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The utility and prognostic value of CA 19-9 and CEA serum markers in the long-term follow up of patients with colorectal cancer: A single-center experience over 13 years

PURPOSE: *To evaluate utility and prognostic value of serum CA 19-9 levels in relation to serum CEA levels in the long-term follow up of patients with colorectal cancer (CRC)*
METHODS: *A total of 315 patients with CRC who were treated over a 13-year period were included in this retrospective study. Data on tumor characteristics, CEA and CA 19-9 levels were recorded. Survival analysis was performed with respect to marker status, while receiver operating characteristics (ROC) curve was plotted to determine the performance of CEA in predicting survival during follow up with calculation of area under curve (AUC) and cut-off value via ROC analysis.*
RESULTS: *Advanced T stage (T3-4, p<0.001), presence of intramural invasion (p=0.019), lymphatic invasion (p=0.003) and larger tumor volume (p=0.02) were associated only with high CEA levels on admission, while poor histological differentiation (p=0.036) was only associated with high CA 19-9 levels on admission. Presence of normal CEA and CA 19-9 levels was associated with the longest survival time (131.6 and 46.8 months, respectively, p<0.001 for each) and 5-year OS rate of 90.5%, while ROC analysis revealed CEA levels >11 (AUC (95% CI): 0.636 (0.580-0.690), p<0.001) to be a potential marker of poor survival with a sensitivity of 75.0% and specificity of 45.9%.*
Conclusion: In conclusion, our findings seem to indicate a weaker poor prognostic value of high CA 19-9 levels when used alone and strongly suggest combined use of CEA and CA 19-9 markers in prognostic assessment and risk-adapted follow-up surveillance in CRC patients.

KEY WORDS: CEA, CA 19-9, Colorectal cancer, Prognosis, Survival

Introduction

Colorectal cancer (CRC) is the most common digestive system malignancy and the leading causes of cancer-related mortality worldwide [1,2]. Although prognosis is favorable in patients with early stage (Stage I-II) CRC, rapid disease progression with dissemination to lymph nodes and distant metastasis is frequent being associated with significantly lower survival rate in patients with advanced CRC stages [3,4].
Accordingly, reliable diagnostic and prognostic biomarkers are considered essential for early screening and diagnosis of CRC, for identification of potential candidates of adjuvant systemic therapy based on the risk of metastatic relapse and for assessment of curative effect and the judgment of prognosis and survival [5-7].

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Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9) are the two widely used blood-based markers for surveillance and for monitoring response to treatment in CRC patients [8-11]. CEA has an established role as a convenient biomarker in diagnosis, treatment and surveillance in CRC [12,13] being recommended by the American Society of Clinical Oncology (ASCO) guidelines for the use in preoperative staging and treatment planning, as well as postoperative follow-up of CRC patients [14,15].

However, ASCO guidelines suggest that there is insufficient evidence for using CA 19-9 in CRC patients and therefore routine use of CA 19-9 is not recommended for screening, diagnosis, staging, or monitoring CRC [14,15]. Hence, while the utility of CA 19-9 as an indicator of prognosis and recurrence was reported in several studies [16-21], the clinical significance of CA 19-9 in terms of prognostic surveillance and outcome in CRC patients remains controversial [12,15,22-24].

Indeed, highly heterogeneous nature of CRC is considered to jeopardize the use of a single tumor marker as a stand-alone diagnostic test with sufficient sensitivity and/or specificity, while the limited data on the interaction between the biomarkers and the clinical parameters of CRC is considered to prevent the optimized use of biomarkers [7].

Besides, since the use of CEA alone has been documented to be insufficiently sensitive in recent studies, using a panel of tumor markers has been suggested to be effective approach for diagnosis and treatment outcomes in CRC patients [7,25]. Hence, addition of another marker such as CA 19-9 has been considered to improve prognostic value of CEA [13,25,26].

This study was therefore designed to evaluate utility and prognostic value of serum CA 19-9 levels in relation to serum CEA levels in a large cohort of CRC patients in the long-term follow up.

Materials and Methods

Study Population

A total of 315 patients (mean(SD) age: 62.0(13.8) years, 54.6% were males) with CRC who were treated in a tertiary center over a 13-year period from February 2006 to February 2019 were included in this retrospective study. Overall, 489 patients were operated due to CRC within the study period in our hospital, while the study population subjected to final analysis was composed of 315 patients with exclusion of 174 patients due to implementation of a palliative intervention (n=75), lost to follow up (n=36) and unavailability of data on admission marker levels (n=63). The study protocol was approved by local ethics committee (Date of Approval: 11/07/2019, Reference number/Protocol No: 2019-12/) and the study was conducted in accordance with the Declaration of Helsinki and its later amendments. Due to the retrospective design of the study, informed consent for study entry was not required.

Study Parameters

Data on patient demographics (age, gender), diagnosis (colon, rectal and synchronous), family history for CRC, previous history for other malignancy, tumor characteristics (localization, volume, TNM stage, histological differentiation, and invasion) and recurrence (local or systemic) were recorded in each patient. CEA and CA 19-9 levels were recorded on admission and during follow up. Marker status was categorized in three ways including a) CEA/CA 19-9 levels: normal/normal, high/normal, normal/high and high/high (first value for CEA and second value for CA 19-9 levels) b) combined CEA+CA-19-9 levels (normal: both markers are normal, high: any of the markers is high) and c) admission/follow up (first value for marker levels on admission and the second for follow up) and evaluated with respect to study parameters. Combined CEA and CA 19-9 assessment was performed in 191 patients. Survival analysis was also performed in the overall study population and with respect to admission and follow up marker status, while receiver operating characteristics (ROC) curve was plotted to determine the performance of CEA in predicting survival during follow up with calculation of area under curve (AUC) and cut-off value via ROC analysis.

CEA and CA 19-9 assay

Serum levels of CA 19-9 and CEA were measured via chemiluminescent immunoassay following the manufacturer's instructions (Roche Diagnostics Deutschland GmbH, Mannheim, Germany), while CEA ≥5 ng/mL (in smokers) or ≥2.5 ng/mL (in none-smokers) and CA 19-9 ≥37 ng/mL levels were regarded as elevated.

Follow up period

Follow up was based on routine outpatient visits (every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter) and involved laboratory tests (including serum CEA and CA 19-9), radioimaging (chest CT and abdominopelvic CT) every 3-6 months or every year in accordance with NCCN guidelines [27]. Peritoneal seeding was diagnosed intraoperatively in cases of stage IV disease, and postoperative recurrence as peritoneal carcinomatosis was diagnosed based on findings during reoperation for recurrence or abdominopelvic CT/PET CT findings indicating the presence of abnormal intraperitoneal nodules or peritoneal thickening.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). The normality of continuous variables was investigated by Shapiro-Wilk's test. Chi-square test (Fisher Exact test where available) was used for analysis of categorical variables. For comparison of two normally distributed groups Student t test was used. Non-parametric statistical methods were used for values with skewed distribution with use of Mann Whitney U test for comparison of two non-normally distributed groups and Kruskall-Wallis test for comparison of three non-normally distributed groups. For post Hoc comparisons, Bonferroni corrected Mann Whitney U test was used. Survival analysis was made via Kaplan Meier analysis and comparisons were made via Log-Rank test. ROC curve was plotted to determine performance of CEA levels on admission in prediction of survival with calculation of AUC values and ideal cut-off value via ROC analysis. Data were expressed as mean±standard deviation (SD), median (minimum-maximum), 95% confidence interval (CI) and percent (%) where appropriate.

Results

Patient Demographics and Clinicopathologic Characteristics

The mean patient age was 62.0 years (ranged, 23 to 103 years) and males composed 54.6% of study population. The diagnosis was colon cancer and rectal cancer in 50.2% and 43.2% of patients, respectively. Family history for CRC was evident in 15.2% of patients (Table I).

The most commonly noted tumor characteristics involved rectal (34.6%) or right colonic (29.2%) location, perineural invasion (47.9%) and intermediate differentiation (60.0%) along with T3 (52.7%), N0 (44.1%) and TNM stage 3-4 (70.5%) tumors (Table I).

Metastasis was evident in 21.0% of patients (isolated liver metastasis in 14.0%) at the time of admission and in 15.2% of patients (isolated liver metastasis in 4.8%) during follow up (Table I).

Marker status on admission and follow up

On admission, both CEA and CA 19-9 levels were normal in 45.4% of patients and both were high in 14.3% of patients, while high CEA per se and high CA 19-9 per se were noted in 36.2% and 4.1% of patients, respectively (Table II).

At follow up, both CEA and CA 19-9 levels were high in 18.3% of patients, while high CEA per se and high CA 19-9 per se were noted in 11.0% and 14.1% of patients, respectively (Table II).

When admission/follow up combined marker status was evaluated, no change in marker status from admission to follow up was noted in 62.1% of patients, involving those with marker levels remained normal (38.3%) or high (23.8%) during the entire study period (Table II). The change in combined marker status from admission to follow up was evident in 37.9% of patients, involving normalization of initially higher marker levels in 31.6%, whereas elevation in marker levels from admission to follow up in 6.4% of patients (Table II).

The presence vs. absence of recurrence was associated with lesser likelihood of marker levels to be normal on admission (15.2 vs. 69.7%, p<0.001) and lesser likelihood of initially high marker levels to be normalized during follow up (38.1 vs. 61.9%, p<0.001) (Table II).

CEA and CA 19-9 levels according to study parameters

Median levels for CA 19-9 and CEA markers and on admission were 13.9 (range, 0.19 to 4855.5) and 3.0 (range, 0.15 to 3065.6), respectively. Both the high CA 19-9 and high CEA levels on admission were associated with presence of family history for CRC (p=0.024 and p=0.002, respectively), advanced TNM stage (stage 4, p<0.001 for each), presence of perineural (p=0.050 and p=0.023, respectively) or extranodal (p=0.011 and p<0.001, respectively) invasion and higher metastatic lymph node count (p<0.001 for each) (Table III).

The tumor localization (left colon, transverse colon and synchronous, p=0.016), advanced T stage (T3-4, p<0.001), presence of intramural venous (p=0.019) or lymphatic (p=0.003) invasion and larger tumor volume (p=0.02) were associated only with high CEA levels on admission, while poor histological differentiation (p=0.036) was associated only with high CA 19-9 levels on admission (Table III).

Survival Data According to Admission and Follow Up CEA and CA 19-9 Marker Status

The 5-year OS rate was 62.8% in the overall study population, 90.5% in patients with normal marker levels (CEA + CA 19-9) in both admission and follow up and 100% in those with high marker levels on admission but normal levels on follow up. Patients with normal marker levels on admission but high marker levels on follow up had 5-year OS rate of 27.8%, while those with high marker levels in both admission and follow up had 5-year OS rate of 26.2%.

Mean survival time was 108.7 months (ranged, 100 to 117.4 months). Presence of normal levels for both CEA and CA 19-9 on admission was associated with the longest survival time (131.6 months), while survival time was significantly shorter in patients with high marker levels on admission, whether or not for CEA per se (88.3 months, log Rank p<0.001), for CA19-9 per se (72.0

TABLE I - *Patient demographics and clinicopathologic characteristics*

Demographic and clinical characteristics		
Age, mean(SD, min-max)	62.0(13.8, 23.0-103.0)	
Gender, n(%)	Female	143(45.4)
	Male	172(54.6)
Diagnosis, n(%)	Colon Ca	158(50.2)
	Rectal Ca	136(43.2)
	Synchronous	21(6.7)
Family history for CRC, n(%)	48(15.2)	
Previous CRC	12(3.8)	
Previous history of another malignancy	17(5.4)	
Tumor characteristics, n(%)		
Tumor localization, n(%)	Rectum	109(34.6)
	Right colon	92(29.2)
	Left colon	57(18.1)
	Rectosigmoid	27(8.6)
	Synchronous	21(6.7)
	Transverse colon	9(2.9)
Tumor invasion, n(%)	Perineural	151(47.9)
	Extranodal	111(35.2)
	Lymphatic	113(35.9)
	Venous	64(20.3)
	Extramural venous	29(9.2)
	Intramural venous	35(11.1)
Histological differentiation, n(%)	Poor	83(26.3)
	Intermediate	189(60.0)
	Well	43(13.7)
T stage	0	3(1.0)
	1	15(4.8)
	2	29(9.2)
	3	166(52.7)
	4	102(32.4)
N stage	0	139(44.1)
	1	94(29.8)
	2	82(26.0)
TNM Stage	0	2(0.6)
	1	30(9.5)
	2	97(30.8)
	3	120(38.1)
	4	66(21.0)
Metastasis on admission, n(%)	66(21.0)	
Isolated liver	44(14.0)	
Isolated extrahepatic	9(2.9)	
Multiple organs/mixed	13(4.1)	
Recurrence, n(%)	46(18.4)	
Isolated liver	12(4.8)	
Isolated extrahepatic	17(6.8)	
Multiple organs/mixed	9(3.6)	
Local recurrence	8(3.2)	
Tumor volume (cm^3), median (min-max)	29.5(0.1-1200)	
Metastatic lymph node count, median (min-max)	1(0-63)	
Time to metastasis (month) , mean±SD (min-max)	21.1± 20.9(0.8-81.2)	

Table II - *Marker status on admission and follow up*

	CEA / CA 19-9[a]				
	Normal Normal/Normal	High/Normal	High Normal/High	High/High	Total
On admission, n(%)	143(45.4)	114(36.2)	13(4.1)	45(14.3)	315(100.0)
At follow up, n(%)	108(56.5)	21(11.0)	27(14.1)	35(18.3)	191(100.0)
	Admission / follow up[b]				
CEA+CA 19-9, n(%)	Normal Normal/Normal	High/Normal	High Normal/High	High/High	Total
Total	108(38.3)	89(31.6)	18(6.4)	67(23.8)	282(100.0)
Recurrence-metastasis					
Absent	101(69.7)	13(61.9)	11(40.7)	20(57.1)	145(75.9)
Present	7(15.2)	8(38.1)	16(59.3)	15(42.9)	46(24.1)
p value	<0.001				

[a]the first value represents CEA levels and second value represents CA19-9 levels as normal or high with respect to reference values;
[b]the first value represents admission levels and the second value represents follow up values for combined marker status Pearson Chi-Square test

months, log Rank p<0.001) or both for CEA and CA 19-9 (90.5 months, log Rank p<0.001) (Table IV, Fig 1).
Presence of normal marker status for both CEA and CA 19-9 on follow up was associated with the longest survival time (146.8 months), while survival time was significantly shorter in patients with high marker levels on follow up, whether or not for CEA per se (31.9 months, log Rank p<0.001), for CA19-9 per se (71.5 months, log Rank p<0.001) or both for CEA and CA 19-9 (40.2 months, log Rank p<0.001) (Table IV, Fig. 2).

ROC Analysis

ROC analysis revealed CEA levels >11 (AUC (95% CI): 0.636 (0.580-0.690), p<0.001) to be a potential marker of poor survival with a sensitivity of 75.0% and specificity of 45.9% (Fig 3).

Discussion

Our findings revealed abnormal serum levels for at least one marker in half of patients on admission or during follow up in CRC patients, along with a tendency for decrease in rate of high CEA levels per se and increase in rate of high CA 19-9 levels per se during follow up. Both CEA and CA 19-9 levels were high in case of family history for CRC, advanced tumor stage and tumor invasion (perineural or extranodal) and they were also associated with higher metastatic lymph node count and higher recurrence rate. The factors associated specifically with high CEA levels on admission were tumor localization, larger tumor volume, advanced T stage, intramural venous or lymphatic invasion, while high CA 19-9 levels were specifically associated with poor histological differentiation. The 5-year OS rate was 90.5% in patients with normal marker levels (CEA + CA 19-9) on both admission and follow up, whereas 26.2% in those with high marker levels (CEA + CA 19-9) on both admission and follow up. Survival time was longer in patients with normal levels for both CEA and CA 19-9 as compared with those with high marker levels including those with high CEA per se, high CA 19-9 per se or high CEA plus CA 19-9.
Both high CEA and high CA 19-9 levels on admission were associated with pathological features such as tumor stage, metastasis and tumor invasion as well as higher metastatic lymph node count, higher recurrence rates and shorter survival time in the current study. This supports the previously reported association of high preoperative serum CEA and CA19-9 levels with increased likelihood of lymph node or perineural invasion, poorly differentiated tumor and pathological tumor-node-metastasis stages [7]. In fact, while both markers were associated with advanced tumor stages and perineural or extranodal invasion, CEA alone was also associated with tumor localization, larger tumor volume, advanced T stage as well as intramural and lymphatic tumor invasion.
In the current study, in accordance with tendency for CEA levels to be initially high at the time of admission and to be associated with several clinicopathological factors, ROC analysis revealed high CEA levels (cut-off value >11) on admission to be a potential marker of poor survival in CRC patients with a sensitivity of 75.0% and specificity of 45.9%.
This supports the consideration of high preoperative CEA levels to be an independent prognostic factor in stage I-III rectal cancer patients as associated with worse overall survival (OS) [25]. Likewise, in a prospective single-center study on assessment of preoperative serum midkine level in comparison to CEA and CA 19-9 in CRC

TABLE III - *CEA and CA 19-9 levels on admission according to study parameters*

		CA19-9 on admission			CEA on admission		
		Normal	**High**	**p value**	**Normal**	**High**	**p value**
Total, n(%)		255(19.0)	60(81.0)		154(48.9)	161(51.1)	
Gender, n(%)	Female	115(45.1)	28(46.7)	0.940[1]	71(46.1)	72(44.7)	0.894[1]
	Male	140(54.9)	32(53.3)		83(53.9)	89(55.3)	
Family history for CRC, n(%)	No	210(82.4)	57(95.0)	0.024[1]	120(77.9)	147(91.3)	0.002[1]
	Yes	45(17.6)	3(5.0)		34(22.1)	14(8.7)	
Previous other malignancy, n(%)	No	241(94.5)	57(95.0)	0.872[1]	145(94.2)	153(95.0)	0.121[1]
	Yes	14()5.5	3(5.0)		9(5.8)	8(5.0)	
Tumor localization, n(%)							
Right colon		72(28.2)	20(33.3)	0.079[2]	50(33.3)	42(26.1)	0.016[2]
Transverse colon		4(1.6)	5(8.3)		1(8.3)	8(5.0)	
Left colon		46(18)	11(18.3)		21(18.3)	36(22.4)	
Rectosigmoid		25(9.8)	2(3.3)		14(3.3)	13(8.1)	
Rectum		90(35.3)	19(31.7)		61(31.7)	48(29.8)	
Synchronous		18(7.1)	3(5.0)		7(5.0)	14(8.7)	
T stage, n(%)							
0		3(1.2)	0(0.0)	0.256[2]	3(1.9)	0(0.0)	<0.001[2]
1		14(5.5)	1(1.7)		10(6.5)	5(3.1)	
2		27(10.6)	2(3.3)		23(14.9)	6(3.7)	
3		131(51.4)	35(58.3)		82(53.2)	84(52.2)	
4		80(31.4)	22(36.7)		36(23.4)	66(41.0)	
N stage, n(%)							
0		124(48.6)	15(25.0)	0.002[2]	80(51.9)	59(36.6)	0.001[2]
1		73(28.6)	21(35.0)		48(31.2)	46(28.6)	
2		58(22.7)	24(40.0)		26(16.9)	56(34.8)	
TNM Stage, n(%)							
0		2(0.8)	0(0.0)	0.001[2]	2(1.3)	0(0.0)	<0.001[2]
1		29(11.4)	1(1.7)		22(14.3)	8(5.0)	
2		85(33.3)	12(20.0)		52(33.8)	45(28.0)	
3		96(37.6)	24(40.0)		65(42.2)	55(34.2)	
4		43(16.9)	23(38.3)		13(8.4)	53(32.9)	
Perineural invasion, n(%)	No	139(54.7)	24(40.0)	0.050[1]	90(58.8)	73(45.3)	0.023[1]
	Yes	115(45.3)	36(60.0)		63(41.2)	88(54.7)	
Intramural invasion, n(%)	No	228(89.8)	51(85.0)	0.409[1]	143(93.5)	136(84.5)	0.019[1]
	Yes	26(10.2)	9(15.0)		10(6.5)	25(15.5)	
Extramural invasion, n(%)	No	235(92.2)	51(85.0)	0.140[1]	143(92.9)	143(88.8)	0.297[1]
	Yes	20(7.8)	9(15.0)		11(7.1)	18(11.2)	
Lymphatic invasion, n(%)	No	167(65.7)	34(56.7)	0.243[1]	111(72.5)	90(55.9)	0.003[1]
	Yes	87(34.3)	26(43.3)		42(27.5)	71(44.1)	
Extranodal invasion, n(%)	No	171(67.9)	29(49.2)	0.011[1]	116(76.3)	84(52.8)	<0.001[1]
	Yes	81(32.1)	30(50.8)		36(23.7)	75(47.2)	
Differentiation, n(%)	Poor	59(23.1)	24(40.0)	0.036[2]	40(26.0)	43(26.7)	0.269[2]
	Intermediate	159(62.4)	30(50.0)		88(57.1)	101(62.7)	
	Well	37(14.5)	6(10.0)		26(16.9)	17(10.6)	
Tumor volume (cm^3), Median(min-max)		28(0-1200.0)	49(1.2-240.0)	0.109[3]	23 (0-1008)	35(2-1200)	0.002[3]
Metastatic lymph node count, Median(min-max)		0(0-55)	3(0-63)	<0.001[3]	0 (0-40)	1 (0-63)	<0.001[3]
Time to metastasis (month), Mean±SD		22.9±21.1	16.3±20.4	0.359[4]	17.9±20.8	24.6±20.8	0.240[4]

[1]Continuity Correction test; [2]Fisher's Exact test; [3]Mann-Whitney U test; [4]Student-t test

patients, amongst the biomarkers studies only CEA was found to be an independent prognostic factor for survival in the multivariate Cox regression analysis [28]. In addition, in a previous study on risk factors for recurrence of patients with stage III CRC, while preoperative serum CEA level (>5 ng/ml) and preoperative serum CA19-9 level (>37 U/ml) were both determined to be the risk factors in the univariate analysis for recurrence, preoperative serum CEA level >5.0 ng/ml was reported to be the only risk factor for recurrence in the multivariate analysis [29].

In the current study, 5- year survival rate was >90%

TABLE IV - *Survival data overall and according to CEA and CA 19-9 marker status*

			Overall survival time (month)			
				95% CI		
			Mean (SE)[a]	LB	UB	Log Rank (Mantel cox) *p* value vs. Normal/Normal
Total			108.7 (4.4)	100.0	117.4	
Admission (n=315)						
CEA	CA19-9	n				
Normal	Normal	143	131.6 (5.9)	120.0	143.2	
Normal	High	13	72.0 (18.9)	35.0	108.9	<0.001
High	Normal	114	88.3 (7.4)	73.8	102.8	<0.001
High	High	45	90.5 (10.3)	70.3	110.7	<0.001
Follow up (n=191)						
CEA	CA19-9	n				
Normal	Normal	108	146.8 (5.6)	135.8	157.8	
Normal	High	27	71.5 (11.3)	49.4	93.7	<0.001
High	Normal	21	31.9 (5.0)	22.2	41.6	<0.001
High	High	35	40.2 (6.5)	27.4	53.0	<0.001

CI: confidence interval
[a]Estimation is limited to the largest survival time if it is censored

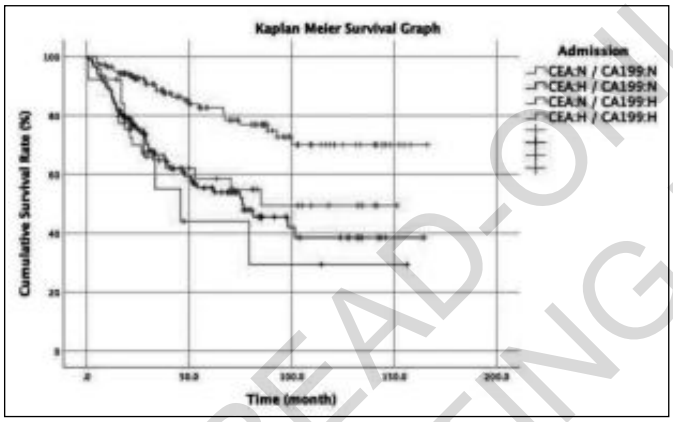

Fig. 1: Kaplan Meier analysis for survival according to CEA and CA 19-9 marker status on admission.

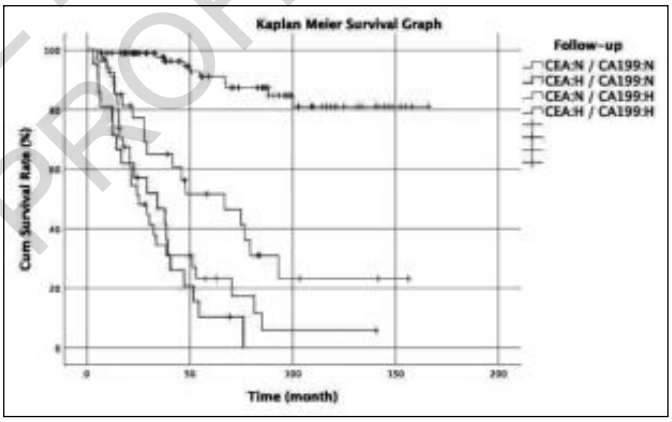

Fig. 2: Kaplan Meier analysis for survival according to CEA and CA 19-9 marker status on follow up.

when both markers remained normal or normalized during follow up, whereas <30% when both markers remained high or increased during follow up. Notably, in a past study with CRC patients, the 5- year OS rates in patients with normal/normal, high/normal, normal/high "CEA/CA 19-9" levels were reported to be 94.1%, 85.2% and 79.6%, respectively [15]. Nonetheless, given the association of high CEA levels vs. high CA 19-9 levels on admission with higher number of aggressive pathological features, identification of high CEA levels >11 on admission to significantly predict poor survival and shorter survival time in patients with high CEA levels during follow up; our findings seem to indicate a weaker poor prognostic value of high CA 19-9 levels when used alone.

Hence, our findings strongly suggest combined use of CEA and CA 19-9 marker levels in diagnostic and prognostic assessment of CRC patients, given the potential superiority of CEA analysis over CA 19-9 analysis in providing better information on tumor stage, tumor invasion and poor prognosis and survival along with association of high CA 19-9 levels on admission per se with poor histological differentiation. Similar advantage of combined use of tumor markers was reported in terms of not only diagnostic efficiency in CRC but also for the estimation of recurrence and metastasis risk in patients with postoperative CRC [7,30,31].

Although previous studies indicated a correlation between preoperative CEA and CA 19-9 levels with tendency of CRC patients with higher CEA levels also to have high-

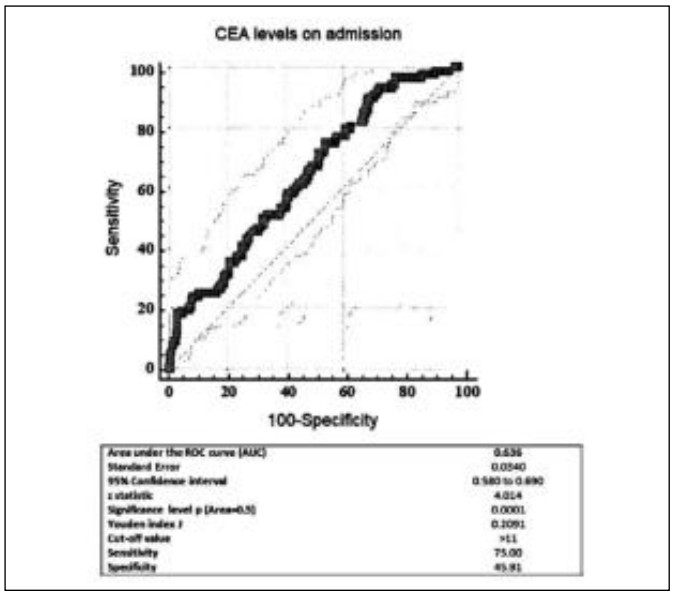

Fig. 3: ROC curve analysis of the role of CEA levels on admission in prediction of poor survival.

er CA 19-9 levels [15,25], our findings revealed a difference in time-dependent change of two markers, such as higher possibility of CEA levels to be high initially on admission but tendency of CA 19-9 levels to increase later on during follow up. In addition, initial marker status (CEA plus CA 19-9) remained unchanged in two thirds of patients during follow up, and in those with change, normalization was more likely than elevation. This seems notable given the past studies in CRC patients indicated the serum CEA and CA 19-9 levels to show increasing trends with the increase of pathological staging [32], association of an exponential decrease of the CEA levels after neoadjuvant treatment with significant tumor down staging and complete pathologic response [33] and that increase in CEA and CA19-9 levels after the third cycle of chemotherapy (by 35% and 28%, respectively) to be associated with a shorter progression-free survival period [34].

Notably, in addition to the higher likelihood of CA 19-9 vs. CEA levels to increase during follow up, higher levels of CA 19-9 were also associated with presence of poorly differentiated tumors in our patients. Indeed, the clinical significance of pre-CA 19-9 is considered to remain controversial [15]. Some studies reported high preoperative serum CA 19-9 levels to be an independent predictor of poor prognosis or recurrence [18,35,36], while others indicated no role of CA 19-9 in prediction of prognosis or detection of recurrence among CRC patients since it has no predictive superiority over CEA in CRC patients [37,38].

Some studies also reported association of high CA 19-9 levels with aggressive pathologic features and poor prognosis in stage III and IV CRC [15], as well as higher likelihood of isolated elevated CA 19-9 to predict highly aggressive disease in metastatic CRC (mCRC) patients with BRAF mutation [23]. In the current study, high CA 19-9 levels per se predicted only the poorly differentiated tumors, suggesting utility of CA 19-9 as a complementary marker to CEA rather than being used alone in prognostic assessment of CRC patients. However, it should also be noted that elevation in marker levels during follow up was uniquely observed for CA 19-9 rather than CEA. Notably, in a past study concerning three serial measurements of CEA and CA 19-9 among CRC patients, although increase in CA 19-9 levels per se (7.3%) was reported to be less commonly observed than concomitant increase of both markers (55.4%), authors reported poorer 5-year survival in patients with increased CA 19-9 levels per se than in those with increased CEA levels per se [13]. Hence, authors suggested that CA 19-9 can be used as additional marker to follow the disease process in patients with CRC without an increase in CEA level [13]. Utility of CA 19-9 in monitoring disease development was also documented in metastatic CRC patients with no elevation of CEA[39], while serum CEA levels were reported to be higher in case of synchronous disease and to be associated with the rate of recurrences in patients with hepatic colorectal cancer metastasis [40].

Nonetheless, given the likelihood of CA 19-9 to increase in other type of malignancies (i.e. gastric, lung, ovary) and comorbid diseases (i.e. DM, chronic hepatitis, inflammatory bowel disease, benign kidney and lung diseases, autoimmune and thyroid disorders) along with the ongoing controversy regarding its prognostic role in CRC patients [13,41], a need for large prospective studies to elucidate the significance of CA 19-9 as a prognostic tumor marker in CRC has been emphasized [42].

Retrospective single center design is the major limitation of the current study, given the impossibility of establishing the temporality between cause and effect as well as generalizing our findings to overall CRC population Nevertheless, given the restricted amount of data available on prognostic role of combined or separate use of CEA and CA 19-9 both preoperatively and postoperatively, our findings represent a valuable contribution to the literature.

Conclusion

In conclusion, our findings revealed abnormal serum levels for at least one marker in half of patients on admission or during follow up and a tendency for increase in the percentage of patients with high CA 19-9 levels per se during follow up. Although combined evaluation of high marker status (CEA plus CA 19-9) on admission was associated with pathological features such as tumor stage, metastasis and tumor invasion as well as higher recurrence rate and shorter survival time, high CEA levels on admission alone was associated with higher num-

ber of aggressive pathological features. CEA levels (cut-off values >11) on admission significantly predicted poor survival. Accordingly, our findings seem to indicate a weaker poor prognostic value of high CA 19-9 levels when used alone and strongly suggest combined use of CEA and CA 19-9 markers in prognostic assessment and risk-adapted follow-up surveillance in CRC patients. Nonetheless, unlike to CEA, CA 19-9 seems to show a tendency for elevation during follow up and to associate with histological differentiation specifically, emphasizing the likelihood of CA 19-9 marker status to have an additional prognostic value in patients with normal preoperative CEA levels.

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Riassunto

Studio retrospettivo per valutare l'utilità e il valore prognostico dei livelli sierici di CA 19-9 in relazione ai livelli sierici di CEA nel follow-up a lungo termine di pazienti con carcinoma del colon-retto (CRC)
Sono stati inclusi in questo studio un totale di 315 pazienti con CRC trattati lungo un periodo di 13 anni. Sono stati registrati i dati sulle caratteristiche del tumore, i livelli CEA e CA 19-9. L'analisi di sopravvivenza è stata eseguita rispetto allo stato del marker, mentre la curva ROC è stata tracciata per determinare l'efficacia del CEA nella previsione della sopravvivenza durante il follow-up con il calcolo dell'area sotto curva (AUC) e il valore di cut-off tramite l'analisi ROC.
Risultati: stadio T avanzato (T3-4, p <0,001), presenza di invasione intramurale (p = 0,019), invasione linfatica (p = 0,003) e volume tumorale maggiore (p = 0,02) sono stati associati solo con livelli elevati di CEA al momento del ricovero , mentre una scarsa differenziazione istologica (p = 0,036) era associata solo a livelli elevati di CA 19-9 al momento del ricovero. La presenza di livelli normali di CEA e CA 19-9 era associata a più lunghi periodi di sopravvivenza (rispettivamente 131,6 e 46,8 mesi, p <0,001 per ciascuno) e un tasso di OS a 5 anni del 90,5%, mentre l'analisi ROC ha rivelato che livelli di CEA> 11 (AUC (IC 95%): 0,636 (0,580-0,690), p <0,001) sono un potenziale marker di scarsa sopravvivenza con una sensibilità del 75,0% e una specificità del 45,9%.
In conclusione, i nostri risultati sembrano indicare un valore prognostico scarso più debole di livelli elevati di CA 19-9 quando usati da soli e suggeriscono fortemente l'uso combinato dei marcatori CEA e CA 19-9 nella valutazione prognostica e nella sorveglianza di follow-up adattata al rischio in Pazienti CRC.

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