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Incidental versus preoperatively diagnosed hepatocellular carcinoma in liver transplantation: a clinicopathologic comparison

Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Despite advances in diagnostic imaging, incidental HCC (iHCC) continues to be detected on histopathologic evaluation of liver explants. The clinicopathologic features and outcomes of iHCC compared with preoperatively diagnosed (known) HCC (kHCC) remain incompletely characterized.

Methods: A retrospective search of pathology databases at two academic institutions (University Hospitals Cleveland Medical Center and Northwestern Memorial Hospital) identified liver explants containing HCC from 2011 to 2025. Clinicopathologic features and follow-up data were collected. Cases were classified as kHCC (detected on preoperative imaging) or iHCC (identified only on explant pathology). Comparisons were performed using chi-square tests for categorical variables and t-tests for continuous variables, with statistical significance defined as $p < 0.05$.

Results: Of 134 HCC cases identified, 120 (89.6%) were kHCC and 14 (10.4%) were iHCC. Patients with iHCC were slightly younger (mean 57.6 vs. 62.1 years, $p = 0.06$) and included a higher proportion of females (35.7% vs. 19.2%, $p = 0.12$). No iHCC patient had multiple underlying liver diseases, compared with 10.0% of kHCC patients ($p < 0.001$). Fatty liver disease was significantly more prevalent in the iHCC group (78.6% vs. 56.7%, $p = 0.04$), whereas hepatitis C virus infection was more common in kHCC (41.7% vs. 7.1%, $p < 0.001$). Alpha-fetoprotein levels at diagnosis and transplantation did not differ significantly between groups. Magnetic resonance imaging was the predominant preoperative modality in kHCC (92.5%) but was used in only 28.6% of iHCC cases. Tumors in the iHCC group were significantly smaller (mean 1.4 cm vs. 3.1 cm, $p < 0.001$), and poorly differentiated morphology was observed exclusively in kHCC. On follow-up, 92.9% of iHCC patients were alive without evidence of disease, with no recurrence, metastasis, or disease-related death.

Conclusions: Incidental HCC represents a distinct subset of small, early-stage, well-differentiated tumors with favorable post-transplant outcomes. Differences in underlying liver disease etiology and preoperative imaging modality may contribute to radiologic-pathologic discordance.

Keywords: hepatocellular carcinoma, incidental hepatocellular carcinoma, liver transplantation, liver explant, radiologic-pathologic discordance, fatty liver disease

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Amna Anzar, MD,[1] Cindy Qian Xue,[2] Jennifer Rytych,[2] Akram Shalaby, MD[1]

[1]Department of Pathology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

[2]Northwestern University, Chicago, Illinois, USA

Correspondence: Akram Shalaby, M.D. Department of Pathology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, USA, Tel + 216-983-3421

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy and the third leading cause of cancer-related mortality worldwide. Its rising incidence is driven primarily by chronic liver disease and cirrhosis, most commonly secondary to chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol-associated liver disease, and metabolic dysfunction-associated steatohepatitis (MASH). Among curative treatment options, orthotopic liver transplantation (OLT) offers the greatest curative potential by simultaneously eradicating both the tumor and the underlying cirrhotic liver. Given limited organ availability, OLT is reserved for patients with early-stage HCC who meet the Milan criteria, which are associated with excellent post-transplant survival and low recurrence rates.

Standard pretransplant evaluation includes contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), along with measurement of serum alpha-fetoprotein (AFP) levels. The hallmark radiologic features of HCC—arterial phase hyperenhancement with portal venous or delayed phase washout—are used to determine whether patients meet the Milan criteria, thereby influencing transplant listing decisions.

Despite advances in imaging, small HCCs may escape preoperative detection. Lesions identified only on histopathologic examination of explanted livers—termed incidental HCC (iHCC)—represent a clinically important subset whose characteristics and impact on post-transplant outcomes remain incompletely understood. Characterizing the factors contributing to radiologic-pathologic discordance is essential for improving diagnostic accuracy and optimizing post-transplant care.

The aim of this study was to characterize iHCC in a two-institution retrospective analysis, compare it with preoperatively detected HCC (known HCC, kHCC), and evaluate factors contributing to radiologic-pathologic discordance.

Materials and methods

Study design and population: This retrospective study was approved by the institutional review boards of both participating centers, and the requirement for written informed consent was waived because of the retrospective design. Pathology databases at University Hospitals Cleveland Medical Center/Case Western Reserve University and Northwestern Memorial Hospital were queried for all liver explants containing HCC between January 2011 and January 2025.

Data collection: Collected data included patient demographics (age, sex), etiology of underlying liver disease, liver function tests, AFP levels at the time of HCC diagnosis and at transplantation, preoperative imaging modalities used, and tumor characteristics including greatest dimension, number of lesions, histologic grade of differentiation, pathologic tumor stage, and presence of lymphovascular invasion. Post-transplant follow-up data, including disease recurrence, metastasis, and cause of death, were also recorded.

Cases were classified as kHCC if HCC was identified on preoperative imaging or as iHCC if HCC was detected only on histopathologic examination of the liver explant.

Statistical analysis: Categorical variables were compared using chi-square tests or Fisher exact tests, as appropriate. Continuous variables were compared using independent-samples *t*-tests. Statistical significance was defined as $p < 0.05$. All analyses were performed using standard statistical software.[1–11]

Results

Patient demographics and clinical characteristics

A total of 134 liver explants with HCC were identified: 120 kHCC (89.6%) and 14 iHCC (10.4%). Patients in the iHCC group were slightly younger than those in the kHCC group (mean 57.6 vs. 62.1 years, $p = 0.06$) and included a higher proportion of females (35.7% vs. 19.2%, $p = 0.12$), although neither difference reached statistical significance. All 14 iHCC patients had a single underlying liver disease, whereas the kHCC group included 12 patients (10.0%) with dual etiologies and 3 (2.5%) with unknown etiologies ($p < 0.001$).

Etiology of liver disease

Fatty liver disease was significantly more prevalent in the iHCC group (78.6% vs. 56.7%, $p = 0.04$), whereas HCV infection was significantly more common in the kHCC group (41.7% vs. 7.1%, $p < 0.001$). The prevalence of HBV infection and other etiologies did not differ significantly between cohorts. A prior history of non-HCC malignancy was noted in 7.1% of iHCC patients compared with 18.3% of kHCC patients ($p = 0.08$).

Biochemical markers and imaging

AFP levels trended lower in the iHCC group at both diagnosis (mean 120.2 vs. 338.9 ng/mL, $p = 0.22$) and transplantation (mean 16.0 vs. 32.7 ng/mL, $p = 0.08$), although neither difference reached statistical significance. Preoperative imaging modalities differed markedly between groups: MRI was used in 92.5% of kHCC cases but only 28.6% of iHCC cases. Among iHCC patients, 42.9% were evaluated with CT alone, 21.4% with ultrasound, and 7.1% with magnetic resonance cholangiopancreatography (MRCP). The clinical features of both groups are summarized in Table 1.

Table 1 Clinical features of known and incidental HCC.

Variables (n, %)	kHCC (n=120)	iHCC (n=14)	p-value
Age [Mean (range)]	62.1 (45-75)	57.6 (42-74)	0.06
Gender			0.12
Male	97 (80.8)	9 (64.3)	
Female	23 (19.2)	5 (35.7)	
Number of underlying liver disease(s)			<0.001
1	105 (87.5)	14 (100)	
2	12 (10)	0 (0)	
Unknown	3 (2.5)	0 (0)	
Underlying liver disease			
Alcoholic liver disease	22 (18.3)	5 (35.7)	
NASH	44 (36.7)	6 (42.9)	
Alcoholic liver disease and NASH	2 (1.7)	0 (0)	
All fatty liver disease	68 (56.7)	11 (78.6)	0.04
HBV infection	9 (7.5)	1 (7.1)	
HCV infection	50 (41.7)	1 (7.1)	<0.001
Autoimmune hepatitis	2 (1.7)	1 (7.1)	
Primary biliary cholangitis	2 (1.7)	0 (0)	
AIH/PBC overlap	1 (0.8)	0 (0)	
Hemochromatosis	2 (1.7)	0 (0)	
Celiac disease	1 (0.8)	0 (0)	
Cryptogenic cirrhosis	3 (2.5)	0 (0)	
History of other malignancy			0.08
Yes	22 (18.3)	1 (7.1)	
No	98 (81.7)	13 (92.9)	
AFP level at diagnosis (mean, ng/mL)	338.9	120.2	0.22
AFP level at transplantation (mean, ng/mL)	32.7	16	0.08
Pre-operative imaging modality used			
MRI	111 (92.5)	4 (28.6)	<0.001
CT	4 (3.3)	6 (42.9)	
CT and MRI	5 (4.2)	0 (0)	
US	0 (0)	3 (21.4)	
MRCP	0 (0)	1 (7.1)	
Follow-up time (Mean, range)	89.6 (7-221)	41.3 (2-153)	
Follow-up data			
Alive with no evidence of disease	88 (73.3)	13 (92.9)	0.01
Alive with recurrence or metastasis	5 (4.2)	0 (0)	0.01
Dead of disease	13 (10.8)	0 (0)	<0.001
Died of other causes	13 (10.8)	1 (7.1)	0.31
Unknown	1 (0.8)	0 (0)	

AIH, autoimmune hepatitis; CT, computed tomography; HBV, hepatitis b virus; HCV, hepatitis c virus; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; US, Ultrasound

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Pathologic tumor characteristics

The mean greatest tumor dimension was significantly smaller in iHCC (1.4 cm; range, 0.3–3.0 cm) compared with kHCC (3.1 cm; range, 0.5–12.0 cm; $p < 0.001$). Unifocal tumors were more frequent in the iHCC group, although this difference did not reach statistical significance (64.3% vs. 44.2%, $p = 0.08$). Poorly differentiated morphology was observed exclusively in the kHCC group (10.8% vs. 0%, $p < 0.001$). Lymphovascular invasion was less frequent in iHCC (7.1% vs. 18.3%, $p = 0.08$). All iHCC tumors were early stage (T1: 57.1%; T2: 42.9%), whereas 59.2% of kHCC cases were staged T2–T4. Histopathologic features are summarized in Table 2.

Table 2 Pathological features of known and incidental HCC.

Variables (n, %)	kHCC (n=120)	iHCC (n=14)	p-value
Focality of HCC			0.08
Unifocal	53 (44.2)	9 (64.3)	
Multifocal	67 (55.8)	5 (35.7)	
Location			
Right lobe	67 (55.8)	8 (57.1)	0.46
Left lobe	17 (14.1)	2 (14.3)	0.49
Bilateral	33 (27.5)	3 (21.4)	0.31
Not specified	3 (2.5)	1 (7.1)	
Mean tumor size	3.1 (0.5-12)	1.4 (0.3-3.0)	<0.001
Differentiation			
Well	22 (18.3)	3 (21.4)	0.44
Moderately	76 (63.3)	11 (78.6)	0.2
Poorly	13 (10.8)	0 (0)	<0.001
Lymphovascular invasion			0.08
Yes	22 (18.3)	1 (7.1)	
No	98 (81.7)	13 (92.9)	
Pathologic stage			
T1	45 (37.5)	8 (57.1)	
T2	65 (54.2)	6 (42.9)	
T3	6 (5)	0 (0)	
T4	0 (0)	0 (0)	
T2-T4	71 (59.2)	6 (42.9)	0.006

iHCC, incidental hepatocellular carcinoma; kHCC, known hepatocellular carcinoma

Post-transplant outcomes

Mean follow-up was 41.3 months for iHCC and 89.6 months for kHCC. At last follow-up, 92.9% of iHCC patients were alive with no evidence of disease, compared with 73.3% of kHCC patients. No iHCC patient experienced tumor recurrence, metastasis, or disease-related death, whereas 10.8% of kHCC patients died of disease ($p < 0.001$). One iHCC patient (7.1%) died of causes unrelated to the malignancy.

Discussion

This two-institution retrospective study demonstrates that iHCC constitutes a clinically and pathologically distinct subset of HCC detected in liver explants. In our cohort, iHCC accounted for 10.4% (14/134) of all HCC cases, consistent with previously reported rates of 3%–16%.[12–15] This variation in prevalence across the literature likely reflects differences in pretransplant imaging protocols, surveillance frequency, patient selection criteria, and pathologic evaluation techniques.

Several clinicopathologic differences between iHCC and kHCC merit discussion. Patients with iHCC tended to be younger and were significantly less likely to have multiple underlying liver diseases (0% vs. 10.0%, $p < 0.001$). The significantly higher prevalence of fatty liver disease in the iHCC group (78.6% vs. 56.7%, $p = 0.04$) and the predominance of HCV infection in the kHCC group (41.7% vs. 7.1%, $p < 0.001$) suggest that etiology-specific factors may influence both tumor biology and detectability. Patients with HCV-related cirrhosis or multiple comorbidities may develop larger, more aggressive tumors that are more readily identified on imaging. Conversely, iHCC appears to arise more frequently in younger patients with a single etiology—often fatty liver disease—which may predispose to the development of smaller, less conspicuous lesions.

AFP levels at diagnosis and transplantation did not differ significantly between groups, underscoring the limited utility of AFP as a standalone biomarker for detecting small, asymptomatic tumors. Although AFP remains valuable for monitoring patients with known HCC, these results emphasize that reliance on serologic markers alone is insufficient for identifying subcentimeter or well-differentiated lesions.

Imaging modality emerged as a critical determinant of tumor detection. MRI, which has superior sensitivity for HCC compared with CT or ultrasound, was used in 92.5% of kHCC cases but only 28.6% of iHCC cases. Notably, four iHCC lesions were missed despite MRI evaluation, indicating that small tumor size, challenging anatomic locations, or background parenchymal changes (such as steatosis or fibrosis) can compromise diagnostic accuracy even with the most sensitive modality. The predominant use of CT (42.9%) or ultrasound (21.4%) in iHCC cases further illustrates the limitations of less sensitive modalities for detecting subcentimeter lesions. These findings support continued optimization of imaging protocols, including the use of hepatobiliary-specific contrast agents and high-resolution MRI sequences, particularly in high-risk patients with fatty liver disease.

The pathologic characteristics of iHCC provide additional insight into its relatively indolent biology. Lesions were significantly smaller (mean 1.4 cm vs. 3.1 cm, $p < 0.001$), predominantly unifocal, and confined to early-stage disease (T1 or T2). The absence of poorly differentiated tumors in the iHCC cohort, compared with 10.8% in the kHCC group ($p < 0.001$), and the lower rate of lymphovascular invasion (7.1% vs. 18.3%, $p = 0.08$) are consistent with previous reports suggesting that iHCC tends to exhibit less aggressive histologic features and a more favorable prognosis.[10] Figure 1 illustrates the gross and microscopic findings of a representative iHCC case from our cohort. The patient was a 41-year-old man with cirrhosis secondary to autoimmune hepatitis. An incidental 0.9 cm, subcapsular lesion was identified on gross examination and was histologically confirmed as a well-differentiated hepatocellular carcinoma.

Post-transplant outcomes further corroborate the indolent behavior of iHCC. During a mean follow-up of 41.3 months, 92.9% of iHCC patients remained alive without disease recurrence, and no cases of metastasis or disease-related death occurred. In contrast, 10.8% of kHCC patients died of disease. However, the substantially longer mean follow-up in the kHCC group (89.6 vs. 41.3 months) must be considered when interpreting these differences, as the extended observation period may have contributed to the higher observed rates of recurrence and disease-related mortality. Despite this limitation, the favorable outcomes in iHCC likely reflect the combined effect of small tumor size, early stage, and well-differentiated histology.

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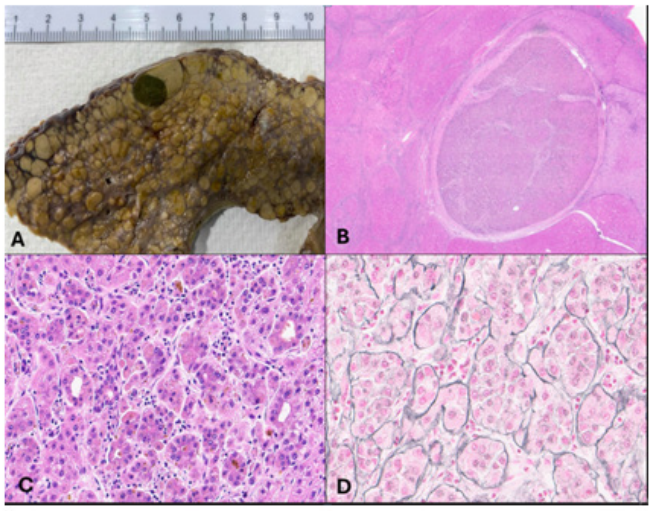

Figure 1 (A) Gross examination of a liver explant from a 41-year-old man with cirrhosis secondary to autoimmune hepatitis reveals an incidental dark green, subcapsular mass, measuring 0.9 cm in greatest dimension. (B) Histological section from the mass shows a well-circumscribed lesion distinct from the background liver parenchyma (hematoxylin-eosin, 2x magnification). (C) High-power view of the lesion shows clusters of hepatocytes with increased cellular density and pseudoglandular formation (hematoxylin-eosin, 20x magnification). (D) Reticulin stain shows thickened hepatocyte trabeculae, supporting the diagnosis of hepatocellular carcinoma (reticulin stain, 20x magnification).

The clinical implications of radiologic-pathologic discordance are significant. Small lesions, particularly those under 2 cm or situated adjacent to vascular structures, may remain undetected, leading to underestimation of tumor burden in transplant allocation systems. These findings highlight the importance of meticulous pathologic examination of explanted livers and support consideration of enhanced imaging strategies for high-risk populations, particularly those with fatty liver disease.

Limitations

This study has several limitations. The retrospective design introduces inherent selection and information biases. The relatively small iHCC sample size (n = 14) limits the statistical power to detect differences in some variables and precludes multivariable analysis. The disparity in follow-up duration between groups complicates direct comparison of long-term outcomes. Additionally, variability in imaging protocols and pathology review practices across the two institutions may have introduced heterogeneity. Nonetheless, this study represents one of the larger multi-institutional analyses of iHCC to date. Future prospective studies with larger cohorts should explore molecular and genetic differences between iHCC and kHCC to elucidate the underlying tumor biology and its implications for surveillance and therapeutic strategies.

Conclusions

Incidental HCC detected in liver explants represents a distinct subset of small, early-stage, well-differentiated tumors associated with excellent post-transplant survival and recurrence-free outcomes. Compared with kHCC, iHCC occurs more frequently in younger patients with fatty liver disease and is significantly less common in the setting of viral hepatitis. Although MRI remains the most sensitive preoperative imaging modality, subcentimeter lesions may still evade detection because of their diminutive size or background parenchymal changes. Although optimized imaging and surveillance strategies may further reduce the incidence of iHCC, its inherently indolent biology and excellent prognosis suggest that these occult tumors have minimal impact on overall post-transplant management and long-term patient survival.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of each participating center, and the need for written informed consent was waived due to the retrospective nature of the study.

Data Availability

The data presented in this study is available upon request from the corresponding author.

Author Contribution

Conceptualization: ASS

Data collection: AMA, JLR

Data analysis and interpretation: CQX, ASS

Drafting the article: ASS, CQX, AMA

Critical revision of the article: ASS

Approval of final manuscript: all authors

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Amna Anzar and Cindy Xue, co-first authors contributed equally to this work.

Conflicts of interests

The authors declare that they have no potential conflicts of interest to disclose.

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