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ORIGINAL ARTICLE

Ultrasound/CT combined with serum CEA/CA19.9 in the diagnosis and prognosis of rectal cancer

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Summary

Purpose: *To explore the significance of computed tomography (CT) and transrectal ultrasonography (TRUS) combined with serum CEA and CA19.9 in the staging, diagnosis and prognosis of rectal cancer.*

Methods: *Fifty-six patients with rectal cancer were recruited from our oncology department. ELISA detected the expression level of CEA and CA19.9 in serum. The hemodynamic parameters of the rectal mucosa and tumor were detected by TRUS [resistance index (RI), pulse index (PI), peak systolic velocity (PSV), end-diastolic volume (EDV)]. All patients were pathologically examined to determine the disease stage and to compare the diagnostic accuracy of serum tumor markers, CT and TRUS. All patients were followed up for 24 months to assess the relationship between the combined examinations and the disease prognosis.*

Results: *CEA and CA19.9 levels were significantly different in patients with different pathological stages ($p<0.05$). RI and PI decreased with increasing pathological stage, while PSV and EDV were increased with increasing pathological stage. The serum CEA+CA19.9 examination showed 12 cases of misdiagnosis, with an accuracy diagnostic rate of 78.57% (44/56). CT examination showed 8 cases of misdiagnosis, with an accuracy diagnostic rate of 85.71% (48/56). TRUS showed 6 cases of misdiagnosis, with an accuracy diagnostic rate of 89.28% (50/56). However, only 2 cases were misdiagnosed and 96.43% (54/56) were accurate, while no statistical difference was noticed between combined detection and pathology ($p<0.05$). Postoperative follow-up showed significant differences in T staging at 6 months, 1 year and 2 years after operation ($p<0.05$).*

Conclusion: *CT and TRUS combined with serum CEA and CA19.9 had great value in the diagnosis and prognosis in rectal cancer.*

Key words: *CT, rectal cancer, tumor markers, tumor staging, ultrasound*

Introduction

Rectal cancer accounts for about 61.4-75.2% in large bowel cancers, which is a common malignant tumor of the digestive tract, showing an increasing trend year by year [1,2]. Tumor cells gain nutrients from the host through new blood vessels formation, and metastasize to distant parts of the body via blood and lymph vessels [3]. In this study, TRUS was used to detect the change in arterial hemodynamics in the tumor, and then its relationship with the pathological staging. CT, as a routine imaging examination method, plays an important role in determining the tumor staging. Detection of serum tumor markers is a noninvasive and effective diagnostic means for tumors. At

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present, more than 10 serum tumor markers for rectal cancer have been reported, and carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA19.9) are well-recognized and broadly used markers for colorectal cancer [4,5]. However, these three detection methods, due to their inherent characteristics, have limitations and lack sufficient sensitivity and specificity for tumors in different stages [6]. Therefore, this study aimed to explore the clinical application value of TRUS and CT combined with serum CEA and CA19.9 in the staging and prognosis of rectal cancer.

Methods

Clinical data

A total of 56 patients with rectal cancer were recruited from the Oncology Department of our hospital from April 2013 to March 2017, including 29 males and 27 females with an average age of 53.82±15.23 years. The main clinical manifestations were bloody stool, constipation, abdominal discomfort and abdominal pain. The mass was 4-10 cm away from the anal verge, and malignant tissues were taken from all patients by colonoscopy and definitely diagnosed via pathological examination. All patients underwent surgical treatment, including low anterior resection (24 cases) and abdominal-perineal resection (32 cases). This study was approved by the Ethics Committee of our hospital, and all patients signed written informed consent.

TRUS examination

In TRUS, Phillip HDI5000 sono CT (Tokyo, Japan) with the transrectal biplane probe was used. Radial plane scanning was performed to examine patients in left lateral position. After the probe was inserted into the rectum, the balloon wrapping the transducer was filled with about 60 mL water. The probe was moved up and down in an interval of 0.5 cm. The transducer performed transverse 360-degree scanning in the rectal longitudinal axis. The parameter values of arterial hemodynamics inside the tumor (RI, PI, PSV and EDV) were routinely detected. After operation, the parameter values were grouped and retrospectively analyzed according to the pathological staging, and were compared in each group.

CT examination

Plain scan and enhancement scan were performed in patients using the 64-slice spiral CT (GE, USA), and the original data were reconstructed with a thickness of 1-2 mm. In most cases, 6-mm-thick transverse sections were scanned from the sacroiliac joint to the anal area. Four patients took contrast agent (2% diatrizoate, 100 mg/mL) orally and were examined within 6 hrs, while the remaining patients were not given contrast agent. The results of CT were analyzed by two experienced radiologists according to the TNM staging system of the Union Internationale Contre le Cancer (UICC) to determine the staging of disease.

Detection of serum CEA and CA19.9 expressions via enzyme-linked immunosorbent assay (ELISA)

After 10 mL whole blood was drawn from patients and centrifuged at 1000 rpm for 15 min, the upper-layer serum was taken away. The levels of inflammatory factors in CEA and CA19.9 were detected using the horseradish peroxidase-labeled double-antibody sandwich immunoassay method. Briefly, CEA (RD, Article Number: D5050, New York, USA) and CA19.9 (RD, Article Number: DY827) were inoculated into a 96-well ELISA plate. An appropriate amount of serum was added for incubation. With tetramethylbenzidine as the substrate, the contents of enzyme and enzyme-bound tumor necrosis factor-α (TNF-α) were determined. The optical density (OD) values were detected at dual wavelength of 450 nm and 600 nm using microplate reader, and the sample concentration was calculated.

Statistics

GraphPad Prism (Version 5.01, GraphPad Software, Santiago, Chile) statistical software was used for analysis. Numerical data were presented as numbers and percents and variables' data were presented as mean±SD. Chi-square test was used to compare the index differences among groups, and independent-samples t test was used to compare the index differences between two groups. Kaplan-Meier method was used to construct the cumulative survival curves of the patients and log-rank test to compare differences between groups. $p<0.05$ suggested that the difference was statistically significant.

Results

Detection of serum CEA and CA19.9 levels via ELISA

The results showed that the serum CEA and CA19.9 levels in patients with different pathological staging were significantly different, been significantly increased with the increase of pathological staging ($p<0.05$; Table 1).

Table 1. Detection of serum CEA and CA19.9 levels in patients via ELISA

Pathological staging	*n*	*CEA (μg/L)*	*CA19.9 (μg/L)*
T1	10	4.21±2.52	1.42±0.27
T2	14	13.75±7.07**	8.62±2.83**
T3	19	45.63±13.04##	28.04±10.09###
T4	13	74.03±26.82Δ	41.27±17.42ΔΔ

Compared with that in T1 stage, **p<0.01; compared with that in T2 stage, ##p<0.01, ###p<0.001; compared with that in T3 stage, Δp<0.05, ΔΔp<0.01.

Detection of intestinal wall and tumor hemodynamic parameters via TRUS

RI and PI were decreased with the increase of pathological staging, but PSV and EDV were significantly increased with the increase of pathological staging ($p<0.05$; Figure 1 and Table 2).

Detection of pathological signs of rectal cancer patients via CT examination

CT examination showed that: (1) there were eccentric irregular soft tissue density lumps with clear or obscure edge in the rectal cavity, and low-density cystic or necrotic areas could be seen in the center of lumps when they were large; (2) there were irregular thickening of the intestinal wall and asymmetric stenosis of the intestinal lumen, and the tumor tissues of some T4 patients broke through the outer membrane of the intestinal wall; (3) when extensive infiltration occurred, the intestinal wall was stiff, the stenosis of intestinal lumen was severe, the serous surface of the intestinal wall was rough, and the density of fat around the rectum was increased; (4) CT showed

Table 2. Detection of arterial hemodynamic parameters of intestinal wall via TRUS

Pathological staging	*n*	*RI*	*PI*	*PSV (cm/s)*	*EDV (cm/s)*
T1	10	1.28±0.11	2.93±0.72	18.83±8.68	2.12 ±0.44
T2	14	0.93±0.07*	2.37±0.52*	23.63±7.36*	11.36±2.17**
T3	19	0.63±0.08$^{\#}$	1.84±0.69$^{\#}$	27.05±9.04$^{\#}$	17.22±5.84$^{\#}$
T4	13	0.27±0.10$^{\Delta}$	1.17±0.42$^{\Delta\Delta}$	34.26±11.36$^{\Delta}$	24.82±10.47$^{\Delta}$

For abbreviations see text. Compared with that in T1 stage, *p<0.05, **p<0.01; compared with that in T2 stage, $^{\#}$p<0.05; compared with that in T3 stage, $^{\Delta}$p<0.05, $^{\Delta\Delta}$p<0.01.

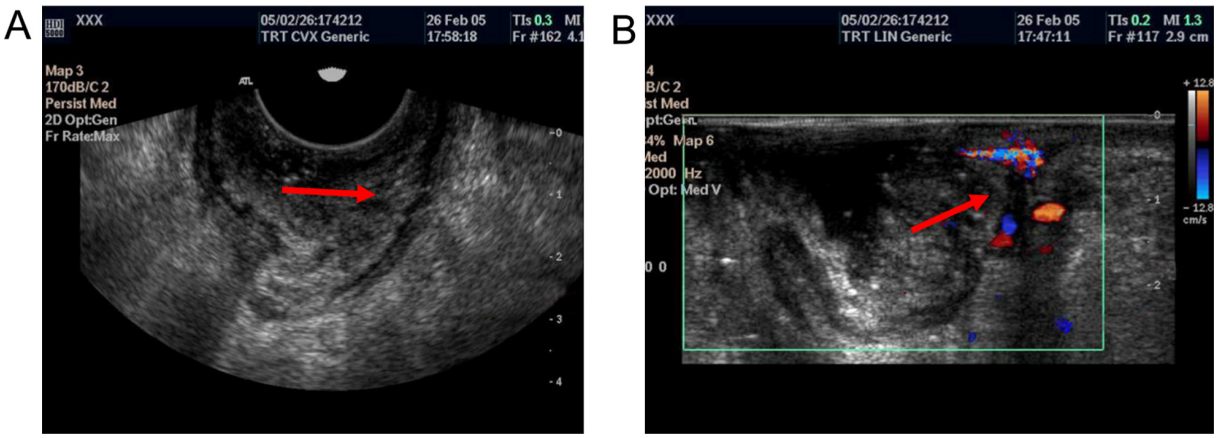

Figure 1. TRUS parameters of rectal cancer. **A:** Low-speed low-resistance arterial spectrum in rectal cancer (arrow); **B:** dotted blood flow signal in the tumor shown in color Doppler flow imaging (CDFI) (arrow).

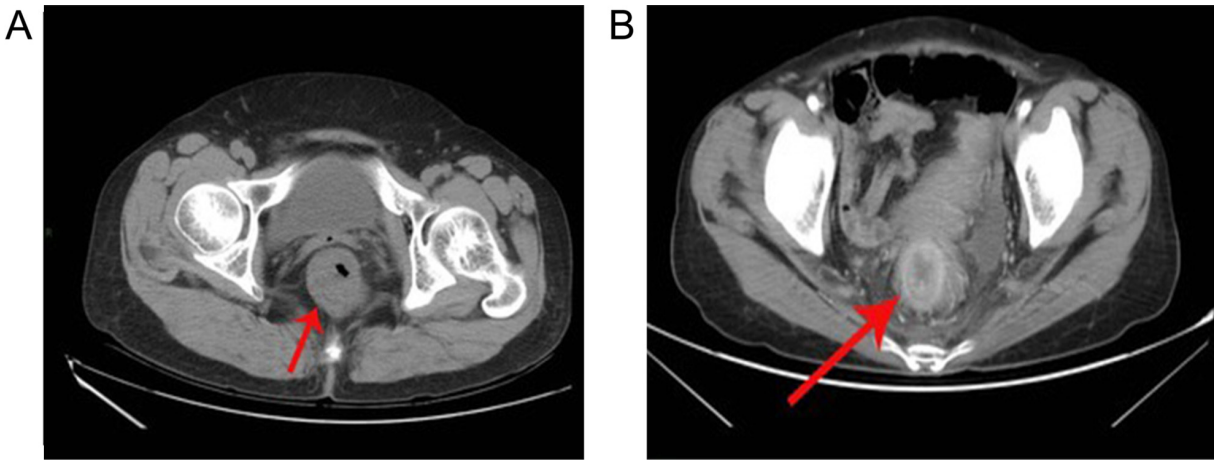

Figure 2. CT signs of rectal cancer. **A:** T4 stage disease determined via CT diagnosis; there are irregular thickening of the intestinal wall and stenosis of the intestinal lumen (arrow). **B:** Lesions break through the outer membrane of the intestinal wall (arrow), and the surrounding normal fat space disappears (arrow).

signs of nodal and distant organ metastases (Figure 2).

Comparison of accuracy in evaluating pathological staging among several examination methods

With pathological examination as a reference standard, there were 12 cases of misdiagnosis in serum CEA + CA19.9 detection, and the accurate diagnosis rate was 78.57% (44/56); there were 8 cases of misdiagnosis in CT examination, and the accurate diagnosis rate was 85.71% (48/56); there were 6 cases of misdiagnosis in TRUS examination, and the accurate diagnosis rate was 89.28% (50/56); there were only 2 cases of misdiagnosis in the evaluation of preoperative staging of rectal cancer via combined application of TRUS, CT and serum CEA + CA19.9, and the accuracy rate was 96.43% (54/56), indicating that there were significant differences among these examination methods ($p<0.05$). There was no statistically significant difference between the combined detection and pathological examination ($p>0.05$; Table 3).

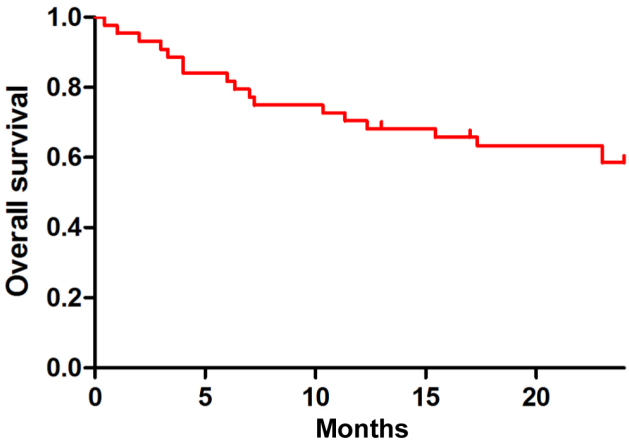

Figure 3. 2-year overall survival rate of patients after operation.

Effects of combined examination on prognosis

All patients were followed up for 24 months after operation. In this time frame, there were 3 cases lost to follow-up. Chi-square test showed that there were significant differences in the T staging of patients who survived at 6 months, 1 year and 2 years after the operation ($p<0.05$; Figure 3 and Table 4).

Discussion

At present, local resection can be performed for T1 and part of T2 stage rectal cancer, while treatment methods via local excision or local irradiation, such as neoadjuvant chemoradiotherapy, can be performed for T3 and T4 cancer stage, which have become generally-recognized treatment methods of rectal cancer [7,8]. Therefore, the accurate analysis of rectal cancer staging is a necessary prerequisite for local treatment. At present, although the CT imaging technique has been significantly improved in spatial resolution

Table 3. Comparison of accuracy in evaluating pathological staging of rectal cancer among three examination methods

Examination method (n=56)	*Pathological staging/n*				*Accuracy (%)*
	T1	*T2*	*T3*	*T4*	
Pathological diagnosis	10	14	19	13	100
CEA+CA19.9	14	16	14	12	78.57
CT examination	14	14	17	11	85.71
TRUS examination	10	15	16	15	89.28
Combined examination	10	13	19	14	96.43
x^2					9.46
p					<0.05

Table 4. Correlation between combined diagnosis and prognosis of patients

Prognosis (n=56)	*T staging*			
	T1	*T2*	*T3*	*T4*
Total cases surviving after 6 months (n=51)	9	13	18	11
Total cases surviving after 1 year (n=44)	9	13	16	6
Total cases surviving after 2 years (n=33)	9	11	11	2
x^2		6.85		
p		0.027		

and contrast, and homogeneous images on any plane in almost any direction can be obtained [9], CT cannot be used to determine whether the tumor involves the submucosal layer, muscular layer or serosal layer due to the large difference between rectal wall density and soft tissue density, so T1 stage, T2 stage and non-progressive colorectal cancer cannot be better differentiated via CT [10,11]. In this study, CT examination showed that: (1) there were eccentric irregular soft tissue density lumps with clear or obscure edge in the rectal cavity, and low-density cystic or necrotic areas could be seen in the center of lumps when they were large; (2) there were irregular thickening of the intestinal wall and asymmetric stenosis of the intestinal lumen, and in umor tissues of some T4 patients broke through the outer membrane of the intestinal wall; (3) when extensive infiltration occurred, the intestinal wall was stiff, the stenosis of the intestinal lumen was severe, the serous surface of the intestinal wall was rough, and the density of fat around the rectum was increased; (4) CT showed signs of nodal and distant organ metastases. Overall, there were 4 cases of misdiagnosis of T1 patients in CT examination, and the accurate diagnosis rate was 85.71%.

TRUS is a noninvasive and nonradiative examination technique, which is characterized by convenient operation and low cost, and considered as the most convenient, quick and accurate imaging method [12,13]. TRUS can clearly show the intestinal wall layer. The size and echo of lymph nodes in the rectum and mesorectal lymph node region can be used as imaging reference indexes for cancer [14]. Tumor cells rely on new vessels formation to obtain nutritional support [15]; therefore, TRUS was used to detect the arterial hemodynamic parameter values inside the tumor in this study. The research of Timmerman et al. showed that the arterial hemodynamic parameter values inside the rectal cancer display "four-low" phenomena: low PI, low RI, low PSV and low EDV [16]. However, the results of our study showed that RI and PI were decreased with the increase of pathological staging, but PSV and EDV were increased with the increase of pathological staging. We think this may be because new vessels inside the tumor lack the normal vascular structure, and the vascular direction is tortuous. In addition, vascular wall lacks smooth muscle, resulting in decline in systolic and diastolic abilities of the vascular wall. Besides, arteriovenous fistula formed inside the tumor causes more arteriovenous communication, resulting in decline in blood flow velocity. In terms of diagnostic efficiency, there was only 1 case of misdiagnosis in T2 stage cancer, 3 cases of misdiagnosis in T3 stage cancer and 2 cases of misdiagnosis in T4 stage cancer in the diagnosis of early rectal cancer via TRUS in this study, and the overall accurate diagnosis rate was 89.28%, consistent with research results of Gearhart et al. [17]. The above mentioned results suggest that TRUS can identify T1 and T2 stage tumors more accurately than CT. However, inflammatory and fibrotic lesions often exist around the tumor, so many studies have argued that there are also staging excess and staging insufficiency of TRUS [18]. In addition, the ultrasound probe cannot go across the lumps due to the severe stenosis of the enteric cavity caused by rectal cancer, and it can only explore the inferior border of lumps; moreover, bleeding caused by excessive force in the examination and other complex situations may lead to diagnostic errors. Therefore, there are some drawbacks in the two kinds of routine imaging examination methods.

CEA is a high-molecular-weight glycoprotein in the molecular immunoglobulin superfamily, which plays a key role in the biological phenomena of tumor cells, such as adhesion, immunity or apoptosis [19]. CA19.9 is a high-molecular-weight glycolipid, which mainly impacts the adhesion cell function and plays an important role in the occurrence and development of tumor [20]. Studies have found that patients with a high CA19.9 levels before operation have a poor prognosis, and the level of CA19.9 in patients with tumor recurrence is increased significantly compared with patients without recurrence [21]. In this study, the serum CEA and CA19.9 levels showed increasing trends with the increase of pathological staging, and the accuracy rate of diagnosis of preoperative staging of rectal cancer via serum CEA and CA19.9 alone was 78.57%, indicating that the preoperative serum CEA and CA 19.9 level still have some reference values for rectal cancer staging.

Conclusion

We conclude that the combined application of serum CEA + CA19.9, TRUS and CT imaging examination had a higher accurate diagnotic rate. In addition, according to the follow-up data, there were significant differences in the T staging of patients evaluated with the combined examination, who survived at 6 months, 1 year and 2 years after the operation. We believe that the combined application of serum CEA + CA199, TRUS and CT examination in evaluating the preoperative staging of rectal cancer in this study has a higher diagnostic efficiency.

Conflict of interests

The authors declare no conflict of interests.

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