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Preliminary Study of Clinicopathological and Computed Tomography Features of Hepatoid Adenocarcinoma in Stomach

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Abstract:
Introduction: Hepatoid adenocarcinoma (HAC) of the stomach is a rare tumor with limited clinical data. This study aims to study the clinicopathological and radiological features of hepatoid adenocarcinoma of the stomach and its two subtypes.

Materials and methods: Histopathologically confirmed 39 gastric hepatoid adenocarcinoma cases (16 pure hepatoid carcinomas and 23 mixed hepatoid carcinomas from 30 males and 9 females) with mean age of 60 years (36 to 78 year) were included in this ethical committee approved retrospective study. Clinicopathological data was extracted from the system. Two radiologists evaluated the radiological features.

Results: The serum Alfa-fetoprotein was higher in the pure group (p=0.008). Pure hepatoid carcinoma group was larger than the mixed group, with average tumor size of 5.75± 2.13 cm Vs 4.27± 1.48 (p=0.02). Pure hepatoid carcinoma group had a substantial association with positive AFP staining of 57.10% Vs 9.10 % in mixed group (p=0.005). On CT, HAC showed significant eccentric wall thickening (p<0.001) and a higher number (74.36%) of tumor in pylorus of the stomach (p<0.001). Liver metastasis and tumor thrombosis were significantly negatively associated with HAC.A single case of tumor thrombus was seen in the pure group. All HAC enhanced heterogeneously and occupied extremes of T and N stage.

Conclusions: HAC of stomach mainly affects middle to older aged males. On CT, it enhances heterogeneously with eccentric wall thickening in pylorus of the stomach. Pure hepatoid carcinoma differs from mixed hepatoid carcinoma only in terms of its large tumor size, high serum AFP level, and high positive AFP staining.

Keywords: Clinicopathological feature; Computed tomography; Hepatoid adenocarcinoma; Pure hepatoid carcinoma; Stomach.

INTRODUCTION

Hepatoid adenocarcinoma (HAC) is a rare type of tumor with features resembling morphologically to hepatocellular carcinoma [1]. It has been mostly reported in the stomach, but it has also been found in other organs like lungs, urinary bladder, uterus, pancreas, esophagus, ovary, gallbladder, colon, duodenal papilla, ureter, extrahepatic bile duct and mediastinum [1-14]. HAC is a rare tumor, coined by Ishikura et al., with very bad prognosis, frequently affecting older age groups with mostly Alfa fetoprotein (AFP) production and aggressive metastasis to liver and lymphatic[15-17]. HAC incidence ranges from 0.17% to 0.36% in recent studies [18,19]. Because of the rarity of this disease and limited information, it is difficult to diagnose and treat with certainty.

We are studying pure hepatoid carcinoma of stomach with only hepatoid cells and mixed hepatoid carcinoma with a mixture of hepatoid and adenocarcinoma cells. Both subtypes are hepatoid adenocarcinoma, but there is a varying proportion of hepatoid differentiated cells. Hepatoid adenocarcinoma is diagnosed using hematoxylin and eosin (HE) stain and histological feature of hepatoid differentiation.

According to World Health Organization, eosinophilic hepatocyte-like large polygonal neoplastic cells arranged in a sheet like pattern is suggestive of HAC [20]. But in cases with difficult histological features, immunohistochemical staining is used. Commonly seen immunohistochemical staining is positivity for Alfa fetoprotein (AFP), Hepatocyte Paraffin 1 antibody (HepPar-1) and Glypican-3 (GPC3). AFP and Glypican-3 are oncofetal proteins that are positive in the tumor with hepatoid content [21]. HepPar-1 is monoclonal antibody denoting hepatoid differentiation [22]. Laboratory parameter frequently used in gastric hepatoid adenocarcinoma is Alfa fetoprotein level in blood. AFP is glycoprotein synthesized in the yolk sac, fetus liver, and other cells of the gastrointestinal tract. Increased level of serum AFP is considered as an abnormality in adults and likely indicates tumor of the yolk sac, gonads, hepatocellular carcinoma (HCC) or gastric tumors [23]. Alfa fetoprotein level in blood is a marker of hepatoid differentiation of gastric tumor [15] and is used along with other findings in diagnosing hepatoid adenocarcinoma.

CT is being widely used to detect the tumor invasion of the gastric wall, along with metastasis to lymph nodes and other organs. There is limited literature about CT features of gastric hepatoid adenocarcinoma due to the limited number of cases. We study the clinicopathological and radiological characteristics of HAC and its two histological types, to increase the understanding of this tumor.

METHOD AND MATERIALS

Study design, setting and Patients

A retrospective study was done using the computer system of The First Hospital of Jilin University. Clinical, pathological and radiological data of pathologically proven hepatoid adenocarcinoma of the stomach was searched from the year 2009 to 2023. All the cases with no hepatocellular carcinoma or tumor elsewhere in the body (other than HAC) were included. Cases with lab findings of hepatitis B and C were excluded.41 cases were collected and only 39 cases were fit for our study due to missing radiological data of those two. Patient data was anonymized and de-identified prior to analysis. 39 HAC cases were evaluated as a single entity and studied by dividing into two groups (16 cases of pure hepatoid carcinoma and 23 cases of mixed hepatoid carcinoma). The average age of the cases was 60 years (36 to 78 year) with 30 males and 9 females.

CT protocol

Images were obtained from dual-energy Gemstone Spectral CT (Discovery CT750HD scanner, GE Healthcare, Waukesha, WI, USA) [n=19] or Siemens second generation DSCT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) [n=20] with patients with 12 hours fasting. All the three scans (unenhanced, arterial phase and portal venous phase) were taken in supine position from the dome of the diaphragm to the iliac crest after patient drank 1 liter of water, using conventional scanning protocol. Non-ionic, water-soluble contrast agent (iohexol, Omnipaque 350, GE Healthcare, Shanghai, China) was injected into the right antecubital vein in the volume of 1.5ml/kg at the rate of 3.5ml/sec through 20-gauge cannula using automated power injector. This was followed by flushing 20ml of saline through the cannula at similar injection rate. Image acquisition was done using bolus tracking technique with a delay of 10s and 40s after ROI in the root of abdominal aorta measured threshold value of 100HU for arterial and portal venous phase respectively. Discovery CT750HD scanner parameters were detector configuration of 64 × 0.625mm, 5mm slice thickness, 1.375 pitch, 0.5s rotation time, 120kVp tube voltage and automatic tube current (290-650 mAs). Siemens Somatom Definition Flash scanner parameters were detector configuration of 64 × 0.6mm, 5mm slice thickness, 0.6 pitch, 0.5s rotation time, 120kVp tube voltage and tube current of 210 mAs.

Image analysis

Picture archiving and communication system (PACS) was used to view the images that were selected. Two radiologists (S.A and M.S with 2 years of experience) assessed tumor location in stomach, growth pattern, T stage, N stage, tumor enhancement pattern, liver metastasis, lymph node metastasis and tumor thrombosis.

The radiologists weren't aware of the diagnosis (single blinded). Where there was confusion, the decision was taken by consensus. T and N staging was done following 7th AJCC classification. The gastric wall is visible in CT as 3 layers; high attenuating mucosal layer, low attenuating submucosal layer, and high attenuating seromuscular layer. T1a is noticed as a focal mucosal irregularity which is missed mostly. T1b is more pronounced as a thickened mucosal layer with a low attenuation stripe of submucosa at the base of the lesion. T2 is a thickened gastric wall with loss of the low attenuation stripe and presence of clear outer stomach margin. T3 stage is seen as a sharply marginated serosa with a very thin spared subserosal layer. T4a stage can be seen as an irregular, nodular lesion disrupting contour of the stomach or with perigastric fat infiltration. T4b stage is a further extension of T4a tumor to adjacent organs. Short axis diameter of >6mm for the perigastric lymph nodes and >8mm for extra perigastric lymph nodes was considered as a metastatic lymph node. The degree of enhancement was interpreted by measuring tumor Hounsfield unit (HU) from the largest possible area in unenhanced, arterial and portal venous phase.

Pathological data

Serum Alpha fetoprotein and serum carcinoembryonic antigen level were evaluated. Pathological information including histological diagnosis, tumor size, alpha fetoprotein staining status, glypican-3 staining status and hepatocyte paraffin-1 staining status were collected from the computer system. T and N stage was evaluated according to 7th AJCC classification using the available pathological findings.

Statistical analysis and data management

Clinical, pathological and radiological data were analyzed using statistics. Results from quantitative variables were presented as mean ± standard deviation (M±SD), whereas results of qualitative variables were written in frequencies. To identify the difference between categorical variables chi-square test was used. Fisher's exact test was used whenever a cell had expected count less than 5. Shapiro-Wilk test was done for data in scale measurement to find its normal distribution. Student's t test was done in normally distributed data to identify significance between those groups. Non-normal scale data was compared using Mann-Whitney U test. IBM SPSS Statistics 22, New York, USA) was used. P value ≤0.05 (two-tailed) was interpreted as statistically significant.

Ethical Consideration

Ethical approval was taken from First Hospital of Jilin University (Reference number 2016-380), and patient consent was waived looking at our retrospective nature of the study.

RESULTS

There was total 39 HAC cases. 30 were males and 9 were females. HAC was significantly more common in males compared to females, $\chi2(1, N =39) =11.31$, $p = 0.001$ (Table 1).

Table 1|Findings on Hepatoid adenocarcinoma of stomach

Variable	Number (%)	χ^2	P value
Sex		11.31	0.001
Male	30(76.92)		
Female	9(23.08)		
Wall thickening[1]		13.56	<0.001
Circumferential	8(20.51)		
Eccentric	31(79.49)		
Tumor location[1]		51.97	<0.001
Cardia	1(2.56)		
Fundus	3(7.69)		
Body	6(15.39)		
Pylorus	29(74.36)		
Liver metastasis[1]		21.56	<0.001
Positive	5(12.82)		
Negative	34(87.18)		
Tumor thrombosis[1]		35.10	<0.001
Positive	1(2.56)		
Negative	38(97.44)		

χ^2 denotes Chi-square test value and [1]represents data from CT image analysis. All the P value are from Chi-square test.

Stomach wall was significantly thickened in eccentric pattern (79.49%) compared to circumferential thickening (20.51%), $\chi2(1, N =39) =13.56$, $p <0.001$. Similarly, there was a significant difference in tumor location in the stomach, with 74.36% of tumor located in the pylorus. However, liver metastasis and tumor thrombosis were negative in HAC, at $p<0.01$ (with positive liver metastasis and tumor thrombosis of 12.82% and 2.56% respectively).

Clinicopathological findings of Pure and Mixed hepatoid carcinoma

In pure hepatoid carcinoma group, there was M: F ratio of 7:1, whereas in mixed hepatoid carcinoma group the ratio was 2:1. The mean age of pure group was 58±10 years (36-78) and that of the mixed group was 60.6±10years (44-78). The serum AFP was significantly higher in the pure group compared to mixed group (U= 86.5, p=0.008). The pure group had AFP level of 577.81± 909.97 ng/ml, with one case having highest AFP level of 3173ng/ml. The mixed group had AFP level of 47.14 ± 124.13 ng/ml, with highest AFP level of 582.91 ng/ml. Carcinoembryonic antigen (CEA) level difference was not significant between these two groups. CEA was higher in the pure group with 19.91±33.89 ng/ml than mixed group with13.24±31.85 ng/ml. But mixed group reported a case with highest CEA level of 155.95ng/ml (Table 2).

Table 2 | Clinicopathological findings			
Variable	**Pure Hepatoid Carcinoma (n=16)**	**Mixed Hepatoid carcinoma (n=23)**	**P value**
Sex[1]			0.46
Male	14(87.50)	16(69.60)	
Female	2(12.50)	7(30.40)	
Age(y) [2]	58 ±10 (36-78)	60.60 ± 10.26 (44-78 yr)	0.26
AFP (ng/ml)[2]	577.81± 909.97 (3.20-3173)	47.14 ± 124.13 (1.32 - 582.91)	0.008
CEA(ng/ml)[2]	19.91±33.89 (0.76-128.80)	13.24±31.85 (0.55- 155.95)	0.943
[2]Data are Mean ± Standard deviation. Parentheses data is Range data. P-value is after Mann-Whitney U test.			
[1]Data in parentheses is percentage within that tumor group. P-value is from Fisher's exact test.			

Pure hepatoid carcinoma group tumor size was larger than mixed hepatoid carcinoma group, with average tumor size of 5.75± 2.13 cm Vs 4.27± 1.48; p=0.02. Largest tumor size of pure hepatoid carcinoma was 9.5cm. There was no significant difference in pathological T and N stage between these groups. 81.3% of pure hepatoid carcinoma group were in T3 stage Vs 47.8% of mixed hepatoid carcinoma in that same stage. 31.3 % of pure hepatoid carcinoma were in N2 and N3a stage each Vs 30.4 % of mixed hepatoid carcinoma in N1 stage. This demonstrated more aggressiveness of pure hepatoid carcinoma.

In immunohistochemistry, pure hepatoid carcinoma group had significant positive staining for AFP (57.10%) Vs mixed tumor (9.10 %), (P=0.005, two-sided Fisher's exact test). With Phi coefficient of 0.52, there was a substantial positive association of pure hepatoid carcinoma with AFP staining compared to mixed hepatoid carcinoma. Whereas, GPC3 had no statistically significant difference. 84.60% of cases in pure group were positive for GPC3 Vs 69.60% in mixed group (P=0.438, two-sided Fisher's exact test). Hep Par 1 comparison finding was also not significant (Table 3).

Table 3 | Pathological characteristics			
Variable	**Pure Hepatoid carcinoma**	**Mixed Hepatoid carcinoma**	**P value**
Tumor size(cm)	5.75± 2.13(3-9.5)	4.27 ± 1.48 (1.4- 7)	0.02 [1]
T stage			0.37
T1a	0(0)	0(0)	
T1b	1(6.3)	3(13)	
T2	1(6.30)	5(21.70)	
T3	13(81.30)	11(47.80)	
T4a	1(6.30)	3(13)	
T4b	0(0)	1(4.3)	
N stage			0.59
N0	2(12.50)	5(21.70)	
N1	2(12.50)	7(30.40)	
N2	5(31.30)	5(21.70)	
N3a	5(31.30)	4(17.40)	
N3b	2(12.50)	2(8.70)	
AFP			0.005
Positive	8(57.10)	2(9.10)	
Negative	6(42.90)	20(90.90)	
GPC-3			0.44
Positive	11(84.60)	16(69.60)	
Negative	2(15.40)	7(30.40)	
Hep Par-1			1.0
Positive	9(60)	15(65.20)	
Negative	6(40)	8(34.80)	
[1]This value is of independent student's t-test. All other p-value are of Fisher's exact test.			

Radiological findings of Pure and Mixed hepatoid carcinoma

Eccentric: circumferential wall thickening ratio was 3:1 in the pure group (Fig 1) and 4:1 in the mixed group (Fig 2). There was no statistically significant difference in between these two groups in terms of pattern of gastric wall thickening, liver metastasis, lymph node metastasis and tumor thrombosis (Table 4).

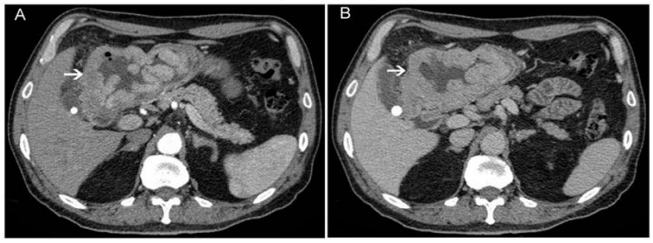

Figure 1 A 78yr old male with Pure hepatoid carcinoma.
A and B are Axial contrast-enhanced CT scans in arterial and portal venous phase respectively, shows circumferential gastric wall thickening (white arrow) of the tumor with heterogeneous enhancement, in pyloric part of the stomach. The tumor appears to involve the serosal layer of the stomach (T4a) with fat stranding around.

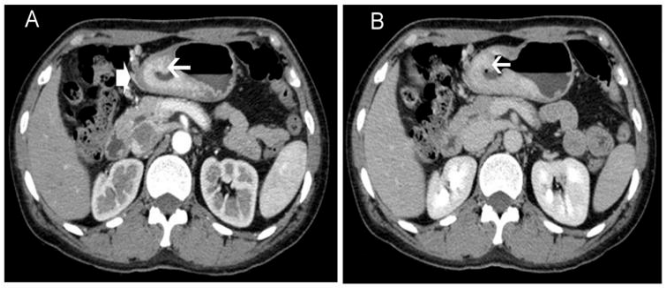

Figure 2 A 47 yr old women with Mixed hepatoid carcinoma.
A, B Axial contrast enhanced CT scan image shows eccentric gastric wall thickening (thin white arrow) in pylorus of the stomach, with hyperattenuating, heterogeneous enhancement pattern in arterial and

Table 4 |Radiological features			
Variable	**Pure hepatoid carcinoma**	**Mixed hepatoid carcinoma**	**P value**
Site of tumor			1
Cardia	0(0)	1(4.3)	
Fundus	1(6.30)	2(8.7)	
Body	3(18.80)	3(13)	
Pylorus	12(75)	17(73.90)	
Wall thickening			0.69
Eccentric	12(75)	19(82.60)	
Circumferential	4(25)	4(17.40)	
T stage			0.12
T1a	0(0)	0(0)	
T1b	0(0)	0(0)	
T2	1(6.30)	0(0)	
T3	1(6.30)	7(30.40)	
T4a	14(87.50)	15(65.20)	
T4b	0(0)	1(4.30)	
N stage			0.42
N0	5(31.30)	11(47.80)	
N1	2(12.50)	1(4.30)	
N2	9(56.30)	8(34.80)	
N3a	0(0)	2(8.70)	
N3b	0(0)	1(4.30)	
Enhancement pattern			
Homogeneous	0(0)	0(0)	
Heterogeneous	16(100)	23(100)	
CT value (HU)			
Unenhanced phase	39± 4.30(30-48)	37.17± 7.11(21-50)	0.35[1]
Arterial phase	79.69±17.30(48-103)	76.78±27.66(40-142)	0.71[1]
Portal-venous phase	79.85± 12.18(60-97)	85.13± 22.98(40-128)	0.37[1]
Liver metastasis			1
Positive	2(12.5)	3(13)	
Negative	14(87.5)	20(87)	
Tumor thrombosis			0.41
Positive	1(6.30)	0(0)	
Negative	15(93.7)	23(100)	

[1]Indicates p-value from Independent student's t-test .All other p-value are from Fisher's exact test.

portal venous phase respectively. Tumor (T3 stage) is separated from the serosa by a layer of hypoattenuating subserosal tissue (thick white arrow). There is no fat stranding around the tumor location. Liver metastasis was seen in 2/16 pure hepatoid carcinoma and 3/23 mixed hepatoid carcinoma (Fig 3). Most of the pure hepatoid cases (12/16) had lymph node metastasis Vs mixed hepatoid cases (12/23). A single case of tumor thrombus was seen in the pure group at the junction of the superior mesenteric vein

and the portal vein (Fig 4). All the HAC of both groups enhanced heterogeneously. There was no statistically significant difference in terms of enhancement phase in CT scan (unenhanced, arterial and portal venous phase). There were statistically significant numbers of HAC located in the pyloric part (74.36%) compared to other parts of the stomach, $\chi 2(3, N = 39) = 51.97$, $p < 0.01$. In the mixed group, 73.90% of the tumors were in the pylorus, and in the pure group, 75% of the tumors were in pylorus. Whereas, within pylorus of the stomach, the mixed hepatoid tumor was more common (58.60%) than the pure tumor (41.40%).

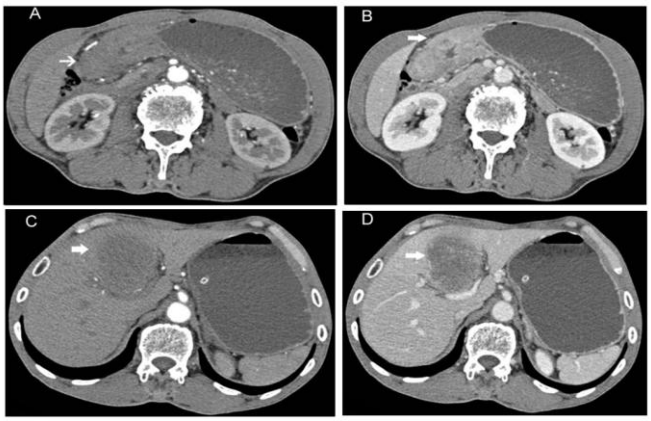

Figure 3 A 66 yr old male with Mixed hepatoid carcinoma. A, B Axial contrast enhanced CT scan with circumferential wall thickening (white arrow) with heterogeneous enhancement in pyloric part of the stomach in arterial and portal venous phase respectively. The tumor appears to involve the serosal layer of the stomach (T4a) with fat stranding around. C Shows liver metastasis (white arrow) from HAC of stomach with hypoattenuating, mostly homogeneous enhancing, ill-defined mass in arterial phase and portal venous phase (D).

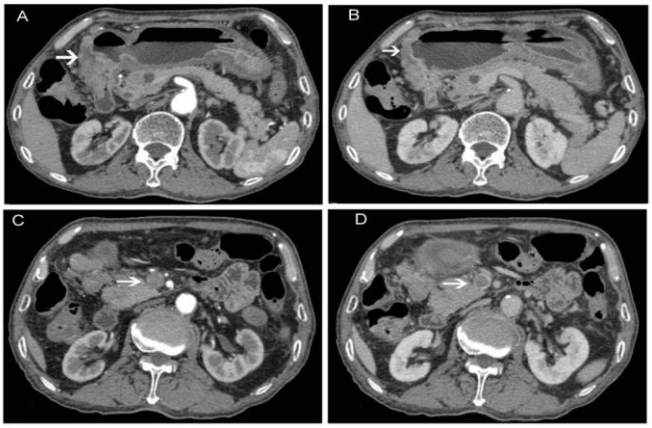

Figure 4 Pure hepatoid carcinoma in a 73-yr old male. A, B shows Axial contrast enhanced CT scan with eccentric heterogeneously enhancing tumor (white arrow) in pyloric part of the stomach during arterial and portal venous phase respectively. The tumor appears to involve the serosal layer (T4a) with fat stranding around. D, C shows tumor thrombus (white arrow) in the superior mesenteric vein with homogenous enhancement in arterial and portal venous phase axial CT scans respectively in the same patient. There was no significant difference while comparing radiological T and N stage of both tumor groups, but 87.5% of pure hepatoid carcinoma images had T4 stage Vs 69.50% of mixed hepatoid carcinomas. Similarly, 56.30 % of pure type had N stage >N1 compared to only 47.80% of mixed type, suggesting aggressiveness of pure hepatoid carcinoma. T4b stage was only seen in one case of Mixed hepatoid carcinoma (among total HAC cases studied) (Fig 5). Mixed hepatoid carcinoma had 8.70% of cases with N3a and 4.30% of cases with N3b stage (with no N3a or N3b stage in pure type). These two findings suggested aggressiveness of mixed hepatoid carcinoma. Large sample would help clarify tumor aggressiveness in between these two types of HAC (in terms of T, N stage). Major percentages of these two types of HAC occupied extreme spectrum of T and N stage at time of diagnosis.

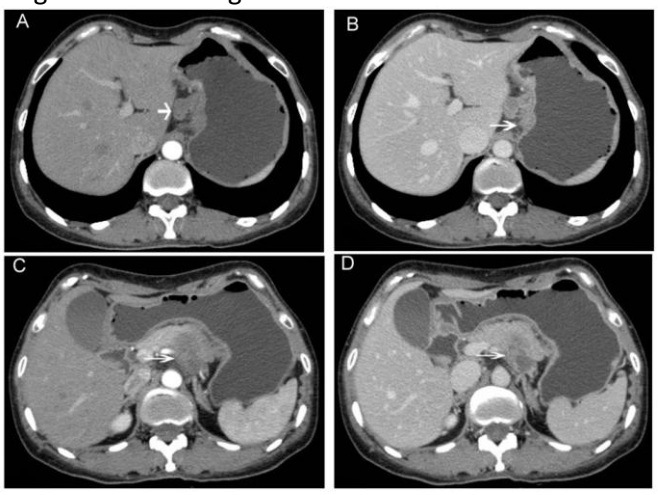

Figure 5 A 47 yr old women with mixed hepatoid carcinoma. A, B Axial contrast enhanced CT scan image showing eccentric wall thickening (white arrow) in body of stomach, with hypoattenuating, heterogenous enhancement in arterial and portal venous phase respectively. Spread of tumor to adjacent pancreas (white arrow) visible as hypoattenuating heterogeneous mass in pancreas with indistinct margin in arterial and portal venous phase respectively (C, D). The fat plane between the pancreas and stomach appears to be obliterated.

DISCUSSION

Hepatoid adenocarcinoma of the stomach predominantly involved males, with the male: female ratio of 3: 1, similar to other studies in the past [1,18]. In this study, the pure hepatoid carcinoma group presented with higher male sex ratio compared to the mixed hepatoid carcinoma group. The serum AFP level of the pure group (578ng/ml) was also statistically significantly higher than the mixed group (47ng/ml). But the AFP level of pure hepatoid carcinoma was far less

than that reported in 2010[24]. The pure hepatoid carcinoma (5.75± 2.13cm) was significantly larger than the mixed hepatoid carcinoma (4.27± 1.48cm) in our study, with pure hepatoid carcinoma reaching upto 7cm, larger than previous study[24]. Larger the size of gastric tumor worse is the prognosis with decreased 5-year overall survival rate [25,26]. There are evidences that increasing tumor size leads to decreased 5-year overall survival rate [25]. These findings suggest poorer prognosis of pure hepatoid carcinoma compared to mixed hepatoid carcinoma.

In our study, immunohistochemical tissue AFP positive staining of the pure hepatoid carcinoma group was statistically significant compared to the mixed group. Whereas tissue GPC3 staining was insignificant in both tumor groups. Positive tissue AFP staining of pure hepatoid carcinoma has been reported in a single case report [24].M Hishinuma et al [27] found positive tissue AFP staining (8/10) and positive GPC3 staining (10/10) in hepatoid component of the tumors. Whereas positive AFP staining (5/10) and positive GPC3 (9/10) was seen in the nonhepatoid adenomatous component of the same tumor population, similar to reposted by M. Osada et al [28]. There was no significant association of Hep Par-1 staining in our study compared to other studies [29].

Our findings for GPC3 and Hep Par-1 are inconclusive to differentiate between pure and mixed hepatoid carcinoma. On CT scan, this study showed both pure and mixed type to have predominantly eccentric wall thickening of the stomach, with eccentric: circumferential thickening ratio of 3:1 and 4:1, respectively. 100% of HAC of the stomach enhanced heterogeneously. This was like the study by M.W. Lee et al, where all the cases had eccentric wall thickening and 7 out of 8 cases had heterogeneous enhancement. Similarly, Wu et al also described 75% of study cases with eccentric thickening pattern and 25% with circumferential thickening pattern. These all cases also had heterogeneous enhancement [30,31]. There was statistically significant absence of liver metastasis (12.8%) in our study, compared to other studies [30,31].

During CT image analysis, combining both the pure and mixed tumor groups, 22 of 24 pT3 tumors and 4 of 6 pT2 tumors were over staged as T4a tumors in CT (over staging of 86.67%), similar to Furukawa et al. [32]. This was mainly due to difficulty in identifying the sub-serosal layer in our study, due to difficulty in identifying this thin layer (due to compression by the tumor). According to the literature, other causes of over staging are due to confusing peri gastric inflammation from benign conditions (fibrosis, inflammation, engorgement of vascular-lymphatics) for fat stranding due to the tumor [33,34]. On the other hand, in our study, the radiological N stage was under staged, compared to the pathological N stage. 40% of N3a stage and 17% of N3b stage were under staged by us. This was better than other study that under staged 54% of N2 and 91% of N3 using 6th edition of TNM staging (N3a and N3b stage respectively according to 7th TNM stage) [35].

In our study, we couldn't appreciate the smaller metastatic lymph nodes, multiple matted lymph nodes and the perigastric lymph nodes in close vicinity of gastric tumor (leading to under staging). In our study, there was a significant difference while we considered tumor location for HAC as a whole, with 74.36% tumor in the pylorus, with no difference between pure and mixed group. There was no clinical research on tumor location about pure hepatoid carcinoma to our knowledge for comparison. But, in a study on mixed HAC of the stomach, tumor predominantly involved the pylorus, similar to our study [18]. Similarly, in another two studies, HAC of the stomach was reported in the lower third of the stomach, but with a higher percentage (87-100%) [29,36].

There were few limitations in our study. Though our study was bigger radiological study, than that reported in the past, it would be better to have a larger sample size to give more power to our results or to clarify conflicting findings compared to those other studies. Another limitation was, our limited available retrospective data and unavailability of patient or specimen for reevaluation.

CONCLUSION

Hepatoid adenocarcinoma of the stomach is a rare gastric tumor, significantly affecting males in their middle to older age. HAC presents on CT as a heterogeneously enhancing gastric tumor, with significant eccentric wall thickening and located mostly in the pyloric part of the stomach. Radiologically, the pure hepatoid carcinoma and the mixed hepatoid carcinoma are aggressive tumors with advanced T and N stage at time of presentation, but without any significant differences. Pure hepatoid carcinoma differs significantly from mixed hepatoid carcinoma only pathologically in terms of its large tumor size, positive serum AFP level, and positive tissue AFP staining. A larger study in future will help us more to clarify these entities of hepatoid adenocarcinoma in future.

ADDITIONAL INFORMATION AND DECLARATIONS

Declaration of conflict: None

Author Contributions: Sunil Adhikari and Shengnan Mu contributed equally to this work; Sunil Adhikari and Shengnan Mu collected and analyzed the data, and drafted the manuscript; Rashmi Aryal and Qiu Xiang reviewed the pathological findings; Sunil Adhikari and Shengnan Mu analysed the radiological findings; Ragni Sinha did Statistical analysis; Huimao Zhang designed

and supervised the study; Sunil Adhikari, Shengnan Mu, Rashmi Aryal, Ragni Sinha and Huimao Zhang revised the manuscript for important intellectual content; all authors have read and approved the final version to be published.

Data Availability: No additional data are available.

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