SURVEILLANCE FACTORS CHANGE OUTCOMES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA DUE TO CHRONIC HEPATITIS C VIRUS INFECTION IN NEW ZEALAND

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HCC

- Second leading and fastest rising cause of cancer-related death in the world
- Most common cause of death in patients cirrhosis
- HCV infection
  - *leading cause of end-stage liver disease*, HCC and liver-related death in the western world

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med. 2003;139(10):817-23.

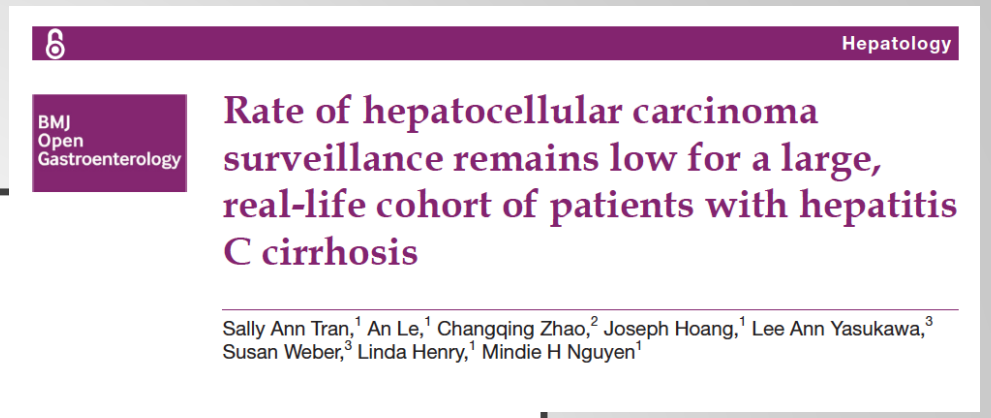
Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

SURVEILLANCE

- 6 monthly Ultrasound Scan (USS) and Alpha-feta protein (AFP)
- Higher rates of early tumour detection, curative treatment receipt and overall survival

Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med. 2014;11(4):e1001624.

ADHERENCE



- Poor
  - 12% "routine HCC surveillance", with most receiving sporadic or none at all
  - 24% underwent HCC surveillance every 6 months
  - 44% had surveillance at least every 12 months.

Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, El-Serag HB. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med 2011;154:85-93.

Tran SA, Le A, Zhao C, Hoang J, Yasukawa LA, Weber S, Henry L, et al. Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis. BMJ Open Gastroenterol 2018;5:e000192.

WHY

- Provider recommendations
- Socioeconomic
- Cultural
- Patient attitudes
- Knowledge
- Practical barriers
  - scheduling, cost and transportation

Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila). 2012;5(9):1124-30.

Singal AG, Li X, Tiro J, Kandunoori P, Adams-Huet B, Nehra MS, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. The American journal of medicine. 2015;128(1):90 e1-7.

Farvardin S, Patel J, Khambaty M, Yerokun OA, Mok H, Tiro JA, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. Hepatology. 2017;65(3):875-84.

ASSOCIATIONS

Lower likelihood of receiving routine HCC surveillance in HCV patients:

- Patient co-morbidity
- Advanced liver disease
- Alcohol intake

Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med. 2011;154(2):85-93.

NZ PROBLEM

- 54,000 living with past or present HCV infection
  - Less than 50% aware of their HCV status (Australia, 25% of 230,000)
- NZLTU: 1998 to 2016: Of patients with HCC (1683)
  - Hepatitis C 26%
  - Hepatitis B 43%
  - ALD11%, NASH 9%
- HBV liver disease decreased from 56% to 32%,
- HCV had increased from 17% to 32%
- Despite DAA's: Peak prevalence of cirrhosis and HCC will occur after 2030

Gane E, Stedman C, Brunton C, Radke S, Henderson C, Estes C, et al. Impact of improved treatment on disease burden of chronic hepatitis C in New Zealand. The New Zealand medical journal. 2014;127(1407):61-74.

Hassan I, Gane E, Prasad D, Bartlett A, Lithgow O. Improving survival in patients with hepatocellular carcinoma related to chronic hepatitis C and B but not in those related to non-alcoholic steatohepatitis or alcoholic liver disease: A 20 year experience from a national programme. Journal of Hepatology. 2018;68(Supplement 1):S424

- Few studies exist that examine the actual **method** of detection of HCC
  - Difficult to get data

STUDY

- NZLTU database
- Primary aim: method of HCC detection
- Impact on subsequent clinical outcomes, in particular treatment and survival.
- 31 January 2001 to 31 May 2018

- Patient demographics, date of definitive HCC diagnosis, treatment modality and date of death (if applicable) from computerized clinical database
- Physical patient records were retrieved
  - GP/secondary care letters

METHOD OF DETECTION: CATEGORIES

- Group 1: Known HCV and cirrhosis diagnosis and receiving optimised HCC surveillance (defined as receiving liver imaging with US, CT or MRI plus serum AFP measurements every 6 months)
- Group 2: Known HCV and cirrhosis diagnosis but nonadherent with scheduled HCC surveillance
- Group 3: Known HCV and cirrhosis diagnosis but not offered HCC surveillance (defined as not having had liver imaging or AFP for 2 or more years)
- Group 4: Known HCV and cirrhosis diagnosis and receiving suboptimal HCC surveillance (imaging less than 6 monthly or isolated AFP monitoring)
- Group 5: Known HCV diagnosis but not known to be cirrhotic
- Group 6: No previous diagnosis of HCV infection (or diagnosed within 2 years of HCC detection).

RESULTS

- 529 patients
- 18 were excluded due to a an inability to obtain complete data
  - 2 patients where the notes had been destroyed.
  - 1 patient with hepatic masses thought to be HCC but died before further characterisation could be undertaken.

- 83% of patients male.
- Mean age at diagnosis was 59.2 years.
- 64% were NZ European, 22% Maori, 8% Asian, 2% Pacific and 4% other.

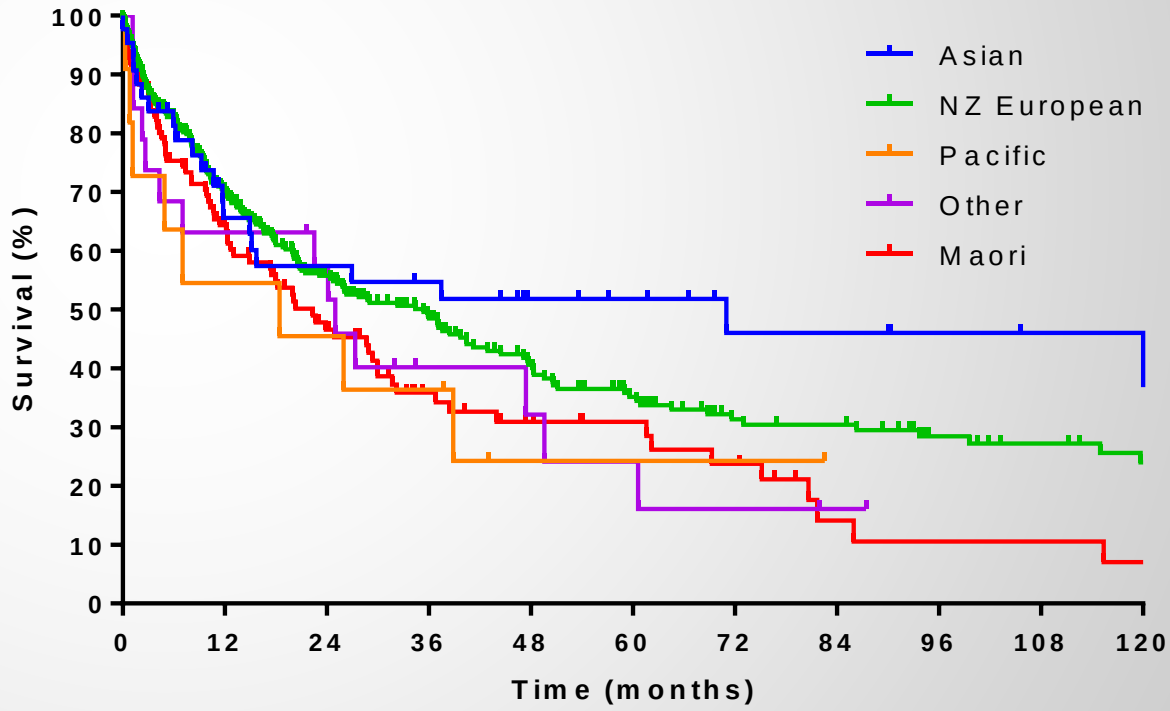
- Mean survival was 64 months (*5.3 years*) (95% CI 55.8,73.6).

GENDER

- Males mean survival 67.8 months, (95% CI 58.0, 77.6) vs 45.0 months females (95% CI, 31.0, 58.8) (p=0.04).

ETHNICITY

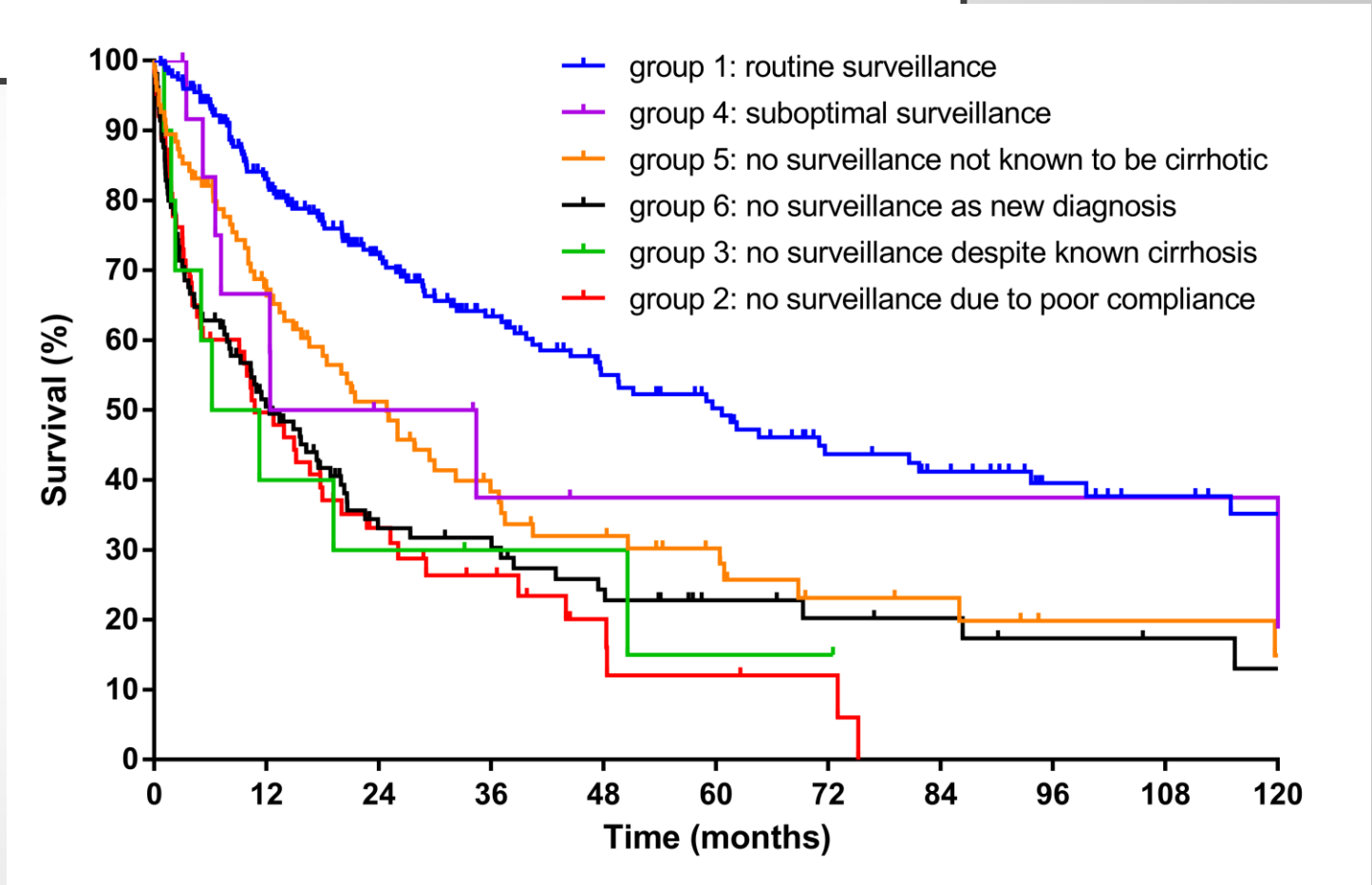
- 67.7 (95% CI 56.4, 79.1) NZ Euro
- 38.6 (95% CI, 29.4, 47.7) Maori
- 90.4 (95% CI 61.4, 119.5) Asian
- 30.1 (95% CI 10.6, 49.5) Pacific
- 33.5 (95% CI 19.1, 47.8) Other



Group Method HCC Detected	1 n=224 (44%)	2 n=63 (12.4%)	3 n=10 (2%)	4 n=13 (2.5%)	5 n=95 (19%)	6 n=105 (21%)	P value
Age at diagnosis (mean)	58.6	59.2	63.9	59.3	60.7	58.4	0.30
Gender							0.829
Male, n (%)	182 (81.3)	51 (81.0)	9 (90.0)	12 (92.3)	80 (84.2)	89 (15.2)	
Female, n (%)	42 (18.8)	12 19.0)	1 (10.0)	1 (7.7)	15 (15.8)	16 (84.8)	
Ethnicity, n (%)							0.741
NZ European	151(67.4)	42 (66.7)	6 (60)	10 (76.9)	60 (63.2)	57 (54.3)	
Maori	42 (18.8)	15 (23.8)	2 (20)	2 (15.4)	23 (24.2)	27 (25.7)	
Asian	16 (7.1)	3 (4.8)	2 (20)	1 (7.7)	9 (9.5)	12 (11.4)	
Pacific	4 (1.8)	2 (3.2)	0 (0)	0 (0)	2 (2.1)	3 (2.9)	
Other	11 (4.9)	1 (1.6)	0 (0)	0 (0)	1 (1.1)	6 (5.7)	

- 224 (44%) of cases were diagnosed up via routine surveillance (Group 1)
- 12.4% were diagnosed without routine surveillance due to documented poor medical compliance, non-attendance or being lost to follow-up (Group 2).
- 2% were diagnosed without routine surveillance despite having known cirrhosis (Group 3).
- 2.5% were diagnosed after apparent intermittent or suboptimal surveillance (Group 4).
- 19% were diagnosed after not receiving surveillance as they were not known to be cirrhotic (Group 5)
- 21% of patients had newly diagnosed HCV either at the time of HCC diagnosis or within 2 years (Group 6)

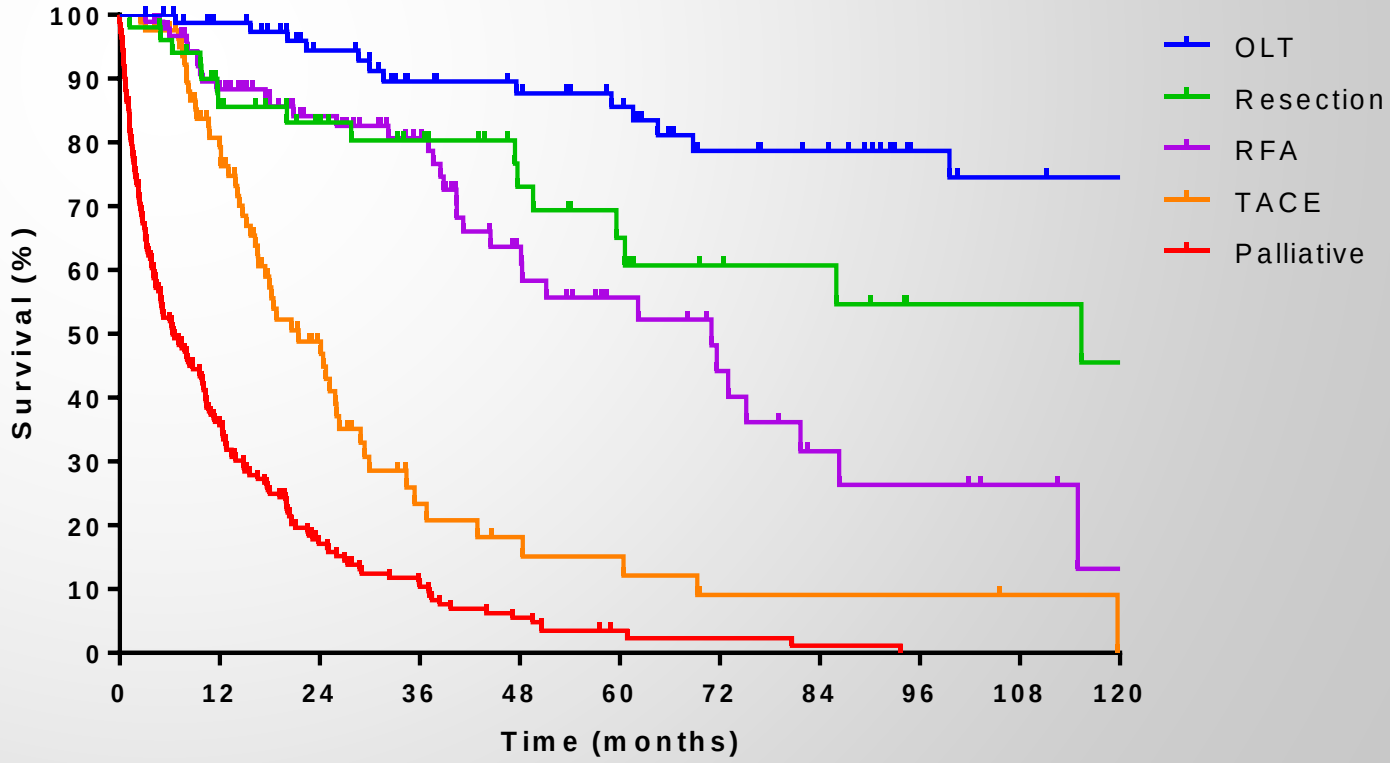
Group Method HCC Detected	1 n=224 (44%)	2 n=63 (12.4%)	3 n=10 (2%)	4 n=13 (2.5%)	5 n=95 (19%)	6 n=105 (21%)	P value
Treatment							<0.01
Transplant	59 (26.3)	1 (1.6)	1 (10)	2 (15.4)	8 (8.4)	11 (10.5)	
Resection	22 (9.8)	2 (3.2)	1 (10.0)	2 (15.4)	18 (18.9)	6 (5.7)	
RFA	66 (29.9)	11 (17.5)	0 (0)	2 (15.4)	10 (10.5)	6 (5.7)	
TACE	41 (18.3)	11 (17.5)	0 (0)	2 (15.4)	15 (15.8)	14 (13.3)	
Palliative	36 (16.1)	38 (60.3)	8 (80.0)	5 (38.5)	44 (46.3)	68 (64.8)	
Survival mean, months (95% CI)	91.5 (76.4-106.6)	22.0 (15.3-28.7)	23.1 (6.6-39.7)	59.1 (23.0-95.3)	53.0 (36.5-69.4)	64.6 (55.8-73.4)	<0.0001



SURVIVAL

- Liver transplant: 157 months (95% CI 135.7, 178.2) – 13 years
- Resection: 106.7 (95% CI 79.1, 134.3),
- RFA: 70.2 (95% CI 56.0, 84.4)
- TACE: 32.2 (95% CI 23.2, 41.2)
- Palliative 13.4 (95% CI 10.8, 16.0)

(p<0.0001)



PREDICTORS OF SURVIVAL

	Univariate Analysis		Multivariate Analysis	
Variable of interest	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.01(1.00-1.03)	0.12	1.00 (0.99-1.02)	0.59
Male	0.73(0.55-0.98)	0.04	0.52(0.38-0.70)	<0.001
Maori	1.36(1.04-1.76)	0.03	1.3 (1.10-1.75)	0.04
Asian	0.67(0.43-1.04)	0.08	0.72(045-1.16)	0.17
Surveillance	0.41(0.32-0.53)	<0.001	0.70(0.54-0.91)	0.01
Palliative	7.04(5.47-9.06)	<0.001	6.63(5.06-8.70)	<0.001

BETTER

- Male
- Asian
- Regular surveillance

WORSE

- Maori
- Palliative

PREDICTORS OF SURVEILLANCE

	Univariate Analysis		Multivariate Analysis	
Variable of interest	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	0.99 (.97-1.29)	0.30	0.99(0.96-1.02)	0.11
Male	0.81 (0.51-0.98)	0.37	0.74(0.44-1.26)	0.27
Maori	0.73 (0.47-1.11)	0.15	0.64(0.40-1.04)	0.07
Asian	0.74 (0.39-1.40)	0.36	0.47(0.23-1.00)	0.05
Palliative	0.14 (0.09-0.22)	<0.001	0.14(0.09-0.22)	<0.001

LACK OF SURVEILLANCE:

- Asian
- Palliative

DISCUSSION

- Adherence to surveillance is poor
- Late diagnosis, low rates of curative therapy and poor outcomes

- Compelling survival evidence in absence of RCT evidence

- NZ Setting:
- Under-diagnosis of HCV infection
- Lack of diagnosis of cirrhosis in patients known to have HCV (staging)

WHERE TO MAKE THE GAINS?

- Patients without surveillance due to non-attendance, non-adherence or lost to follow-up: 12.4%
  - poorest survival at just 22 months.
  - Stress importance of attempting to follow-up this transient population (Liver CNS?)
- 2% diagnosed without routine surveillance despite having known cirrhosis
  - Reassuring that clinicians seem to be aware to image high risk group.
  - Stresses importance and significance of a label of cirrhosis.

ETHNIC DISPARITY

- Māori ethnicity associated with worsened overall survival
- Despite poor surveillance uptake, Asian patients appear to have the longest survival
  - ?better access to health care

NON-CURATIVE

- 278 offered non-curative treatment
- 76 patients (27.3%) were having regular surveillance
  - Missed/aggressive biology?
- Survival 19.0 (15.9-22.2) months compared to 7.33 (5.92-8.74) months if newly diagnosed

LIMITATIONS

- Reliance on chart review/accuracy of clinical record
- -Possible missed cases if not sent for review to central centre.
  - ? Those brought straight for palliative care

- Non-inclusion of patients with likely cirrhosis on clinical grounds
- Lack of other important variables such as tumour size, stage, baseline liver disease, enrolment in primary or secondary care.

SUMMARY

- Outcome following diagnosis of HCC secondary to chronic HCV is determined by early detection

- Under-diagnosis of HCV infection and lack of diagnosis of cirrhosis in patients known to have HCV infection are the largest current barriers in NZ