HHS Public Access

Author manuscript

J Gastrointest Surg. Author manuscript; available in PMC 2024 July 03.

Published in final edited form as:

J Gastrointest Surg. 2023 November ; 27(11): 2474–2483. doi:10.1007/s11605-022-05531-6.

Impact of Biopsy Attempts, Race, and Access on Time to Initiation of Treatment for Pancreatic Cancer

Riley P Bohan[1], **Andrea N Riner, MD MPH**[1], **Kelly M Herremans, MD**[1], **Hanzhi Gao, MS**[2], **Dominique D Szymkiewicz**[1], **Ibrahim Nassour, MD**[1], **Chris E Forsmark, MD**[3], **Steven J Hughes, MD FACS**[1]

[1.]Department of Surgery, University of Florida College of Medicine, Gainesville, FL USA

[2.]Department of Biostatistics, University of Florida College of Public Health and Health Professions & College of Medicine, Gainesville, FL USA

[3.]Department of Medicine, University of Florida College of Medicine, Gainesville, FL USA

Abstract

Background: Biopsy of suspected pancreatic cancer (PDAC) in surgical candidates is informative however not always necessary. Biopsies impact treatment options as histological diagnosis is presently required for neoadjuvant therapy, but not surgical resection. We explored the impact of pursuing tissue diagnosis by endoscopic ultrasound (EUS) biopsy on time to treatment in patients with resectable and borderline resectable PDAC.

Methods: A retrospective review of surgical patients with ultimately proven PDAC was performed (2011-2021). Milestone dates (cancer suspected, biopsy(ies), surgical or neoadjuvant treatment) were collected. Mann-Whitney-Wilcoxon tests, Pearson's Chi-squared tests, Fisher's exact tests, linear regressions, and Cox proportional hazard models were used for data analysis.

Results: Among 131 resectable and 58 borderline resectable patients, the borderline resectable group underwent more biopsies (1.2 vs 0.7, p<0.0001), were more likely to undergo biopsy at tertiary care centers (67.2% vs 30.5%, p<0.0001), and trended toward longer time to treatment (49 vs 44 days, p=0.070). Significant increases in days to treatment were seen in patients with Black race (29 days, p=0.0002), Medicare insurance (22 days, p=0.038) and no biopsies at a tertiary

[1]This research was presented at the 17th Annual Academic Surgical Congress, February 1-3, 2022, Orlando, FL, USA

Corresponding Author: Steven J Hughes, MD FACS, Edward M. Copeland, III MD Professor, Chief of Surgical Oncology, 1600 SW Archer Rd. PO Box 100109, Gainesville, FL 32610, steven.hughes@surgery.ufl.edu.
Work completed at the Department of Surgery of the University of Florida College of Medicine, Gainesville, FL USA

Statement of Author Contribution:
All authors confirm contribution to the paper through (1) concept, design, data acquisition, analysis, or interpretation, (2) drafting or revising, (3) approval for publication, and (4) agreeing to be accountable for all aspects of work.

Conflicts of Interest:
Riley P Bohan: None Declared
Andrea N Riner MD MPH: None Declared
Kelly M Herremans MD: None Declared
Hanzhi Gao MS: None Declared
Dominique D Szymkiewicz: None Declared
Ibrahim Nassour MD: None Declared
Chris E Forsmark MD: None Declared
Steven J Hughes MD FACS: None Declared
This work was previously presented at a scientific meeting1

care center (10 days, p=0.039). After adjusting for covariates, additional biopsies significantly delayed treatment (1 biopsy: 21 days, p=0.0001; 2 biopsies: 44 days, p<0.0001; 3 biopsies: 68 days, p<0.0001).

Conclusions: EUS biopsy significantly impacts time between suspicion and treatment of PDAC. This may be exacerbated by clinical practices increasingly favoring neoadjuvant therapy that necessitates biopsy-proven disease. Time to treatment may also be impacted by access to tertiary centers and racial disparities.

Keywords

EUS-FNA; Pancreatic Ductal Adenocarcinoma; Treatment Delay; Resectable Pancreatic Cancer

Introduction:

Pancreatic ductal adenocarcinoma (PDAC) is a dire diagnosis with a 5-year survival rate of 11% [1]. When discovered at a resectable or borderline resectable stage, surgical resection extends patients' life expectancy and confers a 5-year survival rate of approximately 25% [2]. When diagnosing PDAC, typical features of pancreatic malignancy on contrast-enhanced computer tomography (CT) have a 98% positive predictive value [3]. This is more accurate than Endoscopic Ultrasound Fine Needle Aspiration (EUS-FNAs), with sensitivity and specificity of 85% and 98%, respectively [4, 5]. Given this false-negative rate of biopsy in PDAC, surgical guidelines published by The Society of Surgical Oncology, The National Comprehensive Cancer Network, and The International Study Group of Pancreatic Surgery state that suspected pancreatic cancer should be surgically resected regardless of tissue confirmation of malignancy [6-8].

Despite this lack of requirement, many patients and physicians decide to attempt confirmatory biopsy prior to surgical resection. Recently, the demand for pre-treatment biopsy has been driven by enthusiasm for neo-adjuvant therapy, particularly in the setting of borderline resectable disease [8]. Neoadjuvant therapy also offers a powerful opportunity for clinical trials with biological correlative studies. In our center, we felt this evolution was having unintended consequences for patients including delaying initiation of therapy and patient stress, but this premise is virtually unstudied in pancreatic cancer.

In fact, even minor delays in initiation of therapy of PDAC may not be clinically trivial. A previous study noted that a delay of 32 days between imaging and surgery increased the odds of a progression to unresectable disease from 13% to 26.2% (HR 0.42, p=0.021) [9]. Further, biopsies are emotionally burdensome for patients. False-negative biopsies induce patient confusion and anxiety. The psychological toll when waiting for biopsy of potential malignancy is proven in other malignancies. Patients with suspected breast cancer have high anxiety scores while waiting for biopsy [10]. In fact, anxiety levels are higher during the biopsy process than after the diagnosis [11].

During this transition to favor neoadjuvant therapy at our institution (the timeframe of this study), our center insisted that patients with borderline resectable PDAC receive neo-adjuvant therapy, while resectable disease typically underwent surgery first [8]. On occasion,

neoadjuvant therapy was initiated for borderline resectable lesions without histological confirmation following 2 negative biopsies, provided the multidisciplinary tumor board concurred with a diagnosis of PDAC – accrual to clinical trials was abandoned in this setting. We hypothesized that this paradigm shift was impacting time to initiation of therapy and the patient and family experience. This demarcation also offered an organic control group to compare changes in biopsy practices and downstream delays between patients where first line treatment did require tissue confirmation (neo-adjuvant therapy in borderline disease) versus patients where biopsy was not required for recommended treatment (surgery in resectable disease).

The implications of pursuing biopsy(ies) in patients with surgically-treatable pancreatic cancer is essentially unexplored. The choice to pursue a pre-operative tissue diagnosis is appropriately individualized, but current literature lacks data equipping a physician to weigh evidence-based assessment of the risks and benefits. Thus, to initially explore this concept, this study aimed to determine the time impact associated with biopsy attempts in patients with resectable and borderline resectable PDAC.

Methods:

A retrospective review was performed of patients with PDAC who underwent surgical resection at a tertiary care center from October 2011 to May 2021 and consented to participate in a pancreatic cancer biobank (IRB #201600873). Inclusion required final surgical pathology to confirm PDAC. This specific analysis was approved by the University of Florida IRB (IRB #202101170).

Patient Selection

Study participants were determined as shown in Figure 1. After screening, patients were excluded if PDAC was an unexpected finding upon surgical pathology or if they had a history of 3 or more episodes of pancreatitis. Since this study sought to investigate the diagnostic process of PDAC, patients who were worked up under another leading differential diagnosis (e.g. pancreatic cyst, pancreatitis) were not included. PDAC may be immediately diagnosed through cytological brushings at therapeutic endoscopic retrograde cholangiopancreatography (ERCP). This study sought to explore the clinical implications of pursuing biopsy. Since patients with ERCP brushings usually underwent the procedure for the therapeutic purpose of stenting, the clinical decision of whether to initiate the procedure would not be weighed in the same context as the purely diagnostic EUS-FNA. Therefore, patients with ERCP brushing diagnosis were excluded from analysis. Their time to treatment was calculated with univariate analysis for completeness. Patients who received brushings during ERCP procedure that were not diagnostic were still included. Following the exclusion process, remaining patients were divided into two groups based on surgical resectability at diagnosis as determined by a multi-disciplinary tumor board at our tertiary care center, where a radiologist is universally present as case information, including imaging, is reviewed.

Study Variables

Demographic variables included sex, age, self-reported race and ethnicity, and insurance status. Diagnostic milestones included the dates when PDAC was suspected, biopsies were performed, and treatments were initiated. The date of suspicion of pancreatic cancer was defined as the date (a) imaging showed/was suspicious for mass or showed "double duct sign" with dilated pancreatic and common bile ducts, (2) magnetic resonance cholangiopancreatography (MRCP), ERCP, or EGD showed/was suspicious for mass or malignancy, or (3) patient presented with obstructive jaundice. Given our institution is a tertiary center, most patients were referred from outside institutions along the diagnostic process, from initial presentation to after multiple biopsies have already occurred, thus biopsy attempt locations were also categorized as tertiary or non-tertiary centers. The date of treatment initiation was defined as the date of surgical resection, or initiation of neo-adjuvant therapy.

Statistical Analysis

Descriptive statistics for demographic variables, number of biopsies, and days between diagnostic milestones are reported. Time intervals are recorded with average number of days, standard deviations (SDs), and quartiles (Q1, Q3). Statistical significance was defined as $p < 0.05$ as defined utilizing Mann-Whitney-Wilcoxon tests for continuous variables and with Pearson's Chi-squared tests and Fisher's exact tests for categorical variables. The time between suspicion of cancer and treatment initiation was investigated further with multivariate analyses including Linear Regression and Cox Proportional Hazard Models. In these models, sex, race, ethnicity, biopsy location, and insurance type were included. Subsequently, number of biopsy attempts was added to the model. Analysis was performed based on Intention-to-Treat methodology. Specifically, if surgical resection was attempted but unable to be performed due to advanced disease on initial exploration, the date of surgery was still utilized as the date of treatment initiation.

Results:

Patient Characteristics

Of 189 patients who met inclusion criteria, 58 had borderline resectable disease and 131 had resectable disease. Two of the patients in the borderline group were classified as borderline resectable due to performance status. Women tended to be more likely to have borderline resectable disease, whereas men tended to be more likely to have resectable disease, although this difference was not statistically significant. The majority of patients were White (87.3%) and non-Hispanic (92.6%). Most patients were insured by Medicare (68.8%), aligning with the average age of 67.9 years. Between these groups, patients did not differ significantly based on age, sex, race, ethnicity or insurance status (Table 1).

Characteristics of the 14 patients who were excluded due to receiving diagnosis via ERCP Brushings are displayed in Appendix Table 1. Summary statistics of T and N stages for each group are in Appendix Table 2.

Biopsy Attempts and Time to Treatment

Among all patients, the majority (67.7%) underwent one attempt at biopsy and 23.8% did not undergo attempted biopsy (Table 2). Patients with borderline resectable disease were significantly more likely to have undergone at least 1 biopsy attempt compared to patients with resectable disease (98.3% vs 66.4%, p<0.0001); 33.6% of patients with resectable disease did not have a biopsy. Patients with borderline resectable disease were more likely to have at least one of their biopsy attempts at a tertiary care center compared to patients with resectable disease (67.2% vs 30.5%, p<0.0001). When stratified by number of biopsy attempts, performance of a biopsy at a tertiary center differed significantly only for the 1st biopsy (borderline resectable 64.9% vs resectable 40.2%, p=0.006). The average time from suspicion of pancreatic cancer to treatment initiation was 46 days, with the average time between biopsy attempts ranging between 18 and 26 days (Figure 2).

For completeness, Appendix Table 3 shows patients who were diagnosed via ERCP Brushings had an average time from differential diagnosis to treatment initiation of 32.5 days. Appendix Tables 4a and 4b show univariate data for the Resectable group for T and N staging stratified by number of biopsies and number of days to treatment, respectively.

Multivariate Analysis of Tumor Resectability and Time to Treatment

Patients with borderline resectable disease underwent more biopsy attempts than patients with resectable disease, but their average time to treatment initiation was only 6 days longer, and this trended toward significance (p=0.070) (Table 2). Accordingly, in the multivariate analysis, the difference in time from suspicion to treatment between borderline resectable and resectable groups was not significant (5 days, p=0.334). After adjusting for the number of biopsies, the time difference between groups equalized (−1 day, p=0.860) (Table 4). Importantly, the time between suspicion of pancreatic cancer and treatment initiation became significantly longer as the number of biopsy attempts increased [1 biopsy added 21 days (p=0.0001), 2 biopsies added 44 days (p<0.0001), 3 biopsies added 67 days(p<0.0001)]. Further, race and insurance status were determined to have significant effects on time to treatment (Table 3). The time from suspicion of PDAC to treatment initiation was 29 [95% CI, (13.9, 43.9)] days longer for Black patients compared to White patients (p=0.0002) and Black patients were less than half as likely as White patients to initiate treatment on any given day following biopsy (HR=0.46, p=0.006). Similarly, the time between suspicion of PDAC to treatment initiation for Medicare patients was 22 days longer than those with Medicaid (95% CI, (1.2, 42.1), p=0.038) and 10 days longer than those with private insurance (95% CI, (0.5, 20.1), p=0.061). Medicare-insured patients were less than half as likely to have initiated treatment on any given day following biopsy (HR=0.43, p=0.028). After adjusting for the number of biopsy attempts, the delay for Black patients remained significant (24 days, p=0.001), whereas the delay for Medicaid- and privately-insured patients were no longer statistically significant (17 days, p=0.082; 8 days, p=0.090). Interestingly, after including number of biopsy attempts in the model, whether any biopsy was performed at a tertiary care center became significant (additional 10 days for those with no tertiary center attempts, p=0.039) (Table 4).

Discussion:

This study assessed the time implications of attempting to obtain a tissue diagnosis via biopsy prior to treatment initiation for suspected resectable or borderline resectable PDAC. Our results indicate delays averaging 2-3 weeks for patients who undergo 1 biopsy attempt, with more than 20 additional days for each subsequent biopsy. Of importance in the interpretation of these data is that not all patients who were unsuccessful in achieving a diagnostic sample in their first biopsy proceeded to a second attempt. Therefore, the rates of those progressing from first to second biopsy should be interpreted as the number of patients who had a false negative biopsy and whose treatment team decided that a second attempt was warranted. Some patients with false negative biopsies proceeded to treatment, particularly surgical resection, without a tissue diagnosis. Though the delay incurred per biopsy is statistically similar between resectable and borderline resectable patients, patients with borderline resectable disease underwent nearly twice the number of biopsy attempts, thus extending their wait as a cohort for treatment. Clinically, patients with borderline resectable disease may have additional motivators to achieve tissue diagnosis, including pursuit of neo-adjuvant therapy. The additional biopsy attempts for patients with borderline resectable disease could therefore be interpreted not as a response to an increased false negative rate, but instead as a response to an inability to forgo a tissue diagnosis. For patients with borderline resectable disease, neo-adjuvant therapy is preferred, whereas for patients with resectable disease, either neo-adjuvant therapy or surgical resection are both considered first line treatment. Therefore, patients with resectable disease are not being excluded from the most efficacious treatment if their biopsy is falsely negative, unlike borderline resectable patients. Our own institution requires at least 2 biopsy attempts prior to initiating non-surgical treatment without histological confirmation of malignancy, provided interdisciplinary tumor board and radiological signs all concur on a diagnosis of PDAC. Unfortunately, patients with borderline resectable disease who have compelling clinical reasoning for pursuit of tissue diagnosis are also most vulnerable to progression to unresectable disease, making the time spent awaiting biopsy a delicate assessment for the physician. This is compounded by our findings that demographic variables have significant influence on time to treatment. Black race and Medicare insurance were found to add 2-4 weeks of delay in treatment, independent of number of biopsy attempts, suggesting disparities in access to timely care. Additionally, lack of access to tertiary care centers may contribute to delays in care as patients with no biopsies at a tertiary center had an additional 10-day delay to treatment.

Our findings are similar to the limited number of studies that have investigated implications of EUS-FNA in suspected pancreatic cancer. Mitchell et al. found that the median time between 1st and 2nd EUS-FNAs was 31 days, with a large range of 7-175 days [13]. Another study showed a median time of 27 days between 1st and 2nd EUS-FNAs [14]. In an investigation of the implications of EUS-FNA in suspected resectable pancreatic cancer, Kliment et al. found 83% of patients with false negative EUS-FNAs had delays in surgical management [15]. A meta-analysis found that delaying treatment of resectable PDAC 32 or more days significantly increases the risk of progression to unresectable stages and significantly decreases overall survival [16]. Our study was not adequately powered to assess

whether treatment delays were associated with stage of cancer or survival. Though one possible place for improvement is the biopsy process, the logistic implications of scheduling, completing, and interpreting biopsies is not negligible. The days leading to and between biopsies found in our study reflect efficiency in this process, especially in tertiary care facilities as our results demonstrated decreased delays in patients receiving biopsy at tertiary care centers. This, along with more patients with borderline resectable disease undergoing biopsy at tertiary care centers, may partially explain why the borderline resectable group did not have as substantial of a delay to treatment as would be expected for their significant increase in average number of biopsies (average of 0.5 more biopsies but only 6 more days delay). Addressing the delays in scheduling and interpreting specimens in the plethora of possible biopsy facilities would not be nearly as effective as addressing the beliefs and policies driving the impetus for biopsies in the first place. Early referral of patients to surgical oncologists and tertiary care centers with tumor boards prior or simultaneously to biopsy, as opposed to after histological confirmation, could minimize unnecessary biopsy attempts. Early referral could allow biopsies to be put into overall patient context for determining necessity and be completed with rapid on-site evaluation (ROSE). ROSE has been shown to increase EUS-FNA sensitivity in PDAC (65% to 83%) [17], however, there is still ongoing debate as recent publications have also found lack of ROSE to be non-inferior [18]. In addition to early tertiary center referral, implementing policies that minimize the number of biopsies attempted in resectable and borderline resectable patients have the potential to reduce weeks of delays for these patients. Given classic radiologic and clinical signs of PDAC have 98% positive predictive value [4, 5], biopsies are typically not used to confirm diagnosis but instead are used for a qualification for treatment. Adjusting such qualifications so patients are not forced to delay months for a less accurate test to confirm a nearly assured diagnosis may be the most cost effective and patient-sparing approach to shorten time to treatment.

To the best of our knowledge, there have not been studies that explore the effect of patient characteristics on delays in treatment for PDAC. Though not our primary research question, our study is the first to identify the impact of race and insurance factors on delays in obtaining a tissue diagnosis prior to treatment initiation. Although literature in other settings suggest treatment delays for minority patients [19-21], our study identified a significant increase in days to treatment for Black patients and Medicare-insured patients. With racial/ethnic minority patients and Medicaid-insured patients representing less than 15% and 5% of our study population respectively, further research is warranted to verify the observed disparities. However, our findings of increased delay suggest contributions from demographic and social variables, where minorities are disproportionately affected by lack of access and health education. Our findings align with recent publications where, in early-stage pancreatic cancer, Black and Latinx patients are less likely to receive surgical resection or pre-operative chemotherapy [22-24]. Black PDAC patients are also known to have worse survival than their White counterparts as contributed to by systematically poorer medical care and more biologically aggressive disease [24-26]. Our data suggest Black patients also experience delays in biopsy. It is unknown if these delays are due to implicit bias or other unmeasured factors. The treatment delays found with differing insurances could be explained by each insurance’s relationship with a university-affiliated tertiary care

center, like our own. Though initially surprising for Medicare-insured patients to have the longest delay, this is consistent with the widely used Medicare HMO policies that do not cover healthcare services out of network [27]. With patients being referred from up to hundreds of miles away for specialty care, delays in insurance coverage of biopsies and treatment due to being out-of-network are common. This contrasts with Medicaid-insured patients who are in-network with all non-profit hospitals in our state, including public university academic centers [28]. Therefore, this comparative expedition in our small sample of Medicaid-insured patients likely reflects delay byproducts of insurance company networks and authorization processes which are required for almost all of our Medicare HMO patients. However, Medicare can be a proxy for age, therefore the observed delays among Medicare patients may reflect delays related to older age. Further investigations into the interplay of demographic and social variables is warranted.

This study has several limitations. It does not assess the implications to patients who are eventually proven to have benign disease but still undergo biopsies or even surgery with the suspicion of malignancy (true negatives). Our sample size also precludes us from meaningful investigation of survival differences based on number of biopsies or time to treatment. The low percentage of Medicaid-insured patients also limits our analysis of the association of insurance status with delays in treatment initiation. Additionally, in our patients, there was a mix of diagnostic work up settings, reflective of the nature of a referral center. Biopsies were completed in tertiary care centers, community hospitals, and private facilities. Each setting may vary with regard to patient scheduling, technician experience, and pathologist experience, which could affect timing and results of each biopsy. Further, the combination of the retrospective nature of this study and the variable outside facility locations of biopsy precluded any verification or investigation of the technique and quality of EUS-FNAs such as the size of the needle, number of passes made, or whether cytology was available onsite. Lastly, the need for clear definitions separates this study from the more nuanced and uncertain reality of clinical practice. For instance, a physician may suspect PDAC prior to a patient developing obstructive jaundice or finding a mass on imaging, differing from the definition we used as the “suspicion of cancer” time point.

Conclusion:

These findings have direct and specific application to the decisions physicians face in providing care for a patient with suspected PDAC, particularly in surgical candidates. Though delays are currently more relevant in the context of borderline resectable disease, increasing enthusiasm for neo-adjuvant therapy indicates future expansion of such decisions to include patients with resectable disease as well. The psychological and biological toll of pursuing a pre-operative tissue diagnosis is individual to each patient, but this study contributes to a more explicit understanding of the time associated with obtaining diagnostic confirmation of suspected pancreatic cancer and will serve as a foundation for subsequent studies that assess patient duress during such delays. Additionally, our results indicate possible extension of the factors of consideration to include patient demographic and socio-economic characteristics. Further study to validate these findings and address inequities is warranted. Overall, this study contributes to our understanding of the time risks associated with recommending biopsy for patients with suspected resectable or borderline resectable

PDAC. Early referral to tertiary care centers with a multi-disciplinary tumor board might mitigate such delays.

Financial Support:

Research reported in this publication was supported by NIH 1U01DK108320 – 06 (SJH, CEF), the University of Florida Clinical and Translational Science Institute, which is supported in part by the NIH National Center for Advancing Translational Sciences under award number UL1TR001427, and salary support from the National Human Genome Research Institute (T32 HG008958 to ANR, KMH). ANR is also supported by the National Cancer Institute (U54 CA233444-03S1) of the National Institutes of Health. ANR and KMH are also supported by the Collaborative Alliance for Pancreatic Education and Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix

Appendix Table 1.

Characteristics of Those Excluded due to Diagnostic ERCP Brushings

		Patients Diagnosed via ERCP Brushings N = 14
Age at Treatment (Mean) (Years)		71.3
Sex	Male	8 (57.1%)
	Female	6 (42.9%)
Race	White	14 (100%)
	Black	0 (0%)
	Other	0 (0%)
	Unknown	0 (0%)
Ethnicity	Hispanic/Latinx	0 (0%)
	Not Hispanic/Latinx	14 (100%)
	Unknown	0 (0%)
Insurance	Medicare	11 (78.6%)
	Private	2 (14.3%)
	Medicaid	0 (0%)
	None	1 (7.1%)
Brushing Location	**Tertiary Center**	**6 (42.9%)**
	Not Tertiary Center	**8 (57.1%)**

Appendix Table 2.

Summary Statistics for T and N Stages

		All N = 189	**Borderline N = 58**	**Resectable N = 131**	**P-value**
T Stage	is	1 (0.5%)	0 (0%)	1 (0.8%)	0.0128
	1	14 (7.4%)	9 (15.5%)	5 (3.8%)	
	2	47 (24.9%)	13 (22.4%)	34 (26.0%)	
	3	116 (61.4%)	30 (51.7%)	86 (65.6%)	

		All N = 189	Borderline N = 58	Resectable N = 131	P-value
	4	11 (5.8%)	6 (10.3%)	5 (3.8%)	
N Stage	0	45 (25.6%)	20 (38.5%)	25 (20.2%)	0.013
	1	70 (39.8%)	21 (40.4%)	49 (39.5%)	
	2	61 (34.7%)	11 (21.2%)	50 (40.3%)	

Appendix Table 3.

Resectability, Number of Biopsies, and Time to Treatment for Patients Excluded due to Diagnostic ERCP Brushings

	Patients Diagnosed via ERCP Brushings N = 14
Number of Patients Resectable	12 (85.7%)
Number of Patients Borderline Resectable	2 (14.3%)
Average Number of Biopsies Total	1.4
Average Time from DDX to Tx (Days)	32.5

Appendix Table 4a.

Summary Statistics for T and N Stages Stratified by Number of Biopsies for Patients with Resectable Disease

		Resectable	Number of Biopsies		P-value
			0	1 or more	
Number of records		131	44	87	
T stage	is	1 (0.8%)	0 (0%)	1 (1.1%)	0.2944
	1	5 (3.8%)	3 (6.8%)	2 (2.3%)	
	2	34 (26.0%)	13 (29.5%)	21 (24.1%)	
	3	86 (65.6%)	28 (63.6%)	58 (66.7%)	
	4	5 (3.8%)	0 (0%)	5 (5.7%)	
N stage	0	25 (20.2%)	5 (11.4%)	20 (25.0%)	0.1859
	1	49 (39.5%)	20 (45.5%)	29 (36.2%)	
	2	50 (40.3%)	19 (43.2%)	31 (38.8%)	

Appendix Table 4b.

Summary Statistics for T and N Stages Stratified by Days DDX to Tx for Patients with Resectable Disease

		Resectable	Days DDX to Tx			P-value
			0-30	31-60	60+	
Number of records		131	57	40	34	

		Resectable	Days DDX to Tx			P-value
			0-30	31-60	60+	
T stage	is	1 (0.8%)	0 (0%)	1 (2.5%)	0 (0%)	0.4955
	1	5 (3.8%)	2 (3.5%)	2 (5.0%)	1 (2.9%)	
	2	34 (26.0%)	15 (26.3%)	7 (17.5%)	12 (35.3%)	
	3	86 (65.6%)	38 (66.7%)	27 (67.5%)	21 (61.8%)	
	4	5 (3.8%)	2 (3.5%)	3 (7.5%)	0 (0%)	
N stage	0	25 (20.2%)	10 (18.5%)	8 (21.6%)	7 (21.2%)	0.4342
	1	49 (39.5%)	20 (37.0%)	12 (32.4%)	17 (51.5%)	
	2	50 (40.3%)	24 (44.4%)	17 (45.9%)	9 (27.3%)	

References:

1. American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society; 2022.
2. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73–85. Epub 20160130. doi: 10.1016/S0140-6736(16)00141-0. [PubMed: 26830752]
3. Amin Z, Theis B, Russell RC, House C, Novelli M, Lees WR. Diagnosing pancreatic cancer: the role of percutaneous biopsy and CT. Clin Radiol. 2006;61(12):996–1002. doi: 10.1016/j.crad.2006.07.005. [PubMed: 17097419]
4. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75(2):319–31. doi: 10.1016/j.gie.2011.08.049. [PubMed: 22248600]
5. Yang Y, Li L, Qu C, Liang S, Zeng B, Luo Z. Endoscopic ultrasound-guided fine needle core biopsy for the diagnosis of pancreatic malignant lesions: a systematic review and Meta-Analysis. Sci Rep. 2016;6:22978. Epub 20160310. doi: 10.1038/srep22978. [PubMed: 26960914]
6. Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155(5):887–92. Epub 20140102. doi: 10.1016/j.surg.2013.12.032. [PubMed: 24661765]
7. Evans DB, Jessup JM, Colacchio T. Pancreatic cancer surgical practice guidelines. Pancreatic Cancer Practice Guideline Committee. Oncology (Williston Park). 1997;11(7):1074–9. [PubMed: 9251127]
8. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(8):1028–61. doi: 10.6004/jnccn.2017.0131. [PubMed: 28784865]
9. Sanjeevi S, Ivanics T, Lundell L, Kartalis N, Andrén-Sandberg Å, Blomberg J, et al. Impact of delay between imaging and treatment in patients with potentially curable pancreatic cancer. Br J Surg. 2016;103(3):267–75. Epub 20151117. doi: 10.1002/bjs.10046. [PubMed: 26572509]
10. Miller LS, Shelby RA, Balmadrid MH, Yoon S, Baker JA, Wildermann L, et al. Patient Anxiety Before and Immediately After Imaging-Guided Breast Biopsy Procedures: Impact of Radiologist-Patient Communication. J Am Coll Radiol. 2016;13(11S):e62–e71. doi: 10.1016/j.jacr.2016.09.034. [PubMed: 27814826]
11. Liao MN, Chen MF, Chen SC, Chen PL. Uncertainty and anxiety during the diagnostic period for women with suspected breast cancer. Cancer Nurs. 2008;31(4):274–83. doi: 10.1097/01.NCC.0000305744.64452.fe. [PubMed: 18600114]
12. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18(1):2–11. Epub 20171122. doi: 10.1016/j.pan.2017.11.011. [PubMed: 29191513]

13. Mitchell RA, Stanger D, Shuster C, Telford J, Lam E, Enns R. Repeat Endoscopic Ultrasound-Guided Fine-Needle Aspiration in Patients with Suspected Pancreatic Cancer: Diagnostic Yield and Associated Change in Access to Appropriate Care. Can J Gastroenterol Hepatol. 2016;2016:7678403. Epub 20160825. doi: 10.1155/2016/7678403. [PubMed: 27648440]

14. Eloubeidi MA, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol. 2008;23(4):567–70. doi: 10.1111/j.1440-1746.2007.05119.x. [PubMed: 18397485]

15. Kliment M, Urban O, Cegan M, Fojtik P, Falt P, Dvorackova J, et al. Endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: the utility and impact on management of patients. Scand J Gastroenterol. 2010;45(11):1372–9. Epub 20100714. doi: 10.3109/00365521.2010.503966. [PubMed: 20626304]

16. Lukács G, Kovács Á, Csanádi M, Moizs M, Repa I, Kaló Z, et al. Benefits Of Timely Care In Pancreatic Cancer: A Systematic Review To Navigate Through The Contradictory Evidence. Cancer Manag Res. 2019;11:9849–61. Epub 20191119. doi: 10.2147/CMAR.S221427. [PubMed: 31819622]

17. Lisotti A, Frazzoni L, Fuccio L, Serrani M, Cominardi A, Bazzoli F, et al. Repeat EUS-FNA of pancreatic masses after nondiagnostic or inconclusive results: systematic review and meta-analysis. Gastrointest Endosc. 2020 Jun;91(6):1234–1241.e4. doi: 10.1016/j.gie.2020.01.034. Epub 2020 Jan 30. [PubMed: 32006546]

18. Crinò SF, Di Mitri R, Nguyen NQ, Tarantino I, de Nucci G, Deprez PH, et al. Endoscopic ultrasound-guided fine-needle biopsy with or without rapid on-site evaluation for diagnosis of solid pancreatic lesions: A randomized controlled non-inferiority trial. Gastroenterology. 2021 Sep;161(3):899–909.e5. doi: 10.1053/j.gastro.2021.06.005. Epub 2021 Jun 9. [PubMed: 34116031]

19. Emerson MA, Golightly YM, Aiello AE, Reeder-Hayes KE, Tan X, Maduekwe U, et al. Breast cancer treatment delays by socioeconomic and health care access latent classes in Black and White women. Cancer. 2020;126(22):4957–66. Epub 20200921. doi: 10.1002/cncr.33121. [PubMed: 32954493]

20. Ahmad TR, Susko M, Lindquist K, Anwar M. Socioeconomic disparities in timeliness of care and outcomes for anal cancer patients. Cancer Med. 2019;8(17):7186–96. Epub 20191009. doi: 10.1002/cam4.2595. [PubMed: 31595720]

21. Naghavi AO, Echevarria MI, Strom TJ, Abuodeh YA, Ahmed KA, Venkat PS, et al. Treatment delays, race, and outcomes in head and neck cancer. Cancer Epidemiol. 2016;45:18–25. Epub 20160922. doi: 10.1016/j.canep.2016.09.005. [PubMed: 27664388]

22. Azap RA, Diaz A, Hyer JM, Tsilimigras DI, Mirdad RS, Ejaz A, Pawlik TM. Impact of race/ethnicity and county-level vulnerability on receipt of surgery among older Medicare beneficiaries with the diagnosis of early Pancreatic Cancer. Ann Surg Oncol. 2021 Oct;28(11):6309–6316. doi: 10.1245/s10434-021-09911-1. Epub 2021 Apr 12. [PubMed: 33844130]

23. Murphy MM, Simons JP, Hill JS, McDade TP, Chau Ng S, et al. Pancreatic resection: a key component to reducing racial disparities in pancreatic adenocarcinoma. Cancer. 2009 Sep 1;115(17):3979–90. doi: 10.1002/cncr.24433. [PubMed: 19514091]

24. Murphy MM, Simons JP, Ng SC, McDade TP, Smith JK, Shah SA, Zhou Z, Earle CC, Tseng JF. Racial differences in cancer specialist consultation, treatment, and outcomes for locoregional pancreatic adenocarcinoma. Ann Surg Oncol. 2009 Nov;16(11):2968–77. doi: 10.1245/s10434-009-0656-5. Epub 2009 Aug 11. [PubMed: 19669839]

25. Singal V, Singal AK, Kuo YF. Racial disparities in treatment for pancreatic cancer and impact on survival: a population-based analysis. J Cancer Res Clin Oncol. 2012 Apr;138(4):715–22. Doi: 10.1007/s00432-012-1156-8. Epub 2012 Jan 15. [PubMed: 22246279]

26. Vick A, Hery D, Markowiak S, Brunicardi F. Closing the disparity in Pancreatic Cancer outcomes, Pancreas: February 2019 - Volume 48 - Issue 2 - p 242–249 doi: 10.1097/MPA.0000000000001238 [PubMed: 30629027]

27. Services CfMM. Understanding Medicare Advantage Plans. US Department of Health & Human Services; 2020. p. 16.

28. The 2021 Florida Statutes, Title XXXVI, Chapter 617, 617.2002. In: Legislature F, editor. Online Sunshine: The Florida Legislature; 2021.

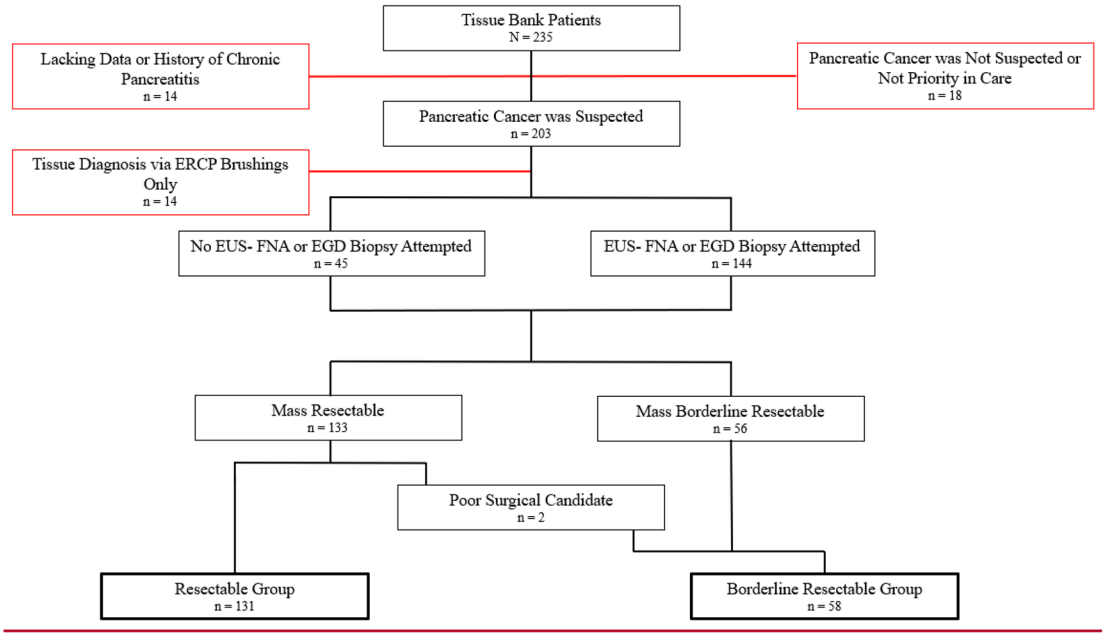

Figure 1. Patient Selection -

Flow diagram depicting study inclusion and exclusion criteria. Red boxes indicate reason for exclusion. Two patients who had anatomically resectable tumors were re-classified as “borderline resectable” due to medical comorbidities that increased risk of surgical resection.

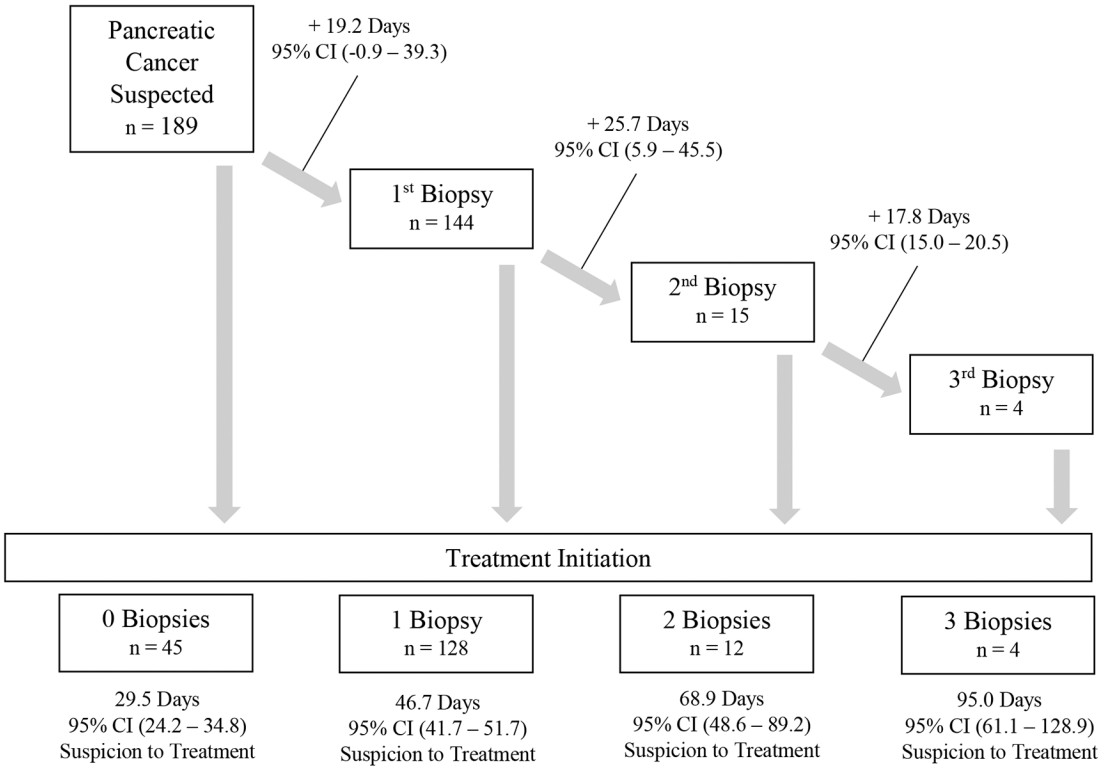

Figure 2. Time Cost of Additional Biopsy Attempts –

Flow chart describing the diagnostic processes from suspicion of pancreatic cancer to initiation of treatment. The average time between given milestones, as well as cumulative time to treatment based on the number of biopsy attempts, are reported with the first and third quartiles.

Table 1.

Patient Characteristics –

Descriptive statistics including age at treatment initiation, as well as sex, race, ethnicity, and insurance provider. Statistical significance was determined using Mann-Whitney-Wilcoxon tests for continuous variables and Pearson's Chi-squared tests and Fisher's exact tests for categorical variables.

		All N = 189	Borderline Resectable N = 58	Resectable N = 131	P-value
Age at Treatment (Mean ± SD)		67.9±9.4	66.2±10.0	68.7±9.0	0.139
Sex	Male	104 (55.0%)	26 (44.8%)	78 (59.5%)	0.086
	Female	85 (45.0%)	32 (55.2%)	53 (40.5%)	
Race	White	165 (87.3%)	51 (87.9%)	114 (87.0%)	1.000
	Black	15 (7.9%)	5 (8.6%)	10 (7.6%)	
	Other	8 (4.2%)	2 (3.5%)	6 (4.6%)	
	Unknown	1 (0.5%)	0 (0%)	1 (0.8%)	
Ethnicity	Hispanic/Latinx	8 (4.2%)	0 (0%)	8 (6.1%)	0.172
	Not Hispanic/Latinx	175 (92.6%)	56 (96.6%)	119 (90.8%)	
	Unknown	6 (3.2%)	2 (3.5%)	4 (3.1%)	
Insurance	Medicare	130 (68.8%)	39 (67.2%)	91 (69.5%)	0.968
	Private	38 (20.1%)	12 (20.7%)	26 (19.9%)	
	Medicaid	8 (4.2%)	3 (5.2%)	5 (3.8%)	
	None	13 (6.9%)	4 (6.9%)	9 (6.9%)	

Table 2.

Biopsies and Time to Treatment –

Descriptive statistics for number of biopsy attempts, whether attempts were at a tertiary care center, and time from suspicion of pancreatic cancer to initiation of treatment.

		All N = 189	Borderline Resectable N = 58	Resectable N = 131	P-value
Number of Biopsies	0	45 (23.8%)	1 (1.7%)	44 (33.6%)	<0.001
	1	128 (67.7%)	48 (82.8%)	80 (61.1%)	
	2	12 (6.4%)	7 (12.1%)	5 (3.8%)	
	3	4 (2.1%)	2 (3.5%)	2 (1.5%)	
Number of Biopsies (Mean±SD)		0.9±0.6	1.2±0.5	0.7±0.6	<0.001
Biopsies in Tertiary Center	1st	72 (50.0%)	37 (64.9%)	35 (40.2%)	0.006
	2nd	12 (75.0%)	6 (66.7%)	6 (85.7%)	0.58
	3rd	4 (100%)	2 (100%)	2 (100%)	1
Any Biopsy in Tertiary Center		79 (41.8%)	39 (67.2%)	40 (30.5%)	<0.001
Days from Suspicion to Treatment (Mean±SD, the first and third quartiles)		45.5±29.3 [23.0, 58]	49.3±28.1 [30.0, 55]	43.9±29.8 [21.5, 62.0]	0.070

Table 3.

Time from Suspicion of Malignancy to Treatment (Days) –

In the linear regression, coefficient values represent the number of days added to the intercept based on patient demographics. These coefficients can be summed to estimate the time interval for patients (e.g. black female prediction: 44.7 + 28.9 + −1.5 = 72.1 days). Cox Proportional Hazard Model ratios indicate the likelihood of treatment being initiated with each additional day of waiting, in comparison to the reference group (male, White race, non-Hispanic, Medicare-insured, with at least one biopsy performed at a tertiary care center).

		Linear Regression		Cox Proportional Hazard Model	
		Coefficient (95% CI)	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
Intercept		44.7 (37.2, 52.3)	<0.001		
Group	Borderline Resectable vs Resectable	4.6 (−4.8, 13.9)	0.334	0.8 (0.6, 1.1)	0.220
Sex	Female vs Male	−1.5 (−9.7, 6.8)	0.722	1.0 (0.8, 1.4)	0.877
Race	Black vs White	28.9 (13.9, 43.9)	<0.001	0.5 (0.3, 0.8)	0.006
	Other or Unknown vs White	−15.8 (−39.8, 8.2)	0.194	2.3 (1.0, 4.9)	0.039
Ethnicity	Hispanic/Latinx/Unknown vs Not Hispanic/Latinx	−0.7 (−20.4, 18.9)	0.942	1.1 (0.6, 2.1)	0.721
Insurance	Private vs Medicare	−9.8 (−20.1, 0.5)	0.061	1.2 (0.8, 1.8)	0.298
	Medicaid vs Medicare	−21.6 (−42.1, −1.2)	0.038	2.3 (1.1, 5.0)	0.028
	None vs Medicare	8.9 (−7.3, 25.1)	0.280	0.7 (0.4, 1.2)	0.214
Location	Any Biopsy Tertiary vs None Tertiary	2.1 (−6.7, 10.8)	0.644	0.9 (0.7, 1.2)	0.481

Table 4.

Time from Suspicion of Malignancy to Treatment (Days), Adjusting for Number of Biopsies –

Linear regression coefficients and Cox Proportional Hazard Model ratios demonstrate longer cumulative time between suspicion of pancreatic cancer and treatment initiation based on number of biopsy attempts, as well as disparities with race, insurance provider, and tertiary location of biopsy.

		Linear Regression		Cox Proportional Hazard Model	
		Coefficient (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Intercept		32.1 (23.4, 40.9)	<0.001		
Group	Borderline Resectable vs Resectable	−0.8 (−9.6, 8.0)	0.860	1.0 (0.7, 1.4)	0.974
Sex	Female vs Male	−0.3 (−7.9, 7.3)	0.939	1.0 (0.8, 1.4)	0.865
Race	Black vs White	23.6 (9.5, 37.7)	0.001	0.6 (0.3, 1.0)	0.034
	Other or Unknown vs White	−15.1 (−37.1, 7.0)	0.179	1.9 (0.9, 4.0)	0.122
Ethnicity	Hispanic/Latinx/Unknown vs Not Hispanic/Latinx	0.07 (−17.9, 18.1)	0.994	1.2 (0.6, 2.2)	0.613
Insurance	Private vs Medicare	−8.3 (−17.9, 1.3)	0.090	1.3 (0.9, 1.9)	0.243
	Medicaid vs Medicare	−16.7 (−35.6, 2.15)	0.082	2.3 (1.1, 5.0)	0.034
	None vs Medicare	7.6 (−7.3, 22.6)	0.316	0.8 (0.4, 1.4)	0.354
Location	Any Biopsy Tertiary vs None Tertiary	−9.5 (−18.6, −0.5)	0.039	1.4 (1.0, 2.0)	0.091
Biopsies	1 vs 0	21.0 (10.7, 31.4)	<0.001	0.4 (0.3, 0.6)	<0.001
	2 vs 0	44.0 (25.7, 62.2)	<0.001	0.2 (0.1, 0.4)	<0.001
	3 vs 0	67.7 (39.8, 95.6)	<0.001	0.1 (0.0, 0.4)	<0.001