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ORIGINAL RESEARCH

Improved Survival of Hepatocellular Carcinoma Patients Diagnosed with a Dedicated Screening Programme—a Propensity Score Adjusted Analysis

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Abstract

Aim To assess the overall survival (OS) in those with hepatocellular carcinoma (HCC) diagnosed within a programmatic, centrally co-ordinated, regional screening programme.

Methods A retrospective cohort analysis of consecutive HCC patients diagnosed between 2004 and 2013. Patients were followed up till death or end of study period (30 April 2015). A dedicated screening programme was commenced in 2009 to screen high-risk patients for HCC. Primary objective is to compare the OS between HCC patients diagnosed within the screening group versus those diagnosed outside this group. Other objectives were to compare tumour stage at diagnosis and the proportion having curative treatments in the two groups. Propensity score adjustments were performed to assess the survival benefit.

Results HCC was diagnosed in 130 subjects during the study period (82.3% males, median [IQR] age 62 [± 19] years and median [IQR] follow-up of 11.3 (± 23.5) months). Ninety-six patients (73.8%) died during the follow-up, and the median (95%CI) OS was 15.7 (9.7–21.8) months. HCC diagnosed within the screening programme had a better OS compared to those diagnosed outside this programme (26.8 vs 11.5 months, $p = 0.01$). Further, those diagnosed within the programme had an earlier stage HCC ([58.3% vs 23.6%], $^2 = 11.3$, $p = 0.001$), and a significant proportion were treated with curative intent ([62.5% vs 31.1%], $^2 = 8.3$, $p = 0.004$). Propensity score adjustment showed a 58% reduction in mortality for HCC diagnosed within the screening programme (HR [95%CI] 0.42 [0.20–0.89], $p = 0.02$).

Conclusion A programmatic, regional HCC screening programme improved the OS and detected tumours at an earlier stage enabling more patients to have curative therapies.

Keywords Hepatocellular carcinoma · Screening · Survival · Mortality · Propensity scores

Introduction

The worldwide incidence and mortality rates of hepatocellular carcinoma (HCC) continue to increase [1, 2]. HCC is a tumour with poor prognosis as it often presents late and without treatment; the 5-year survival is less than 5% [3]. Current recommendation for HCC screening is to use 6-monthly abdominal ultrasound with or without alfa-feto protein (AFP) in high-risk patients [4–7]. However, mortality reduction with this screening strategy is equivocal as there is only limited prospective data. A large Chinese study used a cluster randomisation process to evaluate mortality benefits of a screening programme [8]. The study evaluated more than 19,000 patients with HCC and found that there was a 37% reduction in mortality in the screening group.

Despite randomised controlled data from a single Chinese study of predominantly hepatitis B patients, there is a paucity of data among the Western populations that evaluates the benefit of regular screening programmes. Given the differences in demographics in the Chinese study versus a typical heterogeneous Western population, it is important therefore to evaluate the impact of screening/surveillance programme in the Western

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population. Given the difficulty of conducting randomised controlled trials of HCC screening in the Western populations due to ethical concerns, alternative forms of evidence are required [9].

An alternative form of evidence may be evaluation of real-world effectiveness of surveillance programmes, implemented across whole health regions. Adherence to HCC screening is poor in real-world environments and has been documented by multiple authors, and this may also limit the effectiveness of an HCC screening programme [10, 11]. Despite clear evidence of poor adherence to screening, to the best of our knowledge, no study has attempted to redesign care to address this problem, implement a redesigned screening programme, and then assess its effectiveness across a whole health region.

Our aim in this study was therefore to compare the effectiveness of programmatic surveillance implemented across an entire health region. Specifically, we aimed to compare overall survival (OS) of HCC patients within our health region, comparing those diagnosed within the dedicated and centrally driven screening programme versus those diagnosed outside this group. We also evaluated tumour stage at diagnosis as well as the number of patients offered curative treatment in the two groups. A further aim was to examine the performance of the screening programme with respect to adherence to the 6-monthly screening ultrasound.

Methods

Study Design and Participants

The study was a retrospective, multicentre cohort analysis of consecutive patients diagnosed with HCC from 01 January 2004 to 31 December 2013 within the Southern Adelaide Local Health Network (SALHN) catchment area (estimated population ~ 350,000, one tertiary referral hospital with a liver transplantation centre and two smaller secondary hospitals). Patients were excluded if their primary address did not fall within SALHN postcodes or if they were diagnosed at another facility and subsequently referred to our Liver Transplant Unit or Palliative Care Hospice for ongoing management. Patients were not included in the screening group if they were diagnosed with HCC within 3 months of screening programme entry.

Patients were identified using the ICD-10 Code for HCC (C22.0) from all three hospitals and cross-referenced with the South Australian Cancer Registry to ensure maximal case finding. Diagnosis was confirmed either histologically or with characteristic radiological appearance as per the current guidelines [4]. Although the dedicated, centrally co-ordinated HCC screening programme, run by non-medical clinical staff, was established only in 2009 within our network, we evaluated 5 years prior to this to assess the era effect. The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).

HCC Screening Programme

An audit performed in 2007 within this local health network identified that individuals with high risk of developing HCC were having inadequate screening ultrasounds [10]. High-risk individuals or target population for our study were defined as per the AASLD screening recommendations for HCC [4]. One of the major barriers for this was the tertiary care practice, and this required system redesign for quality improvement. Based on this audit finding, a dedicated, centrally co-ordinated HCC screening programme was established in 2009 along with an easy-to-use patient database with automated recall function. Screening was performed with 6-monthly ultrasound scan of the abdomen, and the additional use of AFP was at the discretion of the treating hepatologist. Booking process for ultrasounds, blood tests and medical reviews were centralised and monitored by HCC co-ordinator. Patients received written reminders about ultrasound appointments prior to their visits which also included the contact details for the HCC co-ordinator. Patients who failed to attend their appointments were contacted and re-educated about the importance of this screening programme, and a subsequent ultrasound appointment was made.

Data Collection

Baseline demographics including age at diagnosis, gender, indigenous status, aetiology of liver disease and stage of liver disease based on the Child-Pugh and MELD score were obtained. Number of AFP measurements and HCC screening ultrasound scans (USS) were recorded for 2 years prior to diagnosis. Those who had at least two screening scans in a 12-month period prior to diagnosis were deemed to have adequate screening. Those with suspicious tumour nodules or with elevated AFP were then evaluated with cross-sectional imaging (either multi-phase CT or contrast enhanced MRI) to confirm the diagnosis. Tumour characteristics were obtained from radiologic and histologic data including number, size and location of tumours, the presence or absence of portal vein thrombosis or invasion and alpha-fetoprotein (AFP) level on diagnosis. Based on the above parameters, the Barcelona Clinic Liver Cancer (BCLC) staging was assessed, and tumours were classified as early (stages O and A) or late (stages B, C and D).

Treatment intent, either curative (resection, liver transplantation or percutaneous ablation therapies) or palliative (trans-arterial chemo-embolization, oral chemotherapy or symptomatic management) was also recorded. Duration of follow-up was from the date of diagnosis (confirmatory scan) until the date of death or date of last follow-up (30 April 2015).

Statistical Analysis

Baseline characteristics were expressed either as median (IQR) for continuous variables or as number (%) for categorical variables. Primary outcome in this study was overall survival (OS), which was calculated using the Kaplan-Meier method and compared between those diagnosed within and outside the screening programme. Secondary outcomes like BCLC stage, size of the largest tumour and treatment intent on diagnosis were also compared between the above two groups using chi-squared tests and Fisher's exact tests as appropriate.

The OS between those diagnosed between 2004 and 2008 (era 1) to those diagnosed between 2009 and 2013 (era 2) was also compared to assess the era effect. Logistic regression analysis was performed to determine the predictors of mortality with a 2- sided p value of < 0.05 being considered statistically significant. We used propensity score (PS) analysis to create an estimated probability of being in the screening programme based on several possible predictors of the screening programme. This allowed adjustment for possible selection bias. The PS analysis consisted of a probit regression model with the screening programme as the binary outcome variable, and age, sex and the year of diagnosis as covariates. The estimated effect of the screening programme on survival was then assessed using Cox regression with the screening programme being the exposure of interest, and the PS, AFP and MELD as covariates. All statistical analysis was performed using IBM SPSS Statistics software for windows, Version 19.0. Armonk, NY: IBM Corp. and Stata (MP Version 14.0, Stata Corp, Texas, USA).

Results

Baseline Characteristics

During the study period, 130 subjects were diagnosed with HCC and met inclusion criteria. Among them, 107 (82.3%) were males with a mean (±SD) age of 63.2 (± 12.3) years at diagnosis and were followed up for a mean (±SD) duration of 20 (± 23.5) months (Table 1).

Chronic hepatitis C (CHC)–related cirrhosis was the predominant underlying aetiology followed by alcohol and non-alcoholic steato-hepatitis (NASH)-related cirrhosis. The majority of patients (56.2%) were well-compensated Child-Pugh A at the time of HCC diagnosis.

Unadjusted Probability of Overall Survival

Ninety-six patients (73.8%) died during the follow-up period, and the median (95% CI) overall survival (OS) was 15.7 (9.7–21.8) months. There was no difference in median survival between the HCC diagnosed in the two eras (12.9 [5.7–20.2] vs 16.3 [7.5–24.9] months, $p = 0.60$). However, those diagnosed within the dedicated screening programme had a better OS compared to those who were diagnosed outside this programme (26.8 vs 11.5 months, $p = 0.01$). The 1-, 2- and 3-year survival was also better in those diagnosed within the programme (Table 2). Even after adjusting for the era of HCC diagnosis, the survival benefit was still seen for those diagnosed within the programme (Fig. 1).

Table 1 Baseline characteristics

Variables	Results
Age at diagnosis (median (IQR)), years	62 (19)
Males (*n* (%))	107 (82.3)
Aetiology (*n* (%))[a]	
Chronic hepatitis C (CHC)	25 (19.2)
Alcohol	23 (17.7)
Non-alcoholic steato-hepatitis	22 (16.9)
Alcohol + CHC	21 (16.2)
Diagnosed 2009–2013 (Era 2) (*n* (%))	81 (62.3)
Diagnosed within the programme (*n* (%))	24 (18.5)
Child-Pugh score (*n* (%))[b]	
A	73 (56.2)
B	39 (30)
C	13 (10)
BCLC stage (*n* (%))	
Early (stages O and A)	39 (30)
Late (stages B, C and D)	91 (70)
Follow-up (median (IQR)), months	11.3 (23.3)

[a] Only four common aetiologies mentioned; [b] Child-Pugh score could not be calculated in 5 (3.8%) patients. *IQR*, inter-quartile range; *BCLC*, Barcelona clinic liver cancer staging

Stage of Disease, Treatments Offered and Proportion with Adequate Screening

Overall, only 39 (30%) patients had a very early or early BCLC stage at diagnosis. Within the screening programme, 14/24 had an earlier stage of diagnosis compared to 25/106 outside the programme ([58.3% vs 23.6%], $^2 = 11.3$, $p = 0.001$). Further, majority (95.2%) of those within the screening programme had a tumour < 5 cm (largest tumour nodule in case of multiple nodules) on diagnosis compared to only 46.3% outside the programme, $p < 0.001$.

Overall, there were 48 patients (36.9%) who were treated with a curative intent. Again, 15/24 (62.5%) within the screening group had a treatment with curative intent compared to only 33/106 (31.1%) outside this group, $^2 = 8.3$, $p = 0.004$.

Overall, 20% (26 out of the 130 patients) had adequate screening (as described in the "Methods" section). Within the screening group, 19 out of 24 patients had adequate screening

Table 2 Overall survival in HCC

Groups	Median survival (95% CI), months	1-year (%)	2-year (%)	3-year (%)
2004–2008, outside the program	12.9 (5.7–20.2)	53.1	29.6	22.4
2009–2013, outside the program	10.4 (3.9–16.8)	45.0	34.5	20.6
2009–2013, within the program	26.8	76.0	61.4	46.0

compared to 7 out of 106 patients diagnosed outside the programme ([79.2% vs 6.6%], $^2 = 64.4$, $p < 0.001$).

Predictors of Mortality

In univariate analysis, increasing age, HCC diagnosis outside the screening programme, AFP > 400, later BCLC stage at diagnosis and non-curative treatment intent were predictors of mortality. In multivariate analysis, after adjustment for gender and era of HCC diagnosis in addition to the above factors, later stages of BCLC, AFP > 400 and non-curative treatment intent were independent predictors of mortality. There was a trend towards increasing mortality in those diagnosed outside the screening programme, but this was not statistically significant (Table 3).

Multivariate Analysis Including the Screening Propensity Score

After adjustment for the propensity score for screening alone, those diagnosed within the screening programme had a 58% reduction in mortality compared to those diagnosed outside the programme (HR [95% CI] 0.42 [0.20–0.89], $p = 0.02$) (Fig. 2). This remained significant after adjusting for the stage of liver disease (based on MELD score) and AFP levels (0.46 [0.22–0.97], $p = 0.04$). However, the significance for screening programme was lost after additional adjustment for MELD score, the stage of HCC on diagnosis and AFP levels (Table 4).

Discussion

The important finding of this study is the improved overall survival in HCC patients diagnosed within a dedicated, centrally co-ordinated screening programme targeting a high-risk population. To the best of our knowledge, this is the first study to provide evidence that high-quality screening programmes, with good screening adherence, can be successfully implemented in real-world populations. Positive outcomes in terms of stage of diagnosis, proportion offered curative therapy and survival were associated with programmatic surveillance.

The effectiveness of the SALHN programme was likely to have been driven by a high adherence to screening protocols. This was confirmed by data showing that patients within the programme had an overall adherence rate of 79%. This adherence rate is a key quality indicator and process measure of any HCC screening programme. Achieving acceptable adherence rates is likely to be a significant challenge for many screening programmes, and therefore a thorough understanding of local

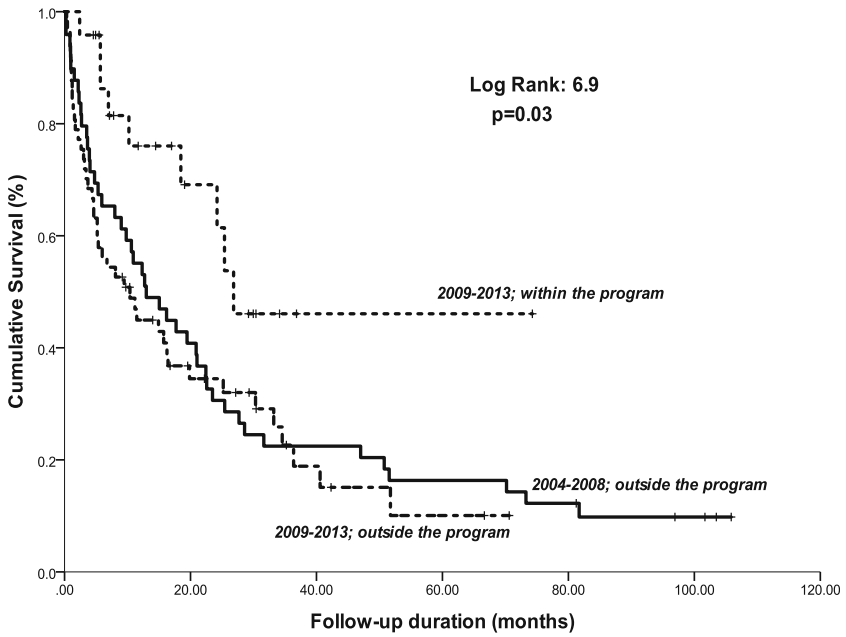

Fig. 1 Overall survival of HCC diagnosed within and outside the programme (unadjusted)

Table 3 Predictors of mortality excluding propensity score adjustment

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Age (per year)	1.02 (1.00–1.03)	0.03	1.0 (0.9–1.0)	0.20
Diagnosed outside the program	2.4 (1.2–4.7)	0.01	1.9 (0.9–3.9)	0.09
AFP > 400	3.2 (2.0–5.0)	< 0.001	3.0 (1.8–4.9)	< 0.001*
Late BCLC stage	2.3 (1.5–3.8)	< 0.001	2.0 (1.2–3.2)	0.007*
Non-curative treatment intent	4.7 (2.9–7.7)	< 0.001	4.5 (2.6–7.8)	< 0.001*

AFP, alpha feto protein; *BCLC*, Barcelona clinic liver cancer stage

*Statistically significant

barriers to screening and strategies to overcome these barriers in a population is fundamental starting points for the effective design of any program. The design of the screening programme used in this study with components of central coordination rather than doctor-led peripheral test ordering is considered the key contributor to the good programmatic adherence rate. The importance of designing effective HCC surveillance programs is highlighted by the recent EASL Clinical Practice Guidelines for HCC, which strongly recommend the improved implementation of screening programs as an important public health care goal [6].

The proportion of screen-detected HCCs in the community is variable, and this has shown to vary widely from 17 to 46% in the studies [11–13]. This would be influenced by various factors including local prevalence, study period, study setting (tertiary vs primary care), robustness of the screening programme etc. In this study, the screen-detected HCC (overall) was 20% (26 out of 130 HCC patients). This was significantly higher post-2009 after the screening programme was commenced—27.2% (22/81) compared to 8.2% (4/49) pre-2009.

Cohort studies reporting survival benefits in the screened population who develop HCC are prone to lead time bias, and we cannot definitely exclude this bias from our findings. We attempted to correct this by using propensity score adjustment for the screened and unscreened population, which matches the subjects on their propensity for treatment. In this study, there was a significant reduction in mortality in the screened population even after propensity score adjustment. The screening benefit remained significant even after adjusting for the underlying liver disease severity but lost its significance when adjusted for the stage of HCC. Lead time adjustment has been estimated at 6.5 months [14], and given the survival difference of 15.3 months between groups in this study, it therefore appears unlikely that the survival difference could be explained solely by lead time bias.

In addition to survival, stage migration is another surrogate end point suggesting effectiveness of this screening program. This term describes the ability of a screening programme to find an earlier stage, curable disease. In this study, there were more patients within the screening programme who had an early-stage disease and had curative treatments, contributing to increased survival. Stage migration is an important goal of any effective screening program; as without diagnosis at an earlier curable stage, programs are unable to positively impact on patient survival. In this study, the screening programme did not translate into survival benefit during multivariate analysis.

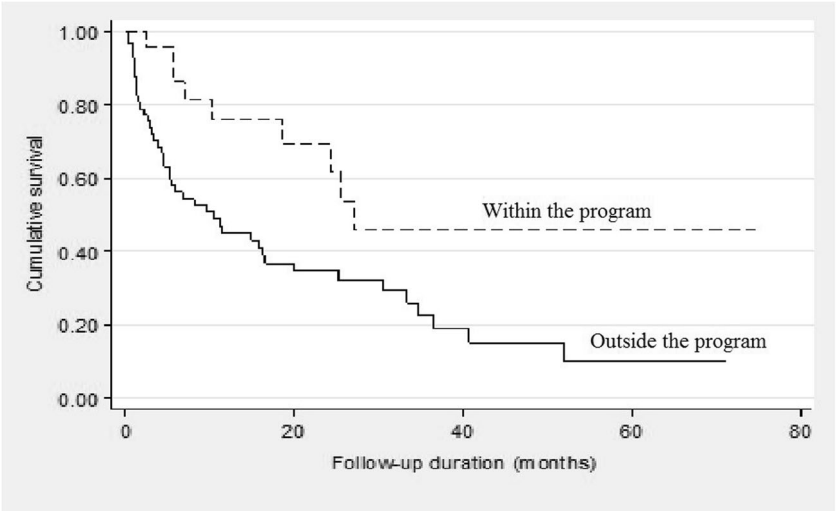

Fig. 2 Overall survival of HCC diagnosed within and outside the programme after propensity score adjustment

Table 4 Predictors of mortality after additional propensity score adjustment

Variables	HR (95% CI)	*p* value
Screening program	0.63 (0.28–1.42)	0.30
AFP > 400	2.02 (1.26–3.24)	0.003*
MELD score (per 10 units)	1.07 (0.61–1.89)	0.80
Late BCLC stage	1.45 (1.02–2.07)	0.04*

AFP, alpha feto protein; *BCLC*, Barcelona clinic liver cancer stage; *MELD*, model for end-stage liver disease

*Statistically significant

One explanation for the loss of statistical significance despite the unadjusted association and the sizeable estimated effect is the low event rate within those screened with < 20% of the overall HCCs diagnosed within the screening program.

In addition to the novelty of this study, another major strength was the detailed epidemiological and clinical data available for HCC patients across an entire health region. Such granular data would not be available from larger registry-based studies and enabled us to adjust the survival benefit seen with the screening programme for various confounding factors.

There are also several limitations to this study. Firstly, HCC treatments continually evolved during the study period, particularly the percutaneous ablation therapies, and this may have influenced survival. Secondly, only a small proportion (< 20%) of HCC patients in the overall cohort were diagnosed within the program. This small sample size could explain why the survival benefit in this group did not reach statistical significance on multivariate analysis, even though there was a trend. The finding that the majority of HCC diagnosed within the health region during this period was at clinical presentation and occurred outside a screening programme remains a concern. This likely reflects the high number of asymptomatic, cirrhotic patients who remain undiagnosed and highlights the need for improved detection of high-risk patients and improved HCC screening uptake in the overall population.

In conclusion, this study showed that the implementation of high-quality programmatic HCC screening across a health care region was associated with improved overall survival of patients diagnosed with HCC within that program. The detection of smaller tumours at an earlier stage suggests that screening reduced the lead time to HCC diagnosis enabling more patients to have curative therapies. High AFP, late BCLC stage and non-curative treatment intent were independent predictors of mortality.

Compliance with Ethical Standards

The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).

Conflict of Interest The authors declare that they have no conflict of interest.

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