TURUN YLIOPISTO

Surgical outcomes and prognosis of pancreatic and periampullary cancer treated with neoadjuvant therapy in Turku University Central Hospital

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Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas. Pancreatic cancer is the third leading cause of cancer related deaths in Finland. Its only curative treatment is surgery. The prognosis of the disease is poor, with an overall 5-year survival rate of only 10 %, and post-operative survival rate of around 20-30 %. Median overall survival after surgery is 16 to 23 months. Periampullary carcinoma is commonly used term to define diverse range of neoplasms originating from the head of the pancreas, the duodenum, and the distal common bile duct. Its prognosis is similar to that of PDAC.

Now the treatment protocol is to proceed directly to surgery if the PDAC is localised or only partially attached to the porta-vein. The median survival rate of patients undergoing surgery can be prolonged by neoadjuvant therapy (NAT), i.e. chemotherapy, radiation therapy or a combination of both. Recently, there have been promising results on the efficacy of NAT for locally advanced and borderline resectable PDACs. NAT is thought to allow a larger patient population to receive an effective dose of chemotherapy in addition to surgical resection, due to chemotherapy often being better tolerated before surgery than after.

The aim of this thesis is to illustrate the effects of NAT on overall survival and disease-free survival of pancreatic and periampullary cancer patients who underwent surgery at the Turku University Central Hospital between the years of 2019-2023.

The most used NAT regimens were Gemcitabine plus Nab-Paclitaxel (60%) and modified FOLFIRINOX (35%). The median duration of NAT was 21 weeks. Fifteen out of 20 NAT patients proceeded to pancreatoduodenectomy. Pathological analysis confirmed eight PDACs and seven periampullary cancers. Seventeen out of 20 patients received adjuvant therapy postoperatively. Eight out of 15 patients had disease recurrence postoperatively (median time of recurrence 15,9 months), and four of them were pathological analysis confirmed PDAC. The median postoperative prognosis free survival (PFS) was 9,3 months (range 2,5-13,7 months), and for only PDAC patients, it was 12,2 months (range 10,7-13,7 months). After follow-up (median follow-up time of 29,0 months, range 8,2-61,5 months) eleven patients were alive. Ten of these eleven patients underwent pancreatoduodenectomy.

Key words: pancreatic cancer, pancreatic ductal adenocarcinoma, neoadjuvant therapy

Contents

1 Review of the literature

1.1 Pancreatic cancer

1.1.1 Epidemiology and survival rates

Pancreatic ductal adenocarcinoma (PDAC) accounts for over 90% of pancreatic neoplasms (Jin and Bai, 2020). PDAC is the 8th most common cancer in Finland; however, it's the third leading cause of cancer related deaths. Its percentage of all cancers is 4% both in men and in women. 1192 new cases were diagnosed in 2021, and 613 (51%) of them were men. ("Cancer statistics – Syöpärekisteri," n.d.) The preliminary incidence of PDAC in Finland in 2022, divided by gender and age, is depicted in **Figure 1**.

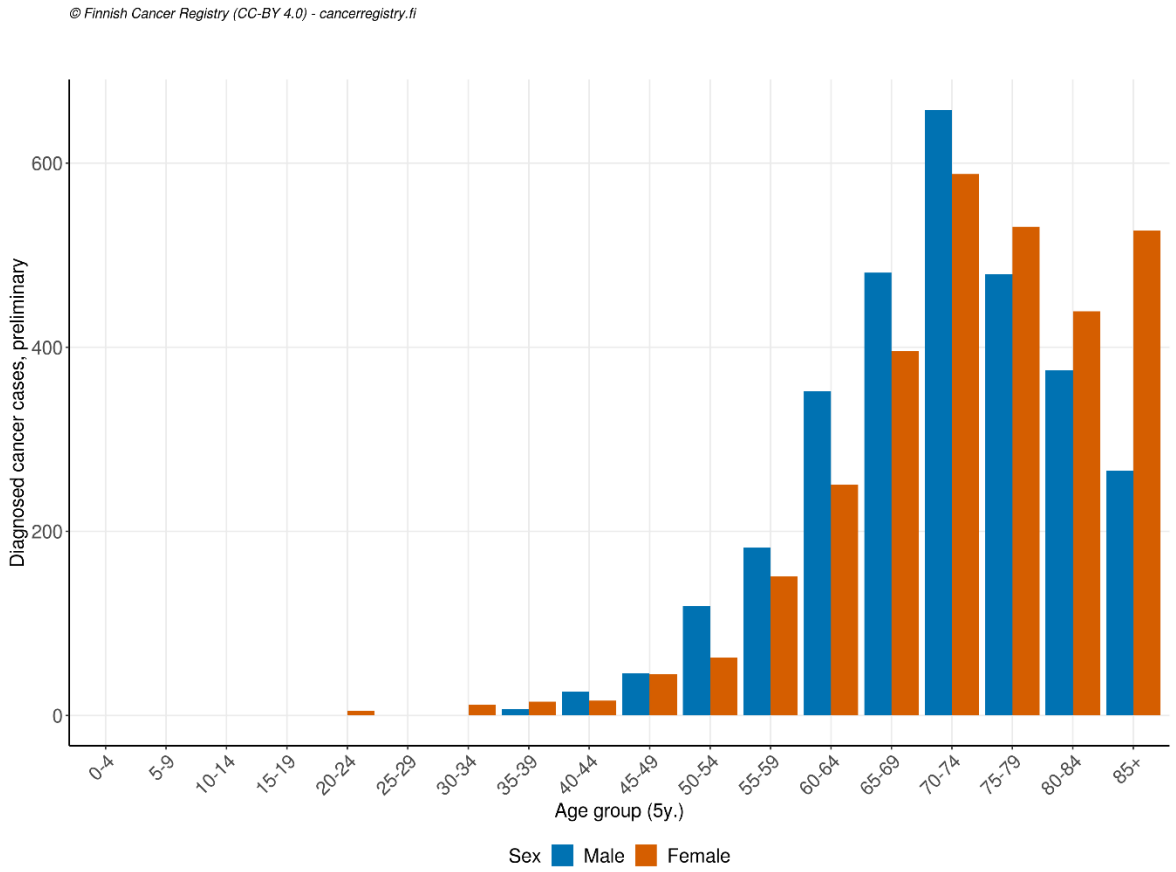

Figure 1. The preliminary incidence of PDAC in Finland in 2022 divided by age and gender. The figure is by *Finnish Cancer Registry* and it's available at *cancerregistry.fi* under CC-BY 4.0 license.

Globally, PDAC is the 12th most common cancer, and 6th in cancer related deaths. The incidence of the disease varies among regions, being highest in developed countries. European countries,

North America, Australia, New-Zealand, Brazil, and South Africa have the highest pancreatic cancer related mortality rates. ("Global Cancer Observatory: Cancer today," n.d.) This implies that lifestyle factors significantly contribute to its etiology, although some of the variation may be attributed to differences in diagnostic and coding practices. Proper diagnosis of PDAC requires modern and expensive imaging modalities and intricate procedures. Without these, many PDAC cases in low-income countries, particularly in patients with metastatic diseases and in elderly might have been misdiagnosed and -registered (Maisonneuve and Lowenfels, 2017).

The incidence of PDAC has increased over the last decades. This can be seen in **Figure 2**, which showcases new cancer diagnoses each year in Finland. Increase in incidence is partly explained by the increasing population longevity and ageing, as PDAC is highly age-dependent. It's estimated that by 2040, the total number of pancreatic cancer cases in the EU will increase by more than 30% (Maisonneuve, 2019).

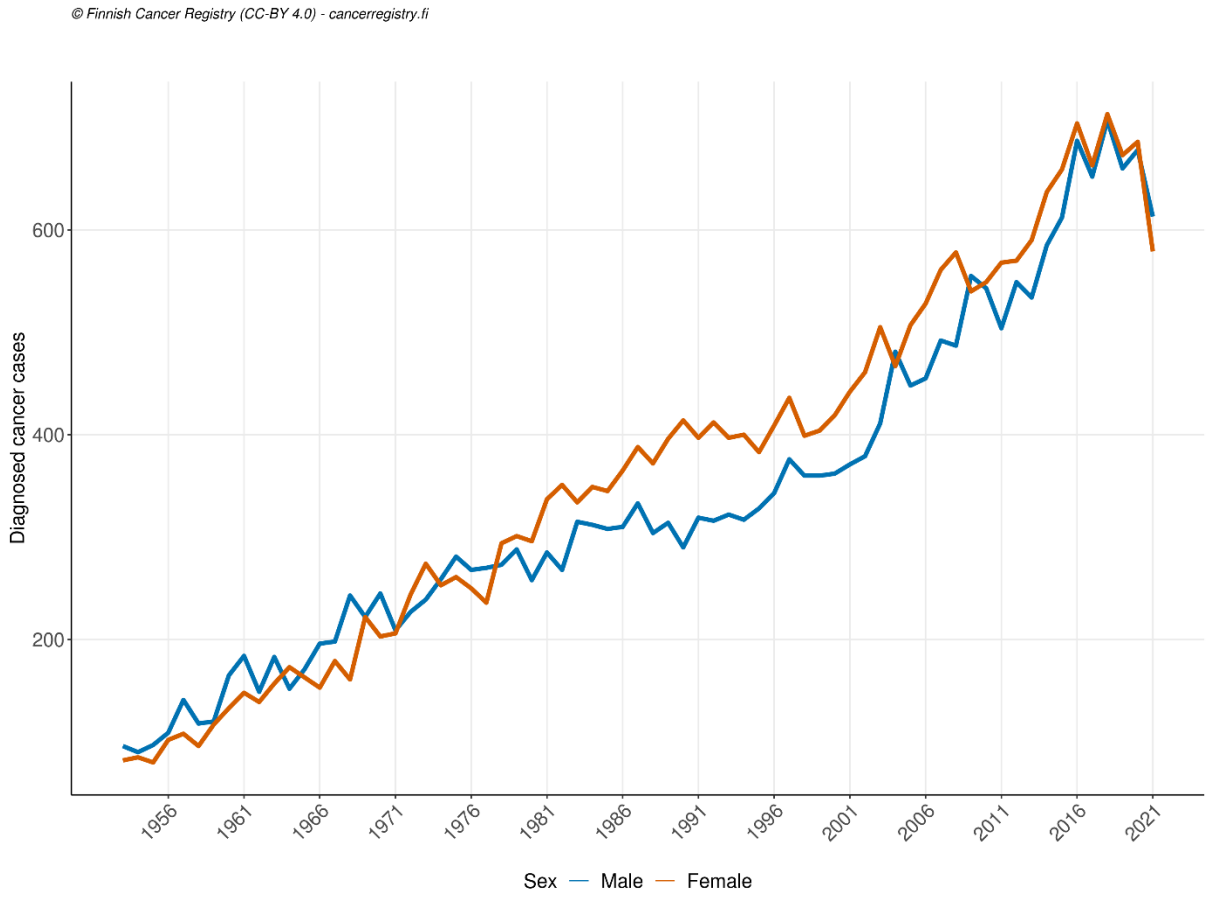

Figure 2. New diagnosed PDAC cases in Finland in recent decades. The figure is by *Finnish Cancer Registry* and it's available at *cancerregistry.fi* under CC-BY 4.0 license.

The survival rates of PDAC remain poor. Its prognosis being the poorest of any common solid malignancy (Howlader et al., 2020). Due to some improvement in diagnosis and treatment methods, the long-term survival rate (>5 years) of 10% has nearly doubled in the last two decades (Siegel et al., 2021). In resectable pancreatic cancer cases, the 5-year survival rate is even higher, about 16-22% (Aaltonen et al., 2021; Luu et al., 2021), and can be up to 39% in the case of stage 1A cancer (van Roessel et al., 2018).

The poor prognosis of PDAC is associated to its location deep in the upper abdomen between aorta and its major upper abdominal branches, where the cancer can grow without causing major symptoms (Grossberg et al., 2021). PDAC displays an aggressive biology characterised by early metastasis. More than 50% of patients present with distant metastatic disease at diagnosis, and majority of operated patients will develop metastasis in the first four years after resection (Conroy et al., 2018; Howlander et al., 2020). Other factors affecting prognosis include PDAC's resistance to many antineoplastic therapies (He at al., 2018) and cachexia, which reduces the tolerability of treatments and occurs in up to 80% of patients at diagnosis (Laviano et al., 2005).

1.1.2 Risk factors

The precise cause of PDAC remains unknown, but its development is linked to various non-modifiable and modifiable risk factors. The non-modifiable risk factors encompass age, gender, diabetes mellitus (DM), ABO blood group, family history and genetic susceptibility. While modifiable risk factors encompass smoking, alcohol consumption, pancreatitis, and obesity. (Hu et al., 2021.) Smoking has the highest positive correlation with the risk of developing pancreatic cancer (Ghadirian et al., 2003). A comprehensive European case-control study confirmed that smoking increased the risk of PDAC by 72 % compared with never-smokers (Molina-Montes et al., 2020). Age is also important factor. The majority of new PDAC cases are diagnosed in people aged 65-74, with median age of diagnosis being 70 years (Surveillance, Epidemiology an End Result Program, 2021). Males have a higher worldwide incidence and mortality rate compared with females.

About every tenth of PDACs are associated with hereditary predisposition, which include hereditary syndromes and familial pancreatic cancer (Ohmoto et al., 2019). Depending on the underlying genetic error, the lifetime risk ranges from 3 to 53% (Klatte et al., 2022). Genetic

mutations affiliated with an increased risk of PDAC include STK11, BRCA1/2, CDKN2A, PRSS1, ATM and PALB2 to name a few (Ghiorzo, 2014). The criteria for familial pancreatic cancer are met when at least two interrelated first-degree relatives have been diagnosed with PDAC and genetic testing has not identified a genetic mutation associated with known cancer hereditary syndromes (Llach et al., 2020).

1.1.3 Diagnosis

PDAC's early diagnosis at a curable stage is extremely difficult because the patients rarely have symptoms and tumours do not have sensitive and specific markers to help with detection (Kleeff et al., 2016). By the time of diagnosis, 80-85 % of cases have spread locally or metastasized (Ryan et al., 2014). Further, the symptoms are often non-specific. Most common of them are weight loss, upper abdominal pain, and jaundice. In addition, symptoms include back pain, nausea, and new-onset diabetes. (Yabar & Winter 2016.) The symptoms depend on the location of the tumour. Mass located in the right side of the pancreas (including head, neck and uncinate process) can cause an obstruction of the common bile duct, leading to jaundice.

Transabdominal ultrasound is the most cost-effective imaging method while being easily accessible (Eurola, 2022). In ultrasound, PDAC can be seen as an irregular hypoechoic mass associated with a cut-off of the main pancreatic duct (MPD) and upstream dilatation of the MPD ("Ultrasonographic diagnostic criteria for pancreatic cancer," 2013). Sensitivity for detecting PDAC on transabdominal ultrasound is only 75-89% depending on factors including operator experience and obesity (Kamisawa et al., 2016), therefore, it cannot be used to exclude pancreatic malignancies.

Computer tomography (CT) is the first-line imaging modality for suspected PDAC (Elbanna et al., 2020). Standard CT can be used in primary phase imaging. But to adequately evaluate the disease, a pancreatic CT is performed with triphasic contrast-enhanced examination, including pancreatic, arterial, and portal venous phases. The location of the tumour in relation to the blood vessels is important in know when choosing a treatment strategy. Typical CT signs of PDAC include a hypoattenuating mass seen in hepatic venous and pancreatic phases. There can also be secondary signs including dilation or cut-off of the pancreatic duct, dilation of the common bile duct, parenchymal atrophy, and outline abnormalities (Yoon et al., 2011). PDAC can be accurately diagnosed using CT with overall sensitivity of 98% and specificity of 90 %

(Treadwell et al., 2016). Challenge occurs in diagnosing smaller tumours (<2 cm) with a lower sensitivity of 77% (Bronstein et al., 2004; Yoon et al., 2011). Diagnostic accuracy of magnetic resonance imaging (MRI) is equivalent to CT with specificity of 89% (Treadwell et al., 2016), but it can help in detecting isoattenuating pancreatic cancer on CT (Zhang et al., 2018). Still CT remains as the primary imaging modality due to MRI's higher cost and inaccessibility compared to CT. Although MRI has an important role in detecting liver metastases.

Endoscopic ultrasound (EUS) offers great help in cases with high clinical suspicion of PDAC without definitive findings on CT, especially for small (≤ 2 cm) tumours. EUS can also be used for PDAC staging, for instance evaluating vascular invasion and lymph node metastases (Ishii et al., 2021). EUS has sensitivity of 87% and specificity of 98%. (Wang et al., 2013.) EUS has an added value in an option to take fine-needle aspiration (FNA) but is less accessible compared to regular ultrasound. Like US, EUS sensitivity depends on operator experience.

Positron emission tomography (PET) -CT detects increased metabolic activity in neoplastic cell tissue. Fluorodeoxyglucose (FDG) is generally used as a marker when suspecting pancreatic cancer. PET-CT can be utilized as a diagnosis tule, particularly in detecting distant metastases, evaluating oncological treatment response and in postoperative controls. It could also play a significant role as independent prognostic factor for overall survival in post-oncological imaging (Kauhanen et al., 2009; Lee et al., 2021).

Endoscopic retrograde cholangiopancreatography's (ERCP) use as a diagnostic method has decreased due to recent progress of other imaging modalities listed above. Hence, ERCP is primarily performed as a therapeutic intervention, such as facilitating biliary drainage for bile duct stricture due to a tumour located in the head of the pancreas. ERCP enables taking of pancreatic juice cytology (PJC) and brush cytology (BC). PJC's sensitivity, including BC in the diagnosis of PDAC, is reportedly 21-64%. This falls well beneath the diagnostic efficacy achieved by EUS-FNA. Due to the invasiveness of ERCP, it is associated with a risk (1-12%) of post-ERCP acute pancreatitis. (Ishii et al., 2021.)

As stated previously, the lack of specific diagnostic markers for PDAC make an early diagnosis difficult. Existing tumour markers lack the required specificity to differentiate effectively between benign and malign forms of the disease. Distinguishing chronic pancreatitis (CP) from PDAC poses a particular challenge. (Ferri et al., 2016.) Two of the most studied tumour markers

assessed in PDAC are carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). Of the two, CA 19-9 is more used in the management of pancreatic cancer; however, it comes with significant limitations, with a sensitivity of 79% and a specificity of 82% (Goonetilleke and Siriwardena, 2007). CA 19-9 can increase in other malignancies and in benign diseases of gastrointestinal tract, and in cholestasis. Therefore, a normal result does not exclude cancer. (Ferri et al., 2016.) Recently, there have been rising interest in utilizing liquid biopsy for diagnosing PDAC. This includes the examination of biomarkers in urine and saliva, as well as circulating tumour cells (CTCs), tumour DNA (ctDNA), microRNAs (miRNAs) and exosomes in blood (Yang et al., 2021).

PDAC is not suitable for screening in healthy population with an average risk due to large number of false positives (Lucas and Kastrinos, 2019). Although, screening should be considered for people with greater than 5% lifetime risk. This includes genetic susceptibility. Genetic mutations can be divided into three groups based on cancer risk and monitoring recommendations. The very high-risk group (7-53%) (Klatte et al., 2022) includes all carriers of STK11, CDKN2A and certain PRSS1 gene defects. According to recommendation, over 40-year-olds in this group should undergo MRI or EUS in alternate years. The high-risk group (3-9,5%) (Klatte et al., 2022), includes carriers of ATM and BRCA2 gene defects. This group should also undergo MRI or EUS in alternate years, if their first-degree relative has been diagnosed with pancreatic cancer. Reduced monitoring is recommended for the moderate risk group, which includes PALB2 gene mutations and familiar pancreatic cancer. Reduced monitoring is done with yearly MRI, if first-degree relative has been diagnosed.

1.1.4 Resectability

Achieving clean resection margins with surgery is crucial in curable pancreatic cancer. Resection margin status stands out as one of the most established prognostic factors. The aim is an R0-rescetion, a macroscopically complete removal with a clean margin of ≥1 mm from the tumour. In R1-resection, removal is macroscopically complete, but microscopically the tumour grows to the margin. In R2-resection, the removal of the tumour is macroscopically incomplete. The ESPAC-4 trial demonstrated better median OS of 39,5 months after R0-resection compared to 23,5 months after R1-resection (Neoptolemos et al., 2017).

Surgical resectability is carefully decided in multidisciplinary meetings at experienced centers. In Finland, pancreatic surgery is done in five university hospitals. The location of the tumour compared to surrounding tissues and blood vessels is carefully defined by triphasic pancreatic CT or contrast MRI and radiological staging. According to these findings, pancreatic tumours are classified into four categories according to their resectability. These are resectable, borderline resectable, locally advanced, and metastatic. However, there is no single standardised definition of this classification (Wei and Hackert, 2021). Typically, locally advanced tumours without distant metastasis are treated with chemotherapy, while resectable tumours undergo upfront surgical resection (Kamisawa et al., 2016; Siegel et al., 2016). The classification within borderline resectable cases varies across institutions, especially in defining the criteria of venous invasion due to differences in vascular reconstruction surgeries (Zins et al., 2018). Metastatic cancer cases are automatically excluded form curative surgical treatment. **Table 1** shows National Comprehensive Cancer Network's (NCCN) definition of the pancreatic tumour's resection criteria.

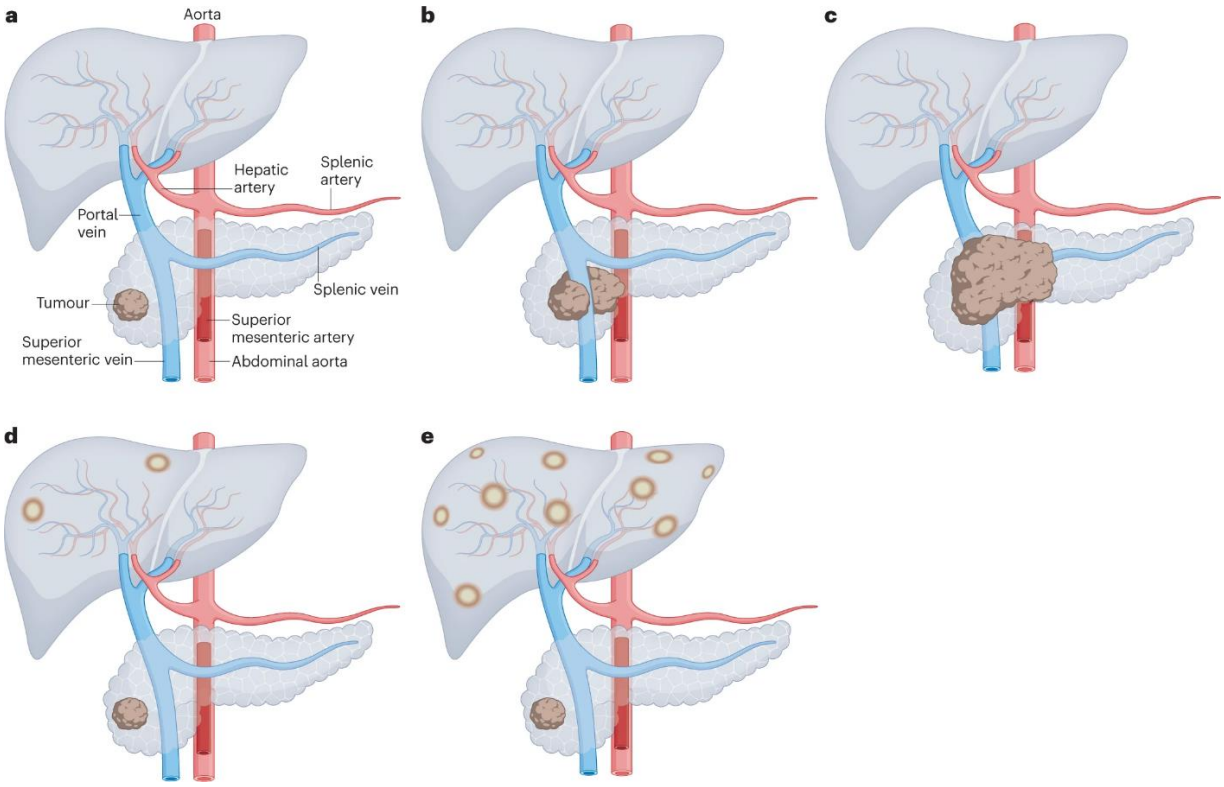

Figure 3: Different stages of pancreatic cancer illustrated in Nature Reviews Clinical Oncology, Springfeld et al., 2023.
a, Resectable, b, Borderline resectable, c, Locally advanced, d, Oligometastatic, e, Metastatic

Table 1 The criteria for tumour resectability in PDAC by National Comprehensive Cancer Network (Eurola, 2022).

Resectability	
Resectable	No tumour-vessel contract ≤ 180˚ contact with SMV/PV without venous contour irregularity
Borderline resectable Vein contact	 > 180˚ contact with SMV/PV ≤ 180˚ contact with SMV/PV with venous contour irregularity or thrombosis Tumour contact with IVC
Artery Contact	≤ 180˚ contact with CA/SMA Tumour contact with CHA without extension to CA or HA Contact with variant arterial anatomy
Locally advanced	>180˚ tumour contact with SMA or CA Contact with the CA and aortic involvement Unreconstructible SMV/PV due to tumour invasion or thrombosis
Unresectable	Metastasis including non-regional lymph nodes

CA, celiac artery; CHA, common hepatic artery; HA hepatic artery; IVC, inferior vena; PV, porta vein; SMA: superior mesenteric artery; SMV, superior mesenteric vein

Radiological TNM-staging is usually performed preoperatively to predict prognosis. It includes the local tumour extent (T), local lymph node metastases (N) and metastatic dissemination to distant organs (M). The American Joint Committee on Cancer's (AJCC) Cancer Staging Manual is used for determining the cancer stage. Its latest 8th edition for staging PDAC is presented in **Table 2.**

Table 2. The American Joint Committee on Carcer's 8th edition manual of staging pancreatic ductal adenocarcinoma, Chun et al., 2017.

TMN category	Description
T1	Tumour diameter ≤ 2 cm
T1a	≤ 0,5 cm
T1b	> 0,5 cm and < 1 cm
T1c	1-2 cm
T2	Tumour diameter > 2 cm and ≤ 4 cm
T3	Tumour diameter > 4 cm
T4	Tumour growth to the SMA or the celiac axis
N0	No regional lymph node metastasis
N1	Metastases in 1-3 regional lymph nodes
N2	Metastases in ≥ 4 regional lymph nodes
Staging	
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T3 N0 M0
IIB	T3 N0 M0
III	T1, T2, T3 N2 M0 T4 any N M0
IV	any T any N M1

SMV, superior mesenteric vein

1.2 Treatment of pancreatic ductal adenocarcinoma

1.2.1 Neoadjuvant treatment

NAT is defined as the administration of chemotherapy, sometimes including radiation therapy, prior to curative surgery. Advantages of NAT include providing more patients with a change to undergo surgery, increased probability of achieving R0 margins, decreased difficulty of the surgical operation due to tumour downsizing, guaranteeing early administration of systemic chemotherapy, and facilitating broader access to chemotherapy for most patients due to chemotherapy being better tolerated preoperatively than postoperatively (Versteijne et al., 2018; Yu et al., 2020). Approximately 50% of patients do not receive adjuvant chemotherapy due to early recurrence of the disease, surgical morbidity, or clinical deterioration (Merkow et al., 2014). Finally, NAT can prevent redundant surgeries in patients with rapidly progressive pancreatic cancer.

Some disadvantages of NAT are clinical deterioration before surgery, toxicity of the chemotherapy, and possibility of disease progression due to tumour insensitivity to the NAT (van Dam et al., 2022). In contrast to many types of cancer, PDACs are relatively resistant to chemotherapy treatments (Springfeld et al., 2019). However, up to 20% of scheduled resections of patients undergoing NAT are cancelled due to early metastases, diminished performance status, or comorbidities during NAT, but very rarely because of local tumour progression alone (Tzeng et al., 2012).

Generally, NAT is recommended for patients with bordeline resectable and locally advanced disease and in cases of resectable disease with high-risk attributes such as larger tumour or high CA19-9 level (Tempero et al., 2021). As mentioned earlier, there is no single consensus on the definition of borderline resectable PDAC (BR-PDAC). To address this issue, a symposium was held during the 20th meeting of the International Association of Pancreatology in Japan, in 2016. They agreed to a broader definition of BR-PDAC derived from the 'ABC' method developed at the MD Anderson Cancer Centre (Katz et al., 2008). This includes the anatomical, biological, and conditional definitions. The anatomical definition is a tumour that is at high risk for margin-positive resection (R1, R2) when proceed directly to surgery. This often entails tumour contact with abdominal vessels. The biological definition is when there are suspicious but not diagnostic radiographic findings for extrapancreatic metastatic disease, including high CA19-9 levels (>1000 U/ml). The conditional definition regards for patients' performance status and co-morbidities that increase the risk of morbidity and mortality after surgery. (Isaji et al., 2018.)

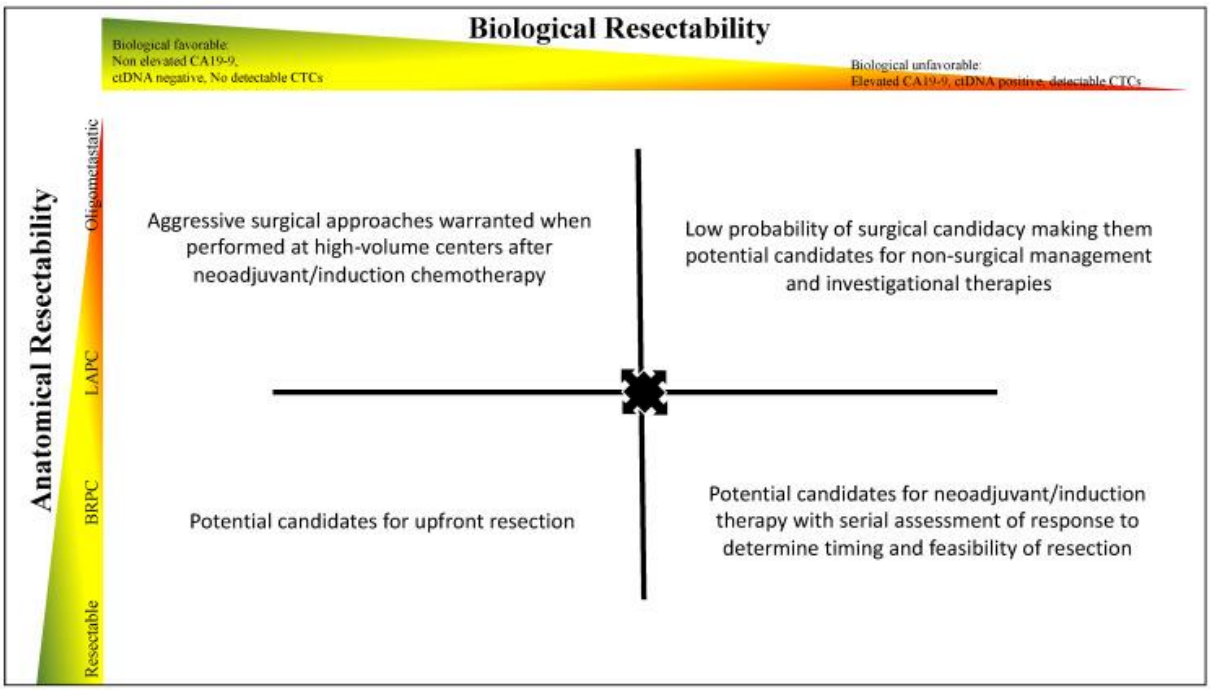

Figure 4. Evaluation of anatomical and biological resectability, Rompen et al., 2024.

Nowadays, the two of the most preferred NAT regimens consist of FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) and Gemcitabine plus Nab-Paclitaxel. The NCCN guideline recommends these two as first-line regimens for NAT in PDAC (Yu et al., 2020). While these regimens have demonstrated significant potential, some challenges persist such as the management of toxicities, especially, with FOLFIRINOX. Therefore, it is primarily used for patients with a good performance status (Smaglo, 2024). A practical approach to reduce toxicities is dose adjustment. Modified FOLFIRINOX can significantly lower the frequency and severity of toxicities without affecting its efficacy compared to the standard FOLFIRINOX (Stein et al., 2016). The duration of NAT varies according to chosen regimen and treatment response, but generally it is approximately 4-6 months (Springfeld et al., 2023).

NAT can also include chemoradiation. Some studies have shown that its implementation could increase the likelihood of R0 resection. Recently, utilization of stereotactic body radiation therapy (SBRT) has increased. Some studies suggest that it may improve R0 resection and overall survival. (Jiang et al., 2019.)

Restaging after NAT is often more challenging than the initial staging, due to the difficulty in confidently distinguishing active tumour from tumour necrosis, tumour associated desmoplasia, and/or inflammation resulting from NAT (Katz et al., 2012). Most commonly used evaluation methods are imaging and tumour markers. Other indicators including circulating tumour cells, circulating tumour cell DNA and Micro RNA are under research. In Turku University Central Hospital, a CT is performed every two months. If the disease progresses, the NAT regimen is changed. Some studies have shown a decrease of accuracy in detecting R0 resectability after neoadjuvant therapy with CT (Katz et al., 2012). Several studies have disputed these findings; however, the limitations of CT for NAT response evaluation must be considered when determining the timing of surgery (Yu et al., 2020). The fluctuation of CA19-9 levels is significant during NAT (Yu et al., 2020). Its normalisation or decrease of more than 50% is a sign of a good prognosis. Patients with BR-PDAC who experienced a decrease of CA19-9 >50% during NAT had higher odds of R0-margin status (Katz et al., 2010).

NAT can influence the choice of surgical technique. Preoperative radiotherapy can make the surgery more difficult. Some of the long-term effects of radiotherapy include microvascular damage and soft tissue fibrosis, resulting in an increased likelihood of developing chronic wounds which are unreceptive to surgical treatment (Dormand et al., 2005). Hackert et al. suggest “the TRIANGLE operation” for patients with borderline or locally advanced pancreatic tumours. It is a technique of radical resection of the tumour with preservation of the arterial vessels (Hackert et al., 2017). It is due to CT’s poor ability to distinguish neoplastic and arterial infiltration from chemotherapy induced fibrosis.

Table 3. Survival outcomes of neoadjuvant therapies in patients with resectable and borderline resectable pancreatic cancer in randomized studies.

Trial	Recruitment period	Treatment arms	Median OS (months)
Resectable			
Prep-02/JSAP-05 (Unno et al., 2019)	2013-2016	GEM-S1 → surgery → S1 (n=182) vs surgery → S1 (n=180)	36.7 vs 26.7
PREOPANC1 (Versteijne et al., 2020; Versteijne et al., 2022)	2013-2017	CRT GEM → surgery → GEM (n=65) vs surgery → GEM (n=68)	15.7 vs 14.3
SWOG S1505 (Sohal et al., 2021)	2015-2018	mFOLFIRINOX → surgery → mFOLFIRINOX (n=55) vs GEM-NabP → surgery → GEM-NabP (n=47)	23.3 vs 23.6
NEONAX-AIO-PAK-0313 (Seufferlein et al., 2022)	2015-2021	GEM-NabP → surgery → GEM-NaP (n=59) vs surgery → GEM-NaP (n=59)	25.2 vs 16.7, primary end point not reached in either arm
PANACHE01-PRODIGE48 (Schwarz et al., 2018)	2017-2020	mFOLFIRINOX → surgery → CTX (n=70) vs FOLFOX → surgery → CTX (n=50) vs surgery → CTX (n=26)	30.6 vs 31.3 vs >36 (NS)
Borderline			
Jag et al., 2018	2012-2014	CRT + GEM → surgery → GEM + CRT (n=27) vs surgery → GEM + CRT (n=23)	21 vs 12
ESPAC-5 (Ghaneh et al., 2023)	2014-2018	Surgery → CTX (n=32) vs NAT (CEMCAP (n=20), FOLFIRINOX (n=20) or CAP-CRT (n=16)) → surgery → adjuvant CTX	1-year OS 39% vs 76% for the combined NAT groups; 1-year OS 78%, 80% and 60%, in GEMCAP, FOLFIRINOX and CAP-CRT
Alliance A021501 (Katz and Russo, 2022)	2016-2019	mFOLFIRINOX → surgery (n=54) vs mFOLFIRINOX → SBRT → surgery (n=56)	29,8 vs 17,1

CAP-CRT, capecitabine plus chemoradiotherapy; CRT, chemoradiotherapy; CTX, chemotherapy; GEM, gemcitabine; GEMCAP, GEM plus capecitabine; mFOLFIRINOX, modified folinic acid; NabP, nab-paclitaxel; NAT, neoadjuvant therapy; NR, not reported; NS, not significant; OS, overall survival.

1.2.2 Surgical treatment

Surgical resection remains as the only curative treatment for PDAC and periampullary cancers. It is a viable approach for only 15-20% of patients with early-stage disease (Park et al., 2021). The main goal for curative surgery is margin-negative (R0) resection of the primary tumour and regional lymph nodes. Other goals include reducing procedural morbidity and mortality, preventing metastatic spread, and improving the patient's overall quality of life (Grossberg et al., 2020). Current treatment practise for resectable PDAC, is upfront surgery combined with adjuvant therapy postoperatively (Tempero et al., 2021).

PDAC is most commonly located (60-70%) in the head of the pancreas (Luchini et al., 2016). In these cases, a pancreatoduodenectomy, known as the Whipple procedure, is performed. It includes the resection of the head of the pancreas, duodenum, proximal part of jejunum, cystic duct, common bile duct and gallbladder. The classical Whipple (CW) also entrails the removal of the lower part of the stomach and pylorus. The pylorus sparing pancreatoduodenectomy (PPPD) was developed in 1980 to reduce post-gastrectomy symptoms including dumping syndrome, dyspepsia and diarrhea. Multiple prospective studies comparing the two techniques in perioperative and long-term outcomes have yielded inconclusive results (Seiler et al., 2005; Hackert et al., 2018). The choice of procedure technique is made by the surgeon according to experience and hospital practices. The PPPD technique is used in Turku University Hospital. After all the resections, three anastomoses are constructed: pancreatojejunostomy, hepaticojejunostomy, and duodenojejunostomy. Due to high technical complexity of this operation, the open technique is the golden standard.

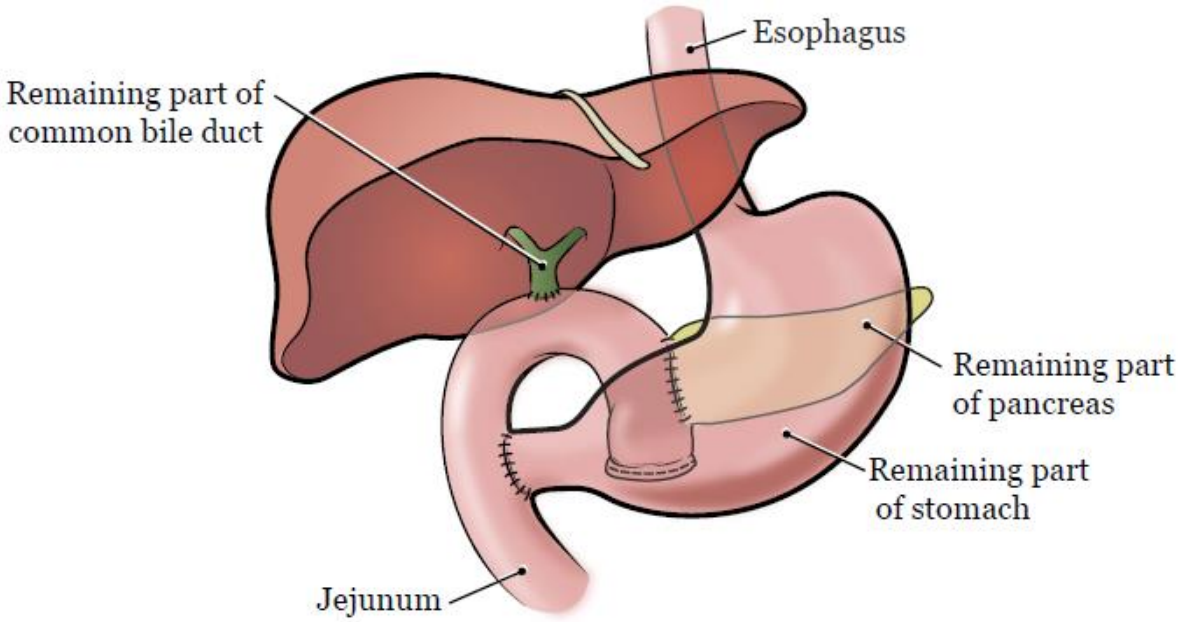

Figure 5. Schematic picture of the anastomoses of pancreatoduodenectomy ("Memorial Sloan Kettering Cancer Center," n.d.)

If necessary, a vascular resection is performed. This can be the case in pancreatic head tumours, where the tumour grows into contact with the portal vein or superior mesenteric vein. Then a segmental resection of vein is done with help of vascular surgeon (D'Cruz et al., 2023).

Distal pancreatectomy is performed when the cancer is located in the tail or the body of the pancreas, which is in 20-25% of PDAC cases (Ryan et al., 2014). During the procedure, a splenectomy is also required as the splenic artery also supplies circulation to the distal part of the pancreas. Minimally invasive technique for distal pancreatectomy is widely used. Studies have inconclusive results regarding which technique is better, open or minimally invasive (Takagi et al., 2022).

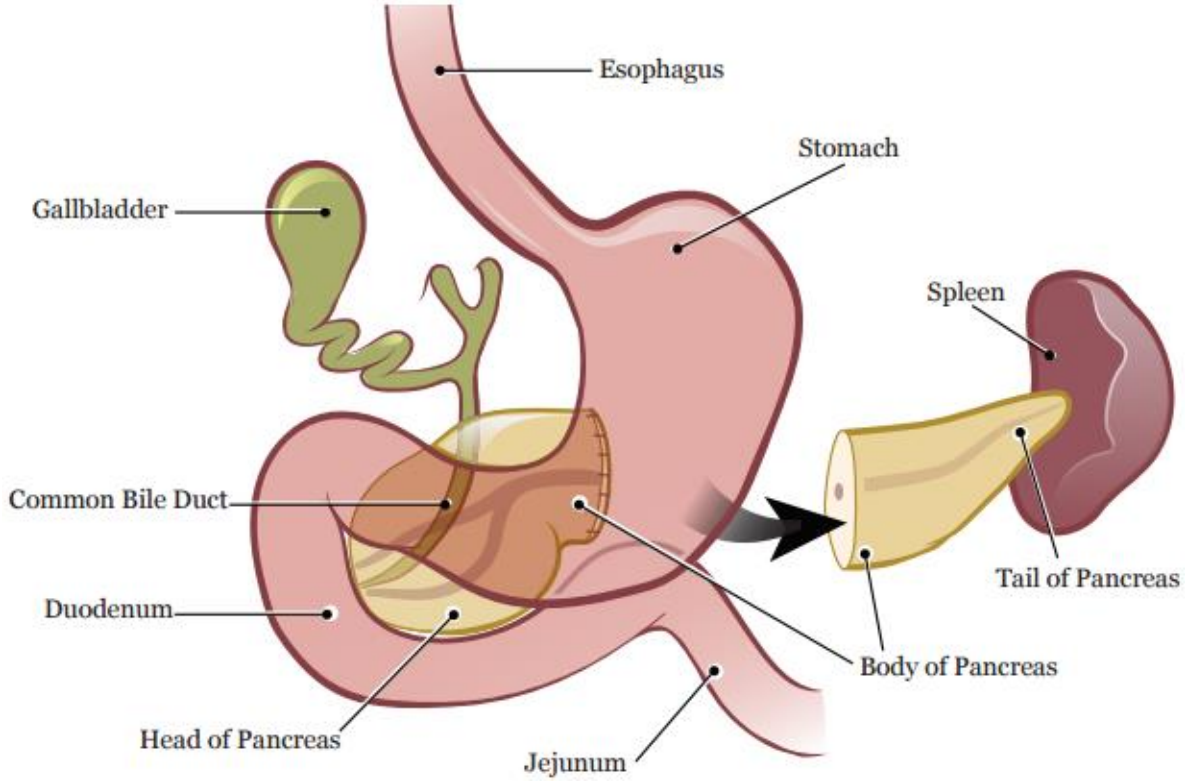

Figure 6. Schematic picture of a distal pancreatotectomy. ("Memorial Sloan Kettering Cancer Center," n.d.)

A lymphadenectomy, resection of local lymph nodes, is done in all pancreatic cancer surgeries. Lymph node metastasis is a central prognostic marker of survival and predictor of recurrence in PDACs (Sarfaty et al., 2023). In standard lymphadenectomy, 13-17 lymph nodes are removed (Tol et al., 2014), and in extended lymphadenectomy, the number is 20-40. Studies have not shown a difference in survival time comparing the two procedures, while the latter is reported to have a higher postoperative morbidity rate (Niesen et al., 2019).

Despite the complexity of the operation, the perioperative mortality is relatively low, around 3,2% (Merath et al., 2020). Multiple studies indicate improved patient outcomes and survival rates by centralization of pancreatic cancer treatment to big volume centers (El Amrani et al., 2020). In Finland, all pancreatic cancer surgeries are centralised in university hospitals.

The risk of postoperative complications (morbidity) remains high, around 50% (Simon, 2021). The high rate of morbidity is attributed to the technical complexity of the operation and the frailty and co-morbidity of the patient population. Specific postoperative complications include postoperative pancreatic fistula (POPF) (20-30%), delayed gastric emptying (DGE) (20%) and haemorrhage (3-10%). The definition of POPF, is a persistent drainage of amylase-rich fluid.

The risk of developing a POPF is 20% after pancreatoduodenectomy and 30 % after distal pancreatectomy. They are classified into three categories according to treatment methods. About 85% of POPFs are grade A and treated conservatively. Grade B fistulas require postoperative treatment, such as endoscopic or percutaneous drainage. Once an organ failure occurs, the fistula is grade C and requires reoperation. DGE is defined as need for nasogastric tube (NGT) for more than three days, need to reinsert the NGT after postoperative day three, or the inability to tolerate an oral diet after postoperative day seven. Postoperative haemorrhages can be defined by the onset of the bleeding. Early haemorrhage (< 24 hours) is due to inadequate haemostasis and is often treated with reoperation. Late bleeding (>24 hours) is usually associated with mild symptomatic POPF, in which pancreatic enzymes corrode a hole in the artery wall. At first, patients haemorrhage a little and then the bleeding stops for a while, until it can later become massive. Therefore, the mortality rate for late haemorrhage can be high, 10-20%. (Kauhanen et al., 2018.) Other common complications include intra-abdominal pustules, wound infections (23,5%) (Simon, 2021) and metabolic complications such as diabetes or exocrine insufficiency.

Table 4. The Clavien-Dindo classification of postoperative complications by *AssesSurgery*.

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. Also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusion and total parenteral nutrition are also included.
Grade III **IIIa** **IIIb**	Requiring surgical, endoscopic, or radiological intervention Intervention not under general anaesthesia Intervention under general anaesthesia
Grade IV **IVa** **IVb**	Life-threatening complication (including CNS complications)* requiring IC/ICU-management Single organ dysfunction (including dialysis) Multiorgan dysfunction
Grade V	Death of a patient

*brain haemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: intermediate care; ICU: intensive care unit.

1.2.3 Adjuvant treatment

When chemotherapy, sometimes combined with radiation therapy, is given in curative intent after surgical resection, it's called adjuvant therapy (AT). In recent trials, AT has reportedly improved median overall survival to 25-28 months (Neoptolemos et al., 2017; Sinn et al., 2017). Adjuvant therapy is recommended for PDAC if there are no metastasis or local recurrence, even if the patient did not receive NAT (Tempero et al., 2021). Adjuvant chemotherapy must be started within a 12-week timeframe following surgical resection (Valle et al., 2014).

PRODIGE-24 trial reported an improved disease-free survival (DFS) of almost nine months with modified FOLFIRINOX (21,6 months) compared to Gemcitabine (12,8 months), establishing it as standard AT for fit patients (Conroy et al., 2018). Other AT regimens include Gemcitabine plus Capecitabine and Fluorouracil plus Leucovorin. In cases of previously received NAT, its response should be taken into consideration when designing the AT regimen.

There is a lot of debate on the role of adjuvant chemoradiation therapy (CRT) in PDAC treatment. No modern level 1 evidence supports its use. However, several large retrospective observational database studies from both SEER and National Cancer Database indicate improved overall survival (OS) among patient who receive adjuvant radiation therapy, particularly those with pN+ disease or microscopically positive surgical markers (Hazard et al., 2007; Rutter et al., 2015).

As stated earlier, patients commonly receive < 50% of planned adjuvant chemotherapy (Neoptolemos et al., 2017; Conroy et al., 2018). This is partly due to intolerance of adjuvant therapy especially in those with postoperative morbidity. This has caused the move toward neoadjuvant approach in many centers.

2 Aims of the study

The principle aim of the thesis is to determine the effect NAT have on the prognosis of pancreatic and periampullary cancer in patients who undergo surgery in the Southwestern Finland between the years 2019 to 2023. In particular, the purpose is to examine PFS and OS from the time of diagnosis and radical surgery.

3 Methods

Data from Varha data system will be collected between the years of 2019-2023 on neoadjuvant-treated pancreatic and periampullary cancer patients who have undergone surgery. The data will be collected by searching for the necessary information per patient, such as type and length of NAT received, surgical technique, surgical complications, survival, and progression-free time after treatment. The data compiled in Excel spreadsheets, followed by an analysis of how pancreatic and periampullary cancer patients who received NAT fared after surgery. Finally, the results will be complied into tables and graphs.

There were 20 patients with pancreatic head tumours treated with NAT who were operated on in Turku University Central Hospital between 2019-2023. Ten of them were men (50%). The median age of diagnosis was 65,6 years (range 46-81-year-old).

Fourteen patients had single-line NAT regimens; Gemcitabine plus Nab-Paclitaxel for nine patients, mFOLFIRINOX for three patients, FOLFIRINOX for one patient, and Gemcitabine plus Cisplatin for one patient. The six out of twenty patients had their NAT regimen changed due to poor disease response. Two patients started with Flox and switched to mFOLFIRINOX. One patient switched from mFOLFIRINOX to Folfiri, one from mFOLFIRINOX to Gemcitabine plus Nab-Paclitaxel, one from FOLFIRINOX to Gemcitabine plus Nab-Paclitaxel and one from IRI-FUFA Nordic to Gemcitabine plus Nab-Paclitaxel. The median number of NAT cycles was 6,7. The median duration of NAT was 21,0 weeks. The indication for NAT was tumour growth into contact with blood vessels for 18 out of 20 patients. Two of these 18 patients also had high CA19-9 levels (>1000 U/ml). One patient was treated with NAT only due to high CA19-9 levels. One patient was inoperable due to post-ERCP pancreatitis in first-line pancreatitis, so he was treated with NAT instead of moving straight to operation

Table 5. Different NAT regimens used, and the number of patients treated with them.

Number of patients	Neoadjuvant therapy regimen
9	Gemcitabine plus Nab-Paclitaxel
3	mFOLFIRINOX
1	FOLFIRINOX
1	Gemcitabine plus Cisplatin
2	Flox → mFOLFIRINOX
1	mFOLFIRINOX → Folfiri
1	mFOLFIRINOX → Gemcitabine plus Nab-Paclitaxel
1	FOLFIRINOX → Gemcitabine plus Nab-Paclitaxel
1	IRI-FUFA Nordic → Gemcitabine plus Nab-Paclitaxel

Five patients could not undergo a curable surgery due to local tumour growth to surrounding tissues and two of them also had distant metastases. Instead, they underwent palliative gastrojejunostomies, where an anastomosis of stomach and jejunum is made to bypass a possible stricture of duodenum due to tumour growth. Fifteen patients had pancreatoduodenectomies and six of them also had vascular resections.

Seven out of the fifteen patients, who underwent pancreatoduodenectomy had surgical complications; Clavien-Dindo one grade I (postoperative pancreatitis treated conservatively), one grade II (postoperative infection needing prolonged antibiotic treatment), four grade IIIa (three intra-abdominal pustules drained by interventional radiologist, one pancreatic fistula) and one grade IIIb (reoperation due to internal haemorrhage and pancreatic fistula). The median duration of hospital stay was 12,4 days (range 5-41 days).

Eight out of 15 patients who underwent surgery had PDAC in histopathological analysis. In addition, three patients had papillary adenocarcinomas, two cholangiocarcinomas, and one duodenal adenocarcinoma. One patient did not have malignancy in pathological analysis but later on had PDAC disease recurrence (liver metastasis). Twelve out of 15 patients had R0-resections. Three out of 15 patients had R1-resections, and all of them had histologically determined PDAC. In none of these three cases was the tumour in the pancreatic resection line, but the distance from the tumour to the resection line was less than 1 mm.

Seventeen out of 20 patients received AT postoperatively. Eleven had single-line AT regimen: four patients had Gemcitabine plus Nab-Paclitaxel, three had mFOLFIRINOX, two had Capox,

and two had Capecitabine. The rest had multiple AT regimens. Four of them had two regimens: one patient switched from Gemcitabine to Gemcitabine plus Nab-Paclitaxel, one from Gemcitabine plus Nab-Paclitaxel to Capiri, one from Gemcitabine to Capecitabine, and one from mFOLFIRINOX to Gemcitabine. One patient had three different regimens: Gemcitabine plus Nab-Paclitaxel, Xelox (Capecitabine plus Oxaliplatin), and IRI-FUFA Nordic. One patient had four different regimens: Gemcitabine plus Na-Paclitaxel, Gemcitabine, Erlotinibi, and IRI-FUFA Nordic. The median number of AT cycles was 4,5. The median duration of AT was 18,2 weeks.

Table 6. Different AT regimens used, and the number of patients treated with them.

Number of patients	Adjuvant therapy regimen
4	Gemcitabine plus Nab-Paclitaxel
3	mFOLFIRINOX
2	Capox
2	Capecitabine
1	Gemcitabine → Gemcitabine plus Nab-Paclitaxel
1	Gemcitabine plus Nab-Paclitaxel → Capiri
1	Gemcitabine
1	mFOLFIRINOX → Gemcitabine
1	Gemcitabine plus Nab-Paclitaxel → Xelox → IRI-FUFA Nordic
1	Gemcitabine plus Nab-Paclitaxel → Gemcitabine → Erlotinibi → IRI-FUFA Nordic

Three patients did not receive AT postoperatively. On two of these patients, the cause was surgical complications and the resulting prolonged postoperative recovery (pancreatic fistula and reoperation due to haemorrhage, postoperative pancreatis). For one patient, the multidisciplinary team decided not to administer AT because of the desirable radicality of the surgery.

4 Results

Seven out of 15 patients who underwent curative surgery, did not have a disease recurrence in median 11,9 months follow-up time from surgery (range 4,3-24,7 months). Eight out of 15 patients had a disease recurrence in median 25,9 months follow-up time from surgery (range 5,9-54,7 months). Two patients had only local recurrence, three had only distant metastases (including one patient who had liver metastasis after not receiving AT due to desirable radicality of the surgery) and the rest had either one or both including lymph node metastasis. Four out of eight of recurrences were histopathological analysis confirmed PDAC. All eight patients with cancer recurrence had R0-resections. Their median follow-up time from surgery was 25,9 months. The three patients with R1-resection did not have cancer recurrence, but their median follow-up time from surgery was 6,1 months. So, the follow-up time was 19,8 months less than in patients with recurrence after R0 resection.

The median PFS after the beginning of NAT was 15,9 months , and for only PDAC patients, it was 21,6 months. The median postoperative PFS was 9,3 months, and for only PDAC patients, it was 12,2 months. Six out of eight patients with cancer recurrence were treated with chemotherapy.

Nine out of 20 patients had deceased during median follow-up time of 29,9 months from the start of NAT (range 8,2-61,5 months). Four out of these nine deceased patient did not undergo curable surgery due to distant metastases and local tumour growth to surrounding tissues. As of now, the median overall survival from the time of diagnosis is 24,4 months (range 9,3-45,5 months) for patients (n=5) who underwent pancreatoduodenectomy, and 14,7 months (range 10,1-21,4 months) for patients (n=4) who did not undergo curable surgery.

Five out of the nine deceased patients underwent pancreatoduodenectomy. Histopathological analysis confirmed one PDAC and four periampullary cancers. The median overall survival from the time of pancreatoduodenectomy was 18,7 months (range 3,9-40,3 months) for all five patients, 33,8 months for PDAC (n=1), and 14,9 months for periampullary cancer (n=4).

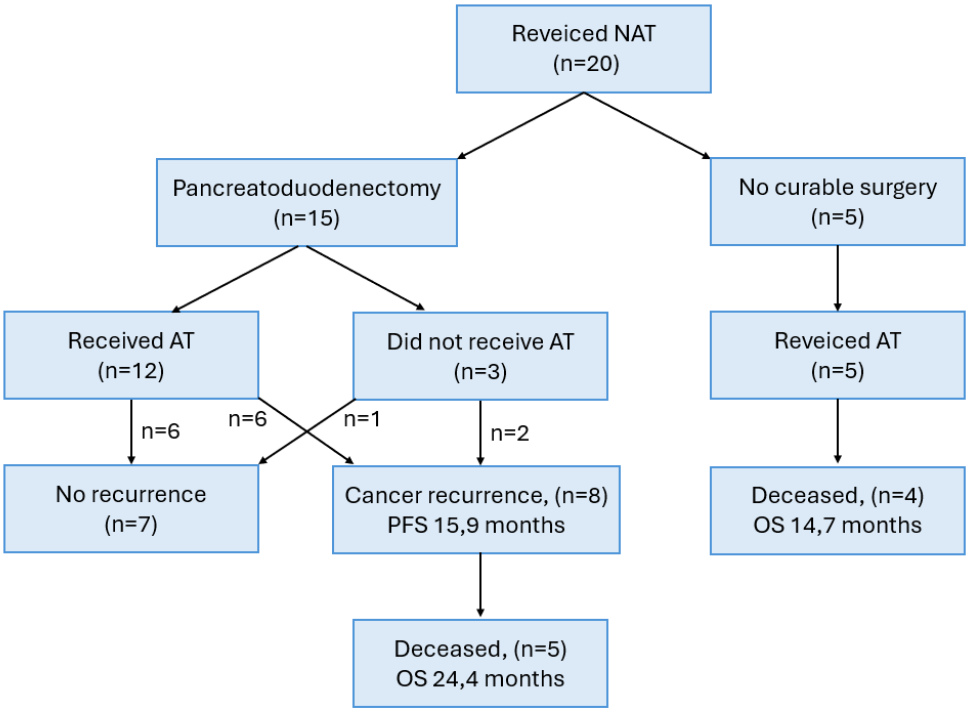

Figure 7. Results summarised in a flowchart. PFS was calculated from the time of operation. OS was calculated from the time of diagnosis.
AT, adjuvant therapy; NAT, neoadjuvant therapy; OS, overall survival; PFS, progression free survival.

5 Discussion

The setting of this thesis was to determine the effect of NAT on the prognosis of pancreatic and periampullary cancers in patients who underwent curative surgery in the Southwestern Finland between the years 2019 to 2023. The median follow-up time was 29,0 months (range 8,2-61,5 months) from the start of NAT. There were 20 patients who received NAT for pancreatic head tumours. Fifteen of them proceeded to pancreatoduodenectomy, and six of the fifteen also had vascular resections. Eight out of the fifteen had a cancer recurrence with median PFS of 15,9 months. The median OS from the time of diagnosis was 24,4 months for patients (n=5) who underwent pancreatoduodenectomy, and 14,7 months for patients (n=4) who did not undergo curable surgery. So, the patients who underwent curable surgery had 9,7 months longer median OS.

NAT offers an early systemic approach to treating PDAC. Generally, NAT is recommended for patients with borderline resectable or locally advanced pancreatic cancer and in cases of resectable disease with high-risk attributes such as larger tumour or high CA19-9 levels (>1000 U/ml). Recently, the discussion on NAT has focused on whether patients with resectable disease should be considered for its administration. The two most recommended NAT regimens for PDAC are FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel.

The benefits of NAT include increased probability of R0-resection status, decreased difficulty of the surgical operation due to tumour downsizing, and providing more patients with a change to undergo surgery, to name a few. Resection margin status stands out as one of the most established prognostic factors for PDAC. This was reflected in the ESPAC-4 trial, where the median OS was 39,5 months after R0-resection and 23,5 months after R1-resection (Neoptolemos et al., 2017). Incorporating vascular resection and reconstruction during pancreatoduodenectomy broadens the patient population eligible for radical resection, and thus enabling the achievement of R0-resections (Kasumova et al., 2016). Other studies have demonstrated 79-93% rates of R0-resections after the implementation of NAT (Katz et al., 2016; Versteijne et al., 2020; Brown et al., 2022). In our study, twelve out of fifteen (80%) patients who underwent pancreatoduodenectomy had R0-resection. Three patients who had R1-resection (tumour < 1 mm from the pancreatic resection line) did not have recurrence yet but the median follow-up time in our study was only six months for these patients.

In our study median OS in patients who underwent radical surgery after NAT was in concordance with the other studies reviewed (Jag et al., 2018; Schwarz et al., 2018; Unno et al., 2019; Versteijne et al., 2020; Sohal et al., 2021; Katz and Russo, 2022; Seufferlein et al., 2022; Versteijne et al., 2022). Other studies showed median OS of 26,4 months (range 15,7-36.7 months) for patients who underwent radical surgery. Their median follow-up time was 31,0 months (range 12-60 months). In our study the median OS was 24,4 months (range 9,3-45,5 months) for patients who underwent radical surgery, and our median follow-up time was 29,0 months (range 8,2-61,5 months).

The sample size (n=20) for this thesis is small, because NAT is relatively new treatment method for PDAC. Before the year 2019, there were no patients treated for pancreatic cancer with NAT in Turku University Central Hospital. In addition, this thesis only looked at patients whose NAT response results were good enough to proceed to curative or exploratory surgery. The follow-up period after surgery was quite short for some patients. Therefore, the full effects of NAT on disease prognosis cannot yet be fully seen. The median postoperative follow-up time for patients whose cancer recurred was 14,0 months longer than for patients whose cancer did not recur.

Future research prospects regarding NAT for PDAC are multifaceted, including several avenues for research and advancement. For example, better understanding of molecular profiling and biomarkers could allow better NAT regimen tailoring. Research in this area and improvement in imaging modalities could also enable earlier diagnosis of pancreatic and periampullary cancers, thus bettering the prognosis. In the future, a prospective study of NAT for PDAC, covering all patients in Finland or in the Nordic countries, could allow for a larger sample size. The result of this type of study could be used to assess different NAT regimens, duration, and treatment effectiveness of NAT. All in all, the use of NAT for PDAC will increase in the future.

6 Conclusions

- The OS was 65% after median follow-up time of 29,0, from the start of NAT in all patients (n=20).
- The median OS from the time of diagnosis was 24,4 months for patients (n=5) who underwent NAT combined with pancreatoduodenectomy, and 14,7 months for patients (n=4) who did not undergo curable surgery.
- The median PFS from the start of NAT was 15,9 months for pancreatic and periampullary cancer, and 21,6 months for only PDAC, and median postoperative PFS was 9,3 months for all patients, and 12,2 months for only PDAC patients.

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Annexes

Annex 1. PDAC and periampullary cancer surgeries after NAT in TYKS 2019-2023