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Revisiting *ab initio* carcinoembryonic antigen and CA19-9 tumor markers in colorectal carcinoma in association with anatomotopographic location and staging of disease

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SUMMARY

OBJECTIVE: This study purposed to evaluate preoperative two tumor markers, namely, carcinoembryonic antigen and carbohydrate antigen (CA)19-9, in colorectal cancer for anatomotopographic location with disease stage and to assess their utility for diagnostic staging purposes.

METHODS: The study retrospectively incorporated patients who had undergone surgery for colorectal cancer at our department in 2015–2018 and in whom carcinoembryonic antigen and CA19-9 tumor markers had been preoperatively analyzed. The obtained data were then statistically processed using R-project.

RESULTS: A total of 155 patients had been incorporated, of whom 96 (62%) were men and 59 (38%) were women. Rectum was the most common location (74 patients, 48%), and the least represented stage was IV (18, 12%). The marker carcinoembryonic antigen was obtained in all 155 cases, while CA19-9 was in 105. The median carcinoembryonic antigen was 3 (0.34–1104.25), and the median CA19-9 was 12 (0.18–840.00). A significance was recognized between median carcinoembryonic antigen and disease stage (p-value=0.016), with stages I, II, and III (medians 2, 3, and 2) different from stage IV (median 13), while no significance for CA19-9 was recognized (p-value=0.343). No significance between either marker and location (carcinoembryonic antigen: p=0.276; CA19-9: p=0.505) was detected. The testing was performed at a significance level of alpha=0.05.

CONCLUSION: This study revealed a significance between the marker carcinoembryonic antigen, but not CA19-9, and the disease stage, while no relationship of either of these markers with tumor location was found. Herewith, the study confirmed that higher carcinoembryonic antigen values may suggest the finding of more advanced forms of colorectal cancer and thus a worse prognosis of this malignant phenomenon.

KEYWORDS: Colorectal cancer. Tumor markers. Carcinoembryonic antigen. Surgery. Pathology.

INTRODUCTION

Colorectal cancer (CRC) is considered a disease of civilization, representing a serious global health and economic problem. In 2020, more than 1.9 million new cases of colorectal (including anus) cancer were diagnosed worldwide and 935,000 patients died of this diagnosis. It is the most common gastrointestinal malignancy in developed countries, and its global incidence keeps increasing. The current incidence rate, of both sexes, ranks CRC as the third most common malignancy after breast cancer and lung cancer, while it is second only to lung cancer in mortality[1]. In the Czech Republic, approximately 8,000 patients are diagnosed with this disease every year and approximately 4,000 die of it. However, in recent years, there has been a decline in both incidence and mortality. Specifically, in 2018, 7,437 patients were diagnosed with CRC and 3,550 patients died of CRC[2].

Many years of research on the available global data show that the carcinogenesis of CRC is associated with lifestyle, type of diet, smoking, and the influence of the environment in which one lives and works. A sedentary lifestyle and a general

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lack of exercise, an inadequate diet low in fiber and vitamins, as well as stress have a significant impact on the development of the disease[3]. Carcinogenesis is a long, complex, and gradual process. Epithelial cells are subject to abnormal proliferation under genetic influence, leading to the creation of new clones. Of note, if new clones pass unrecognized by suppressor genes (or if these genes are damaged so that they are unable to recognize the changes at the level of DNA), then they proliferate unperturbed and form the basis of a tumor[4].

Before initiating treatment of CRC, it is essential to fully examine the patient using imaging modalities and determine the disease's clinical stage. Staging aims to determine the extent of local tumor spread and the extent of lymph node involvement and to evaluate whether distant metastases are present. Colonoscopy, *per se*, is the gold standard in the diagnosis of colorectal neoplasia due to its high sensitivity and the possibility of performing biopsy as well as therapeutic procedures. As such, colonoscopy is usually followed by other imaging modalities, namely, a CT scan of the lungs, abdomen, and small pelvis, contrast-enhanced ultrasonography in order to determine the presence, number, and size of liver metastases, endoscopic sonography, and magnetic resonance imaging (MRI) of the small pelvis where the rectum is involved. Basic laboratory tests (i.e., blood count and biochemistry) including the tumor markers complement the diagnostic procedures. The therapy is then determined based on carefully performed staging[5].

Although carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 are the most commonly used tumor markers in CRC staging, the role of these tumor markers in screening, early detection of disease recurrence, or as prognostic or predictive factors for CRC is still debated. *Grammatici certant.* Therefore, this study aimed to determine whether the preoperative levels of the tumor markers CEA and CA19-9 can indicate the location of the tumor within the colon and whether the preoperative levels of these markers can predict the clinical staging of this malignant phenomena and thus the prognosis of the patients.

METHODS

Study design

The study was designed as a retrospective analysis of preoperative CEA and CA19-9 tumor markers in cases who had undergone surgery for CRC at the Department of Surgery, University Hospital Ostrava, Ostrava, Czech Republic, from 2015 to 2018. All the cases had undergone a preoperative colonoscopy and a biopsy, based on which the diagnosis of CRC was established. Colonoscopy and histopathological examination of the preoperative samples had been performed at multiple departments within the region before referring the cases to the Department of Surgery of the University Hospital Ostrava. We had supplemented the previously determined staging with additional imaging methods, especially CT of the lungs, abdomen, and small pelvis, which was supplemented by MRI or endoscopic ultrasonography for rectal tumors.

Using these examinations, the preoperative staging of the tumor was determined and patients were classified according to the current TNM classification. Based on these data, the optimal treatment strategy was determined. All included cases had been indicated for surgical treatment of CRC (i.e., all had undergone resection); in some of them, surgery was performed after neoadjuvant chemoradiotherapy. The CEA tumor marker had been collected preoperatively in all 155 patients, and the CA19-9 tumor marker had been collected in 105. The laboratory samples had been processed and evaluated by the Institute of Laboratory Medicine, University Hospital Ostrava. The surgically obtained tumor (including the entire colon resection) was sent to the Institute of Pathology of the University Hospital Ostrava for processing and final TNM classification.

Statistical analysis

The Shapiro-Wilk test was used to test the normality of the data. Of note, none of the variables had a normal distribution; therefore, nonparametric tests were used for statistical analysis. The Kruskal-Wallis rank test was used as a nonparametric alternative to the one-factor analysis of variance to test significance across multiple groups. In addition, Dunn's multiple comparison test was utilized for *post hoc* analysis in case of multiple comparisons. Testing was performed at the level of significance of alpha=0.05. Statistical analysis was calculated using R-project[6] with the following packages: dplyr, ggplot2, and Dunn's test.

RESULTS

A total of 155 patients who had undergone surgery for CRC in 2015–2018 and in whom CEA (and, in most instances, CA19-9) tumor markers were collected preoperatively were included in the study, of whom 98 patients (62%) were men and 59 (38%) were women. Laparoscopic surgery had been performed in 107 (69%) cases, while the conventional, i.e., open, surgical technique had been employed in 48 (31%) patients. The median CEA for all patients was 3 (range 0.34–1104.25), and the median CA19-9 was 12 (range 0.18–840.00).

The number of cases and CEA and CA19-9 medians concerning disease stage classification are shown in Table 1.

Statistical analysis was performed to evaluate the significance between the medians of CEA and CA19-9 markers and the disease stage and/or disease location. The analysis revealed a statistically significant association between the median CEA tumor markers according to the disease stage (p-value=0.016, Kruskal-Wallis test). Figure 1A demonstrates that stages I–III formed a relatively homogeneous group with similar CEA medians, and CEA median in stage IV patients was found to have no significance (for clarity, a logarithmic scale was used for the marker values), and the conclusion was confirmed by *post hoc* analysis (Dunn's test). No statistical significance was recognized between CA19-9 medians and the disease stage as shown in Figure 1B (p=0.343, Kruskal-Wallis test). In addition, the possible association of tumor markers with tumor location had been investigated. Figure 2 obviates no statistical significance between medians of CEA (Figure 2A; p-value=0.276, Kruskal-Wallis test) or CA19-9 (Figure 2B; p-value=0.505, Kruskal-Wallis test) and location.

DISCUSSION

De facto, the use of tumor markers in screening for CRC, in early detection of the disease recurrence, or as prognostic or predictive factors still remains under debate, and no clear consensus has been established to date. *Ad fontes,* CEA and CA19-9 are well-known tumor markers used in the preoperative staging and postoperative follow-up of CRC, especially in cases undergoing chemotherapy. As such, CEA is an oncofetal tumor marker discovered by Gold and Freedman[7] and remains the only tumor marker with recognized efficacy in the monitoring of the treatment modalities in CRC. Originally, it was considered to be specific for CRC, but its elevated levels were also detected later in other cancers, such as gastric and pancreatic cancer, as well as in inflammatory conditions, such as ulcerative colitis, liver cirrhosis, chronic bronchitis, and smokers. The European Group on Tumor Markers (EGTM), in line with other societies (i.e., European Society of Medical Oncology and American Society of Clinical Oncology), does not recommend utilizing CEA for screening purposes. However, the EGTM recommends the determination of preoperative CEA levels in newly diagnosed CRC cases. Although diagnosis[8-12] remains crucial for this malignant phenomenon, the preoperative CEA level provides some prognostic information and, in addition, serves as a baseline for follow-up[8-10,13-15]. Our study supports

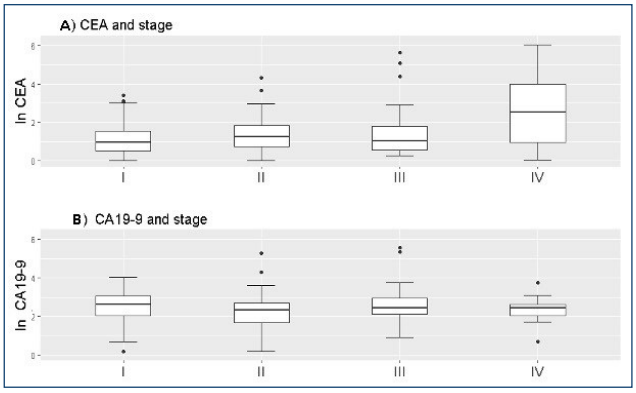

Figure 1. The tumor markers and the stage (logarithm of marker values). (A) Carcinoembryonic antigen – significant association. (B) CA19-9 – no significant association.

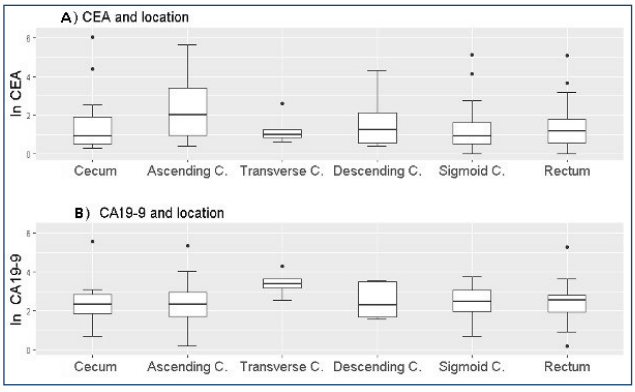

Figure 2. The tumor markers and the location (logarithms of marker values). Neither of the markers has any relationship to the location. (A) Carcinoembryonic antigen; (B) CA19-9.

Table 1. Characteristics of carcinoembryonic antigen and CA19-9 markers according to the disease stage.

Stage	I	II	III	IV	p-value
CEA					
n (%)	47 (30%)	43 (28%)	47 (30%)	18 (12%)	
Median (CI)	2 (2–4)	4 (3–6)	3 (2.5)	31 (8–142)	0.016
CA19-9					
n (%)	30 (29%)	34 (32%)	28 (27%)	13 (12%)	
Median (CI)	14 (11–19)	11 (8–16)	14 (10–20)	22 (9–451)	0.343

these conclusions by demonstrating a statistically significant association between CEA and disease stage (specifically, stage IV). In addition, CA19-9 is a tumor antigen whose elevated serum levels were observed in metastatic CRC, i.e., stage IV[13]. However, this study did not demonstrate an association of CA19-9 with the disease stage. Vukobrat-Bijedic et al.[3], based on their study involving 91 patients, extremely elevated CEA and CA19-9 values in tumors localized in the right colon. On the contrary, Nakatani et al.[16] reported extremely elevated CEA and CA19-9 values in a patient with CRC localized in the sigmoid colon. A CT scan did not reveal metastasis in this case. However, our study did not demonstrate a dependence of either of the two studied markers on tumor location.

The usability of the CEA and CA19-9 tumor markers in the management of CRC is still ambiguous. Several studies focus on these markers but often reach contradictory conclusions. We recorded a higher incidence of tumors in the distal parts of the colon (i.e., rectum and sigmoid colon), which is in accordance with the results mentioned by most authors. Regarding the prediction of tumor location in the colon, however, our study did not confirm any dependence of preoperatively measured values of these markers on tumor location. However, we did demonstrate a statistically significant dependence of preoperative CEA values on the disease stage, i.e., stage IV. Thus, herein, in agreement with most studies, we might postulate that CEA can be utilized as a definite prognostic factor for CRC. However, our study did not state such a relationship for CA19-9.

Limitations

This study has some limitations. CA19-9 had not been collected in all the cases, leading to the sample being limited. As such, it could also be argued that the number of patients included in this study (155 cases) is still relatively limited, especially given the number of cases with tumors in individual locations, but this number of subjects is similar to or higher than those reported in similar studies.

CONCLUSION

This study demonstrated a statistically significant relationship between the tumor marker CEA (but not CA19-9) and disease stage, while neither the CEA nor CA19-9 was associated with the topographic tumor location of CRC. As such, our preliminary outcomes are, therefore, following most of the previously reported studies, i.e., that higher CEA values may suggest the presence of a more advanced form of CRC and, therefore, a worse prognosis which was, however, not valid for marker CA19-9. *Nothing new under the sun.* Nevertheless, although CEA in stage IV disease is significantly elevated compared with others, neither CEA nor CA19-9 appears to be suitable markers for CRC screening. This issue merits further investigation.

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AUTHORS' CONTRIBUTIONS

ML: Conceptualization, Data curation, Formal Analysis, Funding, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. D**S:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **IS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **MP:** Methodology, Project administration, Validation, Visualization. **WG:** Methodology, Project administration, Validation, Visualization. **VJ:** Methodology, Project administration, Validation, Visualization. T**M:** Methodology, Project administration, Validation, Visualization. H**T:** Methodology, Project administration, Validation, Visualization. **LP:** Methodology, Project administration, Validation, Visualization. **AP:** Investigation, Methodology, Validation, Visualization.

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