Aus dem

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„ The Mesopancreas and the Ductal Adenocarcinoma of the Head of the Pancreas ’’

Implications for Prognosis and Therapy

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Directory

1. Introduction

1.1. The Ductal Adenocarcinoma of the Pancreas

The pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic malignancy, accounting for about 90% of all pancreas neoplasms (1, 2). Thus, the terms “pancreatic cancer” and “pancreatic ductal adenocarcinoma” are often used synonymously. A curative resection is in 80% of the patients not possible, as a locally advanced or metastatic stage of disease is already present at the time of diagnosis (3, 4). Although therapeutic strategies have been extended over the past decade with the use of various multimodal therapies, PDAC is estimated to become the second leading cause of cancer-related deaths by 2030 (5).

Despite intensive efforts in basic research and clinical research, it has so far only partially been possible to achieve more than just minor improvements in median survival rates in the palliative stage (1, 6, 7). This is also contributed due to the high resistance of the PDAC to different therapy modalities such as chemotherapy and radiation therapy, as well as so-called “targeted” therapy strategies (8-11).

Confirmed risk factors for the development of pancreatic cancer are smoking, heavy alcohol consumption and obesity (12, 13). Certain diseases (diabetes mellitus, chronic pancreatitis) are also known to increase the risk for PDAC development, whereas occupational exposure to certain substances is discussed as risk factors (14). There is evidence that a healthy lifestyle with sufficient exercise and a healthy diet has a protective effect (15, 16). No drug prophylaxis is currently available (17).

An increased risk of PDAC has been observed in several hereditary syndromes in which pancreatic cancer is not one of the leading phenotypic manifestations (18). Familial pancreatic carcinoma (FPC) is now distinguished from these syndromes. An FPC is considered if at least two first-degree relatives in a family (regardless of the age of the

patient) have developed PDAC without the individuals meeting the clinical or family history criteria of other hereditary syndromes (19).

1.2. Current preoperative analysis

Studies in the literature are not available, in which symptoms and the combination of them that could suspect PDAC were analyzed. Which symptom alone or the combination of symptoms is sufficient to exclude a PDAC is also not known in the literature. While new onset of painless jaundice is highly suspicious for PDAC, new or existing type 2 diabetes mellitus in the absence of other symptoms should not be used as a trigger in extending diagnostic tests (20-22).

Unlike in patients with colo-rectal carcinomas, screening examinations for PDACs are yet not implemented (23). The diagnostic work up is solely started if the patient is presented actively in a medical facility. Various methods such as transabdominal sonography (US), endo-sonography (EUS), multi detector computed-tomography (MDCT), magnetic resonance imaging (MRI) with magnetic resonance cholangiopanreatography (MRCP) or endoscopic retrograde cholangiopanreatography (ERCP) are suitable modalities in order to clarify a suspected pancreatic malignancy (24-27).
Principally, an US already provides the suspected diagnosis of PDACs and possibly also the diagnosis of metastases. While ERCP only detects gait changes, all other methods enable the detection of an intrapancreatic mass (28-30). The MDCT is the gold-standard for pre-therapeutic staging with an at least biphasic contrast medium protocol (pancreatic parenchyma phase and portal venous phase).

MDCT and EUS are preferred in the pre-therapeutic work-up for assessing local tumor staging. Alternatively, an MRI can be performed in the event of contrast agent intolerance or

renal insufficiency. The EUS alone is however not sufficient enough for visual documentation, so that a cross-sectional image procedure (MDCT or MRI) is usually necessary to complete preoperative diagnostic imaging (28, 31).

There are multiple features that raise suspicion for PDAC, many of which also overlap with pancreatitis. These features include in all modalities a hypo attenuating mass, duct dilatation, duct cut-off, and upstream pancreatic atrophy (32, 33). All modalities achieved similar rates in sensitivity, specificity and accuracy with confidence intervals above 95% (34) (Table 1).

Table 1: Accuracy and predictive value of different radiographic modalities for PDAC detection. Modified from (34).

Modality	MRI	MDCT	PET-CT	EUS	US
Sensitivity	93%	90%	89%	91%	88%
Specificity	89%	87%	70%	86%	94%
Accuracy	90%	89%	84%	89%	91%

1.3. Current resectability criteria

The demographic development worldwide will lead to a further increase in the number of PDAC patients with an advanced age (35). Prospective studies in which the surgical and oncological outcome was studied across patients age groups are not available. A patient's advanced age is therefore not a factor against pancreatic surgery (36). Data and results are principally based on retrospective cohort studies supplemented by systematic reviews and meta-analyzes (37). As multimodal therapeutic options have been increased over the past decades, patient selection and the risk assessment regarding existing comorbidities are inevitable in the future to guide the decision-making process for major pancreatic surgery (38, 39).

As a result, the “International Association of Pancreatology” (IAP) published consensus criteria for the resectability of PDACs in 2017 (40) (Table 2). The IAP recommends resection of the pancreatic carcinoma in patients with an ECOG performance status of 0, 1 and 2, especially if the ECOG performance status is restricted due to tumor conditions (40). Criteria were introduced in this consensus paper, which determines the resectability of PDAC not only based on anatomical criteria (A), but also based on biological criteria (B) (e.g., the preoperative CA19-9 value) and defined conditional criteria (C) (e.g., ECOG performance status) (Table 2).

Table 2: ABC criteria for resectability according to International Association of Pancreatology. Modified from (40).

Resectability status	A (Anatomic)	B (Biology)	C (Conditional)
Primary resectable	Preoperative diagnostic imaging	CA 19-9 values	ECOG performance status
Borderline resectable			
Locally advanced			

As mentioned above, MDCT is the gold-standard to access the anatomical resectability of PDACs (Chapter 1.2). The anatomical criteria which determine resectability are based between the radiographic detected mass and the relationship with the portal vein/superior mesenteric vein (PV/SMV) and superior mesenteric artery (SMA). This is based on the established consensus by the International Study Group in Pancreatic Surgery (ISGPS) in 2014 (41, 42). Patients are sub-grouped into primary resectable, borderline resectable and locally-advanced/synchronously metastatic disease. The summary is presented in Table 3.

Table 3: Resectability classification by preoperative imaging studies according to the national comprehensive cancer network (43) (NCCN), the international association of pancreatology (IAP) and the International Study Group in Pancreatic Surgery (ISGPS). Simplified and modified from (40, 43).

<table>
<tr><th>Resectability status</th><th>Arterial vessels</th><th>Venous vessels</th></tr>
<tr><td>Primary resectable</td><td>No tumor contact</td><td>No or <180° tumor contact to PV/SMV</td></tr>
<tr><td>Borderline resectable</td><td>Tumor contact:
AMS <180°
Common hepatic artery without involvement of the celiac trunk</td><td>Tumor contact >180° to PV/SMV</td></tr>
<tr><td rowspan="2">Locally advanced/
Non-resectable</td><td colspan="2">M1 disease</td></tr>
<tr><td>Tumor contact >180°</td><td>Extend of Tumor contact in which no reconstruction is possible</td></tr>
</table>

Borderline resectable pancreatic cancers are defined if the risk of a non-tumor-free resection margin (R1 / R2) is increased during primary surgery. The likelihood of a vascular resection in these patients is high.

In summary, for the PDAC, unlike in the preoperative work up for rectal cancer patients (45-47), the attention lies mainly in the pancreatic parenchyma and the vascular system. The adipose tissue, located between the pancreatic parenchyma and the vascular system, has not adequately been studied yet and was neglected during radiographic examinations (48).

Whereas in eastern countries the dissection of the retropancreatic fatty tissue started to gain attention, this anatomical area has not yet gained sufficient attention in the western literature (49-51). It could be plausible that this region could serve as a novel and more precise cut off point for primary and borderline resectable PDACs. To date, it is not understood how frequently the retropancreatic fat is infiltrated by the PDAC and if these findings are of oncologic relevance.

However, lately implemented pathological pancreas protocols, in which the resection margins are separately analyzed, showed that not only the vascular groove was a major site of tumor infiltration (Section 1.5). These radiographic vascular cut off points between primary and borderline-resectable patients could only partially reflect the local peripancreatic tumor extensions. Since the circumferential pathological outcome was underestimated during pancreatic surgery (section 1.5 (44)), presumably novel MDCT-parameters are needed for all important resection sites.

The radiographic analyses of the tumor dimensions in preoperative staging for rectal or esophageal carcinomas are obligatory components (52-54). Despite numerous publications on MDCT and PDAC, it has so far not been reported if MDCT-estimated tumor size correlates with the redefined size-based T-stage of the 8th TNM classification (55). Since multimodal therapies are evolving and individualized for each patient (56), a precise preoperative staging, incorporating tumor size and the status of the retropancreatic fat, would be of great interest in the future in order to stratify patients for further therapeutic options.

1.4. Surgical therapy for pancreatic cancer, and efforts for extended surgery for colorectal cancer patients

Surgical therapy is the only potentially curative treatment option for pancreatic cancer patients (57). Interventions on the pancreas are among the most complex elective operations in visceral surgery, which are associated with a high rate of complications and mortality. Studies have shown a significant correlation between the 30-days mortality and the amount of conducted pancreatic surgeries (58). The mortality in high-volume centers was significantly lower when compared to centers with a lower quantity of cases. In guidelines, these values (number of cases per year) are used as a surrogate parameter and quality marker. However, perioperative and postoperative care is interdisciplinary and the quality of care differs across medical institutions and hospitals and depends on various factors (surgical bias/interventional radiography/interventional gastroenterology/intensive care unit) (59). National certification committees, for example ''Deutsche Krebs Gesellschaft (DKG)'' or ''Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)'', implemented similar criteria in order to obtain a certification. The pathological assessment quality or the likelihood of margin negative resections (R0) in an institution are not considered as quality indicators (60, 61).

Since the first surgical description of the pancreatic head removal in the beginning of the 20th century (62, 63), anatomic landmarks during surgery remained over the past decades similar (64). Therefore, during pancreatoduodenectomy the duodenum and the pancreatic head are removed from the retroperitoneal embryonic adhesions either with or without preservation of the pancreatic body and tail. In general, the transection plane of the pancreatic parenchyma is dependent on the location of the tumor. If no other contraindication is given, and the tumor is localized in the pancreatic head, formally the pancreatic body and tail can be preserved.

The dissection of the pancreatic tissue is performed posteriorly from the vena cava and abdominal aorta and continued medially from the PV/SMV and SMA. The extend of dissection and the amount of peri-vascular adipose tissue preserved has not been standardized and depends mainly on the philosophical view of the surgeon's degree of radicality (44, 50, 65, 66). The oncological value of the retropancreatic fat remains unknown, and there are only a dismal amount of studies in the literature in which the retropancreatic fat was analyzed with regard on cancerous infiltration (48, 67-70).

Studies in the 1970s have already analyzed the survival outcome in PDAC patients who received extended ''en-bloc'' resections compared to patients who received standardized resections (71). Fortner et al. unfortunately failed to show any survival benefit when compared to patients who received standardized surgery. However, in this era no standardized pathological reporting systems and cross-section examinations as well as chemotherapeutic treatment options were available for PDAC patients (72-74) which could have contributed, next to higher reported mortality rates, to the similar survival outcome. Until two decades ago, R0 resection rates have been propagated high and were underestimated in oncological pancreatic surgery (75). Presumably these two factors have contributed to the marginal interest in performing these extended resections. Much effort was put into decreasing morbidity and mortality rates after pancreatic resections during the past century. However during this surgical ''standstill'', chemotherapeutic regimes have evolved since the introduction of gemcitabine in the 90s (Table 4).

Table 4: Survival rates achieved over past decade by implemented new adjuvant therapeutic modalities. Simplified and modified from (72-74).

	Gemca/5FU/S1 Vs. Surgery	Gemca + Cap Vs. Gemca	mFOLFIRINOX Vs. Gemca
Median OS (months)	24	28	54
5-years OS	20-45%	30%	66% (3-Years OS)

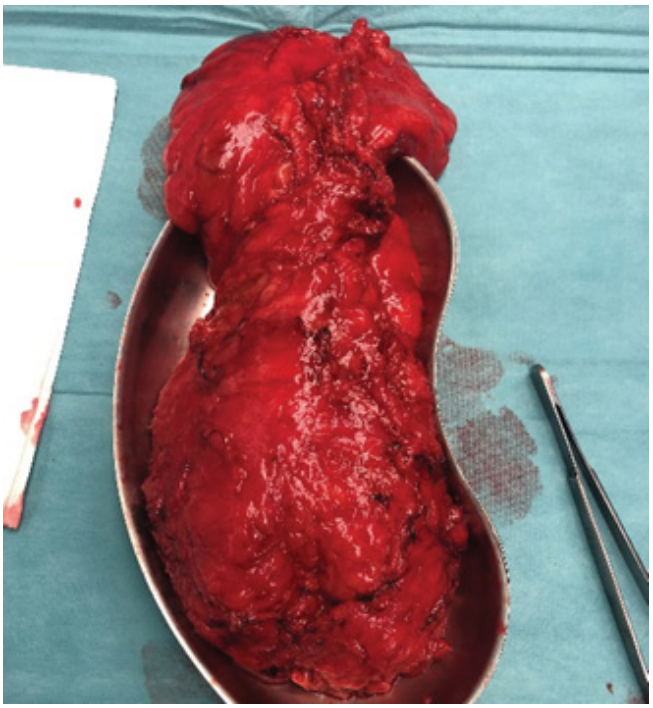
Cap: capecitabine, Gemca: gemcitabine, FOLFIRINOX: folinic acid, fluorouracil, irinotecan and oxaliplatin, OS: overall survival

To this day, local recurrence is a major concern in follow-up examinations for PDAC patients. Studies from 90s and lately published data from multi-centric prospective trials as well as post mortem analysis of deceased patients have confirmed rates of up to 60%-80% (76-78). Since margin ''negative'' resections were believed to be achieved in the majority of the patients, these follow-up results seemed paradox, and were not explained by the surgical results.

On the other hand, surgical treatment strategies have clearly evolved for colo-rectal cancer patients. In the end of the past century, the implementation of extended surgery by means of total mesorectal excision (TME) has become the gold-standard in surgical care for rectal cancer patients (79, 80). Since the rectum is primarily extraperitoneal, from an anatomic view, the term mesorectum is not officially recognized. However, the perirectal tissue with its vasculature arising from the inferior mesenteric artery and further comprising the lymphatic tissue is covered by a macroscopic visible fibrous sheet, the so called ''holy-plane'', allowing to categorize the rectum with its mesentery into a separated compartment (79). The amount of fibrous sheet visible on the resectate is used for pathological quality assessment (Mercury grade 1-3) (81-83). Studies have shown that the quality of surgery, hence the amount of fibrous sheet preserved, has correlated significantly with the survival outcome (Figure 1). Not

only was the surgical quality of the resectate assessed, but more importantly a circumferential resection margin histopathologically implemented and evaluated (84). In order to simplify the technique and standardize it into clinical practice and every-day nomenclature it seems concise to define it total mesorectal excision (85).

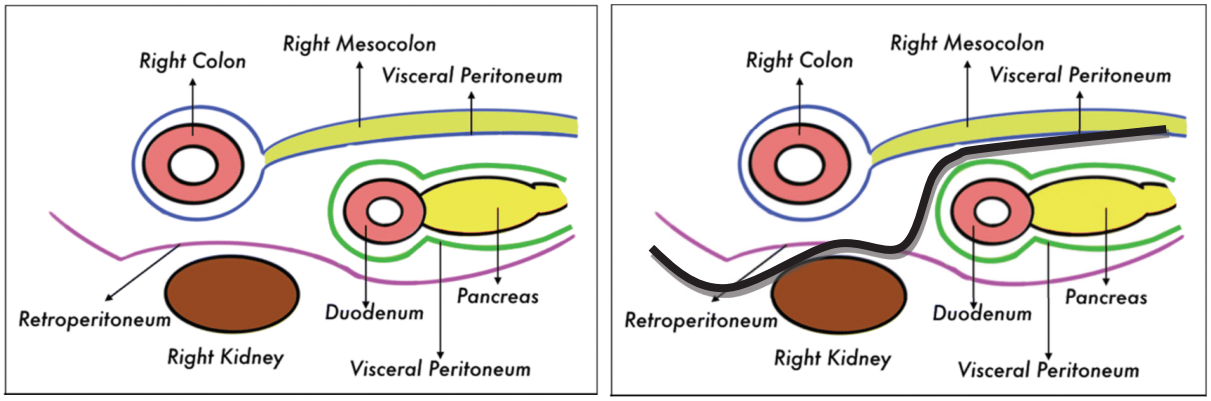
Figure1: Dorsal view after total mesorectal excision. (Safi SA, Department of Surgery (A), University Hospital Duesseldorf, all rights reserved).



Adapted from surgical TME protocols, with standardized dissection between fascial planes of fibrous layers, the Toldts' fascia during mesocolic excision for colon cancer patients has gained clinical attention in the past two decades for colon cancer patients as well (86).

These ''extended techniques'' for colo-rectal carcinomas that are comprised by predefined anatomic-compartment hallmarks have been implemented in international guidelines and represent the current standard in oncological care (87). These implementations were most importantly highlighted by studies that have shown a significant prognostic benefit while local-recurrence rates have decreased. Putting this all together, underlines the oncological value of anatomical layer-specific preparations (Figure 2).

Figure 2: Schematic slide presenting the fusion fascia of Fredet and the Toldt's line (purple). The adhesion plane between visceral peritoneum of the mesocolon of ascending colon and hepatic colonic flexure and the visceral peritoneum of duodenum and pancreas. Black line defines resection margin during mesocolic excision. Copyright and under License by (88).



Since the ascending colon and pancreas are both secondary retroperitoneal, redefined anatomic landmarks during oncological surgery for PDAC patients could be of scientific interest as well. However, the anatomy of the pancreas is more sophisticated when compared to the anatomy of the colo-rectal tract, as the circumferential boarders are limited by a visceral vasculate (i.e. caval vein and abdominal aorta posteriorly; the PV/SMV and SMA medially and the common hepatic artery as well as celiac trunk superiorly). Therefore, extended approaches are more likely to be limited when compared to the circumferential boarders during oncologic colo-rectal surgery.

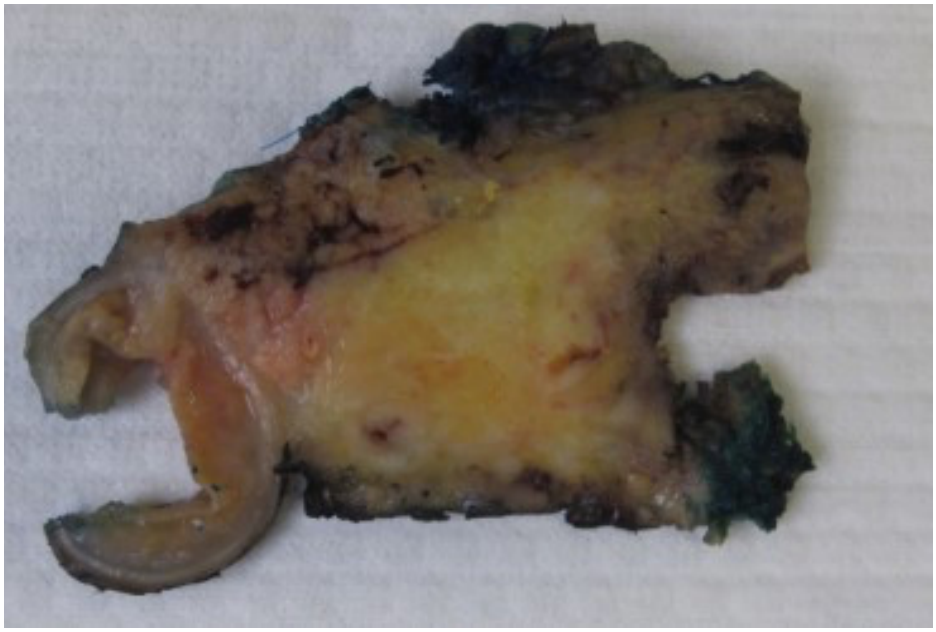
Following two conclusions are drawn: (1) The implementation of the pathological circumferential resection margin seems for PDAC patients necessary as well (Section 1.5). (2) Extended and vascular preserved pancreatic resections using predefined anatomic-hallmarks, synergistically to total mesorectal excision or mesocolic excision, seems to be a promising tool in order to maximize local tumor control (Section 1.6).

1.5. Histopathological Analysis and the dilemma with the R0-status

The PDAC is mostly located in the head of the pancreas rather than the body or tail (2). Since the PDAC of the pancreatic head is often diagnosed in a late stage of the disease, the tumor size (T-stage) is subsequently at an advanced stage of disease (>pT2), or even larger if located in the body or tail of the pancreas (1).

The PDAC presents as solid and firm white-yellowish poorly-defined mass (Figure 3). Regional lymph node metastases are also commonly present at diagnosis (2). The macroscopic grossing of PDAC specimens is of great importance for the qualitative workup of each PDAC case, with the three main aspects being the extent of the primary tumor, which is relevant for the T category of the TNM staging as well as the presence and number of lymph node metastases.

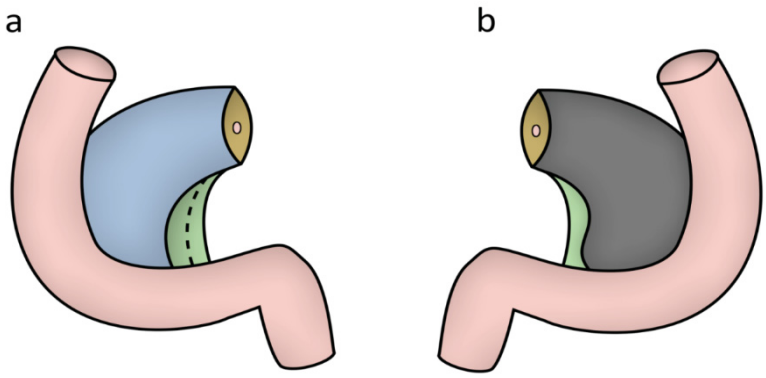
Figure 3: Pathological specimen of the pancreatic head with infiltration of the peripancreatic fatty tissue. The specimen was inked using a pre-defined color code (posterior surface: black, anterior surface: blue, medial surface: green). Grossing was done according to the axial slicing technique (pT3 pN2 (5/47) L1 V0 Pn1). (Haeberle L, Institute of Pathology, University Hospital of Duesseldorf, all rights reserved).



In an era of standardization and quality management, the evaluation of the circumferential resection margin (CRM), a refined histopathological examination protocol, was implemented for PDACs in 2004 according to the recommendations of the Royal College of Pathologists (LEEPP) (89, 90). Due to the growth pattern of ductal adenocarcinomas of the pancreas with strong fibrosis and desmoplastic stromal reaction as well as numerous surgical resection sites, histopathological processing of the circumferential resection margins is sophisticated when compared to the assessment of the CRM for colorectal carcinomas (91).

The following resection margins are separately inked in a predefined color code and histo-pathologically investigated: (1) Medial resection margin: Proc. uncinate (E) and vascular groove (A./V. mes. sup.) (green); (2) dorsal resection margin (formerly retropancreatic resection surface) (black) and (3) ventral resection margin (if tumor is localized macroscopically anteriorly) (blue) (Figure 4).

Figure 4: Schematic view of inking procedure in order to implement and analyze the circumferential resection margins. Copyright and under License by (2).



In addition to the correct application of the internationally valid R classification, uniform standards must apply to the resectate after pancreatoduodenectomy for PDACs. R0-resected PDACs are classified as CRM-positive if the distance between the tumor cells and the resection margin is less than 1mm but does not reach the resection margin (R0CRM+ or R0narrow). If the carcinoma cells are 1mm or more away from all resection margins, patients

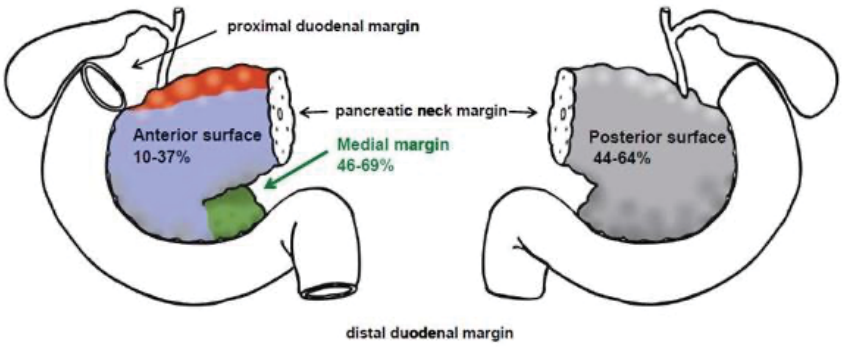
are staged as R0CRM-negative. Studies have shown a prognostic relevance by classifying the R0-status dependent on the tumor distance from the resection margins (1, 2, 44, 92). The survival outcome was significantly prolonged after R0CRM- resections when compared to surgery with insufficient margin clearances R1/R0CRM+ (93). *Most importantly was the resulted decline of R0CRM- resections after the CRM implementation. The once high propagated rates of R0 resections have significantly decreased to about 20%, which presumably have resulted in the high rates of local recurrences (44). The most common margins which are infiltrated are the posterior surface of the uncinate process and the medial groove of the vascular axis (44) (Figure 5). Thus, although the preoperative resectability criteria were published years after the known difficulty in R0CRM- resections, either patients are not adequately stratified (Section 1.3; primary resectable vs. rest) or surgical strategies not maximized yet (Section 1.6).*

Next to the prognostic relevance in R0CRM- resections is the the histopathological staging system as well. *The most important update in the revised 8th UICC edition was the stratification method of the T-stage, which is now strictly size based.* This allows a more precise prediction in survival outcome when compared to the previous version and its stratification power was even superior to the revised N-stage categories (55). *Thus, as already mentioned in section 1.3, predicting the T-stage by radiographic imaging could serve as a useful tool in identifying patients for individualized therapeutic options (upfront surgery vs. neoadjuvant therapy; Section 1.6).*

Since the rate of R0CRM- resections is low, the following two questions arise: (1) Are surgical capacities already maximized, or could the implementation of anatomic layer-specific preparations, synergistically to total-mesorectal or -mesocolic excision provide further margin safety? (Section 1.4 and 1.6) (2) Are the yet implemented preoperative radiographic cut-off

points not precise enough to stratify patients between primary resectable and borderline/non-resectable (Section 1.3).

Figure 5: Schematic view of most common positive resection sites during pancreatoduodenectomy. Note that not only the medial resection but also the posterior surface is at risk. Copyright and under License by (94).



In order to assess intraoperatively the resection margins for tumor infiltration, intraoperative frozen sections are widely applied for other malignancies and are used during pancreatic surgery as well. When frozen sections are positive, these allow subsequent re-resection in order to achieve secondary margin clearance. The study-line is incontenous and it remains unclear if survival outcomes are similar to patients who received primary margin clearances (95, 96). If otherwise proofed differently, primary margin clearances should be the defining goal in oncologic pancreatic resections (93, 97).

In summary, particular attention must be paid to the circumferential resection margin and the tumor size. Since the implementation of the redefined pathological standard, the extend of cancerous infiltration was clearly underestimated, as the rates of true R0 resections have drastically decreased to about 20%. As already mentioned above, in the re-defined ABC resectability criteria, the vascular status determined during diagnostic imaging remained the major factor. This however only reflects the medial resection margin. Since the dorsal resection margin was evenly infiltrated in pathological studies when compared to the medial

resection margin, it could be of further evidence that the retropancreatic adipose tissue could be of oncological interest. The pre-therapeutic analysis of the retropancreatic adipose tissue as well as tumor size and vascular status could be useful as a prediction model to stratify between R0CRM- and R0CRM+ resections instead between R0 and R1 resections.

1.6. The mesopancreas, Toldt's fascia and a possible implication from colorectal surgery?

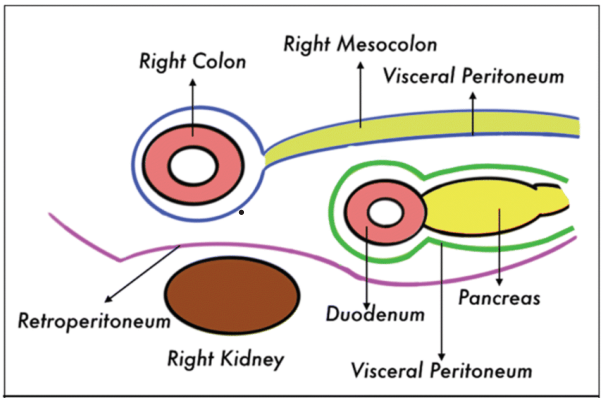
The Pancreas is a secondary retroperitoneal organ. The pancreas develops during the 4th week of gestation from two protuberances of the primitive foregut, the ventral and dorsal pancreatic anlage. The ventral appendix is located in the ventral mesentery below the liver appendix, while the dorsal appendix arises slightly above and opposite the liver appendix. In the following two weeks of gestation, the ventral system moves together with the confluence of the common bile duct around the back of the foregut, behind and under the dorsal system (rotation). Subsequently, both the parenchyma and the excretory ducts of both appendages fuse, with the dorsal appendix forming the body and tail and the ventral appendix forming the head and uncinate process (fusion). The ductus pancreaticus (Wirsung), which becomes the main duct of the pancreas, is created by the fusion of the duct of the ventral system with the distal duct part of the dorsal system. The proximal duct portion of the dorsal attachment either recedes completely or remains as an accessory duct (Santorini duct) (98, 99).

Extended oncological pancreatic surgery was already described in the early 1970s; in an era without adjuvant chemotherapy (71). Since survival outcome was not improved and mortality rates were high, no further efforts have been made. However, margin negative resection rates have drastically dropped and local-recurrence after surgery remains a major dilemma (44), redefined surgical resection strategies are clearly demanded that achieve higher rates of curative resections without the need to perform vascular resection and reconstruction (50).

Since anatomic landmarks have stayed similar during pancreatoduodenectomy for PDAC patients (100), only a marginal amount of studies are known in which local tumor control was achieved with a higher rate and classified by the implemented redefined pathological standards (CRM) (101). In our opinion, insufficient rates of margin negative resections are either a result of inadequate preoperative stratification or surgical bias (44).

Synergistically to the ascending colon, the pancreas lies as well secondary retroperitoneal (86). Thus, the topography of the Toldt's fascia could be transferred to the anatomy of the pancreas as well (86) (Figure 6). Anatomico-surgical studies are missing in which an in-depth study of the retropancreatic area was carried out with the anatomical topography and uniform nomenclature of the fusion fascia. Focus was lied on to the composition of the retropancreatic tissue instead of the extensions of fascia sheets across the pancreas in order to provide evidence for the existence of a separated anatomical-compartment (mesopancreas) (67). Therefore, only the Toldt's fascia has gained clinical relevance during oncological resection in colon cancer patients. Fusion fascia that are known to exist in the retropancreatic area have been forgotten and do not find particular attention in clinical literature on pancreatic surgery.

Figure 6: Schematic trans axial view of upper abdominal organs. Could the Toldt's fascia continue cranio-medially towards the retropancreatic area? Copyright and under License by (88)



The Treitz's fusion fascia is located between the dorsal aspect of the pancreatic head and the aortocaval plane. It is an attachment structure of the pancreatic head and duodenum (pars II, III and (IV)) to the dorsal abdominal wall. When considering the Toldt's fusion fascia of the ascending colon, it could be suggested that this fibrous sheet is a continuous retroperitoneal plane which extends medio-cranially and combines with the Treitz's fusion fascia (102). Clinical studies are missing in which the topography of these two fascies are described with the focus of a possible connection. During embryonic growth, the pancreas is rotating around the superior mesenteric artery, and its arterial vasculate is arising from it, thus it seems coherent that the dorsal retro-pancreatic layer that comprises all the pancreatic vasculate and lymphatic tissue is running from a mesenteric root of the superior mesenteric artery (103). However, current surgical practice and anatomical studies are missing that define surgical resections with an intact fibrous sheet running across the dorsal and medial resection margin that envelops the retropancreatic tissue.

The term mesopancreas is not officially approved by anatomic societies. In the known literature, only a marginal amount of anatomic studies are available, in which the mesopancreatic/retropancreatic tissue was anatomically and histologically studied (48, 67, 69, 70, 104). Surgery with implementing the topography of anatomic fusion fascia is mainly standardized in Japanese pancreatic societies, and studies from the western world is missing that describe the standardized dissection of the mesopancreas/retropancreatic root until the origin of the SMA. Nevertheless current surgical literature is missing in which a uniform nomenclature was implemented with the known historical anatomical findings.

Since the mesopancreatic/retropancreatic adipose tissue is comprised in these extended dissection planes, it yet remains unknown if and with what rate this fatty tissue is infiltrated by the PDAC. Surgical-histopathological studies are missing in which an in-depth

histopathological evaluation of the mesopancreas was performed comprising a survival analysis of consecutive treated patients. It would be also of importance if the dissection of the mesopancreatic/retropancreatic adipose tissue would contribute to a higher R0CRM- rate and if this rate would be dependent of the cancerous infiltration status of the mesopancreas. Only studies are available in the literature that describe such extended pancreatic resection. The histopathological outcome as well as the oncological value with focus on local recurrence rates was not studied yet (105).

1.7. Current literature on neoadjuvant therapy

The following points underline the need to enhance treatment strategies for PDAC patients as well: (1) R0CRM- resections are not common and local-tumor control after pancreatic surgery was not achieved; the extend of infiltration of the PDAC was underestimated. (2) Likewise, to the tumor stage dependent multimodal treatment strategies for rectal cancer patients, neoadjuvant therapy for PDAC patients could enhance local tumor control as well. (3) Most PDAC patients after curative therapy are diagnosed not only with local recurrence but with systemic relapse.

Potential advantages of this neoadjuvant concept are an early systemic treatment of existing micro-metastases, better tolerability of chemotherapy when compared to adjuvant chemotherapy and a potentially increased R0CRM- rate (106, 107). A vast amount of prospective studies on this topic is available for rectal and esophageal as well as gastric cancer patients (53, 54). For PDAC patients, only few prospective randomized studies are currently available which did not yet show a clear advantage for neoadjuvant therapy over upfront surgery regarding overall survival in patients with primary resectable or borderline resectable cases (56, 108-111).

Only a significant benefit in relapse free survival (RFS) and higher R0CRM- rates were achieved of the randomized phase III PREOPANC study in resectable and borderline-

resectable PDACs after neoadjuvant radiochemotherapy with gemcitabine compared to adjuvant chemotherapy with gemcitabine alone (112). An improvement in overall survival (OS) was only reached in a subgroup analysis of patients who underwent curative resection. The current PREOPANC II study which compares two neoadjuvant chemotherapeutic regimes is still running (56). In the Japanese JSAP-05 study patients with primarily resectable PDACs either received neoadjuvant chemotherapy with gemcitabine and S1 or underwent upfront surgery (109). This randomized phase III study showed a significant improvement in the median OS in the neoadjuvant treated group. Results are yet available only as a congress abstract. Since further studies are missing, no clear recommendation for standardized neoadjuvant chemotherapy is given in current guidelines.

However, margin negative resection rates are low and most of the patients are diagnosed with systemic relapse in follow-up examinations. Lately, novel pre-therapeutic imaging applications of PET/CT using radioactive labelled Fibroblast Activation Protein (FAP) - Inhibitors (FAPI-PET/CT) resulted into the diagnosis of an underestimated, previously not detected, systemic stage of disease in patients yet receiving primary surgery (113, 114). Putting this and the above-mentioned dilemma together (known rates in R0CRM- resections, local recurrence and systemic relapse rate as well as resectability criteria with presumed partial estimated tumor extensions), underlines the importance for neoadjuvant chemotherapy.

Since the relation between the mesopancreatic/retropancreatic area and the PDAC is unknown in patients who received upfront surgery, it remains unclear if tumor cells routinely remain in the mesopancreatic/retropancreatic area following neoadjuvant therapy and if the tissue is vital or necrotic. Both for patients who receive upfront surgery or neoadjuvant therapy prior to surgery the mesopancreatic/retropancreatic area is a yet unexplored region.

1.8. Current literature on distant lymph node metastasis or hepatic metastasis

Standardized lymphadenectomy involves the peripancreatic lymph-node (LN) station, right hemi-circumference of the SMA and celiac trunk as well as hepatoduodenal ligament stations. The removal of LNs in those stations is not underlined in randomized trials and are recommended by expert consensus statements. Since most patients are diagnosed with lymphatic metastases, a curative intended therapeutic approach is justified in patients with preoperatively diagnosed enlarged LNs as well. The extend of lymphadenectomy was no prognostic factor (115), which is underlined by the superiority in survival stratification by the updated T-stage when compared to N-stage of the 8th UICC edition (55). Thus, it could be presumed that all PDAC patients with PDAC are at an advanced stage of lymphatic disease.

Since standardized surgical therapy is not recommended in patients with synchronous distant lymphatic para-aortic (PALN) disease (LN station 16), no studies are available in which routinely dissection of the PALN is performed independent on the preoperative staging (116, 117) . Although the para-aortic lymph nodes are in immediate vicinity to the pancreatic head, these are still considered 'distant' lymphatic metastases in PDAC, supposedly indicating a late stage in the lymphatic spread. While some studies propagate no survival difference across the PALN status in PDAC patients, in other studies, the removal of positive PALN correlated with a longer patient survival (118).

There is no study in the literature that compared a patient cohort who received routinely PALN lymphadenectomy in a large study cohort limiting selection bias. Following issues remain elusive: (1) predictive value of MDCT of those retroperitoneal lymph nodes, (2) the difference in lymphatic mapping of other LN stations, (3) the survival outcome in unselected patients and the pattern of metachronous disease across patients stratified according to the PALN status.

The study-line on multimodal therapy for oligometastatic hepatic disease is dismal and heterogeneous. Palliative intended therapy or chemotherapy is the standard of care for patients with metastasized or locally advanced PDACs (119, 120). To date, however, no standardized surgical treatment exists for patients with synchronous or metachronous oligometastatic disease. Therefore, in current clinical practice, unlike in other malignancies, synchronous metastasectomy of PDAC has rarely been performed. In these patients, neoadjuvant chemotherapy with subsequent resection and ablative technologies are possible treatment options for metastasized PDAC. Hence, therapeutic regimes, such as FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) or gemcitabine and nab-paclitaxel, have very recently been established as neoadjuvant or primary treatment options (120, 121). To date, it is unclear which patient group might benefit from such an individual approach of neoadjuvant therapy followed by radical tumor resection. Moreover, it is unclear whether chemotherapy-naive patients with small tumor burdens, patients with a stable disease, or patients with tumor regression after neoadjuvant therapy would benefit from a multimodal approach.

Improved survival outcome by curative surgery, especially in regard to long-term outcome, has never been adequately studied in patients with limited and isolated synchronous hepatic metastases of PDAC. To date, surgery in these cases is not recommended in any current guideline. Curative intended therapy for patients with synchronous hepatic metastasized colorectal cancer or pancreatic neuroendocrine tumors have been neglected in the past. However, over the last decade surgery became the gold standard of care. Moreover, it has been proven to be oncological beneficial, to prolong survival, and to improve the quality of life (45, 122). In PDAC with oligometastatic disease, however, only limited evidence is currently available (123).

In two recent studies, a larger number of patients with synchronously hepatic-metastasized PDACs were analyzed (124, 125). Six European pancreatic centers retrospectively reported on 69 patients diagnosed with synchronously hepatic-metastasized PDACs, who received simultaneous pancreatic and liver resections (125). Patients treated in palliative intent served as a control group. A significant benefit for survival was achieved for patients undergoing this extensive surgical approach with tolerable rates of morbidity and mortality compared to patients who only received an exploration. *Over the past decade chemotherapeutic regimes have evolved with an improved survival outcome when compared to previous standards, presumably allowing to extend indication windows for extended surgery as well in patients with an oligometastatic disease. No study compared the survival outcome synchronously oligometastatic resection to patients with an extended chemotherapeutic regime with localized PDACs who received a single agent chemotherapy.*

1.9. Current literature to metachronous disease

Most PDAC patients after multimodal therapy during follow-up are diagnosed with systemic relapse. After local recurrence, the liver remains the main sight for relapse followed by distant pulmonary and osseous metastases (78, 126). Although pulmonary metastases are located more distantly from the primary tumor site than liver metastases, the survival outcome in pulmonary metastasized patients is somehow paradox, which is superior when compared to patients with hepatic metastases (127-130).

In colo-rectal cancer patients, therapeutic options have been extended in the past decades even for metachronous relapse (53). Since extended surgical approaches revealed significant survival benefits, the indication window for multimodal therapy has been widened (53). To date, no standardized surgical treatment exists for PDAC patients with

oligometastatic metachronous disease. Therefore, in current clinical practice, unlike in other malignancies, metachronous metastasectomy has barely been performed for PDAC.

In these metachronous patients, chemotherapy largely remains the only treatment option on offer. Therapeutic regimes, such as FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin), have very recently been established as primary treatment option and most patients with an adequate clinical condition can tolerate these cytotoxic regimes (120).

To date, it remains uncertain which patients may benefit from surgical metastasis resection. Yet, whether chemotherapy-naive patients with resectable relapse burden, patients with a stable relapse or patients with relapse regression following chemotherapy will benefit from a surgical approach, is hardly investigated.

To date, the survival outcome of metachronous disease has only been evaluated from one compartment (local, hepatic or pulmonary) in a single center cohort (125, 128, 129, 131). Treatment decisions in patients with an early diagnosed technically resectable relapse remain are not yet standardized and recognized. *Early relapse surgery for local recurrence without systemic spread could be beneficial, assuming a less aggressive tumor biology and only insufficient primary margin negativity in this subgroup of patients. Also in patients with late diagnosed isolated pulmonary or hepatic metastases local therapeutic options could be implemented.*

1.10. Summary of the introduction, hypothesis and aim

After the introduction of the histopathological CRM, the rate of R0CRM- resections has drastically declined while local recurrence rates remain a major concern (44). Pre- and intraoperative methods for the resectability evaluation have been studied (40, 42, 132, 133). On one hand these preoperative resectability criteria presumably only reflect partially true tumor extensions, which are needed in order to decide/plan treatment strategies/extend of surgery. On the other hand, intraoperative resectability techniques only stratify patients into primary resectable/non-resectable in order to increase R0CRM- resection rates, while the anatomic hallmarks during surgery have remained the same. It remains unknown if extended surgery could contribute to an even higher R0CRM- resection rate. Literature from the western world is missing in which extended surgery, by using predefined embryologic/anatomic landmarks, are described and analyzed. Since the 1970s after Fortner at al no further studies are available in which standardized extended surgery was performed (71).

Surgery with the excision of the mesentery from the colon and rectum for colo-rectal cancer patients, i.e. mesocolic excision or mesorectal excision achieved international recognition (79, 86). These standards improved survival outcome and significantly decreased local recurrence rates (87). The implementation of such resection techniques, which are based on the idea of the compartment-anatomy and separated by the retroperitoneal fascia systems, could be of interest for oncological pancreatic surgery as well. Mesopancreatic excision during pancreatoduodenectomy has been already implemented in the Japanese pancreatic society (50). Anatomical, histopathological and oncological outcomes have however not been studied yet and the prognostic significance of mesopancreatic excision remains elusive. In-depth evaluation of the mesopancreas in PDAC patients combined with the infiltration status as well as the rate of infiltration and the ability to pretherapeutically identify an infiltration

could serve as a similar important marker likewise to the infiltration status of the mesorectal fascia in rectal cancer patients.

An anatomical review was performed by accessing historical primary anatomical textbooks. The whipple resectate was studied and the mesopancreatic/retro-pancreatic area was histopathologically analyzed for questionable cancer infiltration. A survival analysis was performed with the evaluation of follow-up results. The predictive value of preoperative MDCT staging of mesopancreatic/retro-pancreatic area was analyzed. Since the revised T-stage in the updated 8th UICC edition is strictly size based and of oncological importance, the presumed radiographic tumor size was measured by MDCT slides and correlated with the histopathological outcome.

(134) Safi SA, Haeberle L, Fluegen G, Lehwald-Tywuschik N, Krieg A, Keitel V, Luedde T, Esposito I, Rehders A, Knoefel WT. ***Mesopancreatic excision for pancreatic ductal adenocarcinoma improves local disease control and survival****. Pancreatology. 2021 Jun;21(4):787-795. doi: 10.1016/j.pan.2021.02.024. Epub 2021 Mar 17. PMID: 33775563.*

(135) Safi SA, Haeberle L, Heuveldop S, Kroepil P, Fung S, Rehders A, Keitel V, Luedde T, Fuerst G, Esposito I, Ziayee F, Antoch G, Knoefel WT, Fluegen G. ***Pre-Operative MDCT Staging Predicts Mesopancreatic Fat Infiltration-A Novel Marker for Neoadjuvant Treatment?*** *Cancers (Basel). 2021 Aug 28;13(17):4361. doi: 10.3390/cancers13174361. PMID: 34503170; PMCID: PMC8430607.*

Since neoadjuvant chemotherapy will most likely play a major role in multimodal therapy in the near future (111, 136), it remains unclear if MPE is still warranted after neoadjuvant therapy. MPE is only performed in a few pancreatic centers and neoadjuvant therapy only provided yet for a selected group of patients. The mesopancreatic/retropancreatic fat was

analyzed in patients who received neoadjuvant therapy and compared to patients who received upfront surgery.

(137) Safi, S.-A.; Haeberle, L.; Rehders, A.; Fung, S.; Vaghiri, S.; Roderburg, C.; Luedde, T.; Ziayee, F.; Esposito, I.; Fluegen, G.; Knoefel, W.T. ***Neoadjuvant Treatment Lowers the Risk of Mesopancreatic Fat Infiltration and Local Recurrence in Patients with Pancreatic Cancer****. Cancers 2022, 14, 68. https://doi.org/10.3390/cancers14010068*

Furthermore, it remains unclear if PALN status has any oncological relevance. Only a dismal amount of studies exist in the literature that compared the outcomes of PALN negative and PALN positive patients. Data is missing from a consecutively treated non-selected patient cohort (116, 138). Furthermore, no lymph-node mapping was before performed in patients stratified according to the PALN status. It remains elusive if PALN positive patients have a higher metastatic lymph node burden when compared to PALN negative patients and if PALN positive patients show a different pattern of metachronous disease when compared to PALN negative patients.

(139) Safi SA, Rehders A, Haeberle L, Fung S, Lehwald N, Esposito I, Ziayee F, Krieg A, Knoefel WT, Fluegen G. ***Para-aortic lymph nodes and ductal adenocarcinoma of the pancreas: Distant neighbors?*** *Surgery. 2021 Aug 12:S0039-6060(21)00666-8. doi: 10.1016/j.surg.2021.06.045. Epub ahead of print. PMID: 34392977.*

Since chemotherapeutic regimes have been extended and survival outcome improved, extended surgery combined with a multi-agent chemotherapy in oligometastatic hepatic disease could be beneficial, when compared to patients who received palliative care (74, 120).

The median OS in R0 resected non-metastatic PDAC patients is increased from 20 months to 54 months with the implementation of mFOLFIRNOX when compared to the previous chemotherapeutic standards. For this reason, extended surgery for oligometastatic disease could be beneficial, provided that patients received such extended chemotherapeutic regimes. The oncological outcome was studied between synchronously hepatic metastasized PDAC patients who received surgery and extended multidrug chemotherapy and patients with localized disease who received standard single agent chemotherapy.

(140) Safi SA, Fluegen G, Rehders A, Haeberle L, Fung S, Keitel V, Krieg A, Knoefel WT, Lehwald-Tywuschik N. ***Surgical margin clearance and extended chemotherapy defines survival for synchronous oligometastatic liver lesions of the ductal adenocarcinoma of the pancreas.*** *Int J Clin Oncol. 2021 Oct;26(10):1911-1921. doi: 10.1007/s10147-021-01961-5. Epub 2021 Jun 16. PMID: 34132929; PMCID: PMC8449759.*

To date, no standardized surgical treatment exists for patients with metachronous isolated disease. Therefore, in current clinical practice, unlike in other malignancies, metachronous metastasectomy has barely been performed for PDAC.

In previous studies, the survival outcome of metachronous disease has only been evaluated from one compartment (local, hepatic or pulmonary) in a single center cohort (125, 128, 129, 131). Thus, relapse free survival (RFS) in patients before relapse diagnosis as well as survival after relapse diagnoses (Post relapse survival, PRS) were not studied and compared to each other from results of a single institution. Patients were identified who succumbed to isolated relapse (hepatic, pulmonary or local recurrence) and either received relapse surgery or relapse chemotherapy. RFS before relapse diagnoses was evaluated and correlated across relapse locations. Survival after secondary treatment (PRS) (surgery vs. chemotherapy) was analyzed and compared.

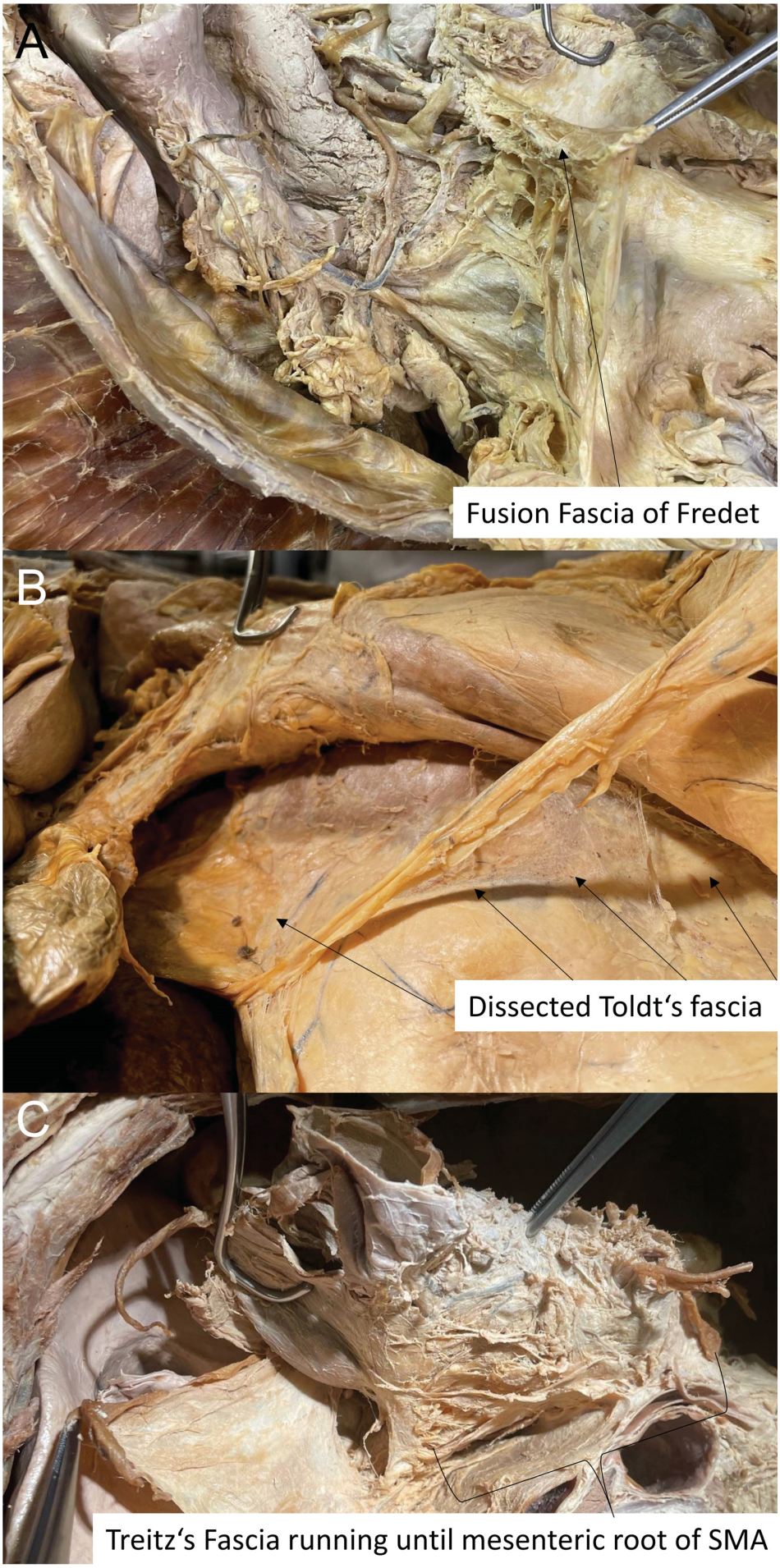
(141) Safi SA, Lehwald-Tywuschik N, Rehders A, Fluegen G, Haeberle L, Keitel V, Knoefel WT. ***Site of relapse of ductal adenocarcinoma of the pancreas affects survival after multimodal therapy.*** *BMC Surg. 2021 Mar 3;21(1):110. doi: 10.1186/s12893-021-01082-w. PMID: 33658016; PMCID: PMC7931536.*

2. Results and Discussion

2.1 The Anatomy of the Mesopancreas

The Toldt's Fascia is an important anatomic landmark during oncologic resection and defines the lateral as well as dorsal borders of the mesentery from the ascending as well as descending colon (86, 88). Since the pancreas is likewise to the ascending colon secondary retroperitoneal located, it seems coherent to suggest that such fusion fascia could be found around the head of the pancreas as well. In an in-depth review of surgical-anatomic literature (48, 67-70, 99, 101, 104, 142, 143), primary anatomic text books of the 19th as well as beginning of the 20th century (144-146) and by re-evaluating the peripancreatic region from body donors, following conclusions were drawn: (1) The fusion fascia of Treitz is a medio-cranial extension of the Toldt's fascia. (2) The Treitz's fusion fascia does run underneath the pancreatic head and continues until the mesenteric root of the superior mesenteric artery. (3) The anatomy of the portal vein should be seen as an atypical variant because the adventitia is not enveloped by the fusion fascia nor the mesopancreatic fat.

Figure 7 (A): Picture from right body-donor side. The right colon flexure and ascending colon are dissected and moved aborally of the picture. The mesentery was dissected until the pancreatic parenchyma. **(B):** Dissection of the right colon flexure and ascending colon with a partial kocher manoeuvre. One dorsal continuous plane from the hepatoduodenal ligament until the mesentery of the ascending colon is seen. **(C):** Transversal dissected body donor with a partial Kocher manoeuvre, displaying the Treitz fascia running continuously until the mesenteric root of the SMA. (W. Neuhuber, Institute of Anatomy, Friedrich Alexander Universität Erlangen-Nürnberg, Universtitätsstraße 19, 91054 Erlangen, all rights reserved).


A
Fusion Fascia of Fredet
B
Dissected Toldt‘s fascia
C
Treitz‘s Fascia running until mesenteric root of SMA

2.2 Mesopancreatic excision; how we do it

After establishing a clear view of the duodenum and pancreas, a wide Kocher manoeuvre is performed to complete the mobilization of the pancreatic head displaying the left renal vein. A simultaneous transection of the mesopancreatic lamina followed by a para-aortic and interaortocaval lymphadenectomy (PALN-LAD) to the right border of the SMA and PV/SMV is performed. The dissection is then accomplished to the inferior border of the pancreatic neck. Following this, dissection of the hepatoduodenal ligament (left and right hepatic artery, common hepatic artery (CHA), gastroduodenal artery (GDA), common bile duct, PV/SMV) completes surgical exploration. Lymphadenectomy and dissection of the common hepatic artery is performed up to its origin from the celiac trunk (CT). The jejunum, the ligament of Treitz and the duodenal bulb (or distal stomach) can then be transected. The jejunum is then mobilized to the patient's right side. After the pancreatic head is completely separated from the PV/SMV and the SMA, the pancreatic neck is divided. Next, lymphadenectomy and dissection of the portal vein and superior mesenteric vein is completed. If a possible tumor infiltration is present, venous resection and reconstruction is routinely performed. Sharp preparation along the SMA and the CT up to their aortic origins is carried out. To avoid persistent diarrhoea only 180°-270° of the right circumference of the SMA are dissected. If cancerous involvement is intraoperatively suspected, dissection of the SMA is extended to the left circumference (Figure 8A and B).

The aim of the procedure is complete dissection of perineural and lymphatic tissue and structures surrounding the pancreatic head/uncinate process (CHA, GDA, CT, SMA, PV, SMV), in an "en bloc" resection in which we preserve a fibrous sheet that runs between the duodenum and the origin of the SMA. We designated this surgical process mesopancreatic excision (Figure 9A and B).

Figure 8 (A): Intraoperative picture demonstrating MPE from patients' right side. **(B):** Intraoperative picture demonstrating the surgical site after structured radical partial pancreatoduodenectomy for hPDAC. Complete skeletonization of the SMA is only carried out for 180° of the right circumference. Only in selected cases in which tumor encasement is intraoperatively suspicious, an extended dissection >180° of the SMA is carried out. Copyright and under License by (134).

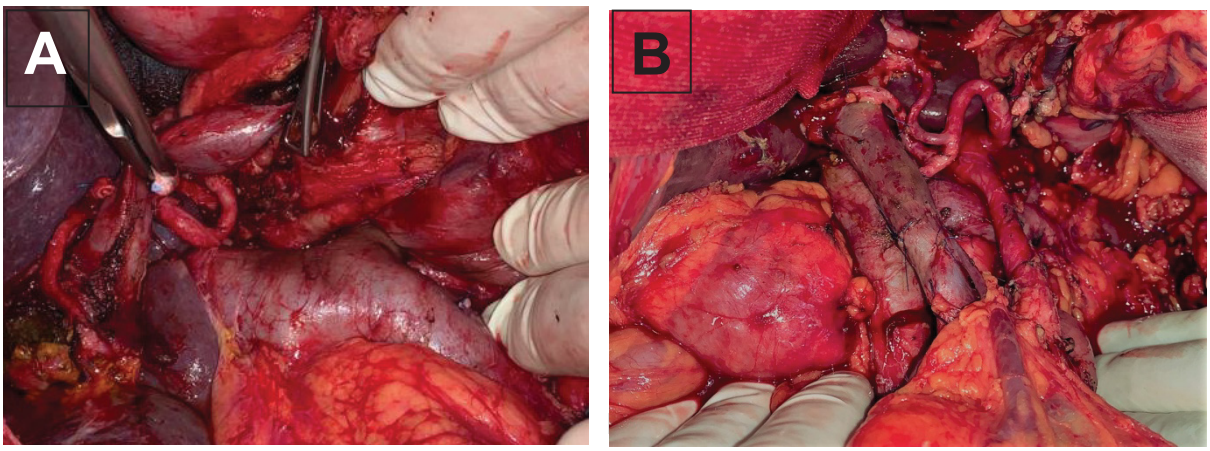
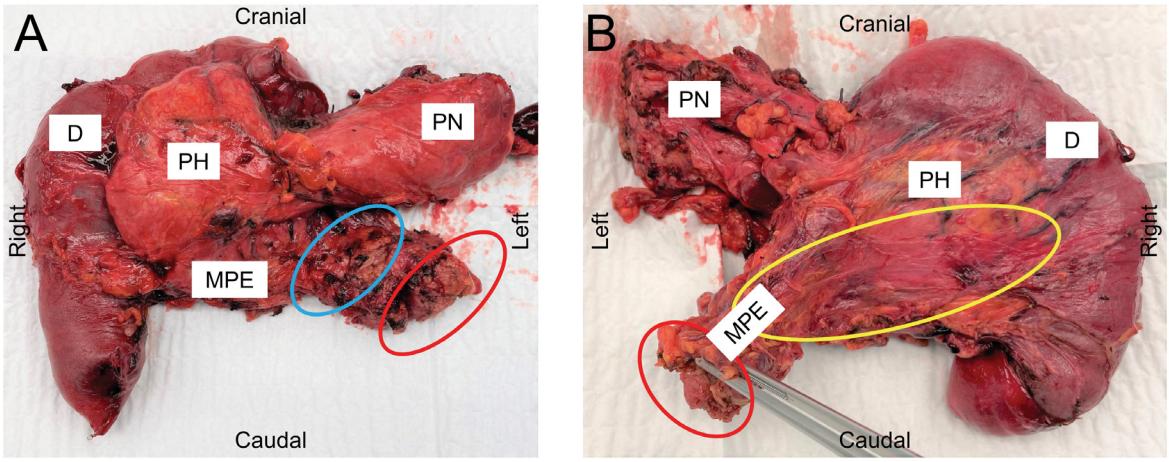
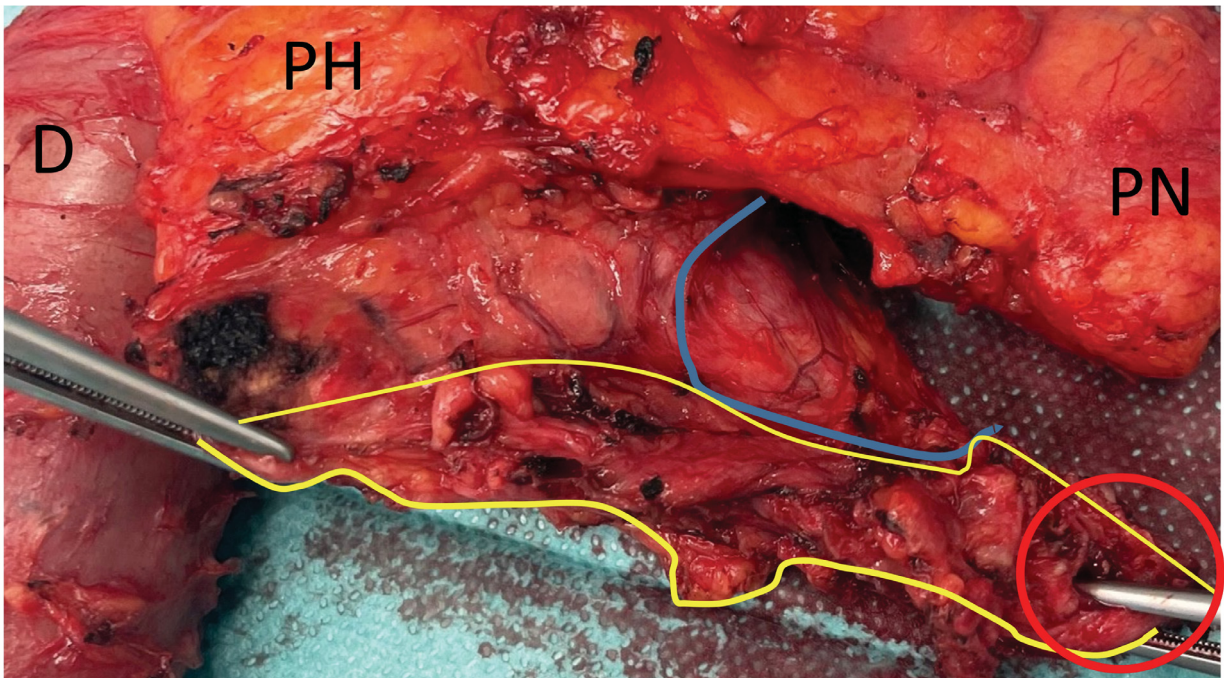


Figure 9 (A): Ventral view of specimen following pancreaticoduodenectomy for PDAC demonstrating mesopancreatic excision. **(B):** Posterior view of specimen. Note the fibrous tissue in B (yellow circle, Treitz's fascia) extending between the mesenteric origin of the superior mesenteric artery and the duodenum. Positional markings indicate the position of specimen in-situ (D: duodenum; MPE: mesopancreatic excision PH: pancreatic head; PN: pancreatic neck). Copyright and under License by (137).



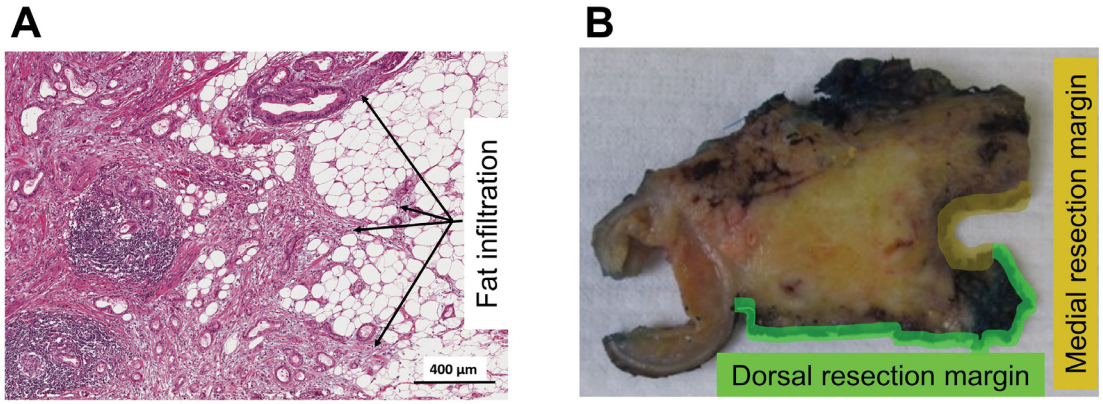
When the mesopancreatic excision until the root of the SMA is compared to the dissection of the tissue around the PV/SMV, it can be concluded that the peritoneum just envelops the PV/SMV which easers the surgical mobilisation when compared to the dissection and the mobilisation of the SMA. This could contribute to possibility of blunt preparation and dissection of the PV/SMV from its adhesions whereas the dissection around the SMA is more sophisticated. As seen in Figure 7C, 8A and 9B the mesopancreas with the enveloped treitz's fascia is running up to the origin of the SMA, whereas the serosa and the peritoneum is running around the PV/SMV (Figure 9A, and 10).

Figure 10: Ventral view of specimen following pancreatoduodenectomy showing the medial groove of the PV/SMV (blue circle). Note the lack of mesopancreatic fatty tissue (yellow lines) around the medial groove. The mesopancreatic arch is extending beneath the medial groove from the duodenum until the origin of the SMA (red circle). D: duodenum; PH: Head of the pancreas; PN: pancreatic neck. (Safi SA, Department of Surgery (A), University hospital of Duesseldorf, all rights reserved)



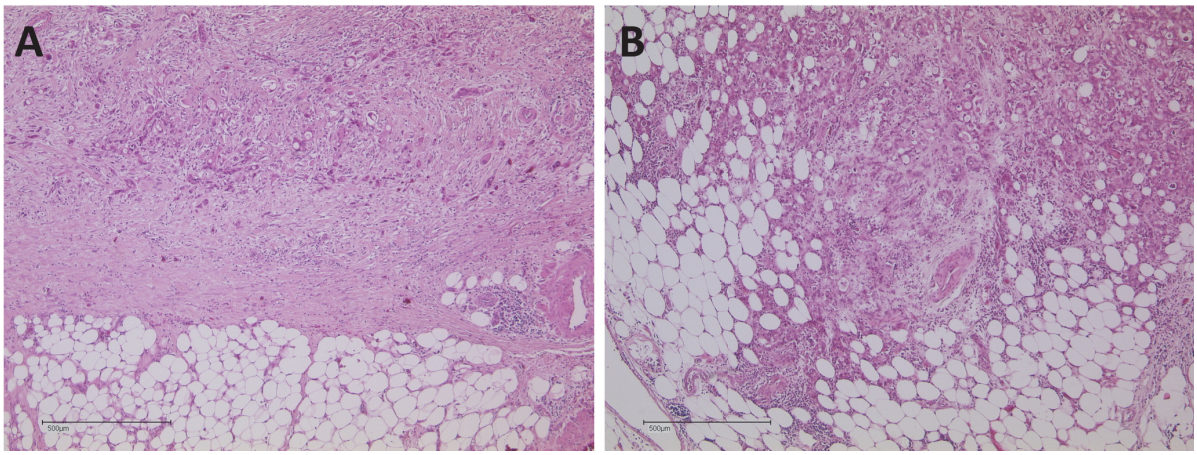
The CRM evaluation was implemented at the University Hospital of Duesseldorf in September 2015. The oral/aboral duodenal, bile duct and pancreatic neck resection margin, as well as the dorsal resection margin and, if applicable, portal vein specimen were examined according to the LEEPPs pathological protocol (Figure 11A and B).

Figure 11 (A): H&E staining of hPDAC with microscopic infiltration of mesopancreatic fatty tissue (50x). **(B):** Pathological specimen of the pancreatic head with infiltration of the peripancreatic fatty tissue. The specimen was inked using a pre-defined color code (posterior surface: black, anterior surface: blue, medial surface: green). Grossing was done according to the axial slicing technique (pT3 pN2 (5/47) L1 V0 Pn1). Copyright and under License by (134)



Additionally the mesopancreatic adipose tissue was histopathologically evaluated for cancerous infiltration (Figure 12). Histopathological slides originating before 2015 were re-visited and if sufficient slides were available, a CRM status with evaluation of the mesopancreatic fat was evaluated. This included the evaluation not only of the dorsal, but also ventral and medial CRM. In addition, the “1-mm rule” was implemented: A minimum margin clearance of 1 mm defined R0(CRM negative), whereas margin clearances between 0 and 1 mm were judged as R0(CRM positive).

Figure 12 (A): Mesopancreatic/Retropancreatic fatty tissue without PDAC infiltration (H&E, 5x). **(B)** Mesopancreatic/Retropancreatic fatty tissue with abundant PDAC infiltration (H&E, 5x). Copyright and under License by (137).



<u>Summary:</u> As seen in Figure 8-10 an extended surgical resection during pancreatoduodenectomy with the preserved peripancreatic vasculature is possible. Whereas the separation of the PV/SMV from the pancreatic tissue is often possible with blunt preparation methods, the mesopancreatic excision until the root of the CT and SMA is more sophisticated and demands sharp preparation techniques (red circles Figure 9 and 10). The Treitz's fascia unlike the Toldt's fascia is a forgotten retroperitoneal structure. It serves as an evenly important landmark for extended surgery as well. Its structure is visible in the dorsal resection margin of the whipple resectate and it runs beneath the serosa of the duodenum and pancreas serving as an additional envelope. The Treitz fascia can be preserved as seen in Figure 9B. In our opinion this is the medio-cranial extension of the Toldt's fascia that combines with the Treitz's fusion facia (Figure 7C).

2.3 Most pancreatic cancer patients are locally advanced – Histopathological results

Histopathological analyses and resection status are summarized in Table 5. Following the 1 mm-rule in all patients (*n*=264) with CRM assessment (2003-2020), 128 patients (48.5%) were staged as R0(CRM-), whereas 78 patients (29.6%) had tumor infiltration into the 1 mm resection margin R0(CRM+). Fifty-eight patients (21.9%) were staged as R1 following re-evaluation (Table 5). All studied clinico-pathological data were homogenously distributed between R0(CRM-) and R1/R0(CRM+) resected patients (Table 6).

Table 5: Resection margin studies after MPE. Copyright and under License by (134).

	All CRM evaluated patients n=269 (2003-2020)	
	n	%
Margin status		
R0(CRM-)	**130**	**48.3**
R0(CRM+)	79	30.0
R0 no CRM	—	—
R1	60	21.7

CRM: circumferential resection margin; R: resection margin

Table 6: Correlation analysis of clinicopathological data across R-status.

	R0(CRM-)		R1/R0(CRM+)		*p-value*
	n=130		n=139		
Age in years					*0.781*
Median (range)	68.5 (41-95)		69 (42-88)		
Gender	**n**	**%**	**n**	**%**	*0.282*
Male	74	56.9	70	50.4	
Female	56	43.1	69	49.6	
T-stage					*0.421*
T1	12	9.2	4	2.9	
T2	63	48.5	73	52.5	
T3	54	41.5	55	39.6	
T4	1	0.8	7	5.0	
N-stage					*0.053*
N0	21	16.2	19	13.7	
N1	66	50.8	56	40.3	
N2	43	33.1	64	46.0	
M-stage					*0.589*
M0	107	82.3	108	77.7	
M1hep	10	7.7	16	11.5	
M1PALN	13	1.0	15	10.8	
Grading					*0.607*
G1/G2	75	57.7	77	55.4	
G3	55	42.3	62	44.6	
Pn					*0.441*
Pn0	23	17.7	29	20.9	
Pn1	98	75.4	97	69.8	
missing	9	6.9	13	9.4	
L					*0.522*
L0	65	50.0	62	44.6	
L1	57	43.8	64	46.0	
missing	8	6.2	13	9.4	
V					*0.121*
V0	95	73.1	88	63.3	
V1	26	20.0	38	27.3	
missing	9	6.9	13	9.4	
Adjuvant Therapy					*0.348*
Gemcitabine	73	56.2	85	61.2	
MD CTx	32	24.6	28	20.1	

CRM: circumferential resection margin; CTx: chemotherapy; hep: hepatic; L: lymphatic invasion; MD: multidrug; PALN: para-aortic lymph nodes; Pn: perineural invasion; V: venous invasion

In all 264 patients with CRM assessment, paraffin embedded histopathologic specimens were available for retrospective re-evaluation of the fatty tissue of the mesopancreatic/retro-pancreatic dorsal resection margin. Tumor infiltration of adipose tissue was evident in 207 patients (78.4%). In only 57 patients, mesopancreatic adipose tissue had no tumor infiltration (21.6%) (Table 7).

Statistical analysis (chi-squared test and fisher exact test) revealed a significantly higher rate of lymphatic metastases (N1 and N2) and positive resection rate (R1/R0(CRM+)) in patients with MP infiltration (Table 7). All other studied clinicopathological variables were homogenously distributed (Table 7). Surprisingly, mesopancreatic fat invasion was equally distributed between the strictly size based T-stage categories and the rate of mesopancreatic fat invasion was not significantly increased in M1 resected patients when compared to M0 patients (Table 7).

Summary: In correlation analysis of the 264 consecutive treated patients two novel aspects were studied. (1) In histopathological analysis of the mesopancreatic/retropancreatic adipose tissue, tumor infiltration was evident in 78% of the patients (Figure 10 and Table 7). These findings underline the underestimated tumor extensions and presumably the cause for low rates of R0CRM- rates since CRM implementation. (2) R0CRM- rate was increased to 48%, which is higher than in previous international studies which implemented the CRM. (3) When compared to margin R0 rates in other carcinomas of the gastrointestinal or colorectal tract, these rates are not adequate. (4) The resection-status was dependent on the mesopancreatic fat infiltration status. Putting these findings together, all tough extended resections are indeed possible, the underestimated local tumor burden might demand either a more precise preoperative stratification system or a neoadjuvant approach to reach even higher levels of R0CRM- resections.

Table 7: Correlation analysis of clinicopathological data across MP status

	No mesopancreatic fat infiltration n=57		**Mesopancreatic fat infiltration** n=207		***p-value***
Age in years					
Median (range)	67.5 (47-90)		69.0 (41-88)		
Gender	**n**	**%**	**n**	**%**	*0.456*
Male	28	49.1	114	55.1	
Female	29	50.9	93	44.9	
T-stage					*0.706*
T1	5	8.8	11	5.3	
T2	31	54.4	110	53.1	
T3	20	35.1	79	38.2	
T4	1	1.8	7	3.4	
N-stage					***0.007***
N0	15	26.3	25	12.1	
N1	17	29.8	102	49.3	
N2	25	43.9	80	38.6	
M-stage					*0.709*
M0	45	78.9	166	80.2	
M1hep	5	8.8	20	9.7	
M1PALN	7	12.3	21	10.1	
Grading					*0.053*
G1/G2	38	67.9	109	52.7	
G3	18	32.1	98	47.3	
Pn					*0.258*
Pn0	15	26.3	36	17.4	
Pn1	40	70.2	151	72.9	
missing	2	3.5	20	9.7	
L					*1.000*
L0	28	49.1	97	46.9	
L1	27	47.4	91	43.9	
missing	2	3.5	19	9.2	
V					*0.379*
V0	38	66.7	142	68.6	
V1	17	29.8	45	21.7	
missing	2	3.5	20	9.7	
R-status					***0.001***
R0(CRM-)	39	68.4	89	48.0	
R1/R0(CRM+)	18	31.6	118	57.0	

CRM: circumferential resection margin; hep: hepatic; L: lymphatic invasion; PALN: para-aortic lymph nodes; Pn: perineural invasion; V: venous invasion

2.3.1 Lymph node mapping according to PALN status (139)

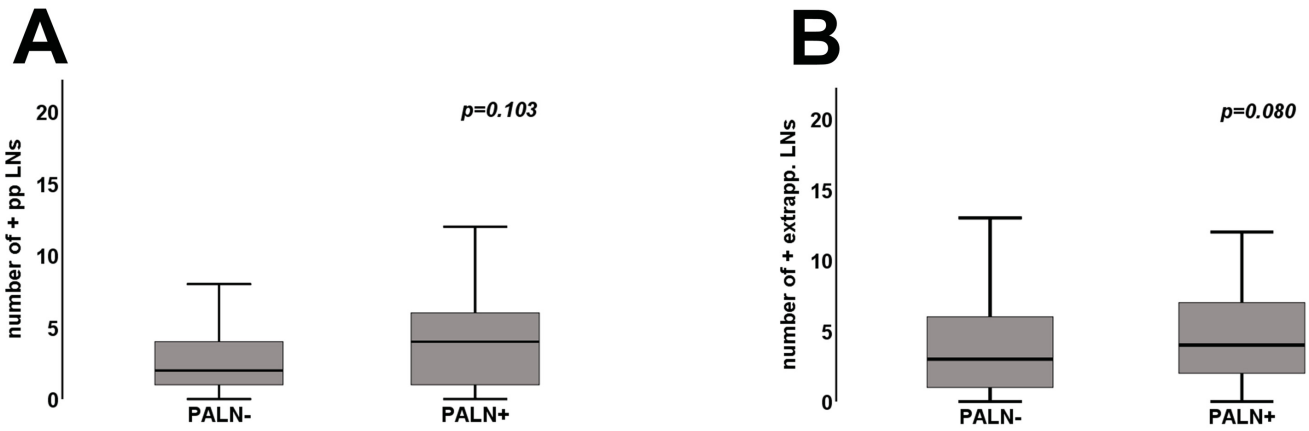
Following a Kocher manoeuver, extended para-aortic lymphadenectomy (group 16a2+b1, Japanese classification) was performed as a standard of care for hPDAC patients. The dissection plane incorporates at least all lymphatic tissue between the right crus of the diaphragm, cranially, and the branching of the inferior mesenteric artery from the aorta caudally, with the aorta and the vena cava as lateral borders of dissection. This area is usually covered by the pancreatic head. During para-aortic lymphadenectomy a bipolar sealing scissor is primarily used. Small para-aortic and inter-aortic vessels which have been missed during dissection are sealed selectively with 5-0 or 6-0 Prolene® sutures. The specimens were harvested for histopathological analysis and were directly preserved in formaldehyde. No fresh frozen sections were performed for intraoperative decision making (Figures 8-10).

The dissected peripancreatic (pp) (LN 5, 6, 13/17), extra-peripancreatic (LN 8, 9, 12, 14, 15) as well as the PALN stations (LN 16a2+b1) were histopathologically analyzed (147). Forty-one patients were diagnosed with metastatic PALN (PALN+, median number of positive PALN: 1.0; range: 1 - 14), the remaining 151 patients were histopathologically free from PALN metastases (PALN-). A median of five (range: 1 - 25) para-aortic lymph nodes were dissected during surgery in the whole cohort (PALN+ and PALN-). All clinicopathological variables were homogeneously distributed between the three studied groups (Table 8). The median age at the time of surgery for all 289 patients was 69 years (range: 41-95 years).

All patients with nodal positive disease (pN+) harbored peripancreatic lymph node metastases. A median of 15 (range: 6 - 42) peripancreatic lymph nodes were dissected during surgery in all patients. Interestingly, in one patient with nodal negative disease (pN0), PALN metastases were histopathologically evident (**Table 8**). We observed no significant correlation between the number of positive peripancreatic lymph nodes and PALN status (*p=0.103*) **(Figure 13)**. The amount of positive extra-peripancreatic LNs was again not

statistically different in patients with positive and negative PALN status (*p=0.080*) **(Figure 13)**. Hence, PALN+ patients did not harbor significantly more peri-pancreatic or extra-peripancreatic LN metastases compared to PALN- patients.

Figure 13 (A): Box-plot of the number of positive peripancreatic (pp) and **(B)** extra peri-pancreatic (extra-pp) lymph nodes (LN) stratified by patients PALN status. Mann-Whitney U test was used to test for significance. Copyright and under License by (139)



Summary: As already mentioned in section 2.1 standardized PALN-LAD is an obligatory component during MPE in our institution. Since analysis is performed in a non-selective study group, surgical bias was removed. Two novel findings were studied: (1) From the performed lymph-node mapping, a similar amount of metastasized peri-pancreatic and extra peri-pancreatic lymph nodes was investigated across the PALN status (Figure 13). (2) In this yet largest PALN-LAD series (41 PALN+ vs. 151 PALN-) clinico-pathological variables were homogenously distributed across PALN status and PALN were infiltrated in 20% of the study collective. Next to the high rate of MP infiltration status, this further underlines the underestimated advanced tumor stage of yet primary resected PDAC patients. These findings could further contribute for the demand in neoadjuvant treatment.

Table 8: Demographic data of patient collective from 2004-2018; n=289

	PALN negative n=151		**PALN positive n=41**		**No PALN LAD n=97**		**p-value**
Age in years							*0.179*
Median (range)	68 (41-90)		67 (51-81)		70 (45-95)		
Gender							*0.231*
Male	83	55.0	16	39.0	51	52.6	
Female	68	45.0	25	61.0	46	47.1	
T-stage							*0.442*
T1	11	7.3	1	2.4	9	9.3	
T2	84	55.6	21	51.2	58	59.3	
T3	53	35.1	18	43.9	28	28.9	
T4	3	2.0	1	2.4	2	2.1	
N-stage							*0.479 (PALN- vs. No PALN LAD)*
N0	26	17.2	1	2.4	22	22.7	
N1	72	47.7	10	24.4	48	49.5	
N2	53	35.1	30	73.2	27	27.8	
Grading							*0.259*
G1/G2	84	55.7	30	73.2	55	56.7	
G3	66	43.7	11	26.8	41	42.3	
n/a	1	0.7	0	0	1	1.0	
Pn							*0.292*
Pn0	25	16.6	10	24.4	22	22.7	
Pn1	114	75.5	26	63.4	63	64.9	
n/a	12	7.9	5	12.2	12	12.4	
L							*0.190*
L0	77	51.0	16	39.0	49	50.5	
L1	62	41.1	22	53.7	36	37.1	
n/a	12	7.9	3	7.3	12	12.4	
V							*0.117*
V0	107	70.9	25	61.0	70	72.2	
V1	32	21.2	12	29.3	15	15.5	
n/a	12	7.9	4	9.8	12	12.4	
R-status							*0.138*
R0CRM-	83	55.0	19	46.3	46	47.4	
R1/R0CRM+	68	45.0	22	53.7	51	52.6	
Adjuvant CTx							*0.331*
Gemcitabine	88	58.3	29	70.7	57	58.8	
MD regime	39	25.8	7	17.1	17	17.5	
n/a	24	15.9	5	12.2	23	23.7	

L: lymphatic invasion; n/a: data not available; MD: multidrug; PALN: para-aortic lymph nodes; Pn: perineural invasion; V: venous invasion

2.3.2 Is MPE after neoadjuvant therapy warranted or excessive?

27 patients met our inclusion criteria (11 females (40.7%) and 16 males (59.3%)). Table 9 summarizes clinico-pathological characteristics of the cohort. All 27 patients received neoadjuvant treatment because of advanced disease. The median age of all patients at the time of surgery was 66 years (range 41-80 years). In total, 3 patients (11.1%) received gemcitabine mono therapy, while 5 patients (18.5%) received a combination therapy including gemcitabine and 3 patients (11.1%) received combined radiochemotherapy including gemcitabine. Fifteen patients (55.6%) were treated with modified FOLFIRINOX. The dosing regimen is stated in a supplemental Table i. One of 27 patients deceased during the first 30 postoperative days (Clavien-Dindo V; 30-day mortality rate: 3.7%). Median length of hospital stay (LOS) was 23 days (range: 12-153 days). All patients received MPE during pancreatic surgery. In all patients a fibrous sheet (Treitz's fascia) was visible at the posterior resection site running between the duodenum and the origin of the SMA/CT (Figures 8-10).

Histopathological analyses and resection status are summarized in Table 9. In all 27 patients, detailed CRM was histopathologically evaluated. Fifteen patients (55.6%) were evaluated before 2015 and needed sophisticated histopathological re-evaluation, whereas in 12 patients (44.4%), CRM evaluation in the context of a standardized pancreatic protocol was primarily applied. When applying the 1mm rule, true negative resection margins were still present after re-evaluation in 17 patients (62.9%). Of the remaining patients, 4 (14.8%) had insufficient tumor clearances (R1) and in 6 patients (22.2%) tumor residues were detected within the 1mm margins (R0(CRM+)).

Table 9: Demographic data of neoadjuvant treated patients prior to MPE

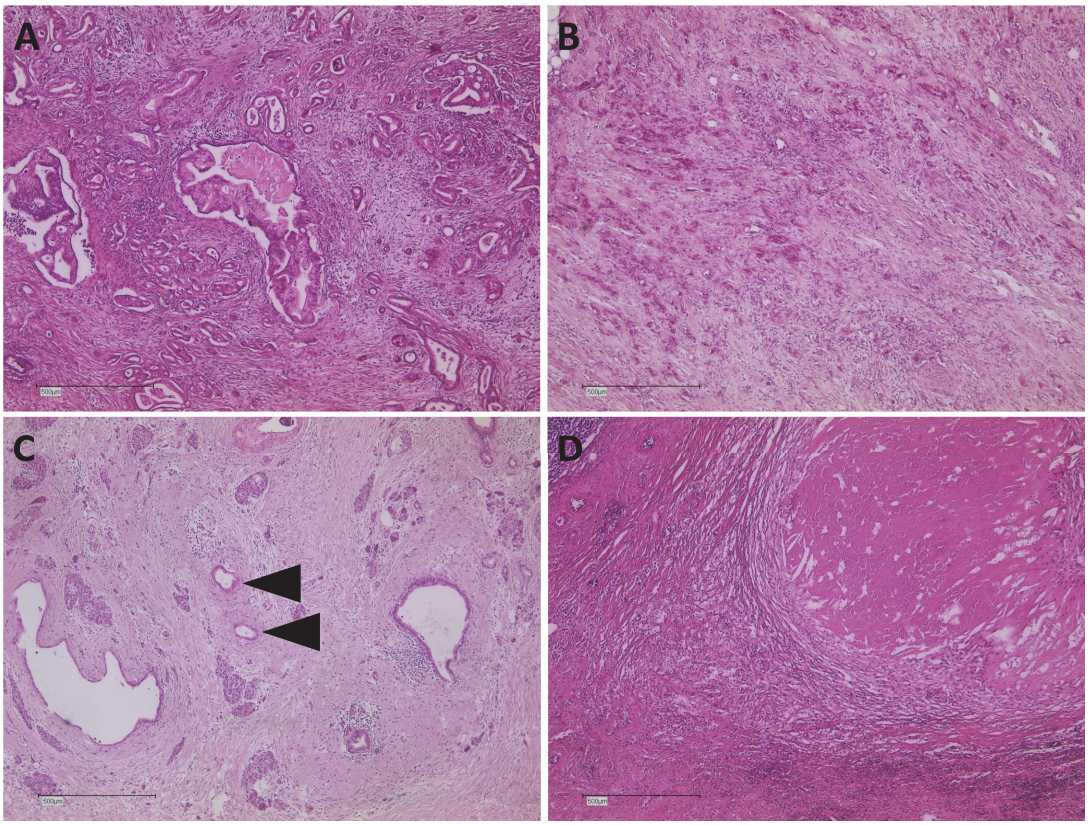
Age in years Median (range)	66 years (41-80)	
Sex	**n**	**%**
Male	16	59.3
Female	11	40.7
T-stage		
ypT0	2	7.4
ypT1	3	11.1
ypT2	13	48.1
ypT3	9	33.3
N-stage		
N0	11	40.7
N1	10	37.0
N2	6	22.2
Grading		
G1/G2	18	66.6
G3	9	33.3
Pn		
Pn0	9	33.3
Pn1	18	66.6
L		
L0	20	74.1
L1	7	25.9
V		
V0	21	77.8
V1	6	22.2
R-status		
R0(CRM-)	17	62.9
R1/R0(CRM+)	10	37.1
MPI		
Positive	17	62.9
negative	10	37.1

CRM: circumferential resection margin; Hep: hepatic; L: lymphatic invasion; MPI: mesopancreatic fat infiltration; Pn: perineural invasion; V: venous invasion

In all 27 patients, paraffin embedded histopathologic specimens were available for retrospective re-evaluation of the mesopancreatic fat tissue of the peripancreatic dorsal resection margin (Figure 14A-D). Tumor infiltration of adipose tissue was evident in 17 patients (62.9%), whereas in only 10 patients (37.1%), mesopancreatic adipose tissue had no tumor infiltration (Table 9). In all 17 patients with mesopancreatic fat infiltration, vital tumor cells were present. Histopathological re-evaluation of tumor response was performed on the complete study cohort (Figure 4A-D). In 2 patients (7.4%), complete tumor response (CAP

grade 0) was detected. In 5 patients (18.5%), a near complete tumor response (CAP grade 1) was diagnosed, whereas in 15 (55.5%) and 5 (18.5%) patients, partial (CAP grade 2) and poor/no tumor response (CAP grade3) was evident (Figure 14A-D).

Figure 14 Spectrum of tumor regression grading in pancreatic cancer. **(A):** PDAC with CAP 3 displays abundant vital residual tumor with nearly no regressive changes (H&E, 5x). **(B):** PDAC with CAP 2 shows partial regression with collagen-rich fibrosis and inflammatory infiltrate, but vital residual tumor exceeding rare small groups of tumor cells (H&E, 5x). **(C):** PDAC with CAP 1 is characterized by near-complete response showing only rare single tumor glands embedded in vast collagen-rich fibrosis with residual normal pancreatic tissue (H&E, 5x). **(D):** PDAC with CAP 0 equals complete response with necrosis, fibrosis and inflammatory resorption, but no vital tumor cells (H&E, 5x). Copyright and under License by (137)



Mesopancreatic fat infiltration was compared in patients with and without histopathological tumor response. Patients lacking mesopancreatic fat infiltration had a significantly better histopathological tumor response, compared to patients with mesopancreatic fat in-filtration (*p=0.003) (Table 10). This correlation was significant in the Pearson correlation (*p=0.005, r=+0.585**). Resection status (R0(CRM-) vs. R1/R0(CRM+)) was compared with mesopancreatic histology. The rate of R0(CRM-) resection was 62.9% in the total cohort. For patients lacking mesopancreatic fat infiltration, this rate was significantly higher compared to patients with histopathological mesopancreatic fat infiltration (*p=0.031; R0(CRM-) in MP- = 80.0% and R0(CRM-) in MP+ = 52.9%) (Table 10).

Table 10: Correlation analysis stratified according to positive and negative mesopancreatic infiltration. Statistical significance was calculated by chi squared test. ** indicates a *p-value* ≤ *0.01*; * indicates a *p-value* ≤ *0.05*. Copyright and under License by (137).

	No mesopancreatic fat infiltration		**Mesopancreatic fat infiltration**		***p-value***
	n=10		**n=17**		
Treatment response	**n**	**%**	**n**	**%**	***0.003*** **
Grade 0	2	20.0	0	0	
Grade 1	4	40.0	1	5.9	
Grade 2	4	40.0	11	64.7	
Grade 3	0	0.0	5	29.4	
R-status					***0.031****
R0(CRM-)	8	80.0	9	52.9	
R1/R0(CRM+)	2	20.0	8	47.1	

CRM: circumferential resection margin

Patients with better treatment response had a significantly higher percentage of complete (R0(CRM-)) resections (*p=0.042). While patients with good histological treatment response (CAP grade 0 and 1) had a 100% rate of complete resections, only 57.1% and 20.0% of the patients with partial and poor/no response (CAP grade 2 and 3), respectively, received a R0(CRM-) resection. None of the R1/R0(CRM+) patients had a good histopathological response (CAP grade 0 and 1) (Table 11).

Table 11: Analysis of patients stratified according resection status, n=27. Patients without mesopancreatic fat infiltration showed a higher rate of R0CRM- resections. Statistical significance was calculated by chi squared test. ** indicates a *p-value ≤ 0.01*; * indicates a *p-value ≤ 0.05*. Copyright and under License by (137).

	R0(CRM-) n=17		**R1/R0(CRM+)** n=10		***p-value***
Treatment response	**n**	**%**	**n**	**%**	
CAP 0	2	11.8	0	0.0	
CAP 1	5	29.4	0	0.0	***0.042*****
CAP 2	9	52.9	6	60.0	
CAP 3	1	5.8	4	40.0	

CAP: College of American Pathologists; *CRM: circumferential resection margin*

During the study period (2010-2021), 173 patients received upfront surgery for primary resectable PDAC. In all patients, the mesopancreatic fat infiltration was analyzed. In 131 patients (75.7%), the mesopancreatic fat was histopathologically infiltrated. We detected a statistical different rate of mesopancreatic fat infiltration between primary resected patients and the 27 patients resected following neoadjuvant therapy (p=0.039) (Table 12).

Table 12: correlation analysis of MP infiltration status and primary treatment modality. Statistical significance was calculated by chi squared test. ** indicates a *p-value ≤ 0.01*; * indicates a *p-value ≤ 0.05*. Copyright and under License by (137).

	Neoadjuvant and surgery n=27		**Upfront surgery** n=173		***p-value***
MP Infiltration					***0.039***
positive	17	62.9	131	75.7	
negative	10	37.1	42	24.3	

MP: mesopancreatic

Follow-up data was available in the 27 neoadjuvant treated patients and the 173 patients who received upfront surgery (Table 13). Follow up analysis revealed that systemic relapse was not prevented by degree of surgical radicality (p=0.143). Irrespective of the treatment strategy, most patients were diagnosed with a systemic relapse during follow up analysis

(46.8% of the patients after upfront surgery and 69.2% of the patients after ne-oadjuvant treatment (p=0.143). Neoadjuvant treated patients showed a significantly lower rate of local recurrence during follow up investigations when compared to patients after upfront surgery (p=0.040) (7.4% vs. 16.8%). secure local tumor control.

Table 13: Analysis of patients stratified according to MDCT predicted tumor response, n=27.MP infriltation status was distributed heterogenously across MDCT tumor response status. Statistical significance was calculated by chi squared test. ** indicates a *p-value ≤ 0.01*; * indicates a *p-value ≤ 0.05*. Copyright and under License by (137).

	MDCT tumor response n=17		**MDCT no tumor response** n=10		***p-value***
Treatment response	**n**	**%**	**n**	**%**	
CAP 0 and 1	6	35.3	1	10.0	*0.122*
CAP 2 and 3	11	64.7	9	90.0	
MP Infiltration					
positive	8	47.1	9	90.0	***0.042**
negative	9	52.9	1	10.0	
R-status					
R0(CRM-)	11	64.7	6	60.0	*0.692*
R1/R0(CRM+)	6	35.3	4	40.0	

CAP: College of American Pathologists; CRM: circumferential resection margin; MDCT: multi-detector computed tomogprahy; MP: mesopancreatic

Summary: The infiltration status of the mesopancreatic/retropancreatic fat after neoadjuvant treatment was not studied before. In 62.9% of the neoadjuvantly treated patients, the mesopancreatic fat was infiltrated and this rate was significantly lower when compared to patients who received primary surgery. Independent on the tumor regression grading, in all neoadjuvant treated patients solely vital tumor cells were present at this invasion front (MP fat). According to these findings (majority of patients with MP+ status and solely vital tumor cells) mesopancreatic excision is still warranted also in patients after neoadjuvant treatment. This is likewise to the extensions during surgery in rectal cancer patients which are, independently whether neoadjuvant treatment was performed or primary surgery conducted, evenly considered.

2.3.3 Complication profile after MPE vs. standard PD

The distribution of postoperative complications is summarized in Table 14. Patients with PALN LAD had a similar rate of postoperative lymphatic fistula when compared to patients without PALN LAD. The rate of other typical postoperative complications specific to pancreatic surgery was not different between the subgroups. We found that PALN LAD did not increase the LOS, compared to PD without PALN LAD (Table 12). In the total cohort of 289 patients, 15 patients succumbed during the first 30 postoperative days (Clavien-Dindo V: 5.2%), which is on par with published mortality rates (148)

Table 14: Complication profile analysis and length of stay. Statistical significance was calculated by Kruskal-Wallis-test for numeric data and chi squared test for ordinal data

	Morbidity					
	No complication	**Bleeding**	**Pancreatic fistula**	**GI bleeding**	**Chyle fistula**	***p-value***
PALN LAD n=192	147 (76.6%)	10 (5.2%)	29 (15.3%)	1 (0.5%)	4 (2.1%)	*p=0.170*
No PALN LAD n=97	81 (83.5%)	4 (4.1%)	10 (10.3%)	1 (1.0%)	1 (1.0%)	
	LOS in days Median (range)		**Clavien-Dindo V**			***p-value***
PALN LAD n=192	23 (9.0 – 262.0)		11 (5.7%)			*p=0.601*
No PALN LAD n=97	20.5 (10.0 – 154.0)		4 (4.1%)			

LAD: lymphadenectomy; LN: lymph nodes; PALN: para-aortic lymph nodes; LOS: length of stay

Summary: Morbidity and mortality rates were on par with the known literature. When further stratifying patients according to LAD status; patients with a PALN-LAD showed a similar complication profile when compared to patients without PALN-LAD.

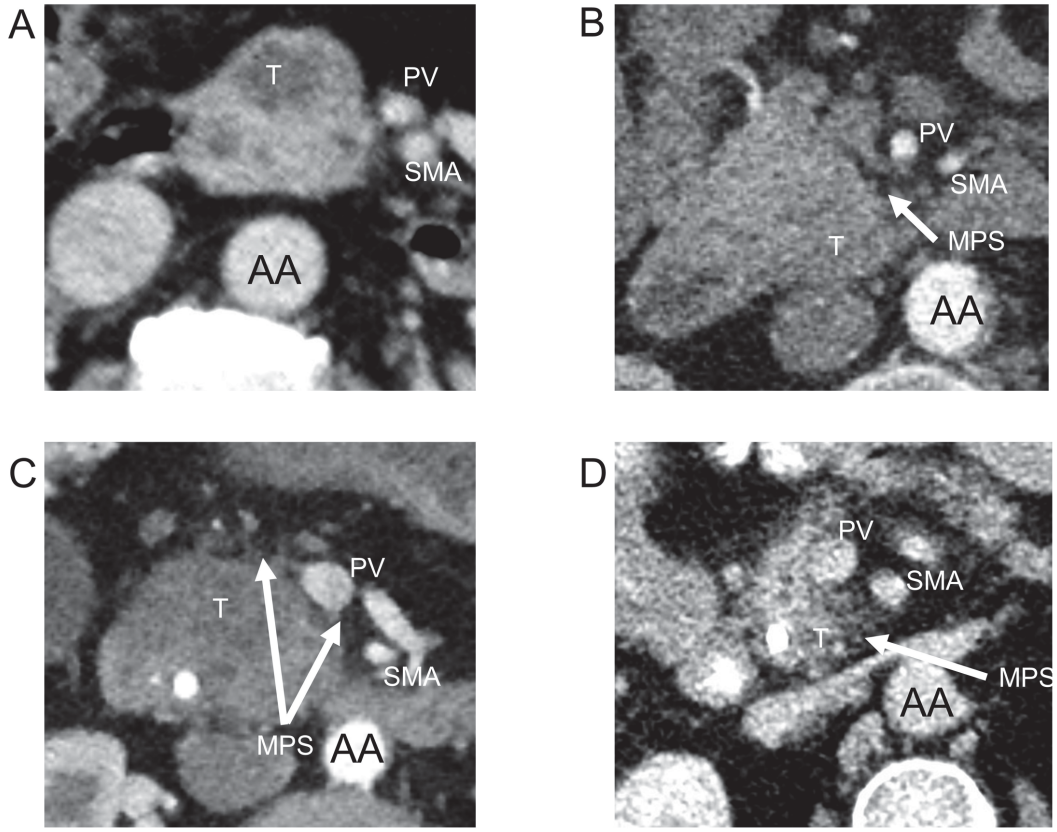
2.4 Pre-operative MDCT and the mesopancreas

Patients who received upfront MPE for PDAC of the pancreatic head were included if the scans of preoperative multiphasic multi-detector CT (MDCT) were available for re-evaluation. These examinations were retrospectively analysed and blinded for resection status and postoperative staging. To further minimize observer bias, scans from patients who did not meet the above-mentioned inclusion criteria and received MDCT for other reasons were re-analysed as well and not included in the study.

Each scan was re-evaluated and the following parameters were recorded: (1) Tumor diameter and distance to posterior and medial anatomic margins, and (2) mesopancreatic fat stranding. Furthermore, the presumed contact of the tumor to the superior mesenteric artery (SMA), common hepatic artery (CHA), gastroduodenal artery (GDA) portal, and superior mesenteric vein (PV/SMV) was analysed and further sub-categorized by the circumferential degree of invasion (Figure 15 and 16).

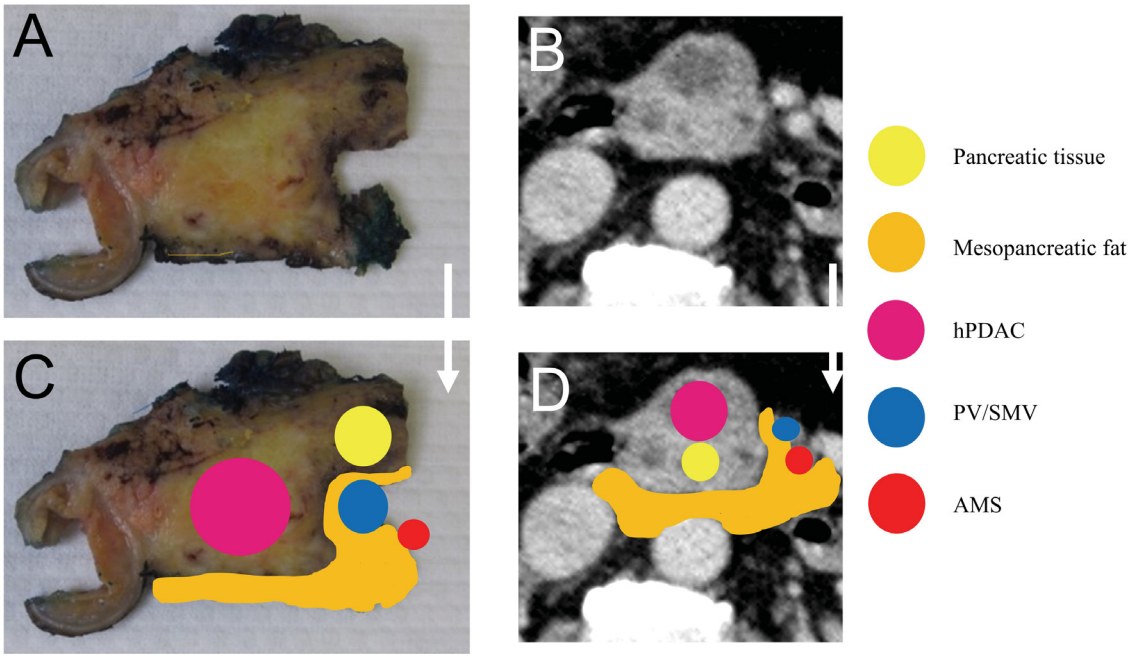
In MDCT, early and sparse tumor invasion of fatty tissue may be visible as “stranding”, an increased attenuation resulting from oedema reminiscent of an inflammatory reaction. Based on the improved preoperative radiologic assessment, patients with even limited mesopancreatic fat infiltration and thus likely to receive R1 or CRM+ resections may be identified for neoadjuvant treatment followed by surgery, while others lacking those signs may benefit from a radical resection.

Figure 15 (A): MDCT slide without mesopancreatic fat stranding; **(B):** MDCT slide with MPS 1; **(C):** MDCT slide with MPS 2; **(D):** MDCT slide with MPS 3 (AA: abdominal aorta; MPS: mesopancreatic fat stranding; PV: portal vein; SMA: superior mesenteric artery; T: tumor). Copyright and under License by (135).



All the radiographic variables are summarized in Table 15. A presumed malignant mass was detected in all patients (Figure 12A–D). Mesopancreatic stranding (MPS) dorsal to the head of the pancreas was sub-grouped as described in Materials and Methods (Figure 12A–D). In only 60 patients, MPS was not visible (24.8%), whereas MPS 1, 2, and 3 were found in 69 (28.5%), 33 (13.6%), and 80 (33.1%) patients, respectively. Out of the 80 MPS, isolated peri-vascular fat stranding around the PV/SMV was detected in eight patients (10.0%), whereas isolated fat stranding around the SMA was detected in 18 patients (22.5%). In 39 patients (48.8%), both PV/SMV and SMA showed a simultaneous fat stranding. Fat stranding around the GDA and CHA was visible in 10 (12.5%) and in five patients (6.25%), respectively (Table 15; Figure 17 A and B).

Figure 16: (A): Pathological specimen of the pancreatic head with infiltration of the peripancreatic fatty tissue. The specimen was inked using a pre-defined color code (posterior surface: black, anterior surface: blue, medial surface: green). Grossing was done according to the axial slicing technique (pT3 pN2 (5/47) L1 V0 Pn1); **(B):** MDCT slide without MPS; (C): Edited pathological specimen visualizing the hPDAC as well as the mesopancreatic fat; (D): edited MDCT slide without MPS visualizing the hPDAC as well as the mesopancreatic fat (hPDAC: ductal adenocarcinoma of the pancreatic head; MPS: mesopancreatic fat stranding; PV: portal vein; SMA: superior mesenteric artery; SMV: superior mesenteric vein). Copyright and under License by (135).



Tumor diameter and tumor distance to the dorsal plane (ICV/AA) in MDCT significantly correlated with the pathological T-stage ($p < 0.001$ and 0.010) (Figure 18 A and B and Table 16). MDCT detected that fat stranding at the dorsal plane correlated significantly with pathologic mesopancreatic tumor infiltration at the dorsal resection margin ($p = 0.001$) (Table 16). Both MDCT detected tumor contact and peri-vascular fat stranding (MPS 3) to the SMA and PV/SMV correlated significantly with the pathologic infiltration of these structures ($p <$

0.001 and p = 0.011 for tumor contact around the SMA and PV, respectively; p = 0.006 and p = 0.037 for MP fat stranding around the SMA and PV, respectively) (Table 16).

Figure 17 (A): Illustration visualizing separate and synchronous histological tumor contact to peripancreatic vessels **(B)** Illustration visualizing separate and synchronous mesopancreatic fat stranding (MPS 3) to peripancreatic vessels. (CHA: common hepatic artery; GDA: gastroduodenal artery; MPS: mesopancreatic fat stranding; PV: portal vein; SMA: superior mesenteric artery; SMV: superior mesenteric vein). Copyright and under License by (135).

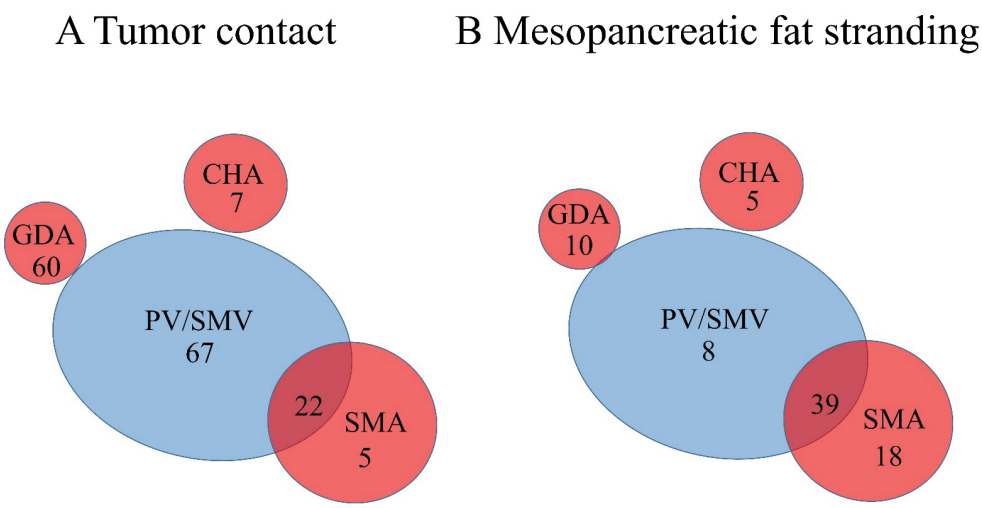


Figure 18 (A): Box plot of radiographically assumed tumor width and pathological T stage. Pearson test was used to test for statistical significance (p=0.001). **(B):** Box plot of radiographically assumed tumor distance to dorsal margin (ICV/AA) in relation to pathological T stage. Pearson/spearman test was used to test for statistical significance (p=0.011). modified from (135).

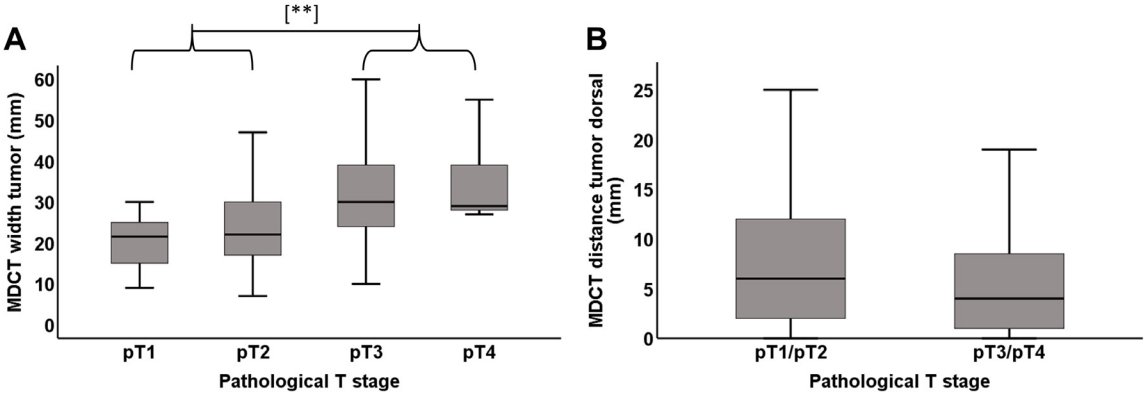


Table 15: Demographic table of all 242 included patients. Staging is revised to the 8th edition of the UICC TNM classification of malignant tumors.

Age in years Median (range)	70 (41-95)		**Tumor width** Median (range)	25mm (7-60mm)	
	n	**%**	**Distance from dorsal margin** Median (range)	5mm (0-25mm)	
Gender				**n**	**%**
Male	134	55.4			
Female	108	44.6	**Tumor contact in MDCT**		
T-stage			SMA	27	11.2
T1	15	6.2	Contact >180°	20	8.3
T2	137	56.6			
T3	85	35.1	CHA	7	2.9
T4	5	2.1	Contact >180°	6	2.5
N-stage					
N0	39	16.1	GDA	60	24.8
N1/2	203	83.9	Contact >180°	32	13.2
M-stage					
M0	193	79.8	PV/SMV	89	36.8
M1	49	20.2	Contact >180°	28	11.6
Grading					
G1/G2	136	56.2	**MPS in MDCT**		
G3	102	42.1	positive MPS	182	75.2
missing	4	1.7			
Pn			stranding to SMA	58	24.0
Pn0	50	20.7			
Pn1	183	75.6	stranding to CHA	5	2.1
missing	9	3.7			
L			stranding to GDA	10	4.1
L0	116	47.9			
L1	117	48.3	stranding to PV/SMV	48	19.8
missing	9	3.7			
V			**LN enlargement in MDCT**		
V0	170	70.2	peripancreatic LN	90	37.2
V1	63	26.0			
missing	9	3.7			
R-status (CRM)			retroperitoneal LN	6	2.5
R0CRM-	86	35.5			
R0CRM+/R1	111	45.8			
missing	45	18.6	hepatoduodenal ligament LN	39	16.1

CHA: common hepatic artery; CRM: circumferential resection margin; GDA: gastroduodenal artery; ICV: inferior caval vein; L: lymphatic invasion; LN: lymph nodes; MPS: mesopancreatic fat stranding; Pn: perineural invasion; PV/SMV: portal/superior mesenteric vein; SMA: superior mesenteric artery; V: venous invasion

Table 16: Correlation analysis of radiographic and histopathological variables.

Histopathology		MDCT scan					
		Tumor width (mm)		*p-value*	Sensitivity/ Specificity	HR	95%CI
T-stage	n	Median	range				
pT1	15	21	9-30		40% / 75%		
pT2	137	23	7-50		30% / 83%		
pT3	85	30	10-60	***<0.001***	57% / 71%	1.690	1.2-2.3
pT4	5	29	27-55		60% / 89%		

Modified contingency tables
Tumor morphology

Histopathology		MDCT scan					
PV/SMV infiltration		PV/SMV tumor contact					
	n		n				
Yes	39	Yes	30 of 39	***<0.001***	77% / 74%	9.375	4.1-21.9
No	122	No	90 of 122				

SMA infiltration		SMA tumor contact					
	n		n				
Yes	14	Yes	6 of 14	***0.010***	43% / 89%	5.893	1.6-22.0
No	63	No	56 of 63				

Modified contingency tables
Mesopancreatic fat

Histopathology		MDCT scan					
MP fat infiltration		MPS (<3)					
	n		n				
Yes	70	Yes	47 of 70	***0.013***	67% / 55%	2.488	1.2-5.2
No	51	No	28 of 51				

Histopathology		MDCT scan					
MP fat infiltration		MPS (1-3)					
	n		n				
Yes	128	Yes	103 of 128	***0.001***	80% / 41%	2.709	1.4-5.3
No	69	No	28 of 69				

PV/SMV infiltration		MPS to PV/SMV					
	n		n				
Yes	39	Yes	5 of 39	***0.037***	12% / 71%	1.040	0.5-2.2
No	122	No	86 of 122				

SMA infiltration		MPS to SMA					
	n		n				
Yes	14	Yes	10 of 14	***0.006***	71% / 70%	5.789	1.6-20.8
No	63	No	44 of 63				

CI: confidence interval; HR: Hazard ratio; MP: mesopancreatic; MPS: mesopancreatic fat stranding; PV/SMV: portal/superior mesenteric vein; SMA: superior mesenteric artery

MDCT variables were correlated with the CRM-implemented resection status. Out of the MDCT variables, tumor diameter and positive MPS significantly correlated with R1/R0CRM+ resection status (Figure 19, Table 17).

Figure 19: Box plot of MDCT-presumed tumor diameter and resection status. Pearson/spearman test was used to test for statistical significance (p=0.033). Copyright and under License by (135).

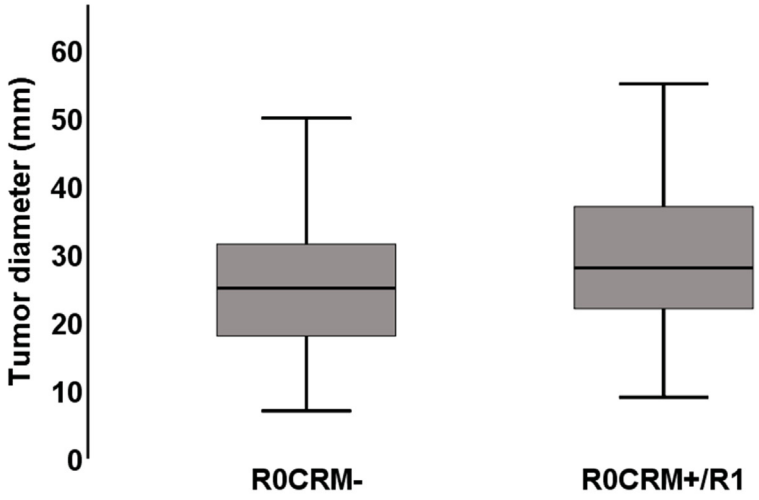


Table 17: Correlation analysis of histopathological mesopancreatic fat infiltration and resection status. Statistical difference was calculated by Fisher's exact test.

	Resection status **R0CRM- vs. R1 / R0CRM+**
Radiographic Variable	***p-value***
</≥ 2cm tumor diameter	***0.048***
</≥ median Tumor distance dorsal plane (AA/ICV)	*0.339*
contact SMA yes/no	*1.000*
contact SMA >180° yes/no	*0.302*
contact PV/SMV yes/no	*0.149*
contact PV/SMV >180° yes/no	*1.000*
MPS yes/no	***0.010***
stranding to SMA yes/no	*0.731*
stranding to PV/SMV yes/no	*0.057*

CI: confidence interval; HR: Hazard ratio; MPS: mesopancreatic fat stranding; PV/SMV: portal/superior mesenteric vein; SMA: superior mesenteric artery

2.4.1 Pre-operative CT evaluation and PALN status:

In 120 PALN LAD patients, preoperative CT scans were available for re-evaluation. Of these 120 patients, 29 were diagnosed with PALN metastases in the dissected specimen. In only 4.2% (5/120), retro-pancreatic lymph node involvement was predicted radiographically. However, only three of these five patients were indeed PALN+ in the histopathological evaluation (sensitivity=10.3%, specificity=97.8%, PPV=60%, NPV=77.4%) (Table 18).

Table 18: Contingency table of radiographic variables and PALN status; n=120. Copyright and under License by (139).

	Radiographic predicted retroperitoneal LN enlargement	
	No	**Yes**
PALN-	89	2
PALN+	26	3

LN: lymph nodes; PALN: para-aortic lymph nodes

Summary: Since the infiltration status of the mesopancreatic/retropancreatic fat could be a future topic of interest, we analysed the predictive value of MDCT in regard to local tumor extensions. Three novel findings were studied: (1) Both MDCT presumed tumor size and mesopancreatic fat stranding correlated significantly with the histopathological outcome and resection status. (2) The predictive value for PALN status analysis was poor, underlining that an advanced lymphatic stage of disease was preoperatively underestimated. (3) Thus, next to the yet implemented ABC-criteria, MDCT could serve with these markers for a precise prediction model to estimate local tumor burden.

2.4.2 Pre-operative CT evaluation after neoadjuvant therapy

In all 27 patients, preoperative MDCT scans following neoadjuvant therapy were performed to investigate local treatment response. In 17 (62.9%) patients, MDCT indicated a treatment response, and these patients were re-staged from non-resectable to borderline resectable. In the other 9 patients, MDCT after neoadjuvant treatment showed a stable disease. Out of the 27 patients, mesopancreatic fat stranding after neoadjuvant treatment was still visible in 20 patients. Mesopancreatic fat infiltration and tumor response was compared to preoperative MDCT variables (Table 19). Radiographically presumed tumor response did predict mesopancreatic fat infiltration (p=0.042), whereas the trend for histopathologically verified treatment response was present but not statistically significant (p=0.112 for treatment response) (Table 19).

Table 19: Analysis of patients stratified according to MDCT predicted tumor response, n=27.MP infiltration status was distributed heterogeneously across MDCT tumor response status. Statistical significance was calculated by chi squared test. ** indicates a *p-value* ≤ *0.01*; * indicates a *p-value* ≤ *0.05*. Copyright and under License by (137).

	MDCT tumor response n=17		**MDCT no tumor response** n=10		***p-value***
Treatment response	**n**	**%**	**n**	**%**	
CAP 0 and 1	6	35.3	1	10.0	*0.122*
CAP 2 and 3	11	64.7	9	90.0	
MP Infiltration					
positive	8	47.1	9	90.0	***0.042**
negative	9	52.9	1	10.0	
R-status					
R0(CRM-)	11	64.7	6	60.0	*0.692*
R1/R0(CRM+)	6	35.3	4	40.0	

CAP: College of American Pathologists; CRM: circumferential resection margin; MDCT: multi-detector computed tomography; MP: mesopancreatic

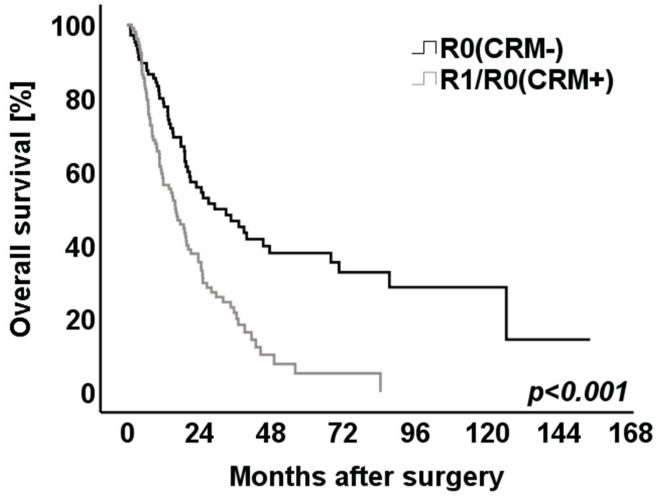
Summary: The mesopancreatic infiltration status after neoadjuvant therapy correlated significantly with the post-neoadjuvant MDCT tumor response status, which again underlines the value of MDCT to access the mesopancreatic fat independent on the applied treatment strategies. Further studies are clearly warranted in which these results are confirmed with a larger study cohort.

2.5 Survival factors after MPE

2.5.1 In M0 Patients

In univariate analysis, the following clinicopathological parameters were associated with prognostic impact: N-status, grading, multidrug chemotherapeutic regime and positive resection margin (Table 20). The median OS was stratified according to the resection status. In the "true'' margin negative patients (R0(CRM-); *n*=106) the median OS was significantly longer, compared to the margin positive patients (R1 and R0(CRM+); *n*=105) (Table 20, Fig. 20). In patients with adjuvant therapy, we observed a significant prolonged OS when multidrug based regimes (Gemcitabine based or FOLFIRINOX) were applied. In multivariate analysis, only negative resection margin (R0(CRM-)) remained as an independent prognostic factor (Table 20).

Figure 20: Kaplan-Meier curve for overall survival in correlation with positive and negative resection status in CRM evaluated patients. Log rank test was used to test for significance. p-value ≤ 0.05 is regarded as significant. Copyright and under License by (134).



	0	24	48	72	96	120	144	168
R0(CRM-)	108	39	20	10	6	3	1	1
R1/ R0(CRM-)	107	31	4	1	n/a	n/a	n/a	n/a

Table 20: Univariate and multivariate survival analyses for overall survival of M0 resected patients. Analyses were performed by log-Rank test and cox logistic forward regression. p-value ≤ 0.05 is considered statistically significant. Copyright and under License by (134).

Univariate analysis	
	p-value
Median age (< vs. > median)	*0.077*
T-stage (T1/T2 vs. T3/T4)	*0.280*
N-stage (N0/N1 vs. N2)	***0.004***
Grading (G1/G2 vs. G3)	***0.010***
Pn (Pn0 vs. Pn1)	*0.727*
L (L0 vs. L1)	*0.979*
V (V0 vs. V1)	***0.012***
R-status (R0(CRM-) vs. R1/R0(CRM)+)	***<0.001***
Gemcitabine mono vs Multidrug CTx	***0.026***

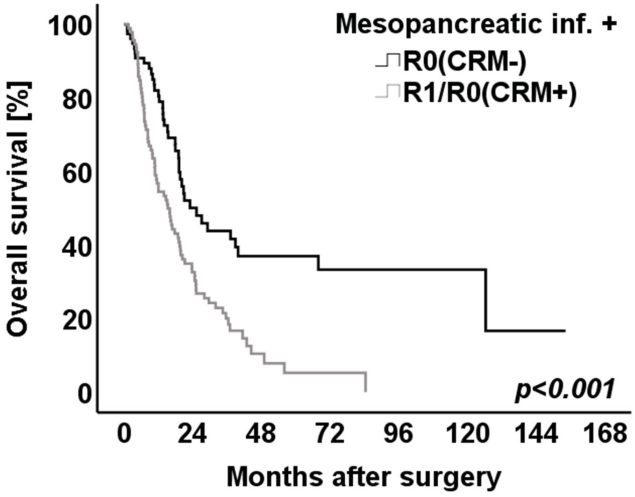
Multivariate analysis			
	p-value	**HR**	**95%CI**
R-status (R0(CRM-) vs.R1/R0(CRM)+)	*0.022*	*1.614*	*1.071-2.431*

CTx: chemotherapy; CI: confidence interval; HR: hazard ratio; multidrug: gemcitabine based or FOLFIRINOX; L: lymphatic invasion; Pn: perineural invasion; V: venous invasion

The median OS in patients with positive mesopancreatic fat infiltration was not significantly different from the median OS in patients with negative mesopancreatic infiltration.

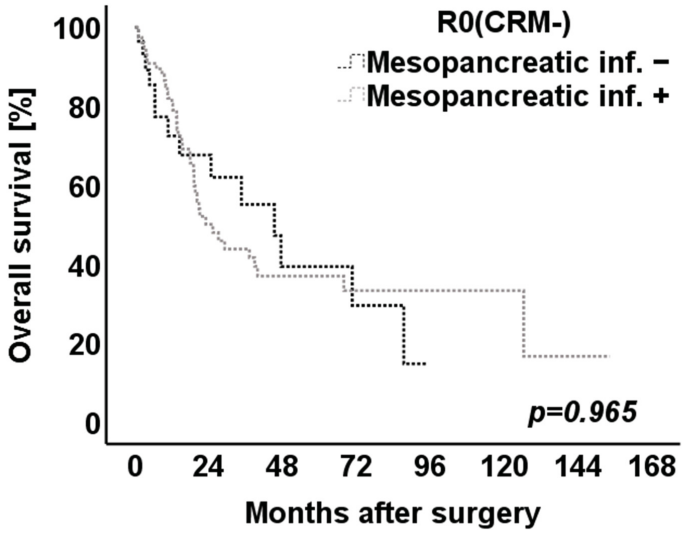
Analyzing those 166 patients with mesopancreatic fat infiltration, patients who received true margin negative resection R0(CRM-) showed a significantly higher median OS when compared to margin positive patients R1/R0(CRM+) (Fig. 21). In the margin negative patients R0(CRM-), the median overall survival was similar in patients with and without mesopancreatic infiltration (Fig. 22).

Figure 21: Kaplan-Meier curve for overall survival of patients with positive mesopancreatic fat infiltration at the dorsal resection margin. Margin negative resections provided survival benefit in patients with mesopancreatic fat infiltration as well, Inf.: infiltration. Log rank test was used to test for significance. p-value ≤ 0.05 is regarded as significant. Copyright and under License by (134).



	0	24	48	72	96	120	144	168
R0(CRM-)	76	25	14	7	6	3	1	n/a
R1/ R0(CRM+)	90	28	4	1	n/a	n/a	n/a	n/a

Figure 22: Kaplan-Meier curve for overall survival of R0CRM- resected patients with mesopancreatic fat infiltration and without mesopancreatic fat infiltration at the dorsal resection margin. Margin negative resection revealed similar survival benefit independent on MP status. Inf.: infiltration; MP= mesopancreatic. Log rank test was used to test for significance. p-value ≤ 0.05 is regarded as significant. Copyright and under License by (134).



	0	24	48	72	96	120	144	168
MP-	30	12	4	3	n/a	n/a	n/a	n/a
MP+	76	24	14	7	6	3	1	n/a

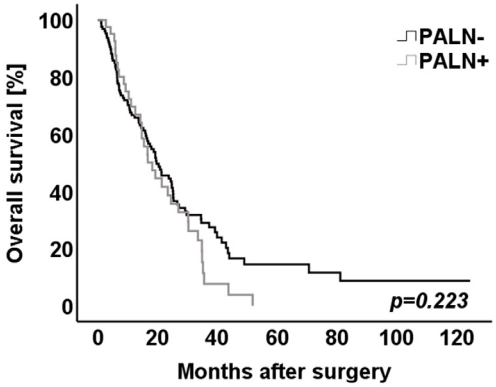
<u>Summary:</u> In par with previous studies, R0CRM- resection status was the most important prognostic factor next to extended chemotherapeutic regimes. Thus margin negativity should be the foremost goal during pancreatic surgery. Mesopancreatic fat infiltration status failed to be of prognostic significance, presuming that MP infiltration is a result of an adverse tumor topography instead of an aggressive tumor biology.

2.5.2 According to PALN status

Only PALN LAD patients were included. 192 patients received PALN LAD, of which 41 were positive for PALN metastases. Currently this represents the largest series on PDAC patients who received PALN lymphanectomy. Overall survival was evaluated using official records from the registration office. 163 patients received an adjuvant treatment. 117 patients received gemcitabine, while 46 patients received a combination therapy of gemcitabine and paclitaxel or capecitabine. None of the patients included received FOLFIRINOX or neoadjuvant treatments.

At univariate survival analysis, higher tumor grading, positive resection margins (R1) and single agent chemotherapy were significantly associated with poor overall survival (OS). Interestingly, nodal and PALN status were not prognostic factors in our cohort (PALN+ vs. PALN-) (Table 18). Thus, the median OS with 19.63 months (95%CI: 14.57 – 24.79 months) in PALN- patients was not statistically different when compared to the median OS with 18.22 months (95%CI: 12.68 – 23.75 months) in PALN+ patients (log-rank test *p=0.223*) (Figure 23). At multivariate analysis, only tumor grading remained a significant prognostic factor (*p=0.001*) (Table 21).

Figure 23: Kaplan-Meier curve for overall survival of all patients stratified by PALN status. Log rank test was used to test for significance. Copyright and under License by (139).



	0	20	40	60	80	100	120
PALN-	141	49	16	8	5	2	2
PALN +	40	16	3	0	0	0	0

Table 21: Univariate and multivariate analysis for overall survival. Copyright and under License by (139).

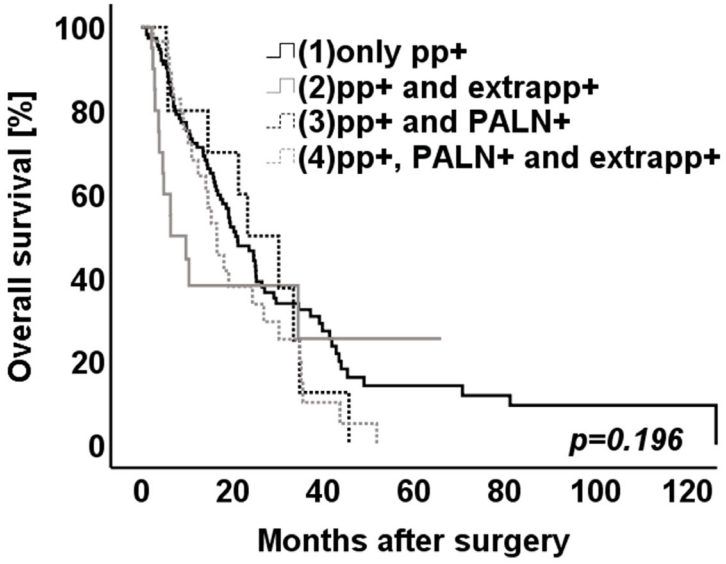
	Univariate analysis	**Multivariate analysis**		
	p-value	***p-value***	**HR**	**CI (95%)**
Age (≥ / <median)	*0.785*	*0.329*	—	—
Gender (male / female)	*0.795*	*0.891*	—	—
T-stage (T1;T2 / T3;T4)	*0.871*	*0.498*	—	—
N-stage (N0 / N1;N2)	*0.305*	*0.334*	—	—
PALN (PALN+/PALN-)	*0.223*	*0.167*	—	—
Grading (G1;G2 / G3)	***0.009***	***0.001***	2.051	1.358 – 3.098
Pn (Pn1 / Pn0)	*0.530*	*0.134*	—	—
L (L1 / L0)	*0.581*	*0.421*	—	—
V (V1 / V0)	*0.120*	*0.295*	—	—
R-status (R0CRM- / R0CRM+; R1)	***0.024***	*0.310*	—	—
CTX (MD regime vs. Gemca mono)	***0.049***	*0.397*	—	—

CI: confidence interval; CTX: chemotherapy; MD: multidrug regime; Gemca: gemcitabine; HR: Hazard ratio; PALN: para-aortic lymph nodes; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

To elucidate the spatial LN involvement and its potential influence on OS, PALN LAD patients were divided into four subgroups, depending on the location of metastatic LN stations: (1) patients with isolated peripancreatic lymph node metastases (LN 5, 6, 13/17; n=120; median OS: 19.63 months (95%CI: 16.93 – 22.34 months)); (2) patients with lymph node metastases in the peripancreatic and extra peripancreatic stations *except* PALN (LN 5, 6, 8, 9, 12, 13/17, 14, 15 ; n=21; median OS: 7.1 months (95%CI: 1.22 – 12.99 months)); (3)

patients with lymph node metastases in the peripancreatic *and* PALN stations (LN 5, 6, 13/17, 16; n=11; median OS: 16.63 months (95%CI: 9.66 – 23.59 months)) and (4) patients with positive lymph node metastases in all locations (LN 5, 6, 8, 9, 12, 13/17, 14, 15 16; n=29; median OS: 18.22 months (95%CI: 9.77 – 26.67 months)). There was no statistical difference in overall survival between the four subgroups (*p=0.196*) (Figure 24).

Figure 24: Kaplan-Meier curve for overall survival of all patients stratified by metastasized lymph node stations. Only pp+: patients with isolated peri-pancreatic lymph node metastases; pp+ and extrapp+: patients with peri-pancreatic and extra peri-pancreatic lymph node metastases except PALN; pp+ and PALN+: patients with peri-pancreatic and PALN involvement; pp+, extrapp+ and PALN+: patients with metastasized peri-pancreatic, extra peri-pancreatic and PALN. Log rank test was used to test for significance. Copyright and under License by (139).



	0	20	40	60	80	100	120
(1)	120	52	21	7	5	2	2
(2)	21	3	1	1	n/a	n/a	n/a
(3)	11	7	1	0	0	0	0
(4)	29	9	2	0	0	0	0

Summary: *Median overall survival rates were similar in patients with or without PALN metastases. When stratifying patients according to the metastasized lymph node stations, survival analysis revealed similar outcomes across subgroups. These findings further underline the yet underestimated advanced stage of disease in patients who receive upfront surgery and may underline the demand for neoadjuvant therapy in order not only to locally down size the PDAC (R0CRM- rate and MP infiltration rate) but also so secure systemic tumor control.*

2.5.3 Oligometastatic disease to the liver

38 patients met the inclusion criteria of oligometastatic disease to the liver (group: M1surg). In the same period, 143 consecutive patients were scheduled for surgery for localized disease (group: M0). 15 patients succumbed during the first 30 postoperative days (Clavien-Dindo V: 7.7%), which is in-line with published mortality rates. These were excluded from the study, which now includes 35 M1surg and 131 M0 patients in the study group (Table 22). There was no statistical difference in mortality rates between groups M0 and M1surg (Clavien-Dindo V: 7.9% for M1surg and Clavien-Dindo V: 8.3% for M0; fisher exact test: p=0.450). Further 14 patients with oligometastatic disease to the liver and a similar ECOG performance status to group M0 and M1surg (group: M1pall), who did not agree on an extended surgical approach, were treated with a palliative intended chemotherapy according to national guidelines. None of the palliative treated patients succumbed during the first 30 chemotherapeutic days. In all 180 patients, an intraoperative ultrasound of the liver was performed and documented for further analysis.

Table 22: Demographic data of patients, n=180. Copyright and under License by (140).

	M0 n=131		**M1surg** n=35		**M1pall** n=14	
Age Median (range)	69 (17-95)		67 (45-80)		71.5 (51-87)	
Gender	**n**	**%**	**n**	**%**	**n**	**%**
Male	80	38.9	20	42.9	7	50
Female	51	61.1	15	57.1	7	50
Tumor location						
Head	119	90.8	27	77.1	13	92.9
Tail	12	9.2	8	22.9	1	7.1
T-stage						
T1	8	6.1	4	11.4	-	-
T2	78	59.5	11	31.4	-	-
T3	44	33.6	18	51.4	-	-
T4	1	0.8	2	5.7	-	-
N-stage						
N0	27	20.6	7	20.0	-	-
N1	99	75.6	27	77.1	-	-
N2	5	3.8	1	2.9	-	-
Grading						
G1/G2	81	61.8	17	48.6	12	85.7
G3	50	38.2	17	48.6	2	14.3
missing	-	-	1	2.9	-	-
Pn						
Pn0	30	22.9	11	31.4	-	-
Pn1	101	77.1	24	68.6	-	-
missing	-	-	-	-	-	-
L						
L0	74	56.5	18	51.4	-	-
L1	57	43.5	17	48.6	-	-
missing	-	-	-	-	-	-
V						
V0	96	73.3	23	65.7	-	-
V1	35	26.7	12	34.3	-	-
missing	-	-	-	-	-	-
R-status						
R0	111	84.7	17	48.6	-	-
R1	20	15.3	18	51.4	-	-

surg: surgical; pall: palliative; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Of all analysed clinicopathological variables, location of the PDAC (head vs. tail), T-stage and R-status were heterogeneously distributed between patients who received curative-intended surgery for localized and metastasized disease respectively (M0 vs M1surg) (Table 23). Thus, a larger tumor size correlated with synchronous hepatic metastases. Of the 18 M1surg patients with R1 resections, in 10 patients (55.6%) margin clearance could not be achieved at site of liver metastasectomy. Thus, the peripancreatic resection status was of no statistical difference between group M0 and M1surg (peripancreatic R0 status in M0=84.7% vs. 77.1% in M1surg; p=0.312).

Out of the 180 patients, 117 patients (65.0%) died during the follow-up period. The median OS of all 180 patients was 15.1 months (95% CI 10.4–19.8 months). Out of patients who received curative-intended therapy (M0 and M1surg, n = 166), 90.9% of the patients received a multimodal therapy. In group M0, 80 patients (61.1%) were given gemcitabine as monotherapy, whereas 35 patients (26.7%) received a combination therapy with paclitaxel. Only five patients (3.8%) were given FOLFIRINOX as a standardized adjuvant treatment regime. None of the M0 patients received neoadjuvant treatment. In the M1surg group, 15 patients received an adjuvant gemcitabine therapy (42.8%), while eight patients received FOLFIRINOX (22.8%) (four perioperative and four postoperative) and two patients received an adjuvant gemcitabine multidrug regime with either erlotinib or paclitaxel (5.7%). Further five patients entered the HEAT study and received adjuvant radiochemotherapy (14.2%). The distribution of chemotherapeutic regimes was heterogeneous between group M0 and M1surg ($p < 0.001$) (Table 24).

Table 23: Correlation analysis of clinicopathological data across M-status. Copyright and under License by (140).

	M1surg vs. M0	**M1surg vs. M1pall**	**M0 vs. M1pall**
	p-value	*p-value*	*p-value*
Tumor location	***0.039***	*0.563*	*0.347*
Age	*0.132*	***0.031***	*0.173*
Gender	*0.701*	*0.703*	*0.833*
T-stage	***0.014***	-	-
N-stage	*0.957*	-	-
Grading	*0.428*	*0.087*	***0.040***
Pn	*0.377*	-	-
L	*0.702*	-	-
V	*0.402*	-	-
R-status	***<0.001***	-	-
Morbidity	*0.665*	***0.003***	***0.001***
Hospital stay (days)	*0.503*	***0.001***	***0.002***

surg: surgical; pall: palliative; Pn: perineural invasion; L: lymphatic invasion; V: venous invasion

Table 24: Distribution analysis of chemotherapeutic regimes between groups M0, M1surgR0 and M1surgR1. p-value ≤0.05 indicates significance. Copyright and under License by (140).

	M0	**M1surg R1**	**M1surg R0**	**Chi-squared test**
	N=131	**n=18**	**n=17**	***p-value***
	n	**n**	**n**	
Chemotherapy				***<0.001***
No CTx	11	5	0	
Gemcitabine mono	80	9	6	
Gemcitabine MD	35	1	1	
FOLFIRINOX	5	2	6	
HEAT study/RCT	0	1	4	

CTx: chemotherapy; Mono: monotherapy; MD: multi-drug; RCT: radiochemotherapy; surg: surgical

Univariate survival analysis was performed for the total cohort. In the univariate analysis of all 166 surgically resected patients (M0 and M1surg), patients with: higher median age, PDACs of the pancreas tail, surgically resected synchronous hepatic metastases, higher tumor grading, positive venous infiltration, positive resection margins and single drug chemotherapy had a significantly worse overall survival (Table 25). Thus, patients who received resection of the primary PDAC with synchronous liver metastases had a median OS of 10.3 months (95% CI 7.2–13.4 months) (M1surg), which was shorter than in patients with localized disease (median 20.6 months, 95% CI 16.7–24.6 months) (M0) (p = 0.001). In multivariate analysis however only positive venous invasion and positive resection margin were left as independent prognostic factors for poor OS (Table 25).

Table 25: Univariate and multivariate analysis for overall survival. Copyright and under License by (140).

	Univariate analysis	**Multivariate analysis**		
	p-value	***p-value***	**HR**	**CI (95%)**
Tumor location (tail vs. Head)	*0.060*	*NS*	—	—
Age (≥ / <median)	***0.002***	*NS*	—	—
Gender (male / female)	*0.653*	*NS*	—	—
T-stage (T1;T2 / T3;T4)	*0.713*	*NS*	—	—
N-stage (N0 / N1;N2)	*0.295*	*NS*	—	—
M1 (M1/M0)	***0.001***	*NS*	—	—
Grading (G1;G2 / G3)	***0.030***	*NS*	—	—
Pn (Pn1 / Pn0)	*0.559*	*NS*	—	—
L (L1 / L0)	*0.606*	*NS*	—	—
V (V1 / V0)	***<0.001***	***<0.001***	2.38	1.54 - 3.67
R-status	***<0.001***	***<0.001***	2.29	1.41 - 3.71
CTx (MD regime vs. Gemca mono)	***0.007***	*NS*	—	—

CI: confidence interval; CTx: chemotherapy; HR: Hazard ratio; Pn: perineural invasion; L: lymphatic invasion; NS: not significant; V: venous invasion

Survival analysis was performed of only R0 resected patients (M0R0 and M1surgR0, n = 128). In univariate analysis, patients with PDACs of the pancreatic head, higher median age and positive venous invasion showed a significantly worse prognosis (Table 23). Thus, the median OS in patients who received histopathologically proven tumor-free extended resection (M1surgR0, n = 17) was not statistically different compared to the median OS in

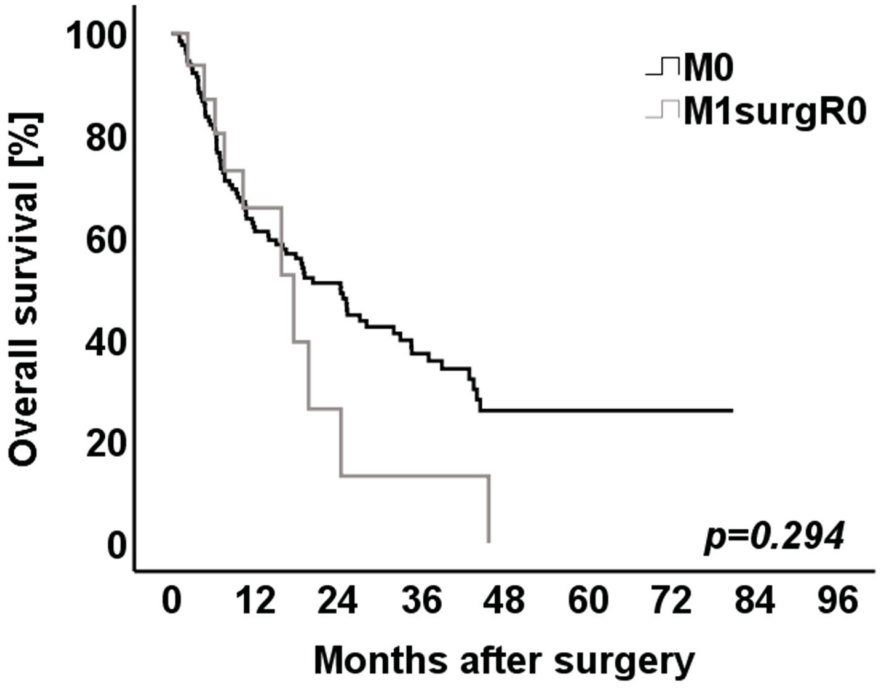
patients who received surgery for localized disease (M0, n = 131) (Figure 25). In multivariate analysis only positive venous invasion was left as an independent prognostic factor (Table 26).

Table 26: Univariate and multivariate analysis for overall survival in R0 patients. Copyright and under License by (140).

	Univariate analysis	**Multivariate analysis**		
	p-value	***p-value***	**HR**	**CI (95%)**
Tumor location (tail vs. Head)	***0.039***	*NS*	—	—
Age (≥ / <median)	***0.006***	*NS*	—	—
Gender (male / female)	*0.920*	*NS*	—	—
T-stage (T1;T2 / T3;T4)	*0.880*	*NS*	—	—
N-stage (N0 / N1;N2)	*0.693*	*NS*	—	—
M1 (M1/M0)	*0.142*	*NS*	—	—
Grading (G1;G2 / G3)	*0.643*	*NS*	—	—
Pn (Pn1 / Pn0)	*0.476*	*NS*	—	—
L (L1 / L0)	*0.779*	*NS*	—	—
V (V1 / V0)	***0.048***	***0.010***	2.07	1.19 - 3.58
CTx (MD regime vs. Gemca mono)	*0.058*	*NS*	—	—

CI: confidence interval; CTx: chemotherapy; HR: Hazard ratio; Pn: perineural invasion; L: lymphatic invasion; NS: not significant; V: venous invasion

Figure 25: Kaplan Meier survival curve for Overall survival of patients without synchronous metastases (M0; n=131) in correlation to patients after margin negative extended surgery (M1surgR0; n=17) Log rank test was used to test for significance. p-value ≤0.05 indicates significance. Copyright and under License by (140).



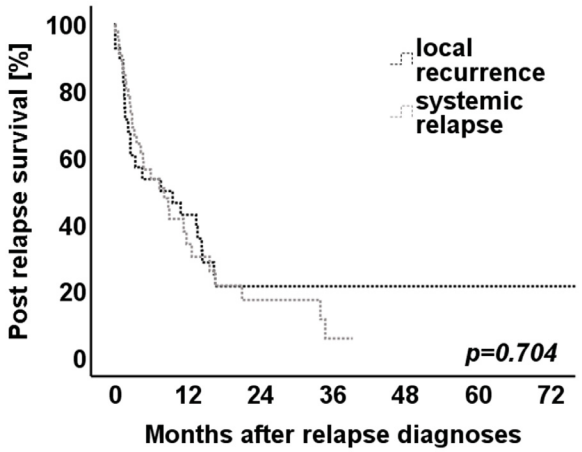
	0	12	24	36	48	60	72	84	96
M0	131	74	51	28	11	8	1	n/a	n/a
M1surgR0	17	8	2	1	0	0	0	0	0

<u>Summary:</u> This study further provides evidence for the underestimated systemic tumor burden in PDAC patients. Selected oligometastatic patients who receive extended chemotherapeutic regimes and surgery showed a similar survival outcome even when compared to patients who received multimodal therapy for localized disease. Since these novel chemotherapeutic regimes offer obvious survival benefits when compared to the previous standards, extended surgery could evenly be a topic of interest in the future.

2.6 Local recurrence vs. distant metastases

Follow up analysis revealed that systematic relapse was not prevented by degree of surgical radicality. Most patients succumbed to metachronous disease independent of the resection margin status (R0(CRM-) vs. R1/ R0(CRM+)) (fisher exact test: p=0.091). However, in R0(CRM-) resected patients, only 10.9% of the patients were diagnosed with local recurrence, compared to 33.3% after insufficient surgical tumor clearance (R1/R0(CRM+)) (p=0.004) (Table 27). The median RFS in patients before diagnosed isolated local recurrence was similar when compared to the median RFS in patients before diagnosed systemic relapse (p=0.853) (Table 27). The median post relapse survival (survival after relapse diagnosis) of patients suffering from isolated local recurrence vs. systemic relapse was again not significantly different (Table 27, Figure 26).

Figure 26: Kaplan-Meier curve for Post relapse survival dependent on relapse location. Survival after isolated local recurrence was similar when compared to after diagnosed systemic relapse. Log rank test was used to test for significance. p-value ≤ 0.05 is regarded as significant. Copyright and under License by (134).



	0	12	24	36	48	60	72
LR	28	12	5	3	2	1	1
Systemic relapse	55	9	3	1	n/a	n/a	n/a

Table 27: Distribution of metastases after upfront surgery and survival stratification.

	No metastases			Systemic relapse			Local recurrence		
	n	**%**	***Fisher exact test (p-value)***	**n**	**%**	***Fisher exact test (p-value)***	**n**	**%**	***Fisher exact test (p-value)***
R0(CRM-) n=73	35	47.9		30	41.1		8	10.9	
R1/ R0(CRM+) n=60	15	25.0	***<0.001***	25	41.7	*0.796*	20	33.3	***<0.001***
				Median (95%CI)			Median (95%CI)		
Relapse-free survival				months			months		
				12.9 (9.9-15.9)			13.1 (8.2-18.1)		
Log rank test (p-value)				*0.853*					
				Median (95%CI)			Median (95%CI)		
Post relapse survival				months			months		
				8.10 (2.6-13.6)			7.57 (0.0-17.2)		
Log rank test (p-value)				*0.704*					

Summary: These results provide evidence that the previous dilemma with the high rates of local recurrence was resulted by the inadequate stratification of resection status prior to CRM implementation. Patients who received mesopancreatic excision not only benefited from a higher rate of margin clearances. In follow-up examinations only 20.1% of the patients were

diagnosed with local recurrence which is lower when compared to values in the known literature. Since survival after diagnosed local recurrence is similar when compared to patients with systemic spread, local and systemic tumor control are evenly important. Patients with isolated local-recurrence are potential candidates for relapse-surgery; in order to secure systemic relapse, chemotherapy must be administered in a greater patient proportion. In a significant amount of patients' adjuvant chemotherapy is not possible, a neoadjuvant concept could therefore serve as a promising tool.

2.6.1 Follow-up results stratified across PALN-status

In 93 PALN LAD patients, a detailed follow up was available to analyze disease free survival (RFS) (79 PALN-; 14 PALN+). Of these, 68.8% (64/93) were diagnosed with relapse during the available follow-up. Anatomic distribution of metachronous disease is summarized in (Table 28). 28.6% (4/14) and 21.4% (3/14) of PALN+ patients were diagnosed with metachronous pulmonary and hepatic metastases, respectively. In the PALN- group, 11.4% (9/79) and 31.6% (25/79) of patients developed metachronous pulmonary and hepatic relapse, respectively (PALN+ vs PALN -: p=0.050).

Table 28: Distribution of metachronous disease according to PALN status (n=93). Copyright and under License by (139).

	PALN- n=79	**%**	**PALN+ n=14**	**%**	**p-value** *0.050*
no metastases	28	35.0	4	26.7	
hepatic	24	30.0	3	20.0	
pulmonary	9	11.3	4	26.7	
local	15	18.8	1	6.7	
peritoneal	2	2.5	2	14.3	
osseous	1	1.2	—	—	

PALN: para-aortic lymph nodes

Summary: *Interestingly, the pattern of metachronous metastasis was statistically different in PALN+ and PALN- patients in our cohort, even if the number of patients included was limited. While the majority of PALN- patients suffered from metachronous hepatic disease, PALN+ patients were more prone to pulmonary metastases. Chemotherapeutic treatment or surgical resection for isolated metachronous pulmonary metastatic disease has been shown to significantly improve survival when compared to patients with relapse in another compartment. Potentially, pulmonary metastasis was caused by lymphatic spread via the thoracic duct, while metachronous hepatic spread is most likely caused by intravasation via the portal vein.*

2.6.2 Follow-up results after neoadjuvant treatment

Follow-up data was available in the 27 neoadjuvant treated patients and the 173 patients who received upfront surgery (Table 29). Follow-up analysis revealed that systemic relapse was not prevented by degree of surgical radicality (p = 0.143). Irrespective of the treatment strategy, most patients were diagnosed with a systemic relapse during follow-up analysis (46.8% of the patients after upfront surgery and 69.2% of the patients after neoadjuvant treatment (p = 0.143). Neoadjuvant-treated patients showed a significantly lower rate of local recurrence during follow-up investigations when compared to patients after upfront surgery (p = 0.040) (7.4% vs. 16.8%). Thus, the negative effect of neoadjuvant treatment on the infiltration status of the mesopancreatic fat presumably resulted in a more secure local tumor control (Tables 29).

Table 29. Analysis of metachronous disease stratified according to treatment constellation. Rate of systemic relapse was similar between neoadjuvant and upfront surgery-treated patient groups (p = 0.143; not shown). Local tumor control was significantly improved after neoadjuvant treatment when compared to patients who received upfront surgery (p = 0.040). Statistical significance was calculated by chi-squared test. Copyright and under License by (137).

Therapy modality	No Metastases		Systemic Relapse		Local Recurrence		p-Value
	n	%	n	%	n	%	
Neoadjuvant n = 27	5	18.5	18	66.7	2	7.4	0.04
Upfront surgery n = 173	63	36.4	81	46.8	29	16.8	

2.6.3 Secondary therapy for isolated relapse

Out of the total study collective, 26 patients received relapse surgery for local recurrence, pulmonary and hepatic metastases (Table 26). For hepatic metastases, one right hemi-hepatectomy and five atypical non-anatomical resections were per- formed. For pulmonary metastases, patients received four right and five left atypical resections via video- assisted thoracoscopy (VATS). For local recurrence, one gastrectomy with atypical resection of the left diaphragm, nine salvage-pancreatectomies with simultaneous right hemicolectomies and one partial psoas muscle resection were performed (Figure 27, Table 30).

In all 26 patients, margin negative resections were achieved. Out of the 62 conservatively treated patients, 44 patients (74.6%) received gemcitabine mono, while a combination therapy with gemcitabine was administered to 15 patients (25.4%). None of the patients received FOLFIRINOX as a secondary therapy line. The distribution of secondary conservative treatment regimens between the isolated relapse compartments was homogenous and without statistical significance (p=0.900) (Table 30).

Table 30: Correlation analysis between relapse compartment and survival time stratified according to secondary therapy, n=111. Pearson test was used to test for statistical significance. p-value ≤0.05 indicates significance. Copyright and under License by (141).

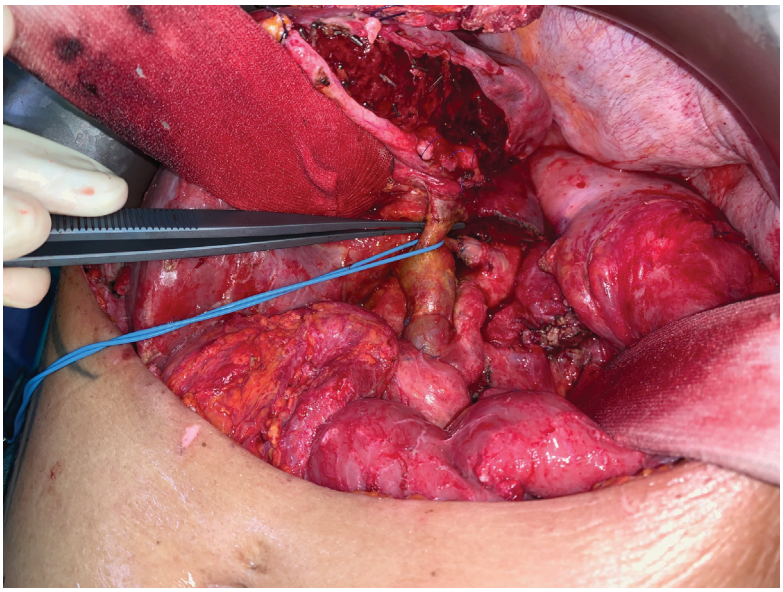
	Total	**Surgery**		**Chemotherapy**		***Fisher-exact test***
Recurrence/metastases	**n**	**n**	**%**	**n**	**%**	*p-value <0.001*
hepatic	43	6	*13.9*	37	*86.1*	
local	28	11	*39.3*	17	*60.7*	
pulmonary	17	9	*52.9*	8	*47.1*	

Relapse Chemotherapy/ procedure	**Hepatic**	**Local**	**Pulmonary**	***Fisher-exact test***
	n	**n**	**n**	*p-value 0.900*
Gemcitabine	27	12	5	
MD regime	10	5	3	
FOLFIRINOX	-	-	-	
BSC	-	-	-	

BSC: best supportive care, MD: multi-drug

Median survival data is summarized in Table 30. The median disease free survival of all 141 patients was 13.09 months (95%CI 9.46–16.72 months). The median disease free survival in the 87 patients with isolated relapse was 13.28 months (95%CI 10.74–15.83 months). In patients in the pulmonary metastasis group, the median RFS of 18.15 months was longer, compared to the RFS of patients in the local recurrence and hepatic metastasis groups (p=0.031) (Table 27). The median RFS of 10.55 months in the local recurrence group was similar to the median RFS of 7.83 months in hepatic metastasis group (p = 0.180) (Table 31)

Figure 27: Intraoperative view after resection of local recurrence. The tumor was infiltrating the left portal vein and left hepatic artery. Tumor resection was performed with synchronous left lateral hemihepatectomy and resection/reconstruction of the left portal vein and resection of the left hepatic artery with reconstruction of the common hepatic artery. Primary tumor staging pT2 pN1 (3/56) L0 V0 Pn1 G2 R0CRM+. Copyright and under License by (141).



To assess post relapse survival, 54 patients without metachronous relapse were removed for further survival analysis. In order to exclude selection bias and differences in tumor biology between the applied treatment modalities for metachronous disease, RFS before secondary relapse treatment initiation was stratified according to the treatment modality applied (Table 30). The median RFS before secondary therapy initiation was similar in patients with isolated hepatic metastases and isolated local recurrence between both treatment modalities (surgery and chemotherapy) (p=0.897 for surghep vs. chemhep and p=0.972 for surglocal vs. chemlocal) (Table 31). However, RFS in patients in the resected pulmonary metastasis group was significantly longer when compared to patients who only received chemotherapy (p=0.012) (Table 31). Hence, a selection bias was detected only in patients with isolated pulmonary metastases.

Table 31: Survival data stratified according to relapse location and treatment modality, n=111. Patients with isolated pulmonary metastases showed the best RFS. Surgery significantly influenced PRS in patients with isolated pulmonary metastases and local recurrence. Copyright and under License by (141).

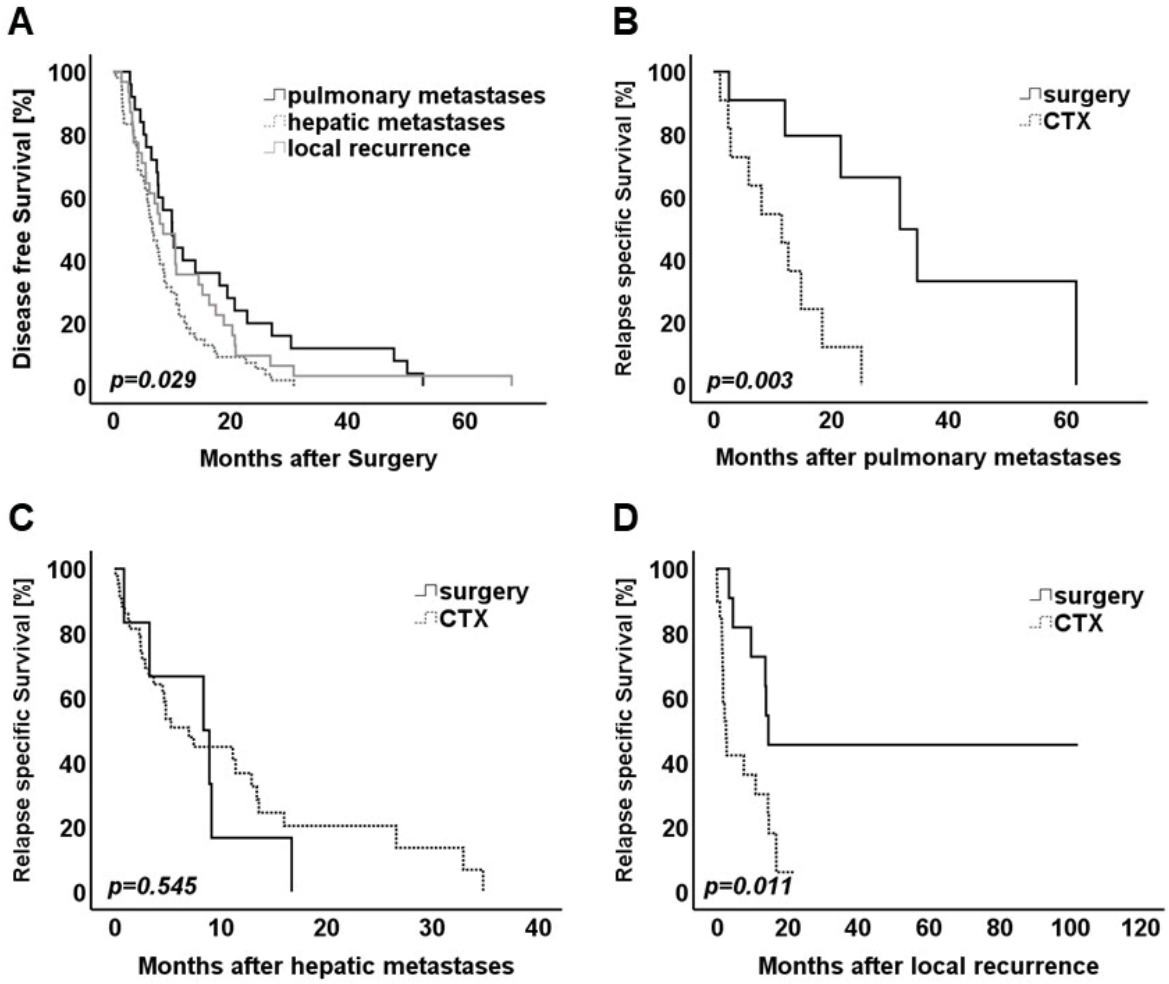
	RFS before 2nd treatment		A RFS before surgery B RFS before chemotherapy			A PRS after surgery B PRS after chemotherapy		
	Median (months)	95%CI		Median (months)	95%CI		Median (months)	95%CI
Pulmonary	18.15	0.30 - 35.99	**A**	22.85	14.10 – 31.64	**A**	61.71	-
			B	7.63	4.76 – 10.49	**B**	5.99	0.0 – 12.3
		Log-rank test	***p-value***		*0.012*	***p-value***		*0.005*
Hepatic	7.83	5.76 – 9.89	**A**	7.47	0.00 – 15.56	**A**	8.39	1.52 – 15.26
			B	7.83	5.75 – 9.90	**B**	4.84	1.25 – 8.42
		Log-rank test	***p-value***		*0.897*	***p-value***		*0.829*
Local	10.55	7.14 - 13.96	**A**	10.75	2.30 – 19.22	**A**	51.85	24.65 – 79.10
			B	7.95	2.10 – 13.84	**B**	6.20	3.41 – 9.89
		Log-rank test	***p-value***		*0.972*	***p-value***		*0.006*

CI: confidence interval; RFS: disease free survival; PRS: relapse specific survival; 2nd treatment: relapse surgery or relapse chemotherapy

To evaluate the post relapse survival benefit after surgery or conservative treatment, the post relapse survival for each analyzed relapse compartment was analyzed after therapy initiation. Surgical therapy significantly improved survival in patients with isolated local recurrence and pulmonary metastases, when compared to chemotherapy (p=0.009 for surgpul vs. chempul; p=0.006 for surglocal vs. chemlocal and p=0.829 for surghep vs. chemhep) (Figure 28). Although the median PRS was similar in the pulmonary metastasis and local recurrence groups, all patients suffering from isolated pulmonary metastases succumbed after

secondary therapy in our study (Table 27, Figure 25). Five of the 11 patients with surgically resected isolated local recurrence were still alive 102 months after relapse surgery. In spite of a dismal median RFS of patients in the local recurrence group, which was similar to the RFS of patients with hepatic metastases, all very long-term survivors (> 5 years) of this cohort were found only in the group of patients with surgically resected isolated local recurrence (Figure 28).

Figure 28: Kaplan-Meier curve for (A) disease free survival of patients dependent on the metastatic location. (B) Post relapse survival of patients with pulmonary metastases. (C) Post relapse survival of patients with hepatic metastases. (D) Post relapse survival of patients with local recurrence. Log rank test was used to test for significance. p-value ≤*0.05* indicates significance. Copyright and under License by (141).



Summary: Although RFS in patients before diagnosed local recurrence was significantly shorter when compared to patients before diagnosed systemic disease recurrence, survival after relapse diagnosis was superior after secondary surgery in patients for local-recurrence when compared to patients after relapse surgery for pulmonary or hepatic metastases. Thus, independent on the period between primary therapy and relapse diagnoses, relapse surgery could be performed if otherwise no other contraindication was given. Since local tumor control can be given even after a secondary surgical trial, systemic tumor control and systemic relapse could be presumably achieved/prevented in a greater amount of patient by a neoadjuvant concept when compared to an adjuvant setting after major pancreatic surgery. To evaluate systemic tumor burden prior to treatment initiation, novel radiographic modalities such as the FAPI-PET-CT could play a future role.

3. Summary/Zusammenfassung

Seit der Jahrhundert-Wende hat sich die Prognose von Patienten mit einem duktalen Adenokarzinom des Pankreaskopfes (PDAC) kaum geändert. Die 5-Jahres Überlebensrate liegt derzeit weiterhin unter 10%. Dies ist unter anderem dadurch bedingt, dass sich zum Zeitpunkt der Diagnosestellung circa 80% der Patienten in einem inoperablen oder einem synchron metastasierten Stadium befinden. Gründe dafür sind unteranderem die lange Symptom-Armut, die aggressive Tumorbiologie und das Fehlen von Vorsorgeuntersuchungen des Pankreaskopfkarzinoms.

Die Therapie der Wahl stellt noch immer die Pankreatoduodenektomie dar. Deren Operationsausmaß hat sich seit der Erstbeschreibung Anfang des letzten Jahrhunderts kaum geändert. Während des 20ten Jahrhunderts wurden Bemühungen zur Senkung der Morbiditäts- und Mortalitätsrate unternommen. Erweiterte, sogenannte en-bloc Resektionen haben in den 70er Jahre des letzten Jahrhunderts keine signifikante Verbesserung des Überlebens erzielen können. Des Weiteren betrug die Rate an mutmaßlichen kurativen Resektionen, also Resektionen im Gesunden, circa 80-90%. Motivationen zu einer radikaleren Resektion waren berechtigterweise somit gering. Eine standardisierte pathologische Beurteilung und eine perioperative Chemotherapie existiere jedoch in diesem Zeitraum noch nicht. Paradox erschienen zudem die Ergebnisse der Nachbeobachtung: Trotz den propagierten hohen Raten an R0 Resektion erlitten die meisten Patienten ein lokalregionales Rezidiv, an dem die viele Patienten verstarben.

In der kolorektalen Chirurgie beobachtete man jedoch während der Jahrhundertwende eine Trendwende. Durch die Integration von embryo-anatomischen Kennlinien in die chirurgische Präparation etablierte sich die sogenannte totale-mesorektale sowie die -mesokolische Exzision. Diese fasziengerechte bzw. schichtgerechte Präparation, wurde auf Grund der guten onkologischen Ergebnisse zum Standard und erlangte weltweite Anerkennung. In

Studien konnte nachgewiesen werden, dass die Rate an kurativen Resektionen (R0) sowie die Prognose und die Rate an Lokalrezidiven signifikant verbessert wurde.

Nach der Implementierung eines pathologischen zirkumferentiellen Resektionsrandes (CRM) ebenfalls für das PDAC am Anfang dieses Jahrhunderts zeigte sich eine drastische Senkung der tatsächlichen Resektionen im Gesunden (R0CRM-). In dieser standardisierten pathologischen Vorgehensweise werden zusätzlich zu den schon zuvor untersuchten Resektionsrändern (orale und aborale Duodenum-Absetzung, Gallengangs-Absetzung, Pankreasparenchym-Absetzung) die chirurgischen peri-pankreatischen Resektionsränder mituntersucht. Die mediale und die posteriore Pankreasabsetzung sind am häufigsten von einer inkompletten Resektion betroffen, was verdeutlicht welchen hohen Stellenwert eine genaue Aufarbeitung des zirkumferentiellen Resektionsrandes einnimmt. Dass die Rate an R1 Resektionen historisch deutlich unterschätzt wurde, passt, wie schon oben beschrieben, zur hohen Rate an Lokalrezidiven. Post-Mortem Analysen aus den 90er Jahre konnten Lokalrezidiv-Raten von bis zu 80% zeigen. Dies wurde auch durch eine aktuelle Analyse der in die ESPAC-4 Studie eingeschlossenen Patienten neuerdings wiederholt bestätigt.

Folgende zwei Punkte haben sich seit der pathologischen CRM Implementierung entwickelt: (1) Während sich das gefäßerhaltende (Vena Portae/Vena mesenterica superior und/oder Arteria mesenterica superior; Truncus Coeliacus) Resektionsausmaß nicht geändert hatte, wurden chirurgische Methoden zur besseren intraoperativen Einschätzung der Resektabilität etabliert. Das Ziel dieser ist die adäquatere intraoperative Patienten-Stratifizierung, um inkomplette Resektionen zu verhindern. In allen beschriebenen Fällen gilt es, bevor eine Resektion vorgenommen und der ‘‘point-of no return‘‘ erreicht wird, die Resektabilität zu überprüfen, um gegebenenfalls den Eingriff zu beenden falls keine R0 Resektion erreicht werden kann. Somit konnte die R0 Rate erhöht werden, jedoch bleibt es ungewiss ob eine radikalere gefäßerhaltende Resektion, ähnlich wie sie durch die totale

mesorektale/mesokolische Exzision möglich ist, auch dazu beizutragen kann die R0CRM-Rate weiter zu steigern.

(2) Auch wurden in dieser Zeit bildgebende Verfahren vertieft re-evaluiert und Anhand des Ausmaßes der tumorösen Gefäßummauerung Einstufungen der Patienten in primär operabel, borderline-operabel und nicht operabel vorgenommen. Hier wird isoliert der Tumor beobachtet und dessen CT-morphologische peri-tumoröse Topographie. Der Tumor-Kontakt wird im Zusammenhang mit den medial gelegenen Gefäßen evaluiert (Vena portae und Vena Mesenterica superior sowie Arteria mesenterica superior). Jedoch unterliegt der dorsale Resektionsrand ebenso stark dem Risiko einer non-in-sano (R1) Resektion, sodass allein durch die Gefäßbetrachtung keine Vollständige radiologische Evaluation vorliegen könnte. Das CT-morphologische Ausmaß der Tumorinfiltration wird so womöglich unterschätzt. Bei Patienten mit Rektum-Karzinom hat unter anderem der Abstand des Tumor zur mesorektalen Faszie und die mögliche Infiltration derselben einen deutlichen Stellenwert in der Entscheidung über die Art der multimodalen Therapie und den Zeitpunkt einer Operation. Es ist also denkbar, dass eine präoperative Begutachtung des peripankreatischen Fettes in Bezug auf die tumoröse Topographie bei PDAC Patienten einen ähnlichen Stellenwert einnehmen könnte.

Während dieses chirurgischen ‘‘Stillstandes‘‘ hat sich die onkologische medikamentöse Therapie sehr stark weiterentwickelt. Nach der Einführung von Gemcitabin in der adjuvanten Monotherapie, etablierten sich im Verlauf Kombinationstherapien, die eine verbesserte Prognose einer noch immer extrem letalen Erkrankung brachten. Der jüngste Durchbruch war die Etablierung des modifizierten FOLFIRNOX-Schema. Da die Nebenwirkungen jedoch sehr ausgeprägt sind, wird dieses Kombinations-Regime nur in ausgewählten Patienten eingesetzt.

Neuerdings rückt analog zur multimodalen Behandlung des Rektumkarzinoms die neoadjuvante medikamentöse Behandlung, auch bei geplanter chirurgischer Therapie, in den Vordergrund. Ziel ist es hierbei, in Patienten bei denen eine primär kurative Resektion (R0) unwahrscheinlich ist, durch eine medikamentöse Therapie ein ‘‘down-sizing‘‘ und gegeben falls eine sekundäre Operabilität zu erreichen. Erste Daten einer verbesserten kurativen Resektionsrate wurden schon veröffentlicht, Daten hinsichtlich einer verbesserten Prognose fehlen allerdings noch. Daher soll die neoadjuvante Therapie aktuell nur in ausgewählten Fällen in Betracht gezogen werden. Von Interesse wäre nun die präoperative Stratifizierung der Patienten welche von einer neoadjuvanten Therapie profitieren könnten. Da es unbekannt ist, ob und wie oft das peripankreatische Fettgewebe von dem PDAC infiltriert ist, kann dessen histologische Beurteilung von therapeutischem Interesse sein. Nicht nur könnte davon das Ausmaß einer standardisierten Operation (Vergleich totale-mesorektale sowie -mesokolische Exzision) abhängen, sondern auch die Entscheidung einer neoadjuvanten Therapie, falls die R0CRM- Rate mit dem Infiltrationsstatus des peripankreatischen Fettes korreliert. Sollten somit Patienten mit einer Fettgewebsinfiltration aber ohne Gefäßbeteiligung eine erhöhte R1 Resektionsrate vorliegen, so stellt sich zukunftsperspektivisch die Frage wie mit Patienten mit einem tumorösen Gefäßkontakt unabhängig vom Infiltrationsgrad (<180° oder >180°) (venöser confluens (Vena portae/Vena mesenterica superior) und/oder Kontakt mit der arteriellen Strombahn (Arteria mesenterica superior, Arteria hepatica communis)) vorgegangen wird und ob diese Subgruppe somit automatisch einer neoadjuvanten Therapie zugänglich gemacht werden sollte.

Da das Pankreas, ähnlich wie das Colon ascendens, sekundär retroperitoneal gelegen ist, wurde in der ersten Dekade diesen Jahrhunderts versucht das Mesopankreas zu definieren. Während die anatomischen Faszienverhältnisse (Toldt’s Faszie) des Kolon und Rektum für die chirurgische Resektion weltweit standardisiert wurden, fehlen entsprechende chirurgische Beschreibungen der Faszienverhältnisse um den Pankreaskopf. Bis auf ein

paar einzelnen Zentren in Japan, welche Operationsmethoden anhand dieser embryo-anatomischen Kennlinien definiert haben, fehlen hierzu jedoch weiteren Daten in der westlichen Welt. Der chirurgische Therapieansatz entspricht dem der kolorektalen Chirurgie, in der mit en-bloc Resektion der lymphatischen und vaskulären Strukturen eine Verbesserung der lokalen Tumorkontrolle erreicht wird. In der Literatur fehlen jedoch pathologische Aufarbeitungen der Resektate und Überlebensanalysen, sodass die Vorteile dieser fasziengerechten Präparation des Pankreaskopfes bisher nicht belegt wurden. Auch fehlen anatomische Definitionen der peripankreatischen Topographie in Bezug auf eventuelle Faszienverhältnisse, die ein separates Kompartiment beschreiben und so eine standardisierte Resektion rechtfertigen (Analog der totalen-mesorektalen Exzision und -mesokolische Exzision).

Analog zu den japanischen Kollegen verfolgen wir während einer Pankreatoduodenektomie für PDAC Patienten eine ähnliche Resektionsstrategie. In dieser kumulativen Habilitationsschrift bzw. Übersichtsarbeit werden neue, potenzielle präoperative sowie operative Strategien beschrieben, welche eine adäquatere Stratifizierung von Patienten bzw. deren operativen Therapie, und damit eine erhöhte Rate an kurativen Resektionen, ermöglichen sollen. Die Operationsstrategie wurde definiert und beschrieben, sowie mit anatomischen Grundlagen untermauert (134). Der Infiltrations-Status des mesopankreatischen Fettgewebes wurde histopathologisch untersucht. Die präoperative CT-Bildgebung wurde im Fokus der Tumorgröße und der mesopankreatischen Fettgewebs-Imbibierung re-evaluiert (135). Da die neoadjuvante Therapie in Zukunft auch in der Pankreaschirurgie wahrscheinlich einen sehr großen Stellenwert besitzen wird, wurde der mesopankreatische Infiltrations-Status und die ersten Ergebnisse der Nachsorge von neoadjuvant vorbehandelten Patienten mit den primär operativ versorgten Patienten verglichen (137). Der klinische Verlauf von Patienten mit einem fortgeschrittenen metastasierten Zustand (positive para-aortale Lymphknotenmetastasen (PALN+) und Oligo-

metastasierung der Leber (M1(hep)) wurde aufgearbeitet und mit Patienten, die wegen einem lokal begrenzten Karzinom behandelt wurden, verglichen (139, 140). Zudem wurde die Prognose nach einer Rezidiv-Resektion bei Patienten mit isolierten Lokal-Rezidiven im Vergleich zu den Patienten mit isolierten metachronen pulmonalen und hepatischen Metastasen, analysiert (141).

Das Pankreas, welches ähnlich dem Kolon ascendens und Kolon descendens, nach Abschluß der intestinalen Rotation sekundär retroperitoneal liegt, entspringt wie die übrigen Anteile des hepatobiliären Systems aus dem unteren Vorderdarm. Somit ist das Vorhandensein eines „Mesenteriums“ des Pankreas, welches die versorgenden Gefäß- und Lymphbahnen enthält und sich analog zu den sekundär retroperitonealisierten Kolonanteilen verhält, nachvollziehbar. Es liegt also der Schluss nahe, dass die Faszien Verhältnisse des Colon ascendens auf die der Anatomie des Pankreas übertragen werden könnten. Aus anatomischer Sicht ist es plausibel das die Toldt’s Faszie nach medio-kranial verfolgt werden kann und dort in die Treitz-faszie übergeht. Aus chirurgischer Sicht kann durchaus nachvollzogen werden, dass die Rotationsachse der embryologischen Pankreasdrehung am Abgang der Arteria mesenterica superior ihren Ursprung nimmt. Eine fasziengerechte Präparation während der Pankreatoduodenektomie wurde, neben den japanischen Erstbeschreibern, in unserer Klinik schon früh implementiert und standardisiert. Dadurch erreichen wir eine routinemäßige komplette Resektion des retropankreatischen Gewebes, welches sich bis zwischen die Abgänge des Truncus Coeliacus und der AMS aus der Aorta abdominalis darstellen und mobilisieren lässt. Um eine klare Sicht auf die retroperitonealen Strukturen zu erlangen und um die dorsale Resektionsfläche sicher zu dissezieren, wird zugleich eine para-aortale Lymphadenektomie nach kranial bis zum Ansatz des rechten Zwerchfellschenkels durchgeführt.

Die Faszienverhältnisse konnte ich intraoperativ bis zum Ursprung der Arteria mesenterica superior nachvollziehen. Unter Berücksichtigung der bekannten Anatomie und der embryologischen Grundlage der Faszienformation kann theoretisch von einem Mesopankreas ausgangengen werden (Kompartiment-Anatomie). Es lässt sich am dorsalen Resektionsrand eines Whipple`schen Resektates, entlang des mesopankreatischen Pedikels so auch ein Bindegewebsüberzug nachvollziehen, welcher als Ausläufer der Treitz Faszie zu verstehen ist. Anatomische Erstbeschreibungen in primären Textbüchern aus dem Ende des 19ten und Anfang des 20ten Jahrhunderts haben bereits auf diese Faszienverhältnisse hingewiesen. Durch den Stellenwert der totalen-mesorektalen sowie -mesokolischen Exzision rückte die Toldt's Faszie in den klinischen Vordergrund, sodass die bekannten Faszienverhältnisse um das Duodenum und den Pankreaskopf in Vergessenheit geraten sind. Anders als die Literatur-Recherche für klinische Fragestellungen, ist diese für anatomische Grundlagendaten schwieriger. Die primäre Literatur stammt aus historischen Textbücher die meist nur in anatomischen Sammlungen vorhanden sind. Somit habe ich herausgefunden, dass die Faszienverhältnisse am dorsalen Bereich des mesopankreatischen Pedikels vom Whipple`schen Resektat mit der historischen Literatur im Einklang ist und diese als Treitz-Faszie zu verstehen ist.

Im Gegensatz zu den übrigen mesenterialen Gefäßen des Intestinums erreicht die Vena portae embyrologisch unabhängig von der Rotationsbewegung der mesopankreatischen Achse ihre adulte anatomische Position. Hierzu durchbricht sie das Pankreas. Bei der chirurgischen Präparation zeigt sich diese Differenz in dem teilweise nur sehr dünnen bindegewebigen Saum, welcher sich teilweise schon durch stumpfe Präparationen vom Pankreas-Gewebe trennen lässt. Hingegen ist die Dissektion der Arteria mesenteria superior (AMS) durch die vorhandenen festen Adhäsionen zu den Faszien und dem umgebenden Gewebe des Mesopankreas deutlich erschwert. Diese anatomische Besonderheit ist durchaus von onkologischem Interesse, da durch das Fehlen des mesopankreatischen

Fettgewebes um den venösen Konfluens somit eine tumoröse Infiltration deutlich erleichtert wird.

Von allen konsekutiven Patienten, die in unserer Klinik einer solchen mesopankreatischen Exzision (MPE) unterzogen wurden, zeigte sich bei erneuter sorgfältiger histologischer Aufarbeitung eine mesopankreatische Fettinfiltration in 78% des Kollektivs. Interessanterweise war die Infiltrations-Rate in Patienten mit einem lokal fortgeschrittenen und einem lokal begrenzten Tumor (T1/T2 vs. T3) ähnlich. Des Weiteren war die Verteilung fast aller weiteren klinisch-pathologischen Variablen zwischen Patienten mit und ohne mesopankreatische Fettgewebs-Infiltration homogen, sodass hier von einer ungünstigen Tumorlokalisation, anstelle einer aggressiveren Tumorbiologie, auszugehen ist.

Das Vorhandensein eines ‘‘fat-stranding‘‘ (Fettgewebs-Imbibierung) des mesopankreatischen Fettgewebes in der präoperativen Computertomographie (CT) korrelierte unabhängig von der radiologisch ermittelten Gefäßinvasion (primär resektabel vs. borderline resektabel) mit dem tatsächlichen histologischen Nachweis einer mesopankreatischen Fettgewebs-Infiltration. Auch konnte ich zeigen, dass die radiologisch ermittelte Tumorgröße mit dem in der neuesten Version der UICC Klassifikation größenabhängigen T-Stadium beim PDAC korrelierte. Dies ist durchaus von prognostischer Bedeutung, da das T-Staging der 8ten UICC Edition im Hinblick auf das Überleben eine bessere Vorhersagekraft hat, die der vorherige Version. Ähnliche Daten existierten zu diesem Zeitpunkt nicht. Zusammengefasst können neben der Ermittlung der Gefäßinvasion weitere präoperative CT-morphologische Marker zur Stratifizierung für zukünftige Therapieeinleitungen verwendet werden. Die Evaluierung des mesopankreatischen Fettgewebes und der Tumorgröße, gemeinsam mit der Beurteilung des Gefäßstatus, erlaubt

so die präoperative adäquate Einschätzung des Resektionsausmaßes und der Radikalität an allen chirurgischen Resektionsränder und ermöglicht eine individuelle Stratifizierung der Patienten.

Im Vergleich zu den international publizierten Daten zur Resektion beim PDAC konnte durch die mesopankreatische Exzision (MPE) in unserer Klinik eine erhöhte R0CRM- Rate erreicht werden; diese war bei einer fehlenden mesopankreatischen Fettinfiltration noch deutlich verbessert. Dennoch betrug die R0CRM- Resektionsrate in allen Patienten nur 48%. Im Vergleich zu kurativen Resektionsraten anderer Karzinome, beispielsweise beim kolorektalen Karzinom, bedarf es einer hier einer weiteren Verbesserung. Somit kann postuliert werden, dass das Infiltrationsverhalten des PDAC weiterhin unterschätzt wird und durch die neoadjuvante Therapie, analog zum Rektumkarzinom, eine mögliche verbesserte lokale Tumorkontrolle erreicht werden könnte. Konklusive Daten hierzu liegen jedoch aktuell noch nicht vor. Da ich jedoch zeigen konnte, dass eine mesopankreatische Exzision durchaus histopathologisch zu rechtfertigen ist (MP+ Rate 78%), und durch diese Maximierung der chirurgischen Radikalität die Patienten mit den aktuellen ABC-Kriterien nicht ausreichend stratifiziert sind (R0CRM- Rate 48%), erscheint es sinnvoll, in der präoperativen Aufarbeitung und Therapieentscheidung (primäre Chirurgie vs. neoadjuvante Therapie) mögliche Ansatzpunkte für eine weitere Steigerung der R0CRM- Rate zu suchen. Nicht nur habe ich den prädiktiven Stellenwert des CT morphologischen „fat-stranding“ in Bezug auf den tatsächlichen Infiltationsstatus zeigen können, sondern auch den Zusammenhang dieses Faktors mit einer signifikant verbesserten R0CRM- Rate. Dies soll, analog zum präoperativen Staging für Patienten mit Rektumkarzinom, als Plattform für weitere multizentrische Studien dienen.

Folgende zwei Punkte können dem sinnvollen onkologischen Stellenwert der neoadjuvante Therapie dienen. (1) Die para-aortale Lymphadenektomie (PALN) ist ein obligater

Bestandteil der MPE. Diese wird in unserer Klinik unabhängig von der präoperativen Bildgebung durchgeführt, sodass dies hier in positiven und negativen Patienten ohne ein Selektionsbias untersucht werden konnte. Ich habe zeigen können, dass Patienten mit einer PALN Metastasierung im Vergleich zu den Patienten ohne eine PALN Metastasierung eine ähnliche Anzahl an peripankreatischen sowie extra-peripankreatische Lymphkontenmetastasen auf aufgewiesen haben. Das Lymphknoten-Mapping war somit zwischen den Gruppen ähnlich. Auch zeigte sich kein signifikanter Unterschied im medianen Gesamtüberleben zwischen den Gruppen. Interessanterweise hatten in der Nachsorge die Patienten mit einer PALN Metastasierung eine erhöhte Tendenz für eine pulmonale Metastasierung. Zur präoperativen Detektion von Lymphknotenmetastasen hatte das CT eine schlechte Aussagekraft. Vor allem die para-aortalen Lymphknotenmetastasen wurden in den meisten Fällen nicht detektiert, sodass prä-therapeutisch die ausgedehntere Tumormanifestation nicht diagnostiziert wurde. (2) In selektierten Fällen unseres Kollektivs wurde bei einer Oligometastasierung der Leber (M1hep) eine simultane Leberresektion durchgeführt. Diese kurativ resezierten Patienten (R0CRM-), die perioperativ und/oder postoperativ eine chemotherapeutische Behandlung erhalten hatten, zeigten interessanterweise ein ähnliches mediane Überleben wie Patienten mit einem lokal beschränkten PDAC welche eine chemotherapeutische Monotherapie erhalten hatten. Auch war zwischen den Gruppen das Lokalisationsmuster der Rezidive in den Nachsorgeuntersuchungen ohne signifikanten Unterschied.

Zusammengefasst kann neben dem prätherapeutisch meistunterschätzten dorsalen Infiltrationsmuster des PDACs (78% MP+ Status, mit dann geringerer R0CRM- Rate), die relativ hohe Rate an PALN-Lymphknotenmetastasen (20%) und das ähnliche median Überleben bei metastasierten PDAC Patienten (PALN+ und M1hep) im Vergleich zu Patienten mit einem lokal beschränktem PDAC (PALN- und M0) weitere Gründe für eine standardisierte neoadjuvante Therapie darstellen.

Aller Voraussicht nach kann die neoadjuvante Therapie somit einen hohen Stellenwert in der Behandlung des PDAC besitzen. Selektiere Patienten unserer Klinik wurden vor der MPE einer neoadjuvanten Therapie unterzogen. Ich konnte zeigen, dass die Rate der mesopankreatischen Fettgewebs-Infiltration im Vergleich zu den Patienten nach einer primären Chirurgie signifikant geringer war. Auch zeigte sich in Patienten die eine neoadjuvante Therapie erhielten und im CT eine ‘‘tumor-response‘‘ aufwiesen eine signifikant geringere Rate an mesopankreatischer Tumorinfiltration im Vergleich zu den Patienten ohne radiologisches Therapieansprechen. Da in der größeren Kohorte der primär chirurgisch behandelten Patienten die R0CRM- Rate mit dem MP Infiltationsstatus korrelierte, wird der Stellenwert des neoadjuvanten „down-sizing“ (signifikant geringere MP+ Rate nach Neoadjuvanz) in dieser Arbeit nochmals untermauert. Interessanterweise waren in allen Patienten die Tumorzellen im mesopankreatischen Fett unabhängig von dem histopathologischen Tumoransprechen vital, sodass ähnlich wie bei der chirurgischen Therapie des Rektumkarzinoms (TME unabhängig von Vortherapien) eine mesopankreatische Exzision empfohlen werden sollte.

Die folgenden Überlebensergebnisse aus meinen Arbeiten unterstreichen die oben beschriebenen Stellenwerte des Mesopankreas in PDAC Patienten. In der Nachsorge aller primär chirurgisch behandelten Patienten unseres Kollektivs zeigte sich, im Vergleich zu den in der Literatur publizierten Daten, eine weitaus geringe Rate an Lokalrezidiven. Diese Rate lag im Gesamtkollektiv bei 20.1% und war im Falle einer kurativen Resektion (R0CRM-) weiter auf 10% gesenkt. In der univariaten sowie in der multivariaten Überlebensanalyse sowohl der metastasierten als auch der nicht-metastasierten (PALN Status und M1hep) Patienten war der Resektionsstatus der stärkste prognostische Faktor. Das Vorhandensein einer Infiltration des mesopankreatischen Fettgewebes korrelierte somit nicht mit einem schlechteren Überleben.

Bei den neoadjuvant vorbehandelten Patienten sank interessanterweise die Wahrscheinlichkeit ein Lokalrezidiv zu erleiden nochmals, auf dann lediglich 7.2%. Die hier vorliegende Analyse ist die bislang Erste, die diesen Zusammenhang zwischen dem Mesopankreas und einer neoadjuvanten Therapie untersucht hat. Die neoadjuvante Chemotherapie kann somit durchaus von Nutzen sein, um die lokale und systemische Tumorausbreitung zu beschränken und schon vorhandene und noch nicht detektierte Metastasen zu erreichen. Somit wird in dieser Arbeit der Stellenwert, ähnlich zur lokalen Kontrolle bei Rektum-Karzinom Patienten, mit einer neoadjvuanten Therapie unterstrichen und verdeutlicht.

Während für metachrone Rezidive des kolorektalen Karzinoms oder bei neuroendokrinen Tumoren Erst- und Zweitlinientherapien angeboten werden können, und auch eine klare Indikation für die chirurgische Therapie bei technisch operablen Rezidiven vorliegen, besteht für PDAC Patienten mit isolierten Metastasen weiterhin nur sehr enge und häufig ungenügende Therapieoptionen. Verbesserungen der Chemotherapie-Regime konnten jedoch in der letzten Dekade eine stable disease bei synchron metastasierten Patienten erreichen, sodass in der Zukunft die Möglichkeit einer chirurgischen Therapie der residuellen Tumore sinnvoll erscheint. Es konnte bislang schon gezeigt werden, dass eine Rezidiv-Chirurgie in selektierten Patienten, die an isolierten Lokalrezidiven oder pulmonaler Oligometastasierung erkrankten, sinnvoll für das Gesamtüberleben sein kann. Wobei Patienten mit isolierten Lokalrezidiven im Mittel früher erkrankten, als solche mit isolierten pulmonalen oder hepatischen Metastasen. Daher konnte im Falle einer Organmetastasierung durch die chirurgische Resektion das längste mediane Überleben erzielt werden.

Im Rahmen meiner Arbeiten konnte ich damit schlussfolgern: Durch eine embryonal-anatomische und fasziengerechte Resektion, analog der TME in der kolorektalen Chirurgie,

kann die lokale Tumorkontrolle verbessert werden. Dennoch beträgt die kurative Resektionsrate (R0CRM-) nach einer adäquaten pathologischen Aufarbeitung nur circa 50%. Vermutlich leiden eine unterschätzte Anzahl der primär chirurgisch behandelten Patienten an einer lokal wie systemisch nicht detektierten Dissemination (MP+ Status bei circa 78%, PALN+ bei circa 20%). Des Weiteren werden im Verlauf der Nachsorge die meisten Patienten mit einer systemischen Metastasierung diagnostiziert. Im Hinblick auf diese Unterschätzung der lokalen wie auch systemischen Dissemination, stellt die neoadjuvante Therapie eine hoffnungsvolle Therapieergänzung dar. Durch eine detaillierte Aufarbeitung der präoperativen oder post-neoadjuvanten Bildgebung können Patienten anhand der erweiterten Risikoparameter (MP Status, R1 Status) besser stratifiziert werden.

4. Abbreviations

5FU	
CA	Cancer antigen
Cap	Capecitabine
CHA	Common hepatic artery
CI	Confidence intervall
CRM	Circumferential resection margin
CT	Celiac trunk
CTX	Chemotherapy
DGAV	Deutsche Gesellschaft für Allgemein und Viszeralchirurgie
DKG	Deutsche Krebsgesellschaft
ECOG	Perfomance status
ERCP	Endoscopic retrograd cholangiopancreatography
EUS	Endoscopic ultrasound
FAPI	Fibroblast activation protein inhibitor
FPC	Familial pancreatic cancer
GDA	Gastroduodenal artery
Gemca	Gemcitabine
HR	Hazard ratio
IAP	International association of Pancreatology
ISGPS	International studygroup of pancreatic surgery
L	Lymphatic invasion
LAD	Lymphadenectomy
LN	Lymphnode
MD	Multidrug
MDCT	Multidetector computed tomography
mFOLFIRINOX	modified folinic acid, fluorouracil, irinotecan, oxaliplatin
MP	Mesopancreas/mesopancreatic
MPE	Mesopancreatic excision
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
N/A	Not available
NCCN	National cancer network
OS	Overall survival
PDAC	Pancreatic ductal adenocarcinoma
PET-CT	Positron emission computed tomography
PH	Pancreatic head
Pn	Perineural invasion
PN	Pancreatic neck
Pp	Peripancreatic
PRS	Post relapse survival
PV/SMV	Portal vein/ superor mesenteric vein
RFS	Relapse free survival
S1	Tegafur/gimeracil/oteracil
SMA	Superior mesenteric artery
TME	Total mesorektal exzision
TNM	Tumor, Nodal and distant metastases staging
UICC	Union for International Cancer Control
US	Ultrasound
V	Venous invasion

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7. Eidesstattliche Versicherung

Ich versichere an Eides statt, dass diese Habilitationsschrift selbstständig und ohne unzulässige fremde Hilfe erstellt worden ist.

Die hier vorgelegte Arbeit wurde nicht von einer anderen Medizinischen Fakultät abgelehnt und ich habe keine anderen Habilitationsverfahren begonnen oder abgebrochen.

Bei den hier vorgelegten wissenschaftlichen Arbeiten wurden die ethischen Grundsätze und die Grundsätze und Empfehlungen zur Sicherung guter wissenschaftlicher Praxis beachtet.

Für alle Forschungsvorhaben wurde vor Beginn ein positives Ethikvotum der Ethikkommission der Heinrich-Heine-Universität Düsseldorf eingeholt. Die Vorgaben des Bundesdatenschutzgesetzes wurden bei allen Arbeiten in der jeweils aktuellen Version eingehalten.

8. Appendix

This thesis was based on the following original articles:

Appendix 1: **Safi SA,** Haeberle L, Fluegen G, Lehwald-Tywuschik N, Krieg A, Keitel V, Luedde T, Esposito I, Rehders A, Knoefel WT. Mesopancreatic excision for pancreatic ductal adenocarcinoma improves local disease control and survival. Pancreatology. 2021 Jun;21(4):787-795. doi: 10.1016/j.pan.2021.02.024. Epub 2021 Mar 17. PMID: 33775563.

Appendix 2: **Safi SA,** Haeberle L, Heuveldop S, Kroepil P, Fung S, Rehders A, Keitel V, Luedde T, Fuerst G, Esposito I, Ziayee F, Antoch G, Knoefel WT, Fluegen G. Pre-Operative MDCT Staging Predicts Mesopancreatic Fat Infiltration-A Novel Marker for Neoadjuvant Treatment? Cancers (Basel). 2021 Aug 28;13(17):4361. doi: 10.3390/cancers13174361. PMID: 34503170; PMCID: PMC8430607.

Appendix 3: **Safi SA,** Rehders A, Haeberle L, Fung S, Lehwald N, Esposito I, Ziayee F, Krieg A, Knoefel WT, Fluegen G. Para-aortic lymph nodes and ductal adenocarcinoma of the pancreas: Distant neighbors? Surgery. 2021 Aug 12:S0039-6060(21)00666-8. doi: 10.1016/j.surg.2021.06.045. Epub ahead of print. PMID: 34392977.

Appendix 4: **Safi, S.-A.;** Haeberle, L.; Rehders, A.; Fung, S.; Vaghiri, S.; Roderburg, C.; Luedde, T.; Ziayee, F.; Esposito, I.; Fluegen, G.; Knoefel, W.T. Neoadjuvant Treatment Lowers the Risk of Mesopancreatic Fat Infiltration and Local Recurrence in Patients with Pancreatic Cancer. Cancers 2022, 14, 68. https://doi.org/10.3390/cancers14010068

Appendix 5: **Safi SA,** Fluegen G, Rehders A, Haeberle L, Fung S, Keitel V, Krieg A, Knoefel WT, Lehwald-Tywuschik N. Surgical margin clearance and extended chemotherapy defines survival for synchronous oligometastatic liver lesions of the ductal adenocarcinoma of the pancreas. Int J Clin Oncol. 2021 Oct;26(10):1911-1921. doi: 10.1007/s10147-021-01961-5. Epub 2021 Jun 16. PMID: 34132929; PMCID: PMC8449759.

Appendix 6: **Safi SA,** Lehwald-Tywuschik N, Rehders A, Fluegen G, Haeberle L, Keitel V, Knoefel WT. Site of relapse of ductal adenocarcinoma of the pancreas affects survival after multimodal therapy. BMC Surg. 2021 Mar 3;21(1):110. doi: 10.1186/s12893-021-01082-w. PMID: 33658016; PMCID: PMC7931536.

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