2019-05-06

Improved Survival after Administration of Neoadjuvant Chemotherapy in Patients with Clinical Stage I/II Pancreatic Ductal Adenocarcinoma

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IMPROVED SURVIVAL AFTER ADMINISTRATION OF NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH CLINICAL STAGE I/II PANCREATIC DUCTAL ADENOCARCINOMA

A Masters Thesis Presented

BY

RYAN J. HENDRIX, MD

Submitted to the Faculty of the
University of Massachusetts Graduate School of Biomedical Sciences, Worcester
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

MAY 6, 2019

BIOMEDICAL SCIENCES
HEALTH SERVICES RESEARCH

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Program
Masters of Science in Clinical Investigation

MAY 6, 2019

ACKNOWLEDGEMENTS

I would like to acknowledge and sincerely thank my mentor, Dr. Jennifer LaFemina, for her mentorship, guidance, and genuine investment in my education; this would not have been possible without her support and significant time commitment. I would also like to thank the contributors to this project, Dr. Eva Rouanet, Dr. Bradley Switzer, Dr. Tasneem Ali, Dr. Venu Bathini, and Dr. Giles Whalen. My Thesis Research Advisory Committee included Dr. Robert Goldberg, Dr. Jeremy Aidlen, and Dr. Mara Epstein, all of whom were instrumental in the completion and success of this project. Lastly, I would like to thank my colleagues in the Surgical Research Scholars Program, Dr. Robert McLoughlin, Dr. David Meyer, Dr. Chau Hoang, Dr. Stacy Sanders, and Dr. Vijaya Daniel. Funding for this study was provided by the Division of Surgical Oncology at the University of Massachusetts Medical School and through generous donations from the Pancreatic Cancer Alliance and the Verville Foundation.

ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of US cancer related deaths. This study assessed the oncologic benefit of a neoadjuvant chemotherapy (NAC) treatment strategy for patients with clinical Stage I/II PDAC.

Methods: Patients with biopsy confirmed PDAC and clinical Stage I/II disease were treated with a protocol of NAC. The primary study endpoint was median overall survival (OS). Kaplan-Meier survival curves were compared using the log-rank test.

Results: 56 patients met inclusion criteria. Of these, 21 patients (38%) had Stage I disease and 35 (62%) had Stage II disease. The median OS for the entire study population was 18.7 months. A total of 22 (39%) patients were managed with NAC+S; 34 (61%) received NAC alone. Median OS and 2-year survival rates were greater in those completing NAC+S compared to NAC alone (median OS 28.8 months vs. 17.3 months: p=0.05; 2-year OS: 55% vs 21%: p=0.01) . Interestingly, patients managed with NAC who were not candidates for surgical resection after restaging demonstrated a survival advantage (17.3 months) compared to what was previously reported in historical controls.

Conclusion: NAC+S provided a significant 11.5 month improvement in median OS compared to treatment with NAC alone. Modern NAC may contribute a significant oncologic benefit in the overall treatment strategy for patients with Stage I/II PDAC, even if surgery is not ultimately pursued.

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Figure 5: Kaplan Meier Analysis of Overall Survival for Stage I/II PDAC According to Treatment Type

For patients with biopsy confirmed Stage I and II Pancreatic Ductal Adenocarcinoma, median OS were determined by the Kaplan Meier method. Results were compared by treatment type: neoadjuvant chemotherapy alone versus neoadjuvant chemotherapy plus potentially curative surgical resection.

LIST OF THIRD PARTY COPYRIGHTED MATERIAL

Supplemental 1: Pancreatic Cancer Stage IA, IB, IIA, IIB - CDR687928, CDR687932, CDR742418 . Terese Winslow.

Stage I pancreatic cancer is found in the pancreas only. In stage IA pancreatic cancer, the tumor is two centimeters in diameter or smaller. In stage IB, the tumor is larger than two centimeters in diameter but not larger than four centimeters. In stage IIA pancreatic cancer the tumor is larger than four centimeters. For stage IIB, the tumor may be any size, however, the cancer has spread to one to three nearby lymph nodes.

LIST OF SYMBOLS, ABBREVIATIONS, OR NOMENCLATURE

PDAC – Pancreatic Ductal Adenocarcinoma

BR – Borderline Resectable

LA – Locally Advanced

NAC – Neoadjuvant Chemotherapy

S – Potentially Curative Surgery

IRB – Institutional Review Board

NAC+S – Neoadjuvant Chemotherapy and Potentially Curative Surgery

OS – Median Overall Survival

ECOG – Eastern Cooperative Oncology Group

FOLFIRINOX – Folinic Acid, Fluorouracil, Irinotecan, Oxaliplatin

R0 – Margin Negative Microscopic Resection

AJCC – American Joint Committee on Cancer

SEER – Survival, Epidemiology, and End Results

BMI – Body Mass Index

CA 19-9 – Carbohydrate Antigen 19-9

COPD – Chronic Obstructive Pulmonary Disease

PREFACE

According to the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) Program, pancreatic cancer represents only 3.2% of all incident cancer cases in the United States; however, it is now the 3rd leading cause of cancer-related deaths.[1] Unlike most solid-organ tumors, the prognosis associated with pancreatic cancer has not changed much over the past 30 years. Despite improvements in diagnostic and therapeutic interventions, 5-year survival rates remain dismal at approximately 8%.[1] This can in large part be attributed to the typically advanced stage at which pancreatic cancer is diagnosed. Only 10% of cases are diagnosed early in the disease progression, when disease is confined to the primary site.[1] Even then, 5-year survival rates are approximately 30%.[1] Greater than 50% of cases have already metastasized at the time of initial diagnosis, and are accompanied by a 5-year survival rate of less than 3%[1]. Historically, early stage pancreatic cancer has been managed with upfront surgery followed by adjuvant chemotherapy and/or radiation, however, the limitations of adjuvant therapy have now been well described. A major area of interest to potentially improve survival relates to the incorporation of neoadjuvant chemotherapy into current management strategies.

CHAPTER I: INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is presently the third leading cause of cancer related mortality in the United States with an estimated 44,000 deaths due to this disease in 2018.[1] Since most cases of PDAC are diagnosed at an advanced stage, overall 5-year survival remains poor at 8%.[1] Only 10-15% of patients are considered to be surgically resectable as defined by tumor size, location, and vascular involvement. As surgical resection represents the only potential for cure, even in this small subset of eligible patients, the 5-year overall survival remains poor at less than 20%.[2,3]

Regardless of the initial clinical and radiographic features, PDAC is largely regarded as a systemic disease at the time of diagnosis.[4,5] Between 20-30% of patients who are treated with surgery at high-volume centers do not receive the intended adjuvant chemotherapy due to a combination of postoperative morbidity, patient refusal, and early disease recurrence.[6-8] This has led to increasing support for neoadjuvant therapies in the management of patients with PDAC.[9-11] Theoretical additional benefits of neoadjuvant chemotherapy (NAC) include (1) delivery of chemotherapy to well-oxygenated tissues which maximizes tumor infiltration thus yielding higher efficacy; (2) improved rates of chemotherapy tolerance by avoiding the setbacks caused by extended postoperative recovery and operative complications; (3) reduced tumor volume resulting in possible downstaging and increased rates of R0 resections; (4) reduction in overall disease burden and the odds of locoregional recurrence; and (5) an opportunity to observe and identify patients who would not benefit from surgical resection due to inherently aggressive

tumor biology.[12] Retrospective studies have demonstrated this treatment approach to be feasible, is associated with an increased percentage of patients receiving all intended therapy, and may provide some oncologic benefit as it relates to margin clearance and long-term patient survival.[13]

In 2012, our institution adopted a protocol incorporating NAC prior to performing a potentially curative resection in patients with Stage I and II PDAC (Supplemental Figure 1). The aims of this observational study were to describe the overall survival of patients with Stage I/II PDAC who were managed with NAC and to assess if there is any added benefit of potentially curative resection beyond that afforded by modern day NAC regimens.

CHAPTER II: METHODS

Data Sources

A retrospective review of a prospectively-maintained pancreatic cancer database was conducted for patients who had a biopsy confirmed diagnosis of clinical stage I/II PDAC from July 1, 2012 to July 31, 2016. Sociodemographic characteristics, chronic conditions, operative characteristics, and long-term mortality were obtained. The study was approved by our Institutional Review Board (IRB).

Study Population

A multidisciplinary tumor board guided the evaluation, treatment, and follow-up of all patients. Standardized definitions and the American Joint Committee on Cancer (AJCC) 7th edition staging system were used in the establishment of our institutional protocol which directed all patients with clinical stage I/II PDAC undergo NAC (Figure 1). Patients received a uniform 25% dose reduction of standard FOLFIRINOX therapy every two weeks (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2 followed by bolus fluorouracil 400 mg/m2 on day 1, then fluorouracil 2,400 mg/m2 as a 46-hour continuous infusion) or standard dose gemcitabine-*nab*-paclitaxel (*nab*-paclitaxel 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 administered on days one, eight, and fifteen) every four weeks. Potentially curative surgery was initially planned for all patients following completion of NAC and restaging, however, if found to have evidence of disease progression to locally unresectable or distant disease, or exacerbation of medical comorbidities, patients were no longer considered surgical candidates. Neoadjuvant

radiation was selectively administered if deemed necessary for local control prior to surgery. For the purposes of data analysis, patients were categorized into two treatment groups; those who completed NAC followed by a potentially curative resection and those who completed NAC and due to disease progression or exacerbation of medical comorbidities were not candidates for resection.

Statistical Analysis

Descriptive statistics were calculated for the entire cohort and compared between study groups using chi-square tests for categorical variables, and student's t-tests and Wilcoxon rank-sum tests for continuous variables. Median OS was the primary study endpoint, which was defined as the time period from diagnosis of PDAC to death. OS was examined using the Kaplan-Meier (KM) method. The significance of NAC and potentially curative resection on survival were assessed using the log-rank test. For all analyses, a p-value ≤ 0.05 was considered the cut-off point for statistical significance. All analyses were performed using STATA software (version 15.1; College Station, TX: StataCorp LLC.).

CHAPTER III: RESULTS

Study Population

Eighty-eight patients with biopsy-confirmed Stage I/II PDAC were evaluated during the study period. Fifty six patients (63%) were offered and completed NAC. Of the 32 (37%) patients not treated with NAC, 15 (17%) patients were excluded due to poor Eastern Cooperative Oncology Group (ECOG) performance status, six (7%) patients refused treatment and elected best supportive care, five (6%) patients were lost to follow-up after their initial diagnosis, five (6%) patients sought immediate surgical resection at an outside institution, and one (1%) patient died from other causes.

Baseline Characteristics

Among the 56 patients who completed NAC, 21 (38%) presented with clinical stage I disease and 35 (62%) with clinical stage II disease. Baseline ECOG scores were higher for patients completing NAC alone (p=0.01). There was no difference in age, gender, or any other preoperative demographic variables or comorbidities (Table 1). Median follow-up time for the entire cohort was 18.7 months.

Neoadjuvant Chemotherapy

Eleven patients (20%) received FOLFIRINOX, 42 patients (75%) received gemcitabine-*nab*-paclitaxel, and 3 patients (5%) were switched from FOLFIRINOX to gemcitabine-*nab*-paclitaxel due to toxicity. None of the patients who switched regimens were ultimately found to have a

resectable tumor on restaging. No difference in chemotherapy regimens was identified between groups (p=0.89). All patients completed their intended course of NAC.

Restaging and Neoadjuvant Radiation Therapy

After completing NAC and restaging, 16 patients (29%) were found to have progression of disease or exacerbation of their medical comorbidities, rendering them unfit for surgical resection (Figure 2). Of the remaining 40 patients (71%), 23 were considered candidates for potentially curative surgery while 17 were treated with neoadjuvant radiation therapy, with no difference between groups (p=0.44). Following radiation, an additional nine patients were found to be candidates for resection, thus resulting in 32 patients (57%) ultimately being offered potentially curative surgery. Of those, four patients refused and opted for no additional treatment.

Operation

Potentially curative resection was pursued in 28 patients (50%). During surgery, six patients were found to have locally advanced or distant metastatic disease, thus leading to abortion of the surgical procedure. For the purposes of analysis, these six patients were included in the NAC alone group. Ultimately, 22 patients (39%) underwent potentially curative resection with pancreaticoduodenectomy (n=16) or distal pancreatectomy (n=6). Of these, 19 (86%) patients had microscopic margin negative (R0) resections; there were no R2 resections. Seven (32%) vein resections were performed. 90-day mortality was 0%.

Oncologic Outcomes

Median OS for the entire study population was 18.7 months. There was no difference in 1-year survival between the NAC+S and NAC groups (86% vs 68%; p=0.11; Fig. 3), however, 2-year survival was significantly increased for the NAC+S group (55% vs 21%; p=0.01; Fig. 4). For patients who were treated with NAC+S, overall survival was greatly increased with a reported median OS of 28.8 months compared to 17.3 months for those who received NAC alone (p=0.05; Fig. 5). Comparing patients by AJCC disease stage, there were no significant differences in median OS (p=0.18). Similarly, while neoadjuvant radiation facilitated surgical resection in nine patients, it was not associated with an increase in patient survival (p=0.67).

CHAPTER IV: DISCUSSION

In our single institution experience evaluating the role of NAC in the management of patients with clinical stage I/II PDAC, patients who underwent potentially curative surgery after NAC achieved an 11.5 month improvement in survival compared to those who underwent NAC alone. Patients who completed NAC but were not candidates for resection demonstrated a significantly improved survival compared to historical controls in prior reports.

Survival, Epidemiology, and End Results (SEER) data from 1992-2002 suggest that approximately one third of patients have clinically resectable or borderline resectable PDAC at diagnosis.[14] Despite the initially favorable findings in this subset of patients, only 33% underwent potentially curative resection.[14] Reasons for this failure to progress to resection are not captured in large database studies. In our study using a NAC approach, we demonstrated a similar estimate as 39% of patients with clinical Stage I/II PDAC ultimately progressed through treatment and received a resection. While early upfront surgery has traditionally been considered the standard of care, our data suggests the administration of NAC does not have a negative impact on the ability to proceed to surgical resection. Additionally, all patients in our study completed their intended NAC course, suggesting that even with modern day therapies, rates of completion of intended therapy are significantly higher than demonstrated with adjuvant regimens in which only 20-30% of patients receive their intended chemotherapy regimen.[6-8]

Modern day systemic chemotherapy regimens, notably FOLFIRINOX and gemcitabine-*nab*-paclitaxel, initially showed efficacy in patients with metastatic pancreatic cancer.[15,16] Increasingly, these regimens have been incorporated into protocols for patients with early stage PDAC. In our institutional experience, application of these regimens in the neoadjuvant setting was associated with a median OS of 18.7 months for the study population, which is consistent with reports in the current literature, including a recent meta-analysis which noted a median OS of 18.8 months after neoadjuvant treatment for resectable or borderline resectable PDAC.[17] Evaluating only the patients who completed NAC and subsequently underwent resection, our study finds a median OS of 28.8 months. Again, our results are consistent with recent studies which reported an increased median OS in this select group of 26.1 months.[17]

There is a paucity of data evaluating the survival of those with resectable or borderline resectable disease who complete NAC but who do not progress to completed potentially curative resection. Historically, this group of patients has done poorly with a median OS around 7-8 months.[7,18] Interestingly, the current study demonstrated a median OS of 17.3 months in this group of patients, which appears greater than previous reports on the topic.[7,18] Understanding the limitation that we are comparing results to external historical controls, the survival difference is notable and may still be very meaningful. As all patients in this group completed the intended course of chemotherapy, it is possible that NAC has impacts on tumor biology that contribute to the observed improvement in median OS.

While one needs to be appropriately cautious in comparing our results with the findings from prior published reports, the survival difference is notable and improvements in survival with modern day NAC alone may be meaningful. Since all patients completed the intended course of chemotherapy, it is possible that NAC favorably impacts tumor biology which contributed to the observed improvement in OS.

Most striking in the current data set is the significant improvement in median and 2 year survival in patients who underwent potentially curative surgery following NAC, compared to those who received NAC alone. Early Phase II trials demonstrated a significant improvement in survival, with an added benefit afforded by resection, using preoperative gemcitabine-based chemoradiation therapies.[11] More recent studies confirmed the findings in resectable patients, but the data was heavily influenced by gemcitabine-based regimens.[18] A recent Phase II trial by Murphy et al demonstrated that incorporation of a FOLFIRONOX-based neoadjuvant approach with individualized radiation for patients with borderline resectable PDAC may yield similar benefits in survival, again with added benefit afforded by potentially curative surgery.[19] With 75% of the study population receiving gemcitabine-*nab*-paclitaxel, the current study is the first to suggest that modern day regimens including gemcitabine-*nab*-paclitaxel—in addition to FOLFIRNOX—may confer a similar oncologic benefit in patients with resectable disease at diagnosis. While there are limited phase II studies and no phase III clinical trials to guide definitive decisions regarding the utility and application of NAC, several trials are ongoing which have the potential to expand on our understanding of the role of NAC in resectable

pancreatic cancer.[20-22] Certainly, the current data suggests the need to evaluate the role of modern day regimens in the resectable, as well as borderline resectable, populations.[11,18,19]

Study Strengths and Limitations

This observational study reports our four year institutional experience in managing patients with biopsy proven stage I/II PDAC using a NAC based approach. The study has limitations inherent to single-institution, retrospective review, including those related to selection bias and an inability to prove causality. Comparison of our data to historical series is limited given the heterogeneity of study populations and lack of consistency in anatomic definitions. The small sample size of the study prevented the ability to perform Cox regression analyses or advanced modeling to identify and quantify predictors of survival.

CHAPTER V: CONCLUSIONS

Management strategies involving NAC with the intent for potentially curative surgery may offer patients with resectable, stage I/II PDAC improvements in survival even in the absence of resection. While patients who were able to complete all components of intended therapy experienced higher survival rates, patients who completed NAC may achieve even greater benefits on long-term survival relative to historical controls. Certainly, however, if surgery can be employed, it may confer an additional one year of improvement in survival and may be done with excellent administration rates and without negative impact on resectability.

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Table 1. Baseline characteristics of the study

Characteristics	NAC+S (n=22)	NAC Alone (n=34)	P value
Age at Diagnosis (years) α	65 (10)	69 (9)	0.08
Male	11 (50)	12 (35)	0.28
Race			
White	22 (100)	30 (91)	
Black	0 (0)	1 (3)	
Hispanic	0 (0)	2 (6)	
BMI (kg/m^2) α	26 (6)	24 (6)	0.22
ECOGα	0.1 (0.4)	0.7 (0.9)	0.01
Initial CA19-9 α	173 (224)	600 (1927)	0.32
Restaging CA19-9 α	470 (1306)	1465 (1948)	0.07
AJCC Clinical Stage			0.67
Stage I	9 (41)	12 (35)	
Stage II	13 (59)	22 (65)	
Diabetes	9 (41)	15 (45)	0.74
Renal Disease	4 (18)	4 (12)	0.53
Heart Disease	3 (14)	9 (27)	0.23
Hypertension	10 (45)	18 (55)	0.51
Current/Previous Smoker	12 (55)	22 (65)	0.45
COPD	1 (5)	2 (6)	0.81
Neoadjuvant Chemotherapy			0.89
FOLFIRINOX	5 (23)	6 (18)	
Gemcitabine-*nab*-paclitaxel	16 (73)	26 (76)	
Switch	1 (4)	2 (6)	
Neoadjuvant Radiation Therapy	5 (23)	12 (35)	0.44

*All values recorded as (n,%) unless otherwise specified

α: Mean (Standard deviation)

BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, COPD: Chronic obstructive pulmonary disease

Figure 1: University of Massachusetts Institutional Protocol for PDAC

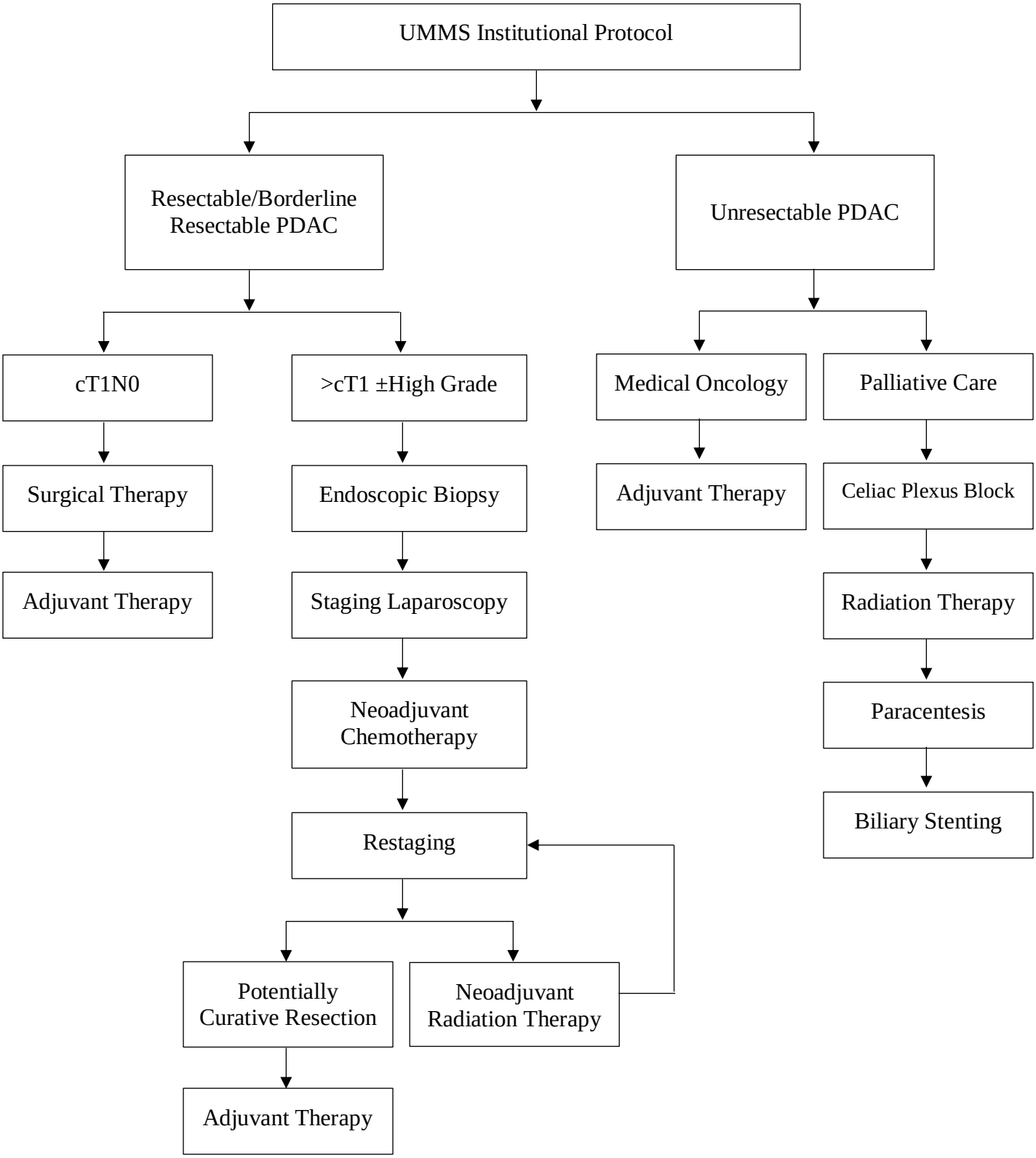
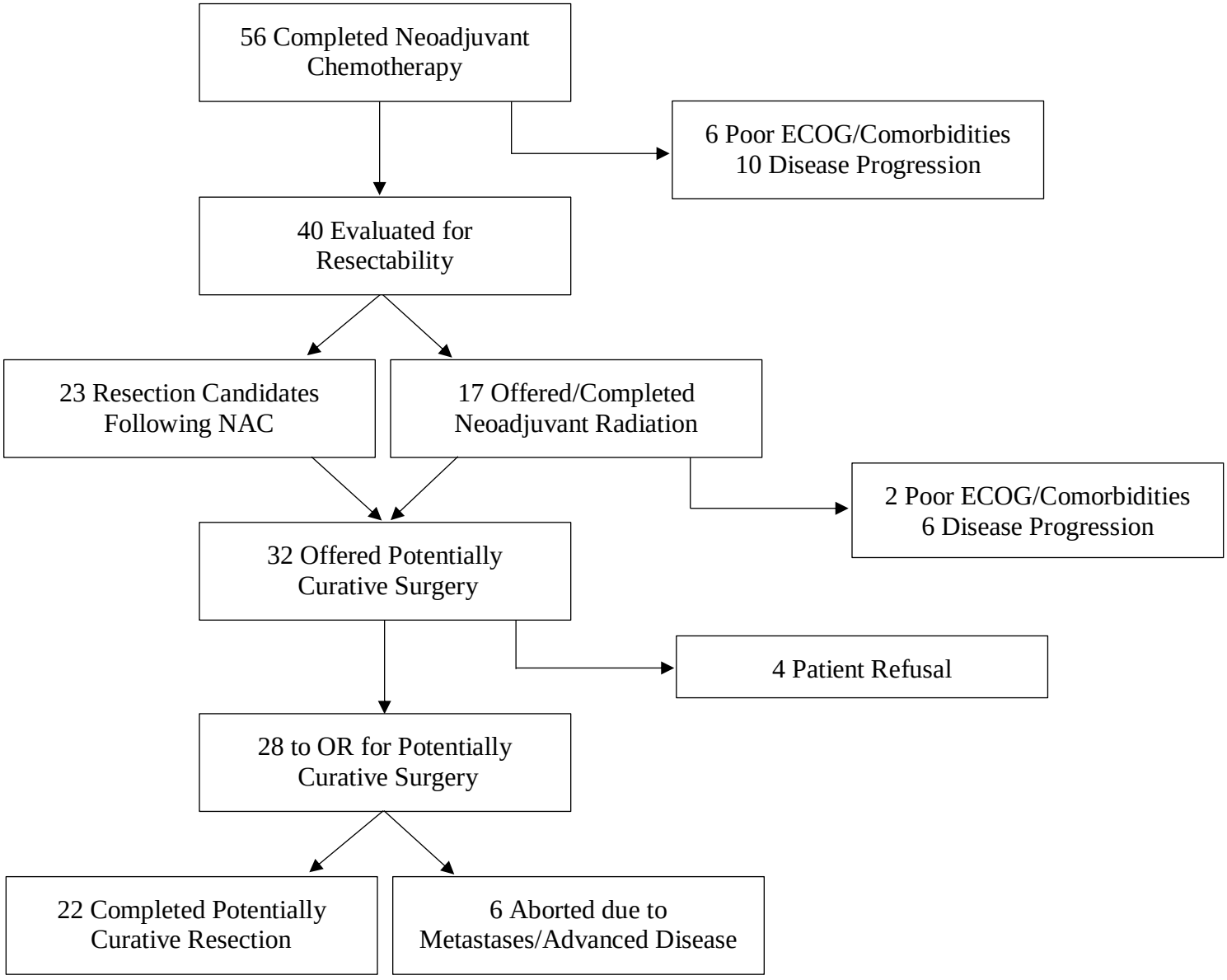
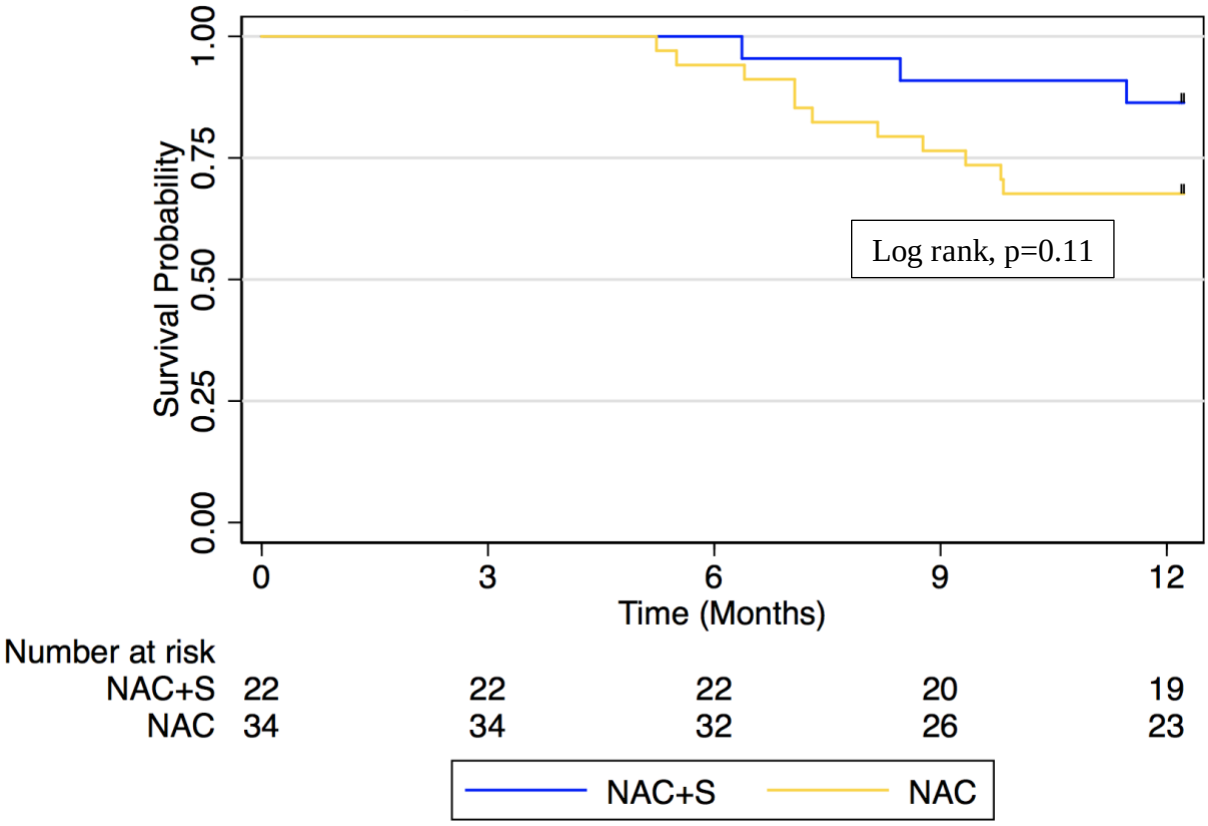


Figure 2: Algorithm of Patient Flow through our Institutional Treatment Protocol



*NAC: Neoadjuvant Chemotherapy

Figure 3: Kaplan Meier Analysis of 1-Year Survival for Stage I and II PDAC According to Treatment Type; NAC+S = neoadjuvant chemotherapy plus surgery; NAC = neoadjuvant chemotherapy only.



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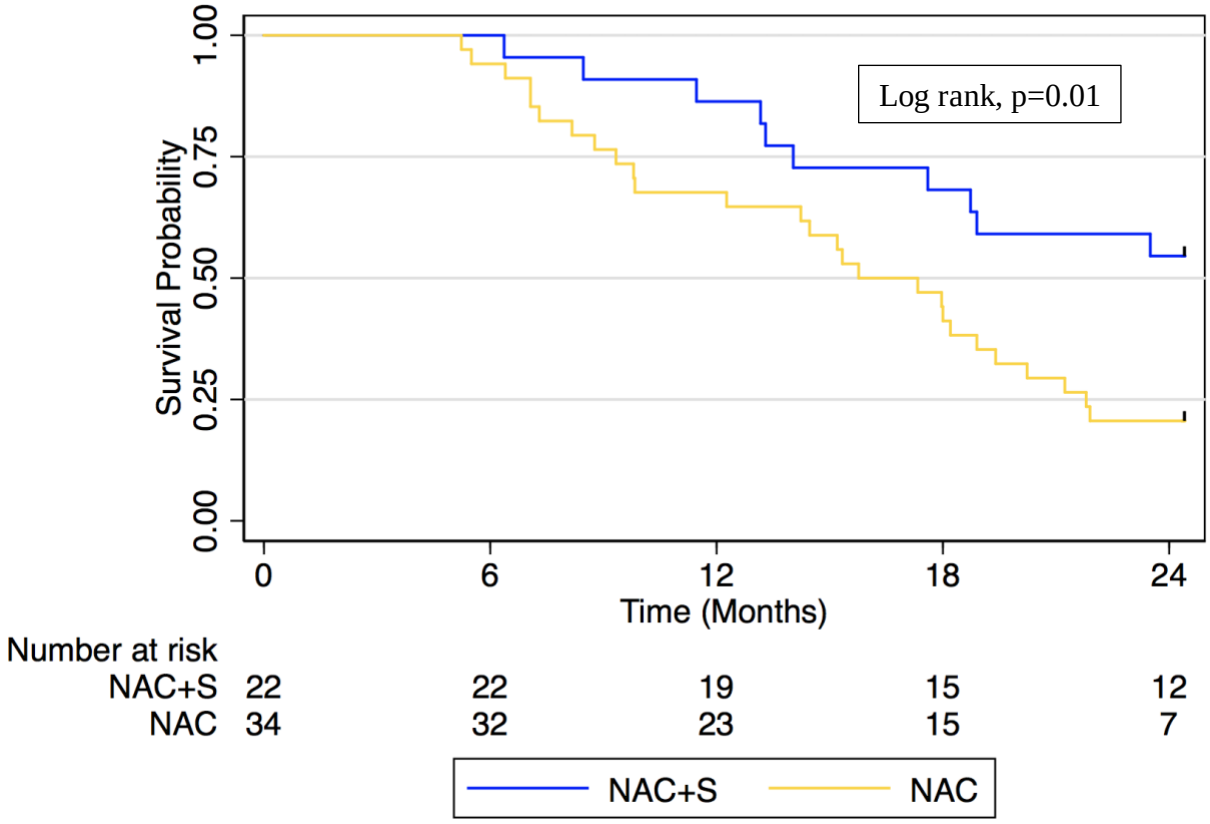

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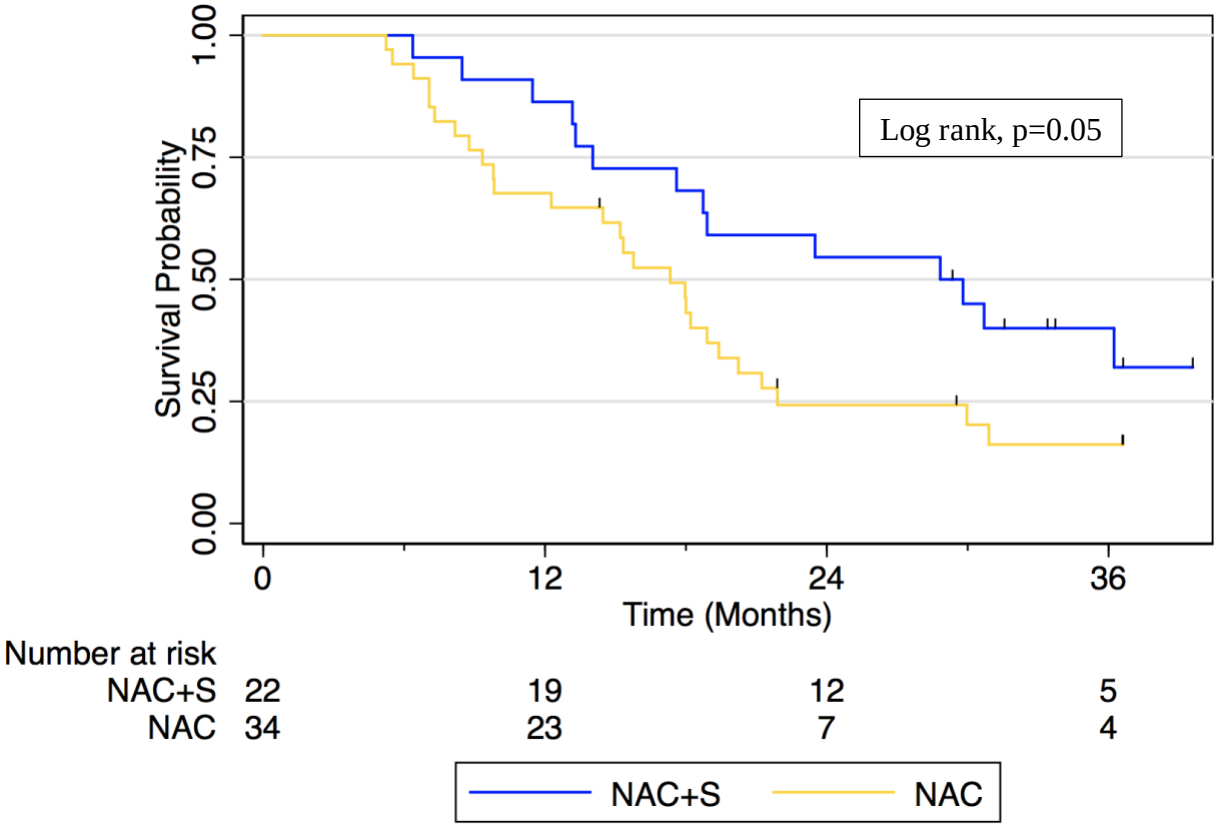

Supplemental Figure 1: Pancreatic Cancer Stage IA, IB, IIA, IIB

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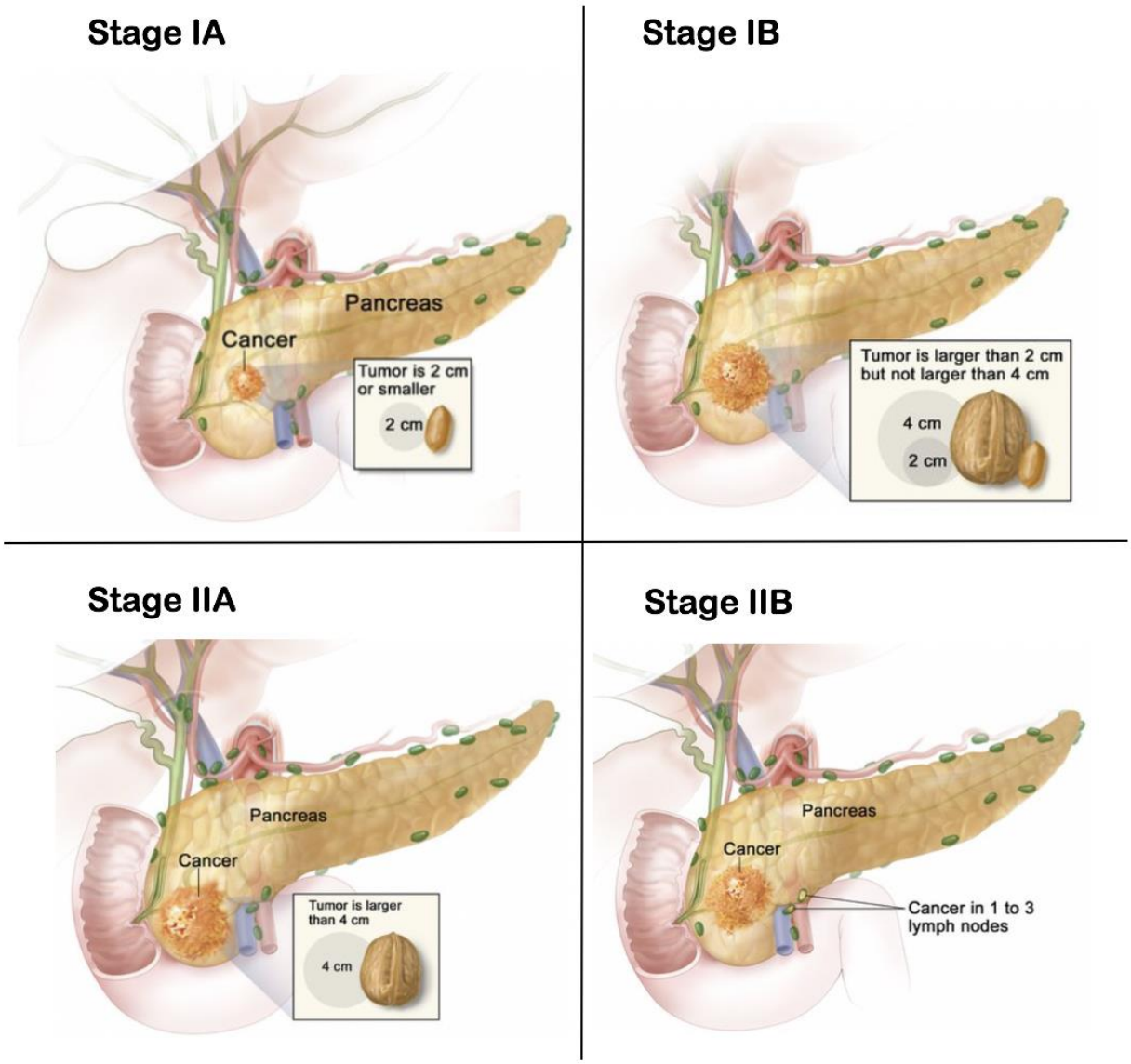

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