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ORIGINAL ARTICLE

Prognostic value of preoperative carcinoembryogenic antigen: Is it useful in all stages of colorectal cancer?☆

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Abstract
Introduction: Recent reports have reopened discussion of the prognostic value of elevated pretreatment carcinoembryonic antigen (CEA) levels in colorectal cancer. Due to the discrepancies in the published results, we aimed to analyze the possible predictive value of CEA, both overall and in different tumoral stages in our environment.
Patients and methods: We retrospectively studied 303 consecutive patients with colorectal cancer resected with curative intent by analysing tumour-related mortality. The frequency of patients with increased CEA levels (>5 mg/L) was registered. Univariate and multivariate analyses of survival curves were performed, comparing patients with increased CEA levels and those with CEA levels within normal limits, both in the overall series and in the different pTNM tumoral stages.
Results: Frequency of patients with CEA > 5 mg/L was 31%. The median clinical follow-up was 83 months. A poor survival rate was registered in the multivariate analysis of the whole series in patients with high CEA levels: hazard ratio (HR) = 1.81; 95% confidence interval (95% CI) = (1.15–3.10); $p = 0.012$. This predictive value was only maintained in stage II in the survival analysis of the distinct tumoral stages (n = 104): HR = 3.02; 95% CI = (1.22–7.45); $p = 0.017$.
Conclusions: Before treatment, 31% of our patients with colorectal cancer resected with curative intent had pathological CEA values. In the overall series, a high pretreatment CEA level showed an independent prognostic value for poor survival. When pTNM tumoral stages were analyzed separately, CEA level had predictive value only in pTNM II tumours.

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PALABRAS CLAVE
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Valor pronóstico pretratamiento del antígeno carcinoembrionario en el cáncer colorrectal operado. ¿Es útil en todos los estadios del tumor?

Resumen
Introducción: Publicaciones recientes han reactivado la discusión sobre el valour pronóstico de la elevación pretratamiento del antígeno carcinoembrionario (CEA) en el cáncer colorrectal. Debido a los resultados discordantes comunicados, pretendemos analizar en nuestro medio esta posible capacidad predictiva, globalmente y en los diferentes estadios tumorales.
Pacientes y métodos: Estudiamos retrospectivamente 303 cánceres colorrectales resecados consecutivamente con intención curativa, analizando la mortalidad debida al tumour. Determinamos la frecuencia de casos con CEA pretratamiento patológico (>5 mg/l). Comparamos mediante análisis univariante y multivariante las curvas de supervivencia entre los casos con CEA normal y patológico, tanto en el global de la serie como en los diferentes estadios pTNM.
Resultados: La frecuencia de pacientes con CEA > 5 mg/l fue del 31%. La mediana de seguimiento clínico alcanzó los 83 meses. En el análisis multivariante de la serie global, la supervivencia fue desfavorable para los casos con CEA elevado: *hazard ratio* (HR) = 1,89; intervalo de confianza al 95% (IC 95%) = (1,15−3,10); p = 0,012. Al efectuar el análisis de supervivencia en los diversos estadios, únicamente se mantiene el valour predictivo en el estadio II (n = 104): HR = 3,02; IC 95% = (1,22−7,45); p = 0,017.
Conclusiones: Antes del inicio del tratamiento, un 31% de nuestros cánceres colorrectales resecados con intención curativa presentaron unos valores patológicos de CEA. Considerando la serie globalmente, la elevación del CEA pretratamiento presenta, de modo independiente, un valour pronóstico desfavorable sobre la supervivencia, pero al analizar su valour predictivo según los diferentes estadios, solo mantiene su significación en el estadio pTNM II.

Introduction

Carcinoembryonic antigen (CEA) is an intracellular glycoprotein belonging to the immunoglobulin superfamily. It is present in low concentrations in embryonic and foetal intestine, and can also be found in insignificant amounts in the blood of healthy adults.[1] As early as 1965, Gold et al.[2] reported overexpression of CEA in 90% of colorectal cancer (CRC) tissue samples. Elevated serum CEA can also be found in other malignant processes, such as lung and breast cancer, or in benign conditions such as inflammatory bowel disease, diffuse liver disease and pancreatitis.[3,4]

CEA has been the most universally accepted and widely-used marker in CRC for decades.[5] Following early publications describing high CEA levels in this disease,[6] a Canadian study[7] reported increased CEA in 35 of 36 CRCs, with no false positives. These results, which suggest a high diagnostic value, have not been confirmed, and the use of CEA for both screening and early diagnosis of CRC is not currently recommended due to its poor cost-effectiveness ratio.[8] Most interest in the study of CEA has therefore centred on the determination of its possible prognostic utility in CRC.

In Spain, more cases of CRC are diagnosed annually than any other cancer.[9] In addition to its high incidence, CRC is also associated with high mortality rates: it is the second leading cause of cancer-related death in Europe,[10] and causes 12,000 deaths annually in Spain.[9] Since risk for mortality varies greatly between individuals, it is very important to establish a prognosis as near to the time of tumour diagnosis as possible. Among the many predictive parameters proposed, postoperative tumour staging or pTNM is still considered the gold standard.[11] However, major variations in mortality have been observed among patients classified in the same tumour stage.[12,13] This limits the utility of the staging system, and raises the need for other prognostic variables not related to the pTNM classification.[14]

The predictive value of CEA has been analyzed in different circumstances. In some studies, levels of this marker measured at tumour diagnosis have been evaluated, both to assess the overall prognosis[14,15] and to predict the response to neoadjuvant treatment,[16–18] while others have examined persistently high CEA levels following surgery or administration of neoadjuvant treatment as a predictor of adverse prognosis.[5] Finally, some authors have suggested periodically monitoring CEA levels during postoperative follow-up, since elevated values would lead to early suspicion of metastases or tumour recurrence, thereby increasing the chances that a new treatment might be curative.[3,5,19]

Despite numerous studies, the use of elevated pretreatment CEA as an independent predictor of prognosis in CRC[1,15,20] remains uncertain, as recent studies have questioned its value.[21,22] The last few years have seen a growing interest in the notion that the prognostic utility of pretreatment CEA differs in different TNM stages, which could help explain the discrepancy in results.[14] Most studies in this context have been conducted in Asian patients, leading to the hypothesis that ethnicity could influence the evolution of CRC,[23] and that this factor could have biased the study results. The few studies carried out in