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ORIGINAL PAPER

Population-based assessment of the national comprehensive cancer network recommendations for baseline imaging of hepatocellular carcinoma

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Abstract
This analysis aims to evaluate the performance characteristics of alternative baseline imaging thresholds in a cohort of hepatocellular carcinoma (HCC) patients from the Surveillance, Epidemiology, and End Results (SEER) database. HCC patients within the SEER database (2010–2015) who had complete information on clinical T and N stages as well as complete information on metastatic sites were eligible for the current study. Various performance characteristics associated with baseline imaging were investigated, including specificity, sensitivity, positive likelihood ratio (LR), negative LR, number needed to investigate (NNI), negative predictive value (NPV), positive predictive value (PPV), and accuracy. A total of 27,201 HCC patients were included. Based on current recommendations that advocate for the use of cross-sectional chest imaging in all newly diagnosed cases of HCC, these recommendations would yield a PPV of 5.0% for the detection of lung metastases. This would translate to an NNI of 20.0. When T1N0 patients were excluded from routine chest or bone imaging, this resulted in a PPV of 6.8% for the identification of lung metastases and an NNI of 14.7. Likewise, this translated to a PPV of 4.6% for the identification of bone metastases and an NNI of 21.7. Similarly, when patients with T1N0 disease and normal alpha-fetoprotein (AFP) were excluded from routine imaging, this resulted in a PPV of 5.6% for the identification of lung metastases and an NNI of 17.8. Also, this translated to a PPV of 3.8% for the identification of bone metastases and an NNI of 26.3. The current study suggests that the omission of routine baseline chest imaging may be considered in selected patients with asymptomatic early-stage HCC and normal AFP.

Keywords HCC · Staging · NCCN · Staging · Prognosis

Introduction

The initial approach to newly diagnosed cases of hepatocellular carcinoma (HCC) requires proper attention to patient characteristics (e.g., age, liver function, and other comorbidities) and disease extent [1]. Determining both intra-hepatic and extra-hepatic disease extent would be achieved with an appropriate baseline imaging approach [2].

According to the National Comprehensive Cancer Network (NCCN) guidelines (version 2.2018), triphasic abdominal imaging in the form of either computerized tomography or magnetic resonance imaging which can illustrate the characteristic vascular patterns of HCC is a prerequisite for the diagnosis of HCC [3]. Moreover, the NCCN guidelines recommend routine cross-sectional chest imaging for all newly diagnosed HCC patients. While NCCN guidelines recommend baseline bone scans only among patients with symptoms suggestive of bone metastasis, other international guidelines (e.g., Alberta) recommend routine bone scans for all comers with newly diagnosed HCC [4]. Given that HCC represents one of the most common incident cancers worldwide, the choice and schedule of baseline imaging studies would carry enormous economic implications for patients as well as for the healthcare systems. Particularly when considering the fact that HCC is more prevalent in countries with low socio-demographic indices, it is important to examine

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the value of these baseline imaging recommendations in real-world scenarios [5, 6]. There are specific baseline factors, such as alpha-fetoprotein (AFP) levels, which have been previously found to be associated with larger primary tumor size and more advanced disease, but it is unclear at this point how these factors should be incorporated into imaging recommendation to better risk stratify patients for investigations [7].

The current study hypothesized that universally recommending cross-sectional chest imaging in all cases of HCC may result in over-investigation for a significant proportion of patients with early-stage disease. Moreover, we hypothesized that most patients with early-stage HCC may not benefit from routine baseline bone scans. Therefore, our study aim was to assess the performance characteristics of different baseline imaging thresholds for staging in a contemporary cohort of HCC patients from the SEER database.

Methodology

Selection of the study cohort

Using the most recent version of the SEER*Stat software (Version 8.3.5), records of eligible patients were extracted from the SEER-18 registry [8]. The eligibility criteria considered for selecting patients in the current analysis included HCC cases diagnosed from 2010 to 2015 with complete data on clinical T and N stages as well as complete information on sites of metastases (lung and bone). Metastatic disease status was determined on the basis of clinical and/or radiological methods. In rare circumstances, this status was supplemented by pathological assessment.

Evaluation of alternative imaging thresholds

For cross-sectional chest imaging, two alternative chest imaging thresholds were evaluated. The first threshold excluded patients with clinical T1N0 disease from routine chest imaging and the second threshold excluded patients with clinical T1N0 disease and normal AFP levels from routine chest imaging. For the purposes of the second threshold, only patients with known AFP status (i.e., normal or raised) were considered. For bone scans, the same two imaging thresholds were evaluated as hypothetical scenarios in which to assess the value of routine baseline bone scans.

Statistical considerations

Descriptive statistics, including frequencies and proportions, were evaluated for baseline characteristics in the study population. These characteristics included age, race, gender, histology, clinical T and N stages, treatments, and the presence of lung and/or bone metastases.

Additional performance characteristics for each imaging threshold were considered including sensitivity, specificity, positive likelihood ratio (LR), negative LR, positive predictive value (PPV), negative predictive value (NPV), number needed to investigate (NNI), and accuracy. The SPSS program 20.0 (IBM, NY) was used to accomplish the above statistical calculations.

Results

Patient characteristics

A total of 27,201 eligible HCC patients were included in the current study (Fig. 1; consort diagram). Most patients within the cohort were aged 40–69 years (70.6%), white race (69.8%), male gender (77.3%), and HCC (not otherwise specified) histology (99.1%) (Table 1). The majority of patients did not receive surgical/ablative treatment (83.9%). Patients with normal AFP levels represented 21.5% of the study population while patients with T1N0 disease represented 44.8%. Bone, lung, and brain metastases were reported in 3.5%, 5.0%, and 0.3% of cases, respectively. Based on the current NCCN recommendations that

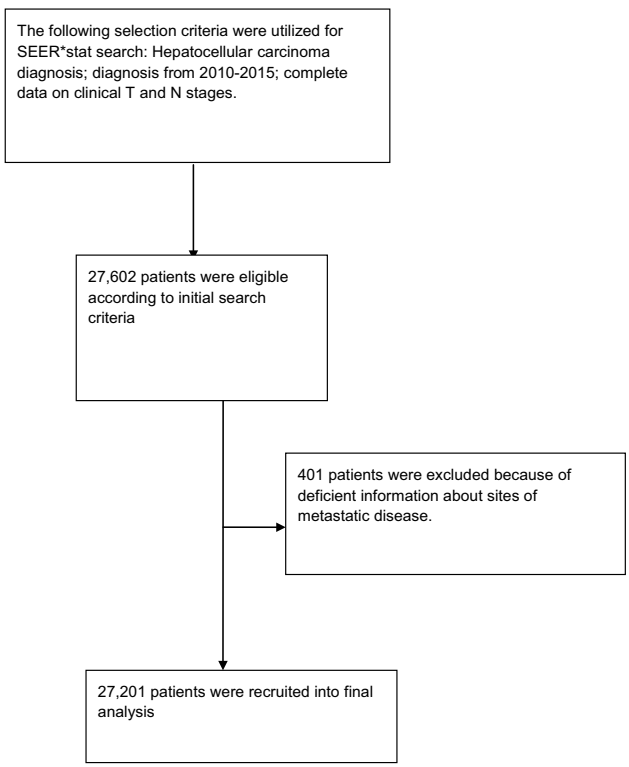

Fig. 1 Flow chart of selection process of the patient cohort

Table 1 Baseline characteristics of patients in the study (N = 27,201 patients)

Parameter	N (%)
Race	
White	18,982 (69.8%)
Black	3835 (14.1%)
Others	4249 (15.6%)
Unknown	135 (0.5%)
Sex	
Females	6198 (22.8%)
Males	21,003 (77.3%)
Age	
< 40 years	242 (0.9%)
40–69 years	19,197 (70.6%)
≥ 70 years	7762 (28.5%)
Histology	
HCC, NOS	26,968 (99.1%)
Other variants	233 (0.9%)
Surgery/local ablation	
No	22,833 (83.9%)
Local ablation	3628 (13.3%)
Resection/transplantation	636 (2.5%)
Unknown	104 (0.3%)
Chemotherapy	
Yes	13,148 (48.3%)
No/unknown	14,053 (51.7%)
Radiotherapy	
Yes	2674 (9.9%)
No/unknown	24,527 (90.1%)
Bone metastases	
Yes	943 (3.5%)
No	26,258 (96.5%)
Brain metastases	
Yes	27 (0.3%)
No	27,129 (99.7%)
Lung metastases	
Yes	1358 (5%)
No	25,843 (95%)
Baseline alpha-fetoprotein	
Normal	5839 (21.5%)
Elevated	16,593 (61%)
Unknown	4769 (17.5%)
TN stage	
T1N0	12,188 (44.8%)
> T1N0	15,013 (55.2%)

endorse the use of cross-sectional chest imaging for all cases of newly diagnosed HCC, these guidelines would yield a PPV of 5.0% for the detection of lung metastases. This would translate to an NNI of 20 for lung metastases. Likewise, based on other international recommendations (e.g., Alberta) that propose the routine use of bone scans for newly diagnosed HCC cases, this would yield a PPV of 3.5% and an NNI of 28.5 for bone metastases.

Evaluation of alternative baseline imaging thresholds

The first hypothetical imaging threshold that was examined consisted of the exclusion of clinical T1N0 patients from routine cross-sectional chest imaging and bone scans. In the study cohort, 12,188 patients had clinical T1N0 disease, whereas 15,013 patients had more advanced disease for which chest imaging and bone scans would still be indicated even after applying the alternative imaging threshold.

Using the new imaging threshold, 330 patients (1.2%) with lung metastases would have been undetected and 245 patients (0.9%) with bone metastases would have been undetected. Conversely, 13,985 patients (51.4%) would have had chest imaging despite the absence of lung metastases, and 14,315 patients (52.6%) would have undergone bone imaging despite the lack of bone metastases.

This resulted in a PPV of 6.8% and an NNI of 14.7 for the identification of one case of lung metastases. Similarly, this resulted in a PPV of 4.6% and an NNI of 21.7 for the identification of one case of bone metastases. Additional endpoints that included sensitivity, specificity, NPV, and accuracy are summarized in Table 2. For lung metastasis, positive LR would be 1.39 and negative LR would be 0.52 in this setting. For bone metastasis, positive and negative LR would be 1.35 and 0.57, respectively.

The second hypothetical imaging threshold that was evaluated consisted of the exclusion of patients with T1N0 disease and normal AFP levels from routine chest and bone imaging. For the purposes of this threshold, only patients with known AFP status were considered (N = 22,432 patients). In the study cohort, 3292 patients had T1N0 disease with normal AFP levels, whereas 19,140 patients had more advanced disease in which chest imaging and bone scans would still be indicated despite applying the new imaging threshold.

Using this alternative imaging threshold, 40 patients (0.1%) with lung metastases would have been undetected and 34 patients (0.1%) with bone metastases would have been undetected. In contrast, 18,065 patients (80.5%) would have undergone chest imaging in the absence of lung metastases, and 18,417 patients (81%) would have received bone scans despite not having bone metastases.

This resulted in a PPV of 5.6% for the identification of lung metastases and an NNI of 17.8. Similarly, this resulted in a PPV of 3.8% for the identification of bone metastases and an NNI of 26.3. Additional performance characteristics are described in Table 3. For lung metastasis, positive and negative LR would be 1.13 and 0.23, respectively. For bone

metastasis, positive and negative LR would be 1.12 and 0.3, respectively.

Discussion

The typical treatment decision-making process for newly diagnosed HCC patients would usually entail a detailed assessment of multiple patient-related and disease-related factors to balance the pros and cons of therapy. Among the many factors that are considered, intra-hepatic and extra-hepatic extensions of the disease are the most important and can be evaluated using cross-sectional imaging (Table 4).

With regard to the detection of lung metastases, the current study suggests that adherence to the current NCCN recommendations for baseline imaging in HCC would fail to detect only very few patients with lung metastases. The specificity of this approach, however, is limited and the omission of routine chest imaging in asymptomatic patients could be considered in selected early-stage patients with normal AFP levels. Similarly, for the detection of bone

Table 2 Performance characteristics when excluding stage T1N0 from routine baseline chest imaging

	Reference: lung metastases as shown on chest imaging		NNI (1/PPV) 14.7
	Lung metastases (1358 patients)	No lung metastases (25,843 patients)	
≥Stage T2N0 (15,013 patients)	TP N = 1028 patients	FP N = 13,985 patients	PPV = TP/(TP + FP) 6.8%
Stage T1N0 (12,188 patients)	FN N = 330 patients	TN N = 11,858 patients	NPV = TN/(TN + FN) 97.3%
	Sensitivity = TP/TP + FN 75.7%	Specificity = TN /FP + TN 45.9%	Accuracy (TN + TP/All) 4.9%

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value, *NNI* number needed to investigate

Table 3 Performance characteristics when excluding stage T1N0 from routine baseline bone imaging

	Reference: lung metastases as shown on bone scan		NNI (1/PPV) 21.7
	Bone metastases (943 patients)	No bone metastases (26,258 patients)	
≥Stage T2N0 (15,013 patients)	TP N = 698 patients	FP N = 14,315 patients	PPV = TP/(TP + FP) 4.6%
Stage T1N0 (12,188 patients)	FN N = 245 patients	TN N = 11,943 patients	NPV = TN/(TN + FN) 98%
	Sensitivity = TP/TP + FN 74%	Specificity = TN /FP + TN 45.5%	Accuracy (TN + TP/All) 4.6%

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value, *NNI* number needed to investigate

Table 4 Performance characteristics when excluding stage T1N0/normal alpha-fetoprotein from routine baseline chest imaging

	Reference: lung metastases as shown on chest imaging		NNI (1/PPV) 17.8
	Lung metastases (1115 patients)	No lung metastases (21,317 patients)	
>Stage T1N0/normal AFP (19,140 patients)	TP N = 1075 patients	FP N = 18,065 patients	PPV = TP/(TP + FP) 5.6%
Stage T1N0/normal AFP (3292 patients)	FN N = 40 patients	TN N = 3252 patients	NPV = TN/(TN + FN) 98.8%
	Sensitivity = TP/TP + FN 96.4%	Specificity = TN /FP + TN 15.3%	Accuracy (TN + TP/All) 19.2%

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value, *NNI* number needed to investigate

Table 5 Performance characteristics when excluding stage T1N0/normal alpha-fetoprotein from routine baseline bone imaging

	Reference: lung metastases as shown on bone scan		NNI (1/PPV) 26.3
	Bone metastases (757 patients)	No bone metastases (21,675 patients)	
>Stage T1N0/normal AFP (19,140 patients)	TP N = 723 patients	FP N = 18,417 patients	PPV = TP/(TP + FP) 3.8%
Stage T1N0/normal AFP (3292 patients)	FN N = 34 patients	TN N = 3258 patients	NPV = TN/(TN + FN) 99%
	Sensitivity = TP/TP + FN 95.5%	Specificity = TN /FP + TN 15%	Accuracy (TN + TP/All) 17.7%

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value, *NNI* number needed to investigate

metastases, the current study further suggests that routine baseline bone scan should not be considered among asymptomatic early-stage patients with HCC (Table 5).

A frequently cited argument when recommending routine baseline chest and bone imaging for all newly diagnosed HCC patients is that some asymptomatic patients with apparent early-stage localized disease may actually be harboring occult metastatic disease. The current study shows that the probability of this is quite infrequent and that the sensitivity of the staging approach can still be maintained when omitting chest/bone imaging for selected early-stage asymptomatic patients.

Our results are largely consistent with those from a Korean research group that evaluated the importance of routine CT chest and bone scans (versus chest-X ray only) among patients with newly diagnosed HCC. Similar to our findings, the Korean study showed that routine CT chest and bone scan revealed additional metastases only in 1.1% of patients [9].

It has to be underscored, however, that the current results apply mainly to asymptomatic patients. For patients with symptoms suggestive of distant metastases, it continues to be clinically important to investigate them properly regardless of their T or N stage.

Before adopting the results of the current analysis, several limitations should be highlighted. These include the fact that the SEER database does not actually provide information regarding specific details of imaging studies performed for each individual patient. Nevertheless, as most patients were treated in academic or community oncology centers within the US, it is expected that most of these patients were thoroughly investigated and imaged prior to starting therapy. Another potential limitation is related to the use of PPV and NPV in this study since these metrics are affected by the prevalence of the condition. To overcome this weakness, positive and negative LRs were reported for each proposed imaging threshold. Additionally, all cases in the current study were diagnosed and treated in the US. Therefore, discretion should be exercised before generalizing the results to other treatment settings or jurisdictions. Due to data not being available, another limitation relates to our inability to differentiate between T1a and T1b disease even though the latter is associated with a worse prognosis. Conversely, these limitations should be weighed against the study's strengths, including its large cohort size as well as the rigorous data quality assurances of the SEER database.

Beyond performance characteristics, other aspects that need to be considered when evaluating the value of a particular baseline imaging approach for HCC should include the potential economic impact of universally recommending a specific imaging modality, the rare possibility of contrast-induced toxicity (e.g., nephrotoxicity or allergy), and the psychological burden on patients associated with more intensive imaging strategies [10, 11]. It should be further noted that imaging, particularly evaluations of the chest, may be necessary if a patient is potentially eligible for a resection or a liver transplant. In this scenario, the purpose of imaging would be to rule out extra-hepatic disease. This is justified because the cost of this imaging is likely significantly less than the cost of proceeding with a futile resection or transplant. More importantly, such an approach also spares the patient from the potential complications of an unnecessary surgical procedure.

In conclusion, the current study suggests that the omission of routine baseline chest imaging could be considered in selected patients with asymptomatic early-stage HCC and normal AFP levels. Moreover, routine baseline bone scan might also be safely omitted among asymptomatic patients with early-stage disease.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

References

1. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii41–8.
2. Oweira H, Petrausch U, Helbling D, Schmidt J, Mehrabi A, Schob O, et al. Prognostic value of site-specific extra-hepatic disease in hepatocellular carcinoma: a SEER database analysis. Expert Rev Gastroenterol Hepatol. 2017;11:1–7.
3. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed 6 Aug 2018.
4. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gi007-hepatocellular-carcinoma.pdf. Accessed 6 Aug 2018.
5. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The global burden of cancer 2013. JAMA Oncol. 2015;1(4):505–27.
6. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3(4):524–48.
7. Abdel-Rahman O. Assessment of the discriminating value of the 8th AJCC stage grouping for hepatocellular carcinoma. HPB (Oxford). 2018;20(1):41–8.
8. Surveillance, Epidemiology and End Results Program. About the SEER Program. http://seer.cancer.gov/about. Accessed 25 June 2016.
9. 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(6):1324–9.
10. Deek H, Newton P, Sheerin N, Noureddine S, Davidson PM. Contrast media induced nephropathy: a literature review of the available evidence and recommendations for practice. Aust Crit Care. 2014;27(4):166–71.
11. Ziegler L, Hill K, Neilly L, Bennett MI, Higginson IJ, Murray SA, et al. Identifying psychological distress at key stages of the cancer illness trajectory: a systematic review of validated self-report measures. J Pain Symptom Manage. 2011;41(3):619–36.