Original Article

Routine Staging Using Chest Computed Tomography in Workup of Treatment-Naïve Hepatocellular Carcinoma Prior to Locoregional Therapy: Is There a Need?

Po Wey Leong, [1]*MBBS, MMED FRCR*, Uei Pua, [1]*MBBS, MMED, FRCR*, Kian Soon Lim, [1]*BM, MRCP, FRCR*

Abstract

Introduction: The lung is the most common site of distal metastasis in patients with hepatocellular carcinoma (HCC), as seen in more than half of patients with extrahepatic disease. The incidence of pulmonary metastasis in all patients with HCC, however, remains low (between 4.5% to 20%). Their presence, nevertheless, contraindicates curative locoregional therapies. The role of staging chest computed tomography (CT) before locoregional treatment is not well defined. This study aimed to assess the utility of pre-treatment chest CT prior to locoregional therapy. Materials and Methods: Retrospective review of continuous cases of treatment-naïve HCC referred for locoregional therapy from 2004 to 2013 was performed. Patients with pre-treatment chest CT were evaluated for the presence of pulmonary metastases. HCC features (size, numbers, vascular invasion, nodal status and bone metastases) were recorded. Univariate analysis and multivariate logistic regression were performed for significant association. Results: A total of 780 patients were reviewed, of which 135 received staging chest CT. Pulmonary metastases (n = 17, 12.6%), benign lesions (n = 41, 30.4%) and indeterminate lesions (n = 11, 8.1%) were detected. Among the indeterminate lesions, there were losses to follow-up (n = 2) and deaths within the study period (n = 3). All patients with pulmonary metastases were declined locoregional therapy. Univariate analysis showed statistical significant association between pulmonary metastases with the number of intrahepatic lesions (*P* <0.01), primary tumour size (*P* = 0.018) and presence of vascular invasion (*P* <0.01). On multivariate analysis, the number of intrahepatic lesions (OR: 9.7; 95% CI, 1.6 to 57.2; *P* = 0.012) and presence of both hepatic and portal venous invasions (OR: 11.8; 95% CI, 1.1 to 128.8; *P* = 0.043) were the 2 independent positive predictors of pulmonary metastases. Conclusion: The prevalence of pulmonary metastasis is low in HCC and our study does not support the routine use of staging chest CT in all treatment-naïve patients. It can, however, be considered in cases with multiple lesions or vascular invasion.

Ann Acad Med Singapore 2017;46:282-6

Key words: Metastasis, Liver, Lung

Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumour of the liver. It is a major health issue, being the fifth most common tumour in the world with an increasing incidence.[1] Despite advances in treatment, it remains a disease with poor prognosis and survival.[2] The incidence of hepatocellular carcinoma is highest in Asia and Africa due to the high prevalence of hepatitis B and C infections and related liver disease.[3,4]

Staging systems are key to prognostication and treatment choice in newly diagnosed HCC. To this end, several staging systems have been proposed, of which the Barcelona Clinic Liver Cancer (BCLC) staging is the most commonly used classification in the Western world. Broadly, surgical resection and locoregional treatment (LRT) such as percutaneous ablation and transarterial chemoembolisation confer the best survival outcome for patients with early and intermediate stage disease, with systemic chemotherapy (sorafenib) reserved for advanced stage disease characterised by extrahepatic metastasis.[5-8]

The lung is the most frequent site for HCC metastasis,[9] as seen in more than half of patients with extrahepatic disease.[10]

[1]Department of Diagnostic Radiology, Tan Tock Seng Hospital, Singapore
Address for Correspondence: Dr Leong Po Wey, Department of Diagnostic Radiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: powey.leong@mohh.com.sg/powey@hotmail.com

Table 1. Association between Pulmonary Metastases and the Size of Intrahepatic Lesions

	Maximum Primary Tumour Diameter			Total
	<5 cm	5 cm to 10 cm	>10 cm	
Benign or no lung lesions	37	30	40	107
Lung metastases	1	4	12	17
Total	38	34	52	124

P value from Fisher's exact test <0.018.

Table 2. Association between Pulmonary Metastases with Increased Number of Intrahepatic Lesions

	Number of Intrahepatic Lesions			Total
	1	2 to 3	>3	
Benign or no lung lesions	65	19	23	107
Lung metastases	2	7	8	17
Total	67	26	31	124

P value from Fisher's exact test <0.018.

The prevalence of pulmonary metastasis in HCC patients, however, is low (between 4.5% to 20%).[10-12] The presence of lung metastasis excludes patients for curative LRT.[5-8] While the value of routine staging chest computed tomography (CT) prior to curative treatment in other common cancers such as colorectal cancer have been well described,[13-16] to date, however, the clinical benefit of a routine staging chest CT for exclusion of metastasis prior to commencement of LRT in HCC remains to be systematically studied.[17] This study aims to assess the value (if any) for routine pre-treatment chest CT in treatment-naïve patients with HCC prior to LRT and identify any potential predictors for lung metastasis based on tumour morphology.

Materials and Methods

A retrospective study involving consecutive cases of treatment-naïve HCC from our institution's HCC registry between 2004 and 2013 was performed. This study was approved by our institutional review board and waiver of informed consent was obtained.

Cases identified from our registry were diagnosed based on either histology or imaging criteria according to the American Association for the Study of Liver Diseases (AASLD) practice guidelines.[18] Patients with newly diagnosed HCC who received pre-treatment chest CT were included in our study and their initial chest and abdomen CT scans were reviewed by 2 consultant radiologists, each with at least 8 years of experience in body imaging. Patients who did not receive pre-treatment chest CT were excluded from further analysis. The chest CT studies were performed based on a combined tumour board decision, typically for intermediate and advanced staged tumours, and all studies were performed for exclusion of lung metastases prior to LRT. The CT scans were performed with either Siemen's Somatom Definition AS 128-slice or Siemen's Somatom Sensation 64-slice CT scanners. The chest and abdominal scans were reviewed separately and the radiologists were blinded to tumour morphology and treatment plan whilst reviewing the chest CT findings.

Based on the chest CT findings, the patients were then grouped into 4 categories—those with no lung lesions, benign lesions, indeterminate lesions and pulmonary metastases. Pulmonary metastases were defined as multiple discrete nodules, nodules of varying sizes and/or nodules randomly distributed in the lungs.[17] Benign lesions included those containing central calcifications or fat, those with tree-in-bud appearances and sub-pleural nodes.[19] Indeterminate lesions were those that could not be catagorised into either benign or metastatic lesions, particularly solitary lung nodules.

Features of the primary tumour, including tumour size and number of hepatic lesions, were studied. The maximum diameter of the tumours in the portovenous phase (either on the axial or coronal plane) were measured and placed into 1 of these 3 groups: <5 cm, 5 cm to 10 cm and >10 cm (Table 1). The number of hepatic lesions were also placed into groups of single lesion, 2 to 3 lesions and >3 lesions (Table 2). Other associated imaging features, including the presence of vascular invasion, nodal status and presence of bone metastases, were also evaluated. Univariate analysis using chi-square or Fisher's exact test (when the cell number was <5) and simple logistic regression was performed to detect any significant association of these features with pulmonary metastases. Multivariate logistic regression was also performed to control potential confounders.

Results

Within the study period, there were a total of 780 patients in our HCC registry, of which 135 patients (male = 108, female = 27) received chest CT for exclusion of pulmonary metastases prior to LRT. The patients had a mean age of 67.4 years (range, 41 to 92 years). The aetiologies for HCC were hepatitis B (n = 63, 47%), hepatitis C-related (n = 3, 2%) and others (e.g. cryptogenic/non-alcoholic steatohepatitis) (n = 69, 51%).

The mean diameter of the tumours was 8.4 cm (range, 1.5 to 18.3). They were grouped as <5 cm (n = 38, 31%), 5 cm to 10 cm (n = 34, 27%) and >10 cm (n = 52, 42%).

Table 3. Association between Pulmonary Metastases with Presence of Vascular Invasion

	No Vascular Invasion	Vascular Invasion (Hepatic/Portal Vein or Both)	Total
Benign or no lung lesions	87	20	107
Lung metastases	9	8	17
Total	96	28	124

P value from Pearson's chi-square = 0.009.

The number of intrahepatic tumours were grouped either as single lesion (n = 67, 54%), 2 to 3 lesions (n = 26, 21%) or >3 lesions (n = 31, 25%). Twenty-eight (23%) of the tumours had vascular invasion, 8 (6%) had nodal invasion, and 7 (5%) demonstrated bone metastases.

Among these 135 patients, 61 patients had abnormal chest CT findings. Seventeen patients were found to have pulmonary metastases (12.7%), 33 patients had benign lung lesions (26.7%) and 11 patients had indeterminate lesions (8.1%). Examples of chest CT findings of all separate categories are shown in Figure 1. Among the patients with indeterminate lesions, 6 were later diagnosed on biopsy or follow-up imaging to be benign lesions. The rest of the 5 patients either defaulted on follow-up (n = 2) or died before the follow-up study (n = 3). These patients were also excluded from further analysis (Fig. 2). Among the 17 patients with pulmonary metastases, locoregional therapy was precluded as a result of the findings.

Table 4. Predictors for Extrahepatic Metastasis: Multivariate Analysis

Variables	Odds Ratio (95% CI)	*P* Value
No. of liver lesions		
1	1	
2 to 3	9.66 (1.63 to 57.16)	0.012
>3	7.61 (1.26 to 45.04)	0.027
Tumour size		
Less than 5 cm	1	
5 cm to 10 cm	1.40 (0.11 to 17.8)	0.80
More than 10 cm	4.48 (0.51 to 39.58)	0.18
Presence of vascular invasion		
No vascular invasion	1	
Portal vein invasion only	2.11 (0.49 to 9.08)	0.312
Hepatic vein invasion only	2.77 (0.21 to 37.2)	0.442
Both hepatic and portal invasion	11.77 (1.08 to 128.82)	0.043

Univariate analysis showed statistically significant associations between pulmonary metastases with larger primary tumour size (Fisher's exact test, $P = 0.018$) (Table 1), increased number of intrahepatic lesions (Fisher's exact test, $P < 0.01$) (Table 2) and presence of vascular invasion (chi-square test, $P < 0.01$) (Table 3). No statistically significant association was detected between pulmonary metastases and presence of nodal involvement (Fisher's exact test, $P = 0.078$) or bone metastases (Fisher's exact test, $P = 0.245$).

On multivariate analysis (Table 4), the presence of multiple intrahepatic lesions (2 to 3 liver lesions [OR: 9.7; 95% CI,

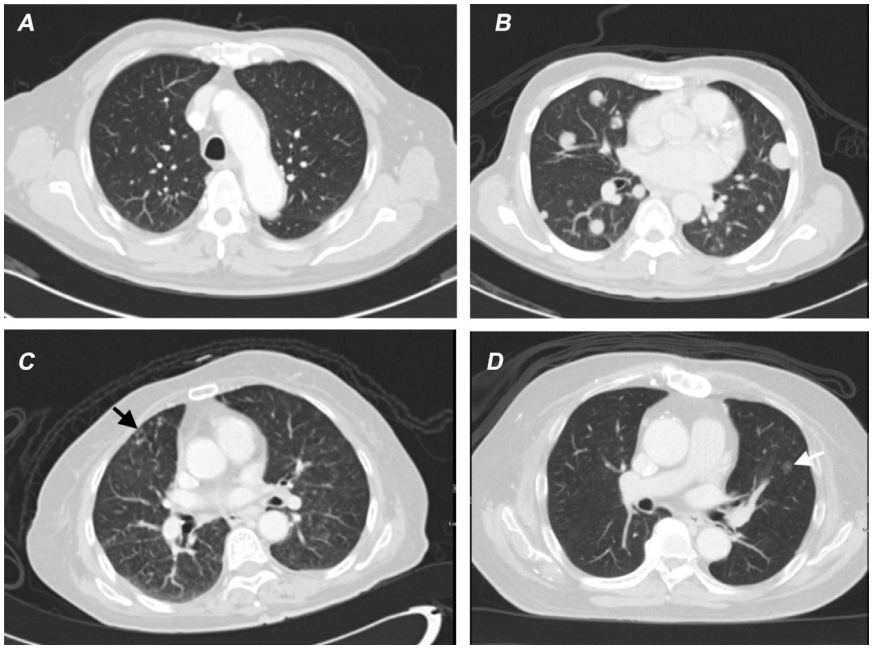

Fig 1. Examples of chest CT findings in all 4 categories. A) No lung lesion. Chest CT shows no focal abnormality. B) Pulmonary metastases. Chest CT shows multiple nodules of varying sizes scattered in both lungs. C) Benign lesion. Chest CT shows tree-in-bud nodules in the periphery of the right upper lobe (black arrow), in keeping with inflammatory change. D) Indeterminate lesion. Chest CT shows a solitary ground glass lesion in the left upper lobe (white arrow).

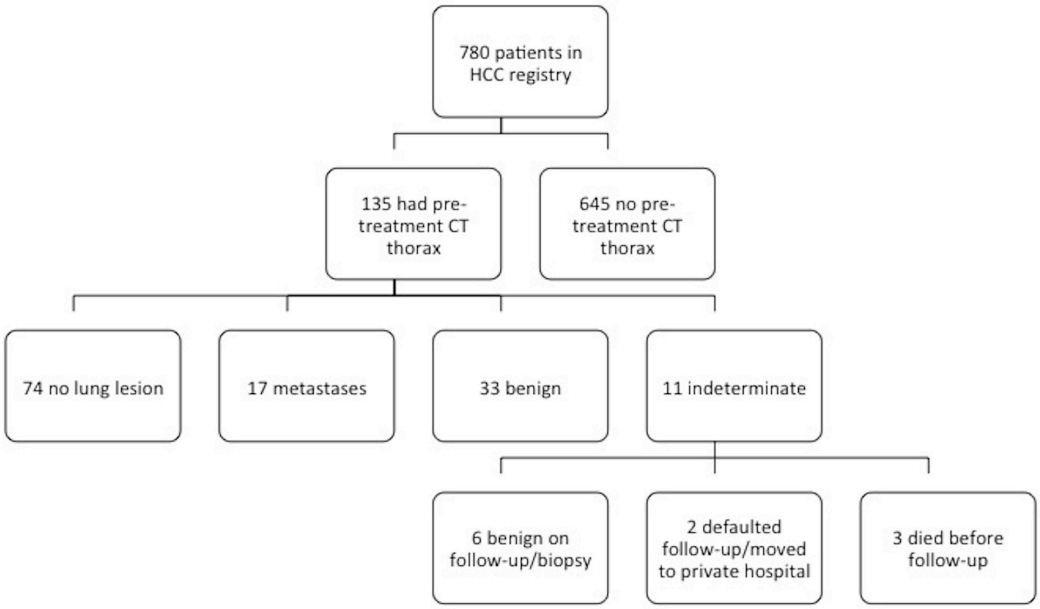

Fig. 2. Flowchart demonstrating CT thorax findings.

1.6 to 57.2; $P = 0.012$]) (more than 3 liver lesions [OR: 7.6; 95% CI, 1.3 to 45.0; $P = 0.027$]) and the presence of both hepatic and portal venous invasion (OR: 11.8; 95% CI, 1.1 to 128.8; $P = 0.043$) were the 2 independent positive predictors of pulmonary metastases with statistical significance. The size of tumour was not found to be a significant independent predictor for pulmonary metastases (5 cm to 10 cm [OR: 1.4; 95% CI, 0.1 to 17.8; $P = 0.8$]) (>10 cm [OR: 4.5; 95% CI, 0.5 to 39.6; $P = 0.2$]).

Discussion

The lung is the most common site of extrahepatic metastasis in HCC[9-11,20] and its presence excludes patients from curative locoregional therapy.[5-8] Chest CT could therefore, in theory, play an important role in pre-treatment stratification. To this end, the role of pre-treatment chest CT has not been described in commonly used staging and treatment systems such as the BCLC.[8] Review of the literature revealed limited recommendations regarding the role of chest CT in pre-treatment staging. The British Society of Gastroenterology recommends a baseline chest CT for newly diagnosed HCC patients.[21] However, this is largely based on consensus and the utility of pre-treatment chest CT remains to be systematically studied.

Issues with additional radiation burden and increased economic cost with routine staging chest CT would also require additional data to be resolved. In addition, false-positives such as indeterminate lung lesions (8% of our patients) also pose a clinical dilemma to the clinicians, resulting in increased patient anxiety and possible treatment delay from additional investigations (e.g. biopsy, positron emission tomography [PET]/CT, etc). Notably, while we identified 17 patients with lung metastasis in our study, of the 11 patients with indeterminate lung lesions, 6 who had undergone subsequent biopsy or follow-up imaging were eventually found to have benign lesions.

Furthermore, the prevalence of lung metastasis is low. The yield of lung metastases in our study population was at 12.7% which correlates with similar low figures of between 4.5% to 20% as reported in other studies that evaluated extrahepatic metastases of HCC,[10,11,20] even though these studies did not directly address the use of chest CT in the pre-treatment staging. A prior study by Jin et al of 381 patients that evaluated the value of staging chest CT with bone scan for HCC concluded that the staging scans did not contribute to significant changes to HCC BCLC staging.[17] Based on our findings, we concur that routine staging chest CT prior to LRT should not be recommended.

The decision for staging chest CT is currently largely dependent on clinician discretion and experience. In our institution, this decision is usually based on a combined tumour board decision and CT thorax is typically reserved for intermediate to advanced staged HCC. There is, however, no fixed criterion and this also presents as an inherent bias in our study group. This lack of standardisation and evidence on the usage of chest CT is part of the impetus for our study to further understand the role (if any) of staging chest CT scans and better strategise its use. Notwithstanding, routine pre-treatment chest CT is not currently practised by our

clinicians as reflected by a majority of our patients (82.7%) who have not undergone a pre-treatment chest CT.

Our study found statistically significant association between pulmonary metastases with tumour size (Table 1), number of intrahepatic lesions (Table 2) and presence of vascular invasion on univariate analysis (Table 3). This result is similar to that in a previous study conducted by Kanda et al which found that the maximum tumour diameter, number of HCC nodules and presence of vascular tumour invasion to be predictors of extrahepatic metastasis (including extrathoracic metastases).[11] On multivariate analysis, our study found the presence of multiple hepatic lesions (2 or more lesions) and the presence of both hepatic and portal venous invasion to be the 2 independent positive predictors of pulmonary metastases. This also corroborates with findings by M Natsuizaka et al that found most patients with extrahepatic metastases (including extrathoracic metastases) had multiple hepatic tumour and vessel invasion.[9] Since hematogenous dissemination to the pulmonary capillaries is the proposed mechanism of the spread of lung metastases,[10] it would explain the positive association between the presence of vascular invasion and lung metastases. Multiple liver tumours may also increase the risk of microvascular invasion and tumour seeding into the lungs. It is therefore reasonable to suggest that staging chest CT could be considered for patients with multiple hepatic lesions or vascular invasion.

Our study was limited by several factors. Most notably, it was a retrospective study with selection bias for patients who received a chest CT, which was compounded by undefined selection criteria by the referring clinicians. There were also losses to follow-up (n = 5). Our small sample size also presents a statistical challenge.

Conclusion

Based on our study results, routine staging chest CT is not necessary in all treatment-naïve HCC patients prior to LRT. Its use, however, should be considered in cases with multiple (2 or more) hepatic lesions or vascular invasion. This deserves further investigation through a prospective study with defined at-risk groups.

Acknowledgement

The authors would like to thank Ms Mira Shen for assisting in the statistical analysis.

REFERENCES

1. Jemal A, Bray F, Centre MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529-38.
5. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
6. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
7. Johnson PJ. Non-surgical treatment of hepatocellular carcinoma. HPB (Oxford) 2005;7:50-5.
8. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005;40:225-35.
9. Natsuizaka M, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol 2005;20:1781-7.
10. Katyal S, Oliver JH, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000;216:698-703.
11. Kanda M, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, et al. Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors. Liver Int 2008;28:1256-63.
12. Yang T, Lu JH, Lin C, Shi S, Chen TH, Zhao RH, et al. Concomitant lung metastasis in patients with advanced hepatocellular carcinoma. World J Gastroenterol 2012;18:2533-9.
13. Restivo A, Zorcolo L, Piga S, Cocco IM, Casula G. Routine preoperative chest computed tomography does not influence therapeutic strategy in patients with colorectal cancer. Colorectal Dis 2012;14:e216-21.
14. Grossmann I, Avenarius JK, Mastboom WJ, Klaase JM. Preoperative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure. Ann Surg Oncol 2010;17:2045-50.
15. Christoffersen MW, Bulut O, Jess P. The diagnostic value of indeterminate lung lesions on staging chest computed tomographies in patients with colorectal cancer. Dan Med Bull 2010;57:A4093.
16. Brent A, Talbot R, Coyne J, Nash G. Should indeterminate lung lesions reported on staging CT scans influence the management of patients with colorectal cancer? Colorectal Dis 2007;9:816-8.
17. Jin YJ, Lee HC, Lee D, Shim JH, Kim KM, Lim YS, et al. Role of the routine use of chest computed tomography and bone scan in staging workup of hepatocellular carcinoma. J Hepatol 2012;56:1324-9.
18. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
19. Soubani AO. The evaluation and management of the solitary pulmonary nodule. Postgrad Med J 2008;84:459-66.
20. Zhang SM, Zeng ZC, Tang ZY, Sun J, Cheng JM, Liu R, et al. Prognostic analysis of pulmonary metastases from hepatocellular carcinoma. Hepatol Int 2008;2:237-43.
21. Ryder SD; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003;52 Suppl 3:iii1-i8.