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Surgical Oncological Textbook Outcome in Patients with Pancreatic Ductal Adenocarcinoma: A Cross-Validation Study of Two National Registries

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1 Introduction

1.1 Pancreatic cancer

Pancreatic cancer poses substantial challenges in the field of surgical oncology. The disease is often asymptomatic in early stages, which results in delayed diagnosis and limited treatment options once patients have been diagnosed. The term "pancreatic cancer" typically denotes pancreatic ductal adenocarcinoma (PDAC) and represents the predominant malignancy originating in the pancreas, accounting for approximately 90% of cases [1, 2]. PDAC emerges from the exocrine component of the pancreas, characterized by uncontrolled epithelial cell proliferation within the pancreatic ductal system [3]. Of note, the term "pancreatic cancer" is not confined solely to PDAC, as the pancreas also hosts other, less prevalent neoplastic entities. This study exclusively concentrates on PDAC, using the term "pancreatic cancer" interchangeably to specifically reference PDAC.

1.1.1 Pancreatic cancer statistics and epidemiology

The incidence of pancreatic cancer has been continuously increasing over the past decades [1, 2]. Rates of pancreatic cancer are nearly equal between men and women, although a slightly higher occurrence is recorded in men [1, 3]. The prevalence of pancreatic cancer is notably higher in high income nations, correlating with risk factors such as obesity and lifestyle-related factors i.e. smoking and increased daily alcohol intake [4]. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program estimates that there will be 64,050 new cases in the United States in 2023, comprising approximately 3.3% of all newly diagnosed cancer cases [5]. Importantly, the incidence of pancreatic cancer closely mirrors its mortality rate, with an estimated 50,550 deaths expected in the year 2023 [5]. Overall, pancreatic cancer is expected to be the 4th leading cause of cancer deaths by 2030. Interestingly, Germany falls within the top 10 countries globally in terms of both pancreatic cancer incidence and mortality rates according to data from the World Cancer Research Fund International (WCRF) [6]. Pancreatic cancer is associated with a dismal overall prognosis associated with a 5-year survival of 9% for all stages, which is amongst the lowest for all cancer entities [7, 8]. Over the past decade, while there have been advancements in cancer care and treatment modalities, the survival rates for pancreatic cancer have seen only modest improvements from previously reported 5-year-survival rates of 5% [9, 10]. In summary, the increasing incidence and rising mortality rates highlight the importance of addressing the topic of PDAC and the essential requirement for advancements in PDAC treatment options and patient outcomes.

1.1.2 Staging of pancreatic cancer

Staging of pancreatic cancer is a critical process that assesses the extent of the disease. It involves classifying tumors based on the size of the primary tumor (T), involvement of regional lymph nodes (N), and the presence of distant metastasis (M). PDAC is categorized into four main stages (stage I–IV) according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging system [11], (Table *1*).

Table 1: PDAC TNM stages according to the 8th edition AJCC/UICC staging system [11].

T1	Maximum tumor diameter ≤ 2 cm
T2	Maximum tumor diameter > 2 cm and ≤ 4 cm
T3	Maximum tumor diameter > 4 cm
T4	Tumor involves the celiac axis or the superior mesenteric artery

N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in ≥ 4 regional lymph nodes

M0	No distant metastasis
M1	Distant metastasis

Annotation. The TNM staging system includes the extent of the tumor (T), the spread to regional lymph nodes (N) and metastasis to distant sites (M).

The 8th AJCC/UICC PDAC classification considers tumor size and expansion, lymph node involvement and metastasis, Table 2.

Table 2: Clinical stages of PDAC according to the 8th edition AJCC/UICC staging system [11].

IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T1–3	N2	M0
	T4	any N	M0
IV	any T	any N	M1

Annotation. The TNM categories are grouped to assign overall clinical stages.

PDAC staging is a multidisciplinary process involving surgeons, radiologists, pathologists, and gastrointestinal oncologists. It is conducted at various points in the patient's journey, both before and after the initiation of surgery or any treatments.

Preoperative staging primarily relies on imaging techniques such as ultrasound and computed tomography (CT) scans to evaluate tumor dimensions and the extent of both local and systemic progression of the disease. Additionally, blood tests are conducted to measure the levels of the biomarker serum carbohydrate antigen 19–9 (CA 19–9). In PDAC patients, CA 19–9 biomarker levels serve as a dynamic indicator to gauge the efficacy of ongoing therapeutic regimens and monitor a patient's trajectory before, during and after treatment phases [12]. Further, CA 19–9 levels exceeding 500 units/ml have been incorporated as biological criteria in the assessment of PDAC resectability [13]. Upon completion of the staging process, the collected data is discussed among a multidisciplinary panel of PDAC care experts to reach a consensus on the optimal treatment approach, tailored to the individual patient.

1.1.3 Treatment of pancreatic cancer

1.1.3.1 Surgical treatment: Resectability, approach and limitations

The treatment of PDAC is complex and necessitates a precise approach. It typically involves a combination of surgical, oncological, and radiation therapies tailored to each patient’s specific condition and stage of the disease. The pancreas presents the surgeon with unique anatomical challenges due to its proximity to major blood vessels such as the superior mesenteric artery and vein, and the portal vein (

Figure 1). Complete surgical resection with tumor free resection margins is widely regarded as the only potential cure for pancreatic cancer [14].

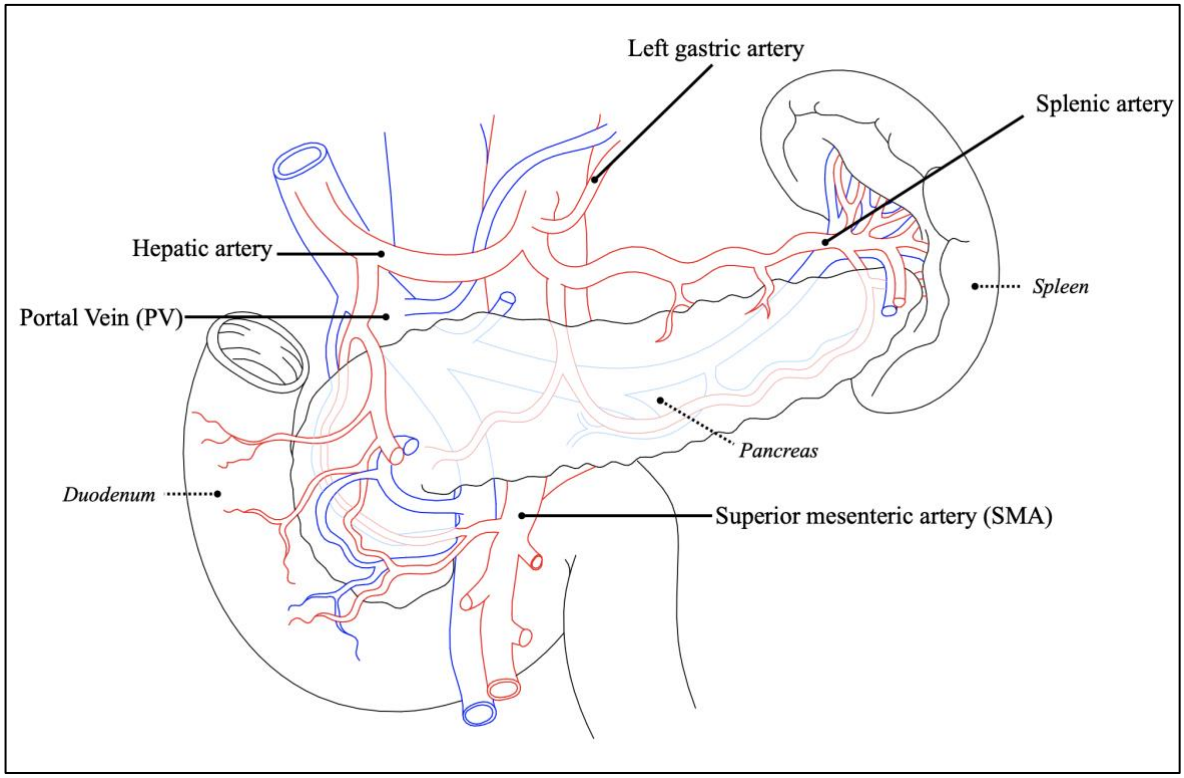

Figure 1: Anatomy of the pancreas in relation to surrounding major blood vessels [14].

The head of the pancreas is closely embedded into the duodenum, while the tail of the pancreas is located at the splenic hilum. The celiac axis (CA) consisting of hepatic artery, splenic artery and left gastric artery emerges from the aortic vessel above the pancreatic body. The superior mesenteric artery (SMA), responsible for supplying both the small intestine and a significant portion of the colon, originates from the aorta just below the pancreas. The confluence of venous drainage from most gastrointestinal organs occurs near the pancreatic head, forming the portal vein (PV) just prior to its entry into the liver. Figure adapted from [14].

PDAC is characterized by late on-set symptoms and about 50–55% of patients present with metastatic disease at time of diagnosis, while only 15–20% patients present with resectable disease [4]. It is essential to determine resectability at time of diagnosis as it will influence the patient's course of treatment. For stage I–III PDAC patients, resectability is categorized into three groups: resectable, borderline resectable and unresectable. Stage IV PDAC is deemed unresectable as it is characterized by the systemic dissemination of cancer cells, evident through distant metastasis. Exceptions may apply as each patient's situation and tumor burden must be individually assessed. PDAC resectability is classified by the joint consensus guidelines of the American Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT) [15]. The AHPBA/SSO/SSAT Classification was later modified by the National Comprehensive Cancer Network (NCCN) [16]. The NCCN resectability classification is supported by the International Study Group of Pancreatic Surgery (ISGPS) [17].

The classification of resectability is based on the extent of involvement of critical adjacent vessels, specifically the celiac axis (CA), superior mesenteric artery (SMA), and the superior

mesenteric vein (SMV) and/or portal vein (P V) [16]. Tumors that do not abut upon these vital vessels are deemed resectable. In contrast, borderline resectable PDAC (BR-PDAC) implies tumor involvement that might not be resectable in its entirety due to significant contact to major vessels, up to a certain degree [16]. For the tumor to be deemed borderline resectable, arterial involvement of the CA or SMA must be less than 180°. Regarding venous involvement, a tumor can possess a contact angle exceeding 180° for borderline resectability unless there is contour irregularity evident in preoperative imaging. In the presence of contour irregularity, only venous involvement lower than 180° is considered borderline resectable [16]. PDAC is deemed unresectable when arterial involvement surpasses 180° at the SMA or CA, and when there is tumor contact with the aorta. Regarding venous involvement, tumors are categorized as unresectable if preoperative imaging suggests that the large venous vessels are likely unable to be reconstructed during surgery, due to extensive tumor involvement [16].

Recently, experts have suggested to expand the definition of BR-PDAC beyond just anatomical criteria. They propose an "ABC system" for defining resectability which includes biological criteria, such as elevated serum levels of CA 19–9 (>500 IU/ml) and or positive regional lymph node metastases, as well as conditional criteria i.e. poor performance status [13]. Once resectability has been deemed, the surgical approach used is dependent on location of the tumor within the gland. The majority of PDAC (67.5%) are located in the head of the pancreas, while approximately 17% of tumors are located in the tail and 15% in the body of the pancreas [18]. Patients with tumors located in the head of the pancreas typically undergo pancreatoduodenectomy (PD), commonly known as the Kausch-Whipple procedure [19]. In recent years though, a pylorus-preserving pancreatoduodenectomy (PPPD), introduced by Traverso and Longmire, has been the preferred approach [20]. The surgical procedure involves dissection of the head of the pancreas, removal of the duodenum and the gall bladder. The dissection is then followed by the reconstruction phase which requires complex anastomoses to restore the anatomical conditions (Figure 2).

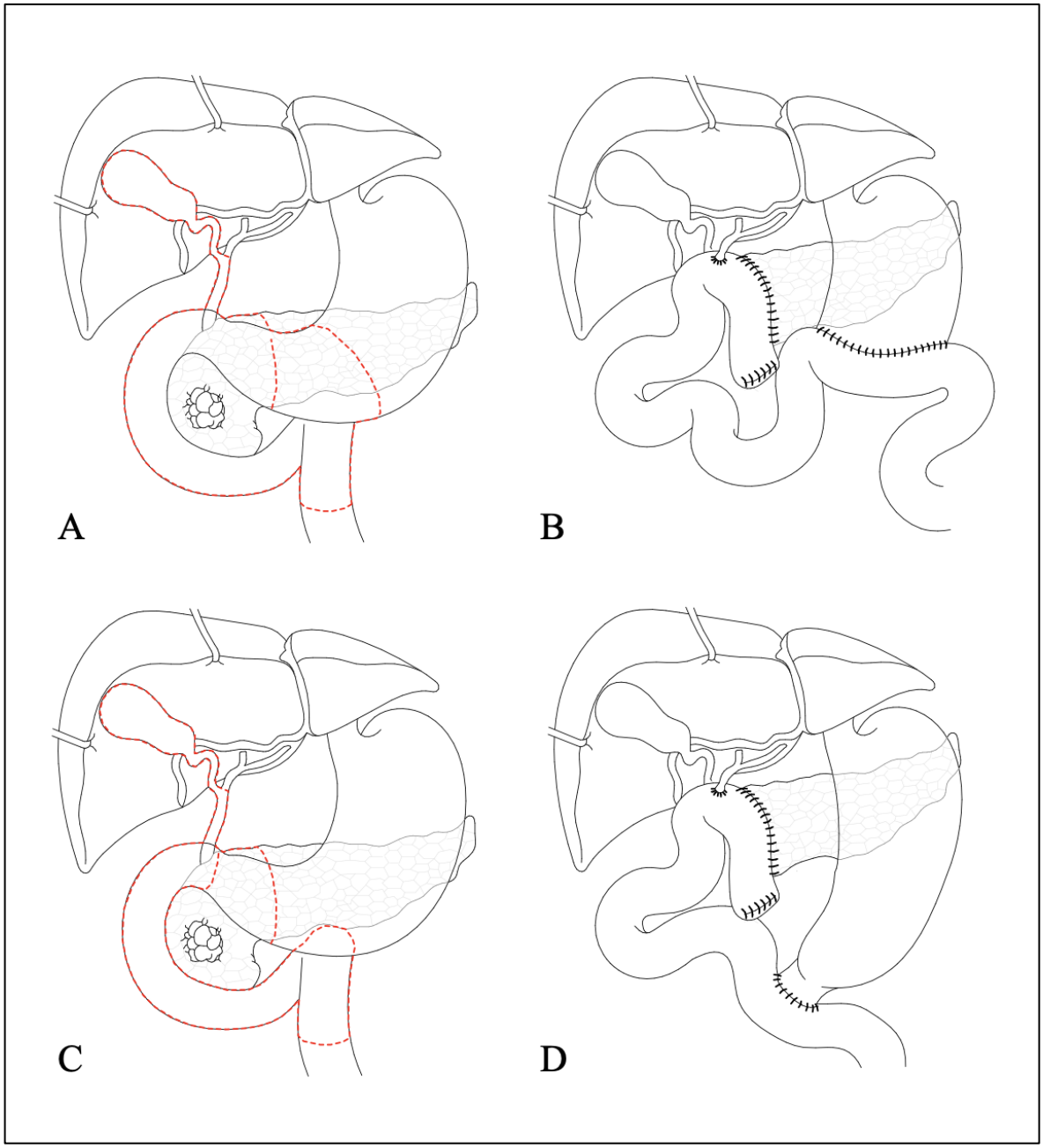

Figure 2: Comparison of the standard Whipple procedure and the pylorus preserving pancreatoduodenectomy [21].

A and B: The Whipple procedure includes resection of the gallbladder, duodenum, pancreatic head, and the gastric pylorus. The reconstruction phase consists of choledochojejunostomy, pancreatojejunostomy and gastrojejunostomy to restore anatomical conditions as closely as possible. C and D: The pylorus preserving pancreatoduodenectomy (PPPD) after Transverso and Longmire preserves the pylorus of the stomach. Preservation of the pylorus aims to maintain control of gastric outflow into the intestines compared to the standard Whipple procedure. Figure adapted from [21].

If preoperative imaging shows that the tumor is located in the tail of the pancreas, the patient will undergo a distal pancreatectomy combined with splenectomy as the tail of the pancreas is closely embedded in the hilum of the spleen. Regardless of the surgical approach to remove the tumor, the achievement of tumor-free resection margins (R0) in PDAC surgery is crucial, given that positive resection margins are associated with poorer survival rates and a higher likelihood of early cancer recurrence [22, 23].

In addition to achieving complete tumor resection, another fundamental aspect of surgical oncology involves the locoregional lymphadenectomy (LAD). Lymph nodes are common sites for early cancer metastasis. Their involvement influences treatment choices and prognosis, as demonstrated by 3- and 5-year survival rates of 60.0% for patients without nodal micrometastasis compared to 19.2% and 0% for those with micrometastasis [24]. Approximately 56% of PDAC patients undergoing resection present with lymph node metastasis [25]. Numerous studies have highlighted the prognostic relevance of factors such as the total number of examined lymph nodes, the count of positive lymph nodes, and the lymph node ratio (LNR) [26–29]. The optimal approach to LAD in PDAC patient is a subject of ongoing debate, primarily evolving around two distinct approaches: standard and extended LAD. Standard LAD involves the removal of a defined set of regional lymph nodes, while extended LAD encompasses a more radical approach, extending the dissection to a broader range of lymphatic structures beyond the standard boundaries [30]. There is uncertainty regarding the survival benefits of extended LAD, as studies have shown mixed results [31–34]. In a consensus statement, the ISGPS define a standard LAD for PDAC as the removal of the lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17ba – totaling 12 lymph nodes, and at the same time do not advocate the use of an extended LAD [35]. In conclusion, regarding surgical interventions for pancreatic cancer aimed at enhancing patient survival, it is crucial to ensure complete resection of the tumor with tumor free margins. Additionally, it is necessary to perform a thorough lymph node harvest, typically involving retrieval of a minimum of 12 lymph nodes.

1.1.3.2 Adjuvant treatment strategies in pancreatic cancer

The reported 5-year survival for PDAC patients that underwent curative-intent resection only is below 20% [36]. PDAC patients treated with a chemotherapy regimen following surgical resection, also known as adjuvant therapy (AT), have shown improved 2- and 5-year survival of 38% and 19%, compared to 28% and 12% in patients that did not receive postoperative chemotherapy [37]. While adjuvant therapy is considered an essential aspect of postoperative care for PDAC patients, the identification of the most effective chemotherapy protocols remains subject of ongoing clinical research. The CONKO-001 study showed significantly improved 5-year survival rates of 20% in patients that received adjuvant therapy with gemcitabine compared to a 5-year survival of 10% in patients that underwent resection alone [38]. Both the CONKO-001 study and the ESPAC-3 trial showed improved median survival of 22.8 and 23.6 months, respectively, in patients treated with single agent therapy of gemcitabine [38, 39]. Following the extensive research on adjuvant therapy with

single-agent chemotherapy protocols, two clinical trials were able to show survival benefits for PDAC patients receiving multi-agent chemotherapy. The ESPAC-4 trial successfully demonstrated enhanced survival outcomes with the combined use of gemcitabine and capecitabine in comparison to gemcitabine alone in the adjuvant treatment of PDAC [40]. The PRODIGE24/ACCORD 24 study aimed to compare gemcitabine monotherapy with a combination chemotherapy consisting of oxaliplatin, irinotecan, and 5-FU/folinic acid, called modified FOLIFIRINOX (mFOLFIRINOX) [41]. The use of mFOLFIRINOX resulted in a reported median overall survival of 54.4 months, while the gemcitabine monotherapy group was associated with 35.0 months of median overall survival [41]. Furthermore, a notable improvement in three-year overall survival rates was observed, increasing from 48.6% with gemcitabine to 63.4% in the mFOLFIRINOX group [41]. In the context of the PRODIGE24/ACCORD 24 study results, it is essential to highlight that the included patients had an Eastern Cooperative Oncology Group (ECOG) status of 0–1 and were all under 80 years of age. Since this multiagent chemotherapy is associated with considerable toxicity burden, treatment regimens are recommended to be tailored to the individual patient's characteristics. In Germany, the current national guidelines recommend using the mFOLFIRINOX protocol for patients with an ECOG performance status of 0–1, aiming for a more comprehensive treatment approach [42]. Conversely, patients with an ECOG status of >1–2, where minimizing toxicity is a priority, are typically advised to consider either gemcitabine monotherapy or a combination of gemcitabine and capecitabine as more suitable treatment options [42]. Lastly, regarding the timing of treatment administration the ESPAC-3 trial provided valuable insights, indicating that adjuvant therapy can be safely administered within up to 12 weeks postoperatively without adversely affecting survival outcomes [43, 44].

1.1.3.3 Neoadjuvant treatment strategies in pancreatic cancer

In the field of oncology, neoadjuvant therapy (NAT) is characterized as a therapeutic intervention administered ahead of the scheduled primary treatment, which is considered the surgical resection of the tumor for stage I–III PDAC. There has been a rising interest in neoadjuvant chemotherapy for patients with PDAC across different resectability categories. In PDAC patients who are considered resectable upon diagnosis, the use of neoadjuvant therapy is a subject of debate. Given the fact that only approximately 20% of resected patients are receiving or completing adjuvant therapy, a neoadjuvant approach in order to administer chemotherapy before surgery seems reasonable. This strategy aims to increase the likelihood of these patients receiving chemotherapy to manage systemic micrometastasis

and to prevent early disease recurrence [45–47]. Additionally, it may increase the odds of achieving tumor-free resection margins, especially at a microscopic level. On the other hand, there is a risk of the disease progressing while the patient is on chemotherapy, which could make them ineligible for resection after completing the treatment [48]. Moreover, the toxicity of the treatment may leave initially resectable patients too weakened to undergo surgery. The limited studies available regarding neoadjuvant therapy in resectable PDAC patients have failed to demonstrate a significant improvement in overall survival [49, 50]. As a result, the application of neoadjuvant therapy is currently not recommended for resectable PDAC patients, except within the context of clinical trials [42].

In the specific context of borderline PDAC, the NCCN guidelines advocate for the use of neoadjuvant therapy, whereas in Germany, until recently, it was recommended to consider NAT for borderline resectable patients primarily within the framework of clinical trials. The German S3 guidelines were last updated in 2022 and now recommend NAT routinely for BR-PDAC [42, 51]. Multiple studies have reported improved survival rates in patients diagnosed with BR-PDAC after receiving neoadjuvant therapy [52, 53]. The long-term results of the multicenter phase III PREOPANC trial by the Dutch Pancreatic Cancer Group further validate the benefits of neoadjuvant chemoradiotherapy compared to surgery and adjuvant therapy, particularly in patients with borderline resectable PDAC. Both overall and disease-free survival were significantly longer with neoadjuvant therapy (17.6 vs 13.2 months, $p = 0.0029$; 6.3 vs. 6.2 months; $p = 0.013$) [54]. Notably, patients who received neoadjuvant therapy were less likely to exhibit pathologic lymph node involvement (33% compared to 78%; $p < 0.001$) [55]. The benefit of neoadjuvant therapy for BR-PDAC patients is also represented in the results of ESPAC-5, a feasibility study. While the resection rates exhibited no significant difference among patients subjected to immediate surgery and those who received neoadjuvant therapy, neoadjuvant therapy demonstrated a higher one-year survival rate in comparison to upfront surgery (77% vs. 40%; $p < 0.001$) [56].

Finally, locally advanced PDAC (LA-PDAC) is primarily considered irresectable. At time of diagnosis, it is often uncertain whether the potential of resectability over the course of treatment exists, or whether the patients are ultimately undergoing definitive chemotherapy. Multiple studies have reported improved overall survival for patients with LA-PDAC after resection, therefore achieving secondary resectability with the use of neoadjuvant therapy plays an indispensable role in the management of LA-PDAC [57–60]. Further, R0 resection in up to 80% of LA-PDAC patients that underwent neoadjuvant therapy has been reported [59, 60]. Evaluating and comparing different neoadjuvant protocols in LA-PDAC and unresectable PDAC, Hackert et al. demonstrate successful resection in 50% of patients after

neoadjuvant therapy [61]. Resection rates were highest using FOLFIRINOX (61%), closely followed by gemcitabine and radiotherapy (52%) [61].

While current national guidelines and recommendations differ in their treatment recommendations, emerging data underscores the substantial influence of neoadjuvant therapy on patients with BR-PDAC and LA-PDAC, emphasizing the importance of ongoing research to establish collective recommendations.

1.1.3.4 The role of radiotherapy in pancreatic cancer

Radiotherapy can be employed both in a neoadjuvant and an adjuvant setting for PDAC. Radiotherapy is often administered alongside chemotherapy as a radiosensitizer, constituting the approach known as chemoradiotherapy. The benefits of radiotherapy in enhancing PDAC outcomes are subject to controversial debate. There are only limited studies available investigating adjuvant chemoradiotherapy with heterogenous results [62–64]. In 2004, Neoptolemos et al. published data of the ESPAC-1 trial indicating that adjuvant chemoradiotherapy has a negative impact on survival in PDAC patients [65]. Patients receiving adjuvant chemoradiotherapy had a lower estimated five-year survival rate (10%) compared to those who did not receive chemoradiotherapy (20%) [65]. The TCOG T3207 study, conducted by the Taiwan Cooperative Oncology Group, focused on evaluating the role of adjuvant chemotherapy versus chemoradiotherapy in PDAC patients after curative intent surgery. The study observed a marginal improvement in locoregional control in the chemoradiotherapy arm (17.6% vs 15.1%, $p = 0.068$), but no significant increase in median recurrence-free (RFS) and overall survival (OS) when compared to the chemotherapy group (RFS: 13.3 vs 12.1 months; OS: 21.5 vs 23.5 months) [66, 67]. Presently, the NCCN guidelines support the use of radiotherapy in an adjuvant setting only for patients at higher risk for local recurrence such as those with positive resection margins [16]. Similarly, the German guidelines support radiotherapy in addition to chemotherapy after R1, though only within clinical trials [42].

Neoadjuvant radiotherapy primarily finds application in cases of BR- PDAC and LA-PDAC. The aim is to improve the rates of margin-negative resection and local control [68]. Nevertheless, the impact of neoadjuvant radiotherapy on the survival of PDAC patients remains uncertain [69]. The phase 3 PREOPANC trial revealed potential benefits of neoadjuvant gemcitabine-based chemoradiotherapy in BR-PDAC patients, with an improved overall survival of 17.6 months in patients that received neoadjuvant chemoradiotherapy, compared to 13.2 months in those who underwent initial surgery. Following resection, both treatment cohorts also received adjuvant gemcitabine therapy [55].

The multicenter, randomized phase 2 ALLIANCE A021501 trial compared neoadjuvant mFOLFIRINOX to mFOLFIRINOX followed by hypofractionated image-guided or stereotactic body radiotherapy in borderline resectable PDAC patients. The recently published results demonstrate a positive impact on overall survival and higher R0 resection rates in the chemotherapy only arm, compared to the chemoradiotherapy arm [64]. Recent technical advancements in the domain of radiotherapy enable the utilization of stereotactic body radiotherapy (SBRT), which allows for the precise delivery of a higher radiation dose to a confined target area while effectively shielding the adjacent healthy tissues [70]. De Geus et al. [71] investigated the potential of SBRT in unresected PDAC patients, comparing the outcomes of SBRT combined with chemotherapy against external beam chemoradiotherapy (EBRT) and chemotherapy alone. The findings suggest that SBRT in conjunction with chemotherapy results in improved median survival as compared to chemotherapy alone [71]. These developments highlight the promise of SBRT as an emerging radiotherapy treatment approach for PDAC, emphasizing the need for further investigation across all PDAC stages. At this time, the US-American NCCN guidelines support the concurrent use of neoadjuvant chemoradiotherapy for treatment of BR-PDAC and LA-PDAC [16, 51]. The German S3 guideline recommends chemoradiotherapy in a neoadjuvant setting for BR-PDAC patients, and only to be applied within clinical trials for LA-PDAC [42].

1.2 Clinical benchmarking

The term "benchmarking" finds its origins in the manufacturing industries. It was initially defined by Robert C. Camp as the "continuous process of measuring products, services, and practices against the toughest competitors or those companies recognized as industry leaders" [72]. In 2006, Ellis et al. expanded the definition of benchmarking to healthcare, describing it as a systematic procedure for comparative assessment. They emphasized its role in identifying factors that contribute to high performance, thereby facilitating improved quality and best practices in the healthcare sector [73]. Since then several approaches have been described to determine the best way of implementing benchmarking processes in medicine and surgery in particular [74–77].

Clinical benchmarking is now considered a crucial process in healthcare that involves systematically measuring and comparing healthcare performance against recognized standards or peers [78, 79]. In healthcare, where patient lives are at stake, ensuring the highest standards of care is essential. Further, clinical benchmarking fosters transparency, allowing patients and the public to make informed decisions about their healthcare providers.

Benchmarking has recently evolved from being solely of interest to individual hospitals and care providers to becoming a valuable tool on an national and international level [74, 80]. This development is well represented in the establishment of the International Cancer Benchmarking Partnership (ICBP) in 2009. The ICBP represents a collaborative initiative formed to benchmark and compare disparities in cancer outcomes across participating nations; the ultimate goal is to improve cancer care worldwide [81].

In the multifaceted world of surgical oncology, clinical benchmarking is more than a quality assurance tool; it is a patient-centric approach, striving to enhance the lives and well-being of individuals facing cancer. By embracing benchmarking principles, surgeons and oncologists ensure that cancer patients receive the highest standard of care, incorporating the most up-to-date evidence-based practices.

1.3 Textbook Outcome

Textbook Outcome (TO) is a novel parameter in the context of clinical benchmarking. TO was first introduced in 2013 by a Dutch group of colorectal surgeons, proposing TO as a composite measure to assess the surgical process within one simplified variable [82]. The measure is used to evaluate whether a surgical treatment is achieving outcomes that are similar to those that would be expected in a well-conducted textbook case. Since its first introduction, TO has gained popularity in surgical research, and several efforts in proposing TO definitions in different surgical disciplines have been made [83–85]. The use of TO has been introduced as potentially of interest for patients, care providers and insurance companies to compare quality of care [86].

The focus on quality improvement research including assessment of surgical hospital care and benefits of perioperative therapy regimens has been one of the pillars in clinical pancreatic cancer research. In this regard, many national and multi-center registries have been established recently [87–90]. Especially cancer registries on a national level like the US-American National Cancer Database (NCDB) and the German Cancer Registry Group (GCRG) of the Society of German Tumor Centers – Network for care, quality, and research in Oncology (ADT) are ideal platforms for assessing “real world” data and can help to identify best surgical and oncological practices, as well as areas for improvement in cancer care and control. Van Roessel et al. have previously defined TO for pancreatic surgery using expert consensus, focusing on variables regarding surgical efficacy and evaluating complications following pancreatic resection for any indication [91]. At this time, a uniform definition of TO regarding desired outcomes in PDAC surgery and the perioperative journey has not been proposed yet.

1.4 Research objective

The primary objective of this thesis is to conduct a cross-validation study of the US-American National Cancer Database (NCDB) and the German Cancer Registry Group (GCRG). This study proposes a PDAC-specific TO definition which includes both surgical and oncological care goals by differentiating surgical-oncological TO and an extended composite TO. This novel definition is intended to comprehensively encompass desirable oncological treatment outcomes for PDAC patients. Additionally, the study seeks to investigate whether the achievement of TO differs between the United States and Germany. A key aspect of this study is to thoroughly assess TO and identify the predominant factors contributing to failure of achieving this benchmark in PDAC treatment. The objective is to evaluate TO on a nationwide scale and to analyze the correlation between the attainment of TO and long-term outcomes in stage I–III PDAC. This exploration is vital for understanding the variations in treatment outcomes and for guiding improvements in PDAC patient care on an international scale.

The research was guided by the following specific objective and questions:
1: Define Textbook Outcome for PDAC patients including oncological long-term goals.
2: Does achieving TO correlate to improved overall survival in PDAC patients?
3: What are the limiting factors of achieving TO in Germany and the United States?

2 Materials and methods

2.1 Study design

The study design is a retrospective investigation. Patient data were retrieved from two extensive databases: the US-American National Cancer Database (NCDB) supported by the American College of Surgeons and the Commission on Cancer, and the German Cancer Registry Group (GCRG) of the Society of German Tumor Centers – Network for care, quality, and research in Oncology (ADT). The study period was 2010–2020 for both cohorts. The study received approval from the ethics commission of the University of Lübeck on the 17th of August 2020, reference number: 20-319.

2.2 Study population

A search was conducted in the NCDB and GCRG databases to identify patients with histologically confirmed PDAC who underwent curative-intent resection. Patient data was received in an anonymized form. Patients with preoperative clinical stage I–III PDAC were included in the study population. The selection of patients for this study followed the criteria outlined in the Consort Statement and flow diagram [92]. Exclusion criteria were clinical stage IV, no resection, missing follow-up data and patients where the surgical margins were not specified.

2.3 Study parameters

The analysis incorporated the following patient baseline parameters: age, gender, presence of comorbidities, surgical variables, clinical stage, and perioperative treatment regimens. Presence of comorbidities was categorized into two groups: absence and presence of comorbidities. Clinical stage was defined according to the AJCC 8th edition. Surgical variables recorded were type of resection: pancreatoduodenectomy (PD) versus distal pancreatectomy (DP). Perioperative treatment regimens from both registries were assessed and encompassed the following categories: no perioperative chemotherapy was administered (Surgery Alone), surgery and adjuvant chemo- and/or radiotherapy only (AT Alone), surgery and neoadjuvant chemo- and/or radiotherapy only (NAT Alone), and combination of neoadjuvant chemo- and/or radiotherapy combined with adjuvant chemo- and/or radiotherapy (NAT and AT).

Histopathological parameters, such as T stage, N stage, lymphovascular invasion, perineural invasion, grading (G) according to Broders [93], and R status were systematically included

from both registries. R status was defined according to the AJCC Cancer Staging Manual 8th edition: complete oncologic resection with no residual tumor (R0), grossly complete resection with microscopic residual tumor (R1), incomplete resection with macroscopic residual tumor (R2) and resection where residual tumor presence was not assessable (Rx) [11, 94]. Lymph node status (N) was determined by the presence or absence of cancer cells in lymph nodes, with N0 indicating no nodal involvement, N1 indicating cancer spread to 1–3 regional lymph nodes and N2 indicating tumor spread to more than 4 lymph nodes. In this study, overall survival referred to the duration from the patient's diagnosis to their date of death.

2.4 Textbook Outcome definition

The definition of surgical-oncological and composite Textbook Outcome for PDAC patients was established in expert consensus of two pancreatic cancer study groups: the pancreatic cancer working group led by Prof. Wellner of the department of surgery at the University Hospital Schleswig-Holstein (UKSH), Campus Lübeck, and the Qadan research group of the department of surgery at Massachusetts General Hospital (MGH) and Harvard Medical School (HMS) in Boston, United States.

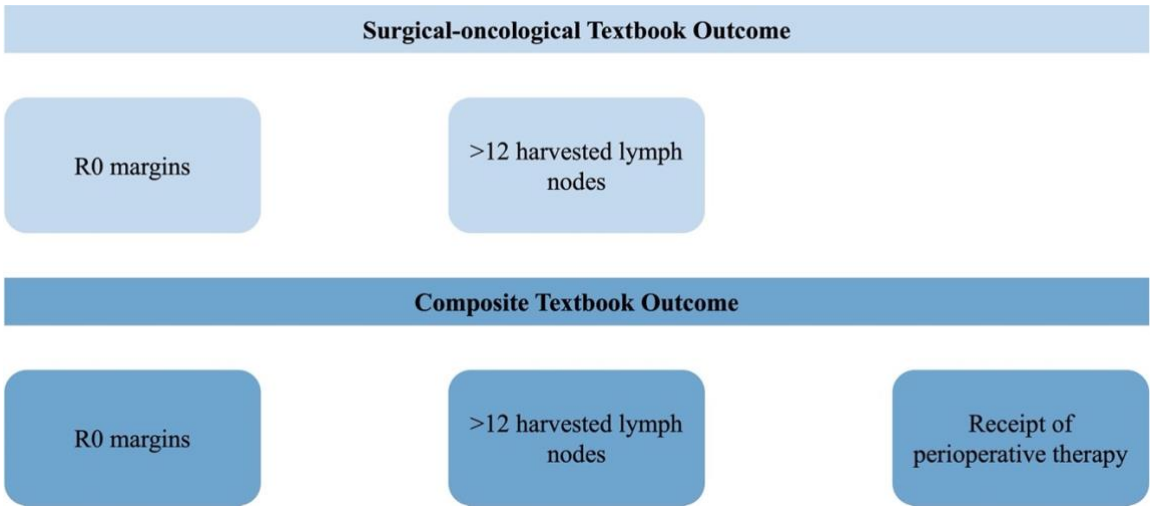

Figure 3: The individual parameters that encompass both surgical-oncological Textbook Outcome and composite Textbook Outcome.

Textbook surgical-oncological Outcome was defined as complete oncologic resection with R0 margins and ≥12 harvested lymph nodes. Composite Textbook Outcome was defined as R0 resection, ≥12 harvested lymph nodes, and receipt of perioperative therapy (Figure 3). The retrieval of a minimum of 12 lymph nodes is mandated by the German S3 guideline for pancreatic cancer treatment as the standard for oncological lymphadenectomy [42], while the US-American NCCN guidelines do not specify a minimum yield for lymph node retrieval

[16]. The minimum of 12 lymph nodes, as stipulated by the German guidelines, was chosen for our analysis; evidence also supports that this number is significant for the correct assessment of nodal status [95, 96].

2.5 Statistics

The software IBM SPSS Statistics for Windows (Version 25.0) was used for statistical analysis. Continuous variables were presented as medians with absolute frequencies. Categorical variables were presented by their range and expressed as relative frequencies in percentages. The chi-square test was utilized to analyze and assess associations between categorical variables. The Kaplan Meier method was used to estimate median overall survival estimates. Additionally, Kaplan Meier graphs were used to visualize the survival experience in both patient cohorts. Survival analyses in this study utilized Cox proportional hazards regression models, enabling the assessment of hazard ratios, and offering insights into the relative risks associated with different variables. To ascertain statistical significance, the threshold for acceptance was set at a p-value of less than 0.05 ($p < 0.05$). All tests were performed using a two-sided approach. The reported confidence intervals (CI) are all set at a 95% confidence level.

3 Results

3.1 Patient cohort

The NCDB and the GCRG registries were searched for patients with histologically confirmed PDAC. Patients were selected based on the criteria outlined in the CONSORT flow charts. 241,144 patients were identified from the NCDB. 207,656 patients were excluded from the study. Exclusion criteria were clinical stage IV (*n* = 124,338), no surgical resection (*n* = 74,671), missing follow-up (*n* = 4,669), and unspecified surgical margins (*n* = 3,978). Among the 33,498 patients included in the study, 16,967 achieved the composite Textbook Outcome, while 16,531 patients did not (Figure 4).

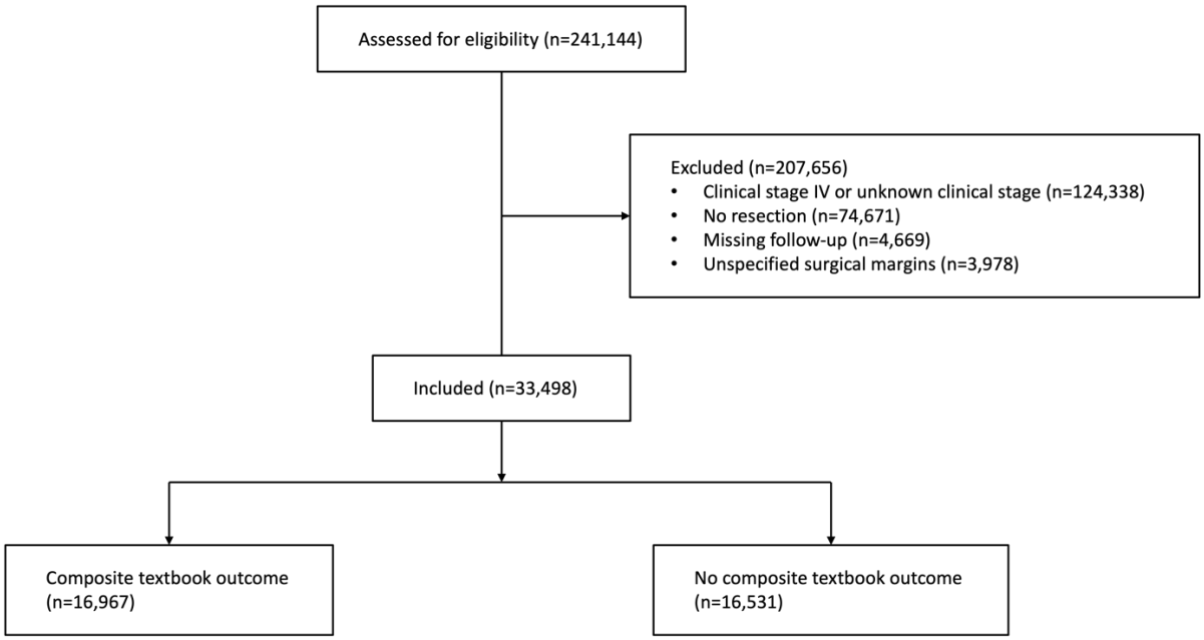

Figure 4: Consort Flow Chart for Patient Selection in the NCDB registry.

From the GCRG registry, 103,914 patients with histologically confirmed PDAC were initially identified. 89,316 patients were excluded from the study because of clinical stage IV (*n* = 84,434), no surgical resection (*n* = 165), and missing follow-up (*n* = 4,917). Out of the 14,598 patients included, 7,878 patients achieved the composite Textbook Outcome, while 6,720 patients did not (Figure 5).

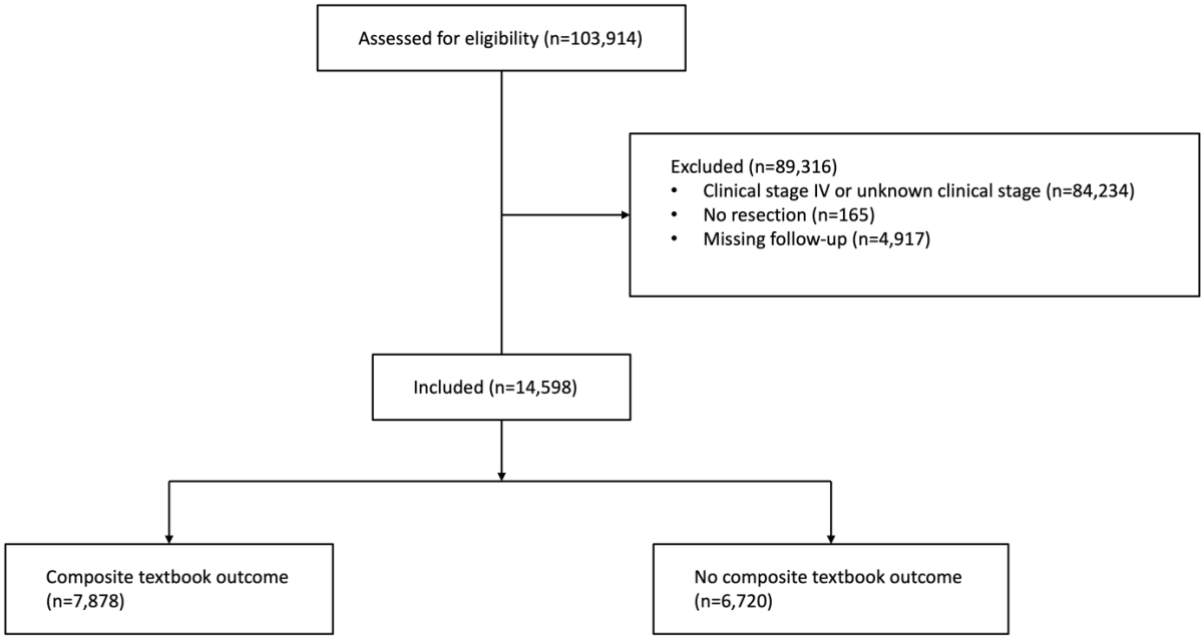

Figure 5: Consort flow chart for patient selection in the GCRG registry.

3.2 Baseline and histopathological parameters

The final NCDB cohort included 33,498 patients. PDAC patients included from the NCDB registry displayed a median age of 67 (range 18–90). 49.7% of the patients were female. 63.8% of the patients had no comorbidities. 16,539 patients (49.4%) presented with stage I disease, 15,111 (45.1%) with stage II disease and 1,848 (5.5%) of patients presented with stage III PDAC (Table 3). 28,249 patients (84.3%) underwent PD, and 5,249 patients (15.7%) underwent DP. The median duration from diagnosis to surgery was 30 days in the NCDB registry.

14,589 patients with histologically confirmed PDAC were included from the GCRG registry. Among patients in the GCRG registry, the median age was 69, spanning from 24 to 96, with female patients comprising 47.4% of the cohort. Comorbidities were recorded in 18.0 % of patients. A total of 10,256 patients (70.3%) underwent PD, while 2,022 patients (13.9%) underwent DP. In the GCRG registry, the median time from diagnosis to surgery was 23 days. Stage I disease was observed in 2,412 patients (16.6%), stage II disease in 9,318 patients (63.9%), and stage III PDAC was present in 2,859 patients (19.6%).

Table 3: Patient baseline parameters in the NCDB and GCRG registries.

		NCDB		GCRG	
Parameter	*condition*	*n/median*	*%/range*	*n/median*	*%/range*
total		33,498		14,589	
Age		67	18–90	69	24–96
Gender	female	16,646	49.7	6,926	47.4
Co-morbidities		12,134	36.2	2,629	18.0
Clinical stage	stage I	16,539	49.4	2,412	16.5
	stage II	15,111	45.1	9,318	63.9
	stage III	1,848	5.5	2,859	19.6
Surgical procedure	PD	28,249	84.3	10,256	70.3
	DP	5,249	15.7	2,022	13.9
Time from diagnosis to surgery		30	0–1,854	23	2–68

Annotation. NCDB = National Cancer Registry; GCRG = German Cancer Registry Group; PD = pancreatoduodenectomy; DP = distal pancreatectomy

Histopathological parameters recorded in both national registries were analyzed (Table 4). In the NCDB cohort, 8,454 (27.1%) PDAC patients presented with a T stage of 1–2 and 22,474 (72.1%) patients with T3–4. T status was not determined in 262 (0.8%) patients. Lymph node negativity (N0) was documented in 11,963 (38.3%) patients. In 18,223 patients (58.4%) tumor spread to 1–3 regional lymph nodes (N1) was documented, and 704 (2.3%) patients displayed dissemination of cancer cells to four or more lymph nodes (N2). In 311 (1.0%) patients, there was no record of lymph node invasion available. Lymphovascular invasion was noted in 13,608 (40.6%) cases. Data on perineural invasion were not available as it is not recorded in the NCDB. Tumor cell differentiation of G3–4 was observed in 9,355 (28.2%) PDAC patients.

In the GCRG registry, 1,849 (12.7%) patients exhibited a tumor stage of T1–2, whereas 12,740 (87.3%) patients presented with stage T3–4. Lymph node negativity was observed in 5,670 (38.8%) patients. 7,489 patients (51.3%) patients displayed lymph node invasion of N1, and in 1,430 (9.9%) patients lymph node status was classified as N2. Within the GCRG registry, lymphovascular invasion was documented in 6,431 (44.1%) patients, and perineural invasion was evident in 8,148 (55.8%) patients. Moreover, 5,404 (37%) identified PDAC patients exhibited tumor cell differentiation of G3–4.

Table 4: Histopathological parameters recorded from the NCDB and GCRG registries.

		NCDB		GCRG	
Parameter	*condition*	*n/median*	*%/range*	*n/median*	*%/range*
T stage					
	T1–2	8,454	27.1	1,849	12.7
	T3–4	22,474	72.1	12,740	87.3
	Tx	262	0.8	-	-
N stage					
	N0	11,963	38.3	5,670	38.8
	N1	18,223	58.4	7,489	51.3
	N2	704	2.3	1,430	9.9
	Nx	311	1	-	-
Grading	G3–4	9,355	28.2	5,404	37.0
Lymphovascular invasion		13,608	40.6	6,431	44.1
Perineural invasion		NA	NA	8,148	55.8

Annotation. NCDB = National Cancer Registry; GCRG = German Cancer Registry Group; T = tumor; N = lymph node.

3.3 Surgical oncological and composite Textbook Outcome endpoints

In the NCDB cohort, complete oncologic resection (R0) was achieved in 28,931 (86.4%) patients. 4,355 (13.0%) cases resulted in R1 resections and in 212 (0.6%) patients the tumor was resected with tumor margins classified as R2 resection. The median lymph node yield for patients documented in the NCDB was n=17 (0–90). In 8,723 (26.2%) patients less than 12 lymph nodes were harvested during curative-intent surgery, respectively. In the GCRG, in 11,595 (79.5%) patients had recorded R0 resection while in 2,674 (18.3%) patients R1 resection was recorded. Lastly, 329 (2.2%) patients presented R2 tumor resection margins. For the GCRG registry patients, median lymph node yield was 18 (0–116). In 556 (3.8%) PDAC patients less than 12 lymph nodes were harvested for pathological assessment (Table 5).

Table 5: Comparison of Textbook Outcome parameters between the NCDB and the GCRG

		NCDB		GCRG	
Parameter	*Condition*	*n/median*	*%/range*	*n/median*	*%/range*
n total		33,498		14,589	
Surgical margins					
	R0	28,931	86.4	11,595	79.5
	R1	4,355	13.0	2,674	18.3
	R2	212	0.6	329	2.2
Lymph node yield total n		17	0–90	18	0–116
Lymph node yield n < 12		8,723	26.2	556	3.8
Perioperative therapy					
	None	7,363	22.0	6,389	43.8
	NAT alone	7,276	21.7	2,165	14.8
	AT alone	17,037	50.9	5,992	41.1
	NAT + AT	1,822	5.4	43	0.3
Surgical Textbook Outcome		21,198	63.3	11,234	77.0
Composite Textbook Outcome		16,967	50.7	7,878	54.0

Annotation. NCDB = National Cancer Database, GCRG=German Cancer Registry Group, R0 = complete oncologic resection with no residual tumor; R1 = grossly complete resection with microscopic residual tumor; R2 = incomplete resection with macroscopic residual tumor; NAT = neoadjuvant chemo- and/or radiotherapy only; AT = adjuvant chemo- and/or radiotherapy only; NAT and AT = neoadjuvant chemo- and/or radiotherapy combined with adjuvant chemo- and/or radiotherapy.

From the NCDB, 26,135 (78.0%) of patients underwent perioperative therapy. 7,276 (21.7%) received neoadjuvant therapy alone (NAT alone), 17,037 (50.9%) received adjuvant therapy alone (AT alone) and 1,822 (5.4%) received both (NAT+AT). In the NCDB patient cohort, 2,853 (8.5%) patients received NAT chemotherapy and 2,791 (8.3%) were administered NAT chemoradiotherapy. 10,291 (30.8%) patients received AT chemotherapy. NAT + AT chemotherapy was recorded in 1,738 (5.2%) of patients (Table 6).

In the GCRG, a total of 8,200 (56.2%) patients underwent perioperative therapy. 2,165 (14.8%) patients received NAT alone, with 135 (0.9%) patients receiving chemoradiotherapy and 2,030 (13.9%) receiving NAT chemotherapy. 5992 (41.1%) patients received AT alone, including 5,325 (36.5%) who had chemotherapy alone and 667 (4.6%) who received chemoradiotherapy. In 43 (0.3%) PDAC cases both adjuvant and neoadjuvant chemo- and or radiotherapy was administered, with 23 patients (0.2%) receiving chemotherapy alone and 20 patients (0.1%) undergoing chemoradiotherapy (Table 6).

Table 6: Perioperative treatment concepts in the NCDB and GCRG registries

			NCDB		GCRG	
Parameter	*Condition*		*n/median*	*%/range*	*n/median*	*%/range*
n total			33,498		14,589	
Perioperative Therapy	**None**		7,363	22.0	6,389	43.8
	NAT alone		7,276	21.7	2,165	14.8
		NAT chemotherapy	2,853	8.5	2,030	13.9
		NAT chemoradiotherapy	2,791	8.3	135	0.9
	AT Alone		17,037	50.9	5,992	41.1
		AT chemotherapy	10,291	30.8	5,325	36.5
		AT chemoradiotherapy	5,861	17.5	667	4.6
	NAT + AT		1,822	5.4	43	0.3
		NAT + AT chemotherapy	1,738	5.2	23	0.2
		NAT + AT chemoradiotherapy	13	0.0	20	0.1
	Sequence unspecified		2,588	7.7		

Annotation. NCDB = National Cancer Database; GCRG=German Cancer Registry Group; NAT = neoadjuvant chemo- and/or radiotherapy only; AT = adjuvant chemo- and/or radiotherapy only; NAT and AT = neoadjuvant chemo- and/or radiotherapy combined with adjuvant chemo- and/or radiotherapy.

In the National Cancer Database (NCDB), 58% of patients with more than 12 lymph nodes received adjuvant therapy, compared to 51% of patients with fewer than 12 lymph nodes. Similarly, in the GCRG study, adjuvant therapy was administered to 45.1% of patients with a lymph node yield greater than 12, and to 48.3% of patients with a lymph node yield of less than 12.

Surgical oncological TO was achieved in 21,198 (63.3%) patients in the NCDB and in 11,234 (77.0%) patients from the GCRG (Figure 6). The endpoint of composite Textbook Outcome, defined as the combination of surgical TO and the receipt of perioperative therapy, was attained in 16,967 (50.7%) patients in the NCDB and 7,878 (54.0%) patients in the GCRG (Table 5, Figure 7).

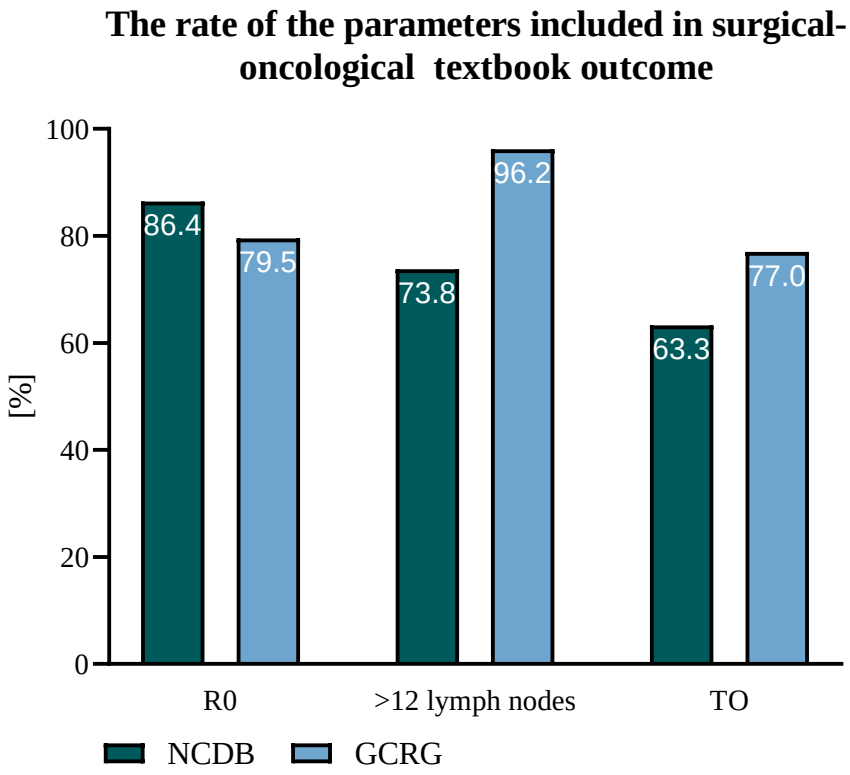

Figure 6: Surgical-oncological Textbook Outcome percentages (per parameter and cumulative for the National Cancer Database (NCDB) and the German Cancer Registry (GCRG).

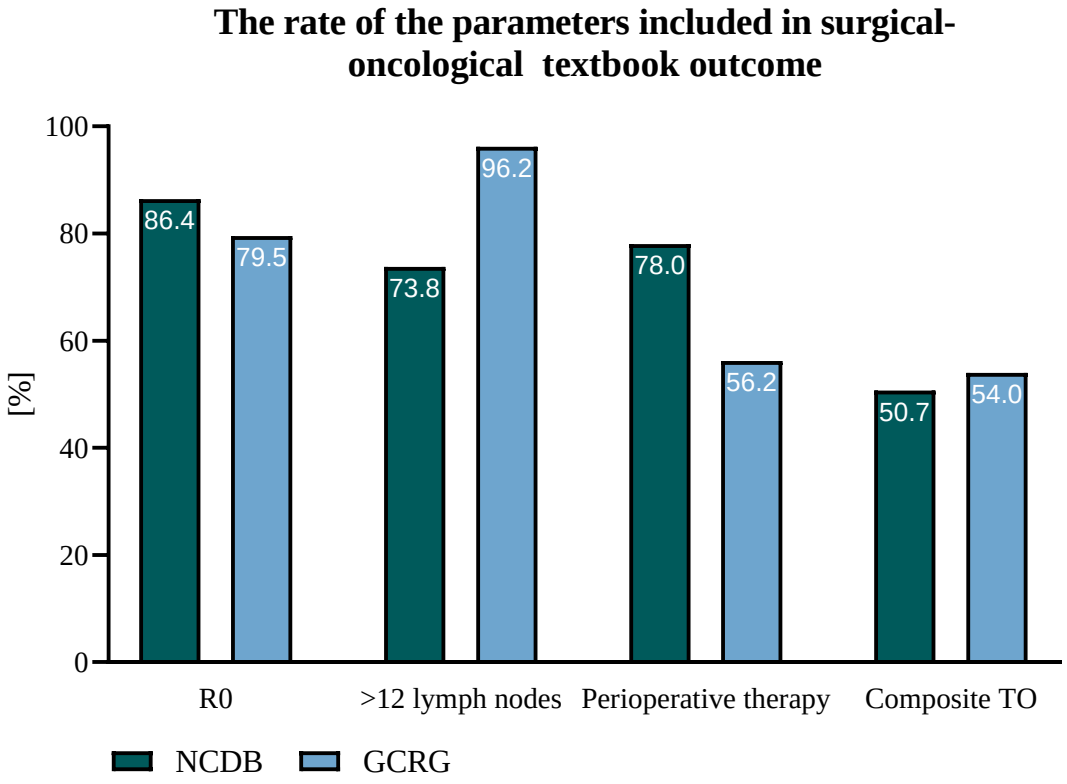

Figure 7: Composite Textbook Outcome percentages (per parameter and cumulative for the National Cancer Database (NCDB) and the German Cancer Registry (GCRG).

3.4 Textbook outcome and overall survival estimates

Survival analysis of PDAC patients recorded in the NCDB illustrates a distinct separation between patients that were considered Textbook Outcome and those that are not for both surgical and composite Textbook Outcomes (Figure 8). In the NCDB, patients who achieved surgical-oncological TO showed a median overall survival (OS) of 29.7 months. In contrast, patients failing to achieve surgical-oncological TO had a lower median OS of 22.9 months in the NCDB (Hazard Ratio (HR): 0.78, 95% CI: 0.76–0.80, $p < 0.001$). The median OS for patients who achieved both surgical-oncological Textbook Outcome and completed perioperative therapy was observed to be 31.5 months. Conversely, NCDB patients who did not achieve composite TO exhibited a median OS of 22.5 months (HR 0.73, 95% CI 0.71–0.75, $p < 0.001$), Table 7.

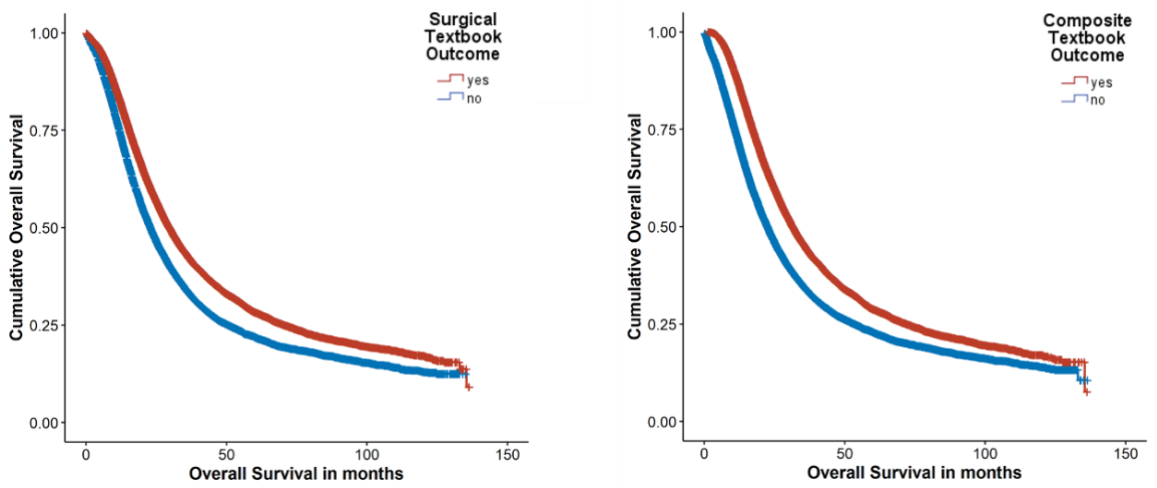

Figure 8: Overall survival in patients with surgical and composite Textbook Outcome, NCDB registry.

Similarly, survival analysis of PDAC patients in the GCRG demonstrated increased overall survival for patients considered to have attained a surgical-oncological and a compositive TO, Figure 9. In the GCRG dataset, the median OS for patients who achieved surgical-oncological TO was 33.2 months. Conversely, for those who did not achieve surgical TO in the GCRG, the median OS was 21.9 months (HR:0.68, 95% CI: 0.41–0.72, $p < 0.001$). Further, in the GCRG, patients who attained a composite TO demonstrated a median OS of 27.1 months. In comparison, in patients failing to achieve the composite TO a median OS of 20.3 months was observed (HR: 0.84, 95% CI 0.70–0.96, $p < 0.001$) (Table 7).

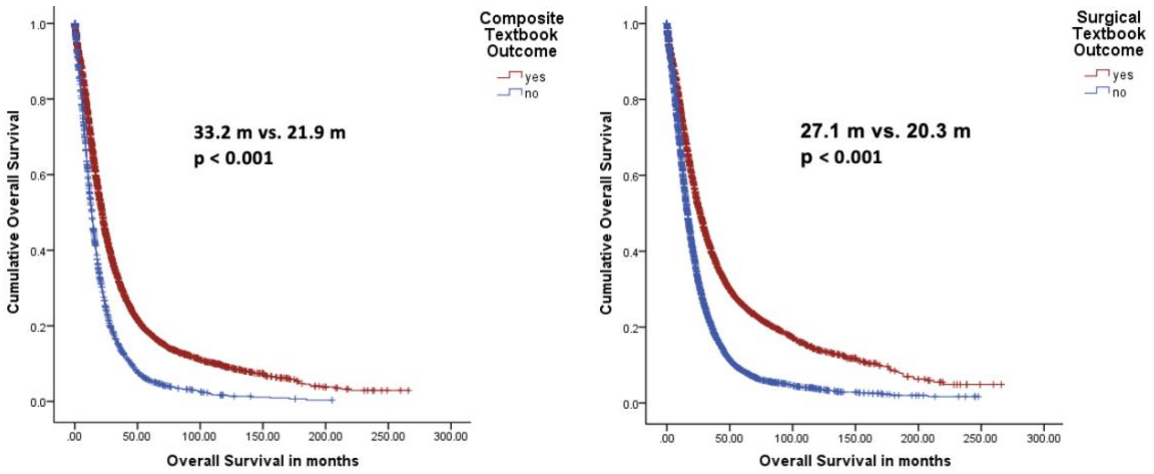

Figure 9: Overall Survival in patients with surgical and composite Textbook Outcome, GCRG registry.

In the NCDB, patients with more than 12 lymph nodes harvested exhibited a median OS of 27.6 months. In contrast, those with fewer than 12 lymph nodes collected had a median OS of 25.3 months (HR: 0.93, 95% CI 0.90–0.96, p < 0.001). Notably, the GCRG data did not demonstrate a difference in OS based on the number of lymph nodes harvested (28.8m vs 25.5m; HR: 0.89, 95% CI: 0.68–0.94, p = 0.112).

Patients with complete oncologic resections and tumor-free margins (R0) versus those with R+ resection exhibited differences in OS in both the NCDB (R0: 29.1 months vs R+: 17.3 months, HR: 0.57, 95% CI 0.55–0.59, p < 0.001) and the GCRG (R0: 35.3 months vs R+: 22.4 months, HR: 0.53, 95% CI 0.41–0.67, p < 0.001).

Within the NCDB, median OS for patients undergoing resection was 18.0 months, in contrast to 30.8 months for those receiving NAT alone (HR: 0.670, 95% CI 0.65–0.70, p < 0.001). AT alone was linked to a median OS of 27.7 months (HR: 0.750, 95% CI 0.72–0.77, p < 0.001), while the combination of NAT and AT was associated with a median OS of 35.5 months (HR: 0.580, 95% CI 0.54–0.62, p < 0.001). The GCRG registry data also showed a reduced overall survival for surgery alone compared to NAT alone (24.2 vs 41.7 months, HR: 0.872, 95% CI 0.734–0.976, p < 0.001), AT alone (24.2 vs 35.4 months, HR: 0.934, 95% CI 0.834–0.976, p = 0.030), and the combination of NAT and AT (24.2 vs 46.8 months, HR: 0.711, 95% CI 0.631–0.837, p < 0.001) (Table 7).

Table 7: Overall survival estimates in the NCDB and GCRG registries.

		NCDB				GCRG			
Parameter	*condition*	*median OS (m)*	*HR*	*95% CI*	*p-value*	*median OS (m)*	*HR*	*95% CI*	*p-value*
all patients		27.1				24.4			
Surgical Textbook Outcome	yes	29.7	0.78	0.76–0.80	< **0.001**	33.2	1.711	1.629–1.796	< **0.001**
	no	22.9				21.9			
Composite Textbook Outcome	yes	31.5	0.73	0.71–0.75	< **0.001**	27.1	1.262	1.166–1.366	< **0.001**
	no	22.5				20.3			
Lymph node yield	n > 12	27.6	0.93	0.90–0.96	< **0.001**	38.8	1.128	0.889–1.274	0.112
	n < 12	25.3				35.5			
Surgical margins	R0	29.1	0.57	0.55–0.59	< **0.001**	35.3	1.773	1.598–1.803	< **0.001**
	R+	17.3				22.4			
Perioperative therapy	None	18.0				24.2			
	NAT alone	30.8	0.67	0.65–0.70	< **0.001**	41.7	0.872	0.734–0.976	< **0.001**
	AT alone	27.7	0.75	0.72–0.77	< **0.001**	35.4	0.934	0.834–0.976	**0.030**
	NAT and AT	35.5	0.58	0.54–0.62	< **0.001**	46.8	0.711	0.631–0.837	< **0.001**

Annotation. Bold values denote statistical significance at the p < 0.05 level. NCDB = National Cancer Registry; GCRG = German Cancer Registry Group; R0 =complete oncologic resection with no residual tumor; OS =overall survival; m= months; NAT = neoadjuvant chemo- and/or radiotherapy only; AT = adjuvant chemo- and/or radiotherapy only; NAT and AT = neoadjuvant chemo- and/or radiotherapy combined with adjuvant chemo- and/or radiotherapy.

4 Discussion

This cross-validation study between the US-American NCDB and the German GCRG provides evidence of the impact of surgical-oncological Textbook Outcomes on the prognosis of stage I–III PDAC patients. Notably, over 60% of patients across both registries achieved surgical-oncological Textbook Outcome, with more than half of the patients completing perioperative therapy, thus additionally reaching the composite Textbook Outcome, a benchmark of comprehensive care. The study underscores the correlation between achieving Textbook Outcome and improved long-term survival. Insufficient lymph node retrieval translated into impaired overall survival rates. Disparities in international clinical practices were evident, such as the lymph node harvest rate; less than 12 nodes were retrieved in 26% of NCDB cases, but in less than 4% of GCRG cases. While receipt of perioperative therapy significantly improved overall survival in PDAC patients across both registries, this study highlights significant treatment care gaps regarding the administration of perioperative therapy. The application of perioperative therapy varied between registries, with the GCRG reporting no administration of perioperative therapy in 43% of patients. In comparison, only about 22% of NCDB PDAC cases did not receive perioperative therapy. This disparity extends to neoadjuvant therapy use, which was more frequently used in the NCDB (21.7%) as compared to the GCRG (14.8%). The longest overall survival times could be seen in patients receiving neoadjuvant and adjuvant therapy (NCDB: 35.5 months, GCRG: 46.8 months), which also was the perioperative treatment that was administered in only a minority of patients (NCDB: 5.4%, GCRG: 0.3%). This substantial survival benefit merits further investigation to potentially establish this combined approach as a more standard practice in PDAC treatment protocols.

4.1 Study design and patient cohort

This study uses PDAC patient data from the German Cancer Registry Group (GCRG) and National Cancer Database (NCDB). The GCRG is a unique network of cancer registries in Germany. Following the implementation of a federal law on clinical cancer registries in 2013, all German states have established population-based registries that fulfill the national criteria for complete clinical cancer registration [97]. Mandatory reporting by clinicians at time of diagnosis and subsequent treatment stages contributes to the GCRG's complete case coverage of all cancer incidences throughout Germany [97]. In this sense, the GCRG represents a unique data collection of cancer patients in Germany, making it a distinctive and important resource for cancer research on a nationwide level. Unlike Germany, the

United States do not have one singular cancer registry. The NCDB is a joint project of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that captures approximately 64–70% of all newly diagnosed cancer cases in the United States at accredited facilities [98, 99]. An in-depth analysis of the NCDB case coverage from 2012–2014 revealed a 75% case coverage for pancreatic cancer cases [98]. The NCDB provides considerable case coverage for white, black, and Asian/Pacific Islander groups, with rates between 64.7% and 67.4%, but this coverage significantly decreases for American Indians/Alaskan Natives at 32.8% and Hispanics at 51.1% [99]. Additionally, there is an age-related coverage gap in the NCDB, with 63.0% for those aged 65 and older compared to 73.0% for individuals under the age of 65 [99]. Another large cancer registry in the US is the SEER Program which is a population-based registry. The SEER program is maintained by the National Cancer Institute (NCI) and covers approximately about 50% of the population [100]. Both registries collect cancer-related data but are distinct in the amount of data they collect, coverage, and user access. The NCDB collects a larger dataset than the SEER registry and access to the NCDB is limited, while access to the SEER registry is public [101, 102]. Given that the SEER registry is population-based with an epidemiological emphasis, it contains limited data related to therapy specifics. Consequently, the type of analysis we have conducted would not be feasible with data from the SEER registry. While the GCRG serves as a national representative of all German cancer patients, the NCDB in contrast does not capture the entirety of cancer cases in the US, with about 25% of pancreatic cancer patients potentially unrepresented. This discrepancy in case coverage between the registries should be considered when making comparisons, as the NCDB may also not fully reflect the diverse American population. Looking ahead, it would be beneficial to explore ways for the different US cancer registries to overlap to enhance national case coverage. Future comparative assessments between German and US cancer registries would be particularly intriguing once US-American registries achieves higher case coverage, potentially offering new insights into how the currently unreported cases might modify results and perspectives on cancer patient care.

The gender distribution amongst PDAC patients in both cohorts was nearly equal, with a slightly higher percentage of men diagnosed with pancreatic cancer (NCDB: 50.3%, GCRG: 52.6%). This aligns with the understanding that PDAC prevalence is not distinctly attributed to gender, and while rates have historically been slightly higher in men, this has been contributed to lifestyle factors in the past. The average age at PDAC diagnosis was 67 in the NCDB and 69 in the GCRG, aligning with prior analyses [103]. The comparable age

distribution in both registry cohorts enables a reliable comparison across the two patient populations.

There is a notable disparity for stage distribution between the NCDB and the GCRG. The NCDB cohort shows a more uniform distribution among stages I and II, with 49.4% and 45.1% respectively, whereas stage III accounts for only a small fraction at 5.5%. In contrast, the GCRG presents a different pattern, with a predominant 63.9% of cases at stage II and a higher proportion of patients reported at stage III at 19.6%, compared to the NCDB. In the US, the prevalent use of NAT tends to result in downstaging of PDAC cases. Further, as demonstrated by this study, insufficient lymph node retrieval in the US could contribute to under-staging, where patients may postoperatively be categorized at a lower stage of PDAC. Conversely, the prevalence of higher-stage III cases in the German data may reflect a tendency towards more 'aggressive surgery'. There seems to be a greater likelihood of upfront surgery on advanced-stage PDAC patients. This could account for the observed differences in stage distribution between the NCDB and GCRG.

The distribution of surgical approaches for PDAC in both the NCDB and the GCRG is similar, with pancreatoduodenectomy (PD) being the predominant procedure over distal pancreatectomy (DP) in both registries. This reflects the common clinical presentation of PDAC in the pancreatic head, which typically necessitates a PD to remove the tumor [18].

The median time from diagnosis to surgery in the NCDB is slightly higher than in the GCRG, which may be explained by the more frequent use of neoadjuvant therapy in the United States before proceeding to surgery.

4.2 Defining Textbook Outcome for PDAC oncological care goals

The current study proposes a novel definition of Textbook Outcome for PDAC patients. The proposed surgical-oncological Textbook Outcome and composite Textbook Outcome focus on long-term oncological outcomes. By excluding short-term variables, the proposed TO definition shifts its focus to parameters that are important in obtaining improved long-term outcomes in PDAC patients. The approach breaks TO down into three key categories, each critically relevant to PDAC care: tumor free resection margins, sufficient lymph node dissection and perioperative therapy.

Tumor-free resection margins (R0) are considered an important prognostic factor in PDAC as R0 resected patients demonstrate significantly prolonged survival compared to R1 resected patients [35, 104]. Until recently, R0 resection margins have not been included in TO definitions in pancreatic surgery. Textbook Outcome, as a multifaceted metric, should encompass both surgical proficiency as well as the broader scope of oncological care. This

shift in perspective towards adjusting TO for oncological surgical indications is evident in the definition created by the pancreatic neuroendocrine cancer group specifically for pancreatic neuroendocrine tumors (PNETs) [105]. In addition to emphasizing postoperative complications, the inclusion of R0 margins was a significant aspect of their TO criteria [105]. Similarly, in their evaluation of TO as a measure of quality of care in elective rectal cancer surgery, Warps et al. included R0 resection margins in their TO definition amongst 30-day and primary hospital admission survival, no reintervention, no postoperative complications, a hospital stay of less than 14 days and no readmission [106].

Following the emphasis on tumor-free resection margins, another key criterion is appropriate lymph node dissection in surgical oncology. Lymph nodes represent a common site for early metastasis in PDAC and are crucial for accurately assessing the extent of the disease postoperatively [27, 107, 108]. The retrieval of a minimum of 12 lymph nodes is mandated by the German S3 guideline for pancreatic cancer treatment as the standard for oncological lymphadenectomy [42]. A retrieval of a minimum of 12 lymph nodes as a standard lymphadenectomy is also recommended by the ISGPS [35]. In contrast, the US-American NCCN guidelines do not specify a minimum yield for lymph node retrieval [16].

The decision to include perioperative therapy into the definition of a composite Textbook Outcome was made based on the results of several large clinical randomized trials showing significant survival benefits in patients that received perioperative therapy [39, 41, 64, 65, 109]. Perioperative therapy is considered an essential part in the treatment of pancreatic cancer, a consensus widely accepted within the surgical oncology community.

In conclusion, these criteria are critical for the long-term overall survival of PDAC patients, as evidenced by the current cross-validation study. The focus here expands from surgical success to the effectiveness of the entire oncology care team in managing complex cancer treatment protocols. In the case of PDAC patients and cancer patients in general, reaching Textbook Outcome encompasses more than just the surgical aspect, as surgery often represents just one step in the patient's journey towards, ideally, cancer remission. The ideal outcome goes beyond having minor complications from surgery, instead aiming for long-term cancer treatment goals that are linked to better survival outcomes.

4.3 Textbook Outcome rates in pancreatic cancer

The surgical-oncological TO rates of 63.3% in the NCDB and 77.0% in the GCRG align closely with previously reported surgical TO rates. Presently, the most widely adopted definition of TO in pancreatic surgery can be attributed to van Roessel et al. [91]. TO was defined as the absence of critical postoperative complications like pancreatic fistula, bile leak, hemorrhage, and in-hospital mortality. Their analysis, utilizing data from the Dutch Pancreatic Cancer Audit, encompassed patients undergoing PD or DP for various indications, not limited to cancer. TO was reported in 60.3% of patients. The metric 'no Clavien-Dindo grade III or higher complications' emerged as the primary obstacle for achieving TO [91]. Using the Dutch Study Group's definition, Wu et al. evaluated TO following laparoscopic PD at 16 high-volume pancreatic cancer centers in China [110]. TO was accomplished in 68.9% of cases (709 out of 1029 patients), with the achievement rate varying between 46.4% to 85.0% across different hospitals [110]. TO rates were notably higher in high and medium-volume hospitals compared to low-volume ones, and they increased with a surgeon's cumulative experience in minimally invasive surgery [110]. Subsequent studies utilizing the definition have shown comparable rates, albeit with a variation ranging from 55% to 74% [110–112].

Although different criteria were used to define surgical Textbook Outcome in this current study due to the focus being on oncological-surgical goals, the TO rates of this study are similar (NCDB: 63.3%, GCRG: 77.0%). Interestingly, the surgical-oncological TO rates in the current study are higher. This could be explained by the omission of postoperative complications as parameters into the definition. Future investigations how the addition of postoperative complications to our proposed definition would affect the surgical-oncological TO rates are warranted.

This current study proposes administration of perioperative therapy as an essential component of what defines TO for pancreatic cancer patients, creating a composite TO. The composite TO rates are considerably lower than the surgical-oncological TO rates in this study, at 50.7% in the NCDB and 54.0% in the GCRG. The decline in the composite TO rate reveals a substantial care gap in pancreatic cancer treatment, indicating that over 10% of patients meeting surgical-oncolgical TO criteria—a presumptive steppingstone to composite success—did not receive perioperative therapy.

Limited TO studies which include perioperative therapy as a variable are available. Aquina et al. aimed to validate "Textbook Oncologic Outcome" (TOO) as a measure of hospital

quality in cancer surgery [86]. Their study involved patients who underwent curative-intent resection of various cancers, including pancreatic, between 2006–2017, using data from the NCDB. TOO was defined based on criteria including adequate lymph node yield, R0 resection, hospital stay duration, readmission rates, and adherence to chemotherapy and radiation guidelines. In their study, pancreatic cancer cases had the lowest TOO rate of all evaluated cancer entities, recorded at 25% [86]. In a NCDB analysis, focusing on PDAC patients who underwent PD from 2006 to 2016, Sweigert et al. characterized TOO by several criteria: margin-negative resection, compliant lymph node evaluation, absence of prolonged hospital stay, no 30-day readmission or mortality, and the administration of adjuvant chemotherapy [113]. Despite high achievement rates for individual TOO factors, such as R0 margin and no 30-day mortality, overall, only 16.8% of patients achieved TOO [113].
Comparing the two proposed TOO's to our composite TO it is of note that the achievement rate differs significantly even though all three T(O)O benchmarks include negative tumor margins, lymph node yield and administration of perioperative therapy. The TOO definitions additionally include postoperative complications into the evaluation, to which the significantly lower rates could be attributed too. Sweigert et al. highlighted that starting adjuvant chemotherapy within 12 weeks post-surgery (48.2%) and absence of prolonged length of hospital stay (53.7%) showed the lowest achievement rates. Of note, in their study the consideration of perioperative therapy was limited to adjuvant therapy, potentially overlooking patients who underwent neoadjuvant therapy [113].

The proposed composite TO definition, consisting of three criteria, offers a focused yet concise perspective on pancreatic cancer TO. While the proposed TO definition of this study includes core elements of pancreatic cancer care, it does not imply these are the only relevant factors; rather, it aims to establish a baseline using metrics essential for improved overall survival in PDAC patients. The significantly low rates of TOO presented by Aquina et al. [86] as well as Sweigert et al. [113], support our approach of separating general oncological care goals from short term surgical goals. Very low TO rates could potentially overshadow essential variables where significant achievements can be seen. For example, the rate of R0 resections have increasingly been improving in the past decades. By including postoperative complications, which are not uncommon in complex procedures like pancreatic surgery, there is a risk of overlooking the areas of oncological care where favorable variables towards patient outcome are consistently achieved. Regarding long-term outcomes, postoperative complications and duration of hospital stay often play a minor role and should therefore be regarded separately. The TO definition proposed in this study is intended to represent a

long-term oncological level of success in PDAC care as a benchmark. Future work could involve defining TO subcategories and assessing their individual impact on long-term outcomes.

4.4 Application and implications of Textbook Outcome as a clinical benchmark

Textbook Outcome is emerging as a novel measure of quality management in oncology, especially due to its proven association with enhanced overall survival across various cancer types, including but not limited to PDAC. As shown in this current cross-validation study, both surgical-oncological TO and the composite TO were significantly associated with increased overall survival in PDAC patients across two large national registries. Previous studies reporting on TO confirm the association of achieving TO and improved overall survival for PDAC patients and in pancreatic surgery in general [86, 91, 113–116].
In gastric adenocarcinoma patients, TO was linked to increased survival post-gastrectomy, though achieved in only 23.8% of cases [117]. Similar results of improved survival are reported for patients achieving TO following gastrectomy and esophagectomy [118]. For retroperitoneal sarcoma patients, achieving TO significantly extended median survival (12.7 vs 5.9 years) [119]. In colon cancer, patients that were considered to have a Textbook Outcome, demonstrated better five-year disease-free survival [120]. An analysis by Hyer et al. that concentrated on patients undergoing complex gastrointestinal surgeries, including pancreatic procedures, revealed a rising trend in the achievement rates of TO over recent years. In their study, TO rates were associated with enhanced patient survival across all surgical categories [121]. Collectively, these findings, along with the results presented in this study, highlight the significant correlation between achieving 'Textbook Outcome' and improved overall survival in cancer patients, establishing it as a valuable composite measure for evaluating the quality of oncological care.

Demonstrating broad applicability, TO represents a valuable tool for a range of stakeholders in the healthcare system and the usefulness of the composite measure extends beyond clinical outcomes. Textbook outcome can serve as a critical measure for identifying social and racial vulnerabilities in current healthcare systems, on both national and regional levels. Several studies have demonstrated that socially vulnerable groups and residents in underserved areas have lower odds of achieving TO following cancer surgery [122–124]. An analysis of patients that underwent hepatic and pancreatic surgery from the Medicare Standard Analytic

Files showed that Textbook Outcome was more likely to be achieved in patients from high upward economic mobility counties (in the US) as compared to low upward economic mobility counties [124]. Further, Moazzam et al. were able to show that black patients had lower odds of achieving Textbook Outcome and higher risks of complications and longer hospital stays after pancreatic surgery [124]. Similarly, Diaz et al. demonstrated that patients in the least racially or ethnically integrated counties had a 16% lower chance of achieving Textbook Outcome following pancreatic surgery [123]. Their data, indicating lower odds for both minority and non-minority patients in these areas, suggests broader implications for the oncological care of socially vulnerable patient groups. Access to high-quality healthcare remains less attainable and affordable for minority patients, often compounded by socioeconomic barriers [125]. Recent discourse has increasingly highlighted the impact of racial discrimination in healthcare settings [126–131]. Racial discrimination in healthcare settings contributes to a mistrust that often delays patients from seeking necessary care [132]. Studies have shown that black men are notably less likely to undergo screenings or treatments for prostate cancer [133, 134]. Additionally, the likelihood of black patients being screened for lung cancer is up to 61% lower compared to white patients [135]. This disparity extends to Asian-American populations as well, who are less frequently screened for conditions like cancer and diabetes [136]. Additionally, the described low TO rates could be linked to the proven higher prevalence of chronic health conditions in economically disadvantaged patients and minorities, such as cardiovascular disease, diabetes and obesity [137–140]. Obesity, as an example, is a significant preoperative risk factor; it is linked with a heightened risk of postoperative complications and greater post-surgery morbidity [141–143]. There is a notable gap in research regarding the achievement of oncological care goals within low-economic mobility areas and among minority groups in the US. Collectively, these findings emphasize the significant role of social determinants of health, including race and ethnicity, in influencing access to surgical and oncological care and shaping postoperative outcomes. The use of Textbook Outcome as a metric effectively identifies areas or groups that require more targeted healthcare interventions.

Textbook Outcome is also emerging as an appealing composite measure for insurance companies, particularly regarding cost management. Average Medicare payments for patients following hepatopancreatic surgery were significantly higher in patients who did not achieve TO [144]. In line with these findings, a 2023 Medicaid analysis on TO following surgery found that failing to achieve TO resulted in more than a 95.1% increase in cumulative healthcare costs [145]. In their analysis, the definition of TO focused on

postoperative short-term goals such as absence of major complications and no prolonged length of hospital stay [145]. Given these findings, insurance companies might consider using TO as a criterion for directing patients to certain high standard care hospitals for specific treatments. This approach could lead to a scenario where treatment at hospitals with higher rates of TO achievement would be more encouraged, aligning financial incentives with quality healthcare outcomes. Future research could focus on how achieving key oncological goals, such as obtaining R0 negative margins and administering perioperative therapy, influences healthcare costs, given their association with improved patient outcomes. Understanding this cost dynamic could provide valuable insights into the economic impact of cancer care protocols.

Additionally, TO is proposed as a metric for assessing the performance of both individual surgeons and hospital performance. For instance, in pancreatic surgery, Chen et al. demonstrated that patients operated on by surgeons in the bottom quartile of performance experienced higher rates of postoperative complications and were less likely to achieve TO [146]. The current international trend towards centralization of healthcare and increased focus on specialty hospitals, thus moving away from ‘regular’ hospitals offering a wide array of procedures, has led to a heightened focus on evaluating and comparing hospital performance. Hospital case volume has been linked to improved survival in PDAC patients . With TO established as linked to improved survival, various studies have examined its achievement in relation to different hospital volumes. Despite treating more patients with complex health issues, dedicated cancer centers (DCCs) showed higher rates of achieving Textbook Outcomes in hepatopancreatic surgery compared to hospitals in the U.S., indicating that DCCs may offer superior surgical care for hepatopancreatic malignancies [151]. Similarly, patients had higher odds of achieving TO after pancreatic and hepatic surgery at major teaching hospitals compared to minor ones, with this trend being largely influenced by the volume of hepatopancreatic procedures [152]. Contrary to these results, an analysis by Mehta et al. showed that patients undergoing surgery for lung, esophageal, liver, pancreatic and colorectal cancer experienced similar rates of Textbook Outcome at both honor roll and non-honor roll hospitals [153]. Honor roll hospitals were defined as the top 20 institutions recognized for the quality of cancer care on the U.S. News & World Report (USNWR) Best Hospitals rankings, one of the most commonly used hospital ranking system in the United States [153]. Institutions named to U.S. News & World Report's honor roll achieved this distinction by scoring highly in one or more medical specialties and being recognized as ‘high performing’ in various procedures and conditions by U.S. News analysts

[154]. In 2023, the USNWR hospital rankings faced significant criticism, with calls for greater transparency in their evaluation processes [155]. Given that patients frequently rely on these rankings to select their healthcare providers, concerns have been raised about the potential financial relationships between U.S. News and the hospitals they rank. These issues have been increasingly publicized with one top-ranking hospital distancing themselves from the ranking system in 2023 [156].

A study by Kalaga et al. analyzing PDAC patients in the NCDB suggests that long-term survival post-pancreatic surgery is more closely associated with achieving a Textbook Outcome than with the surgical volume of a hospital [116]. Patients that underwent surgery at low-volume hospitals were less likely to achieve TO compared to those at high-volume hospitals. However, the significance of hospital volume as a determinant of overall survival decreased when the achievement of TO was considered: Attaining TO itself was found to be associated with a substantial 31% decrease in the risk of death, independent of the hospital's surgical volume [116]. In conclusion, when examining long-term survival rates, the literature presents mixed findings on the correlation between improved survival and hospitals with high case volumes or honor status. However, when introducing TO as a metric, this association appears less pronounced. There is a tendency for higher TO rates in patients treated at high case load hospitals, yet the primary conclusion is that TO serves as a more effective measure for assessing patient outcomes than merely considering hospital case volume. In the future, TO may serve as an effective benchmark for identifying proficient care providers, extending beyond the size, case volume and reputation of hospitals.

For patients, Textbook Outcome may serve as a summary measure of the quality of care which aids and enables patients in making informed decisions about their healthcare options [157]. As a comprehensive measure of healthcare quality, TO encompasses various aspects of patient care, from surgical proficiency to postoperative recovery, and as with this current study, oncological care goals. When choosing a healthcare provider, patients often face many options and complex information. The benchmark TO simplifies this decision-making process by offering a summary measure of the quality of care. Indeed, patients seem to prefer a summary measure of quality care over many detailed measures [158]. By comparing the TO rates of different hospitals, patients can make more informed choices about where to receive treatment, ideally leading to improved outcomes.

In summary, the versatility of Textbook Outcome as a measure makes it a powerful tool for assessing healthcare quality across various levels, from individual surgeons to entire

hospitals. It also aids in addressing broader issues like social vulnerabilities in healthcare, making it an essential component of modern healthcare quality assessment and improvement efforts. To ensure the highest relevance, it is important to customize Textbook Outcome to the specific goal or aspect of care that is being measured. Our definition of surgical-oncological Textbook Outcome and composite Textbook Outcome enables assessing the overall achievement of PDAC cancer care goals internationally. Analyzing real-world data on a nationwide scale using this approach allows for the identification of treatment areas where care gaps are most pronounced, and it pinpoints where future improvements are necessary.

4.5 The prognostic significance of R0 resection in PDAC treatment

The central objective in curative-intent surgical resection for PDAC remains achieving a margin-negative (R0) resection [14]. Achieving R0 margins is not only a clinical goal but also an outcome highly valued by patients. From the patients' perspective, achieving an R0 resection is regarded as an 'extremely important' endpoint of cancer treatment, as indicated by the vast majority of patients in a recent study [159]. Failure to achieve R0 resection has consistently been shown to correlate with unfavorable long-term outcomes and multiple studies highlight the reduced survival rates associated with margin-positive resections in PDAC patients [54, 90, 95, 160, 161]. The current cross-validation study confirms these findings, with the results revealing a marked improvement in median overall survival rates: 29 (NDCB) and 35 (GCRG) months for margin-negative resections, which is significantly higher compared to the 17 (NCDB) and 22 (GCRG) months observed in patients with margin-positive resections. R0 resection was achieved in 79–86% of the patients resected for stage I–III PDAC.

Sweigert et al. conducted a comprehensive analysis of oncological Textbook Outcomes using data from over 18,000 patients in the NCDB, revealing R0 resection rates of 77.9% up to the year 2016 [114]. Similarly, the nationwide Dutch Pancreatic Cancer Audit reported a 29% incidence of direct margin involvement among 595 patients from 2014–2016 [162]. Anger and colleagues examined 3,079 PDAC patients from the German StuDoQ pancreatic surgery registry (2014–2019) and found margin positive resections in 21–27% of cases [163]. Collectively, these studies benchmark the R0 resection rates, aligning the findings of the current cross-validation study with the international standard of 70 to 80% for stage I–III PDAC.

The presented results reaffirm the critical role of R0 resection in PDAC treatment, validating its significance as a key predictor of patient survival and its resonance with patient expectations for optimal cancer care outcomes. Our findings, coupled with previously reported R0 resection rates, indicate that the international standards for achieving R0 resection rates are affirmatively high. The improvement in R0 resection rates over the past decades can be attributed to advances in surgical techniques, imaging technologies and the addition of neoadjuvant therapy to PDAC treatment regimens [14, 164, 165]. The on average remaining 20–30% of patients with R1 resections might be associated with a preoperative misjudgment of tumor resectability. While modern imaging techniques offer high precision and the ability to make detailed assessments, the actual intraoperative scenario may differ from the preoperative expectations. It may be valuable to investigate the cohort of R1 resected patients to identify any commonalities that could, in the future, aid in enhancing preoperative assessments and more accurately determine tumor resectability.

4.6 Lymph node dissection: Impact on oncological care goals and PDAC prognosis

The median number of lymph nodes dissected in the current cross-validation study was 17 to 18 lymph nodes across both registries. While supposedly appropriate lymph node yields were achieved in the median, more than 25% of the patients in the NCDB but only 4% in the GCRG had fewer than 12 lymph nodes dissected. Lymph node retrieval of less than 12 lymph nodes translated to impaired median overall survival rates. It may therefore be concluded that sufficient lymph node retrieval is a major component of surgical-oncological Textbook Outcome and determines long-term oncological outcomes.

Inadequate lymph node dissection was observed in other registry studies, too [96, 166]. A 2008 study conducted by Hellan et al. analyzed data from the SEER registry, focusing on N0 PDAC patients treated between 1988 and 2003 [96]. The median number of lymph nodes examined in this N0 cohort was only seven (7), and a significant portion of patients (71%) had fewer than 11 lymph nodes examined [96]. Although this study exclusively focused on N0 patients, limiting its direct comparison to the present study that encompasses all stage I–III PDAC patients, it is worth noting that lymph node dissections rates seem to have improved over the past 20 years. Wang and colleagues performed an analysis of 9,945 patients from the SEER registry and found the median number of lymph nodes retrieved to be as low as 13 [166]. The authors defined 15 lymph nodes as the minimum required number to be dissected and concluded that 56% of the patients had an inadequate lymph node

dissection [166]. Maegawa et al. report significant differences in lymph node dissection rates between Academic/Research cancer programs (APCs) and non-academic hospitals (nAPCs) in their 2006–2016 analysis of PDAC patients in the NCDB [167]. More than 15 lymph nodes were examined in 49.6% of patients at APCs and in 36.3% of patients at nAPCs [167]. Setting 15 lymph nodes as the adequate dissected number of nodes, Wang et al. reference the consensus statement by the ISGPS [166]. However, a detailed examination of the consensus statement discloses that, the group considered a minimum of 12 or 15 lymph nodes to be crucial. Ultimately, the final statement specifically recommends standard lymphadenectomy to include lymph nodes stations no. 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b (a total of 12) for pancreatoduodenectomy [36]. However, it should be noted that both this recommendation and the German S3 guideline are grounded in expert consensus rather than rather than direct empirical evidence. Considering the variation in cut-off points between our study and prior registry analyses, a secondary analysis within our dataset, with a set minimum requirement of 15 dissected nodes, would enable a more accurate comparison. This could help identify trends in lymph node dissection rates within our 2010–2020 patient cohort compared to past cohorts.

The most recent international consensus statement was published 2013, and there have been no subsequent updates on the subject. While there is a consensus that performing an extended LAD offers no added benefits, supporting the use of standard LAD, there is currently a lack of evidence-based recommendations regarding the minimum number of nodes required for a standard LAD. In 2019, Huang et al. highlighted the significance of the number of examined lymph nodes (ELNs) in tumor staging. They reported an increased risk of insufficient staging with a lower number of ELNs, proposing that at least 11 ELNs are necessary to achieve dependable accuracy [97]. In their 2022 analysis of the SEER registry involving 2610 patients who underwent DP, Wang et al. found that the median number of ELNs was 12, with the most common count being 9 lymph nodes examined [168]. The study revealed that a minimum of 19 ELNs was essential for a high quality and comprehensive lymph node examination in patients that underwent DP, yet this standard was only achieved in approximately 25% of the cases examined [168]. As the trend of recently is moving towards a higher threshold for what constitutes as a sufficient number of lymph nodes, the incidence of inadequate lymph node dissection, as highlighted in this study, could be even more prevalent.

Under-sampling of lymph nodes in pancreatic cancer surgeries represents a potential source of error that can significantly influence patient prognosis. Accurate staging and outcome predictions hinge on the retrieval and examination of an adequate number of lymph nodes. Importantly, adequate lymph node dissection significantly enhances survival rates in PDAC patients, as demonstrated in our study. As such, comprehensive lymph node dissection stands as a critical component of PDAC treatment, directly affecting the accuracy of cancer staging and subsequent therapeutic decisions. Ensuring the surgical quality of radical lymph node dissection is therefore essential, warranting establishment as a benchmark standard and a key indicator of surgical quality in surgical-oncological Textbook Outcome. It is imperative for future research to concentrate on creating a universally accepted standard for the minimum number of lymph nodes examined in a standard lymphadenectomy, as this will enable more accurate conclusions and enhance the assessment of cancer care globally. Further, a comprehensive examination of the reasons behind the common occurrence of insufficient lymph node dissection in the United States compared to Germany is warranted. A detailed analysis within the NCDB could identify trends or patterns of suboptimal lymphadenectomy within states and counties, specific hospitals and individual surgeons.

4.7 Optimizing perioperative care in PDAC: Systemic challenges

The current study reveals that a significant number of patients (22% – 44%) do not receive perioperative therapy, with the GCRG particularly reporting high rates of surgery alone (44%). This underutilization is notably reflected in the overall survival rates, with the GCRG cohort demonstrating a shorter median survival (27.1 months) as compared to the NCDB cohort (31.5 months). The discrepancy in survival outcomes between the two registries may largely be attributed to the differences in the administration of perioperative therapy; when such therapy is provided, it significantly extends overall survival in both registries. Failure to provide perioperative therapy directly correlates with poor long-term outcomes, indicating that enhancing access to and acceptance of perioperative therapy is critical for improving overall survival rates and achieving better Textbook Outcomes.

This study highlights the considerably low rates of administered neoadjuvant therapy in Germany. The rate of neoadjuvant therapy in the GCRG is as low as 15%, but 22% in the NCDB. While adjuvant therapy has been a standard of care for stage I–III PDAC in both the United States and Germany, the role of neoadjuvant therapy is emerging for BR-PDAC in particular [53, 54]. The NCCN has recommended neoadjuvant therapy for BR-PDAC since 2014, predominantly due to its potential for making inoperable tumors resectable through

tumor size reduction [17, 52]. Conversely, the German S3 guideline only recently embraced neoadjuvant therapy in its 2022 update [43]. A previous cross-validation study of the NCDB and GCRG (study period: 2000–2018) by our research group, reported neoadjuvant therapy rates of 13.7% in the GCRG and 16.3% in the NCDB [104]. Though the rates of administered therapy remain low, the number of patients receiving neoadjuvant therapy has been increasing.

While the longest median survival can be seen in patients that received both neoadjuvant and adjuvant therapy (NAT + AT) (NCDB: 35.5 months, GCRG: 46.8 months), it is also the minority of patients that received both NAT and AT (NCDB: 5.4%, GCRG: 0.3%). So far limited data is available on the benefits of additional AT in PDAC patients that previously received NAT. Van Roessel et al. reported that AT following NAT significantly improved survival, but notably only in node-positive PDAC patients (median OS: 26 vs. 13 months, $p = .004$) [169]. A 2021 analysis of the NCDB by Kamarajah et al. indicated that patients receiving both NAT and AT had a considerably better survival rate (median OS: 29.4 vs. 24.9 months; $p < 0.001$), with the survival benefit persisting regardless of nodal status [170]. More recently, Lee et al. found that the combination of NAT and AT not only enhanced OS, but also disease-free survival (DFS) in PDAC patients (DFS:13.8 months vs. 8.2 months, $p < 0.001$; OS: 38.0 months vs. 25.7 months) [171]. Given the emerging evidence, it is justified to consider the integration of adjuvant therapy into the treatment plans of PDAC patients who have undergone neoadjuvant therapy, particularly considering the significant enhancement in survival rates observed.

The study at hand demonstrates that perioperative therapy, whether neoadjuvant, adjuvant, or both, markedly improves long-term outcomes compared to surgery alone, with the highest median overall survival rates observed in patients receiving both. Therefore, administration of perioperative therapy in addition to surgical-oncological Textbook Outcome is crucial and should be acknowledged as a composite oncological Textbook Outcome parameter. The current healthcare infrastructure faces challenges in ensuring that eligible patients receive perioperative therapy, a trend observed across this presented cross-validation study of two national registries. This issue is partly structural; the entities responsible for surgical resection and those administering perioperative therapy often operate independently. Complex surgeries, such as pancreatic surgery, are typically performed in specialized centers, recommended for their expertise and better outcomes in managing complex procedures, whereas perioperative therapy is frequently administered in outpatient settings

by local oncologists [172, 173]. While large medical centers typically adhere to the latest medical guidelines and treatment protocols, local practices may not always be as current with these standards [174–176]. This discrepancy can increase the likelihood of care deviations, as individual oncologists in the community setting have more autonomy in decision-making, potentially leading to physician bias and a variability in treatment approaches [174–176]. Additionally, patient preference plays a significant role in instances where there is a departure from the recommended perioperative treatment [174, 177, 178]. Cheville et al. conducted a study to evaluate the impact of a structured, multidisciplinary Quality of Life (QOL) intervention on chemotherapy completion in gastrointestinal cancer patients [179]. This intervention, conducted two to three times a week and led by psychologists or psychiatrists, encompassed activities such as gentle exercise and guided relaxation. The study observed a significant increase in the completion rate of chemotherapy regimens among participants in the intervention group compared to those in the control group, with completion rates of 77.8% versus 38.2% [179]. It is noteworthy that such seemingly minor additions to cancer care, like the QOL intervention, can have a substantial impact, markedly improving the rate of completed chemotherapy regimens. This finding suggests that, in future strategies, there should be a consideration for restructuring perioperative therapy to incorporate elements that enhance the quality of life, potentially leading to better treatment adherence and outcomes.

The value of systemic therapy as a key factor in influencing long-term outcomes for PDAC patients cannot be understated. Increasing the rate of neoadjuvant therapy, offers a promising strategy to ensure more patients benefit from systemic therapy, even those with prolonged postoperative recovery. It is crucial to provide patients with comprehensive information about their treatment options and their benefits and to de-stigmatize chemotherapy, ensuring that patients can make informed decisions about their treatment plans without preconceived biases or misconceptions. Enhancing understanding and acceptance of chemotherapy could significantly improve adherence to treatment protocols and, consequently, patient outcomes. Looking ahead, a strategic approach to promote treatment completion could involve the identification and implementation of additional therapies or patient support systems. These should be designed to not only enhance patient adherence to perioperative treatment protocols but also to improve the overall tolerability of the treatment process.

4.8 Limitations

This registry-based study is subject to several limitations due to its design and data sources. Firstly, the retrospective nature of the data from national registries carries potential biases, particularly in patient selection. Such biases could influence the generalizability of the findings. The retrospective approach also means that instances of missing or incomplete data are difficult to address or trace back. The study is dependent on the quality and accuracy of available data in the NCDB and the GCRG. Incomplete or inaccurately recorded information may affect the accuracy and completeness of the analysis. Additionally, the NCDB does not encompass 100% coverage of all cancer patients in the US [91, 103], which could introduce a selection bias in the data. Critical surgical short-term outcome parameters, particularly those related to postoperative pancreas-specific complications, were not included in the registries. This omission restricts a complete evaluation of surgical outcomes and their implications. Next, detailed oncological data, including specific chemotherapy agents used in treatment, were not accessible for this analysis. The lack of this information limits the scope of the analysis, particularly in understanding the impact of different chemotherapy regimens on patient outcomes. Furthermore, patients with stage III cancer may be underrepresented in the NCDB cohort, potentially skewing results and limiting the applicability of findings to this subset of the patient population. The interpretation of the analysis results requires careful consideration of these factors.

The concept of a "Textbook Outcome" as a benchmark in healthcare is a novel parameter that has been introduced only recently. As such, it presents several limitations that warrant careful consideration. Firstly, due to its recency, there is still a lack of clarity and consensus regarding its final application in healthcare and the potential implications it may have. This ambiguity stems partly from the abstract nature of the concept, which does not have a universally accepted definition or set of criteria yet. The novelty of Textbook Outcome has generated significant interest across the medical scientific community, leading to a surge in efforts to contribute to its definition and understanding. This keen interest among researchers to contribute to the establishing of this novel benchmark, is evidenced by the multiple definitions of 'Textbook Outcome' that have emerged [92, 114, 147, 153]. The varied definitions highlight the benchmarks dynamic character yet underscore the necessity for unification. In the future, systematic reviews of the different established Textbook Outcome definitions may be helpful in developing a more uniform and empirically grounded standard for 'Textbook Outcome' for both future academic research and clinical application.

4.9 Outlook

In the future, a second cross-validation of the data from these two national registries would be very interesting, particularly once the national coverage of the NCDB has ideally expanded. This follow-up comparison could provide further insights into trends and patterns that may not be fully evident in the current dataset. A more comprehensive coverage would allow for an additional analysis, potentially revealing new aspects of pancreatic cancer outcomes across all PDAC stages.

Further, there have been no detailed analyses focusing on social, economic, and racial vulnerabilities in the context of pancreatic cancer in the United States and Germany to date. While Germany may not exhibit the same level of racial diversity as the United States, it is still crucial to identify vulnerable groups, and areas in the nation. Understanding these dynamics is essential for enhancing healthcare delivery and ensuring equitable access to cancer care for all populations and guide interventions to improve outcomes in underserved communities. Furthermore, it will be of interest, to observe the development and establishment of the benchmark TO. Once this novel benchmark is officially established, revisiting national cancer registry data with the criteria will offer insightful comparisons, revealing how current treatments measure up to the defined “gold standard”.

Moving forward, a critical research objective should be the examination of patient outcomes associated with currently available treatment agents and regimens. A comparative analysis of patient cohorts, such as patients treated with FOLFIRINOX versus patients receiving capecitabine, could yield novel insights into treatment efficacy beyond the scope of clinical trials. Analyzing real-world data from a nationwide cohort has the potential to identify which treatments present the greatest advantages to patients, offering essential information that could shape clinical decision-making and future research directions.

5 Conclusion

In conclusion, this thesis has extensively explored the concept of “Textbook Outcome” as an innovative benchmark for assessing the quality of oncological care in pancreatic ductal adenocarcinoma treatment. The primary goal of the study was to define surgical-oncological Textbook Outcome, focusing on long-term oncological care goals in PDAC patients. Additionally, it sought to assess whether Textbook Outcomes vary between nations, to examine the correlation between achieving Textbook Outcomes and overall survival in PDAC patients, and to identify the limiting factors in achieving these outcomes. A retrospective cross-validation study was conducted, utilizing data from two large national registries: the National Cancer Database in the United States and the German Cancer Registries. The results of this study are novel. Surgical-oncological Textbook Outcome and the composite Textbook Outcome were only achieved in half of all stage I–III PDAC patients across both registries. More importantly, there was a clear correlation between the achievement of Textbook Outcomes and improved survival rates across both national registries. Surgical-oncological Textbook Outcome and the composite Textbook Outcome including the receival of perioperative therapy can be ideal simple benchmarking tools to assess and maintain quality of care in PDAC patients. A critical limiting factor identified in achieving Textbook Outcomes across both registries was the administration of perioperative therapy. This study discloses the very low rates of administered perioperative treatment in Germany, drawing on real-world data from the German Cancer Registry. Given that the German Cancer Registry data encompasses 100% of pancreatic cancer cases in Germany, it offers a comprehensive insight into the realities of everyday pancreatic cancer care within the country. Thus, this study highlights areas for improvement in the management of pancreatic cancer. Both surgical-oncological Textbook Outcome and composite Textbook Outcome summarize the most important oncological outcome parameters of multidisciplinary pancreatic cancer treatment. Currently there is no internationally standardized definition of Textbook Outcome in pancreatic cancer care. This would be an important step toward standardized quality control in multidisciplinary oncological pancreatic cancer therapy. An expert panel could evaluate previous definitions, with the goal of reaching an agreed-upon, standardized consensus. Patient surveys could be conducted to understand what aspects of treatment and care patients prioritize.

6 Thesis summary in German

Hintergrund

Das duktale Adenokarzinom des Pankreas ist der häufigste maligne Tumor der Bauchspeicheldrüse [1, 2]. Die chirurgische Resektion des Tumors stellt bis heute die einzige kurative Option dar [14]. Die Krankheit ist in den frühen Stadien oft asymptomatisch, was zu einer verzögerten Diagnose führt und in begrenzten Behandlungsmöglichkeiten resultiert [14, 59]. Der Parameter "Textbook Outcome" hat in der klinischen Forschung zunehmend an Bedeutung gewonnen, da er ein umfassendes Bewertungskriterium darstellt, das verschiedene Aspekte und Standards eines idealen Behandlungsverlaufs berücksichtigt [84, 86, 180]. Textbook Outcome (TO) wurde erstmals von einer niederländischen Kolorektal-Karzinom Forschungsgruppe im klinischen Kontext eingeführt [83]. Seitdem wurde TO auch für die Pankreaschirurgie definiert, jedoch bisher noch nicht spezifisch für die Versorgungsziele des Pankreaskarzinoms definiert [92]. Das Hauptziel dieser Arbeit ist die Kreuzvalidierung von Daten aus der US-amerikanischen Nationalen Krebsdatenbank (NCDB) und der Deutschen Krebsregistergruppe und der Arbeitsgruppe Deutscher Tumorzentren (GCRG/ADT). Die Studie schlägt eine PDAC-spezifische Definition für TO vor, die chirurgische und onkologische Versorgungsziele umfasst. Die Studie untersucht zudem, ob die TO-Erfolgsrate zwischen den USA und Deutschland variiert. Ein zentraler Aspekt ist die Analyse der Gründe für das Nichterreichen des TO in der PDAC-Behandlung.

Methodik

Diese retrospektive Studie analysierte Patientendaten aus der Nationalen Krebsdatenbank (NCDB) der USA und der Deutschen Krebsregistergruppe der Gesellschaft Deutscher Tumorzentren (GCRG/ADT). Die Ethikkommission der Universität zu Lübeck genehmigte die Studie am 17. August 2020 (Aktenzeichen: 20-319). Die Kohorten umfassten Patienten mit histologisch bestätigtem PDAC, die zwischen 2010 und 2020 einer kurativen Resektion unterzogen wurden. Einschlusskriterien waren präoperatives PDAC Stadium I-III, während Patienten im Stadium IV, ohne Resektion, fehlende Nachsorgedaten oder unspezifizierten chirurgischen Rändern ausgeschlossen wurden. Die "Textbook Outcome“ Definitionen wurde durch Expertenkonsens definiert. Chirurgisch-onkologisches TO umfasste vollständige onkologische Resektion mit R0-Rändern und mindestens 12 entnommenen Lymphknoten. Das kombinierte TO wurde definiert als R0-Resektion, mindestens 12 entnommene Lymphknoten und Erhalt einer perioperativen Therapie. Die Arbeitsgruppe

„Bauchspeicheldrüsenkarzinom“ der Klinik für Allgemein-und Viszeralchirurgie am Universitätsklinikum Schleswig-Holstein (UKSH), Campus Lübeck, und das Qadan-Labor am Massachusetts General Hospital (MGH) in Boston, USA, waren beteiligt. Statistische Auswertungen wurden mit IBM SPSS Statistics (Version 25.0) durchgeführt. Zur Bestimmung statistischer Signifikanz wurde ein Schwellenwert von $p < 0.05$ festgelegt.

Ergebnisse

Im NCDB-Register wurden 241 144 Patienten mit histologisch bestätigtem Pankreaskarzinom (PDAC) identifiziert. Aus dem GCRG/ADT-Register wurden 103 914 Patienten mit histologisch bestätigtem PDAC identifiziert. Die endgültige NCDB-Kohorte umfasste 33.498 Patienten, von denen 28 249 (84,3%) mittels Pankreatoduodenektomie (PD) versorgt wurden und 5 249 (15,7%) eine distale Pankreatektomie (DP) erhielten. Aus dem GCRG/ADT Register wurden 14 589 Patienten mit histologisch bestätigtem PDAC in die Analyse aufgenommen. Bei 10 256 (70,3%) Patienten wurde eine PD durchgeführt und bei 2 022 (13,9%) Patienten eine DP. Die mediane Zeit von der Diagnose bis zur Operation betrug im NCDB-Register 30 Tage und im GCRG/ADT-Register 23 Tage. In der NCDB wurde bei 28 931 Patienten (86%) eine vollständige onkologische Resektion (R0) erreicht, in der deutschen Kohorte bei 11 595 Patienten (79%). Von der GCRG/ADT Kohorte wurden bei 556 Patienten (4%) weniger als 12 Lymphknoten entfernt, und in der NCDB bei 8 723 (26,2%) Patienten. In der NCDB erhielten 26 135 Patienten (78%) eine perioperative Therapie; 7 276 Patienten (21,7%) erhielten neoadjuvante Therapie (NAT). Bei 17 037 Patienten (50,9%) wurde eine adjuvante Therapie (AT) administriert. 1 738 (5,2%) Patienten erhielten sowohl NAT als auch AT. Im GCRG/ADT wurde bei 8 200 Patienten (56,2%) eine perioperative Therapie dokumentiert; davon erhielten 2 165 Patienten (14,8%) eine neoadjuvante Therapie. 5 992 Patienten (41,1%) dagegen adjuvante Therapie. Bei 43 Patienten (0,3%) aus dem deutschen Krebsregister wurde NAT und AT dokumentiert. Chirurgisch-onkologisches TO wurde von 21 198 (63,3%) Patienten in der NCDB und von 11 234 (77,0%) Patienten aus dem GCRG/ADT erreicht. Das kombinierte TO, definiert als die Kombination aus chirurgischem TO und dem Erhalt perioperativer Therapie, wurde bei 16 967 (50,7%) Patienten in der NCDB und bei 7 878 (54,0%) Patienten in der GCRG erreicht. Patienten in der NCDB, die das chirurgisch-onkologische TO erreichten, zeigten eine mediane Gesamtüberlebenszeit (OS) von 29,7 Monaten, im Vergleich zu 22,9 Monaten bei Patienten, die es nicht erreichten (HR: 0,78, 95%CI: 0,76-0,80, $p < 0,001$). Patienten, die das kombinierte TO erreichten, wiesen eine mediane OS von 31,5 Monaten auf, im Gegensatz zu 22,5 Monaten bei denen, die kein kombiniertes TO erreichten (HR 0,73,

95%CI 0,71-0,75, p < 0,001). In den GCRG/ADT-Daten zeigten Patienten mit chirurgisch-onkologischem und kombiniertem TO erhöhte Überlebensraten, mit mittleren OS-Werten von 33,2 bzw. 27,1 Monaten, im Vergleich zu 21,9 bzw. 20,3 Monaten bei denen, die TO nicht erreichten (HR: 0,68 bzw. 0,84, p < 0,001).

Diskussion

Diese Kreuzvalidierungsstudie zwischen der NCDB und der GCRG/ADT liefert Belege für den Einfluss chirurgisch-onkologischer Textbook Outcomes auf die Prognose von PDAC-Patienten der Stadien I-III. Die Vielseitigkeit von "Textbook Outcome" als Maßstab macht es zu einem leistungsstarken Instrument zur Bewertung der Qualität der Versorgung auf verschiedenen Ebenen, vom individuellen Chirurgen bis hin zu gesamten Krankenhäusern. Es trägt dazu bei, breitere Probleme wie soziale Vulnerabilität im Gesundheitswesen anzugehen und ist ein wesentlicher Bestandteil moderner Bemühungen zur Bewertung und Verbesserung der medizinischen Versorgung. Um höchste Relevanz sicherzustellen, ist es wichtig TO an das spezifische Ziel oder den zu messenden Aspekt der Versorgung anzupassen. Die vorgeschlagene Definition des TO bietet eine fokussierte und dennoch prägnante Perspektive auf die Versorgung von Bauchspeicheldrüsenkrebs. Während sie Kernaspekte berücksichtigt, strebt sie danach, allgemeine onkologische Versorgungsziele von kurzfristigen chirurgischen Zielen zu trennen.

Internationale Unterschiede in klinischen Praktiken waren offensichtlich, wie etwa die Rate der entnommenen Lymphknoten; in 26% der NCDB-Fälle wurden weniger als 12 Knoten entnommen, während dies nur bei weniger als 4% der GCRG/ADT-Fälle der Fall war. Die Kreuzvalidierung dieser Studie ergab eine Medianzahl von 17 bis 18 entfernten Lymphknoten. Allerdings wurden bei über 25% der Patienten in der NCDB und nur bei 4% im GCRG weniger als 12 Lymphknoten entnommen. Ungenügende Dissektionsraten korrelierten mit einer schlechteren Gesamtüberlebensrate. Andere Registerstudien haben ähnliche Tendenzen einer unzureichenden Lymphknotendissektion aufgezeigt. Beispielsweise berichtete eine SEER-Registerstudie von Hellan et al., dass bei N0-PDAC-Patienten im Median nur sieben Knoten untersucht wurden, wobei 71% weniger als 11 Knoten untersucht hatten [96].

Das Nichterreichen einer R0-Resektion wird konsistent mit ungünstigen Langzeitergebnissen in Verbindung gebracht [54, 90, 95]. Die aktuelle Kreuzvalidierungsstudie bestätigt diese Befunde. Die Ergebnisse zeigen eine deutliche Verbesserung der medianen Gesamtüberlebensraten: 29 Monate (NCDB) und 35 Monate (GCRG) für Resektionen mit tumor-negativen Rändern, was signifikant höher ist als die 17

Monate (NCDB) und 22 Monate (GCRG), die bei Patienten mit Resektionen mit tumor-positiven Resektionsrändern beobachtet wurden. Eine R0-Resektion wurde bei 79-86% der Patienten, die wegen PDAC der Stadien I-III reseziert wurden, erreicht. Mehrere Studien, darunter aktuelle Arbeiten von Sweigert et al. und Anger et al., weisen R0-Resektionsraten von 77,9% bis 80% für PDAC auf, was den vorliegenden Ergebnissen der Kreuzvalidierungsstudie entspricht [114, 163]. Die internationalen Standards für R0-Resektionsraten sind hoch, wobei Fortschritte in Chirurgie und Bildgebungstechnologien dazu beigetragen haben [14, 181]. Die verbliebenen 20-30% der Patienten mit R1-Resektionen könnten auf präoperative Fehleinschätzungen der Tumorresektabilität zurückzuführen sein.

In der Studie wurde festgestellt, dass nur knapp über 60% der Patienten in beiden Registern chirurgische Textbook Outcomes erreichten. Zusätzlich erhielten nur die Hälfte der Patienten eine perioperative Therapie, und somit erreichten sie das kombinierte chirurgisch-onkologische Textbook Outcome. Die Studie betont die Korrelation zwischen dem Erreichen des Textbook Outcomes und einer verbesserten Langzeitüberlebensrate. Interessanterweise offenbart die aktuelle Studie, dass eine bedeutende Anzahl von Patienten (22% bis 44%) keine perioperative Therapie erhält. Insbesondere das deutsche Krebsregister verzeichnet hohe Quoten von Patienten, die alleinig chirurgisch (44%) behandelt wurden. Diese geringe Nutzung der perioperativen Therapie spiegelt sich in den Gesamtüberlebensraten wider. Die GCRG-Kohorte zeigt ein niedrigeres Gesamtüberleben mit einer medianen Überlebenszeit von 27,1 Monaten, im Vergleich zur NCDB-Kohorte mit 31,5 Monaten. Der Unterschied in den Überlebensergebnissen zwischen den Registern kann größtenteils auf die unterschiedliche Anwendung der perioperativen Therapie zurückgeführt werden. Wenn diese Therapie angewandt wird, verbessert sie signifikant das Gesamtüberleben in beiden Registern. Der Nicht-Erhalt einer perioperativen Therapie steht in direktem Zusammenhang mit schlechteren Langzeitergebnissen. Die längsten Gesamtüberlebenszeiten wurden bei Patienten beobachtet, die neoadjuvante und adjuvante Therapie erhielten (NCDB: 35,5 Monate, GCRG: 46,8 Monate). Interessanterweise war dies auch die perioperative Behandlung, die jedoch nur bei einer Minderheit der Patienten durchgeführt wurde (NCDB: 5,4%, GCRG: 0,3%). Dieser bedeutsame Überlebensvorteil sollte künftig verstärkte Aufmerksamkeit erhalten, um die Möglichkeit einer breiteren Anwendung von neoadjuvanter Therapie kombiniert mit adjuvanter Therapie in PDAC-Behandlungsprotokollen zu prüfen.

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8 Appendix

8.1 Ethics committee approval

UNIVERSITÄT ZU LÜBECK

Ethik-Kommission

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Aktenzeichen: 20-319
Datum: 17. August 2020

Verkürztes Verfahren
Titel: „Multimodale Therapie und Subtypen beim Pankreaskarzinom – Analyse anhand des Registers der Arbeitsgemeinschaft Deutscher Tumorzentren"
Ihr Schreiben vom 11. August 2020

Sehr geehrter Herr Prof. Keck,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Es werden ausschließlich anonymisierte Daten verarbeitet.

Folgende Unterlagen lagen vor:

- Ihr Anschreiben vom 11. August 2020
- Studienprotokoll undatiert

Die Ethik-Kommission nimmt das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis. Eine Behandlung im normalen Antragsverfahren wird nicht für notwendig erachtet.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

8.2 Abbreviations

ADT	*Society of German Tumor Centers - Network for care, quality, and research in Oncology*
AHPBA	*American Hepato-Pancreato-Biliary Association*
AJCC	*American Joint Committee on Cancer*
APC	*Academic/Research Cancer Programs*
AT	*Adjuvant therapy*
AT Alone	*Surgery followed by adjuvant therapy*
BR-PDAC	*Borderline resectable Pancreatic ductal adenocarcinoma*
CA	*Celiac axis*
CA 19-9	*Carbohydrate antigen 19-9*
CI	*Confidence interval*
CT	*Computed tomography*
DCC	*Dedicated cancer center*
DFS	*Disease-free survival*
DP	*Distal Pancreatectomy*
EBRT	*External beam radiotherapy*
ECOG	*Eastern Cooperative Oncology Group*
ELN	*Examined lymph nodes*
G	*Grading*
GCRG	*German Cancer Registry Group*
ICBP	*International Cancer Benchmarking Partnership*
ISGPS	*International Study Group of Pancreatic Surgery*
LA-PDAC	*Locally advanced Pancreatic ductal adenocarcinoma*
LAD	*Lymphadenectomy*
M	*Metastasis*
m	*Months*
mFOLFIRINOX	*Modified FOLFIRINOX*
N	*Lymph node*
nAPC	*Non-Academic/Research Cancer Programs*
NAT	*Neoadjuvant therapy*
NAT + AT	*Surgery accompanied by Neoadjuvant and adjuvant therapy*
NAT Alone	*Neoadjuvant therapy followed by surgery*
NCCN	*National Comprehensive Cancer Network*
NCDB	*National Cancer Database*
OS	*Overall survival*
PD	*Pancreatoduodenectomy*
PDAC	*Pancreatic ductal adenocarcinoma*
PNET	*Pancreatic neuroendocrine tumor*
PPPD	*Pylorus-preserving pancreaticoduodenectomy*
PV	*Portal vein*
QOL	*Quality of life*
R	*Resection margin*
R0	*Tumor negative resection margins*

R1	*Tumor positive resection margins*
RFS	*Recurrence-free survival*
SBRT	*Stereotactic body radiotherapy*
SEER	*Surveillance, Epidemiology and End Results*
SMA	*Superior mesenteric artery*
SMV	*Superior mesenteric vein*
SSAT	*Society for Surgery of the Alimentary Tract*
SSO	*Society of Surgical Oncology*
T	*Tumor*
TO	*Textbook Outcome*
TOO	*Textbook Oncologic Outcome*
UICC	*Union for International Cancer Control*
UKSH	*University Hospital Schleswig-Holstein*
US	*United States*
USNWR	*U.S. News & World Report*
WCRF	*World Cancer Research Fund International*

8.3 List of figures

8.4 List of tables

9 Acknowledgements

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10 Curriculum Vitae

11 List of Publications

Peer-Review Journal Articles:

1. **Petruch N**, Servin Rojas M, Lillemoe KD, et al. The impact of surgical-oncologic textbook outcome in patients with stage I to III pancreatic ductal adenocarcinoma: A cross-validation study of two national registries. Published in Surgery on December 12, 2023. doi: 10.1016/j.surg.2023.11.004. Epub ahead of print. PMID: 38092633.

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Oral Presentations:

Petruch N, Bolm L, Zemskov S, Zeller M, Baba T, Roldan J, Harrison JM, Sato H, Petrova E, Lapshyn H, Braun R, Honselmann KC, Hummel R, Dronov O, Kirichenko AV, Klinkhammer-Schalke M, Kleihues-van Tol K, Zeissig SR, Rades D, Keck T, Fernandez-Del Castillo C, Wellner UF, Wegner RE: "A Cross-Validation of Perioperative Therapy Concepts in the National Cancer Database (NCDB) and the German Cancer Registry of the Working Group of German Cancer Centers (WGCC)."

Presented at the Pancreas Club 2021 Annual Meeting, October 27, 2021, Washington D.C. (Virtual).

Poster Presentations:

Petruch N, Bolm L, Zemskov S, Zeller M, Baba T, Roldan J, Harrison JM, Sato H, Petrova E, Lapshyn H, Braun R, Honselmann KC, Hummel R, Dronov O, Kirichenko AV, Klinkhammer-Schalke M, Kleihues-van Tol K, Zeissig SR, Rades D, Keck T, Fernandez-Del Castillo C, Wellner UF, Wegner RE: "Perioperative Therapy Concepts in Pancreatic Cancer: A Cross-Validation of Two National Registries."

Presented at Deutscher Pankreas Club, January 28-31, 2022, Lübeck, Germany.

Petruch N, Bolm L, Pisuchpen N, Sondermann S, Müller K, Harrison JM, Baba T, Zelga P, Roldan J, May K, Petrova A, Lapshyn H, Honselmann KC, Braun R, Keck T, Wellner UF, Kambadakone A, Férnandez-del Castillo C **:** "Impact of Radiological Borderline Resectability Features on R Status After Neoadjuvant Therapy versus Upfront Surgery."

Presented at the 14th E-AHBPA Congress, September 15-17, 2021, Bilbao, Spain (Virtual).