Evaluation of disease recurrence and incidental findings from an imaging surveillance programme for hepatocellular carcinoma post liver transplant: experience of a UK transplant centre.

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List of abbreviations:

HCC, Hepatocellular Carcinoma
RETREAT, Risk Estimation of Tumour Recurrence After Transplant
OS, Overall survival
RFS, Recurrence free survival
UKELD, United Kingdom model for End-stage Liver Disease
NHS, National Health Service
BSG, British Society of Gastroenterology
EASL, European Association for Study of the Liver
AASLD, American Association for Study of Liver Disease
EPR, Electronic Patient Record
CI, Confidence Interval
AFP, Alpha Fetoprotein
MASLD, Metabolic Dysfunction Associated Steatotic Liver Disease
VATS, Video assisted thoracoscopic surgery
ERCP, Endoscopic Retrograde Cholangio Pancreatography
EUS, Endoscopic Ultrasound

Abstract

Background and Aims:
Hepatocellular carcinoma (HCC) is an increasingly common indication for liver transplantation. The study purpose was to explore the benefits and drawbacks of surveillance imaging in this patient group and further assess the use of prognostic scoring systems such as the Risk Estimation of Tumour Recurrence After Transplant score (RETREAT).

Methods:
A retrospective, single centre, analysis of imaging findings in patients undergoing computed tomography (CT) surveillance following liver transplantation for HCC from 2008 – 2014. Subsequent five-year imaging follow-up and ten-year overall follow-up period. Primary outcomes were recurrence free survival (RFS) and overall survival (OS). Validation of the RETREAT Score was undertaken.

Results:
135 patients underwent liver transplantation for HCC. At five years, 8 patients (6%) were diagnosed with recurrence through surveillance, all of whom died despite some receiving treatment. At ten years, one further patient died of recurrence. 826 surveillance scans were performed resulting in 59 incidental findings, mostly benign. Recurrence free survival (RFS) post liver transplant and overall survival (OS) were 94% (95% CI's:89 – 98%) and 85% (95% CI:79 – 81%) respectively at five years. RETREAT score validation achieved a C-index for prediction of RFS of 0.88 (95% CI:0.80 – 0.95) and 0.63 (95% CI:0.52 – 0.75) for OS at five years.

Conclusion:
The results suggest regular surveillance imaging with curative intent for HCC recurrence post transplantation may not be of benefit to RFS. The use of prognostic scoring systems such as the RETREAT score provide valuable prognostic information and may negate the need for regular imaging.

Keywords:
Hepatocellular carcinoma, Liver Transplant, Imaging, Computed Tomography, Magnetic Resonance Imaging.

Key Points:

- Liver transplantation or surgical resection is the only cure for HCC. Despite this, there remains no standardised imaging surveillance protocol post liver transplantation to assess for recurrence in this patient group.
- There was no mortality benefit to surveillance imaging in relation to HCC recurrence specifically.
- Imaging surveillance is costly to a state funded healthcare system, including detection of incidental findings.
- Further studies investigating long-term survival, cost analysis and impact on quality of life of differing surveillance regimes would be indicated to establish if there is benefit of selective follow up.

Introduction

Hepatocellular carcinoma (HCC) is an increasingly common indication for transplantation, accounting for 27% of all liver transplants[1,2]. Transplant surgery is the only truly curative treatment for HCC[3]. Decision to transplant relies on stringent guidelines and objective scoring systems[4–6] in order to minimise post-transplant morbidity and mortality. In the UK, radiological assessment of tumour burden is based on the modified MILAN criteria[7,8] which together with the United Kingdom model for end-stage liver disease (UKELD) has been incorporated into the National Health Service (NHS) Blood and Transplant liver criteria for transplantation[8].

Notwithstanding, after transplantation, the risk of HCC recurrence remains significant, estimated at a rate of 8 – 20%[9]. Cancer recurrence is usually within the first 3 years of surgery[10] and, if present, treatment is usually palliative. Despite regular surveillance for both acute and chronic complications[11], there is a paucity of research focusing on the efficacy of follow up imaging for HCC recurrence. Guidelines from the British Society of Gastroenterology (BSG), European Association for Study of the Liver (EASL) and the American Association for Study of Liver Disease (AASLD)[5,11,12] are incongruent and may explain the heterogeneity in practice in post-operative imaging follow up across transplant centres. At present there are no standardised imaging follow-up guidelines in patients post liver transplantation.

The long-term survival benefit of surveillance post-transplant for HCC recurrence remains unclear. Theoretically, the early identification of recurrent disease may allow curative therapy. This is supported by Lee *et al*[13] who reported increased imaging surveillance was associated with a higher probability of aggressive treatment and improved post-recurrence survival. However, in contrast, Liu *et al*[14] demonstrated that reducing surveillance scan frequency did not affect recurrence free survival time, in particular when other surveillance methods are used, such as tumour markers.

Given the incongruity on the benefits of surveillance imaging, exploring different methods of predicting recurrence risk is important, hence the development of prognostic indicator scores. The MILAN criteria is one such score that calculates the suitability of patients for liver transplantation. Further and more novel scores such as the Risk Estimation of Tumour Recurrence After Transplant (RETREAT) score, are being increasingly investigated to predict HCC recurrence with good performance in validation studies[15–18]. The RETREAT score is a composite of both pre-surgical biochemical parameters, and explant pathology markers, placing less emphasis on post-surgical imaging. With increasing research into pathological tumour markers along with blood results and monitoring, prognostic indictor scores show promise as a valid and cost-effective method of stratifying risk of recurrence.

The purpose of this study was to explore the efficacy of routine surveillance for HCC recurrence post-transplant and consider the benefits and drawbacks of surveillance in the state-funded National Health Service (NHS). Factors including HCC recurrence and incidental findings (intra-and extra-hepatic) were assessed in terms of impact on patient survival and ability to cure, as well as burden on resources for the service provider. Further, we aimed to externally validate the RETREAT score on our cohort of patients.

Methods

Patient Selection

Formal ethics committee approval and informed written consent was waived for this study which was considered by the institutional review board to represent evaluation of a routine clinical service.

All consecutive patients transplanted for HCC, or with incidental HCC on explant, at Leeds Teaching Hospitals NHS Trust between 2008 – 2014 were included. There was a subsequent five year imaging follow up and overall ten year follow up period. Leeds Transplant Centre is a large tertiary centre and one of only seven national centres that offers a liver transplant service in the UK.

Patients were identified retrospectively from the institution's Electronic Patient Record (EPR, Patient Pathway Manager, Leeds, UK) and cross-referenced with a prospectively maintained database to ensure all patients were captured.

Data were collected on baseline demographics, clinical and biochemical parameters, time to transplant, underlying liver disease, histology on explant, surveillance imaging findings including any HCC recurrence / incidental findings along with management and outcome over the follow up period.

Image acquisition and analysis

Follow up CT imaging was performed, using one of four Siemens scanners, on every patient that underwent liver transplant at the centre. As per standard HCC post-transplant follow up, an arterial phase thoracic acquisition in addition to dual-phase abdominal and pelvic imaging in arterial and portal venous phases was completed during each imaging study.

CTs were performed every six months for three years, and annually for a further two years to complete a five year follow up. Images were reviewed and reported by a small group of experienced gastrointestinal consultant radiologists and any adverse findings or recurrence were discussed in a multi-disciplinary meeting.

Outcome Measures

The study outcomes were cancer recurrence post liver transplant, overall survival (OS) and recurrence free survival (RFS). Recurrence included both intra-hepatic and extra-hepatic sites of disease. OS was calculated from transplant date to date of death (from any cause) or last day of follow up if alive. RFS was defined as the time between liver transplant to cancer recurrence. For patients without recurrence, the censor date was taken to be the last time each individual was seen in clinic or by a doctor.

An exploratory analysis was conducted of the data to identify unexpected benefits and possible harms of the surveillance programme as well incidental imaging findings along with the additional investigations generated and final outcomes. The aim of follow up imaging was the detection of HCC recurrence, however incidentally, complications of transplant, intra- or extra-hepatic incidental findings and metachronous malignancies were also identified and reported.

Statistical analysis

Primary outcome measures were OS and RFS in patients with HCC post liver transplant. Five- and ten-years follow-up OS and RFS estimation was performed using Kaplan-Meier analysis. The predictive value of the RETREAT score in our cohort was assessed with univariable Cox proportional hazards models using RETREAT score as a predictor of both RFS and OS for five- and ten-year end-points. Model discrimination was assessed with Harrell's C index and 95% confidence intervals (CIs). Kaplan-Meier analysis and Cox proportional hazards modelling was performed in R (Version 4.2.2, 2022-10-31).

RETREAT Score

The RETREAT score encompasses alpha fetaprotein (AFP), vascular invasion, sum of the largest viable tumour diameter (cm) and number of viable tumours on explanted liver.

Results

Patient characteristics

135 patients underwent liver transplantation for HCC at the Leeds Liver Unit between 2008 – 2014. Mean age at transplant was 57 years (range 25-72) with variable aetiology of underlying liver disease. Viral infection was the prevailing disease, with Hepatitis C being the most common (60, 44%). Mean time on the transplant waiting list was 164 days (range 0-1510).

Survival analysis

Over the five-year follow up period, 8 out of 135 (6%) patients were diagnosed with recurrent HCC. On follow up to ten years, there was one more case of recurrence. Recurrence was diagnosed in 8 out of 9 patients on routine surveillance, the final case presented due to symptomology.

RFS five years post liver transplant was estimated at 94% (95% CI's: 89 – 98%) and 93% (95% CI's: 89 – 97%) at ten years. OS was estimated to be 85% (95% CI: 79 – 91%) at 5 years and 80% (95% CI: 73 – 87%) at ten years.

Despite treatment with surgical resection or palliative therapy, all 9 patients with recurrence died. The commonest site of recurrence was the lung (*Table 1*).

Table 1.

Patient	Age	Site of recurrence	Presentation	Treatment
1	58	Bone	Routine surveillance	Radiotherapy kinase inhibitor
2	61	Bone	Routine surveillance	Spinal decompression
3	45	Lung	Routine surveillance	Resection via VATS
4	60	Lung	Routine surveillance	Kinase inhibitor
5	64	Lung	Symptomatology	Resection via VATS
6	52	Lymph nodes	Routine surveillance	Nil
7	57	Lung	Surveillance imaging	Nil
8	55	Lung	Surveillance imaging	Nil
9	56	Paraspinal	Surveillance imaging	Nil

Table 1: Result breakdown of patients with HCC recurrence (VATS = Video assisted thoracoscopic surgery).

Within the post-transplant follow up period of 5 years, 73 of 135 patients were found to have a total of 87 incidental findings, inclusive of malignant and benign pathology. 16 (12%) metachronous malignancies were identified which included post-transplant lymphoproliferative disorder (3), skin (5), lung (4), gastrointestinal cancers (2), lymphoma (1) and sarcoma (1). The remaining 71 findings were classified as benign and encompassed transplant related complications, such as anastomotic strictures or portal vein thrombosis (34), or incidental findings such pancreatic cysts and hyper-vascular liver lesions (37).

During follow up, 826 surveillance CT scans were undertaken. Of the total incidental findings highlighted above, 59 pathologies were identified in 44 patients through surveillance imaging

only. This was inclusive of 3 metachronous malignancies (lung (2) and sarcoma (1)), and the remainder classified benign (56).

The benign findings prompted a total of 86 additional investigations inclusive of further multimodality imaging (46), multidisciplinary team meeting (MDT) discussion (23) and further procedures (17).

Retreat score validation

As part of our analysis we aimed to externally validate the RETREAT score[15] in our cohort of patients. See *Table 2* for a summary of features.

Table 2.

RETREAT score variable	HCC non-recurrence (n =127)	HCC recurrence (n = 8)
Max lesion diameter (mean, mm)	23	28
No of lesions (n, %)		
1 - 3	111 (87)	3 (38)
4 - 6	12 (9)	2 (25)
≥7	3 (2)	2 (25)
Microvascular invasion (n, %)	32 (25)	4 (50)
AFP at LT (ng/ml)		
0-20	100 (79)	4 (50)
21 -99	14 (11)	2 (25)
100 -999	13 (10)	2 (25)

Table 2: Summary of retreat score variables in the different cohorts.

The distribution of RETREAT scores was 0 – 6 in our group. A breakdown of retreat scores for patients with recurrence and non-recurrence can be seen in *Table 3.*

Table 3.

RETREAT score	Recurrence		% Recurrences per RETREAT score
	No	Yes	
0	3	0	0
1	56	1	1.8
2	20	2	9
3	25	0	0
4	15	2	12
5	6	2	25
6	0	1	100

Table 3: Summary of retreat scores in the different cohorts.

One patient had no histology results on record. The following bar chart (Figure 1) summarises the distribution of patients with and without recurrences per RETREAT score category.

Figure 1.

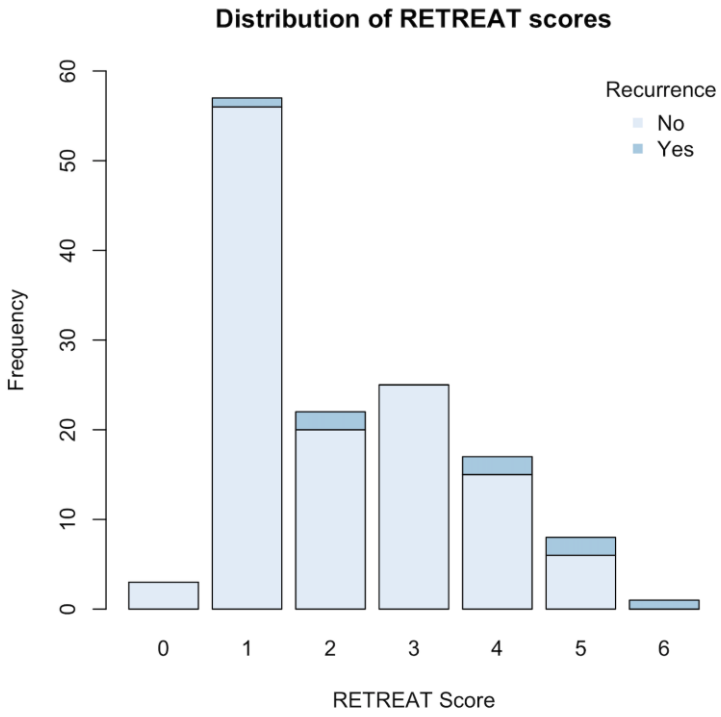

Figure 1: Distribution of patients with and without recurrence per score category.

Cox regression was used to assess the prognostic relationship between the RETREAT score and RFS and OS post liver transplant for HCC. At five years post-transplant, the C-index for prediction of RFS was 0.88 (95% CI 0.80 – 0.95) and for ten years was 0.84 (95% CI 0.72 – 0.96). For OS, the C-index at five years was 0.63 (05% CI 0.52 – 0.75) and at ten years follow up was 0.60 (95% CI 0.52 – 0.68). In summary, the RETREAT score showed good discrimination in our cohort.

Discussion

There remains a paucity of evidence supporting HCC surveillance imaging post-transplant surgery, particularly with a curative intent for any detected recurrence. As a result, Leeds liver transplant unit has since stopped routine follow up imaging in this patient group. Routine surveillance imaging identified 8 out of 9 cases of HCC recurrence, however early identification through imaging alone did not lead to successful curative treatment for any of these patients.

It is acknowledged that patients with early recurrence generally have poorer outcomes[16]. Limited evidence suggests that treatment of recurrence with surgical resection or ablation is associated with increased survival, with no difference in survival time between intra-hepatic or extra-hepatic recurrence[13]. Such studies are challenging to interpret since these are uncontrolled and are at risk of bias from both length and lead time bias. Early detection of recurrence has previously utilised blanket surveillance imaging protocols which are resource intensive and a financial burden on state funded health care systems such as in England, particularly if subsequent treatment is palliative only. More optimised patient stratification and surveillance of high-risk groups may be of advantage to both patients and healthcare providers in the future. This is particularly relevant in patients diagnosed and transplanted in an era of criteria defined recipient selection such as those within Milan criteria and where, as we have described, the overall risk of recurrence is low.

Newer surveillance methods encompassing prognostic scoring to help quantify future risk of recurrence may help guide optimal use of imaging resources for those at higher risk and need. A novel development is the RETREAT score; a pre- and post-surgical scoring system that incorporates biochemical and explant pathology to predict risk, helping stratify surveillance for those at highest risk of recurrence. This scoring system has been recently validated as a prognostic tool in a UK centre[15,16], showing a decrease in recurrence free survival with increasing RETREAT score whilst also outperforming the MILAN index[16]. The RETREAT index is scored out of eight, and studies suggest those with a total score of equal to or lower than two are within a very low risk category[17]. It has further been validated in European and Northern American cohorts[17,18]. Very low risk is defined as a recurrence rate of under 3% at ten years post-transplant. Given the extremely low risk of recurrence it remains unclear whether the risk of radiation exposure and psychological burden associated with returning for repeated imaging studies yields a net benefit in this subgroup and whether imaging surveillance is warranted at all. In our cohort, the RETREAT Score achieved a C-index of 0.88 at five years follow up for RFS. Our results concur with previous studies[15,16,18] suggesting there is benefit to use of prognostic scoring in this specific population.

In our overall cohort 79/135 (59%) patients scored ≤ 2 with 3/79 (3.8%) cases of recurrence. These patients scored as low risk on the RETREAT score and therefore may not have been deemed suitable to targeted surveillance. These figures are slightly higher than the defined low risk of recurrence rate of 3%. If surveillance for recurrence had been omitted in the 79 patients with a score of ≤ 2 then approximately 474/826 CT scans could have been avoided (average 6/person). From an economical perspective this would have made considerable savings over a 5 year follow up period. In our cohort, a further 5/46 (11%) patients with a RETREAT score of >2 had recurrence of HCC.

Using a risk stratification tool such as this is of major clinical interest to help identify those at highest risk of recurrence and better concentrate finite healthcare resources and imaging on this group if clinically indicated. However, further research is needed within the high-risk groups assessing the effect on quality of life and survival benefit.

Many incidental findings were identified in our cohort on surveillance imaging, which were all subsequently treated if needed. At conclusion of the five-year follow up, three patients had been diagnosed with a metachronous malignancy. Of these, one patient died due to progression. Though surveillance had no benefit for cure in HCC recurrence, it could be inferred that in certain cases there may be a significant overall survival benefit in detection of metachronous malignancies. However, this would be regardless of pre-transplant HCC status and would have to apply to all patients post liver transplantation, with or without history of HCC, given that all receive immunosuppressive therapy and are at generally greater risk of developing malignancy. It is also unclear how earlier detection of metachronous malignancies affects overall survival compared to detection of these cancers only once they become symptomatic. Nonetheless, any benefits of cross-sectional imaging need to be weighed against the need for further investigation of non-significant incidental findings and the added burden on both the patient and the healthcare provider.

Biliary and vascular complications are not uncommon post liver transplant, and one consequence of surveillance imaging was the detection of these incidental transplant specific complications. Of these incidents, some required intervention such as stenting, whilst others were managed conservatively. However, again it is unclear if these interventions were necessary and, in some cases, caused management dilemmas in asymptomatic patients who were otherwise well. It is uncertain what the incidental asymptomatic complication rate would be in other liver transplant recipients not undergoing surveillance.

The remainder of incidental findings mainly encompassed hypervascular liver lesions, lung nodules or pancreatic cysts, of which some needed treatment. These required follow up, further imaging or inter disciplinary team discussion, as well as creating unmeasured disruption and anxiety for the patient. The impact of regular follow up and incidental findings on patients is often not considered. Although historically good outcome post-transplant has concentrated on survival, success should also be measured on the impact on the patient's quality of life[11]. To the best of our knowledge, there are no related publications reporting the number or consequences of incidental findings in this cohort of patients, and further exploration of their impact is warranted.

Our study had several limitations. The number of recurrent cases were small, thus subgroup analysis was difficult. Further, accurate cost estimations for surveillance imaging was not carried out. Imaging costs are likely to vary amongst institutions and health care systems depending on locally negotiated rates. Further studies investigating survival, cost analysis and impact on quality of life of differing surveillance regimes would be indicated to establish if there is benefit of selective follow up. The long-term outcomes of patients receiving treatment for HCC recurrence in this setting need to be better understood. In addition, it would be prudent to address all-cause morbidity and mortality, especially the presence of non-HCC cancers.

Conclusion

The results of this single centre study suggest prognostic scoring such as RETREAT can provide valuable prognostic information in this specific group of patients and aid in the assessment of HCC recurrence.

We conclude that regular surveillance imaging with a curative intent for HCC recurrence post transplantation is not indicated. There may be some benefit with regards to offering life-prolonging treatment, but it is unclear how this would compare with treatment of symptomatic disease only and, should be weighed up alongside the significant burden placed on the service provider.

The incidental findings of non-HCC malignancy in an immunosuppressed cohort and asymptomatic transplant-related complications were not the purpose of the surveillance programme, and it is probable that a similar rate of these findings would be present in liver transplant recipients with no history of HCC i.e., not part of the surveillance programme. It is important to continue to explore how to best serve this patient group and work from other studies on risk stratification scores is likely to drive practice in the coming years along with new treatment options.

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