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Original Research Article

Integrated Diagnostic Approach to Liver Lesion: Cyto–Histo and Relevant Tumor Marker Correlation

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Abstract

Introduction: Focal liver lesions encompass a wide spectrum from benign cystic and inflammatory conditions to primary and metastatic malignancies. Accurate differentiation is essential for clinical management and staging. Fine-needle aspiration cytology (FNAC) offers rapid cellular assessment, while core biopsy provides architectural detail and grading. Hepatocellular carcinoma is the most common primary hepatic malignancy, whereas metastatic tumors are frequent due to the liver's vascular connections. Serum biomarkers such as AFP, CEA, CA 19-9, and CA-125 may support diagnosis but have variable performance depending on context. This retrospective observational study was conducted at a tertiary care hospital to analyze demographic, histopathological, cytological, and tumor-marker features of patients with focal liver lesions, aiming to generate internally consistent data for clinical and academic application.

Objective: To evaluate the cytological and histopathological spectrum of focal liver lesions and assess their correlation with relevant serum tumor markers.

Methods: A retrospective observational study was conducted on 73 patients evaluated for focal liver lesions. Age, sex, cytological diagnosis, histopathological diagnosis, hepatocellular carcinoma (HCC) grade, metastatic status and available serum CEA, AFP, CA 19-9 and CA-125 results were analyzed. Diagnostic performance of definitive cytology was calculated using histopathology as the reference standard.

Results: The study included 35 males (47.9%) and 38 females (52.1%); mean age was 59.7±11.9 years. Sixty-seven lesions (91.8%) were malignant/neoplastic and 6 (8.2%) non-malignant/degenerative. Twenty-four HCCs were identified: 6 (25.0%) well differentiated, 11 (45.8%) moderately differentiated and 7 (29.2%) poorly differentiated. Twenty-five cases (34.2%) showed definite/favored metastatic involvement. Among 58 definitive cytological interpretations, sensitivity was 98.2%, specificity 66.7%, positive predictive value 98.2%, negative predictive value 66.7% and accuracy 96.6%; Cohen's kappa was 0.65. Tumor-marker positivity among available results was 88.0% for CEA, 66.7% for AFP, 70.6% for CA 19-9 and 71.4% for CA-125 (U/mL; cutoff 35 U/mL).

Conclusion: Cytology demonstrated high sensitivity and positive predictive value for malignant liver lesions when a definitive interpretation was possible. Histopathology remained essential for tumor characterization and HCC grading, while serum tumor markers served as supportive adjuncts.

Keywords: Liver Lesions; Fine-Needle Aspiration Cytology; Histopathology; Hepatocellular Carcinoma; Metastatic Carcinoma; Tumor Markers; Cyto-Histological Correlation.

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Introduction

Focal liver lesions represent a heterogeneous group of pathological conditions ranging from benign cystic and inflammatory lesions to primary hepatic malignancies and metastatic tumors. Accurate distinction among these entities is important for clinical management and staging. Fine-needle aspiration cytology (FNAC) provides a minimally invasive method for rapid cellular assessment, whereas core biopsy and histopathological examination permit evaluation of tissue architecture and grading.[1,4,7,10,11]

Hepatocellular carcinoma is the most common primary malignant tumor of the liver and may show variable differentiation.[10,11,20] Metastatic tumors are also common in the liver because of its dual blood supply and extensive vascular connections.[3,13,17] Serum biomarkers such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and cancer antigen 125 (CA-125) may provide supportive information in selected clinical settings, but their diagnostic performance is dependent on clinical context.[5,18-20]

The present analysis evaluates a case-level study dataset to provide internally consistent demographic, histopathological, cytological and tumor-marker statistics suitable for an Original Article.

Study design: This was a retrospective observational study conducted on patients evaluated for focal liver lesions at a tertiary care hospital.

Materials and Methods

Study design and setting: This was a retrospective observational analysis of 73 patients evaluated for focal liver lesions. The dataset was compiled at the individual-case level from the source project records.

Data variables: Age, sex, cytological interpretation, histopathological diagnosis, HCC differentiation grade, metastatic status and available serum tumor-marker results were analyzed. Cases were classified as malignant/ neoplastic or non-malignant/ degenerative according to the recorded histopathological diagnosis.

Cytology–histology analysis: Diagnostic performance was calculated using histopathology as the reference standard, consistent with prior cytology accuracy studies.[9,12] Only cases with a definitive cytological interpretation were included in the 2 × 2 diagnostic-performance analysis. Indeterminate, inadequate or non-diagnostic cytology was excluded from sensitivity, specificity, predictive-value and accuracy calculations rather than being incorrectly treated as negative.

Tumor markers: Positivity was determined using the reference limits documented in the source project. CA-125 was standardized to the conventional clinical reporting unit U/mL, with 35 U/mL used as the upper reference limit. The source dataset contained incomplete tumor-marker testing; therefore, positivity percentages were calculated using the number of available results as the denominator.

Statistical Analysis: Continuous variables were summarized using mean, standard deviation, median and range. Categorical variables were summarized as frequencies and percentages. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated from the 2 × 2 table. Cohen's kappa was used to assess agreement between definitive cytology and histological malignancy classification.

Results

Demographic characteristics: The study included 73 patients. There were 35 males (47.9%) and 38 females (52.1%). Mean age was 59.7 ± 11.9 years, median age was 59 years and the age range was 33–92 years.

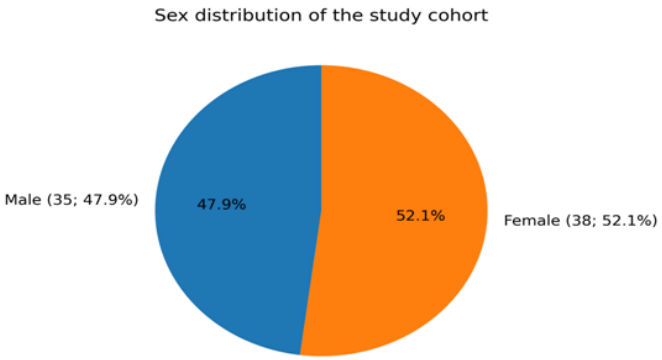

Figure 1: Sex distribution of the 73-patient study cohort

Table 1: Demographic and broad histopathological classification of the study cohort

Sr No	Variable	N	%
1	Total cases	73	100.0
2	Male	35	47.9
3	Female	38	52.1
4	Malignant/neoplastic	67	91.8
5	Non-malignant/degenerative	6	8.2

Histopathological spectrum: Malignant/neoplastic lesions accounted for 67/73 patients (91.8%), while 6/73 (8.2%) were non-malignant/degenerative. HCC constituted 24/73 patients (32.9%). Definite or favored metastatic involvement was identified in 25/73 patients (34.2%).

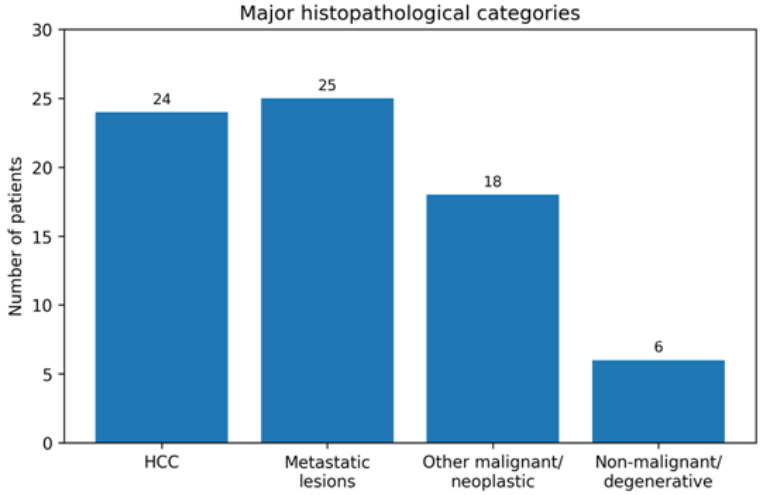

Figure 2: Major histopathological categories in the study cohort

Table 2: Major histopathological categories

Sr No	Category	n	% of 73
1	Hepatocellular carcinoma	24	32.9
2	Definite/favored metastatic lesions	25	34.2
3	Other malignant/neoplastic lesions	18	24.7
4	Non-malignant/degenerative lesions	6	8.2

HCC grading: Of the 24 HCC cases, 6 (25.0%) were well differentiated, 11 (45.8%) moderately differentiated and 7 (29.2%) poorly differentiated.

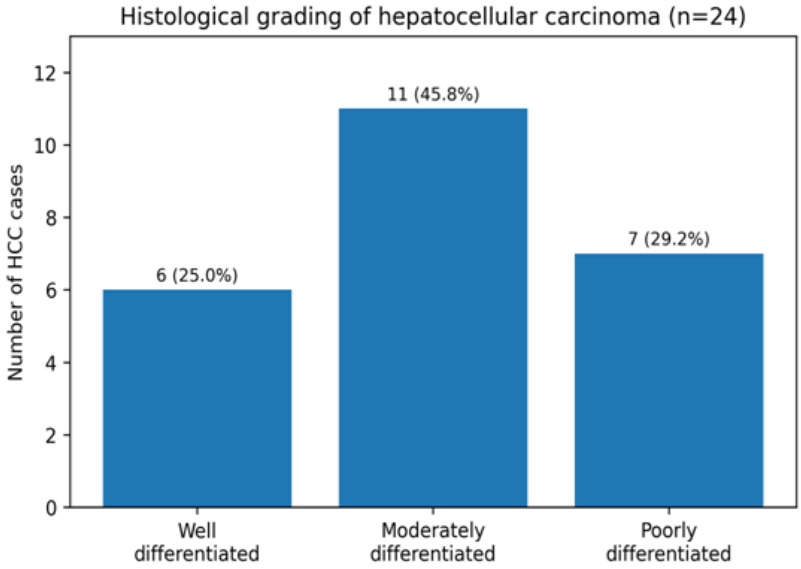

Figure 3: Histological grading of hepatocellular carcinoma (n=24)

Table 3: Histological grading of hepatocellular carcinoma (n=24)

Sr No	HCC grade	n	% of HCC
1	Well differentiated	6	25.0
2	Moderately differentiated	11	45.8
3	Poorly differentiated	7	29.2

Tumor markers: Marker testing was incomplete. Among available results, CEA was positive in 22/25 (88.0%), AFP in 10/15 (66.7%), CA 19-9 in 12/17 (70.6%) and CA-125 in 5/7 (71.4%). CA-125 was reported in U/mL, using 35 U/mL as the upper reference limit.

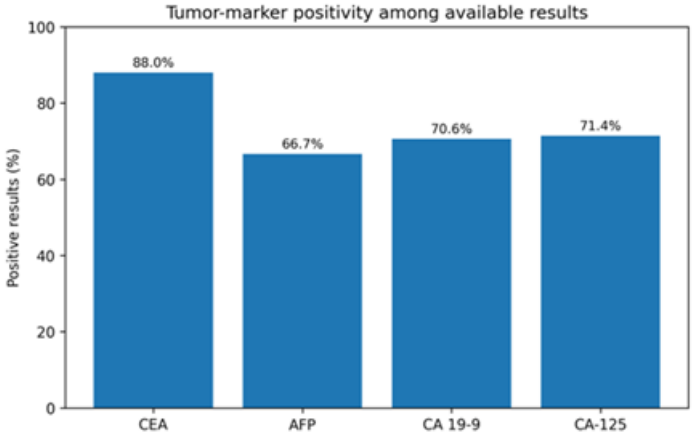

Figure 4: Tumor-marker positivity among cases with available results

Table 4: Serum tumor-marker positivity among cases with available results

Sr No	Marker	Unit	Upper reference limit	Available n	Positive n	Positive %
1	CEA	ng/mL	5	25	22	88.0
2	AFP	ng/mL	40	15	10	66.7
3	CA 19-9	U/mL	37	17	12	70.6
4	CA-125	U/mL	35	7	5	71.4

CA-125 is standardized to U/mL; cutoff 35 U/mL.

Cytology–histology concordance and diagnostic performance: Definitive cytological interpretation was available in 58 cases. The binary comparison yielded 54 true-positive, 2 true-negative, 1 false-positive and 1 false-negative results. Fifteen cases had indeterminate, inadequate or otherwise non-definitive cytology and were excluded from the performance calculation.

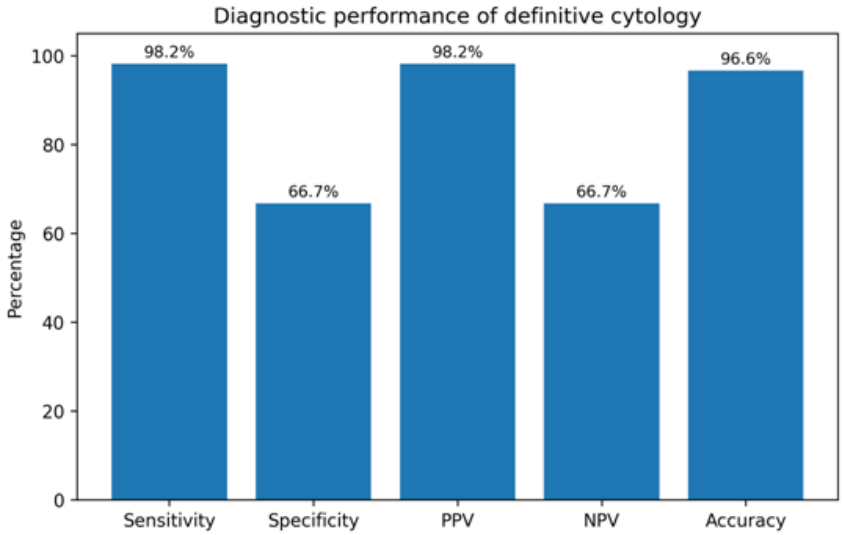

Figure 5: Diagnostic performance of definitive cytology using histopathology as the reference standard

The resulting diagnostic performance was: sensitivity 98.2%, specificity 66.7%, positive predictive value 98.2%, negative predictive value 66.7%, accuracy 96.6% and Cohen's kappa 0.65.

Discussion

This study cohort demonstrates the broad pathological spectrum encountered in focal liver lesions and highlights the complementary roles of cytology and histopathology. The cohort was concentrated in middle-aged and older adults, with a slight female predominance. The high proportion of malignant/neoplastic lesions probably reflects the referral pattern of patients undergoing tissue or cytological evaluation.

HCC represented approximately one-third of the cohort. Moderately differentiated HCC was the largest grade category, followed by poorly and well differentiated tumors. Histological grading provides information beyond the binary distinction between benign and malignant disease and may have prognostic and therapeutic relevance.

Metastatic lesions were frequent, comprising 25 cases (34.2%). Cytology can be particularly useful for recognition of metastatic carcinoma, but scant or inadequate specimens remain a limitation.[4,13,14,17] An indeterminate cytological specimen should not be interpreted as a negative result; tissue confirmation remains important when architecture or definitive tumor classification is required.

The definitive-cytology analysis showed high sensitivity and positive predictive value. Specificity and negative predictive value were lower and were based on only three definitive cytology cases with a non-malignant histological reference diagnosis; consequently, these estimates have wide uncertainty and should not be generalized to all focal liver lesions.

Tumor-marker results were heterogeneous because testing was not uniform.[5,18-20] CEA showed the highest observed positivity in the available data, followed by CA-125 and CA 19-9, with AFP positive in approximately two-thirds of tested cases. These findings should not be interpreted as estimates of population-level diagnostic sensitivity because marker testing was selective and incomplete.

A major strength of the present analysis is use of reconstructed case-level data rather than relying on inconsistent aggregate tables in the source project. The source project contained discrepancies between aggregate counts and case-level classifications. Accordingly, the case-level dataset was used for the primary statistical analysis.

Limitations include the retrospective single-center design, modest sample size, incomplete tumor-marker testing, indeterminate cytology in a proportion of cases, and reliance on recorded histological wording rather than independent slide re-review. Difficult primary-versus-metastatic diagnoses may require immunohistochemistry and clinical/radiological correlation.

Conclusion

In this 73-patient study, definitive cytology demonstrated high sensitivity and positive predictive value for identifying malignant liver lesions. Histopathology remained essential for architectural assessment, HCC grading and characterization of metastatic disease. Serum AFP, CEA, CA 19-9 and CA-125 provided supportive information but were limited by incomplete testing. A combined cyto-histological and biochemical approach can improve diagnostic confidence, while inadequate or indeterminate cytology should prompt tissue confirmation rather than being interpreted as negative.

Declarations

Conflict of Interest: Nil.

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