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Ultrasound surveillance for hepatocellular carcinoma: service evaluation of a radiology-led recall system in a tertiary-referral centre for liver diseases in the UK

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AIM: To review the radiology-led ultrasound (US) surveillance programme for the detection of hepatocellular carcinoma (HCC) in cirrhotic patients in a UK tertiary-referral centre.

MATERIALS AND METHODS: The radiology information system was searched for patients who had undergone US for surveillance of cirrhosis from September 2009 to May 2013. Patient demographics and cirrhosis aetiology were documented. Data including numbers of surveillance scans, abnormal findings suspicious for HCC, subsequent radiological investigations, numbers of HCC and survival for HCC patients were recorded. Service performance data, such as rates of attendance and rebooking, were also recorded.

RESULTS: Eight hundred and four patients entered surveillance and 2,366 surveillance US examinations were performed; 368 (46%) underwent follow-up (6-monthly US). Abnormalities leading to further radiological investigations were found in 81 patients. Reasons for incomplete surveillance included non-attendance and radiology failure to re-book appointments. HCC was diagnosed in 22 patients. Fourteen had HCC diagnosed on a surveillance scan, eight had HCC diagnosed on a scan performed for other reasons. Patients diagnosed with HCC on a surveillance scan were more likely to be treated with curative intent and had longer survival.

CONCLUSION: Even with a radiology-led recall service for HCC surveillance, the proportion of patients receiving scans 6-monthly was low, due in part to the lack of organisational support that is available for other screening programmes. This study gives a realistic representation of the implementation of surveillance in a UK hospital at the current time and of the rates of HCC proceeding to treatment.

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Introduction

Hepatocellular carcinoma (HCC) incidence is rising in the UK and globally, constituting part of a wider trend of increased mortality from chronic liver disease.[1,2] The majority of HCC cases occur in patients with cirrhosis. The rise in cirrhosis has been attributed to an increased prevalence of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infections in addition to non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD).[3,4] Globally, HCC is the third leading cause of cancer death, due to the impact of CHB infection in Africa and Asia.[5]

The prognosis of HCC is related to the stage of disease at presentation and is dependent on several variables including: tumour size; the number of cancerous nodules; extra-hepatic disease; portal vein invasion by tumour; and underlying liver function. Patients with cancers that are potentially amenable to curative treatment (transplantation, resection, or ablation) have a 3-year survival rate between 60–80%.[6] In comparison, the prognosis for patients presenting with advanced HCC remains poor with 3 year survival rates as low as 10%.[7,8]

Small tumours are asymptomatic and the aim of surveillance is to identify patients with early, curable tumours using ultrasound (US) screening followed by cross-sectional imaging (Figs 1–2). HCC surveillance, in selected high-risk patient groups, is recommended by several international liver associations (e.g., the American Association for the Study of Liver Diseases [AASLD], the European Association for the Study of the Liver [EASL], and the British Society of Gastroenterology [BSG]).[9–11] The most common surveillance regimen is US with or without alpha-fetoprotein (AFP) measurement every 6 months in patients with compensated cirrhosis.

Robust evidence supporting the benefit of surveillance is lacking.[12] This was acknowledged in a Royal College of Radiology (RCR) position statement published in September 2014.[13] In the UK, there is currently no specific funding for surveillance, nor is there the organisational support that is available in other screening programmes such as for breast and colon cancer. Yet, both patients and clinicians have an expectation that surveillance will be offered. The provision of US surveillance for HCC in the UK is inconsistent and poorly performed. This was confirmed by a recent survey of current practice amongst British and Irish gastroenterologists and hepatologists (A.H., unpublished data).

The Royal Liverpool Hospital is a tertiary-referral centre for liver diseases. In September 2009, the Radiology Department implemented a 6-monthly recall protocol for US surveillance of all cirrhotic patients who were referred by the hepatology and infectious diseases teams for HCC surveillance. It had been observed that US booked as part of clinic attendances were haphazard and results had the risk of being overlooked. In addition, the US examinations were frequently not performed in the recommended 6-monthly time frame.

The present study originated as an internal service evaluation of performance of the recall surveillance programme. The primary aim was to evaluate the detection rate of HCC in surveillance. Secondary objectives were to determine type and number of follow-up imaging investigations required, stage of disease at the time of

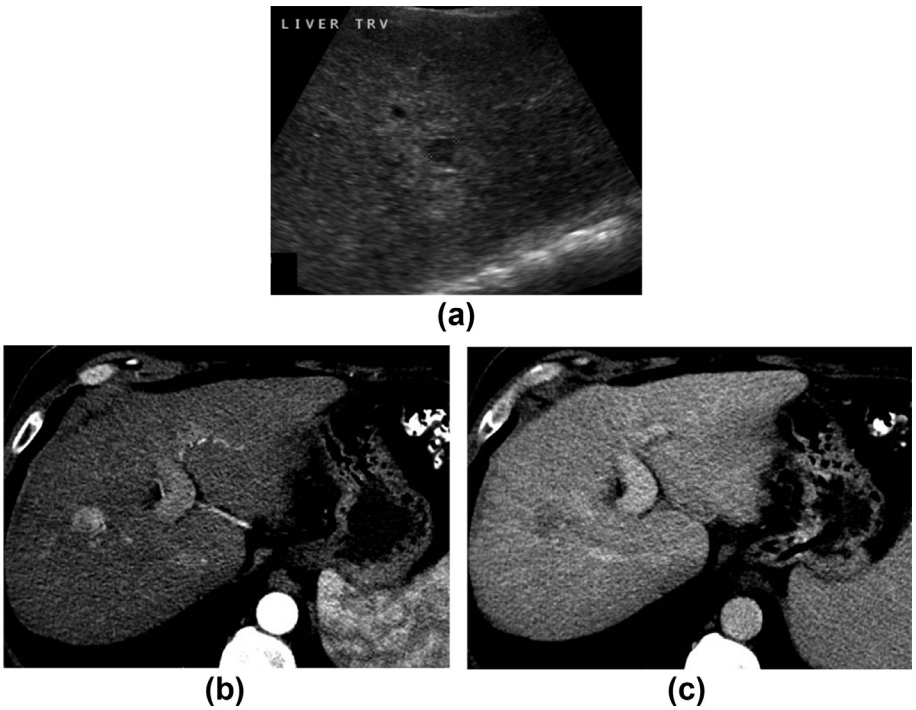

Figure 1 (a) US image of a cirrhotic patient shows a nodule in the right lobe of the liver. (b) Arterial-phase CT. The liver lesion identified at US shows avid arterial enhancement. (c) Portal venous phase CT shows washes of the lesion, diagnostic of HCC.

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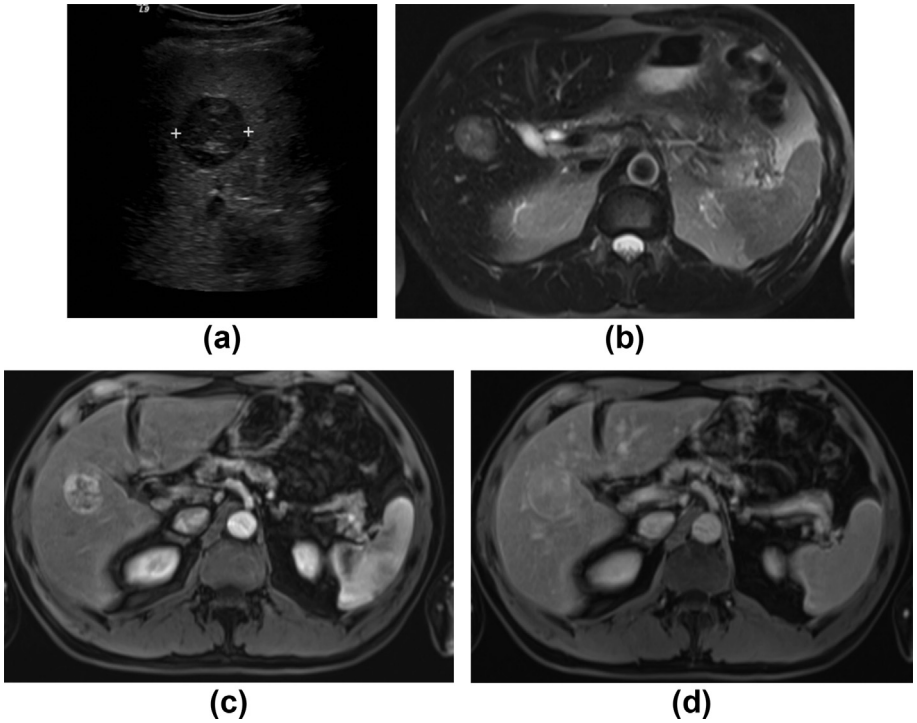

Figure 2 (a) Surveillance US shows a large nodule in the right lobe of the liver. (b) Axial T2-weighted MRI. The lesion is T2 bright and heterogeneous. (c) Arterial phase MRI shows avid peripheral enhancement with central necrotic areas of hypo-enhancement. (d) Portal venous phase MRI shows contrast washout with a peripheral enhancing pseudo-capsule. A radiological diagnosis of HCC was made.

diagnosis, number of patients proceeding to treatment with curative intent and assessment of adherence to surveillance.

Materials and methods

A single-centre, retrospective study of patients who underwent US HCC surveillance at The Royal Liverpool Hospital between September 2009 and May 2013 was performed. As the study was a service evaluation of recommended practice, ethics committee approval was not required. The hospital's radiology information system (RIS) was searched using relevant key terms to identify all surveillance scans between 1 September 2009 and 30 May 2013 (Electronic Supplementary Material Appendix S1). This search strategy was necessary as there was no formal US surveillance patient database. Liver US examinations for patients not in surveillance were excluded from further study.

Patients with a diagnosis of Child–Pugh class A or B cirrhosis of any aetiology were eligible for surveillance. Non-cirrhotic patients with hepatitis B and a family history of HCC were also offered surveillance. Patients with a prior history of HCC or liver transplantation together with patients with Child–Pugh class C cirrhosis (who were not liver transplant candidates) or with significant co-morbidities were to be excluded. A targeted US of the liver was performed by a general radiologist or sonographer. If the examination did not identify lesions suspicious for HCC, the patients were rebooked by the reporting radiologist or sonographer for a follow-up scan in 6 months. The date of the first surveillance US served as the index date. The number of subsequent scans and their interval dates were recorded. Complete follow-up was defined as the patient receiving 6 monthly scans until either the end of the study, when HCC was detected on surveillance and confirmed, or if cessation of surveillance was requested by the referring clinical team. Reasons for cessation of HCC surveillance were not recorded. Data collection included: patient demographics, cirrhosis aetiology, total time period on surveillance, actual number of scans performed, and projected number of scans for each patient if surveillance had been completed. In addition, the numbers of lesions suspicious for HCC requiring further investigation and the modality used in further investigations was recorded. For confirmed HCCs, the following data were collected from a hepatology departmental database: number of tumour nodules, size of the largest nodule, Barcelona Clinic Liver Cancer (BCLC) stage, and treatment provided. All HCCs were identified: both those found on routine surveillance scans and those found on scans performed for other indications. Where HCC was found on a scan performed for an indication other than surveillance, the indication for the scan was recorded. Duration of survival for the HCC cases was recorded; survival data were available until 28/6/16. The overall survival and outcomes for the patients who did not have HCC was not documented. Patients with inconsistent surveillance, defined as receiving at least one scan, but without appropriate follow-up scans, were considered "lost to follow-up" if no reason for the incomplete surveillance could be identified. Patients whose scans were delayed by 6–12 weeks were deemed to have suffered "minor delays."

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Statistical analysis

Continuous variables were presented as medians with interquartile ranges. Frequencies were expressed as whole numbers and percentages. Categorical variables were compared using Fisher's exact test where appropriate. Hepatocellular cancers detected were expressed as number of cases per 100 patients per year.

Results

Of the 6,725 patients identified via the RIS search criteria, 804 were confirmed to be in the HCC surveillance programme and were included in the analysis. The median age of the entire cohort was 55 years (IQR 46–63) and 307 (38%) were female. The aetiologies of the liver diseases are summarized in Table 1. A total of 2,366 US surveillance scans were performed. Abnormalities suspicious for HCC, requiring further radiological investigation, were detected in 81 patients (10% of patients, 3.4% of US examinations). Twenty-three of these were characterised using computed tomography (CT), 42 with magnetic resonance imaging (MRI), 14 had both MRI and CT, and two had contrast-enhanced US (CEUS) to characterise the lesion. Fourteen of these 81 (17%) were confirmed as having HCC, either on imaging criteria or at biopsy. The US surveillance detection rate of HCC for the whole group was 1.2 per 100 patients per year or 1.2%. A further eight patients were diagnosed with HCC during the study period following an US examination that was performed for an indication other than surveillance. In total, 22 HCC cases were found in the surveillance population, 14 (63%) on surveillance scans and eight (36%) on scans other than surveillance US. Results are summarised in Fig 3.

Confirmed HCC cases

Twenty-two cases of HCC were identified. The median age of patients with HCC was 65 years (IQR 51–71), of which seven (31%) were women. The aetiology of liver disease was similar to that found in the overall surveillance population, with ALD being the most frequent cause (Table 1). Haemochromatosis showed a strong trend towards higher prevalence in the HCC group, compared to the non-HCC group (3/22 HCC cases versus 19/782 non-HCC cases, $p=0.02$, Fisher's exact test); however, numbers were small. A summary of lesion characteristics is presented in Table 2. There was no significant difference in the size or number of lesions in those HCC cases found via surveillance US compared with those cases found at US performed for other reasons. There was also no difference in the stage of disease; however, the numbers of HCC cases were small, precluding detailed analysis.

The patients in whom HCC was diagnosed on surveillance US all attended for and received complete surveillance. Of the eight patients who had HCC diagnosed on US performed for a reason other than surveillance, six out of eight (75%) received complete surveillance. The two patients who had not received complete surveillance had both failed to attend for appointments.

Where HCC was diagnosed on US requested for indications other than surveillance, in four cases the examination was performed for the investigation of raised AFP, in two cases for abdominal symptoms, and in two cases for vascular mapping pre-transjugular intrahepatic portosystemic shunt (TIPSS) placement.

Survival

Of 22 HCC patients, 16 (73%) had died as of 28 June 2016. All patients who had HCC found at US performed for indications other than surveillance had died, median survival 192 days (IQR 132–324). Of the patients with HCC found on surveillance, six (43%) were still alive as of 28 June 2016, median time from diagnosis 1,201 days (IQR 1,091–1,754). The remainder of this group had a median survival of 782 days.

Treatment

On radiological criteria alone, 15/22 (68%) of the HCC cases were eligible for curative treatment (BCLC 0-A), a summary of stage and treatment intent are presented in Table 2. Of the 14 patients whose HCC was identified on a surveillance scan, 13 (93%) were treated with curative intent. Eleven were treated with radiofrequency ablation (RFA), one with RFA and irreversible electroporation, one with RFA, and transarterial chemoembolisation (TACE) as a bridge to transplant. This patient was listed for transplant but was later delisted following disease progression. No patients had local tumour resection. One patient was treated palliatively with TACE.

Of the eight patients whose HCC was identified on a scan other than a surveillance scan, two (25%) were treated with curative intent. One underwent TACE as a bridge to transplant and was placed on the transplant list, but was later delisted following disease progression. One patient was scheduled for RFA, but was found to have progression and the ablation was not performed.

Of the six patients not treated with curative intent, four were not offered any specific treatment, one was treated with TACE and one was treated with systemic chemotherapy. Patients with HCC found on a surveillance scan

Table 1
Aetiology of liver disease in surveillance population and hepatocellular carcinoma group.

Aetiology of liver disease	*n* (%)	*n* (%)
Alcoholic liver disease	308 (38%)	12 (39%)
HCV	154 (19%)	8 (26%)
HBV	113 (14%)	2 (6%)
Non-alcoholic hepatic steatosis	78 (10%)	5 (16%)
Primary biliary cirrhosis	37 (5%)	1 (3%)
Mixed aetiology	38 (5%)	–
Haemochromatosis	22 (3%)	3 (10%)
Others	54 (7%)	–

HCV, hepatitis C virus; HBV, hepatitis B virus.

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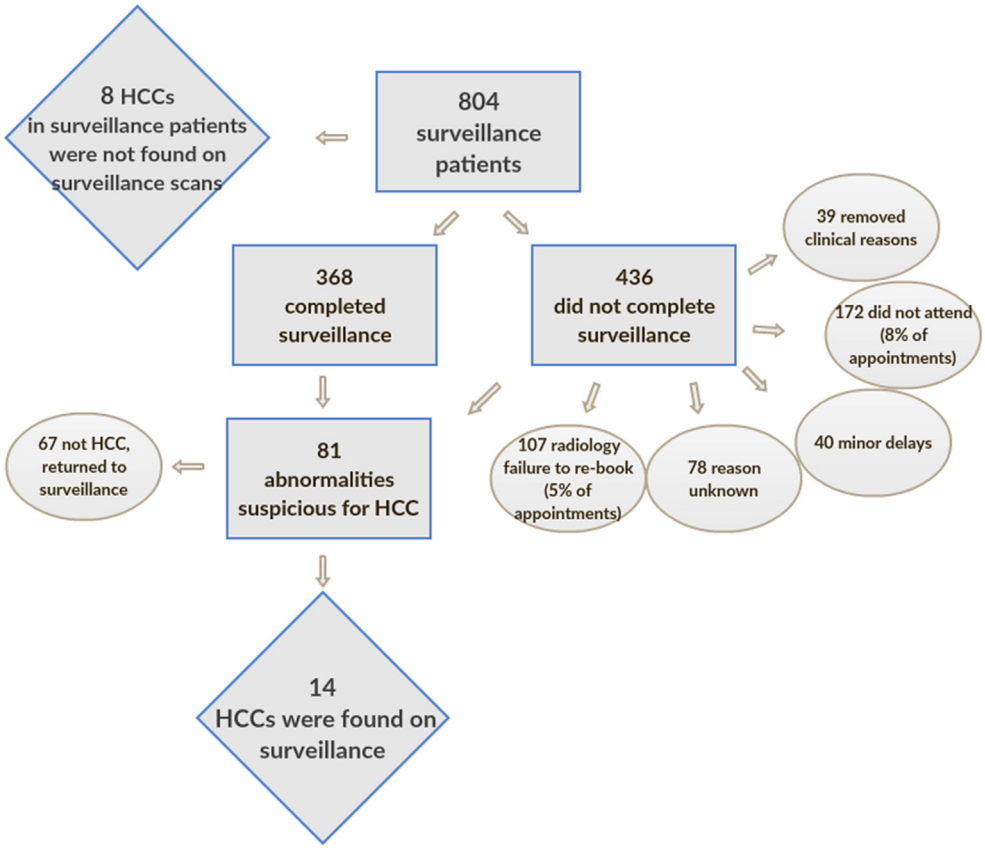

Figure 3 Summary of surveillance patients: reasons for failure to complete surveillance, numbers of abnormalities found, HCCs, and treatment intention.

were more likely to be treated with curative intent than those patients who had HCC found on a scan performed for another indication (p=0.002, Fisher's exact test).

Uptake and adherence

The median number of surveillance US examinations per patient was three (range 1–8) and the mean length of time spent in surveillance was 17.4 months (range 6–42 months). New patients were continuously enrolled into the programme over the study period. The total number of surveillance scans performed was 2,366. Had all patients received complete surveillance, the number of scans performed would have been 3,495. Of all patients referred for surveillance, 368 (46%) completed their expected follow-up over the study period; 172 (21%) patients did not attend at least one appointment (7% of scans). Radiologists/sonographers failed to rebook the next scan in 107 (13%) patients, (this represents 5% of scans). In 78 (10%) patients, it was not possible to identify the reason why surveillance was incomplete. Forty (5%) patients suffered minor delays. Thirty-nine (5%) were removed from surveillance either temporarily or permanently for clinical reasons (e.g., other co-morbidities, too ill to attend). Eighty-one patients (10%) died during the surveillance period, or 6.85 per 100 patients per year. It was not possible to ascertain cause of death by searching the RIS.

Discussion

The present study evaluated the feasibility and performance of an informal, radiology led, 6-monthly US surveillance programme for the detection of HCC. Evidence for surveillance is limited, but a 2014 meta-analysis on early detection, curative treatment, and survival rates for HCC surveillance by Singal *et al.*[14] reported significant benefits, with increases in early detection and curative treatment rates, (odds ratio 2.24). A survival benefit was found in surveillance compared with non-surveillance patients (odds ratio 1.9), which persisted in those studies adjusting for lead time bias. The paper acknowledged that none of the studies included in their analysis assessed harm or cost-effectiveness. Current guidelines on surveillance and expectations of patients and clinicians mean that informal surveillance programmes are increasingly being implemented, while randomised, controlled trials (RCTs) are no longer considered ethical.[9–11,15] An impasse has, therefore, arisen in which funding for surveillance is withheld due to lack of evidence, yet the investigations can no longer be refused on clinical grounds.

In the present study, 81 abnormal US examinations were identified out of 2,366, of which 83% were false positives, while 17% of patients with a detected abnormality on US were subsequently diagnosed with HCC. Positive survival

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Table 2
Lesion number, size, staging, treatment intent, and survival in hepatocellular carcinoma (HCC) cases.

	All cases	HCC found on surveillance ultrasound	HCC not found on surveillance ultrasound
	22	14	8
Number of lesions			
1	13 (59)	6 (43)	7 (88)
2	3 (14)	3 (21)	0 (0)
3	2 (9)	2 (14)	0 (0)
≥4	4 (18)	3 (21)	1 (12)
Size of largest lesion, cm			
≤2	10 (45)	6 (43)	4 (50)
2.1–5	12 (55)	8 (57)	4 (50)
Barcelona Clinic Liver Cancer (BCLC) stage			
0	5 (23)	3 (21)	2 (25)
A	10 (45)	7 (50)	3 (38)
B	4 (18)	2 (14)	2 (25)
C	1 (5)	1 (7)	0 (0)
D	2 (9)	1 (7)	1 (12)
Within Milan Transplant Criteria			
Yes	17 (77)	11 (79)	6 (75)
No	5 (23)	3 (21)	2 (25)
Treatment with curative intent			
Yes	15 (68)	13 (93)	2 (25)
No	7 (32)	1 (7)	6 (75)
Alive as of June 2016	6 (27)	6 (43)	0 (0)
Median survival post diagnosis for deceased patients (days)	387	782	192

outcomes were achieved in this group with six patients (43%) alive between 2.8 and 5.4 years after diagnosis, and a median survival for the remainder of these patients of 782 days.

In contrast, eight patients in the surveillance cohort presented with HCC found as a result of investigations other than surveillance US. Six (75%) of these patients had received complete surveillance and can, therefore, be classified as interval cancers, a marker used as an important statistical benchmark to assess the efficacy of other screening programmes, particularly mammographic screening.[16] There are several possible explanations for interval presentation: the lesions were truly new, were misinterpreted as benign, or were missed (false-negative examinations). Although numbers are small, it is worth noting that a single lesion was present more frequently in this group. This may have increased the likelihood of a false-negative scan. Interestingly, although the HCC stage at presentation in these patients was not significantly different from the HCC cases found on surveillance, only two of these patients were treated with curative intent and all had died by 28 June 2016 with a median survival of 192 days. Two were undergoing investigation of abdominal symptoms, and two were awaiting TIPSS. In contrast, the HCC cases found at surveillance were likely asymptomatic. Although numbers are small, the present findings are in keeping with the published literature suggesting a survival benefit for surveillance.

The false-negative rate in this population is unknown, as follow-up of patients with negative scan results was not conducted. A significant number of patients dropped out (12%) or died (10%) during surveillance for which a cause could not be identified and some of these could be attributed to HCC. In addition, the present detection rates were not compared with rates of HCC in patients who had never been in surveillance.

Although the overall adherence to surveillance was only 46% in this informal recall programme, interestingly, the attendance rate was significantly higher in the group with HCC (91%) and more in line with other, established, and well-funded screening programmes. Attendance currently stands at 72% for breast cancer,[17] 70% for cervical cancer,[18] and 55–60% for bowel cancer.[19] A total of 2,447 US examinations would have been performed at a presumed attendance rate of 70%. Failings in the recall protocol were exposed with 112 patients not being recalled for examination. This was mainly due to operators not adding the rebook code to the scan report; a failure that might not have occurred in a formal screening setting with better recall mechanisms in place. At 8%, the rate of non-attendance for rebooked scans was similar to that for other appointments in the department. The failure of patients to attend is likely multifactorial. As well as common causes, such as forgetting an appointment, illness, or change of address, a misunderstanding as to why the US was being performed may have contributed, in particular as patients under surveillance are generally asymptomatic. Should surveillance continue to be recommended, these factors will also need to be clarified in further studies and appropriate information material developed to support adherence. Although there is no robust evidence on the benefits versus harm of surveillance, nor on cost-effectiveness, it is likely that current practice will continue and expand, at least until any information to the contrary should become available. Indeed, in the UK, the present government has set targets to reduce cancer deaths by earlier disease detection and HCC surveillance may be promoted as one of the means of achieving this. In 2014, the Royal College of Radiologists issued a position statement on the use of US surveillance for HCC.[13] It alludes to the absence of strong data indicating a decrease in disease-specific mortality and the lack of financial and administrative support seen in other screening programmes. The present findings illustrate that an informal system, run by goodwill from the radiology department without appropriate support and funding is suboptimal and may leave early cancers undetected in patients who do not receive complete surveillance. A large number of US examinations was required to detect a small number of potentially curable cases, but an even larger number of scans would have been required to reach acceptable standards of screening attendance. The resource implications are significant, and it is unlikely that high-quality surveillance will be adopted widely without appropriate funding.

The limited accuracy of US for the detection of liver lesions, in particular in cirrhotic and obese patients, is another area of concern as it invariably leads to further imaging in suspected cases, although in this study the number of referrals for further imaging was relatively small (10%). As it may potentially become higher, once data on false-negative rates become available and more vigorous additional imaging may be recommended, this will also need to be taken into account in the funding of surveillance.

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Ideally, new methods to improve the quality of surveillance are required such as biomarkers and/or composite scores to gauge the risk of HCC in a particular individual. At present, US is the best modality available and informal surveillance is the best available option for at risk patients.

To resolve the above-mentioned impasse, in the absence of a fully funded surveillance programme, at the very least, funding should be provided for high-quality studies of current surveillance practice to obtain the evidence that can no longer be acquired through RCTs. With limited access to funding, the evaluation of current service provision suffered from a number of limitations: most data were obtained from the RIS and only clinical notes of patients with a confirmed HCC could be reviewed. Subsequently, no follow-up data are available on patients with negative scan results. The accuracy of US in this population could not be assessed, nor exactly why a significant number of patients dropped out of surveillance or why operators did not arrange the agreed recalls.

In conclusion, the present study supports previous findings that surveillance can lead to improved survival rates for HCC; however, it also highlights the challenges of performing US surveillance for HCC in the absence of appropriate funding and administrative frameworks. The finding that adherence to surveillance and patient inclusion were suboptimal, even in an environment dedicated to successful surveillance, supports the argument that high-quality surveillance is unlikely without appropriate investment. Despite the limitations, this study provides an indication of expected HCC detection rates in a UK population, the frequency of further investigations required, and the number of HCC cases actually proceeding to treatment with curative intent. This information, given the paucity of UK data in this area, could act as a benchmark against which much needed future studies are designed and compared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.crad.2016.10.019.

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