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Original Research Article

A Hospital-Based Study to Explore the Impact of Pursuing Tissue Diagnosis by Endoscopic Ultrasound (EUS) Guided Biopsy for Primary Diagnosisin Patients with Pancreatic Cancers

Sanjay Kumar[1], Ravikant Kumar[2], Lajpat Agarwal[3], Mamta Kumari[4], Manish Mandal[5]

[1]Additional Professor, Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

[2]Additional Professor, Department of Gastroenterology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

[3]Senior Resident, Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

[4]Assistant Professor, Department of Pathology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

[5]Professor and Head, Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

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Corresponding author: Dr. Sanjay Kumar
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Abstract

Aim: The aim of the present study was to explore the impact of pursuing tissue diagnosis by endoscopic ultrasound (EUS) guided biopsy for primary diagnosis in patients with Pancreatic ductal adenocarcinoma.

Methods: The present study was conducted at Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India in patients who were diagnosed and/or treated with PC at our high-volume tertiary center were prospectively included in a patient database. 50 patients were included in the study.

Results: Median age at diagnosis was 66 years. A majority of patients were male (56%; n = 28); had a good performance status and initially presented with synchronous metastatic disease. Most patients were treated with single-agent gemcitabine or gemcitabine-containing combination chemotherapy, followed by 5-FU-based regimens. We calculated TTI as time from first imaging study showing a suspicion of advanced PC and administration of the first cycle initiation was 29 days (range: 1–124 days), with a 75th and 90th percentile of 43 and 60 days, respectively. Prior to the conduct of our study, we assumed that a TTIinterval of more than 21 days represents a "treatment delay". Applying this strict definition, a delay in treatment initiation was found in 30 patients (60%). Treatment delay was significantly more frequent in patients who initially presented with synchronous metastatic disease than in patients who relapsed after surgery in curative intent.

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

Keywords: endoscopic ultrasound (EUS) biopsy, resectable and borderline resectable Pancreatic ductal adenocarcinoma.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the seventh most common cause of cancer-related death worldwide, and its incidence is increasing. [1-3] In the United States and Japan, it ranks as the fourth leading cause of cancer-related mortality. [4,5] Its 5-year survival rate remains as low as 6% in the United States. [6] Without novel diagnostic methods and/or treatments, it is expected to become the second leading cause of cancer-related deaths by 2030. [7] Due to its early metastatic nature, up to 20% of patients with PDAC are eligible for initial resection. [6] The poor prognosis results from the low respectability rate at diagnosis, with surgery being the only potentially curative treatment. However,

even with radical resection, most patients relapse within a year. Moreover, due to the high resistance rate to chemotherapy, radiotherapy, and immunotherapy [8], non-operative treatment has a poorer prognosis with a median survival of 5-9 mo. [9] A variety of genetic and molecular alterations have been identified in PDAC, including mutations in KRAS, p16, p53, BRCA2, Smad4, etc. [10]

Pancreatic cancer is a devastating disease with a poor prognosis, which is partially due to delayed diagnosis because of the late onset of symptoms. [11] Despite the many advancements that have been made in medical therapy in the past decade, there are still limited treatment modalities for advanced disease. Many epidemiologic surveys have shown that the 5-year survival rate is below 5%. [12,13] A significant proportion of patients could extend their survival time by surgery if their tumors were diagnosed at an early stage. [14] So early detection and accurate staging are crucial for the right treatment choice.

Tissue acquisition is of great importance to confirm diagnosis and guide treatment in pancreatic solid mass. The endoscopic ultrasound (EUS)-guided minimally invasive tissue acquisition techniques have become the standard of choice to sample pancreatic tissue that could only be biopsied through open techniques in the past. [15] The EUS method can detect lesions that are not seen by other imaging modalities and fine needle aspiration (FNA) is reported to be able to give a definitive cytological diagnosis4. A recent meta-analysis reported that the sensitivity and specificity of EUS-guided FNA (EUS-FNA) for pancreatic neoplasms were 85% and 98%, respectively. [16] The complication rate of EUS-FNA is approximately 1%–2%. [17] Having become widely accepted as safe and effective, EUS-FNA is considered a minimally invasive method of diagnosing pancreatic cancer. [18]

The aim of the present study was to explore the impact of pursuing tissue diagnosis by endoscopic ultrasound (EUS) biopsy guided biopsy for primary diagnosisin patients with Pancreatic ductal adenocarcinoma. And start of chemotherapy.

Materials and Methods

The present study was conducted atDepartment of G.I. Surgery,Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India for 36 months in patients who were diagnosed and/or treated with PC at our high-volume comprehensive cancer center were prospectively included in a patient database. 50 patients were included in the study. For the current study, medical records were retrospectively analyzed to screen for eligible patients. Inclusion criteria were: histologically or cytologically confirmed advanced PC patients (locally advanced or metastatic disease) who received palliative chemotherapy. Exclusion criteria were: histology other than pancreatic adenocarcinoma, second malignancy, surgery in palliative intent, no imaging study prior to initiation of palliative chemotherapy or insufficient data quality. The following data were evaluated: patient and tumor characteristics including age, performance status, carbohydrate antigen 19-9 (CA 19-9) levels at time of initial diagnosis of advanced PC, date of first imaging study (e.g. ultrasound, CT or MRI scan) showing a suspicion of advanced PC, treatment of PC (surgery, radiotherapy, chemotherapy). Patients treated outside of clinical trials received chemotherapy based on the decision of the supervising medical oncologists (SB and VH) until disease progression, unacceptable toxicity or patient refusal. TTI was calculated as time from first imaging study showing advanced PC to time of first receipt of chemotherapy in palliative intent. Survival status was determined by (a) review of medical records at our institution, (b) consultation of patient's primary care physician or (c) consultation of patient's civil registrar office. The study was approved by the local ethics committee of Indira Gandhi Institute of medical sciences, Patna.. This report was writ- ten according to the most recent reporting recommendations for tumour MARKer prognostic studies (REMARK). [19]

Results

Table 1: Patient characteristics at time of initiation of palliative first-line chemotherapy

Age (years) Median Range Gender	*n* 66 37–84	%
Male	28	56
Female	22	44
Stage of disease		
Metastatic (relapse after surgery in curative intent)	14	28
Metastatic(synchronous)	28	56
Locally advanced	8	16
Primary tumor site		
Head of pancreas	31	62

Body of pancreas	8	16
Tail of pancreas	10	20
Missing	1	2
Performance status		
ECOG0	20	40
ECOG1	20	40
ECOG2	5	10
ECOG3	4	8
Missing	1	2
Histology		
Ductal adenocarcinoma	48	96
Adenosquamous Carcinoma	1	2
Mucinousadeno carcinoma	1	2
First-line chemotherapy		
Chemoradiotherapy	4	8
Gemcitabine Monotherapy	10	20
Gemcitabine- based combination chemotherapy	23	37
5-FUorcapecitabine monotherapy	2	4
5-FU- based combination chemotherapy	11	27
Other	2	1
Missing	6	3

Median age at diagnosis was 66 years. A majority of patients were male (56%; n = 28); had a good performance status and initially presented with synchronous metastatic disease. Most patients were treated with single-agent gemcitabine or gemcitabine-containing combination chemotherapy, followed by 5-FU-based regimens.

Table 2: Time to treatment initiation (TTI)

Time To Treatment Initiation			
Median TTI	30days		
Range TTI	1–124days		
75th percentile	43days		
90th percentile	60days		
Treatment delay (TO>21 days) according to initial stage of disease	No treatment delay (TTI≤21days)(*n*)	Treatment delay (TTI>21 days)	
All patients	20	30	$p<0.001$
Initial Presentation with advanced disease	11	20	
Relapsed after surgery in curative intent	9	10	
Reasons for treatment delay (TO>21 days)	*n*	%	
Additional Biopsy (initial biopsy inconclusive)	10	20	
Additional Diagnostic studies to establish pancreas cancer primary	2	4	
Comorbidities	6	12	
Initially Deemed Respectable On Preoperative Staging	2	3	
Patient's request	2	1	
Referral From Tertiary Cancer Center	13	26	
No Specific Reason	16	32	

We calculated TTI as time from first imaging study showing a suspicion of advanced PC administration of the first cycleinitiation was 29 days (range: 1–124 days), with a 75th and 90th percentile of 43 and 60 days, respectively. Prior to the conduct of our study, we assumed that a TTInterval of more than 21 days represents a "treatment delay". Applying this strict definition, a delay in treatment initiation was found in 30 patients (60%). Treatment delay was significantly more frequent in patients who initially presented with synchronous metastatic disease than in patients who relapsed after surgery in curative intent.

Discussion

Despite a declining overall cancer mortality in the western world, pancreatic cancer (PC)-related mortality has been on the rise in recent years. [20,21] A further increase in incidence is predicted to make PC the second leading cause of cancer-related mortality by 2030 in the US and Europe, respectively. [22,23] Treatment options for other solid malignancies were substantially expanded by the advent of targeted therapy and immunotherapy in recent years. For advanced PC patients, treatment efficacy was only modestly improved by the development of two intensified chemotherapy regimens, resulting in a median overall survival of still less than 1 year for patients with good performance status without significant comorbidities. [24-26] This leaves patients and physicians in a dissatisfactory situation with limited therapeutic options

Median age at diagnosis was 66 years. A majority of patients were male (56%; n = 28); had a good performance status and initially presented with synchronous metastatic disease. Most patients were treated with single-agent gemcitabine or gemcitabine-containing combination chemotherapy, followed by 5-FU-based regimens. We calculated TTI as time from first imaging study showing a suspicion of advanced PC administration of the first cycleinitiation was 29 days (range: 1–124 days), with a 75th and 90th percentile of 43 and 60 days, respectively. Prior to the conduct of our study, we assumed that a TTIinterval of more than 21 days represents a “treatment delay”. Applying this strict definition, a delay in treatment initiation was found in 30 patients (60%). Treatment delay was significantly more frequent in patients who initially presented with synchronous metastatic disease than in patients who relapsed after surgery in curative intent. Median TTI in our study was 30 days. This is longer than we expected prior to the initiation of our study (our predefined cutoff for treatment delay was 21 days). We identified four other studies that reported TTI in advanced PC patients. [27-30] In the most recent study,median TTI for patients with advanced PC was reported to be only 14 days, but the definition of TTI differed from the one used in our study. [29]

For resectable PC a prolonged TTI correlates with an adverse prognosis for patients treated at low but not high volume Cancer centers. [31] Because of the monocentric design of our study, it is unclear, whether the effect of TTI in advanced PC does also vary between low- and high-volume cancer centers. It is therefore important to note that our results should be only translated with caution to patients exclusively treated at tertiary centers. For patients transferred from local hospitals to high-volume cancer centers, the absence of a strong correlation between TTI and prognosis in our study is reassuring. Prognosis of advanced PC has been reported to depend on size of the treating cancer center. [20] If possible, advanced PC patients should therefore be referred to a specialized cancer center irrespective of a possible TTI prolongation.

Conclusion

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

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