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Article

Fluctuation of Serum CEA in the Conventional Normal Range and The Risk of Relapse Following Curative Intent Treatment of Colorectal Cancer

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Abstract: Carcinoembriogenic antigen (CEA) is a routine marker for follow-up of colo-rectal cancers. We aimed to determine whether a CEA increase within the normal range can be linked to a recurrence risk. We included 78 consecutive patients with colo-rectal cancer, who underwent curative surgical treatment with or without chemo- or radiotherapy. As reference, we used the smallest value of the CEA during follow-up. A total of 34/78 patients (43.6%) had fluctuations of CEA of at least 1.1 ng/ml, with or without increases above 5 ng/ml. In 27/34 patients (79.4%) increases of CEA were explained either by recurrence (15/34 patients, 44.1%), adjuvant chemotherapy (7/34 patients, 20.6%) or benign pathology (5/34 patients, 14.7%). In 5 of 22 recurrences (23%) a CEA increase of at least 1.1 ng/ml, but below 5 ng/ml preceded the clinical relapse by a median of 8 months (range 3-22 months). The 4-year disease-free survival was 89% in patients with postoperative CEA <2.5 ng/ml, and 55% in patients with CEA >2.5 ng/ml. CEA increase by at least 1.1 ng/ml within the normal range, after curative treatment of colorectal cancer can be either an early sign of relapse or can be usually explained by other pathological processes.

Keywords: CEA 1; colorectal cancer 2; follow-up 3 ; tumor markers 4 ; early intervention 5 ; adjuvant chemotherapy 6

1. Introduction

Colorectal cancer, a leading cause of mortality worldwide, is the third most common type of cancer in men and the second in women [1]. In the case of relapse, a modern aggressive approach consisting of radical treatment of oligometastatic disease, chemotherapy, molecular targeted therapy and local approaches (radiotherapy, surgery) can achieve cure or at least offer longer survival. Therefore, theoretically, early diagnosis and therapeutic intervention for relapse seems to be crucial. Circulating tumor cells, novel proteic tumor markers or serum genetic markers are probably the future of a more sensitive follow-up.

CEA (carcinoembryonic antigen) and CA 19-9, although not sensitive enough for screening and early diagnosis, are the two standard tumor markers at diagnostic workup (for prognosis) and post treatment follow-up (for detection of a relapse). Among the two, CEA is the most employed and its periodical use as an indicator of relapse has been well established in several studies, even rendering routine periodic CT scans unnecessary based on some data [2,3]. For follow-up after curative multimodal treatment of ≥T2 or N+ tumors, its measurement is mandatory, usually every 2-3 months in the first 2-3 years, then every six months until 5 years [4]. Even if the initial CEA value at diagnosis falls in

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the normal range it is still useful to follow-up its values, as shown in the analysis of the Dutch TME trial data [5].

The normal value for CEA is considered < 5 ng/ml (μg/l) by most guidelines and laboratories. Some go as low as < 2.5 ng/ml or < 3.4 ng/ml in non-smokers and < 4.3 ng/ml in smokers, but usually only heavy smoking can increase CEA values above 3.4 ng/ml [6-8].

The aim of this study was to analyze the fluctuation of CEA and to determine whether a certain increase in the conventional normal range of values can predict clinical recurrence (local recurrence, regional recurrence, i.e. lymph node recurrence, or metastasis).

The second aim of this study was to determine whether the post-surgery value of CEA has a significant influence on the disease-free survival.

2. Materials and Methods

Our retrospective observational study was performed at a tertiary academic cancer center and included consecutive patients with rectal and non-rectal colon cancer diagnosed between January 2006 until December 2013, who underwent curative surgical treatment with or without chemo- or radiotherapy.

Inclusion criteria:

- Primary confirmed colorectal adenocarcinoma
- Clinical stage II and III
- Curative surgical treatment
- Negative resection margins (R0)
- Post-surgery follow-up of the CEA values

Exclusion criteria:

- Multiple synchronous colorectal tumors
- Clinical stage IV
- Other cancers (several other tumors express and secrete CEA)

The database used for this study was selected by browsing through 2620 files concerning patients treated with colorectal cancer from our institution to identify patients that fulfill the inclusion criteria. As a result, only 78 patients were selected in this period.

We collected all available CEA values measured during the postoperative follow-up. The first measurement of CEA was performed within 1 to maximum 3 months after surgery. CEA was measured in the same laboratory using the same method by electrochemiluminescence immunoassay (ECLIA). CEA is considered normal in our laboratory at values < 3.4 ng/ml in non-smokers and < 4.3 ng/ml in smokers. For the purpose of this study however we used the convention of < 5 ng/ml for CEA values that were considered "normal". As reference, we used the smallest value of the CEA observed during follow-up.

To analyze the association between the increase of CEA and tumor recurrence we arbitrarily defined an "alarm value" for the CEA, defined as the first increase of at least 1.1 ng/ml registered during follow-up, compared to the smallest previous value. We defined clinical recurrence as either local, regional or distant relapse, documented by imaging studies. For patients with CEA increase of more than 1.1 ng/dl without documented recurrence, we searched the patients' records for possible benign causes of the fluctuation.

All data were collected in a FileMaker database and analysis was performed through Excel Microsoft Office.

The 4-year overall survival and disease-free survival (DFS) were determined through the Kaplan-Meier method. Survival differences were evaluated through the log-rank test. To analyze the influence of post-surgery CEA on DFS, we chose the cut-off value 2.5 ng/ml with the aid of a ROC curve and chi-squared test (using Yate's correction). The cut- off value was chosen by the minimum distance of ROC curve to point (0,1). The odds ratio was calculated with the chi square test.

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The confidence intervals were estimated at 95% confidence level. Statistical significance was defined by value of $p \leq 0.05$.

3. Results

From the 78 patients included in the study 49 were men (69%). Patients' age ranged between 25 and 79 years and the median age was 59 years. The median follow-up was 42.1 months (range 12.4-93.1). Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Variable	Number	(%)
Sex		
Male	49	69
Female	29	31
Subsite		
Rectosigmoid	60	76.9
Non-rectal colon	18	23.1
Tumor stage		
IIA	26	33.2
IIB	2	2.6
IIIA	2	2.6
IIIB	41	52.6
IIIC	7	9
Neoadjuvant / Adjuvant chemotherapy	51	65.4
Neoadjuvant / Adjuvant radiotherapy	50	64.1

From the entire group of patients, 22 (28.2%) presented recurrences, of which most had metastasis as the only type of relapse (12 patients, 54.5%), seven patients (31.8%) had both metastasis and local recurrence, and three patients (13.6%) had only local recurrence.

In 5 of 22 relapsed patients (22.7%), we observed an increase in the CEA values of at least 1.1 ng/ml, during follow up, before the clinical recurrence, with values positioned in the normal range interval. (Table 2.) Notably the CEA increase of at least 1.1 ng/ml preceded the clinical relapse by a median of 8 months (range 3-22 months).

Table 2. Patients with increase of CEA of at least 1.1 ng/ml, but not reaching 5 ng/ml, before clinical recurrence.

Patient number	Date of clinical recurrence on CT/MRI/PET-CT/US/ endoscopy	Baseline value after surgery	Alarm value	Date of alarm value	Difference of at least 1.1 ng/ml
6.	21.09.2009	1.70	2.89	13.12.2007	1.19
8.	1.11.2008	0.63	1.91	29.01.2007	1.28
24.	11.05.2009	0.64	1.90	03.12.2008	1.26
37.	02.02.2009	1.40	4.50	08.12.2008	3.10
78.	01.02.2015	1.40	3.70	05.06.2014	2.30

In Figure 1 we represent the fluctuation of CEA with an increase of at least 1.1 ng/ml, but below 5 ng/ml in patients with clinical recurrence.

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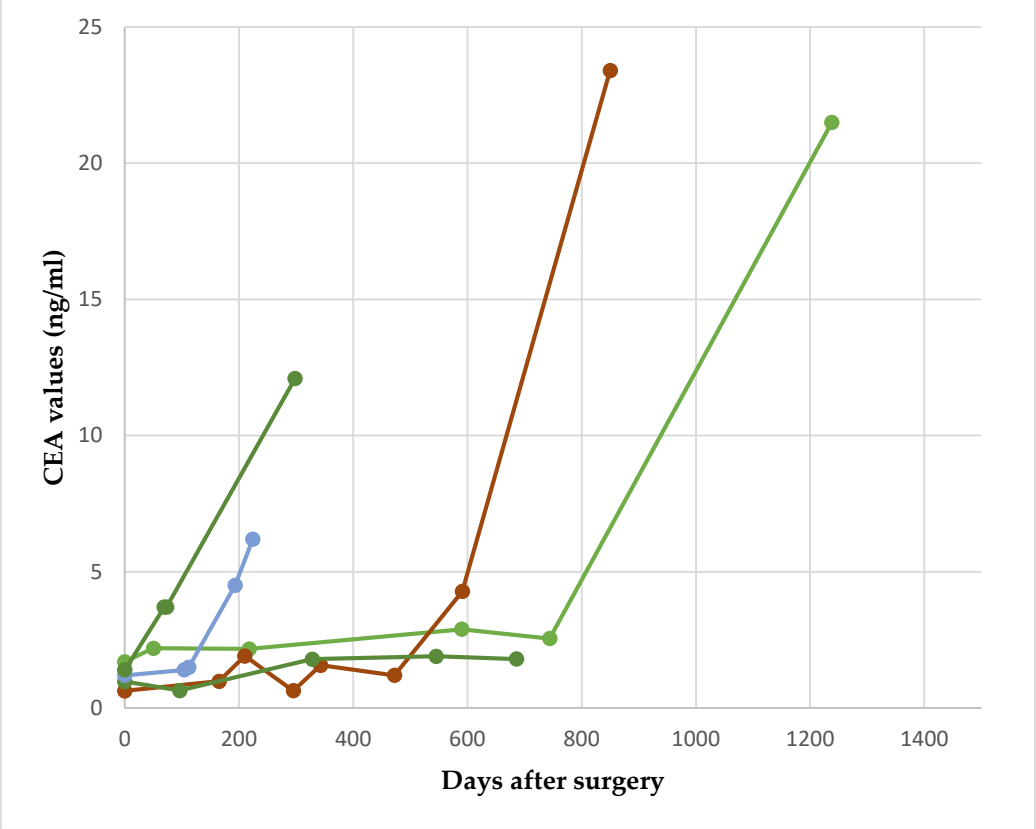

Figure 1. Increases of CEA below 5 ng/ml, but at least 1.1 ng/ml which predicted relapse in 5/22 patients.

Seven patients out of the 22 (31.8%) presented relapse but had no increase of CEA neither above 5 ng/ml nor with the defined alarm value of ≥1.1 ng/ml. The median of the peak CEA values was 1.63 ng/ml (range 1.39-3.38).

The remaining subjects with clinical recurrence (10/22, 45.5%) presented an abrupt increase of CEA above 5 ng/ml with no preceding alarming increase of more than 1.1 ng/ml. Altogether 15/34 (44.1%) of CEA increases with at least 1.1 ng/ml (either gradually or abruptly increasing above 5 ng/ml) were related to a clinical recurrence.

Out of the 78 patients, 56 subjects (71.7%) had no recurrence during follow-up. Still, 19 patients out of these 56 (33.9%), presented an increase of CEA marker that exceeded 1.1 ng/ml. In 7 patients (36.8%) the only evident cause for this fluctuation was adjuvant chemotherapy (Table 3 and Figure 2.)

Table 3. Increase of CEA by at least 1.1 ng/ml associated with adjuvant chemotherapy.

Patient number	Minimum value	Maximum value	Date of first increase with >1.1 ng/ml	Date of start of chemotherapy	Last chemotherapy cycle
13.	2.45	2.52	07.12.2006	14.08.2006	30.10.2006
28.	2.04	1.51	20.11.2007	11.10.2007	05.03.2008
43.	1.20	3.80	08.07.2009	26.05.2009	28.10.2009
54.	4.00	1.10	29.09.2011	30.03.2011	24.08.2011
63.	3.10	1.50	21.11.2011	25.07.2011	21.11.2011
50.	1.60	3.20	20.06.2011	07.02.2011	07.06.2011
55.	5.80	11.60	19.08.2011	04.03.2011	29.07.2011

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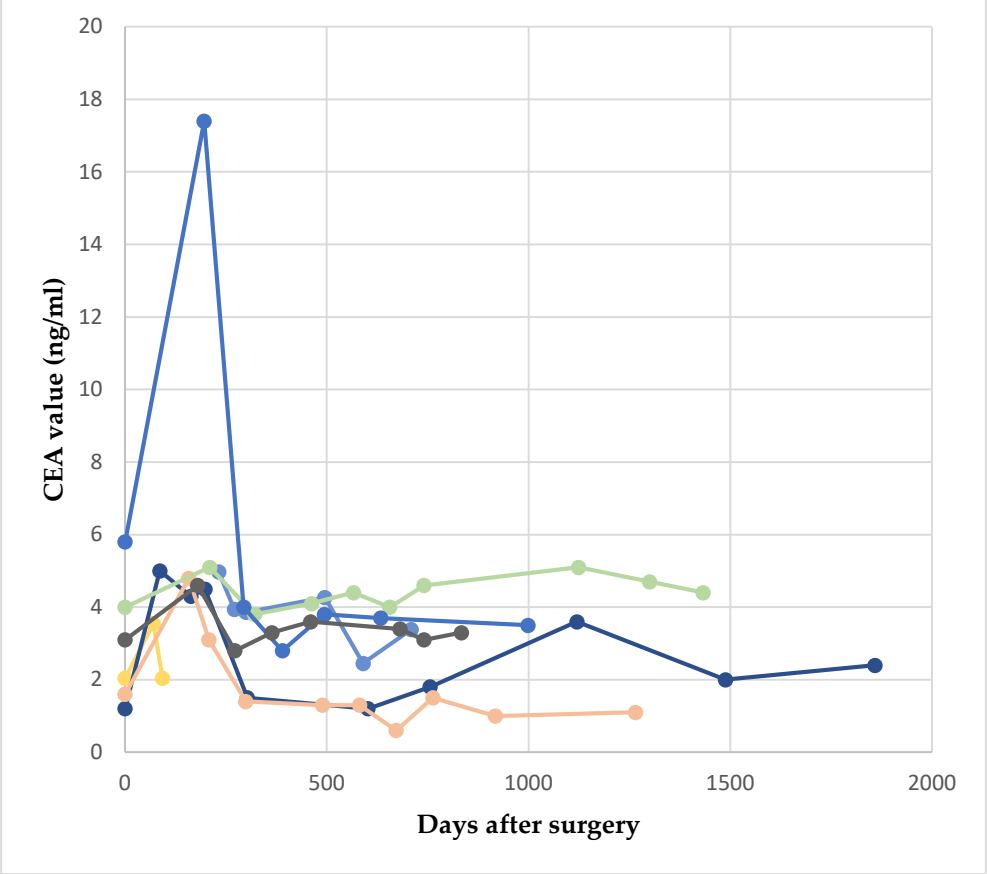

Figure 2. CEA fluctuation of at least 1.1 ng/ml under adjuvant chemotherapy.

The transient growth of CEA values occurred either during chemotherapy (5 patients), or in a minority (2 patients) the increase was detected at one month or maximum two months post chemotherapy. Some of the CEA values were slightly above the normal range (median increase of 4.9 ng/ml, range 2.2-17.4 ng/ml and a median difference from the minimum value of 1.54 ng/ml). In 6 out of 7 cases the values returned to "normal" (<5ng/ml).

In 12/34 of the patients with a fluctuation of at least 1.1 ng/ml neither due to relapse nor to adjuvant chemotherapy (35.3% of patients with fluctuation) a possible association between the growth of the marker and a benign pathology was found in 5 patients, who were fully investigated for all possible benign pathology such as *colorectal adenomas* and *liver disease* to name just the most frequent possible causes (Table 4, Figure 3).

Table 4. CEA increase at least 1.1 ng/ml for patients with no relapse and no adjuvant chemotherapy (probably benign causes and non-relevant fluctuations).

Patient number	Possible cause for CEA fluctuation	Min. value	Max. value	Difference of at least 1.1 ng/dl
9.	Not investigated for all benign causes	2.49	3.83	1.34
4.	Not investigated -//-	3.22	4.69	1.47
16.	Not investigated -//-	1.60	5.78	4.18
19.	Ulcerative colitis	2.97	35.50	32.5
18.	Colic adenoma	1.00	2.40	1.40
53	Cholecystitis	2.30	4.50	2.20

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75	Not investigated -//-	1.50	3.10	1.60
44	Not investigated -//-	1.20	3.60	2.40
45	Not investigated -//-	2.90	4.50	1.60
59	Not investigated -//-	1.60	2.90	1.30
61	Gastritis	9.20	13.5	4.30
70	Colic adenoma	2.70	8.40	5.70

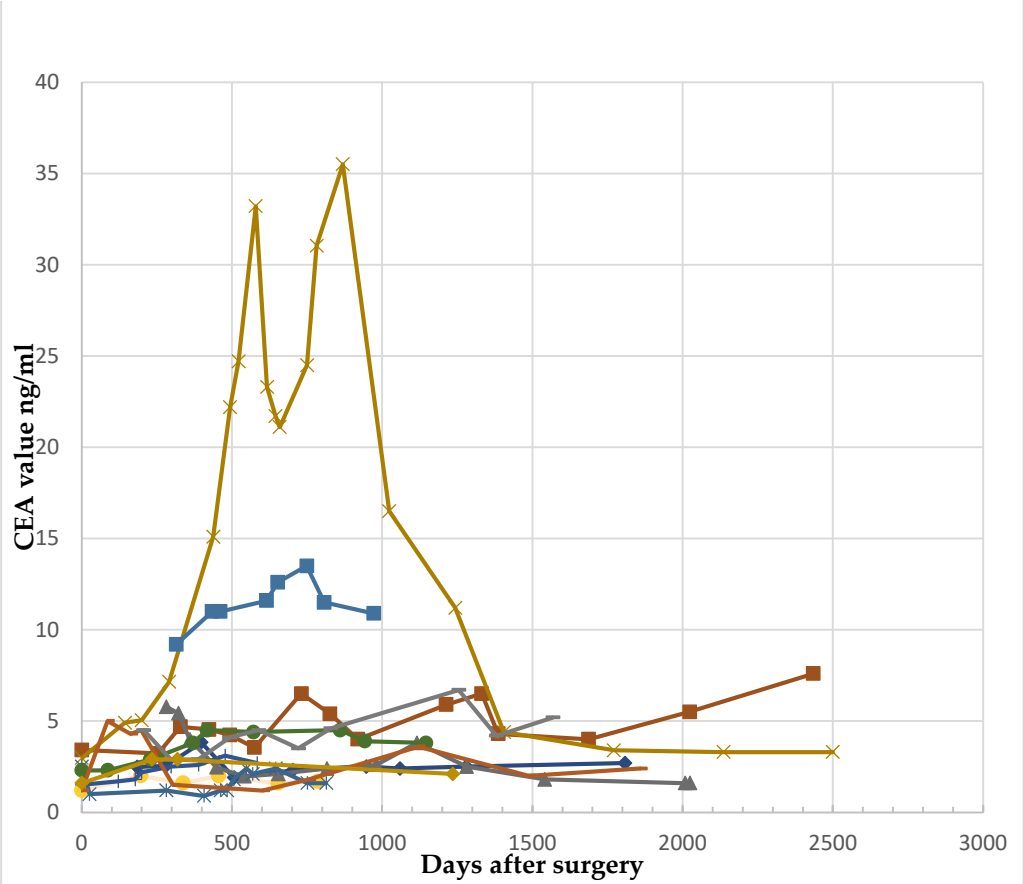

Figure 3. CEA fluctuation at least 1.1 ng/ml for patients with no relapse and no adjuvant chemotherapy

A total of 44/78 (56.4%) patients had no increase in CEA values of at least 1.1 ng/ml and no relapse.

All in all, 34/78, 43.6% of patients had fluctuations of CEA of at least 1.1 ng/ml. From these 34 patients in 27 (79.4%) increases of CEA were explained by recurrence, adjuvant chemotherapy or benign pathology. The odds ratio of a relapse in the presence of a CEA increase of at least 1.1 ng/ml was 4.17 (95% CI 1.45-11.97, p=0.0079). (Table 5.)

Table 5. CEA fluctuation and clinical recurrence

Variable	Clinical recurrence	No clinical recurrence	Total
CEA fluctuation	15	19	34
No CEA fluctuation	7	37	44
Total	22	56	78

[1] OR 4.17 (95% CI 1.45-11.97, p=0.0079).

The estimated overall survival at 48 months (4 years) and disease-free survival rate, for the same period is shown in Fig. 4.

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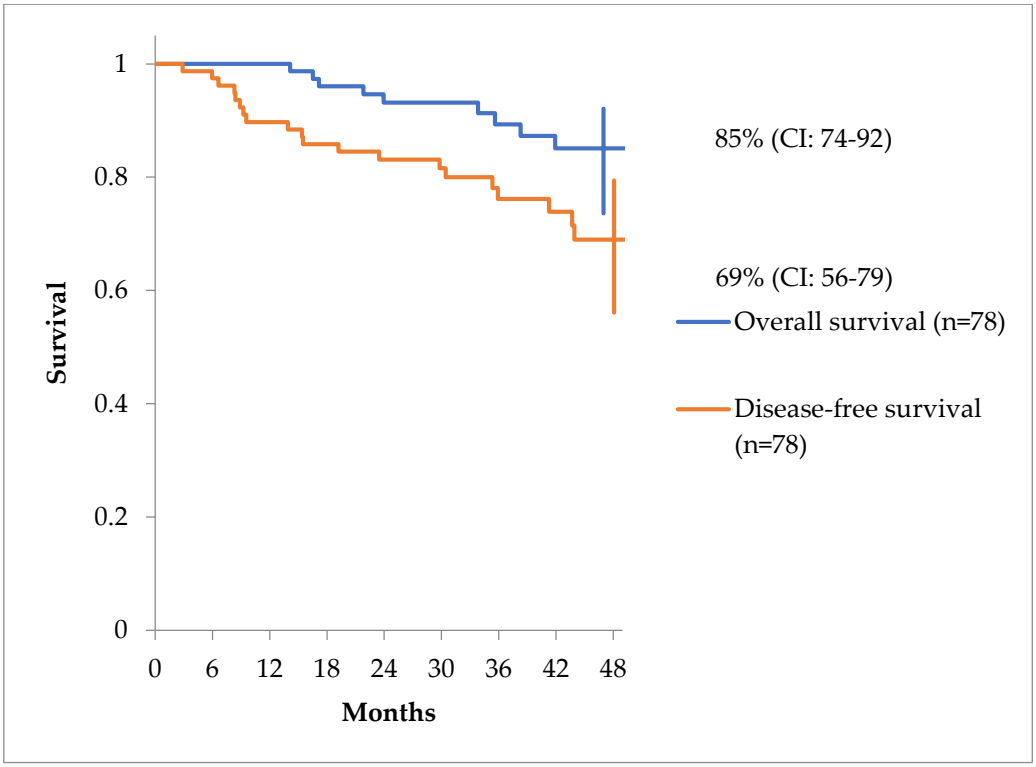

Figure 4. OS and DFS at 4 years.

The disease-free survival was significantly influenced by the post-surgery value of CEA. Patients with CEA values < 2.5 ng/ml had a disease-free survival (DFS) at 4 years of 89%, while patients with values > 2.5 ng/ml had a DFS rate of only 55%. (Fig. 5)

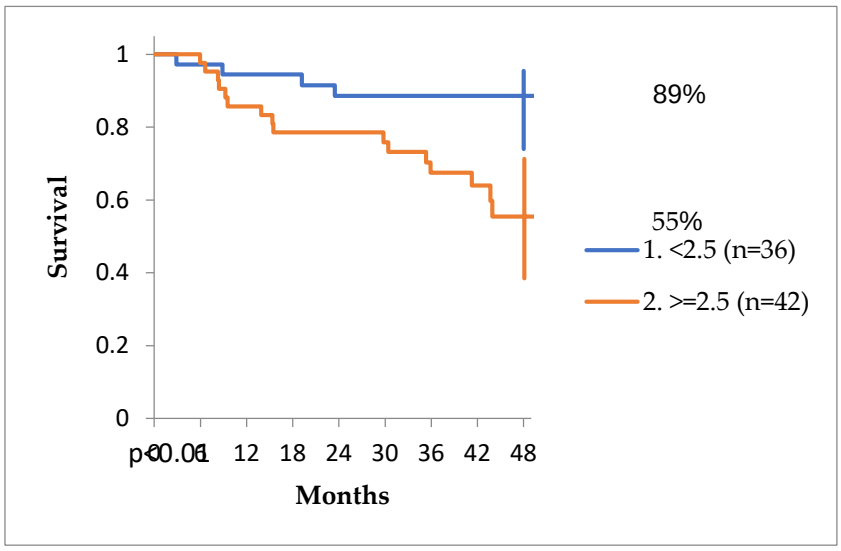

Figure 5. The post-surgery value of CEA marker and the DFS.

4. Discussion

The disease-free survival was significantly influenced by the post-surgery value of CEA, being almost double in patients with values < 2.5 ng/ml compared to patients who had values >2.5 ng/ml. Several studies have demonstrated that the *pre-treatment* value of this marker affects survival (values > 4-6 ng / ml) [9-10]. However, only scarce data is available about postoperative levels. In this study we demonstrated a correlation be-

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tween disease free survival and "post-curative" value of CEA. This result is similar to that published in the post hoc analysis of the MOSAIC and PETACC-8 trials. In this analysis the 3-year DFS rate was 75%, 65%, and 45% in a group of patients with CEA level of 0–1.30 ng/mL (n = 630), 1.30–5 ng/mL (n = 613), and >5 ng/mL (n = 49). [11]

Metastases as the only form of relapse, represented the majority (54 %) among patients with treatment failure, followed by metastasis along with local recurrence, meanwhile the fewest subjects had only local recurrence. This data is consistent with the literature, metastasis alone being the leading cause of treatment failure [12].

Five patients (22.7 %) with clinical recurrence presented an earlier increase of the CEA, although its value remained in standard normal range of values (<5 ng/ml for smokers). The ability to suspect a relapse at lower values of CEA is important, since CEA climbs up gradually as shown in the Dutch TME clinical trial: when relapse was diagnosed during follow-up, CEA values were normal at the first measurement in 81% of patients at a threshold of 5 ng/ml and in 66% at a threshold of 2.5 ng/ml.

Seven patients, 31.8% of the clinically relapsed patients did not present neither fluctuations of CEA > 1.1ng/ml nor increases above 5 ng/ml, underlining the need of combined CEA-CT follow-up. These relapsed patients lack of CEA secretion above a certain arbitrarily defined level. CEA cellular expression and secretion is around 50-70% [13], depending on primary or relapsed cancer and is thus cannot be used as an universally sensitive tumor marker. In our study "CEA-silent" relapsed patients had CEA values of less than 3.4 ng/ml.

Twenty-one patients had increases of CEA of at least 1.1 without presenting relapse. These elevations were transitory, even though in some cases the values exceeded by far 5 ng/ml. Only 5/21 patients underwent general investigations to determine non-oncological causes of CEA growth. The cause of CEA increase in these cases were colic adenoma, cholecystitis, ulcerative colitis and antral gastritis. These were all benign diseases which were worth addressing with treatment, in other words the alarm value of 1.1 ng/ml can be useful in these pathologies.

A study of the literature shows that several types of benign pathologies, including gastric, liver and lung diseases and premalignant lesions can result in increase of CEA over normal values in the absence of a malignancy [14-17]. The values in these cases are rarely over 10 ng/ml, although not exceptional[14]; in our study there were only two patients with values over 10 ng/ml. In our study in almost all cases there was a subsequent return to the normal range of values.

Hypothyroidism can be a cause for abnormal CEA and TSH and fT4 should be measured if there is an otherwise unexplained increase of CEA [18].

Age and even blood groups influence CEA but its values are rarely over 3.4-5 ng/ml [19].

There are proponents of an adjusted CEA value based on age, BMI, WBC count, Hb, fasting glucose, AST, creatinine, triglyceride and HbA1c levels [20].

Another possible cause to take into consideration when examining CEA elevations is adjuvant chemotherapy. A hypothesis that would explain this phenomenon, is the release of CEA from the apoptotic cells during chemotherapy, similar in patients receiving palliative chemotherapy. Another more likely explanation for the CEA increase could be the gastrointestinal toxicity or liver toxicity of chemotherapy. (Physiologically the liver clears CEA efficiently from the serum.) Mitchell et al also observed a transient increase of CEA during adjuvant chemotherapy with influence on the relapse risk [21].

5. Conclusion

An increase of CEA marker with at least 1.1 ng/ml, detected in the post-surgery follow up, even though in the normal range of values, should raise the hypothesis of a relapse and prompt close monitoring of patients, since it can predict a clinical recurrence with several months in advance. Other causes, such as adjuvant chemotherapy, gastric

pathology and adenomas are important factors to be taken into consideration in post-surgery follow up regarding CEA dynamics, causing transient increases of the values even above 5 ng/ml. Disease-free survival is significantly influenced by the postoperative value of the CEA with a cut-off value of 2.5ng/mL.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*., **2021**. doi:10.3322/caac.21660
2. Lepage C, Phelip JM, Cany L, et al. Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer: The FFCD PRODIGE 13 randomised phase III trial. *Digestive and Liver Disease*. **2015**, 47, 529-31. doi:10.1016/j.dld.2015.03.021
3. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: The FACS randomized clinical trial. *JAMA - J Am Med Assoc*. **2014**, *311*, 263-270. doi:10.1001/jama.2013.285718
4. Benson AB, Al-Hawary MM, Arain MA, et al. *NCCN Guidelines Version 1.2021 Rectal Cancer Version 1.*; 2021.
5. Grossmann I, de Bock GH, Meershoek-Klein Kranenbarg WM, van de Velde CJH, Wiggers T. Carcinoembryonic antigen (CEA) measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery. A retrospective study of CEA values in the TME trial. *Eur J Surg Oncol*. **2007**, *33*, 183-7. doi:10.1016/j.ejso.2006.10.035.
6. Stevens DP, Mackay IR. Increased carcinoembryonic antigen in heavy cigarette smokers. *Lancet*. **1973**, *2*, 1238-9. doi: 10.1016/s0140-6736(73)90975-6.
7. Fukuda I, Yamakado M, Kiyose H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. *Journal of Medical Systems*. **1998**, *22*., 89-93. doi:10.1023/A:1022643102208.
8. Sajid KM, Chaouachi K, Mahmood R. Hookah smoking and cancer: Carcinoembryonic antigen (CEA) levels in exclusive/ever hookah smokers. *Harm Reduct J*. **2008**, *5*, 19. doi:10.1186/1477-7517-5-19.
9. Sung S, Son SH, Kay CS, Lee YS. Prognosis Can Be Predicted More Accurately Using Pre- and Postchemoradiotherapy Carcinoembryonic Antigen Levels Compared to Only Prechemoradiotherapy Carcinoembryonic Antigen Level in Locally Advanced Rectal Cancer Patients Who Received Neoadjuvant Chemoradiotherapy. *Medicine (Baltimore)*. **2016**, *95*, e2965. doi:10.1097/MD.0000000000002965
10. Giessen C, Nagel D, Glas M, et al. Evaluation of preoperative serum markers for individual patient prognosis in stage I-III rectal cancer. *Tumor Biol*., **2014**, 35, 10237-48. doi:10.1007/s13277-014-2338-6
11. Auclin E, Taieb J, Lepage C, et al. Carcinoembryonic antigen levels and survival in stage III colon cancer: Post hoc analysis of the MOSAIC and PETACC-8 trials. *Cancer Epidemiol Biomarkers Prev*. 2019;28(7):1153-1161. doi:10.1158/1055-9965.EPI-18-0867
12. Smoragiewicz M, Lim H, Peixoto RDA. Surveillance for asymptomatic recurrence in resected stage III colon cancer: Does it result in a more favorable outcome? *J Gastrointest Oncol*, **2015**, 6, 268-73. doi:10.3978/j.issn.2078-6891.2015.019
13. Saito G, Sadahiro S, Okada K, Tanaka A, Suzuki T, Kamijo A. Relation between Carcinoembryonic Antigen Levels in Colon Cancer Tissue and Serum Carcinoembryonic Antigen Levels at Initial Surgery and Recurrence. *Oncology*, **2016**, *91*, 85-9.
14. Hao C, Zhang G, Zhang L. Serum CEA levels in 49 different types of cancer and noncancer diseases. In: *Progress in Molecular Biology and Translational Science*. Vol 162. Elsevier B.V.; 2019:213-227. doi:10.1016/bs.pmbts.2018.12.011
15. Rule AH, Goleski-Reilly C, Sachar1 DB, Vandevoorde J, Janowitz HD. Circulating carcinoembryonic antigen (CEA): Relationship to clinical status of patients with inflammatory bowel disease. *Gut*. **1973**, *14*, 880-4. doi:10.1136/gut.14.11.880

16. Turk O. The diagnostic value of tumor markers and endoscopy in patients with gastric disorders. *Arch Clin Exp Surg*. **2015**, 4, 74-8. doi:10.5455/aces.20140531053930
17. Kojima O, Tanioku T, Kitagawa N, et al. Immunoreactive carcinoembryonic antigen in gastric juice in patients with gastric cancer. *Jpn J Surg*. **1983**, *13*, 324-30. doi:10.1007/BF02469514
18. Sekizaki T, Yamamoto C, Nomoto H. Two cases of transiently elevated serum CEA levels in severe hypothyroidism without goiter. *Intern Med*. **2018**, *57*, 2523-6. doi:10.2169/internalmedicine.0764-18
19. Liang Y, Tang W, Huang T, et al. Genetic variations affecting serum carcinoembryonic antigen levels and status of regional lymph nodes in patients with sporadic colorectal cancer from southern China. *PLoS One*. **2014**, 9. doi:10.1371/journal.pone.0097923
20. Kang HY, Choe EK, Park KJ, Lee Y. Factors Requiring Adjustment in the Interpretation of Serum Carcinoembryonic Antigen: A Cross-Sectional Study of 18,131 Healthy Nonsmokers. *Gastroenterol Res Pract*. **2017**. doi:10.1155/2017/9858931
21. Mitchell NJ, Hinder V, Murray M, et al. Transient increase in serum CEA while on adjuvant chemotherapy for colon cancer: Is this of prognostic importance? *J Clin Oncol*. **2014**, *32*, 654. doi:10.1200/jco.2014.32.3_suppl.654