Diagnostic Imaging and Biopsy Use Among Elderly Medicare Beneficiaries With Hepatocellular Carcinoma

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Abstract

Purpose: Diagnostic imaging is effective for evaluating patients suspected of having hepatocellular carcinoma (HCC). Although the diagnosis can be established with imaging alone, diagnostic biopsy may be useful for patients with tumors measuring 1 to 2 cm. To date, biopsy and imaging use among patients with HCC has not been evaluated in the general community.

Patients and Methods: This cohort study used Surveillance, Epidemiology, and End Results (SEER) -Medicare data (2002-2005) evaluating biopsy, imaging modalities (ultrasound, computed tomography [CT] scan, and/or magnetic resonance imaging [MRI]), and HCC risk factors.

Results: Of 3,696 patients, 1,197 (32.4%) underwent one or more biopsies, with no change in yearly biopsy rate (trend test,

$P = .64$). Patients with tumors > 5 cm were most likely to receive biopsies (35.3%), with increasing rates of biopsy for larger tumors ($P = .001$). Patients who received biopsies underwent more imaging than those who did not ($P < .001$) and were more likely to have an HCC risk factor. Tumor size > 5 cm in the setting of a concurrent HCC risk factor increased the odds of biopsy. In 47.8% of patients, the diagnostic sequence was not consistent with contemporary evidence-based guidelines.

Conclusions: Despite widespread availability and use of CT scan and MRI, one third of HCC patients undergo biopsy, suggesting a problem with the performance and/or quality of diagnostic imaging or that providers do not believe imaging alone is sufficient to establish the diagnosis. Understanding factors that drive biopsy use may help improve the care of patients with HCC.

Introduction

For patients with hepatocellular carcinoma (HCC), treatment of localized disease offers the best chance for prolonged survival. However, achieving this hinges on early diagnosis. In this regard, the role of biopsy has been debated. Although the diagnostic yield for computed tomography (CT) and magnetic resonance imaging (MRI) alone are quite good, the false-positive rate in the setting of chronic liver disease or cirrhosis may be as high as 7.5%–15.2%.¹ As a result, 7% of donor livers in the United States may be transplanted into patients thought to have HCC but subsequently discovered to only have cirrhotic nodules.² With regard to biopsy, the risks of needle track seeding,³ tumor dissemination or recurrence,⁴ and a possible negative impact on disease-free survival after resection are worthy of discussion.⁵ Because of these and numerous other controversies in the treatment of patients with HCC, the European Association for the Study of Liver (EASL) created international consensus guidelines for HCC surveillance, diagnosis, and treatment.⁶ These recommendations include patients for whom biopsy was considered most appropriate: those with lesions 1 to 2 cm in diameter.

EASL guidelines have been adopted by the American Association for the Study of Liver Diseases (AASLD) and the National Cancer Care Network (NCCN), which further restricted recommendations for biopsy to patients with 1- to 2-cm lesions for whom dual modality multiphase imaging cannot establish

the diagnosis.^{7,8} To our knowledge, diagnostic biopsy and imaging use in the management of HCC has not been assessed in the United States to date. Thus, we used a population-based approach to evaluate diagnostic biopsy and imaging use among patients with HCC; identify patient characteristics associated with receipt of biopsy; and compare care provided in the general community to the only available, fully defined diagnostic criteria of the time (NCCN guidelines during this study period did not explicitly describe the role of diagnostic imaging in the work-up of a liver nodule suspected to be HCC). Our underlying hypothesis was that biopsy is overused in the treatment of patients with HCC.

Patients and Methods

Data

This cohort study was approved by the National Cancer Institute (NCI) and the University of Washington institutional review board. The NCI reviews all manuscripts submitted to peer-reviewed publications to ensure the confidentiality of all patients and practitioners contained within the database. This article was approved on February 26, 2010. The most current linkage (including incident HCC cases through 2005) of the Surveillance, Epidemiology, and End Results (SEER) -Medicare data set was used. SEER is a national tumor registry sponsored by NCI that captures 26% of incident cancers in the United States.⁹ SEER records for Medi-

care beneficiaries are subsequently linked to their Medicare claims. A complete discussion of content, quality, and generalizability of results using SEER-Medicare has been detailed elsewhere.¹⁰⁻¹²

Study Participants

From SEER records, we identified 13,327 patients with an incident diagnosis of HCC between 2002 and 2005. Sequential exclusions were then made for the following: diagnosed at autopsy or by death certificate ($n = 694$); histology inconsistent with HCC ($n = 2,578$; [International Classification of Diseases (ICD) -O-3 codes other than 8170-8175 were excluded]); age less than 66 years ($n = 3,374$); second malignancy diagnosed within 6 month before the HCC diagnosis ($n = 104$); and concurrent enrollment in a health maintenance organization (HMO) and/or not continuous fee-for service status for 1 year before diagnosis ($n = 2,881$). This resulted in a final cohort of 3,696 patients. To enhance the generalizability of our findings, we chose to exclude patients younger than 66 years, because nonelderly patients enrolled in Medicare are either disabled, have end-stage renal disease, or both. Because the data set does not provide information on procedural indication and because liver biopsy and noninvasive imaging techniques may be used in the management of other malignancies, patients with a second malignancy within 6 months before their HCC diagnosis were excluded. Patients who were not entirely fee-for-service over the time period of interest were excluded because Medicare claims are not consistently submitted by HMOs.

Variables

A Klabunde-modified Charlson comorbidity index was calculated by using ICD-9-CM diagnosis codes from both the Physician/Carrier and Hospital Outpatient claims files in the year before diagnosis.¹³ Patient demographic and clinical information was available from SEER records. Indicators of low income and low education were based on the lowest quartile of median income and the proportion without a high school education within a given patient's zip code, respectively. Biopsy procedures and imaging modalities were defined using either the Healthcare Common Procedure Coding System within the Physician/Carrier and Outpatient files or ICD-9-CM procedure codes from the MEDPAR and Outpatient files (Appendix Table A1, online only). Common HCC risk factors⁸ were ascertained from all available diagnosis codes (Physician/Carrier, Outpatient, and MEDPAR).

We considered a biopsy as performed for diagnostic purposes if it occurred within 3 months before diagnosis. Claims consistent with diagnostic imaging procedures or diagnostic codes for HCC risk factors were sought between the earliest biopsy date and 1 year before diagnosis and used to calculate the total number of imaging studies and the total number of risk factors for each patient. Claims and diagnostic codes before the earliest biopsy were considered because only existing risk factors or known imaging results would likely bear on the decision to perform a biopsy. For patients who did not undergo biopsy, all claims and diagnostic codes in the year before diagnosis were

evaluated for ascertainment of risk factors and imaging. In a sensitivity analysis, we restricted ascertainment of imaging counts and HCC risk factors to a 6-month window before the earliest biopsy date or diagnosis.

The sequence of imaging and biopsies was also examined and compared with guidelines, which recommended the following: lesion <1 cm—interval follow-up ultrasound (US); lesion 1 to 2 cm—diagnostic biopsy; lesion >2 cm—two contrast-enhanced imaging studies (CT and MRI) to identify classic enhancement.⁶ In the United States, contrast-enhanced US is not used, and therefore US alone cannot be considered a diagnostic imaging modality. Thus, the following diagnostic sequence was considered to be inconsistent with guidelines: lesion 1 to 2 cm receiving multiple imaging procedures (because immediate biopsy would have been indicated); lesion >2 cm receiving only US or a US and either CT or MRI (because both CT and MRI would have been recommended); lesion >1 cm receiving US after a CT/MRI or a noncontrast CT/MRI after a contrast-enhanced study (because US or noncontrast studies would not provide additional diagnostic information).

Statistical Analyses

Statistical analyses were performed with STATA 10.1 (StataCorp, College Station, TX). All comparisons were two-sided, with significance at the $P < .05$ level. Categorical and continuous comparisons across biopsy status were obtained by using χ^2 and t test, respectively. Parametric and nonparametric trend tests were used to evaluate changes in rates. Multiple logistic regression, using robust SEs and adjusting for regional clustering, was used to evaluate the association between patient demographic and clinical factors and receipt of diagnostic biopsy. An interaction term between the presence of an HCC risk factor and tumor size was statistically significant by a 2-degree of freedom Wald test ($P = .007$). To deal with missing values, the regression analysis was performed using five sets of imputed covariate data obtained through multiple imputation by chained equations.¹⁴

Results

Overall, 3,696 patients met study inclusion criteria. The mean age ($\pm$ standard deviation) of the cohort was 76.3 ± 6.4 years; 66.0% were male, 68.3% were white, and 70.8% had a comorbidity index of ≥ 1 . One third (32.4%) of patients underwent at least one diagnostic biopsy (11.4% received two or more biopsies). Yearly biopsy rate remained stable (31.9%–33.1%; trend test, $P = .64$).

Biopsy Use

Table 1 shows the demographic and clinical characteristics of patients who did and did not undergo diagnostic biopsy. Demographic characteristics were generally evenly distributed between both groups. Patients who underwent a biopsy had significantly higher comorbidity indices ($P < .001$), more often had a prior malignancy ($P = .002$), and had larger tumors ($P = .01$). Table 2 shows biopsy use stratified by tumor size. Among

Table 1. Demographic and Tumor Characteristics of the HCC Cohort (N = 3,696)

Characteristic	No Biopsy (n = 2,499)	Biopsy (n = 1,197)	P
Mean age $\pm$ SD, years	76.3 $\pm$ 6.5	76.4 $\pm$ 6.2	.60
Age, years (%)			.19
$\leq$ 70	25.0	23.1	
71-75	26.9	26.1	
76-80	25.1	26.7	
81-85	15.4	17.6	
$\geq$ 86	7.7	6.6	
Male sex (%)	66.8	64.2	.11
Race, %			.05
White	67.6	70.5	
Black	7.6	8.7	
*Other	24.8	20.8	
Low income, %	17.3	18.0	.61
Low education, %	4.4	3.8	.69
Missing	4.3	4.4	
Married, %	57.3	55.0	.22
Missing	3.3	2.8	
Geographic region			< .001
West	56.1	46.3	
East	19.0	24.1	
Midwest	11.2	13.8	
South	13.8	15.9	
Residence, %			.47
Metropolitan	88.8	88.9	
Urban/rural	11.2	11.1	
Comorbidity index, %			< .001
0	32.1	23.3	
1	28.8	27.4	
2	15.4	17.0	
$\geq$ 3	23.8	32.3	
HCC risk factor, %	50.1	55.9	.001
Prior malignancy, %	18.3	22.7	.002
Tumor size, %			.01
$\leq$ 2 cm	5.4	4.0	
2.1-5 cm	24.6	21.8	
$>$ 5 cm	34.9	39.7	
Missing	35.2	34.5	
$>$ 1 lesion, %	55.3	53.6	.55
Missing	17.2	17.3	

Abbreviations: HCC, hepatocellular carcinoma; SD, standard deviation.

* In the biopsy and nonbiopsy groups, information on race was missing for < 1% of patients.

patients with known tumor size, those with tumors $>$ 5 cm were most likely (35.3%) to undergo a biopsy (60.6% of all biopsies), with a significant trend toward use of biopsy for larger tumors ($P = .001$).

Imaging Use

Overall, 48.4% of patients underwent at least one US (62.0% biopsied v 41.8% nonbiopsied; $P < .001$), 56.3% at least one

CT scan (77.0 v 46.3%; $P < .001$), and 15.1% at least one MRI (18.7 v 13.4%; $P < .001$). CT scan was the most commonly used individual imaging modality (26.1 v 16.8%). More commonly (40.4%), patients underwent more than one kind of imaging modality (55.8 v 33.0%). Patients who received biopsy underwent more imaging ($P < .001$) than those who did not, particularly patients with tumors $>$ 2 cm (Table 3).

The proportion of diagnostic sequences that were inconsistent with guideline recommendations (47.8%) was constant over the study period (45.4%–54.2%; trend test, $P = .87$). Only 25.2% of patients with a 1- to 2-cm lesion received a diagnostic biopsy. The majority of patients with tumors $\leq$ 2 cm (56.8%) received multimodal imaging. Patients who underwent biopsy more commonly (65.6% v 39.2%; $P < .001$) received a diagnostic sequence that was inconsistent with guidelines. Increasing tumor size was associated with decreasing guideline nonconformity among patients who did not receive biopsy ($P < .001$). By comparison, among patients who received biopsy, there was a consistently high rate ($>$ 50%) of nonconformity unassociated with tumor size (Table 2).

Associated Factors

Patients who received biopsy had more HCC risk factors (Appendix Table A2, online only) than those who did not (55.9% v 50.1%; $P = .001$). Comparing patients with lesion $>$ 5 cm, those who underwent biopsy had a higher prevalence of HCC risk factors than those who did not undergo biopsy (49.3 v 38.8%, $P < .001$). Factors associated with the receipt of diagnostic biopsy were evaluated (Appendix Table A3, online only). A diagnostic sequence that was inconsistent with guidelines was associated with a nearly three-fold increase in the odds of biopsy (odds ratio [OR] 2.98; 95% CI, 2.67 to 3.34). Increasing comorbidity was associated with a monotonic increase in the odds of biopsy. As compared to patients with a comorbidity index of 0, those with comorbidity indices of 1, 2, or $\geq$ 3 were at 30% (95% CI, 1.08 to 1.57), 54% (95% CI, 1.31 to 1.82), and 80% (95% CI, 1.22 to 2.67) higher odds of undergoing biopsy, respectively. Patients who had a prior malignancy were at 32% (95% CI, 1.17 to 1.51) higher odds of undergoing biopsy. As compared to patients with lesions $\leq$ 2 cm and no HCC risk factors, those with tumors $>$ 5 cm and at least one HCC risk factor were at a more than two-fold higher odds (OR 2.17; 95% CI, 1.36 to 3.45) of biopsy.

Sensitivity Analyses

The cohort was restricted to those patients with diagnostic codes consistent with chronic liver disease or cirrhosis (n = 1,440). Although the amount of imaging remained higher among cirrhotic patients who underwent biopsy, differences were only significant among patients with tumors $>$ 5 cm. There were also no significant differences in the mean number of risk factors among cirrhotic patients who did or did not undergo biopsy. All remaining parts of the analysis were similar. In a second sensitivity analysis, we restricted ascertainment of prebiopsy or prediagnosis imaging to a 6-month, rather than 1-year, window. Results from this analysis were also similar.

Table 2. Biopsy Use Stratified by Tumor Size

Characteristic	≤ 2 cm (n = 183)		2.1-5 cm (n = 875)		> 5 cm (n = 1,346)		Unknown (n = 1,292)*		P†
	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI	
≥ 1 biopsy	26.3	20.0 to 33.2	29.8	26.8 to 33.0	35.3	32.7 to 37.9	32.0	29.4 to 34.6	.001
Guideline nonconformity‡									
Biopsy	58.3	43.2 to 72.4	67.8	61.8 to 73.4	65.1	60.6 to 69.3	N/A		.90
No biopsy	55.6	46.8 to 64.1	43.2	39.2 to 47.2	33.9	30.7 to 37.1	N/A		< .001

Abbreviation: N/A, not applicable.

* Those with unknown tumor size were excluded from the trend tests.

† Parametric test for trend.

‡ Guideline nonconformity represents the proportion of patients (stratified by biopsy status) whose diagnostic sequence did not conform to European Association for the Study of Liver consensus guideline recommendations.

Table 3. Mean (± standard deviation) No. of Imaging Studies, by Biopsy Use and Tumor Size

Imaging use and tumor size	No Biopsy	Biopsy	P
Non-ultrasound imaging			
≤ 2 cm	1.6 ± 1.4	1.5 ± 1.0	.82
2.1-5 cm	1.2 ± 1.3	1.7 ± 1.2	< .001
> 5 cm	0.8 ± 1.0	1.5 ± 0.9	< .001
Unknown	0.9 ± 1.2	1.5 ± 1.1	< .001
Total	1.0 ± 1.2	1.5 ± 1.0	< .001
No. of imaging studies			
≤ 2 cm	2.4 ± 2.1	2.4 ± 1.4	.93
2.1-5 cm	2.1 ± 1.8	2.8 ± 1.6	< .001
> 5 cm	1.3 ± 1.4	2.3 ± 1.7	< .001
Unknown	1.4 ± 1.7	2.3 ± 1.6	< .001
Total	1.6 ± 1.7	2.4 ± 1.7	< .001

Discussion

The goal of this population-based study was to characterize the use of diagnostic imaging and biopsy among patients with HCC. We found that one in three patients underwent diagnostic biopsy, with greater use among patients with larger tumors. Also, when we compared care in the general community with the only established evidence-based diagnostic guidelines of the time, we found that half of patients received a diagnostic sequence inconsistent with these recommendations. Furthermore, patients who received a guideline-inconsistent diagnostic sequence were three times more likely to undergo biopsy.

There are several reasons to suspect that the most likely explanation for these findings is difficulty establishing the diagnosis by using imaging alone. First, biopsy was increasingly used among patients with the largest tumors—tumors requiring only properly performed, contrast-enhanced imaging to arrive at a diagnosis. Also, patients who underwent biopsy (in particular those with > 5 cm lesions) had a higher prevalence of HCC risk factors. The presence of a large lesion in the setting of one or more risk factors should raise a practitioner's suspicion of HCC. Finally, when comparing patients with the same-sized lesions, those who underwent biopsy on average received more imaging studies. The proper timing of contrast administration

during a CT/MRI is crucial for identifying characteristic HCC contrast enhancement. The manner in which imaging is requested (which could affect the contrast administration protocol), quality of imaging protocols, and radiologic interpretation may vary among hospitals that treat patients with HCC infrequently. Taken in combination, diagnostic confusion resulting from improperly requested or inadequately performed/interpreted imaging seems a likely contributing factor to the higher-than-expected biopsy rate among patients with large tumors.

Another possible reason is unnecessary biopsy use as a confirmatory procedure if providers did not believe imaging alone was sufficient to establish an HCC diagnosis. As compared with the paradigm for many other cancers, biopsy for HCC is not necessary when imaging alone is potentially adequate (ie, in patients with lesions > 2 cm). Because we excluded patients with other malignancies diagnosed within 6 months of their HCC diagnosis, the likelihood that biopsies were performed for reasons other than evaluation of a possible HCC lesion (ie, diagnosing metastatic disease from an extrahepatic primary) is low. It is also possible that biopsy use may have reflected prevailing misconceptions about the disease, (ie, HCC is always large, symptomatic, and rapidly lethal). For example, a practitioner may have been reluctant to diagnose HCC in a patient who presented in good health and might therefore have performed a biopsy.

Prior work has shown that guideline adherence for various stages of cancer care is generally poor for other common (breast, colon, and cervical)¹⁵⁻¹⁸ and less common (testicular)¹⁹ cancers. Similarly, as many as 30% to 50% of patients in the United States may not be receiving recommended care.²⁰ Much of this nonadherence may be explained by rapid and continual evolution of technology and expert opinion. It has been estimated that primary care practitioners need to read an average of 20 research studies per day, every day, to keep pace with current evidence-based practice.²¹ In the face of decreasing physician reimbursement (requiring higher patient turn-over to ensure practice sustainability) and increasing regulatory pressure to practice evidence-based medicine, our findings may reflect a systematic problem within the U.S. health care system. If community practitioners do not have access to (or are unaware of) guidelines, the guidelines cannot be expected to affect cur-

rent practice. Future work evaluating the impact of AASLD and/or NCCN diagnostic guidelines for HCC might be useful to help ascertain the extent to which guidelines penetrate into the general community.

Alternatively, if physicians are aware of but do not have the resources to properly implement evidence-based guidelines, a more feasible approach might be prudent. One possible alternative might be referring patients with a liver mass in whom the diagnosis of HCC seems likely to a referral center with experience in the diagnosis and treatment of these patients. Rather than subjecting patients to excess imaging studies and an invasive diagnostic procedure, prompt referral could potentially shorten time to diagnosis, decrease patient risk from additional invasive procedures, and decrease unnecessary health care use. Furthermore, current NCCN and AASLD guidelines are even more restrictive regarding biopsy. Therefore, biopsy use and diagnostic nonconformity in the context of the revised guidelines are likely to be even more widespread. Future studies focusing on practitioner and institutional factors associated with guideline compliance and imaging accuracy would be helpful in this regard. Quality improvement initiatives should also focus on the quality of imaging and on increasing general adherence to evidence-based guidelines.

There are several notable limitations to this study. This cohort was limited to elderly Medicare beneficiaries with fee-for-service coverage. If diagnostic biopsy is used differently among nonelderly/non-Medicare beneficiaries, our results may not be broadly generalizable. Also, we compared care provided in the general community to international consensus guidelines (because no such guidelines existed in the United States during this study period). Although we did not expect that providers would have been aware of these European guidelines, we found this comparison informative because EASL guidelines were based on the best available evidence of the time. Ascertainment of biopsy and imaging procedures was based on provider billing claims; therefore, some patients might have been nondifferentially misclassified if incorrect billing codes were filed. There was a relatively high proportion of missing data on several tumor variables, which may have biased our results. However, the degree of missingness was similar between patients who did and did not undergo biopsy. In addition, even if all patients with missing data had lesions ≤ 2 cm, that still cannot explain why patients with tumors > 2 cm required so much imaging before biopsy (relative to those who did not receive biopsy) and why such a high proportion of these same patients with large lesions required biopsy. Certain clinical data such as tumor location, size of each lesion (for patients with > 1 lesion), and total number of lesions (other than one or > 1) were not available. This might have been helpful in identifying patients who would not have been expected to undergo subsequent therapeutic intervention(s). Data on the indication for biopsy and the indication for, results of, and quality of imaging procedures were also not available. Such data could have allowed ascertainment of the degree of diagnostic uncertainty associated with each imaging technique and the necessity of biopsy for a given patient. In addition, without the indication for a given imaging

procedure, the amount of diagnostic imaging used may have been overestimated, or certain patients could have been misclassified as having received a nonconforming imaging sequence (eg, patients might have undergone US for a reason other than evaluation of their liver lesion). However, our results were robust in a sensitivity analysis using a shorter prediagnosis time window. Data on α -fetoprotein level might have also been useful to identify patients at higher risk for a positive HCC diagnosis. Finally, although we were able to ascertain the presence of diagnostic codes consistent with common HCC risk factors, it is unclear how strongly correlated the presence of the actual condition is with these billing codes. In particular, data on the severity of a patient's cirrhosis (Child-Pugh classification) might have been useful.

We identified a high overall rate of biopsy, with a high proportion of use among patients with larger tumors, suggesting a problem either with the quality of diagnostic imaging or with how these results are interpreted and used by providers evaluating patients with HCC. Furthermore, much of the diagnostic care provided for patients with HCC was not consistent with evidence-based guidelines, which may indicate suboptimal or wasteful care. At least one prior study has also documented poor adherence to treatment-based guidelines for HCC in the general community.²² This could indicate a widespread lack of knowledge about proper care for these patients. Understanding factors that drive biopsy use and how to improve the diagnostic yield of imaging may be important parts of quality improvement initiatives focusing on the care provided to patients with HCC.

Accepted for publication on November 17, 2010.

Acknowledgment

The authors had full access to the data used in this study and take responsibility for the integrity of the data and the accuracy of the analysis. This study used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. We acknowledge the efforts of the Applied Research Program, National Cancer Institute (NCI); the Office of Research, Development and Information, Centers for Medicare & Medicaid Services (CMS); Information Management Services; the SEER Program tumor registries in the creation of the SEER-Medicare database. The views expressed do not necessarily represent those of the NCI, NIH, CMS, or the University of Washington. Neither funding body played a role in the conduct of this study.

N.N.M. was supported by the National Institutes of Health under a Ruth L. Kirschstein National Research Service Award (1F32CA136135-01) from the NCI. Dr Bruix was supported by a grant from the Instituto de Salud Carlos III (Grant No. PI08/0146).

This work was presented at the annual meeting of the American Society of Clinical Oncology, June 5-9, 2010, Chicago, IL.

We thank Kara E. MacLeod, MPH, for her help in constructing the data set.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.2010.000116

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