Hepatocellular Carcinoma Surveillance At A Quaternary Centre In The United Kingdom

An Assessment Of Local Adherence And Deviations To;

European Association For The Study Of The Liver (EASL) &
American Association For The Study Of Liver Diseases Guidance(AASLD)

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Introduction

Hepatocellular cancer (HCC) is the most common type of primary liver cancer in adults, and most common cause of death in people with cirrhosis. The prognosis of HCC is poor except in cases of early diagnosis where potentially curative treatments such as surgery or transplantation can be undertaken. With this in mind, the European Association for the Study of Liver (EASL) published clinical practice guidelines for the management of HCC[2], which includes recommendations for surveillance programmes.

University Hospitals Birmingham (UHB) NHS Foundation Trust Liver and HPB Unit is one of the largest in the UK, providing a comprehensive range of hepatology services, including a surveillance programme for patients at-risk for HCC. In this report the authors present a 5-year retrospective cohort study of patients under the surveillance imaging programme at the centre. The study utilises EASL guidance as the gold-standard, assessing for adherence and deviations to the pathways outlined. A null hypothesis is proposed; deviation from EASL guidance will negatively effect patient outcomes.

Methods

1. Acquiring data

UHB utilises a radiology information system named CRIS for vetting, reporting and analytics of the department. A specific search was undertaken of CRIS to identify a targeted cohort to survey for the audit. The request text for all ultrasounds in the system dating between 01 Jan 2015 to 30 June 2015 (six-month period) were filtered for the keywords "HCC", "hepatocellular carcinoma" and/or "surveillance". Any identified ultrasounds with the mentioned keywords were marked and all subsequent imaging for that patient (up to a maximum of 20) were extracted from the system. Through the above process 8634 scans were originally identified from 1460 unique individuals.

2. Sift process

From the original raw data set, we manually sifted and included only individuals that had imaging requests including or specific to HCC surveillance, and removed all others. This left 5227 scans from 853 unique individuals on the surveillance programme. Of the remaining dataset, a further manual sift was completed with the following exclusion criteria; Remove cases that never reported a measurable mass on surveillance, remove cases with incomplete data, e.g. no initial surveillance scan at QEHB, no follow up on system, imported images with no reports, remove cases where follow up investigation was undertaken for 'nodular' livers on surveillance USS but no specific measured mass. This left a working dataset of 1010 scans from 140 unique individuals.

3. Extracting and transposing

In order to take the dataset and compare it to EASL guidance it needed to be transposed to a new excel sheet. From here we were able to identify mass sizes, follow up investigations, time intervals and whether diagnosis of HCC was made. If HCC was diagnosed or patient returned to routine surveillance the event was considered complete and any further masses on surveillance USS were deemed as new events. If repeat surveillance scans identified previously known masses, these were not considered new events unless there was a growth of previous mass or further new masses identified. Any missing data, e.g. no imaging request text provided, was attempted to be further extracted from trust electronic informatics system to fill in possible gaps.

4. Analysing data

Analysing time intervals between scans was done by calculating whole number of days between the dates, giving integer values. This allowed for calculation of mean and median time intervals. The pathway for nodule investigation was recorded through serial scans and request data, utilising binary code as yes/no whether EASL guidance was followed or deviated from. The modality of surveillance or further investigative scans were also analysed. As these were discrete data (USS/CT/MRI/IR) they were easily measured by frequency.

Results

1; EASL guidance states for nodules detected on surveillance USS with a size of less than 1cm should be followed up within 4 months with further USS to assess for stable or growing appearances.

Number of events of nodules on routine surveillance USS less than 1cm was 35. Of these 35 events, 26 events were appropriately followed up by repeat USS, the remaining 9 events had inappropriate follow up with either CT or MRI imaging. Therefore, the correct follow up rate was 74.3%. The mean days was 133.0 with standard deviation of 68.9, and median days of 108.5.

2; EASL guidance states for nodules detected on surveillance USS with a size of less than 1cm, should continue with 4 monthly ultrasounds for 1 year.

Of the 26 events correctly followed up by USS, 24 showed stable appearances and 1 was lost to further follow up. This left 23 events eligible for further USS follow up within 4 months. The mean days was 189.8 with standard deviation of 69.1, and median days of 182.0.

3; EASL guidance states for nodules detected on surveillance USS with a size of more or equal to 1cm, should be reviewed by either CT or MRI follow up, no stated time interval.

Number of nodules on routine surveillance USS more or equal to 1cm were 127 events. Of these 127 events, 119 events were appropriately followed up by CT or MRI imaging, the remaining 8 events were inappropriately followed up with USS. Therefore, the correct follow up rate was 93.7%.

Of the correctly followed up 119 events, CT and MRI were utilised 34 and 85 times respectively. Of the 34 CT events, the mean days was 28.4 with standard deviation of 20.9, and median days of 23.0. Of the 85 MRI events, the mean days was 56.7 with standard deviation of 51.3, and median days of 41.0.

12 events were diagnosed with HCC at 1st modality (10.1%), and remaining 107 events required second modality investigation.

4; EASL guidance states when 1st modality CT or MRI shows no positive technique for HCC imaging hallmark, should be followed up with 2nd modality (other of the two) CT or MRI, no stated time interval.

Number of nodules seen at 1st modality with report of either no nodule seen (0), no evidence of HCC (1) or indeterminate nodule (2), were 107 events. Of these 107 events, 2 reports were unavailable, and 5 patients' follow up could not be followed. Of these 100 events for 2nd modality scanning; 13 went to 2nd modality, 7 went to biopsy, and 80 returned to routine surveillance. Therefore, the correct further investigation rate was 26%.

Of the correctly further investigated 13 events, 4 were for 2nd modality CT, and 9 were for 2nd modality MRI. The combined 2nd modality mean days was 48.8 with standard deviation of 39.8, and median days of 46.0. Of these 13 events, 2 were diagnosed with HCC at 2nd modality (15.4%).

Results

5; EASL guidance states if 2nd modality CT or MRI shows no positive technique for HCC imaging hallmark, should be followed with biopsy, no stated time interval.

Of the 13 2nd modality events, 2 were diagnosed with HCC and 1 was lost to follow up, leaving 10 events eligible for biopsy.

In the dataset, of all events, the total number of biopsies undertaken was 9. 2 events underwent biopsy after 2nd modality scan could not confirm HCC (appropriate follow up), 7 events were fast tracked biopsied after 1st modality scan only.

Of all 9 biopsy events, the time interval to biopsy had mean days of 80.7 with standard deviation of 47.8, and median days of 66.0. Of these 9 biopsy events, 2 were diagnosed with HCC, 1 diagnosed with Cholangiocarcinoma. No re-biopsies undertaken; all events returned to a form of routine surveillance.

6: EASL guidance post-all investigation recommends 4 monthly ultrasounds for 1 year

Of all 162 events in the dataset, 26 events did not have post investigation follow up available, leaving 136 events. Of these 136 events, 116 events were followed up by routine USS, 1 event with a routine CT, and 19 events with a routine MRI.

Actual follow up data for post-all investigation follow up had a mean days was 177.9 with standard deviation of 78.3, and median days of 175.5.

7; Statistics

- Period prevalence of nodule incidence on surveillance USS of cohort over 5 years is 0.164319 (16.4%) (140/852)

- Period prevalence of HCC diagnosis on surveillance programme of cohort over 5 years is 0.018779 (1.9%) (16/852)

- Incidence proportion of HCC for cohort on surveillance programme over 5 years is 0.018779 (1.9%) (16/852)

- Incidence rate of HCC in cohort under surveillance programme is 3.75597 cases per 1000 person-years.

- Ultrasound (surveillance modality) has a 10.1% (12/119) positive predictive value to pick up HCC when compared to gold-standard first modality imaging. Thus, it has an 89.9% false discovery rate.

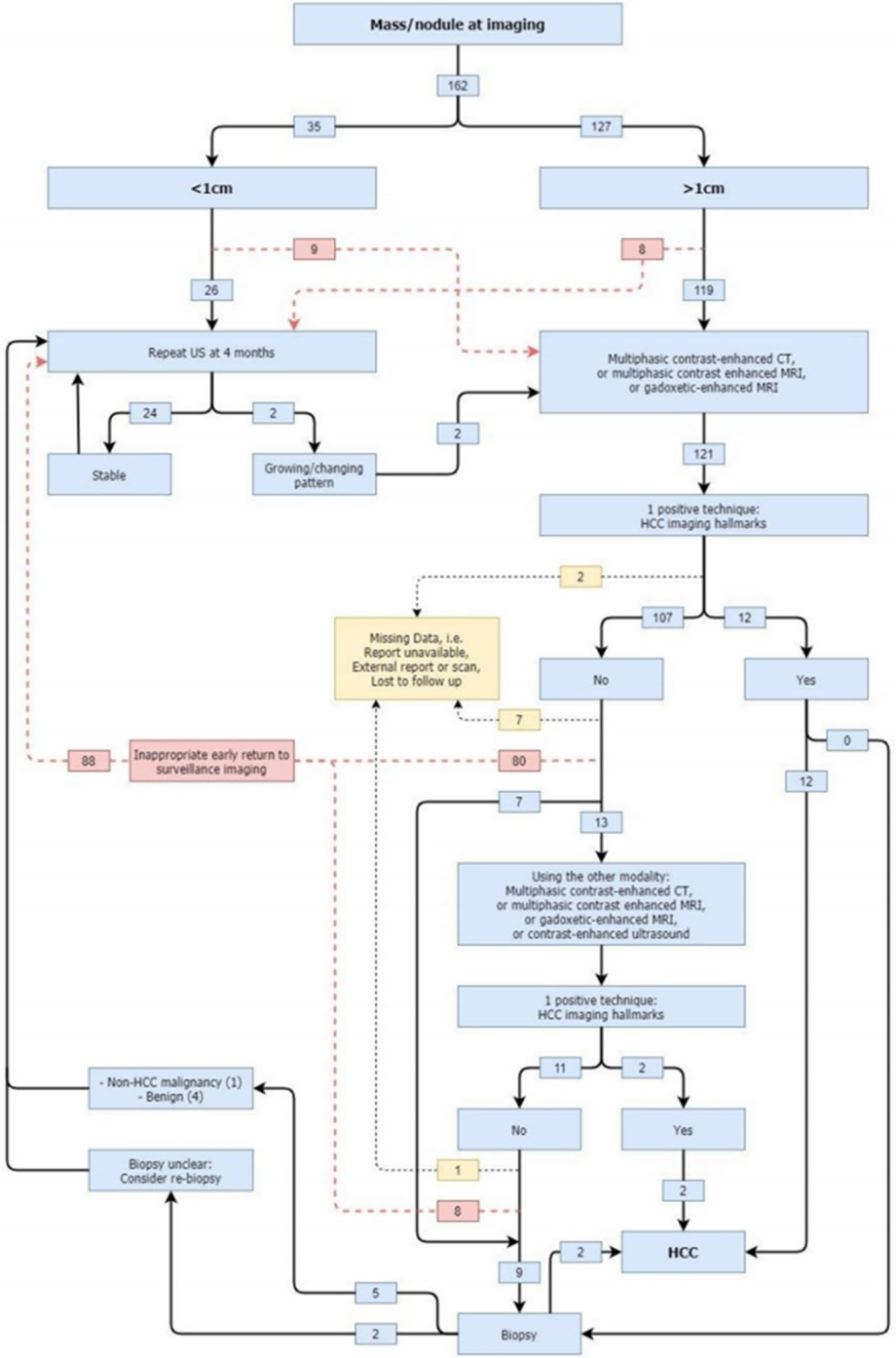
Summary of Findings

The results indicate that there is strong adherence to EASL guidance for following up nodules with USS when less than 1cm, and CT/MRI when 1cm or larger. However, from here there is clear deviation from guidance when first modality CT/MRI does not report one positive technique from HCC imaging, whereby majority of cases return to routine surveillance instead of continuing to second modality imaging.

The data suggests our centre has a high straight to biopsy rate for indeterminate lesions, bypassing second modality imaging. This is considered acceptable for specialist centre-based programmes. There was no case of biopsy undertaken when imaging had already shown one or more positive technique for HCC imaging, though this additional step of biopsy confirmation is optional within the guidance.

The analysis shows that post-all investigation surveillance imaging was, in most cases, returned to 6 monthly whereas guidance advises 4 monthly USS follow up. A portion of the cohort instead returned to routine MRI surveillance over USS. In both cases this deviates from the guidance provided.

A summary of investigation of our studied cohort overlaid to guidance can be seen in the Figure opposite. EASL guidance is shown in blue, with significant deviations to guidance in red. Yellow displays missing data within the study that was removed. Numbers at each stage refer to frequency of cases at each stage on the nodule investigative process.



Discussion

Expediting earlier return to routine USS surveillance, and quicker return to 6-monthly intervals, does not affect outcomes

For new nodules <1cm identified on USS EASL guidance advises repeat USS surveillance at 4 monthly intervals for one year before returning to 6 monthly routine surveillance. The significant deviation may stem from the confidence gained from the first repeat USS showing stable appearances of a small nodule, or often the nodule not being seen on this repeat imaging. It could be argued that there is resultant very low clinical suspicion of HCC and thus there is unlikely to be great clinical benefit to repeating a scan at 4 months, with radiologist reports often recommending an early 'return to routine 6-monthly surveillance'. In this study, it was found that in the cases of early return to routine there was no evidence of subsequent detriment to the patients. Conversely AASLD recommends repeat USS at 3-6 months, allowing for clinician discretion for what would be a return to routine surveillance to be within guidance – which is more in line with our specialist programme.

1st Modality CT vs MRI choice perceptual, CT faster than MRI

EASL guidance offers CT or MRI as a first characterising modality imaging option with no advised preference, nor any specified interval. Our data shows a clear preference for MRI over CT within our Unit in the first instance. Though there may be a preference for MRI in this study, this comes with the potential drawback that patients wait on average twice as long for this imaging modality; roughly 1 month for CT vs. 2 months for MRI. This discrepancy is difficult to explain, although patient (ability to breathold, BMI, claustrophobia etc.), service configuration (availability, cost, time) and clinician preference (perceived sensitivity/specificity of each modality, historical availability) parameters may all contribute. Interestingly, within our Unit the total number of HCC diagnoses at this stage were too few to confidently substantiate either as the superior modality.

Discussion

Very low 2nd modality imaging, preference to either biopsy & TACE/RFA, or a quick return to routine/expedited surveillance

EASL guidance recommend second modality alternate imaging (or direct to biopsy) when first modality imaging does not definitively characterise HCC. In this study an overwhelming majority of cases returned to routine surveillance after first modality imaging, deviating heavily from EASL guidance. This indicates strong confidence in first modality imaging, and that a report of 'no evidence of HCC' may only be made when there is high confidence in negative characterisation, as it was often accompanied alongside a recommendation to return to routine surveillance. This likely reflects the experience provided within our Unit where all characterising examinations are reported by subspecialist hepatobiliary radiologists. The modality of scan requested on this expedited return to routine surveillance is predominately USS as per EASL guidance, however MRI does feature a non-trivial amount. This may represent a cohort of patients where USS surveillance could be inaccurate e.g. fatty and/or macronodular disease. It is also possible there is intermediate clinical suspicion of HCC despite no formal diagnosis obtained through imaging or biopsy, and so these high-risk patients are followed up with surveillance MRI (omitting second modality imaging) – through imaging requests it was evident this was a conscious return to routine MRI surveillance as opposed to delayed 2nd modality imaging. Of the 88 cases with early return to routine surveillance, only on one occasion was there progression to HCC shown. This, alongside the low incidence and prevalence of HCC in the studied cohort, suggests that this earlier return to routine surveillance does not convincingly affect the outcomes for future HCC and mortality rate over the 5-year surveyed period.

The use of biopsy, TACE and RFA

Our data shows a high straight to biopsy rate following indeterminate 1st characterising examination, as is optional for specialist centre-based programmes. Though 9 biopsies were seen in this study, only 2 of these had undergone second modality imaging prior in their pathway. Biopsies seem to be pursued in cases where there was high clinical suspicion of HCC with indeterminate first modality imaging. The apparent early preference for biopsy, bypassing second modality imaging, may be due to the availability of RFA at our centre, allowing for both earlier diagnosis and potential treatment to overlap which provide more immediate benefit to the patient than awaiting second modality imaging before proceeding.

Discussion

Addressing the Null Hypothesis

Our null hypothesis states that deviation from EASL guidance worsens patient outcomes. The summary of findings highlights key deviations in repeat USS surveillance in nodules <1cm and large deviations beyond first modality imaging in nodules >1cm, especially with very low second modality imaging and high early return to routine surveillance USS. The null hypothesis, if true, would mean this study should show high rates of HCC detection. In this study, the rate of diagnosis for HCC was 11.4% of the surveyed population in which a nodule was seen during routine surveillance imaging, and a 1.9% diagnosis rate of the total surveyed population undergoing surveillance imaging over the 5-year period. As discussed previously, deviations from guidance do not demonstrably affect patient outcomes. Therefore, we feel it is reasonable to reject the null hypothesis, and state that the deviations to EASL guidance by our specialist centre-based programme are not shown to worsen patient outcomes.

Is strict surveillance worth it? Very low diagnosis rates, resource management

In England, imaging activity within the National Health Service (NHS) increases significantly year on year, as shown by the Annual Statistic Release 2019/2020 by NHS England , with upwards of 44 million scans each year. It is thus important to recognise that resources must be allocated appropriately and to where the greatest benefit can be obtained. Within this study, the low positive predictive value of (10.1%) of surveillance ultrasound and the overall low rate of diagnosis of HCC brings into question the cost-benefit of the current surveillance programme; however there was limited scope to formally assess this in any required detail. Future research exploring novel HCC risk stratification tools to allow personalised assessment of HCC predictability would be of great interest to more finely ascertain and identify those that do or do not require routine imaging surveillance. With huge international meta data-sets available, Artificial Intelligence could play a pivotal role in achieving this. There is also a need to revisit available models for HCC surveillance to optimise cost-effectiveness.

EASL vs. AASLD

AASLD and EASL guidance for HCC surveillance have some key differences to be highlighted. Nodules <1cm are advised for 4-monthly strict USS follow up by EASL, whereas AASLD advise 3-6 months, allowing for clinician discretion based on suspicion of HCC. Within our centre we seem to align more so with AASLD and most patient return to 6 monthly routine surveillance.

AASLD has clearer guidance on further investigation of patient post first modality imaging (CT/MRI for nodules >1cm) through its use of Liver Imaging Reporting and Data System (LI-RADS) classification. Though EASL elements of this, it advises progression to second modality based on negative HCC imaging hallmark. Conversely, AASLD uses seven LI-RADS categories in which first modality should be reported and thus provides clear guidance how the patient should be further investigated.

In this study a large majority of cases were returned to routine surveillance from first modality imaging when no nodule was seen or it was deemed to be (probable) benign, which conflicts with EASL guidance to progress to second modality imaging. Interestingly, AASLD aligns with our data as it advises a return to routine surveillance (of varying time intervals) when there is negative characterisation for HCC.