Hepatoid Adenocarcinoma of the Stomach: Current Perspectives and New Developments

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Hepatoid adenocarcinoma of the stomach (HAS) is a rare malignant tumor, accounting for only 0.17–15% of gastric cancers. Patients are often diagnosed at an advanced disease stage, and their symptoms are similar to conventional gastric cancer (CGC) without specific clinical manifestation. Morphologically, HAC has identical morphology and immunophenotype compared to hepatocellular carcinoma (HCC). This is considered to be an underestimation in diagnosis due to its rare incidence, and no consensus is reached regarding therapy. HAS generally presents with more aggressive behavior and worse prognosis than CGC. The present review summarizes the current literature and relevant knowledge to elaborate on the epidemic, potential mechanisms, clinical manifestations, diagnosis, management, and prognosis to help clinicians accurately diagnose and treat this malignant tumor.

Keywords: hepatoid gastric carcinoma, pathology, diagnosis, prognosis, treatment

INTRODUCTION

Hepatoid adenocarcinoma of the stomach (HAS), the Primer’s focus, is a scarce primary extrahepatic malignant neoplasm. The estimated annual incidence of HAS is 0.58–0.83 cases per million individuals. Most tumors have metastasized at diagnosis with a poor prognosis due to their aggressive behavior (1, 2). Hepatoid adenocarcinoma(HAC) has been reported to occur in the stomach (3), esophagus (4, 5), duodenum (6), jejunum (2), colon (7), peritoneum (8), pancreas (9–13), lung (14), ovary (15, 16), gallbladder (17), uterus (16, 18) and other sites (19). Of these locations, the stomach is the most common site of HAC. Histologically, HAC has similar morphology and immunohistochemistry to hepatocellular carcinoma (HCC). This is considered to be an underestimation in diagnosis due to its rare incidence, and no consensus is reached regarding therapy (20). Although numerous cases and a small sample of retrospective reports on HAS have been reported over the years, it has not been sufficiently identified. Herein, to deepen the comprehensive understanding of HAS, we elaborate on the epidemic, potential mechanisms, clinical manifestations, diagnosis, management, and prognosis of this neoplasm based on current literature and relevant materials to assist clinicians in diagnosing and treating this disease.
Epidemiology

HAS is a rare neoplasm and the annual incidence of HAS is approximately 0.58–0.83 cases per million people (2, 21). It is also a rare entity with an inconsistent reported incidence between 0.17% and 15.0% in all gastric carcinomas across several studies (20, 22). A large number of HAS case reports come from the Asian region, mainly from the Japanese and Chinese cohort (22). According to previously published reports, HAS predominantly occurred in around 65 years old male patients (21, 23). Although no specific risk factors have been reported to influence the occurrence and progression of HAS positively, several cases described patients diagnosed as HAS with HBsAg seropositivity (8, 24).

Pathogenesis

The exact molecular mechanism of HAS remains unclear. A possible hypothesis is that based on the stomach and liver, with a common embryonic and histological origin, originating from the endoderm and the primitive foregut during the development of the embryo (25–27). The major genotypes of gastric malignancy have been defined by The Cancer Genome Atlas (TCGA) Research Network as Epstein–Barr virus-positive (EBV), microsatellite-instable (MSI), genomically stable tumors (GS), and chromosomally instability tumors (CIN): HAS is excluded from any of these due to its scarcity and characteristics of geographical distribution (28). Nevertheless, HASs are genetically heterogeneous groups with a majority of HAC are “CIN” and a small number of HAC with “MSI” (29, 30). It has been speculated that HAS is the result of trans-differentiation, transitioning from the intestinal type to hepatoid phenotypic (31); and the emergence of Alpha-fetoprotein (AFP) leading to hepatoid and intestinal mucin phenotype differentiation (33). The intestinal component usually stains for CDX-2 (33, 38). HepPar-1 and Arginase-1 immunostainings are regarded as highly sensitive and specific markers of HCC, while the positive staining of these markers can be detected in some HAC, causing certain difficulties in distinguishing HAS from HCC (37, 39). Among epithelial markers, CK8/18, CK19, and AE1/AE3 are always positive for hepatoid adenocarcinoma; nevertheless, the expression of CK7, CK14, CK20 rarely appears in HAS (37). It has been reported that staining for CEA, CK19, and CK20 is detected more frequently in HAS than in HCC. Furthermore, palate, lung, and nasal epithelium clone protein (PLUNC) is a good marker for distinguishing HAS from HCC because it is often positive in the papillary and tubular adenocarcinoma components of HAS. Anecdotally, PLUNC-positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP (40). Though LIN28 is not as sensitive as SALL4, it is a particular marker (98% positive tumor cells cannot be stained by AFP.
related to more adverse bio-behavior than nonamplified tumors, including lower differentiation, greater nerve and vascular invasion, and more significant liver metastasis and is associated with worse prognosis (29, 42, 43). Moreover, the signaling pathway, including ErbB, PI3K-Akt, HIF-1 and p53 pathway regulating the pluripotency of stem cells, were specifically enriched in the mutated genes. In terms of Epigenetic modifications, GATA4 is not responsible for forming and maintaining the hepatocellular carcinoma-like phenotype (44).

Serum Tumor Markers
The majority of cases reported the elevations in AFP concentration in patients with HAS (Figure 2), and the serum AFP concentration was associated with HAC cell component percentage: the higher HAC cell component ratio in a tumor, the more AFP could be secreted by the tumor (22, 42). Although a majority of cases reported the patient had been diagnosed as HAS with the elevation of serum AFP (22), it is of note that there were still patients with HAS whose serum AFP levels were negative despite pathological results that confirmed the presence of Hyaline globule and canalicular structures morphologically (26). Accordingly, HAS’s clinicopathological entity was extended, involving adenocarcinomas performing histological patterns of similarity to HCC morphologically regardless of AFP expression/production (36, 39, 45). Other hematological markers, such as the concentration of CA19-9, CA125, CEA, and CA72-4 in the blood, were also elevated in some cases.

IMAGING DIAGNOSIS
For primary sites, the findings of computed tomography (CT), covering the longest and mean short diameter of malignancy, the ratio of lesion attenuation to aorta CT attenuation, the ratio of the number of accrete lymph nodes (LN) on CT to the number of histologically proven metastatic LN and the strengthening indexes in arterial phase minus portal venous phase, were significant predictors for distinguishing HAS from other gastric cancer (46–48). For HAC liver metastasis, arterial phase hypoenhancement was more frequently encountered than HCC. Furthermore, the diffusion-weighted magnetic Resonance Imaging (MRI) was performed for a suspected HAS and clarified the diagnosis of HAS (49). The significance of positron emission tomography (PET)/CT had in diagnosing and staging HAS accurately (50–52).
CLINICAL PRESENTATIONS

HASs were often diagnosed at an advanced disease stage with lymphatic permeation, blood vessel, and regional lymph node metastasis. Among retrospective analysis, 61.5% of HAC patients were in the III or IV stages at the diagnosis time. The relapse rate of early-stage or locally advanced stage patients was 47% (53, 54). The most common sites in which HAC developed include LNs, liver, lungs, peritoneum, and the spleen from existing literature (2, 37). Lacking specific clinical symptoms, the clinical manifestation of HAS is similar to common gastric cancer with many initial symptoms cover epigastric pain (55), abdominal distention (8), backache (55), fatigue (56), reduced appetite, weight loss (57), hematochezia, hematemesis (57) and shortness of breath (58). The most common presentation of HAS is abdominal pain (Table 1). Moreover, paraneoplastic hypercholesterolemia has been demonstrated in one case of HAS accompanied by liver metastasis (76).

TREATMENT

Surgery

For patients with early-stage HAS, radical surgery is a cornerstone of therapy with curative intent (21, 35). Radical surgery in combination with adjuvant chemotherapy is regarded as the optimal treatment approach (2). Gastric and liver metastasis resection is occasionally performed for palliation in advanced/metastatic HAS patients (85). And it was suggested that salvage surgery following chemotherapy could achieve curative resection of HAS with portal vein tumor thrombus (PVTT) (70).

Chemotherapy

No standard therapies for HAS were recommended by randomized controlled trials currently. Although the feasibility of neoadjuvant or adjuvant therapy for HAS patients and indications and concrete proposals for auxiliary treatments is illegible (21), adjuvant chemotherapy has been reported as one of the independent factors for a better outcome (35, 68) especially for HAS patients diagnosed with LNs or/and distant organ metastasis (2, 68). It was also reported that FOLFOX might be a potential adjuvant therapy for HAS (72). Cisplatin-based chemotherapy is judged as a standard first-line systemic regimen for metastatic HAS (55). Two advanced HAS patients treated with a first-line chemotherapy regimen of cisplatin and etoposide achieved a complete response (21, 86). The effectiveness of other regimens like oxaliplatin, irinotecan, gemcitabine, and 5-FU, as the first- or second-line treatment, either alone or combined, for advanced HAS situations remains obscure (86).

Interventional Therapy

Transcatheter arterial chemoembolization (TACE)/hepatic arterial infusion chemotherapy (HAIC), local intra-arterial chemotherapy for liver metastasis of HAS, has a lower frequency of toxicity reactions than systemic chemotherapy because of high resistance and lower systemic toxicity (86).
| Sex/age | Family history | Tumor location | Clinical Manifestation | Lymph nodes | Liver met | TNM | Clinicopathologic stage | Surgery | Treatment except surgery | Survival | Progression | PFS (month) |
|---------|----------------|---------------|------------------------|-------------|-----------|-----|------------------------|---------|-------------------------|----------|-------------|------------|
| Zhang et al. (26) | M/68 | NO | Antrum | NA | NO | T4aN3aM0 | IIIB | YES | 5-FU | YES | NO | 56 |
| Zhang et al. (26) | M/63 | NO | Cardia | NA | YES | T4aN2M0 | IIIA | YES | 5-FU | NO | YES | 28 |
| Zhang et al. (26) | M/58 | NO | Body | NA | YES | T2N0M0 | IIB | YES | 5-FU | NO | YES | 56 |
| Zhang et al. (26) | M/66 | NO | Body | NA | NO | T4N0M0 | IIIB | YES | 5-FU | NA | NO | 27 |
| Zhang et al. (26) | M/59 | NO | Antrum | NA | YES | T4N1M0 | IIB | YES | 5-FU | NA | NO | 6 |
| Zhang et al. (26) | F/65 | NO | Antrum | NA | NO | T4N3aM0 | IIIB | NO | 5-FU | NA | NO | 56 |
| Zhang et al. (26) | M/70 | NO | Antrum | NA | YES | T4N1bM0 | IIC | YES | 5-FU | NO | NO | 6 |
| Zhang et al. (26) | M/74 | NO | Antrum | NA | NO | T4bN2M0 | IV | YES | 5-FU | NO | YES | 11 |
| Zhang et al. (26) | M/71 | NO | Antrum | NA | NO | T4bN1M0 | IIB | YES | 5-FU | NO | NO | 1 |
| Yahaya et al. (5) | M/26 | NA | Gastroesophagael junction | Colon | shortness of breath; loss of appetite/weight | NO | NA | NA | NA | NO | NA | NA |
| Ilyas et al. (59) | M/62 | NA | Colon | Hematemesis/melena | NO | YES | T4aN2aM1a | IV | NO | L-OHP + Cap | RT | NO | YES | 5 |
| Li et al. (60) | M/60 | NA | Colon | Hematemesis/melena | NO | YES | T2N1Mx | NA | NA | L-OHP + Cap+ bevacizumab | RT | NO | NA | NA |
| Yoshizawa et al. (55) | M/61 | NA | Antrum | Gastrointestinal obstruction; left-sided back pain | YES | YES | T4N2M1 | IV | YES | FT/ CDHP/ S-1 | YES | 2 |
| Valle et al. (1) | M/61 | NA | Lung | Abdominal distention; swelling of his bilateral lower extremities, jaundice, and dark urine, fatigue, melena; loss of weight | NO | NO | NA | NO | IMRT | YES | YES | 12 |
| Hu et al. (61) | M/63 | NO | Gastric | Abdominal distention; swelling of his bilateral lower extremities, jaundice, and dark urine, fatigue, melena; loss of weight | NO | NO | IVB | NO | NO | NA | NA | 18 |
| Soreide et al. (56) | M/49 | NA | Gastric | Fatigue, epigastric discomfort, nausea, anemia | YES | NO | T4bN1M0 | NA | YES | NO | NO | 3 |
| Soreide et al. (56) | F/81 | NA | NA | Hematemesis/melena; loss of appetite/weight | NO | NO | NA | NO | L-OHP+5-Fu + Ca; TAX+ Cap# | NO | NO | YES | 7 |
| Sun et al. (62) | M/66 | NA | Antrum; Body | Hematemesis/melena | NO | NO | NA | NA | 5-FU | NO | NA | NO |
| Tong et al. (11) | M/56 | NA | Antrum | Hematemesis/melena | NO | NO | T3N1 | NA | YES | DCX+ Trastuzumab | NO | YES | 9 |
| Fakhruddin et al. (63) | F/41 | NO | Antrum | Hematemesis/melena; epigastric pain | NO | NO | T3N1 | NA | YES | YES | NO | 18 |

(Continued)
| Sex/age Family history | Tumor location | Clinical Manifestation | Lymph nodes | Liver met | TNM | Clinicopathologic stag | Surgery | Treatment except surgery | Survival | Progression | PFS (month) |
|------------------------|---------------|------------------------|-------------|----------|-----|-----------------------|---------|------------------------|----------|-------------|-------------|
| Lakshmanan et al. (64) | M/75 | NA | Antrum | fatigue epigastric pain | NO | NO | NA | NA | D2 | NO | YES | NO | NA |
| Shen et al. (65) | M/70 | NA | Antrum | muscle weakness; palpitations | NO | YES | NA | NA | YES | L-OHP + Cap# | YES | NA | NA |
| Ogbonna et al. (6) | M/66 | NO | Duodenum | nausea, vomiting, constipation loss of appetite/weight epigastric pain | NA | YES | NA | IV | NO | NO | NO | YES | 1 |
| Gaeta et al. (66) | M/72 | NA | NA | Fatigue | NA | NO | T3N2M0 | IIIb | YES | NA | NA | NA | NA |
| Cheng et al. (57) | M/83 | NA | NA | hematemesis/melena loss of appetite/weight | YES | YES | T3N3M1 | IV | NO | NO | NO | NA | NA |
| Zhou et al. (67) | F/72 | NO | Antrum | abdominal distension | YES | NA | NA | NA | YES | L-OHP+ 5-FU+ olivic acid, | YES | NO | NA |
| Xiao et al. (68) | M/47 | NA | Body/5*3 | abdominal distension | NA | NO | pT2aN3aM0 | IIA | D2 | SOX6 | YES | NO | NA |
| Xiao et al. (68) | M/63 | NA | Antrum/5*3 | abdominal distension | NA | NO | pT4aN3bM0 | IIIC | D2 | FOLFOXx4/#, TS-1 | YES | NO | NA |
| Xiao et al. (68) | F/76 | NA | Cardia/7*5*3 | abdominal distension | NA | NO | pT1bN0M0 | Ia | D2 | Cap+ TAX | YES | YES | 18 |
| Xiao et al. (68) | M/61 | NA | Antrum/5.5*4 | abdominal distension | NA | NO | pT4aN2M0 | IIIB | D2 | SOX/# | YES | YES | 11 |
| Xiao et al. (68) | M/69 | NA | Antrum/3*2.5 | abdominal distension | NA | NO | pT3N1M0 | IIB | D2 | SOX | YES | NO | NA |
| Xiao et al. (68) | M/57 | NA | Antrum/3*4 | abdominal distension | NA | NO | pT4aN3M0 | IIIC | D2 | SOX | YES | NO | NA |
| Xiao et al. (68) | M/67 | NA | Cardia/4*3.2 | abdominal distension | NA | NO | pT4aN3M0 | IIIB | D2 | SOX | YES | NO | NA |
| Xiao et al. (68) | M/58 | NA | Antrum/4.5*4 | abdominal distension | NA | NO | pT4aN2M0 | IIIB | D2 | SOX | YES | YES | 22 |
| Xiao et al. (68) | M/72 | NA | Antrum/4*6 | abdominal distension | NA | NO | pT4aN2M0 | IIIb | D2 | NO | YES | 1 |
| Xiao et al. (68) | F/73 | NA | Gastric/4*6 | YES | YES | pT3N3am1 | IV | NA | NA | NA | NA | NA |
| Velut et al. (49) | M/63 | NA | Distal stomach | abdominal pain | NA | NO | pT2aN1M0 | NA | YES | FOLFOX | YES | NO | NA |
| Nakao et al. (70) | M/63 | NA | Body | positive fecal occult blood | NA | NO | NA | IB | D2 | S-1+ CDDP | NA | NA | NA |
| Liu et al. (34) | M/47 | NA | NA | upper abdominal ache, nausea, vomiting, melena | YES | NO | NA | NA | YES | Chemotherapy + radical | YES | NO | NA |
| Lin et al. (71) | M/64 | NA | Body; Antrum | Epigastric discomfort | YES | YES | NA | NA | YES | Chemotherapy + TACE | NO | YES | 19 |
| Lin et al. (71) | M/69 | NA | Antrum | Body weight loss | NA | YES | NA | NA | YES | Chemotherapy | NO | YES | 3 |
| Lin et al. (71) | M/78 | NA | Antrum | Epigastric discomfort | YES | YES | NA | NA | YES | Chemotherapy | NO | YES | 5 |
| Lin et al. (71) | M/63 | NA | Cardia | Epigastric discomfort | YES | YES | NA | NA | YES | Chemotherapy + TACE | NO | YES | 6 |
| Lin et al. (71) | F/70 | NA | Body; Antrum | Palpable mass | YES | YES | NA | NA | NO | Chemotherapy + TACE | NO | YES | 23 |
| Lin et al. (71) | F/69 | NA | Body; Antrum | Epigastric discomfort | YES | YES | NA | NA | NO | Chemotherapy | NO | YES | 9 |
| Lin et al. (71) | M/60 | NA | Antrum | Epigastric discomfort | YES | YES | NA | NA | NO | Chemotherapy | NO | YES | 3 |
| Lin et al. (71) | M/75 | NA | Body | Body weight loss | YES | YES | NA | NA | NO | Chemotherapy | NO | YES | 3 |
| Velut et al. (72) | M/63 | NA | Epigastric pain, weight loss, anemia | YES | NA | T2N1 | NA | NA | YES | FOLFOX4 | YES | NO | NA |
| Sun et al. (50) | M/73 | NA | upper abdominal pain | YES | NA | T2N1M0 | NA | NA | YES | FOLFOX4 | YES | NO | NA |
| Osada et al. (45) | F/66 | NA | Body/5 | Epigastric pain | YES | NA | NA | NA | NO | NA | NO | YES | 13 |
| Osada et al. (45) | M/62 | NA | Body/3.5 | Epigastric pain | YES | NA | NA | NA | NO | NA | NO | YES | NA |
| Osada et al. (45) | M/61 | NA | Antrum/3.5 | Epigastric pain | YES | NA | NA | NA | NO | NA | NO | YES | NA |
| Sex/age | Family history | Tumor location | Clinical Manifestation | Lymph nodes | Liver met | TNM | Clinicopathologic stage | Surgery | Treatment except surgery | Survival | Progression | PFS (month) |
|---------|----------------|----------------|------------------------|-------------|----------|-----|------------------------|---------|------------------------|----------|-------------|------------|
| Osada et al. (45) | M/78 | NA | Antrum/7 | Epigastric pain | NA | NA | NA | NA | NA | NO | NA | NA | NA | NA |
| Osada et al. (45) | M/61 | NA | Body/7 | Fatigue, weight loss | NA | YES | NA | NA | NA | NA | NO | YES | NA | NA |
| Osada et al. (45) | M/75 | NA | Diffuse/3.2 | Fatigue, weight loss | NA | YES | NA | NA | NA | NA | NO | YES | 3 |
| Mahajan et al. (73) | M/60 | NA | Antrum | pain abdomen | NA | NO | NA | NA | D2 | Chemotherapy | NA | NA | NA | NA |
| Lipi et al. (74) | M/50 | NA | NA | Pain abdomen | YES | NA | NA | NA | NA | NO | YES | NA | NA |
| Ye et al. (75) | F/58 | NA | NA |  | NO | YES | T2N0M1 | NA | YES | L-OHP+ Cap, TACE, CT-guided radiofrequency ablation | YES | NO | NA | NA |
| Osada et al. (45) | M/61 | NA | Body/7 | Fatigue, weight loss | NA | YES | NA | NA | NA | NA | NO | YES | NA | NA |
| Ye et al. (75) | M/54 | NA | Gastroesophageal junction/4 | retrosternal pain | NO | NO | pT2N0M0 | IB | YES | L-OHP + 5-FU/ # | NO | YES | 18 |
| Ye et al. (75) | M/67 | NO | Body; Antrum | epigastric pain, weight loss | NA | NA | NA | NA | NA | NA | L-OHP + S-1 | NO | YES | 8 |
| Sohda et al. (76) | M/68 | HBV | Body/6 |  | NO | YES | NA | NA | NA | NO | TS-1/adjuvant Cap+ CDDP/ 4M, FOLFI R | NO | YES | 2 |
| Nuevo et al. (77) | F/67 | HBV | Antrum/3 | fatigue, anorexia, weight loss, anemia | NO | NA | NA | NA | YES | CDDP+ EPI+ Cap/# | NA | YES | 12 |
| Verma et al. (78) | M/59 | HBV | Cardia/4 | anemia | YES | NO | NA | NA | NA | NA | Subtotal/ D4 | NO | NA | NA |
| Deng et al. (79) | M/49 | HBV | Body/6 |  | YES | NA | pT3N2M1 | NA | NO | NA | TAX+ CBP | NO | YES | 6 |
| Yamanoi et al. (80) | M/100 | NA | Body | abdominal distension, dyspnea, abdominal pain, weakness, weight loss | NA | YES | NA | NA | NA | NO | Distal | NA | NA | NA |
| Metzgeroth et al. (41) | M/21 | NA | NA | melena | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Lu et al. (81) | M/59 | NA | Cardia | epigastric and right upper quadrant abdominal pain, weight loss | YES | YES | NA | NA | total | TACE | NA | YES | 6 |
| Vlachostergios et al. (82) | F/85 | NA | Antrum/7 | YES | YES | NA | NO | NO | YES | 4 |
| Lin et al. (83) | M/56 | HBV | Body |  | NA | NA | NA | NA | NA | MMC+ 5-FU+ ADM | NO | YES | 20 |
| Gálvez-Muñoz et al. (84) | M/75 | NA | Cardia; Gastroesophageal junction |  | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
concentrations of the drug injected locally (87). Both are also effective for the remission of the liver nodules of mHAS, accompanied with radical surgery or/and systemic chemotherapy.

Radiotherapy
Radiotherapy (RT) may be an inappropriate therapeutic option for HAS patients due to limited efficacy data. A scarce event reported that one patient with HAC of lung metastasizing to tonsils obtained an extraordinary symptomatic remission after the therapy of intensity-modulated radiation therapy (IMRT) (1). The palliative fractionation of RT was delivered to patients with PS (≥2) purely for symptom control, developing an unusual radiological adverse reaction to RT (59).

Anti-Angiogenesis Drugs
The introduction of anti-angiogenesis drugs has expanded treatment options of HAS. A case demonstrated that a HAS patient's resistance to chemotherapy had an evident clinical response to ramucirumab (RAM) monotherapy (87). The AFP concentration might be a potential marker to predict the response to ramucirumab and other anti-angiogenic drugs in gastric cancer. Besides, the positive Her-2 test rate of HAS patients was around 25%. Combined with chemotherapy, such as capecitabine and cisplatin, Trastuzumab could improve HER2-positive advanced HAS patients’ overall survival compared with those who received chemotherapy alone (63, 87–90). Sorafenib, a molecularly targeted drug via the unclear mechanism of its direct pro-apoptotic effects or anti-angiogenic properties, has been administrated in some HAC patients. But it was suspended attributable to early adverse reactions (21). No convincing evidence about the sensitivity of HAS to Sorafenib was reported. In addition, HAC of the ovary and peritoneum were insensitive to Sorafenib (8).

Immunotherapy
Immune checkpoint antibodies have been approved to be administrated in multiple solid tumors, incorporating carcinomas of lungs, liver, esophagus, kidney, and stomach. Currently, immunotherapy applied to HAS is rare to report. Only one case showed that one HAS patient managed with PD-L1 inhibitor represented a low curative effect, which might be related to its low expression of PD-L1. Further experimental verification is expected to be reached in future clinical trials (8).

PROGNOSTIC FACTORS
The prognosis of HAS is poor. HAS patients had notably lower survival rates and disease-free survival (DFS) compared to those with other types. It is revealed that the 5-year DFS of HAS patients was only 20.7% (2, 33, 91). It was concluded that pTNM stage, portal vein thrombosis, vascular invasion, and adjuvant treatments were independent risk factors for DFS and pTNM stage, entirely surgical resection, and adjuvant therapy were independent risk factors for disease-specific survival (DSS) (2). However, some case reports argued that survival was not associated with sex, location, type, the serum AFP level, the degree of differentiation, or the type of therapy received. Although the relationship between neuroendocrine differentiation and the prognosis of HAS remained vague, it was inclined to an unfavorable factor to give rise to low differentiation and prognosis (92).

Morphologically, clear cell histology, more than a threshold of 10% about the ratio of clear cells, harmed prognosis in patients within HAS (33, 38). No evidential relations were deemed between immunohistochemical staining and prognosis in HAC. Among epithelial markers, including CEA, CK7 and CK20 were crucial for survival assessment by immunohistochemistry stains (8). Patients with CEA, CK20, and CK7 staining positive lived a shorter life. Furthermore, the combination of PLUNC, SALL4, and Hep-Par-1 might be a way of a tried prognostic factor in HAS (40).

Also, the patients with higher AFP expression had a significantly more inferior OS (58). AFP was assumed to be adverse to tumor suppression due to inhibiting lymphocyte transformation (27). However, The AFP-positive cases had shown better outcomes than the AFP-negative instances in a series of HAC with enteroblastic differentiation (GAEDs) (43). Meanwhile, It was observed the expression of β-catenin has a significant correlation with survival time (27).

FUTURE PERSPECTIVES
Although the standard surgical and systemic chemotherapies have been proved to improve the prognosis of HAS, it still shows a poor clinical outcome. Cisplatin-based chemotherapy regimens are regarded as the first-line treatments for metastatic HAS, while the second-line systemic approaches for optimal management remain unclear. Further researches should be directed at exploring the radiobiological sensibility and radiational therapeutic effects in these patients (59). A significant step toward applying anti-angiogenesis drugs covering RAM combining with chemotherapy, the overall survival of advanced HAS patients has been significantly increased. Of note, the development of molecularly targeted treatments related to Sorafenib should be validated. Immunotherapy as a possible therapeutic means is to be further explored in patients with HAS.

CONCLUSION
HAS is a scarce subtype of gastric cancer. It is often diagnosed with lymph node metastasis and distant organ metastasis and has a poor prognosis, which poses a significant challenge to clinicians’ diagnosis and treatment. Several immunohistochemical markers covering AFP, CEA, CK8/18, CK19, glypican 3, SALL4, CDX-2, and HepPar-1 can be performed to assist in pathological confirmation. The level of AFP serum is propitious to the early detection of HAS. The available radical surgery, chemotherapy, radiotherapy, and
Author Contributions

RX collected data, reviewed the literature, and wrote the manuscript. YZ collected data and wrote and revised the manuscript. YW collected data and rechecked the manuscript. JY assisted in drawing. XM designed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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