cumulative Risk

CT – Computer Tomography

DVT – deep venous thrombosis

ECOG – Eastern Cooperative Oncology Group

EGFR – epidermal growth factor

ERCP – Endoscopic Retrograde Cholangiopancreatography

ESMO – European Society for Medical Oncology

FAMMM – Familial atypical multiple mole melanoma syndrome

FF – Folinic Acid, Fluouracil

Gy – Gray

HBOC – Hereditary Breast and Ovarian Cancer

HP – Helicobacter Pylori

KI – Karnofsky Index

LAPC – Locally advanced pancreatic cancer

mFOL – modified FOLFIRINOX regime

mPC – metastatic pancreatic cancer

MRCP – Magnetic Resonance Cholangiopancreatography

MRT – Magnetic Resonance Tomography

OFF – Oxaliplatin, Folinic Acid, Fluouracil

OR – Odds Ratio

OS – overall survival

PC – Pancreatic Cancer

PE – pulmonary embolism

PFS – progression free survival

PJS – Peutz- Jehgers syndrome

THR - transition hazard ratio

TKI – Tyrosine Kinase Inhibitor

Transabdominal US – transabdominal ultrasound

VTE – venous thromboembolism

vWV – van Willebrand factor

5 – FU – 5 – Fluouracil

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Zusammenfassung

Hintergrund:

Die Tumortyp spezifische Charakterisierung venöser und arterieller Thrombembolien bei PatientInnen mit Pankreaskarzinom kann individuelle Präventionsmaßnahmen verbessern. Diese retrospektive multizentrische Kohorten Studie liefert umfassende und aktuelle Untersuchungen von Inzidenz, Risikofaktoren und der Prognose venöser und arterieller Thrombembolien bei Patientinnen mit fortgeschrittenem Pankreaskarzinom unter palliativer Erstlinientherapie mit Gemcitabine/ nab-Paclitaxel oder FOLFIRINOX.

Material und Methoden:

PatientInnen mit fortgeschrittenem Pankreaskarzinom aus drei akademischen Zentren, die eine palliative Erstlinientherapie mit Gemcitabine/nab- Paclitaxel (GN) oder FOLFIRINOX erhalten haben wurden in die Studie eingeschlossen (n=455). Primäre Endpunkte waren objektiv bestätigte venöse Thrombembolien (tiefe Venenthrombose, Pulmonalarterienembolie, Eingeweidethrombosen) und/oder arterielle Thrombembolien (Myokardinfarkt, ischämischer Insult oder periphere Embolien). Kumulative Inzidenzen und Gruppenvergleiche von VTE/ATE Risiko wurden mittels competing risk Analysen berechnet. Der Einfluss von venösen und arteriellen Thrombembolien auf das Gesamtüberleben sowie auf das progressionsfreie Überleben wurden durch Multistate Modelle untersucht.

Ergebnisse:

Während einer medianen Beobachtungszeit von 26 Monaten [IQR: 14-144] wurden 86 VTE (kumulative Inzidenz: 20.0% [95% Konfidenzintervall (CI): 16.3-24.0]) und 11 ATE (kumulative Inzidenz: 2.8% [95% confidence interval (CI): 1.5-4.9]) beobachtet. Das Auftreten von VTE war mit einem statistisch signifikant höherem Sterblichkeitsrisiko (transition hazard ratio (THR) for VTE occurence: 1.59 [95% confidence interval (CI): 1.21-2.09])] und einem erhöhten Progressionsrisiko (THR 1.47 [95%CI: 1.08-2.01]) assoziiert, während das Auftreten von ATE mit einer numerisch, aber statistisch nicht signifikant höheren Mortalität einher ging (THR: 1.85 [95%CI: 0.87-3.94]). Hinsichtlich der Risikostratifizierung war der stärkste Risikofaktor für das Auftreten einer VTE eine VTE in der Vorgeschichte [sub-distribution HR (SHR) 3.29 [95%CI: 2.09-5.18]). Zwei validierte Risikostratifizierungsmodelle für das Auftreten der krebsassoziierten VTE, i.e. der Khorana- Score (SHR 0.78 [0.57-1.06]) und der CONKO- Score (SHR 0.87 [0.60-

1.03]) zeigten keine statistisch signifikante Assoziation mit dem Auftreten einer VTE. Das Vorliegen einer zentralen arteriellen Verschlusskrankheit (ZAVK) war mit einem deutlich erhöhten ATE Risiko (SHR: 22.05 [95% CI: 6.83-71.22], p<0.001), vor allem mit dem Auftreten ischämischer Insulte assoziiert. Das Risiko von VTE oder ATE zeigte keinen signifikanten Unterschied in Abhängigkeit der Art der erhaltenen Erstlinientherapie.

Conclusio:

PatientInnen mit fortgeschrittenem Pankreaskarzinom unter palliativer Erstlinientherapie mit FOLFIRINOX oder GN haben ein hohes Risiko einer VTE /ATE. Des Weiteren ist die Diagnose einer VTE/ATE mit schlechtem klinischem Outcome assoziiert. VTE Risikomodelle haben nur eine limitierte Fähigkeit, thrombotische Ereignisse zu klassifizieren.

Abstract

Introduction:

Cancer-type specific characterisation of venous- and arterial thromboembolism (VTE/ATE) risk in pancreatic cancer patients might improve personalized prevention strategies. This multicenter retrospective cohort study provides a comprehensive and contemporary investigation of incidence, risk factors and outcomes of VTE/ATE in homogenously treated patients with advanced pancreatic cancer (aPC).

Material and Methods:

Patients with aPC undergoing palliative 1st-line chemotherapy (Gemcitabine/nab-Paclitaxel (GN) or FOLIRINOX) at three Austrian academic centers were included (n=455). Primary outcomes were objectively confirmed VTE (deep-vein thrombosis, pulmonary embolism, splanchnic vein thrombosis) and/or ATE (myocardial infarction, ischemic stroke, or peripheral embolism). Cumulative incidences and between-group comparisons of VTE/ATE risk were obtained in a competing-risk framework. The impact of VTE/ATE on overall- and progression free survival was studied by multi-state modelling.

Results:

Over a median follow-up of 26 months (interquartile range: 14-44), 86 VTE (cumulative incidence: 20.0% [95% confidence interval (CI): 16.3-24.0]) and 11 ATE events (cumulative incidence: 2.8% [95%CI: 1.5-4.9]) were observed. VTE diagnosis was associated with increased mortality (transition hazard ratio (THR): 1.59 [95%CI 1.21-2.09]) and increased risk of disease progression (THR: 1.47 [95%CI: 1.08-2.01]), while the impact of ATE on mortality was numerically but not statistically significant (THR: 1.85 [95%CI: 0.87-3.94]). The strongest predictor for VTE risk was history of cancer-associated VTE (SHR 3.29 [95%CI: 2.09-5.18]), while two validated prediction models for cancer-associated VTE, the Khorana-score (SHR 0.78 [0.57-1.06]) and CONKO-score (0.78 [0.60-1.03]) failed to predict VTE risk. A history of cerebrovascular disease was associated with markedly increased ATE risk (SHR: 22.05 [95%CI: 6.83-71.22], $p<0.001$) especially of ischemic stroke. Risk of VTE/ATE did not significantly differ according to type of 1st line chemotherapy.

Conclusion:

Patients with aPC undergoing palliative 1st-line chemotherapy with FOLFIRINOX or GN face a high risk for VTE/ATE and its diagnosis is linked with worse clinical outcomes. VTE-risk prediction models have limited ability to sub-stratify thrombotic events in this high-risk scenario.

1. Introduction

Venous thromboembolism (VTE) is a frequent complication in patients with cancer and is associated with high morbidity and mortality (81,100,140). Overall, patients with cancer have a 9-fold increased risk of developing VTE compared to the general population (141). Among cancer patients, the risk of developing VTE strongly differs according to underlying thrombotic risk profiles. This risk is associated with patient characteristics such as age and comorbidities, depends on cancer-related risk factors and is further influenced by cancer specific treatment interventions (103, 142-147). The strongest risk factors for cancer associated VTE are the presence of high-risk tumour types and advanced cancer stage. With a cumulative incidence estimated of up to 20%, advanced pancreatic cancer accounts for the highest VTE risk among all tumour types (141,148). However, recently, the implementation of two novel chemotherapy regimens (FOLFIRINOX and Gem/nab-Paclitaxel) have transformed the palliative first line treatment of patients with advanced pancreatic cancer and good ECOG performance status. These novel treatment modalities have led to higher disease control rates and longer survival. (33,35) The more intense chemotherapy combination and a longer time at risk due to increased survival might significantly affect the VTE risk of patients in this setting.

In parallel, recently updated guidelines recommend risk-stratified prophylactic anticoagulation in ambulatory patients with cancer and a Khorana score ≥2 based on the results of two randomized controlled trials (149-152). However, the number needed to treat to prevent VTE events remains high indicating sub-optimal risk discrimination (153). Further, risk stratification based on the Khorana score is mainly driven by the underlying tumour type, preventing tumour-type specific sub-stratification of VTE risk (142). Consequently, the application of risk stratified prophylactic anticoagulation in ambulatory patients with cancer remains low in routine clinical practice. This burden might be overcome by the identification of tumour-specific prediction of VTE risk, particularly in high-risk cancer entities such as advanced pancreatic cancer, resulting in a lower number needed to treat to prevent VTE events. The high-risk scenario in combination with recent developments in treatment approaches warrants an updated, thorough analysis of the pattern, risk factors and clinical consequences of VTE in patients with advanced pancreatic cancer.

In contrast to VTE, patterns of arterial thromboembolism (ATE) in patients with cancer remains ill-defined. Recent studies suggest that the risk of ATE is increased in patients

with cancer and its occurrence is associated with poor outcome. (116) However risk profiles and clinical consequences of ATE in patients with pancreatic cancer have been poorly investigated to date.
The aim of this study was to thoroughly characterise the clinical pattern and outcome of both VTE and ATE in a homogenously treated, multi-center cohort of patients with advanced pancreatic cancer undergoing palliative first-line chemotherapy with Gemcitabine/nab-Paclitaxel or FOLFIRINOX and to explore a broad panel of clinical variables towards its predictive capability towards risk of VTE and ATE in this cohort.

1.1.1.1.Incidence

In 2018, 458.981 people were diagnosed with pancreatic cancer (PC) worldwide. There is a rare difference between the incidence rates of male and female. In Europe, 67.206 new cases within men and about 65.353 new cases within women have been documented. (1)
In Austria 1.806 new cases of PC were documented in 2018. Of these 945 patients were male, and 861 patients were female. Over time, the incidence rarely changed as it is shown in Table 1. In 1992 about 23 new cases per 100.000 males were documented and in 2017 there were 25 cases per thousand. In females, in 1992 17 new cases per 100.000 occurred, and this number remained unchanged in 2017. (3)
In the United States, about 57.600 cases of PC are diagnosed annually. The comparative incidence ratio for men and women is about 1.3:1. We can therefore see that males are slightly more prone to PC than females in the United States as well. (2)
The GLOBOCAN database from 2018 confirms these findings. Worldwide there were 243.033 new cases in men and 215.885 new cases in women, which is a ratio of about 1,12:1. (1)
The incidences increase with advanced age of the patients. This trend is similar in male as well as in female patients. There is a peak between the age of 65 – 69 years in male and between 75 and 79 years a peak was observed among women. Before the age of 45 years, PC is rare. (6)

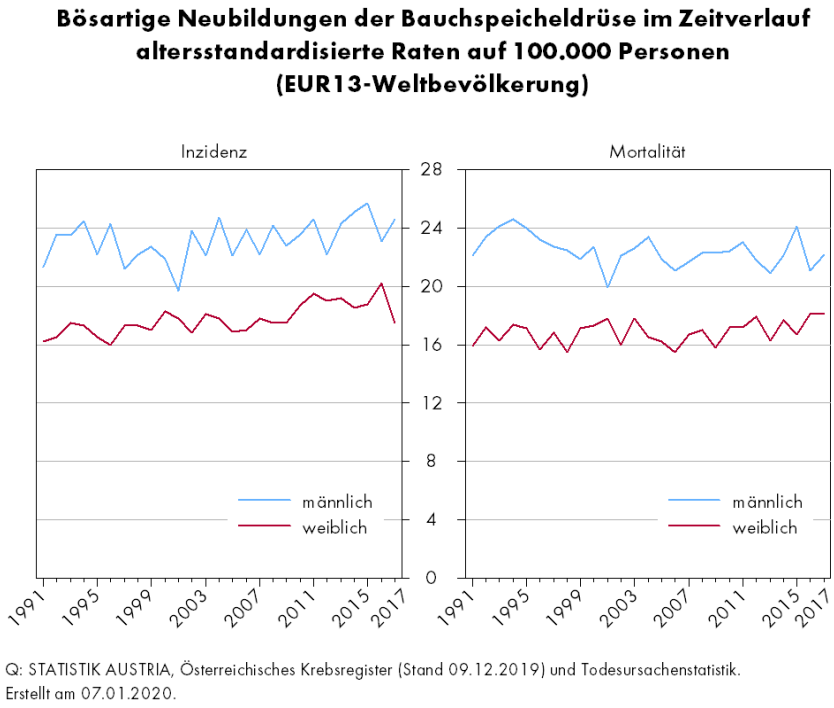

Figure 1: Austrian cancer register and statistic of causes of death

1.1.1.2.Mortality

In 2018, PC was the seventh most likely cancer to cause death amongst male and female patients worldwide. (1) The development in the last decades showed, that the mortality of PC has not decreased over the last 50 years. In 1955 the mortality rate was 4 per 100.000 among female and 6 per 100.000 within male patients. In 2000 the mortality rose to 6.5 per 100.000 amongst females and 8 per 100.000 amongst males. In 2015 the mortality of male patients was 9 per 100.000 people and nearly 7 per 100.000 amongst female patients. In the United States the mortality went up from 4 per 100.000 female in 1955 up to 5.5 per 100.000 in 2015. The mortality amongst men in the USA increased from 7 per 100.000 up to 7.5 per 100.000 in 2015. (5)

Similar to the findings of incidence for the global burden disease study, also the mortality increases with increased age. (6)

1.1.2. Etiology

The etiology of pancreatic cancer is not completely understood yet, but there are several genetic as well as non-genetic risk factors, that are implicated with pancreatic cancer.

1.1.2.1.Non genetic risk factors

The Global Burden Disease Study 2017 showed that smoking cigarettes, a lack of physical activity as well as obesity and Diabetes Mellitus are conditions that frequently occurred in patients who died of pancreatic cancer. (1)

Cigarette Smoking:

An analysis from the International Pancreatic Cancer Case-Control Consortium in 2012 has shown, that the odds ratio (OR)[1] to suffer from pancreatic cancer was 2.1 for former smokers and almost 2.2 for current smokers. Furthermore, the risk to contract PC increased, the more cigarettes a person smoked (OR = 3.4 for ≥35 cigarettes per day). The risk also increased with the duration of cigarette smoking. Up to 40 years of cigarette smoking showed an OR of 2.4, which means that people who smoke up to 40 years have a 2.4 higher chance to suffer from pancreatic cancer than non-smoking people. (7) Maisoneuve et Lovenfeld (2015) conducted a meta-analysis study about the risk factors for PC. Their findings suggest that 11%-32% of patients contract PC due to cigarette smoking (8).

Adiposities and physical inactivity, Diabetes Mellitus:

Two US cohort studies have shown that a Body Mass Index (BMI) of more than 30 kg/m^2 is associated with an increased risk of developing pancreatic cancer (RR 1.72, CI 95%) compared with people with a BMI lower than 23 kg/m^2. It was also evaluated, that physical inactivity has a negative influence of developing PC, especially among people who are overweight with a BMI of at least 25 kg/m^2. (9)

[1] Odds ratio: An **odds ratio** (OR) is a measure of association between an exposure and an outcome. The OR represents the **odds** that an outcome will occur given a particular exposure, compared to the **odds** of the outcome occurring in the absence of that exposure

There exist several studies that have shown a connection between obesity, physical inactivity, and PC (10,11,12).
The tumor genesis is triggered by the high amount of adipose tissue, supposedly through an abnormal metabolism of glucose. Moreover, Meta-analysis has shown a connection between Diabetes Mellitus Type I and Diabetes Mellitus Type II and PC. The OR is 2.0 among DM I and 1.7 among DM II. (13)

Chronic Pancreatitis and Alcohol Consume:

Chronic Pancreatitis is responsible for about 5% of PC. The main cause for chronic pancreatitis is an excess alcohol consume (13).
However, there is little evidence to suggest that there is a direct correlation between high alcohol consumption and PC. Cigarette smoking is believed to be the primary confounding factor leading to the onset of PC (2,14). There have been two studies that investigated the impact of alcohol to PC, but the results have shown, that if there is a correlation it is very weak and merely due to heavy alcoholic drinks. (2)

Helicobacter Pylori Infection:

Some studies have shown that there is a link between HP Infections and PC. (15-19)

1.1.2.2. Genetic risk factors

Not only environmental risk factors are associated with pancreatic cancer. There also exist several genetic risk factors that have an impact on the development of pancreatic cancer. The two most prominent hereditary risks are familial pancreatic cancer (FPC) and inherited cancer syndromes. It is estimated, that about 10-15% of PC are attributed to genetic causes (20). In the following paragraphs, the genetic risk factors for PC are going to be discussed shortly.

Inherited cancer syndromes associated with increased risk of PC:

Hereditary breast/ovarian cancer:
The hereditary breast and ovarian cancer (HBOC) is characterized by a germline mutation in one of the two breast cancer genes (BRCA genes) BRCA1 and BRCA2. According to

findings from Broses et al. (2002), BRCA 1 mutation carriers have a three times higher risk for PC (49). Thompson et al. (2012) described in their cohort study, that BRCA1 mutation carriers were at a statistically significantly increased risk for several cancers, including pancreatic cancer (RR = 2.26, 95% confidence interval [CI] = 1.26 to 4.06, P =.004) (50). Lynch et al. (2005) found an apparent association between BRCA1 and PC (51). However, it must be noted that there are studies that contradict those findings. For example, Axilbund et al. (2009) found no connection between the mutation of BRCA 1 and PC. Their findings suggest that there is neither a connection between an aggregation of pancreatic cancer in families and a mutation in BRCA1 genes nor a connection between breast cancer and PC with germline mutations of BRCA1 (52).
Within BRCA2, the data availability is much more established. According to studies from Murphy et al. (2002), Hahn et al. (2003) and Couch et al. (2007), this mutation was found in 5-17% of patients that suffered from FPC (20, 53, 54, 55).

Familial atypical multiple mole melanoma syndrome:

The familial atypical multiple mole melanoma syndrome (FAMMM) is characterized by a mutation in the cyclin-dependent kinase inhibitor 2A gene (CDKN2A gene). Within this syndrome, patients typically show multiple nevi, cutaneous malign melanoma as well as ocular malign melanoma and pancreatic cancer.
There exists a variant FAMMM- pancreatic carcinoma syndrome that is characterized by a specific mutation. In the p16 gene a 19-base-pair deletion could be established. This mutation is characterized with an increased risk of PC up to nineteen percent by the age of 75 (22).

Peutz- Jeghers syndrome:

The Peutz- Jeghers syndrome (PJS) is an autosomal dominant disorder. Mutations of the germline in the serine/threonine kinase 11 gene (STK11 gene) is common in PJS. This syndrome is characterized by multiple hamartomatous polyps in the gastrointestinal tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and non-gastrointestinal cancer (21). According to Chung et al. (2019), patients with this mutation have a lifetime risk of about 11-36% to suffer from pancreatic cancer. Other common carcinomas within PJS are colorectal cancer (lifetime risk of 39 percent), stomach cancer (lifetime risk of 29%) as well as small bowel cancer (lifetime risk of 13 percent) (21).

Lynch II Syndrome:

The Lynch syndrome is an autosomal dominant disorder. It is characterized by a germline mutation in one of several DNA mismatch repair (MMR) genes or loss of expression of mutS homolog 2 gene (MSH2 gene). The MMR genes that are associated with Lynch syndrome include the MLH1 gene, located on chromosome 3p22.2, MSH2 gene on chromosome 2p21-16, MSH6 gene located on chromosome 2p16.3 as well as the PMS 2 gene located on chromosome 7p22.1 (23).

Kastrinos et al. (2009) investigated the risk of PC in families with Lynch Syndrome. They found that the cumulative risk to suffer from PC in this families was 1,3% (95% CI: 0.31, 2.32) up to the age of 50 years and 3.68% (95% CI:1.45, 5.88) up to the age of 70 years. This constitutes a 8.6 -fold increase compared to the general population (24).

Hereditary pancreatitis:

Hereditary pancreatitis, an autosomal dominant disorder, causes a minor part of chronic pancreatitis. It is associated with a mutation in the in-serine protease 1 gene (*PRSS1*) on chromosome 7q35. Most of the people who suffer from this mutation develop a chronic pancreatitis before the age of 20, sometimes even before the age of five. The chronic inflammation, and thereby the mutation and clonal expansion of genes can lead to development of pancreatic cancer. Only a very small fraction of PC is caused by hereditary pancreatitis, but the patients who suffer from hereditary pancreatitis have a very high risk to develop PC. The lifetime risk is estimated at about 25-44% (20).

Ataxia telangiectasia:

Ataxia telangiectasia is related to mutations in the ataxia-telangiectasia mutated (*ATM*) gene. This mutation is associated with a higher risk of developing PC, despite the lifetime risk of developing PC being uncertain within this illness (25).

The following table (Table 1.) shows a summary about the inherited cancer syndromes that are referred to have an increased risk for pancreatic cancer with the important genes, their locus, and the lifetime risk for PC.

Inherited cancer syndromes associated with increased risk of pancreatic cancer

Syndrome	Gene(s)	Lifetime risk of pancreatic cancer, percent	Locus
Hereditary breast/ovarian cancer	BRCA2, BRCA1	3 to 5	13q
	PALB2	Unknown	16p
Familial atypical multiple mole melanoma syndrome	CDKN2A	10 to 19	9p
Peutz-Jeghers syndrome	STK 11	11 to 36	19p
Familial adenomatous polyposis	APC	Unknown	5q
Hereditary nonpolyposis colon cancer (Lynch II)	DNA mismatch repair genes	4	2p, 3p, 7p
Hereditary pancreatitis	PRSS1, SPINK1	25 to 40	7q, 5q
Ataxia telangiectasia	ATM	Unknown	11q
Li-Fraumeni syndrome	P53	Unknown	17p

Adapted with permission from: Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. Curr Treat Options Oncol 2005; 6:437. Copyright © 2005 Current Medicine.

Graphic 61283 Version 4.0

Table 1: Inherited cancer syndrome associated with increased risk of pancreatic cancer

FPC: Familial Pancreatic Cancer

Familial Pancreatic Cancer is defined as an inherited susceptibility to pancreatic cancer in families, where at least two first degree relative also suffers from pancreatic cancer without any known genetic syndrome. So far, a special genetic defect was not identified within FPC.

For a member of a family with FPC, the risk of PC was nine times higher than for sporadic PC. People with a first degree relative with PFC even have an eighteen-fold higher risk to suffer from PC. The risk for developing PC is increasing with the increasing number of affected blood relatives. (26)

1.1.3. Pathology, Histology, Grading, Staging

85% to 90% of pancreatic carcinoma are adenocarcinomas of the pancreas.

Most of the adenocarcinomas are in their macroscopic appearance hard, gritty, and grey – white mass and badly circumscribed because of invasion of the pancreas and other neighbored tissues.

The majority of PC is localized in the head of the pancreas. The ratio from head to tail/body is 3:1 (27).

1.1.3.1.Grading

Most of the adenocarcinomas are differentiated moderately to poorly. Most common is a variety of mucine and duct like structures (Figure 2).

In general, the histological grading, that is based on the grade of the differentiation of the cells of the tumor, is graded into three groups.
Grade 1 (G1) is a histological picture of a well differentiated tumor, as it is shown on the left picture (A) in figure 2. In **grade 2 (G2)**, moderately differentiated cells are dominate. In **grade 3 (G3)** are predominantly poor differentiated cell groups (right picture (B), figure 2). Sometimes a fourth grade is used, grade 4 (G4) when the tumor cells are highly anaplastic (27).

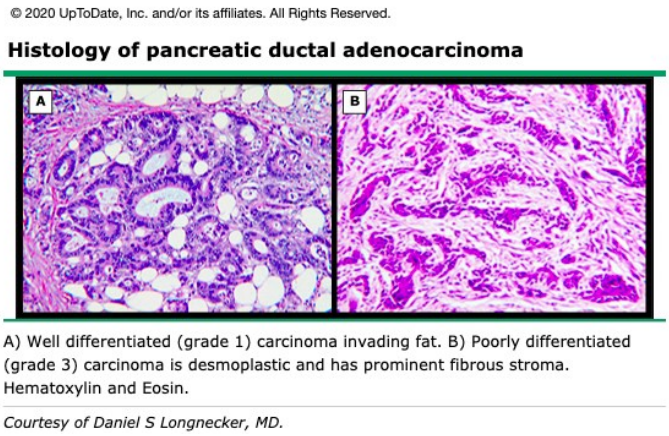

Figure 2: Histology of pancreatic ductal adenocarcinoma

1.1.3.2.Staging

The most common staging system for pancreatic cancer is the TNM classification of the Combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).
The abbreviation TNM stands for T= tumor, N= (lymph) node and M=metastasis (28). The T stands for the depth of the tumor infiltration. The N gives information about the lymph node status and the M describes the occurrence of distant metastasis.
With this classification, the pancreatic cancer can be categorized according to five stages. Stage 0 is classified as carcinoma in situ. The tumor has not infiltrated yet and there are no lymph nodes that are affected and no distant metastasis. The carcinoma in situ includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous

neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.

Stage I is defined as tumors with a maximal dimension of four centimeters, no lymph node and no metastasis.

When the tumor shows metastasis in one to three regional lymph nodes, and no distant metastasis, it is classified as stage II, as well as tumors with a maximal distension of more than four centimeters with no lymph nodes and no distant metastasis are also classified as stage II.

Stage III is defined as tumors larger than four centimeters in dimension with metastasis in four or more reginal lymph nodes and no distant metastasis.

Tumors that affect the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size with any N and no M are classified as stage IV. If distant metastasis are present, the tumor is classified as stage IV, despite the classification of T or N. The stages are subdivided, due to the dimension of the tumor and the different lymph nodes affected, which is shown in table 3.

The five-year survival rate for resected PC was estimated as shown in the following table:

Stage	5-year survival rate
I A	39%
IB	34%
II A	28%
II B	21%
III	11%

Table 2: 5- year survival rate for resected PC depending on the stage

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in suit
T1	Tumor <=2 cm in greatest dimension
T1a	Tumor <= 0,5cm in greatest dimension
T1b	Tumor >0,5 and >1cm in greatest dimension
T1c	Tumor 1-2 cm in greatest dimension
T2	Tumor >2 and <= 4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Table 3: TNM classification by AJCC 8th edition

Prognostic stage groups			
When T is…	And N is…	And M is…	Stage group
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

Table 4: Stage groups of pancreatic cancer

1.1.4. Clinical presentation

According to the actual guidelines from the German society of hematology and oncology (DGHO) (56), the symptoms of PC can be divided into the following four groups:
The most common **localized symptoms** that occur in PC are:

- epigastric pain
- jaundice
- diarrhea
- steatorrhea

The initial symptoms can vary due to the localization of the tumor. Roughly 60% to 70% of PC are located in the pancreatic head. Tumors of the pancreatic head frequently show an earlier jaundice due to a compression of the common bile duct than tumors of the body or the tail (28, 29).

Unspecific symptoms:

- abdominal pain
- back pain
- newly diagnosed or declined diabetes mellitus.

General symptoms:

- a loss of weight
- intolerance versus glucoses
- paraneoplastic symptoms
    - such as thrombophilia, thrombophlebitis, or panniculitis nodularis

Further symptoms can be caused by distant metastasis:

- Icterus or liver insufficiency caused by liver metastasis
- cough
- dyspnea caused by pulmonary or pleural metastasis
- ascites because of peritoneal metastasis
- neurological symptoms due to cerebral metastasis
- bone pain caused by bone metastasis

PC metastasis are mostly located in the liver, the lung as well as the peritoneum. Bone metastasis are detected less often.

1.1.5. Diagnosis of pancreatic cancer

Medical history and clinical examination

A general anamnesis as well as a clinical examination of the patient should be done at first (56).

Imaging:

Transabdominal ultrasound (transabdominal US):

Transabdominal ultrasound is the first choice, if there is a clinical suspicion for pancreatic cancer. The transabdominal US has a high sensitivity for detecting dilatations of the biliary tract as well as for detecting a pancreatic mass. Karlson et al. (1999) have shown that the sensitivity for detecting all tumors of the pancreas with US was 88.6% (n=140), the sensitivity for detecting exocrine tumors was higher at approximately 90% (57). Investigations have shown that the sensitivity for tumors that are smaller than three centimetres is lower (57, 58, 59). The quality of transabdominal ultrasound also depends on the expertise of the examiner as well as if there is a bile duct obstruction or not. (28)

Abdominal computed tomography:

An abdominal computed tomography (CT) is often carried out if either the US is unclear or to complement the US image. It is helpful in defining the accurate advancement and localization of the tumor and detecting distant metastasis (28). The sensitivity of CT to detect PC is dependent on the technique. Following Valls et al. (2002) it is the highest within triple- phase helidedector multical row CT. The sensitivity reached from 89% to 97% (60). Similar as it is in US, the sensitivity is higher, the larger the tumors are. Bronstein et al. (2004) investigated a sensitivity of 100% within tumors that are two centimeters or larger, but only a sensitivity of about 77% for tumors that have been smaller than two centimeters (61).

Magnetic resonance (MRT):

As an alternative to the computed tomography, an abdominal magnetic resonance can also be done. A MRT can be done if the CT is not possible because of contraindications, for example a bad renal function. Furthermore, it can be done if the findings of US and the CT are mainly unclear (56). Special techniques allow a good presentation of the pancreatic and the bile duct as well as upper abdominal blood vessels, without using contrast agent.

Endoscopic retrograde cholangiopancreatography (ERCP):

The ERCP is very useful in detecting abnormalities of the pancreatic duct and the biliary tree (62). Niederau et al. (1992) found in their analysis a specificity from 92 percent and a sensitivity from 96 percent in detecting pancreatic cancer by doing an ERCP. Also, tissue samples for further examinations can be taken by an ERCP (63).

Laboratory values:

CEA (carcinoembryonal antigen):

CEA can also be extended within pancreatitis or liver cirrhosis and is therefore no marker for diagnosing pancreatic cancer. Though it can be used for evaluating the response of a therapy and as a prognostic marker (56).

CA19-9:

The sensitivity from CA19-9 for diagnosing pancreatic cancer ranges from 70% to 92% (128-133). The sensitivity of CA19-9 closely relates to the size of the pancreatic tumor (133). Furthermore, CA 19-9 requires the presence of the Lewis blood group antigen. However, approximately 5% - 10% of the population are Lewis blood group antigen negative genotypes, which can lead to false negative findings. CA19-9 is not very useful for screening patients for detecting PC, but it can be useful as a prognostic marker as well as for checking the response of a chemotherapy or postoperative recurrence (128).

Biopsy with histological and cytological analysis:

An accurate histopathologic diagnosis requires a biopsy and a histological analysis. A histopathological analysis is important, because of the wide range of pancreatic neoplasms. Some forms of pancreatitis can imitate as a pancreatic mass; therefore, a biopsy is the only chance to find out if the tumor is benign or malignant (134).

A diagnostic biopsy is indispensable for the planning of the palliative treatment, if the disease is already spread, and locally unresectable. Patients with an entire staging, who appear to have a resectable tumor and are fit for operation do not essentially need a preoperative biopsy (28).

1.2. Treatment of pancreatic cancer

The treatment strategy of PC mainly depends on the stage of the tumor. It depends on the progress of the disease, the advancement and stage of the disease and the existence of distant metastasis. The only curative treatment for PC is the surgical resection. For more advanced stages, chemotherapy or an adjuvant chemotherapy can be used as treatment (56).

The next section will discuss the therapy of pancreatic cancer in more detail.

1.2.1. Treatment of localized pancreatic cancer

Surgical resection

The main goal of the curative treatment of PC is to achieve a R0 resection, which means to achieve negative resection margins, where no tumor cells can be detected anymore (31). When establishing the respectability, the tumor can be respectable, borderline respectable or locally advanced. This classification is based on the distance between the tumor and the vessels. Borderline tumors are at a high risk not to be resected in R0 but in R1, which significantly lowers the chance for cure. Tumors that are locally advanced are treated as not respectable (135).

The chirurgical procedure of the resection depends on the localization of the tumor.

If the tumor is in the head of the pancreas, usually the Whipple maneuver, a pancreatoduodenectomy, is done. If the veins are involved, they should be resected completely. Arterial resections come together with a higher mortality and morbidity and are therefore not recommended (136). If the tumor is in the body, a total pancreatoduodenectomy is done. If it is in the tail, usually a subtotal resection of the left pancreas as well as a splenectomy is recommended (56).

A total lymphadenectomy is not recommended but there are parts that should be resected as seen in the following table.

Pancreatoduodenectomy	Suprapyloric (station 5)
	Infrapyloric (station 6)
	Anteriosuperior group along the common hepatic artery (station 8a)
	Along the bile duct (station 12b)

	Around the cystic duct (station 12c)
	posterior aspect of the superior (station 13a)
	Inferior portion of the head of pancreas (13a)
	Right lateral side of SMA (station 14a and 14b)
	Anterior surface of the superior (station 17b) and inferior portion of the head of pancreas (station 17b)
Tumor of body and tail	Splenic hilum (station 10)
	Along the splenic artery (station 11)
	Inferior margin of pancreas

Table 5: Lymphadenectomy

After the chirurgical resection, a further treatment is recommended. In general, the options are adjuvant chemotherapy or adjuvant radio chemotherapy. Usually, an adjuvant chemotherapy is done after chirurgical resection.

Adjuvant chemotherapy and radio chemotherapy

The **PRODIGE** Group tested a modified FOLFIRINOX (mFOL) regimen compared to Gemcitabine as an adjuvant therapy for patients with resected pancreatic cancer. The patients suffered from a pancreatic ductal adenocarcinoma. The modified FOLFIRINOX regimen is characterized by not using a Fluouracil bolus. That was introduced to decrease the hematologic toxic effects as well as diarrhea and did not result in reducing the treatment efficacy. The modified FOLFIRINOX regimen included Oxaliplatin, Irinotecan, Leucovorin as well as Fluouracil. 493 patients were included, and they received the treatment for 24 weeks. Only patients who were between 18 to 79 years and underwent R0 or R1 resection within 3 to 12 weeks before, were included in the randomized trial. They did not have any evidence of metastatic disease, pleural effusion, or malignant ascites. The primary end point was defined as disease- free survival, the secondary end points were defined as safety as well as overall survival.

The disease- free survival was 21.6 months among the mFOL group, and 12.8 months among the group that received gemcitabine alone as a therapy (stratified HR for cancer-related event, second cancer, or death, 0.58; 95% confidence interval [CI], 0.46 to 0.73; P<0.001).
Adverse events of grade three or four were determined in 75.9% of patients in the modified FOLFIRINOX regimen and in 52.9% of patients treated with gemcitabine. The mFOL regimen showed more likely up with adverse events like diarrhea, paranesthesia, nausea, vomiting, abdominal pain, sensory peripheral neuropathy, and mucositis, therefore thrombocytopenia was significantly more common in the gemcitabine group.
The median overall survival was 35.0 months in the gemcitabine group, compared to 54.4 months in the modified FOLFIRINOX group (stratified HR for death, 0.64; 95% CI, 0.48 to 0.86; P = 0.003).
To summarize, the PRODIGE study showed, that patients that had undergone an entire resection of PC and an adjuvant chemotherapy with the modified FOLFIRINOX regimen showed a significantly longer disease- free survival as well as overall survival compared to an adjuvant treatment with Gemcitabine. However toxic effects were more common in the mFOL group than in the Gemcitabine group (39).

Another possibility of adjuvant treatment is according to the **ESPAC-4** trial a combination of Gemcitabine and Capecitabine. 732 patients were assigned 1:1 to receive either Gemcitabine or Gemcitabine and Capecitabine within 12 weeks after the surgical intervention (complete macroscopic resection with RO or R1). They were treated for six months. The primary endpoint was defined as the overall survival, this was measured from the randomization until death. The secondary end points have been survival estimates at 24 months, the five-year survival and relapse-free survival (minimum time from randomization to date of local tumor recurrence, lymph node spread, distant metastases or death from any cause).
The median overall survival in the Gemcitabine plus Capecitabine group was 28.0 months compared to 25.5 months (HR 0.82 [95% CI 0·68–0·98], p=0.032) of median overall survival in the gemcitabine group.
The estimated overall survival after 24 months was 52.2% in the gemcitabine group and 53.8% in the gemcitabine plus Capecitabine group. Adverse events of grade three to grade four were more common in the Gemcitabine plus Capecitabine group. However, it is

important to note that the toxicity was manageable. There seem to be some differences with regard to the subgroups. Patients who had a R0 resection had the benefit of getting Gemcitabine plus Capecitabine (median OS 39.5 months with the combined therapy versus 27.9 months with gemcitabine alone). However, patients with a R1 resection did not have any advantage of getting the combined therapy instead of the monotherapy with Gemcitabine (Median OS 23.7 in combined group and median OS 23.0 among monotherapy) (40).

Furthermore, the **ESPAC-1** trial is an important study for the treatment of resected pancreatic cancer. The European study group for pancreatic cancer (2001) compared an adjuvant treatment with a chemotherapy versus an adjuvant treatment with a chemo radiotherapy. The chemo radiotherapy included 20 Gray (Gy) in daily ten fractions over two weeks with 500mg/m^2 Fluouracil intravenously on days one to three and repeated after two weeks. The chemotherapy was based on intravenously 425mg/m^2 Fluouracil and Folfinic Acid 20mg/m^2 daily for five successive days every 28 days, over a period of six months. 541 patients were included in the trial. The primary endpoint was death. The results showed no benefit for patients with an adjuvant chemo radiotherapy (median survival 15.5 months in 175 patients with chemo radiotherapy vs 16.1 months in 178 patients without (hazard ratio 1.18 [95% CI 0.90-1.55], p=0.24). Patients with an adjuvant chemotherapy showed minor improvements in life expectancy (median survival 19.7 months in 238 patients with chemotherapy vs 14.0 months in 235 patients without; hazard ratio 0.66 [0.52-0.83], p=0.0005) (64).
Following these trials, the recommendation for an adjuvant chemotherapy within patients with resected pancreatic cancer is like the following:

- mFOLFIRINOX for patients with a good perfo status (ECOG 0 or ECOG 1)
- Gemcitabine plus Capecitabine in more frail patients
- Gemcitabine Monotherapy only in frail patients

Figure 3 shows the recommended treatment of resected pancreatic cancer.

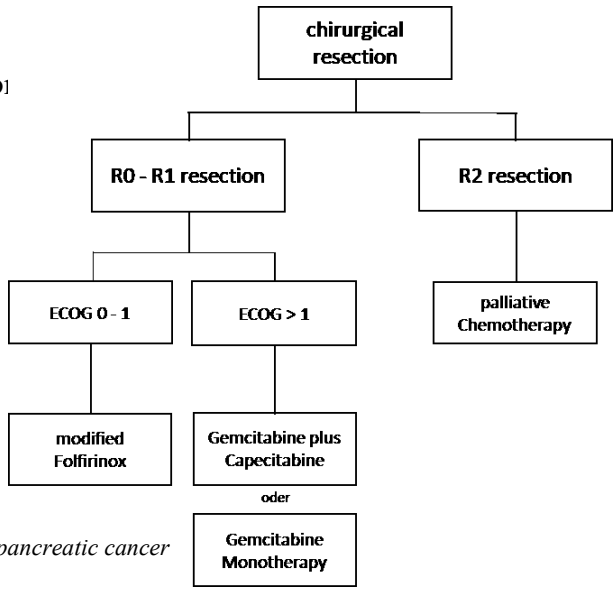

Figure 3: Treatment of resected pancreatic cancer

1.2.2. Treatment of locally advanced pancreatic cancer (LAPC)

About 30 to 40 percent of the patients that suffer from PC, suffer from locally advanced pancreatic cancer. LAPCs are tumors that are not resectable, as they have extensive local vascular involvement. Generally, these patients are treated with the help of neoadjuvant chemotherapy or less frequently with chemoradiotherapy or radiotherapy (31).

Rombouts et al. (2016) have shown that a treatment with **Folfirinox** for patients with LAPC has led to an increased overall survival from 9 months to 16 months (68). Further studies have showed an increase of LAPC to a resectable tumor in 10% to 35% with an adjuvant chemotherapy with Folfirinox (69-71).

Following the actual Onkopedia Guidelines for pancreatic cancer, also **nab-Paclitaxel** is an option for a neoadjuvant chemotherapy within LAPC (56).

Radio chemotherapy is only recommended in patients that develop distant metastasis during the inductive neoadjuvant chemotherapy. Capecitabine has shown to increase the survival rate as well as progression free survival preferable to Gemcitabine within the Radio chemotherapy (72).

1.2.3. Palliative treatment of advanced pancreatic cancer

About 80% of patients diagnosed with PC are suffering from advanced disease at primary diagnosis and the vast majority of patients who are treated in curative intent primarily enter the palliative stage later. Therapy modalities for the palliative setting are palliative chemotherapy as well as supportive measures.
The aim of palliative chemotherapies is to increase the lifetime and to improve the quality of life, but it is no curative treatment (73). The chemotherapy mostly depends on the patient's performance status. Supportive therapy measures primary concern is the relief of biliary, and / or duodenal obstruction (74), malnutrition, and pain management (75).

1.2.3.1.First Line chemotherapy

Over a time of more than ten years, the only therapy for metastatic pancreatic cancer was Gemcitabine monotherapy. This chemotherapy was established in 1997 as a standard of care for PC, as it showed a minimal survival benefit versus weekly 5 – Fluouracil (5-FU) (65). Many Gemcitabine chemotherapy combinations have been tested and evaluated thereafter but none was successful. Combinations with cytotoxic agents like Irinotecan, 5-FU, Cisplatin, Oxaliplatin and Capecitabine have been evaluated. A statistically significant survival advantage has been shown by using chemotherapy combinations versus using only Gemcitabine monotherapy. The combination of Gemcitabine with Capecitabine or Cis-Platin showed the greatest benefit (66) but the level of evidence was too low to bring about changes in routine clinical practices (31).
Gemcitabine plus Erlotinib, that is an epidermal growth factor receptor (EGFR) showed in a phase three study from Moore et al. (2007), that with an addition of 100 to 150 mg of Erlotinib to Gemcitabine daily, a significant, but slightly increase of the overall survival was achieved (6.24 months (HR of 0.82 (95% CI, 0.69 to 0.99; p=038)
within the combined chemotherapy versus 5.91 months within Gemcitabine monotherapy). Unfortunately, the toxicity was higher in the combined chemotherapy, with commonly leading to side effects such as rush, fatigue, and diarrhea. Since the severity of the side-effects outweighed the efficacy of the treatment success, the combination of Erlotinib and Gemcitabine did not become a method for treating mPC (32).
Apart from the Tyrosine kinase inhibitor Erlotinib that showed in combination with Gemcitabine a small but clinically irrelevant survival benefit, modern treatments like other tyrosine kinase inhibitors (TKI) or specific antibodies combined with gemcitabine did not show any benefit in efficacy (31).

Major advance in treatment of metastatic cancer came in 2011, within the trial of the **PRODIGE** group that evaluated **FOLFIRINOX** versus Gemcitabine for the treatment of mPC.
In this study, 342 patients with metastatic pancreatic cancer and an ECOG performance status of 0 or 1 have been included. Participants had to be at least 18 years old, diagnosed with mPC and no prior exposure to chemotherapy. The patients were randomly assigned to receive either FOLFIRINOX or Gemcitabine as first line chemotherapy.

The FOLFIRINOX regimen included Oxaliplatin (85mg/m^2 body surface), Irinotecan (180mg/m^2), Leucovorin (400mg/m^2) and Fluouracil (400mg/m^2) as an intravenous bolus followed by Fluouracil 2400 mg per square meter over a time of 46 hours as a permanent infusion, every two weeks.
Gemcitabine was administered at a dose of 1000 mg/m^2 body surface trough a 30-minute intravenous infusion weekly for seven weeks, one-week rest, and then weekly for another three weeks.
In both groups one cycle of chemotherapy lasted two weeks.
The median overall survival was 6.8 months (95% CI, 5.5 to 7.6) in the Gemcitabine group, compared to 11.1 months (95% CI, 9.0 to 13.1) in the FOLFIRINOX group (HR for death, 0.57; 95% CI, 0.45 to 0.73; p<0,001). The overall survival rate after 6, 12 and 18 months was higher in the FOLFIRINOX group (75.9%, 48.4%, 18.6%) compared to the Gemcitabine group (57.6%, 20.6% and 6.0%).
The progression free survival was 6.4 months (95% CI, 5.5 to 7.2) within the FOLFIRINOX group, and 3.3 months (95% CI, 2.2 to 3.6) within the gemcitabine group (HR for disease progression, 0.47; 95% CI, 0.37 to 0.59; p<0.001).
More adverse effects were documented in the FOLFIRINOX group. Febrile neutropenia occurred in 5.4% of the patients treated with FOLFIRINOX. After six months of treatment, 66% of patients within the Gemcitabine group had a definitive degradation of their quality of life, versus 31% of patients in the group treated with FOLFIRINOX. (HR, 0.47; 95% CI, 0.30 to 0.70; p<0.001) (33).
Findings of PRODIGE trial suggest that FOLFIRINOX has a positive impact on the overall survival rate as well as the progression free survival rate. According to these findings, FOLFIRINOX is a recommended first line therapy for patients with metastatic pancreatic cancer and a good performance status with ECOG 0 or 1.

Due to the high toxicity of the FOLFIRINOX chemotherapy, the modified FOLFIRINOX (mFOLFIRINOX) regimen can be used as an alternative. Stein et al. (2016) reported about this treatment in a phase II study. In the study, the Fluouracil bolus as well as the dose of Irinotecan were reduced at 75% of the original doses of the FOLFIRINOX regimen. It has been found that this combination leads to less severe side-effects, such as fatigue, vomiting, emesis, or neutropenia (34).

In 2013, another great advancement was made in the treatment of PC. The **MPACT** trial evaluated the success rate of a combined chemotherapy of **Gemcitabine with albumin-bound Paclitaxel** (nab Paclitaxel) and compared it to Gemcitabine monotherapy. A phase 1 and 2 trial showed an essential clinical activity of Gemcitabine and Capecitabine in patients with advanced PC.

In total, 431 patients have been randomly assigned to the group nab- Paclitaxel plus Gemcitabine, and 430 to the Gemcitabine Monotherapy group. Patients with advanced pancreatic cancer who had a Karnofsky Index (KI) of 70 or more were included in the study and either got Gemcitabine plus nab-Paclitaxel or Gemcitabine monotherapy. Only patients who had not previously received chemotherapy for the metastatic disease and had a histologically or cytologically confirmed metastatic adenocarcinoma, were eligible to take part in the study. The disease had to be diagnosed maximal six weeks prior to randomization.

The tumor response was investigated every eight weeks trough spiral computed tomography or magnetic resonance imaging.

The primary end point was the overall survival. The median survival in the nab- Paclitaxel group was 8.5 months (95% CI, 7.89 to 9.53) compared to 6.7 months (95% CI, 6.01 to 7.23) in the Gemcitabine group (HR for death, 0.72; 95% CI, 0.62 to 0.83; $p<0.001$). Furthermore, the progression free survival was significantly higher in the nab- Paclitaxel group. It was 5.5 months ((95% CI, 4.5 to 5.9) within the nab- Paclitaxel plus Gemcitabine group compared to the PFS in the Gemcitabine monotherapy group where it was 3.7 months (95% CI, 3.6 to 4.0) (HR for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; $p<0.001$). The time to treatment failure[2] was lower in the Gemcitabine group with 3.6 months (95% CI, 3.5 to 3.9) compared to the nab- Paclitaxel group with 5.1months (95% CI, 4.1 to 5.5) (HR 0.70; 95% CI, 0.60 to 0.80; $p<0.001$). Most common adverse events in the nab- Paclitaxel plus Gemcitabine group have been fatigue (54%), alopecia (50%) and nausea (49%). Adverse events that were related to the treatment more often occurred in the group of nab- Paclitaxel plus Gemcitabine. Especially neutropenia, leukopenia, fatigue as well as peripheral neuropathy were documented (35).

The combined chemotherapy of nab- Paclitaxel plus Gemcitabine showed a benefit in the overall survival, as well as progression free survival and the response rate of patients with

[2] Time to treatment failure: the interval from initiation of chemotherapy to its premature discontinuation.

metastatic pancreatic cancer. For patients with mPC and a good performance status, Gemcitabine plus nab- Paclitaxel is an alternative for the first line treatment.

To summarize, there are three main first line therapies for metastatic pancreatic cancer. For patients with mPC and a good performance status, such as ECOG 0 or EGOC 1 or a Karnofsky Index of 70% or more, and less or no comorbidities, the combination chemotherapy regimens (m)FOLFIRINOX and nab- Paclitaxel plus Gemcitabine are possible first line treatments.
For patients with mPC and a poorer performance status or relevant comorbidities, which are still deemed feasible for cytotoxic treatment Gemcitabine monotherapy is recommended.
When patients, who suffer from mPC, have a very bad performance status, no chemotherapy should be administered, and the treatment should be focused on a patient centered best supportive care (BSC) (Figure 2).

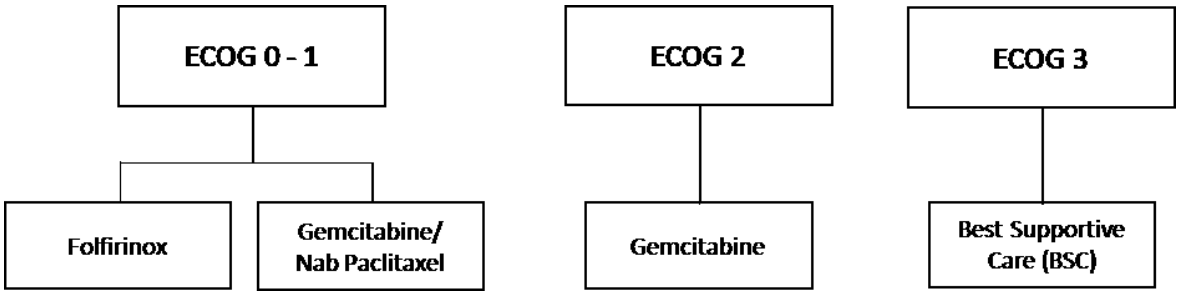

Figure 4: Palliative first line treatment of metastatic pancreatic cancer

1.2.3.2.Second Line oncological treatment

The second line treatment can be performed if the patient exhibits a good performance status (ECOG 0 or 1) after progression on first line treatment.
The most important studies concerning the second line oncological treatment of mPC are the NAPOLI – I study, CONCO003 trial and the PANCREOX study. These trials are going to be discussed in detail in the following.

The **NAPOLI-I** study evaluated liposomal Irinotecan (nal-IRI) plus 5- Fluouracil and Leucovorin (5-FU/LV) compared to 5-FU/LV alone in patients with metastatic pancreatic and ductal adenocarcinoma that was treated with gemcitabine previously.
The combination of nal-IRI plus 5-FU/LV showed an advantage in overall survival (6.2 months within nal-IRI + 5-FU/LV compared to 4.2 months within 5-FU/LV). Moreover,

the progression free survival was longer in the combined group (3.1 months compared to 1.5 months). The most common treatment side-effect in the nal-IRI treatment group were neutropenia, vomiting, fatigue, and diarrhea (36).

The **CONKO-003** trial investigated the second line treatment Oxaliplatin, Folinic Acid plus Fluouracil (OFF) and compared it to the success rate of Folinic Acid and Fluouracil (FF) in patients with Gemcitabine refractory pancreatic cancer. It was a randomized, open label, phase III study conducted in 16 institutions throughout Germany. 186 patients, who were at least 18 years old were included. The inclusion criteria were disease progression during first- line Gemcitabine monotherapy, KPS of 70% or more, adequate renal function, adequate hepatic function and a second line start within four weeks of progression of disease. The patients were randomly assigned to receive either FFO or FF and both groups were additionally supported by Best Supportive Care (BSC).
The OFF group had a significantly longer median duration of overall survival at5.9 months compared to 3.3 months within the FF group. Furthermore, the time to disease progression was significantly extended within the OFF treatment (2.9 months) compared to FF treatment (2.0 months).
Most adverse events were grade one or two. Most frequent nonhematologic adverse events have been diarrhea, nausea and emesis and sensory neuropathy. 4% within the OFF group suffered from grade three neuropathy. Rates of nausea and emesis or diarrhea have not been different in the two treatment groups (37).

The **PANCREOX** study evaluated the second line therapy with Fluouracil/Leucovorin with or without Oxaliplatin for patients with Gemcitabine based first line therapy. Patients were either treated with infusional Fluouracil/Leucovorin (FU/LV) or with mFOLFOX6 which consists of FU/LV plus Oxaliplatin.
The findings showed that there is no benefit in using mFOLFOX6 compared to the infusional FU/LV. The progression free survival of mFOLFOX6 was 3.1 months compared to 2.9 months within the FU/LV group. The median overall survival was higher in FU/LV group with 9.9 months compared to 6.1 months within mFOLFOX6 group. Adverse events grade three or four occurred in 63% of patients in the mFOLFOX6 group, and in 11% of patients in the FU/LV group (38).

Following the findings of NAPOLI-1 data, the second line therapy after progression on Gemcitabine/nab-Paclitaxel should be based on liposomal Irinotecan (nal-IRI) combined with Fluouracil. Another possibility is a combination of Oxaliplatin and Fluouracil, following the OFF regime. After progression on FOLFIRINOX in first line Gemcitabine/nab-Paclitaxel is the preferred chemotherapy regimen in patients who retain a good performance status. This approach however is not supported by any prospective data. In the second line therapy of metastatic pancreatic cancer, the risk benefit for every individual patient is a major concern. If the patients show a good performance status, the therapy based on nal-IRI may be a good treatment option (Figure 3).

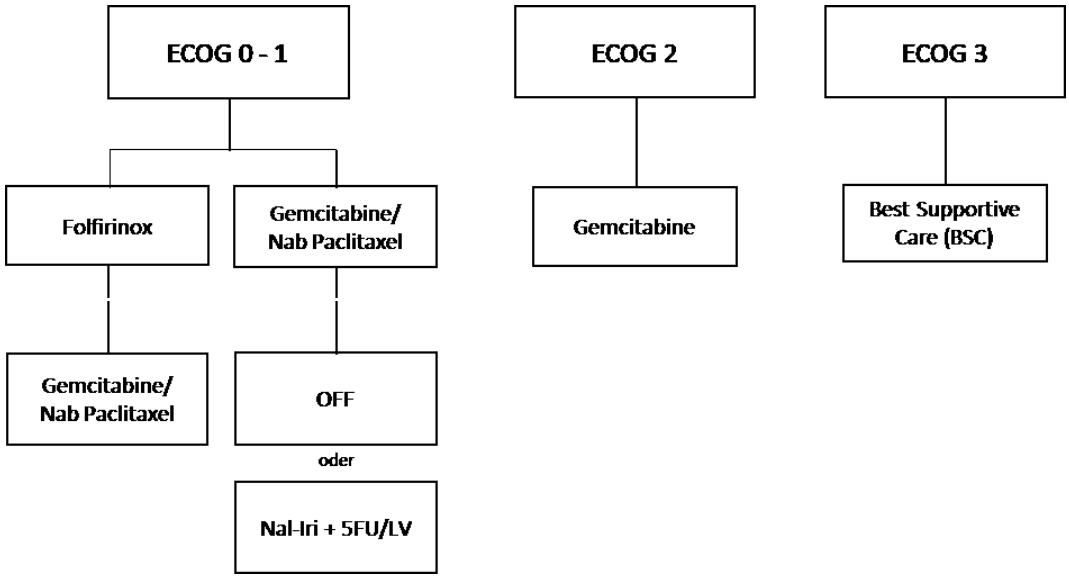

Figure 5: Second Line Treatment of metastatic pancreatic cancer

1.3. Thrombosis in cancer

Venous thromboembolism, that imports deep vein thrombosis (DVT), as well as pulmonary embolism (PE), is a major factor influencing cancer- and treatment- related mortality and morbidity (81, 82). Mandala et al. (2011) validated the connection between thrombotic events and a decreased survival of the patients in a prospective case control study (83).

Patients with malignancy are significantly more fragile to evolve a VTE than people without any malignancy. Especially pancreatic cancer is associated with a very high risk of thrombotic events (76-81).

The connection between venous thromboembolism and cancer was firstly reported by Trosseau in the 19th century (42). More precisely, it was first described in 1865 by Armand Trousseau, who discovered the migratory superficial thrombophlebitis in patients that suffered from cancer. Thereafter, the connection between cancer and a hyper coagulate state was often described as the "Trousseau Syndrome". The Trousseau's syndrome is defined, as shown in table 6, by disturbed blood flow, vessel wall injury as well as hypercoagulability (45).

Disturbed blood flow	Immobility, surgery, compression syndromes, indwelling CVCs
Vessel wall injury	Tumor infiltration, chemotherapy, hypoxia, CVC insertion
Hypercoagulability	TF, microparticles, mucins, cytokines, inflammation, nucleic acids, NETS

Table 6: Trousseau's syndrome

A thrombotic event can precede the tumor diagnosis for months or years. It can be presented in different ways. Examples are migratory superficial thrombophlebitis (Trousseau's syndrome), idiopathic deep venous thrombosis and other sites of venous thrombosis, nonbacterial thrombotic endocarditis (marantic endocarditis), disseminated intravascular coagulation (DIC), thrombotic microangiopathy (e.g. thrombotic thrombocytopenic purpura) as well as arterial thrombosis (43). All these events can be detected by chance or because of symptomatic patients.

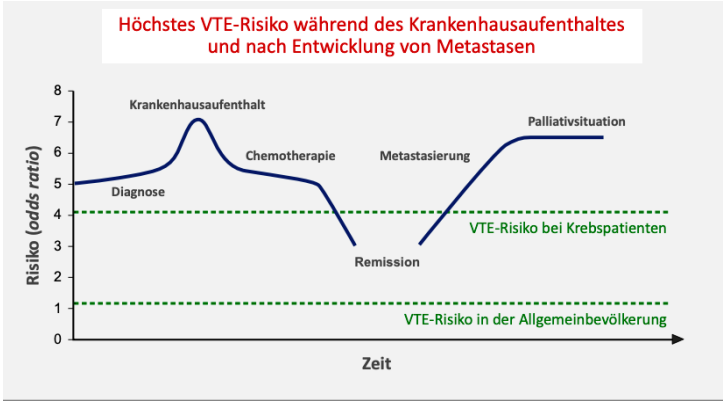

Figure 6: Risk of VTE during hospitalisation and after developing distant metastasis

1.3.1. Pathophysiology

Many patients that suffer from cancer are in a hypercoagulable state. The severity of states can range from hypercoagulable state without VTE up to massive venous thromboembolism or pulmonary embolism. The pathophysiology behind this phenomenon is very complex and not completely understood yet.
The mechanism that is underlying the hypercoagulative state is multifactorial.

Tissue Factor (TF):
Tissue factor is a transmembrane protein. It is expressed among malignant diseases such as melanoma, sarcoma, pancreatic as well as colorectal cancer, lymphoma, neuroblastoma, acute promyelocytic leukemia and ovarian cancer. A few normal human parenchymal and connective tissue cells also express this tissue factor. The main feature of this factor is to activate factor IX and factor X and thus activating the blood coagulation. The level of TF is different but intensifies with advanced and metastatic disease (84-86).
Investigations from White et al. (2007) showed, that patients with a higher level of TF had a higher risk of suffering from VTE than patients that had a lower level of TF. Particularly, patients who suffered from an aggressive tumor, such as pancreatic cancer, in an advanced stage, were at a high risk for VTE (44).
In 1989 Silberberg et al. investigated the TF activity in two different PC cell lines and showed that there is a higher activity of TF (88). Haas et al. (2006) also investigated the expression of TF in eight human pancreatic carcinoma cell lines and showed that all cell

lines expressed a higher level of TF (87). In 2011, Delluc et al. also observed a higher level of TF within patients with PC (89).

Tissue factor bearing microparticles (TFBM): Tumor cells can express tissue factor bearing microbodies. Zwicker et al. (2009) showed that higher levels of TFBM were associated with VTE. Furthermore, the microparticles were detected in advanced malignancy, and proven to exist in two thirds of pancreatic cancer (90).

Cancer procoagulant: Cancer procoagulant is a cysteine protease that shows its coagulant effect through affecting factor X directly. It can be found in malignant tissues, as well as in fetal tissue, but cannot be detected in normal tissues (91). It plays an important role in breast cancer, melanoma, kidney cancer, colon cancer, leukemia as well as acute promyelocytic leukemia (92, 93).

Normal tissues and cells can stimulate and express procoagulant activity, such as **monocytes, platelets, endothelial cells, neutrophils**. **Monocytes** can be stimulated by tumor specific antigens or even indirect by cytokines that are stimulated by tumor cells and can therefore show a higher procoagulant activity (94). Within **platelets**, tumor- platelet interactions or an increased platelet reactivity can lead to hypercoagulation (95). Increased levels of the von Willebrand factor (vWF), thrombin generation caused by the tumor, as well as an ADP expression by the tumor cells, play a role in the coagulative activity of the platelets (96).
Endothelial cells reveal their procoagulant activity trough the influence of inflammatory cytokines and other peptides. Especially TNF and IL-1 have important roles (97).
Moreover, **tumor specific mechanisms** contribute to the procoagulant activity. In particular, the **polyphosphate**, that provides a negative surface and therefore activates the intrinsic coagulation (98), as well as the **MET oncogene** that is a tyrosine kinase receptor and is present at numerous malignancies (99).

1.3.2. Incidence

About 15% of patients with malignancy develop a clinical VTE (101). Investigations showed, that approximately 20% of patients with a symptomatic deep vein thrombosis suffer from any known malignancy (102). In 5-10% of patients with an idiopathic VTE, a

malignancy is going to be detected in the next one or two years. Malignant tumors increase the risk for venous thromboembolism four to seven times, and if a thrombotic event occurs, the prognosis gets even poorer. (46)

1.3.3. Risk factors and prognostic model

Risk factors for VTE are multivariable.

Tumor type: Not all malignancies have the same risk to develop VTEs. Tumors with a higher risk are for example hematological malignancies, followed by lung cancer and gastrointestinal tumors (103).

Tumor stage: The tumor stage also affects the risk to develop a VTE. Patients that are in an advanced or already metastatic disease, have a higher risk for a thrombotic event (103,104).

Tumor specific factors: As already discussed before, tumor specific factors have an impact on developing VTE. Tumor cells as well as normal tissue can express procoagulant factors that can increase the risk for a VTE, such as Tissue Factor or cancer procoagulant.

Anatomic factors can have an impact on the development of thrombosis. Some tumors compress or even infiltrate large vessels. Hepatocellular carcinomas, for example, can compress or infiltrate the hepatic vein, large abdominal tumors can compress or infiltrate major veins (104,105), renal cell tumors infiltrate the inferior vena cava in 5% to 9% of patients (106).

Patients' characteristics can also increase the risk of developing a VTE. An advanced age (107), prior VTE (46), obesity (108,109) or thrombocytosis (108, 110) are the most important factors.

The administration of **chemotherapy** can also contribute to develop a VTE. Following Moore et al. (2008) especially cisplatin – containing chemotherapy regimen have a high risk for VTE (137). Furthermore, also common interventions like surgery or central venous catheters are well known risk factors for developing VTEs (138,139).

Predictive models for cancer associated VTE:

KHORANA risk score:

- Patients with a general cancer diagnosis (solid tumors and lymphomas) starting chemotherapy.
- Do not use in patients with brain tumors or myelomas.
- Categorizes cancer patients for VTE risk.
- Higher risk cohorts (e.g. inpatients, lower performance scores) have even higher risks than shown.
- Most validations were completed in outpatients' settings with higher risk cancer patients.
- Not intended to be used for diagnosis (i.e., clinical suspicion of DVT or PE) but to predict future risk of VTE
- Predicting VTE in cancer patients is complicated and likely improved by a scoring system

This score includes the **cancer type** (stomach +2 points, pancreas +2 points, lung +1-point, lymphoma +1 point, gynecologic +1-point, bladder +1 point, testicular +1 point, other 0 points), **platelet count** before the Chemotherapy ≥350x10^9/L (yes/no), **Hemoglobin level** <10 g/dL or using **RBC growth factors** (yes/no), Pre-chemotherapy **leukocyte count** >11x10^9/L, **BMI** ≥35 kg/m^2

Risk group	Score	2.5-month rate of VTE
Low	0	0.3-0.8%
Intermediate	1-2	1,8-2.0%
High	>= 3	6.7 – 7.1%

Table 7: Score interpretation Khorana risk score

PROTECHT score:

The Protecht score is a modified Khorana risk score for patients receiving Chemotherapy. In addition to the Khorana criteria below, the Protecht score considers the two criteria **Gemcitabine chemotherapy** and **Platinum Chemotherapy**, both are cited with one point.

Following the Protecht risk score patients are at a high risk for venous thrombosis with a score of three or more points. (111)

CONKO score:

The criteria for the Conco risk score are the same as within the Khorana risk score but the BMI criteria was removed and therefore ECOG performance score with two or higher was added. (112)

Vienna CAT SCORE:

In addition to the criteria of the Khorana score, the Vienna CATS score also includes D-dimer >1.44mg/L (1 point) and soluble P- selectin >53.1ng/L (1 point). (113)

1.3.4. Arterial thromboembolism

Contrary to VTE that is known as a common complication in patients with cancer the risk and consequences of arterial thromboembolism (ATE) in patients with cancer have been overlooked for a long time and just came into focus recently. ATE includes strokes, myocardial infarct as well as other peripheral arterial occlusions.

Epidemiology:
Prior investigations have shown, that in about 1.5 – 5.2% of patients that suffer from cancer, an arterial thrombotic event occurs (114,115). A recent study from Grilz et al (2018) showed, that during a follow up period of two years, 2.6% of the observed cancer patients developed an ATE (116).

Pathophysiology of ATE in patients with cancer:
The classic pathway of thrombotic events is described by the Virchow trias. The blood flow, the blood vessels, especially the endothelium and the composition of blood cells are the three parts of the Virchow's trias.
The blood contents: Blann et al. (2011) have shown that patients with cancer have a higher reactivity of platelets and also a higher number of circulating platelets specific products, such as beta- thromboglobulin, solube P- selectin or platelet factor 4 (117). Furthermore, Mezouar et al. (2016) reported about a bidirectional interaction between cancer cells and platelets. Paraneoplastic cells activate platelets. In experimental cell lines, a direct interaction of platelets with the tumor cells lead to thrombocyte aggregation (118).

The vascular wall: In patients with cancer, the endothelium is damaged by multiple factors. Studies from Pavo et al. (2015) have shown, that an increased circulation of vWF induces wall injury. Furthermore, a loss of expression of thrombomodulin on the surface of endothelium plays an important role by reducing the capacity to activate protein C that promotes a procoagulant activity. (119) These abnormal conditions lead to vascular inflammation, proliferation as well as vasoconstriction that promotes ischemic vascular diseases (120).
The blood flow: The blood flow has a minor role in the development of ATE in patients with cancer (117).

Risk factors:

The risk factors for ATE within cancer are multivariable. A part of ATE within cancer may be explained by overlapping of the risk factors for cancer and ATE, for example, smoking or prior arterial thrombotic events (121). However, the risk factors for ATE within cancer can be split in different groups. In the following, the most important groups are going to be discussed shortly.

Cardiovascular risk factors:

The classic cardiovascular risk factors play a role in the development of ATE. Obesity, hypertension, diabetes mellitus, hyperlipidemia and smoking are common risk factors for cardiovascular diseases, and therefor also play a role in the occurrence of arterial thrombotic events within patients with cancer (121)

Anti-neoplastic treatment related risk factors:

Anti-cancer treatments are known to increase the risk for developing an ATE. Radiotherapy (122), as well as VEGF inhibitors (123,124), tyrosine kinase inhibitors (124), cisplatin (125) or monoclonal antibodies (126) tend to increase the risk for an arterial thrombotic event.

Type of cancer: Similar to VTEs, arterial thrombotic events also depend on the type of malignancy. Navi et al. (2017) showed that especially lung cancer, as well as gastric and pancreatic cancer have a higher risk to develop ATEs (127).

2. Methods

2.1. Study design and patient cohort

We conducted a tri-center retrospective cohort study including all consecutively treated patients with aPC who underwent palliative first line treatment with either FOLFIRINOX or Gemictabine/nab-Paclitaxel at three academic medical centers (Medical University of Graz, Paracelsus Medical University Salzburg and Medical University of Innsbruck) in Austria. Patients were identified using the respective in-house electronic healthcare databases as well as the in-house pharmacy prescriptions program thus obtaining full local coverage of treated patients. All eligible patients were aged 18 years old or older, had histologically confirmed pancreatic ductal adenocarcinoma, had radiologically confirmed advanced disease and had received at least one cycle of the mentioned palliative first line regimens between August 2010 and October 2019. Advanced disease stage was defined as a composite of locally advanced inoperable tumors and tumors with distant metastatic spread. Patients who were treated with FOLFIRINOX or Gemcitabine/nab-Paclitaxel as induction treatment for locally advanced resectable or borderline resectable tumors were excluded from this study. Patients with a prior history of a VTE or ATE event as well as patients who were on continuous anticoagulation or antiplatelet therapy at treatment start were deemed eligible in order to ensure a real-world scenario.

2.2. Data acquisition and outcome

Baseline and outcome data were retrospectively collected from the respective in-house electronic healthcare database as well as from the central registry of the Austrian Social Security Providers Association (for all-cause death) as reported previously. Data collection and analysis was approved by the institutional review board of the leading center (Ethics Committee of the Medical University of Graz, Austria; document number 31-035 ex 18/19). All methods were performed in accordance with the relevant local and national guidelines and regulations.

The primary outcome of this study was the occurrence of VTE or ATE from the day of start of palliative first line treatment. VTE was defined as a composite of objectively confirmed symptomatic or incidental deep vein thrombosis (DVT), pulmonary embolism, central venous catheter related thrombosis and splanchnic vein thrombosis. ATE was defined as a composite of acute coronary syndrome, ischemic stroke, acute peripheral arterial occlusion

and acute mesenteric ischemia. All VTE or ATE events had to be confirmed by objective imaging including deep vein sonography, CT angiography or MRI depending on the type of event.

The co-secondary endpoint were disease progression and all-cause mortality.

2.3. Statistical analysis

Baseline characteristics of the study cohort were summarized by reporting absolute frequencies with percentages for categorical variables and distribution median with interquartile range for quantitative variables, as appropriate. The reverse Kaplan-Meier method was used to estimate follow-up time. The cumulative incidences of VTE and ATE were obtained in competing risk analysis, accounting for all-cause mortality as competing outcome event to avoid overestimating the risk of non-fatal outcome events given the high underlying mortality in this cohort. (154) A proportional sub-hazard regression model was applied for uni- and multivariable analysis of potential risk factors for VTE and ATE. (155) Variable selection for multivariable analysis was based on previous knowledge on pro-thrombotic risk factors and results from univariable analysis, limiting the number of variables as appropriate to the number of outcome events to ensure sufficient statistical power in multivariable analysis. The association of VTE and ATE occurrence on survival times (PFS, OS) was estimated within a multi-state model, splitting survival times at the day of VTE/ATE diagnosis, respectively, and reporting the transition hazard ratio (THR) for disease progression / mortality after thrombotic events compared to the non-thrombotic state. (156,157) For visualisation, a landmark analysis was conducted, comparing survival times (PFS, OS) of patients experiencing VTE within the first 3 months of observation, to those without VTE at 3 months, applying Mantel-Byar test for between-group comparisons. Statistical analysis was conducted with the commercially available package STATA 15.0 (Stata Corp., Houston, TX, USA).

3. Results

3.1. Study cohort

A total of 455 patients initiating first line chemotherapy with either Gemcitabine/Nab-Paclitaxel or FOLFIRINOX for advanced pancreatic cancer were included (**Table 8**). Median age at therapy initiation was 67 years (IQR: 58-72] and 41% were female (n=187). Most patients had distant metastasis at the time of therapy initiation (n=359; 79%), and 96 patients had locally advanced, inoperable disease (21%). Two-hundred ninety-seven patients (65%) received Gemcitabine/Nab-Paclitaxel as first line therapy and 158 patients (35%) received FOLFIRINOX.

Eighty-one patients (17.8%) had a history of VTE prior to the initiation of palliative chemotherapy, including 57 patients (12.5%) with cancer associated VTE events and 24 patients (5.3%) with VTE unrelated to cancer. Most patients presented with a baseline Khorana score of 2 (n=276; 61%), followed by a score of 3 in 116 patients (25.5%) and of 4 or 5 in 63 patients (13.8%), with 2 points allocated to all patients due to the diagnosis of pancreatic cancer. Baseline characteristics of the study cohort, both overall and stratified by the occurrence of VTE/ATE during follow-up, are presented in detail in **Table 8**.

Variable	N (% missing)	Median (IQR), n (%)						
		All patients	VTE	No VTE	p*	ATE	No ATE	p*
All patients		**455**	**86**	**369**	**/**	**11**	**444**	
Demographics & Comorbidities								
Female	455 (0%)	187 (41%)	33 (38%)	154 (42%)	0.568	3 (27%)	184 (41%)	0.345
Age	455 (0%)	67 [58-72]	64.4 [59.5-71.1]	67.4 [59.4-72.4]	0.129	70.9 [63.6-74-1]	66.9 [59.2-72.2]	0.194
ECOG	447 (1.8%)	/	/	/	0.055	/	/	0.649
0	/	186 (42%)	45 (54%)	141 (39%)	/	6 (55%)	180 (41%)	/
1	/	223 (50%%)	34 (40%)	189 (52%)	/	5 (45%)	218 (50%)	/
≥2	/	39 (9%)	5 (6%)	33 (9%)	/	0 (0%)	38 (9%)	/
BMI	447 (1.8%)	23.5 [21.3-26.2]	23.2 [21.2-26.0]	23.5 [21.2-26.3]	0.457	26.9 [21.3-28.4]	23.5 [21.3-26.0]	0.426
BMI ≥35	/	17 (4%)	2 (2%)	15 (4%)	0.751	0 (0%)	17 (4%)	1.00
Charlson Comorbidity Index	446 (2%)	6 [6-7]	6 [6-7]	6 [6-7]	0.028	7 [6-9]	6 [6-7]	0.045
- History of myocardial infarction	450 (1%)	27 (6%)	3 (4%)	24 (7%)	0.445	1 (9%)	26 (6%)	0.498
- Chronic heart failure	450 (1%)	17 (4%)	2 (2%)	15 (4%)	0.751	0 (0%)	17 (4%)	1.00
- Peripheral artery disease	450 (1%)	6 (1%)	1 (1%)	5 (1%)	1.00	0 (0%)	6 (1%)	1.00
- History of cerebrovascular disease	450 (1%)	25 (6%)	3 (4%)	22 (6%)	0.598	6 (55%)	19 (4%)	<0.001
Atrial fibrillation	450 (1%)	41 (9%)	6 (7%)	35 (10%)	0.465	2 (18%)	39 (9%)	0.264
Khorana-Score	455 (0%)	/	/	/	0.153	/	/	1.00
- Intermediate risk (Score=2)	/	276 (61%)	58 (67%)	218 (59%)	/	7 (64%)	269 (61%)	/
- High risk (Score: ≥3)	/	179 (39%)	28 (33%)	151 (41%)	/	4 (36%)	175 (39%)	/
Prior VTE	455 (0%)	81 (17.8%)	30 (35%)	51 (14%)	<0.001	4 (36%)	77 (17%)	0.113
-not related to cancer	/	24 (5.3%)	5 (6%)	19 (5%)	0.804	0 (0%)	24 (5%)	1.00
-cancer-associated	/	57 (12.5%)	25 (29%)	32 (9%)	<0.001	4 (36%)	53 (12%)	0.037

Cancer and treatment specifics								
Histology	416 (8.6%)	/						
- Adenocarcinoma	/	409 (98%)	74 (96%)	335 (99%)	0.122	10 (100%)	399 (98%)	1.00
Grade (Differentiation)	283 (37.8%)	/	/	/	0.041	/	/	0.328
- G1 (Well differentiated)	/	24 (8%)	6 (10%)	18 (8%)	/	1 (14%)	23 (8%)	/
- G2 (Moderately differentiated)	/	150 (53%)	38 (66%)	112 (50%)	/	5 /71%)	145 (53%)	/
- G3 (Poorly differentiated)	/	109 (39%)	14 (24%)	95 (42%)	/	1 (14%)	108 (39%)	/
Tumour location	415 (4.2%)	/	/	/	0.103	/	/	0.314
- Head	/	249 (60%)	42 (53%)	207 (62%)	/	4 (40%)	245 (60%)	/
- Body	/	95 (23%)	18 (23%)	77 (23%)	/	4 (40%)	91 (22%)	/
- Tail	/	71 (17%)	20 (25%)	51 (15%)	/	2 (20%)	69 (17%)	/
Stage	448 (1.8%)	/	/	/	0.356	/	/	0.131
- Locally advanced	/	96 (21%)	15 (17%)	81 (22%)	/	0	96 (22%)	/
- Distant metastatic	/	359 (79%)	71 (83%)	288 (78%)	/	11	348 (78%)	/
Metastatic burden	352 (2%)	/	/	/	0.658	/	/	0.197
- metastasis to 1 organ		233 (66%)	44 (64%)	189 (67%)	/	5 (45%)	228 (67%)	/
- metastasis to 2 organs		88 (25%)	17 (25%)	71 (25%)	/	5 (45%)	83 (23%)	/
- metastasis to ≥3 organs		31 (9%)	8 (12%)	23 (8%)	/	1 (9%)	30 (9%)	/
Prior tumour resection	455 (0%)	83 (18%)	16 (19%)	67 (18%)	0.923	2 (18%)	81 (18%)	1.00
Prior chemotherapy (neo-/adjuvant)	455 (0%)	68 (15%)	14 (16%)	54 (15%)	0.700	0 (0%)	68 (15%)	0.383
Primary palliative treatment intent	454 (0.2%)	382 (84%)	72 (84%)	310 (84%)	0.906	10 (91%)	372 (84%)	1.00
First line chemotherapy	455 (0%)	/	/	/	0.430	/	/	0.107
- Gem/Abraxane	/	297 (65%)	53 (62%)	244 (66%)	/	10 (91%)	287 (65%)	/
- FOLFIRINOX	/	158 (35%)	33 (38%)	125 (34%)	/	1 (9%)	157 (35%)	/
Therapy cycles palliative first-line chemotherapy	451 (0.9%)	4 [2-6]	4 [3-7]	3 [2-6]	0.012	3 [1-6]	4 [2-6]	0.856
GCSF use during palliative chemotherapy	452 (0.7%)	106 (23%)	27 (31%)	79 (22%)	0.053	1 (9%)	105 (24%)	0.471
EPO use during palliative chemotherapy	442 (2.9%)	0 (0%)	/	/	/	/	/	/

Laboratory values at start of palliative chemotherapy								
Haemoglobin (mg/dl)	442 (2.9%)	12.7 [11.2-13.6]	12.9 [11.8-13.9]	12.6 [11.2-13.6]	0.067	13.1 [12.0-13.6]	12.7 [11.2-13.6]	0.470
WBC (G/L)	441 (3.1%)	8.1 [6.2-10.3]	7.9 [6.1-10.3]	8.2 [6.2-10.3]	0.661	9.6 [8.4-12.2]	8.0 [6.1-10.3]	0.119
Platelet count (G/L)	444 (2.4%)	251 [195-320]	245 [179-309]	252 [197-325]	0.503	276 [207-330]	250 [195-320]	0.471
CA 19-9 (ng/ml)	442 (2.9%)	1086 [94-8647]	1612 [184-11067]	969 [88-8000]	0.437	10939 [1080-15427]	1018 [89-8000]	0.046
CEA (U/ml)	344 (24.4%)	7.2 [2.8-24.6]	5.8 [2.5-21.7]	7.6 [3.0-25.0]	0.457	5.8 [2.8-11.2]	7.2 [2.8-26.1]	0.651
Albumin (g/dl)	199 (56.3%)	4.0 [3.5-4.3]	3.9 [3.3-4.2]	4.0 [3.6-4.3]	0.415	4.0 [3.7-4.6]	4.0 [3.5-4.3]	0.505
CRP (mg/dl)	383 (15.8%)	3.4 [1.1-9.7]	2.1 [1.0-6.4]	3.5 [1.1-10.1]	0.057	4.3 [1.8-7.8]	3.3 [1.1-9.7]	0.558
Creatinine (mg/dL)	428 (5.9%)	0.8 [0.7-1.0]	0.8 [0.7-0.9]	0.8 [0.7-0.9]	0.991	0.9 [0.8-1.0]	0.8 [0.7-1.0]	0.088

Table 8: Baseline characteristics of the study cohort (n=455)

Table legend: Baseline characteristics overall and stratified by occurrence of either VTE or ATE during follow-up.

*p: Wilcoxon rank-sum test, Chi^2 -test or Fisher exact test, as appropriate.

Abbreviations: ATE – arterial thromboembolism, BMI – Body Mass Index, CEA – Carcinoembryonic antigen, CA19-9 – Carbohydrate antigen 19-9, dl – deciliter, ECOG – Eastern Cooperative Oncology Group performance status, EPO – erythropoietin, G – giga, GCF – granulocyte-colony stimulating factor, IQR – interquartile range, L – liter, mg – milligram, ml – milliliter, ng – nanogram, U – unit, VTE – venous thromboembolism, WBC – white blood count

3.2. Risk of VTE and ATE

Over a median follow-up of 26.2 months [IQR: 14-44] we observed 86 VTE and 11 ATE. The cumulative incidence of VTE in competing risk analysis was 20.0% [95% CI: 16.3-24.0]. The corresponding cumulative incidence estimates of VTE at 3-, 6-, 12-, and 24 months were 10.0% [95%CI: 7.5-13.0], 14.4% [95% CI: 11.3-17.9], 18.1% [95%CI: 14.6-21.9] and 19.6% [16.3-24.0], respectively, with a median time to VTE of 3.8 months [95% CI: 2.7-4.5]. (**Figure 7**). The most frequent type of VTE was DVT alone in 34 patients (40% of all observed VTE), followed by DVT in combination with PE in 24 patients (28%), PE alone in 7 patients (8%), catheter-related thrombosis in 11 patients (13%) and splanchnic vein thrombosis in 9 patients (11%). Most patients presented with symptomatic VTE (n=56; 66%) whereas no symptoms were present and VTE was diagnosed incidentally on imaging studies obtained for different purposes in 27 patients (32%). One patient (1%) died due to fatal PE (**Table 9**).

ATE events were observed in 11 patients, with a cumulative incidence estimate in competing risk analysis of 2.8% [95% CI:1.5-4.9]. Corresponding cumulative incidence estimates at 3-, 6-, 12- and 24 months were 1.1% [95%CI: 0.4-2.4], 1.6% [0.7-3.1], 2.1% [1.0-3.8], and 2.3% [1.2-4.1], respectively (**Figure 7**). The most frequently observed ATE event was ischaemic stroke in 10 patients (91% of all observed ATE) and one patient suffered myocardial infarction (18%). Two patients (18%) suffered fatal ATE, including one stroke and one myocardial infarction (**Table 9**).

VTE*	**86**
- DVT	34 (40%)
- PE	7 (8%)
- DVT + PE	24 (28%)
- CRT	11 (13%)
- SVT	9 (11%)
Symptomatic	56 (66%)
Asymptomatic / Incidental	27 (32%)
Fatal	1 (1%)
ATE	**11**
- Ischaemic stroke	10 (91%)
- Myocardial infarction	1 (9%)
Fatal	2 (18%)

Table 9: Clinical characteristics of VTE and ATE

Table legend: Crude number of thrombotic events, type of event and symptoms during follow-up.

*1 patient with missing information on type of VTE, 3 with missing information on symptoms

Abbreviations: ATE – arterial thromboembolism, DVT – deep vein thrombosis, CRT – catheter-related thrombosis, PE – pulmonary embolism, SVT – splanchnic vein thrombosis, VTE – venous thromboembolism

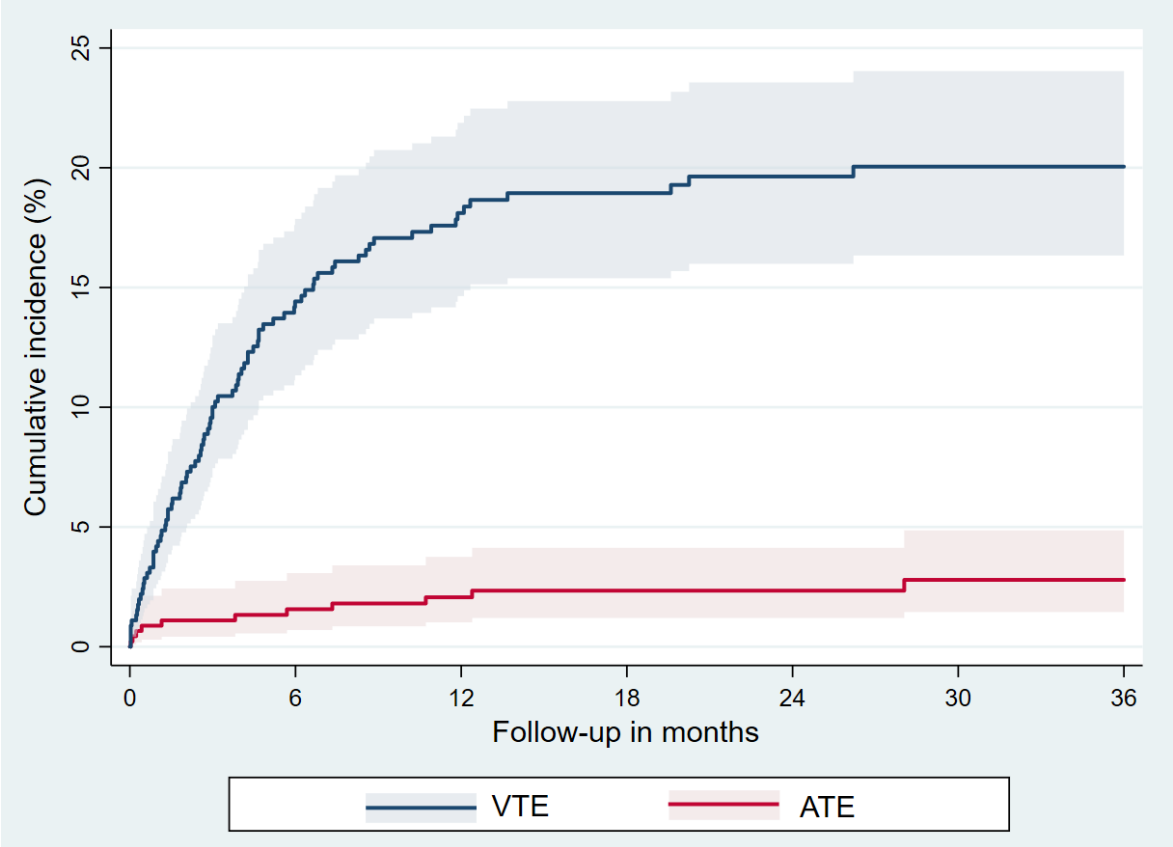

Figure 7: Cumulative incidence of VTE and ATE

3.3. Risk factors for VTE

A uni- and multivariable competing risk regression analysis (**Table 3**) including baseline clinical characteristics, risk prediction scores for cancer-associated VTE, and laboratory parameters was performed for risk factor exploration of VTE and ATE risk. In univariable analysis, a prior history of VTE was identified as a strong predictor for VTE under palliative chemotherapy (subdistribution hazard ratio (SHR): 2.70 [95%CI: 1.75-4.18], p<0.001). Prior

VTE events related to the current cancer diagnosis (n=57) were found to be the strongest predictor for VTE (SHR 3.29 [95%CI: 2.09-5.18], p<0.001), whereas prior VTE unrelated to the current cancer diagnosis (n=24) was not associated with VTE under palliative chemotherapy (SHR: 1.06 [95%CI: 0.44-2.57], p=0.891). In total, of the 86 patients who developed VTE after initiation of palliative chemotherapy, 25 (29.1%) had a prior history of cancer associated VTE. In reverse, this corresponds to 25 of 57 (43.9%) patients with a prior history of cancer associated VTE who developed VTE after initiation of palliative chemotherapy. Worse ECOG performance status (≥1 vs 0) was associated with lower risk of VTE (SHR: 0.59 [95%CI: 0.39-0.92], p=0.020) in univariable analysis. No association of VTE-risk with the Charlson Comorbidity Index was detected (SHR per point increase: 0.79 [95%CI: 0.58-1.07], p=0.121). Further, no difference in VTE-risk was observed between patients with stage IV disease compared to locally advanced, unresectable tumors (SHR: 1.31 [95%CI: 0.76-2.26], p=0.338) and between types of first line palliative chemotherapy (SHR for FOLFIRINOX vs Gemcitabine/Nab-Paclitaxel: 1.16 [0.75-1.79], p=0.502). The Khorana-score and the CONKO-score failed to predict for VTE risk in this patient cohort, both per point increase in scores (Khorana-score: SHR: 0.78 [95%CI: 0.57-1.06], p=0.115) ; CONKO: SHR: 0.78 [0.60-1.03], p=0.086) and when comparing patients with ≥3 points to patients with 2 points (Khorana-score: 0.73 [95%CI: 0.46-1.16], p=0.180) ; CONKO: 0.49-1.19], p=0.226). Baseline, pre-therapeutic levels of haemoglobin were associated with VTE risk (SHR per unit increase[mg/dl]: 1.13 [95%CI: 1.00-1.28], p=0.049), whereas other laboratory parameters were not associated with risk of VTE, including white blood cells (SHR per unit increase [G/L]: 0.99 [95%CI: 0.94-1.04], p=0.629), platelets (SHR per 10 units increase [G/L]: 1.00 [95%CI: 0.98-1.02], p=0.910), CA 19-9 (SHR per double: 1.03 [95%CI: 0.96-1.10], p=0.470), CEA (SHR per double: 0.96 [95%CI: 0.83-1.10], p=0.537), Albumin (SHR per unit increase [g/dl]: 0.87 [95%CI: 0.57-1.32], p=0.503), and CRP (SHR per unit increase [mg/dl]: 0.99 [95%CI: 0.97-1.01], p=0.269).

In multivariable analysis, a prior history of cancer associated VTE emerged as a strong and single independent predictor of VTE risk (SHR: 3.13 [95%CI: 1.92-5.10], p<0.001). In contrast, other variables such as ECOG (SHR: 0.71 [95%CI: 0.44-1.15], p=0.166), Charlson Comorbidity Index (SHR: 0.80 [95%CI: 0.58-1.11], p=0.181), cancer stage (SHR: 1.23 [95%CI: 0.69-2.21], p=0.483), and haemoglobin (SHR: 1.16 [95%CI: 0.99-1.36], p=0.066) were not significantly associated with VTE risk.

Variable	Subdistribution hazard ratio [95% confidence interval]	Multivariable hazard ratio [95% confidence interval]
VTE	/	
History of VTE	2.70 [1.75-4.18]; p<0.001	/
--Cancer-associated	3.29 [2.09-5.20], p<0.001	3.13 [1.92-5.10]; p<0.001
---Not associated	1.06 [0.44-2.57], p=0.891	1.14 [0.44-2.93]; p=0.784
ECOG (≥1 vs 0)	0.59 [0.39-0.92]; p=0.020	0.71 [0.44-1.15]; p=0.166
Charlson Comorbidity Index (per point increase)	0.79 [0.58-1.07]; p=0.121	0.80 [0.58-1.11]; p=0.181
Chemotherapy (FOLFIRINOX vs Gem/Abraxane)	1.16 [0.75-1.79]; p=0.502	1.15 [0.61-2.15]; p=0.671
Distant metastasis vs locally advanced	1.31 [0.76-2.26]; p=0.338	1.23 [0.69-2.21]; p=0.483
BMI (per unit increase)	0.98 [0.92-1.03], p=0.410	0.97 [0.91-1.01]; p=0.306
Haemoglobin (per unit increase[mg/dl])	1.13 [1.00-1.28]; p=0.049	1.16 [0.99-1.36]; p=0.066
WBC (per unit increase [G/L])	0.99 [0.94-1.04]; p=0.629	0.99 [0.93-1.06]; p=0.770
Platelet count (per 10 units increase [G/L])	1.00 [0.98-1.02], p=0.910	1.00 [0.99-1.01]; p=0.687
Albumin (per unit increase [g/dl])	0.87 [0.57-1.32]; p=0.503	0.74 [0.42-1.30]; p=0.294
CRP (per unit increase [mg/dl])	0.99 [0.97-1.01]; p=0.269	1.00 [0.98-1.01]; p=0.615
CA 19-9 (per double)	1.03 [0.96-1.10]; p=0.470	/
CEA (per double)	0.96 [0.83-1.10]; p=0.537	/
Creatinine	0.67 [0.32-1.42]; p=0.299	/
Khorana-score (per point increase)	0.78 [0.57-1.06]; p=0.115	/
Khorana-score (≥3 points vs 2 points)	0.73 [0.46-1.16]; p=0.180	/
CONKO-score (per point increase)	0.78 [0.60-1.03]; p=0.086	/
CONKO-score (≥3 points vs 2 point	0.76 [0.49-1.19]; p=0.226	/

ATE	/	/
History of myocardial infarction	1.56 [0.21-11.78]; p=0.667	/
Atrial fibrillation	2.18 [0.48-9.96]; p=0.313	/
History of cerebrovascular disease	22.05 [6.83-71.22]; p<0.001	/
Charlson Comorbidity Index (per point increase)	1.33 [1.07-1.67]; p=0.012	/
Chemotherapy (FOLFIRINOX vs Gem/Abraxane)	5.59 [95%CI: 0.71-44.28], p=0.103	/
ECOG (per category increase)	0.61 [0.18-1.99]; p=0.411	/
ECOG (≥1 vs 0)	0.56 [0.23-1.38]; p=0.206	/

Table 10: Evaluation of risk factors for VTA and ATE in competing risk regression

Table legend: Risk factor exploration for VTE and ATE was conducted by means of a proportional sub-distribution hazard regression model. Adjustment in a joint multivariable model was based on variables selected upon previous knowledge on predictive utility for cancer associated VTE and results from univariable analysis. In multivariable analysis, missing values were imputed within a chained equation algorithm. Due to the low number of outcome events, no multivariable analysis was feasible for risk of ATE.

Abbreviations: ATE – arterial thromboembolism, BMI – Body Mass Index, CEA – Carcinoembryonic antigen, CA19-9 – Carbohydrate antigen 19-9, CONKO CRP – C-reactive protein, ECOG – Eastern Cooperative Oncology Group performance status, L – liter, mg – milligram, ml – milliliter, ng – nanogram, U – unit, VTE – venous thromboembolism, WBC – white blood count

3.4. Risk factor exploration for ATE

Risk of ATE was increased with a higher number of comorbidities (SHR per point increase in Charlson Comorbidity Index: 1.33 [95%CI: 1.07-1.67], p=0.012). Most prominently, a positive history of cerebrovascular disease (CVD) was associated with ATE risk (SHR: 22.05 [95%CI: 6.83-71.22], p<0.001), with a prior history of CVD in 6 of 11 patients experiencing ATE. No significant association with ATE risk was observed for prior myocardial infarction (SHR: 1.56 [95%CI: 0.21-11.78], p=0.667), atrial fibrillation (SHR: 2.18 [95%CI: 0.48-9.96], p=0.313) or differences in ECOG performance status (SHR per point increase: 0.61 [95%CI: 0.19-1.99], p=0.411). Interestingly, ATE was observed mostly in patients undergoing chemotherapy with Gemcitabine/Nab-Paclitaxel (10 of 11 ATE).

However, this numerical difference did not translate into statistical significance (SHR for Gemcitabine/Nab-Paclitaxel vs FOLFIRINOX: 5.59 [95%CI: 0.71-44.28], p=0.103). Due to the low number of outcome events (n=11), multivariable analysis was deemed infeasible.

3.5. Association of thrombotic events with clinical outcomes

The occurrence of VTE during follow-up was associated with increased risk of death (transition hazard ratio (THR): 1.59 [95%CI: 1.21-2.09], p<0.001). The median survival estimate after VTE diagnosis was 5.2 months [95%CI: 0.1-8.2], compared to 11.0 months [95%CI: 9.9-12.3] in those without VTE (Mantel-Byar: p<0.001). Further, risk of disease progression was increased after VTE (THR: 1.47 [95%CI: 1.08-2.01], p=0.014), with a median PFS estimate after VTE of 3.0 months [95%CI: 0.7-4.53] compared to 4.8 months [95%CI: 4.3-5.7] in patients without VTE (Mantel-Byar: p=0.013). The occurrence of ATE was not statistically significantly associated with increased mortality (THR: 1.85 [95%CI: 0.87-3.94], p=0.108) or risk of disease progression (THR: 1.17 [95%CI: 0.29-4.70], p=0.828). **Figure 8** displays the results of a landmark analysis comparing OS and PFS estimates between patients experiencing VTE in the first 3 months of observation and patients without VTE.

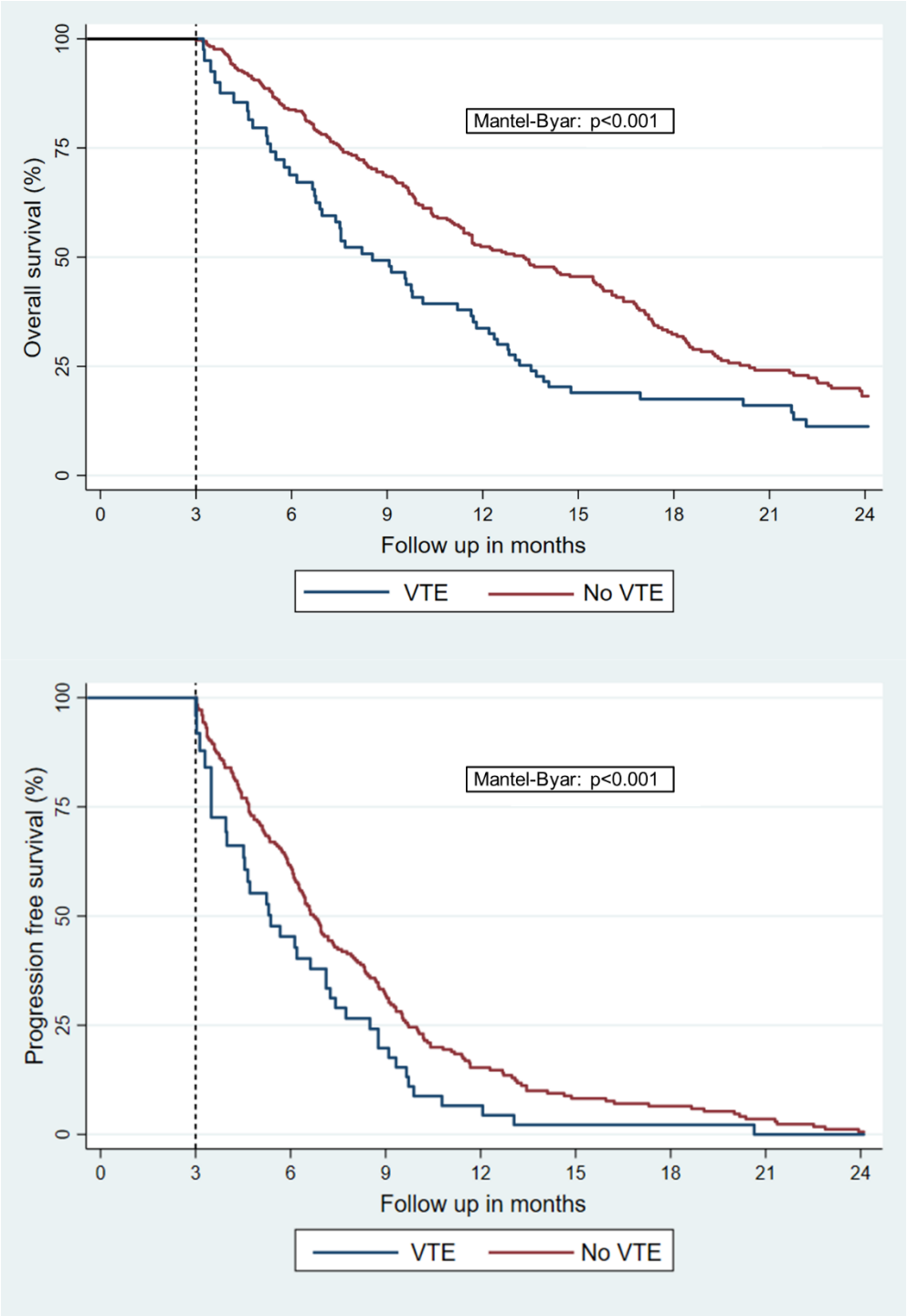

Figure 8: Landmark analysis of overall survival (OS) and progression free survival (PFS) stratified by the occurrence of VTE within the first 3 months of follow-up

4. Discussion

In this study, we sophisticated the incidence, risk factors and outcome of cancer- related ATE and VTE in a homogenously treated group of patients with advanced pancreatic cancer. The patients were undergoing the currently recommended palliative first line treatment with FOLFIRINOX or Gemcitabine/nab- Paclitaxel. Altogether, we found a high risk for thrombotic events in this cohort. The occurrence of VTE was associated with worse outcomes. Especially a prior history of cancer- associated thrombotic events was a high predictor for the occurrence of VTE. Risk prediction models and well known prothrombotic risk factors did not stratify VTE in this special setting. A high risk for ATE, especially the ischemic stroke, was found in patients with a prior history of cerebrovascular disease at treatment start.

4.1. Patterns of VTE

In the past, the epidemiology and pathophysiology of VTE in patients with pancreatic cancer has been comprehensively studied. The findings of prevalence rates were varying according to cancer stage, duration of follow up, the cancer stage as well as the definition of outcome. (158) The study cohort in our study was treated homogenously with the recommended palliative first line chemotherapy for advanced pancreatic cancer FOLFIRINOX or Gemcitabine/ nab Paclitaxel. In our study the median overall survival was 10.1 months and the cumulative incidence for VTE was 25%. These investigations are similar to recently presented findings. (159,160) An investigation of the BACAP consortium about VTE risk in a prospectively collected cohort of stage I-IV patients with newly diagnosed pancreatic cancer, found in the subset of locally advanced and metastatic pancreatic cancer that 25% of the patients developed VTE. 40% of the BACAP study population have been treated with single agent therapy, and none of them were undergoing a combined treatment with Gemcitabine/ Nab- Paclitaxel. (160) Importantly, no statistically significant difference in VTE risk was found between FOLFIRINOX and Gemcitabine/nab-Paclitaxel in uni- and multivariate risk factor analysis in our cohort, which indicates that the VTE risk is mainly driven by underlying cancer-specific risk factors instead of treatment type in this setting. In accordance with previous reports, risk of VTE was highest during the first months after treatment start supporting the hypothesis of upfront prophylactic anticoagulation (141). Whether permanent prophylactic anticoagulation should be routinely performed in patients with advanced pancreatic cancer remains a matter of debate (161). Current guidelines from the American Society of Clinical Oncology (ASCO) and the International Initiative on

Thrombosis and Cancer (ITAC) do recommend an expanding of VTE prophylaxis for ambulatory cancer patients with a Khorana score of 2 or higher (149,150). However, the clinical application of this approach is still low. Further, the Khorana score which currently represents the most established and externally validated tool for VTE risk prediction in an overall outpatient cancer population, was not designed to distinguish VTE risk within specific cancer types. This is supported by a study from the Vienna CATS group which showed that of the five constituents incorporated in the Khorana score only primary tumour site was associated with risk of VTE, whereas the other components had poor predictive value (162). In line with these findings, the cancer type specific predictive value of the Khorana score for VTE prediction is limited, as demonstrated by a large retrospective cohort study of lung cancer patients in which the Khorana score was not associated with risk of VTE (163). Accordingly, the Khorana- and CONKO score did not discriminate patients at highest risk of VTE in our study. These findings align well with two smaller studies previously investigating risk stratification tools for VTE in pancreatic cancer (164,165). In multivariable risk factor analysis, history of VTE emerged to be the strongest risk factor of developing VTE. Interestingly, this strong association was driven by prior cancer associated VTE alone, whereas VTE unrelated to the current cancer diagnosis was not associated with an elevated VTE risk during the study period. This supports the hypothesis of stringent and prolonged anticoagulation in patient with PC developing VTE.

The lack of additional clinical and laboratory variables identified for the stratification of VTE risk in this cohort challenges the concept of utilizing baseline risk prediction in a tumour type specific setting. Novel concepts including longitudinal risk prediction and the identification of biomarkers that might reflect the underlying prothrombotic risk are needed to improve risk prediction and thereby advance personalized thromboprophylaxis strategies to reduce the number needed to treat to prevent VTE events. (166)

Previous studies have reported conflicting results whether the onset of VTE was associated with an increased risk of death in patients with aPC (81,159, 160, 164, 167). We found that VTE diagnosis was associated with adverse outcomes as demonstrated by a significantly decreased OS and PFS. In detail, patients who developed VTE during the study period had a median OS of only five months after occurrence of VTE and lived less than half as lang long compared to patients without a VTE. Since only one patient developed fatal VTE, the increased mortality cannot be attributed to direct effects of VTE, but rather should be interpreted as a consequence of more aggressive cancer biology accompanied by a hypercoagulable state. Thereby, VTE might be used as an indicator for dismal prognosis,

cancer progression, and treatment failure during palliative chemotherapy in patients with advanced pancreatic cancer.

4.2. Patterns of ATE

The implications of ATE in patients with cancer are increasingly recognized (168). Although the event rate of cancer associated ATE is much lower than for VTE, the risk of ATE was shown to be significantly elevated in cancer patients compared to the general population, particularly in stage IV disease (115). Further, the onset of ATE is accompanied by a higher case fatality rate than VTE and often causes devastating consequences including physical disability and cessation of oncologic treatment (169). These aspects underscore the importance to properly characterise ATE events in patients with cancer, especially given the increase in cancer-specific survival in recent years. In our study the cumulative incidence of 2.8% was slightly lower compared to previous studies reporting frequencies of ATE in stage IV pancreatic cancer (115, 170, 171). Given that patients who were not fit enough to receive FOLFIRINOX or Gemcitabine/nab-Paclitaxel were not enrolled in this study this might be partly explained by the overall lower rates of comorbidities and better performance status in our cohort. Consistently, patients who experienced ATE had significantly more comorbidities and were slightly older compared to patients with no ATE event. Interestingly, in our cohort the vast majority of ATE events were ischaemic strokes, whereas only one patient developed myocardial infarction, and none had critical limb ischemia or acute mesenteric ischemia. This aligns well with one recent Taiwanese study which reported a cumulative rate of 4, 3% for stroke and 0, 6% for myocardial infarction in patients with aPC, respectively. (171) Different pathophysiological mechanisms that might explain the elevated risk of ATE in cancer patients have been proposed so far, including cancer-induced hypercoagulability, endothelial injury due to the systemic inflammatory stimulus in cancer, as well as vascular toxicity of chemotherapy, in particular of platinum agents. Further, shared common cardiovascular risk factors such as chronic nicotine consumption, higher age, obesity and diabetes mellitus type II might contribute to the observed co-prevalence of ATE and cancer (168).

The case fatality rate of 18% for ATE in our cohort underlines the urgency to identify patients at the highest risk of ATE. In our study the Charlson Comorbidity Index and a prior history of cerebrovascular disease (CVD) emerged as the only significant predictors of ATE risk, whereas for other risk factors only a non-significant association could be observed. Most prominently, a positive history of cerebrovascular disease (CVD) at treatment start was

associated with a vastly increased ATE risk. In detail, 6 of 11 patients experiencing an ATE had a history of CVD at baseline conferring to a 23-fold increased risk of ATE. Considering the detrimental effects of ATE on physical well-being and the fact that the primary treatment goal in this setting is palliation, this finding suggests, that less aggressive treatment strategies as well as prophylactic anticoagulation or antiplatelet therapy might be considered in patients with advanced pancreatic cancer and CVD. Interestingly, albeit not reaching statistical significance, patients who underwent fist line treatment with Gemcitabine/nab-Paclitaxel had a markedly elevated risk of ATE compared to patients treated with FOLFIRINOX. This could potentially be explained by the higher age and worse comorbidity profile in the GN group, however, might also be related to the administered treatment itself, warranting further exploration. In contrast to previous studies, no significant association between onset of ATE and worse outcome was observed in our cohort, however this observation is limited as of the low statistical power given the small number of outcome events (116, 171).

4.3. Limitations

Several limitations of this study have to be discussed. First, due to the retrospective study design, underreporting of thromboembolic events, especially after termination of chemotherapy, cannot be excluded (172). However, as patients with terminal illness often are not referred to hospital for further diagnostic work up, this is reflective of a real-world scenario. Second, information on baseline long term medication which might have affected the thromboembolic risk were missing. Third, biomarkers including D-dimer, soluble P-selectin, fibrinogen or plasminogen-activator inhibitor 1, which have been proposed as prothrombotic markers, were not assessed before treatment start in routine clinical practice and therefore, their predictive utility for risk of thrombotic events could unfortunately not be assessed in this setting (110, 173). Fourth, due to low number of ATE events in our cohort, multivariable risk factor analysis was deemed infeasible. Despite these limitations, this study provides a comprehensive investigation of real-world patterns of VTE and ATE in a well characterized and homogenously treated multi-center cohort and thereby contributes valuable data on cancer type specific prediction of thrombotic events in patients with advanced pancreatic cancer undergoing palliative chemotherapy.

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