


Therapeutic Approaches to Gastric Hepatoid Adenocarcinoma: Current Perspectives

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Abstract: Hepatoid adenocarcinoma of the stomach (HAS) is a rare subgroup of gastric cancer (GC). Morphologically, this tumor exhibits both adenocarcinomatous and hepatocellular differentiation, and most tumors show immunohistochemical staining for alpha-fetoprotein (AFP) or elevated AFP serum levels. The diagnosis of HAS is frequently delayed, and at least half of patients have advanced disease at the time of diagnosis. Despite a lack of evidence, treatment approaches have mostly followed principles for the treatment of common gastric cancer (CGC), including radical surgery in eligible patients with curative intent. The indications for and the type of adjuvant systemic treatments remain unclear. Additionally, there is a lack of evidence allowing any firm conclusions to be drawn regarding the best treatment for patients with metastatic HAS (mHAS). Chemotherapy regimens, including cisplatin-based chemotherapy, are considered the most efficient first-line systemic treatment in advanced situations. Their combination with targeted therapy (i.e., trastuzumab) in HER2-positive tumors seems promising. The rarity of these patients and the scarce and heterogeneous literature on this particular subgroup of GC make it difficult to provide any robust evidence for the clinical management of patients with HAS.

Keywords: hepatoid adenocarcinoma, stomach, gastric, alpha-fetoprotein, therapy, prognosis

Introduction

The seminal case report by Bourreille et al¹ in 1970 entertained for the first time the distinct entity of an alpha-fetoprotein (AFP)-producing malignant tumor of the stomach. However, the term “hepatoid carcinoma of the stomach” (HAS) was coined by Ishikura et al² in 1985. This rare subtype of primary gastric cancer (GC) exhibits both adenocarcinomatous and hepatocellular differentiation. HAS is prone to early metastasis, specifically to lymph nodes, the liver and lung, and the prognosis is regarded as dismal.^{3–5} This tumor may also arise in other extrahepatic organs, including the esophagus, biliary tract, pancreas, colon and lungs.^{4,6–11}

Due to its rarity, a timely and proper identification and a correct diagnosis may be delayed and sometimes challenging.^{7,12,13} This may further jeopardize the prognosis of these patients.

The scientific literature on this topic comprises mostly single case reports and some small single-institution patient series. Accordingly, scientific evidence for proper clinical decision-making and for the evaluation of various treatment outcomes is limited. Nevertheless, efforts have been made to extract some core knowledge.^{3–5,7,14–17}

In this article, we want to provide pertinent and novel knowledge from the recently available literature to enable a better understanding of the appropriate clinical management of patients with HAS.

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Materials and Methods

A literature search in PubMed was performed, and articles published until July 2019 were included. Various terms, including “hepatoid adenocarcinoma”, “stomach”, “gastric”, “gastric cancer”, “adenocarcinoma”, “alpha-fetoprotein”, “treatment”, “prognosis”, and “surgery”, were included. We performed a rather extensive review of the recent, pertinent literature.⁷ The current search was not a true systematic review. However, emphasis was placed on articles that could add useful clinical information with regard to a correct diagnosis and timely and proper treatment decision-making for patients with HAS. Specifically, we considered publications from the last few years that could provide novel information on treatments and prognostication. Only articles written in English were evaluated.

Results

The Literature

A variety of papers were identified, most comprising single case reports and small single-institution series. Articles other than single case reports, including some selected small patient series and reviews of collected single case reports, are displayed in Table 1. In 2003, Adachi et al¹⁴ reported on 270 cases described in the Japanese literature, and in 2016, a systematic review of case reports and series from China was published by Qu et al¹⁶ Recently, Zeng et al³ described 34 patients from their institution and included 294 cases reported in the literature in their review. Of note is that the majority of papers beyond single case reports typically comprised between 10 and 30 patients from each institution,¹⁴ mostly originating from Japan,^{14,18–20} or China.^{5,15,21,22}

HAS as a Rare Disease

HAS is a rare GC subtype and accounts for 0.38–1.6% of all GCs,^{5,20} although others have suggested an incidence between 1.3–15% of all gastric carcinomas.²⁴ The estimated annual incidence is reported to be between 0.58–0.83 cases per million inhabitants.^{25,26} There is a male predominance (between 2–3-fold), and most patients are in their 60s or 70s at diagnosis (Table 1). Moreover, the majority of patients (i.e., at least 70–80%) have elevated serum alpha-fetoprotein (AFP) levels. At the time of diagnosis, clinical work-up, including imaging, will reveal advanced disease, including distant metastases (predominately in the liver and lung), in many patients and is confirmed in at least half of

the patients. Accordingly, the prognosis for patients with HAS is generally dismal.^{3–5,15–17}

Clinical Diagnosis

Clinical symptoms and signs are unspecific. Hence, the diagnosis of a gastric tumor is mostly made at gastroscopy with biopsy after referral due to abdominal pain, epigastric discomfort, hematemesis/melena, loss of weight, or clinical manifestations related to liver metastases.^{3,4} In particular, if elevated serum AFP levels have been encountered as a single sign, the diagnosis can be delayed or misdiagnosed as hepatocellular carcinoma (HCC).^{3,7,12,13} No correlation between preoperative AFP levels and tumor size has been found.²⁰

Imaging

Computed tomography (CT) is now readily available and remains a cornerstone in the staging of patients with malignant solid tumors. However, with obvious lesions encountered on imaging, it is not always easy to define the true nature of this imaging feature. A spectrum of imaging features of HAS liver metastasis has been reported.^{27,28} On dynamic CT of the liver, an arterial hyperattenuation followed by a late wash is common. Notably, this pattern resembles a pattern similar to that of HCC. However, if an isolated portal vein thrombosis and a tendency for tumor necrosis are encountered related to liver nodules, a diagnosis of HAS is more likely.^{27,28} Magnetic resonance imaging (MRI) adds to the tools, and MRI diffusion-weighted imaging was recently introduced for the identification and diagnosis of primary HAS.²⁹

With scarce pooled information in imaging aspects,³ the exact usefulness of PET/CT in the management of HAS patients remains to be shown.³⁰

Pathology

HAS belongs to the indeterminate type of GC according to Lauren’s classification.^{31,32} The pathological diagnosis is based on morphological characteristics irrespective of the serum AFP levels or tissue AFP staining by immunohistochemistry (IHC).^{13,19,33} The primary HAS lesion comprises tubular as well as hepatoid components.¹⁷ For poorly differentiated adenocarcinoma of the solid type and small cell neuroendocrine cell carcinoma, the growth pattern resembles that of HAS, except for the lack of positive staining for AFP by IHC. Of note, Liu et al¹⁷ claimed that the diagnosis of HAS should be strictly based on a combination of hepatoid features and the

Table 1 Characteristics of Patients with Hepatoid Adenocarcinoma of the Stomach (HAS)

Author, Year	Origin & Time Period	Number of Pts.	Study Type	Serum AFP	M:F Ratio	Age at Diagnosis, Years (Range)	Location of the Primary Tumor	Tumor Size (Cm)	Gross Classification (Bormann I-IV)	Metastases	Survival
Ishikura et al 1986 ¹⁹	Japan	7	Retrospective; several institutions	↑ in all	4:3	Median 63 (44-77)	Fundus I; whole stomach I; antrum 5	Median 7 (5-12)	I=14.3% II=71.4% III=14.3%	None 2; liver, lung, and LN 5	N/A
Adachi et al 2003 ¹⁴	Japan 1982-2001	270	Cases reported in the Japanese literature	↑ in 77% (i.e., >100 ng/mL)	2.8:1	68% ≥60 yr	Cardia and body antrum	N/A	N/A	LN 83%; liver 33%	Median 14 mo; 5-yr survival rate 22%; after curative gastrectomy: median 29 mo; 5-yr survival rate 42%
Liu et al 2010 ²¹	China 1996-2007	45	Retrospective; single institution		3.5:1	58% ≥60 yr			0/I=6.7% II=4.4% III=82.2% IV=6.7%	Liver 75.6%	I-, 3-, and 5-yr overall survival rates were 30%, 13%, and 9%, respectively
Inoue et al 2010 ²⁰	Japan 1992-2001	53	Retrospective; single institution	↑ in 71.7% (i.e., >40 ng/mL)	4.9:1	Median 61 (27-84)	Cardia 19%; body 38%; antrum 43%	N/A	0/I=8% II=49% III=32% IV=9% Unclassified=2%	Stage IV 47%; LN mets. 87; liver mets. • synchr: 17% • metachr: 36%	5-yr survival rate 34%
Zhang et al 2011 ¹⁵	China 1998-2009	20	Retrospective; single institution	Mostly not tested	4:1	Median 60 (40-81)	Cardia 50%; body 10%; antrum 40%	N/A	I=5% II=35% III=35% Missing=25%	None 15; liver and celiac 5	Median 12 mo (2-99); 3-yr survival rate 17.2%
Su et al 2013 ²³	Worldwide 2001-2011	182	Literature review	↑ in 87.5%	3.2:1	Mean 63.3 ±12.8 (28-100)	N/A	N/A	N/A	Liver (48.8%); lung (2.9%); other (5.2)	N/A
Yang et al 2014 ⁵	China 2005-2012	31	Retrospective; single institution	↑ in 87.1%	2.1:1	Mean 51.2 ±20.8 (32-87)	Cardia 10; body 12; antrum 1	N/A	I=3.2% II=6.5% III=9.7 Missing=67.8%	LN 25.8%; distant mets. 54.8%	Median 6 mo; 3-yr survival rate 22.6%

(Continued)

Table 1 (Continued).

Author, Year	Origin & Time Period	Number of Pts.	Study Type	Serum AFP	M:F Ratio	Age at Diagnosis, Years (Range)	Location of the Primary Tumor	Tumor Size (Cm)	Gross Classification (Bormann I-IV)	Metastases	Survival
Lin et al 2015 ²²	North Taiwan 2001–2010	10	Retrospective; single institution	↑ in 70%	3:2	Median 65.5 (46–77)	Cardia 1; body 4; angle 2; antrum 3	N/A	I=30% II=10% III=66%	87.1% either LN or distant mets.	Median 7.2 mo (0.7–131.8); 5-yr survival rate 20% (40% in those undergoing chemotherapy)
Qu et al 2016 ¹⁶	China 1987–2016	180	Systematic review of reported cases from China	↑ in 87.2% (i.e., > 40 ng/mL)	3.2:1	Median 61	Fundus 14; body 41; antrum 96; various 29	N/A	N/A	N/A	Median 10 mo; 3-yr survival rate 7.36%
Fujimoto et al 2018 ¹⁸	Japan 2004–2017	16	Retrospective; single institution	N/A	1.7:1	Median 78 (58–87)	Upper 3rd 5; middle 3rd 6; lower 3rd 5	N/A	I=25% II=18.8% III=56.2%	4 (25%) with distant mets.	N/A
Zeng et al 2018 ⁴	China 2010–2016	34 from a single institution and 294 from a literature review	Retrospective; single institution and literature review	(n=93)* ↑ in 64.5% (i.e., >300 ng/mL)	(n=305) * 3.4:1	Median 63 (12–100)	(n=252)* Cardia 20.6%; body 31.3%; antrum 45.6%; gastric remnant and fundus 2.5%	Median 5.5 (1.5–20)	(n=143)* I = 12.6% II = 16.1% III = 68.5% IV = 2.8%	(n=121)* Liver 78.5%; lung 11.6%; peritoneum 6.6%; spleen and brain 3.3%	(n=122)* 1-, 3-, and 5-yr disease-free survival rates were 51.3%, 26.2%, and 20.7%, respectively

Note: *Information on this specific variable was missing for a large proportion of patients.

secretion of AFP. Thus, while evaluating the incidence of HAS and making a consistent diagnosis, it is important to distinguish between HAS, AFP-producing GC without hepatoid features (AFPPGC) and common gastric cancer (CGC).¹⁷ The same authors also reported that vascular invasion is more often found in HAS compared to AFPPGC and CGC, which is likely associated with the observation that liver metastasis is more often encountered at the time of diagnosis, and patients with HAS have a shorter time until metachronous liver metastasis is diagnosed compared to patients diagnosed with AFPPGC or CGC.¹⁷

Human epithelial growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor (EGFR) family. Amplification of this receptor has been observed in approximately 20% of GCs³¹ and has also been introduced as a marker for targeted therapy in advanced GC.³⁴ HER2 overexpression has been frequently observed in the subgroup of patients with HAS.^{12,17,18} In contrast, no EGFR, KRAS or BRAF overexpression has been observed in the same subgroup.¹⁸

Recently, other molecular characteristics of HAS have also been revealed, showing that TP53, as the most frequently encountered mutation, was found in 30% of the tumors.³² The same authors reported that other genes, including CEBPA, RPTOR, WISP3, MARK1, and CD3EAP, were identified with rather high mutation rates (10–20%), and copy number gains (CNGs) at 20q11.21–13.12 were the most frequent genetic alteration in HAS patients.³²

A more extensive morphological work-up using hepatocellular markers has been recommended.³⁵ Researchers have found that AFP, SALL4, Hep-Par-1 and glypican 3 were significantly more positive in HAS than in nonhepatoid gastric adenocarcinoma, and the frequency of distant metastasis was significantly higher in SALL4-negative cases compared to SALL4-positive cases. Hep-Par-1 positivity was associated with liver metastases, and palate, lung, and nasal epithelium clone (PLUNC) positivity was correlated with lymph node metastases. In addition, the combination of PLUNC, Hep-Par-1 and SALL4 could serve as a reliable prognostic factor in HAS.³⁵

Treatments

Primary Treatment

Surgery is a cornerstone for treatment with curative intent. Gastric resection is sometimes also indicated for palliation, and surgery is generally employed in most patients

(90%).^{3,7,15,20} Operative principles in line with surgery for CGC are recommended.^{36,37} Whether neoadjuvant or adjuvant therapy should be a part of the primary treatment of this particular subgroup of GC patients is not clear. In a single-institution study from Japan during a ten-year time period, adjuvant chemotherapy including 5-fluorouracil, cisplatin, irinotecan, docetaxel, paclitaxel, methotrexate, mitomycin C or tegafur/uracil was offered to 28 (52.3%) of 53 patients at the discretion of each attending doctor, but details on the doses, frequencies, treatment durations and outcomes related to chemotherapy were not given.²⁰ Moreover, Zhang et al¹⁵ described 14 patients who were surgically treated for a cure, including 8 patients who were given postoperative adjuvant chemotherapy. Without providing details on the specific adjuvant chemotherapy treatment employed, they claimed that adjuvant chemotherapy was an independent factor for improved survival.

Treatment of Metastatic Disease

The treatment of metastatic HAS (mHAS) remains even less elucidated. While a number of various drugs (e.g., 5-fluorouracil, cisplatin, irinotecan, docetaxel, paclitaxel, methotrexate, and mitomycin C) and various treatment schedules have been used for the treatment of mHAS, the scarce literature provides only fragmental information. Nevertheless, in a recent systematic review based on 18 case reports on the treatment of metastatic hepatoid gastric adenocarcinomas (n=11) or other primary locations (n=7), the authors concluded that cisplatin-based chemotherapy is the most efficient first-line systemic treatment in advanced situations, with a clinical response observed in 75% of the patients.³⁸

The introduction of molecular targeted therapy has expanded the therapeutic tool box and improved the survival of patients with certain types of solid tumors, including GC.^{31,39} HER2 is overexpressed in 25% of patients with HAS,¹⁸ and trastuzumab in combination with chemotherapy has been offered to patients with HER2-positive CGC.³⁴ Moreover, ramucirumab, a monoclonal antibody for VEGF receptor-2, has been approved as the first antiangiogenic drug for the treatment of advanced CGC. Arakawa et al⁴⁰ recently reported a significant clinical response to ramucirumab monotherapy in an HAS patient with chemotherapy-resistant recurrent disease.

Anecdotally, Wang et al⁴¹ recently described a 56-year-old male with progressive therapy-resistant metachronous liver metastases, as judged by increased biomarker levels

(CEA and AFP), despite transcatheter arterial chemoembolization (TACE) and radiofrequency ablation. Sorafenib had to be stopped due to early adverse reactions. The patient underwent ex vivo hepatectomy and a partial liver autotransplantation, and 20 months after the liver autotransplantation, he was reported to be relapse-free and still alive.⁴¹

Prognosis and Prognostication

The prognosis of HAS is regarded as poor and is predominantly related to the stage of the disease.^{15,20} As a distinct entity, the particular dismal prognosis of HAS patients is emphasized when comparing the prognosis of patients with AFP-producing GC without hepatoid features (AFPPGC) to those with CGC¹⁷ (Figure 1). Neither age, sex nor preoperative serum AFP levels are associated with prognosis.²⁰ Nevertheless, elevated preoperative serum AFP levels ≥ 500 ng/mL are significantly associated with poor overall survival and tend to be associated with poor disease-free survival.³²

The presence of distant metastases, including synchronous or metachronous liver metastases, is significantly associated with poor survival.^{16,20} Improved survival is observed in patients surgically treated for a cure.^{3,20} However, information on the true importance of other employed treatments with regard to overall survival is conflicting.¹⁵

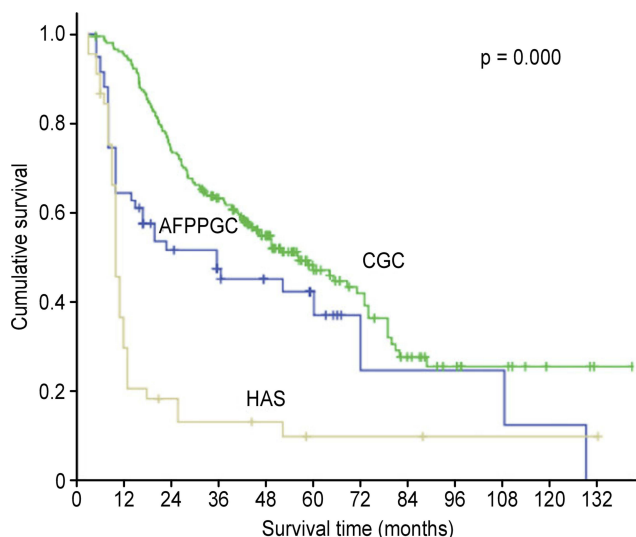


Figure 1 Differences in survival among the three groups (AFPPGC, HAS and CGC).
Notes: Copyright © 2012 Wiley Periodicals, Inc. Reproduced from Liu X, Sheng W, Wang Y. An analysis of clinicopathological features and prognosis by comparing hepatoid adenocarcinoma of the stomach with AFP-producing gastric cancer. *J Surg Oncol.* 2012;106(3):299–303.¹⁷

Abbreviations: AFPPGC, AFP producing gastric cancer; HAS, hepatoid adenocarcinoma of the stomach; CGC, common gastric cancer.

A more extensive morphological work-up using hepatocellular markers seems warranted.³⁵ Researchers have found that AFP, Sal-like protein 4 (SALL4), Hepatocyte paraffin 1 (Hep-Par-1) and glypican 3 are significantly more positive in HAS than in nonhepatoid adenocarcinoma, and the frequency of distant metastasis was significantly higher in SALL4-negative cases compared to SALL4-positive cases. Hep-Par-1 positivity was associated with liver metastases, and PLUNC positivity was correlated with lymph node metastases. The combination of PLUNC, Hep-Par-1 and SALL4 could serve as a reliable prognostic factor in HAS.³⁵

Discussion

HAS, as a particular subgroup of gastric carcinomas, is rare, with a suggested incidence between 1.3–15% of all gastric carcinomas.²⁴ This wide incidence range reported in the literature likely mirrors some uncertainty or discrepancy with regard to criteria for the diagnosis of HAS.²⁰ Others have reported the incidence to be between 1–6%,⁴² and from a Japanese single-institution series of 3374 GC patients, only 1.6% met the given criteria to be diagnosed with HAS.²⁰

While a large proportion of the literature on HAS originates from authors from the East (i.e., Japan or China), this is most likely explained by the much higher incidence of GC, in general, in this part of the world. If the percentage of HAS differs between the East and the West (i.e., Europe and the US), the total number of patients with GC worldwide remains to be further evaluated.

HAS should be diagnosed by the characteristic histologic features of a gastric tumor resembling hepatocellular carcinoma.^{13,21,22,31} A distinction between HAS and AFP-positive carcinoma without hepatoid features is necessary.³³ While Liu et al²¹ claim that the diagnosis of HAS should be based strictly on the combination of hepatoid morphological features and the secretion of AFP, the summarized results displayed in Table 1 indicate that a strict and consistent definition has not always been used by all researchers. Moreover, it remains uncertain which cut-off levels have been used in various studies for the definition of increased AFP levels.

A main obstacle when reviewing the pertinent literature on HAS is the heterogeneous reports available for data extraction. Important information on the definitions used, details on employed treatments and follow-up is frequently missing. Thus, incomplete data make it difficult to arrive at any firm conclusion and to provide evidence-based recommendations for treatment decision-making.

Nevertheless, the daily routine clinical challenge of suspecting the presence of HAS in a patient with unspecific symptoms or in a biopsy to confirm “endoscopic suspicious GC” remains.^{7,16} Another clinical scenario is faced by the clinician who encounters a patient with elevated AFP levels and is diagnosed with hepatic lesions on imaging. Thus, distinguishing a patient with metastatic HAS from a patient with HCC may not always be straightforward.^{17,27,35}

The prognosis of HAS is regarded as dismal. Whether this is attributed to a more aggressive biology only or whether clinical challenges, including a delayed diagnosis and misinterpretation, play a role remains uncertain. As shown by Liu et al¹⁷ patients with HAS more often have liver metastases, and the time to the diagnosis of liver metastasis is shorter in HAS patients than in non-HAS AFP-producing GC patients and in those with CGC. A number of reports support this finding. However, in contrast, a recent report found a 5-year overall survival rate of 34%, and the authors suggested that the prognosis of HAS is not as poor as previously believed.²⁰ Moreover, they found no correlation between preoperative AFP levels and prognosis, and long-time survivors had a primary tumor <10 cm in size, no peritoneal disease and had undergone R0/1 resection.²⁰

As for most solid tumors, the confirmation of advanced disease with distant metastases is of great prognostic importance. While metastases to lymph nodes, the liver and lungs are the most frequently reported locations, cerebral metastasis has also been reported.⁴³

Nevertheless, clinical evidence for the management of these patients is limited. Attention to various challenges, including the proper and timely identification of the patients, is of importance.⁷ If or how novel technologies, including artificial intelligence (AI)⁴⁴ and liquid biopsies,⁴⁵ may add to the clinical tools in this context remain to be shown. The diagnostic criteria and classifications should be discussed and acknowledged. In this regard, scrutinizing the radiomic signatures of the primary gastric tumor to predict occult peritoneal metastases may have important clinical implications.⁴⁶ Treatments should be applied according to the stage of the disease, and the therapeutic principles in line with those for CGC should be followed.

Conclusions

HAS, as a rare disease, poses distinct diagnostic and therapeutic challenges for clinicians. The diagnosis is often delayed, and advanced disease is frequently found at the time of diagnosis. Accordingly, the prognosis is severe for many of these patients. Despite the fact that

therapeutic approaches in line with principles for the treatment of CGC have been applied in single patients, true evidence for the indication and type of adjuvant chemotherapy and for the choice of drugs or a combination of drugs for the systemic chemotherapy treatment of patients with advanced disease is flawed.

Abbreviations

AFP, alpha-fetoprotein; AFPPGC, AFP-producing gastric cancer; AI, artificial intelligence; BRAF, proto-oncogene B-raf; CNG, copy number gain; CT, computer tomography; CGC, common gastric cancer; EGFR, epidermal growth factor receptor; GC, gastric cancer; HAS, hepatoid adenocarcinoma of the stomach; HCC, hepatocellular carcinoma; Hep-Par-1, hepatocyte paraffin 1; HER2, human epithelial growth receptor 2; IHC, immunohistochemistry; KRAS, K-ras gene; MRI, magnetic resonance imaging; PET, positron emission tomography; PLUNC, palate, lung, and nasal epithelium clone; SALL4, sal-like protein 4; TACE, transcatheter arterial chemoembolization; VEGF, vascular endothelial growth receptor.

Disclosure

Professor Jon Arne Søreide, MD, PhD, FACS, FISS is an approved specialist in general- and gastrointestinal surgery. The author reports no conflicts of interest in this work.

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