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Can we optimize CEA as a response marker in rectal cancer?

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ABSTRACT

Background and aim: carcinoembryonic antigen (CEA) is a biomarker commonly used in colorectal cancer. However, its prognostic value is still controversial. Recent studies demonstrate that CEA produced locally by tumor cells has a higher prognostic value compared to serum CEA. This study aimed to determine whether there was an association between the CEA/tumor size ratio (CEA/ExT) and the pathological tumor response in patients with rectal adenocarcinoma (ADC), who underwent neoadjuvant chemoradiotherapy (N-CRT), followed by surgical tumor resection.

Methods: a retrospective study was performed of rectal ADC patients who underwent N-CRT followed by curative surgery between March/2012 and October/2017. CEA and tumor extension for pre-treatment CEA/ExT calculation and the pathological response in the surgical specimen after treatment were analyzed.

Results: eighty-nine patients were included, 60.7 % were male and the mean age was 63.8 ± 10.42. There was a good response to N-CRT in 41.6 % of the patients, tumor downstaging occurred in 83.1 % and a complete pathological response in 23.6 % of cases. The average CEA/ExT was 2.01 ng/ml/cm. In the univariate analysis, higher CEA/ExT values were related to a lower frequency of pathological response (p = 0.04)

and to a lower frequency of tumor downstaging (p = 0.02). In the multivariate analysis, CEA/ExT was independently related to tumor downstaging (OR: 0.72; 95 % IC: 0.53-0.98, p-0.036).

Conclusions: lower pre-treatment CEA/ExT values seem to be associated with tumor downstaging and this parameter may be a promising predictor of a more favorable response in patients with rectal ADC undergoing treatment with N-CRT.

Keywords: Rectal neoplasm. Carcinoembryonic antigen. Chemoradiotherapy. Surgical oncology. Prognosis.

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. The incidence of rectal cancer increases with age, with a median diagnosis around 70 years in most European countries (1-4). Neoadjuvant chemoradiotherapy (N-CRT) followed by surgical resection with total mesorectal excision (TME) is the standard treatment for locally advanced rectal adenocarcinoma. This therapeutic approach leads to a decrease in the rate of recurrence, particularly in tumors of the middle and lower rectum and a higher rate of complete pathological responses (CPR) (5-8). The response to N-CRT varies widely between individuals and approximately 20 % of patients achieve a CPR, defined as ypT0N0M0 or the absence of viable tumor cells in the surgical anatomical specimen (8-11).

Given that patients with a CPR have a better prognosis and their treatment strategy may be different, the ability to predict the tumor response to N-CRT is of great clinical importance (9,10). Several studies have identified clinical factors and biomarkers that predict this response, namely small tumor size, low N staging and low pre-treatment serum carcinoembryonic antigen (CEA) level (9,10,12). Knowledge of these factors can be useful to tailor treatment to the patient and predict outcomes.

CEA is an oncofetal glycoprotein that may increase in certain carcinomas and is a commonly used biomarker in colorectal cancer. The serum levels of CEA have a good correlation with tumor development and the appearance of liver or lung metastases. However, controversy exists regarding the insufficient prognostic value of preoperative

serum CEA alone in rectal cancer (13-16). Some studies demonstrate that the direct measurement of CEA produced and secreted by the tumor cells is an independent prognostic factor for the CRC and is more important than serum CEA (17).

Du Cai et al. (13) tried to use the combination of preoperative serum CEA and the maximum tumor diameter in rectal cancer to correct the CEA level, which may better reflect the malignancy of rectal cancer. This study concluded that preoperative serum CEA/maximum tumor size ratio (CEA/ExT) is an independent prognostic factor for patients with stage I-III rectal cancer (13).

There seems to be a great advantage of CEA/ExT ratio as it reflects the intra-tumor CEA concentration without omission of the tumor extension. Thus, it will be much more accurate than a classic serum CEA test. This implies that adjusting the confounding effect of tumor size may improve the prognostic value of CEA and might be a better marker to assess the biological activity of the tumor and refine the insufficient prognostic value of serum CEA. In this sense, the authors intended to combine preoperative serum CEA levels and the maximum tumor diameter to correct the CEA level, so that it reflects the ability of tumor cells to secrete CEA and better reflects the malignancy of rectal cancer.

This study aimed to determine the pre-treatment serum CEA/maximum tumor diameter ratio (CEA/ExT) and relate this value with tumor response, in patients with stage II-III rectal adenocarcinoma (ADC) undergoing N-CRT, followed by surgical tumor resection. This new ratio was applied as it intends to represent the CEA level adjusted by tumor size, to investigate the prognostic impact in patients with rectal cancer.

MATERIALS AND METHODS

A retrospective cohort study was performed that included 175 patients with carcinoma of the rectum, admitted to the Digestive Oncological Disease clinic between March 2012 and October 2017. All adult patients with stage II or III adenocarcinoma of the rectum who underwent neoadjuvant chemoradiotherapy followed by surgical resection were included. Data were collected from patients' clinical files and the study project was previously submitted and approved by the hospital Ethics Committee.

Pre-treatment variables were demographic, clinical, serum CEA and tumor characteristics (location, extension, clinical staging measured by magnetic resonance imaging [MRI] and degree of differentiation). The CEA/Ext was defined as the ratio to CEA level to the maximum tumor diameter that was measured on MRI before treatment (N-CRT and surgical resection). The optimal discriminator value for the CEA/tumor size was based on the cut-off of 2.429 (literature cut-off [13]) to divide the cohort into two groups: high CEA/ExT group and low CEA/ExT group.

The patients underwent *standard* neoadjuvant chemoradiotherapy protocols, with external, conventional or intensity-modulated radiation therapy (IMRT), with 45Gy in 25-28 fractions and a boost with 5.4Gy in three fractions (five weeks treatment). During this period, chemotherapy was combined with radiotherapy, with 5-fluorouracil IV, 225 mg/m^2/day in continuous infusion, or capecitabine 825 mg/m^2 orally twice a day, according to the choice of the oncologist via clinical evaluation. Subsequently, the patients underwent surgery, protectomy with total excision of the mesorectum.

Post-treatment (after N-CRT and surgical resection) variables included tumor response characteristics analyzed in a surgical specimen such as pathological stage and degree of tumor regression, using the Mandart classification. GRT1 and GRT2 were a good response and GRT3, GRT4 and GRT5 were a poor response.

The main clinical outcomes analyzed were tumor downstaging (TD), which was defined as a pathological staging (ypT/ypN) lower than clinical staging (cT/cN); complete pathological response (CPC), which was defined as the absence of tumor/ganglionic metastasis in the surgical specimen (ypT0, N0 or GRT1); and disease recurrence (DR), locoregional or metastatic and the occurrence of death. In addition, disease-free survival (DFS), which was defined as the time in months from surgery to disease recurrence, and overall survival (OS), which was defined as the time in months from surgery to death, were also investigated.

In the statistical analysis, the data were analyzed using the program Software Package for the Social Sciences (SPSS for Windows, version 24.0). A p-value < 0.05 was considered as statistically significant.

A descriptive analysis was performed using frequencies for categorical variables and measures of central tendency, such as the mean or median, as well as dispersion

measures, such as standard deviation or interquartile range. The intergroup comparisons of the demographic, clinicopathological and tumor characteristic variables were performed using the two independent samples t-test or Mann-Whitney U test (if non-normal distribution) for continuous variables, and the Chi-squared test and Fisher's exact test for discrete variables. Binary logistic regressions were applied to construct multivariable prediction models and to identify independent risk factors for the outcome, after a univariate analysis test for individual relevant variables (variables with a p-value < 0.05) to integrate into the model. Results are reported as odds ratios with 95 % confidence intervals. The Kaplan-Meier method and log-rank test were used to plot the survival curve and to compare the survival data.

RESULTS

Of the 175 cases of patients with carcinoma of the rectum, 89 patients met the inclusion criteria. Eighty-six patients were excluded: 16 who received a short regimen with only neoadjuvant radiotherapy, 14 who went directly for surgery and did not receive neoadjuvant treatment, 13 had insufficient data, eleven were referred for palliative care, nine were followed at another institution, nine were awaiting surgery, eight died during staging and six refused treatment.

Of the 89 patients included, the majority were male (n = 54; 60.7 % of cases), with a median age of 63.8 ± 10.42 years, and the majority (n = 71; 79.8 %) had an ECOG performance status of zero. More than half of the patients had a tumor extension of less than 5 cm (n = 51; 57.3 %), almost half were tumors in the lower rectum (n = 39; 43.8 %) and mostly well-differentiated tumors (n = 76; 85.4 %), in stage III (n = 79; 88.8 %) (Table 1).

The median CEA values were 4.2 ng/ml, with 38.3 % (n = 34) of the patients having high initial values of this tumor marker (CEA > 5 ng/ml). The mean CEA/ExT was 2.01 ng/ml/cm (Table 1). Patients underwent surgery mostly between 6-10 weeks after RQT-NA (58.4 %).

A good response was observed to neoadjuvant chemoradiotherapy (GRT1 and GRT2 in Mandart classification) in 41.6 % of patients, tumor downstaging occurred in 83.1 % (tumor progression in 5.4 %) and there was a complete pathological response in 23.6 %

of patients. Approximately 28 patients (31.5 %) had tumor recurrence, either local or metastatic, and a mean recurrence-free time of 37 ± 18.6 months. Twenty-one of the patients (23.6 %) died and the mean overall survival was 40 ± 17.6 months.

Of all the variables analyzed, there was only a statistically significant association between the lowest levels of CEA/ExT and the outcome. As shown in table 2, the high CEA/ExT group (> 2.429) had TD less frequently (p-0.02) and less CPR (p-0.04) compared to the low CEA/ExT group. Similarly, as shown in table 3, patients in the high CEA/ExT group had DR more frequently and a higher death rate compared with patients with low CEA/ExT group (p-0.03). Demographic, clinical, serum CEA values and tumor characteristics (location, extension, clinical staging, degree of differentiation) did not differ significantly between the two groups analyzed.

Kaplan-Meier curves showed (Fig. 1) that there was no difference between the groups (high and low CEA/ExT groups) regarding the DFS or OS with statistical significance (p > 0.05). In the multivariate analysis, the low CEA/ExT group was independently related with the TD (OR: 5.6; 95 % CI 1.14-26.9, p-0.034), but not to the CPR (OR: 1.2; 95 % CI 0.27-5.25, p-0.80), DR (OR: 0.34; 95 % CI 0.09-1.17, p-0.08) or death (OR: 0.30; 95 % CI 0.74-1.22, p-0.09).

DISCUSSION

Colorectal cancer is the third most commonly diagnosed cancer and one of the leading causes of cancer-related mortality in men and women worldwide. Rectal cancer accounts for approximately 30 % of colorectal cancer and is associated with major challenges for treatment options and a worse clinical outcome (1-4). N-CRT followed by total mesorectal excision has become the standard of care for patients with clinical stages II and III rectal cancer. However, the response to this treatment varies among individuals and those with CPR are associated with a better outcome. For those patients with CPR, *a watch-and-wait* policy is safe and feasible (8-11). However, selecting optimal treatments for individuals remains a great challenge due to the lack of effective biomarkers. Thus, the ability to predict the response to neoadjuvant CRT is of great clinical importance (9,10).

The present study was developed to identify if the serum CEA/ExT had a prognostic

impact on patients with stage II-III rectal adenocarcinoma, who underwent N-CRT, followed by surgical tumor resection. The characteristics of our cohort are in line with the global trends in rectal carcinoma, being mostly made up of males, with an average age close to that described in the literature. Regarding the characteristics of the tumor, the predominance of well-differentiated carcinomas, less than 5 cm in length and located in the lower rectum are also consistent with the descriptions in the main series (2).

The proportion of patients with high serum CEA values (n = 34, 38.2 %) was relatively similar to those in most of the current literature, in the range of 17-47 % (19). The serum CEA level is widely used as a tumor biomarker in patients with colorectal cancer. Pretreatment CEA level is useful to assess prognosis and postoperative CEA testing is used for the early detection of recurrent disease (13,18). However, controversy still exists regarding the prognostic value of the absolute preoperative serum CEA level in colorectal cancer (13-16). CEA evaluates the biological activity of malignancies, but biological activity will also be affected by tumor volume (13). When the tumor grows with proliferating adenocarcinoma cells, there is more expression of CEA and serum CEA levels will increase (13). Therefore, tumor size may be a confounding factor that should be minimized (13).

The most frequent interval between the end of the RQT-NA and the surgical intervention varied between six to ten weeks. This variation originated from the protocol used at our institution, which indicates that surgery should be performed in the 8th week, also considering the restrictions of the clinical practice and the scheduling limitations. Currently, the state-of-the-art indicates that surgery should be performed between eight to 12 weeks after neoadjuvant RQT (8).

In our series, DT occurred in 83.1 % (n = 74) of cases. There was a good pathological response to treatment (GRT1 or GRT2 in the Mandart classification) in 41.6 % (n = 37) of the patients and there was PRC in 23.6 % (n = 21) of patients. These are excellent results and very similar to most series (5,9).

The mean CEA/ExT was 2.01 ng/ml/cm and this variable had a statistically significant association with all the outcomes: DT, RPC, DR and death, contrary to the serum CEA levels. In our sample, CEA/ExT was an independent predictive factor for the occurrence

of DT, with a significance level < 0.05. According to the literature, this is the first study to evaluate the prognostic value of pre-treatment CEA/ExT for stage II to III rectal cancer, undergoing N-CRT followed by surgical tumor resection. However, there is a recent study by Du Cai et al. that reviewed stage I to III rectal cancer patients who underwent a curative tumor resection, but not submitted to N-CRT. In this study, univariate and multivariate analyses showed that CEA/ExT was independently associated with OS and DFS, while absolute serum CEA was not. Furthermore, patients with a high CEA/ExT (over 2.429 ng/ml/cm) had a significantly worse five-year OS and DFS (13).

Tumor size has been used in other studies, such as the one by Jun KH et al., to demonstrate the prognostic value. This study demonstrated that tumor size, especially the maximum horizontal tumor diameter, was a valuable prognosticator in gastric cancer. Furthermore, Tayyab M et al. showed a direct relationship between tumor volume in rectal cancer and overall survival (20,21).

Other studies have demonstrated the insufficient sensitivity of serum CEA to be used alone, such as a recent study that indicated that postoperative tissue CEA rather than serum CEA is an independent prognostic factor in stage I to III CRC (17). This study showed that we should pay more attention to the local CEA produced by tumor cells rather than the overall serum CEA level (13,17). Using tumor size to adjust the prognostic value of a tumor marker is not pioneering. Volume-adjusted prostate-specific antigen has been widely studied as a useful marker in prostate cancer or tumor- infiltrating CD8+ T-cell density in oral squamous cell carcinoma (22-24). However, the combination of CEA levels and tumor size as a prognostic factor for rectal cancer remains unexplored.

Despite this, CEA/ExT showed a statistically significant association with DT, RPC, DR and OS in the univariate analyses in our study. In the multivariate analyses, the CEA/ExT was an independent predictive factor only for the occurrence of DT, but not with RPC, OS and DFS. These results may be related to the need to optimize the sample, such as increasing the number of the samples, performing prospective and controlled studies and eventually trying to use tumor volume instead of its diameter in the formula.

In our study, as in that of Du Cai et al. (13), we defined the CEA/Ext as the ratio of the CEA level to the maximum tumor diameter, which was measured by MRI before treatment (N-CRT and surgery resection). However, the maximum tumor diameter is not an accurate indicator of tumor volume. For example, Huo et al. used the spherical formula $(4 \times \pi \times \text{radius}^3)/3$ to represent tumor volume because they assumed that pulmonary tumors were spherical (25). Rectal tumors do not have a fixed geometric shape, so it is difficult to predict a way to represent the tumor and to calculate its volume. This difficulty may represent a limitation of our study. Alternatively, the careful delineation of the tumor boundary combined with specific software may provide a more accurate estimation of tumor volume.

Finally, we consider that the study is subject to the limitations and selection trends inherent to the retrospective nature of the analysis. The sample size and the lack of control over the preoperative evaluation of the tumor and histological examination of the anatomical specimen may compromise the results. A large-scale prospective study and longer follow-up are needed to further validate our conclusions.

We believe that it is extremely important to carry out studies to identify biomarkers capable of predicting PRC at an early stage of diagnosis. This will aid to select patients with rectal carcinoma who may benefit from N-CRT and consequently choose the most appropriate treatment: assume the “watch and wait” strategy, prolong surgery interval, or reduce toxicity associated with ineffective chemoradiotherapy.

In summary, preoperative CEA/ExT may play an important role in the prognosis of patients with stage II-III rectal ADC, who undergo N-CRT followed by surgical tumor resection, which may influence the decision-making process for a specific treatment regimen.

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Table 1. Sample characteristics regarding the demographic, clinical and tumor data analyzed

Variable	*n = 89 (%)*
Gender	
Male	54 (60.7 %)
Female	35 (60.7 %)
Age - mean (SD)	63.83 (10.42)
Performance status	
0	71 (79.8 %)
1	9 (10.1 %)
Omitted	9 (10.1 %)
Clinical stage	
II	10 (11.2 %)
III	79 (88.8 %)
Tumor location	
Lower rectum	39 (43.8 %)
Middle rectum	30 (33.7 %)
Superior rectum	20 (22.5 %)
Tumor extension	
≤ 5 cm	51 (57.3 %)
> 5 cm	29 (32.6 %)
Degree of differentiation	
Well differentiated	76 (85.4 %)
Moderately differentiated	12 (13.5 %)
Omitted	1 (1.1 %)
CEA (ng/ml) - median (IQR)	4.2 (1.7-8)
CEA/ExT (ng/ml/cm) - mean (SD)	2.01 (4.88)

Table 2. Univariate analysis of demographic, clinical and tumor characteristics to predict tumor downstaging and complete pathological response

Variable	*Tumor downstaging Yes/No*	*p*	*Complete pathologic response Yes/No*	*p*
Gender				
Male (n = 54)	48 (64.9 %)/6 (42.9 %)	0.126	14 (60.7 %)/40 (59.7 %)	0.567
Female (n = 35)	26 (35.1 %)/8 (57.1 %)		7 (33.3 %)/27 (40.3 %)	
Age (mean)	64.7/58.3	0.068	65.8/63.0	0.234
Performance status				
0 (71)	60 (81.1 %)/11 (78.6 %)	0.492	16 (76.2 %)/55 (82.1 %)	0.875
1 (9)	6 (8.1 %)/2 (14.3 %)		2 (6.5 %)/6 (9 %)	
Clinical stage				
II (10)	8 (10.8 %)/2 (14.3 %)	0.657	4 (19 %)/6 (9 %)	0.241
III (79)	66 (89.2 %)/12 (85.7 %)		17 (81 %)/61 (91 %)	
Tumor location				
Lower rectum (39)	32 (43.2 %)/7 (50 %)	0.084	10 (47.6 %)/29 (43.3 %)	
Middle rectum (30)	23 (31.1 %)/7 (50 %)		7 (33.3 %)/23 (34.3 %)	0.925
Superior rectum (20)	19 (25.7 %)/0		4 (19 %)/15 (22.4 %)	
Tumor extension				
≤ 5 cm (51)	41 (55.4 %)/9 (64.3 %)	0.083	14 (66.7 %)/36 (53.7 %)	0.413
> 5 cm (29)	28 (37.8 %)/1 (7.1 %)		5 (23.8 %)/24 (35.8 %)	
Degree of differentiation				
Well differentiated (76)	63 (85.1 %)/12 (85.7 %)	0.953	18 (85.7 %)/57 (85.1 %)	0.940
Moderately differentiated (12)	10 (13.5 %)/2 (14.3 %)		3 (14.3 %)/9 (13.4 %)	
CEA (ng/ml)				
≤ 5 (47)	42 (56.8 %)/5 (35.7 %)	0.22	12 (57.1 %)/35 (52.2 %)	0.61
> 5 (34)	27 (36.5 %)/7 (50 %)		7 (33.3 %)/27 (40.3 %)	
CEA/ExT (ng/ml/cm)				
≤ 2.429 (59)	54 (73 %)/5 (35.7 %)	0.02	14 (66.7 %)/45 (67.2 %)	0.04
> 2.429 (14)	11 (14.7 %)/3 (21.4 %)		3 (14.3 %)/11 (16.4 %)	

Table 3. Univariate analysis of demographic, clinical and tumor characteristics to predict disease recurrence and death

Variable	*Disease recurrence* *Yes/No*	*p*	*Death* *Yes/No*	*p*
Gender				
Male (n = 54)	19 (67.9 %)/35 (57.4 %)	0.41	14 (66.7 %)/37 (58.7 %)	0.58
Female (n = 35)	9 (32.1 %)/26 (42.6 %)		7 (33.3 %)/26 (41.3 %)	
Age (mean)	64.4/64.6	0.40	63.8/63.8	0.96
Performance status				
0 (71)	22 (78.6 %)/49 (80.3 %)	0.48	14 (66.7 %)/53 (84.1 %)	0.17
1 (9)	4 (14.3 %)/5 (8.2 %)		4 (19 %)/5 (7.9 %)	
Clinical stage				
II (10)	3 (10.7 %)/7 (11.5 %)	0.32	3 (14.3 %)/5 (7.9 %)	0.12
III (79)	25 (89.3 %)/54 (88.5 %)		18 (85.7 %)/58 (92.1 %)	
Tumor location				
Lower rectum (39)	18 (64.3 %)/21 (34.4 %)	0.06	14 (66.7 %)/23 (36.5 %)	
Middle rectum (30)	5 (17.9 %)/25 (41 %)		3 (14.3 %)/24 (38.1 %)	0.90
Superior rectum (20)	5 (17.9 %)/15 (24.6 %)		4 (19 %)/16 (25.4 %)	
Tumor extension				
≤ 5 cm (51)	16 (57.1 %)/35 (57.4 %)	0.58	1 (52.4 %)/36 (57.1 %)	0.54
> 5 cm (29)	7 (25.0 %)/22 (36.1 %)		5 (23.8 %)/23 (36.5 %)	
Degree of differentiation				
Well differentiated (76)	26 (92.9 %)/50 (82.0 %)	0.47	20 (95.2 %)/53 (84.1 %)	0.46
Moderately differentiated (12)	2 (7.1 %)/10 (16.4 %)		1 (4.8 %)/9 (14.3 %)	
CEA (ng/ml)				
≤ 5 (48)	34 (55.7 %)/14 (50 %)	0.56	10 (47.6 %)/37 (58.7 %)	0.53
> 5 (34)	22 (36.1 %)/12 (42.9 %)		9 (42.9 %)/24 (38.1 %)	
CEA/ExT (ng/ml/cm)				
≤ 2.429 (60)	18 (64.3 %)/42 (68.9 %)	0.03	14 (66.7 %)/45 (71.4 %)	0.03
> 2.429 (14)	4 (14.3 %)/10 (16.4 %)		1 (4.8 %)/12 (19 %)	

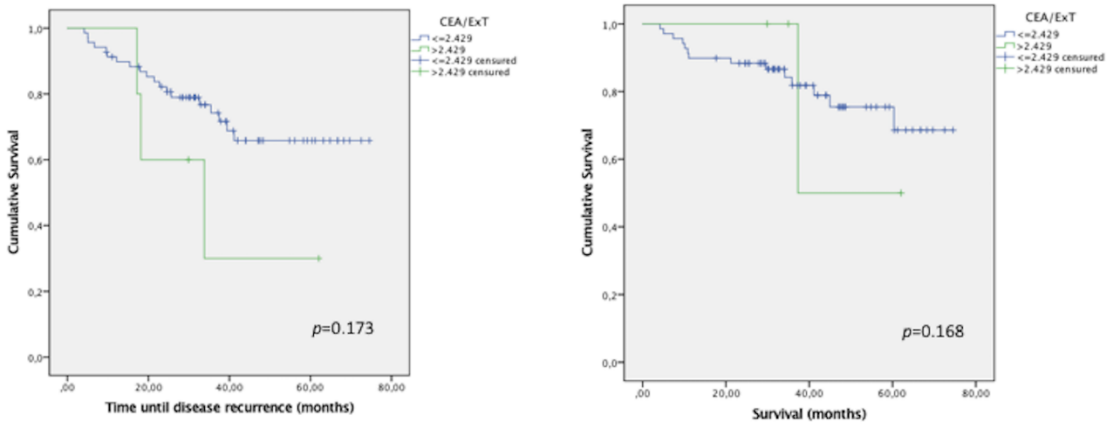

Fig. 1. Kaplan-Meier curves.