Aus der Klinik für Hämatologie, Onkologie und Tumorimmunologie

der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

# The Use of Prognostic Factors to Identify the Group of Beneficiaries for Secondary Resection in Patients with Primarily Not-Resectable Pancreatic Adenocarcinoma

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# Der Nutzen von prädiktiven Faktoren zur Identifikation von Patienten mit primär nicht resektablem Adenokarzinom des Pankreas, welche von einer sekundären Resektion profitieren

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## List of Abbreviations

| | |
|---|---|
| ASA | American Society of Anesthesiologists |
| BMI | Body Mass Index |
| BRPC | Borderline Resectable Pancreatic Cancer |
| c | clinical stage |
| CA 19-9 | Carbohydrate Antigen 19-9 |
| CEA | Carcinoembryonic Antigen |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DNA | Deoxyribonucleic Acid |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Endothelial Growth Factor Receptor |
| EUS | Endosonographic Ultrasound |
| FNA | Fine-needle Aspiration |
| FPC | Familial Pancreatic Cancer |
| HR | Hazard Ratio |
| IAP | International Association of Pancreatology |
| IPMN | Intraductal Papillary Mucinous Neoplasm |
| ISGPF | International Study Group for Pancreatic Fistula |
| LAPC | Locally Advanced Pancreatic Cancer |
| m | modified |
| MDCT | Multislice Detector Computed Tomography |
| mOS | median Overall Survival |
| MRI | Magnetic Resonance Imaging |
| NCCN | National Comprehensive Cancer Network |
| NET | Neuroendocrine Tumor |
| OS | Overall Survival |
| p | pathological stage |
| PanIN | Pancreatic Intraepithelial Neoplasia |
| PDAC | Pancreatic Ductal Adenocarcinoma |

| | |
|---|---|
| PET | Positron Emission Tomography |
| PPPD | Pylorus-preserving Pancreaticoduodenectomy |
| R | Residual |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SMA | Superior Mesenteric Artery |
| TNM | Tumor/Nodus/Metastases |
| y | After Neoadjuvant Therapy |
| 5-FU | 5-fluorouracil |
| 95 % CI | 95 % Confidence Interval |

# 1. Abstract

## 1.1. Abstract (English)

**Background**

The pancreatic ductal adenocarcinoma is one of the most lethal tumor entities. Most patients suffer from a locally advanced or metastasized disease at the time of diagnosis. In this stage, patients regularly receive palliative chemotherapy. However, current studies show a benefit of neoadjuvant intended therapy and subsequent secondary resection for some patients. This investigation aimed to find factors that help identify patients with a good prognosis to justify an intensified neoadjuvant intended therapy with consecutive secondary resection.

**Methods**

Data of patients with pancreatic cancer were collected consecutively within the Comprehensive Cancer Center database of Charité – Universitätsmedizin Berlin. The database was screened for patients with primarily not-resectable adenocarcinoma of the pancreas who underwent a secondary resection after receiving neoadjuvant chemotherapy from March 2017 to May 2019. We analyzed the data retrospectively regarding the overall survival (OS) dependent on clinical and pathological characteristics.

**Results**

Forty patients were identified for the period mentioned above. The median overall survival (mOS) was 20 months (95 % CI: 17.2 – 22.9). The following factors had a positive impact on the OS of the patients: a normal CA 19-9 (Carbohydrate Antigen 19-9) level (< 37 U/ml) at the time of diagnosis (29 vs. 19 months, $p = 0.02$) or after neoadjuvant therapy (26 vs. 18 months, $p = 0.04$) and a BMI (body mass index) below 25 kg/m² after neoadjuvant therapy (15 vs. 24 months, $p = 0.01$). Additionally, there was a benefit for patients who received at least four cycles of neoadjuvant chemotherapy (18 vs. 24 months, $p = 0.02$). Furthermore, nodal negativity had a positive impact on the OS (25 vs. 15 months, $p = 0.003$). Overall, neoadjuvant therapy led to a significant decline of CA 19-9 by 44.7 % from a mean value of 4358.3 U/ml to 138.5 U/ml ($p = 0.001$). Twenty-seven patients (73 %) reached partial remission.

**Conclusion**

In this investigation, the tumor marker CA 19-9 before and after neoadjuvant therapy and the BMI after neoadjuvant therapy were predictive for the OS of the patients. Thus, these factors were predictive for the benefit of a secondary resection. Furthermore, a minimum number of four neoadjuvant cycles led to a significant benefit in survival. Additionally, patients who achieved

nodal negativity after neoadjuvant therapy had a significantly prolonged OS. Thus, the diagnosis of the presurgical nodal status should gain more importance.

## 1.2. Abstrakt (Deutsch)

**Einleitung**

Das Adenokarzinom des Pankreas weist eine der ungünstigsten Prognosen aller Tumorentitäten auf. In den überwiegenden Fällen liegt bei Diagnose ein lokal fortgeschrittener oder bereits metastasierter Befund vor. Für die lokal fortgeschrittene, jedoch nicht metastasierte Situation stand bisher lediglich die palliative Chemotherapie zur Verfügung. Neuere Untersuchungen zeigten jedoch einen möglichen Vorteil einer neoadjuvant intendierten Therapie mit anschließender sekundärer Resektion für ausgewählte Patienten. Die vorliegende Untersuchung dient dazu, prädiktive Faktoren zu identifizieren, mithilfe derer wir Patienten mit einer besseren Prognose identifizieren können, um somit für diese Patientengruppe eine intensivierte Therapie und sekundäre Resektion zu begründen.

**Methoden**

Daten von Patienten mit einem Pankreaskarzinom wurden fortwährend in der Datenbank des Comprehensive Cancer Centers der Charité – Universitätsmedizin Berlin gesammelt. Es erfolgte ein Screening auf Patienten mit einem Adenokarzinom des Pankreas, welche im Zeitraum von März 2017 bis Mai 2019 nach neoadjuvanter Chemotherapie sekundär reseziert wurden. Die Daten der Patienten wurden pseudonymisiert und retrospektiv auf das Gesamtüberleben in Abhängigkeit von klinisch-pathologischen Charakteristika untersucht.

**Ergebnisse**

Im genannten Zeitraum konnten 40 Patienten mit ausreichender Datenlage identifiziert werden. Das mittlere Gesamtüberleben der Patienten betrug 20 Monate (95 % CI: 17,2 – 22,9). Präoperative Faktoren, welche sich positiv auf das Gesamtüberleben der Patienten auswirkten, waren ein normwertiger CA 19-9 Wert (< 37 U/ml) bei Diagnose (29 vs. 19 Monate, $p = 0,02$) und nach neoadjuvanter Chemotherapie (26 vs. 18 Monate, $p = 0,04$) sowie ein BMI unter 25 kg/m² nach neoadjuvanter Therapie (15 vs. 24 Monate, $p = 0,01$). Zudem profitierten die Patienten von einer Applikation von mindestens vier Chemotherapiezyklen (18 vs. 24 Monate, $p = 0,02$). Ein negativer histopathologischer Nodalstatus wirkte sich deutlich positiv auf das Gesamtüberleben aus (25 vs. 15 Monate, $p = 0,003$). Insgesamt konnte durch die neoadjuvante Therapie ein relevanter Abfall des CA 19-9 um 44,7 % von einem Mittelwert von 4358,3 U/ml

auf 138,5 U/ml ($p$ = 0,001) sowie eine partielle Remission bei 27 Patienten (73 %) erreicht werden.

**Schlussfolgerung**

In dieser Untersuchung waren der CA 19-9 Wert bei Diagnose und nach neoadjuvanter Therapie sowie der BMI nach Chemotherapie prädiktiv für das Überleben der Patienten und somit auch prädiktiv für den Nutzen einer sekundären Resektion. Zudem brachte die Applikation von mindestens vier neoadjuvanten Zyklen einen deutlichen Überlebensvorteil. Aufgrund des Nutzens für Patienten, die nach neoadjuvanter Therapie einen negativen histopathologischem Nodalstatus aufwiesen, sollte vermehrte Aufmerksamkeit auf dessen prächirurgische Diagnostik gelegt werden.

# 2. Synopsis

## 2.1. Introduction

### 2.1.1. Epidemiology and Risk Factors of Pancreatic Cancer

Pancreatic cancer is one of the most aggressive malignancies and ranks as the fourth leading cause of cancer deaths in western countries. Despite progress in surgical techniques, radiation, and chemotherapy, the prognosis of this type of cancer remains poor. The 5-year survival rate is described at 8 % and is the lowest of all cancer entities (1). In particular elderly patients suffer from this disease (median age of onset 72 to 75 years), which leads to a rising incidence of pancreatic cancer in our population due to demographic changes (2). Moreover, age-standardized incidence and mortality rates increase, especially in patients over 65 years (3). These facts lead to the prediction of pancreatic cancer becoming the second leading cause of cancer deaths in western countries by 2030 (4).

Smoking and obesity are proven risk factors for the development of pancreatic cancer. The relative risk of ever-smokers compared to never-smokers is described at 1.6. The relative risk for patients with a body mass index > 25 kg/m² compared to a normal BMI is described with 1.3 (5). Patients suffering from chronic pancreatitis and diabetes type 2 are also more likely to develop pancreatic cancer (6, 7). Despite lifestyle factors being mainly responsible for this neoplasm, genetic dispositions also increase its risks, such as Peutz-Jeghers syndrome and familial pancreatic cancer (8, 9). BRCA1 or -2 germline mutations are detected in four to seven percent of pancreatic cancer patients and can have an impact on therapy strategies in advanced or metastatic disease (10, 11).

### 2.1.2. Pathogenesis of Pancreatic Cancer

An accumulation of mutations over time is responsible for progressive degrees of dysplasia of ductal epithelial cells that lead to pancreatic cancer. Four genetic alterations are the most common ones: an activation of KRAS oncogene and the inactivation of tumor suppressors CDKN2A, TP53, and SMAD4. Many further alternating genetic mutations are present that affect the same few pathways, such as NOTCH, WNT, or Hedgehog (12). Genetic instability caused by telomere dysfunction leads to ongoing genetic alterations and heterogeneity within the pancreatic tumor and its metastases (13). Furthermore, the tumor`s microenvironment inhibits vascularization and creates fibrosis surrounding the tumor as a shield against chemotherapeutic agents and immune cell reactions (14).

### 2.1.3. Histopathological Types of Pancreatic Cancer and its Prognoses

The pancreatic gland histologically consists of exocrine (acinar and ductal) and endocrine cells. Derived from this we distinguish between adenocarcinomas of the pancreatic gland and neuroendocrine tumors (NET). NETs, such as insulinoma and gastrinoma derive from cells of the neuroectoderm. They represent about one to two percent of pancreatic tumors and have a relatively good prognosis (5-year survival rate 52 %). About 85 % of these tumors are active, which means that they produce hormones or hormone-like transmitters (15).

The majority of pancreatic malignancies are adenocarcinomas. Depending on the lineage of neoplastic cells in this tumor we differentiate between acinar and ductal adenocarcinoma. The ductal adenocarcinoma of the pancreas (PDAC) is the most common tumor of the pancreatic gland. It represents over 85 % of pancreatic malignancies (16). The 5-year survival rate is described at 11.5 % (2). PDACs are mostly located at the pancreatic head and form solid masses that rarely reach sizes over seven centimeters. At least by that size, they start to disseminate to the abdomen. The neoplastic glands of the tumor easily infiltrate the surrounding stroma, which causes stromal fibrosis and reactive atypia in epithelial cells. For that reason, it may be difficult for pathologists to differentiate between chronic pancreatitis and PDAC in small biopsies. Next to ordinary PDAC, which is characterized by a well-differentiated structure and glands out of mucin-filled cuboidal cells, other cancers of ductal types with different characteristics and prognoses exist, such as undifferentiated carcinoma, osteoclastic giant-cell carcinoma, adenosquamous carcinoma, or colloid carcinoma (16).

Microscopic lesions called Pancreatic Intraepithelial Neoplasia (PanIN) are the presumed precancerous lesions of PDAC. They are not detectable by common clinical imaging modalities

and often are incidental findings in resected pancreatic glands. In more than 80 % PanINs of any grade are coexistent with PDAC and PanINs of grade 3 are highly suspicious for PDAC (17). Infrequently, cystic lesions that are macroscopically visible and detectable by clinical imaging, such as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN), are precursor lesions for PDAC. Nevertheless, in about 30 % of cases, IPMNs contain invasive cancer (16). Often, it remains unclear, whether PDAC arose from these lesions in such cases or whether they developed independently of each other. A study by Scarpa et al. showed few genetic similarities between coexistent PDAC and IPMN in 18 % of cases, consequently, they were likely independent (18).

Although acinar cells are the most numerous cells of the pancreatic gland, cancers with acinar differentiation, such as acinar cell carcinoma, are rather uncommon and represent approximately two percent of pancreatic neoplasms (19). The 5-year survival rate is described at 16.7 % (2).

#### 2.1.4. Stages of Pancreatic Cancer

The TNM-criteria of the American Joint Committee on Cancer (AJCC) are commonly used for postoperative staging. However, this staging system does not apply to preoperative diagnostics as it tends to underestimate the final stage (20). Therefore, criteria of the National Comprehensive Cancer Network (NCCN) are used for the clinical staging. This staging system classifies pancreatic cancer into the following categories: resectable cancer, borderline-resectable cancer (BRPC), locally advanced (and thus, unresectable) cancer (LAPC), and metastatic cancer. PDAC is considered resectable if radiographic imaging shows no signs of encasement or thrombosis of the portal vein or the superior mesenteric vein and if clear fat planes separate the tumor from the celiac axis, the common hepatic artery and superior mesenteric artery (SMA) (21). This early stage can be found in approximately 10 % of cases (22). Resection is not recommended in the presence of unreconstructable occlusions of the named vessels or a circumferential encasement (> 180°) of the SMA or the coeliac axis (23). These tumors are classified as locally advanced pancreatic cancer and represent about 30 % of cases (22). Tumors that do not meet the named criteria are classified as borderline resectable. In these cases, curative intended resection is still feasible but is associated with a higher risk of R1-resections, and thus, a higher rate of local or distant recurrences (23). The neoplasm is categorized as BRPC if it is located at the pancreatic head and shows a limited involvement of the SMA (encasement of less than 180°) and no involvement of the coeliac axis. If the neoplasm is located at the pancreatic body or tail and encases the celiac axis by more than 180°, resection is still feasible, as long as there is no involvement of the aorta and gastroduodenal artery. In that case, an appley procedure

(resection of the celiac axis) can be performed (21) (Table 1). BRPC is present in about 10 % of cases. About 60 % of patients with adenocarcinoma of the pancreatic gland show distant metastases at the time of diagnosis (2, 22).

**Table 1.** Criteria Defining Resectability Status. Source: based on Tempero et al., 2021, page 27 (21)

| | **RPC** | **BRPC** | **LAPC** |
|---|---|---|---|
| **PV/SMV** | No tumor contact or ≤ 180° contact without vein contour irregularity | Solid tumor contact > 180° or tumor contact < 180° with vein contour irregularity or thrombosis that allows reconstruction | Unreconstructable involvement or occlusion |
| **Celiac Axis** | No tumor contact | Pancreatic Head: no tumor contact<br>Pancreatic Body/Tail: solid tumor contact ≤ 180° or > 180° if Appleby procedure is anatomically feasible | Pancreatic Head: solid tumor contact > 180°<br>Pancreatic Body/Tail: solid tumor contact > 180° or with aortic involvement |
| **SMA** | No tumor contact | Solid tumor contact < 180° | Solid tumor contact > 180° |

RPC - Resectable Pancreatic Cancer, BRPC - Borderline Resectable Pancreatic Cancer, LAPC - Locally Advanced Pancreatic Cancer, PV – Portal Vein, SMV – Superior Mesenteric Vein, CA – Celiac Axis, SMA – Superior Mesenteric Artery.

Although postoperative morbidity and mortality rates are increased in patients older than 80 years, there is no general contraindication for surgery depending on the age of patients (24). Nevertheless, there is a trend to include conditional characteristics of patients into the evaluation for curative resection and staging. An investigation by Tas et al. showed a significantly shorter OS in patients with an ECOG performance status of at least 2, independent of the tumor stage (25). Thus, patients with an ECOG performance status of 2 or more are now staged as borderline resectable (BR type C) by the International Association of Pancreatology (IAP) according to the ABC-criteria (A – anatomical, B – biological, C – conditional) even though they were anatomically resectable. Those patients should undergo further medical consultations to improve nutritional conditions and performance before resection. Further conditional characteristics are not included yet. However, another circumstance leads to a borderline resectable staged pancreatic cancer, even if it is anatomically resectable. Biological factors have been identified

that negatively influence resectability and postoperative overall survival. Thus, patients that have a preoperative CA 19-9 level of more than 500 U/ml or have regional lymph node metastases that have been confirmed by either PET-CT or biopsy are staged as borderline resectable (BR type B – biological) by the IAP (26).

### 2.1.5. Diagnosis of Pancreatic Adenocarcinoma

Pancreatic cancer often is diagnosed in a locally advanced and not-resectable stage. Therefore, we would benefit from a screening method that identifies patients at an early stage. The general screening of the population for pancreatic cancer is not recommended due to the low lifetime incidence of this cancer entity. Nevertheless, patients with at least two first-degree relatives with pancreatic cancer are recommended to be screened for familial pancreatic cancer (FPC). Furthermore, patients with Peutz-Jeghers syndrome, hereditary non-polyposis colorectal cancer (HNPCC), and patients with p16- or BRCA2-mutations are worth screening via endosonographic ultrasound (EUS) or magnetic resonance imaging (MRI) (27).

Abdominal sonography is the first necessary diagnostic step when the first symptoms occur. Typical signs for a pancreatic tumor are hypoechoic lesions, the dilatation of the pancreatic duct, and the dilatation of the bile duct (double-duct sign). If the suspicion of a pancreatic tumor arises, a multi-detector row computed tomography (MDCT) is the diagnostic method of choice to evaluate the grade of infiltration of the surrounding organs, resectability, and metastasis (22). Intravenous injections of contrast are used to enhance the arterial and portal venous phase. During the arterial phase, the pancreatic adenocarcinoma and its vasculature become visible. In comparison to NET, PDAC is hypovascular and poorly enhancing. The venous phase depicts the venous involvement, as well as distant metastases and lymphadenopathy (28). MRI is an alternative if contraindications for CT exist. To further evaluate pancreatic findings, EUS can be performed with the option for fine-needle aspiration (FNA). A biopsy is not crucial in cases of unequivocal imaging with the option for curative resection. The suspicion of pancreatic cancer must be histologically confirmed before the initiation of palliative therapy (22).

CT does not always offer clarity about the dignity or the exact extent of the pancreatic tumor. Focal chronic pancreatitis can mimic the appearance of pancreatic cancer. Furthermore, in five to ten percent pancreatic cancer appears with iso-attenuated tissue. Consequently, radiologists need to pay attention to potential secondary signs of pancreatic cancer, such as an abnormal contour of the pancreas, the abrupt cutoff of the pancreatic duct, or pancreatic atrophy (28, 29). Yet, the sensitivity and specificity of CT detecting pancreatic cancer are described at 90 % and 87 %

(30). Furthermore, it happens that curatively intended laparotomy reveals peritoneal metastases or extended infiltration of the surrounding vessels. In particular, small metastases are hard to identify by CT scan (31). Finally, the resectability stage can be correctly interpreted by MDCT with a sensitivity of 94 % and a specificity of 89 % (32).

MRI generally shows a better soft-tissue contrast than CT resulting in its superiority concerning small or iso-attenuated lesions. Furthermore, in situations in which CT only shows a hypertrophic pancreatic head, MRI may reveal the presence of a tumor. While fatty infiltrations of the pancreatic head can lead to the wrong assumption of the presence of pancreatic cancer in CT scan, T1-weighted images of MRI can reveal this misinterpretation. In summary, MRI offers slightly better sensitivity (93 %) and specificity (90 %) than MDCT (30). However, MDCT remains the diagnostic method of choice because of its high availability, low costs, and speed (28). Nevertheless, after having performed a CT scan, it is recommended to additionally perform an MRI of the liver as the sensitivity for detecting small metastatic lesions is higher (33).

In cases of equivocal signs in common imaging modalities, it may be helpful to perform EUS as it provides high-resolution images of the pancreatic tissue. Especially, small lesions with sizes smaller than three centimeters are better visualized with EUS than with CT scans, MRIs, or abdominal ultrasounds (31, 34). The sensitivity and specificity of EUS are described at 92.3 and 68.9 % (35). While difficulties may occur differentiating between chronic pancreatitis and malignant masses, an additional FNA can be performed. EUS-FNA reaches a specificity of 95.8 % (36). Furthermore, new non-invasive EUS techniques, such as EUS elastography increase specificity rates compared to conventional B-mode images of EUS to 80 % (35).

Positron-emission tomography (PET) can additionally be performed to identify distant metastases. For this cause, PET-CT is a very suitable method as it depicts the whole body with all possible evidence for metastases, though the chance for false-positive results is high because of the physiologic uptake of FDG (fluorodeoxyglucose ($^{18}$F)) in many organs or increased uptake caused by inflammatory reactions. Furthermore, false-negative results are possible, especially in cases with metastases smaller than five millimeters (31, 37, 38). Nevertheless, the detection of bone metastases reaches a sensitivity of up to 100 %. On the other hand, PET-CT is not suitable for the primary diagnosis of pancreatic cancer as it has a sensitivity of only 72 %. But it has the main advantage in monitoring the response to the previous therapy, especially in cases of LAPC. While MDCT cannot differ between therapy-destroyed tissues and viable tumors, PET-CT shows metabolically active tissue and cancer (28). However, in Germany PET-CTs are not

covered by the statutory health insurance companies, unless there is a suspicious pulmonary tumor of unknown dignity.

Diagnostically intended laparoscopy can additionally be performed and changes therapy decisions in about one third of initially resectable staged pancreatic cancer patients (39). An additional laparoscopy should be considered in cases of CA 19-9 levels above 150 U/ml or a CT-staged tumor size of more than three centimeters as these factors may predict unresectability and the presence of peritoneal carcinosis (40).

### 2.1.6. Therapy of Pancreatic Adenocarcinoma

#### *2.1.6.1. Surgery*

Surgery is the only treatment option with curative intention. That, for instance, was demonstrated in a randomized trial by Doi et al., where patients who received radiochemotherapy had a very limited median OS of 10.8 months in comparison to resected patients (mOS 22.6 months) (41).

The aim of surgery is an R0-resection. There are different statements about the influence of R1-resection on the OS of patients. An investigation by Neoptolemos et al. resulted in prolonged OS for patients with R0-resection (42). Other investigations with smaller numbers of included patients showed no significant difference (43, 44). Nonetheless, there is a significant increase of local recurrence in patients with R1-resection (45, 46). However, different definitions for R0-resection in pancreatic cancer led to heterogeneous results according to the rate of R1-resections varying from 16 to 75 % (47). Analyses have led to the result, that chances for prolonged OS are increased depending on the distance to the resection margin (48). To aim R0-resection special resection methods and additional organ and vessel resections are possible (49, 50).

The classical surgical treatment techniques for pancreatic cancer of the head are the Whipple procedure or the pylorus-preserving pancreaticoduodenectomy (PPPD) by Traverso-Longmire. Both procedures are equal according to survival, postoperative mortality, complications, and quality of life. Nevertheless, PPPD is the preferred method as it shows advantages in blood loss, shorter operation time, and preservation of the stomach. The Whipple procedure can still be performed to gain R0-resection in cases of stomach infiltration (51). After the resection of the pancreatic head, the resection margin of the pancreatic head and bile duct are histologically examined by frozen section analysis. In cases of a positive resection margin, an additional total pancreatectomy can be performed if R0-resection seems possible (52). Total pancreatectomy can be contemplated in further situations, such as the presence of precancerous lesions in patients with FPC to not leave undetected lesions behind, in cases of arterial reconstruction, or in cases of

extremely soft pancreatic tissue to decrease the risk for postoperative fistula. However, total pancreatectomy is associated with high rates of metabolic complications, such as severe diabetes and its consequences, and a decreased quality of life. Thus, partial resection should be aimed if it is justifiable (53, 54). Indications for distal pancreatectomy are cancers of the pancreatic tail or corpus. Because of its anatomical proximity and its venous drainage to the splenic vein, an additional splenectomy is classically performed. Splenic preservation is possible and is associated with lower rates of infectious complications and clinically relevant pancreatic fistula (ISGPF grade B and C). However, the procedure is technically difficult and can cause complications like spleen infarctions. Further investigations are necessary to prove a possible long-term benefit of this procedure (55).

In about 78 % of cases, lymphogenic metastases are found in the resected specimen (56). Thus, a lymphadenectomy is recommended during every pancreatectomy. The standard lymphadenectomy in PPPD includes the resection of peripancreatic, suprapyloric, and infrapyloric lymph nodes, lymph nodes of the hepatoduodenal ligament, and right-sided lymph nodes of the celiac trunk and superior mesenteric artery. In distal pancreatectomy, the standard lymphadenectomy includes lymph nodes along the splenic artery, at the splenic hilum, and along the inferior portion of the pancreas (57). An extended lymphadenectomy is not recommended because of its increased postoperative morbidity and missing long-term benefits (58). German guidelines recommend the resection of at least 12 lymph nodes, although the nodal stage seems to be more accurate with a tendency to more resected lymph nodes (59-61). Furthermore, the number of positive nodes, the ratio of positive to resected nodes, and the level of nodal metastatic spread may be prognostic factors for OS (62-64).

Infiltration of the superior mesenteric and portal vein is a common problem because of the anatomical proximity to the pancreatic gland. An additional vessel resection can be performed if R0-resection is possible. In some high-volume centers, vessel resection is performed in up to 46 % of cases and is not associated with higher mortality or morbidity rates if performed regularly (65).

As mentioned above, pancreatic surgery often leads to R1-resections. Predisposed localizations are the posterior margins of the resected specimen, adjacent to the so-called mesopancreas which includes the tissue between the pancreatic head and the superior mesenteric vessels and coeliac axis. It further contains high numbers of lymphatic tissue and vessels, and the arterial nerve plexus (66, 67). As pancreatic cancer has a strong tendency towards a discontinuous perineural

invasion of the arterial plexus, it is recommended to perform a resection of the periarterial plexus of the mesopancreas. To ensure R0-resection in this area, special surgical techniques have been established, such as the artery-first approach. During this procedure, the superior mesenteric artery gets dissected first to evaluate resectability (50). In cases of an arterial abutment to the SMA of more than 180°, the response to neoadjuvant therapy decides upon a possible arterial resection. However, SMA-resection remains controversial because of its risks for intestinal ischemia, severe diarrhea caused by denervation, and high mortality rates (68). In cases of coeliac axis involvement, a (subtotal) distal pancreatectomy with simultaneous celiac axis resection can be performed if the tumor has initially responded to chemotherapy. This so-called Appleby procedure is technically possible due to retrograde blood flow from the gastroduodenal artery to the common hepatic artery and right gastric artery to maintain liver and stomach perfusion (68). However, severe side effects such as liver and gastric necrosis are possible (69). Therefore, this procedure should only be performed by high-volume centers in selected patients.

Despite the classical open procedure, laparoscopic approaches are possible. The procedures are associated with shorter hospitalization times, reduced blood loss, and comparable postoperative complication rates. However, operation times are prolonged, and advanced laparoscopic skills are required (70).

Common side-effects and complications after pancreatoduodenectomy are delayed gastric emptying, pancreatic fistula, intra-abdominal abscess, wound infections, hemorrhage, and endocrine and exocrine insufficiency of the pancreatic gland (71).

#### *2.1.6.2. Chemotherapy*

Chemotherapy is part and parcel of therapy in pancreatic cancer. First established as adjuvant and palliative chemotherapy, it now gains more importance as a neoadjuvant option as well.

An adjuvant application of chemotherapy increases the progression-free and overall survival of patients with resectable pancreatic cancer (72). The standard regimen for patients in a good general condition is the application of modified FOLFIRINOX (mFOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan) (73). The application of a full dose FOLFIRINOX (additional 5-fluorouracil bolus) did not show to be more efficient. However, patients suffer from side effects more often if treated with unmodified FOLFIRINOX (74). The mOS for resected patients in a good postoperative condition undergoing adjuvant chemotherapy with mFOLFIRINOX is described with up to 54.4 months. The 3-year survival rate is described at 63.4 % (73). High rates of side effects within the mFOLFIRINOX protocol require a different therapy for patients

with worse general conditions (ECOG > 1). Therefore, either a monotherapy with gemcitabine (mOS 23-35 months), 5-fluorouracil (mOS 23.6 months), or a combination of gemcitabine and capecitabine (mOS 28 months) can be applied and increases the 5-year survival rate to 20.7-28.8 % in comparison to 10.4 % without adjuvant chemotherapy. Gemcitabine in combination with capecitabine gained the best survival results with slightly increased rates for severe neutropenia and diarrhea and should thus be favored (72, 75, 76). Due to the significantly increased incidence of severe mucositis and diarrhea and the missing option for oral application, 5-FU should only be applied in cases of a gemcitabine-intolerance (75). The JASPAC-1 trial conducted with adjuvant application of S-1, an orally active fluoropyrimidine, gained even better 5-year survival rates described at 44.1 %. Though, patients that were included in this trial were more likely to have a negative nodal stage and an ECOG performance status of 0 and thus, had favorable prognostic factors (77).

Adjuvant chemotherapy is recommended to be initiated within 12 weeks after surgery. There seems to be no survival benefit for an earlier initiation (78, 79). Instead, the completion of six cycles of gemcitabine or 5-FU was shown to have a significant positive influence on OS (79).

The rate of metastatic findings at the time of late diagnosis is high. About 60 % of patients are diagnosed at a metastatic stage. In addition, locally advanced non-resectable pancreatic cancer is diagnosed in about 30 % of cases (22). For these two groups, a palliative intended chemotherapy is the therapy of choice. A sole supportive therapy has been shown to have no survival or quality of life benefit (80). In particular, the rate of tumor-associated weight loss and analgesic use is decreased with the help of effective palliative chemotherapy (81). Preferred first-line therapy for patients in a good general condition (ECOG 0-1) is FOLFIRINOX or gemcitabine with nab-paclitaxel (nano-particle albumin-bound paclitaxel) (82, 83). The mOS for patients who are treated with gemcitabine and nab-paclitaxel is described at 8.5 months. The 1-year survival rate is described at 35 %. The response rate is described at 23 %. This therapy protocol is associated with higher rates for neutropenia and peripheral neuropathy in comparison to monotherapy with gemcitabine (83). The mOS for patients who are treated with FOLFIRINOX is described at 11.1 months. The overall survival rate at 12 months was described at 48.4 %. The response rate is described at 31.6 %. This intensified therapy protocol is associated with higher rates for severe adverse events in comparison to monotherapy with gemcitabine as well. Severe side effects are febrile neutropenia, thrombopenia, diarrhea, and sensory neuropathy. Despite higher rates for side effects, quality of life is more persistent during therapy with FOLIRINOX in comparison to monotherapy with gemcitabine (82). A further option for patients in a good to poor general

condition (ECOG 0-2) is the application of gemcitabine in combination with erlotinib, a HER1/EGFR-targeted tyrosine kinase inhibitor. The mOS with this therapy is described at 6.2 months and the 1-year survival rate at 23 %. Except for diarrhea and rush, no further severe adverse events are significantly increased in comparison to monotherapy with gemcitabine, but the incidence for interstitial lung disease (ILD) is increased due to the additive effect of gemcitabine and erlotinib, both known for causing this syndrome (84). A monotherapy with gemcitabine can be applied in cases of good to poor general condition (ECOG 0-2) or intolerable adverse events during other chemotherapy protocols. The response rate is described at 23.8 % and the 1-year survival rate at 18%. The mOS is described at 5.7 months. At all points, monotherapy with gemcitabine is superior to monotherapy with 5-FU (81). Patients with an ECOG status of 2 or worse do not seem to benefit from an intensified chemotherapy protocol with multiple agents (85). However, combination therapy with dose-reduced gemcitabine and nab-paclitaxel or erlotinib are useful options for symptom control in patients with poor general conditions (84, 86). Trials that investigated the use of chemotherapeutic agents only included patients with an ECOG of 0 to 2. Thus, the use for patients in a worse general condition remains unclear (80-85).

A different therapy strategy is required in patients with a germline mutation of BRCA1 or -2. As DNA-repair mechanisms are defective in those tumor cells, chemotherapy agents that inhibit DNA-repair or cause interstrand-crosslinks are suitable in that case. Thus, platin-based therapy is recommended. Common options are a combination of gemcitabine with cisplatin or the FOLFIRINOX-protocol. The mOS is described at 15.5 to 18.1 months (10, 11). Maintenance therapy can be performed with Olaparib, a PARP-inhibitor (poly-(adenosine diphosphate-ribose) polymerase-inhibitor) if primary platinum-containing therapy was conducted for at least 16 weeks and results in a significantly prolonged progression-free survival (10). With the help of this agent, single-strand breaks cannot be repaired, and damaged DNA accumulates in the cell, which causes tumor cell death (87).

A platin- or irinotecan-based therapy combined with 5-fluorouracil infusions is a proven second-line regimen for patients who progressed during a gemcitabine-based first-line therapy (88-90). Patients reached a significantly prolonged progression-free survival (2.9 months) and mOS (5.9 months) if they had been treated with oxaliplatin, 5-FU, and folinic acid (OFF-protocol) in comparison to 5-FU and folinic acid alone (88, 89). However, a study conducted with oxaliplatin and higher dosages of 5-FU and folinic acid (mFOLFOX6-protocol) showed significantly increased severe side effects, in particular neuropathy and hematologic toxicity, and higher rates

of discontinued therapy due to side effects in 20 % of patients. Thus, oxaliplatin-based second-line therapies should only be considered in patients with a good general condition (ECOG < 2) and controlled neuropathy (CTCAE grade < 3) (91, 92). The use of nanoliposomal irinotecan in combination with 5-FU and folinic acid (NAPOLI-protocol) significantly increases mOS to 6.1 months in comparison to 5-FU and folinic acid alone. Severe side effects are as well increased within the NAPOLI-protocol. In particular, the presence of neutropenia, diarrhea, vomiting, and fatigue are significantly increased. However, severe side effects led to therapy withdrawal in only 11 % of patients treated within the NAPOLI-protocol (90). In case of progression during therapy with FOLFIRINOX and stable ECOG performance status (ECOG 0-1), the protocol can be changed to gemcitabine/nab-paclitaxel, but phase-III-trials are missing to prove an OS benefit for this change of course (92). The application of second-line monotherapy gemcitabine or 5-FU is recommended for patients with poor general conditions (ECOG 2 or worse) (92).

#### *2.1.6.3. (Chemo-)Radiation*

Within therapy for PDAC, radiochemotherapy plays a tangential role. So far, randomized controlled studies showed no benefit for chemoradiation in adjuvant therapy. However, most studies showed deficits according to the study design, the study power for pancreatic cancer patients, or deficits due to a deviation from the technical standard of radiotherapy (93, 94).

In palliative situations, radiochemotherapy with capecitabine has been shown to have no survival benefit over chemotherapy with gemcitabine (+ erlotinib) after induction therapy with gemcitabine (+ erlotinib). However, radiochemotherapy gained better tumor control with prolonged progression-free survival and can be considered in patients with good to poor general conditions (ECOG 0-2) (95). Capecitabin is superior to gemcitabine as an agent of radiochemotherapy according to mOS, progression-free survival, and toxicity levels (96). Stereotactic body radiotherapy (SBRT) along with chemotherapy is a further option for unresected pancreatic cancer and has been shown to increase mOS in comparison to chemotherapy alone (97). However, randomized-controlled trials are missing to prove the benefit.

#### *2.1.6.4. Other Therapeutic Agents*

According to the pathogenesis of pancreatic cancer with its underlying mutations, multiple investigations have been initiated to evaluate the efficacy of targeted therapies. For instance, the EGFR-receptor inhibitor erlotinib has been shown to increase mOS in combination with gemcitabine in locally advanced and metastatic pancreatic cancer (84). A meta-analysis by

Ciliberto et al. demonstrated a survival benefit for at most EGFR-receptor inhibitors. Other targeted therapy agents, such as sorafenib (multi-kinase inhibitor), aflibercept or bevacizumab (VEGF-receptor inhibitor), or trametinib (MEK-inhibitor) did not lead to significant survival benefits (98). An exception is the JAK1/JAK2-inhibitor Ruxolitinib which plays a role within the Jak/Stat-inflammatory pathway. This agent led to a survival benefit in PDAC patients with elevated CRP (C-reactive protein) in a randomized phase-II trial (99). Phase-III trials are expected soon (100).

The checkpoint-inhibitor pembrolizumab (PD-L1-inhibitor) is an off-label therapy option if first- and second-line therapies have failed (92). So far, few studies investigating the effectiveness of pembrolizumab in metastatic pancreatic cancer exist and case numbers are small. Nevertheless, complete remissions have been described (101). The condition for the effectiveness of pembrolizumab is a mismatch repair deficiency or high microsatellite instability, which occurs in about one percent of pancreatic cancer patients (101, 102). However, pancreatic tumor stroma is not characterized by effector T-lymphocyte infiltrations. Thus, it is known as non-immunogenic cancer. That is why checkpoint-inhibitors that mainly work by blocking the inhibitory checkpoints of t-lymphocytes are not expected to gain importance in the therapy of pancreatic cancer (100).

Different approaches for new therapy strategies exist. Hedgehog-signaling inhibitors aim to deplete stromal tissue, that surrounds the pancreatic tumor and builds a physical barrier against chemotherapy agents. However, a randomized phase-II study that has been conducted to investigate the effectiveness of these agents resulted in worsened survival. Some further agents change the stromal structure of pancreatic cancer in different ways. However, phase-II trials are not completed or even started yet (100).

#### 2.1.7. Neoadjuvant Therapy as a new Approach in LAPC / The Scientific Issue

Most patients with PDAC are diagnosed in a locally advanced or metastasized, and thus, a non-resectable stage. However, intensified chemotherapy protocols like FOLFIRINOX and gemcitabine with nab-paclitaxel have not only reached increased mOS, but also high remission rates that allow the possibility for a secondary resection. For instance, up to 50 % of patients diagnosed with LAPC or metastasized pancreatic cancer underwent secondary resection in a study by Hackert et al. The OS of resected patients was significantly increased (mOS 15.3 months) in comparison to patients who received chemotherapy alone (mOS 8.5 months). Most patients in this study received chemoradiation with gemcitabine as a neoadjuvant treatment

option. Further treatment protocols were FOLFIRINOX or other combination regimens excluding FOLFIRINOX. However, the highest resection rate was achieved by the FOLFIRINOX-protocol (60.8 %) (103). The rate for partial remission with the gemcitabine and nab-paclitaxel protocol is described at 30 % in metastatic PDAC. Furthermore, this therapy protocol reaches a secondary resection rate of 35.9 % and thus, is suitable as an induction therapy protocol as well (83, 104). However, no randomized controlled trials exist that compare FOLFIRINOX and gemcitabine/nab-paclitaxel.

Despite the henceforth existing possibility for secondary resection, the question arises whether all patients benefit from this intensified therapy. Some patients suffer from early recurrence even though R0-resection was achieved. Other patients suffer from physical degeneration due to the straining procedures that were performed. Not all secondary resected patients gain prolonged survival. Therefore, it is important to select the right patients that benefit from this approach. So far, some retrospective studies have been performed to identify prognostic factors that predict resectability and long-term benefit (105, 106). However, few factors have been identified and no randomized controlled studies exist that prove their practicability. Nevertheless, it is difficult to design prospective trials to answer those questions because of the comparatively small number of patients to be included and possibly high number of patients that do not reach secondary resectability. Therefore, we need to collect data from multiple cancer centers to combine our experiences and knowledge to find answers.

To support the establishment of prognostic factors that predict long-term benefit, we conducted a retrospective analysis of patients with primarily not resectable PDAC who received neoadjuvant chemotherapy and were subsequently resected at our Charité Pancreatic Cancer Center. We focused on factors that have been described to predict resectability and outcome, such as CA 19-9 and ECOG. Further variables have been analyzed to increase the pool of possible predictive factors and improve therapy in PDAC.

## 2.2. Methods

### 2.2.1. Inclusion Criteria

The Comprehensive Cancer Center of Charité – Universitätsmedizin Berlin database was searched to identify suitable patients for this investigation. The main inclusion criterion was the presence of a primarily not resectable adenocarcinoma of the pancreatic gland confirmed by biopsy. In addition, patients had to have received chemotherapy before resection, either palliative intended or as induction therapy. The number of applied cycles and the regimen did not

influence the inclusion of patients. Other tumor subtypes, such as duodenal, periampullary, or neuroendocrine tumors, were excluded from further analysis. The carcinoma was defined as not resectable if anatomical signs of BRPC, LAPC, or distant metastases were detected according to the NCCN guidelines. Diagnosis of primarily unresectable PDAC was confirmed by CT or MRI imaging or, if preoperative radiology underestimated tumor extent, during surgical exploration. Additional radiotherapy did not serve as exclusion criteria either. The chemotherapy was either conducted inpatient or outpatient by our clinic or by specialized external oncologists. Overall, 40 patients fitting the named inclusion criteria and undergoing secondary resection between March 2017 and May 2019 were identified and analyzed. Every patient was discussed in our interdisciplinary tumor conference pre-and postoperatively to determine therapy procedures.

#### 2.2.2. Data Collection

The data were collected consecutively within the clinical information system *SAP*® (Walldorf, Germany) and the Gießener Tumordokumentationssystem (GTDS, Gießen, Germany). Subsequently, they were transferred to a digital data table in a pseudonymized form and were analyzed retrospectively. All medical interventions were performed within the medical standard of care. No more data, as recommended by guidelines, were collected. For named reasons, the ethics committee vote was waived. All patients agreed to the storage of medical data in the clinic's system by a treatment contract.

#### 2.2.3. Analyzed Variables and Definitions

Following characteristics were analyzed: preoperative factors such as age at the time of surgery, the ECOG- Performance status, the BMI of the patients before and after neoadjuvant therapy, the characteristics and side effects of neoadjuvant therapy, and the course of tumor markers CA 19-9 and CEA (Carcinoembryonic Antigen) during therapy. Additionally, operative and postoperative factors were analyzed, such as the surgical procedure, operative and postoperative complications, and histopathological characteristics.

Side effects during neoadjuvant therapy were classified according to the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). CT scans or MRIs were used for staging and restaging. The radiographic response of the tumor during neoadjuvant therapy was categorized according to the RECIST-criteria 1.1 (Response Evaluation Criteria in Solid Tumors) by different radiologists as follows: "Complete response (CR): Disappearance of all target lesions (…). Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions (…). Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions

(…). Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease" (107).

#### 2.2.4. Statistical Analysis

OS times were calculated and related to the different patients` characteristics to identify factors that may have predicted which patients benefited from the multimodal concept consisting of neoadjuvant therapy and secondary resection. The program SPSS version 26 (IBM, Armonk, United States) was used for the statistical analysis. Log-rank tests were used for survival analyses. Hazard ratios (HR) were prepared for significant results. OS times were calculated from diagnosis to the date of death or the last documented contact with the patient. The latter were defined as "lost to follow up" and were censored. Reasons for death were irrelevant for statistical analysis. The Fisher exact test was used to calculate the dependency of the grade of side effects on the chosen chemotherapy protocol and the dependency of complications on the surgical procedure. To assess the influence of age, ECOG performance status, and BMI of the patients before treatment on the choice of the neoadjuvant chemotherapy protocol, we conducted a Kruskal-Wallis test. A one-way ANOVA was performed if the distribution for each group was normal and if the variance was homogeneous (Levene's test, $p > 0.05$). The t-test or the Wilcoxon-test were used depending on the distribution of the variables to compare ECOG performance status, tumor markers, and T- and N-status of the patients at the time of diagnosis to the time after neoadjuvant therapy. The variables are normally distributed with $p > 0.05$. Two-sided p-values were calculated and were significant with $p < 0.05$. Patients with missing values were not included in the calculation.

#### 2.2.5. Publication

Our group published the results of this investigation in the special issue "Current Progress in the Multidisciplinary Treatment for Pancreatic Cancer" of the journal „Medicina" on 18th January 2021 (108).

### 2.3. Results

#### 2.3.1. Patients` Characteristics

Forty patients (22 men and 18 women) who fulfilled the inclusion criteria were identified within March 2017 to May 2019. The mean age at the time of surgery was 61 years (range from 37 to 82 years). Information about ECOG analyses before treatment was available in 33 patients. Most patients had an ECOG of 0 (22 patients, 66.7 %) or 1 (10 patients, 30.3 %) before the initiation of chemotherapy. Only one patient (3 %) had an ECOG of 2. The ASA (American Society of

Anesthesiologists) score was evaluated before the surgical resection. Information about 35 patients were available. Most patients had mild (ASA 2, 15 patients, 42.9 %) or severe systemic diseases (ASA 3, 18 patients, 51.4 %). Two patients (5.7 %) had no relevant comorbidities (ASA 1). Pre-therapeutic information about the BMI was available for 27 patients. The median BMI was 23.9 kg/m² (range from 17.2 to 28.7 kg/m²). Eighteen patients (66.7 %) had a normal BMI (18.5–25 kg/m²), eight patients (29.6 %) were overweight (25.1–30 kg/m²), and one patient (3.7 %) was underweight (< 18.5 kg/m²). A CT scan, MRI, or surgical exploration offered reasons for primary irresectability. In 21 cases (52.5 %), the tumor was located at the head of the pancreas.

**Table 2.** Patient Characteristics at Diagnosis and after Neoadjuvant Therapy. Source: based on Rosumeck et al., 2021, page 4 (34)

| **Baseline Characteristics (n=40)** | | | | | |
|---|---|---|---|---|---|
| **Age** | Mean: 60.6 [37-82] years | | | | |
| **Gender** | ♂ 22 patients (55.0 %), ♀ 18 patients (45.0 %) | | | | |
| **Primary Localization** | Head: 21 (52.5 %) patients,<br>Body: 13 (32.5 %) patients,<br>Tail: 6 (15 %) patients | | | | |
| | **At Diagnosis** | | **After Induction/ Before Resection** | | |
| | **N** | **%** | **N** | **%** | ***p*** |
| **ECOG** | | | | | |
| **0** | 22 | 66.7 | 10 | 37 | |
| **1** | 10 | 30.3 | 12 | 44.4 | 0.003 |
| **2** | 1 | 3 | 5 | 18.5 | |
| **n.a.** | 7 | | 13 | | |
| **ASA Score** | | | | | |
| **1** | | | 2 | 5.7 | |
| **2** | | | 15 | 42.9 | |
| **3** | | | 18 | 51.4 | |
| **n.a.** | | | 5 | | |
| **BMI [kg/m²]** | Median 23.9 [range 17.2 - 28.7] | | Median 22.6 [range 16.8 - 29.9] | | |
| **< 18.5** | 1 | 3.7 | 1 | 2.9 | |
| **18.5 – 24.9** | 18 | 66.7 | 23 | 67.6 | 0.25 |
| **≥ 25** | 8 | 29.6 | 10 | 29.4 | |
| **n.a.** | 13 | | 6 | | |

n.a.—not available, BMI—body mass Index, ASA—American Society of Anesthesiologists, ECOG—Eastern Cooperative Oncology Group.

In 13 cases (32.5 %), it was located at the body, and in six cases (15 %), it was located at the tail of the pancreas (Table 2). Information about reasons for irresectability was available for 37

patients. In 29 cases (78.4 %), vessel encasement or infiltration was the reason for irresectability. In 8 cases (21.6 %), distant metastases led to a palliative therapy concept at first.

### 2.3.2. Neoadjuvant Treatment and Side Effects

Induction therapy with FOLFIRINOX was performed in 23 cases (57.5 %). One of them de-escalated therapy to gemcitabine mono due to side effects after four applications. Nab-paclitaxel and gemcitabine were applied in seven cases (17.5 %). Two external patients received gemcitabine mono or cisplatin/capecitabine. A change of induction therapy between FOLFIRINOX and nab-paclitaxel/gemcitabine was performed in eight patients (20 %). Four of these patients suffered from severe toxicity during induction therapy. Consequently, the therapy protocol was switched from FOLFIRINOX to gemcitabine/nab-paclitaxel. In one patient, the switch was administered when a significant increase of the tumor marker CA 19-9 suggested a progression of the disease. A clinical investigation planned a change from nab-paclitaxel/gemcitabine to FOLFIRINOX in two patients (Table 3).

**Table 3.** Therapeutic Characteristics. Source: based on Rosumeck et al., 2021, page 5 (34)

| Parameter | Category | N | % |
|---|---|---|---|
| **Induction Therapy** | | | |
| | FOLFIRINOX | 23 | 57.5 |
| | Nab-Paclitaxel/Gemcitabine | 7 | 17.5 |
| | FOLFIRINOX ► Nab-Pac/Gem | 8 | 20 |
| | Gemcitabine mono | 1 | 2.5 |
| | Cisplatin/Capecitabine | 1 | 2.5 |
| **Number of Cycles** | | | |
| | Median | 6 (1 – 25) | |
| | > 3 Cycles | 30 | 76.9 |
| | ≤ 3 Cycles | 9 | 23.1 |
| | n.a. | 1 | |
| **Duration of neoadjuvant Therapy** | | | |
| | Median (months) | 3 (1 – 24) | |
| | > 3 months | 18 | 48.6 |
| | ≤ 3 months | 19 | 51.4 |
| | n.a. | 3 | |
| **Adjuvant Therapy** | | | |
| | Yes | 15 | 75 |
| | No | 5 | 25 |
| | n.a. | 20 | |
| **Surgical Procedure** | | | |
| | PPPD | 16 | 40 |
| | Whipple´s Procedure | 2 | 5 |
| | Distal pancreatectomy | 13 | 32.5 |
| | Total pancreatectomy | 9 | 22.5 |

| Parameter | Category | N | % |
|---|---|---|---|
| **Additional Resection** | | | |
| | Splenectomy | 19 | 47.5 |
| | Gastrectomy (total/partial) | 2 | 5 |
| | Partial hepatectomy | 3 | 7.5 |
| | Resection of portal vein | 7 | 17.5 |
| | Resection coeliac axis | 4 | 10 |
| | Hemicolectomy | 1 | 2.5 |
| | Nephrectomy | 1 | 2.5 |
| **Post Op-Complications** | | 26 | 65 |
| | BDA-Insufficiency | 5 | 12.5 |
| | Pancreatic fistula | 9 | 22.5 |
| | Postpancreatectomy haemorrhages | 1 | 2.5 |
| | Postoperative Infections and Wound Healing Disorder | 11 | 27.5 |

n.a.—not available, PPPD—Pylorus-Preserving Pancreaticoduodenectomy, BDA—Biliodigestive Anastomosis, Nab-Pac/Gem—Nab-Paclitaxel/Gemcitabine.

A median number of eight applications was administered. It ranged from three to 25. A median number of six cycles was administered, ranging from one to 25 (one cycle of nab-paclitaxel/gemcitabine consisting of three applications within 28 days, one cycle of FOLFIRINOX consisting of one application once every two weeks, one cycle of gemcitabine mono consisting of three applications within 28 days, one cycle of cisplatin/capecitabine consisting of one cisplatin application once every 22 days). The median duration of neoadjuvant therapy was three months, ranging from one to 24 months (Table 3). There was no significant difference in the age of patients at the time of surgery comparing the groups of neoadjuvant chemotherapy protocols ($x^2 = 5.91$, $p = 0.12$). There was no difference in between the groups depending on the ECOG status ($x^2 = 2.29$, $p = 0.52$) or BMI at the time of diagnosis ($F(2, 24) = 0.81$, $p = 0.46$). The protocol groups showed a significant difference in the number of applied cycles ($x^2 = 11.72$, $p = 0.008$). Patients being treated with FOLFIRINOX received a higher number of cycles than patients being treated with gemcitabine/nab-paclitaxel ($z = 2.87$, $p = 0.025$). There was no difference in the duration of neoadjuvant treatment ($x^2 = 3.11$, $p = 0.38$).

Information about side effects was available for 31 patients. Sixteen patients (51.6 %) suffered from side effects of grades 3 to 4. Patients who underwent a switch from FOLFIRINOX to nab-paclitaxel/gemcitabine or the other way around suffered significantly more often from severe side effects (grade 3 to 4) ($x^2 = 8.48$, $p = 0.007$, $\varphi = -0.52$). There were no other significant differences in the type of side effects depending on the performed induction therapy (Table 4).

**Table 4.** Side Effects during Induction Therapy. Source: based on Rosumeck et al., 2021, page 6 (34)

| | | Total | | FOLFIRINOX | | Nab-Pac/Gem | | FOLFIRINOX ►Nab-Pac/Gem | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Category** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | |
| **General Side Effects** | | | | 19 | | 5 | | 7 | | |
| | 0-2 | 15 | 48.5 | 12 | 63.2 | 3 | 60 | 0 | 0 | 0.009 |
| | 3-4 | 16 | 51.6 | 7 | 36.8 | 2 | 40 | 7 | 100 | |
| **Neutropenia** | | | | 15 | | 5 | | 7 | | |
| | 0-2 | 16 | 59.3 | 11 | 73.3 | 3 | 60 | 2 | 28.6 | 0.16 |
| | 3-4 | 11 | 40.7 | 4 | 26.7 | 2 | 40 | 5 | 71.4 | |
| **Anemia** | | | | 17 | | 5 | | 8 | | |
| | 0-2 | 26 | 86.7 | 15 | 88.2 | 4 | 80 | 7 | 87.5 | 1 |
| | 3-4 | 4 | 13.3 | 2 | 11.8 | 1 | 20 | 1 | 12.5 | |
| **Thrombopenia** | | | | 9 | | 3 | | 4 | | |
| | 0-2 | 15 | 93.8 | 8 | 88.9 | 3 | 100 | 4 | 100 | 1 |
| | 3-4 | 1 | 6.3 | 1 | 11.1 | 0 | 0 | 0 | 0 | |
| **Infections** | | | | 16 | | 4 | | 7 | | |
| | 0-2 | 24 | 88.9 | 15 | 93.8 | 4 | 100 | 5 | 71.4 | 0.2 |
| | 3-4 | 3 | 7.5 | 1 | 6.2 | 0 | 0 | 2 | 28.6 | |
| **Diarrhea** | | | | 4 | | 1 | | 3 | | |
| | 0-2 | 5 | 62.5 | 3 | 75 | 1 | 100 | 1 | 33.3 | 0.68 |
| | 3-4 | 3 | 37.5 | 1 | 25 | 0 | 0 | 2 | 66.7 | |
| **Nausea** | | | | 6 | | 3 | | 6 | | |
| | 0-2 | 15 | 93.8 | 6 | 100 | 2 | 66.7 | 5 | 83.3 | 0.66 |
| | 3-4 | 2 | 13.3 | 0 | 0 | 1 | 33.3 | 1 | 16.7 | |
| **Neurological Side Effects** | | | | 10 | | 3 | | 3 | | |
| | 0-2 | 13 | 81.3 | 7 | 70 | 3 | 100 | 3 | 100 | 0.52 |
| | 3-4 | 3 | 18.8 | 3 | 30 | 0 | 0 | 0 | 0 | |

Nab-Pac/Gem—Nab-Paclitaxel/Gemcitabine.

### 2.3.3. Surgical Procedure and Complications

The surgical procedure was chosen depending on the localization of the tumor and the extent of infiltration. In 16 cases (40 %), a pylorus-preserving pancreaticoduodenectomy (PPPD) was performed. In two cases (5 %), the chosen procedure was a classical Whipple's procedure. 13 patients (32.5 %) received a distal pancreatectomy, and nine patients (22.5 %) received a total pancreatectomy. Four of the patients who underwent distal pancreatectomy received a simultaneous resection of the celiac axis (Appleby procedure). An additional splenectomy was performed in 19 cases, and seven patients received a resection and reconstruction of the portal vein. Additional organ resections were performed depending on the extent of local tumor infiltration. One patient received a hemicolectomy, one received a nephrectomy, and two received a partial or total gastrectomy. Due to distant metastasis, three patients received additional liver resection (Table 3).

The overall complication rate was 65 %, including postoperative pancreatic fistulae (POPF) in 22.5 % (nine patients), insufficiency of hepaticojejunostomy in 12.5 % (five patients), wound healing disorders or other postoperative infections in 27.5 % (eleven patients), and a postpancreatectomy hemorrhage in 2.5 % (one patient) of the cases (Table 3). The resection of the portal vein ($x^2 = 0.23$, $p = 0.68$) or coeliac axis ($x^2 = 0.44$, $p = 0.60$) was not associated with higher complication rates. The rate of overall complications did not differ depending on the performed surgical procedure ($x^2 = 1.37$, $p = 0.78$). There was no impact on the performance of an adjuvant therapy depending on surgical complications either ($x^2 = 1.37$, $p = 0.37$).

#### 2.3.4. Effect of Preoperative Therapy

During neoadjuvant therapy the ECOG performance status worsened significantly ($z = -2.97$, $p = 0.003$, $r = 0.57$). The number of patients with an ECOG status of 2 increased from one patient (3 %) to five patients (18.5 %), the number of patients with an ECOG status of 1 increased from ten patients (30.3 %) to twelve patients (44.4 %) and the number of patients with an ECOG status of 0 decreased from 22 patients (66.7 %) to ten patients (37 %). The BMI of the patients was stable during neoadjuvant therapy (mean BMI at diagnosis: 23.40 kg/m², 95 % CI = 22.17 – 24.63 kg/m²; mean BMI after neoadjuvant therapy: 23.06 kg/m², 95 % CI = 21.95 – 24.17; $t(99) = 1.17$, $p = 0.25$) (Table 2). Ten patients (37 %) suffered from weight loss of more than five percent.

A significant decline of CA 19-9 was registered during neoadjuvant therapy. The mean value of the tumor marker decreased from 4358.3 U/ml (95 % CI = -3251.33 – 11967.98 U/ml) at the time of diagnosis to 138.5 U/ml (95 % CI = 11.71 – 265.29 U/ml) after neoadjuvant therapy ($z = -4.008$, $p < 0.001$, $r = 0.76$). On average, the CA 19-9 values decreased by 44.7 % (95 % CI = -0.77 – (-0.12)). Furthermore, the mean value of the tumor marker CEA dropped during neoadjuvant therapy from 10.55 µg/L (95 % CI = 1.08 – 20.02 µg/L) at the time of diagnosis to 3.53 µg/L (95 % CI = 2.65 – 4.41 µg/L) after neoadjuvant therapy. However, this decline was not significant ($z = -1.42$, $p = 0.16$) (Table 5).

Information about the radiographic response measured by RECIST-criteria was available for 37 patients. Partial response after neoadjuvant therapy was seen in 27 patients (73 %). The disease was stable in eight patients (21.6 %). Radiographic signs for a progressive disease were seen in two patients (5.4 %). Complete radiographic remission was not achieved by any patient, whereas the histopathological analysis showed the absence of malignant cells (ypT0) in five patients (12.5 %). Eight patients (20 %) had a ypT1-stage, eleven patients (27.5 %) had a ypT2-stage

[cT2 in three patients (8.1 %) before neoadjuvant therapy], ten patients (25 %) had a ypT-stage of 3 [cT3 in 14 patients (37.8 %) before neoadjuvant therapy] and six patients (15 %) still had a ypT- stage of 4 [cT4 in 20 patients (54.1 %) before neoadjuvant therapy]. Consequently, neoadjuvant therapy led to a significant decline of the T-stage ($z = -4.33$, $p < 0.001$, $r = 0.71$) (Table 5).

While distant metastases were present in eight patients at the time of diagnosis, five patients remained to have metastases after neoadjuvant therapy. Nineteen patients (47.5 %) were nodal positive. R0-resection was achieved in 18 patients (46.2 %) (Table 5). Six of them had a margin clearance of at least one millimeter. Information about the margin clearance was missing from four patients.

**Table 5.** Clinical-Pathological Characteristics. Source: based on Rosumeck et al., 2021, page 7 (34)

| | | At Diagnosis | | | | After Induction Therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Category** | **N** | **%** | **Mean** | **IQR** | **N** | **%** | **Mean** | **IQR** | ***p*** |
| CA 19-9 (U/ml) | | | | 4358.3 | 64.8 - 830 | | | 138.5 | 12.1 – 65.4 | |
| | ≤ 37<br>37 – 400<br>> 400<br>n.a. | 5<br>14<br>12<br>9 | 16.1<br>45.2<br>38.7 | | | 15<br>17<br>2<br>6 | 44.1<br>50<br>5.9 | | | 0.001 |
| CA 19-9 Course | | | | | | | | | | |
| (-%) | | 29 | | 44.7 | 18 – 94.75 | | | | | |
| CEA (ng/ml) | | | | 10.6 | 2.5 - 7 | | | 3.5 | 2 – 5.3 | |
| | ≤ 5<br>> 5<br>n.a. | 15<br>8<br>17 | 65.2<br>34.8 | | | 18<br>8<br>14 | 69.2<br>30.8 | | | 0.16 |
| c/pT-Status | | | | | | | | | | |
| | 0<br>1<br>2<br>3<br>4<br>n.a. | 0<br>0<br>3<br>14<br>20<br>3 | 0<br>0<br>8.1<br>37.8<br>54.1 | | | 5<br>8<br>11<br>10<br>6<br>0 | 12.5<br>20<br>27.5<br>25<br>15 | | | 0.001 |
| pN-Status | | | | | | | | | | |
| | 0<br>1 | | | | | 21<br>19 | 52.5<br>47.5 | | | |
| c/pM-Status | | | | | | | | | | |
| | 0<br>1<br>n.a. | 30<br>8<br>2 | 78.9<br>21.1 | | | 35<br>5<br>0 | 87.5<br>12.5 | | | 0.18 |

| | | At Diagnosis | | | | After Induction Therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Category** | **N** | **%** | **Mean** | **IQR** | **N** | **%** | **Mean** | **IQR** | ***p*** |
| R-Status | | | | | | | | | | |
| | 0 | | | | | 18 | 46.2 | | | |
| | 1 | | | | | 21 | 53.8 | | | |
| | n.a. | | | | | 1 | | | | |
| Response | | | | | | | | | | |
| | Partial | | | | | 27 | 73 | | | |
| | Stable | | | | | 8 | 21.6 | | | |
| | Progressive | | | | | 2 | 5.4 | | | |
| | n.a. | | | | | 3 | | | | |

n.a.—not available, c/pT—clinical/histopathological tumor expansion, pN—histopathological nodal status, c/pM—clinical/histopathological distant metastasis, R—residual tumor, CA 19-9—carbohydrate-antigen 19-9, CEA—Carcinoembryonic antigen.

Infiltration of the lymphatic vessels was present in five patients (12.5 %). From one patient, the information about lymphatic vessel infiltration was missing. An infiltration of venous vessels was present in four patients (10 %). Information about perineural invasion was not available in three cases. Twenty-nine of the remaining 37 patients (72.5 %) had a perineural invasion.

### 2.3.5. Overall Survival

The median observation time was 19.5 months. Patients had a mOS of 20 months from the time of diagnosis (95 % CI: 17.2–22.9 months, range from four months to 56 months) and 17 months from the time of resection (95 % CI: 11.6–22.4, range from less than one month to 44 months). The 2-year survival rate was 41.2 % (+/- 8.2 %). Nine patients (22.5 %) were lost to follow up and censored.

### 2.3.6. Predictors of Overall Survival

#### *2.3.6.1. Pretherapeutic Factors*

One pretherapeutic factor positively influenced the OS. Patients with a normal CA 19-9 level (< 37 U/ml) at the time of diagnosis profited with a significantly increased mOS (29 months vs. 19 months, $p = 0.02$; HR = 3.44, 95 % CI = 1.14 – 10.36, $p = 0.03$). A normal CEA value (< 5 ng/ml vs. ≥ 5 ng/ml) at the time of diagnosis had no impact on the survival of the patients ($p = 0.33$). Furthermore, neither a normal pretherapeutic BMI (> 25 kg/m² vs. ≤ 25 kg/m², $p = 0.91$) nor the ECOG performance status at the time of diagnosis (0 vs. > 0, $p = 0.75$), nor the presence of distant metastases had a significant impact. Patients with distant metastases controversially showed a longer mOS compared to non-metastatic patients (24 months vs. 20 months, $p = 0.35$). However, this result was statistically not significant.

#### *2.3.6.2. Presurgical Factors*

The tumor marker CA 19-9 and CEA, as well as the BMI of the patients after neoadjuvant therapy had a significant impact on the OS of the patients. If CA 19-9 values were normalized

after neoadjuvant therapy, patients were more likely to have a better mOS (26 vs. 18 months, $p$ = 0.04; HR = 2.23, 95 % CI = 0.99 – 5.03, $p$ = 0.05). Furthermore, if CA 19-9 values did not fall below 400 U/ml during neoadjuvant therapy, patients had a significant shorter mOS (7 months vs. 24 months, $p$ = 0.001; HR = 17.2, 95 % CI = 2.38 – 124.45, $p$ = 0.005). There was no impact of the degree of decline on the OS (exemplary ≥ 75 % vs. < 75 %, $p$ = 0.41). However, if CA 19-9 values dropped by more than 90 %, patients were more likely to have tumor free resection margins ($x^2$ = 4.49, $p$ = 0.034). Furthermore, patients with a normal CEA level after neoadjuvant therapy had a prolonged mOS (25 months vs. 18 months, $p$ = 0.047; HR = 2.67, 95 % CI = 0.96 – 7.48, $p$ = 0.06).

Patients with a normal or an underweight BMI after neoadjuvant therapy had a significantly prolonged OS in comparison to patients who were overweight (≤ 25 vs. > 25 kg/m², mOS 24 vs. 15 months, $p$ = 0.01; HR = 0.36, 95 % CI = 0.15 - 0.83, $p$ = 0.02). There was no significant influence of the ECOG performance status (ECOG 0 vs. ECOG > 0, $p$ = 0.75), the ASA-score (< 3 vs. ≥ 3, $p$ = 0.49) after neoadjuvant therapy or the age of the patients at the time of surgery (≤ 60 vs. > 60 years, $p$ = 0.3). There was no impact of the degree of weight loss during neoadjuvant therapy on the OS (exemplary < 5% vs. ≥ 5 %, $p$ = 0.45). Patients who showed radiographical signs for partial remission during neoadjuvant therapy had no survival advantages over patients with stable or progressive disease ($p$ = 0.82).

*2.3.6.3. Therapeutical Factors*

Patients who received more than three cycles of neoadjuvant chemotherapy had a significantly prolonged mOS (≤ 3 cycles vs. > 3 cycles, 18 months vs. 24 months, $p$ = 0.02; HR = 0.38, 95 % CI = 0.16 – 0.88, $p$ = 0.02). Furthermore, there was a correlation between the application of more than three cycles and the probability of achieving a normal CA 19-9 level after neoadjuvant therapy ($x^2$ = 5.061, $p$ = 0.041). Additionally, the application of more than four (mOS 26 months vs. 18 months, $p$ = 0.02; HR = 0.4, 95 % CI = 0.17 – 0.92, $p$ = 0.03) or five cycles (mOS 26 months vs. 18 months, $p$ = 0.006; HR = 0.34, 95 % CI = 0.15 – 0.78, $p$ = 0.01) led to a better outcome of the patients as well. However, there was no benefit if the patients received more than six cycles ($p$ = 0.61). The duration of the period in which the neoadjuvant therapy was applied had no significant influence on the outcome of the patients (exemplary ≤ 3 months vs. > 3 months, $p$ = 0.89). Furthermore, the chosen neoadjuvant chemotherapy protocol had no significant influence on the OS of the patients (FOLFIRINOX vs. other, $p$ = 0.88; nab-paclitaxel/gemcitabine vs. other, $p$ = 0.54; FOLFIRINOX ► nab-pac/gem vs. other, $p$ = 0.22). Patients who received FOLFIRINOX had a mOS of 20 months (95 % CI = 13.6 – 26.4 months)

as well as the patients who received gemcitabine/nab-paclitaxel (95 % CI = 17.4 – 22.6 months). Patients who received both protocols sequentially had a mOS of 18 months (95 % CI = 0 – 53.1 months).

Patients who received an adjuvant chemotherapy had a significantly prolonged mOS (25 months vs. 10 months, $p = 0.001$; HR = 0.21, 95 % CI = 0.08 – 0.55, $p = 0.002$). The performance of an appleby procedure ($p = 0.11$) or the resection of the portal vein ($p = 0.42$) as well as the presence of postoperative complications ($p = 0.63$) had no negative impact on the survival of the patients.

#### *2.3.6.4. Histopathological Factors*

Nodal negativity after neoadjuvant therapy leads to a significant survival advantage (mOS 25 months vs. 15 months, $p = 0.003$, HR = 2.99, 95 % CI = 1.39 – 6.41, $p = 0.005$). Furthermore, patients with a ypT-stage of less than 2 had a significantly prolonged mOS (43 months, vs. 19 months, $p = 0.008$, HR = 3.09, 95 % CI = 1.26 – 7.62, $p = 0.01$). In five patients the histopathological examination showed the absence of malignant cells. Thus, those patients seemed to have been cured by neoadjuvant chemotherapy. However, those patients did not have a significant survival benefit over patients with remaining malignant cells (ypT0: mOS = 43 months, ypT1-4: mOS = 20 months, $p = 0.22$).

In six patients, there was a persistent suspicion of distant metastases of the liver after neoadjuvant therapy. Consequently, partial liver resection was performed in three of those patients. In one case, no malignant cells were detected. The five remaining patients with proven or suspected distant metastases had no survival disadvantage (yM0: mOS = 20 months, yM1: mOS = 35 months, $p = 0.67$; mOS from the time of resection: yM0 = 16 months, yM1 = 21 months, $p = 0.66$). There was no survival disadvantage for those three patients whose metastases were not resected (not resected metastasis: mOS = 35 months, resected metastasis or M0: mOS = 20 months, $p = 0.65$).

Patients without perineural invasion trend towards prolonged OS without statistical significance (mOS  35 months vs. 19 months, $p = 0.06$; HR = 2.46, 95 % CI = 0.92 – 6.56, $p = 0.07$). There was no impact of a lymphatic or vessel invasion on the OS ($p = 0.12$ and $p = 0.33$). A tumor free resection margin (R0) did not lead to a survival advantage ($p = 0.7$). However, if the clearance of the resection margin was at least one millimeter, patients profited from a significantly prolonged mOS (R0 with margin clearance of ≥ 1mm vs. R1 or resection margin < 1mm, 43 months vs. 20 months, $p = 0.048$, HR = 2.79, 95 % CI = 0.95 – 8.18, $p = 0.06$). Patients without information about the margin clearance were valued as R1/resection margin < 1mm (Table 6).

**Table 6.** Impact Factors on Overall Survival. Source: based on Rosumeck et al., 2021, page 8 (34)

| Parameter | Category | OS (months) | *p* | HR | 95%CI | *p* |
|---|---|---|---|---|---|---|
| **CA 19-9 at Diagnosis** | ≤ 37 vs. > 37 U/ml | 29 vs. 19 | 0.02 | 3.44 | 1.14 – 10.36 | 0.03 |
| **CA 19-9 after Induction** | ≤ 37 vs. > 37 U/ml | 26 vs. 18 | 0.04 | 2.23 | 0.99 – 5.03 | 0.05 |
| | < 400 vs. ≥ 400 U/ml | 24 vs. 7 | 0.001 | 17.2 | 2.38 – 124.45 | 0.005 |
| **CEA after Induction** | ≤ 5 vs. > 5 ng/ml | 25 vs. 18 | 0.047 | 2.67 | 0.96 – 7.48 | 0.06 |
| **BMI after Induction** | > 25 vs ≤ 25 | 15 vs. 24 | 0.01 | 0.36 | 0.15 – 0.83 | 0.02 |
| **pN-status** | 0 vs. 1 | 25 vs. 15 | 0.003 | 2.99 | 1.39 – 6.41 | 0.005 |
| **pT-status** | 0 – 1 vs. 2 - 4 | 43 vs. 19 | 0.008 | 3.09 | 1.26 – 7.62 | 0.01 |
| **Pn** | 0 vs. 1 | 35 vs. 19 | 0.06 | 2.46 | 0.92 – 6.56 | 0.07 |
| **Resection Margin Clearance** | R0 vs. R1-2 | 19 vs. 20 | 0.7 | 1.16 | 0.55 – 2.44 | 0.71 |
| | ≥ 1 mm vs. < 1mm | 43 vs. 20 | 0.048 | 2.79 | 0.95 – 8.18 | 0.06 |
| **Neoadjuvant Protocol** | FOLFIRINOX vs. other | 20 vs. 20 | 0.88 | 0.95 | 0.46 – 1.97 | 0.89 |
| | Nab-Pac/Gem vs. other | 20 vs. 20 | 0.54 | 0.77 | 0.33 – 1.81 | 0.55 |
| | FOLFIRINOX ► Nab-Pac/Gem vs. other | 18 vs. 20 | 0.22 | 1.86 | 0.68 – 5.11 | 0.23 |
| **Number of neoadjuvant Cycles** | ≤ 3 vs. > 3 | 18 vs. 24 | 0.02 | 0.38 | 0.16 – 0.88 | 0.02 |
| | ≤ 5 vs. > 5 | 18 vs. 26 | 0.006 | 0.34 | 0.15 – 0.78 | 0.01 |
| **Adjuvant Therapy** | no adjuvant therapy vs. adjuvant therapy | 10 vs. 25 | 0.001 | 0.21 | 0.08 – 0.55 | 0.002 |

CA 19-9—carbohydrate-antigen 19-9, CEA—Carcinoembryonic antigen, BMI—body mass index, pN—histopathological nodal status, pT—histopathological tumor expansion, Pn—perineural invasion, Nab-Pac/Gem—Nab-Paclitaxel/Gemcitabine.

## 2.4. Discussion

### 2.4.1. Factors that Predict the Benefit of a Secondary Resection

The main aims of neoadjuvant therapy in BRPC and LAPC are to minimize local recurrences by increased R0-resection rates on the one hand and on the other hand to reach long-term survival by increasing general resection rates. However, it remains uncertain which patients benefit from

this procedure. Some patients suffer from local recurrences and metastases after resection. Others achieve a similar survival time to primarily resected patients (109).

Our analysis resulted in an mOS of 4 to up to 56 months for patients who were not resected initially but responded to chemotherapy, and thus, were suitable for a secondary resection. The mOS for patients in whom a secondary resection was not feasible is described with exemplary 16.3 months (110). Consequently, secondary resection can be justified if the patient responds to the previous therapy. Not all patients seemed to have profited from this procedure. Therefore, we need to use prognostic factors to identify those benefiting patients.

#### 2.4.1.1. Nodal Status after Neoadjuvant Therapy

It is well known that nodal negativity is associated with significantly prolonged OS in a primarily resectable specimen (111). This characteristic was reproduced in our analysis with primarily not resectable pancreatic cancer. Patients with nodal negativity reached a significantly prolonged mOS of 25 months. Patients with a positive nodal status had an mOS of 15 months. As it has been proven that neoadjuvant therapy has a positive effect on nodal metastases in BRPC (112), it is reasonable to use this effect in LAPC as well. However, we should use our knowledge about the positive impact of nodal negativity for preoperative diagnostic investigations by identifying those patients with nodal metastases before resection. Based on that, we could discuss further treatment options. For instance, additional neoadjuvant radiation was shown to increase the likelihood of nodal negativity (113). Primary single-agent chemoradiation does not seem to have a survival benefit over polychemotherapy with FOLFIRINOX (103). Thus, radiation after neoadjuvant polychemotherapy and before secondary resection might be an option to improve the patients` outcome by nodal downstaging. To get to this point of drawing therapy consequences, we need to find an accurate diagnosis. However, radiographic diagnosis of the nodal status displays some fundamental flaws. CT scan is no reliable diagnostic tool to identify positive lymph nodes, as not all metastases lead to lymphadenopathy, and not all lymphadenopathies are caused by metastases. Particularly, this counts after neoadjuvant treatment when fibrotic tissue appears as vital tumor in a CT scan. Exemplary, an investigation by Diehl et al. revealed a correctly interpreted nodal status by CT scan in only 54 % of patients who have been resected subsequently (114). Moreover, PET-CT is a method that is not suitable for preoperative diagnosis as it only reaches a sensitivity of 42 % (115). Endosonographic ultrasound (EUS) with fine-needle aspiration (FNA) solely gives a nearly one hundred percent guarantee for the correct histopathology of a lymph node (116).

However, the success of an endosonographic biopsy is strongly dependent on the investigator and the localization of the pathological lymph node. Thus, the risk of false-negative results is high, and the sensitivity decreases. Exemplary, EUS, and FNA were performed in 101 patients with esophageal cancer that were treated with neoadjuvant chemoradiation and were resected subsequently. The EUS nodal staging was compared to the final histopathological examination and resulted in a sensitivity of only 50 % and a specificity of 78 %. Especially, most lymph nodes of false-negative patients were located at lymph node stations that were difficult to reach and did not fulfill the criteria for FNA (round, hypoechogenic, > 5mm). Finally, if FNA was performed, sensitivity and specificity were 100 % for biopsied lymph nodes. Consequently, the investigators recommend performing FNA generously, even in cases of low endosonographic suspicion (117). This recommendation could be used on pancreatic cancer as well. All things considered, an additional endosonographic biopsy, especially in the case of lymphadenopathy, could influence therapy decisions.

#### 2.4.1.2. Body Mass Index as an Expression of Physical Performance

The body mass index is another factor that may have prognostic relevance for pancreatic and other cancer types. It is well known that obesity is correlated with an increased risk for PDAC and a worsened outcome for those patients (118). An explanation might be the higher production of proinflammatory cytokines by fat cells, what leads to insulin resistance, and higher levels of insulin-like growth factor. This factor enhances the proliferation of cells, and thus, the development and progress of pancreatic cancer (119, 120). Moreover, obesity is associated with the development of other complications such as diabetes or cardiovascular diseases. Our analysis shows a survival advantage for patients with a not obese body mass index, including one underweight patient. In contrast, an investigation by Naumann et al. showed a significantly shorter OS for patients who suffered from weight loss of more than 5 % during induction chemoradiation (12 months vs. 27 months) (121). Thus, excessive weight loss might be a sign of high tumor activity. Furthermore, patients with a low BMI have fewer energy reserves for straining procedures such as pancreatectomy, chemotherapy and, the disease itself. Seika et al. support the thesis that both- obese and especially underweight BMI- have a negative effect on the OS. Their study investigated the effect of the BMI on the outcome of patients after pancreatectomy. Although underweight patients had fewer postoperative complications, obese patients showed lower perioperative mortality, and better long-term survival. However, this investigation did not include resection after neoadjuvant therapy and included distal cholangiocarcinoma, duodenal carcinoma and ampullary carcinoma next to PDAC (122).

#### 2.4.1.3. Number of Neoadjuvant Cycles

Another factor that positively influenced the OS of patients in our analysis was the number of applied chemotherapy cycles. Patients who received at least four and a maximum number of six cycles of neoadjuvant therapy survived significantly longer. Additionally, these patients had a higher chance for normalized CA 19-9 values after neoadjuvant therapy. Consequently, we should strive to apply a minimum number of cycles to our patients independent of radiographical or laboratory response. At the same time, we need to find the right moment to stop neoadjuvant chemotherapy before the severity of side effects exceeds the benefits. Other studies have supported the opinion that a specific number of cycles is needed to achieve a survival advantage. For example, in an investigation by Truty et al., patients had no benefit until a number of at least six cycles of FOLFIRINOX or gemcitabine/nab-paclitaxel in patients with LAPC (123). Another study by Okada et al. already showed a benefit from a number of four cycles of modified FOLFIRINOX. However, this study investigated patients with BRPC. Thus, the number of needed cycles might be smaller. Moreover, the number of investigated patients in this study was very small (124). To establish clinical guidelines for neoadjuvant treatment of initially not resectable pancreatic cancer, further investigations are necessary.

#### 2.4.1.4. CA 19-9 - The most Predictive Factor

The tumor marker CA 19-9 has an essential role in identifying suitable patients for this multimodal concept. In our investigation, patients who had a normal value before and after neoadjuvant therapy profited from the secondary resection. The decline of this marker symbolizes a good response to the previous therapy and might be an indicator for less aggressive tumor biology. Supporting this, patients who still had an elevated CA 19-9 level of more than 400 U/ml after neoadjuvant therapy had a notable shorter survival. Different studies have analyzed the OS dependent on presurgical CA 19-9 values after neoadjuvant therapy. Most of them showed that patients with a threshold value of more than 100 U/ml had a significantly shorter OS (105, 125). Therefore, a resection that is performed in such patients should be very well justified.

The extent of the decline of CA19-9 had an impact on the resection stage but not the OS. If CA 19-9 had dropped by more than 90 %, it was more likely to achieve an R0-resection. However, these patients did not reach prolonged OS. Another study supports the role of CA 19-9 concerning R0-resection rates. An investigation by Boone et al. showed that patients with BRPC

were more likely to achieve an R0-status if their CA 19-9 level had dropped by more than 50 % (126).

Furthermore, the CA 19-9 value at the time of diagnosis showed to be predictive for the outcome of the patients in our cohort. Experimental investigations showed that CA 19-9 itself functions as a factor that enhances proliferation by promoting the activation of EGFR (Epidermal Growth Factor Receptor) signaling in mice. Consequently, it might play an essential role in the initiation and acceleration of pancreatic cancer and can provide insight into the spreading biology of the respective tumor (127). Additionally, an investigation by Gao et al. demonstrated the role of the gene FUT 3 (Galactoside 3(4)-fucosyltransferase), also referred to as Lewis` gene. The primary function of Lewis` gene is the fucosylation of proteins and the synthesis of CA 19-9, and it was shown to be upregulated in metastatic PDAC. Consequently, Lewis` gene and CA 19-9 might affect the promotion of cell motility in pancreatic cancer (128). Other investigations confirmed a correlation between the upregulation of FUT genes and the poor prognosis in some cancer entities (129).
Five to ten percent of all individuals are homozygous for the recessive allele of the gene FUT 3. These Lewis-negative patients have a lower or missing secretion of CA 19-9 (130), and thus, might have a lower risk for uncontrolled cell proliferation and invasion. Controversially, a study by Liu et al. showed a correlation between Lewis-negative patients and a significantly shorter OS and higher rates for distant metastases (130). An investigation by Truty et al. showed similar results. Patients who did not secrete CA 19-9 had comparable OS to patients with initially elevated CA 19-9 that stayed elevated after neoadjuvant therapy. Those groups had a significantly worsened OS in comparison to responders (123). Different reasons could be possible for this incidence. Firstly, a compensatory upregulation of CA 125, which also functions as a promotor for cell proliferation, was detected in those patients. Secondly, the absence of the fucosyltransferase, and thus, the downregulated fucosylation of proteins, can impair the human body`s physiological processes, such as the adhesion of leucocytes to the wall of vessels for migration (130). Further studies are necessary to investigate the impact of the inactivation of FUT 3 or CA 19-9 on the prognosis of patients. New therapeutical approaches could be derived from that.

#### 2.4.1.5. Oligometastasis – an exclusion criterion for secondary resection?

The presence of metastases in a limited number restricted to a finite number of organs is described as oligometastasis (131). Locoregional treatments of liver metastases, such as

resection, ablation, and embolization, are well established in colorectal cancer and NET of the pancreas. Over the last decade, treatment techniques have improved and have increasingly been used on metastatic PDAC. A systematic review by Timmer et al. reveals survival benefits for resection of the primary tumor and metastases in oligometastatic patients. Patients who received resection of the primary cancer and hepatic lesions have an OS described with 7.8 to 14.5 months from the time of resection. In comparison, the mOS of patients who underwent sole primary resection is described with 9.2 months (131). However, this review excluded downstaged metastatic PDAC. Furthermore, an investigation by Hackert et al. showed a chance of long-term OS for patients who receive a resection of the pancreatic tumor after neoadjuvant therapy and simultaneous or delayed resection of metastases. Their patients had an mOS of 12.3 months and a 5-year survival rate of up to 10 % (132). Compared to the outcome of patients who receive palliative intended chemotherapy with FOLFIRINOX (mOS 11.1 months (82)), those patients have a slightly prolonged OS and the chance for long-term survival.
In our investigation, secondary resection was performed in eight patients with initial distant metastasis. However, radiological signs for distant metastasis were persistent in only six patients after neoadjuvant therapy. In three of those patients, an additional resection of liver metastases was performed. In one case, no malignant cells were detected. The survival from the time of resection was six and 27 months (12 and 32 months from the time of diagnosis) for the patients who received additional liver resection and had malignant cells detected. On the other hand, the patients who did not receive additional metastasis resection had a survival of ten, 14, and 21 months from the time of resection (18, 20, and 35 months from the time of diagnosis). Thus, additional liver resection led to a long-term survival that is worth mentioning in one case. Furthermore, the survival of the patients who did not receive additional metastasis resection was noticeably prolonged compared to the mOS of palliative-treated patients. Consequently, the resection of the primary tumor and potential additional liver resection in case of oligometastasis can be considered to gain local tumor control. To prove this concept of resection in oligometastatic disease but operable primary, the DFG-funded European METAPAC study (Göttingen, Essen, Berlin) will be started in 2022.

### 2.4.2. Factors that Predict the Probability of a Secondary Resection

Another purpose of this investigation was to analyze factors that are assumed to predict the probability of a secondary resection based on our patient cohort. Moreover, tumor marker CA 19-9 is the most conclusive factor for this question. In a study by Michelakos et al., patients with BRPC who had undergone secondary resection had normal CA 19-9 values after neoadjuvant

therapy (median CA 19-9: 21 U/ml). In comparison, patients with not feasible secondary resection had slightly elevated CA 19-9 values (median CA 19-9: 40 U/ml) after neoadjuvant therapy. However, the CA 19-9 level had dropped to normal values during neoadjuvant therapy with FOLFIRINOX in nearly all cases of those patients (105). In comparison, the patients of our investigation had a median CA 19-9 level of 138.5 U/ml after neoadjuvant therapy. Thus, they had a notable higher level than patients who were not resected in the investigation by Michelakos et al. Therefore, based on our data, we suggest that it is not reasonable to determine a common strong threshold value of CA 19-9 to decide for secondary resection - but a careful look at the individual course of these selected patients.

In our investigation, there were many patients (73 %) with partial remission after neoadjuvant therapy. In comparison, other studies showed partial remission rates in only 31 % of patients being treated with FOLFIRINOX and only 23 % (82) in patients that were treated with gemcitabine/nab-paclitaxel (83). At first, the radiographic response seems to be a good factor to predict resectability. However, a previous study demonstrated the inaccuracy of grading and evaluation of response in pancreatic cancer after neoadjuvant therapy with FOLFIRINOX. In Katz et al., resection was finally feasible in 66 % of patients with BRPC that initially were predicted to be not resectable by CT scan (133). This incidence results from the inability of CT scans to differentiate vital tumors from fibrotic tissue as it results from neoadjuvant therapy. For this reason, some specialists recommend an operative exploration for all patients independently of the radiological assessment. In this way, intraoperative biopsies can be taken from adjacent vessels, and the decision for resection can be made dependent on frozen section analysis (134).

To finally fathom why resection was feasible in our cohort of patients, we need to combine different criteria. Many of those are already essential components for decision-making within multidisciplinary tumor conferences. With the help of polychemotherapy like FOLFIRINOX, we can achieve higher resection rates (103). To be suitable for polychemotherapy, patients should have an ECOG performance status of at least 1. 96 % of our patients fulfilled this criterion at the time of diagnosis, and 81.4 % of our patients still had an ECOG performance status of at least 1 after neoadjuvant therapy. Thus, those patients are most likely to tolerate further intensive multimodal therapy. Additionally, our patients had a significant decrease of CA 19-9 from a mean value of 4358.3 U/ml to 138.5 U/ml. Even though the degree of CA 19-9 decrease had no significant impact on the OS of patients, this variable might have predicted the probability of a secondary resection. Another indication was the high rate of radiographic response in our cohort.

### 2.4.3. The Perspective for Neoadjuvant Therapy in PDAC

Chemotherapy is a systemic therapy aiming to reach disseminated tumor cells in the body. In this way, chemotherapy stops the tumor from developing distant metastases. In turn, pancreatic cancer is a tumor entity that early disseminates (135). Up to 60 % of patients are diagnosed in a metastatic stage (22). In all other cases, the tumor has time to find connections to the vessel system and to disseminate unnoticed to distant lymph nodes and organs or to extend discontinuously along the perineurium while initially resectable or borderline resectable patients get prepared for surgery. This leads to high rates of local and distant recurrence (50). These recurrences are supposed to be prevented or reduced by adjuvant therapy. However, because of this early dissemination, it might be more effective to offer neoadjuvant chemotherapy to borderline and initially resectable PDAC patients as well instead of performing the systemic therapy after surgery, shutting the stable door after the horse has bolted. In addition, adjuvant therapy can be completed in only two-thirds of cases. In about 10 % of the patients, adjuvant therapy is not even initiated due to postoperative complications, wound healing disorders, or other exacerbated comorbidities (72, 75, 76). Thus, it might be an advantage to apply chemotherapy in advance to surgery before complications delay or hinder an adjuvant application. Another positive effect of neoadjuvant chemotherapy is the additional local effect. Next to the possibility of downstaging in LAPC, R0-resection rates in BRPC patients can be increased to more than 90 % by neoadjuvant therapy (136, 137). The R0-status is considered a positive predictive factor for the OS in primarily resected and BRPC patients as it decreases the risk for local recurrences (48). For these reasons, we should not only use neoadjuvant chemotherapy to downstage LAPC but to increase survival chances in BRPC and initially resectable PDAC as well.

Neoadjuvant therapy has already been proven to significantly increase overall survival in BRPC (138). A meta-analysis of 1,808 patients with borderline resectable pancreatic cancer by Versteijne et al. reported an mOS of 19.2 months for patients who received neoadjuvant chemotherapy in comparison to 12.8 months for patients that were initially resected (139).

Some investigations exist that indicate the benefit of neoadjuvant therapy in resectable pancreatic cancer as well. Three underpowered randomized controlled trials were pooled and analyzed by Birrer et al. This analysis revealed a significantly prolonged disease-free survival for initially resectable patients that underwent neoadjuvant chemotherapy (+ radiation). The mOS was prolonged as well but did not reach statistical significance (139, 140).

The downside of this neoadjuvant approach needs to be mentioned as well. Some patients with PDAC might not respond to the chosen neoadjuvant chemotherapy protocol, and the initially (borderline) resectable cancer continues to grow to a locally advanced tumor. This problem gets reflected by decreased overall resection rates after neoadjuvant treatment compared to initially resected patients (139, 141). On the other hand, those patients might have suffered from early recurrence anyway if the missing response to neoadjuvant chemotherapy indicates more aggressive tumor biology. However, this disadvantage of neoadjuvant therapy does not exist for LAPC.

Concerns might exist, that postoperative complications are increased due to increased fibrotic tissue and reduced regenerative ability after neoadjuvant chemotherapy. However, in BRPC and initially resectable cancer postoperative complications are not increased (140, 142). On the contrary, an Italian study with 445 patients (including 305 patients with neoadjuvant therapy) showed reduced rates for postpancreatectomy hemorrhage and postoperative pancreatic fistula (POPF) in patients that have been treated with neoadjuvant therapy in comparison to initially resected patients. Merely, rates for delayed gastric emptying were increased (143).

Nevertheless, adjuvant or additive chemotherapy should remain an important part in therapy for PDAC in all stages as it has been proven to improve OS and reduce recurrence. The risk of R1-resections or intraoperative tumor cell spread is not excluded. Thus, a postoperative systemic chemotherapy is still necessary.

#### 2.4.4. Summary

In summary, neoadjuvant chemotherapy is already recommended by clinical guidelines in BRPC but still needs to be further evaluated in resectable PDAC (59). The use of chemotherapy in LAPC is undoubted. Contrarily, we are working on finding prognostic factors that identify suitable patients for secondary resection. On one hand, the initial CA 19-9 value at diagnosis gives indications on the biology of the tumor and its aggressiveness and might be predictive for the outcome of the patient. Nevertheless, it is important to evaluate further characteristics in the course of therapy. The BMI of the patients after neoadjuvant chemotherapy can give insights into the physical health of the patients to predict resilience during subsequent therapy. CA 19-9 expresses the response to the previous neoadjuvant chemotherapy and might predict the response to further treatment. On the other hand, we can optimize therapy conditions and positively influence the course of treatment. For instance, it is necessary to define the right number of neoadjuvant cycles that need to be applied to reach the best outcome. Furthermore, the nodal

stage of pancreatic cancer is an important predictive factor in initially not-resectable PDAC as well. Thus, we should concentrate on a more accurate preoperative diagnosis of the nodal stage by, for instance, EUS and FNA. Knowing the nodal stage after neoadjuvant chemotherapy, we could either integrate this predictive factor into decision-making for secondary resection or decide over possible further non-operative treatment options to gain nodal negativity before secondary resection. Lastly, the resection of oligometastasis can result in long-term survival and can be considered in selected cases.

#### 2.4.5. Limitations of this Study

The present study is limited by common biases that are mainly due to the retrospective character of this analysis. Our patients had initially profited from neoadjuvant therapy with a high rate of partial remission. Retrospectively, we cannot interpret whether these patients might have also profited from continued chemotherapy. Prospective controlled randomized trials are necessary to answer this question. Notwithstanding, we should bear in mind the disadvantages of continued, and thus, not curative chemotherapy. Cumulative cycles of chemotherapy lead to high rates of side effects due to toxic bone marrow damage. Furthermore, tumor tissue can develop resistances against chemotherapeutic substances what leads to a progression of the disease. For these reasons, secondary resection should be discussed on a patient-to-patient basis.

Further limitations are the small number of analyzed patients, the short observation time, and the missing differentiation between LAPC and BRPC. However, we should question the current classification as it becomes obsolete when initially not resectable LAPC becomes resectable with the help of neoadjuvant therapy and, in some cases, even reaches comparable OS to initially resectable pancreatic cancer (109).

Furthermore, limitations exist for the interpretation of radiographic response and clinical T-status of LAPC. As described above, CT scans are inappropriate to differentiate between viable tumors and fibrotic tissue. Moreover, an analysis carried out by the National Cancer Data Base showed a poor correlation between clinical and histopathological T-stage in patients with primarily resected cancer (144). Consequently, results regarding the clinical stage should be considered with caution.

## 2.5. Conclusion

Pancreatic cancer remains a disease with poor outcome but heterogenous course. Nevertheless, we should strive to identify those patients with a possibly less aggressive tumor biology and good general condition that might profit from this individualized therapy strategy. The initial CA

19-9 value provides first indications for a possible outcome but does not seem to be appropriate to predict the probability of a secondary resection. However, the clinical course during neoadjuvant therapy could be decisive for further therapy decisions. Following factors should be involved in decision-making for secondary PDAC resection within experienced interdisciplinary tumor conferences in high volume centers: the radiographic response, values of the tumor marker CA 19-9 before and after neoadjuvant therapy and the BMI and ECOG performance status of the patients. Additionally, we should strive to apply a minimum number of chemotherapy cycles to increase survival chances.

Furthermore, more attention should be paid to the preoperative diagnosis of the nodal status as nodal positivity after neoadjuvant therapy has an important role in the OS of the patients. If it is clinically feasible, additional endosonographic biopsies should be performed in cases of a suspicious lymphadenopathy to identify those patients, that possibly profit from a strategy change.

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## 3. Statutory Declaration

I, Nathalie Wetterauer, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "The Use of Prognostic Factors to Identify the Group of Beneficiaries in Patients with Primarily Not-Resectable Pancreatic Adenocarcinoma / Der Nutzen von Prädiktiven Faktoren zur Identifikation von Patienten mit primär nicht resektablem Adenokarzinom des Pankreas, welche von einer sekundären Resektion profitieren", independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

## 4. Declaration of my own Contribution to the Publication

Nathalie Wetterauer contributed the following to the below listed publications:

Publication 1: Nathalie Rosumeck, Lea Timmermann, Fritz Klein, Marcus Bahra, Sebastian Stintzig, Thomas Malinka and Uwe Pelzer, "Induction Chemotherapy for Primarily Unresectable Locally Advanced Pancreatic Adenocarcinoma—Who Will Benefit from a Secondary Resection?", Medicina, 2021

Contribution:

The search for better multimodal therapy concepts with the help of intensive systemic chemotherapy protocols has been one of the main topics that have been worked on by the center for pancreatic diseases of Charité. Therefore, the topic of finding predictive factors for the probability and benefit of a secondary resection in LAPC was provided for promotion. With the collaboration of my co-authors, the main question was specified over time.

The consecutive collection of data within the clinic`s SAP database was done by employees within the daily work routine. The identification of patients with pancreatic cancer who received chemotherapy and were resected subsequently was made by Lea Timmermann. I identified the patients with an adenocarcinoma of the pancreatic gland, collected all relevant data from the clinic`s database, and transferred it to a digital data table. Furthermore, I conducted the statistical analysis and performed the interpretation of the results. In doing so, I regularly conferred with my supervisors and co-authors to discuss the results and interpretation. Subsequently, I wrote the publication and created all tables and graphs. After revisions and corrections by my supervisor and co-authors, I finalized the publication.

_____

Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

# 5. Extract from the Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, GENERAL and INTERNAL"**
Selected Category Scheme: WoS
**Gesamtanzahl: 165 Journale**

| Rank | Full Journal Title | Total Cites | Journal Impact Factor | Eigenfactor Score |
|---|---|---|---|---|
| 1 | NEW ENGLAND JOURNAL OF MEDICINE | 347,451 | 74.699 | 0.660800 |
| 2 | LANCET | 256,199 | 60.392 | 0.437300 |
| 3 | JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION | 158,632 | 45.540 | 0.290050 |
| 4 | Nature Reviews Disease Primers | 7,567 | 40.689 | 0.032310 |
| 5 | BMJ-British Medical Journal | 118,586 | 30.223 | 0.145170 |
| 6 | ANNALS OF INTERNAL MEDICINE | 58,033 | 21.317 | 0.091210 |
| 7 | JAMA Internal Medicine | 17,260 | 18.652 | 0.086180 |
| 8 | PLOS MEDICINE | 32,312 | 10.500 | 0.065990 |
| 9 | Journal of Cachexia Sarcopenia and Muscle | 3,553 | 9.802 | 0.007860 |
| 10 | Cochrane Database of Systematic Reviews | 67,763 | 7.890 | 0.134360 |
| 11 | CANADIAN MEDICAL ASSOCIATION JOURNAL | 15,212 | 7.744 | 0.016160 |
| 12 | JOURNAL OF TRAVEL MEDICINE | 2,659 | 7.089 | 0.006360 |
| 13 | MAYO CLINIC PROCEEDINGS | 15,627 | 6.942 | 0.024990 |
| 14 | JOURNAL OF INTERNAL MEDICINE | 10,912 | 6.871 | 0.014180 |
| 15 | BMC Medicine | 15,204 | 6.782 | 0.042500 |
| 16 | MEDICAL JOURNAL OF AUSTRALIA | 11,075 | 6.112 | 0.011070 |
| 17 | Translational Research | 4,043 | 5.411 | 0.008350 |
| 18 | JOURNAL OF THE ROYAL SOCIETY OF MEDICINE | 4,214 | 5.238 | 0.002580 |
| 19 | JAMA Network Open | 2,239 | 5.032 | 0.007660 |

| Rank | Full Journal Title | Total Cites | Journal Impact Factor | Eigenfactor Score |
|---|---|---|---|---|
| 97 | PRESSE MEDICALE | 2,193 | 1.388 | 0.002430 |
| 98 | SINGAPORE MEDICAL JOURNAL | 3,312 | 1.359 | 0.002480 |
| 99 | WIENER KLINISCHE WOCHENSCHRIFT | 2,126 | 1.323 | 0.002440 |
| 100 | REVISTA CLINICA ESPANOLA | 650 | 1.304 | 0.000720 |
| 101 | MEDICAL PRINCIPLES AND PRACTICE | 1,924 | 1.295 | 0.002390 |
| 102 | Libyan Journal of Medicine | 370 | 1.294 | 0.000410 |
| 103 | SAMJ SOUTH AFRICAN MEDICAL JOURNAL | 4,300 | 1.285 | 0.005030 |
| 104 | CROATIAN MEDICAL JOURNAL | 1,619 | 1.247 | 0.001200 |
| 105 | Australian Family Physician | 1,787 | 1.220 | 0.001970 |
| 106 | International Journal of Osteopathic Medicine | 259 | 1.208 | 0.000270 |
| 107 | Medicina-Lithuania | 1,446 | 1.205 | 0.001170 |
| 108 | Open Medicine | 424 | 1.204 | 0.001000 |
| 109 | Bratislava Medical Journal-Bratislavske Lekarske Listy | 1,251 | 1.200 | 0.001290 |
| 110 | SAUDI MEDICAL JOURNAL | 3,575 | 1.195 | 0.003050 |
| 111 | Revista de Investigacion Clinica-Clinical and Translational Investigation | 618 | 1.192 | 0.000650 |
| 112 | Journal of Postgraduate Medicine | 1,289 | 1.167 | 0.000860 |
| 113 | ACTA CLINICA BELGICA | 941 | 1.111 | 0.001370 |
| 114 | IRISH JOURNAL OF MEDICAL SCIENCE | 1,537 | 1.100 | 0.002310 |
| 115 | Atencion Primaria | 1,249 | 1.087 | 0.000970 |
| 116 | Sao Paulo Medical Journal | 1,148 | 1.044 | 0.001350 |



Selected JCR Year: 2019; Selected Categories: "MEDICINE, GENERAL und INTERNAL"

## 6. Publication „Induction Chemotherapy for Primarily Unresectable Locally Advanced Pancreatic Adenocarcinoma – Who Will Benefit from a Secondary Resection?"

*medicina*

MDPI

*Article*

# Induction Chemotherapy for Primarily Unresectable Locally Advanced Pancreatic Adenocarcinoma—Who Will Benefit from a Secondary Resection?

**Nathalie Rosumeck [1,*], Lea Timmermann [2], Fritz Klein [2], Marcus Bahra [2], Sebastian Stintzig [1], Thomas Malinka [2] and Uwe Pelzer [1]**

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**Abstract:** *Background and Objectives:* An increasing number of patients (pts) with locally advanced pancreatic cancer (LAPC) are treated with an intensive neoadjuvant therapy to obtain a secondary curative resection. Only a certain number of patients benefit from this intention. The aim of this investigation was to identify prognostic factors which may predict a benefit for secondary resection. *Materials and Methods:* Survival time and clinicopathological data of pts with pancreatic cancer were prospective and consecutively collected in our Comprehensive Cancer Center Database. For this investigation, we screened for pts with primarily unresectable pancreatic cancer who underwent a secondary resection after receiving induction therapy in the time between March 2017 and May 2019. *Results:* 40 pts had a sufficient database to carry out a reliable analysis. The carbohydrate-antigen 19-9 (CA 19-9) level of the pts treated with induction therapy decreased by 44.7% from 4358.3 U/mL to 138.5 U/mL ($p = 0.001$). The local cancer extension was significantly reduced ($p < 0.001$), and the Eastern Cooperative Oncology Group (ECOG) performance status was lowered ($p = 0.03$). The median overall survival (mOS) was 20 months (95% CI: 17.2–22.9). Pts who showed a normal CA 19-9 level (<37 U/mL) at diagnosis and after neoadjuvant therapy or had a Body Mass Index (BMI) below 25 kg/m$^2$ after chemotherapy had a significant prolonged overall survival (29 vs. 19 months, $p = 0.02$; 26 vs. 18 months, $p = 0.04$; 15 vs. 24 months, $p = 0.01$). Pts who still presented elevated CA 19-9 levels >400 U/mL after induction therapy did not profit from a secondary resection (24 vs. 7 months, $p < 0.001$). Nodal negativity as well as the performance of an adjuvant therapy lead to better mOS (25 vs. 15 months, $p = 0.003$; 10 vs. 25 months, $p < 0.001$). *Conclusion:* The pts in our investigation had different benefits from the multimodal treatment. We identified the CA 19-9 level at time of diagnosis and after neoadjuvant therapy as well as the preoperative BMI as predictive factors for overall survival. Furthermore, diagnostics of presurgical nodal status should gain more importance as nodal negativity is associated with better outcome.

**Keywords:** pancreatic cancer; neoadjuvant therapy; induction therapy; secondary resection; pancreatic surgery



**Citation:** Rosumeck, N.; Timmermann, L.; Klein, F.; Bahra, M.; Stintzig, S.; Malinka, T.; Pelzer, U. Induction Chemotherapy for Primarily Unresectable Locally Advanced Pancreatic Adenocarcinoma—Who Will Benefit from a Secondary Resection?. *Medicina* **2021**, *57*, 77. https://doi.org/10.3390/medicina57010077

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## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies and a leading cause of cancer death worldwide. It is expected to become the second leading cause of cancer-related death within this decade [1,2]. The lack of effective targeted agents as well as missing validated predictive biomarkers that can probably facilitate therapeutic decision-making are major barriers in the treatment of pancreatic cancer.

In patients (pts) with inoperable disease and better performance status, two chemotherapy options, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and nab-paclitaxel/gemcitabine, have emerged in the last decade as frontline standards of care, with response rates around 30–40%. Gemcitabine monotherapy is reserved for pts with lower performance status, substantial comorbidities, or other contraindications.

However, in each of these studies [3,4], the median overall survival of the pts remained less than one year, supporting the ongoing need to develop more beneficial therapies for this disease.

Pts who showed progression while receiving gemcitabine (+nab-paclitaxel) had a phase III-proven chance of further therapy, with a platinum- or irinotecan-based strategy combined with fluoropyrimidine infusion, if the performance status was sufficiently maintained [5–7]. After the first line with FOLFIRINOX, a strategy change to gemcitabine/nab-paclitaxel is possible but is rarely feasible and lacks any phase III-proven overall survival benefit.

In a small number of pts without significant vascular involvement (approximately 15–20%), radical cancer resection followed by adjuvant chemotherapy can offer a curative option [8–10]. Several classifications exist to define PDAC subgroups mainly by means of vascular contact or invasion. The National Cancer Centre (NCC) guidelines is the most commonly used to define the PDAC subtypes of resectable, borderline resectable (BRPC), and locally advanced pancreatic cancer (LAPC). While, in LAPC, primary resection is not recommended due to major venous thrombosis of the portal vein or superior mesenteric vein (SMV) or to circumferential encasement of the superior mesenteric artery (SMA), celiac axis, or proximal hepatic artery, BRPC, which is defined as the presence of tumor abutment on the portal vein or SMV and limited encasement of the mesenteric vein and portal vein, offers the option of a curative surgical resection [11]. However, in up to 50% of resected cancers, microscopic residuals are found in the resection margin. Consequently, the rate of local recurrence is high [12]. Preoperative therapy being mainly favored for BRPC increases R0 resection rates as a prognostic factor and for survival [13].

For pts with locally advanced inoperable PDAC but no evidence of distant metastasis, radio-chemotherapy is lacking effectiveness over chemotherapy alone [14]. However, with the use of a more effective systemic chemotherapy regimen developed in the last decade [3,4], the chance of response and furthermore of a secondary, curative-intended resection increases [15]. Resection rates for LAPC are described as up to 60% when treated with FOLFIRINOX [16], and the mOS can be significantly increased by secondary resection (35.3 vs. 16.3 months) [17]. This chance must be discussed in an interdisciplinary cancer conference of a high volume center at time of first diagnosis, especially since new operative methods such as celiac axis resection offer increased disease control with high rates of negative resection margins without increased perioperative mortality and complications [18,19]. As pancreatectomy with or without additional vessel resection remains a mayor surgical procedure with risks of complications, it is important to justify this procedure. In this context, it is the aim of current studies to identify prognostic factors that predict operability and the benefit of a secondary resection. While radiographic response alone has been proven to be misleading in terms of resectability [20], the tumor marker carbohydrate-antigen 19-9 (CA 19-9) might be a suitable and promising factor to support the selection of pts that benefit from this procedure [21].

The aim of this investigation was to identify factors that could predict or affirm the usefulness of a multimodal concept with a secondary resection after response to an induction treatment.

## 2. Materials and Methods

Pts undergoing systemic induction treatment followed by secondary resection for initially non-resectable PDAC in our cancer center in the period between March 2017 and May 2019 were identified from our Comprehensive Cancer Database. We collected the data prospectively. The analysis was done in a retrospective way. Inclusion criteria

were the histologically proven presence of primarily non-resectable PDAC as well as the application of an undefined number of chemotherapy cycles before performed resection. We excluded other tumor-subtypes such as duodenal carcinoma, periampullary cancer, and neuroendocrine carcinoma. The PDAC was assessed as primarily non-resectable when anatomical signs for BRPC or LAPC were seen. The induction therapy was performed either inpatient or outpatient in our center or in an associated outpatient department. We discussed all pts upfront in our multidisciplinary cancer conference to assess for primary or secondary resectability and the suitability for appropriate chemotherapy treatment.

Data were analyzed for pre-, post-, and operative characteristics such as patient' characteristics including ECOG and Body Mass Index (BMI), therapeutic characteristics including the chosen neoadjuvant therapy, surgical procedures, side effects and complications, clinicopathological characteristics including CA 19-9 and Carcinoembryonic antigen (CEA) levels at diagnosis and after neoadjuvant treatment, and the pTNM status (histopathological state of tumor expansion, nodal state and metastasis) of the pts.

The classification and graduation of side effects during induction therapy were defined by Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Initial staging and restaging were performed via 3-phase CT scans. The radiographic response was defined by the RECIST criteria (1.1) (Response Evaluation Criteria in Solid Tumors) by varying specialists for radiology as follows: complete response (CR)—Disappearance of all target lesions; Partial Response (PR)—At least a 30% decrease in the sum of diameters of target lesions; Progressive Disease (PD)—At least a 20% increase in the sum of diameters of target lesions; Stable Disease (SD)—Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD [22].

Statistics were performed using SPSS version 26 (IBM, New York, NY, USA). Fisher's exact test, Chi-Square-test, *t*-test, and Wilcoxon's test were used depending on scaling level. *p*-values were two-sided and considered to be statistically significant if $p < 0.05$. Kaplan–Meier curves were provided for survival estimations. We calculated survival from time of diagnosis to the death of the pt independent of the reason for death or to the last documented contact with the pt. The last group was defined as lost to follow up and was censored.

## 3. Results

### 3.1. Patient Characteristics

Forty pts (22 men and 18 women) fulfilled the inclusion criteria for analysis. The mean age at time of surgery was 61 years (37–82 years). Pretreatment parameters, such as ECOG status, American Society of Anesthesiologists (ASA) score, and BMI can be found in Table 1. The majority of the pts had an ECOG of 0 (66.7%) or 1 (30.3%) before initiation of chemotherapy. Only 2 pts (3%) showed an ECOG of 2. None of the pts had an ECOG below 2. Data for ASA score were captured before performance of the surgical resection and showed a majority for mild (ASA 2) and severe systemic diseases (ASA 3) in these pts (42.9% and 51.4%); 66.7% of the pts had a normal BMI (18.5–25 $kg/m^2$), 29.6% were overweight (25.1–30 $kg/m^2$), and 3.7% were underweight (<18.5 $kg/m^2$). A 3-phase CT scan or surgical exploration offered reasons for primary irresectability.

**Table 1.** Patient characteristics.

| Baseline Characteristics (*n* = 40) | | | | | |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Mean | 60.6 (37–82) years | | | | |
| **Gender** | | | | | |
| Male | 22 (55.0%) pts. | | | | |
| Female | 18 (45.0%) pts. | | | | |
| **Primary Localization** | | | | | |
| Head | 21 (52.5%) pts. | | | | |
| Korpus | 13 (32.5%) pts. | | | | |
| Tail | 6 (15%) pts | | | | |
| | **At Diagnosis** | | **After Induction/Before Resection** | | |
| | ***N*** | **%** | ***N*** | **%** | ***p*** |
| **ECOG** | | | | | |
| 0 | 22 | 66.7 | 10 | 37 | |
| **1** | 10 | 30.3 | 12 | 44.4 | 0.03 |
| 2 | 1 | 3 | 5 | 18.5 | |
| n.a. | 7 | | 13 | | |
| **ASA Score** | | | | | |
| **1** | | | 2 | 5.7 | |
| 2 | | | 15 | 42.9 | |
| 3 | | | 18 | 51.4 | |
| n.a. | | | 5 | | |
| **BMI [kg/m²]** | Median 23.9 (17.2–28.7) | | Median 22.6 (16.8–29.9) | | |
| <18.5 | 1 | 3.7 | 1 | 2.9 | |
| 18.5–24.9 | 18 | 66.7 | 23 | 67.6 | 0.25 |
| ≥25 | 8 | 29.6 | 10 | 29.4 | |
| n.a. | 13 | | 6 | | |

n.a.—not available, BMI—body mass Index, ASA—American Society of Anesthesiologists, and ECOG—Eastern Cooperative Oncology Group.

### 3.2. Neoadjuvant Treatment

Most pts (57.7%) received induction therapy with FOLFIRINOX. One of them deescalated therapy to gemcitabine mono due to side effects after four applications. Seven pts (17.5%) received nab-paclitaxel and gemcitabine, whereas two external pts were treated with gemcitabine mono and cisplatin/capecitabine. In 8 pts (20%), a change in induction therapy between FOLFIRINOX and nab-paclitaxel/gemcitabine was performed. Four of the pts suffered from severe toxicity during induction therapy, which lead to a switch from FOLFIRINOX to nab-paclitaxel/gemcitabine. In one pt, the switch was administered because a significant increase in the tumor marker CA 19-9 was suspected to be progression of the disease. For two pts, a change from nab-paclitaxel/gemcitabine to FOLFIRINOX was planned within a clinical investigation.

### 3.3. Surgical Procedure

Depending on the localization of the tumor (Table 1) and the extent of infiltration, a surgical procedure was chosen. Performed surgeries were pylorus preserving or classical Whipple's procedure and distal or total pancreatectomy (Table 2). Four pts underwent distal pancreatectomy with simultaneous resection of the celiac axis (Appleby procedure); 19 pts underwent an additional splenectomy; and 7 pts received a resection and reconstruction of the portal vein. Depending on the extent of local tumor infiltration, additional organ resections were performed (Table 2).

**Table 2.** Therapeutic characteristics.

| Parameter | Category | *N* | % |
|---|---|---|---|
| Induction Therapy | | | |
| | FOLFIRINOX | 23 | 57.5 |
| | Nab-Paclitaxel/Gemcitabine | 7 | 17.5 |
| | FOLFIRINOX ► Nab-Pac/Gem | 8 | 20 |
| | Gemcitabine mono | 1 | 2.5 |
| | Cisplatin/Capecitabine | 1 | 2.5 |
| Number of Applications | | | |
| | Median | 8 (3–25) | |
| | ≥8 Applications | 20 | 51.3 |
| | <8 Applications | 19 | 48.7 |
| | n.a. | 1 | |
| Duration of neoadjuvant Therapy | | | |
| | Median (months) | 3 (1–24) | |
| | >3 months | 18 | 48.6 |
| | ≤3 months | 19 | 51.4 |
| | n.a. | 3 | |
| Adjuvant Therapy | | | |
| | Yes | 15 | 75 |
| | No | 5 | 25 |
| | n.a. | 20 | |
| Surgical Procedure | | | |
| | PPPD | 16 | 40 |
| | Whipple's Procedure | 2 | 5 |
| | Distal pancreatectomy | 13 | 32.5 |
| | Total pancreatectomy | 9 | 22.5 |
| Additional resection | | | |
| | Splenectomy | 19 | 47.5 |
| | Gastrectomy (total/partial) | 2 | 5 |
| | Partial hepatectomy | 3 | 7.5 |
| | Resection of portal vein | 7 | 17.5 |
| | Resection coeliac axis | 4 | 10 |
| | Hemicolectomy | 1 | 2.5 |
| Post Op-Complications | | | |
| | BDA-Insufficiency | 26 | 65 |
| | Pancreatic fistula | 5 | 12.5 |
| | Postpancreatectomy | 9 | 22.5 |
| | haemorrhages | 1 | 2.5 |

n.a.—not available, PPPD—Pylorus-Preserving Pancreaticoduodenectomy, and BDA—Biliodigestive Anastomosis.

### 3.4. Side Effects and Complications

Of the pts, 51.6% suffered from side effects of grades 3 to 4 during preoperative therapy. Especially pts who received FOLFIRINOX and nab-paclitaxel/gemcitabine suffered from severe side effects (grades 3 to 4) significantly more often ($p = 0.009$). There was no difference in between the types of side effects depending on the performed induction therapy (Table 3). Of the pts, 56% sustained postoperative complications. Nine pts developed pancreatic fistulae. Five pts suffered from insufficiency of the biliodigestive anastomosis. One pt died from postoperative complications seven days after surgery due to a post pancreatectomy hemorrhage. The remaining seven pts with postoperative complications had either an impairment of wound healing or systemic inflammation and infection such as pneumonia. Resection of the portal vein or coeliac axis was not associated with a higher complication rate ($p = 0.68$; $p = 0.60$). There was also no difference in the rate of overall complications depending on the performed surgical procedure ($p = 0.78$).

**Table 3.** Side effects during induction therapy.

| | | Total | | Folfirinox | | Nab-Paclitaxel/Gem | | Folfirinox ► Nab-Pac/Gem | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Category** | ***N*** | **%** | ***N*** | **%** | ***N*** | **%** | ***N*** | **%** | |
| General Side effects | 0–2 | 15 | 48.5 | 19<br>12 | 63.2 | 5<br>3 | 60 | 7<br>0 | 0 | 0.009 |
| | 3–4 | 16 | 51.6 | 7 | 36.8 | 2 | 40 | 7 | 100 | |
| Neutropenia | | | | 15 | | 5 | | 7 | | |
| | 0–2 | 16 | 59.3 | 11 | 73.3 | 3 | 60 | 2 | 28.6 | 0.16 |
| | 3–4 | 11 | 40.7 | 4 | 26.7 | 2 | 40 | 5 | 71.4 | |
| Anemia | | | | 17 | | 5 | | 8 | | |
| | 0–2 | 26 | 86.7 | 15 | 88.2 | 4 | 80 | 7 | 87.5 | 1 |
| | 3–4 | 4 | 13.3 | 2 | 11.8 | 1 | 20 | 1 | 12.5 | |
| Thrombopenia | | | | 9 | | 3 | | 4 | | |
| | 0–2 | 15 | 93.8 | 8 | 88.9 | 3 | 100 | 4 | 100 | 1 |
| | 3–4 | 1 | 6.3 | 1 | 11.1 | 0 | 0 | 0 | 0 | |
| Infections | | | | 16 | | 4 | | 7 | | |
| | 0–2 | 24 | 88.9 | 15 | 93.8 | 4 | 100 | 5 | 71.4 | 0.2 |
| | 3–4 | 3 | 7.5 | 1 | 6.2 | 0 | 0 | 2 | 28.6 | |
| Diarrhea | | | | 4 | | 1 | | 3 | | |
| | 0–2 | 5 | 62.5 | 3 | 75 | 1 | 100 | 1 | 33.3 | 0.68 |
| | 3–4 | 3 | 37.5 | 1 | 25 | 0 | 0 | 2 | 66.7 | |
| Nausea | | | | 6 | | 3 | | 6 | | |
| | 0–2 | 15 | 93.8 | 6 | 100 | 2 | 66.7 | 5 | 83.3 | 0.66 |
| | 3–4 | 2 | 13.3 | 0 | 0 | 1 | 33.3 | 1 | 16.7 | |
| Neurological side effects | 0–2 | 13 | 81.3 | 10<br>7 | 70 | 3<br>3 | 100 | 3<br>3 | 100 | 0.52 |
| | 3–4 | 3 | 18.8 | 3 | 30 | 0 | 0 | 0 | 0 | |

### 3.5. Effect of Preoperative Therapy

Under induction therapy, the level of the tumor marker CA 19-9 changed from a mean of 4358.3 U/mL to 138.5 U/mL ($p < 0.001$), which is a decrease by 44.7%. The mean value of the tumor marker CEA dropped from 10.5 ng/L before induction therapy to 3.5 ng/L before surgery ($p = 0.16$). In 73% (27 of 37 pts) of the pts, CT scans showed partial response during induction therapy; 21.6% (8 of 37 pts) showed stable disease; and 5.4% (2 of 37 pts) showed progression of the disease. For three pts, there was no information available. The initial clinical tumor formula showed a cT4 stage in 54.1% (20 pts), a cT3 stage in 37.5% (14 pts), and a cT2 stage in 8.1% (2 pts). Histopathological analysis of the tumor showed a significant decrease of the T stage to pT4 in 15% (6 pts), to pT3 in 25% (10 pts), to pT2 in 27.5% (11 pts), and to pT1 in 20% (8 pts). In 5 pts (12.5%), there were no malignant cells detected at all ($p = 0.000015$) (Table 4). Meanwhile, the ECOG performance status of the pts worsened ($p = 0.03$) and the median BMI of the pts decreased slightly ($p = 0.25$) (Table 1). Ten pts (37%) suffered from weight loss of more than 5%.

**Table 4.** Clinical-pathological characteristics.

| | | At Diagnosis | | | | After Induction Therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Category** | ***N*** | **%** | **Mean** | **IQR** | ***N*** | **%** | **Mean** | **IQR** | ***p*** |
| CA 19-9 (U/mL) | | | | 4358.3 | 64.8–830 | | | 138.5 | 12.1–65.4 | |
| | ≤37 U/mL | 5 | 16.1 | | | 15 | 44.1 | | | |
| | 37–400 U/mL | 14 | 45.2 | | | 17 | 50 | | | 0.001 |
| | >400 U/mL | 12 | 38.7 | | | 2 | 5.9 | | | |
| | n.a. | 9 | | | | 6 | | | | |
| CA 19-9 trend (-%) | | 29 | | 44.7 | 18–94.75 | | | | | |
| CEA (ng/mL) | | | | 10.5 | 2.5–7 | | | 3.5 | 2–5.3 | |
| | ≤5 ng/ml | 15 | 65.2 | | | 18 | 69.2 | | | 0.16 |
| | >5 ng/ml | 8 | 34.8 | | | 8 | 30.8 | | | |
| | n.a. | 17 | | | | 14 | | | | |
| c/pT Status | | | | | | | | | | |
| | 0 | 0 | 0 | | | 5 | 12.5 | | | |
| | 1 | 0 | 0 | | | 8 | 20 | | | |
| | 2 | 3 | 8.1 | | | 11 | 27.5 | | | 0.001 |
| | 3 | 14 | 37.8 | | | 10 | 25 | | | |
| | 4 | 20 | 54.1 | | | 6 | 15 | | | |
| | n.a. | 3 | | | | 0 | | | | |
| pN Status | | | | | | | | | | |
| | 0 | | | | | 21 | 52.5 | | | |
| | 1 | | | | | 19 | 47.5 | | | |
| c/pM Status | | | | | | | | | | |
| | 0 | 30 | 78.9 | | | 35 | 87.5 | | | 0.18 |
| | 1 | 8 | 21.6 | | | 5 | 12.5 | | | |
| | n.a. | 2 | | | | 0 | | | | |
| R Status | | | | | | | | | | |
| | 0 | | | | | 18 | 46.2 | | | |
| | 1 | | | | | 21 | 53.8 | | | |
| | n.a. | | | | | 1 | | | | |

n.a.—not available, c/pT—clinical/histopathological tumor expansion, pN—histopathological nodal status, c/pM—clinical/histopathological distant metastasis, R—residual tumor, CA 19-9—carbohydrate-antigen 19-9, and CEA—Carcinoembryonic antigen.

### 3.6. Overall Survival

The median observation time was 19.5 months. The median OS from the time of diagnosis was 20 months (CI 95%: 17.2–22.9 months). The median OS from the time of resection was 17 months (CI 95%: 11.6–22.4). Nine patients (22.5%) were lost to follow up and censored.

### 3.7. Predictors of Overall Survival

Performing an adjuvant therapy (10 vs. 25 months, $p < 0.001$) as well as nodal negativity (25 vs. 15 months, $p = 0.003$) had positive impacts on the OS of the pts in our investigation. Pts who showed a normal weight or underweight after induction therapy ($p = 0.01$), pts who had a normal CA 19-9 levels (≤37 U/mL) at the time of diagnosis ($p = 0.02$) or after neoadjuvant therapy ($p = 0.04$) (Figure 1), and pts with a normalized CEA level (≤5 ng/L) after induction therapy profited from resection ($p = 0.047$). An elevated CA 19-9 level (>400 U/mL) after induction therapy tended towards significantly shorter OS ($p < 0.001$) (Table 5). The percentage of decrease in CA 19-9 level under induction therapy had no impact on the OS (exemplary decrease ≥ 75% vs. <75%, $p = 0.41$). Nevertheless, pts with a decrease in CA 19-9 levels over 90% were significantly more likely to receive R0 resection afterwards ($p = 0.03$). The age of the pts (≤60 vs. >60 years, $p = 0.3$), the pre- or post-therapeutic ECOG status (ECOG = 0 vs. >0, $p = 0.75/0.6$), the ASA score

(ASA < 3 vs. ≥3, $p = 0.5$), the pretherapeutic BMI of the pts (≤25 vs. >25 kg/m$^2$, $p = 0.91$), or the extent of weight loss during induction therapy (<5% vs. ≥5%, $p = 0.45$) had no impact on the OS. There was also no impact of the chosen induction therapy regimen (Table 5), whereas the number of applications of neoadjuvant chemotherapy had a significant influence on the OS (≤5 vs. >5 applications, $p = 0.033$) (Table 5, Figure 1). The total duration of neoadjuvant therapy had no impact on the OS of the patients (exemplary <3 months vs. ≤3 months, $p = 0.89$). There was no correlation between the number of applications and the presence of perineural ($p = 0.16$) or venous invasion ($p = 1$), or the pN ($p = 0.71$), R ($p = 0.7$), or pT stages ($p = 0.69$). Aside from the nodal status, the pT stage also had an impact on the OS. Pts with a pT stage of 0 or 1 showed significantly prolonged OS (43 vs. 19 months, $p = 0.008$) in comparison to higher T stages (Table 5). Although the absence of malignant cells in the histopathological reseced part did not lead to a significantly prolonged OS ($p = 0.22$). A negative perineural infiltration had an impact on the OS, which was statistically not significant ($p = 0.058$) (Table 5). Further histopathological characteristics did not have an impact on the OS (pM 0 vs. 1, $p = 0.67$; R0 vs. ≥R1, $p = 0.7$; L0 vs. L1, $p = 0.12$; and V0 vs. V1, $p = 0.33$). The radiographic response measured by RECIST criteria (partial remission vs. stable/progressive disease, $p = 0.82$) as well as the presence of postoperative complications ($p = 0.63$) had no impact on the OS.

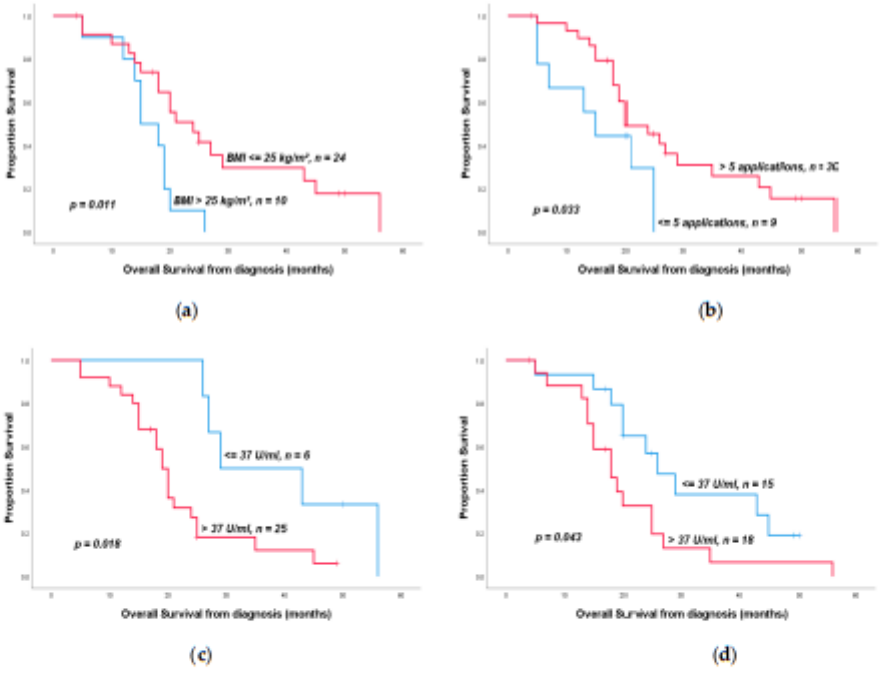


**Figure 1.** Kaplan–Meier overall survival curves in pts who underwent surgical resection after receiving neoadjuvant therapy: (**a**) overall survival depending on the body mass index (BMI) at the time after neoadjuvant therapy, (**b**) overall survival depending on the number of applications of neoadjuvant chemotherapy, (**c**) overall survival depending on the CA 19-9 level at the time of diagnosis, and (**d**) overall survival depending on the CA 19-9 level after neoadjuvant therapy.

**Table 5.** Impact factors on overall survival.

| Parameter | Category | OS (Months) | *p* | HR | 95%CI | *p* |
|---|---|---|---|---|---|---|
| CA 19-9 at diagnosis | ≤37 vs. >37 U/ml | 29 vs. 19 | 0.02 | 3.44 | 1.14–10.36 | 0.028 |
| CA 19-9 after induction | ≤37 vs. >37 U/mL | 26 vs. 18 | 0.043 | 2.23 | 0.99–5.03 | 0.054 |
| | <400 vs. ≥400 U/mL | 24 vs. 7 | 0.001 | 17.2 | 2.38–124.45 | 0.005 |
| CEA after induction | ≤5 vs. >5 ng/ml | 25 vs. 18 | 0.047 | 2.67 | 0.96–7.48 | 0.061 |
| BMI after induction | >25 vs. ≤25 | 15 vs. 24 | 0.01 | 0.36 | 0.15–0.83 | 0.017 |
| pN status | 0 vs. 1 | 25 vs. 15 | 0.003 | 2.99 | 1.39–6.41 | 0.005 |
| pT status | 0–1 vs. 2–4 | 43 vs. 19 | 0.008 | 3.09 | 1.26–7.62 | 0.014 |
| Pn | 0 vs. 1 | 35 vs. 19 | 0.058 | 2.46 | 0.92–6.56 | 0.072 |
| Neoadjuvant protocoll | FOLFIRINOX vs. other | 20 vs. 20 | 0.88 | 0.95 | 0.46–1.97 | 0.89 |
| | Nab-Pac/Gem vs. other | 20 vs. 20 | 0.54 | 0.77 | 0.33–1.81 | 0.55 |
| | FOLFIRINOX ► Nab-Pac/Gem vs. other | 18 vs. 20 | 0.22 | 1.86 | 0.68–5.11 | 0.23 |
| Number of neoadjuvant applications | ≤5 vs. >5 | 15 vs. 20 | 0.033 | 0.41 | 0.17–0.98 | 0.044 |
| Adjuvant therapy | no adjuvant therapy vs. adjuvant therapy | 10 vs. 25 | 0.001 | 0.21 | 0.08–0.55 | 0.002 |

CA 19-9—carbohydrate-antigen 19-9, CEA—Carcinoembryonic antigen, BMI—body mass index, pN—histopathological nodal status, pT—histopathological tumor expansion, and Pn—perineural invasion.

## 4. Discussion

Increasing the intended R0 resection rates is the main aim of preoperative treatment for initially non-resectable PDAC. When the option of resectability after initial treatment appears, it remains unclear which pts benefit from a secondary resection and if they reach a comparable OS to those with a primarily resected specimen [23] or rather suffer from early recurrence.

Our analysis showed an OS of up to 20 months for selected pts with initially non-resectable pancreatic cancer that mainly responded to induction chemotherapy. The mOS for pts with LAPC who did not undergo secondary resection is exemplarily described at 16.3 months [17]. We therefore believe that a secondary resection in pts after responding can be justified. However, the group of beneficiaries has to be narrowed down using prognostic or predictive factors.

Prognostic factors that are associated with an improved OS have been identified before, such as post-resectional nodal negativity [24]. Our results support this thesis once more as pts with nodal negativity had a significant longer OS compared to pts with nodal positivity. Preoperative treatment has a significant positive effect on nodal status [25]. Thus, we should establish a method to identify nodal positivity before secondary resection to discuss the benefit of an invasive surgery. An interpretation of the clinical nodal status via CT scan is difficult. Not every lymph node metastasis is suspicious in a CT scan and not every lymphadenopathy hides a metastasis especially after induction treatment when scar tissue may mimic viable tumor. In one study, only 54% of nodal statuses were interpreted correctly with the help of a CT scan [26]. Interpretation via PET-CT only reaches a sensitivity of 42% [27]. Finally, endosonographic biopsy of lymph nodes offers an almost hundred percent certainty about the histopathology of the tissue when an appropriate biopsy is succeeded [28]. Maybe pts would benefit from an upfront endosonographic biopsy of a suspicious lymphadenopathy to discuss further treatment in case of positivity.

Naumann et al. recently proved the impact of BMI on the outcome of pts treated with radiotherapy as induction [29]. Weight loss of more than 5% during induction therapy lead to a significant shorter overall survival (12 vs. 27 months). This result may outline weight loss as a symbol of high tumor activity, implying a missing benefit for secondary resection in these pts. On the contrary, our study showed a benefit for pts with normal weight and

underweight compared to pts who are overweight. Obesity is associated with a higher risk for concomitant disease. Additionally, fat cells are identified as one cause for chronic inflammation [30]. Earlier works already showed the negative impact of obesity on the outcome of pts with pancreatic cancer [31]. Therefore, further studies should examine the role of obesity or even cachexia on the outcome of pts with PDAC.

Our study also revealed a benefit of secondary resection for pts with normal pretherapeutic CA 19-9 levels. These types of cancer may have a less aggressive spreading biology than those with elevated CA 19-9. A previous research showed that the tumor marker CA 19-9 itself promotes the activation of EGFR (Epidermal Growth Factor Receptor) signaling in mice, suggesting an important role in the initiation and acceleration of pancreatic cancer [32]. Additionally, Gao et al. demonstrated the role of the gene FUT 3 (Galactoside 3(4)-L-fucosyltransferase) or the Lewis gene that is responsible for fucosylation of proteins and the synthesis of CA 19-9. Fucosylation by FUT 3 was shown to be upregulated in metastatic PDAC, suggesting a relation to the promotion of motility in pancreatic cancer [33]. Five to ten percent of the individuals were homozygous for the recessive allele of the gene FUT 3. These pts showed lower levels of fucosylation and thus no or low CA 19-9 secretion [34]. This leads to the supposition that pancreatic cancer in Lewis-negative pts should have a less aggressive biology. A previous study showed the opposite. In Liu et al., Lewis-negative pts with pancreatic cancer had a significant shorter overall survival and showed a higher proportion of metastasis. Possible reasons for this phenomenon could be the upregulation of CA 125 in these cases acting as a promotor for tumor cells or the lack of fucosylation playing an important role in human body physiology [34].

Furthermore, supporting the role of CA 19-9, the pts in our study who had an elevated CA 19-9 level >400 U/mL after induction therapy did not profit from resection. A normalized CA 19-9 level through induction therapy even lead to a significantly better OS for the pts, suggesting the tumor marker as a convenient predictive factor. The extent of the decrease in CA 19-9 did not have an impact on overall survival but on resection rate quality. If there was a decrease by more than 90%, these pts showed a higher rate of R0 resections. Similar results were seen in Boone et al., where a decrease of more than 50% was associated with a higher R0 resection rate in borderline pancreatic cancer [35].

Another impact on the OS of pts was the number of applications of neoadjuvant chemotherapy. Pts who were able to receive at least 5 applications benefited more from a secondary resection. Possible reasons could be the reduction of perineural or venous infiltration by prolonged chemotherapy, although our analysis did not show significant results to support this thesis. A limitation of this finding might be the unsuitability of the unit "applications" instead of "cycles" as one cycle consists of a different number of applications. Nevertheless, based on this result, we should consider finding-specific ranges for the duration of neoadjuvant therapy. Few studies exist that have investigated this question. While Truty et al. showed a significant benefit for pts who received at least 6 cycles of FOLFIRINOX or gemcitabine/nab-paclitaxel [36], another study proposed 4 cycles of modified FOLFIRINOX as sufficient for neoadjuvant therapy in BRPC [37]. Further investigations are necessary to establish a recommendation.

The second interest of this study was to identify factors which predict the ability of resection after induction treatment. CA 19-9 was one of the promising factors, although several studies revealed heterogeneous results. Michelakos et al. demonstrated the role of CA 19-9 in BRPC by showing that pts who were resected after induction therapy had a lower CA 19-9 level after induction than pts who could not be resected (21 vs. 40 U/mL) although CA 19-9 level was normalized in almost all of the pts [38]. The pts in our study had a mean CA 19-9 level of 138.5 U/mL after induction therapy, which is still higher than that in those not resected in the study of Michelakos et al. Therefore, we cannot support the approach of using specific strong threshold values of CA 19-9 by itself for decision making in PDAC.

The rate of radiographically measured by partial remission under induction therapy was particularly high in this study, at 73%. Compared with other studies where

partial response under induction therapy with FOLFIRINOX reached 31% [3] and under gemcitabine/nab-paclitaxel reached in 23% [4], radiographic response offers itself as a promising factor. Oppositely, studies have shown that RECIST criteria being used in order to interpret response under induction therapy with FOLFIRINOX are diagnostically less conclusive. Katz et al. demonstrated that 66% of their pts with borderline resectable pancreatic cancer were resected after induction therapy although CT scans showed non-resectable situations [20]. The borders of CT imaging for PDAC treated with neoadjuvant therapy lie in the disability of distinguishing between viable cancer and fibrosis as it occurs after neoadjuvant treatment. Therefore, specialists suggest exploring all pts independently of radiographic results and deciding on resection depending on frozen-section biopsies of involved arteries and venous structures [39].

Finally, to evaluate the reasons for worthwhile resectability in our cohort, it is necessary to combine multiple criteria. Many of those are already essential components for decision making within multidisciplinary tumor conferences. To be suitable for an intensive neoadjuvant therapy such as FOLFIRINOX, pts need to have an ECOG level of at least 1, which fulfilled 96% of our pts. Even after induction treatment, 81.4% had an ECOG of at least 1, suggesting a good tolerance for further multimodal treatments. Secondly, our pts showed a significant decrease in the tumor marker CA 19-9 from a mean of 4358.3 U/mL to 138.5 U/mL. Even though the degree of decline of CA 19-9 after neoadjuvant therapy had no significant influence on the survival of the pts, this sharp decline in the tumor marker in combination with the high number of radiographic response could have been seen as predictive for the success of a secondary resection.

The present study is limited by common biases that are mainly due to the retrospective character of this analysis. Pts that are able to undergo secondary resection initially profited from the selected chemotherapy and might also profit from continuing with this therapy regime. Prospective randomized trials are necessary to evaluate the benefit of a secondary resection over a continued chemotherapy in these cases. However, ongoing chemotherapy in cases of initial remission might eventually lead to higher rates of side effects due to toxic bone marrow damage and resistances against the chosen chemotherapy, which furthermore supports the role of a definite resection. Another limitation of this investigation is the small number of pts as well as the missing differentiation between LAPC and BRPC. However, we need to discuss whether this classification becomes obsolete in this new era of neoadjuvant therapy when LAPC becomes resectable and, in some cases, even reaches comparable OS to initially resectable pancreatic cancer [23].

Furthermore, interpretation of the radiographic response and clinical T status of locally advanced PDAC is limited. As already described above, CT scans have limitations in distinguishing viable cancer tissue and fibrosis. Additionally, a review of the American National Cancer Data Base showed a poor correlation between the clinical and pathological stages in pts who received initial surgery [40]. Consequently, results regarding clinical stage should be considered with caution.

## 5. Conclusions

Pancreatic cancer remains a disease with a generally poor outcome but heterogeneous clinical course. To identify the small but important number of pts who could potentially benefit from individual strategies, interdisciplinary, experienced cancer boards must involve the following factors in decision-making: the radiographic response, the course of tumor markers, and the general performance status of the pts. The initial CA 19-9 level does not seem to be suitable to predict the probability of a secondary resection; however, it provides the opportunity to predict the chance of a resection and prolonged survival during the course and should influence decision-making.

Nodal status plays an important role in the OS of pts, suggesting a non-localized disease. Special attention should be paid to the diagnosis of nodal positivity after induction treatment either by endosonographic biopsies of suspicious lymphadenopathies or by explorative surgeries with frozen-section analyses of lymph nodes.

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**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to private property of Charité–Universitätsmedizin Berlin.

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## 7. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

## 8. List of Publications

1. Rosumeck N, Timmermann L, Klein F, Bahra M, Stintzig S, Malinka T, et al. Induction Chemotherapy for Primarily Unresectable Locally Advanced Pancreatic Adenocarcinoma—Who Will Benefit from a Secondary Resection? 2021;57(1):77.

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