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Comparison of double contrast-enhanced ultrasonography and contrast-enhanced computed tomography in preoperative TNM stages of gastric cancer

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Abstract

Background: China accounts for about 40% of new cases of Gastric Cancer (GC) in the world every year. Preoperative TNM stages (gastric wall invasion, lymph node metastasis, and distant organ metastasis of gastric tumors) of GC patients are important to develop a correct therapeutic strategy.

Objective: The comparison between values of Double Contrast-Enhanced Ultrasonography (DCEUS) and contrast-enhanced Computed Tomography (CECT) in preoperative TNM stages of gastric cancer has been explored.

Methods: This retrospective study consisted of 82 patients confirmed as gastric cancer by pathology. All patients underwent DCEUS (oral contrast-enhanced ultrasonography combined with intravenous contrast-enhanced ultrasonography) and CECT 1 week before surgery, and TNM preoperative stages were carried out for both of them.

Results: The overall accuracies of DCEUS and CECT in evaluating the T stage of gastric cancer were 74% (61/82) and 76% (62/82), respectively (P>0.999). The overall accuracies of DCEUS and CECT in evaluating the N stage of gastric cancer were 66% (54/82) and 50.0% (41/82), respectively (P>0.05). Moreover, DCEUS and CECT demonstrated good overall accuracies of 95% (78/82) and 98% (80/82), respectively (P>0.05) in assessing the M stage of gastric cancer. There were no significant differences between the accuracies of two methods for T, N and M stages (p = 1.000, 0.058, 0.068). The goodness of fit in TNM stages of the gastric cancer between DCEUS and pathology were κ = 0.580, 0.449, 0.320. The goodness of fit in TNM stages of the gastric cancer between CECT and pathology were κ = 0.606, 0.280, 0.787.

Conclusions: The overall accuracy of DCEUS and CECT for T stage was comparable, CECT was superior to DCEUS for M stage, and both methods have lower assessed values for N stage. The two modalities can complement each other in evaluating TNM stages of gastric cancer.

Background

Gastric Cancer (GC) is the fourth most common malignant tumor, and the second most deadly cancer worldwide [1]. China has a high incidence of GC, which accounts for about 40% of new cases of GC in the world every year and therefore it is a major public health problem [2]. Preoperative TNM stages (gastric wall invasion, lymph node metastasis, and distant organ metastasis of gastric tumors) of GC patients are important to develop a correct therapeutic strategy ultimately to provide patients with the best chance of recovery [3]. Therefore, it is of great clinical application value to evaluate the TNM stages of GC.

Until now, double contrast barium meal, Endoscopic Ultrasonography (EUS), Contrast-Enhanced Computed Tomography (CECT), and Magnetic Resonance Imaging (MRI) have been frequently used for evaluating GC [4]. It is well known that EUS is the most widely used in different GC stages, but some factors including equipment differences, operator factors, lesion location, size, tissue type, presence of ulcers, and other factors can affect the diagnostic accuracy of EUS for clinical stages of GC [5]. Especially for larger GC lesions, it is difficult for EUS to show the complete boundary of the lesion and to determine whether the tumor has infiltrated the perigastric and adjacent structures or not. The EUS is also unable to perform clinical stages of GC when the gastric lumen is narrow and the probe cannot pass through. In addition, EUS is not accepted by all the patients due to the discomfort during examination [6,7]. The CECT is an accurate and effective tool for preoperative stages of GC [8,9], However, it also has certain disadvantages, such as radiation, high cost, requiring large instruments and special rooms.

Transabdominal Oral Contrast-Enhanced Ultrasonography (OCEUS) combined with intravenous contrast-enhanced ultrasonography, also known as Double Contrast-Enhanced Ultrasonography (DCEUS), can enhance signal-to-noise ratio, better display the blood perfusion of the internal and surrounding tissues of the lesion and provide richer diagnostic information for the qualitative diagnosis of the lesion. So, it is considered more common and important for the diagnosis of digestive tract diseases in recent years [10-12]. Some studies have profiled that DCEUS is superior to traditional diagnostic techniques such as conventional transabdominal ultrasound and OCEUS in the assessment of stages [13]. But most of them focus on T stage only, and few assess N and M stages [14-17]. It is well-documented that lymph nodes metastasis is easy to occur in the early and middle stages of GC, and distant metastases often happen in the late stage, which have been reported to indicate poor prognosis [18]. In this study, we are aimed to evaluate and compare the diagnostic values of DCEUS and CECT for preoperative TNM stages of GC so that clinicians can better understand the advantages and disadvantages of these two imaging methods for preoperative stages of GC and provide reference values for treatment plans.

Methods

Patients

The study was approved as a retrospective study by the Institutional Review Board, and patient informed consent was waived. Between July 2021 and July 2022, 82 consecutive patients with gastric cancer were examined with DCEUS and CECT within a week before the operation. The exclusion criteria were (1) Patients had contraindications of contrast-enhanced ultrasound or CECT, such as severe allergic history, asthma or heart disease, severe pulmonary hypertension; (2) Uncontrolled essential hypertension and adult respiratory distress syndrome; and (3) Patients with other tumors and cachexia before surgery. This clinical study was approved by our hospital ethics committee, the First Affiliated Hospital of Chongqing Medical University Medical Ethnic Committee (2020-807).

Double contrast-enhanced ultrasonography

Equipment

Ultrasound imaging was performed using an Aplio i800 ultrasound system (Canon Medical, Tokyo, Japan) with a choice of convex array probes (2.5-5.0 MHz) and linear array probes (7-10 MHz).

Transabdominal gastric DCEUS

All the patients were required to fast at least 8 hours before the examination. The Contrast Pulse Sequencing (CPS) technology was used for ultrasound imaging. The oral contrast agent (Tianxia Brand, East Asia Institute of Gastrointestinal Ultrasound, Huzhou city, Zhejiang Province, China, 50 g/pack, the main ingredient is grain), was reconstituted into 400 mL boiling water and made into pasty liquid. After the liquid was cooled down to a comfortable temperature, the patient was asked to drink it as quickly as possible to reduce inhalation of gas. Abdominal ultrasound scan was performed before oral contrast agent to be consumed [19]. During scanning, if the lesions are in the cardia or the fundus, the supine and left lateral positions are convenient for observation; but if the lesion is in the fundus, gastric body or antrum, the supine and right lateral positions are used [7,20]. For a complete examination of the entire stomach, some rare positions can be used, such as half-sitting, sitting, and standing position. When the gastric lesion was shown using transabdominal OCEUS, a bolus of 2.4 mL of SonoVue (Bracco SpA, Milan, Italy) suspension was injected into median elbow vein, flushed with 5 mL saline. the contrast mode was activated, the mechanical index was set to less than 0.08, and the entire procedure was videotaped. The whole lesion and the entire video sequence (at least 3 min) was stored on disks for analysis [16]. In addition, perigastric lymph nodes, and adjacent tissues and organs, such as pancreas and liver were also investigated. The DCEUS findings for stages of GC were classified according to previous criteria [14].

Contrast-enhanced CT scanning

Contrast-enhanced CT examinations were performed with a 64-detector row CT scanner (Light Speed; GE Healthcare, Milwaukee, WI) within 3 days before or after the DCEUS investigations. Before the CT examination, each patient needed to fast for at least 6 hours and drink 600 mL to 1200 mL of water to dilate the stomach. After a plain scan, 90 mL of the intravenous contrast agent Omnipaque (Shanghai GE Healthcare, Shanghai, China) was administrated *via* an antecubital vein at a rate of 3 mL/s, followed by 30 mL of 0.9% saline. Enhanced CT findings for stages of GC were classified according to previous criteria [21].

Image observation and pathological analysis

Both the ultrasonography and enhanced CT scan were completed within two weeks. The TNM stages of GC based on those imaging data were performed in a double-blinded manner by two radiologists with more than 5 years of abdominal imaging experience, respectively.

According to the American Joint Committee on Cancer [AJCC]/International Union against Cancer [UICC] TNM stage system category [22,23], the TNM stages criteria are as follows. T1: tumor invasion limited to the mucosa or submucosa; T2: tumor invasion to the muscularis propria; T3: tumor invasion to the serosa layer; T4: tumor invasion to adjacent tissues or organs. N0: no lymph node metastasis; N1: 1~2 lymph nodes metastases; N2: 3~6 lymph nodes metastases; N3: more than 7 lymph nodes metastases. M0: no distant metastasis; M1: there are distant metastases. Both DCEUS and CECT examinations were reviewed according to the histopathologic tumor stages as shown above.

Statistical analysis

All statistical analyses were performed using SPSS v.22.0 (χ^2 test). P value < 0.05 was considered statistically significant. Goodness of fit was analyzed using consistency test. κ (consistent coefficient) ≥ 0.7 meant strong goodness of fit, 0.7 > κ ≥ 0.4 meant general goodness of fit, and κ < 0.4 meant weak goodness of fit.

Results

Clinical data

The patients included 58 men and 24 women with a median age of 65 years, ranging from 33 to 87 years. There were 23 cases of gastric cardia and fundus cancer, 19 cases of gastric body cancer, and 40 cases of gastric fundus and cardia cancer. The pathological diagnosis was as follows: 15 cases were identified as stage T1, 8 cases were acknowledged as stage T2, 12 cases were staged T3, 47 cases were staged T4; 41 cases were identified as stage N0, 16 cases were recognized as stage N1, 10 cases were identified as stage N2, 15 cases were staged N3.

Comparison of T stage by two imaging methods and pathology

Herein, T stage according to DCEUS evaluation is as follows: 10 cases in T1 stage, 8 cases in T2 stage, 17 cases in T3 stage, and 47 cases in T4 stage. The results of CECT scanning evaluation of T stage shows 7 cases were in T1 stage, 14 cases in T2 stage, 15 cases in T3 stage, and 46 cases in T4 stage. The comparison of both methods in the evaluation of gastric T stage is shown in Table 2. The overall diagnostic accuracies of DCEUS and CECT in assessing the T stage of GC are 74% (T1 89%, T2 90%, T3 87%, T4 83%) and 76 % (T1 90%, T2 85%, T3 89%, T4 87 %), respectively (p >0.999). In addition, no significant difference was noted between them.

DCEUS of GC appears as a restricted elevation or thickening or depression of the gastric wall with uniform or heterogeneous rapid enhancement in the arterial phase and rapid fading in the venous phase. Whereas, on CECT, a thickened gastric wall with heterogeneous enhancement is shown (Figure 1,2).

Comparison of N stage by two methods and pathology

N stage according to DCEUS evaluation is as follows: 53 cases in N0 stage, 12 cases in N1 stage, 12 cases in N2 stage, and 5 cases in N3 stage. While the results of CECT scanning evaluation of N stage demonstrate 35 cases in N0 stage, 17 cases in N1 stage, 21 cases in N2 stage, and 9 cases in N3 stage (Figure 3). The comparison of both methods in the evaluation of gastric T stage is shown in Table 3. The overall diagnostic accuracies of DCEUS and CECT in estimating the N stage of GC are 66 % (N0 76%, N1 80%, N2 93%, N3 83%) and 50.0% (N0 71%, N1 74 %, N2 74%, N3 80%), respectively (p>0.05). Hence, no significant difference is noted between them.

Comparison of M stage by two methods and pathology

The comparison of both methods in the evaluation of gastric M stage is shown in Table 4, where 81 cases in M0 stage and 1 case in M1 stage are shown by DCEUS. On the other hand, 77 cases in M0 stage and 5 cases in M1 stage are displayed by CECT (Figure 4). The overall diagnostic accuracies of DCEUS and CECT in assessing the M stage of GC are 95 % (M0 95%, M1 95 %) and 98% (M0 98%, M1 98 %), respectively (p>0.05). And there was no significant difference noted between them.

Consistency test of DCEUS and CECT in TNM stage with pathology

According to Table 5, the Kappa consistency test of DCEUS and pathology in TNM stages are 0.580, 0.449, 0.320, and CECT and pathology in TNM stage are 0.606, 0.280, 0.787, respectively. It shows general goodness of fit in the evaluation of TN stages, and weak goodness in M stage by DCEUS and pathology of GC. On the other hand, general goodness of fit in the evaluation of T stage, weak goodness in N stage, and strong goodness of fit in the evaluation of M stage by CECT and pathology of GC.

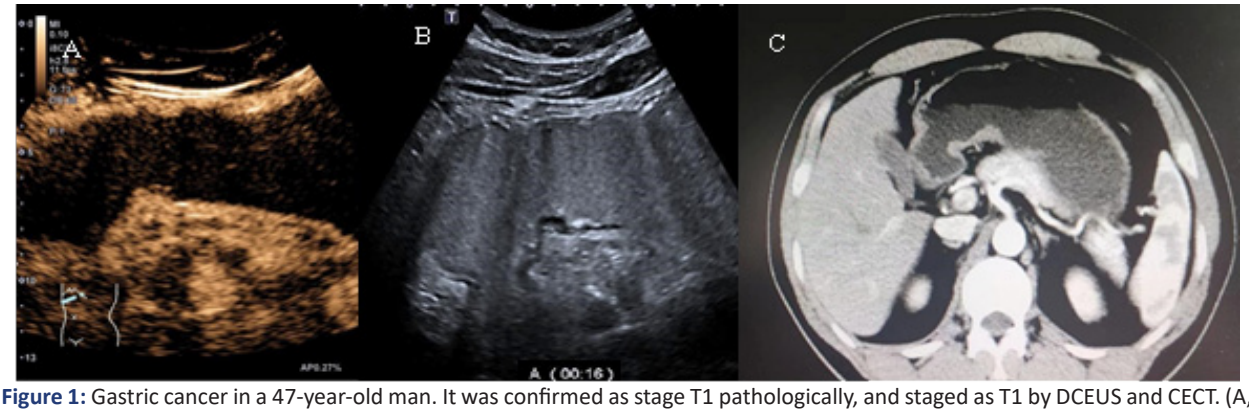

Figure 1: Gastric cancer in a 47-year-old man. It was confirmed as stage T1 pathologically, and staged as T1 by DCEUS and CECT. (A, B). DCEUS showed that the lesion is confined to submucosa (Fig B arrows), inhomogeneous enhancement in the arterial phase (Fig A arrows), and it was staged as T1. (C). CECT showed the gastric mucosa of gastric angle was not smooth, and significant enhancement in the arterial phase (arrows), and it is classified as T1, too.

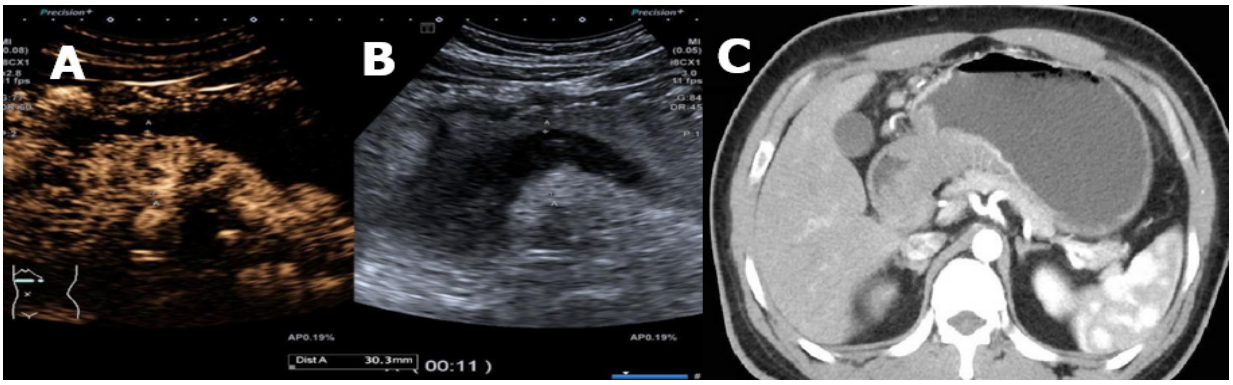

Figure 2: Gastric cancer in a 36-year-old man. It was confirmed as stage T4 pathologically, and staged as T4 by DCEUS and CECT. (A,B). DCEUS showed the diffuse thickened wall of the gastric antrum and invaded into the surrounding fatty tissue (Fig B arrows). The arterial phase of the lesion showed inhomogeneous enhancement, and the area of the enhanced lesion is significantly larger than the area of the lesion shown by gray-scale ultrasound (Figure A arrows). (C). CECT showed the diffuse thickened wall of the gastric antrum and invasion into the surrounding fatty tissue, with significant enhancement in the arterial phase (arrows).

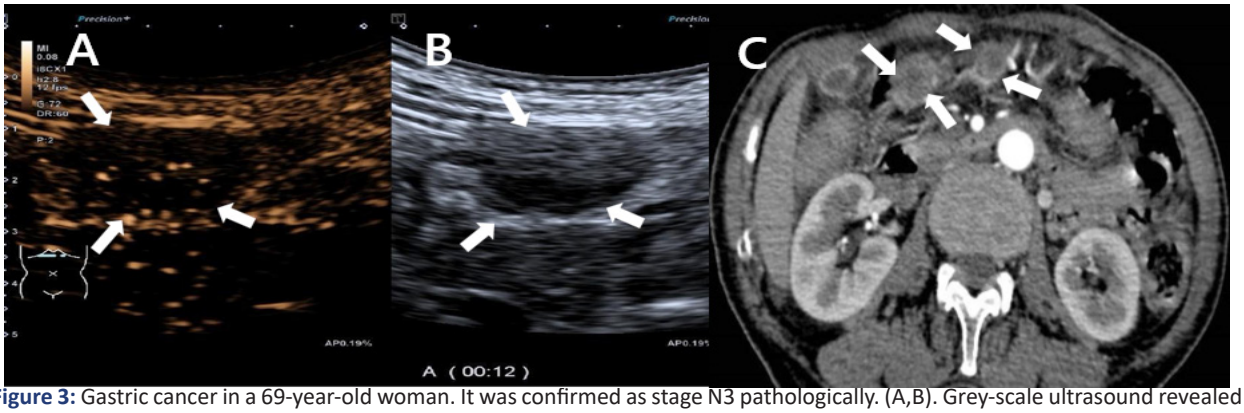

Figure 3: Gastric cancer in a 69-year-old woman. It was confirmed as stage N3 pathologically. (A,B). Grey-scale ultrasound revealed multiple enlarged lymph nodes were seen in the greater omentum (Figure B arrows), CEUS showed with centripetal heterogeneous enhancement in the arterial phase, considering metastatic lymph nodes (Figure A arrows). (C). CECT showed multiple enlarged lymph nodes can be seen in the greater omentum, and circumferential enhancement in the arterial phase (arrows). They were both correctly diagnosed as stage N3.

Figure 4: Gastric cancer in a 45-year-old woman. It was pathologically confirmed liver metastases, M1. (A,B). Grey-scale ultrasound revealed a mass in the liver (Figure B arrows), CEUS showed a "black hole" sign in the venous phase of this liver tumor (Figure A arrows). (C). CECT shows a ring-like enhancement in the arterial phase of this liver tumor (arrows). They were both correctly diagnosed as stage M1.

Discussion

Currently, surgery is the main treatment for GC, endoscopic resection for early GC [17], and neoadjuvant chemotherapy for advanced GC. Previous studies have demonstrated that TNM stages correlate closely with survival [24]. Thus, accurate preoperative stage is critical to the appropriate treatment and prognosis of patients with GC [25]. In clinical diagnosis of GC, EUS and CECT scanning are the two mostly employed imaging methods for stages of GC [26,27]. Ultrasonography possesses some advantages including convenience, low cost, and no radiation. With the development and advancement of technology, DCEUS can clearly show the five layers of the gastric wall, evaluate the microvessels and tissue perfusion, and diagnose GC with high accuracy [28]. Recently, DCEUS is considered as very promising imaging method for stages of GC [13]. Therefore, here we sought to evaluate and compare the accuracy and value of DCEUS and CECT for preoperative TNM stages of GC.

In this retrospective analysis, the overall accuracy of T stage using DCEUS (74%) is comparable with that of employing CECT (76%), which are generally consistent with the reported data

Table 1: Patient and Clinical data of gastric cancer for the study (n=82).

Variables		Clinical data
Median age		65 (33-87).
Gender	Male	58 (70.7%)
	Female	24 (29.3%)
Tumor location, n	Cardia and fundus (upper segment)	23 (28.0%)
	Gastric body (middle segment)	19 (23.2%)
	Gastric angle and antrum (lower segment)	40 (48.8%)
Pathologic stage, n	T1	15
	T2	8
	T3	12
	T4	47
	N0	41
	N1	16
	N2	10
	N3	15
	M0	77
	M1	5

Table 2: Comparison of T stage by two imaging methods and pathology.

Tumor Stage by Imaging	Pathologic Stage, n				Accuracy	Sensitivity	Specificity
	T1	T2	T3	T4			
	(n=15)	(n=8)	(n=12)	(n=47)	%	%	%
DCEUS*							
T1	8	1	1	0	89	53	97
T2	3	4	0	1	90	50	95
T3	1	1	9	6	87	75	89
T4	3	2	2	40	83	85	80
CECT* *							
T1	7	0	0	0	90	47	100
T2	5	5	1	3	85	63	90
T3	2	1	9	3	89	75	94
T4	1	2	2	41	87	87	86

*Kappa = 0.580 (p<0.01); **Kappa = 0.606 (p<0.01).

Table 3: Comparison of N stage by two methods and pathology.

T stage	Pathologic Stage, n				Accuracy	Sensitivity	Specificity
	N0	N1	N2	N3			
	(n=41)	(n=16)	(n=10)	(n=15)	%	%	%
DCEUS*							
N0	37	9	1	6	76	90	61
N1	2	6	1	3	80	38	91
N2	1	0	8	3	93	80	94
N3	1	1	0	3	83	20	97
CECT* *							
N0	26	7	0	2	71	63	78
N1	7	6	3	1	74	38	83
N2	7	1	5	8	74	50	78
N3	1	2	2	4	80	27	93

*Kappa = 0.449 (p<0.01); **Kappa = 0.280 (p<0.01).

Table 4: Comparison of M stage by two methods and pathology.

Tumor stage by imaging	Pathologic Stage, n		Accuracy	Sensitivity	Specificity
	M0	M1			
	(n=77)	(n=5)	%	%	%
DCEUS*					
M0	77	4	95	100	20
M1	0	1	95	20	100
CECT* *					
M0	76	1	98	99	80
M1	1	4	98	80	99

*Kappa = 0.320 ($p<0.01$); **Kappa = 0.787 ($p<0.01$).

Table 5: Consistency test between DCEUS and CECT in TNM stages.

Pathologic stage			
Tumor stage by imaging	T Stage	N Stage	M Stage
DCEUS	0.58	0.449	0.32
CECT	0.606	0.28	0.787

All p <0.01.

[20,29,30]. And there is no significant difference in overall accuracy between them. Among them, our results show that the accuracies of DCEUS and CECT are high for both T1 and T2 stages, the accuracy of DCEUS for T1 and T2 stages is 89% and 90%, and the accuracy of CECT for T1 and T2 stages is 90% and 85%, but the sensitivities are 53%, 50%, 47%, and 63%, respectively, which are relatively low. It means that the two methods would have a higher miss rate for T1 and T2 stages. The reasons may be due to the fact that generally the depth of tumor infiltration in T1 and T2 stages is shallow, if the tumor size is small, which may not easily be detected by imaging, and especially in the presence of gastritis or ulcers. The presence of inflammation and neovascularization may lead to blur the layers among the mucosa, muscularis mucosa, submucosa, and muscularis propria, and this ultimately results in poor diagnosis. By analyzing the data in Table 3, we find that the two methods have not only high accuracies but also high sensitivities for T3 and T4 stages. We believe that the possible reasons are as follows: the serosa is distinctly hyperechoic on ultrasound, when the tumor invades the serosa (T3 stage) or even adjacent tissues or organs (T4 stage), which is extremely obvious on ultrasound. With the help of intravenous contrast agents in ultrasound, the blood supply of the tumor is clear, which is more helpful to clarify its stage. On CECT images, the prominent feature of stage T3 GC is the blurring of the serosa and fatty gap, and the prominent feature of T4 stage is the invasion of surrounding tissues or organs, and these imaging features have high specificity. The kappa value of CECT (0.606) was higher compared to DCEUS (0.580), which indicates that both methods have general goodness of fit in the evaluation of T stage, and the consistency of CECT with pathological findings is better than DCEUS in fact.

Lymph node metastasis is one of the most crucial indicators of postoperative cure of GC. It is also an important criterion for determining whether to give patients neoadjuvant chemotherapy before surgery or not [31]. At present, imaging diagnosis of lymph nodes metastases of GC is quite difficult. Various systematic literature reviews concluded that the available imaging modalities cannot reliably confirm or exclude the presence of lymph nodes metastases [5,32,33]. In our study, overall accuracies of both DCEUS and CECT for N stage are relatively high with no statistical difference. However, the sensitivity of both methods for stage N1 and N3 are very low, the sensitivities of DCEUS for N1 and N3 stage are 38% and 20%, and the sensitivities of CECT for N1 and N3 stage are 38% and 27%. This means that a small number (1~2) or large number (>7) of metastatic lymph nodes can be easily missed by both methods. And the number of metastatic lymph nodes in N2 (3~6) is the easiest to observe, so the sensitivity is higher. Metastatic lymph nodes are considered on ultrasound and CT only if they are significantly enlarged, deformed, or fused with each other. Even if perigastric lymph nodes are found to be enlarged, the enlarged lymph nodes are not necessarily metastatic, but may also be caused by GC combined with inflammation. Hence, it is difficult to distinguish them from metastatic lymph nodes, and not to mention the assessment of the number of metastatic lymph nodes. The kappa value of DCEUS (0.449) is higher as compared to CECT (0.280), which indicates that DCEUS has general goodness of fit in the evaluation of N stage, but CECT has weak goodness of fit in the evaluation of N stage. Therefore, for the current DCEUS and CECT technology, they have limited diagnostic value for N stage, and can only provide some reference value for the presence or absence of metastatic lymph nodes, and are not sensitive to the number of metastatic lymph nodes.

In addition to lymph node metastasis, GC can also metastasize to liver, lung, peritoneum, bone and other parts of the body through bloodstream [34,25]. In our 82 patients with GC, distant metastases occurred in 5 cases, one case of liver metastasis, 2 cases of lung metastasis, one case of peritoneal metastasis and one case of lung metastases combined with bone metastasis. DCEUS and CECT both have high accuracies for M stage, but the sensitivity of DCEUS to stage M1 is particularly low, only 20%, where one of them is found to have liver metastases by DCEUS, “black holes” sign is found in venous phase, while 4 cases are confirmed to have distant metastases by pathology. It noteworthy that DCEUS has limitations for distant metastases beyond the liver, therefore, metastases in the lungs, bone or small metastases in peritoneum are difficult to detect on ultrasound. Numerous studies have found that CEUS has a high sensitivity for liver metastases and is even more sensitive than CECT for millimeter metastatic lesions [36,37]. In our study, only one small peritoneal metastasis is missed by CECT with an accuracy rate of 98%. The kappa value of DCEUS is 0.320, and the kappa value of CECT is 0.787. It indicates that DCEUS has a weak goodness of fit in the evaluation of M stage, but CECT has a strong goodness of fit in the evaluation of M stage. Consequently, we believe that DCEUS has greater diagnostic potential for patients with liver metastases from GC, but it has limited diagnostic value for distant metastases outside the liver. While CECT has high accuracy, sensitivity and specificity for most sites of distant metastases. Overall speaking, it has greater value than DCEUS in diagnosing distant metastases.

Limitation of this study may be as follow: (1) The number of patients included in the study who underwent both DCEUS and CECT preoperatively is small, especially in the few cases with M1 stage, further studies are needed to increase the sample size to make the results more valid. (2) In terms of lymph node stage, for example, the lymph nodes above and below the cardia are easily missed because of their deep location.

Conclusion

In conclusion, the diagnostic value of DCEUS and CECT for T stage was comparable, and both of them have less diagnostic

value for T1 and T2 than T3 and T4. Both the DCEUS and CECT have limited diagnostic value for N stage, and can only provide some reference value for the presence or absence of metastatic lymph nodes, but cannot make an accurate diagnosis of the number of metastatic lymph nodes. In general, CECT is superior to DCEUS for M stage, and DCEUS can be supplemented for gastric cancer with liver metastases. Therefore, the two modalities can complement each other in evaluating TNM stages of gastric cancer.

Declarations

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Data availability statement: The data that support the findings of this study are available on request from the corresponding author.

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