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Pre-diagnostic delays caused by gastrointestinal investigations do not affect outcomes in pancreatic cancer

Jeyakumar R. Apollos[a,*], Sharukh Sami[a], Manju Nadh Prasanth[a], Jerusha Jeyakumar[b], Angus K. McFadyen[c]

[a] Department of General Surgery, Dumfries and Galloway Royal Infirmary, Dumfries, DG2 8RX, UK
[b] University of Aberdeen, King's College, Aberdeen, AB24 3FX, UK
[c] AKM-stats, Glasgow, UK

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ABSTRACT

Background: Pancreatic ductal adenocarcinomas are poor prognostic cancers accounting for 3% of all cancer cases in the UK. They often present late in the course of the disease process with non-specific symptoms, including gastro-intestinal(GI) symptoms. Delays in diagnosis occur when investigations are carried out in a primary care setting for GI symptoms. The aim of this study was to assess delays in pancreatic cancer diagnosis when patients were referred for GI investigations and evaluate its effect on survival.

Methods: Retrospective cohort study of all patients diagnosed with pancreatic adenocarcinoma in a Scottish district general hospital over a seven year period from January 2010 to December 2016. Patients were divided into two groups, those who had a GI investigation 18 months prior to the pancreatic cancer diagnosis and those who did not have GI investigations. Data on demographics, symptoms on referral, stage of disease at diagnosis, treatment undergone and length of survival collected and analysed.

Results: One hundred and fifty-three patients were diagnosed with pancreatic cancer in the study period. Forty (26%) of the 153 underwent gastrointestinal investigations in the 18 months prior to diagnosis. The remaining 113 (74%) had no gastro-intestinal investigations in the same time period. Demographic data were comparable. Significant delays occurred from referral to diagnosis in the GI investigated group compared to those who did not have GI investigations. (64.5days vs 9 days, $p = 0.001$). No difference was noted in disease stage or treatments undergone between the groups. There was no difference in the average survival after diagnosis between the two groups with median of 108 days for those who underwent GI investigations to 97 days for those who did not. ($U = 2079.5$, $p = 0.454$).

Conclusion: Delays caused by pre-diagnostic GI investigations do not appear to contribute to the poor prognosis of pancreatic cancer. Recently updated NICE Guidelines recommends early ultrasound or CT in patients with GI symptoms and weight loss which may reduce delays in diagnosis. Screening tests in future may become cost effective and diagnose this condition at a curable stage which in turn may improve survival rates.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for 3% of all cancer cases in the UK with 9618 new cases recorded in 2014. This condition has a poor prognosis with less than 4% of patients surviving 5 years following diagnosis and treatment [1]. At the time of diagnosis, almost 80% of patients have stage III or IV disease [2,3]. Median survival is stage dependent; metastatic disease has a median survival of 2–6 months, locally advanced disease-6 to 11 months and resectable disease-11 to 20 months [1,4]. Gastrointestinal (GI) symptoms are frequent in pancreatic cancer [5,6]and patients are often referred for endoscopic investigations that may delay diagnosis.

2. Aims

The aim of this study was to assess delays in pancreatic cancer diagnosis when patients were referred for GI investigations from primary care, either by open access or through gastroenterology clinics and evaluate its impact on survival outcomes.

* Corresponding author.
E-mail address: japollos@yahoo.com (J.R. Apollos).

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3. Patients and methods

This retrospective cohort study was conducted in a Scottish District General Hospital (Dumfries and Galloway Royal Infirmary) and approved by the local Quality Improvement department. All patients diagnosed with pancreatic cancer between January 2010 and December 2016 were identified from a prospective cancer database maintained by the local Cancer Audit team. Demographic details, dates of referral and diagnosis, site of tumour, stage at diagnosis and treatment details were collected. Data on principal symptoms triggering referral, GI investigations (endoscopy, colonoscopy or CT Colonogram) in the 18 months prior to diagnosis, treatment details and date of death were obtained by cross referencing each patient's unique Community Health Index (CHI) number with electronic patient records (SCI Store, Information Services Division, NHS Scotland) and our department's gastro-intestinal endoscopy reporting software database (GI Reporting Tool, Unisoft Medical Systems, UK). Patients were allocated to two groups - those who underwent GI investigations in the 18 months prior to their pancreatic cancer diagnosis and those who had no GI investigations in the same period.

Data were anonymised and statistical analysis was performed using IBM SPSS v24.0. Testing between groups was performed using the chi-square test for categorical variables and, either the two independent sample *t*-test or Mann-Whitney *U* test for other measurements, depending on checks for normal distributions. STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) guidelines were followed in the reporting of this study [7].

4. Results

One hundred and fifty-three patients were diagnosed with pancreatic cancer between January 2010 and December 2016. Forty (26%) of the 153 underwent gastro-intestinal investigation with endoscopy, colonoscopy, endoscopy and colonoscopy or CT colonography in the 18 months prior to diagnosis. The remaining 113 (74%) had no gastro-intestinal investigations performed in the same period.

Dyspepsia, abdominal pain, weight loss, bloating, diarrhoea or constipation and unexplained iron deficiency anaemia were the main triggers for referral for GI investigation. One patient had an upper GI endoscopy for Barrett's surveillance and was asymptomatic. Three symptomatic patients had colorectal cancer on colonoscopy; the pancreatic lesion being identified on staging CT scans. Two patients had pancreatic cancers invading the stomach and duodenum allowing tissue biopsy at the time of endoscopy. A pancreatic lesion was not identifiable in one of three patients who underwent a CT colonogram but became apparent in a subsequent CT scan 8 months later. Patients undergoing surgery or chemotherapy had biopsy or cytology proven pancreatic ductal adenocarcinoma.

There were no significant difference in the average age between the group that underwent GI investigations and the group that did not have GI investigations, 72 (range 43–84) vs 72 (range 39–94) respectively [t = 0.811, p = 0.419; 95% CI -5.49, 2.29] or gender profiles, M%:F% = 57.5:42.5 vs 50.4:49.6 respectively [χ^2 = 0.341, p = 0.559] (Table 1).

Patients who underwent GI investigations had a significantly higher occurrence of GI symptoms such as nausea, early satiety, bloating, altered bowel habits, constipation or diarrhoea. Abdominal pain and weight loss were reported more frequently in this group [72.5% v 51.3% and 77.5% v 42.5% respectively]. Presentation with obstructive jaundice was more common in the group that did not undergo GI investigations [12.5% v 47.8%]. There was no difference in other symptoms such as shortness of breath, cough, tiredness and new onset diabetes (Table 2).

Table 1
Demographics.

	GENDER		AGE	
	Male 80 (52.3%)	Female 73 (47.7%)	Mean	Median (Range)
GI Investigation n = 40	23 (57.5%)	17 (42.5%)	70	72 (43–84)
No GI investigation n = 113	57 (50.4%)	56 (49.6%)	72	72 (39–94)

Table 2
Presenting symptoms of both groups.

Symptoms	GI Investigation group n = 40	No GI investigation group n = 113	
GI Symptoms	24 (60%)	27 (23.9%)	X^2 = 15.74 P < 0.001
Abdominal pain	29 (72.5%)	58 (51.3%)	X^2 = 4.57 P = 0.033
Weight loss	31 (77.5%)	48 (42.5%)	X^2 = 13.14 P < 0.001
Jaundice	5 (12.5%)	54 (47.8%)	X^2 = 14.07 P < 0.001
New onset diabetes	3 (7.5%)	10 (6.5%)	X^2 = 0.0 P = 1.0
Other symptoms	16 (40%)	31 (27.4%)	X^2 = 1.64 P = 0.200

We found significant delays from referral to diagnosis in the group that underwent GI investigations with a median delay of 64.5 days (range 1–509) compared to 9 days (range 0–414) for the group not undergoing GI investigation, (U = 768.5, p < 0.001) (Fig. 1).

Head of pancreas tumours were more frequent in patients who did not have GI investigations (65.5% vs 32.5%), body of pancreas tumours were more frequent in the group that underwent GI investigations (42.5% vs 17.7%) and tail of pancreas was involved more frequently in the GI investigation group also (25% vs 16.8%) (Fig. 2). There was no significant association between the groups and the stages of disease. Similarly, there was no significant difference between the groups in treatments undergone.[X^2 = 5.834, p = 0.212] (Table 3). Of the 19 patients with potentially operable lesions, only 3 were from the group that had GI investigations. Seven of these nineteen patients (36%) went on to have a Whipple's resection (4/19) or distal pancreatectomy with splenectomy (3/19) and adjuvant chemo therapy. Only one patient of the three potentially operable patients from the GI investigations group

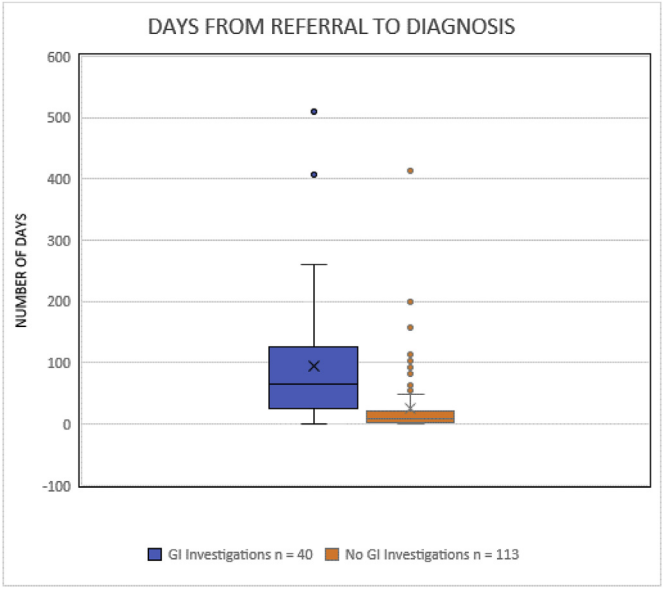

Fig. 1. Days from referral to diagnosis.

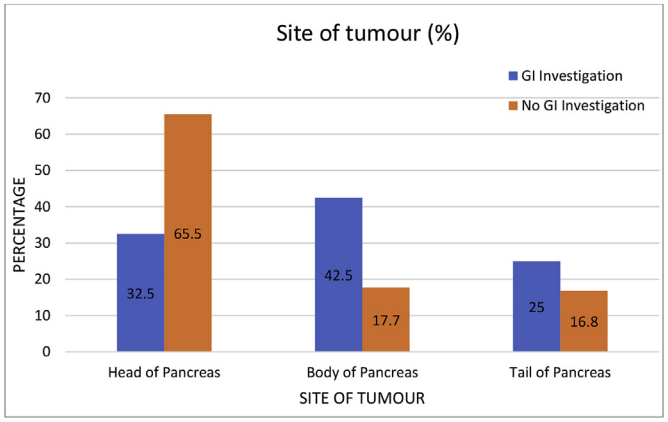

Fig. 2. Site of tumour.

Table 3
Stage at diagnosis and treatment.

	GI Investigation group n = 40	No GI investigation group n = 113
Stage at diagnosis		
Potentially operable	3 (7.5%)	16 (14.2%)
Locally advanced	16 (40%)	35 (31%)
Metastatic	21 (52.5%)	62 (54.9%)
Treatment		
Curative Surgery	1 (2.5%)	6 (5.3%)
Palliative Chemotherapy	10 (25%)	19 (16.8%)
ERCP/PTC Stenting	4 (10%)	21 (18.6%)
ERCP/PTC Stenting with Chemotherapy	0	7 (6.2%)
Best Supportive Care	25 (62.5%)	60 (53.1%)

had surgery which was a distal pancreatectomy. The others in the potentially operable group received palliative treatment by biliary stenting, palliative chemotherapy or best supportive care due to advanced age of an average of 82 years or above at diagnosis and co-morbidities. The patients who underwent surgery in this potentially operable group survived an average of 21 months compared to 4 months in those who did not.

All except three patients had died at the time of data collection for this study which ended on 31 December 2017. One patient who was endoscopically investigated is receiving best supportive care and currently alive, but bed bound 580 days after diagnosis. One patient from the no GI investigation group who underwent distal pancreatectomy and splenectomy is alive at 843 days and a second patient from this group, who had palliative stenting and chemotherapy, is alive 467 days after diagnosis.

There was no significant difference in average survival between the two groups. The median survival was 108 days for patients undergoing GI investigation (range 5–700) compared to 97 days for those who did not (range 2–843) [U = 2079.5, p = 0.454].(Fig. 3). When survival was evaluated according to stage at diagnosis, there was a significant difference for patients presenting with the locally advanced disease, with a higher median survival noted in the group that underwent GI investigations [341 days (range 39–700)] compared to those who did not have GI investigations [130 days (range 8–833), U = 152.0, p = 0.009] (Table 4).

5. Discussion

Pancreatic cancer is the 11th most common cancer in the UK and its incidence has increased by 14% since the1990's. This is projected to increase by 6% by 2035. Prognosis is dependent on stage of disease and overall remains poor with only around 1% surviving 10 years. This has

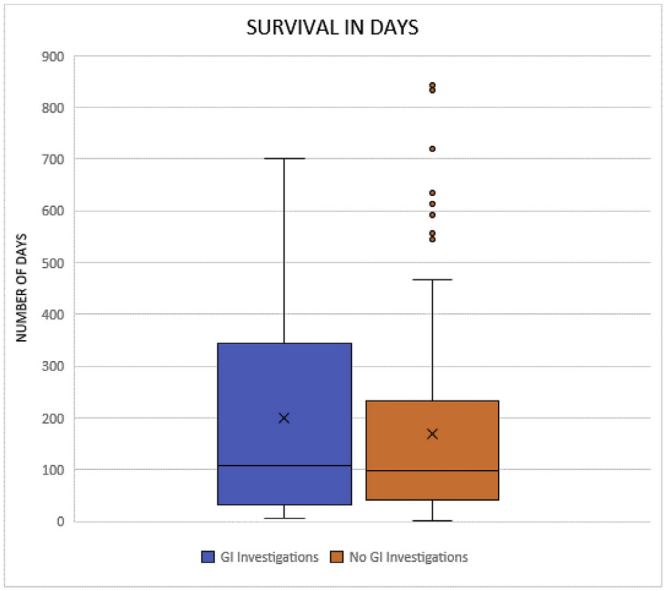

Fig. 3. Survival in days.

remained unchanged in 40 years [1].

This apparent lack of improvement is due to patients rarely exhibiting specific symptoms until the disease is significantly advanced [2]. Tumour location dictates symptomatic presentation, with most head of pancreas tumours presenting sooner with obstructive jaundice [3]. Body and tail tumours tend to present later with abdominal pain, weight loss and other non-specific symptoms [4]. These include anorexia, early satiety, weight loss, abdominal pain, nausea and vomiting, constipation and diarrhoea [5,6]. A large observational study of 3635 patients with pancreatic cancer found that 10.6% complained of diarrhoea and 11.8% described new onset constipation [8]. Such symptoms are common in primary care [8,9] and differentiating between the myriad of benign and malignant gastro-intestinal disorders can be challenging.

Delays in diagnosis of pancreatic cancer, which is considered to be a 'harder to suspect' cancer [10], may occur as GI investigations are performed in a primary care setting through 'Open access' pathways or via GI clinics. Over 40% of patients with pancreatic cancer visit their general practitioners three or more times before referral to secondary care [10,11]. To try and reduce such delays, updated National Institute for Clinical Excellence (NICE) guidelines recommend that "an urgent access CT or ultrasound (within two weeks) should be considered in patients aged 60 or over with weight loss and any one of diarrhoea, nausea, vomiting, constipation and abdominal pain" [12]. This study involves the years before this guidance was available but does identify the need for general practitioners to consider scans along with luminal investigations when seeing patients with the above-mentioned symptoms.

The UK government implemented the NHS Cancer Plan [15] in 2000 to combat the UK's high mortality rates when compared to other European countries and the USA, which are thought to be partly linked to longer waiting times in the UK [13,14]. Cancer waiting time targets were introduced and it was recommended that the overall time from referral of the patient to treatment should not exceed 62 days [15]. In our study, 26% of patients with pancreatic cancer were referred for GI investigations which delayed diagnosis by around 64 days and therefore delayed treatment well beyond the target period. Previous studies have shown that delays in diagnosis and treatment beyond 62 days do not affect the poor survival outcomes in pancreatic cancer [14]. Our study also suggests that this delay in patients undergoing GI investigations prior to their diagnosis did not affect the stage of the cancer at the time of diagnosis or their overall survival when compared with

Table 4
Survival by stage at diagnosis.

	Potentially operable t = 0.955, p = 0.353			Locally advanced U = 152, p = 0.009			Metastatic U = 597.5, p = 0.575		
	n	Mean(Median)	Range	n	Mean(Median)	Range	n	Mean(Median)	Range
GI Investigation n = 40	3 (7.5%)	207(134)	17 to 471	16 (40%)	356.6(341)	39 to 700	21 (52.5%)	81.1(50)	5 to 371
No GI investigation n = 113	16 (14.1%)	360(290)	44 to 843	35 (30.9%)	214(130)	8 to 833	62 (55%)	95.2(57)	2 to 556

the group that had an earlier diagnosis. Paradoxically, patients with locally advanced disease in the delayed diagnosis group survived longer than the corresponding group where there was no delay in diagnosis. This may partly be due to a selection bias as there are a higher proportion of persons aged 60 or over in our catchment region (31.5%) compared to rest of Scotland (24.2%) [16]. As fewer potentially curable lesions were operated upon due to advanced age and co-morbidities in our cohort, this may have caused a type 2 statistical error. However, survival in our region does mirror other studies which report median survival of 16–18 months in spite of increased resection rates in centralised units [17].

Mathematical modelling based on genetic tests predict that the vast majority of pancreatic cancer patients are not diagnosed until the last two years of the tumorigenic process though the cancer may be present for at least 10 years before diagnosis. This is likely to explain the poor survival currently observed in most studies including ours where almost all patients died at two years. An average of 6.8 years is thought to elapse between formation of the index parental clone cell with metastatic potential and the seeding of the first distant metastasis [18]. This highlights the feasibility of screening tests to detect pancreatic cancer at an earlier stage [18]. The incidence of pancreatic cancer is relatively low and therefore, there is no suitable cost-effective test for screening pancreatic cancer in the general population [19]. However, in high risk persons over the age of 40 with a history of hereditary pancreatitis and genetic risk for pancreatic cancer such as a BRCA2 mutation, Hereditary Pancreatitis, Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome, Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Familial Pancreatic cancer(FPC) and Peutz-Jeghers syndrome, it is cost effective. The current recommendation for this group of patients is to undergo either annual or 3 yearly CT scans, Endoscopic Ultrasound scans, genetic tests of pancreatic juice samples collected at ERCP, blood glucose and CA19-9 levels depending on the risk stratification [19–21].

CA 19-9 is a carbohydrate tumour associated antigen but has a low sensitivity and specificity, making it unsuitable for widespread screening [21,22]. When used in combination with other biomarkers such as IGF-1 and albumin, its accuracy can be improved [23]. Within the limitations of screening such as lead time bias, length-biased sampling and overdiagnosis [24], such blood tests to detect cancer-specific proteins, transcripts, mutations in cell-free DNA [21,25,26], and focussed non-invasive imaging methods [21,27] may make population screening and surveillance cost effective in the years to come, as the burden of disease is projected to increase.

6. Conclusion

Pancreatic cancer is usually diagnosed late and carries a poor prognosis, as it largely remains asymptomatic until it is locally advanced or metastasized. Further delays occur due to non-specificity of symptoms resulting in multiple consultations and other investigations such as GI endoscopies being carried out. These delays do not appear to contribute to current poor survival outcomes. The updated NICE recommendation may improve clinical and radiological diagnosis in primary care which in turn may reduce delays in diagnosis. Whether this significantly impacts overall survival remains to be seen. With incidence of pancreatic cancer expected to increase, screening blood tests for the general population may become cost effective in the future and facilitate diagnosis of this condition at a curable stage, which in turn may improve survival outcomes.

Ethical approval

Ethical approval was not required as this is a retrospective anonymised study. However, study approval was given by NHS Dumfries and Galloway Quality Improvement and Educational department.

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None.

Author contribution

Jeyakumar R. Apollos – Concept, design, data collection, writing.
Sharukh Sami – Design, data collection, data verification.
Manju Nadh Prasanth - Design, data collection, data verification.
Jerusha Jeyakumar – Data analysis, literature review, writing.
Angus K McFadyen – Statistical analysis, writing.

Conflicts of interest

None.

Research registration unique identifying number (UIN)

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Guarantor

Jeyakumar R Apollos.

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