Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is currently the fourth leading cause of cancer-related death in the US and is predicted to rise to second by 2020 (1). For patients diagnosed with PDAC, surgical resection is the only chance for long term survival and potentially curative therapy (2). However, only 15–20% of cases are amenable to surgical resection due to local extension or metastasis (3). The median survival for patients with unresectable disease is less than one year (4).
PDAC is a relatively aggressive tumor with the potential
to progress to an advanced stage quickly. Metastases often
occur early in the course of disease, most often to the liver,
at which point the disease is usually incurable (5). The
estimated time for a PDAC tumor to progress from a T1 to
a T4 stage is estimated to be approximately 14 months (6).
Another factor that contributes to the late presentation of
PDAC is the lack of a safe and effective screening strategy.
Symptoms of PDAC often do not appear until the later
stages of progression and may be triggered by the presence
of symptomatic metastasis (7). In addition, symptoms of
PDAC are often nonspecific, with an intermittent course
that can be falsely reassuring to patients (8). When patients
present to medical attention with symptoms that could be
consistent with PDAC, many alternative diagnoses must also
be considered. The workup for patients is not standardized
and multiple follow-up appointments and studies are
often required before a final diagnosis is reached (9).
These factors are thought to contribute to diagnostic delays
and unnecessary healthcare expenditures in the workup of
PDAC (10,11).

Prior research has investigated the effects of diagnostic
delays on the resectability of breast, colon, and bladder cancer,
however, little is known about the impact of such delays on the
surgical resectability of PDAC (12). In this retrospective cohort
study, we investigated the relationship between the time it takes
to present, diagnose and treat the disease and the likelihood of
upfront surgical resection for patients with symptomatic PDAC.

Methods

Study cohort

All patients who were evaluated for PDAC at the Center for
Pancreas Cancer at Johns Hopkins in 2014 were reviewed
using the Johns Hopkins Pancreas Database, a repository of
patient clinical data. Patients were included if they presented
with symptoms, were diagnosed on the bases of clinical testing
arising from these symptoms and had clear documentation
of medical presentation and tests. Patients who were
asymptomatic and diagnosed from an incidental finding were
excluded from analysis. We also excluded any patients for
whom either the initial medical presentation for symptoms of
PDAC, or workup of tests performed to arrive at the diagnosis
and treatment, was incomplete. This study was approved by
the Institutional Review Board at Johns Hopkins Hospital.

Data collection

Demographic information on patient age, sex, race, tumor
histology, clinic of diagnosis, date of diagnosis and stage
of PDAC at diagnosis were collected directly from the
database. The date and type of presenting symptoms,
initial medical visit, treatment, and diagnostic tests were
collected by a single investigator (AB Deshwar) through
retrospective review of the patient’s physician encounter
notes and imaging documentation. The date and type of the
symptoms were extracted from the physician’s note. The
date of diagnosis was obtained from data available through
the Pancreatic Tumor Registry, defined as the earliest date a
primary cancer was diagnosed clinically or microscopically
by a recognized medical practitioner. The date of treatment
was extracted from patient operative and encounter notes,
defined as either the date of surgery or the first day that
chemotherapy or radiation treatment began. All tests and
procedures that were performed on the patient from their
first medical presentation up until, but not including, the
first day of treatment for PDAC were recorded.

The course of diagnosis and treatment was divided into
three intervals: patient, diagnostic, and treatment intervals.
The patient interval was defined as the time from the
first onset of PDAC symptoms to the first medical visit to
investigate these symptoms. The diagnostic interval was
defined as the time from first medical visit to the time of
clinical or pathologic diagnosis of PDAC (whichever came
first). The treatment interval was defined as the time from
diagnosis to first treatment for PDAC.

Presenting symptoms were then grouped into
16 categories based upon shared characteristics: abdominal
pain, back pain, bloating, change in stools, chest pain, chills/
fever, discolored urine, early satiety, fatigue, gastric reflux,
lower extremity edema, nausea, pruritus, vomiting and
weight loss.

Tests were categorized into one of 12 groupings based
upon modality and relevance towards the workup of PDAC:
CT abdomen, CT other, MRI abdomen, MRI other,
endoscopic ultrasound (EUS) and/or fine needle aspiration
(FNA), esophagogastroduodenoscopy (EGD)/colonoscopy,
endoscopic retrograde cholangiopancreatography (ERCP),
X-Ray, ultrasound, nuclear medicine, fluoroscopy and
other [e.g., biopsy of sites unrelated to PDAC diagnosis
and gastrointestinal (GI) function studies]. Diagnostic tests
were defined as all imaging and procedures performed from
first medical presentation after experiencing symptoms of PDAC, up to and including the day of their diagnosis.

Treatment planning tests were defined as all imaging and procedures performed after the date of their diagnosis of PDAC until the day before the patients first treatment.

Statistics

The demographic and disease characteristics of the cohort were summarized using medians with interquartile ranges (IQR, 1st–3rd quartile ranges) for continuous variables and counts with proportions for categorical variables. Shaded bar charts and timelines were used to graphically summarize the timing of the patient, diagnostic, and treatment intervals. Fisher’s exact tests and Wilcoxon rank-sum tests were used to compare categorical and continuous outcomes, respectively, between subgroups of interest. Univariable and multivariable logistic regression was used to assess the impact of demographic and clinical characteristics as well as interval durations on the odds of surgical resection and stage at diagnosis.

Results

Study cohort

Of 453 charts with PDAC that were reviewed, 337 were excluded from the analysis: 283 had an unclear documentation of initial medical presentation or an incomplete progression...
of tests leading to up to diagnosis and treatment, and 54 had asymptomatic (incidentally diagnosed) disease. The remaining 116 patients met our inclusion criteria for symptomatic PDAC (Table 1). At the time of diagnosis, 7 patients (6%) had stage 1, 53 (46%) had stage 2, 24 (21%) had stage 3, and 32 (28%) had stage 4 disease. The median interval from the beginning of patient symptoms to the first day of treatment for all patients was 74 days (IQR: 45–131 days) (Figure 1). The patient, diagnostic, and treatment intervals for each of the patients included in the analysis is shown in Figure 1. The median number of tests performed from initial medical presentation until treatment was 8 (IQR: 6–11).

**Patient interval**

The median patient interval was 14 days (IQR: 6–30 days) and 89 (77%) patients presented to a physician within 1 month after first reporting experiencing symptoms. At initial medical presentation, patients reported a median of 2 (IQR: 2–4) symptoms potentially related to the eventual diagnosis of PDAC. The most common symptoms were abdominal pain (70%), a change in stool habits (34%), and jaundice (29%). Patients with abdominal pain waited significantly longer until their first medical visit as compared to those without (medians: 15.0 vs. 7.0 days, P=0.003). In contrast, patients with jaundice had a shorter wait time compared to those without (medians: 10.0 vs. 14.5 days, P=0.035). No other symptom types were significantly associated with the duration of the patient interval (P>0.05).

**Diagnostic interval**

The median diagnostic interval was 22 days (IQR: 8–46 days) and 92 (79%) patients were diagnosed with PDAC within 2 months after their first presentation to a physician. All 116 individuals had at least 1 test performed between the first medical visit and diagnosis (median 5, IQR: 3–7, range: 1–12). The most common tests performed were abdominal CT (175, 29%), ultrasound (76, 13%), and EUS (12%). We also examined the last test performed immediately prior to a diagnosis of PDAC being made. The most common test was EUS/FNA (59, 30%) followed by abdominal CT (52, 26%).

**Treatment interval**

The median treatment interval was 25 days (IQR: 15–35 days). A total of 92 (79%) individuals had additional procedures during the treatment interval, i.e., after their diagnosis but prior to treatment. The median number of treatment planning tests per individual was 4 (IQR: 1–6, range: 0–19). Abdominal
CT (n=152, 33%) and Other CT (n=139, 30%) made up the majority of treatment planning tests (Table 2).

**Patient, diagnostic, and treatment intervals and surgical resectability**

A total of 38 patients (33%) received upfront surgery for treatment of PDAC and 78 (67%) received nonsurgical upfront treatment. Although the decision to proceed to upfront surgery was made on a case by case basis by the consulting surgeon, as a general practice purely resectable pancreas cancers in operative candidates with a CA19-9 <200 were routinely provided upfront surgery. Patients with locally advanced disease, high CA19-9s, or high-risk medical comorbidities were generally provided with nonsurgical treatment. Of those who received upfront surgery, 34 (89%) had stage I or II disease whereas only 26 (33%) of patients who received nonsurgical upfront treatment had stage I or II disease.
II disease. There was no significant association between age at the first medical visit or gender and the odds of upfront surgical resection (P>0.05, Table 3). However, non-white patients had lower odds of upfront surgical resection than those who were white [adjusted odds ratio (aOR): 0.09, 95% confidence interval (CI): 0.004–0.480, P=0.023]. Patients treated with upfront surgery underwent fewer tests, both diagnostic (median: 4 vs. 5, P=0.61) and treatment planning (median: 2 vs. 4, P<0.001), then those who did not receive upfront surgery.

We examined the relationship between patient, diagnostic, and treatment intervals and surgical resectability (Table 3). The odds of resection were more than 3 times higher for those who had a medical visit within 30 days of symptom onset (aOR: 3.41, 95% CI: 1.08–13.20, P=0.050). The median patient interval for those receiving upfront surgery was 10 days (IQR: 6–21 days) as compared to 16 days (IQR: 7–40 days) for those without upfront surgery. Individuals diagnosed within 60 days of the first medical visit had higher odds of upfront surgical resection (aOR: 15.68, 95% CI: 2.95–291.00, P=0.009) (Figure 2). The median diagnostic interval for those receiving upfront surgery was 18 days (IQR: 6–28 days) as compared to 30 days (IQR: 11–72 days) for those who did not receive upfront surgery. The odds of receiving surgery did not differ significantly for those treated within 30 days of diagnosis after adjusting for other risk factors, including the patient and diagnostic intervals (aOR: 1.81, 95% CI: 0.68–5.01, P=0.240).

**Discussion**

We find that patients who wait 30 days or less to present to medical attention after the start of PDAC symptoms, and patients with a diagnostic interval for PDAC after presentation to medical attention of 60 days or less, have increased odds of receiving upfront surgical resection for PDAC. These associations are hypothesis generating, but suggest that delays in PDAC diagnosis may lead to the identification of PDAC at a more advanced stage, when it is less likely to be surgically resectable. Alternatively, advanced PDAC may present with more nonspecific findings than localized PDAC, resulting in longer diagnostic intervals. Our observation that non-white participants may be less likely to receive upfront surgical resection for PDAC could be a reflection of barriers to care, and warrants further investigation. We did not identify any significant association between length of the treatment interval and the odds of upfront surgical resection. This may be because treatment plans are often established at the beginning of the treatment interval and are unlikely to change despite the passage of additional time.

Prior studies across multiple tumor types investigating the relationship between interval lengths in patient care and clinical outcomes have yielded mixed results (12). There have only been three previous studies that have investigated a component of the diagnostic interval and patient outcomes in PDAC. Two of these studies identified a positive association between shorter intervals and improved patient outcomes (13,14), and one found no association (15). Gobbi et al. (13) found a positive association between the “time to diagnosis” (symptom onset–diagnosis) and survival and Raptis et al. (14) found a shorter “pre-hospital” delay (symptom onset–referral to a specialist) to be positively associated with survival. McLean et al. (15) found no association between “wait times” (symptoms–surgical consultation and surgical consultation–procedure) on resectability or survival. However, directly comparing these studies to each other, or to the present investigation has some challenges.

To be able to isolate the impact of the patient, diagnostic and treatment intervals respectively, we followed the protocols for intervals set out by the Aarhus statement on improving designs of early cancer diagnosis studies (16). Historically, these intervals have not been consistently defined, making comparison difficult. For example,
these three previous studies used the date symptoms began to begin the diagnostic interval; the result being a measurement that combines what we identified as the patient (date of first symptoms–first medical appointment) and diagnostic (first medical appointment–diagnosis of PDAC) intervals. Instead, using the date of first medical presentation allows for a more consistent and representative anchor from which to begin the diagnostic interval. A well-defined patient vs. diagnostic interval is crucial, to be able to contextualize findings such as Lyratzopoulos et al. observing that 41% of patients eventually diagnosed with pancreatic cancer, visited their general practitioner three or more times before hospital referral; second only to multiple myeloma amongst major cancers (9). This parallels findings in previous investigations, observing that PDAC patients are often subject to a large variance in the diagnostic workup of testing that they receive, and this often has correlates to greater delays and higher healthcare costs (10,11).

A strength of this investigation includes the use of a large and well-characterized cohort of PDAC patients. However, this study also has certain limitations. We cannot exclude the possibility of selection or recall bias in our study, resulting from the retrospective nature of the data, the study selection criteria, and the reliance on patient self-report to their physicians for ascertainment of the patient interval. In addition, causality cannot be inferred from the observed relationship between patient and diagnostic intervals and the odds of upfront surgical resection. Finally, the majority of the patients in this cohort were treated at a single tertiary referral center, which may limit the generalizability of our findings. Since it is not ethically feasible to delay surgery for patients with PDAC to determine the effect of treatment delays on outcomes, additional retrospective analyses will be necessary to confirm our findings. In summary, a patient interval of less than 30 days and a diagnostic interval of less than 60 days for symptomatic PDAC, are associated with a clinically meaningful improved probability of upfront surgical treatment. These data suggest that efforts to reduce delays may lead to improved outcomes in PDAC.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board (IRB) at Johns Hopkins Hospital (NA_00068179).

References


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