Assessment of staging, prognosis and mortality of colorectal cancer by tumor markers: receptor erbB-2 and cadherins[1]

Avaliação do estadiamento, prognóstico e mortalidade do câncer colorretal mediante marcadores tumorais: receptor erbB-2 e caderinas

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ABSTRACT

Purpose: To evaluate the prognostic significance and correlation with staging and degree of cell differentiation of the tumoral expression of the proteins c-erbB-2 and E-cadherin, in patients with colorectal adenocarcinoma. **Methods**: The study included 117 patients with an average age of 63.1 years and an average follow-up duration of 28.1 months. The disease-free interval, survival, incidence of recurrence and specific mortality were evaluated. c-erbB-2 anti-oncoprotein antibodies (Dako) were utilized via the streptavidin-biotin technique. Samples were considered to be positive for c-erbB-2 if 10% or more of the tumor cell membranes were stained.The anti-E-cadherin antibodies (Dako), evaluated this protein and is considered positive, if 50% or more of the cell membranes were stained. Statistical analysis was performed using Pearson's chi-squared test, Fisher's exact test, Kaplan-Meier's estimator, the log-rank test and Wilcoxon's test (Breslow version), setting the level of statistical significance at 5% ($p<0.05$). **Results**: 52 of 108 patients studied for c-erbB-2 were positive (48,1%), 47 of 93 patients studied for E-cadherin were negative (50,5%). These data do not express any correlation with TNM (tumor, node and metastasis) staging and the degree of cell differentiation or with the tumor recurrence rate. The disease-free interval among patients who were positive for c-erbB-2 and negative for E-cadherin was 68.0 months and did not differ from those with c-erbB-2 negative and E-cadherin positive (55.0 months - $p = 0.5510$). The average survival among patients positive for c-erbB-2 and negative for E-cadherin was 75 months without statistical significance difference with the other group (61 months - $p = 0.5256$). Specific mortality occurred in 20.0% of the cases and did not correlate with the expression of c-erbB-2 ($p=0,446$), E-cadherin ($p=0,883$). **Conclusion**: The tumoral expression of c-erbB-2 and E-cadherin did not demonstrate a correlation with the staging and degree of cell differentiation, and it did not present prognostic value regarding disease recurrence, disease-free interval, survival and specific mortality among patients with colorectal adenocarcinoma.

Key words: Colorectal neoplasms. Tumor markers, biological. Receptor, erbB-2. Cadherins. Immunohistochemistry. Prognosis.

RESUMO

Objetivo: Avaliação da expressão tumoral das proteínas c-erbB-2 e E-caderina e sua relação com o prognóstico, estadiamento e grau de diferenciação celular, em doentes com câncer colo-retal . **Métodos**: O estudo incluiu 117 doentes com média de idade de 63.1 anos e com acompanhamento médio de 28.1 meses. O intervalo livre de doença, sobrevida, índice de recidiva e mortalidade específica foram os parâmetros avaliados. Anticorpos anti-oncoproteína c-erbB-2 (Dako) foram utilizados pela técnica da estreptavidiva-biotina. Considerou-se como positiva a presença desta proteína quando mais de 10% das células tumorais estivessem coradas. A proteína E-caderina foi estudada pelo anticorpo anti-E-caderina (Dako), sendo computada como positiva a amostra que apresentasse 50% ou mais das células coradas. A análise estatística utilizou o teste do qui-quadrado de Pearson, o teste exato de Fischer, a curva de Kaplan-Meier, o teste de log-rank e o teste de Wilcoxon (variante de Breslow),sendo estabelecido nível de significância de 5%($p<0,05$). **Resultados**: 52 de 108 doentes estudados para c-erbB-2 foram positivos (48,1%), 47 de 93 doentes estudados para E-caderina foram negativos (50,5%). Estes dados não mostraram relação com estadiamento TNM (tumor, nódulo e metástase), com o grau de diferenciação celular e índice de recidiva tumoral. O intervalo livre de doença para os doentes positivos para c-erbB-2 e negativos para E-caderina foi de 68.0 meses e não diferiu daqueles que foram negativos para c-erbB-2 e positivos para E-caderina (55.0 meses - $p = 0.5510$). A sobrevida média para os doentes positivos para c-erbB-2 e negativos para E-caderina foi 75 meses sem diferença estatisticamente significante com o outro grupo de comparação(61 meses - $p = 0.5256$). A mortalidade específica foi de 20.0% dos casos e não se correlacionou com a expressão do c-erbB-2 ($p=0,446$) ou da E-caderina($p=0,883$).

Conclusão: A expressão das proteínas c-erbB-2 e E-caderina em doentes portadores de adenocarcinoma colo-retal não apresentou correlação com o estadiamento e grau de diferenciação celular. Não houve da mesma forma relação com o prognóstico, no que diz respeito ao índice de recidiva da doença, intervalo livre de doença, sobrevida e mortalidade específica.

Descritores: Neoplasias colorretais. Marcadores biológicos de tumor. Receptor, erbB-2. Caderinas. Imunohistoquímica. Prognóstico.

Introduction

Although the advances in the surgical treatment of colorectal cancer have given rise to improvements in survival among patients with tumors in their initial stages, treatment of more advanced cancer has not resulted in such significant improvements in patient survival. Patients'prognoses have mainly been based on their anatomopathological staging. However, differences have been observed among patients within the same anatomopathological staging group. The significant differences observed in the evolution of such patients justify why the search for tumor markers has taken on great relevance within clinical research. Such markers would enable the classification of patients into subgroups with specific markers for staging and prognosis and would thus assist in the recognition and treatment of new patients with these same markers, especially in relation to those at Dukes stages B and C [1]. Study of the molecular biology of the tumor by means of tumor markers could therefore, for example, assist in the identification of patients with a greater capacity to benefit from adjuvant therapy at stage III. Thus, the present study had the objective of evaluating the tissue expression of the proteins c-erbB-2 and E-cadherin, separately and in association, and correlating this with the anatomopathological staging, the degree of cell differentiation, disease-free interval, disease recurrence rate, survival and specific mortality, among patients who had been submitted to surgical resection due to colorectal adenocarcinoma.

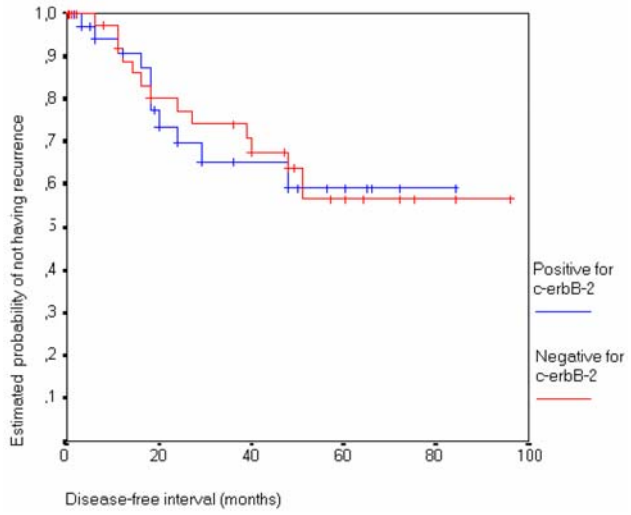
Methods

The study was approved by the Institution Ethics Committee and included 117 patients with colorectal adenocarcinoma undergoing surgical treatment, of whom 53 (45.3%) were male and 64 (54.7%) were female. Their ages ranged from 30 to 87 years, with an average of 63.1 years. Among these patients, 90 (76.9%) had been submitted to surgery that had a curative aim, while in 27 cases (23.1%), the surgery was considered to be palliative. With regard to TNM (tumor, node and metastasis) staging, 30 patients were in stage I (25.6%), 21 in stage II (18.0%), 30 (25.6%) in stage III and 36 (30.8%) in stage IV. Concerning the degree of cell differentiation presented, there was predominance of patients with tumors of grade I (well differentiated - 55 patients - 47.0%) and grade II (moderately differentiated - 60 patients - 51.3%), while grade III (poorly differentiated) was only seen in two cases (1.7%). The follow-up was directed towards the disease-free interval, incidence of recurrence, average survival and specific mortality. The duration of the patients' follow-up ranged from 1 to 96 months, with an average of 28.1 months. The biological samples were fixed in formalin and embedded in paraffin. Sections of 4 µm in thickness were cut for the immunohistochemical reaction. These were mounted on slides that had previously been silanized (3-aminopropyl triethoxysilane, Sigma A-3648, USA) and were left in a glass cabinet at 60º C for 24 hours to maximize the adhesion of the sections. Areas of representative sections were stained using hematoxylin-eosin to allow identification of regions of interest within the tumor tissue, for the immunohistochemical reaction. The streptavidin-biotin-peroxidase technique was utilized with the following monoclonal antibodies: c-erbB-2 anti-oncoprotein antibodies, code 1:485 (Dako, Denmark); and anti-E-cadherin antibodies, clone NCH-38 (Dako, Denmark). For the evaluation of the expression of the protein c-erbB-2, the sections were examined semi-quantitatively under an optical microscope, with sweeping of the slide at a magnification of 400x, over at least ten fields. For the analysis of the immunohistochemical and morphological associations, the tumors were also classified as positive or negative for c-erbB-2. They were considered to be positive only when there was immunological reactivity of the cell membrane that involved at least 10% of the tumor cells. For the marker E-cadherin, the slides were also examined under the optical microscope. Positivity was evaluated via the presence of brown staining on the cell membrane, and the tumors were considered to be positive for E-cadherin when such staining was present in 50% or more of the cells analyzed. The following were utilized in the statistical analysis: Pearson's chi-squared test[2], Kaplan-Meier, log-rank test, Wilcoxon's test (Breslow version)[3], Pearson's chi-squared test and Fisher's test. $P < 0.05$ was considered statistically significant.

Results

Among these patients, 48.1% were positive for c-erbB-2 (52/108), 50.5% were negative for E-cadherin (47/93) and 24.0% were positive for c-erbB-2 and negative for E-cadherin (20/83). The expression of the markers did not have a significant association with TNM (tumor, node and metastasis) staging and the degree of cell differentiation. The tumor recurrence rate had no correlation with each marcher: c-erbB-2 positive ($p = 0.815$), E-cadherin negative ($p = 0.761$), or its association (c-erbB-2 positive and E-cadherin negative - $p = 0.972$). The disease-free interval was 68 months (range: 54.0-83.0) for patients with tumors that were positive for c-erbB-2 and 67 months (54.0-83.0) for those negative for c-erbB-2, without a statistical difference ($p = 0.9164$) (Figure 1). In the case of E-cadherin, the disease-free interval was 67 months (53.0-81.0) for patients who are positive and 68 months (54.0-83.0) for those negative, without a statistical difference ($p = 0.9164$) (Figure 2). The patients with combination of tumors markers (c-erbB-2 positive and E-cadherin negative) the disease-free interval was 68.0 months (56.0-80.0), without a significant difference ($p = 0.5510$) in relation of no presence of this association 55.0 months (33.0-76.0) (Figure 3). The average

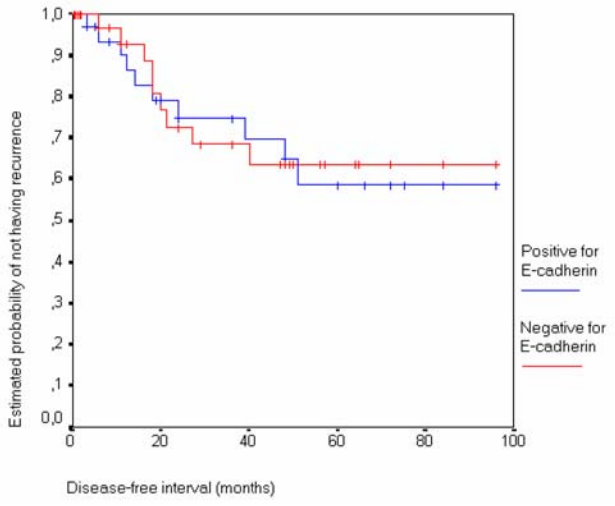
survival among patients with tumors that were positive for c-erbB-2 was 68 months (range: 57.0-83.4) and 73 months (61.0-84.0) for those negative for c-erbB-2, without a significant difference (p = 0.9164)(Figure 4). For those positive for E-cadherin it was 68 months (57.0-83.4), and for those negative for E-cadherin it was 75 months (62.0-89.0), without a significant difference (p = 0.9164) (Figure 5). When the patients show the combination of c-erbB-2 positive and E-cadherin negative, the average survival was 75 months (65.0-88.0), without a significant difference (p = 0.5744) in relation to patients where there was not this association (average survival - 61 months - range : 40.0-83.0) (Figure 6). The specific mortality rate was 20.0% (18/90 patients). Mortality was associated with positivity for c-erbB-2 in 28.8% (15/35), with p = 0.446; negativity for c-erbB-2 in 35.7% (20/35); positivity for E-cadherin in 32.6% (15/31), with p = 0.883; and negativity for E-cadherin in 34.0% (16/31), with p = 0.883. No significant difference was found between the expression of the biological markers and the specific mortality.



c-erbB-2	*Average*	*Confidence interval*
Negative	67.0	53.0 – 81.0
Positive	68.0	54.0 – 83.0

Wilcoxon's test (Breslow version): p = 0,9164

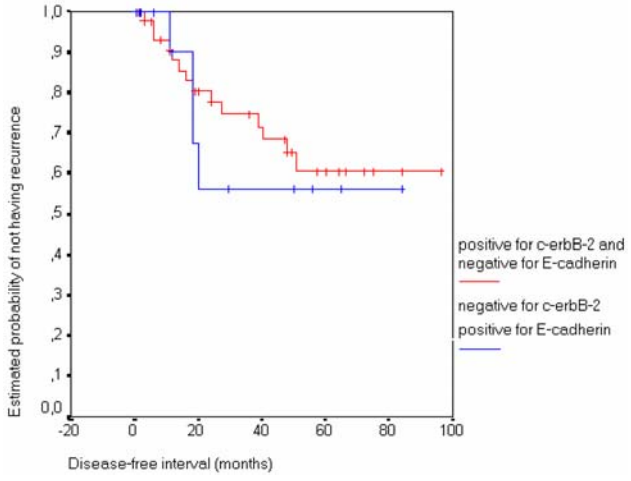
FIGURE 1 - The correlation between the expression of the protein c-erbB-2 and the disease-free interval.



E-cadherin	Average	Confidence interval
Negative	68.0	54.0 – 83.0
Positive	67.0	53.0 – 81.0

Wilcoxon's test (Breslow version): p = 0,9164

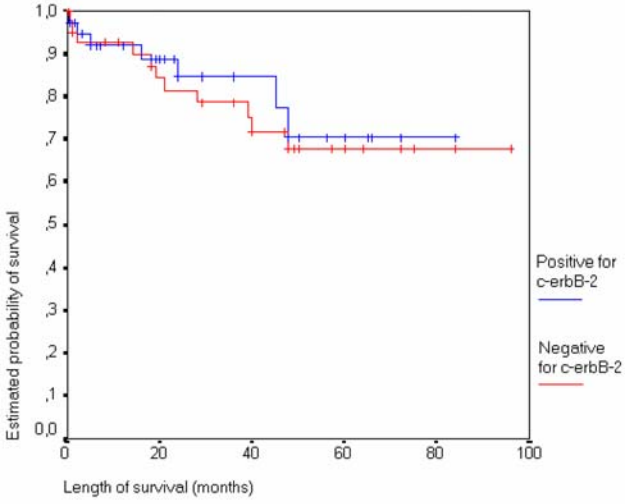
FIGURE 2 - The correlation between the expression of the protein E-cadherin and the disease-free interval.



c-erbB-2 and E-cadherin	*Average*	*Confidence interval*
Negative for c-erbB-2 and positive for E-cadherin	55.0	33.0 – 76.0
Positive for c-erbB-2 and negative for E-cadherin	68.0	56.0 – 80.0

Wilcoxon's test (Breslow version): p = 0,5510

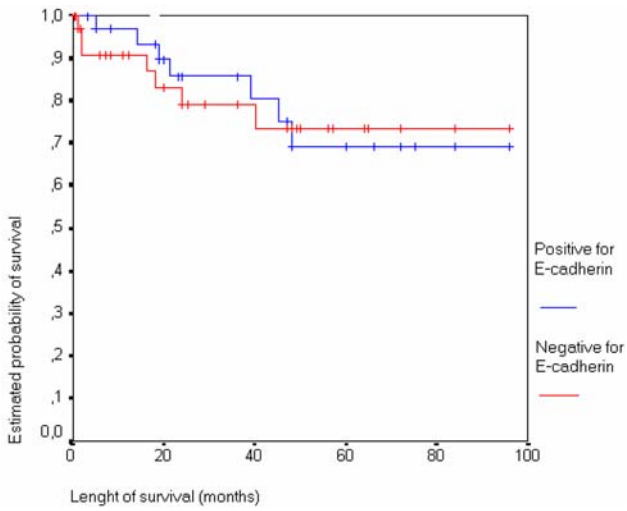
FIGURE 3 - The disease-free interval in relation to the tumor expression of both c-erbB-2 and Ecadherin.



c-erbB-2	Average	Confidence interval
Negative	73.0	61.0 – 84.0
Positive	68.0	57.0 – 83.4

Wilcoxon's test (Breslow version): p = 0,9164

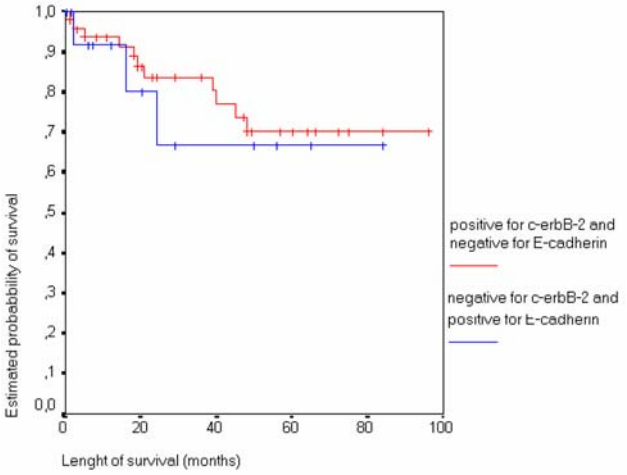
FIGURE 4 - Survival curve for the patients in relation to the tumor expression of c-erbB-2.



E-cadherin	Average	Confidence interval
Negative	75.0	62.0 – 89.0
Positive	68.0	57.0 – 83.4

Wilcoxon's test (Breslow version): p = 0.9164

FIGURE 5 - Survival curve for the patients in relation to the tumor expression of Ecadherin.



c-erbB-2 and E-cadherin	Average	Confidence interval
positive for c-erbB-2 and negative for E-cadherin	75.0	65.0 – 88.0
negative for c-erbB-2 and positive for E-cadherin	61.0	40.0 – 83.0

Wilcoxon's test (Breslow version): p = 0.5744

FIGURE 6 - Survival curve for the patients in relation to the tumor expression of both c-erbB-2 and E-cadherin.

Discussion

Even with improvements in surgical treatment and its association with adjuvant chemotherapy, colorectal cancer still causes high mortality today. Hepatic metastases occur in up to 50% of such patients [4], which justifies the search for new prognostic markers in relation to this disease. Histopathological evaluation of the disease, by means of identifying the degree of tumor invasion, infiltration of the lymphatic ganglia and distant organs, is utilized for defining patients' prognoses. This procedure allows the patients who are at advanced stages to be distinguished from those who are at early stages of the disease [5]. The information obtained from staging using the TNM system, however, is insufficient for making prognoses for patients who are at intermediate stages of tumor invasion, as is the case with patients in stage II, T3-T4N0M0 [6]. In this group, the TNM system is incapable of distinguishing which patients may or may not benefit from having, for example, postoperative chemotherapy associated with their surgical treatment [7]. Thus, the utilization of tumor markers could improve the clinical staging of the disease. Among the large numbers of tumor markers that have been described in the literature, it was decided to study the proteins c-erbB-2 and E-cadherin. The correlation between these two tumor markers is believed to involve hyperexpression of the protein c-erbB-2 caused by amplification of the c-erbB-2 gene, which would lead to reduced transcription of the E-cadherin and alpha-2 integrin genes, with consequent reduction in the expression of the E-cadherin and alpha-2 integrin proteins, thereby causing the loss of cell adhesion, tumor progression and metastasis [8, 9]. The great controversy in the literature and the lack of conclusive studies regarding the real prognostic value of the c-erbB-2 and E-cadherin tumor markers in patients with colorectal adenocarcinoma gave rise to an interest in investigating these variables together. This had the aim of verifying whether they would together acquire some prognostic value. In this respect, the present study would take on great relevance. The transmembrane protein c-erbB-2 is the product of the c-erbB-2 gene. It was identified using the immunohistochemical technique, through observation of the brown staining of the tumor cell membrane, by utilizing anti-c-erbB-2 monoclonal antibodies. The interpretation of immunohistochemical findings regarding c-erbB-2 varies in the literature. The quantity of positive cells needed for defining a result as positive differs according to the study. Some authors have considered that tumors were positive for the c-erbB-2 protein when at least 5% of the tumor cells were stained [10], while others considered that positivity was reached with 10% stained [11]. In the present study, whenever slides presented staining of more than 10% of the tumor cells, they were considered positive for the presence of the c-erbB-2 protein. Thus, 51.9% of the patients in the sample studied were positive for the expression of this protein. This rate is similar to findings in the literature [9,10,11]. The protein E-cadherin was also identified using the immunohistochemical technique, through observation of the brown staining of the tumor cell membrane. The cutoff point for positivity of the expression of E-cadherin varies in the literature. Some authors have defined that tumor cells are positive for the expression of E-cadherin, when 90% of these cells are stained using the immunohistochemical technique [12,13]. Other authors have defined positivity as 80% and 50% of the cells stained, respectively[14, 15]. Great diversity in the results obtained using the immunohistochemical method in colorectal adenocarcinoma, regarding the expression of E-cadherin, can be seen in the literature. The detection rates for E-cadherin have varied from 29% [12] to 79% [15] of patients. Other studies have obtained results that are similar to each other, with an E-cadherin detection rate of around 50% of

the colorectal tumors analyzed [16, 17]. In the present study, patients who presented staining of more than 50% of the tumor cell membranes were considered to be positive for the expression of E-cadherin. The detection rate for E-cadherin expression in the present study was 50.5%, a result that is in agreement with the latter authors cited above. There are studies in the literature that have identified a correlation between expression of the c-erbB- 2 protein and the Dukes classification system[18,19], while others[20,21] have not observed such a correlation. In the present study, no correlation was identified between expression of c-erbB-2 and the TNM staging system. In other words, it was found that positivity for this protein was not related to the grade of the disease, contrary to the findings of some authors cited above. The same can be seen in relation to the protein E-cadherin. Some authors have obtained results that demonstrate a correlation between the presence of this protein and the more advanced stages of the disease [15,16], while others were unable to detect such a correlation [13,17]. In the present study, as in the case of c-erbB-2, no correlation was observed between the expression of E-cadherin and the TNM staging. In other words, the loss of expression of this protein was unrelated to the more advanced stages of the disease. In the present study, in relation to the degree of cell differentiation, there was a predominance of patients with grade I tumors (well differentiated) and grade II tumors (moderately differentiated), while grade III (undifferentiated) was observed in only two patients. There are studies in the literature that have detected correlations of the proteins c-erbB-2[22] and E-cadherin[23] with the degree of tumor differentiation. However, in the present study, no such correlation with the degree of cell differentiation was identified, which may have resulted from the small number of cases of undifferentiated tumors. No studies were found in the literature that reported any relationship between these two markers and the relapse rates for neoplastic disease in colorectal adenocarcinoma. Likewise, the present study did not show a statistically significant association between the proteins studied and tumor relapse. Some authors have observed a correlation between disease-free interval and the expression of c-erbB-2[24] and E-cadherin [16]. In the present study, no correlation was identified between the expression of the tumor markers studied and the disease-free interval. Nor was there a correlation between positivity for c-erbB-2 and negativity for E-cadherin, a situation in which it would be expected that there would be an increase in the invasive potential of the tumor, according to the understanding of carcinogenesis. Studies evaluating the association between the expression of c-erbB-2 and survival have shown controversial results. Some studies have demonstrated reduced survival among patients with immunohistochemical hyperexpression of the protein c-erbB-2[19,24], and also in relation to reduced expression of E-cadherin, in colorectal cancer patients[25]. In other studies, however, no association has been detected between prognosis and the expression of the protein c-erbB-2[21] or, furthermore, between prognosis and the absence of the protein E-cadherin[17]. Similarly, the present study did not present any statistically significant association between the expression of these proteins and survival, either separately or together. Some studies in the literature have been able to find a significant correlation between increased expression of the protein c-erbB-2 and mortality [24], and also between the absence of E-cadherin expression and mortality[16]. However, in the present study, just as for the other clinical variables studied, the tumor markers c-erbB-2 and E-cadherin did not correlate with mortality among the patients studied. The first resultant implication of the present study is that new investigations into tumor markers must be made, with the objective of contributing towards the knowledge of carcinogenesis. Despite not finding a correlation for the tumor markers c-erbB-2 and E-cadherin with the staging and prognosis of colorectal carcinoma in the present study, positivity rates similar to those reported in the literature were found. This demonstrates the reliability of the results obtained and it can therefore be inferred that this study makes a valid contribution to the literature. Correlations between single tumor markers and the prognosis for colorectal cancer do not appear to be encouraging. We believe that research into such correlations should not involve single tumor markers but, rather, this research should be done through a panel of markers. The choice of these markers should be based both on the understanding of carcinogenesis and also on their clinical importance in the prognosis of patients with colorectal cancer.

Conclusion

The tumoral expression of c-erbB-2 and E-cadherin did not demonstrate a correlation with the staging and degree of cell differentiation, and it did not present prognostic value regarding disease recurrence, disease-free interval, survival and specific mortality among patients with colorectal adenocarcinoma.

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