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The survival benefit of using neoadjuvant therapy for resectable and unresectable tumours in pancreatic cancer patients estimated with multi-centred real-world data of the PURPLE registry.

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Master thesis report

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Foreword

The completion of this master thesis report is the last missing piece for finalising my student career, which has been an enjoyable journey that lasted almost 7.5 years. I had the privilege to meet extraordinary people along the way. I'd like to thank several of them in particularly.

My journey would not have been possible without the help of Regien Bloch, who has been my coach of the Orientation Track. I'm very grateful for her support, thoughts and guidance concerning my study choice and personal development. She wrote "Groei en bloei in Twente" on a piece of paper, which she handed over to me on our last day of the track. I still have it and this phrase reminds me of how happy I'm that I moved to Enschede for studying.

For almost 7 years, Huize Badeendt was my home and I could not think of a better home base to start and conclude my student life with. I thank each and every former housemate for the great time we shared at Calslaan 22. I'll gladly revisit Huize Badeendt each year with Eendtenvoedertijd. A green rubber duck will always accompany me on vacation.

Although Technical Medicine did not suit me very well, I'm eventually happy that choose this particular bachelor program. It did confirm my wish to pursue a profession in the medical domain, but, even more important, I got the chance to meet everyone from the ÜGGG. The name of the group may be poorly chosen, but our friendship remains. I'm in particular grateful for the friendship with Jeroen, Rob, Jasper, Rutger W, and also Rutger A, which was accompanied with coffee at lectures and accompanied with beer and Risk after lectures.

When I came, Kronos was an association of fading glory with a poor training accommodation. When I left, the glory was restored and has bright future ahead on the UTrack. I have to thank Joris, Verena and Tineke for their trust, help and company with the governance of Kronos in 2013-2014. Also, I'd like to express my deepest gratitude to the board of Ruud, Leon, Daniël and Joep, because, in the end, Kronos might have been gone without them.

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Abstract

Introduction: Pancreatic cancer (PC) is the fifth leading cause of cancer-related deaths in Australia. Moreover, the Australian five-year survival rate for PC remains less than 10%. Surgical resection of the tumour is considered as the only chance of cure. However, less than one-fifth of the PC patients is classified as surgical candidates. Neoadjuvant therapy has the potential advantage to improve the resection rate. Meta-analysis have observed the added value of neoadjuvant therapy, but multi-centred randomised trials have not been completed. Real-world data (RWD) are an alternative source of clinical data. This study aimed to analyse the potential survival benefit of using neoadjuvant therapy for resectable and unresectable tumours in PC patients by using multi-centred RWD of the PURPLE registry.

Methods: Data of 1,492 PC patients from 27 hospitals across Australia, New Zealand and Singapore were obtained from PURPLE. The effects of neoadjuvant therapy were studied within three tumour resectability classifications of non-metastatic PCs: potential resectable (PR), borderline resectable (BR), and locally advanced unresectable (LA). The role of the type of therapy, the neoadjuvant regimen, and the therapy duration were analysed as well. Overall survival (OS) was determined as the primary outcome. Kaplan-Meier estimators and Cox Proportional Hazards models were applied as evaluation methods for investigating the role of neoadjuvant therapy to the OS. Backwards stepwise selection was applied for determination of the most valuable features in an attempt to develop a Cox regressive model.

Results: This study identified 648 (43.4%) non-metastatic PC patients, whose tumours were classified as PR (n = 368), BR (n = 118), or LA (n = 162). Twelve (3.2%), 89 (75.4%), and 4 (2.5%) patients received neoadjuvant therapy, respectively. These neoadjuvant therapy patients (n = 105) were younger ($P < 0.001$) and had lower ECOG scores ($P = 0.002$) compared to the group without neoadjuvant therapy (n = 543). The median OS (mOS) was lower for the neoadjuvant therapy group compared to those without neoadjuvant therapy in case of PR tumours (22.7 months vs. 29.9 months $P = 0.58$) and BR tumours (21.6 months vs. 22.1 months; $P = 0.80$). The mOS was higher for LA cases treated with neoadjuvant therapy (17.1 months vs. 14.8; $P = 0.49$). This study was unable to conduct the survival analysis of neoadjuvant chemo-radiotherapy against neoadjuvant chemotherapy alone. FOLFIRINOX resulted in a higher mOS compared to gemcitabine nab-paclitaxel (22.0 months vs. 12.0 months; $P < 0.001$). Neoadjuvant therapy duration of at least 6 cycles had a mOS of 24.4 months and was therefore higher compared the 21.6 months for those with shorter therapy durations ($P = 0.68$). Multivariate Cox regression did not demonstrate neoadjuvant therapy as conclusive prognostic factor (HR: 0.91; $P = 0.81$) and was therefore not adopted as feature in any model proposal due to its insufficient regressive property to the OS.

Discussion & conclusion: This RWD analysis did not provide conclusive evidence to support the hypothesis that neoadjuvant therapy contributes to better survival outcomes for PC patients with either PR, BR or LA classified tumours. Most observations were not supported with a significant statistical test result due to the limited number of patients in certain research arms, the relative short follow-up period, and the influence of potential confounders. However, if neoadjuvant therapy is used, FOLFIRINOX seemed to be the best chemotherapy regimen compared to gemcitabine nab-paclitaxel. We recommend clinicians to discuss neoadjuvant treatment as possible treatment option, which might potentially lead to more variation in PURPLE registry. If more data is available in PURPLE and the follow-up period is majorly increased, then we recommend a re-conduction of the survival analysis and a further identification of potential confounders.

Contents

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List of abbreviations

AGITG	Australasian Gastrointestinal Trials Group
AHPBA	Americas Hepatopancreatobiliary Association
AIHW	Australian Institute of Health and Welfare
BR	borderline resectable
CA	cancer antigen
CCI	Charlson comorbidity index
CI	confidence interval
COSA	Clinical Oncology Society of Australia
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FLX	FOLFIRINOX
FU	fluorouracil
GNP	gemcitabine nab-paclitaxel
IQR	interquartile range
JPS	Japan Pancreas Society
LA	locally advanced
MDACC	M.D. Anderson Cancer Center
MOGA	Medical Oncology Group of Australia
NCCN	National Comprehensive Cancer Network
NCERG	National Cancer Expert Reference Group
OS	overall survival
P	P-value
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
PR	potential resectable
PURPLE	Pancreatic cancer: Understanding Routine Practice and Lifting End results
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	recurrence-free survival
RWD	real-world data
SSAT	Society for Surgery of the Alimentary Tract
SSO	Society of Surgical Oncology
UR	unresectable

1 Introduction

The pancreas is a human organ in the abdomen, located posterior to the stomach, between the duodenum on the right and the spleen on the left. The pancreas is a gland with an exocrine and endocrine function, which is part of the digestive system and the endocrine system, respectively (Moore et al., 2011). Unrestrained cell division may occur in the pancreas and is referred in this thesis as *pancreatic cancer (PC)*.

This chapter of the thesis introduces PC in terms of statistics, diagnosis, and treatments in Sections 1.1, 1.2, and 1.3, respectively. Neoadjuvant therapy is a possible addition to the various treatment options for PC and is therefore discussed in Section 1.4. Real-world data reflects on the actual usage and benefits of therapies in practice and is therefore introduced in Section 1.5. This chapter is concluded with Section 1.6, which describes the intention of the study of this master's thesis.

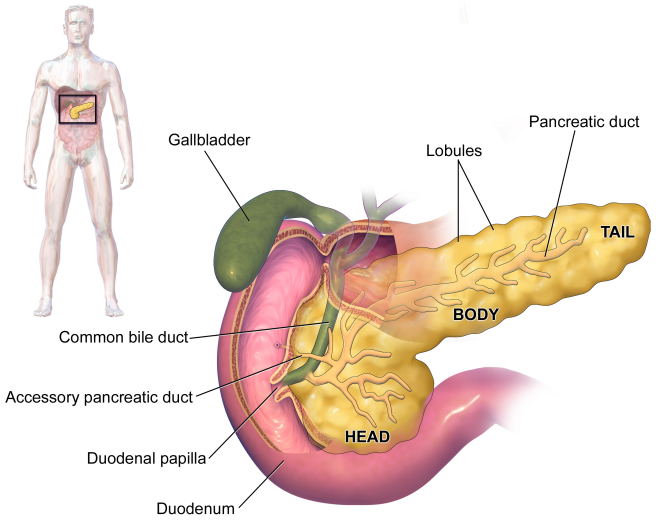

Figure 1.1: The anatomy of the pancreas (Blausen Medical, 2014).

1.1 Pancreatic cancer statistics

The pancreatic ductal adenocarcinoma (PDAC) accounts for the majority of all PC type occurrences (Moore et al., 2011). Adenosquamous carcinoma and undifferentiated carcinomas with osteoclast-like giant cells are other variants of PC. Observations, reported by the European Society for Medical Oncology (ESMO), have shown that PC generally develops in the head and neck of the pancreas (60%-70%), but PC occurs likewise in the body and tail (20%-25%), or in the whole organ (10%-20%) (Ducreux et al., 2015).

Studies around the globe have been reporting that PC is one of the most lethal cancer types worldwide, with a mortality rate almost equal to the incidence rate (Torre et al., 2015). From an Australian point of view, comparable observations were reported by Cancer Australia (2019), given the estimated annual incidence of 3,364 Australian citizens and annual mortality estimation of 3,006 people, resulting in a mortality-incidence ratio of 0.89. PC was therewith determined as the fifth leading cause of cancer-related deaths is Australia in 2018. Moreover, the overall survival (OS) rate from PC is equally limited for males and females in Australia, despite an increase in the average 5-year survival from 3.3% in 1986-1990 to 9.8% in 2011-2015, as displayed in Figure 1.2.

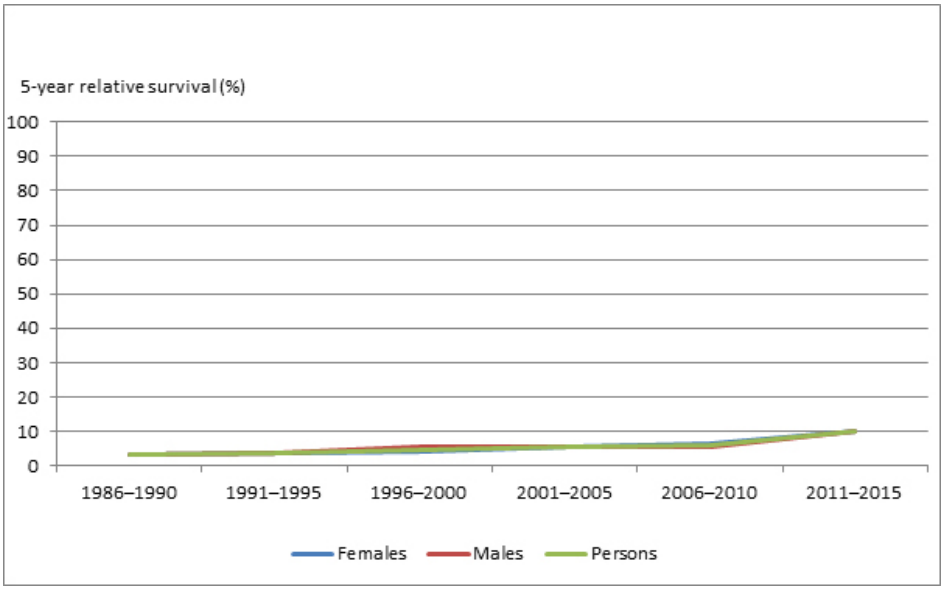

Figure 1.2: 5-year relative survival from pancreatic cancer, by sex with data from 1986–1990 to 2011–2015 (Cancer Australia, 2019).

The rather limited OS is affected by two phenomenons: cancer stage and recurrence. On one hand, Yu et al. (2012) observed, from population-based cancer data registry of New South Wales, that the majority of the PC patients (53%) were diagnosed with cancer stage IV, and that these patients had worse survival compared to other three cancer stages. Simultaneously, long-term survival is limited by the recurrence of PC, which is common in 5-year survivors, thus Speer et al. (2012). According to their analysis in Victoria, only sixteen (2.1%) of the 747 patients were confirmed to be alive after 6 years of follow-up.

1.2 Presenting symptoms and diagnosis

The survival from PC is highly depending on the presentation of symptoms. In the end, an early discovery of PC would benefit the OS outcomes in the short- and long-term, as stated by the National Cancer Expert Reference Group (NCERG). Pancreatic tumours located in the head and neck of the pancreas commonly cause PC-symptoms, whereas tumours in the body and tail are less presenting and the cancer remains therefore easily undetected (Artinyan et al., 2008). Nevertheless, the most common presenting symptoms are jaundice (64%), pain (63%), and weight loss (54%), but anorexia, vomiting, and lethargy were also reported by Wylie et al. (2013). Ducreux et al. (2015) added steatorrhoea and new-onset diabetes as other presenting symptoms.

A computed tomography (CT) scan of the abdomen is the most commonly used diagnostic method in case of a clinical suspicion of PC or evidence of a stricture of the bile duct, according to the clinical guidelines of National Comprehensive Cancer Network (NCCN) written by Tempero et al. (2017). Depending on the results of the CT-imaging, additional diagnostic methods may be considered for non-metastatic diseases, such as endoscopic ultrasonography, liver function tests, chest-CT, magnetic resonance imaging, or endoscopic retrograde cholangiopancreatography. Moreover, biopsies are performed to clarify the metastatic site of the tumour when the tumour is suspected as such. Furthermore, high blood levels of the protein *cancer antigen (CA) 19-9* are often an indication of PC, making CA 19-9 the most useful *biomarker*, but remains unusable for primary diagnosis (Ducreux et al., 2015).

1.3 Treatment options

The treatment strategy depends on the severity of the PC stage. Possible treatment options are categorised in *curative therapy*, *anti-cancer therapy* (without expectation of cure), and *palliative care* (NCERG, 2016). Early staged and locally advanced tumour cases are considered for curative surgery, which results in a surgical removal of the pancreatic tumour. Otherwise, these patients are referred to chemo(-radiation) therapy for minimising the probability of a metastatic disease. Patients with metastatic diseases are primary considered as incurable and ultimately receive palliative care. Nonetheless, these patients might be considered for a clinical trial enrolment with potential positive health and survival outcomes.

1.4 Potential and implementation of neoadjuvant therapy

As mentioned in the previous section, the surgical removal of the tumour, referred in this report as *tumour resection*, is generally considered as the only potential chance of curing PC (Tempero et al., 2017). Alas, only 8% till 12% of the PC patients are considered as surgical candidates, according to NCERG (2016). A consideration rate, or *resection rate*, between the 15% and 20% is given in the introduction of the review by Russo et al. (2016). So, less than one-fifth of the PC patients qualifies for a curative surgery. This low resection rate is confirmed by pancreatic medical oncologist dr. Belinda Lee, who has been providing clinical expertise to this thesis.

Preoperative therapy, referred in this report as *neoadjuvant therapy*, is the application of chemotherapy or chemo-radiation therapy prior to the patient's surgery. The review of Desai et al. (2015) summarised the potential advantages and disadvantages of the usage of neoadjuvant therapy in the PC domain, as reported in Table 1.1. Improving the resection rate is one of the potential advantages, in which the neoadjuvant therapy aims to convert the unresectable tumour into a resectable one by shrinking, or *down-staging*, the tumour. This particular advantage is also acknowledged by the Australasian Gastrointestinal Trials Group (AGITG), stating that neoadjuvant therapy might lead to better selection of patients for tumour resection (Segelov et al., 2017).

However, the disadvantage of neoadjuvant therapy is the limited opportunity window to surgically treat PC. In other words, it might be undesirable to provide any neoadjuvant therapy to those who are already considered as resection candidates, because *unresectability* is the potential consequence due to the opportunity for the tumour to grow even further when the tumour resists the intended effects of the neoadjuvant therapy (Desai et al., 2015).

Table 1.1: Potential advantages and disadvantages of the application of neoadjuvant therapy in pancreatic cancer patients (Desai et al., 2015).

Advantages	**Disadvantages**
Intact tumour vasculature not disrupted by surgery.	Progression of disease during neoadjuvant treatment leading to missed window of opportunity for resection.
Early treatment of micrometastatic disease.	Toxicity from neoadjuvant treatment precluding definitive surgical resection.
Ensures delivery of systemic treatment.	Need tissue confirmation of neoplastic process.
Improved R0 resection rate, especially in borderline resectable cases.	
Ideal in vivo platform for research.	

The application of the neoadjuvant therapy as treatment option has been adopted in the clinical guidelines of the United States and Europe by the NCCN and the ESMO, respectively. Neoadjuvant therapy is generally recommended for patients with a pancreatic tumour close to the main arteries and vessels of the pancreas, as summarised in the overview of Figures A.1 and A.2 of the Appendix. The NCCN and ESMO guidelines do admit though that there is still "limited evidence to recommend specific neoadjuvant regimens off-study and practices vary with regard to the use of chemotherapy and radiation" (Tempero et al., 2017).

The scientific uncertainty could be the reason why neoadjuvant therapy is not prominently recommended by the Australian Cancer Council in the guidelines of the NCERG (2016), as summarised in Figure 1.3. In fact, the potential advantage of increasing the resection rate for (unresectable) PC cases is not mentioned in the guidelines. The treatment of unresectable tumours is solely focused on palliative care. Any motivation of rejecting the possibilities of neoadjuvant therapy for the initial unresectable tumours is not included in the report of the NCERG. Other sources have been consulted to find more information concerning general recommendations for clinical practice in Australia, but Clinical Oncology Society of Australia (COSA), Medical Oncology Group of Australia (MOGA) or Australian Institute of Health and Welfare (AIHW) have not communicated any general guidelines or recommendations about neoadjuvant therapy for PC.

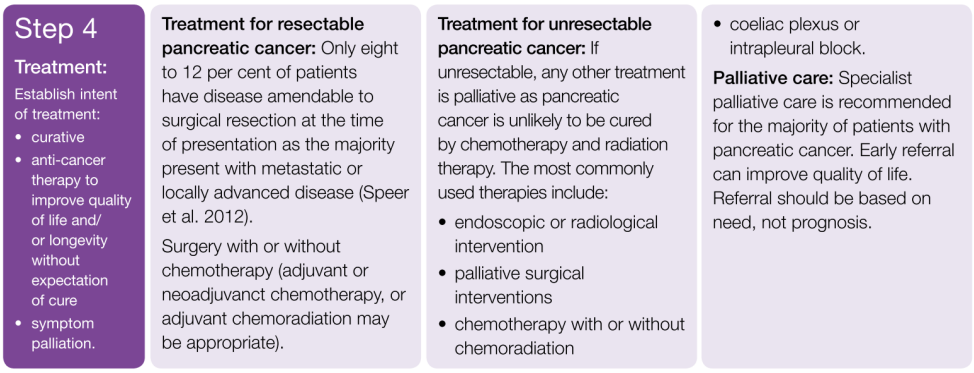

Figure 1.3: Summary of the treatment options for resectable and unresectable pancreatic cancers according to the National Cancer Expert Reference Group (NCERG, 2016).

1.5 Real-world data analysis

The most conventional way of demonstrating the added value of an intervention, compared to the standard care, is by means of a multi-centred randomised controlled trial (RCT), also known as phase III study. This type of research needs a great number of patients to demonstrate the power of the trial and might therefore lead to difficulties in the recruitment of patients. This issue led to the cancellation of two phase III studies about neoadjuvant therapy in PC (Segelov et al., 2017). Up to now, no phase III study has been completed and it remains challenging to deliver any significant observations about the intervention of neoadjuvant therapy by means of these trials.

Although neoadjuvant therapy is not widely recommended in Australia due to limited multi-centred scientific publications, that does not automatically mean that this preoperative therapy has not been applied at all. Some patients may have been enrolled in a clinical trial and others might be treated with neoadjuvant therapy on the basis of the clinician's and/or patient's preference. These variations within a medical centre, or between medical centres, are documented in the health records. Accessing these observational data, or *real-world data (RWD)*, would shed a light on the actual usage of neoadjuvant therapy and accompanying outcomes for PC patient from an Australian perspective. Hence, RWD might be seen as substitute to the absent phase III studies.

RWD is defined by the U.S. Food and Drug Administration (2019) as "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources". This is one perspective of RWD, but an overall definition is not agreed upon by reviewing relevant literature and interviewing relevant stakeholders (Makady et al., 2017). RWD may be derived from electronic health records, making RWD observational and therefore different from experimental data used in RCTs, thus the U.S. FDA.

Since 2016, Pancreatic cancer: Understanding Routine Practice and Lifting End results (PURPLE) is a world-leading PC registry, which contained 1,492 patients from 27 medical centres across Australia, New Zealand and Singapore on 29 November 2019. PURPLE aims to increase data sharing and collaboration between the cancer centres "to combat the alarming trend" of PC incidence and mortality in Australia (BioGrid, 2019). PURPLE may be considered as a source of RWD and is therefore used in this research for a further clarification of the survival outcomes following the usage neoadjuvant therapy.

1.6 Intention of the study

This section will discuss the intention of the study via the problem formulation, the study objective and main research question, the scope, and the further outline of this report in Subsections 1.6.1, 1.6.2, 1.6.3, and 1.6.4, respectively.

1.6.1 Problem formulation

This chapter has provided an overview about the occurrence of PC in Australia and an introduction to the potential of neoadjuvant therapy in the treatment pathway for PC. This chapter discussed the following observations and statements:

(i) PC is one of the most lethal cancer types in Australia with a 5-year survival of less than 10% ever since this was first monitored in 1984;

(ii) Surgical resection of the tumour is considered to be the only cure to PC;

(iii) Less than 20% of the PC patients is classified as surgical candidates;

(iv) Neoadjuvant therapy has the potential advantage to convert an unresectable tumour into resectable one, which would increase the resection rate;

(v) Progression of the cancer in resectable tumours is the potential disadvantage of neoadjuvant therapy, which would decrease the resection rate;

(vi) Clinical guidelines from the U.S. and Europe have adopted neoadjuvant therapy as treatment option, but Australia has not, due to a lack of multi-centred RCT publications;

(vii) No phase III study has been completed about neoadjuvant therapy in PC due to the difficulties with recruiting patients;

(viii) Multi-centred RWD of PURPLE are potential valuable sources of clinical information which could clarify the effects of neoadjuvant therapy on the survival outcomes.

So, one can derive from these observations and statements that there is still an urgency to further investigate the effects of various treatment options to improve the resectability of PC tumours in Australian patients. Resection of the tumour is the only potential cure to PC, but not everyone is suitable for this procedure. Neoadjuvant therapy has the potential to improve the resectability, which might lead to more surgeries and therefore better survival outcomes for individual PC patients. Alas, the effectiveness of this preoperative therapy is still discussed, and multi-centred RWD provides thus a new view on the matter, which could lead to a further optimisation of the clinical practice and, moreover, the survival of patients who suffer from PC.

1.6.2 Study objective and main research question

The aim of this master's thesis was to investigate retrospectively the potential survival benefit of using neoadjuvant therapy for resectable and unresectable tumour in PC patient by analysing multi-centred RWD of the PURPLE registry. Hence, the following main research question is formulated:

What is the survival benefit of using neoadjuvant therapy in pancreatic cancer patients estimated with multi-centred real-world data collected in the PURPLE registry?

1.6.3 Scope of the research

This research focused on the tumour resection rates and survival outcomes of the eventual usage of neoadjuvant therapy in non-metastatic pancreatic cancer patients from Pancreatic cancer: Understanding Routine Practice and Lifting End results (PURPLE) registry and is limited by the available documented data in this particular registry.

1.6.4 Outline of the report

The report consists of multiple chapters that are necessary to answer the research questions.

Chapter 2 (Literature review) will provide an retrospective in-depth analysis about the scientific attempts to assess the added value of neoadjuvant therapy to the survival outcomes of PC patients with either resectable or unresectable tumour.

Chapter 3 (Methods) will discuss the manner in which this study selects the population of interest and the most important techniques for analysing associations and regressions of clinical factors with the survival outcomes by using RWD.

Chapter 4 (Results) will summarise the most important findings of the survival analysis from three research perspectives.

Chapter 5 (Discussion) will compare the main findings of this research with the observations from other authors about neoadjuvant therapy in the PC domain. Furthermore, the main limitations of the study are being presented.

Chapter 6 (Conclusion) will complete the report with the conclusions and recommendations. The main research question will be answered in this particular chapter.

2 | Literature review

Chapter 1 addressed the severity of PC in Australia and the urgency to look further into the potential added value of neoadjuvant therapy to the patients with resectable and unresectable pancreatic tumours. This chapter of the master's thesis report provides an overview of the recent published literature about the influence of neoadjuvant therapy to the resectability of the tumour and the OS of patients. The search matrix, which has been used to find the available literature, is attached to this report in Table B.1 of the Appendix.

Firstly, Section 2.1 explains the manner in which the resectability of the patient's tumour is determined. Thereafter, Section 2.2 shortly discusses the treatment options for various classified patient groups according to the American and European clinical guidelines. Systematic reviews and meta-analysis about neoadjuvant therapy in PC have been published since 2010 and their main findings and limitations are discussed in Section 2.3. In addition, Sections 2.4 and 2.5 describe several mathematical models and RWD studies, respectively, which assessed the benefits of neoadjuvant therapy. This chapter is finalised with a summary and conclusion in Section 2.6.

2.1 Resectability of the tumour

The diagnosis is commonly determined by means of a CT scan of the abdomen when there is significant suspicion of PC. Clinicians primarily focus on the presence of a pancreatic tumour, because presenting symptoms might be caused by something else. Secondly, if a pancreatic tumour is present, then the tumour stage is determined and one assesses whether there is any *tumour-vessel involvement*, which is any direct contact of the tumour with a main artery or vein, close or within the pancreas (Tempero et al., 2017). The gradation of tumour-vessel involvement influences the possibilities of curative surgical removal of the tumour. The so-called *resectability* of the tumour is evaluated and classified as precise as possible from the CT scan, as further explained in Subsection 2.1.1. International guidelines differ in their criteria of *resectability classification* and the consequences of these variations are shortly discussed in Subsection 2.1.2.

2.1.1 Tumour classification based on tumour involvement with blood vessels

The outcome of the abdominal CT is crucial to decision-making process and possible management of the patient's PC. A minimal tumour-vessel involvement increases the probability for patients to be considered as surgical candidates. The celiac artery, the common hepatic artery, and the superior mesenteric artery are evaluated for arterial tumour involvement using the CT-imaging of the pancreas. Any venous tumour-vessel involvement is determined by studying the portal vein and superior mesenteric vein on the CT image.

Based on the involving tumour-vessel gradation, tumours are thereafter classified into four groups: *potential resectable (PR)*, *borderline resectable (BR)*, *locally advanced (LA) unresectable*, and *unresectable (UR)*. This tumour classification reflects on the resectability of the tumour and therefore determinative for the decision-making about the treatment. Patients without any tumour-vessel involvement, as displayed in Figure 2.1A, are classified as PR or resectable, considering them as surgical candidates for tumour resection. However, if any minor contact is detected between the tumour and one of the vessels, but the tumour surrounds less than 180 degrees in the cross-sectional plane of the vessel, as seen in Figure 2.1B, tumours tend to be classified as BR, but they might be considered as LA as well. Patients are mostly considered as LA when the tumour majorly involves at least 180 degrees in the cross-sectional plane of the vessel, as shown in Figure 2.1C. The resectability of BR and LA patients is debated within multidisciplinary setting of the clinic due to the various resectability criteria in international guidelines. Patients with a metastatic cancer are categorised as UR and are subsequently referred to palliative care (Tempero et al., 2017).

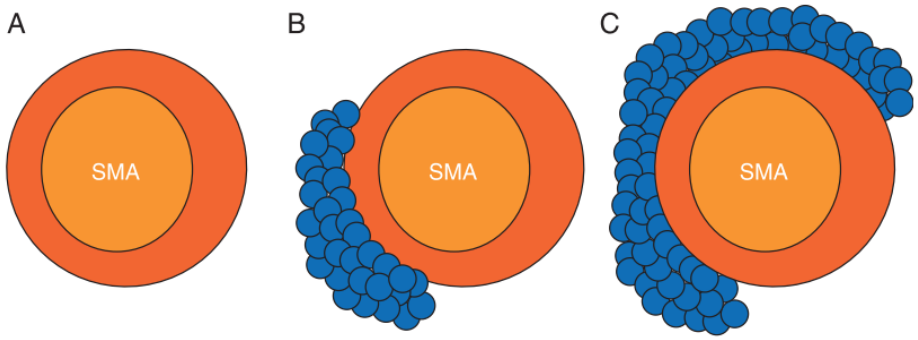

Figure 2.1: Schematic figure of tumour-vessel involvement around the superior mesenteric artery (SMA) in the cross-sectional plane (Gilbert et al., 2017). **A:** no tumour-vessel involvement. **B:** tumour-vessel involvement of less than 180 degrees. **C:** tumour-vessel involvement of more than 180 degrees.

2.1.2 The influence of classification criteria

As mentioned in Subsection 2.1.1, there remains uncertainty concerning the definition of BR and LA tumours. The gradation of tumour-vessel involvement is worldwide discussed. Unfortunately, a standard definition of resectability has not been developed in the PC domain due to a lack of consensus between major guidelines (Gilbert et al., 2017, Russo et al., 2016). M.D. Anderson Cancer Center (MDACC), Alliance A021101, NCCN, Americas Hepatopancreatobiliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT), and Japan Pancreas Society (JPS) classification 7th edition are five prominent sources of classification criteria regarding the resectability of the tumour, but they use slightly different anatomic criteria to classify patients into BR or LA. These variations are summarised in Figure A.3 of the Appendix. It could vary from hospital to hospital which guidelines are used for the tumour classification process.

The variations in the guidelines have drastic consequence for the individual tumour classification, which has been demonstrated by Katz et al. (2012) by comparing the MDACC guidelines with AHPBA/SSO/SSAT guidelines. In this study, 129 BR patients were reclassified, for which 122 (95%) patients were considered as BR following the guidance of AHPBA/SSO/SSAT, whereas only 77 (60%) patients were seen as BR using the MDACC criteria. The remaining 52 patients from the MDACC criteria were classified as PR, while the remaining seven patients from the AHPBA/SSO/SSAT criteria were tagged as LA. Fig-

ure 2.2 summarises these classification findings of Katz et al. (2012). So, this study exposed the danger of the inconsistency between prominent guidelines with up- and down-scaling as consequence. The probability of referral for tumour resection is certainly influenced by using one over the other four published guidelines.

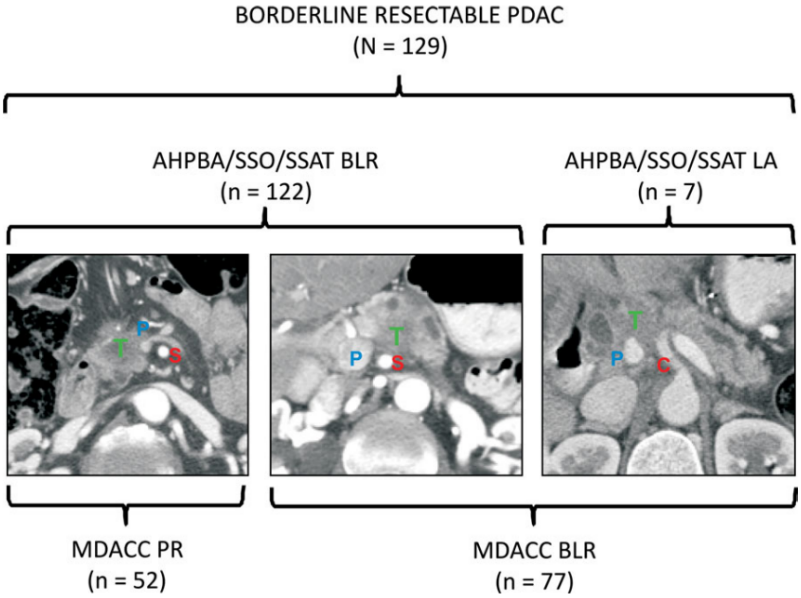

Figure 2.2: Variations in tumour classification of borderline resectable pancreatic ductal adenocarcinoma (PDAC) tumours based on CT using the guidelines from Americas Hepatopancreato- biliary Association (AHPBA), Society of Surgical Oncology (SSO) and Society for Surgery of the Alimentary Trac (SSAT), and guidelines from the M.D. Anderson Cancer Center (MDACC) (Katz et al., 2012).
PR: potential resectable; *BLR*: borderline resectable; *LA*: locally advanced unresectable; *C*: celiac artery; *P*: portal vein; *S* mesenteric artery; *T*: tumour.

2.2 Guidelines for neoadjuvant therapy

The majority of the diagnosed PC cases are labelled as metastatic and will not be referred for any curative therapy. The remaining minority of the patients will be classified as PR, BR or LA, but less than one-fifth of those patients are amendable for surgical resection, as discussed in Section 1.3. A limited number of resection candidates could cause lagging survival outcomes for the entire PC population and individual patients. Therefore, it might be desirable to apply neoadjuvant therapy to increase the resection rate, because, ultimately, surgical removal of the tumour is the only potential possibility of curing PC.

As discussed in Chapter 1, the American NCCN and European ESMO guidelines have adopted neoadjuvant therapy as treatment option in the PC domain, as seen in the publications of Tempero et al. (2017) and Ducreux et al. (2015), respectively. Both guidelines use the NCCN tumour classification criteria, which are attached to this report in Appendix A.4. The two guidelines have similarities in their recommendations concerning the treatment options for PR and BR patients, but they differ with regard to LA patients, as displayed in Table 2.1. Firstly, neoadjuvant therapy is not recommended for those who are classified as PR and this might have to do with limited surgical opportunity window as stated by Desai et al. (2015), but is not explicitly motivated in both guidelines. Instead, PR cases are directly referred to surgery. Secondly, if biopsy confirms the presence of PC, then BR patients should receive neoadjuvant therapy instead of upfront surgery, because of the well-tolerated

outcomes of neoadjuvant therapy in BR patients from several trials, like Gillen et al. (2010) and Assifi et al. (2011). Thirdly, LA patients are not considered for neoadjuvant therapy in guidelines by ESMO, because it is "too early" to conclude anything from the promising results for down-staging LA tumour, thus Ducreux et al. (2015). Tempero et al. (2017), on the other hand, stated in the NCCN guidelines that in unique cases, when a significant tumour response is observed due to neoadjuvant therapy, LA patients may be considered as surgical candidates for tumour resection. Otherwise, without any significant response, this therapy is considered as palliative care. A schematic (simplified) overview of the NCCN and ESMO guidelines are included in Appendix A.1 and A.2, respectively.

Table 2.1: Recommendation of the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) about the use of neoadjuvant therapy for certain tumour classifications within the pancreatic cancer domain.

	NCCN	**ESMO**
Resectable (PR)	Not recommended	Not recommended
Borderline Resectable (BR)	Recommended	Recommended
Locally Advanced (LA)	Recommended	Not recommended

2.3 Systematic reviews and meta-analysis

Many prospective and retrospective phase I and II studies have been conducted over the last five decades to gain more clarity about the advantages and disadvantages of neoadjuvant therapy in the PC domain. No multi-centred RCTs (phase III studies) were published so far. However, the conducted phase I and II studies were bundled in the first systematic review and meta-analysis by Gillen et al. (2010). This publication is quite comprehensive and may thus be considered as the starting point for a better understanding of neoadjuvant therapy in PC, moreover because this study is cited by the NCCN and ESMO for the development of their clinical guidelines. Hence, this thesis highlights the most important observations and limitations from this study in Subsections 2.3.1 and 2.3.2, respectively. In addition, comparable meta-analysis have been published since Gillen et al. (2010) and their findings are shortly highlighted in Subsection 2.3.3.

2.3.1 Observations from Gillen et al. (2010)

The study of Gillen et al. (2010) included 111 studies from 1966 to 2009, of which 78 were prospective (phase I, I/II, and II) and 33 were retrospective. All studies together contained a comined study population of 4,394 PC patients, with a median of 31 patients per study. Two major conclusions were drawn from the meta-analysis of Gillen et al. (2010) with regard to the effects of neoadjuvant therapy on the patient's survival outcomes. The accompanying survival medians and resection rates of these two conclusions are displayed in the summary overview of Figure 2.3 from the review of Gillen et al. (2010).

First, patients with an initial resectable tumour (10%-20%) did not seem to benefit from the application of neoadjuvant therapy compared to upfront surgery (with subsequent adjuvant therapy). The median survival of patients with neoadjuvant therapy was 23.3 months, which was similar to the survival of those with the opposing upfront surgery with adjuvant therapy. Also, the resection rate was 73.6% (95% CI: 65.9% - 80.6%) for the neoadjuvant therapy group, which is a slightly lower rate compared to the upfront surgery group (78%-96%).

Second, 33.2% (95% CI: 25.8% - 41.1%) of the unresectable PC tumours (BR and LA) were converted into resectable tumours after applying neoadjuvant therapy. Moreover, these particular patients gained a median survival of 20.5 months, which is a similar survival outcome as that of those who were initially classified as resectable.

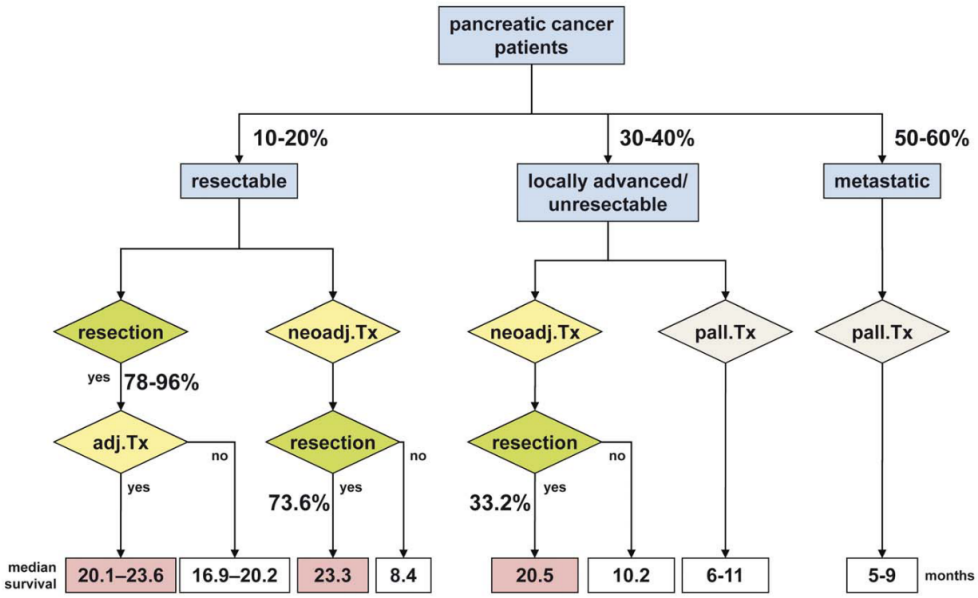

Figure 2.3: Overview of the median survival and resection rate of the resectable arm, unresectable (borderline and locally advanced) arm, and the metastatic arm (Gillen et al., 2010).

So, the usage of neoadjuvant therapy resulted in an increase of the surgical candidates for initially unresectable tumours and therefore improved the survival outcomes for these particular patients. This phenomenon relates back to one of the potential advantages of neoadjuvant therapy from Desai et al. (2015) about increasing the resection rate and thus a better selection of surgical candidates. However, neoadjuvant therapy for initially resectable tumour did not seem to improve the survival outcomes and decreased the resection rate to 73.6%, possibly due to the missed opportunity window for resection, which is one of the potential disadvantages mentioned by Desai et al. (2015), as seen in Section 1.4.

2.3.2 Limitations from Gillen et al. (2010)

This systematic review, and its meta-analysis, has several limitations. Some main limitations are itemised in this subsection.

- The meta-analysis was based on 111 studies, but none were phase III studies. The median study population was around the 30 patients. Together with the non-randomised characteristic of the included prospective and retrospective studies, the limited study populations might have resulted in a possible selection bias.
- In addition, the conclusions of Gillen et al. were based on the descriptives from the included studies. In other words, Gillen et al. did not posses any patient-level data and were therefore constrained by what was reported by the authors of the included study. Direct group comparison was not possible in this meta-analysis, so the influence of potential confounders was not tested, such as patient characteristics, conditional features, tumour details, regimen and duration decisions, and surgery type.

- To assess the survival estimations, Gillen et al. had to assume that there was time-independent hazard rate and a similar censoring rate due to lost to follow-up. But, in reality, the hazard might change over time and it can differ per study why and how many patients drop out of a trial. So, the survival analysis are not fully truthful.
- The guidelines with the resectability criteria are variable between the individual studies. The criteria of the NCCN were used in seven (6.3%) studies. Forty-five studies had clearly defined criteria of resectability, but it is unsure whether one of the five prominent guidelines was used as basis. Also, the resectability criteria were not clearly stated or not stated in 59 studies (53.2%). As seen in the example of Katz et al. (2012) in Subsection 2.1.2, unclear definition of resectable and unresectable tumours influence the classification of patient's tumour and therefore the outcomes of the survival analysis. More than half of the included studies did not clarify their definition of tumour resectability and this may be considered as a major limitation to the results.
- Clinical practices change over time, so published articles from 1966 might not represent the clinical practice of articles from 2009, which could have affected the observation from the included studies. Even the studies from recent history might be considered as outdated, for instance because chemotherapy regimen FOLFIRINOX was available for clinical practice since 2010 and is now considered as one of the most important chemotherapy drugs in the neoadjuvant setting, but its effects are obviously not taken into account in this meta-analysis, so one might question the clinical relevance based on specific clinical details.
- As displayed in Table 2.2, the resection rates might be skewed, because not all patients were examined, or *explored*, for their resectability: 88.1% (95% CI: 82.9% - 92.4%) of the resectable tumours were explored, which is significantly higher than the rate of just 46.9% (95% CI: 36.9% - 57.1%) for the group with the initial unresectable tumours. Moreover, the resected-explored ratio is also significantly different between resectable and unresectable tumours: 85.7% (95% CI: 78.9 - 91.2%) versus 69.9% (95% CI: 61.2% - 77.9%), respectively. These contrasts in exploration rates between resectable and unresectable tumours should be taken into consideration while presenting the promising one-third resection rate for unresectable tumours.

Table 2.2: The exploration and resection rates of the resectable tumours (Group 1), unresectable tumours (Group 2), and all tumours after the neoadjuvant therapy application (Gillen et al., 2010).

Group	**Explored/All (95% CI)**	**Resected/All (95% CI)**	**Resected/Explored (95% CI)**	**R0 resection/Resected (95% CI)**
Resectable	88.1% (82.9%-92.4%)	73.6% (65.9%-80.6%)	85.7% (78.9%-91.2%)	82.1% (73.1%-89.6%)
Unresectable	46.9% (36.9%-57.1%)	33.2% (25.8%-41.1%)	69.9% (61.2%-77.9%)	79.2% (72.4%-85.2%)
All	*69.5% (62.1%-76.4%)*	*50.7% (44.0%-57.4%)*	*77.9% (72.4%-82.9%)*	*79.6% (74.8%-83.9%)*

The systematic review adds a new chapter in the pancreatic neoadjuvant therapy domain by comprehensively reviewing that initially unresectable staged tumour may be resectable in one-third of the cases when neoadjuvant therapy is applied. But this result should be taken cautiously if one would take into account the study's limitations. New questions raise as a result of the limitations to this meta-analysis, especially with regard to the possible

confounders that affect the survival outcomes, which should be considered in the analysis of this thesis.

2.3.3 Other work since Gillen et al. (2010)

Since Gillen et al. (2010), other meta-analysis have also aimed for a better understanding of the added value of neoadjuvant therapy for the several PC patients populations. Firstly, Assifi et al. (2011) analysed 14 phase II studies (n = 536 patients) and found similar post-neoadjuvant results as Gillen et al.: resection rate of 65.8% for initially resectable tumours and 31.6% for BR/LA tumours, and comparable median survivals of 23 months and 22 months, respectively.

Patient-level data of 315 PC patients with LA tumours from 11 studies were used in the meta-analysis of Suker et al. (2016). The resection rate was observed to be 25.9% after the provision of FOLFIRINOX as neoadjuvant chemotherapy regimen. The accompanying pooled median survival was determined at 24.2 months.

Furthermore, Schorn et al. (2017) determined from 35 studies that neoadjuvant therapy reduced the tumour size and lymphatic nodes, and increased R0 (microscopic negative margin) resection rates, favouring neoadjuvant therapy over upfront surgery for BR and LA patients.

Versteijne et al. (2018) reviewed 38 studies (n = 3,448 PR/BR patients) and reported a lower resection rate (66%) for neoadjuvant therapy group compared to upfront surgery group (81%), but, ultimately, the weighted median OS was better for patients with neoadjuvant therapy compared to the upfront surgery: 18.8 months versus 14.8 months.

In summary, Gillen et al., and other analysis, have demonstrated that the advantages and disadvantages of neoadjuvant therapy from Desai et al. are more than just potential. Although there remains limitations to the studies, these observation justify any reconsideration to the role of neoadjuvant therapy as treatment option for PC patients in clinical practice guidelines, like the ones from the NCCN and the ESMO.

2.4 Decision trees and Markov models

Models have been created to contribute to the development of optimal care pathways within the PC domain. As displayed in Table 2.3, eight studies have been conducted which hypothetically tested the added value of an intervention compared to a comparator. This added value is expressed in, among other things, OS, disease-free survival, and cost-effectiveness. This section highlights the most important findings of these models.

Just like the meta-analysis from Section 2.3, the models of Van Houten et al. (2012), Abbott et al. (2013), de Geus et al. (2016), and Bradley & Van Der Meer (2019) were interested in the added value of neoadjuvant therapy as alternative to the upfront surgery. Their models favoured this pre-operative intervention over upfront surgery, although they all solely focus on PC patients with PR tumours. This particular focus is striking, because neoadjuvant therapy is not recommended by any of the clinical guidelines for PR tumours.

On the other hand, Choi et al. (2018) created a Markov model in which neoadjuvant chemotherapy of FOLFIRINOX (FLX) was compared to upfront surgery with adjuvant chemotherapy and patient group of interest consisted of BR and LA hypothetical patients. The usage of FLX favoured over the comparator, but this conclusion was drawn from a hypothetical co-

hort of one million individuals, whereas Van Houten et al. (2012) and Abbott et al. (2013) used patient-level information from studies or data bases.

Furthermore, metastatic patient cohorts were also adopted in the Markov models of Tam et al. (2013) and Attard et al. (2014), in which the authors observed FLX as the best alternative regimen for first-line neoadjuvant chemotherapy compared to gemcitabine. By researching patient-level information from 21 prospective studies, Sharma et al. (2015) concluded that neoadjuvant chemotherapy is preferred over adjuvant chemotherapy for PR tumours in terms of survival outcomes.

These studies have attempted to provide a modelling view on the decision-making process in the PC domain. Neoadjuvant therapy is unanimously favoured over the alternatives. However, these conclusions should be interpreted with caution, because these models created a hypothetical view on reality. This is especially the case for the Markov models due to used a fixed time frame for the health status. Discrete event simulations are able to cope with the complexity of patient-level details in empirical studies (Standfield et al., 2014), but, for what we know, such simulations have yet not been developed for any neoadjuvant therapy purposes.

Table 2.3: Published studies with mathematical model about the pancreatic cancer domain. Abbreviations: adjuvant chemotherapy (AC), borderline resectable (BR), FOLFIRINOX (FLX), health status (HS), locally advanced (LA), neoadjuvant chemotherapy (NAC), potential resectable (PR), radio-therapy (RT), unresectable (UR).

Author and year	**Model type**	**Patient group**	**Intervention**	**Comparator**
Van Houten et al. (2012)	Decision tree	PR	NAC	Upfront surgery
Abbott et al. (2013)	Markov model 1 month HS	Unknown	NAC-RT	Upfront surgery
Tam et al. (2013)	Markov model 1 month HS	Metastatic UR	NAC-FLX	NAC-gemcitabine
Attard et al. (2014)	Markov model 1 week HS	Metastatic UR	NAC-FLX	NAC-gemcitabine
Sharma et al. (2015)	Markov model 1 month HS	PR	NAC	AC
de Geus et al. (2016)	Markov model 3 months HS	PR	NAC	Upfront surgery
Choi et al. (2018)	Markov model 1 month HS	BR and LA	NAC-FLX	Upfront surgery + AC
Bradley & Van Der Meer (2019)	Markov model 1 month HS	PR	NAC	Upfront surgery

2.5 Real-world data publications

To the best of our knowledge, the retrospective study of Itchins et al. (2017) is the only RWD study worldwide about neoadjuvant therapy within PC. Patient records from two hospitals in Northern Sydney were obtained and, between 2010 and 2016, 87 PC patients were treated with neoadjuvant therapy, whereas 133 patients underwent upfront surgery instead. The authors determined a median OS of 25.9 months for the neoadjuvant group and 26.9 months for the upfront surgery group. Though the study population was relative small and the result is considered as inconclusive ($P = 0.579$), this study provided nonetheless a real-world view on the two treatment options in an Australian context.

2.6 Summary and conclusion

Desai et al. (2015) provided an overview of the potential advantages and disadvantages to the application to neoadjuvant therapy in PC. The uncertainty around neoadjuvant therapy is still discussed around the globe and the optimal neoadjuvant therapy strategy therefore remains inconclusive. The lack of standardisation in the various developed tumour classification criteria makes it hard to distinguish BR from LA cases, despite that up- or down-scaling between these two classifications easily affects the recommended treatment options from the clinical practice guidelines, like the ones from NCCN and ESMO.

In the search for evidence regarding the benefits of neoadjuvant therapy, one might conclude that the conducted meta-analysis discourage the usage of neoadjuvant therapy for PR pancreatic tumours, possibly because of limited opportunity window for surgery. On the other hand, these same analysis observed an improved survival for one-third of the initial unresectable (BR and LA) tumours after neoadjuvant therapy prior to tumour resection. However, this promising advantage is still debated, because no single multi-centred phase III study has been published so far.

Modelling approaches, like Markov models, were developed as substitute to absence of conducted RCTs. This mathematical approach eventually favoured neoadjuvant therapy over upfront surgery for all resectability classifications, but, unfortunately, Markov models have limitations concerning the invariability of the health status in a fixed time frame. Another option to gain evidence is by means of RWD, which provides a view on neoadjuvant therapy in real life and has not been explored broadly worldwide. Only one small study was conducted in Australia and this particular study was not able to favour neoadjuvant therapy over upfront surgery.

So, up to now, there are indications of preferring neoadjuvant therapy over upfront surgery for certain types of resectability in the PC domain. However, it remains uncertain which treatment option is the most optimal for the three tumour classification types, because of opposing findings and study limitations. The patient-level details from multi-centred RWD sources might overcome some of the limitations of the meta-analysis and mathematical models, and is therefore able to provide a more realistic view on the actual usage of neoadjuvant therapy and the survival outcomes of the PC patients due to the treatment strategy.

3 | Methods

This master's thesis is a retrospective study using patient-level variables, referred in this report as *features*, from PURPLE. These features may be potential explanatory factors to the patient's survival. This chapter aims to motivate the manner in which this research selects the data from PURPLE. Also, this chapter presents the appropriate survival analysis techniques for assessing the explanatory property of individual features to the patient's survival.

In the end, from a clinician's perspective, he or she wants to prescribe the most desirable treatment to a particular patient and thus contributing to the optimisation of the clinical cancer care strategy. Hence, Section 3.1 motivates from which angles the evaluation is conducted regarding the role of neoadjuvant therapy. Section 3.2 defines the primary and secondary outcomes in the interest to this research. Section 3.3 provides the necessary information with regard to the inclusion and exclusion of features from the PURPLE registry. Section 3.4 clarifies the definitions of these features and accompanying outcomes used in this thesis, because this may deviate from scientific literature. Thereafter, multiple exclusion criteria are presented in Section 3.5 for the creation of the patient cohort in such a way that we can deal with data flaws or scope-related issues. Also, the statistical survival analysis techniques are being discussed in Section 3.6. Lastly, Section 3.7 concludes the chapter with a summary and conclusion.

3.1 Study approach

The study approach is subdivided into three different parts or perspectives: *intention to treat* perspective, *successful resection* perspective, and *neoadjuvant therapy specific* perspective. These sub-views are further motivated in Subsections 3.1.1, 3.1.2, and 3.1.3, respectively.

3.1.1 Intention to treat perspective

The focus of this thesis is to clarify whether the neoadjuvant therapy is able to contribute to the improvement of survival outcomes in PC. As mentioned earlier in Chapter 1, tumour resection is the only chance of curing PC, but not every patient is considered for such a curative surgery due to resectability of the tumour. Even though neoadjuvant therapy has the potential to convert unresectable tumours into resectable ones, this particular advantage of neoadjuvant therapy is not guaranteed. Prior to the treatment, the clinician has no certainty how the tumour will respond to the neoadjuvant therapy, despite the necessity to decide whether a particular patient should be enrolled into a neoadjuvant therapy program. Hence, it is important to take this *intention to treat* perspective of the clinician in mind for the survival analysis. For this reason, this thesis focuses on the effects of neoadjuvant therapy on the survival outcomes given the probability that patients are not considered as surgical

candidates later in the PC care pathway. The schematic overview of Figure 3.1 displays the neoadjuvant-therapy-decision-nodes (green diamonds) within each tumour resectability classification. Ultimately, for each tumour classification, we compare the survival outcomes of the neoadjuvant subgroup with subgroup without neoadjuvant therapy.

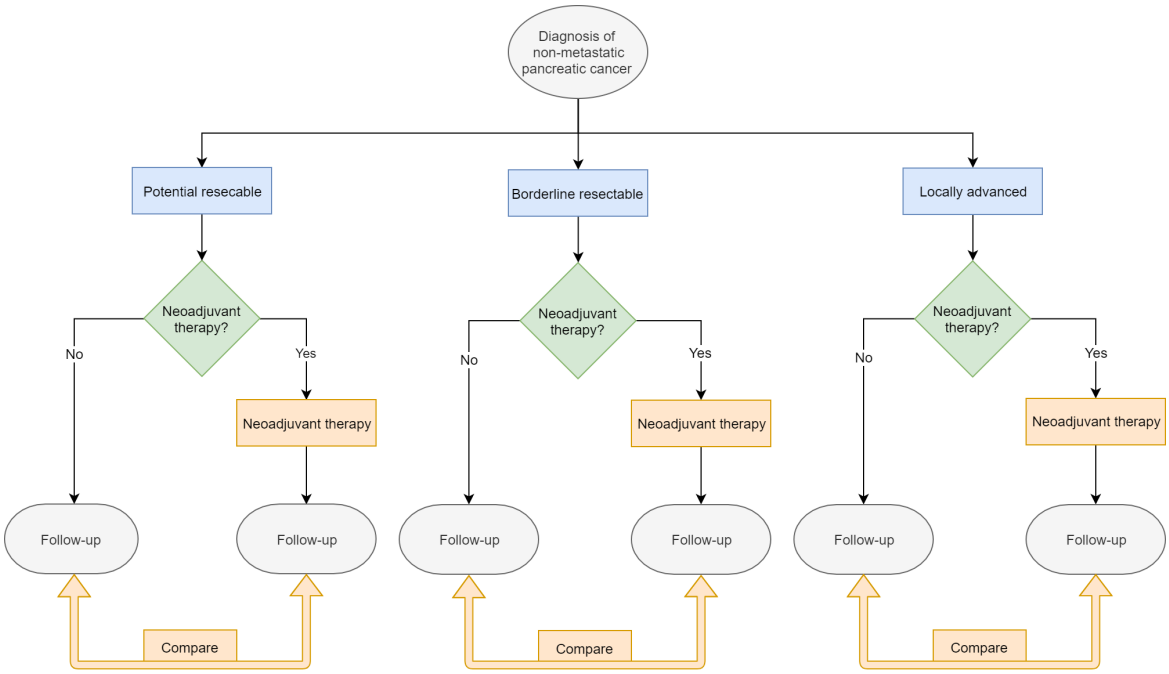

Figure 3.1: Schematic flowchart of the possible strategies within each tumour classification of the pancreatic cancer pathway. This *intention to treat* perspective attempts to compare the survival outcomes after the neoadjuvant therapy decision-node.

3.1.2 Successful resection perspective

Within the *intention to treat* perspective of Subsection 3.1.1, an extra layer of the PC care pathway is added which eventually deals with the uncertainty in the surgical procedure, which is visualised in Figure 3.2. The figure displays how the survival outcomes from the follow-up are compared between the neoadjuvant and no neoadjuvant subgroups of patients who underwent a successful tumour resection. This extra stratification of the patient cohort would most likely lead to more homogeneous, and thus comparable, subgroups in the neoadjuvant therapy survival analysis. The outcomes from this *successful resection* perspective align with the survival analysis of discussed literature from Chapters 1 and 2, like the meta-analysis of Gillen et al. (2010). Therefore, the insights from this sub-view contribute to a better understanding of the role of neoadjuvant therapy in PC populations with successfully resected tumours.

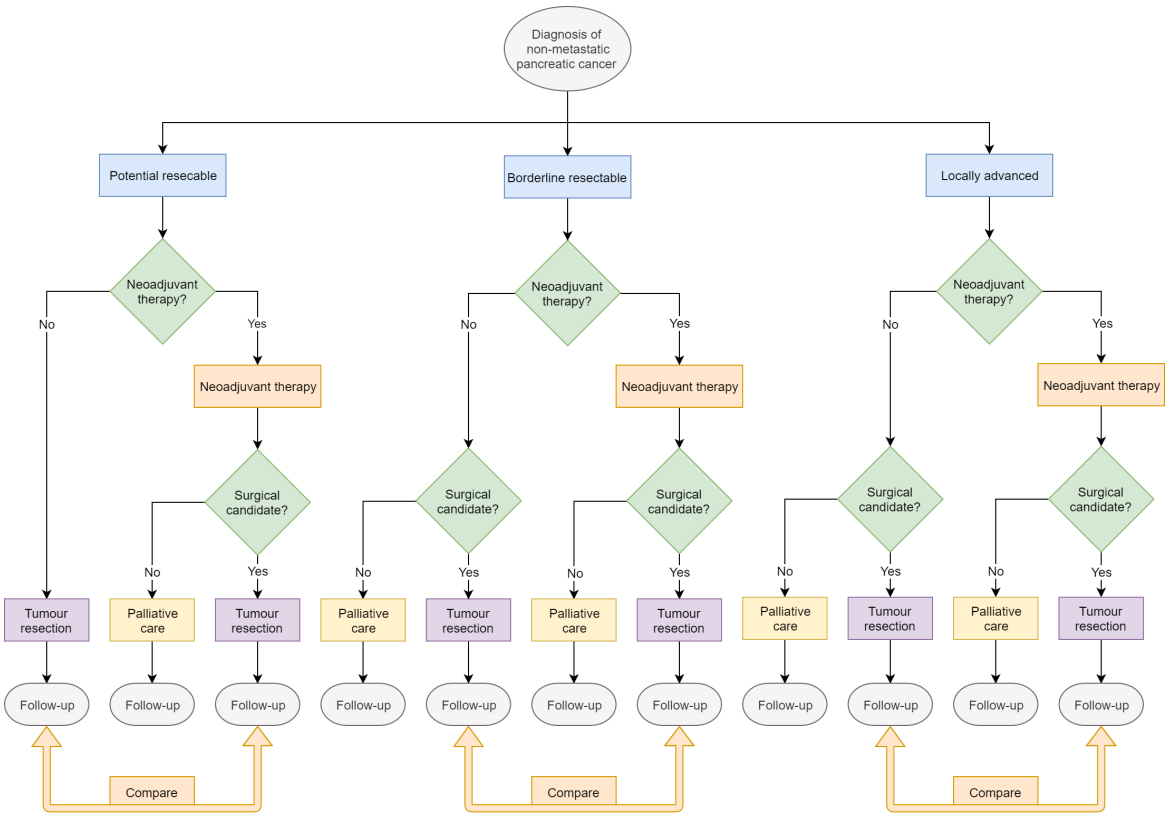

Figure 3.2: Schematic flowchart of the possible strategies within each tumour classification of the pancreatic cancer pathway. This *successful resection* perspective attempts to compare the survival outcomes after the completing the surgery.

3.1.3 Neoadjuvant therapy specific perspective

As discussed in Subsection 2.3.2, amongst the limitations of the meta-analysis of Gillen et al. (2010) were the outdated inclusion of literature and the unknown treatment practices of neoadjuvant therapy in PC. In order to help clinicians with in their decision-making process, especially with the neoadjuvant therapy prescription for the various tumour classifications, it is vital to understand the effectiveness of treatment variations within the neoadjuvant therapy domain to the tumour response and subsequent survival outcomes. For instance, the NCCN and ESMO recommend FOLFIRINOX (FLX) as chemotherapy regimen, but gemcitabine nab-paclitaxel (GNP) is a considerable alternative. Including the *neoadjuvant therapy specific* perspective to this research is desirable for a further understanding of the relation of various neoadjuvant therapy strategies with the survival outcomes. These results could contribute to the clinician's and patient's clinical decision-making process, the optimisation of PC care pathway, and thus the improvement of survival outcomes. For this sub-view, the type of neoadjuvant therapy (chemotherapy versus chemo-radiation therapy), the chemotherapy regimen (FLX versus GNP), and the therapy duration are analysed for their contribution to the outcomes of interest within each of the tumour classification. These analysis are further visualised in a schematic flowchart of Figure 3.3.

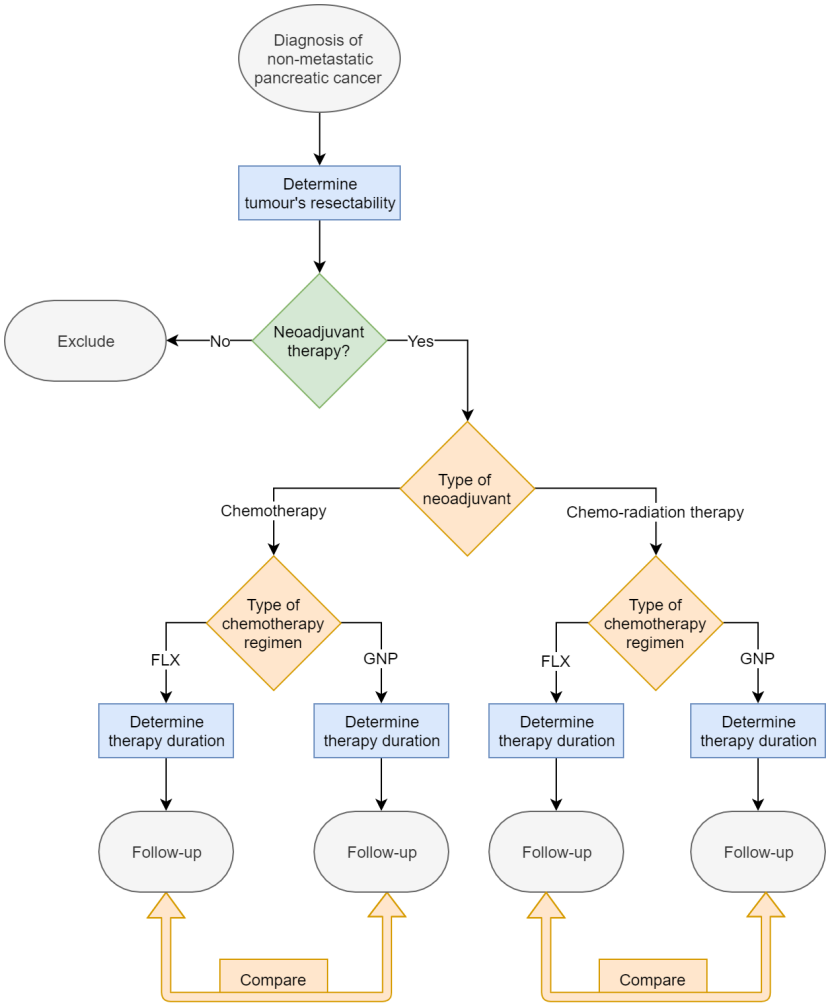

Figure 3.3: Schematic flowchart of the possible strategies within each tumour classification of the pancreatic cancer pathway. This *neoadjuvant therapy specific* perspective attempts to compare the survival outcomes after certain neoadjuvant therapy application.

3.2 Outcomes of interest

The primary outcome of this thesis was the OS. The resection rate and recurrence-free survival (RFS) were secondary outcomes. RFS was solely optional for analysis with patients who underwent a successful curative surgery. All outcomes are defined in Section 3.4.

3.3 Data collection from PURPLE

The data was downloaded from PURPLE on November 29, 2019, and contained 1,492 patients from 27 hospitals. PURPLE consisted of 238 patient-level features within 28 linked tables. Relevant features from the following nine tables were obtained for this research: *chemotherapy regimen*, *medical history*, *patient*, *patient summary*, *recurrence*, *specimen details*, *surgery details*, *treatment*, and *tumour details*. The exact inclusion and exclusion of features from these tables are documented in Tables B.2-B.6 of the Appendix.

3.4 Definitions

Descriptions, associated values and other data attributes were obtained per feature from the *PURPLE Data Dictionary* document of 28 May 2018, provided by BioGrid Australia. However, several additional definitions were developed to align the way in which medical-related data is documented in PURPLE, and the way that this thesis has discussed the content of features in Chapters 1 and 2. This section clarifies the necessary definitions under the themes *ECOG and CCI*, *resectability*, *therapy duration*, *cycle length*, *tumour response*, *resection rate*, *survival outcomes*, and *unreported data*.

ECOG and CCI
Multiple international scoring systems have been developed to assess the patient's conditional status. The Eastern Cooperative Oncology Group (ECOG) and Charlson comorbidity index (CCI) are used in this thesis and we interpret the scoring mechanism as motivated in Tables B.7 and B.8 of the Appendix, respectively.

Resectability
Tumour classifications *resectable disease* (PR), *borderline resectable* (BR), and *unresectable* (UR) were documented in PURPLE under the feature *resectability*. LA cases are mostly considered as UR and feature *tstage* has been used to distinguish LA cases from actual metastatic UR cases. This thesis assumes that those who were reported as *locally advanced* (*tstage*) and *unresectable* (*resectability*) were thus LA. Patients with a metastatic PC, who are reported as *unresectable*, are truly UR and therefore not part of this study.

Therapy duration
If the *therapy duration* was unknown, but the *therapy start date* and *therapy stop date* were documented, then these dates were used to determine the therapy duration. However, if the therapy duration and the stop date were both unknown, then the date of death was used for patients who were not alive. The date on which the PURPLE tables were downloaded, was applied for calculating the therapy duration for those who were still alive.

Cycle length
The number of days to complete a full treatment cycle of gemcitabine nab-paclitaxel (GNP) was determined at 28 days (Pharmaceutical Benefits Scheme, 2014), and a full cycle of FOLFIRINOX (FLX) was set at 14 days (eviQ, 2019). The number of therapy cycles was determined by dividing the number days of the patient's therapy duration by the duration of a complete cycle (either GNP or FLX) and rounded down if a cycle was not fully completed.

Tumour response
The tumour response after (chemo)therapy is documented in PURPLE using the categories of the RECIST by Eisenhauer et al. (2009), which are *complete response*, *partial response*, *stable disease*, and *progressive disease*. The precise definition of each response type are summarised in Table B.9 of the Appendix.

Resection rate & successful resection
Patients contributed to the resection rate if the patient underwent surgery (feature *surgery performed*) and the tumour was actual removed from the pancreas (feature *tumour resected*), also referred in this report as *successful resection*. If the tumour was not removed during surgery (due to circumstances), then the surgery is considered as unsuccessful.

Survival outcomes
Overall survival (OS) is defined as the time between the date of the actual cancer diagnosis (feature *cancer diagnosis date*), and the date of death (*date of death*) or the date of last review (*date of review*) if the patient is still alive according to the feature *vital status*. The OS is expressed in months and one month is one-twelfth of 365.25 days counting year.

Furthermore, RFS is defined as the time between the date of the actual cancer diagnosis (feature *cancer diagnosis date*), and the date of the documentation of the recurrence of the cancer (*progression date*). The RFS is expressed in months, which is likewise one-twelfth of 365.25 days counting year.

Unreported data
Empty cells may occur in the tables of PURPLE and these undocumented cells were therefore labelled as *not reported* or *not registered* (NR). However, in case of unreported values for the features *surgery performed* or *tumour resected*, we assumed that no surgery had been performed, rather than processing this missing data as NR.

3.5 Selection of patient cohort

Documentation flaws and scope-related issues led to the development of exclusion criteria for selecting a patient cohort of interest from the PURPLE registry. Ultimately, exclusion was justified if the patient met one of the following exclusion criteria:

- The patient was deleted from PURPLE (see feature *patient deleted*);
- The patient suffered from a metastatic PC or the tumour stage was unknown;
- The patient was referred directly to best supportive care or care was not clarified;
- No therapy was offered or commenced to the patient;
- Patient-related characteristic (e.g. gender or age) was not reported;
- The patient's clinical-related information (e.g. ECOG score or CCI) was not reported;
- Tumour-related information (e.g. cancer diagnosis date) was not reported;
- The resectability classification of the patient's tumour was not reported;
- The patient's documentation (e.g. linkages of several PURPLE tables) was opposing.

3.6 Statistical analysis

Statistical analysis was performed with with *RStudio, Inc.*, version 1.1.456, software for Windows (RStudio Team, 2015). The performed analysis are shortly described in this section with their accompanying R packages. For the various analysis of this thesis, a P-value (P) ≤ 0.05 is considered as statically significant and therefore 95% confidence intervals (CIs) were applied if necessary as such. This section is subdivided into patient demographics & association analysis, survival analysis, comparison of hazards, and survival modelling in Subsections 3.6.1, 3.6.2, 3.6.3, and 3.6.4, respectively.

3.6.1 Patient demographics & association analysis

The patient demographics are primarily presented by means of tables from the R package *arsenal*, in which continuous features are presented as mean, standard deviation, median and interquartile range (IQR), and categorical features are expressed as frequencies and percentages. Association analysis were performed to test the relationship of a certain feature between two or multiple subgroups of the patient cohort. The Fisher's test was applied for categorical features in case of two subgroups, otherwise the chi-square test was used. The Kruskal-Wallis test was performed for continuous features, independent from the number of subgroups. The patient demographics are secondarily visualised in graphs or plots using the R packages *ggplot2* and *cowplot*.

3.6.2 Comparison of survival

Kaplan-Meier plots were created to graphically display the difference in probability of survival between two groups over the course of time. This technique is generally adopted as the most conventional descriptive method for processing and analysing survival data (Hosmer et al., 2008). R packages *survminer* and *survival* were applied for this type of analysis.

The date of the actual cancer diagnosis was considered to be the start of all Kaplan-Meier plots, given our definitions of OS and RFS. In case of computing the survival function for OS, death was set as *event* and still alive patients (according to feature *vital status*) were *right censored* (patient who does not experience the event of interest) using the last known review date. The *event* changed to cancer recurrence in case of RFS survival analysis. Furthermore, the log-rank test was applied to statistically test the significant difference in survival outcomes between two Kaplan-Meier curves (Hosmer et al., 2008). Wilcoxon signed rank test may be considered as conservative alternative to the log-rank test, because of its allocation of weights to the survivals. CIs were added to curves for a better view on the uncertainty of the survival probability estimator. Also, risk tables were sometimes added to display the absolute number of patients on various moments in time within the Kaplan-Meier curves.

Amongst the important limitations of the Kaplan-Meier survival estimator is the incorporation of solely categorical features, because Kaplan-Meier cannot cope with continuous features. Also, censoring observations results into uncertainties in the Kaplan-Meier curves due to incomplete information concerning the patient's survival. Furthermore, the log-rank test is not able to adjust for confounders, so promising Kaplan-Meier trends were therefore subsequently tested for confounders by means of Cox Proportional Hazard analysis, as further described in Subsection 3.6.3. Lastly, Kaplan-Meier is non-parametric, meaning that we are not able to summarise a survival curve into a single number. However, as seen in the next subsection, the computation of hazard ratio for all features of interest allows the possibility of comparing the prognostic value of each feature.

3.6.3 Comparison of hazards

Cox Proportional Hazard models, or Cox models, were used as a survival regression means for the determination of the feature's hazard to a certain event of interest (e.g. death). This method allows us to evaluate the influence of features on the survival outcomes and simultaneously identify possible confounders (Hosmer et al., 2008). This influence is expressed in a hazard ratio, consisting of the feature's hazard against the baseline hazard of one or multiple features. Depending on the outcome of the ratio, this particular feature may be seen as a prognostic factor for the patient's survival. R package *survivalAnalysis* was applied for

the computation of univariate and multivariate hazard ratios, and the visualisation of these hazard ratios within so-called Forest plots.

This Cox model computes the hazard of a certain patient at a certain time given the outcomes of the features, but has no self-evident meaning, also due to the unspecified character of the baseline hazard. However, the ratio of the hazard functions allow us to understand the difference in hazard between two groups at a given point in time, known as the proportional hazard. In the end, the ratio of the hazard at time t and the baseline hazard at time t provides better understanding of the hazard of the group of interest against the reference hazard. Hazard ratios with a value above 1 should be interpret as an increase in hazard of the group of interest against the reference group and may have a bad prognostic value. On the other hand, values of hazard ratios below 1 indicates a reduction in hazard and may thus be considered as good prognostic factors.

The Cox model is able to cope with categorical and numerical explanatory features, so both types are incorporated into the analysis. The events of interest are death in case of OS and cancer recurrence for RFS. The Wald test was performed to assess the significance of the computed hazard ratios. Also, CIs were created to provide a clear view on the hazard's uncertainty. Univariate Cox models assessed the hazard ratio of a certain features, independent of the influence from other features. Multivariate Cox models assessed the hazard ratios of multiple features, taking into account the influence of all the included features into account. Multivariate analysis are therefore applied to justify the promising outcomes from features that are considered as statistically significant by univariate analysis. Lastly, the Cox model does not assume a constant hazard and may thus change over time, but the proportion of the hazards must remain the same. Hence, the cumulative hazard or the Schoenfeld's test may be used to justify the proportion hazard property over the course of time.

3.6.4 Survival modelling

When the hazards of the various features are clarified in the (multivariate) Cox model, then one is able to fit Cox proportional hazard model using the *coxph()* function of the R package *survminer*. One or multiple feature can be incorporated to built a regression model that attempts to explain the survival outcomes over time. As defined earlier, the *event* was considered to be death in case of OS. If RFS was used as endpoint, then cancer recurrence is set as the *event* for the model.

Features were initially considered for the model when they have significant outcomes from the multivariate Cox model. Other clinical relevant features should be considered for adoption as well, despite their potential poor Cox regression results. The individual relationship between the feature and the survival outcome of interest are statistically tested with the Wald test. Considered features were subsequently tested for their predictive, or regressive, property by means of a subset selection approach. This thesis used the backwards selection approach of the R package *pec*. The inclusion of features is based on the evaluation from the Akaike information criterion (AIC), which is an appropriate approach (Steyerberg et al., 2010).

In order to test the influence of a neoadjuvant therapy as a potential predictive feature, a conceptual model with this particular feature is tested against a model without this particular feature. Eventually, a feature was not adopted into the survival model if the inclusion of the feature does not lead to an improvement of model's prediction. This is determined by testing the model with this particular feature against the similar model, but without this particular feature. The statistical comparison is performed by means of the Likelihood ratio test.

3.7 Summary & conclusion

The role of neoadjuvant therapy within the PC domain can be clarified by using the RWD properly. This chapter therefore aimed to determine the data-selection related issues such that one is able to compare the neoadjuvant therapy arm with the alternative arm without the usage of neoadjuvant therapy. This comparison can be conducted within each tumour resectability classification from multiple moments, or perspectives, in the care pathway. The *intention to treat* perspective will determine the value of neoadjuvant therapy, independent from what happens after this therapy. On the other hand, the *successful resection* perspective takes into account the knowledge of a successful completion of the tumour resection when the role of neoadjuvant therapy is investigated. Lastly, the *neoadjuvant therapy specific* investigates how the type of neoadjuvant therapy, the regimen of chemotherapy, and the duration of the therapy are actually affecting the survival outcomes.

In order to perform the survival analysis from these perspectives, the PURPLE data is cleaned and processed such that we have representative and comparable subgroups. Nine tables have been selected, which contain the necessary patient-level information. Definitions with regard to the descriptive values from features were primarily based on the descriptives of the PURPLE Data Dictionary, otherwise assumptions were made. The various exclusion criteria have been presented to aim for an appropriate baseline patient cohort.

This research is interested in the difference between the subgroup with and the subgroup without the application of neoadjuvant therapy. The Fisher's exact test, Chi-square test and Kruskal-Wallis test are included to perform the association analysis for all features in order to test the comparability of two (or more) subgroups. The Kaplan-Meier estimator and the Cox Proportional Hazard model are adopted as the relevant survival analysis techniques for assessing the survival probabilities over time and for determining the hazard ratio, respectively. Neoadjuvant therapy is the primary feature of interest for the analysis and OS is defined as the primary survival outcomes of interest for this study. Neoadjuvant therapy should eventually be incorporated into Cox models to determine the the regressive relationship with OS.

4 | Results

This chapter presents the results from the survival analysis of the PURPLE registry. The exclusion of patients and the ultimate identified baseline patient cohort is explained in Section 4.1. Section 4.2 describes subsequently the basic patient demographics of the cohort. The actual results of the survival analysis are presented in Section 4.3. This chapter is concluded with Section 4.4 about the outcomes of the survival modelling.

4.1 Patient cohort selection

The exclusion criteria of Section 3.5 were applied on the relevant features of the 1,492 patients from the PURPLE registry. The patient selection process towards the baseline patient cohort is summarised in Figure 4.1. One patient was removed from PURPLE, according to feature *patient deleted*. A total of 597 patients were removed from the study due to non-metastatic cancer scope of our research. Despite the local advanced character of the cancer, a total of 152 patients were directly referred to best supportive care or the subsequent care was unknown. In 58 cases, patients declined treatment or any treatment was ultimately not commenced. Critical patient-, clinical-, or tumour-related characteristics were not reported for 31 patients and they were therefore not included. Moreover, the tumour resectability classification was unknown for four patients. Lastly, some opposing documentation with relation to the survival was noticed for one patient, hence the exclusion of this particular case. In the end, we identified 648 (43.3%) non-metastatic PC patients suitable for analysis. One hundred and five patients (16.2%) in baseline cohort received neoadjuvant therapy and the remaining 543 (83.8%) patients were not exposed to any preoperative treatments.

4.2 Patient demographics

Detailed cohort demographics are summarised in Table 4.1. This patient cohort had a median age of 67 years (IQR 59-74), and the distribution of the patients' age is presented in the histograms of Subfigure A.5A and A.5B of the Appendix. A slight majority of patients were male (55.1%), especially from the age of 50, whereas there are more women if the patient's age is younger than 50 (Subfigure A.5C). Almost all patients were classified with a ECOG score of either 0 (48.3%) or 1 (44.4%), and the CCI was determined at 0 for 56.5% of the cohort. The cancer tumours were located in the head (76.7%), body (14.0%), tail (8.3%), or the whole pancreatic organ (0.9%). Three hundred and sixty-eight tumours were classified as PR (56.8%), 118 as BR (18.2%), 162 as LA (25.0%), but proportions differ per age category. As displayed in Subfigure A.5D, more LA cases occurred in proportion to the BR classification from an age of 60, whereas this distribution is more balanced for younger patients. Furthermore, adjuvant therapy and palliative therapy were applied for 294

(45.4%) and 279 (43.1%) patients of the cohort, respectively. Lost to follow-up was reported in 75 cases (11.6%) and 59 (9.1%) patients enrolled into clinical trials regarding neoadjuvant therapy. Lastly, 497 patients (76.7%) were treated in a public hospital or medical centre. Patients from 24 hospital of the initial 27 centres are contributing to this thesis because of the exclusion process. The histogram of Subfigure A.6 displays the number of included patients per hospital, stratified for the neoadjuvant therapy usage. A great portion of the patient cohort originate from Cabrini Health, Western Health, and Royal Melbourne Hospital, with a total of 95, 85, and 77 PC patients, respectively.

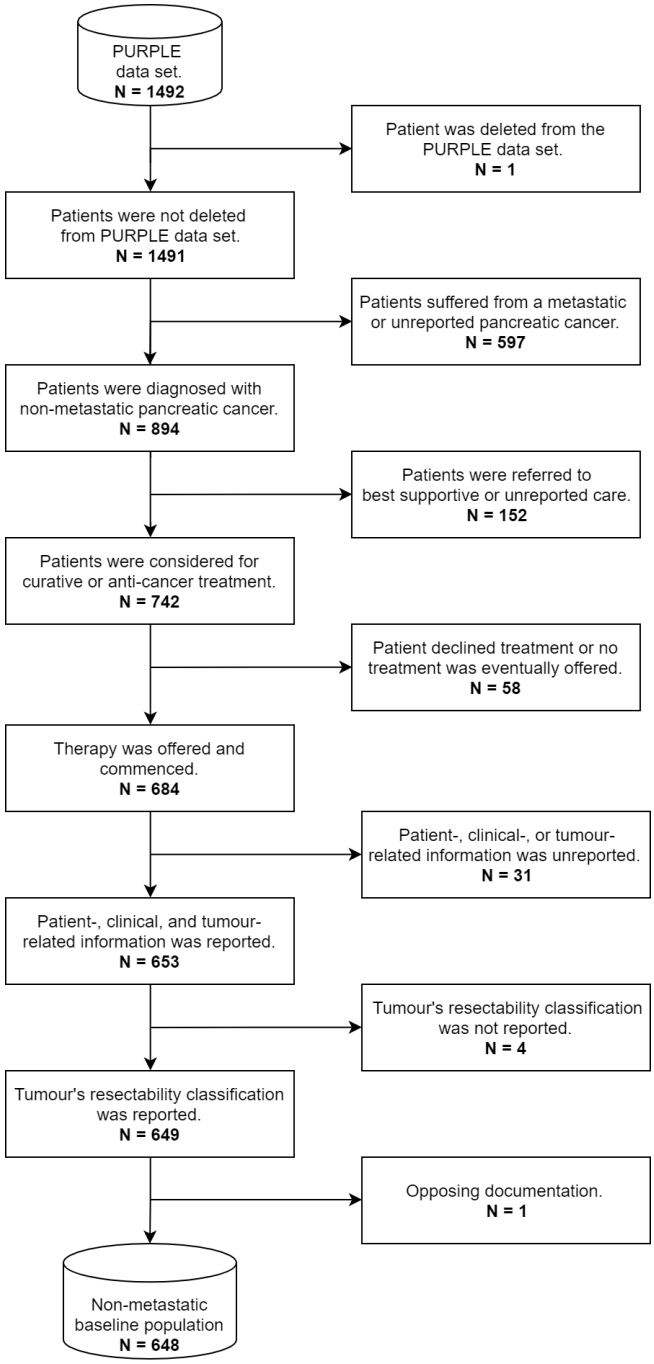

Figure 4.1: The patient cohort selection process of the non-metastatic baseline population.

Table 4.1: Demographics and clinical characteristics of the non-metastatic patient cohort, stratified for neoadjuvant therapy. Kruskal-Wallis and Fisher's Exact tests were applied.

Feature	**No neoadjuvant therapy (n = 543)**	**Neoadjuvant therapy (n = 105)**	**Total (n = 648)**	***P*-value**
Gender				0.592
- Male	302 (55.6%)	55 (52.4%)	357 (55.1%)	
- Female	241 (44.4%)	50 (47.6%)	291 (44.9%)	
Age at primary diagnosis				<0.001
- Mean (SD)	66.236 (10.818)	62.514 (10.443)	65.633 (10.838)	
- Median	68	63	67	
- Q1, Q3	60, 74	55, 71	59, 74	
ECOG score				0.002
- 0	246 (45.3%)	67 (63.8%)	313 (48.3%)	
- 1	253 (46.6%)	35 (33.3%)	288 (44.4%)	
- 2/3	44 (8.1%)	3 (2.9%)	47 (7.3%)	
Charlson Comorbidity Index				0.205
- 0	299 (55.1%)	67 (63.8%)	366 (56.5%)	
- 1	161 (29.7%)	29 (27.6%)	190 (29.3%)	
- 2	50 (9.2%)	4 (3.8%)	54 (8.3%)	
- 2<	33 (6.1%)	5 (4.8%)	38 (5.9%)	
Tumour location				0.023
- Head	412 (75.9%)	85 (81.0%)	497 (76.7%)	
- Body	73 (13.4%)	18 (17.1%)	91 (14.0%)	
- Tail	52 (9.6%)	2 (1.9%)	54 (8.3%)	
- Whole organ	6 (1.1%)	0 (0.0%)	6 (0.9%)	
Tumour's resectability				<0.001
- Potential resectable	356 (65.6%)	12 (11.4%)	368 (56.8%)	
- Borderline resectable	29 (5.3%)	89 (84.8%)	118 (18.2%)	
- Locally advanced	158 (29.1%)	4 (3.8%)	162 (25.0%)	
Tumour resected				0.002
- Yes	320 (58.9%)	45 (42.9%)	365 (56.3%)	
- No	38 (7.0%)	16 (15.2%)	54 (8.3%)	
- Surgery was not performed	185 (34.1%)	44 (41.9%)	229 (35.3%)	
Adjuvant therapy provided				0.007
- Yes	259 (47.7%)	35 (33.3%)	294 (45.4%)	
- No	284 (52.3%)	70 (66.7%)	354 (54.6%)	
Palliative therapy provided				0.010
- Yes	246 (45.3%)	33 (31.4%)	279 (43.1%)	
- No	297 (54.7%)	72 (68.6%)	369 (56.9%)	
Lost to follow-up				0.404
- Yes	66 (12.2%)	9 (8.6%)	75 (11.6%)	
- No	477 (87.8%)	96 (91.4%)	573 (88.4%)	
Enrolled in neoadjuvant clinical trial				0.357
- Yes	47 (8.7%)	12 (11.4%)	59 (9.1%)	
- No	496 (91.3%)	93 (88.6%)	589 (90.9%)	
Institution type				0.450
- Public	413 (76.1%)	84 (80.0%)	497 (76.7%)	
- Private	130 (23.9%)	21 (20.0%)	151 (23.3%)	

4.3 Survival analysis

The results from the *intention to treat*, the *successful resection*, and the *neoadjuvant therapy specific* perspectives are being presented in Subsections 4.3.1, 4.3.2, 4.3.3, respectively.

4.3.1 *Intention to treat* perspective

Association analysis
In addition to the overall patient demographics, Table 4.1 also displays the performed association analysis for each feature between the neoadjuvant therapy subgroup (n = 105) and the subgroup without neoadjuvant therapy (n = 543). The neoadjuvant subgroup was significantly younger and fitter, according to age ($P < 0.001$) and ECOG score ($P = 0.002$). Furthermore, the neoadjuvant subgroup consisted mostly of tumours classified as BR, whereas more than 90% of other subgroup was either PR or LA ($P < 0.001$). With regard to the tumour location, the tail or whole organ were mostly represented in the subgroup without neoadjuvant therapy ($P = 0.023$). Tumour resections were more observed in the subgroup without neoadjuvant therapy. Surgery was ultimately not proceeded in 41.9% of the neoadjuvant cases ($P = 0.002$). Furthermore, referring patients to adjuvant or palliative care had been carried out mostly for those without neoadjuvant therapy compared to the alternative ($P = 0.007$ and $P = 0.001$, respectively). Other features were not associated with any of the two subgroups.

Survival analysis
As addressed earlier, the tumour classification varied in the patient cohort and the effects of using neoadjuvant therapy are therefore further stratified by the tumour resectability classification. As seen from association analysis of Table B.10 of the Appendix, the various subgroups statistically differ with regard to age ($P = 0.026$), ECOG score ($P < 0.001$), tumour location ($P < 0.001$), surgery performance ($P < 0.001$), neoadjuvant therapy ($P < 0.001$), adjuvant therapy ($P < 0.001$), and palliative care ($P < 0.001$). A successful tumour resection resulted in significant better median OS (mOS) compared to those who ultimately did not undergo surgery: 34.4 months versus 13.9 months, $P < 0.001$ (Subfigure 4.2A).

Subfigure 4.2B displays the survival curves of the patients with PR tumours (n = 368), in which the median mOS was lower for neoadjuvant therapy, though not significantly proven (22.7 months versus 29.9 months, $P = 0.58$). A similar trend, regarding a lower mOS for those who were exposed to neoadjuvant therapy, was also visible in the BR subgroup (n = 118), as shown in Subfigure 4.2C: 21.6 months versus 22.1 months, $P = 0.80$. On the other hand, the data indicated a potential survival benefit from neoadjuvant therapy (17.1 months versus 14.8 months, $P = 0.49$) within the LA classification (n = 162), but, as seen in Subfigure 4.2D, this observation remains uncertain with the limited number of patients in the neoadjuvant arm. An overview of these stratified results are presented in Figure 4.3.

In addition to the Kaplan-Meier analysis, the univariate Cox model of each tumour classification indicated good prognostics for those treated with neoadjuvant therapy, given hazard ratios of 0.55 ($P = 0.395$), 0.68 ($P = 0.230$), and 0.60 ($P = 0.392$), for PR, BR, and LA tumours, as displayed in the Forest plots of Figures A.7, A.8, and A.9 of the Appendix, respectively. The actual added value of neoadjuvant therapy remained uncertain due to the accompanying CIs and P-values, and the role of confounders. The resection of the tumour was the primary feature with the best prognostic value within PR (HR: 0.27, $P < 0.001$) and BR (HR: 0.19, $P < 0.001$) resectability classifications, which is in line with the observation from Subfigure 4.2A. None of the LA cases eventually completed surgery.

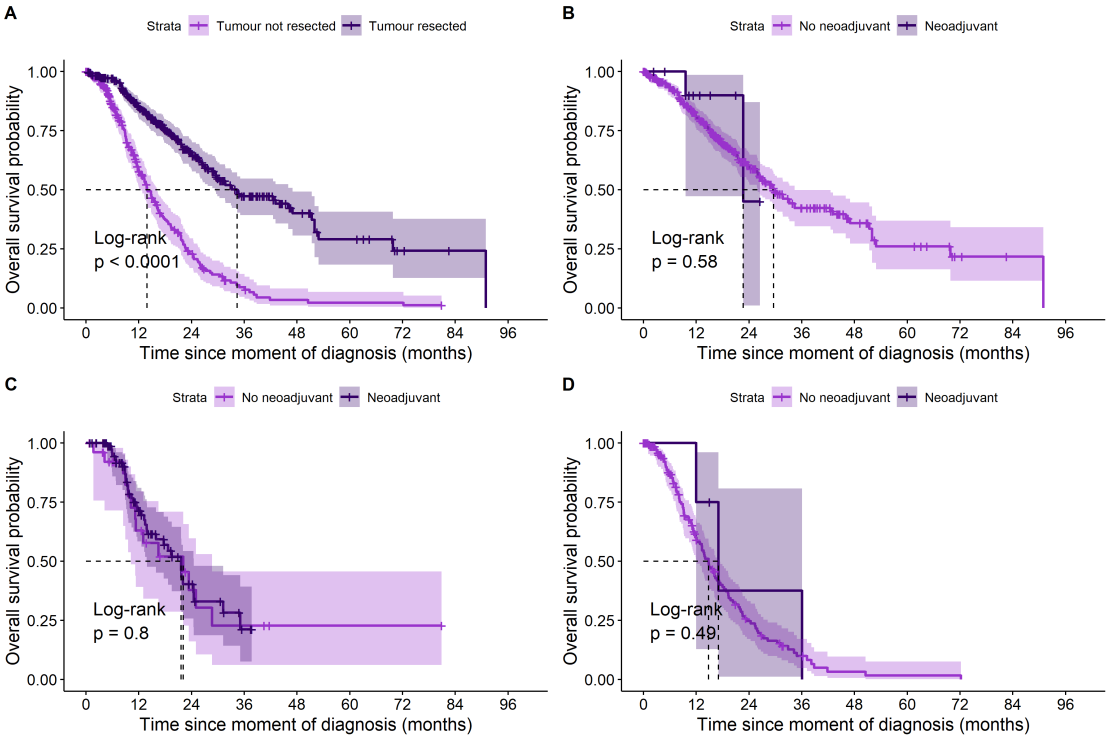

Figure 4.2: Kaplan-Meier plots regarding the overall survival as result of **A:** tumour resection for resectable, borderline resectable, and locally advanced subgroups together. Also, Kaplan-Meier plots regarding the overall survival following the usage of neoadjuvant therapy for **B:** the resectable subgroup; **C:** the borderline resectable subgroup; and **D:** the locally advanced subgroup. Log-rank test was applied for the statistical comparison.

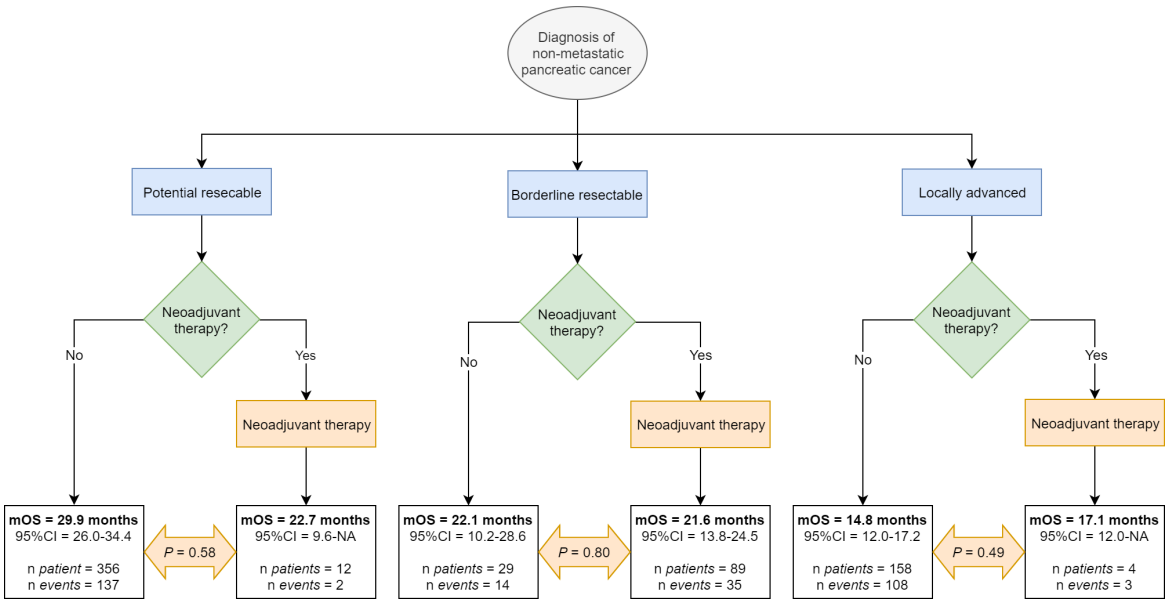

Figure 4.3: Overview of the survival outcomes of different groups of patients in the *intention to treat* perspective (n = 648). *mOS*: median overall survival; *95%CI*: 95% confidence interval; *P*: P-value; *n*: number of patients.

4.3.2 *Successful resection* perspective

As seen in the analysis of the previous subsection, the actual tumour resection heavily affects the patient's probability of survival. The inclusion of solely patients with a successful tumour resection (n = 365) would potentially provide a less skewed overview of the effectiveness of neoadjuvant therapy in PC patients. Ultimately, 45 (12.3%) patients of this sub-population received neoadjuvant therapy prior to the surgery, whereas the remaining 320 (87.7%) patient were not treated with neoadjuvant therapy.

Association analysis
The detailed patient demographics are presented in Table B.11 of the Appendix. According to the association analysis within the same table, the neoadjuvant subgroup remained to be younger ($P = 0.001$) and fitter (ECOG: $P = 0.042$). Again, the neoadjuvant subgroup consisted primary of BR tumours ($P < 0.001$). LA tumours were absent in the successful resection sub-population. Tail and whole organ cancers were solely represented in the subgroup without neoadjuvant therapy ($P = 0.038$). Furthermore, adjuvant therapy was more applied for those without neoadjuvant therapy ($P = 0.014$). Other features did not seem to differ.

Survival analysis
There were too few cases (n = 6 versus n = 315) in the neoadjuvant arm of the PR subgroup to assess the potential benefit of neoadjuvant therapy in terms of OS and RFS, as seen from the survival curves of the Kaplan-Meier plots in Subfigures 4.4A and 4.4C, respectively. Moreover, the mOS is never reached in the neoadjuvant therapy subgroup for those who with PR tumours, whereas the mOS is determined at 33.0 months for patient without neoadjuvant therapy. In addition, the resection rate was determined at 50% for those with neoadjuvant therapy, which is lower to the 88% of for patients without neoadjuvant therapy.

An opposite phenomenon is seen in the BR subgroup: the mOS is not reached for those without neoadjuvant therapy (n = 5), whereas patients treated with neoadjuvant therapy (n = 39) had a mOS of 35.1 months, as displayed in Subfigure 4.4B. In addition, the median RFS (mRFS) was 20.1 months for neoadjuvant therapy and 11.0 months for those who were not treated with neoadjuvant therapy ($P = 0.65$, Subfigure 4.4D). Likewise, the resection rate were 44% and 17% for those with and without neoadjuvant therapy, respectively.

As summarised in the overview of Figure 4.5, the survival results of this perspective were inconclusive due to the unbalanced number of patients in the research arms. If one would combine all the cases together, then there is still much uncertainty concerning the role of neoadjuvant therapy in the successful resection sub-population: the mOS of 35.1 months was observed in the neoadjuvant therapy subgroup (n = 45) and is therefore higher compared to the mOS of 33.0 months in the other subgroup (n = 320), though there is no significant indication to determine neoadjuvant therapy as a good prognostic factor ($P = 0.33$), as shown in Figure A.10. Moreover, the mRFS was very comparable between the neoadjuvant subgroup and those without neoadjuvant therapy: 18.2 months versus 17.3 months, $P = 0.77$ (Figure A.11).

Given the results from the univariate Cox models in Figures A.12 and A.13 of the Appendix, neoadjuvant therapy was considered to be beneficial compared to withholding neoadjuvant therapy in terms of OS (HR: 0.71, $P = 0.330$) and RFS (0.93, $P = 0.775$), if one would combine the PR and BR cases together. There are no Cox regression analysis performed for the PR and BR subgroups in this particular sub-population due to the insufficient number of patients in one of the research arms.

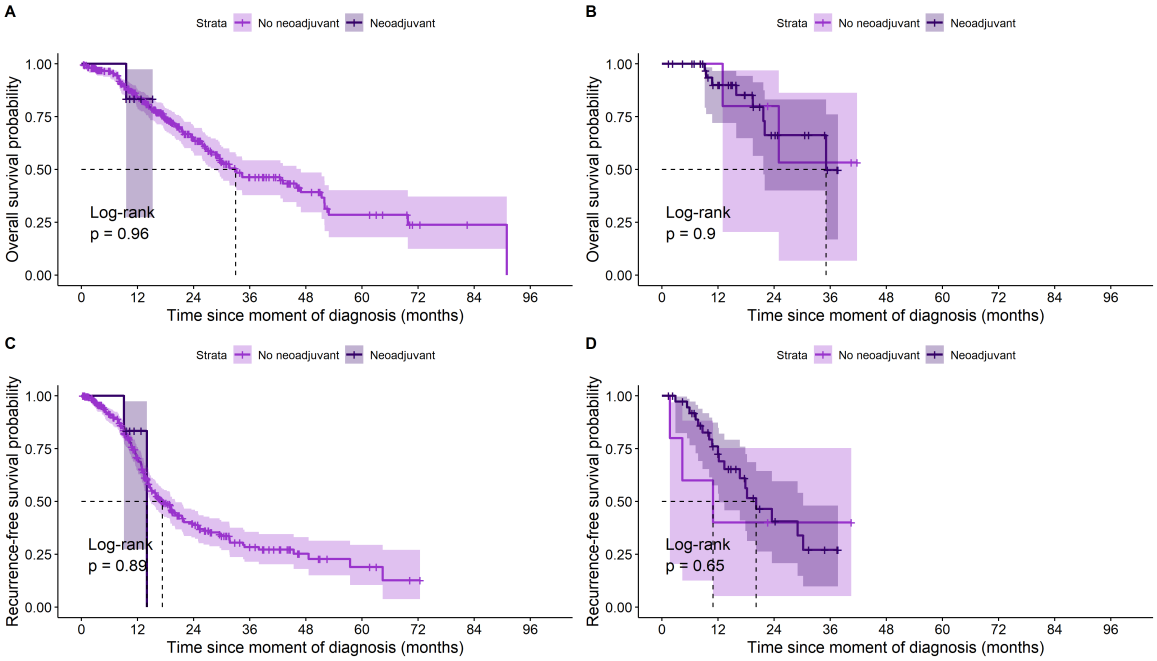

Figure 4.4: Kaplan-Meier plots regarding the overall survival following the usage of neoadjuvant therapy in **A:** the resectable subgroup and **B:** the borderline resectable subgroup. Kaplan-Meier plots regarding the recurrence-free survival following the usage of neoadjuvant therapy in **C:** the resectable subgroup and **D:** the borderline resectable subgroup. Log-rank test was applied for the statistical comparison.

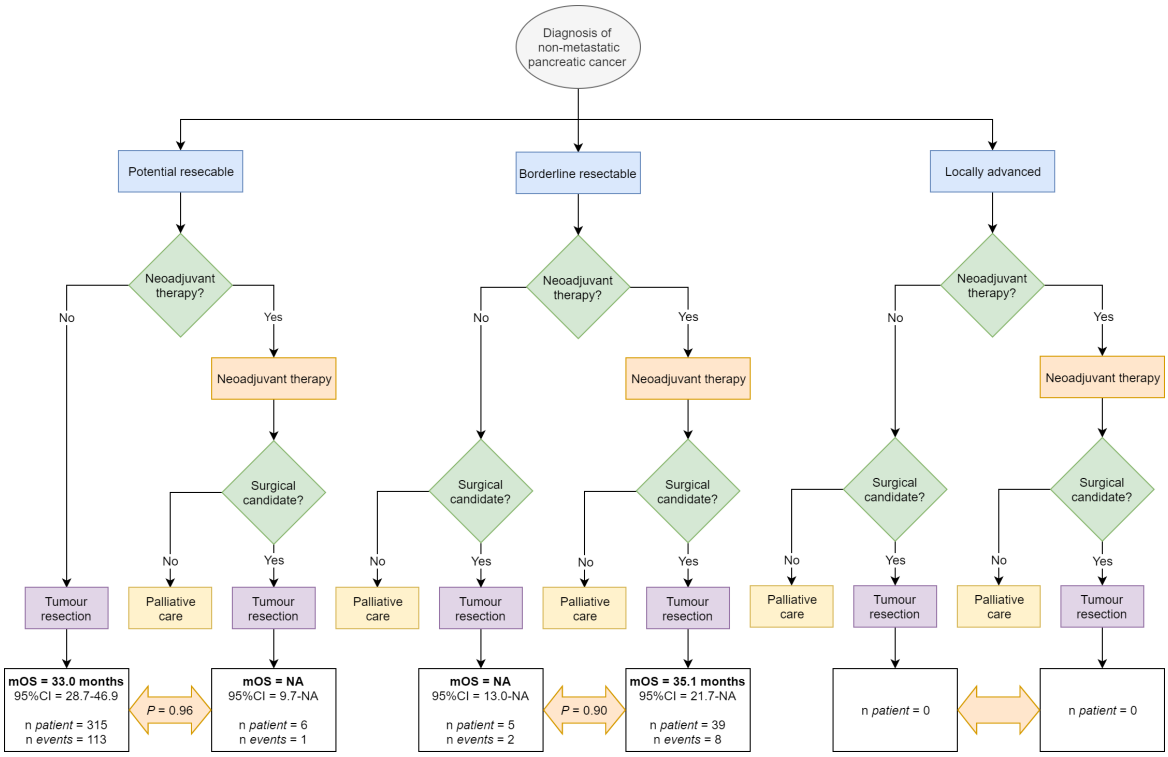

Figure 4.5: Overview of the survival outcomes of different patient groups from the *successful resection* perspective (n = 365). *mOS*: median overall survival; *95%CI*: 95% confidence interval; *P*: P-value; *n*: number of patients.

4.3.3 *Neoadjuvant therapy specific* perspective

From the initial 105 patients who received neoadjuvant therapy, there were eventually eight patients who underwent multiple chemotherapy regimens, possibly because these patients did not tolerate their initial chemotherapy regimen. These cases were excluded from the survival analysis in this perspective because of comparability purposes of chemotherapy regimen FLX and GNP. Also, as presented later, there were too few patients who underwent chemo-radiation therapy (n = 3), so, ultimately, no survival analysis was performed in which the effects of chemotherapy (n = 94) was compared to chemo-radiation therapy.

Association analysis
Given this new sub-population (n = 97), detailed patient demographics and, moreover, the association analysis between the FLX (n = 64) and GNP (n = 33) subgroups, are presented in Table B.12 of the Appendix. As a result of the analysis, those who treated with FLX were determined to be younger ($P < 0.001$) and had a better ECOG score ($P = 0.023$). No one from the FLX subgroup underwent chemo-radiotherapy, which is contrast to the GNP subgroup with a total of 3 patient ($P = 0.037$). Those treated with FLX underwent significant more neoadjuvant therapy cycles ($P < 0.001$), but there is a possibility that the absolute therapy duration is more or less the same between the two subgroups, given 14-day cycle of FLX and the 28-day cycle of GNP. Other features, including tumour location and tumour response, did not significantly differ between the two subgroups.

Survival analysis
The usage of neoadjuvant chemotherapy regimen FLX resulted in a mOS of 22.0 months and this is significantly better than mOS of 12.0 months of the GNP subgroup ($P < 0.001$, Subfigure 4.6A). Prolonging the neoadjuvant therapy indicated in slightly better mOS of 24.4 months than the 21.6 months for those who received less than 6 cycles of neoadjuvant therapy ($P = 0.68$, Subfigure 4.6B). But, if one would stratify the data for their regimen, as displayed in Figure A.14 of the Appendix, than there is no clear survival benefit of prescribing at least 6 cycles of neoadjuvant FLX ($P = 0.65$) or GNP ($P = 0.81$). Furthermore, any observed tumour response (complete response or partial response) after neoadjuvant therapy was associated with significant better mOS: 24.5 months versus 13.9 months, $P < 0.001$ (Subfigure 4.6C). In addition, the tumour response might depend on the initial tumour classification, but there are not enough cases to motivate this with certainty (Table B.13 of the Appendix). Lastly, if patients were treated in a private medical institution instead of a public alternative, then there was an higher survival gain, given the mOS of 36.1 months versus 20.3 months of the alternative ($P = 0.002$, Subfigure 4.6D). The actual survival overview of this particular perspective is displayed in Figure 4.7.

The observations from the Kaplan-Meier analysis are supported by the results from the univariate Cox model, which are displayed in the Forest plot of Figure 4.8. Private institution (HR: 0.16, $P = 0.013$), surgical resection (HR: 0.18, $P < 0.001$), FLX chemotherapy regimen (HR: 0.34, $P < 0.001$), tumour response after neoadjuvant therapy (HR: 0.36, $P = 0.003$), and adjuvant therapy (HR: 0.49, P 0.037) seemed to have contributed in favour of the OS compared to their reference. The therapy duration is inconclusive with the hazard ratio of 0.87 ($P = 0.677$).

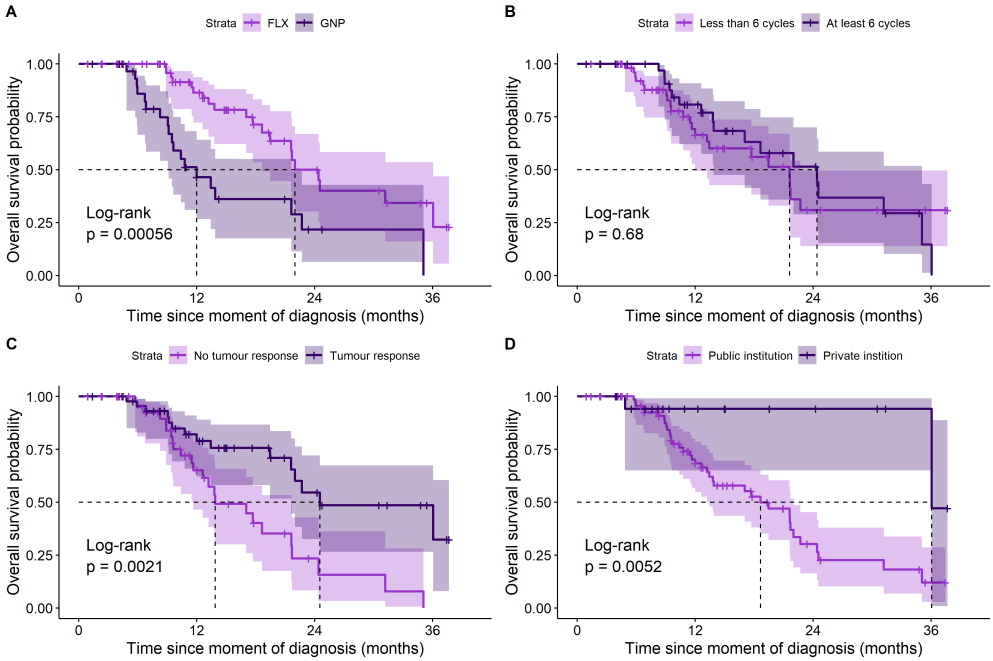

Figure 4.6: Kaplan-Meier plots regarding the overall survival following **A:** the neoadjuvant therapy regimen, **B:** the duration of the neoadjuvant therapy, **C:** the tumour response due to the neoadjuvant therapy, and **D:** the institution type. Log-rank test was applied for the statistical comparison.

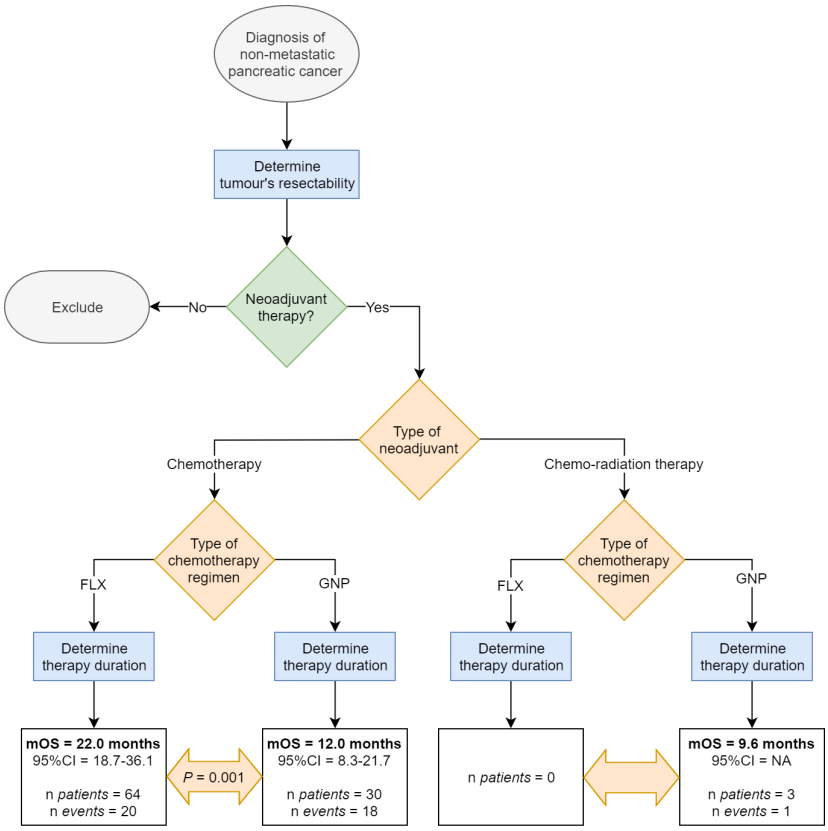

Figure 4.7: Overview of the survival outcomes of different patient groups from the *neoadjuvant specific* perspective (n = 97). *mOS*: median overall survival; *95%CI*: 95% confidence interval; *P*: P-value; *n*: number of patients.

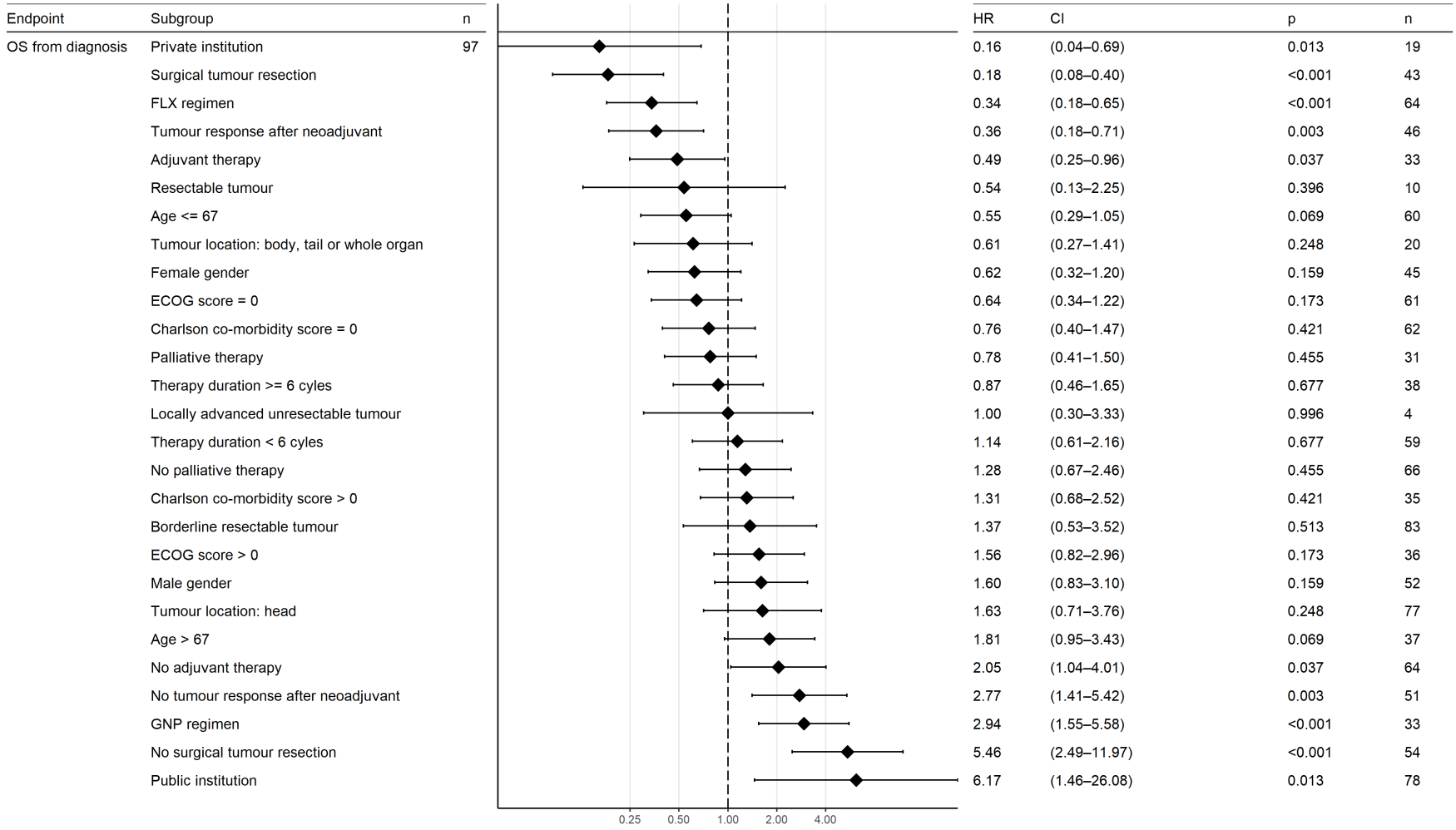

Figure 4.8: Forest plot of the outcomes from the univariate Cox proportional hazards model about the influence of features to the overall survival (OS) in the neoadjuvant sub-population (n = 95). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

4.4 Survival modelling

The added value of neoadjuvant therapy is now assessed by means of survival analysis, but the Kaplan-Meier estimators and univariate Cox models did not take into account the influence from potential confounders. This section presents the results from the multivariate Cox models and offers survival models that might contribute to the decision regarding prescribing neoadjuvant therapy in the *intention to treat* scenario. As seen earlier, the number of patients varied enormously between the two research arm within the PR and LA classifications. These unbalanced data might therefore be considered as not suitable with regard to modelling of neoadjuvant therapy. Therefore, we solely focused on the BR cases of PURPLE, because the data seemed better suitable for modelling. Moreover, patients with BR tumours are more likely to benefit from neoadjuvant therapy in terms of OS, given the theoretical background of this thesis.

Multiple patient-related factors were taken into account for the scenario, in which a clinician has to decide whether neoadjuvant therapy has to be applied on a particular patient. Age and ECOG score differed significantly in the neoadjuvant therapy subgroup compared to those who were not treated with neoadjuvant therapy (Table 4.1), but gender, CCI and tumour location are also pre-neoadjuvant features that should be considered from an *intention to treat* perspective, despite their *P*-value above the 0.05 from the univariate Cox model. So, all these patient-related features were ultimately incorporated with neoadjuvant therapy in a multivariate Cox model, as seen in the Forest plot of Figure 4.9. Combining the various features resulted in a very inconclusive multivariate Cox model with regard to OS, given the accompanying *P*-values and CIs of each feature, especially for neoadjuvant therapy: HR = 0.91, CI = 0.44-1.88, *P* = 0.808.

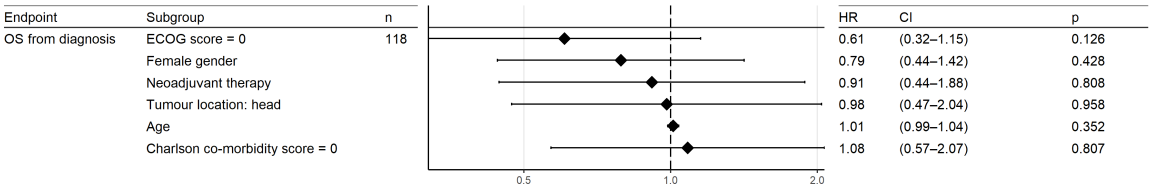

Figure 4.9: Forest plot regarding the multivariate Cox proportional hazards model about the influence of features to the overall survival (OS) of those with borderline resectable tumour from the non-metastatic population (n = 118). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

The outcomes from the Forest plot of Figure 4.9 indicated that neoadjuvant therapy has an insufficient regressive property with the patient's OS and the adaption of neoadjuvant therapy in any future models is therefore debatable. This was confirmed by a performance comparison of two models in which neoadjuvant therapy is adopted in one version and was excluded in the opposing version. For now, all other features, as discussed in the previous multivariate Cox model, were incorporated in both models. As displayed in Figure 4.10, the addition of the neoadjuvant therapy feature did not result in a better prediction of the model, given the *P*-value of 0.165 from the likelihood ratio test.

In addition, the backwards selection procedure was applied as subset selection approach in an attempt to assess whether neoadjuvant therapy could be considered as predictor of the OS in a Cox regression model. Eventually, the backwards subset selection of R package *pec* solely discovered regressive properties for ECOG score 1, 2 and 3, but neoadjuvant therapy was not

adopted in the best model. This was extra confirmed if one would compare a model, solely containing ECOG as predictive feature, with a opposing model which includes ECOG and neoadjuvant therapy. As shown in Figure 4.11, the Likelihood ratio test determined a *P*-value of 0.356, which means that the addition of neoadjuvant therapy on top of the ECOG-feature did not result in a better predictive value of the model. Moreover, as presented by Table 4.2, only minor changes were noticeable in the coefficients and in the standard deviations of the coefficients if one would compared the two models, meaning that neoadjuvant therapy did not drastically affect the implementation of other features in the model.

```
Analysis of Deviance Table
 Cox model: response is  Surv(diagnosis_survival, status)
 Model 1: ~ age + gender + ecog + cci + tumour_location
 Model 2: ~ age + gender + ecog + cci + tumour_location + neoadjuvant_therapy
   loglik Chisq Df P(>|Chi|)
1 -174.77
2 -173.81 1.928  1     0.165
```

Figure 4.10: Assessment regarding the added value of neoadjuvant therapy in a multivariate Cox regression model with features *age*, *gender*, *ECOG score*, *CCI* and *tumour location*, in which Model 1 (without neoadjuvant therapy) is compared to Model 2 (containing neoadjuvant therapy). The Likelihood ratio test was applied.

```
Analysis of Deviance Table
 Cox model: response is  Surv(diagnosis_survival, status)
 Model 1: ~ ecog
 Model 2: ~ ecog + neoadjuvant_therapy
   loglik  Chisq Df P(>|Chi|)
1 -182.22
2 -181.79 0.8519  1     0.356
```

Figure 4.11: Assessment regarding the added value of neoadjuvant therapy in a multivariate Cox regression model with feature *ECOG score*, in which Model 1 (without neoadjuvant therapy) is compared to Model 2 (containing neoadjuvant therapy). The Likelihood ratio test was applied.

Table 4.2: Properties of the model with neoadjuvant therapy and the model without neoadjuvant therapy. The Wald test was applied as statistical test.

Feature	**Coef.**	**exp(coef)**	**se(coef)**	**Z-value**	***P*-value**
Model without neoadjuvant therapy					
ecog = 1	0.4128	1.5111	0.3035	1.360	0.1738
ecog = 2	1.5057	4.5074	0.5522	2.727	0.0064
ecog = 3	0.3733	1.4525	1.0251	0.364	0.7157
Model with neoadjuvant therapy					
ecog = 1	0.4937	1.6384	0.3145	1.570	0.11646
ecog = 2	1.7866	6.0288	0.6417	2.800	0.00512
ecog = 3	0.6706	1.9554	1.0791	0.621	0.53432
neoadjuvant therapy = yes	0.3428	1.4088	0.3804	0.901	0.36763

5 | Discussion

The discussion starts with the remarks on the analysis from the *intention to treat*, *successful resection* and *neoadjuvant therapy specific* perspectives in Sections 5.1, 5.2 and 5.3, respectively. Section 5.4 continues with discussing the survival modelling outcomes and techniques. Limitation to this research are divided in general RWD issues and PURPLE specific ones, which are presented in Sections 5.5 and 5.6, respectively. This chapter is finalised with some remainder discussion points in Section 5.7.

5.1 Remarks on the *intention to treat* analysis

This study was unable to find conclusive indications with regard to the usage of neoadjuvant therapy in either PR, BR or LA tumours of PC patients from the PURPLE registry. This was mainly caused by the unbalanced number of patients in the various research arms. Only 12 of the 365 (3.2%) PR tumours and 4 of the 162 (2.5%) LA tumours were treated with neoadjuvant therapy. The distribution was slightly better, but remained skewed, in the BR subgroup: 89 of the 118 (75.4%) patients received neoadjuvant therapy. These skewed populations in PURPLE limited our attempts to compare the research arms with each other and draw any meaningful conclusions from the observations.

Besides the absolute number of patients in each arm, the observations from the several survival analysis are also restricted by the lack of actual deaths in each arm. For instance, only 2 (1.4%) patients have passed away in the neoadjuvant therapy arm of the PR subgroup against 137 patients in the opposing arm. Such unbalanced distribution is also noticed for the LA tumours: 3 (2.7%) patients died in neoadjuvant therapy research arm versus 108 in the other arm. Again, the representation was slightly better in the BR subgroup, which contained 35 (71.4%) mortalities in the neoadjuvant arm against 14 in the other arm. Many patients were thus censored in our survival analysis due to the incomplete individual survival information. This might be the result of the relative short follow-up time for many of the included patients our population, which is further motivated in Subsection 5.6.6.

On the other hand, the RWD study of Itchins et al. (2017) reported inconclusive results as well: neoadjuvant subgroup gained a mOS of 25.9 months versus 26.9 months for upfront surgery (P = 0.579; Figure 5.1). Surprisingly, the mOS improved to 29.2 months for the neoadjuvant subgroup if eighteen cases were removed when the tumours were re-classified as UR in the post-neoadjuvant setting. The study contained mostly PR and BR cases and was therefore comparable with our population. However, Itchins et al. did not stratify the survival analysis for each classification, which hardens reflecting our results with this particular study. If our PR and BR cases were combined, then we would most likely have similar results as Itchins et al. (2017), but the added value of our analysis is observing the role of neoadjuvant therapy compared to an alternative treatment option within each tumour classification type.

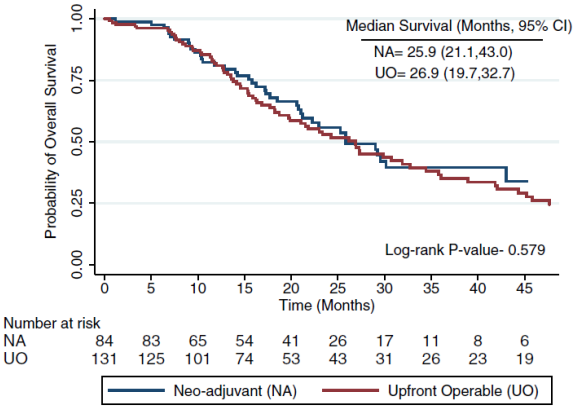

Figure 5.1: Kaplan-Meier regarding the overall survival of patients with neoadjuvant therapy versus patients with solely upfront surgery (Itchins et al., 2017).

Although no definitive observations were noticeable due to these discussed population limitations, this thesis is unique compared to other published articles from the PC domain because of this particular *intention to treat* perspective. To the best of our knowledge, almost all retrospective analysis, that have been reviewed in (preparation to) this thesis, excluded patients whose surgery was uncompleted. In other words, the authors were solely interested in those who underwent a successful tumour resection. These studies may therefore have a potential selection bias. Also, studies generally looked into one or two tumour resectability classifications, but focusing on PR, BR and LA within the same study is not commonly done. In conclusion, this thesis included a broad spectrum of patients given the resectabilities and the individual surgery considerations, which makes the observations from PURPLE represent the clinical reality more compared to other scientific work in the PC domain. Alas, although this *intention to treat* perspective is thus more desirable for the clinical purposes, uncertainty remains regarding the added value of neoadjuvant therapy as treatment option for PC patients from various tumour classifications.

5.2 Remarks on the *successful resection* analysis

Just as in the previous section, not enough data existed in the *successful resection* perspective to create two comparable arms within each tumour resectability classification. For instance, with regard to those with PR tumours, only 6 (1.9%) of the neoadjuvant therapy arm underwent a tumour resection and only one passed away according to the data. The resection rate of 50% was also not completely reliable better due to the limited number of patients in the arm, despite that a similar observation was noticeable in the resection rates of our PR cases compared to the work of Gillen et al. (2010).

Although the BR classification was better distributed compared to PR subgroup, we still had too few patients and events in both arm to draw any conclusion regarding the effect of neoadjuvant therapy. Only 8 patients died in the follow-up period within the neoadjuvant therapy arm and only 2 patients in opposing arm. The resection rate of 44% for the neoadjuvant therapy arm is a bit higher compared to what is reported in other studies, but this rate is unreliable for comparison due to the absence of any LA cases. Non of the LA tumours were eventually removed from the patient's pancreas and therefore resulted in a resection rate of 0%. This poor rate is obviously caused by the low number of patient (n = 4) in the neoadjuvant therapy arm and is therefore not representative.

The actual survival outcomes are thus very hard to compare with other PC related work, though this particular perspective is commonly used in the retrospective analysis. For instance, the retrospective study of Michelakos et al. (2019) included 110 patients who were treated with neoadjuvant FLX and another 155 patients were not treated with neoadjuvant therapy. All patients ultimately completed surgery. Different to our findings, Michelakos et al. suggested that the neoadjuvant therapy arm, consisting of BR and LA cases, gained a better OS (37.7 months versus 25.1 months, $P = 0.01$) and RFS (29.1 months versus 13.7 months, $P < 0.001$). Comparable with our data, the authors reported that the neoadjuvant therapy subgroup was younger and fitter. The tumour sizes did not differ between the subgroups of Michelakos et al., but we were unable to check this particular observation with the patients of PURPLE, because tumour size was not reported for all patients.

5.3 Remarks on the *neoadjuvant therapy specific* analysis

Multiple elements of the neoadjuvant therapy have been investigated in the *neoadjuvant therapy specific* perspective. This section attempts to compare the observations from this perspective with what has recently been published about the type of neoadjuvant therapy (Subsection 5.3.1), regimen choice (5.3.2), treatment duration (5.3.3), tumour response (5.3.4), and institution type (5.3.5).

5.3.1 Usage of chemo-radiotherapy over chemotherapy

This thesis was unable to compare the survival results of the chemotherapy arm with the chemo-radiotherapy arm in an attempt to assess which treatment option should be favoured in future PC cases. Merely three patients underwent chemo-radiotherapy and only one had died in the follow-up period, so there were too few data for any analysis. However, Hammel et al. (2016) (n = 221), Pietrasz et al. (2019) (n = 203) and Macedo et al. (2019) (n = 270) investigated the survival benefit of those with chemo-radiotherapy compared to solely chemotherapy in the neoadjuvant setting. According to their Kaplan-Meier plots, the data of these various studies seemed to result in better survival outcomes for the chemo-radiotherapy arm, but these observations remain inconclusive due insignificant difference of the survival curves. Du & Wang-Gillam (2017) mentioned that studies are still exploring the best neoadjuvant chemo-radiotherapy approach and this might affect the observations of the various phase II studies.

5.3.2 Regimen choice: FOLFIRINOX or gemcitabine nab-paclitaxel

Historically, 5-fluorouracil (FU) was mostly applied as neoadjuvant chemotherapy until Burris et al. (1997) demonstrated the clinical benefit of the gemcitabine regimen over 5-FU. FOLFIRINOX (FLX) became available in clinics since 2010 and is a mix of four chemotherapy regimens. The data from the *neoadjuvant therapy specific* perspective seem to associate FLX with a longer OS compared the GNP regimen.

The recent conducted retrospective multi-centred study of Macedo et al. (2019) (n = 274), and the single-centred studies from Dhir et al. (2018) (n = 193) and Chapman et al. (2018) (n = 120), assessed the difference in survival of PC patients treated with either FLX or GNP in a neoadjuvant application. Alas, no significant difference has been determined in these studies, which is striking compared to the observation in this thesis. It might be explained by the manner in which patients were included into these three studies, because the authors were solely interested in those who successfully underwent surgery. Furthermore, there was

no variations in survival reported between patients with either PR, BR, or LA classified tumours. However, similar to our population, those who underwent the FLX regimen were younger and fitter in all three studies. It is unsure whether particular patients appeal to FLX because of their age and condition, or that there is another explanation to the association the FLX regimen with younger and fitter patients. In addition, there was a tendency noticeable in favouring FLX over GNP in the conclusions of the studies, despite the fact that they were unable to demonstrate conclusive evidence about the preferred neoadjuvant chemotherapy regimen. The review of Du & Wang-Gillam (2017) concluded that some studies have shown promising outcomes in the application of FLX. However, more analysis are most desirable for a better understanding of the regimen choice in the neoadjuvant therapy application for PC patients. After all, not all patients from PURPLE tolerated the FLX regimen and eventually switched to an alternative, like GNP.

5.3.3 Treatment duration

The data of the *neoadjuvant therapy specific* perspective did not result in a striking observation regarding the role of the neoadjuvant therapy duration on the OS. The univariate hazard ratio was 0.87 for a treatment duration of 6 cycles or more, but uncertainty remains given the CI of 0.46 till 1.65. This might have been affected due to the merging of the FLX and GNP regimens in this univariate Cox analysis. On the other hand, the single-centred retrospective studies of Williams et al. (2016) (n = 102) and Truty et al. (2019) (n = 196) reported significant better OS and RFS outcomes for those who underwent at least six cycles of neoadjuvant treatment compared to patients with less than six cycles, regardless of the regimen. However, these studies included solely patients who successfully completed the tumour resection attempt.

Based on the multi-centred analysis of Macedo et al. (2019) (n = 270), clinicians may strive for a prolonged neoadjuvant chemotherapy duration when one is specifically applying FLX as regimen. Patients who were treated with at least 7 cycles of FLX gained a better OS compared to a shorter treatment duration. Such a significant phenomenon has not been observed with GNP as neoadjuvant chemotherapy regimen. Nevertheless, there seems to be a causality between the prolonged neoadjuvant chemotherapy duration and the survival from these various retrospective studies. Alas, the definition of a short and a long therapy duration is not unified. One study determines the threshold to be 6 cycles, while another nominates 7 cycles. These variations should be further explored in the future with a large patient population, including patients who were not considered as surgical candidates after provision of neoadjuvant therapy.

5.3.4 Relationship between tumour response and survival

As seen from the Kaplan-Meier plot of Subfigure 4.6C, the data suggests a relationship between tumour response and survival. Those with a complete or partial tumour response have a potential better OS compared to those with a stable disease or progressive disease. This outcome is not very surprising. After all, patients are more likely to be considered as surgical candidates if the tumour shrinks. Alas, tumour shrinkage is not documented in PURPLE, nor investigated in this thesis. Besides re-classification of the tumour after neoadjuvant therapy, the tumour response could also not be reasoned back to the provided chemotherapy regimen (Table B.12) and there was no clear association of the initial tumour classification with the response due to the restricted PR and LA cases (Table B.13).

Nevertheless, the probability of any tumour response due to the neoadjuvant therapy seems not be associated with the initial tumour resectability classification: the meta-analysis of Gillen et al. (2010) did not report any significant response deviations between the resectable and unresectable tumours when neoadjuvant therapy was provided. In the end, 3.9% and 29.1% of the response cases were either complete or partial, respectively. Moreover, the tumour response, as defined in the RECIST criteria, is not an effective way to determine the resectability or associate with OS, according to the publication Barreto et al. (2019). The authors reviewed 15 studies, among which Katz et al. (2012) of Subsection 2.1.2, in an attempt to associate the anatomic changes of the tumour from the CT images with the consideration for surgery and accompanying survival, but the authors considered CT imaging as an unreliable method because of the poor examination accuracy.

A similar conclusion has been drawn by Wagner et al. (2017) and Marchegiani et al. (2018), who both used the AHPBA guidelines as substitute to the RECIST criteria. Wagner et al. (2017) observed no correlation between the post-neoadjuvant (pre-surgery) tumour classification and the R0 resection, as seen from Figure 5.2. Marchegiani et al. (2018) observed a significant tumour response ($P < 0.001$), but the R0/R1-ratio was comparable in the PR (72%/14%) and BR (64%/21%) post-neoadjuvant population. Furthermore, the authors concluded that "the CT scan was able to define the resectability of PC with a sensitivity of 86% and a specificity of 29%". So, in conclusion, a CT-detected tumour response did not automatically lead to a better understanding prediction of neither R0 or R1 resection types.

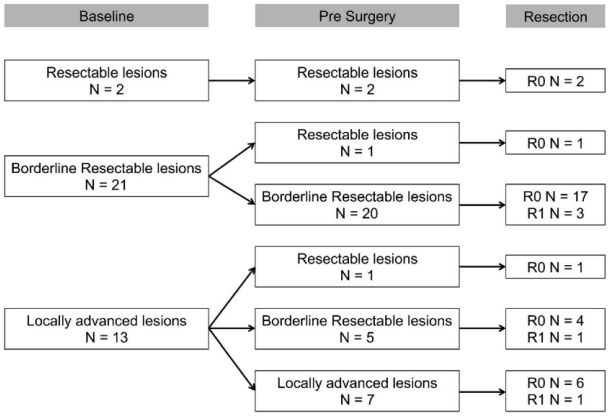

Figure 5.2: Usage of the NCCN criteria to evaluate the tumour classification before (baseline) and after (pre-surgery) neoadjuvant FOLFIRINOX application in pancreatic cancer patients (Wagner et al., 2017).

5.3.5 Role of private and public medical centres

As seen in the results, treatment in a private hospital seems to be associated with better survival outcomes than for those who were handled in a public institution, despite the limited number of patients in our *neoadjuvant therapy specific* perspective. One could question the quality of care between the private and public institutions, but other factors are more likely to play a role in this phenomenon. Van Gaans & Dent (2018) identified *availability*, *accessibility*, *accommodation*, *affordability*, and *acceptability* as dimensions of care which could differ between private and public institutions in Australia. Any suspicion of PC is faster examined for those who are able to afford private care. Most people appeal for public care, which limits the accessibility in the short-term. So, the patients from our neoadjuvant therapy sub-population might have been better of with private care, probably because of its relative early accessibility.

5.4 Remarks on the survival analysis and modelling

Analysis methods and tests
The inclusion of features into the survival model was initially based on the results from the Kaplan-Meier estimators and univariate Cox models. A feature was considered as promising when a statistical significant observation ($P \leq 0.05$) had been determined from the log-rank test or Wald test. However, the outcomes of these tests would be affected if the patients' survivals were evaluated differently. For instance, the various survivals from the patient cohort are now equally weighted with the log-rank test, but Tarone-Ware test, Peto-Prentice test, and Wilcoxon test have different statistical weighting approaches. Especially this last type is considered as the most conservative test compared to the conventional log-rank test (Hosmer et al., 2008). In addition, the log-log method is the most conventional estimator of the 95% CIs, but the other estimators, like Hall & Wellner Band (as mentioned by Hosmer et al.), could have led to slightly different interpretation of the CIs of the survival curves. Furthermore, the Likelihood ratio test and log-rank test could be potential substitutes to the conventional Wald test in the Cox regression domain. Ultimately, the variations in the test outcomes have not been determined in this thesis, but it might be worth considering for future research.

Modelling
Backwards stepwise selection is proposed by Steyerberg et al. (2010) for selecting features in the model developing procedure. Despite the disadvantages, like instability of the selection and biased estimation of coefficients, this method has the relatively straightforwardness and the objectiveness as advantages. Alas, the R package *pec* has no option to apply forwards stepwise or best subset selection, so our analysis remained quite basic. In addition, as mentioned in the work of James et al. (2015), shrinkage methods (ridge regression and the Lasso) are valuable alternatives of subset selection techniques, but these approaches are for more advanced and maybe not applicable on survival data. Polynomial properties have also not been addressed, which would potentially result in different understanding of the features and subsequently lead to a better association of these features with the actual survival outcomes. These variations in subset selection and subset alteration might be worthwhile to explore in future research. In addition, the AIC stopping rule was incorporated in the analysis, but alternatives, like BIC and adjusted R-squared, should be considered in future research. On the other hand, given the multivariate Cox model of Section 4.4, one could question whether using different approaches would have led to a more meaningful model. There remained too much uncertainty for each included feature with regard to the OS.

Simulation
The multivariate Cox model, as proposed in Section 4.4, is only a basic attempt for associating certain patient-related features with the patient's survival. To gain a better understanding of the data on major scale, developing simulation models is available to estimate the patient's survival probability in hypothetical scenarios, as described in the work of Law (2007) and Hosmer et al. (2008). Our research has not been able to demonstrate the intended effect of neoadjuvant therapy in PC patients, partially caused by the number of patient in some of the research arms. There seems not enough basis to conduct any Markov modelling or discrete event simulation for further exploration of the neoadjuvant therapy potentials in various hypothetical scenarios within the PC domain. Therefore, it has not been an obvious choice to include and develop a simulation model in this thesis, which makes this thesis more a survival analysis study rather than a survival estimation study.

5.5 Limitations of real-world data

Working with RWD resulted in several general limitations to the research in this thesis. First of all, we are unable to retrace or to recreate the decision-making process for each individual patient in the registry. In the end, we are limited by what is documented in PURPLE and it is impossible to obtain the protocols, motivations or preferences of the involved clinician(s) (and the patient) with regarding to the usage of neoadjuvant therapy. This uncertainty is a main limitation of working with RWD. It might have led to a heterogeneous selection of patients in the research cohort, so a possible selection bias.

Also, one is depending on the quality of documentation by those who are responsible for the administrative side of the patient's health care. Although PURPLE has fixed associated values for most patient-level features, there remains a possibility for errors in the documentation of the patient's health record by the administrative user or users. Nevertheless, these types of flaws will most likely occur in a very slim proportion of the patient cohort.

5.6 Limitations of PURPLE

Besides the most general drawbacks of RWD, there are multiple PURPLE specific limitation to this research with regard to the tumour classification (Subsection 5.6.1), tumour detection (5.6.2), neoadjuvant therapy procedure (5.6.3), tumour response (5.6.4), survival details (5.6.5), and follow-up time (5.6.6).

5.6.1 Tumour classification means

The tumour resectability classification is conducted in the diagnosis phase of the PC care pathway and forms therefore the basis for any continuation of treatment. This classification was documented per patient in PURPLE, but whether these tumours were appropriately classified and documented in registry is uncertain due to the absence of any documentation regarding applied tumour criteria. As explained in Subsection 2.1.2, the world knows five prominent guidelines with classification criteria for PCs and these do differ, especially in their definitions of BR and LA tumours. Katz et al. (2012) demonstrated the consequences of using one guideline over the other. Therefore, any potential classification flaws have to be taken into account within the initial classification and documentation of PC tumours in PURPLE, which would ultimately have affected the the findings of this research. Future researchers should include a sensitivity analysis by up- and down-scaling the initial classification, especially with regard to simulation studies. This might lead to new sub-populations with different observations compared to the original and thus potentially providing new insights.

5.6.2 Quality of radiographic tumour detection

In addition to the tumour classification process, the quality of the CT imaging might also have played a role of significance the tumour classification process for the patients from PURPLE. Russo et al. (2016) mentioned that imaging from the CT scan might be misleading, because one of their included studies had observed undetected metastases in 10% to 20% of the resection cases. Simultaneously, Gilbert et al. (2017) reviewed two studies and concluded that the sensitivity for PC is between the 89% and 97%. So, there remains quite the discussion about the accuracy of CT imaging for the evaluation of the anatomic features of the PC tumour.

Isaji et al. (2018) proposed therefore the adoption of biological and conditional features, as additions to the traditional anatomic classification means. Despite the lack of consensus regarding the interpretation of the CT imaging variations, Isaji et al. claimed that there is consensus in the scientific literature about the associations between the BR patient and his biological and conditional features. The proposed classification system, as displayed in Figure 5.3, has not yet been evaluated on a non-metastatic PC population, which is a drawback for clinical practices today. Nevertheless, the system can be taken into account for future (simulation) studies or sensitivity analysis in the PC domain if the biological and conditional features are available for each individual. Our research did not apply this proposed model, but the CA (cancer antigen) 19-9 levels, regional lymph node metastases, and performance status (PS) can be obtained from PURPLE.

Type of definition	**Anatomical**	**Biological**	**Conditional**
R	R-Type A	No: R-Type A	No: R-Type A
		Yes: BR-Type B	Yes: BR-Type C
BR	BR-Type A	No: BR-Type A	No: BR-Type A
		Yes: BR-Type AB	Yes: BR-Type AC
Locally advanced: LA	LA-Type A	No: LA-Type A	No: LA-Type A
		Yes: LA- Type AB	Yes: LA-Type AC

Biological definition:
- CA 19-9 more than 500 IU/ml
- Regional lymph node metastasis (biopsy or PET-CT)

Conditional host-related definition:
- Depressed performance status (PS: 2 or more)

Figure 5.3: Proposal to classify pancreatic cancer patients based on anatomic, biological and conditional features (Isaji et al., 2018).

5.6.3 Neoadjuvant therapy procedure

Our research was able to obtain the regimen and assess the number cycles, but we had no knowledge about the (individual) clinical procedure details or handled clinical protocols from the 27 medical centres of PURPLE. Clinical decisions that might have affected the treatment outcomes are, amongst other things, the dose of chemotherapy or chemo-radiation therapy and the possible toxicity exposure from these treatments. However, this specific information remained unknown and we were thus unable to identify certain clinical factors, like toxicity, as potential confounders to the observed survival outcomes.

5.6.4 Tumour response evaluation

This research is uncertain about the applied criteria for the tumour response from the neoadjuvant therapy provision in post-neoadjuvant therapy phase of the care pathway. Tumour response evaluation can be assessed from a radiographic or pathological perspective, which are both accompanied with different criteria means and examination procedures.

The pathological protocol of the College of American Pathologists, developed by Kakar et al. (2017), is generally used for examining pancreatic tissue specimen during or after pancreatic surgery, but Yin et al. (2019) identified five other evaluation systems with slightly different interpretations of the pathological tumour response after neoadjuvant therapy.

Nevertheless, the radiographical tumour examination, using the 1.1 version of RECIST of Eisenhauer et al. (2009), seems to be the applied in PURPLE, because the tumour response categories of RECIST are similar to what is documented in the registry: complete response, partial response, stable disease, and progressive disease. However, this is an assumption and it might also be possible that another version or another type of tumour response examination is applied for the radiographical evaluation of the tumour after neoadjuvant therapy.

5.6.5 Survival details

The OS was in our study defined as the time from the moment of cancer diagnosis until the last review date for those who are still alive, according to the feature *vital status*. Although the BioGrid staff attempts to collect the PURPLE data as complete as possible, there is a probability that the *last review date* and *vital status* are not fully up-to-date for every patient. The staff made a great effort in updating the PURPLE registry for this thesis, but some of the patient's survival information will be incomplete, due to lost of follow-up. However, only 75 (11.6%) patients were lost to follow-up, which would not change our results drastically.

5.6.6 Follow-up period

The follow-up time was possibly too short for a long-term analysis about the added value of neoadjuvant therapy in PC. The PURPLE registry was established in 2016 and the patient with the oldest cancer diagnosis dated from 2009. As shown in the histogram of Figure 5.4, a majority of the patients from PURPLE were diagnosed between 2015 and 2018, and this is, medically speaking, not so long ago. Moreover, four of the original fourteen patients, who were diagnosed in 2012, are still alive today. This is quite extraordinary for a cancer type with a 5-year survival rate of less than 10%. One might say that it is too early to conduct this RWD study if one would use the data content of PURPLE. On the other hand, the longer research is postponed because of follow-up related arguments, the higher the probability that the research is no longer representative to the clinical field because practices change constantly. So, in the end, the short follow-up period has limited our findings, but a longer follow-up period might affect the relevance to the PC domain.

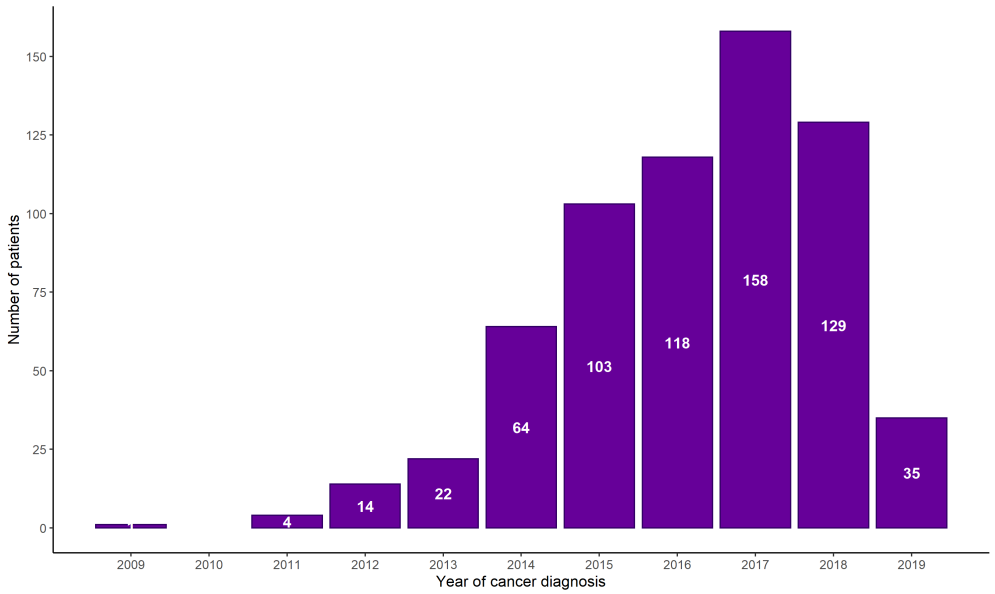

Figure 5.4: Histogram regarding the year of cancer diagnosis of the patients from PURPLE.

5.7 Other remarks to the analysis

This final section highlights some other general remarks that have not been illuminated yet.

Morbidity and quality of life
Our research solely focused on the survival measurements OS and RFS. However, mortality is just one aspect in the decision-making process for treatment. Another important aspect in the patient-centred considerations is morbidity, in which the consequences from the treatment are assessed in terms of quality of life. As seen from the various tables in this thesis, quite some patients have a high ECOG score and/or CCI. Sometimes due to jaundice or other PC-related co-morbidities. It might therefore be less desirable to confront these particular patients with neoadjuvant therapy and a possible surgical procedure if these worsen their morbidity afterwards. After all, neoadjuvant therapy could be accompanied with toxicity from the chemotherapy. Also, major blood loss may occur during surgery. Patients should have the ability to decline neoadjuvant treatment if research addresses a significant decrease in quality of life for patients who have a major morbidity. Treatments in PURPLE were not commenced if one was unsure about the post-treatment quality of life consequences, but this research did not contribute to this specific morbidity theme.

Truty et al. (2019) looked into factors associated with major morbidity in PC patients who were treated with neoadjuvant therapy and underwent subsequent surgery. In the end, the authors determined only excessive blood transfusion as an independent multivariate predictor for major morbidity. Features regarding neoadjuvant therapy were not associated with major morbidities.

Biomarker CA 19-9
The role of biomarker CA 19-9 had been studies during the exploration phase of our research proposal. Elevation of the CA 19-9 levels in the blood stream might indicate the presence of PC or a biliary obstruction, but several studies unsuccessfully attempted to associate *pre-neoadjuvant* CA 19-9 levels with the PC patient's survival outcomes and one therefore hypothesised that the pre-neoadjuvant CA 19-9 does not contain any predictive values (Ducreux et al., 2015).

However, Aldakkak et al. (2015) reported that the *post-neoadjuvant* CA 19-9 level had a better predictive value, because patients with a normalised CA 19-9 levels after neoadjuvant therapy gained a significant better OS compared to those with abnormal levels. In addition, Williams et al. (2016) retrospectively reviewed the records of 109 patients with either BR or LA tumours, and determined from the multivariate Cox models that a normalised CA 19-9 levels was associated with better survival outcomes. Moreover, even if a normalised CA 19-9 level is not reached, but an enormous decline was noticeable after neoadjuvant treatment compared to the situation beforehand, then this CA 19-9 drop leaded to promising survival of PC patients (Dhir et al., 2018). Williams et al. (2016) even proposed the adoption of CA 19-9 decline for whether a patient should by treated with an additional neoadjuvant therapy cycle (in case of elevated CA 19-9 level) or stop the therapy (in case of normalised CA 19-9).

So, CA 19-9 has the potential to further optimise the PC care pathway with regard to the provision of neoadjuvant therapy. This particular research recommendation had not been explored in this thesis due to the absence of post-neoadjuvant or post-treatment CA 19-9 levels in the PURPLE registry. It might be desirable to include all the CA 19-9 measurement throughout the complete care pathway of individual patients into PURPLE for a better understanding of the relation between cancer care and this particular biomarker.

6 | Conclusion

The aim of this master's thesis was to investigate retrospectively the potential survival benefit of using neoadjuvant therapy for resectable and unresectable tumour in PC patient by analysing multi-centred RWD of the PURPLE registry. Therefore, the following main research question was formulated:

What is the survival benefit of using neoadjuvant therapy in pancreatic cancer patients estimated with multi-centred real-world data collected in the PURPLE registry?

The multi-centred data from the PURPLE registry did not provide conclusive evidence to support the hypothesis that neoadjuvant therapy contributes to better survival outcomes for PC patients with either PR, BR or LA classified tumours. Most observations were not supported with a significant statistical test result due to the limited number of patients in certain research arms, the relative short follow-up period, and the influence of potential confounders. As feature for modelling, neoadjuvant therapy was therefore not related to OS because of its insufficient regressive property, as seen in the developed multivariate Cox regression model by using backwards stepwise selection. However, if neoadjuvant therapy is applied, then chemotherapy regimen FLX seems to be a better alternative compared to GNP in terms of OS. However, it is unsure whether FLX is applicable for patients of all ages and ECOG scores. This thesis is finalised with the following recommendations for future research:

- More variation in the neoadjuvant treatments is necessary to estimate the overall effects of neoadjuvant therapy in general and for specific cases based on the tumour's resectability classification. We recommend clinicians to discuss neoadjuvant treatment as possible treatment option, despite this might not be the first choice from a medical point of view. The potential increase of neoadjuvant therapy cases will contribute to worldwide knowledge of this treatment's effects within the PC domain.
- If more data is available and the follow-period is significantly prolonged, then we recommend re-conduction of the general survival analysis and a further identification of the confounders regarding the neoadjuvant therapy and the survival outcomes.
- We recommend to determine whether the type of therapy (chemotherapy versus chemoradiation), the regimen choice, and the duration of the neoadjuvant therapy affect the patient's survival, if more neoadjuvant therapy cases have been added to PURPLE.
- We recommend the adoption of all CA 19-9 biomarker data, such that one is able to investigate possible relation of the decline in CA 19-9 levels, due to neoadjuvant therapy, with the survival outcomes.

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A | Appendix: Figures

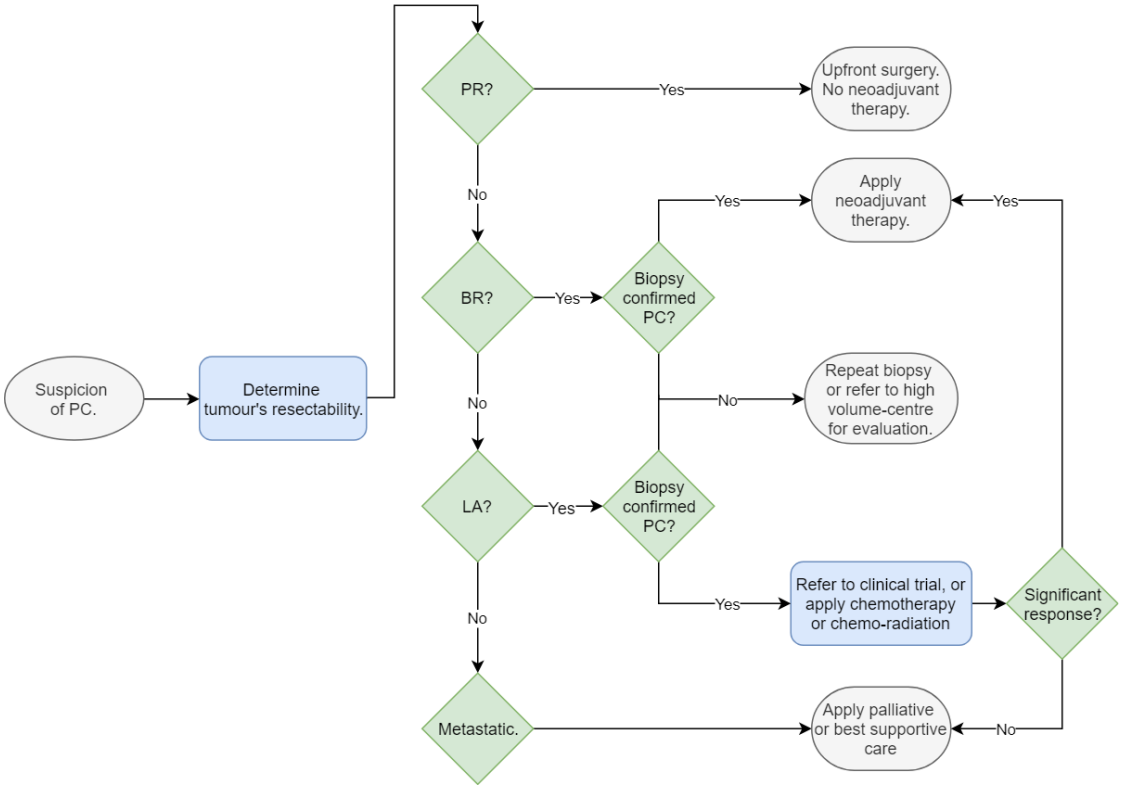

Figure A.1: Simplified overview of the clinical guidelines from the National Comprehensive Cancer Network about the application of neoadjuvant therapy in pancreatic cancer (PC) for resectable (PR), borderline resectable (BR), locally advanced (LA), and metastatic tumours (Tempero et al., 2017).

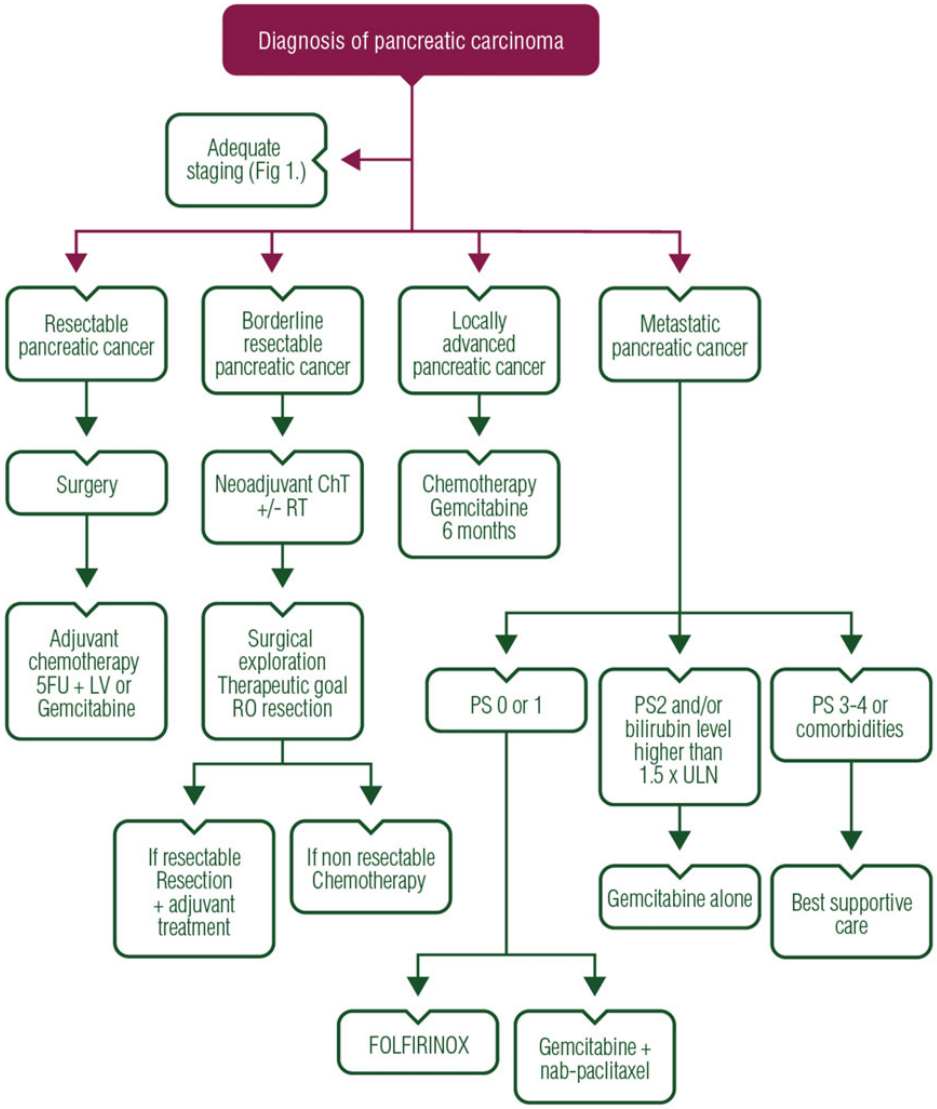

Figure A.2: Overview of the clinical guidelines from the European Society of Medical Oncology about the treatment of pancreatic cancer (PC) for resectable, borderline resectable, locally advanced, and metastatic pancreatic tumours (Ducreux et al., 2015).

		MD Anderson [8, 15]	AHPBA/SSAT/SSO [19]	NCCN (Version 2.2016) [22]	Alliance [23]
Celiac	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	No involvement	No involvement	Solid tumor[b] contact ≤180°, *or* >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery[a] (body/tail only)	Tumor-vessel interface <180°
	Locally Advanced	Any involvement	Any involvement	>180° solid tumor contact (any portion of pancreas), or any degree of solid tumor contact with aortic involvement (body/tail only)	Tumor-vessel interface ≥180°
SMA	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	Abutment ≤180°	Abutment ≤180°	Solid tumor contact ≤180°	Tumor-vessel interface <180°
	Locally Advanced	>180° involvement	>180° involvement	>180° solid tumor contact (any portion of pancreas), or any solid tumor contact with the first jejunal branch off SMA (head/uncinate only)	Tumor-vessel interface ≥180°
CHA	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	Short segment abutment <180° or encasement ≥180° amenable to reconstruction	Short segment abutment <180° or encasement ≥180° amenable to reconstruction	Solid tumor contact without extension to celiac axis or hepatic bifurcation, allowing for safe/complete reconstruction	Any degree of reconstructible involvement
	Locally Advanced	Involvement not amenable to reconstruction	Involvement not amenable to reconstruction	Any solid tumor contact with extension to celiac axis or hepatic bifurcation	Nonreconstructible involvement
SMV/PV	Resectable	Any involvement without occlusion	No involvement	No tumor contact with the SMV/PV *or* ≤180° contact without vein contour irregularity	Tumor-vessel interface <180°, no occlusion
	Borderline	Short segment occlusion only, with patent vein above and below the occlusion amenable to surgical reconstruction	Abutment, encasement, and/or occlusion amenable to surgical reconstruction (any involvement)	Solid tumor contact with the SMV/PV of > 180°, contact of ≤ 180° with contour irregularity of the vein, or thrombosis of the vein but with suitable vessel proximal and distal to the site allowing for safe and complete reconstruction	Tumor-vessel interface ≥180° and/or occlusion amenable to surgical reconstruction
	Locally Advanced	Non-reconstructible occlusion	Any non-reconstructible involvement or major venous thrombosis extending for several cm	Unreconstructible SMV/PV due to tumor involvement or occlusion (tumor or bland thrombus) *Head/uncinate only:* Contact with most proximal draining jejunal branch into SMV	Any non-reconstructible involvement

[a]This is a point of some controversy and would be considered unresectable according to certain NCCN 2016 panel members as noted in the most recent guidelines.
[b]'Solid tumor contact' can also be considered hazy density or stranding of the fat surrounding relevant peripancreatic vessels, reported on staging and follow-up imaging, with resectability decisions made through consensus at multidisciplinary meetings per most recent NCCN guidelines [22].

Figure A.3: Table from the review of Gilbert et al. (2017) in which the tumour criteria differences are displayed for each classification guideline per vessel and per classification.

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Figure A.4: The NCCN criteria for tumour classification of resectable (PR), borderline resectable (BR) and unresectable (LA) cases based on the arterial and venous tumour involvement (Tempero et al., 2017).

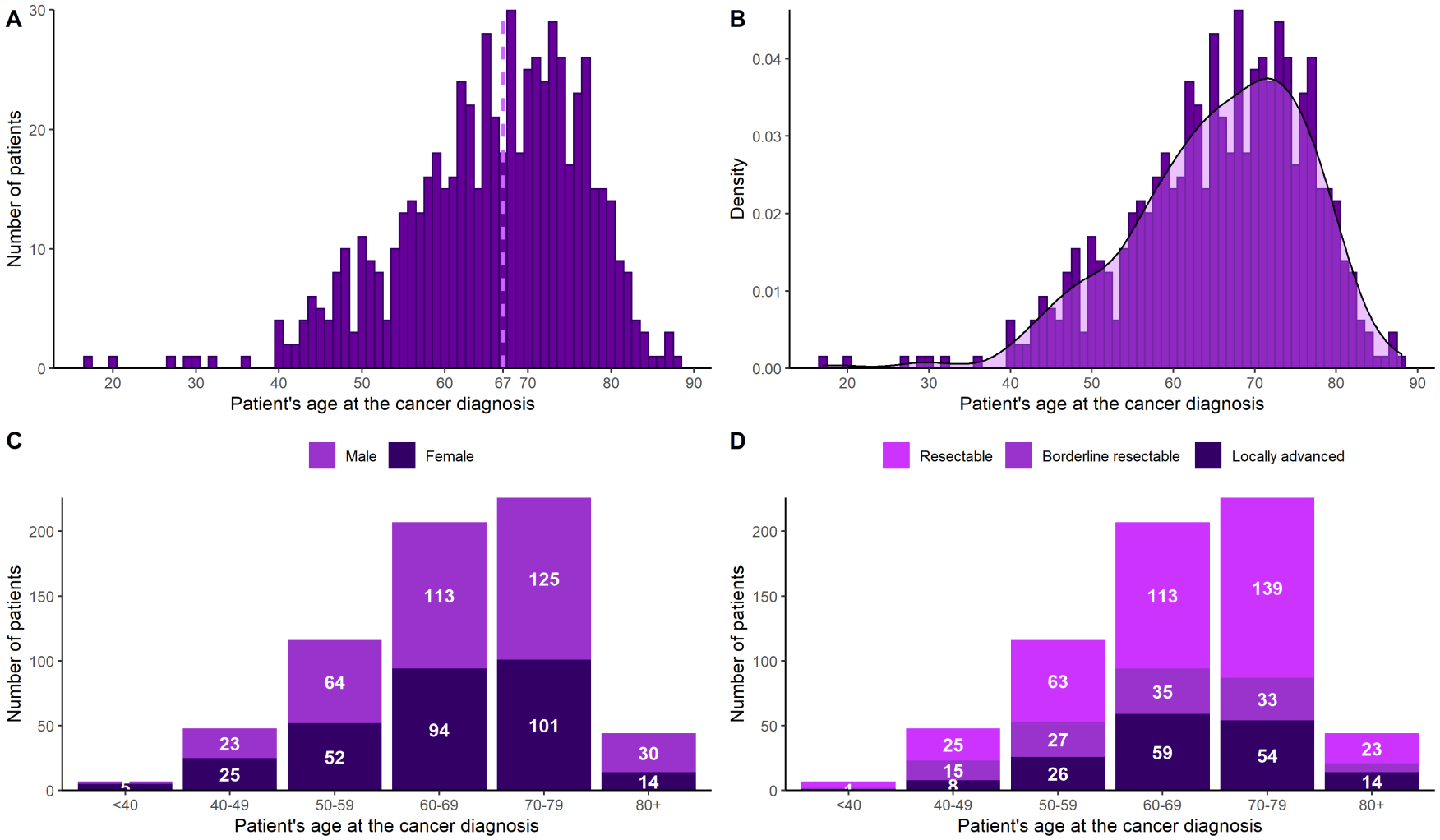

Figure A.5: Age related overview of the non-metastatic patient cohort (n = 408). **A** displays the median age. **B** displays the distribution of age at the cancer diagnosis. **C** displays the distribution of male and female patients per age category. **D** displays the distribution of the tumour resectability classification per age category.

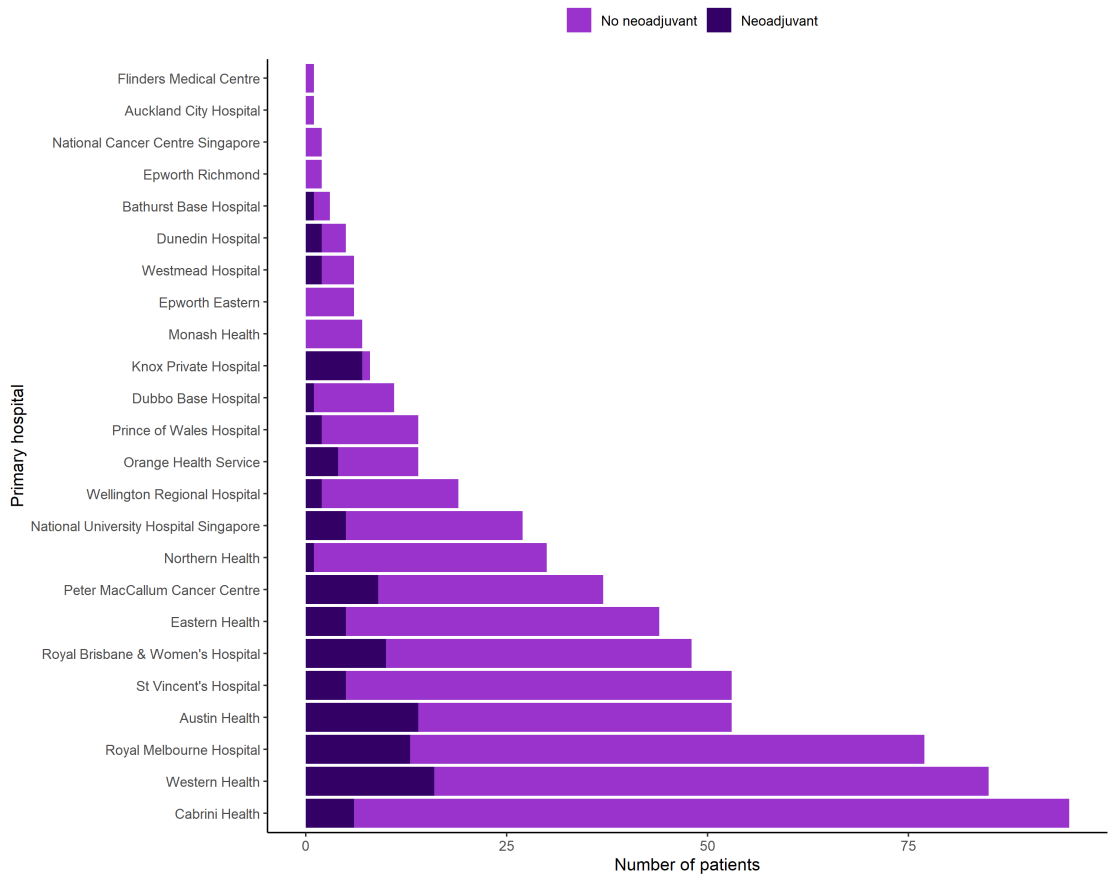

Figure A.6: Histogram of the primary treatment location, stratified for the neoadjuvant therapy.

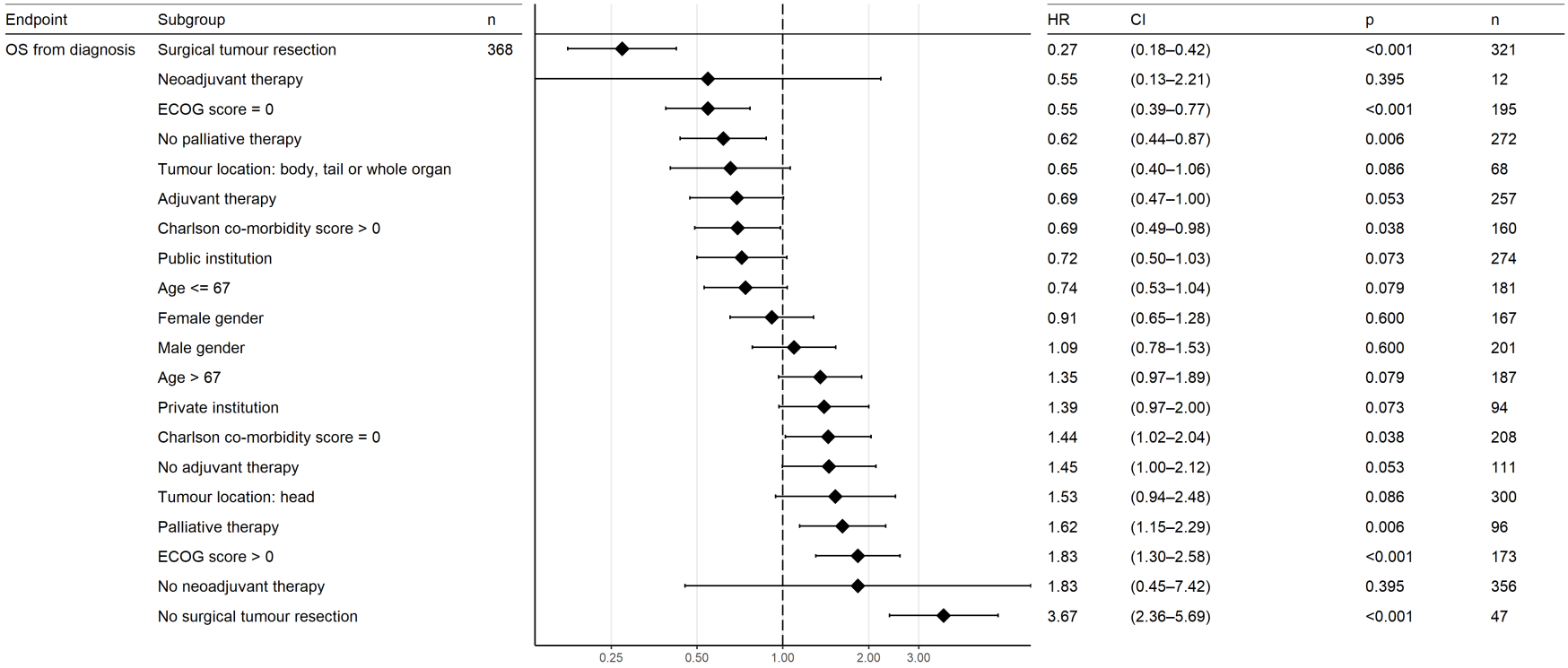

Figure A.7: Forest plot regarding the outcomes from the univariate Cox regression analysis about the influence of features to the overall survival (OS) in patients with a resectable (PR) pancreatic cancer tumour (n = 368). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

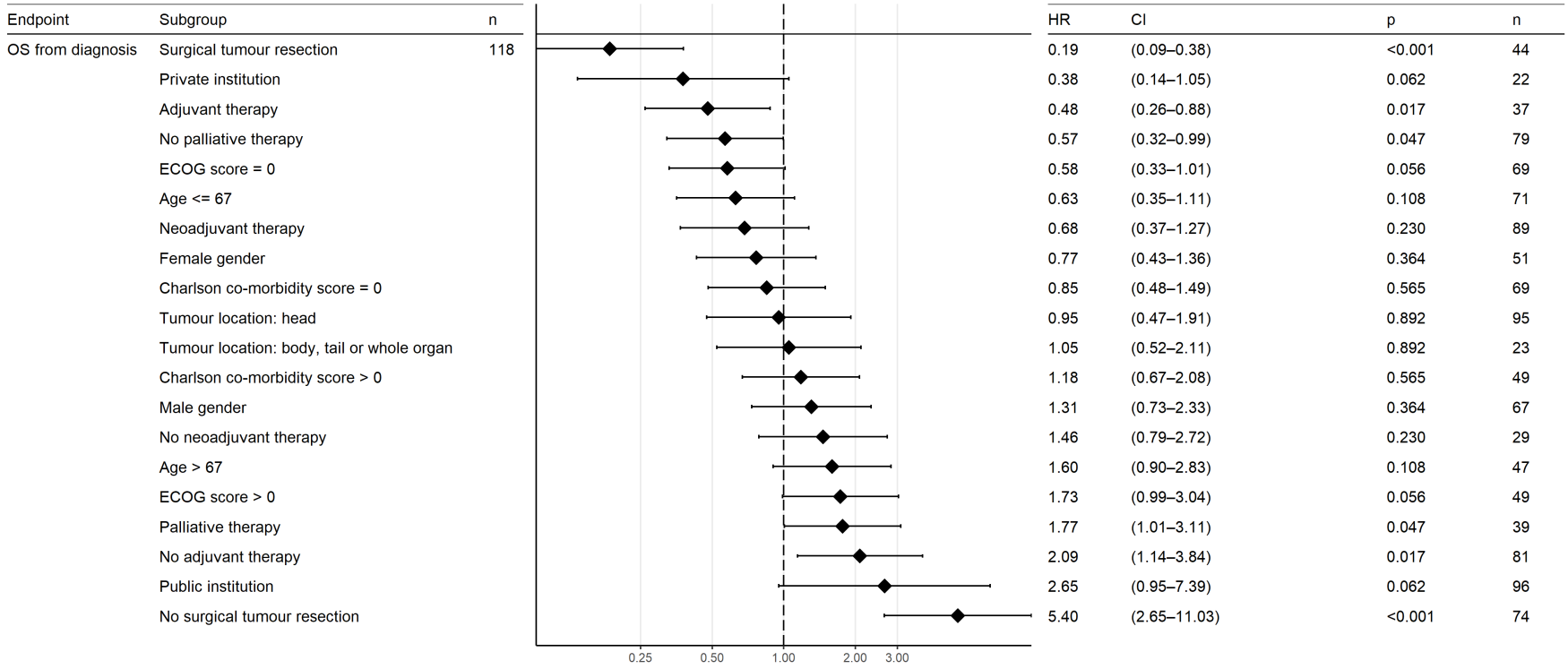

Figure A.8: Forest plot regarding the outcomes from the univariate Cox regression analysis about the influence of features to the overall survival (OS) in patients with a borderline resectable (BR) pancreatic cancer tumour (n = 118). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

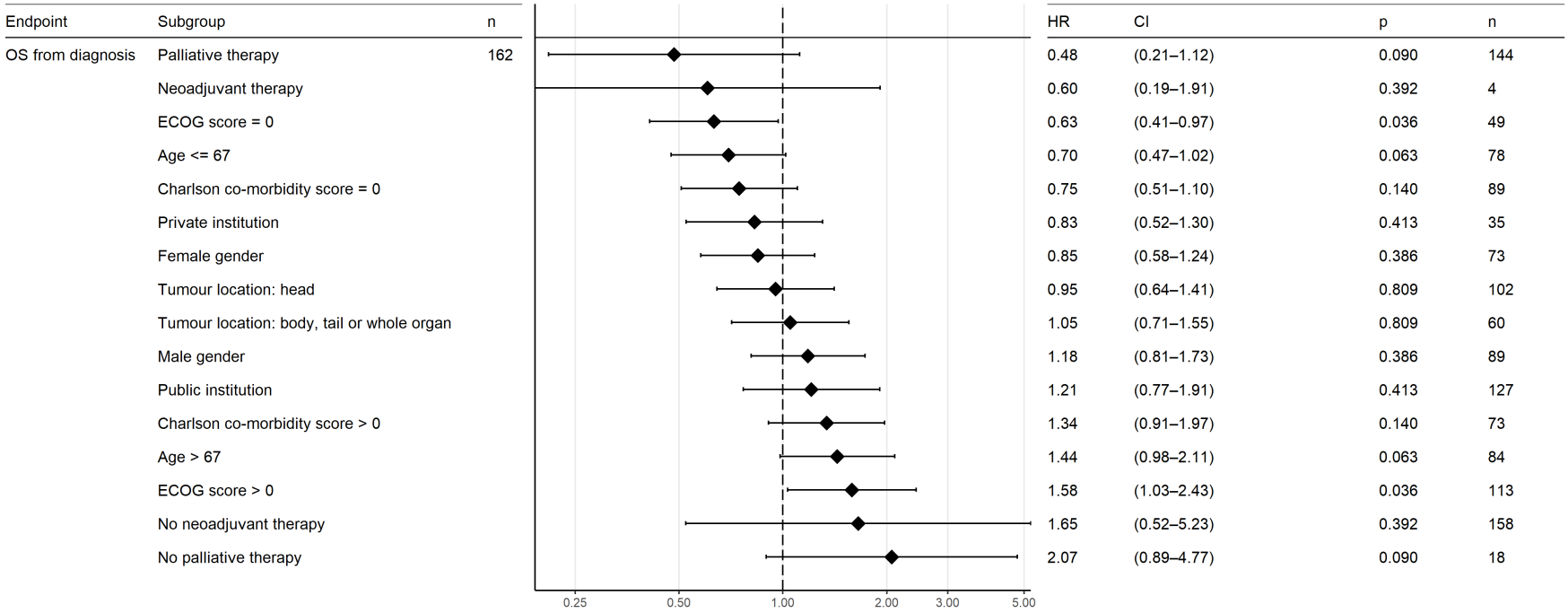

Figure A.9: Forest plot regarding the outcomes from the univariate Cox regression analysis about the influence of features to the overall survival (OS) in patients with a locally advanced (LA) unresectable pancreatic cancer tumour (n = 162). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

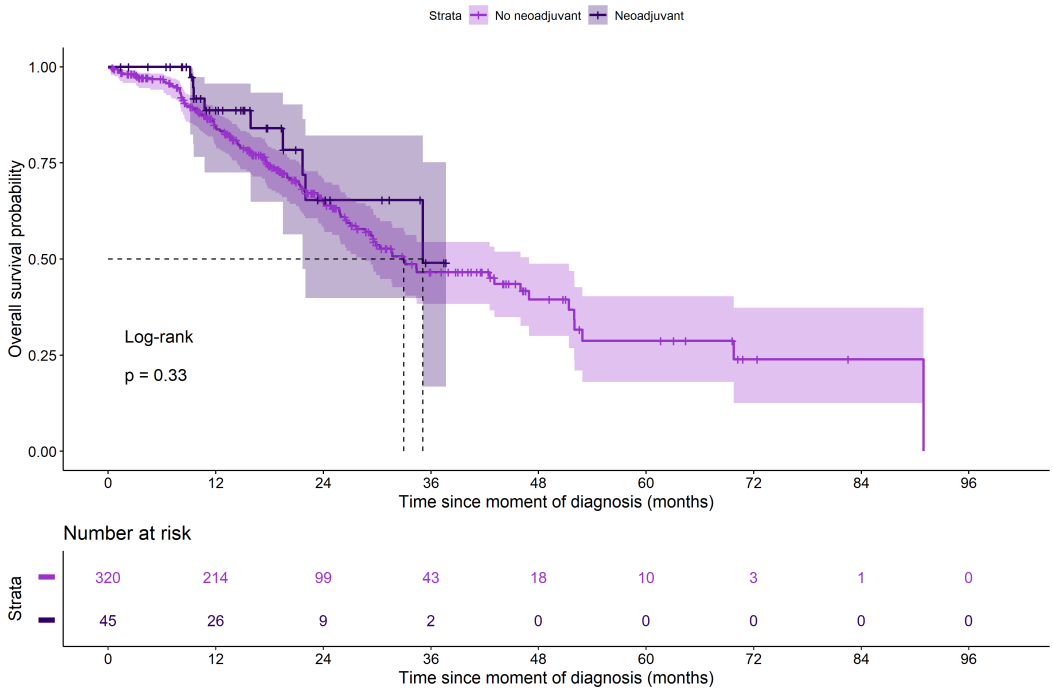

Figure A.10: Kaplan-Meier plot and risk table regarding the overall survival (OS) following the usage of neoadjuvant therapy in the successful resection sub-population (n = 365), containing resectable, borderline resectable and locally advanced cases together. Log-rank test is applied for the statistical comparison.

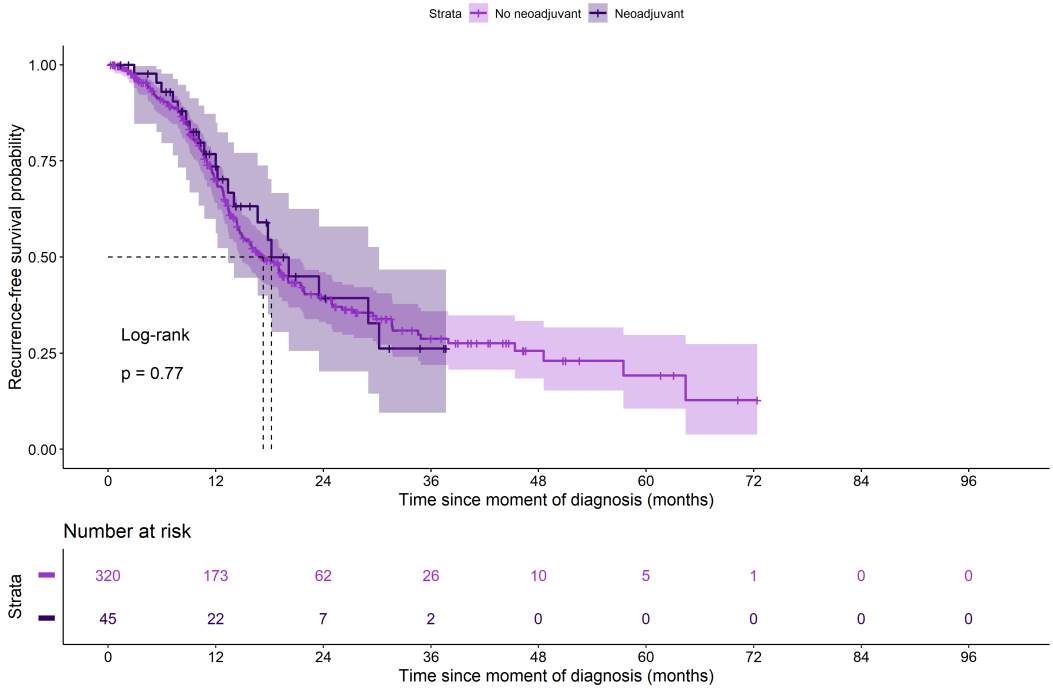

Figure A.11: Kaplan-Meier plot and risk table regarding the recurrence-free survival (RFS) following the usage of neoadjuvant therapy in the successful resection sub-population (n = 365), containing resectable, borderline resectable and locally advanced cases together. Log-rank test is applied for the statistical comparison.

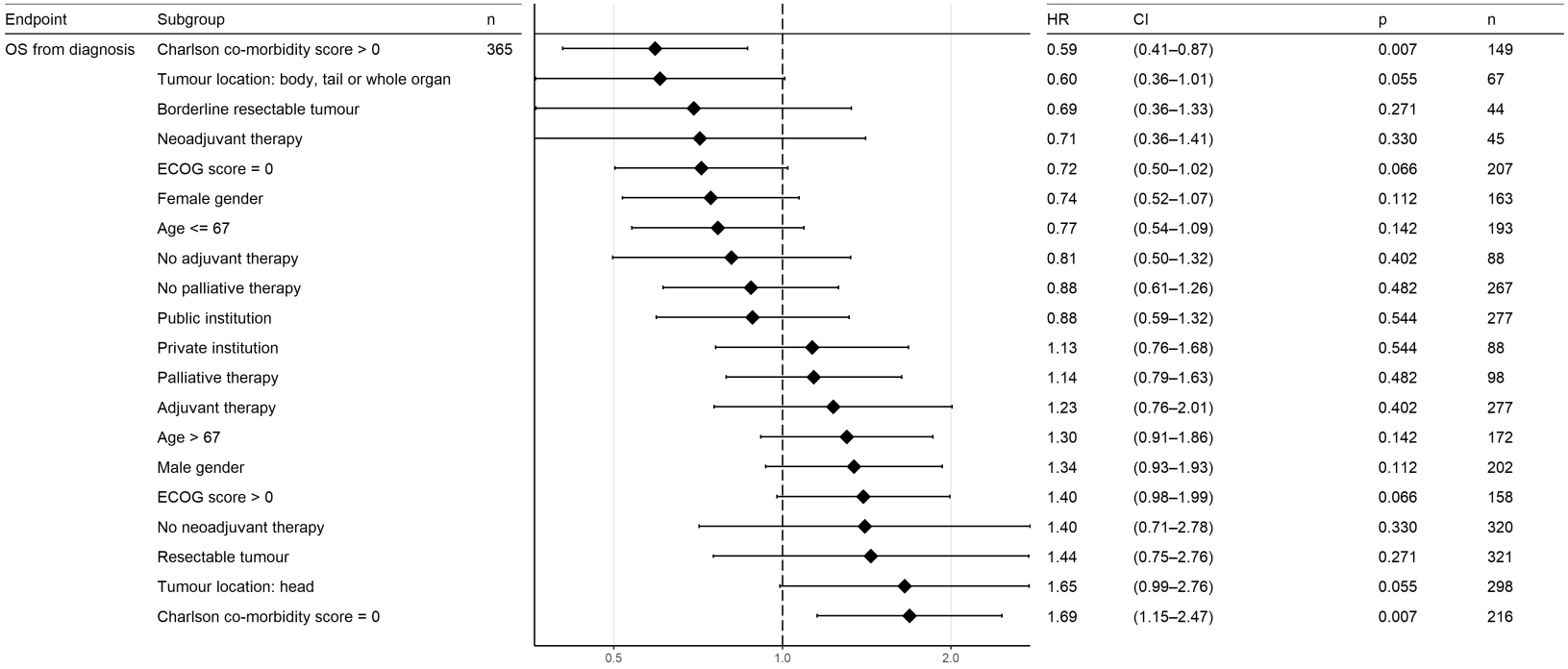

Figure A.12: Forest plot regarding the outcomes from the univariate Cox proportional hazards model of features affecting the overall survival (OS) in the successful resection sub-population (n = 365). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

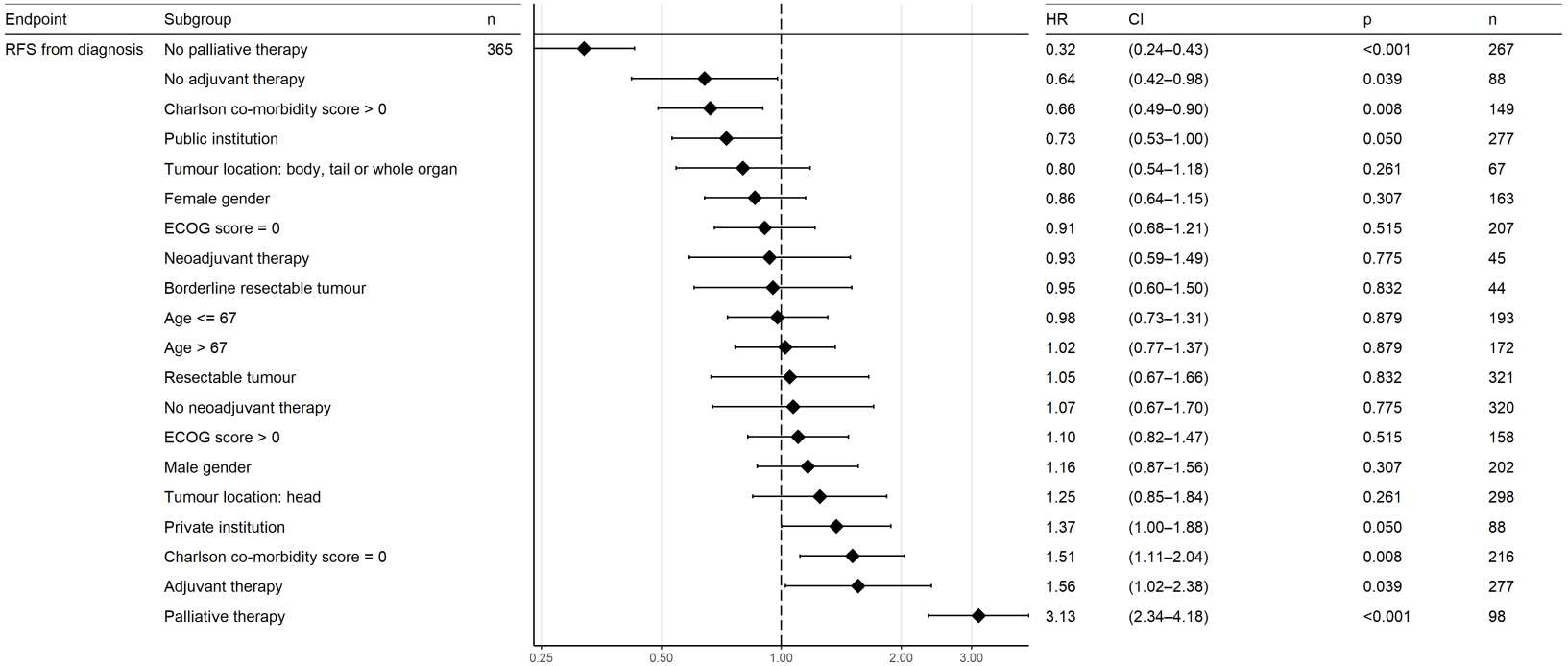

Figure A.13: Forest plot regarding the outcomes from the univariate Cox regression analysis of features affecting recurrence-free survival (RFS) in the successful resection sub-population (n = 365). The Wald test was applied as statistical test.
HR: hazard ratio; *CI*: confidence interval; *p*: P-value; *n*: number of patients.

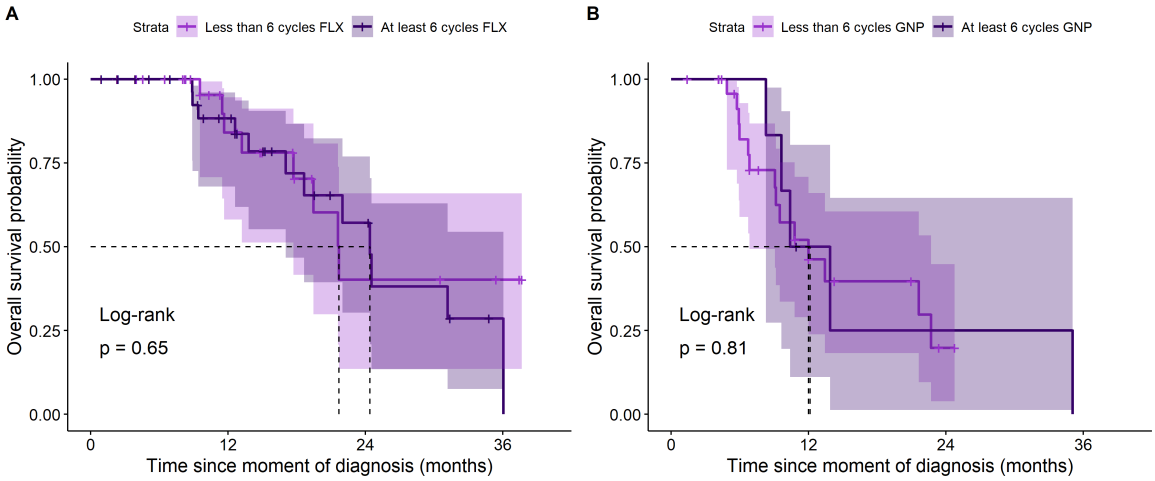

Figure A.14: Kaplan-Meier plot regarding of the overall survival (OS) following the neoadjuvant therapy duration for **A:** FOLFIRINOX (n = 64); and **B:** gemcitabine nab-paclitaxel (n = 33) in the neoadjuvant therapy specific sub-population (n = 97). Log-rank test is applied for the statistical comparison.

B | Appendix: Tables

Table B.1: Search matrix of the thesis.

No.	Data base	Key 1	Key 2	Key 3	Key 4	No. results	Sort on	Document type
1	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy	Resection		884	Cited by (high)	All
2	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy	Resection		206	Relevance	Reviews
3	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy	Resection		206	Date (newest)	Reviews
4	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy OR preoperative chemotherapy	Resection	Model	97	Relevance	All
5	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy OR preoperative chemotherapy	Resection	Simulation	3	Relevance	All
6	PubMed	Pancreatic cancer	Neoadjuvant chemotherapy OR preoperative chemotherapy	Resection OR resectable	Model OR simulation OR cost-effectiveness OR cost effectiveness	109	Best match	All
7	PubMed	Pancreatic cancer	Neoadjuvant chemotherapy OR preoperative chemotherapy	Resection OR resectable	Markov OR discrete-event simulation	2	Best match	All
8	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy	Australia		5		
9	Scopus	Pancreatic cancer	Neoadjuvant chemotherapy	Phase III	Randomised controlled trial	34	Relevance	All
10	Scopus	Pancreatic cancer	Borderline resectable	CA 19-9		40	Relevance	All
11	Scopus	Pancreatic cancer	Borderline resectable	Locally advanced	Resectable	289	Relevance	All
12	Scopus	Pancreatic cancer	Neoadjuvant therapy	Regimen		78	Relevance	Reviews
13	Pubmed	Pancreatic cancer	Neoadjuvant therapy	Real-world data		2	Best match	All

Table B.2: Included and excluded features from tables *Patient summary* and *Patient*.

Patient summary		*Patient*	
Included features	**Excluded features**	**Included features**	**Excluded features**
UNIVID	Clinician	UNIVID	Medicare NUM
Vital status	Last review disease status	Date of birth	Last name
Date of death	Summary comments	Gender	First name
Death date estimated		Patient deleted	Middle initial
Cause of death			Address
Lost to follow-up			Postcode
Date of review			Country
Primary Hospital			URN
Institution type			Comment

Table B.3: Included and excluded features from tables *Medical history* and *Chemotherapy regimen*.

Medical history		*Chemotherapy regimen*	
Included features	**Excluded features**	**Included features**	**Excluded features**
UNIVID	ID	UNIVID	ID
Agescore	Prior malignancy	Chemotherapy regimen	Chemotherapy regimen other
Co-morbidity score	Prior malignancy type	Trigger point	
Total score	Smoking history	Line	
ECOG	Family history of cancer		
	Alcohol history		

Table B.4: Included and excluded features from tables *Tumour details* and *Specimen details*.

Tumour details		*Specimen details*	
Included features	**Excluded features**	**Included features**	**Excluded features**
UNIVID	ID	UNIVID	ID
Initial detection method	Adjuvant treatment	Specimen type	Specimen ID
Cancer diagnosis date	Treatment plan	Tumour locating	Histology
Age at primary diagnosis	Treatment plan other	T staging	TILS
Tumour stage	Biomarkers	N staging	Number of nodes examined
Tumour location	Stenting required	M staging	Number of positive nodes
Resectability	Stent location	R status	Nodal count unknown
Biopsy proven	Referred to palliative care	Tumour grade	Pancreatic intraepithelial neoplasia
Presenting symptoms	Date of palliative care reference		Lymphatic invastion
			Perineural invasion
			Tumour confirmed
			Tumour size length
			Tumour size width
			Tumour size depth
			Mediapath number

Table B.5: Included and excluded features from tables *Treatment* and *Surgery details*.

Treatment		*Surgery details*	
Included features	**Excluded features**	**Included features**	**Excluded features**
UNIVID	Master ID	UNIVID	ID
Trigger point	Biomarkers	Interval	No tumour resected reason
Line	Therapy type other	Tumour resected	Palliative
Therapy type	Radiotherapy	Surgery performed	Palliative procedure type
Clinical trial		Surgery date	Procedure type
Patient therapy			Location
Therapy interval			Location other
Therapy duration			Stent insertion required
Therapy response			Stent type
Therapy start date			Stent location
Therapy stop date			Splenectomy
Therapy stopped			Metastatic sites
Therapy indented			Specimen
			Neoadjuvant
			Adjuvant

Table B.6: Included and excluded features from table *Recurrence*.

Recurrence	
Included features	**Excluded features**
UNIVID	ID
Progression date	Specimen details
Biopsy proven	Detection method
	ECOG
	Subsequent treatment
	Biomarkers
	Medipath number

Table B.7: Eastern cooperative oncology group (ECOG) score.

Score	Performance status
0	Fully active.
1	Able to carry out light work.
2	Unable to work, but up >50% of waking hours.
3	Limited self-care, bed or chair bound >50% of waking hours.
4	Completely bed or chair bound.

Table B.8: Comorbidities for the Charlson Comorbidity Index (CCI).

Score	Co-morbidity status
0	No comborbidities
1	- Myocardial infarction (history, not ECG changes only) - Congestive heart failure - Peripheral vascular disease (includes aortic aneurysm >6cm) - Cerebrovascular disease: CVA with mild or no residual deficits or TIA - Dementia - Chronic obstructive pulmonary disease - Connective tissue disease - Peptic ulcer disease - Mild liver disease - Diabetes: no end-organ complications
2	- Diabetes: end-organ complications (retinopathy, neuropathy, nephropathy, brittle) - Hemiplegia/stroke - Mod-severe renal disease (dialysis, renal transplant, estimated GFR <30ml/min) - Mod-severe renal disease (dialysis, renal transplant, estimated GFR <30ml/min) - Lymphoma (Lymphoma or myeloma) - Leukaemia (acute or chronic)
3	- Mod-severe liver disease (cirrhosis with portal hypertension)
6	- Acquired immune deficiency syndrome (not just HIV positive) - Second Metastatic solid tumour (separate to metastatic breast cancer)

Table B.9: Tumour response definitions from the 1.1 version of RECIST by Eisenhauer et al. (2009) for radiographic tumour evaluation.

Tumour response	Description
Complete response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
Progressive disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Table B.10: Demographics and clinical characteristics of the non-metastatic patient cohort, stratified for tumour's resectability. Kruskal-Wallis and Chi-square tests were applied.

Feature	**Potential resectable (n = 368)**	**Borderline resectable (n = 118)**	**Locally advanced (n = 162)**	**Total (n = 648)**	**P-value**
Gender					0.918
- Male	201 (54.6%)	67 (56.8%)	89 (54.9%)	357 (55.1%)	
- Female	167 (45.4%)	51 (43.2%)	73 (45.1%)	291 (44.9%)	
Age at primary diagnosis					0.026
- Mean (SD)	65.812 (10.937)	63.331 (11.178)	66.901 (10.147)	65.633 (10.838)	
- Median	68	65	68	67	
- Q1, Q3	59, 73	56, 72	61, 75	59, 74	
ECOG score					<0.001
- 0	195 (53.0%)	69 (58.5%)	49 (30.2%)	313 (48.3%)	
- 1	159 (43.2%)	41 (34.7%)	88 (54.3%)	288 (44.4%)	
- 2/3	14 (3.8%)	8 (6.8%)	25 (15.4%)	47 (7.3%)	
Charlson Comorbidity Index					0.224
- 0	208 (56.5%)	69 (58.5%)	89 (54.9%)	366 (56.5%)	
- 1	103 (28.0%)	40 (33.9%)	47 (29.0%)	190 (29.3%)	
- 2	37 (10.1%)	3 (2.5%)	14 (8.6%)	54 (8.3%)	
- 2<	20 (5.4%)	6 (5.1%)	12 (7.4%)	38 (5.9%)	
Tumour location					<0.001
- Head	300 (81.5%)	95 (80.5%)	102 (63.0%)	497 (76.7%)	
- Body	28 (7.6%)	18 (15.3%)	45 (27.8%)	91 (14.0%)	
- Tail	36 (9.8%)	4 (3.4%)	14 (8.6%)	54 (8.3%)	
- Whole organ	4 (1.1%)	1 (0.8%)	1 (0.6%)	6 (0.9%)	
Tumour resected					<0.001
- Yes	321 (87.2%)	44 (37.3%)	0 (0.0%)	365 (56.3%)	
- No	25 (6.8%)	23 (19.5%)	6 (3.7%)	54 (8.3%)	
- Surgery was not performed	22 (6.0%)	51 (43.2%)	156 (96.3%)	229 (35.3%)	
Neoadjuvant therapy provided					<0.001
- Yes	12 (3.3%)	89 (75.4%)	4 (2.5%)	105 (16.2%)	
- No	356 (96.7%)	29 (24.6%)	158 (97.5%)	543 (83.8%)	
Adjuvant therapy provided					<0.001
- Yes	257 (69.8%)	37 (31.4%)	0 (0.0%)	294 (45.4%)	
- No	111 (30.2%)	81 (68.6%)	162 (100.0%)	354 (54.6%)	

Palliative therapy provided					<0.001
- Yes	96 (26.1%)	39 (33.1%)	144 (88.9%)	279 (43.1%)	
- No	272 (73.9%)	79 (66.9%)	18 (11.1%)	369 (56.9%)	
Lost to follow-up					0.355
- Yes	37 (10.1%)	15 (12.7%)	23 (14.2%)	75 (11.6%)	
- No	331 (89.9%)	103 (87.3%)	139 (85.8%)	573 (88.4%)	
Enrolled in neoadjuvant clinical trial					0.193
- Yes	38 (10.3%)	12 (10.2%)	9 (5.6%)	59 (9.1%)	
- No	330 (89.7%)	106 (89.8%)	153 (94.4%)	589 (90.9%)	
Institution type					0.256
- Public	274 (74.5%)	96 (81.4%)	127 (78.4%)	497 (76.7%)	
- Private	94 (25.5%)	22 (18.6%)	35 (21.6%)	151 (23.3%)	

Table B.11: Demographics and clinical characteristics of the successful resection patient cohort, stratified for neoadjuvant therapy. Kruskal-Wallis and Fisher's Exact tests were applied.

Feature	**No neoadjuvant therapy (n = 320)**	**Neoadjuvant therapy (n = 45)**	**Total (n = 365)**	**P-value**
Gender				0.424
- Male	180 (56.2%)	22 (48.9%)	202 (55.3%)	
- Female	140 (43.8%)	23 (51.1%)	163 (44.7%)	
Age at primary diagnosis				0.001
- Mean (SD)	65.459 (11.164)	59.911 (11.151)	64.775 (11.296)	
- Median	67	62	66	
- Q1, Q3	59, 73	52, 68	58, 73	
ECOG score				0.042
- 0	174 (54.4%)	33 (73.3%)	207 (56.7%)	
- 1	134 (41.9%)	12 (26.7%)	146 (40.0%)	
- 2/3	12 (3.8%)	0 (0.0%)	12 (3.3%)	
Charlson Comorbidity Index				0.268
- 0	183 (57.2%)	33 (73.3%)	216 (59.2%)	
- 1	91 (28.4%)	9 (20.0%)	100 (27.4%)	
- 2	31 (9.7%)	2 (4.4%)	33 (9.0%)	
- 2<	15 (4.7%)	1 (2.2%)	16 (4.4%)	
Tumour location				0.038
- Head	259 (80.9%)	39 (86.7%)	298 (81.6%)	
- Body	24 (7.5%)	6 (13.3%)	30 (8.2%)	
- Tail	34 (10.6%)	0 (0.0%)	34 (9.3%)	
- Whole organ	3 (0.9%)	0 (0.0%)	3 (0.8%)	
Tumour's resectability				<0.001
- Potential resectable	315 (98.4%)	6 (13.3%)	321 (87.9%)	
- Borderline resectable	5 (1.6%)	39 (86.7%)	44 (12.1%)	
- Locally advanced	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Adjuvant therapy provided				0.014
- Yes	250 (78.1%)	27 (60.0%)	277 (75.9%)	
- No	70 (21.9%)	18 (40.0%)	88 (24.1%)	
Palliative therapy provided				0.858
- Yes	87 (27.2%)	11 (24.4%)	98 (26.8%)	
- No	233 (72.8%)	34 (75.6%)	267 (73.2%)	
Lost to follow-up				0.598
- Yes	32 (10.0%)	3 (6.7%)	35 (9.6%)	
- No	288 (90.0%)	42 (93.3%)	330 (90.4%)	
Enrolled in neoadjuvant clinical trial				0.623
- Yes	36 (11.2%)	6 (13.3%)	42 (11.5%)	
- No	284 (88.8%)	39 (86.7%)	323 (88.5%)	
Institution type				0.710
- Public	244 (76.2%)	33 (73.3%)	277 (75.9%)	
- Private	76 (23.8%)	12 (26.7%)	88 (24.1%)	

Table B.12: Demographics and clinical characteristics of the neoadjuvant therapy patient cohort, stratified for regimen: FOLFIRINOX (FLX) or gemcitabine nab-paclitaxel (GNP). Kruskal-Wallis and Fisher's Exact test were applied.

Feature	**FLX (n = 64)**	**GNP (n = 33)**	**Total (n = 97)**	**P-value**
Gender				0.669
- Male	33 (51.6%)	19 (57.6%)	52 (53.6%)	
- Female	31 (48.4%)	14 (42.4%)	45 (46.4%)	
Age at primary diagnosis				<0.001
- Mean (SD)	60.016 (9.695)	67.455 (10.906)	62.546 (10.671)	
- Median	61	70	64	
- Q1, Q3	53, 67	65, 75	55, 71	
ECOG score				0.023
- 0	46 (71.9%)	15 (45.5%)	61 (62.9%)	
- 1	17 (26.6%)	16 (48.5%)	33 (34.0%)	
- 2/3	1 (1.6%)	2 (6.1%)	3 (3.1%)	
Charlson Comorbidity Index				0.237
- 0	45 (70.3%)	17 (51.5%)	62 (63.9%)	
- 1	15 (23.4%)	13 (39.4%)	28 (28.9%)	
- 2	2 (3.1%)	1 (3.0%)	3 (3.1%)	
- 2<	2 (3.1%)	2 (6.1%)	4 (4.1%)	
Tumour location				0.155
- Head	51 (79.7%)	26 (78.8%)	77 (79.4%)	
- Body	13 (20.3%)	5 (15.2%)	18 (18.6%)	
- Tail	0 (0.0%)	2 (6.1%)	2 (2.1%)	
Tumour's resectability				0.638
- Potential resectable	8 (12.5%)	2 (6.1%)	10 (10.3%)	
- Borderline resectable	53 (82.8%)	30 (90.9%)	83 (85.6%)	
- Locally advanced	3 (4.7%)	1 (3.0%)	4 (4.1%)	
Offered therapy				0.037
- Chemotherapy	64 (100.0%)	30 (90.9%)	94 (96.9%)	
- Chemo-radiotherapy	0 (0.0%)	3 (9.1%)	3 (3.1%)	
Number of completed therapy cycles				<0.001
- Mean (SD)	7.891 (8.231)	3.939 (6.159)	6.546 (7.788)	
- Median	5.500	2.000	5.000	
- Q1, Q3	4.000, 9.000	2.000, 4.000	2.000, 8.000	
Number of completed chemo-cycles >5				0.002
- Yes	32 (50.0%)	6 (18.2%)	38 (39.2%)	
- No	32 (50.0%)	27 (81.8%)	59 (60.8%)	
Tumour response				0.242
- Complete response	3 (4.7%)	0 (0.0%)	3 (3.1%)	
- Partial response	26 (40.6%)	17 (51.5%)	43 (44.3%)	
- Stable disease	15 (23.4%)	5 (15.2%)	20 (20.6%)	
- Progressive disease	9 (14.1%)	9 (27.3%)	18 (18.6%)	
- No evidence of disease	4 (6.2%)	0 (0.0%)	4 (4.1%)	
- Unknown	7 (10.9%)	2 (6.1%)	9 (9.3%)	
Tumour resectected				0.254
- Yes	32 (50.0%)	11 (33.3%)	43 (44.3%)	
- No	9 (14.1%)	5 (15.2%)	14 (14.4%)	
- Surgery was not performed	23 (35.9%)	17 (51.5%)	40 (41.2%)	
Adjuvant therapy provided				0.655
- Yes	23 (35.9%)	10 (30.3%)	33 (34.0%)	
- No	41 (64.1%)	23 (69.7%)	64 (66.0%)	
Palliative therapy provided				0.646
- Yes	22 (34.4%)	9 (27.3%)	31 (32.0%)	
- No	42 (65.6%)	24 (72.7%)	66 (68.0%)	

Lost to follow-up				0.714
- Yes	7 (10.9%)	2 (6.1%)	9 (9.3%)	
- No	57 (89.1%)	31 (93.9%)	88 (90.7%)	
Enrolled in neoadjuvant clinical trial				0.100
- Yes	5 (7.8%)	7 (21.2%)	12 (12.4%)	
- No	59 (92.2%)	26 (78.8%)	85 (87.6%)	
Institution type				0.280
- Public	49 (76.6%)	29 (87.9%)	78 (80.4%)	
- Private	15 (23.4%)	4 (12.1%)	19 (19.6%)	

Table B.13: Association analysis between the tumour resectability classification and the tumour response after neoadjuvant therapy. Chi-squared test is performed for the statistical analysis.

Feature	**Potential resectable (n = 10)**	**Borderline resectable (n = 83)**	**Locally advanced (n = 4)**	**Total (n = 97)**	***P*-value**
Therapy response					<0.001
- Complete response	0 (0.0%)	3 (3.6%)	0 (0.0%)	3 (3.1%)	
- Partial response	1 (10.0%)	39 (47.0%)	3 (75.0%)	43 (44.3%)	
- Stable disease	4 (40.0%)	15 (18.1%)	1 (25.0%)	20 (20.6%)	
- Progressive disease	0 (0.0%)	18 (21.7%)	0 (0.0%)	18 (18.6%)	
- No evidence of disease	4 (40.0%)	0 (0.0%)	0 (0.0%)	4 (4.1%)	
- Unknown	1 (10.0%)	8 (9.6%)	0 (0.0%)	9 (9.3%)	

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