Is non-contrast-enhanced magnetic resonance imaging cost-effective for screening of hepatocellular carcinoma?

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Abstract

Introduction: Ultrasonography (US) is the current standard of care for imaging surveillance in patients at risk of hepatocellular carcinoma (HCC). Magnetic resonance imaging (MRI) has been explored as an alternative, given the higher sensitivity of MRI, although this comes at a higher cost. We performed a cost-effective analysis comparing US and dual-sequence non-contrast-enhanced MRI (NCEMRI) for HCC surveillance in the local setting.

Methods: Cost-effectiveness analysis of no surveillance, US surveillance and NCEMRI surveillance was performed using Markov modelling and microsimulation. At-risk patient cohort was simulated and followed up for 40 years to estimate the patients’ disease status, direct medical costs and effectiveness. Quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio were calculated.

Results: Exactly 482,000 patients with an average age of 40 years were simulated and followed up for 40 years. The average total costs and QALYs for the three scenarios — no surveillance, US surveillance and NCEMRI surveillance — were SGD 1,193/7.460 QALYs, SGD 8,099/11.195 QALYs and SGD 9,720/11.366 QALYs, respectively.

Conclusion: Despite NCEMRI having a superior diagnostic accuracy, it is a less cost-effective strategy than US for HCC surveillance in the general at-risk population. Future local cost-effectiveness analyses should include stratifying surveillance methods with a variety of imaging techniques (US, NCEMRI, contrast-enhanced MRI) based on patients’ risk profiles.

Keywords: Cost-effectiveness analysis, hepatocellular carcinoma, magnetic resonance imaging, ultrasound surveillance

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fifth most common cancer among males in Singapore.¹⁻² This can in part be attributed to the high prevalence of chronic hepatitis B and C in the Asia-Pacific region, where chronic viral hepatitis-induced liver disease is a major risk factor for HCC.²⁻³ Surveillance for HCC is, therefore, the standard of care for this group of patients, and imaging plays a central role. Conventionally, surveillance for HCC is performed with ultrasonography (US). Various international guidelines, including the American Association for the Study of Liver Diseases, European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver, recommend six-monthly US with or without alpha-fetoprotein, as imaging surveillance of HCC has been shown to reduce mortality.³⁻⁴

Ultrasonography of the liver is generally cheap, does not involve ionising radiation and is, therefore, suitable for mass population surveillance. However, it is highly dependent on operator technique and patient factors. Lesions near the diaphragm are also easily missed due to tissue depth and respiratory motion. Studies have shown that US has a low sensitivity for detection of HCC, ranging from 30% to 70%.

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Potential alternatives to US with higher accuracy for detection of HCC include contrast-enhanced computed tomography (CECT)\(^\text{[4–7]}\) and contrast-enhanced magnetic resonance imaging (CEMRI)\(^\text{[9,10]}\). However, the risks associated with repeated radiation exposure with CECT as well as the lower accessibility and higher cost of CEMRI make these imaging modalities less attractive for surveillance. Furthermore, current standard CEMRI liver protocols involve multiple sequences, which can be relatively time-consuming to scan and subsequently report. Hence, recent studies have proposed cheaper abbreviated magnetic resonance imaging (MRI) protocols in HCC surveillance.\(^\text{[11–15]}\)

Non-contrast-enhanced MRI (NCEMRI) has been shown to perform reasonably well for HCC diagnosis,\(^\text{[11,12]}\) with at least one study demonstrating no significant difference in sensitivity and specificity between CEMRI and NCEMRI for detecting hepatic malignancies and distinguishing them from benign entities.\(^\text{[15]}\) The absence of intravenous contrast in NCEMRI reduces cost while at the same time allays concerns over gadolinium toxicity. A large prospective trial that provides a head-to-head comparison between NCEMRI and US is underway in South Korea (MIRACLE-HCC).\(^\text{[16]}\) In terms of sensitivity, NCEMRI has been shown to be superior to US for HCC detection (range 76%–95%).\(^\text{[11,12,15,17]}\) In addition, NCEMRI will be significantly cheaper than CEMRI. Yet, to our knowledge, there is no dedicated study on cost-effectiveness of routine use of NCEMRI for HCC surveillance. Therefore, we performed a cost-effective analysis comparing US (which is the standard of care) and NCEMRI for surveillance of HCC in at-risk patients.

**METHODS**

This cost-effectiveness analysis was performed using Markov modelling and microsimulation. A disease transition model with seven states has been developed to mimic stepwise disease progression, from at-risk to cancer stage 0, A, B, C, D, and death, based on the Barcelona Clinical Liver Cancer (BCLC) staging system for staging of HCC.\(^\text{[18]}\) The five cancer stages are stage 0 and stages A–D [Figure 1]. There is a precancerous stage, and progression from precancerous stage to early-stage HCC (stage 0/A) has been reported to be about 6%–8% annually.\(^\text{[19,20]}\)

At-risk patient cohort was simulated, and the patients in the cohort were followed up for 40 years to estimate their disease status as well as their direct medical costs and effectiveness following three surveillance approaches: no surveillance, US surveillance and dual-sequence NCEMRI surveillance using T2-weighted and diffusion-weighted imaging. A total of 482,000 patients with an average age of 40 years were simulated. The cost analysis was conducted from the patient’s perspective. Although the majority of local patients were eligible for government subsidy, the total bill size without government subsidy was used for cost calculation to reflect overall burden to the healthcare system. Discounting is a technique commonly used in cost-effectiveness analysis to make ‘fair’ comparisons of programmes, whose costs and outcomes occur at different times, given the time value of money, and most guidelines recommend equal discounting costs and effects at 3%.\(^\text{[21]}\) Hence, for this study, both cost and effectiveness were discounted at an annual rate of 3%. Direct medical costs for surveillance, treatment and follow-up care management were collected for evaluation. The incremental cost-effectiveness ratio (ICER) was calculated and applied to identify the most cost-effective surveillance approach for HCC among at-risk patients in the Singapore context. The Markov transition cycle, which is defined as equal increments of time during which the patient may make a transition from one disease state to another,\(^\text{[22]}\) is taken to be 6 months. Cost-effective analysis threshold was taken as per capita gross domestic product (GDP) as recommended by the

![Figure 1: Disease progression of hepatocellular carcinoma through seven stages.](image-url)
World Health Organization, as this allows a patient to avoid disability-adjusted life years (DALYs) at a low cost.\(^{[23]}\)

The following assumptions were made:

1. At-risk patients undergo first-tier scan (either dual-sequence NCEMRI or US), and the outcome of the surveillance test is either positive or negative; only positive patients will then be scanned using full CEMRI study for final diagnosis of HCC.
2. Disease either progresses in a stepwise fashion from one stage to the next or remains at the same stage.
3. Cancer stages 0, A and B can be cured or reversed to a previous stage.
4. Cancer stages C and D cannot be cured or reversed to a previous stage.
5. Once diagnosed with HCC, patients follow the same treatment protocol; average treatment effects and costs apply to all patients at the same stage.
6. False-positive patients will be correctly diagnosed at the next MRI scan.
7. No treatment for false-negative patients; they are likely to be picked up in the follow-up scan in 6 months.
8. Death is all-cause death.
9. All stages can lead to death with different mortality rates.
10. If no surveillance is done, patients are most likely to be diagnosed at stages B, C or D.

Cost data were collected from local healthcare providers and Singapore’s Ministry of Health (MOH), while other model parameters like disease transition probabilities, quality of life values, mortality rates, treatment effects, etc., at various disease stages were derived via literature search.

Sensitivity and specificity of US and NCEMRI for surveillance of patients at risk of HCC were pooled from the literature. A literature search was performed using the PubMed database. Pooled point sensitivity and specificity of US were estimated to be 55.6% and 97.3%, respectively.\(^{[48]}\) This is comparable to a recent meta-analysis that reported the sensitivity and specificity of US to be about 59% and 93%, respectively, for detection of HCC in both surveillance and non-surveillance settings.\(^{[24]}\) Pooled point sensitivity and specificity of NCEMRI were estimated to be 90% and 91.5%, respectively, based on proof-of-concept studies.\(^{[11,12,15]}\) This is similar to a recent meta-analysis that reported pooled sensitivity and specificity of 86% and 94%, respectively.\(^{[25]}\)

There were 2,346 cases locally from 2011 to 2015,\(^{[56]}\) giving an average of 469 cases annually in Singapore. The major risk factors for HCC are chronic hepatitis B infection, non-alcoholic steatohepatitis (NASH) and cirrhosis. The estimated prevalence of chronic hepatitis B locally is about 180,000 and the estimated prevalence of cirrhosis locally is about 45,000, of which the top causes are chronic hepatitis B (63.3%), alcohol-related cirrhosis (11.2%), cryptogenic cirrhosis (9%) and chronic hepatitis C (6.9%).\(^{[27]}\) Based on this data, the prevalence of non-hepatitis B-related cirrhosis is estimated at 12,200. Non-alcoholic steatohepatitis lies on a spectrum of non-alcoholic fatty liver disease (NAFLD) and is increasingly being recognised as an important aetiology of HCC and liver cirrhosis, with the local prevalence of NAFLD reported to be around 29%.\(^{[28]}\) Recent evidence suggests that majority of cases of cryptogenic cirrhosis are likely secondary to NASH.\(^{[29]}\) For this analysis, NASH-related cirrhosis is, therefore, categorised as a subtype of cryptogenic cirrhosis. Similar to chronic hepatitis B, it is also known that HCC can develop in NASH without evidence of cirrhosis.\(^{[30]}\) The prevalence of NASH and NASH-related cirrhosis is estimated based on the following probabilities: 20% of patients with NAFLD progress to NASH, of which another 20% progress to cirrhosis.\(^{[31,32]}\) The prevalence of NASH without cirrhosis is, therefore, estimated at about 290,000. The estimated total at-risk population comprising chronic hepatitis B, NASH without cirrhosis and non-hepatitis B-related cirrhosis is, therefore, around 482,000 locally.

A pooled estimate of 83.4% of surveillance US were normal,\(^{[5–9]}\) while about 4.5% were BCLC stage 0/A cancers, 5.9% were stage B cancer, 3.3% were stage C cancer and 2.3% were stage D cancer.\(^{[33]}\) No corresponding data was available for NCEMRI surveillance.

A local study showed that 0.8% of patients with chronic hepatitis B, with or without cirrhosis, develop HCC annually.\(^{[34]}\) Based on available literature, about 1.6% of patients with alcoholic cirrhosis, 4% of patients with chronic hepatitis C cirrhosis and 2.6% of patients with NASH (with or without cirrhosis) develop HCC annually.\(^{[35,36]}\) This gives an estimated pooled transition probability per annum of about 1.1%. Annual mortality for liver cirrhosis is estimated at 2.7%.\(^{[37]}\) Patients with chronic hepatitis B infection without cirrhosis are generally asymptomatic, and annual mortality is assumed to be baseline for the general population at an estimated 0.5% per year.\(^{[38]}\) This gives an estimated pooled base mortality for at-risk patients of about 1.3% annually.

Based on local surveillance programmes, at-risk patients routinely undergo six-monthly consultations and laboratory tests, as well as six-monthly imaging surveillance using hepatobiliary US. Based on a tumour doubling time of 117–195 days,\(^{[39]}\) 40% of HCCs progress from early/very early stage (stage 0/A) to advanced stage (C/D) without treatment. The annual percentage increase in mortality is estimated to be 2%.\(^{[40]}\) Based on BCLC stage, the annual mortality without treatment was estimated as follows: 36% for stage 0/A, 63% for stage B, 87% for stage C and 93% for stage D.\(^{[41]}\)

Treatment for each stage is based on BCLC recommendations. For stage 0/A, treatment options include liver resection and local percutaneous ablation therapy for curative treatment. For stage B, treatment options include transhepatic arterial chemoembolisation (TACE). For stage C, treatment options include chemotherapy (sorafenib) or transhepatic arterial radiotherapy with Y-90. For stage D, there is no specific
Impact of treatment on mortality depends on the type of treatment and cancer stage. Local percutaneous ablation therapy for stage 0/A HCC has been shown to reduce mortality from 36% to 17%, while surgical resection for stage 0/A reduces mortality from 36% to 23% within the first year of treatment.[42,43] While TACE improves long-term survival in advanced HCC, it appears to have little effect on annual mortality of stage B HCC within the first year of treatment, reducing the annual mortality from 63% to 61%.[44] Chemotherapy with sorafenib for stage C HCC shows improvement in mortality within the first year from 87% to 68%.[45] Symptomatic treatment for stage D HCC does not confer improvement in mortality. Based on available literature, for purposes of computational analysis, it can be assumed that treatment for early-stage disease (stages 0/A) allows a reduction in annual mortality by up to 50% within the first year of treatment, while treatment of intermediate and late-stage disease (stage B, C, D) does not result in significant reduction in mortality.

Routine surveillance of at-risk patients is assumed to be performed six monthly. Direct medical costs for routine surveillance of at-risk patients and direct medical costs of treatment are summarised in Tables 1 and 2, respectively. Costs were obtained from a local institution, Tan Tock Seng Hospital, or estimated from the MOH Guidelines on Fees. Direct non-medical costs such as transportation, as well as indirect costs such as caregiver expenditure and absenteeism are estimated. For purposes of cost calculation, curative treatment (surgery or percutaneous local ablation therapy) is assumed to be a one-off treatment per year, an average of one course of treatment per year is assumed for TACE and Y-90 radiotherapy, and chemotherapy cost is based on monthly cost.

Patients on treatment are assumed to be followed up six monthly. Direct medical costs for follow-up of patients who have undergone treatment are as follows: full MRI study with contrast (SGD 1,200), laboratory tests (SGD 50) and clinic consultation (SGD 110). Duration of follow-up is assumed to be lifelong.

RESULTS

A simulated cohort of 482,000 at-risk patients with an average age of 40 years was analysed. After 40 years, all at-risk patients will die if there is no surveillance. For at-risk patients who underwent surveillance by US and NCEMRI, the percentage of patients still alive after 40 years would be around 9% and 10%, respectively. The average total costs and quality-adjusted life years (QALYs) for the three scenarios are as follows: no surveillance, SGD 4,675/7.483 QALYs; surveillance with US, SGD 23,803/11.242 QALYs; and surveillance with NCEMRI, SGD 177,876/11.426 QALYs [Figure 2].

The cost, effectiveness and ICER of the three surveillance approaches are presented in Table 3. Overall, the incremental QALYs of US and NCEMRI surveillance over no surveillance were SGD 5,088 and SGD 43,924 per QALY gained, respectively. The incremental QALY of NCEMRI surveillance over US surveillance is SGD 837,353 per

Table 1. Estimated direct medical cost of surveillance for patients at risk of hepatocellular carcinoma

| Component                  | Cost (SGD) |
|----------------------------|------------|
| Imaging surveillance       |            |
| Ultrasoundography          | 140        |
| NCEMRI                     | 660 a      |
| Laboratory tests           | 50         |
| Clinic consultation        | 110        |

aEstimated for dual-sequence NCEMRI using T2 and diffusion-weighted imaging. NCEMRI: non-contrast-enhanced magnetic resonance imaging

Table 2. Estimated cost of HCC treatment at each cancer stage.

| BCLC stage | Treatment                  | Cost (SGD) |
|------------|----------------------------|------------|
| A          | Liver resection            | 14,000     |
|            | Percutaneous local ablation| 4,000      |
| B          | TACE                       | 4,300      |
| C          | Chemotherapy               | 9,000 /mth |
| D          | Y-90 radiotherapy          | 10,000     |
|            | Supportive care            | No specific cost |

*Based on a combination of Barcelona Clinical Liver Cancer and local treatment guidelines. HCC: hepatocellular carcinoma, TACE: transhepatic arterial chemoembolisation

Table 3. Comparison of costs, effectiveness and ICER of the three surveillance approaches.

| Approach     | Total cost | Total QALYs | Incremental cost (SGD) | Incremental QALYs | ICER |
|--------------|------------|-------------|------------------------|--------------------|------|
| No surveillance | 4,675 (263) | 7.483 (0.044) | 19,128 (299) | 3,759 (0.052) | 5,088 |
| US surveillance | 23,803 (367) | 11.242 (0.074) | 173,201 (1135) | 3,943 (0.051) | 43,924 |
| MRI surveillance | 177,876 (1111) | 11.426 (0.074) | 154,073 | 0.184 | 837,353 |

ICER: incremental cost-effectiveness ratio, MRI: magnetic resonance imaging, QALY: quality-adjusted life year, SE: standard error, US: ultrasonography
DISCUSSION

Diagnostic superiority of MRI, even without the use of gadolinium chelate contrast agents, over US is well established. However, cost is always cited as a reason against population-based surveillance of at-risk patients in HCC using MRI. Our study confirms that NCEMRI is indeed a less cost-effective surveillance strategy compared to US, with an overall ICER of over SGD 800,000 per QALY gained, which is much higher than Singapore’s GDP. One explanation could be the relatively low transition probability of 1.1% used in our study. This would result in a higher number of at-risk patients undergoing surveillance to detect an early-stage HCC, reducing the cost-effectiveness of NCEMRI. This is because the simulation in our study included all patients at risk of HCC, including those with chronic hepatitis B without cirrhosis. This low transition probability could also be attributed to improving control over the natural disease progression of chronic hepatitis B, given that chronic hepatitis B remains the major contributing risk factor for HCC in this region. Other studies on cost-effective analysis simulated cohorts with liver cirrhosis, and in regions where other risk factors such as chronic hepatitis C or alcoholic cirrhosis may contribute significantly to HCC, higher transition probabilities were applied, ranging from 1.5% to 5%. The higher transition probabilities applied in these studies will tend to lead to increased cost-effectiveness, as more cases of early HCC are picked up when the disease is still curable.

Although the majority of patients locally are eligible for government subsidy for medical treatment, in the context of population health screening and surveillance, the overall cost to the government, healthcare system and taxpayers has to be considered. Therefore, based on our analysis, NCEMRI, while superior to US for detection of HCC, should currently not be recommended as an alternative to US for HCC surveillance in the general at-risk population.

Kim et al. performed a similar analysis comparing CEMRI versus US for HCC surveillance and found CEMRI to be a cost-effective alternative. Our study showed a lower overall gain in QALY of 0.18 using NCEMRI instead of US, compared to 0.22 incremental QALY using CEMRI compared to US shown by Kim et al. Furthermore, the study by Kim et al. showed that CEMRI incurred USD 5,562 incremental cost and an estimated ICER of USD 25,202 per QALY gained when compared to US, which are considerably lower than the incremental cost of SGD 154,073 and an estimated ICER of SGD 837,353 per QALY gained using NCEMRI, as found in our study. The differences in cost-effectiveness are also very likely related to differences in cost of surveillance and HCC treatment in different geographical regions. In addition, that study analysed patients with cirrhosis, which can be considered a higher-risk subgroup. The reported transition probability of 3% could also have accounted for superior cost-effectiveness, compared to our cohort, which included patients with chronic hepatitis B and NASH without cirrhosis.

Other cost-effective analyses compared a variety of imaging surveillance strategies (US vs. MRI vs. CT) and surveillance intervals (annual vs. semi-annual). Andersson et al., on comparing six imaging surveillance strategies modelled within the USA, found an ICER exceeding USD 100,000 for MRI surveillance and deemed MRI least cost-effective compared to US or CT. This could be because in the study by Andersson et al., full multisequence CEMRI was performed, which increases the cost of the scan compared to CT or US. The findings are similar to that of our study, which showed that NCEMRI is not a cost-effective surveillance modality, even without intravenous contrast. Andersson et al. analysed a subgroup of patients with compensated cirrhosis, similar to Kim et al., but with a higher transition probability of 5%. A more recent study by Lima et al. also simulated a cohort of patients with cirrhosis within Canada. In contrast, despite a transition probability of 1.5%, which is close to that used in our study (1.1%), the study by Lima et al. found an ICER of about CAD 40,000 for abbreviated MRI surveillance.
and concluded that abbreviated MRI protocol could be cost effective in high-risk cirrhotic patients, where compliance to surveillance is not 100%.[47] Different findings from our study and previous analyses from the available literature suggest that there is no ‘one-size-fits-all’ imaging surveillance strategy and cost-effectiveness is dependent on factors such as demographics, varying epidemiology of HCC in different geographical regions, national healthcare policies and willingness to pay. Although our study does not demonstrate cost-effectiveness of NCEMRI as a surveillance tool in all patients at risk for HCC, our findings are in line with the current recommendation that US remains the modality of choice for HCC surveillance. It is possible that by further risk-stratifying patients within our local at-risk population, NCEMRI could potentially be cost-effective for a subgroup of patients at ‘super-high’ risk with higher incidence of HCC, such as those with advanced cirrhosis.

There are several limitations in our study. Owing to the need to generate a model for evaluation even with a lack of supporting published evidence, we assumed that false-positive patients and false-negative patients would be correctly diagnosed at subsequent visits. Furthermore, given the limited data available, we attributed deaths to all-cause deaths rather than cancer-specific deaths. However, we believe that this may be meaningful since the lifespans of HCC patients are often prolonged by locoregional therapies and surgeries within Asia. Also, for the purpose of analysis, we assumed that all patients with a positive surveillance test would undergo CEMRI to confirm the diagnosis of HCC in our study. In practice, such patients may undergo CECT or even contrast-enhanced US instead, which will affect cost-effectiveness.

For this study, we did not take into account the availability of MRI scanners as a resource because MRI costs typically factor in the depreciation of MRI scanners. Furthermore, the ‘cost’ of surveillance (such as costs of scans, clinic visits and treatment costs) utilised in our studies reflected the price paid out by patients and/or government and may not take into account the actual expense incurred, such as scan time and manpower costs. We believe that this better reflects the true cost-effectiveness of the procedure. The calculation of costs incurred by patients at risk and at different cancer stages was based only on local institutional or MOH guidelines, and we recognise that this may vary between institutions. However, the published costs from individual institutions were not readily accessible.

Furthermore, although liver transplant is an established treatment option for BCLC stage A HCC, it was not included in our analysis, as liver transplant is an uncommon treatment option locally due to organ shortage.[48] This omission could potentially have influenced the cost-effectiveness of NCEMRI due to the relatively high cost of liver transplant. Also, while some studies evaluated the cost-effectiveness of multiphasic CT for HCC surveillance,[46,47] we omitted a comparison against CECT, which, in our opinion, is not acceptable for HCC surveillance imaging due to radiation exposure and the need for potentially nephrotoxic iodinated contrast. Lastly, model parameters, such as disease transition probabilities, quality of life values, mortality rates as well as treatment effects at various disease states, were derived from a mix of local and international data, resulting in a very heterogeneous data set. This could not be avoided due to lack of local data or evidence for certain parameters.

In conclusion, despite NCEMRI having a superior diagnostic accuracy, it is a less cost-effective strategy than US for HCC surveillance in the general at-risk population, from an overall healthcare perspective. Future local cost-effectiveness analyses should include stratifying surveillance methods with a variety of imaging techniques (US, NCEMRI, CEMRI) based on patients’ risk profiles. This would enhance our understanding of the cost-effectiveness and impact on the overall outcome of patients using various imaging tools for HCC surveillance.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Ministry of Health, Singapore. Disease burden: 2017. Available from: https://www.moh.gov.sg/resources-statistics/singapore-health-facts/disease-burden. [Last accessed on 2020 May 12].
2. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut Liver 2016;10:332-9.
3. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-22.
4. Miller WJ, Federle MP, Campbell WL. Diagnosis and staging of hepatocellular carcinoma: Comparison of CT and sonography in 36 liver transplantation patients. AJR Am J Roentgenol 1991;157:303-6.
5. Dodd GD 3rd, Miller WJ, Baron RL, Skolnick ML, Campbell WL. Detection of malignant tumors in end-stage cirrhotic livers: Efficacy of sonography as a screening technique. AJR Am J Roentgenol 1992;159:727-33.
6. Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: Correlation of pretransplantation sonography and liver explant pathology in 200 patients. AJR Am J Roentgenol 2002;179:75-80.
7. Shapiro RS, Katz R, Mendelson DS, Halton KP, Schwartz ME, Miller CM. Detection of hepatocellular carcinoma in cirrhotic patients: Sensitivity of CT and ultrasonography. J Ultrasound Med 1996;15:497-504.
8. Libbrecht L, Bielen D, Verslype C, Vanbekevoort D, Pirenne J, Nevens F, et al. Focal lesions in cirrhotic explant livers: Pathological evaluation and accuracy of pretransplantation imaging examinations. Liver Transpl 2002;8:749-61.
9. Kim HL, An J, Park JA, Park SH, Lim YS, Lee EK. Magnetic resonance imaging is cost-effective for hepatocellular carcinoma surveillance in high-risk patients with cirrhosis. Hepatology 2019;69:1599-13.
10. Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of
hepatocellular carcinoma. JAMA Oncol 2017;3:456-63.

11. Han S, Choi JI, Park MY, Choi MH, Rha SE, Lee YJ. The diagnostic performance of MRI without intravenous contrast for detecting hepatocellular carcinoma: A case-controlled feasibility study. Korean J Radiol 2018;19:568-77.

12. Min JH, Kim YK, Choi SY, Kang TW, Jeong WK, Kim K, et al. Detection of recurrent hepatocellular carcinoma after surgical resection: Non-contrast MR imaging with diffusion-weighted imaging versus gadoxetic acid-enhanced MR imaging. Br J Radiol 2018;91:20180177.

13. Besa C, Lewis S, Pandharipande PV, Chhatwal J, Kamath A, Cooper N, et al. Hepatocellular carcinoma detection: Diagnostic performance of a simulated abbreviated MRI protocol combining diffusion-weighted and T1-weighted imaging at the delayed phase post gadoxetic acid. Abdom Radiol (NY) 2017;42:179-90.

14. Marks RM, Ryan A, Heba ER, Tang A, Wolfson TJ, Gamst AC, et al. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. AJR Am J Roentgenol 2015;204:527-35.

15. Kim YK, Kim YK, Park HJ, Park MJ, Lee WJ, Choi D. Noncontrast MRI with diffusion-weighted imaging as the sole imaging modality for detecting liver malignancy in patients with high risk of hepatocellular carcinoma. Magn Reson Imaging 2014;32:610-8.

16. An C, Kim DY, Choi JY, Han KH, Roh YH, Kim MJ. Noncontrast magnetic resonance imaging versus ultrasonography for hepatocellular carcinoma surveillance (MIRACLE-HCC): Study protocol for a prospective randomized trial. BMC Cancer 2018;18:915.

17. Park HJ, Jang HY, Kim SY, Lee SJ, Won HJ, Byun JH, et al. Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: Comparison with ultrasound. J Hepatol 2020;72:718-24.

18. Pons-F, Varela M, Lovet JM. Staging systems in hepatocellular carcinoma. HPB (Oxford) 2005;7:35-41.

19. Seki S, Sakaguchi H, Kitada T, Tamori A, Takeda T, Kawada N, et al. Outcomes of dysplastic nodules in human cirrhotic liver: A clinicopathological study. Clin Cancer Res 2000;6:3469-73.

20. Kobayashi M, Ikeda K, Hosaka T, Szakaki H, Someya T, Akuta N, et al. Dysplastic nodules frequently develop into hepatocellular carcinoma in patients with chronic viral hepatitis and cirrhosis. Cancer 2006;106:636-47.

21. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. Pharmacoeconomics 2018;36:745-58.

22. Sonnenberg FA, Beck JR. Markov models in medical decision making: A practical guide. Med Decis Making 1993;13:322-38.

23. Leech AA, Kim DD, Cohen JT, Neumann PJ. Use and misuse of cost-effectiveness analysis thresholds in low- and middle-income countries: Trends in cost-per-DALY studies. Value Health 2018;21:759-61.

24. Chou R, Cvekas C, Fu R, Devine B, Wasson N, Ginsburg A, et al. Imaging techniques for the diagnosis of hepatocellular carcinoma. A systematic review and meta-analysis. Ann Intern Med 2015;162:697-711.

25. Gupta P, Soudagarajan R, Patel A, Kumar-M P, Sharma V, Kalra N. Abbreviated MRI for hepatocellular carcinoma screening: A systematic review and meta-analysis. J Hepatol 2021. doi: 10.1016/j.jhep.2021.01.041.

26. National Registry of Diseases Office, Health Promotion Board, Singapore. Singapore Cancer Registry Annual Registry Report 2015. Available from: https://www.nrdo.gov.sg/docs/librariesprovider3/Publications-Cancer/cancer-registry-annual-report-2015_web.pdf?sfvrsn=10. [Last accessed on 2020 May 12].

27. Mathiah M, Chong CH, Lim SG. Liver disease in Singapore. Euroasian J Hepatogastroenterol 2018;8:66-8.

28. Estes C, Chan HLY, Chien RN, Chuang WL, Fung J, Goh GB, et al. Modelling NAFLD disease burden in four Asian regions-2019-2030. Aliment Pharmacol Ther 2020;51:801-11.

29. Younossi Z, Stepanova M, Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, et al. The comorbidity of cryptocogenic cirrhosis: Adverse outcomes without treatment options. J Hepatol 2018;69:1365-70.

30. Dhamija E, Paul SB, Kedia S. Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: An increasing concern. Indian J Med Res 2019;149:9-17.

31. Satapathy SK, Sanyal AJ. Epidemiology and natural history of nonalcoholic fatty liver disease. Semin Liver Dis 2015;35:221-35.

32. Loomba R, Adams LA. The 20% rule of NASH progression: The natural history of advanced fibrosis and cirrhosis caused by NASH. Hepatology 2019;70:1885-8.

33. Chen K, Chang PE, Goh GBB, Tan CK. Surveillance for hepatocellular carcinoma-current status and advances. Hepatoma Res 2018;4:72.

34. Poh Z, Goh BB, Chang PE, Tan CK. Rates of cirrhosis and hepatocellular carcinoma in chronic hepatitis B and the role of surveillance: A 10-year follow-up of 673 patients. Eur J Gastroenterol Hepatol 2015;27:638-43.

35. Fattovich G, Strufilli T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. Gastroenterology 2004;127 (5 Suppl 1):S35-50.

36. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-8.

37. Chang PE, Wong GW, Li JW, Liu HF, Chow WC, Tan CK. Epidemiology and clinical evolution of liver cirrhosis in Singapore. Ann Acad Med Singap 2015;44:218-25.

38. Ministry of Health, Singapore. Population and vital statistics: 2019. Available from: https://www.moh.gov.sg/resources-statistics/singapore-health-facts/population-and-vital-statistics. [Last accessed on 2020 May 12].

39. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: A multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16:132-7.

40. Kim D, Li AA, Perumpail BJ, Gaidaparti C, Kim W, Cholankeril G, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019;69:1064-74.

41. Giannini EG, Farinati F, Cicerese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015;61:184-90.

42. Yang W, Yan K, Goldberg SN, Ahmed M, Lee JC, Wu W, et al. Ten-year survival of hepatocellular cancer patients undergoing radiofrequency ablation as a first-line treatment. World J Gastroenterol 2016;22:2903-3005.

43. Zhao HC, Wu RL, Liu FB, Zhao YJ, Wang GB, Zhang ZG, et al. A retrospective analysis of long term outcomes in patients undergoing hepatic resection for large (>5 cm) hepatocellular carcinoma. HPB (Oxford) 2016;18:943-9.

44. Kong JY, Li SM, Fan HY, Zhang L, Zhao HJ, Li SM. Transarterial chemoembolization extends long-term survival in patients with unresectable hepatocellular carcinoma. Medicine (Baltimore) 2018;97:e11872.

45. Kok VC, Chen YC, Chen YY, Su YC, Ku MC, Kuo JT, et al. Sorafenib with transarterial chemoembolization achieves improved survival vs. sorafenib alone in advanced hepatocellular carcinoma: A nationwide population-based cohort study. Cancers (Basel) 2019;11:985.

46. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008;6:1418-24.

47. Lima PH, Fan B, Bérubé J, Cerny M, Olivié D, Giard JM, et al. Cost-utility analysis of imaging for surveillance and diagnosis of hepatocellular carcinoma. AJR Am J Roentgenol 2019;213:17-25.

48. Tan EK, Goh BKP, Lee SY, Krishnamoorthy TL, Tan CK, Jeyaraj PR. Liver transplant waitlist outcomes and the allocation of hepatocellular carcinoma model for end-stage liver disease exception points at a low-volume center. Transplant Proc 2018;50:3564-70.