Profiling for primary care presentation, investigation and referral for liver cancers – evidence from a national audit

Short title - Profiling of liver cancer diagnosis

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Declaration: This study provides a detailed profile of liver cancer recognition and investigation from within primary care. The National Audit of Cancer Diagnosis in Primary Care (NACDPC) enables the assessment of diagnostic time intervals for common cancers. We describe measures and markers of diagnostic timelines for patients with liver cancer to raise awareness of the need for further research and improvement initiatives in this area. A comparison of these time intervals is made to diagnostic time intervals of other cancers to help better contextualise the size of the challenge.

Abstract

The incidence of liver cancer across Europe is increasing. There is a lack of evidence within the current literature regarding the identification and investigation of liver cancer within primary care. We aimed to profile liver cancer recognition, assessment and the timeliness of liver cancer diagnosis from within the primary care setting in the United Kingdom. Data were obtained and analysed from the National Audit of Cancer Diagnosis in Primary Care 2009-10. We calculated the patient interval, primary care interval and the number of pre-referral consultations for liver cancer. We then compared these data with prior evidence on the respective time variables for other common cancers. The median patient interval was 9 days (IQR 0-31 days), and the median primary care interval for liver cancer was 11 days (IQR 0-40 days). 21/90 (23.3%) patients had three or more consultations with their general practitioner prior to specialist referral. For the three metrics (patient interval, primary care interval, and number of pre-referral consultations), liver cancer has average or longer intervals when compared with other cancers. The most common symptomatic presentation of liver cancer within primary care was with right upper quadrant pain (11%) followed by decompensated liver failure (9%). 12% of patients were diagnosed with liver cancer due to an incidental finding of an abnormal liver function test. This information provides a detailed and thorough overview of the recognition and promptness of liver cancer identification in an English context, and should inform strategies for hastening diagnosis pathways.

Key words

Liver cancer, diagnosis, promptness, primary care interval, patient interval, symptoms, investigations

Introduction

Primary care plays a crucial role in delivering a high quality health service to the general population. In diagnosing cancers, General Practitioners must differentiate between benign and malignant conditions. Prompt referral for investigation or specialist opinion is essential to try to achieve early diagnosis [1]. Direct comparison with European data regarding 5 year cancer survival rates has revealed that approximately between 6600 to 7500 premature cancer deaths can be avoided annually in the United Kingdom, and prompt diagnosis has a role in preventing a proportion of these [2]. The English National Awareness and Early Diagnosis Initiative (NAEDI) was set up to facilitate earlier diagnosis and improve cancer outcomes [3]. It is well documented that early identification of cancer is associated with an improved survival rate [4-7]. In liver cancer, there is evidence that the early diagnosis of liver cancer increases the amount of curative treatment strategies available [8-9]. Difficulties arise when liver cancer presents with symptoms of low predictive value, therefore the need for further investigations and use of formal diagnostic pathways may not be apparent initially.

The incidence of liver cancer (comprising hepatocellular and intrahepatic cholangiocarcinoma) across Europe is increasing [10]. In 2012, nearly 4,000 new cases of liver cancer were diagnosed within the United Kingdom [11]. A recent report from the National Office for Statistics highlighted that the incidence of liver cancer has increased by 70% for males and 60% for females within the United Kingdom between 2003 and 2012 [11]. It is now the 18th most common cancer in England [11]. Despite this we are unaware of any previous reports of time intervals in the diagnostic journey for liver cancer, apart from one recent paper which reported patients with biliary tract cancer consulting their GPs a median of 22 times in the year prior to diagnosis [12]. Hence, we aimed to determine the commonest presentation of liver cancer, the patient interval, primary care interval, and the number of pre-referral consultations for liver cancer and compare these metrics with existing data for other cancers. This is important as it should inform policy for the diagnosis of liver cancer.

Methods

The National Audit of Cancer Diagnosis in Primary Care (NACDPC) 2009–2010 was a collaborative effort between about 1170 general practices across England (approximately 14% of all practices) [13,14]. GPs were asked to complete a template regarding their patient's cancer diagnosis. Participation was voluntary for GPs. Individual patients who were diagnosed with cancer through national screening programmes were not included. Both the patient population and the characteristics of participating practices have a high degree of representativeness compared with incident cancer cases and non-participating practices. [14,15]For each case, GPs selected the type of cancer from a drop-down menu, with both 'liver cancer' and 'gall bladder cancer' as options. It is possible cholangiocarcinomas may have been reported as either liver or gall bladder. The data include patient demographics, social-economic status, ethnicity, and various time measures in the diagnostic journey. From the dataset, we calculated the patient interval, the primary care interval and the number of pre-referral consultations for liver cancer, in the same way as reported for other cancers [16,17]. Specific time intervals were calculated, and median intervals were reported in days with inter-quartile ranges. Direct comparison with previously published data was made for each of the three metrics [16,17]. From the data, we were able to determine the most common presentation of liver cancer, in addition to which initial diagnostic investigations were requested from within primary care. No ethical approval was required for this study as data were anonymous and non-disclosive.

Results

130 cases of liver cancer were reported. 70 cases of gall bladder cancer were also reported. The data for liver cancer, compared with other cancers are presented in Table 1.

Patient interval

Data were available on the patient interval for 70 (54%) patients with liver cancer. The median patient interval was 9 days (IQR 0-31 days). When compared with other cancers for which this interval is available [17], liver cancer is eighth equal of the 19 cancers, and similar to other gastro-intestinal cancers (stomach, pancreas).

Primary care interval

Data were available on the patient interval for 85 (66%) patients with liver cancer. The median patient interval was 11 days (IQR 0-40 days). When compared with other cancers for which this interval is available [16], liver cancer is thirteenth out of the 19 cancers.

Number of pre-referral consultations

Data were available for the number of pre-referral consultations for 90 (69%) patients with liver cancer. The median number was two, with a range from one to 'in excess of five' consultations 44 patients (49%) were referred to a specialist centre following one consultation, and 6 (7%) required in excess of five consultations with their GP prior to a specialist referral being made. The proportion of patients requiring three or more was 21/90 (23.3%). When compared with other cancers [16], liver cancer is twelfth out of 19 cancers, and similar to oesophageal cancer.

Liver cancer presentation

Clinical information regarding the presentation of liver cancer was available for 130 patients. Table 2 highlights the diversity of the initial presentation of liver cancer within primary care. The most common presenting symptom of liver cancer was right upper quadrant pain in 14 patients (11%), decompensated liver failure in 12 patients (9%) and unintentional weight loss in 12 patients (9%). 16 patients (12%) were asymptomatic but were diagnosed incidentally with liver cancer following abnormal liver function tests. It was noted that 8 patients (6%) presented with metastatic liver

disease. The anatomical location of these metastases were bone (4 cases), lung (2 cases), brain (1 case) and bladder (1 case).

Liver cancer investigation

Initial diagnostic tests requested were recorded for each patient. Table 3 presents the diagnostic tests requested from within primary care. The most common were blood tests (including liver function) in 50 cases (38%), followed by abdominal ultrasound in 38 cases (29%).

Discussion

This study has highlighted key diagnostic time intervals for liver cancer. This information is both useful and informative, especially when compared to similar data for a range of other commoner cancers within primary care. Prompt diagnosis of liver cancer is crucial – a recent study has reported that survival of patients with hepatocellular cancer was adversely effected when treatment was delayed [18]. This highlights the importance of identifying liver cancer early, thus allowing prompt referral to tertiary care. These findings serve as a benchmark upon which future improvement can be monitored by repeat studies. They can also help stimulate comparative studies in other country populations and settings.

For all three interval measures, liver cancer was in the middle of the spectrum of diagnostic promptness for all three measures examined. Liver cancer does not produce early specific symptoms; presentation is usually with large volume tumour disease. Some cancers have been labelled as 'easier to diagnose' as most patients present with 'alarm' symptoms (such as a lump – breast cancer, or a visible skin lesion – melanoma) [19,20]. As the proportion of patients who present with 'alarm' symptoms varies greatly by cancer, the number of pre-referral consultations also varies greatly between cancers. Whilst almost half were referred after just one consultation, just a under a quarter had three or more. Overall, the metrics were similar to other gastro-intestinal and solid tumours. Our findings highlight that some patients with liver cancer appear to have had fairly typical symptoms (with adequate enough specificity / predictive value) and others not , this is very similar to the diverse symptom signature of colorectal cancer.

Our study highlights the issue that liver cancer can present with a great number of symptoms, none of which is dominant among all liver cancer patients. Patients with hepatocellular carcinoma may present with jaundice (which will be an 'alarm' symptom) but also a variety of much less-specific symptoms, ranging from malaise, fatigue, unintentional weight loss to right upper quadrant pain [12, 21]. This study confirms the great diversity in the presentation of liver cancer. A large case series reviewing hepatocellular cancers presenting symptoms to a tertiary unit, demonstrated that the most common symptoms were non-specific abdominal pain and hepatomegaly [22, 23]. Studies have highlighted that patients with hepatocellular cancer often present with decompensated liver cirrhosis, prior to their formal diagnosis of liver cancer [22]. These patients will present severely decompensated, often meeting the criteria of Child's class B or C cirrhosis [24]. A small proportion (9%) may be asymptomatic and be diagnosed incidentally [22]. This finding was consistent with the results from this study as 16 patients (12%) were asymptomatic and diagnosed with liver cancer following abnormal liver function tests. Therefore general practitioners must have a low threshold for requesting relevant investigations when assessing patients with vague and non-specific symptoms. This is especially the case when dealing with a cohort of patients who possess risk factors for liver cancer, notably individuals with known cirrhosis or hepatitis B or C infection [25]

This study has highlighted the difficulty of investigating the potential symptoms of liver cancer within primary care. There is no uniformity with regard to the initial investigations requested. They vary from cheap, readily available blood tests to advanced imaging of the abdomen. Only 38% of the patients within this study had blood tests. This investigation is cheap, minimally invasive and provides a wealth of clinical information. This may reflect the fact that general practitioners are unfamiliar with the vague , non specific presentation of liver cancer. The difficulty within clinical practice is that general practitioners see many patients with non specific symptoms, where the underlying pathology is benign. The diagnostic challenge is identifying individuals with non specific symptoms that are due to an underlying malignancy. One may argue that when dealing with such a clinical scenario that a low threshold for investigating cancers that could potentially present insidiously should be adopted.

This would consist of undertaking screening bloods and basic abdominal imaging such as ultrasonography (as this may identify an early mass lesion). Unfortunately this approach would accumulate a significant cost to the health service due to the fact of the large number of general practitioner consultations that involve vague, non specific symptoms. The percentage of advanced imaging tests for the investigation of liver cancer within this study is low, less than 5%. Perhaps a possible solution to this would be to train general practitioners and specialist nurses to be able to conduct ultrasonographic assessment and interpretation of results from within primary care [26]. This would allow quick access to a non invasive investigation that would be able to be used as a screening tool in patients with non specific, vague abdominal symptoms. Ultrasound assessment could be used to assess for other cancer that present insidiously, such as ovarian and pancreatic cancer. However there are financial aspects to consider, mostly the cost of purchase and maintenance for an ultrasound machine. In addition one must factor in the cost for formal training of conducting the ultrasound assessment and the subsequent interpretation of the images. Long term this may be a cost effective solution as it would decrease the number of referrals to secondary care for basic investigations, thus releasing invaluable resources form within the hospital setting. Specialist liver units should conduct the definitive diagnostic tests for liver cancer. The role of primary care is to identify individuals with underlying malignant disease, instigate initial simple investigative and diagnostic tests (such as blood tests, tumour markers and abdominal ultrasound scans) and to refer to the specialist units.

This study has produced novel and quantifiable data regarding key diagnostic time intervals for liver cancer. The main strength of this work is that it draws on a good quality and established data source [16,17]. The main limitations are the relatively small numbers of patients with liver cancer in the dataset, and missing data preventing calculations of intervals for some patients. Our study is not able to discriminate whether the interval measures that we describe are any different for the two dominant liver cancer types (hepatocellular carcinoma and cholangiocarcinoma), and this is a limitation to be addressed by future research. There are other issues inherent with the dataset. These have previously been reported [16,17], and include: selected self-inclusion of interested, motivated practices; potential inaccuracies of the GPs' recordings or patient intervals; and potential

inconsistency in the ways GPs interpreted recorded 'first symptomatic presentation'. A comparison between this dataset and the cancer registration statistics suggests that the data is representative of the demographics of English cancer patients.

In conclusion, we have reported time intervals in liver cancer diagnosis for the first time and compared these with other cancers. Whilst many patients are diagnosed quickly, there remains considerable room for improvement in the primary care diagnosis of liver cancer for many patients. The initial presentation of liver cancer may by vague and non-specific. Therefore patients presenting in such a way must be assessed with a low threshold for further investigations. If there is any clinical doubt, these patients should be investigated with baseline blood tests and simple radiological investigations prior to specialist referral. These findings should inform policy and practice to hasten the primary care diagnosis of liver cancer.

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Tables

Table 1. Comparison of the diagnostic time intervals of liver cancer with 18 other common cancers

Cancer type	Median Patient Interval (IQR)	Median Primary Care Interval (IQR)	% patients with 3+ consultations prior to secondary care referral
Bladder	2 (0 -16)	4 (0 –18)	14.6
Brain	7 (1 – 26)	4 (0 –19)	21.4
Breast	7 (0 – 23)	0 (0 - 1)	2.9
Colorectal	19 (1 – 60)	7 (0 – 32)	21.3
Endometrial	14 (1 – 57)	1 (0 – 19)	9.8
Leukaemia	7 (0 – 30)	6.5 (0 – 23)	17.6
Liver	9 (0 – 31)	11 (0 – 40)	23.3
Lung	12 (0 – 33)	14 (3 – 40)	32.8
Lymphoma	14 (1 – 43)	9 (0 – 32)	25.8
Melanoma	20 (0 – 69)	0 (0 – 6)	5.4
Myeloma	14 (0 – 40)	21 (5 – 55)	46.0
Oesophageal	22 (7 – 46)	7 (0 – 33)	22.6
Oro-pharyngeal	30 (7 – 62)	6 (0 – 27)	21.9
Ovarian	14 (2 – 51)	8 (0 – 27)	27.8
Pancreatic	9.5 (1 – 31)	8 (1 – 35)	31.1
Prostate	6 (0 – 42)	12 (3 – 28)	15.2
Renal	3 (0 – 19)	12 (1 – 37)	22.1
Stomach	9 (0 – 33)	14 (0 – 57)	32.1
Unknown Primary	7 (0 – 23)	14 (0 – 37.5)	41.2

Except for liver, other data are reproduced from previous work [11, 14]

Table 2. The presentation of liver cancer within primary care

Presentation of liver cancer	Number of patients
Incidental diagnosis	16
Right upper quadrant pain	14
Decompensated liver disease	12
Weight loss	12
Jaundice	10
Epigastric pain	10
Symptoms from metastatic disease	8
Abdominal mass	6
Nausea	5
Anaemia	4
Fatigue	4
Loss of appetite	2
Pruritus	1
Rising alpha-feta protein (AFP) level	1
Found on follow up for a previously treated colon cancer	1
Not recorded	24

Table 3. Diagnostic investigations requested within primary care

Diagnostic investigation	**Percentage of tests requested from primary care (n=130)**
Blood tests	50 cases (38%)
Abdominal Ultrasound	38 cases (29%)
Chest X-ray	9 cases (7%)
Abdominal CT scan	7 cases (5%)
Abdominal MRI	2 cases (2%)