Tackling cancers of unmet need: the pancreatic cancer pathway

Pancreatic cancer outcomes are unyieldingly poor even despite improvement in the overall picture for many cancers. Pancreatic cancer is the tenth most common cancer in the UK, and demographic changes, such as ageing and the increasing prevalence of diabetes, have precipitated a rise in incidence. Survival, however, has remained steady since the 1970s, with 10-year survival of 1%. Such figures justify the positioning of pancreatic cancer as a cancer of significant unmet need.

Reasons for the persistently poor outlook are complex, but the diagnostic pathway is clearly important. Prompt diagnosis of pancreatic cancer is challenging: common early symptoms typically signify benign disease, and are often attributed to the ageing process or coexisting disorders. Symptom appraisal issues are common across several cancer types, and delays can occur both within the patient interval (the time from first symptom onset to first consultation) and the primary care interval (the time from consultation to specialist referral). The total diagnostic interval is longer for pancreatic cancers than for other cancers, including others of unmet need.[1] Moreover, almost half of all pancreatic cancers are diagnosed via emergency presentation.[2]

Disentangling delay is notoriously complex. Models that categorise the total diagnostic interval show the many influences, including patient, practitioner, and social and environmental factors, that can affect the diagnostic pathway,[3] but much of what we know has been learnt retrospectively. Retrospective accounts are far from ideal because they can compromise accurate recall and, even unwittingly, the symptom appraisal period will be strongly influenced by the subsequent diagnosis.[4]

In *The Lancet Gastroenterology & Hepatology*, Fiona Walter and colleagues[5] attempt to overcome this difficulty with the latest study from the suite of SYMPTOM studies,[6,7] which include lung, colorectal, and, of interest here, pancreatic cancer. The studies provide an important prospective exploration of the time from symptom recognition to referral for specialist care, thus allowing a comparison of symptom profiles in patients with and without cancer. The pancreatic cancer study explores influences on the total diagnostic interval, including symptom and other patient factors, such as age, sex, and socioeconomic deprivation.

With data from various sources (patients, and primary care and hospital records) the investigators report a thorough investigation of the prevalence of symptoms among people referred with symptoms associated with pancreatic cancer.

Of 391 people sampled, 119 (30%) participants were diagnosed with pancreatic cancer and 47 (12%) were diagnosed with other cancers. Of participants with pancreatic cancer, 56% had non-metastatic disease. Despite a poor response rate (24%), which is acknowledged as a key limitation of the study, the investigators present important findings related to patterns of presenting symptoms relevant to primary care and specialist audiences alike, most notably the tendency towards the presence of multiple rather than single symptoms.

A total of 161 (41%) patients presented with a single first symptom, whereas 212 (54%) patients had multiple first symptoms. The most common initial symptoms were indigestion, loss of appetite, fatigue, and feeling different, none of which were reported more frequently in the cancer group than in the no cancer group. Subsequent symptoms of jaundice, change in stool or urine colour, weight loss, fatigue, change in bowel habits, loss of appetite, and feeling different were all more common in patients with pancreatic cancer than in those with no cancer. As with symptom patterns, no notable differences in total diagnostic interval were reported between patients with and those with no cancer (median 117 days [IQR 57–234] vs 131 days [66–284]; p=0·32). However, patients with metastatic pancreatic cancer had longer overall diagnostic intervals than did those with non-metastatic disease (136 days [86–323] vs 108 days [47–222]; p=0·13). The investigators also reported notable associations between type of symptom and diagnostic intervals, for example, jaundice and loss of appetite resulted in shorter total diagnostic intervals, whereas a range of common symptoms, such as back pain and self-reported anxiety or depression, or both, were associated with longer intervals. Diabetes was also associated with longer intervals.

Walter and colleagues' findings echo those of previous studies,[8] but the absence of predictive initial symptoms coupled with the reporting of multiple symptoms
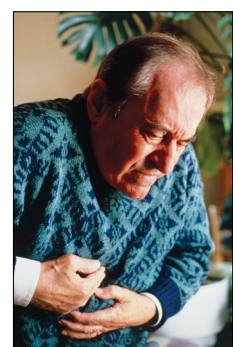
is noteworthy and poses particular challenges for both patients and health professionals. Evans and colleagues[9] found that the intermittent nature of symptoms, including indigestion, wrongly reassured patients that their symptoms did not indicate serious disease and consequently prolonged help-seeking. In this study, longer health system intervals were associated with problems commonly seen in primary care, including coexisting morbidity, such as diabetes and anxiety and depression. Awareness campaigns tend to focus on alarm or red-flag symptoms, and emphasise pervasiveness. Evans and colleagues' report suggests that such an approach requires a considerable rethink if pancreatic cancer is to be diagnosed more promptly. Such a rethink would be challenging because an emphasis on vague, intermittent, or mild symptoms is likely to have a considerable effect on an already stretched primary care system; importantly, it could lead to over investigation, which can also be harmful,[10] because one test could lead to a cascade of further investigations that might themselves carry risks and result in adverse effects. The lowering of referral thresholds by the National Institute for Health and Care Excellence will, if adhered to, along with any further attempts to shorten the total diagnostic interval, have repercussions for health services as a whole, and additional resources will be needed to meet increased demand.[11] Advancing screening options might offer a promising solution to overdiagnosis, but this requires not only the identification of an effective test, but also agreement about its suitability within the target high-risk population. In the absence of adequate screening options at present, work that seeks to better understand and therefore improve the diagnostic pathway of pancreatic cancer should continue.

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