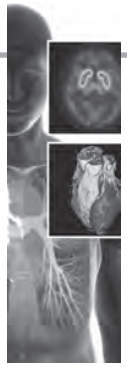

Radiation burden of hepatocellular carcinoma screening program in hepatitis B virus patients should we recommend magnetic resonance imaging instead?

Background: Current Hepatocellular Carcinoma (HCC) surveillance guidelines in high risk patients recommends characterization of a lesion detected on ultrasound with CT. Despite the superior diagnostic utility of MRI compared to CT, MRI is used as a problem solving tool after CT.

Our aim was to assess the radiation burden of CT in a HCC screening program and assess the risk/benefit compared with MRI as the second step after ultrasound in a HCC screening program.

Methods: We conducted a retrospective cohort study of chronic hepatitis B (CHB) patients in a tertiary centre screening program from 2004 to 2014. Imaging modality, number of scans and radiation dose were calculated.

Findings: 382 CHB patients were engaged in an average 5 years of HCC surveillance. Those with 1-3 year follow up received a total dose per patient of 5 mSv, 4-6 years follow up received 11 mSv, >7 years follow up received 18 mSv of radiation.

In the patients with over 7 years follow up the risk of radiation induced cancer was 1 in 850. Some patients had over 100 mSv resulting in radiation induced cancer risk of 1 in 146. 3 patients out of all 382 (0.79%) patients were diagnosed with HCC during surveillance. 99% of CTs were for false positive findings on ultrasound.

Review of literature demonstrated better sensitivity and specificity for small HCC using MRI in addition to improved cost effectiveness of MRI in a screening program.

Conclusion: A significant number of CHB patients received multiple CT scans for false positive findings on ultrasound. Utilizing MRI instead of CT to further characterize US lesions has no radiation exposure and therefore no associated radiation induced cancer risk.

Utilizing MRI instead of CT to further characterize US lesions has greater sensitivity and no radiation exposure compared to the current surveillance model.

KEYWORDS: hepatitis B virus ▪ radiation dose burden ▪ CT ▪ MRI ▪ hepatocellular carcinoma

Background

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer related death worldwide. Hepatitis B virus (HBV) infection accounts for 50% of HCC cases and is the leading risk factor worldwide [1-3]. HCC related prognosis is poor if diagnosed at an advanced stage with estimated five year survival of <5% [4]. Improved survival rates are associated with early detection of small tumours [5,6]. Surveillance programs of at-risk asymptomatic patient cohorts such as those with chronic hepatitis B (CHB) may detect tumours at an early stage and increase their suitability for curative resection or liver transplantation [1,4,5,7,8]. 51% of HCC were detected by surveillance of patients among studies in the USA, 45% of patients were detected in Europe and 37% detected in Asia [7].

Imaging studies play a pivotal role in the surveillance and diagnosis of HCC with the use of ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). Ultrasound is the main modality used in preliminary screening due to its low cost, availability and minimal risks. Practice guidelines from the American Association for the Study of Liver Diseases (AASLD), European

Ophelia Wong, Suong Le, Ronnie Ptasznik, Gideon Ptasznik & Mark Page*

School of Health Sciences, University of Newcastle, NSW, Australia

**Author for correspondence:*

drmarkpage@gmail.com

Association for the Study of Liver Diseases (EASL) and Asian Pacific Association for the Study of the Liver (APASL) recommend regular six monthly ultrasound in high-risk patients [6]. CT or MRI is endorsed for surveillance only when US is limited by factors such as obesity [7,8-12]. This is due to the increased costs and related harms from radiation exposure in CT and adverse events of contrast agents [13]. There has however been an increasing problem with the increased prevalence of obesity in the general community which has increased the flow-on dependence on CT for HCC surveillance [14,15].

CT is the clinically accepted modality to further characterize a suspicious lesion detected on US due to its speed, widespread availability and ability to characterize a tumour. MRI is currently reserved to further characterize a hepatic lesion when CT findings are indeterminate despite its distinct advantages compared to CT [6]. MRI is considered the most sensitive imaging modality for HCC detection. It has no radiation exposure compared with CT [8,15]. As MRIs are becoming more accessible and widely available, there is a potential for MRI to be utilized in preference to CT as the confirmatory test for a lesion detected on ultrasound [16]. Our aim was to assess the frequency of CT in a screening program with the associated radiation dose and to explore the advantages of MRI compared to CT to further characterize lesions detected on US as part of routine HCC screening among patients with chronic hepatitis B (CHB). Our hypothesis was the use of MRI as the second step to screening instead of CT imaging may be associated with less radiation exposure and improved sensitivity to detect early HCC [6].

Methods

■ Study population

This retrospective cohort study was performed following institutional ethics board authorization at Monash Health, Australia. We conducted an imaging review of CHB patients from 2004 through 2014 in our tertiary institutional HBV database, which contains information on 399 adult patients over the age of 30 with HBV based on serology treated at our institution. Only patients with over 1 year of follow up and imaging were included. Scans performed after diagnosis of HCC were not included. HCC was diagnosed based on imaging findings on CT (Barcelona Clinic Liver Cancer guidelines), ultrasound guided biopsies were not performed for confirmation.

■ Data collection

Medical records and imaging reports were reviewed for the type of imaging performed on this cohort as part of HCC surveillance. Only scans performed for HCC screening or diagnoses were included. The majority of the scans were performed within the health network. We included scans performed outside our health care network if a copy of the report was available in our medical records.

We used our institutional average dose per weight per scanner in dose length product (DLP) for single phase and 4 phase CT and converted to effective dose in mSv using K of 0.015 as per ICRP 103 data.

■ Exclusions

17 patients with less than 1 year follow up (5 males and 12 females) were excluded from the study.

Results

■ Demographics

224 males and 158 females. Average age was 51.7 years, standard deviation +/- 9 (range 31-86 years).

■ HCC detection rate within cohort

3 patients out of all 382 (0.79%) patients were diagnosed with HCC during surveillance. 251 out of 254 CTs (99%) were for false positive findings on ultrasound. Due to the very low incidence of HCC in our cohort, sensitivity and specificity for US, CT and MRI were not calculated.

■ Average follow up and adherence

Average follow up was 5 years. Adherence to the program of 6 monthly ultrasound was 65%.

■ Radiation dose analysis

TABLE 1 demonstrates the number of patients who were in the HCC screening cohort with follow up periods separated into three groups: 1-3 years follow-up, 4-6 years follow-up and >7 years follow-up with the corresponding imaging and radiation dose they received. The total dose and the total dose per patient were

Table 1. Number of patients in the HCC screening cohort separated in 3 groups.

HCC screening	1-3 years follow up	4-6 years follow up	>7 years follow up
Number of patients	84	170	128
US	313	1203	1212
CT (both single and 3/4 phase CT)	21	100	133
MRI	21	34	43
Total dose (mSv)	384	1798	2332
Total dose per pt (mSv)	5	11	18

HCC: Hepatocellular Carcinoma
mSv: millisievert

calculated using our institutional average dose per weight per scanner in dose length product (DLP) for single phase and 4 phases CT. This average is obtained by a yearly audit conducted within the radiology department and includes all 5 CTs in the hospital network with the averages doses calculated and divided by 5. The range was +/- 0.8mSv. The DLP was as follows:

■ Average dose per scanner in dose length product (DLP)

Avg dose single phase* (DLP): 504

Avg dose 4 phase (DLP): 1293

* Single phase=post contrast portal venous phase

■ Radiation dose

Avg dose single phase (mSv): 7.5

Avg dose 4 phase (mSv): 19.4

TABLE 2 demonstrates the total amount of patients and separates imaging in study for screening and number of CTs not for screening as well as the number of ultrasound guided biopsies completed in the cohort (biopsies were done for cirrhosis grading).

TABLE 3 demonstrates the percentage chance of having a particular imaging modality within the 3 follow-up cohorts.

It shows that:

- Of patients in the 1-3 years follow up, there is a 25% chance of having a CT and 25% of having a MRI
- Of patients in the 4-6 years follow up, there is a 59% chance of having a CT and 20% of having a MRI
- Of patients in the >7 years follow up, there is a 104% chance of having a CT and 34% of having a MRI. (Note that the percentage is higher than 100% as there is a higher instance of these patients having more than one CT)

TABLE 4 demonstrates the total chance of having a particular imaging in the cohort throughout our study. Of note, there is a 66% chance of having a CT within our study cohort compared to 26% chance of having an MRI in our cohort.

■ Current model and radiation risk

Our study investigated a well defined cohort of ambulatory and asymptomatic CHB patients in a tertiary institute engaged in HCC surveillance program. Our data demonstrates increasing likelihood of having multiple CT scans as these patients extend their follow-up period. This was demonstrated in our study

Table 2. Number of various imaging modalities our cohort were exposed to.

Total No. of patients	Sex	Avg age	No. of US for screening	No. of single phase CT for screening	No. of 3/4 phase CT for screening	No. of MRI for liver	No. of ultrasound guided biopsies	No. of CT not for screening
382	Male 224 Female 158	51.7	2728	35	219	98	103	63

Table 3. Percentage chance of having a particular imaging modality.

Chance of having imaging (%)	1-3 years follow up	4-6 years follow up	>7 years follow up
CT	25	59	104
MRI	25	20	34

Table 4: Chance of having a particular imaging modality.		
Total chance of having imaging (%) in cohort	**Sum of imaging from all three groups**	**Percentage chance of imaging (%)**
CT	254	66
MRI	98	26

Table 5. Specificity and Sensitivity for various imaging modalities in surveillance and non-surveillance settings.		
Imaging modality for surveillance settings	Sensitivity	Specificity
US	0.78	0.89
CT	0.84	0.99
MRI	No data	No data
Imaging modality for non-surveillance settings	Sensitivity	Specificity
US	0.73	0.93
CT	0.83	0.91
MRI	0.86	0.89

cohort in TABLE 5 with patients generally having a 66% chance of having a CT compared to 26% chance of having an MRI in our cohort. Separating the cohort into various follow up periods, the longer the follow up period the larger the likelihood of having a CT and they would be subjected to an increasingly higher dose of ionizing radiation with patients in 1-3 years follow up receiving a total dose per patient of 5 mSv, 4-6 years follow up receiving 11mSv , >7 years follow up receiving 18mSv.

Various studies have shown that ionizing radiation increases the risk of the development of cancer. [17-20]. The median effective dose of an abdomen and pelvis CT scan is around 8-10 mSv. For a multiphase abdomen and pelvis CT scan, the mean effective dose was 31mSv which corresponds to a lifetime attributable risk of 4 cancers per 1000 patients [18].

The severity of the effects of ionizing radiation can vary depending on the amount of radiation a person is exposed to. The American College of Radiology also echo this notion and state that the risk of cancer death for CT patients is comparable with that of 1 year of smoking in a similar population (12.5/10000 for each abdomen CT) [17]. This is an issue for the cohort of patients who have had multiple CT scans as increases the lifetime risk of having a fatal cancer. Therefore, patients who are in the surveillance program with a longer follow-up period have a higher risk of radiation induced cancer from multiple CT. Average dose of patient in our study was 13 mSv giving an additional risk of cancer 1 in 1138. In the patients with over 7 years follow up who received over 18mSv the risk was 1 in 850. Some patients had over 100mSv resulting in risk of 1 in 146. (Risk calculated based on Risk Calculator [21]).

In our cohort, only 0.79% developed HCC. Most CTs performed on this cohort (251 out of 254 CTs (99%)) were for false positive findings on ultrasound. This is especially relevant for the common clinical scenario of a patient having a screening ultrasound which detects a possible lesion. The patient then has a CT which is normal and returns to US screening. A few screening ultrasounds later, a different technologist or radiologist performs the scans and detects a lesion which appears different to the previously detected lesion due to operator dependent factors and the patient has another CT which often comes back normal and once again returns to ultrasound. This process leads to patient anxiety, clinician uncertainty and increased radiation burden.

The large number of CTs in our cohort is likely due to a number of factors including different sonographers, radiology registrars and consultants reviewing the follow up ultrasound scans. As mentioned above, it is likely that there is a very low threshold of recommending a CT for any abnormality seen. These often turned out to represent pseudo-lesions, focal fatty liver and stable cirrhotic nodules which appeared larger on follow up ultrasound but were stable in size on CT/MRI.

The low incidence of HCC in our cohort is probably due to adequate medical treatment and low cirrhosis prevalence. Cirrhosis data was not added to our analysis as less than 30% had biopsy grading.

■ Proposed surveillance model

To minimize the radiation dose and negate the lifetime attributable risk of developing a radiation induced cancer from multiple CTs, we have proposed a new surveillance program which utilizes MRI where available as the next step after US and minimise the use of CT as part of the surveillance program.

This model was proposed as MRI is becoming increasingly accessible in various countries and has a higher sensitivity and specificity in the detection of HCC. MRI is superior in tissue contrast and also has increased sensitivity for the detection of HCC due to its increased sensitivity to gadolinium chelates compared with CT with iodine based agents [13,15].

To determine the effectiveness of the study, we utilized specificity and sensitivity of imaging modalities in detecting HCC based on the systematic review and meta-analysis by [3] which is seen in TABLE 5.

Unfortunately, there was no data which to support the sensitivity and specificity for MRI under surveillance settings as it is not currently done in practice.

In surveillance settings, having a high sensitivity would be more useful than specificity as it would enable early treatment of a potential low grade HCC. MRI is more sensitive compared with both US and CT. The specificity of CT was better than US in surveillance settings. However, in non-surveillance settings, specificity was very similar between imaging ranging from 0.89 to 0.93.

Schutte et al. [4] looked at HCC size at detection between the imaging modalities and found higher sensitivity and specificity of MRI compared to ultrasound and CT for lesions under 1 cm and 2 cm, which would be the ideal size for detection.

The cost of MRI and CT vary in different countries and institutes. However, MRI is often more expensive and less available. At the moment there is no Medicare/government rebate in Australia and several other countries' for MRI liver for the characterization of a suspicious lesion in a HCC screening program and the cost is covered by the patient or hospital [16].

Replacing CT with MRI is likely to reduce costs and the number of repeat test due to is higher accuracy for smaller lesions and increased radiologist confidence. By Using MRI instead of CT and the second imaging test after US we also remove the need for an additional problem solving scan as is the occasional outcome with CT. The proposed model is likely to be more cost effective than the current model in terms of the no radiation exposure, highest sensitivity and lowest cost. There has been one recent study which compares MRI and CT as initial imaging procedures in patients with suspected HCC in South Korea and Thailand [8]. Cost effectiveness was demonstrated with MRI having a greater cost saving as the first imaging procedure compared with multi-detector CT [8].

Recently MRI has become the first test of choice in diagnosis and monitoring patients with Crohn's disease partly due to the high burden of radiation in young patients and also due to better diagnostic performance. Our cohort of screening patient who enter the program at the age of 40 would have similar benefits.

Limitations

Our study has a number of limitations. CT scans were performed on different scanners within and outside of our network. We were unable to obtain the exact dose for each patient and based our estimates on the average dose per scan on CTs in our network.

It is possible that patients had additional scans outside our network which were not captured in our study. This however would only increase the total radiation burden and cost.

Only 0.79% of the study population was found to have HCC during surveillance. This restricted our ability to calculate negative and positive predictive values for each imaging modality due to the low prevalence of this condition.

Conclusion

The current HCC surveillance model utilising CT as the diagnostic test poses an additive risk of radiation induced cancer over the lifetime of engagement in a surveillance program. By utilising MRI instead of CT to further characterise US lesions we receive the added benefits of greater sensitivity, no

radiation exposure and possibly lower cost. The implementation of this model in the major guidelines for HCC surveillance offer significant benefits to both patients and clinicians.

REFERENCES

1. Wang CH, Wey KC, Mo LR *et al.* Current trends and recent advances in diagnosis, therapy and prevention of hepatocellular carcinoma. *Asian. Pac. J. Cancer. Prev.* 16, 3595-3604 (2015).
2. Chou R, Cuevas C, Fu R *et al.* Imaging techniques for the diagnosis and staging of hepatocellular carcinoma. *Comparative. Effectiveness. Review. No. 143.*
3. Chou R, Cuevas C, Fu R *et al.* Imaging techniques for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Ann. Intern. Med.* 162, 697-711 (2015).
4. Schütte K, Schulz C, Malfertheiner P. Hepatocellular carcinoma: current concepts in diagnosis, staging and treatment. *Gastrointest. Tumors*. 1, 84-92 (2014).
5. Cicalese L. Hepatocellular Carcinoma. WebMD. *LLC*. (2015).
6. Joo I, Choi BI. New paradigm for management of hepatocellular carcinoma by imaging. *Liver. Cancer.* 1, 94-109 (2012).
7. 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. ONE.* 11 (2014).
8. Lee JM, Kim MJ, Phongkitkarun S *et al.* Health economic evaluation of Gd-EOB-DTPA MRI vs. ECCM-MRI and multi-detector computed tomography in patients with suspected hepatocellular carcinoma in Thailand and South Korea. *J. Med. Econ*. 19 (2016).
9. Terrault NA, Bzowej NH, Chang KM *et al.* AASLD Guidelines for treatment of chronic hepatitis B. *Hepatology.* (2015).
10. Omata M, Lesmana LA, Tateishi R *et al.* Asian Pacific Association for the study of the liver consensus recommendations on hepatocellular carcinoma. *Hepatol. Int.* 4, 439-474 (2010).
11. Bruix J, Sherman M. AASLD practice guideline: Management of hepatocellular carcinoma: An update. *Hepatology*. 53, 1020-1022 (2011).
12. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO–ESDO Clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 23, vii41-vii8 (2012).
13. Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: Part I. Development, growth and spread: Key pathologic and imaging aspects. *Radiology*. 272, 635-654 (2014).
14. Bartolozzi C, Battaglia V. Imaging in hepatocellular carcinoma. *Guidelines. and. Future. Prospects*. 29, 72-77 (2013).
15. Yu NC, Chaudhari V, Raman SS *et al.* CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. *Clin. Gastroenterol. Hepatol*. 9, 161-167 (2011).
16. Qian MY, Yuwei RJ, Angus P *et al.* Efficacy and cost of a hepatocellular carcinoma screening program at an Australian teaching hospital. *J. Gastroenterol. Hepatol.* 25:951-956 (2010).
17. Tsapaki V, Rehani M, Saini S. Radiation safety in abdominal computed tomography. *Semin. Ultrasound. CT. MR.* 31, 29-38 (2010).
18. Smith-Bindman R, Marcus JLR, Kim KP *et al.* Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch. Intern. Med.* 169, 2078-2086 (2009).
19. González ABd, Mahesh M, Kim KP *et al.* Projected cancer risks from computed tomographic scans performed in the United States in 2007. *JAMA. Intern. Med.* 169 (2009).
20. American College of Radiology (ACR) and Radiological Society of North America (RSNA). Radiation Dose in X-Ray and CT Exams. Radiological. Society. of. North. America. Inc. (2016).
21. Hanley M. Risk Calculator. *Xrayrisk.* (2013).