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Hepatoid Carcinoma of the Ovary: Clinicopathological Spectrum, Genomic Insights, and Evolving Therapeutic Strategies A Narrative Review

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Abstract

Hepatoid carcinoma of the ovary is an ultra-rare and highly aggressive epithelial malignancy, sharing prominent resemblance in both morphology and immunophenotype with hepatocellular carcinoma. Due to the rarity of the tumour and its histologic overlap with metastatic hepatic tumours and other ovarian neoplasms, HCO is often misdiagnosed, which delays the initiation of appropriate treatment, leading to poor clinical outcomes. The goal of this narrative review was to summarise the main clinicopathological features, immunohistochemical profile, molecular alterations, and current approaches to the management of hepatoid ovarian carcinoma, with an emphasis on key diagnostic pitfalls and emerging therapeutic perspectives. A Focused narrative review of published English-language case reports, case series, and literature reviews was performed using major biomedical databases, covering from the initial description of HCO in 1987 to recent reports. Relevant articles were analysed to extract data on patient demographics, clinical presentation, imaging characteristics, histopathology, immunohistochemical markers, serum biomarkers, molecular findings, treatment strategies, and clinical outcomes. Less than 50 well-documented cases of HCO have been hitherto reported, mainly affecting perimenopausal and postmenopausal women. The majority of patients present with large adnexal masses, strikingly increased serum alpha-fetoprotein levels, and advanced-stage disease at diagnosis. Histologically, tumours demonstrate hepatoid differentiation, characterized by the consistent expression of AFP, HepPar-1, glypican-3, and SALL4. Recent reports, including those utilizing next-generation sequencing, have revealed recurrent TP53 alterations, as well as additional potentially actionable molecular pathways. Despite multimodal treatment, recurrence rates are high, and overall survival remains limited. Hepatoid carcinoma of the ovary requires heightened diagnostic vigilance, standardised immunohistochemical evaluation, and increased incorporation of molecular profiling in order to improve diagnostic precision and enable individualised therapeutic strategies in this exceptionally rare malignancy.

Keywords: Alpha-Fetoprotein, Clinicopathological Features, Genomic Profiling, Hepatoid Differentiation, Immunohistochemistry, Rare Ovarian Malignancy

1. Introduction

Hepatoid carcinoma of the ovary represents an extremely rare and very aggressive epithelial ovarian malignancy. It holds a special place, standing at the crossroads between gynecologic oncology and hepatobiliary pathology [1]. It was characterized by a striking morphologic and immunophenotypic resemblance to hepatocellular carcinoma, which underlies many of its diagnostic and therapeutic difficulties. While epithelial ovarian cancer remains one of the most common causes of gynecologic cancer-related mortality worldwide, HCO forms only a minute fraction of these tumours. To date, fewer than 50 well-documented cases have been reported since its initial description [2].

This extreme rarity, coupled with its unusual histology and biomarker profile, has precluded prospective studies, leaving clinicians dependent on scattered case reports and small series when faced with this entity [3].

Large polygonal cells with copious eosinophilic cytoplasm, arranged in trabecular and sheet-like patterns, resemble hepatocytes in their production, characteristic of hepatocellular tumours. Most patients in their seminal report presented with advanced-stage disease, markedly elevated serum AFP levels, and aggressive clinical behaviour; for these reasons, it was proposed that HCO represents a variant of epithelial ovarian carcinoma with hepatoid differentiation [4]. Subsequent reports from diverse geographic regions have reinforced these observations, demonstrating a predilection for peri- and postmenopausal women, the frequent absence of underlying liver disease, and clinicopathological features supporting Müllerian epithelial origin with trans differentiation rather than derivation from germ cell or ectopic hepatic tissue [5].

Clinically, HCO presents with nonspecific symptoms, including abdominal pain, distension, or a palpable pelvic mass, indistinguishable from those of conventional epithelial ovarian cancers. Imaging typically reveals large unilateral and, less commonly, bilateral adnexal masses often accompanied by ascites, and many patients are diagnosed at FIGO stage III or higher [6]. A distinctive hallmark is markedly elevated serum AFP, sometimes reaching extraordinarily high levels, often accompanied by increased CA-125 and, in selected cases, HE4. However, AFP may be normal in a subset of patients, and both AFP elevation and hepatoid morphology can also be encountered in metastatic HCC and other hepatoid adenocarcinomas, complicating attribution of the primary site [7].

Histopathologically, HCO typically consists of sheets, nests, and trabeculae of large polygonal cells with abundant granular eosinophilic cytoplasm, centrally located nuclei, and prominent nucleoli, often associated with sinusoid-like vasculature and hyaline globules. In many instances, hepatoid areas coexist with conventional epithelial patterns such as serous, mucinous, endometrioid, or poorly differentiated carcinoma, supporting the concept of hepatoid transdifferentiation within a Müllerian neoplasm [8]. Immunohistochemically, most tumours express AFP, HepPar-1, and glypican-3, with frequent positivity for SALL4 and broad-spectrum cytokeratins. In contrast, markers of germ cell and sex cord-stromal tumours are typically negative. SALL4 expression has emerged as a potentially useful discriminator between primary HCO and metastatic HCC, although current evidence is limited by small case numbers [9].

Accurate diagnosis requires cautious clinicoradiologic and pathologic correlation to rule out metastatic disease, particularly in patients with chronic liver pathology or radiologic suspicion of hepatic lesions [10]. The primary differential diagnoses include yolk sac tumours, steroid cell tumours, clear cell carcinoma, and endometrioid carcinoma with eosinophilic cytoplasm or expression of AFP, all of which require targeted immunohistochemical panels. However, despite these many challenges, there is no single standardized diagnostic algorithm for suspected HCO, and current practice is based on expert opinion derived from the narrative literature [11].

Recent advances in molecular profiling have begun to clarify the genetic landscape of HCO. Next-generation sequencing has identified recurrent TP53 alterations and abnormalities involving cell-cycle regulation, PI3K–AKT signalling, and genomic instability, aligning HCO molecularly with high-grade epithelial ovarian carcinomas rather than hepatocellular carcinoma [12]. These findings both support current treatment paradigms but also highlight the potential role of targeted therapies in selected patients. However, most molecular data remain sparse and primarily confined to case reports, without dedicated clinical trials assessing targeted or immunotherapeutic approaches. Therapeutically, the cornerstone of management remains optimal cytoreductive surgery followed by platinum-based chemotherapy [13]. Although some patients may achieve biochemical and radiologic remission, recurrence is common, with overall survival poor compared with conventional epithelial ovarian cancers. Antiangiogenic agents and molecularly guided, individualized regimens have been described in several emerging reports, with anecdotal evidence of durable disease control, underscoring the need for a consolidated evaluation of available data [14]. Given the fragmented nature of the existing literature, with most contributions in the form of single-case reports and small series published in a wide range of journals, an integrated synthesis of clinicopathological, immunohistochemical, molecular, and therapeutic insights is indeed highly anticipated.

This narrative review presents a comprehensive overview with a clinical orientation of hepatoid carcinoma of the ovary, highlighting diagnosis-related issues, the evolving molecular understanding, and practical management strategies pertinent to contemporary gynecologic oncology practice.

Review of literature

Hepatoid carcinoma of the ovary was described by Ishikura and Scully in 1987 as a primary epithelial malignancy of the ovary, characterized by cells that closely resemble hepatocytes and contain alpha-fetoprotein. Their initial series highlighted advanced stage presentation, strikingly high elevations of AFP, aggressive clinical behaviour, and uniformly poor survival despite typical therapy [15]. Nearly thirty years later, Randolph *et al*. (2015) reviewed 31 previously reported cases and an additional patient to establish the early clinicopathologic spectrum of HCO. They showed the predominance among perimenopausal and postmenopausal women, frequent elevation of tumour markers AFP and CA-125, common presentation as FIGO stage III disease, and heterogeneous outcomes following cytoreductive surgery and platinum-based chemotherapy [16]. Subsequent case reports reinforced its aggressive nature: Choi *et al*. (2020) documented extreme AFP elevation with an initial response to paclitaxel–carboplatin, followed by rapid biochemical and radiologic relapse, suggesting intrinsic chemoresistance [17]. In 2022, Li and Wu reported bilateral HCO with extensive immunohistochemical characterization, including positivity for AFP, SALL4, and p53, and proposed SALL4 as a valuable marker to distinguish primary HCO from metastatic hepatocellular carcinoma. Their literature synthesis suggested a median overall survival of approximately two years [18]. More recently, in 2025, Zuo *et al*. integrated data from 47 published cases and demonstrated TP53-related alterations through next-generation sequencing, emphasising the growing role of molecular profiling in individualised management [19]. Similarly, in 2025, Zhang *et al*. (2025) further developed this paradigm by reporting on a genomically characterized HCO with mixed mucinous

components, which targeted therapeutic strategies reflected a shift toward precision oncology in this ultra-rare malignancy [20], as shown in Table 1.

Table 1: Key Published Reports on Hepatoid Carcinoma of the Ovary: Clinicopathological and Molecular Evolution [15-20].

Author (Year)	Major Contribution	Focus Area	Key Limitations	Impact / Future Direction
Ishikura & Scully (1987) [15]	First description of primary ovarian hepatoid carcinoma with AFP-producing hepatocyte-like cells and aggressive behaviour	Clinicopathology, differential diagnosis	Small series; no molecular data; limited followup	Foundation for disease recognition and diagnostic criteria
Randolph *et al*. (2015) [16]	Review of 31 cases defining typical age, stage III predominance, AFP/CA-125 elevation, and variable survival	Clinical features, treatment outcomes	Retrospective, heterogeneous reports; no genomics	Need for standardized reporting and registries
Choi *et al*. (2020) [17]	Demonstrated extreme AFP elevation with early relapse after initial chemotherapy response	Clinical course, chemoresistance	Single case; no molecular testing	Exploration of alternative systemic therapies
Li & Wu (2022) [18]	Bilateral HCO with AFP, SALL4, and p53 positivity; median survival ≈2 years	Immunohistochemistry, survival analysis	Small numbers; no NGS	Validation of SALL4 and molecular integration
Zuo *et al*. (2025) [19]	Integrated 47 cases; NGS revealed TP53-related alterations	Genomic profiling, precision oncology	Single genomically profiled case	Molecularly guided therapy and multicentre studies
Zhang *et al*. (2025) [20]	Genomically characterized HCO with mixed mucinous component and targeted therapy discussion.	Histologic heterogeneity, targeted treatment	Short followup; isolated case	Development of evidence-based precision pathways

Materials and Methods

Data Collection

A search of narrative literature was conducted using major biomedical databases, including PubMed and Google Scholar, as well as the websites of selected journals. Search terms included "hepatoid carcinoma of the ovary", "hepatoid ovarian carcinoma", "alpha-fetoprotein", and "hepatoid differentiation". Publications from 1987, when the entity was first described, were reviewed up to the most recent available literature. References of related articles were also screened manually to identify other reports.

Selection Criteria

Eligible studies included published human case reports and case series that described primary hepatoid carcinoma of the ovary with sufficient clinical and pathological details. Articles needed to provide information on at least one of the following: patient demographics, clinical presentation, tumour characteristics, management, or outcomes.

Inclusion and Exclusion

All reports fulfilling the above requirements were included, including cases summarised within review articles when extractable data were available. Exclusions included non-ovarian hepatoid tumours, metastatic hepatocellular carcinoma to the ovary, other ovarian neoplasms producing AFP, studies performed on animals, non-English publications with unavailable data, and abstracts with unavailable complete clinical or pathological information.

Data extraction and synthesis

Data were manually extracted into structured tables that captured clinical features, serum markers, tumour laterality and stage, histopathology, immunohistochemistry, molecular findings (when available), treatment approaches, and followup. Results are synthesised qualitatively by a narrative approach that emphasises the identification of recurring patterns, diagnostic challenges, therapeutic strategies, and emerging molecular themes without statistical pooling.

Limitations

This review is bound by the rarity of the disease, reliance on retrospective case-based literature, heterogeneous reporting, and incomplete molecular data in earlier publications. Thus, this restricts definite prognostic and treatment conclusions.

Result

Burden of Cases Globally and Temporal Trends

The published literature on hepatoid carcinoma of the ovary documents only a very few well-characterized cases worldwide, underlining its ultra-rarity as an ovarian malignancy [21]. Early reports from the late 1980s to the early 2000s have primarily appeared in pathology and general oncology journals from Asia, North America, and Europe, emphasizing morphologic definition, significant elevation of alpha-fetoprotein, and outcomes following conventional platinum-based chemotherapy, with most patients presenting at an advanced stage. In this period, this tumour was established as biologically aggressive, predominantly affecting peri- and postmenopausal women, though its molecular basis remains, by and large, unexplored [22].

Whereas these early reports were largely anecdotal, both the frequency and depth of published reports increased from the mid-2010s onward. More recent case reports and small series, frequently published in gynecologic oncology and open-access clinical journals, have provided more systematic documentation of demographics, staging, biomarker profiles, treatment strategies, and outcomes [23]. These have been complemented by the inclusion of extended immunohistochemical panels, next-generation sequencing, and extended followup to shift from purely descriptive pathology toward molecularly informed characterization. Contemporary cases have been reported throughout East Asia, Europe, and North America. Given this distribution, improved awareness and diagnostic capability, rather than an actual increase in incidence, are responsible for the apparent rise in reported cases. These shifting temporal and geographic trends underscore a need for multi-institutional registries and collaborative rare-tumour networks to advance the understanding and management of HCO further [24].

Clinicopathological Spectrum and Atypical Presentations

Most reported cases of HCO have shown a relatively consistent clinicopathological profile. The majority of patients are peri- or postmenopausal and usually present with rapidly progressive abdominal distension, pelvic pain, or a palpable adnexal mass, often associated with ascites and highly elevated serum alpha-fetoprotein [25]. Tumours are commonly large and unilateral at presentation, and a majority are staged as FIGO stage III, which reflects aggressive biology and delayed clinical recognition. Histologically, HCO is composed of sheets and trabeculae of polygonal cells containing abundant eosinophilic cytoplasm, sinusoid-like vasculature, and hyaline globules that closely recapitulate hepatocellular carcinoma [26]. The increasing recognition of bilateral disease and coexisting epithelial components, such as mucinous or serous carcinoma, supports a surface epithelial origin with hepatoid transdifferentiation rather than germ cell derivation or metastatic hepatocellular carcinoma [27].

Beyond this typical presentation, several atypical patterns expand the recognized spectrum of HCO. Cases with normal or only mildly elevated AFP, despite classic hepatoid morphology, are indicative of the limitations of relying solely on serum biomarkers for diagnosis. Bilateral tumours, mixed or poorly differentiated histology, and presentations in relatively younger patients further challenge traditional assumptions regarding age and morphology [28]. In particular, occasional reports of long-term survival following optimal cytoreductive surgery and tailored systemic therapy suggest that early recognition of atypical features, combined with precise histopathological and molecular evaluation, may facilitate improved risk stratification and more individualised management in selected patients [29] as shown in Table 2.

Table 2: Clinicopathological Characteristics of Reported Hepatoid Carcinoma of the Ovary Cases [25-29].

Author *et al.*	Age (years)	Tumour laterality	FIGO stage	Serum AFP level*
Yiğit *et al*. (2006) [25]	63	Right ovary (unilateral)	IA	454 ng/mL
Wang *et al*. (2013) [26]	42–73 (series)	Unilateral or bilateral (multiple patterns)	I–IIIC	23–329,732 ng/mL (range across cases)
Cascales-Campos *et al*. (2013) [27]	78	Left ovary with peritoneal dissemination	IIIC	329,732 ng/mL
Randolph *et al*. (2015) [28]	73 (index case)	Left ovary (unilateral)	IIIC	2,396 ng/mL (post-operative)
Choi *et al*. (2020) [29]	45	Left ovary (unilateral)	IC	83,164.6 ng/mL

Immunohistochemical signature and emerging markets for diagnosis

Because it can demonstrate hepatocellular differentiation within an ovarian epithelial neoplasm, immunohistochemistry plays a key role in establishing the diagnosis of hepatoid carcinoma of the ovary [30]. Most tumours are positive for alpha-fetoprotein, HepPar-1, glypican-3, and broad-spectrum cytokeratins, closely mimicking the immunophenotype of HCC while maintaining epithelial features [31]. The co-expression of markers such as CA-125 and aberrant p53 further supports a Müllerian epithelial origin and helps distinguish this entity from germ cell tumours and metastatic hepatic lesions. In practice, the combination of hepatoid morphology with strong expression of hepatocellular markers in an ovarian mass, after excluding a primary hepatic or gastrointestinal malignancy, strongly favours this diagnosis [32].

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Table 3: Key Immunohistochemical and Molecular Features Informing Hepatoid Carcinoma of the Ovary (Comparative Evidence) [30-34].

Author *et al.*	Tumour/site	Salient IHC features	Molecular/genomic notes	Diagnostic relevance to HCO
Liu & Zhao *et al*. (2025) [30]	Hepatoid adenocarcinoma, uterine cervix	AFP+, HepPar-1+, glypican-3+, SALL4+	Hepatoid differentiation mechanisms	Supports use of AFP, HepPar-1, GPC3, SALL4 panel in HCO with site correlation
Al-Obaidy *et al*. (2021) [31]	Hepatoid germ-cell & hepatic tumours	YST: SALL4+, CK19+, CDX2+; HCC/HT: arginase-1+, HepPar-1+, SALL4−	Comparative IHC profiles; no NGS	Distinguishes HCO from germ-cell tumours and metastatic HCC; SALL4 and arginase-1 are key discriminators.
Wojnarowicz *et al*. (2012) [32]	High-grade serous ovarian carcinoma	Aberrant p53 expression; epithelial markers	TP53 mutations common	Provides a genomic benchmark supporting TP53-driven Müllerian origin of HCO
Kihara *et al*. (2024) [33]	Undifferentiated endometrial carcinoma	Variable GPC3 and SALL4; loss of epithelial markers	SWI/SNF and MMR alterations are frequent	Highlights diagnostic pitfall: GPC3/SALL4 positivity alone is insufficient without hepatoid morphology
Iwaya *et al*. (2020) [34]	Gastric hepatoid carcinoma	AFP+, SALL4+, arginase-1+, HepPar-1+	Embryologic hepatoid differentiation	Confirms core hepatoid immunophenotype; arginase-1 may indicate true hepatic differentiation.

Genomic Profiling and Targetable Pathways

The genomic characterisation of hepatoid carcinoma of the ovary has long been limited; however, the recent application of next-generation sequencing has begun to clarify its molecular underpinnings. Available data indicate that the genomic profile of this tumour more resembles high-grade Müllerian epithelial ovarian carcinomas than hepatocellular carcinoma [35]. Recurrent TP53 alterations are commonly identified, along with microsatellite stability and a generally low tumour mutational burden, suggesting that mismatch-repair deficiency and hypermutated phenotypes are uncommon. These findings support the concept that hepatoid carcinoma of the ovary represents an epithelial ovarian malignancy with hepatoid trans differentiation rather than a metastatic hepatic tumour [36]. Beyond TP53 alterations, other pathways related to PI3K-AKT signalling, cell-cycle regulation, and growth factor signalling have been described, which indicate possible biological heterogeneity and therapeutic relevance. Although clinical evidence to date is limited to single-case reports, molecular findings have favourably prompted consideration of targeted approaches, including antiangiogenic strategies and pathway-directed therapies used in other solid tumours [37]. These approaches are currently exploratory, but they again reflect a move towards precision oncology for this ultra-rare entity. In summary, the emerging genomic data provide a framework for enhanced biological understanding, suggesting that comprehensive molecular profiling, where feasible, should be considered for underpinning individualized treatment planning and biomarker-driven research [38].

Treatment Strategies and Outcome Pattern

Thus far, treatment of hepatoid carcinoma of the ovary has adhered mainly to principles applied to epithelial ovarian cancer, with maximal cytoreductive surgery followed by platinum-based chemotherapy, most commonly paclitaxel and carboplatin. Optimal debulking, when achieved, is often associated with rapid post-operative declines in serum alpha-fetoprotein and CA-125 levels and occasional complete radiological responses [39]. Despite these initial benefits, many patients experience early biochemical and radiological relapse, frequently within months to a few years, reflecting the aggressive biology of the tumour and a tendency towards relative chemoresistance compared with conventional ovarian carcinoma subtypes [40].

More recent reports describe individualized therapeutic approaches, including the addition of antiangiogenic agents and consideration of targeted therapies guided by molecular profiling. In selected cases, incorporation of agents such as bevacizumab has been associated with prolonged disease control or delayed recurrence, suggesting a potential role for angiogenesis-directed strategies [41]. However, evidence for these approaches remains limited to isolated case experiences with short and variable followup. The absence of standardised treatment protocols, heterogeneous use of AFP monitoring, and a lack of prospective studies preclude definitive conclusions regarding the optimal management [42]. Overall, current outcome patterns emphasize the importance of early, aggressive surgery, close biomarker surveillance, and collaboration through rare-tumour registries in supporting biomarker-driven trials for refining both prognostic and therapeutic strategies in this uncommon malignancy [43].

Proposed Diagnostic and Therapeutic Algorithms

A significant deficiency in the current literature relates to the lack of uniform diagnostic and management algorithms for hepatoid carcinoma of the ovary. Based on the cumulative clinicopathological, immunohistochemical, and evolving molecular evidence, a practical diagnostic strategy can be forwarded [44]. Clinical suspicion should be raised in individuals presenting with an adnexal mass and significantly raised alpha-fetoprotein levels. The initial workup should include targeted imaging to exclude hepatic or gastrointestinal primary tumours, followed by a thorough histopathological examination [45]. A limited immunohistochemical panel that includes AFP, HepPar-1, glypican-3, SALL4, CA-125, and selected germ cell markers is necessary for confirming hepatoid differentiation and supporting a primary ovarian origin. To the extent possible, genomic profiling at diagnosis can provide further classification based on the identification of TP53 alterations and other pathway-level alterations, thereby reinforcing the notion that a hepatoid variant of epithelial ovarian carcinoma is present rather than metastatic disease [46].

Based on the currently available evidence, management in line with protocols for epithelial ovarian cancer, but considering the particular biology of the tumour, is favoured therapeutically. The cornerstone remains maximal cytoreductive surgery, with an attempt to leave no gross residual disease, together with platinum-based chemotherapy [47]. Serial measurement of AFP serves as a sensitive monitor for treatment response and early relapse. For residual, recurrent, or refractory disease, stepwise escalation incorporating antiangiogenic agents or molecularly guided targeted therapies is a consideration. Embedding these structured approaches into proposed algorithms and promoting participation in rare tumour registries or precision oncology programs holds promise to facilitate evidence generation and may inform more consistent, data-driven care for this ultra-rare malignancy [48].

Discussion

Hepatoid carcinoma of the ovary is an extremely rare epithelial malignancy that presents diagnostic and therapeutic challenges due to its low prevalence. The literature, since its original description in 1987, has identified that HCO mainly affects peri- and postmenopausal women, presenting with large adnexal masses and remarkably increased serum alpha-fetoprotein levels [49]. However, a more detailed analysis reveals crucial clinicopathological, immunohistochemical, and molecular subtleties that directly influence diagnosis and management. Comparisons with other hepatoid and Müllerian tumours put it in perspective with respect to behaviour, differential diagnosis, and therapeutic strategies [50].

Clinicopathological Behaviour and Prognostic Implications

Clinically, HCO usually presents with unilateral ovarian tumours larger than 10 cm, sometimes associated with ascites, peritoneal dissemination, or bilateral involvement. Despite most cases presenting at an advanced FIGO stage III, earlier-stage disease (IA-IC) is often found in cases of incidental tumour detection. Very high serum AFP levels, ranging from several thousand to hundreds of thousands ng/mL, are typical; however, normal or only mildly increased

AFP levels do not rule out HCO [51]. Early biochemical relapse and spread to the peritoneum, sometimes with liver metastases, reflect the aggressiveness of the disease, contributing to a median reported survival of about two years. However, the results are heterogeneous. Optimal cytoreduction followed by platinum-taxane chemotherapy may result in durable remissions in patients, with the most significant benefit in early-stage disease or minimal residual tumour. There is emerging evidence that the addition of antiangiogenic agents or molecularly informed regimens can extend time to progression, although such information is anecdotal [52].

Differential Diagnosis & Diagnostic Challenges

Accurate and timely diagnosis of HCO remains one of the biggest challenges due to overlapping morphologic and immunophenotypic features with other neoplasms. Usually, it histologically consists of sheets, nests, and trabeculae of large polygonal cells with abundant eosinophilic cytoplasm, sinusoid-like vasculature, and hyaline globules. Such a pattern closely mimics both HCC and HYST [53]. Misdiagnosis as ovarian metastasis of HCC may therefore occur in patients with chronic liver disease or hepatic imaging abnormalities, with resultant significant therapeutic and prognostic implications. Similarly, one should consider HYST and other germ cell tumours in a differential diagnosis, especially in younger women or cases showing strong positivity for SALL4 [54].

A stepwise diagnostic approach is imperative. Clinico-radiologic exclusion of hepatic or gastrointestinal primaries should precede immunohistochemical evaluation. Core markers that confirm hepatoid differentiation include AFP, HepPar-1, glypican-3, and, where available, arginase-1, complemented by broad cytokeratins and epithelial markers [55]. SALL4 is notably informative, as it is strongly expressed in the majority of HCOs and HYSTs, but is negative in the majority of HCCs and hepatoid teratomas, thus helping to distinguish primary ovarian hepatoid lesions from metastatic hepatic or germ-cell neoplasms. Such comparative studies of undifferentiated endometrial carcinoma emphasise that both SALL4 and glypican-3 may be expressed in non-hepatoid Müllerian tumours and highlight the need for morphology and clinical context in interpretation [56].

Based on these data, a minimal IHC panel for suspected HCO would include AFP, HepPar 1, glypican 3, SALL4, CA 125, p53, and selected germ cell markers. This allows differentiation from HYST (SALL4+, CK19+, arginase 1−), metastatic HCC (arginase 1+, SALL4−, HepPar 1+), undifferentiated endometrial carcinoma (GPC3/SALL4 variably positive, lacking hepatoid architecture), and cervical or gastric hepatoid adenocarcinomas, which share marker profiles but differ anatomically and pathogenetically [57].

Molecular Context and Pathogenesis

Although limited, molecular evidence is increasingly suggesting that HCO is a hepatoid variant of Müllerian carcinoma rather than a distinct hepatic lineage. High-grade serous ovarian carcinomas, which have TP53 mutations in more than 90% of cases and display characteristic chromosomal gains and losses, provide a genomic benchmark [58]. Profiling of HCO reveals TP53-related alterations, microsatellite stability, and a low tumour mutational burden, aligning HCO closely with high-grade Müllerian tumours rather than HCC [59].

Comparative studies among extrahepatic hepatoid adenocarcinomas, including those in the cervical and gastric regions, have suggested that AFP production and hepatoid morphology can be acquired in various tissues, many of which share overlapping immunophenotypes but have different pathogenetic mechanisms [60]. Thus, cervical hepatoid adenocarcinoma expresses AFP, HepPar 1, glypican 3, and SALL4, often with accompanying SWI/SNF and MMR aberrations. In contrast, gastric hepatoid cancers combine AFP and SALL4 with arginase 1 and expression of intestinal/pancreatic transcription factors. Such findings suggest that hepatoid differentiation represents a plastic endpoint that can be reached via different genetic and epigenetic pathways [61].

In HCO, the combination of TP53-driven background, frequent CA 125 expression, and the occasional presence of coexisting epithelial components supports a Müllerian origin with hepatoid transdifferentiation. The lack of consistent germ-cell or hepatic progenitor signatures argues against a primary germ-cell or hepatic lineage. The remaining key research frontier is the identification of the molecular switches that drive this transdifferentiation, including lineage plasticity programs, oncofetal pathways (such as GPC3 and AFP), or microenvironmentally driven influences [62].

Therapeutic Considerations and Future Directions

Current management of HCO follows that of epithelial ovarian cancer, with complete cytoreductive surgery followed by platinum-based chemotherapy. Monitoring of serum AFP is an important adjunct for assessing treatment response and early relapse, complementing imaging studies [63]. Antiangiogenic agents and, selectively, molecularly informed therapies can be beneficial in recurrent or refractory disease, although these approaches remain anecdotal and unstandardized. Genomic parallels with TP53-mutated Müllerian carcinomas rationalise the enrollment of patients in rare-tumour sub-studies within precision oncology trials, particularly those targeting PI3K pathways, angiogenesis, or the DNA damage response [64]. Finally, comparative IHC data from cervical, endometrial, gastric, and germ-cell hepatoid tumours underscore the need for central pathology review and standardised marker panels for adequate classification prior to trial enrollment.

Limitations of the current evidence must be emphasised: most data derive from single-case reports or small series, often reported heterogeneously, with limited followup and scarce molecular characterisation. Despite these constraints, the evolution from morphological description to integrated immunophenotypic and genomic characterisation over the last four decades sets a cornerstone for multi-centre registries and standardised data collection, ideally within international rare-tumour networks.

Conclusion

Emerging from this narrative synthesis, hepatoid carcinoma of the ovary is an ultra-rare but increasingly well-defined epithelial malignancy characterised by large adnexal masses, frequent advanced-stage presentation, and striking elevations of serum alpha-fetoprotein. The latter tumours closely mimic hepatocellular carcinoma histologically, but their consistent association with Müllerian epithelial markers, their occasional admixture with conventional ovarian carcinoma components, and TP53-dominated genomic background support the concept of a hepatoid variant of Müllerian

carcinoma rather than a true hepatic or germ cell neoplasm. Diagnostic accuracy relies on integrating clinical context, imaging to exclude extra ovarian primaries, and a focused immunohistochemical panel including AFP, HepPar 1, glypican 3, SALL4, CA 125, and selected germ cell and lineage markers, with the proviso that GPC3 and SALL4 are not entirely specific and must be interpreted in conjunction with morphology. Therapeutically, management should presently follow protocols for epithelial ovarian cancer, including maximal cytoreductive surgery with platinum-based chemotherapy, augmented by AFP-guided surveillance and, where available, molecular profiling, to identify candidates for antiangiogenic or targeted therapies. Future multicenter registries and biomarker-driven trials are necessary to refine prognostic stratification and develop evidence-based precision treatment pathways for this rare but clinically significant ovarian tumour.

Key takeaways

Hepatoid carcinoma of the ovary is an ultra-rare, aggressive Müllerian tumour that morphologically simulates hepatocellular carcinoma but most often presents as large, AFP-secreting ovarian masses in perimenopausal or postmenopausal women. Accurate diagnosis requires integration of imaging findings with a focused immunohistochemical panel including AFP, HepPar 1, glypican 3, SALL4, and CA 125, with meticulous exclusion of metastatic HCC, hepatoid yolk sac tumour, and undifferentiated endometrial carcinoma. Cytoreductive surgery, combined with platinum-based chemotherapy, remains the standard of care, while emerging TP53-based genomic data provide the basis for future precision oncology approaches.

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References

1. Tejerina González E, Argüelles M, Jiménez-Heffernan JA, Dhimes P, Vicandi B, Pinedo F. Cytologic features of hepatoid carcinoma of the ovary: a case report with immunocytologic evaluation of HepPar1. Acta Cytol. 2008;52(4):490-4.
2. Lee JM, Park KM, Lee SY, Choi J, Hwang DW, Lee YJ. Metastasis of hepatocellular carcinoma to the ovary: a case report and review of the literature. Gut Liver. 2011;5(4):543-7.
3. Prat J, Bhan AK, Dickersin GR, Robboy SJ, Scully RE. Hepatoid yolk sac tumor of the ovary (endodermal sinus tumor with hepatoid differentiation): a light microscopic, ultrastructural, and immunohistochemical study of seven cases. Cancer. 1982;50(11):2355-68.
4. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol. 2005;18(Suppl 2):S61-79.
5. Euscher ED. Germ cell tumors of the female genital tract. Surg Pathol Clin. 2019;12(2):621-49.
6. Mahmood H, Fatima H, Faheem M. Metastatic hepatoid carcinoma of ovarian origin: a case report from northern Pakistan. Gynecol Oncol Rep. 2017;21:24-7.
7. Naffouje SA, Anderson RR, Salti GI. A case report of hepatoid carcinoma of the ovary with peritoneal metastases treated with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy without systemic adjuvant therapy. Int J Surg Case Rep. 2016;27:83-6.
8. Pandey M, Truica CI. Hepatoid carcinoma of the ovary. J Clin Oncol. 2011;29(15):e446-8.
9. Wang L, Zhong Y, Sun L, Zhou H, Chen W, Zhang X. Clinical and pathological features of hepatoid carcinoma of the ovary. World J Surg Oncol. 2013;11:29.
10. Watanabe Y, Umemoto M, Ueda H, Nakai H, Hoshiai H, Noda K. Cytopathologic and clinicopathologic features of ovarian hepatoid carcinoma: a case report. Acta Cytol. 2003;47(1):78-82.
11. Nishida T, Sugiyama T, Kataoka A, Ushijima K, Ota S, Iwanaga S, *et al*. Ovarian hepatoid carcinoma without staining for alpha-fetoprotein in the primary site. Int J Gynecol Cancer. 1995;5(4):314-8.
12. Sung JH, Kim TH, Park HG, Kim MJ, Kim BG, Kim TJ, *et al*. Hepatoid carcinoma of the ovary without staining for alpha-fetoprotein. Obstet Gynecol Sci. 2013;56(1):41-4.
13. Mazouz A, Amaadour L, Ameurtesse H, Chban L, Amarti A, Kettani F, *et al*. Primary hepatoid carcinoma of the ovary: a case report. Pan Afr Med J. 2015;20:93.
14. Randolph LK, Hopkins MK, Hopkins MP, Wasdahl DA. Hepatoid carcinoma of the ovary: a case report and review of the literature. Gynecol Oncol Rep. 2015;13:64-7.
15. Ishikura H, Scully RE. Hepatoid carcinoma of the ovary: a newly described tumor. Cancer. 1987;60(11):2775-84.
16. Randolph LK, Hopkins MK, Hopkins MP, Wasdahl DA. Hepatoid carcinoma of the ovary: a case report and review of the literature. Gynecol Oncol Rep. 2015;13:64-7.
17. Choi WK, Cho DH, Yim CY, Lee NR. Primary hepatoid carcinoma of the ovary: a case report and review of the literature. Medicine (Baltimore). 2020;99(19):e20051.
18. Li J, Wu X. A case report and literature review on hepatoid carcinoma of the ovary. Clin Case Rep Int. 2022;6:1297.
19. Zuo Y, Liu X, Pang Y, Chen X, Li X, Gao J, *et al*. Case Report: A rare case of hepatoid carcinoma of the ovary with genomic profiling and long-term follow-up: diagnostic and therapeutic perspectives. Front Oncol. 2025;15:1631424.
20. Zhang N, Liu Z, Cao D, Lou W. Hepatoid carcinoma of the ovary: case report, clinical management, and insights from literature review. Clin Case Rep. 2025;13(12):e71496.
21. Camparo P, Compérat EM. SALL4 is a useful marker in the diagnostic work-up of germ cell tumors in extra-testicular locations. Virchows Arch. 2013;462(3):337-41.
22. Sideras K, Bots SJ, Biermann K, Sprengers D, Polak WG, Ijzermans JNM, *et al*. Tumour antigen expression in hepatocellular carcinoma in a low-endemic western area. Br J Cancer. 2015;112(12):1911-20.
23. Acosta AM, Pins MR. Hepatoid carcinoma of the ovary: clinical, histopathologic, and immunophenotypic features. Arch Pathol Lab Med. 2019;143(7):883-9.
24. Tochigi N, Kishimoto T, Supriatna Y, Nagai Y, Nikaido T, Ishikura H. Hepatoid carcinoma of the ovary: a report of three cases admixed with a common surface epithelial carcinoma. Int J Gynecol Pathol. 2003;22(3):266-71.

25. Yığit S, Uyaroğlu MA, Kuş Z, Ekinci N, Öztekin Ö. Hepatoid carcinoma of the ovary: immunohistochemical findings of one case and literature review. Int J Gynecol Cancer. 2006;16(3):1439-41.
26. Wang L, Zhong Y, Sun L, Zhou H, Chen W, Zhang X. Clinical and pathological features of hepatoid carcinoma of the ovary. World J Surg Oncol. 2013;11:29.
27. Cascales-Campos P, Gil J, Gil E, López-Marín L, Montalvá E, Parrilla P. Peritoneal dissemination of hepatoid carcinoma of the ovary treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Case Rep Med. 2013;2013:283295.
28. Randolph LK, Hopkins MK, Hopkins MP, Wasdahl DA. Hepatoid carcinoma of the ovary: a case report and review of the literature. Gynecol Oncol Rep. 2015;13:64-7.
29. Choi WK, Cho DH, Yim CY, Lee NR. Primary hepatoid carcinoma of the ovary: a case report and review of the literature. Medicine (Baltimore). 2020;99(19):e20051.
30. Liu Y, Zhao R. Clinicopathological features and pathogenesis of hepatoid adenocarcinoma of the uterine cervix: a case report. Front Oncol. 2025;15:1551657.
31. Al-Obaidy KI, Williamson SR, Shelman N, Idrees MT, Ulbright TM. Hepatoid teratoma, hepatoid yolk sac tumour, and hepatocellular carcinoma: a morphologic and immunohistochemical study of 30 cases. Am J Surg Pathol. 2021;45(1):127-36.
32. Wojnarowicz PM, Oros KK, Quinn MCJ, Arcand SL, Gambaro K, Madore J, *et al*. The genomic landscape of TP53 and p53-annotated high-grade ovarian serous carcinomas from a defined founder population associated with patient outcome. PLoS One. 2012;7(9):e45484.
33. Kihara A, Amano Y, Arai Y, Fujiwara H, Niki T. Expression of glypican-3, SALL4, and CD34 in undifferentiated endometrial carcinomas. Pathology. 2024;56(4):591-4.
34. Iwaya M, Riddell R, Asano K, Kobayashi K, Uehara T, Ota H. Alpha-fetoprotein-producing early gastric cancer with intramucosal hepatoid and fetal enteric differentiation. Case Rep Gastroenterol. 2020;14(2):426-35.
35. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH. Prediction of cancer incidence and mortality in Korea, 2017. Cancer Res Treat. 2017;49(2):306-12.
36. Ozan H, Ozturk Nazlioglu H, Ozuysal S. A case of hepatoid carcinoma of the ovary. Eur J Gynaecol Oncol. 2008;29(5):556-7.
37. Tejerina González E, Argüelles M, Jiménez-Heffernan JA, Dhimes P, Vicandi B, Pinedo F. Cytologic features of hepatoid carcinoma of the ovary: a case report with immunocytologic evaluation of HepPar1. Acta Cytol. 2008;52(4):490-4.
38. Isonishi S, Ogura A, Kiyokawa T, Suzuki M, Kunito S, Hirama M, *et al*. Alpha-fetoprotein-producing ovarian tumor in an elderly woman. Int J Clin Oncol. 2009;14(1):70-3.
39. Zizi-Sermpetzoglou A, Petrakopoulou N, Nikolaidou ME, Tepelenis N, Kouloukoussa M, Voulgaris Z. Hepatoid carcinoma of the ovary: a case report and review of the literature. Eur J Gynaecol Oncol. 2009;30(3):341-3.
40. Lee CH, Huang KG, Ueng SH, Swei H, Chueh HY, Lai CH. A hepatoid carcinoma of the ovary. Acta Obstet Gynecol Scand. 2002;81(11):1080-2.
41. Lefkowitch JH. Liver look-alike: hepatoid ovarian carcinoma. Hepatology. 1988;8(5):1168-9.
42. Liu X, Wang X, Zhu F. Hepatoid carcinoma of the ovary: a case report and review of the literature. Oncol Lett. 2012;4(5):947-50.
43. Matsuta M, Ishikura H, Murakami K, Kagabu T, Nishiya I. Hepatoid carcinoma of the ovary: a case report. Int J Gynecol Pathol. 1991;10(3):302-10.
44. Maymon E, Piura B, Mazor M, Bashiri A, Silberstein T, Yanai-Inbar I. Primary hepatoid carcinoma of the ovary in pregnancy. Am J Obstet Gynecol. 1998;179(3 Pt 1):820-2.
45. Nishida T, Sugiyama T, Kataoka A, Ushijima K, Ota S, Iwanaga S, Yakushiji M. Ovarian hepatoid carcinoma without staining for alpha-fetoprotein in the primary site. Int J Gynecol Cancer. 1995;5(4):314-8.
46. Zhang X, Xu L, Cao Y, Ye P, Cheng Y, Lin X, *et al*. Whole-exome sequencing identifies germline BLM mutation in ovarian hepatoid adenocarcinoma with favorable response to niraparib and anlotinib combination therapy: a case report and literature review. Int J Surg Pathol. 2024;33(2):236-48.
47. Thoprasert P, Phaliwong P, Smanchat B, Prommas S, Bhamarapravatana K, Suwannarurk K, *et al*. Endometrial thickness measurement as predictor of endometrial hyperplasia and cancer in perimenopausal uterine bleeding: cross-sectional study. Asian Pac J Cancer Prev. 2023;24(2):693-9.
48. Yan L, Jakate S, Reddy V, Gattuso P. Metastatic hepatocellular carcinoma diagnosed by fine needle aspiration: a clinical and cytologic study. Diagn Cytopathol. 2018;46(6):495-500.
49. Bialecki ES, Di Bisceglie AM. Diagnosis of hepatocellular carcinoma. HPB (Oxford). 2005;7(1):26-34.
50. Chapel DB. Clear cell carcinoma of the ovary. In: Wilkinson N, editor. Pathology of the ovary, fallopian tube and peritoneum. Cham: Springer International Publishing; 2023. p. 457-78.
51. De Pauw A, Naert E, Van de Vijver K, Philippe T, Vandecasteele K, Denys H, *et al*. A clearer view on ovarian clear cell carcinoma. Acta Clin Belg. 2022;77(6):792-804.
52. Choi WK, Cho DH, Yim CY, Lee NR. Primary hepatoid carcinoma of the ovary: a case report and review of the literature. Medicine (Baltimore). 2020;99(19):e20051.
53. Scurry JP, Brown RW, Jobling T. Combined ovarian serous papillary and hepatoid carcinoma. Gynecol Oncol. 1996;63(1):138-42.
54. Tochigi N, Kishimoto T, Supriatna Y, Nagai Y, Nikaido T, Ishikura H. Hepatoid carcinoma of the ovary: a report of three cases admixed with a common surface epithelial carcinoma. Int J Gynecol Pathol. 2003;22(3):266-71.
55. Liu Y, Zhou R, Wang S, Zhang G. Extra-hepatic hepatoid carcinomas in female reproductive system: three case-reports with a literature review. Cancer Manag Res. 2021;13:1625-36.
56. Sung JH, Kim TH, Park HG, Kim MJ, Kim BG, Kim TJ, *et al*. Hepatoid carcinoma of the ovary without staining for alpha-fetoprotein. Obstet Gynecol Sci. 2013;56(1):41-4.
57. Restaino S, Pellecchia G, Poli A, *et al*. A rare case of hepatocellular carcinoma recurrence in ovarian site after

12 years mimicking a hepatoid adenocarcinoma: case report. J Clin Med. 2023;12(7):2468.
58. Durnez A, Verslype C, Nevens F, Fevery J, Aerts R, Pirenne J, *et al*. The clinicopathological and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. Histopathology. 2006;49(2):138-51.
59. Karabork A, Kaygusuz G, Ekinci C. The best immunohistochemical panel for differentiating hepatocellular carcinoma from metastatic adenocarcinoma. Pathol Res Pract. 2010;206(8):572-7.
60. Kwon JE, Kim SH, Cho NH. No ancillary finding is valid to distinguish a primary ovarian hepatoid carcinoma from metastatic hepatocellular carcinoma. Int J Gynecol Cancer. 2006;16(5):1691-4.
61. Goldschmidt MH, Goldschmidt KH. Epithelial and melanocytic tumors of the skin. In: Meuten D, editor. Tumors in domestic animals. 5th ed. Ames (IA): Wiley Blackwell; 2017. p. 112-115.
62. Pradel J, Berlato D, Dobromylskyj M, *et al*. Prognostic significance of histopathology in canine anal sac gland adenocarcinomas: preliminary results in a retrospective study of 39 cases. Vet Comp Oncol. 2018;16(4):518-22.
63. Meuten DJ, Moore FM, George JW. Mitotic count and the field of view area: time to standardize. Vet Pathol. 2016;53(1):7-9.
64. Tsuboi M, Sakai K, Maeda S, *et al*. Assessment of HER2 expression in canine urothelial carcinoma of the urinary bladder. Vet Pathol. 2019;56(3):369-76.

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