Original Article

Prognostic value of the ratio of pretreatment carcinoembryonic antigen to tumor volume in rectal cancer

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Background: As a commonly used biomarker in rectal cancer (RC), the prognostic value of carcinoembryonic antigen (CEA) remains underexplored. This study aims to evaluate the prognostic value of pretreatment CEA/tumor volume in RC.

Methods: This retrospective study included patients who underwent pretreatment magnetic resonance imaging (MRI) with histologically confirmed primary rectal adenocarcinoma from November 2012 to April 2018. Patients were divided into high-risk and low-risk groups according to the median values of CEA/Dia_{path} (CEA to pathological diameter), CEA/Dia_{MRI} (CEA to MRI tumor diameter), and CEA/Vol_{MRI} (CEA to MRI tumor volume). Cox regression analysis was utilized to determine the prognostic value of CEA, CEA/Dia_{path}, CEA/Dia_{MRI}, and CEA/Vol_{MRI}. Stepwise regression was used to establish nomograms for predicting disease-free survival (DFS) and overall survival (OS). Predictive performance was estimated by using the concordance index (C-index) and area under curve receiver operating characteristic (AUC).

Results: A total of 343 patients [median age 58.99 years, 206 (60.06%) males] were included. After adjusting for patient-related and tumor-related factors, CEA/Vol_{MRI} was superior to CEA, CEA/Dia_{path}, and CEA/Dia_{MRI} in distinguishing high-risk from low-risk patients in terms of DFS [hazard ratio (HR) =1.83; P=0.010] and OS (HR =1.67; P=0.048). Subanalysis revealed that CEA/Vol_{MRI} stratified high death risk in CEA-negative individuals (HR =2.50; P=0.038), and also stratified low recurrence risk in CEA-positive individuals (HR =2.06; P=0.024). In the subanalysis of stage II or III cases, the highest HRs and the smallest P values were observed in distinguishing high-risk from low-risk patients according to CEA/Vol_{MRI} in terms of DFS (HR =2.44; P=0.046 or HR =2.41; P=0.001) and OS (HR =1.96; P=0.130 or HR =2.22; P=0.008). The nomograms incorporating CEA/Vol_{MRI} showed good performance, with a C-index of 0.72 [95% confidence interval (CI): 0.68–0.79] for DFS and 0.73 (95% CI: 0.68–0.80) for OS.

Conclusions: Higher CEA/Vol_{MRI} was associated with worse DFS and OS. CEA/Vol_{MRI} was superior to CEA, CEA/Dia_{path}, and CEA/Dia_{MRI} in predicting DFS and OS. Pretreatment CEA/Vol_{MRI} may facilitate risk stratification and treatment decision-making.

Keywords: Rectal cancer (RC); carcinoembryonic antigen (CEA); tumor volume; prognosis; magnetic resonance imaging (MRI)

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Introduction

Globally, colorectal cancer (CRC) ranks third in terms of cancer incidence and second in terms of cancer-related mortality (1). Rectal cancer (RC), accounting for approximately one-third of CRC, has shown an increasing incidence and mortality (2). Previous studies have shown that approximately 15% to 50% of patients with non-metastatic stage I–III RC experienced relapses within 5-year postoperative follow-up (3,4). In recent years, with the rapid advancements of neoadjuvant chemoradiotherapy, targeted therapy, and immunotherapy, personalized therapeutic approaches emerged as a pivotal part in prolonging survival and improving the quality of life for patients (5-7). However, lacking effective biomarkers, clinicians still face a challenge in making patient-individualized choices for interventions.

Carcinoembryonic antigen (CEA) is one of the most commonly used prognostic biomarkers recommended by the American Society of Clinical Oncology (ASCO) and the European Group on Tumor Markers (EGTM) (8). Studies have shown that elevated pretreatment CEA levels are intricately linked to unfavorable prognosis in patients with RC (9,10). However, the prognostic value of CEA for RC remains insufficient, which rarely leads to better outcomes for patients (11-13). Several studies have revealed that the combination of CEA and postoperative pathologies, such as lymph node metastasis, differentiation, lymphovascular invasion (LVI), and perineural invasion (PNI), holds the potential to augment the accuracy of prognosis evaluation (14,15). Unfortunately, heavily relying on pathology, the majority of studies offered limited assistance regarding preoperative interventions. There is an urgent need to identify effective pretreatment biomarkers for risk stratification and treatment decision-making.

Magnetic resonance imaging (MRI) is the first-line imaging method for RC patients recommended by the National Comprehensive Cancer Network (NCCN) due to its exceptional capacity to evaluate the characteristics of the primary tumor and adjacent structures (16-18). The tumor size exerts a profound influence on surgical management and prognosis evaluation. It has been firmly established as an independent predictor for treatment response and postoperative survival in diverse malignant tumors, such as gastric cancer, non-small cell lung cancer, and CRC (19-22). Considering the robust positive correlation between serum CEA and tumor size, two studies revealed that the CEA/tumor diameter as an independent prognostic factor was superior to CEA in predicting postoperative recurrence and death in CRC (23,24). Unlike tumor diameter which solely refers to the longest distance across single-section, tumor volume encompasses the entirety of the tumor space, regardless of shape (25). The ratio of CEA to tumor volume represents the relative CEA per unit volume, which may reflect the proliferation and aggressiveness of tumor cells (26). Aminsharifi *et al.* have illustrated that the prostate-specific antigen density (prostate-specific antigen/prostate volume) augmented the negative predictive value in the identification of prostate cancer (27). However, the prognostic value of CEA/tumor volume for RC patients is currently unclear.

Thus, the purpose of this study was to evaluate the prognostic value of pretreatment CEA/tumor volume (measured on pretreatment MRI) and to compare it with CEA/tumor diameter (measured on pretreatment MRI and postoperative specimen). We present this article in

Highlight box

Key findings

- Carcinoembryonic antigen (CEA)/Vol_{MRI} [CEA to magnetic resonance imaging (MRI) tumor volume] was superior to CEA, CEA/Dia_{path} (CEA to pathological tumor diameter), and CEA/Dia_{MRI} (CEA to MRI tumor diameter) in stratifying the risk of recurrence and death.

What is known and what is new?

- CEA is a commonly used biomarker for auxiliary detection, prognostic evaluation, and follow-up in rectal cancer. Nevertheless, CEA still presents limitations in terms of sensitivity and specificity in tumor detection and prognosis evaluation.
- Higher CEA/Vol_{MRI} was associated with worse disease-free survival and overall survival. CEA/Vol_{MRI} was superior to CEA, CEA/Dia_{path}, and CEA/Dia_{MRI} in the prognosis evaluation of rectal cancer patients.

What is the implication, and what should change now?

- Pretreatment CEA/Vol_{MRI} may facilitate risk stratification and treatment decision-making.

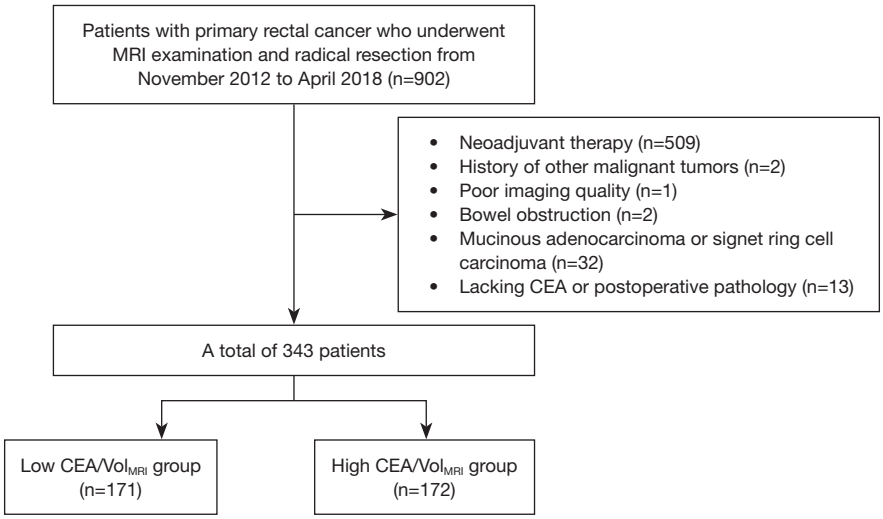

Figure 1 Flowchart. MRI, magnetic resonance imaging; CEA, carcinoembryonic antigen; Vol$_{MRI}$, MRI tumor volume.

accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-683/rc) (28).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of The Sixth Affiliated Hospital of Sun Yat-sen University (No. 2023ZSLYEC-109). Individual consent for this retrospective study was waived.

Patients

This study included consecutive patients with primary RC who underwent pelvic MRI examination and radical resection surgery at The Sixth Affiliated Hospital of Sun Yat-sen University from November 2012 to April 2018 (*Figure 1*). The inclusion criteria were as follows: (I) patients pathologically confirmed primary rectal adenocarcinoma and underwent radical resection surgery; (II) pelvic MRI performed within 2 weeks before surgery; (III) non-metastatic stage I–III according to the 8th edition of the American Joint Committee on Cancer (AJCC). The exclusion criteria were as follows: (I) patients who underwent neoadjuvant chemoradiotherapy; (II) history of other malignant tumors; (III) poor imaging quality that affected tumor assessment; (IV) bowel obstruction; (V) mucinous adenocarcinoma or signet ring cell carcinoma; (VI) lacking pretreatment CEA or postoperative pathology.

All patients underwent pretreatment evaluations including physical examination, medical history, biochemical tests, chest and abdominopelvic computed tomography (CT), and pelvic MRI. The clinical and pathological characteristics, including age, sex, weight, body mass index (BMI), tumor location, differentiation, tumor stage (T stage), nodal stage (N stage), LVI, and PNI, were collected and analyzed. The CEA reference range was 0 to 5 ng/mL as conventional.

MRI

MRI scans were acquired with a 1.5T GE scanner [Optima MR360, General Electric (GE) Company, Piscataway, USA] with the use of phased-array pelvic coils. The imaging protocol included: (I) sagittal, coronal, and oblique axial T2-weighted imaging (T2WI) [sequence: T2 fast spin echo (FSE), slice thickness: 5 mm, repetition time/echo time (TR/TE): 4,235/129.2, flip angle: 90°, echo train length: 19, acquisition voxel size: 0.569×0.569, number of acquisitions: 2]; (II) oblique axial diffusion-weighted imaging (DWI) (sequence: HR DWI, slice thickness: 6, TR/TE: 3,873/84.3, flip angle: 90°, echo train length: 1, acquisition voxel size: 1.5625×1.5625, number of acquisitions: 4).

Diameter and volume evaluation

As shown in Figure S1, the regions of interest (ROIs) were delineated by a junior radiologist (D.M., 3 years of

experience in pelvic MRI diagnosis) on oblique axial T2WI, avoiding visible necrotic tissue, blood vessels, RC intestinal wall, and rectal mucosa, which were subsequently reviewed by a senior radiologist (P.X., 10 years of experience in pelvic MRI diagnosis). The MRI tumor diameter (Dia_{MRI}) was independently measured by the junior radiologist based on the largest available tumor area on a single representative section of oblique axial T2WI, and subsequently reviewed by the senior doctor. The MRI tumor volume (Vol_{MRI}) was calculated by multiplying the number of ROI pixels (N) by section thickness and voxel size. The pathological tumor diameter (Dia_{path}) was measured by at least two pathologists at the maximum level of the tumor. The ratio of CEA to pathological diameter was represented as CEA/Dia_{path}. The ratio of CEA to MRI tumor diameter was represented as CEA/Dia_{MRI}. The ratio of CEA to MRI tumor volume was represented as CEA/Vol_{MRI}. Considering the non-normal distribution of these indicators, we divided patients into high- and low-risk groups with the same number of individuals according to the median values of CEA/Dia_{path}, CEA/Dia_{MRI}, and CEA/Vol_{MRI}.

Surveillance protocol

All patients were postoperative followed up every 3–6 months in the first 2 years, and every 6 months in the following 3–5 years. Chest and abdominopelvic CTs were performed at least every 6–12 months in the first 5 years after surgery. Disease-free survival (DFS) was calculated as the time from curative resection to local recurrence, distant metastasis, or the last follow-up. Overall survival (OS) was calculated as the time from the pretreatment MRI scan to death or the last follow-up.

Statistical analysis

Continuous variables with normal distributions were described as mean (mean ± standard deviation), while continuous variables with non-normal distributions were described as median (quartiles). Categorical variables were described as frequencies (percentages). The Student's *t*-test or Mann-Whiteney *U* test was used for continuous variables, and the χ^2 test was used for categorical variables. Completely random missing data, such as weight and sex, were imputed by using random sampling. Survival curves were generated by using the Kaplan-Meier method and compared by log-rank test. Univariate and multivariate Cox proportional hazard regressions were used to associate DFS and OS with the clinicopathological parameters. Nomograms were constructed for predicting DFS and OS using bidirectional stepwise Cox regression determined by the Akaike information criterion (AIC). Calibration curves were used to evaluate the consistency between predicted probabilities and actual probabilities. Predictive performance was estimated by using the concordance index (C-index) and area under curve receiver operating characteristic (AUC) calculated through 2,000 bootstrap resampling iterations. A two-tailed P value less than 0.05 was considered statistically significant. Statistical analysis was performed using R software (version 4.2.2, http://www.R-project.org) and SPSS software (version 25.0, IBM). The R packages used are listed in Table S1.

Results

Patients characteristics

This study included 343 patients with primary rectal adenocarcinoma from November 2012–April 2018 (*Figure 1*). All RC patients were divided into a high-risk group and a low-risk group based on the median value of CEA/Dia_{path} (*Figure 2A*), CEA/Dia_{MRI} (*Figure 2B*), CEA/Vol_{MRI} (*Figure 2C*).

In comparison to the low CEA/Vol_{MRI} group, the high CEA/Vol_{MRI} group was correlated with older age (73.10% *vs.* 82.56%, P=0.048), high pretreatment CEA levels (18.13% *vs.* 56.40%, P<0.001), and worse differentiation. During the follow-up period, a higher proportion of individuals in the high CEA/Vol_{MRI} group experienced recurrence (18.13% *vs.* 33.14%, P=0.002) and death (15.79% *vs.* 26.74%, P=0.019). The detailed clinicopathological characteristics are shown in *Table 1*.

HR of pretreatment CEA, CEA/Dia_{path}, CEA/Dia_{MRI}, and CEA/Vol_{MRI}

According to univariate Cox regression analysis, pretreatment CEA, tumor location, differentiation, clinical stage, N stage, LVI, PNI, CEA/Dia_{path}, CEA/Dia_{MRI}, and CEA/Vol_{MRI} were significantly associated with DFS (P<0.05). The univariate Cox regression indicated age, tumor location, differentiation, clinical stage, N stage, LVI, PNI, adjuvant therapy, and CEA/Vol_{MRI} were significantly associated with OS (P<0.05). Detailed results of univariate Cox analysis are shown in Table S2.

As shown in *Table 2*, after adjusting for age, gender, weight, BMI, tumor location, differentiation, T stage, N

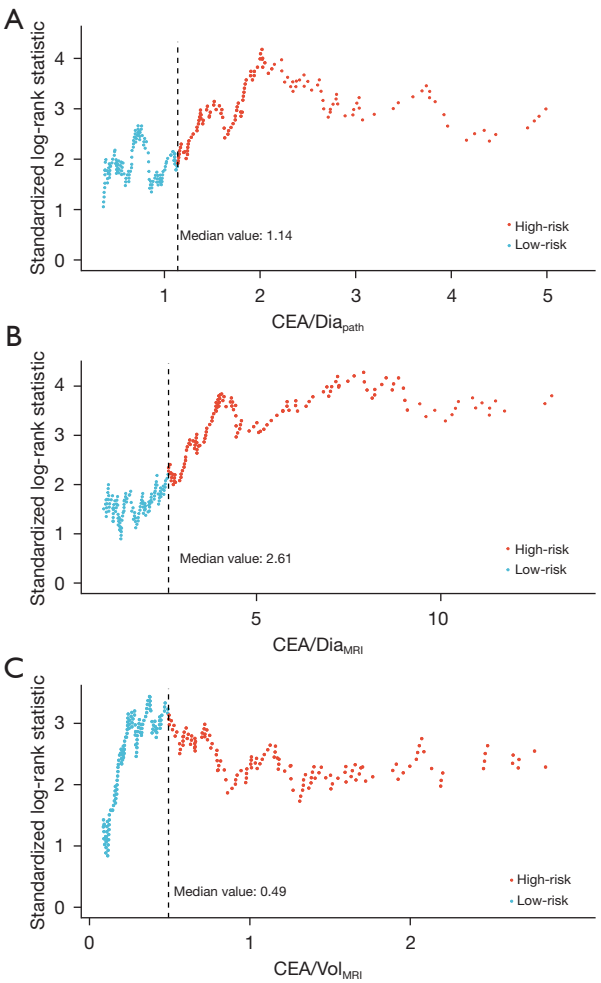

Figure 2 The standardized log-rank statistic according to the median value of CEA/Dia$_{path}$, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (A) Recurrence risk was grouped according to the median value of CEA/Dia$_{path}$. (B) Recurrence risk was grouped according to the median value of CEA/Dia$_{MRI}$. (C) Recurrence risk was grouped according to the median value of CEA/Vol$_{MRI}$. Considering the non-normal distribution of these indicators, patients were divided into high- and low-risk groups with equal numbers according to the median value of CEA/Dia$_{path}$, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. Red and blue dots indicate high- and low-risk patients, respectively. CEA, carcinoembryonic antigen; Dia$_{path}$, pathological tumor diameter; Dia$_{MRI}$, MRI tumor diameter; MRI, magnetic resonance imaging; Vol$_{MRI}$, MRI tumor volume.

stage, LVI, PNI, and adjuvant therapy, positive pretreatment CEA remained poor DFS [HR =1.70; 95% confidence interval (CI): 1.07–2.70; P=0.023], but critical OS (HR =1.19; 95% CI: 0.71–1.99; P=0.504). By contrast, no significant difference (P>0.05) was observed between high- and low-risk patients according to CEA/Dia$_{path}$ or CEA/Dia$_{MRI}$. After adjusting for patient-related and tumor-related factors, the highest HR and lowest P values were observed between high- and low-risk patients in terms of DFS (HR =1.83; 95% CI: 1.16–2.89; P=0.010) and OS (HR =1.67; 95% CI: 1.01–2.77; P=0.048) according to CEA/Vol$_{MRI}$.

Subgroup analyses of patients with negative or positive pretreatment CEA

The Kaplan-Meier curves in Figure S2 display the risk stratification of DFS and OS in subgroups of RC patients (pretreatment CEA negative and positive) according to CEA/Vol$_{MRI}$. In the CEA-negative population, CEA/Vol$_{MRI}$ distinguished patients at high risk of postoperative recurrence and death, with HRs of 1.42 (P=0.248) and 2.06 (P=0.024), respectively. In the CEA-positive population, CEA/Vol$_{MRI}$ distinguished patients at high risk of postoperative recurrence and death, with HRs of 2.50 (P=0.038) and 1.41 (P=0.449), respectively.

Subgroup analyses of patients with stage I, stage II or stage III

The Kaplan-Meier curves in *Figure 3* show the risk stratification of DFS in subgroups of RC patients (stage I, stage II, and stage III) according to CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. Among 58 patients with stage I RC (*Figure 3A-3C*), we did not notice a significant difference (P>0.05) in DFS between high- and low-risk patients according to CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. Among 142 patients with stage II RC (*Figure 3D-3F*), no significant difference was observed between high- and low-risk patients according to CEA or CEA/Dia$_{MRI}$. By contrast, we noticed patients with high CEA/Vol$_{MRI}$ had a higher recurrence risk than patients with low CEA/Vol$_{MRI}$ (HR =2.44; 95% CI: 1.02–5.84; P=0.046). In the subgroup analysis, within stage III cases (*Figure 3G-3I*), we could observe two distinct predicted high- and low-risk groups according to CEA/Vol$_{MRI}$, with the highest HRs and the smallest P values as evidence (HR =2.41; 95% CI: 1.42–4.10; P=0.001).

The Kaplan-Meier curves in *Figure 4* show the risk stratification of OS in subgroups of RC patients (stage I, stage II, and stage III) according to CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. Among patients with stage I or II RC (*Figure 4A-4F*), we did not notice a significant difference

Table 1 Patient characteristics

Parameter	All (n=343)	Low CEA/Vol_{MRI} (n=171)	High CEA/Vol_{MRI} (n=172)	P value
Age				0.048*
≤50 years	76 (22.16)	46 (26.90)	30 (17.44)	
>50 years	267 (77.84)	125 (73.10)	142 (82.56)	
Sex				0.354
Female	137 (39.94)	73 (42.69)	64 (37.21)	
Male	206 (60.06)	98 (57.31)	108 (62.79)	
Weight (kg)†	60.86 (10.57)	60.50 (10.51)	61.22 (10.65)	0.526
BMI (kg/m^2)‡	22.49 [20.58–24.90]	22.66 [20.62–24.74]	22.48 [20.58–25.07]	0.842
Dia_{path} (mm)‡	35.00 [25.00–40.00]	40.00 [30.00–50.00]	30.00 [23.00–35.00]	<0.001*
Dia_{MRI} (mm)‡	13.00 [11.00–16.00]	14.00 [12.00–17.00]	12.00 [10.00–15.00]	<0.001*
Vol_{MRI} (cm^3)‡	8.30 [3.86–16.63]	15.00 [8.07–23.12]	4.63 [2.15–8.90]	<0.001*
Pretreatment CEA				<0.001*
Negative	215 (62.68)	140 (81.87)	75 (43.60)	
Positive	128 (37.32)	31 (18.13)	97 (56.40)	
Location				0.219
Lower	78 (22.74)	39 (22.81)	39 (22.67)	
Middle	169 (49.27)	91 (53.22)	78 (45.35)	
Upper	96 (27.99)	41 (23.98)	55 (31.98)	
Differentiation				0.008*
Well	87 (25.36)	49 (28.65)	38 (22.09)	
Moderate	240 (69.97)	109 (63.74)	131 (76.16)	
Poor	16 (4.66)	13 (7.60)	3 (1.74)	
Clinical stage				0.082
I	58 (16.91)	26 (15.20)	32 (18.60)	
II	142 (41.40)	81 (47.37)	61 (35.47)	
III	143 (41.69)	64 (37.43)	79 (45.93)	
T stage				0.129
T1/2	74 (21.57)	33 (19.30)	41 (23.84)	
T3	255 (74.34)	134 (78.36)	121 (70.35)	
T4	14 (4.08)	4 (2.34)	10 (5.81)	
N stage				0.137
N0	200 (58.31)	107 (62.57)	93 (54.07)	
N1	143 (41.69)	64 (37.43)	79 (45.93)	

Table 1 *(continued)*

Table 1 *(continued)*

Parameter	All (n=343)	Low CEA/Vol_{MRI} (n=171)	High CEA/Vol_{MRI} (n=172)	P value
LVI				0.686
Negative	314 (91.55)	155 (90.64)	159 (92.44)	
Positive	29 (8.45)	16 (9.36)	13 (7.56)	
PNI				>0.99
Negative	314 (91.55)	157 (91.81)	157 (91.28)	
Positive	29 (8.45)	14 (8.19)	15 (8.72)	
Adjuvant therapy				0.212
No	199 (58.02)	93 (54.39)	106 (61.63)	
Yes	144 (41.98)	78 (45.61)	66 (38.37)	
Recurrence				0.002*
No	255 (74.34)	140 (81.87)	115 (66.86)	
Yes	88 (25.66)	31 (18.13)	57 (33.14)	
Death				0.019*
No	270 (78.72)	144 (84.21)	126 (73.26)	
Yes	73 (21.28)	27 (15.79)	46 (26.74)	
DFS (months)‡	64.73 [26.27–76.42]	66.50 [46.67–79.58]	62.38 [18.49–73.95]	0.001*
OS (months)‡	67.60 [53.23–77.30]	69.53 [60.15–80.18]	65.82 [47.98–74.86]	0.007*

Unless stated otherwise, data were numbers of patients, with percentages in parentheses. †, data were means, with standard deviations in parentheses; ‡, data were medians, with IQRs in parentheses; *, P value was <0.05 and considered statistically significant. CEA, carcinoembryonic antigen; Vol_{MRI}, MRI tumor volume; MRI, magnetic resonance imaging; BMI, body mass index; Dia_{path}, pathological tumor diameter; Dia_{MRI}, MRI tumor diameter; T stage, tumor stage; N stage, nodal stage; LVI, lymphovascular invasion; PNI, perineural invasion; DFS, disease-free survival; OS, overall survival.

Table 2 Multivariable Cox regression of DFS and OS

Parameter	DFS		OS	
	HR [95% CI]	P value	HR [95% CI]	P value
Pretreatment CEA (positive *vs*. negative)	1.70 [1.07–2.70]	0.023*	1.19 [0.71–1.99]	0.504
CEA/Dia_{path} (high *vs*. low)	1.48 [0.99–2.31]	0.092	1.23 [0.75–2.01]	0.417
CEA/Dia_{MRI} (high *vs*. low)	1.35 [0.85–2.12]	0.202	1.12 [0.68–1.83]	0.652
CEA/Vol_{MRI} (high *vs*. low)	1.83 [1.16–2.89]	0.010*	1.67 [1.01–2.77]	0.048*

The data in parentheses were 95% CI. HRs were adjusted by age, sex, weight, BMI, location, differentiation, T stage, N stage, LVI, PNI, and adjuvant therapy. *, P value was <0.05 and considered statistically significant. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; Dia_{path}, pathological maximum tumor diameter; Dia_{MRI}, MRI tumor diameter; MRI, magnetic resonance imaging; Vol_{MRI}, MRI tumor volume; BMI, body mass index; LVI, lymphovascular invasion; PNI, perineural invasion.

(P>0.05) in DFS between high- and low-risk patients according to CEA, CEA/Dia_{MRI}, and CEA/Vol_{MRI}. In the subgroup analysis of stage III cases (*Figure 4G-4I*), we still observed two distinct high- and low-risk groups according to CEA/$Vol_{MRI,}$ with the highest HR and the smallest P values as evidence (HR =2.22; 95% CI: 1.23–4.01; P=0.008).

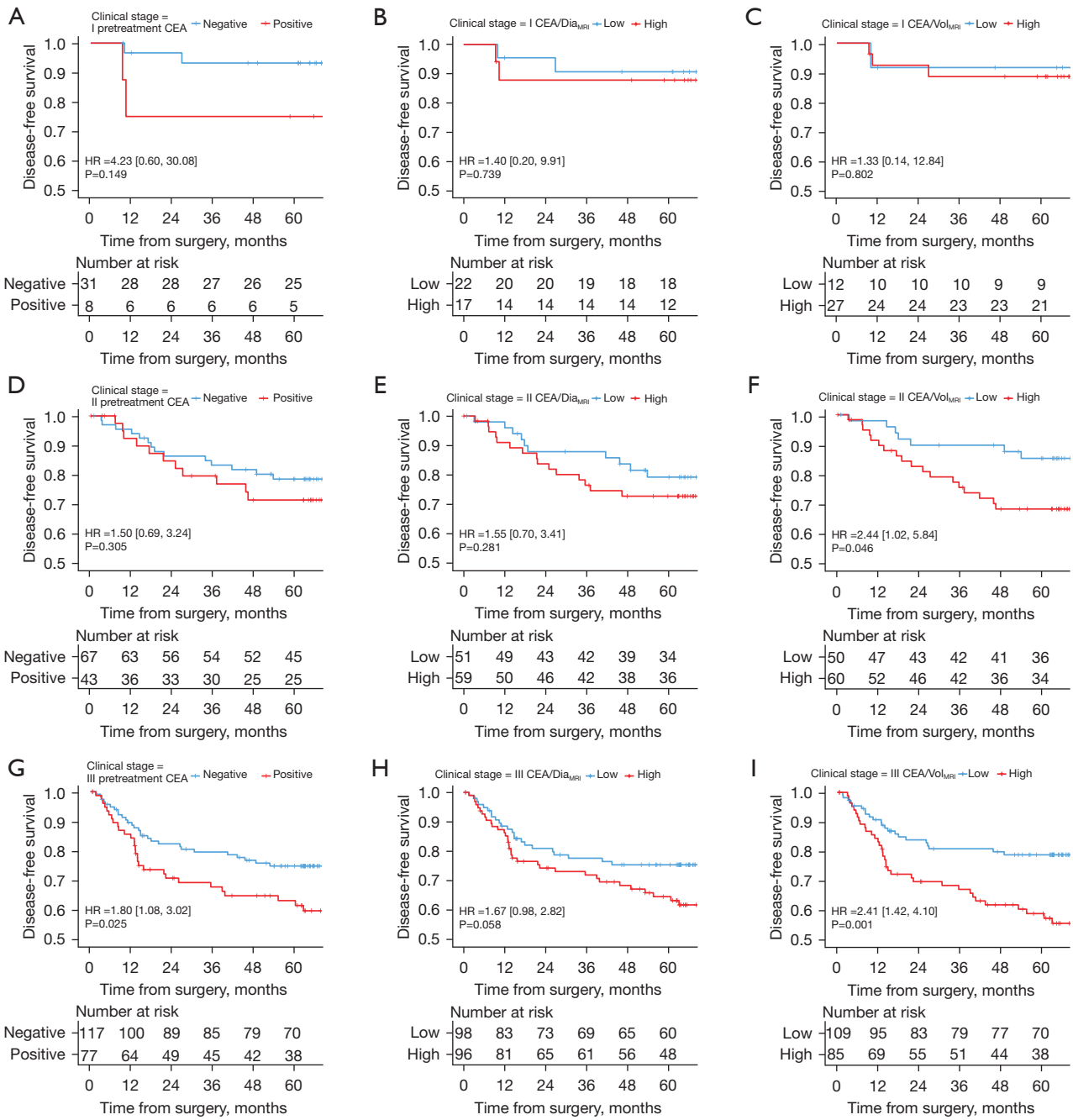

Figure 3 The Kaplan-Meier curves of DFS according to clinical stage and pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (A-C) The Kaplan-Meier curves of DFS are shown for clinical stage I patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (D-F) The Kaplan-Meier curves of DFS are shown for clinical stage II patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (G-I) The Kaplan-Meier curves of DFS are shown for clinical stage III patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. P values were calculated using two-sided log-rank test. The data in parentheses were 95% confidence interval. CEA, carcinoembryonic antigen; HR, hazard ratio; Dia$_{MRI}$, MRI tumor diameter; MRI, magnetic resonance imaging; Vol$_{MRI}$, MRI tumor volume; DFS, disease-free survival.

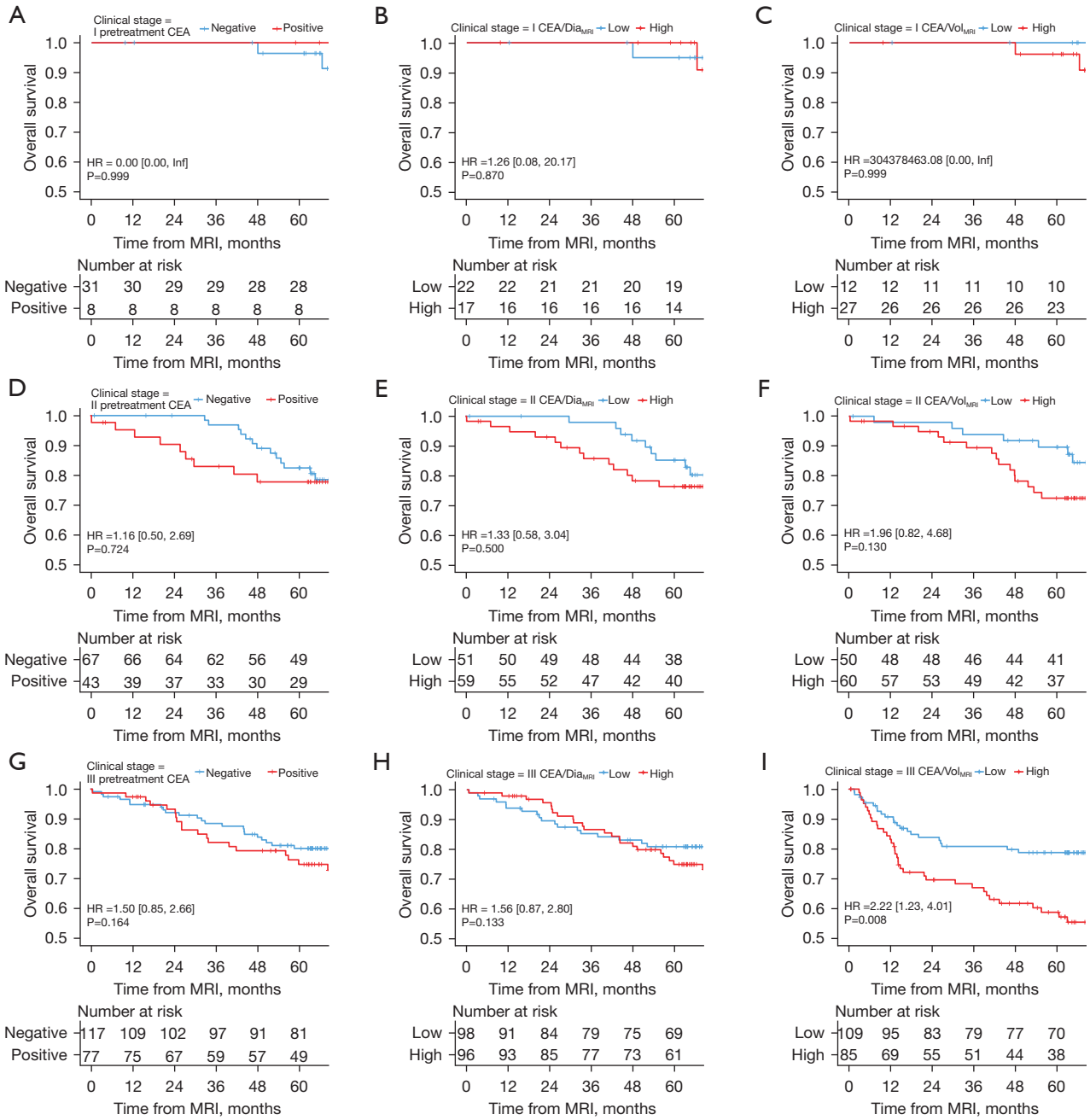

Figure 4 The Kaplan-Meier curves of OS according to clinical stage and pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (A-C) The Kaplan-Meier curves of OS are shown for clinical stage I patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (D-F) The Kaplan-Meier curves of OS are shown for clinical stage II patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. (G-I) The Kaplan-Meier curves of OS are shown for clinical stage III patients according to pretreatment CEA, CEA/Dia$_{MRI}$, and CEA/Vol$_{MRI}$. P values were calculated using two-sided log-rank test. The data in parentheses were 95% confidence interval. CEA, carcinoembryonic antigen; HR, hazard ratio; Inf, infinite; MRI, magnetic resonance imaging; Dia$_{MRI}$, MRI tumor diameter; Vol$_{MRI}$, MRI tumor volume; OS, overall survival.

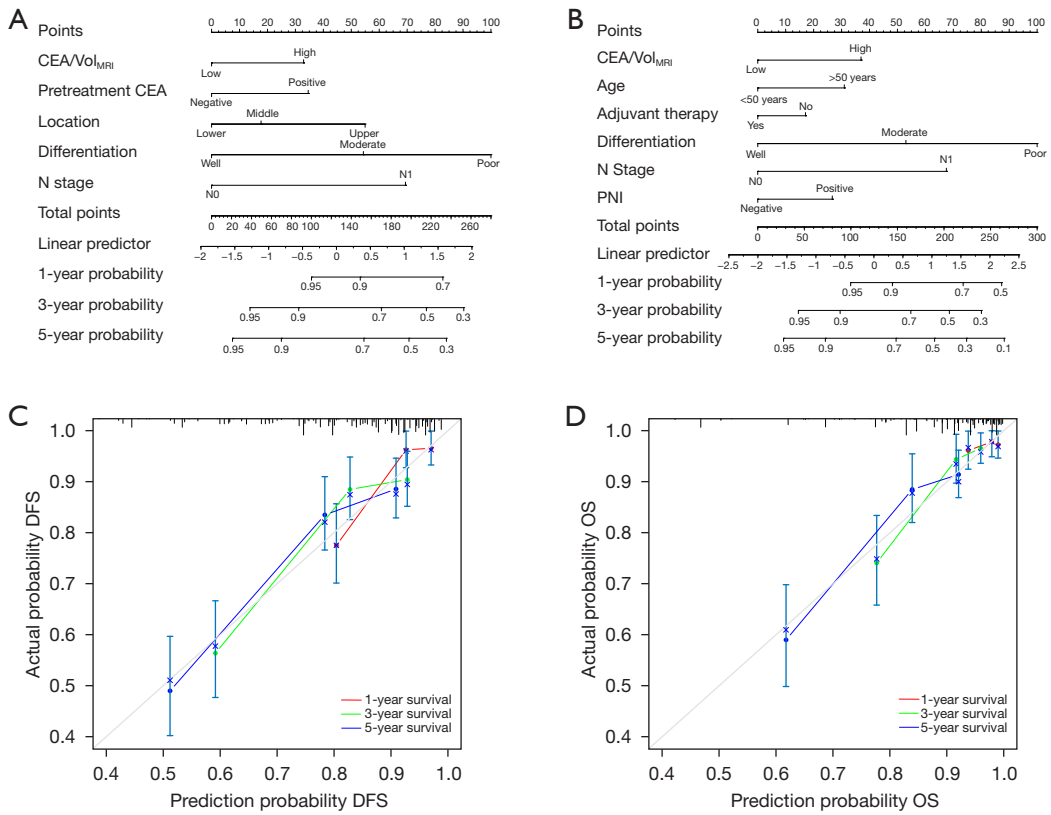

Figure 5 The nomograms and calibration curves of DFS and OS. (A) The nomogram for estimating DFS. (B) The nomogram for estimating OS. (C) The calibration curve for nomogram to estimate DFS. (D) The calibration curve for nomogram to estimate OS. CEA, carcinoembryonic antigen; Vol$_{MRI}$, MRI tumor volume; MRI, magnetic resonance imaging; N stage, nodal stage; PNI, perineural invasion; DFS, disease-free survival; OS, overall survival.

Survival according to CEA/Vol$_{MRI}$

The survival analysis revealed a significant decrease within 5-year DFS (81.5% *vs.* 66.7%, P=0.001) and OS (85.8% *vs.* 76.4%, P=0.008) in high- and low-risk patients according to CEA/Vol$_{MRI}$. The 1- to 5-year DFS and OS for the high CEA/Vol$_{MRI}$ group and low CEA/Vol$_{MRI}$ group are presented in Table S3.

Nomogram and predictive performance

Table S4 shows the results of stepwise Cox regression determined AIC based on significant clinicopathologic factors. Concerning DFS, CEA/Vol$_{MRI}$, pretreatment CEA, location, differentiation, and N stage were finally retained to nomogram for predicting DFS (*Figure 5A*). CEA/Vol$_{MRI}$, age, adjuvant therapy, differentiation, N stage, and PNI were finally retained to nomogram for predicting OS by using stepwise Cox regression (*Figure 5B*). The calibration curves for DFS and OS at 1-, 3-, and 5-year showed great agreement between predicted probabilities and actual probabilities (*Figure 5C*,*5D*).

The C-index and AUCs for predicting DFS and OS are shown in Table S5. The nomogram for predicting DFS demonstrated a C-index of 0.72 (95% CI: 0.68–0.79), with AUCs of 0.80 (95% CI: 0.72–0.90) at 1-year, 0.75 (95% CI: 0.69–0.83) at 3-year, and 0.76 (95% CI: 0.71–0.83) at 5-year. The nomogram for predicting OS demonstrated a C-index of 0.73 (95% CI: 0.68–0.80), with AUCs of 0.68 (95% CI: 0.66–0.91) at 1-year, 0.81 (95% CI: 0.75–0.89) at 3-year, and 0.76 (95% CI: 0.71–0.84) at 5-year. The nomogram incorporating CEA/Vol$_{MRI}$ showed good performance in predicting DFS and OS.

Discussion

Early-stage (stage I) and locally advanced (stages II–III) RC

account for approximately 25% and 60% of RC respectively, with about 15% to 50% 5-year recurrence rates (29). Currently, the prognostic evaluation for RC heavily relies on pathology, posing difficulties in preoperative risk stratification and pretreatment decision-making (6). CEA is a commonly used biomarker for tumor detection, prognostic evaluation, and follow-up in RC. Nevertheless, it is important to note that the limitations in sensitivity and specificity restrict its potential to improve patient outcomes (11,26). In our study, we explored the prognostic value of pretreatment CEA/Vol_{MRI} (CEA to MRI tumor volume) and found that CEA/Vol_{MRI} was superior to CEA, CEA/Dia_{path} (CEA to pathological tumor diameter), and CEA/Dia_{MRI} (CEA to MRI tumor diameter) in stratifying postoperative recurrence and death risk.

CEA is a macromolecular glycoprotein associated with cell adhesion, proliferation, and migration (30). Elevated CEA indicates increased proliferation and invasiveness of tumor cells, suggesting a poor prognosis (26). Previous studies have shown that CEA remains an independent prognostic factor for DFS and OS in patients with RC (31,32). However, approximately 70% of RC patients do not have elevated serum CEA levels (33). Moreover, previous studies revealed that serum CEA correlates to various confounding factors such as age, smoking, and tumor diameter (34,35). Li *et al.* and Cai *et al.* identified that the CEA/tumor diameter (measured on postoperative specimens) is a more reliable predictor of DFS and OS in patients with CRC (23,24). In our study, we confirmed that patients with high CEA/Dia_{path} encounter unfavorable outcomes. In addition, our study further demonstrated that the prognostic value of CEA/Dia_{MRI} measured on pretreatment MRI was not inferior to CEA/Dia_{path} measured on postoperative specimens (DFS: HR =1.63 *vs.* HR =1.51, OS: HR =1.50 *vs.* HR =1.29).

Tumor volume has been proven to be an effective indicator for evaluating treatment response and predicting prognosis (36-38). Jiang *et al.* exemplified that for early-stage RC, a tumor volume <18 cm^3 has exhibited a significant association with improved recurrence-free survival (HR =0.473) and local recurrence-free survival (HR =0.417) (39). Han *et al.* also found that MR volumetric measurement helps predict DFS in patients with local advanced RC (40). Moreover, tumor volume provides a more accurate characterization of the size, morphology, and growth of the whole tumor compared to tumor diameter (25). Therefore, we further explored the prognostic value of the ratio of CEA to tumor volume and compared it to the ratio of CEA to tumor diameter. Our results showed that CEA/Vol_{MRI} as an independent prognostic factor was superior to CEA, CEA/Dia_{path}, and CEA/Dia_{MRI} in predicting DFS (HR =2.04; P=0.001) and OS (HR =1.91; P=0.008) in RC patients. After adjusting for patient-related and tumor-related factors using multivariate analysis, the highest HR and the smallest P value were observed in distinguishing high-risk from low-risk patients according to CEA/Vol_{MRI} in terms of DFS (HR =1.83; P=0.010) and OS (HR =1.67; P=0.048). These results demonstrated that CEA density, which represents the proportionate CEA per unit volume, is superior to CEA and CEA/tumor diameter in evaluating prognosis and indicating tumor invasiveness.

In the subgroup analysis, our study demonstrated that CEA/Vol_{MRI} not only stratified high death risk individuals (HR =2.06; P=0.024) within the CEA-negative population but also stratified low-recurrence risk individuals (HR =2.50; P=0.038) within CEA-positive population. Subanalysis of patients with stage II or III RC revealed that CEA/Vol_{MRI} was effective in distinguishing between high-risk and low-risk patients in terms of DFS (P<0.05) and OS (P<0.05). These findings further indicated that it is possible to utilize pretreatment CEA/Vol_{MRI} to make patient-individualized choices for interventions.

Nomograms can provide a visual representation of clinical predictive models and help clinicians evaluate prognosis simply and rapidly (41). In this study, we developed two nomograms using bidirectional stepwise Cox regression, and CEA/Vol_{MRI} was finally retained in the two nomograms for predicting DFS and OS determined by AIC. The results for C-index, AUCs, and calibration curves demonstrated that both nomograms had good predictive and discriminative abilities. These results revealed that pretreatment CEA/Vol_{MRI} could serve as an efficacious supplementary biomarker for prognostic evaluation in RC patients.

This study has several limitations. Firstly, it was a retrospective study, that might inevitably lead to selective bias. Additionally, we did not perform independent external validation to verify the performance, further multi-center study containing external validation cohorts is going to be done. Thirdly, our study focused on patients who did not receive neoadjuvant therapy, for tumor shrinkage after neoadjuvant therapy making it challenging to consider tumor size at two time points simultaneously.

Conclusions

In conclusion, patients with high pretreatment CEA/

Vol_{MRI} measurements had a significantly worse prognosis. CEA/Vol_{MRI} as a prognostic risk factor was superior to CEA, CEA/Dia_{path} CEA/Dia_{MRI}. Pretreatment CEA/Vol_{MRI} facilitated risk stratification and treatment decision-making.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-683/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-683/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of The Sixth Affiliated Hospital of Sun Yat-sen University (No. 2023ZSLYEC-109). Individual consent for this retrospective study was waived.

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