Prognostic value of preoperative carcinoembryonic antigen level in colorectal cancer in Tunisia

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Valeur pronostique du taux préopératoire de l'antigène carcinoembryonnaire dans le cancer colorectal en Tunisie

LA TUNISIE MEDICALE - 2012 ; Vol 90 (n°01) : 41 - 44

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RÉSUMÉ

But : Evaluer la valeur pronostique du taux sérique préopératoire de l'antigène carcino-embryonnaire (ACE) chez des patients atteints d'un cancer colorectal.

Méthodes: Etude rétrospective ayant concerné 125 patients âgés de 14 à 87 ans présentant un cancer colorectal traité entre Janvier 2001 et Décembre 2006. Le dosage sérique de l'ACE en période préopératoire a été réalisé par méthode chemiluminescente.

Résultats: Notre population comportait 57 hommes et 68 femmes répartis selon la classification de Dukes en 2 patients stade A, 24 stade B, 53 stade C et 46 patients stade D. la médiane de la période de suivie était de 24 mois avec des extrêmes de 4 à 72 mois.

Le taux de survie sans rechute était significativement plus élevé chez les patients avec un taux préopératoire d'ACE < 5 ng/ml que chez ceux ayant un taux d'ACE ≥ 5 ng/ml ($p < 0.0001$). Par ailleurs, nous avons observé que le taux de survie sans rechute varie significativement selon le taux d'ACE chez les patients classés stade B ($p = 0.007$) et C ($p < 0.0001$). Cette différence n'existait pas chez les patients classés stade D. L'analyse multi variée montre que le taux préopératoire de l'ACE est un facteur pronostique indépendant (risque relatif : 6.49, 95% CI, 3.09 à 13.62, $p < 0.0001$).

Conclusion: le taux sérique préopératoire de l'ACE est un facteur prédictif de la survenue de rechute des cancers colorectaux. Ce marqueur pourrait être utilisé dans la classification du cancer et être utile pour la sélection des patients pour un traitement donné.

Mots-clés

Cancer colorectal, CEA, facteur Pronostique

SUMMARY

Aim: To evaluate the prognostic value of preoperative serum carcino-embryonic antigen (CEA) level in patients with colorectal cancer.

Methods: This retrospective study included 125 colorectal cancer patients aged from 14 to 87 years, surgically treated between January 2001 and December 2006. Preoperative serum CEA was measured by chemiluminescence assay.

Results: within the patients, 57 were males and 68 females. They have tumours classified Dukes A in 2 patients, B in 24 patients, C in 53 patients and Dukes D in 46 patients. Median follow-up period was 24 months (range, 4 - 72 months).

The relapse-free survival was significantly higher in patients with CEA < 5 ng/ml compared to CEA ≥ 5 ng/ml, ($p < 0.0001$). We observed significant differences in relapse-free survival between patients with CEA < 5 ng/ml and those with CEA ≥ 5 ng/ml among patients classified as Dukes stage B ($p=0.007$) and C ($p < 0.0001$). However, there was no significant difference in relapse-free survival among those classified as Dukes stage D. Cox multivariate analysis demonstrated that preoperative serum CEA level was a significant independent prognostic factor for relapse-free survival (hazard ratio: 6.49, 95% CI, 3.09 to 13.62, $p < 0.0001$).

Conclusion: Preoperative serum CEA is a reliable predictor factor for recurrence in patients with CRC. CEA might be used in staging system and will be useful for therapeutic orientation in patients undergoing curative resection of CRC.

Key-words

Carcino-embryonic antigen, colorectal cancer, prognostic factor

Colorectal cancer (CRC) remains one of the leading causes of cancer related death worldwide (1). Its prognosis is mainly linked to several pathological, clinical and biological parameters. Tumour stage is generally considered the strongest prognostic factor in CRC (2, 3). Several classifications have been proposed for CRC, the Dukes classification from A to D stages still remains the simplest (4). Although, it is well known, that patients with the same Dukes stage display survival heterogeneity, with some patients exhibiting relatively short survival times. Accordingly, the identification of more promising prognostic factors that are highly predictive of CRC patients undergoing surgical treatment is mandatory. To date, a number of studies have been extensively conducted to explore the role of prognostic factors for survival in patients with CRC. Of these parameters, preoperative carcino-embryonic antigen (CEA) level had previously been demonstrated to be a predictive factor of recurrence (5, 6).

The aim of this retrospective study was to evaluate the prognostic significance of preoperative CEA level in Tunisian patients with colorectal cancer.

PATIENTS AND METHODS

This retrospective study included 125 patients with histologically proven CRC who received surgical treatment between January 2001 and December 2006, at Salah Azaiez Institute. Patients with history of other neoplasias (whether benign or malignant), or/and incomplete record of medical charts were excluded. The follow-up period ranged from 4 to 72 months, with a median of 24 months and a mean of 28 months (SD = 23). Any local recurrence and/or distant recurrence following treatment were defined as a postoperative relapse.

Preoperative CEA levels were determined by the Access Immunoassay Systems, based on immuno-chemiluminescence, and values less than 5 ng/ml were considered normal. Samples can be accurately measured inside range: of 0.1 to 1000 ng/ml. We dichotomized continuous variables into two categories for statistical analysis including age: those aged < 55 years (n = 64) and those ≥ 55 years (n = 61); serum CEA level: < 5 ng/ml (n = 58) and ≥ 5 ng/ml (n = 67). All data were analysed using SPSS software version 11.5 for windows. The clinical endpoint of this study was relapse-free survival calculated using the Kaplan-Meier estimation method. Comparisons were done by the Log-Rank test. For univariate statistical analysis, Chi-square test was used. A Cox regression model was applied for multivariate analysis. Variables were included in the multivariate analysis only if the p value less than 0.05 in the univariate analysis. In this analysis five variables were employed: age, sex, tumour location, Dukes stage and preoperative CEA level.

RESULTS

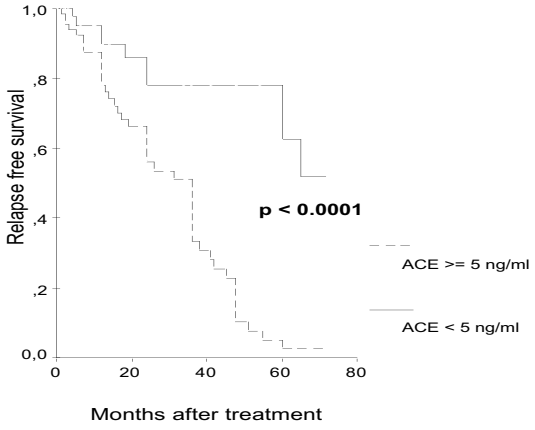
The clinical and pathologic data regarding 125 CRC patients are summarized in table 1. There were 57 (45.6%) males and 68 (54.4%) females. 71 (56.8%) patients had carcinoma of the colon, 52 (41.6%) had carcinoma of the rectum and 2 (1.6%) had carcinoma of colon and rectum. The median age of these patients was 55 years with a range of 14 to 87 years. Sixty four (51.2%) cases were < 55 years old and sixty one (48.8%) cases were ≥ 55 years old. With regard to pathologic classification, according to Dukes stage, as modified by Tumbull et al. (4), there were 2 patients (1.6%) A stage, 24 (19.2%) B stage, 53 (42.4%) C stage and 46 (36.8%) D stage.

Table 1 : Patients characteristics

Variables	Case number	Percentage (%)
Age		
< 55 years / ≥ 55 years	64 / 61	51.2 / 48.8
Gender		
Male / Female	57 / 68	45.6 / 54.4
Tumour location		
Colon / Rectum / Colorectal	71 / 52 / 2	56.8 / 41.6 / 1.6
Dukes Stage		
A / B / C / D	2 / 24 / 53 / 46	1.6 / 19.2 / 42.4 / 36.8
Recurrence		
Presence / Absence	62 / 63	49.6 / 50.4
CEA levels		
< 5 ng/ml / ≥ 5 ng/ml	58 / 67	46.4 / 53.6

Log-Rank test showed that the relapse-free survival was significantly higher in patients who were CEA < 5 ng/ml than those with CEA ≥ 5 ng/ml, p < 0.0001 (figure 1).

Figure 1 : Relapse-free survival in patients according to preoperative CEA serum level



The comparison of relapse-free survival according to Dukes stage showed significant differences in relapse-free survival between patients with CEA < 5 ng/ml and CEA ≥ 5 ng/ml among patients classified as Dukes B stage (p=0.007, figure 2) and C (p < 0.0001, figure 3). However, there was no significant difference in patients classified as Dukes D stage (p = 0.12, figure 4).

Figure 2 : Relapse-free survival in patients with Dukes B according to preoperative serum CEA level

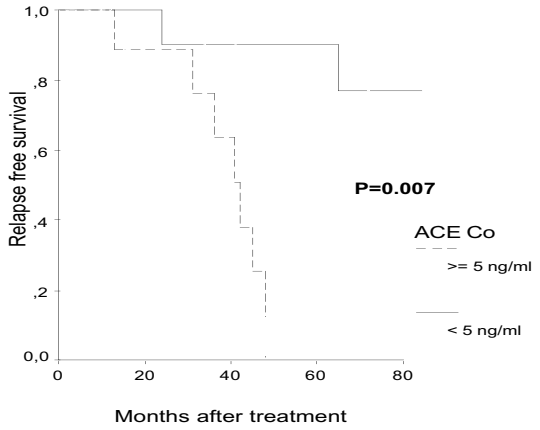


Figure 3 : Relapse-free survival in patients with Dukes C according to preoperative serum CEA level

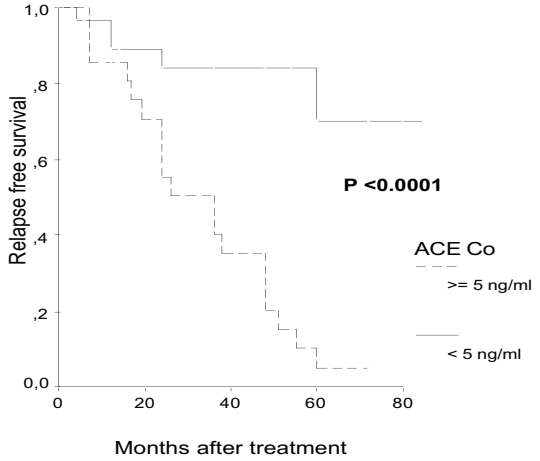
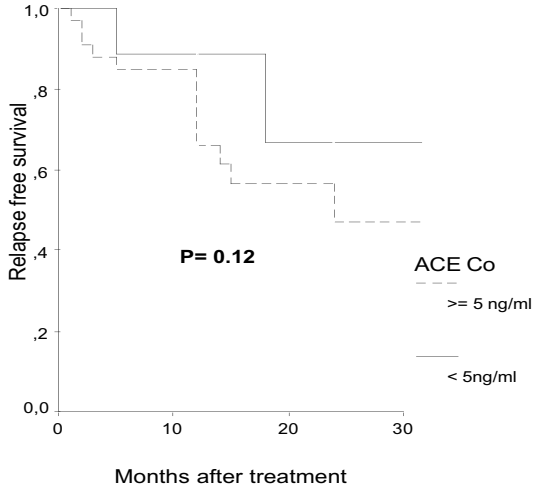


Figure 4 : Relapse-free survival in patients with Dukes D according to preoperative serum CEA level



Using univariate analysis, relapse-free survival was found to be associated with preoperative serum CEA levels (p<0.0001) and Dukes stage (p=0.002), but not with age, gender and tumour location (table 2). Multivariate analysis showed that preoperative CEA levels and Dukes stage were independent prognostic factors for relapse free survival (table 3). Patients with preoperative serum CEA levels ≥ 5 ng/ml were 6.49 times more likely to have postoperative relapse than those whose preoperative serum CEA levels were < 5 ng/ml (HR: 6.49, 95% CI, 3.09–13.62; p <0.0001). patients with Dukes D stage were 1.59 times more likely to have postoperative relapse than those with Dukes B and C stages (HR: 1.59, 95% CI, 1.03–2.47; p=0.035).

Table 2 : Univariate analysis of prognostic factors for relapse free survival

Variables	Odd- ratio (95% CI)	p value
Age (< 55 / ≥ 55) years	1.35 (0.80 - 2.29)	0.25
Sex (Male / Female)	0.89 (0.52 – 1.52)	0.68
Tumour location (Colon/ Rectum)	1.23 (0.75 – 2.03)	0.40
Dukes stage		
B / C	1.34 (0.62 – 2.87)	0.45
B +C / D	1.68 (1.21 – 2.33)	0.002
CEA (< 5 ng/ml / ≥ 5 ng/ml)	7.24 (3.48 – 15.07)	<0.0001

Table 3 : Multivariate analysis of prognostic factors for relapse free survival

Variables	Hazard ratio (95% CI)	p value
Dukes stage (B +C / D)	1.59 (1.03 – 2.47)	0.035
CEA (< 5 ng/ml / ≥ 5 ng/ml)	6.49 (3.09 – 13.62)	< 0.0001

DISCUSSION

CEA is an intracellular glycoprotein released by about 90% of CRC cells, measurable in serum that can be useful as a reliable tumour marker (7). Our study analyzed the prognostic value of preoperative CEA level in Tunisian CRC patients and showed that relapse-free survival was higher for subjects with CEA < 5 ng/ml compared to those with CEA ≥ 5 ng/ml. Multivariate analysis demonstrated that CEA had a significant prognostic impact for relapse-free survival (HR = 6.49, p < 0.0001). As CEA levels reflect tumour volume and tumoral cell number (8), We may speculate that patients with CEA ≥ 5 ng/ml had larger tumour that results in higher risk of local, regional and general dissemination.

Several studies explored the association between preoperative CEA level and CRC recurrence, giving conflicting data. Some investigators reported that preoperative CEA levels don't affect survival rate in patients with Dukes B stage (5, 9-12). Goslin et al. (10) studied 113 patients who had undergone curative

resection and had been followed for 36 to 72 months. They didn't find any adverse impact of abnormal CEA level on survival among patients with stage B. However, the recurrence rate was significantly correlated with the preoperative CEA value ($p<0.005$) among stage C patients. Similarly, Lewi et al. (11) study including 217 Dukes B and C colorectal cancer patients found no correlation between survival and preoperative CEA values in patient with Dukes B stage. However, in C stage patients, a preoperative CEA value >10 ng/ml was associated with significantly decreased five-years survival rate ($p<0.05$). Other authors found that higher preoperative CEA levels are associated with poorer prognosis in different Dukes stage CRC patients (6, 13-16). Discrepancy between these studies may be related to their different serum CEA cut-off and/or to different kits used for CEA measurement, as well as to the lack of tumour volume consideration in Dukes classification. However in our study, the relapse free survival was not significantly different in patients with Dukes stage B compared to Dukes stage C. this is probably due to the lack of differentiation between some bulky B and stage C tumour.

CONCLUSION

Preoperative serum CEA level is a reliable predictor factor for recurrence in patients with CRC. This parameter might therefore be a candidate for use in the staging system, in addition to conventional factors such as lymph node, metastasis or depth of invasion, and will be useful for therapeutic orientation in patients undergoing curative resection of CRC.

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