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Original Article

Predicting rectal tumor response to neoadjuvant chemoradiotherapy using plasma levels of carcinoembryonic antigen (CEA): Results from a tertiary center in Iran

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الملخص

أهداف البحث: تم اقتراح العلاج غير الجراحي لسرطان القولون والمستقيم، الذي يشكل ثالث أكثر أنواع السرطانات انتشارا في جميع أنحاء العالم، باستخدام العلاج الكيميائي الإشعاعي لتحقيق هدأة كاملة. في هذا الصدد، تم استخدام المستضد السرطاني الجنيني كعلامة مرشح. تهدف هذه الدراسة إلى تقييم قابلية تطبيق مستويات المستضد السرطاني الجنيني في التنبؤ بالاستجابة للعلاج الكيميائي الإشعاعي، وخاصة الاستجابة المرضية الكاملة.

طرق البحث: تم تصميم دراسة مستعرضة بأثر رجعي، من خلال استخراج مرحلة الورم ومستويات CEA قبل وبعد العلاج الكيميائي الإشعاعي الجديد من السجلات الطبية للمرضى الذين يعانون من أورام المستقيم الذين خضعوا للعلاج الكيميائي الإشعاعي الجديد قبل الجراحة في مستشفى سينا، طهران، إيران من 2010م-2015م.

النتائج: ارتبطت مستويات المستضد السرطاني الجنيني ما قبل العلاج الكيميائي الإشعاعي بشكل إيجابي بمرحلة الورم، كما أدى العلاج الكيميائي الإشعاعي إلى خفض مستويات المستضد السرطاني الجنيني بشكل كبير. في حين أن المستويات المنخفضة من المستضد السرطاني الجنيني قبل العلاج الكيميائي الإشعاعي ومرحلة الورم كانت مرتبطة بشكل كبير بالاستجابة الكاملة للعلاج الكيميائي الإشعاعي، ولم تظهر مستويات المستضد السرطاني الجنيني اللاحقة للعلاج الكيميائي الإشعاعي أي ارتباط مع الاستجابة الكاملة. بالإضافة إلى ذلك، في تحليل منحنى خصائص فعل المستقبلات، تم إظهار القيمة الحدية البالغة 2.6 لمستوى المستضد السرطاني الجنيني للتنبؤ بالاستجابة الكاملة للعلاج الكيميائي الإشعاعي (الخصوصية = 82.6٪ ، الحساسية = 40.5٪).

الاستنتاجات: على الرغم من أن العديد من العوامل الأخرى غير مستويات المستضد السرطاني الجنيني ومرحلة الورم مهمة أيضا في تحديد الاستجابة للعلاج الكيميائي الإشعاعي، فقد أظهرت هذه الدراسة أنه يمكن استخدام مستويات المستضد السرطاني الجنيني الأولية ومرحلة الورم كعوامل لتحديد الاستجابة الكاملة للعلاج الكيميائي الإشعاعي الجديد في سرطان المستقيم.

الكلمات المفتاحية: سرطان المستقيم؛ المستضد السرطاني الجنيني؛ العلاج الكيميائي الإشعاعي الجديد؛ الاستجابة المرضية الكاملة؛ جراحة القولون والمستقيم.

Abstract

Objectives: Nonsurgical treatment of colorectal cancer, the third most prevalent cancer worldwide, through chemoradiotherapy (CRT) has been suggested to induce complete remission. Carcinoembryonic antigen (CEA) has been used as a candidate marker to predict treatment response. In this study, we aimed to assess the applicability of plasma levels of CEAs in predicting the response to CRT, particularly complete pathological response.

Methods: We designed a retrospective, cross-sectional study in which tumor stage and plasma levels of CEAs before and after neoadjuvant CRT were extracted from the medical records of patients with rectal tumors who underwent neoadjuvant chemoradiotherapy before surgery at Sina Hospital, Tehran, Iran from 2010 to 2015.

Results: Pre-CRT plasma levels of CEA positively correlated with tumor stage, and chemoradiotherapy significantly decreased plasma levels of CEA. Whereas lower pre-CRT plasma levels of CEA and tumor stage were significantly associated with complete response to CRT, post-CRT plasma levels of CEA showed no association with complete response. In addition, in ROC

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curve analysis, a CEA cut-off value of 2.6 ng/mL predicted complete response to CRT (specificity = 82.6%, sensitivity = 40.5%).

Conclusion: Although several factors other than plasma levels of CEA and tumor stage are important in determining the response to CRT, preliminary plasma levels of CEA and tumor stage can be used as factors for determining complete response to neoadjuvant chemoradiotherapy in rectal cancer.

Keywords: Carcinoembryonic antigen (CEA); Colorectal surgery; Complete pathological response; Neoadjuvant chemoradiotherapy; Rectal cancer

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer worldwide, and it ranks second among cancers in mortality.[1] On the basis of the most recent report on the global burden of disease, the age-standardized incidence rate of CRC in 2017 was approximately 23.2 per 100,000 person-years, which is almost 10% higher than that in 1990.[2] The risk of occurrence of CRC increases with aging; moreover, several environmental and genetic risk factors contribute to the development of CRCs.[3]

Despite progress in adjuvant and neoadjuvant chemotherapy and radiotherapy methods, as well as newly developed immunotherapies, surgery remains the mainstay for the treatment of CRCs.[4,5] However, on the basis of tumor extension, tumor type, and patients' underlying conditions, neoadjuvant therapy may also be a possibility for inducing complete remission.[6] In rectal adenocarcinoma with wide tumor extension, neoadjuvant chemoradiotherapy has been found to effectively eliminate metastatic cells and decrease tumor size and staging.[6] Overall, 10−30% of cancers show complete pathologic response to chemoradiotherapy before surgery.[7,8] In special cases, such as squamous cell carcinoma of the rectum, oncologic treatments such as chemo/radiotherapy can replace surgery and consequently are considered the only treatment for these cancers. Thus, neoadjuvant chemotherapy before surgery can be beneficial in decreasing tumor size, but whether it can be used more extensively as the main treatment and whether it might replace surgical treatment remain to be elucidated.

Importantly, because neoadjuvant therapy is followed by surgical treatment, the extent to which such oncologic/medical treatments might be effective in decreasing tumor size cannot be determined. Therefore, surrogate markers such as specific tumor markers have been suggested for estimating changes in tumor size.[9] Carcinoembryonic antigen (CEA) can be used to determine the response to treatments, and to aid in diagnosis and prognostication.[10] Approximately 40−60% of patients with CRCs test positive for circulating levels of CEA before surgery,[11] and levels are higher in advanced tumor stages and tumor invasion.[12] Studies have shown that presurgical levels of CEA are positively correlated with tumor recurrence after surgery.[13,14] Furthermore, if the levels of CEA after surgery remain high and do not return to normal, the prognosis is poor, irrespective of the tumor staging.[15,16] However, some studies have shown that although the decrease in levels of CEA after chemotherapy is considered a prognostic factor for patient survival, the factors associated with surgery, tumor staging, and tumor location are also important.[14,17,18]

In this study, we aimed to assess the changes in plasma levels of CEA before and after neoadjuvant chemoradiotherapy, and their association with rectal tumor pathologic response. Although similar studies are available, we aimed to elucidate whether this marker might aid in determining the net effects of neoadjuvant chemoradiotherapy in our sample of patients with rectal cancer at Sina Hospital, a tertiary center in Iran.

Materials and Methods

Study design and participants

We designed a retrospective cross-sectional study by extracting the required data from the medical records of patients with rectal cancer who had undergone surgery at Sina Hospital, Tehran, Iran between 2010 and 2015. This study was approved by the ethics committee of Tehran University of Medical Sciences and Sina Hospital, and all data were extracted anonymously and remained confidential. The inclusion criteria were as follows: 1) diagnosis of rectal cancer accompanied by pathological confirmation of the tumor; 2) neoadjuvant chemoradiotherapy (CRT) before surgery; and 3) complete tumor resection by surgery. The exclusion criteria were as follows: 1) incomplete records, e.g., incomplete data on plasma levels of CEA before and after CRT and after surgery; 2) failure to track patients' follow-up; and 3) familial colon cancer syndromes. No additional limitations were set for patient demographics, such as age or sex.

Data collection

The following parameters were extracted from patient medical records: demographic data (age and sex), tumor characteristics (tumor site, type, and staging), applied therapies (surgery, chemotherapy, radiotherapy, and mixed interventions), response to therapy (complete remission, no progression, relapse or progression, and death), plasma levels of CEA measured with the radioimmunoassay method (normal range: 0−2.5 ng/dL) before (at the initial visit before CRT) and after (at the initial visit after CRT and just before surgery) CRT, and imaging findings (before and after CRT). The diagnosis of rectal cancer was made by one of three pathologists, and tumor staging was performed on the basis of the American Joint Committee on Cancer TNM system.[19] The patients were categorized according to the changes in tumor stage after treatment. Regression to

stage 0 was considered complete, regression to lower stages of 2–3 was considered moderate, and regression to a lower stage of 1 was considered poor. Some patients' tumors remained in the same stage (no response) or showed tumor progression.

For neoadjuvant chemoradiotherapy, patients underwent long-course radiotherapy with 45–50 Gy in 25–28 fractions for approximately 6 weeks, and capecitabine or 5-fluorouracil was used simultaneously as the chemotherapy. Sphincter-sparing surgical tumor resection was applied for all patients, except those with low rectal tumors with a distance less than 5 cm from the anal verge, who underwent abdominal perineal resection. After surgery, all patients underwent maintenance chemotherapy, and most received FOLFOX (including 5-fluorouracil plus leucovorin plus oxaliplatin) every 14 days. A smaller number of patients received CapeOx/XELOX (capecitabine plus oxaliplatin) every 21 days.

Statistical analysis

The power of the study was set to be 80%, and α and β were set as 0.05, 0.2, respectively. To estimate the required sample size for observing the expected clinical difference (20%), the sample size was calculated (n = 100). For comparison of tumor stages and plasma levels of CEA before and after CRT, paired-sample t-tests were used. For assessing the relationship between independent variables and study outcomes, chi-square and Pearson statistical analyses were conducted. Univariate and multivariate regression analyses were conducted with the Cox proportional hazard model, with the aim of predicting risk factors for patients' pathologic responses.

Results

Demographics

Among the 107 participants included in this study, 45 were women, and 62 were men; the age ranged from 26 to 83, and the mean age was 55.30 ± 11.7. No patients had distant unresectable metastases. Among the included patients, four had liver metastases, one had peritoneal invasion, and one had liver metastasis and omental invasion. The details of demographics and tumor stages are summarized in Table 1.

Table 1: Demographics, plasma levels of CEA and tumor stage before and after CRT.

	Mean ± *SD (n=107)*	*Minimum:maximum*	*P value*
Age	55.30 ± 11.7	26:83	
Sex (female:male)	45:62	–	
Pre-CRT CEA (ng/dL)[§]	10.72 ± 14.62	0.5:101	<0.001*
Post-CRT CEA (ng/dL)[§]	2.44 ± 2.7	0.5:20.02	
Pre-CRT tumor stage	Median: 3	2:4	<0.001*
	Stage 2: 23 (21.4%)		
	2A: 13 (12.1%)		
	2B: 10 (9.3%)		
	Stage 3: 76 (71.2%)		
	3A: 15 (14.0%)		
	3B: 44 (41.1%)		
	3C: 17 (15.9%)		
	Stage 4: 8 (7.2%)		
	4A: 6 (5.6%)		
	4B: 2 (1.4%)		
Post-CRT tumor stage	Median: 2	0:4	
	Stage 0: 32 (29.9%)		
	Stage 1: 17 (15.8%)		
	Stage 2: 30 (28.0%)		
	Stage 3: 24 (22.4%)		
	Stage 4: 4 (3.7%)		
Treatment (CRT) response	Complete response: 32 (29.9%)	–	
	Moderate response: 12 (11.2%)		
	Poor response: 34 (31.8%)		
	No response: 27 (25.2%)		
	Progression: 2 (1.9%)		
Death rate	2:1.8%	–	

Abbreviations: CEA: carcinoembryonic antigen, pre-CRT: before chemoradiotherapy, post-CRT: chemoradiotherapy, SD: standard deviation.

[§] Plasma CEA level normal range (chemiluminescence measurement): 0–2.5 ng/dL.

* Paired sample t-test was used for comparison.

Table 2: Pearson correlation between plasma levels of carcinoembryonic antigen before chemoradiotherapy and tumor stage before and after chemoradiotherapy.

	P value	95% Confidence interval	R^2	r
Pre CRT tumor stage	0.005	to 0.43680.0836	0.072	0.2692
Post CRT tumor stage	0.343	0.0991 to −0.2774	0.008	0.092
Post CRT CEA level	0.0001	to 0.52040.1902	0.134	0.366

Abbreviations: CEA: carcinoembryonic antigen, pre-CRT: before chemoradiotherapy, post-CRT: chemoradiotherapy.

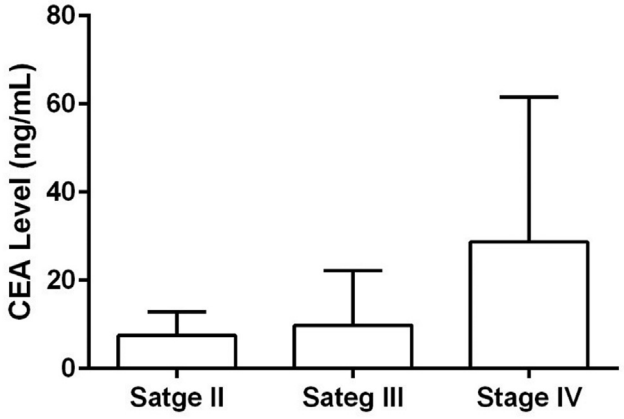

Figure 1: Plasma levels of carcinoembryonic antigen (CEA) before chrmoradiotherapy in different tumor stages. Abbreviations: Pre-CRT: before chemoradiotherapy.

Comparison between plasma levels of CEA and tumor stage before and after CRT

On average, the tumor stage decreased from stage 3 to stage 2 after CRT ($t = 12.16$, $p < 0.001$). In contrast, the CEA level significantly decreased from 10.72 ± 14.62 to 2.44 ± 2.7 after CRT ($t = 3.832$, $p < 0.001$). The related data are summarized in Table 1.

Correlation between plasma levels of CEA and tumor stage before and after CRT

A significant positive correlation was observed between the pre-CRT plasma levels of CEA and the tumor stage before CRT ($p < 0.01$). Moreover, a significant association between pre-CRT and post-CRT plasma levels of CEA ($p < 0.001$) was found. However, pre-CRT plasma levels of CEA were not associated with post-CRT tumor stage, as shown in Table 2.

Difference between plasma levels of CEA in patients with different tumor stages

Patients with a pre-CRT tumor stage of 2 or 3 had significantly lower levels of CEA than patients with a pre-CRT tumor stage of 4 ($p < 0.01$) (Figure 1). Comparison between pre-CRT and post-CRT plasma levels of CEA with two-way repeated measures ANOVA revealed that the plasma levels of CEA significantly decreased in patients with stage 3 and 4 tumors ($p < 0.01$) but not in those with stage 2 tumors ($p > 0.05$) (Figure 2).

Effects of CRT on tumor stage in patients with different tumor stages

Among the 23 patients whose tumors were in stage 2 before CRT, 12 tumors (52.17%) regressed to stage 0, 5 tumors (21.7%) regressed to stage 1, 5 tumors remained at stage 2 (21.7%), and 1 tumor (4.3%) progressed to stage 3 after CRT. Among the 76 patients whose tunors were in stage 3 before CRT, 19 tumors (25%) regressed to stage 0, 12 tumors (15.7%) regressed to stage 1, 25 tumors (32.8%) regressed to stage 2, 19 tumors (25%) remained at stage 3, and 1 tumor (1.3%) progressed to stage 4. Among the eight patients whose tumors were in stage 4 before CRT, one tumor (12.5%) regressed to stage 0, and four tumors (50%) regressed to stage 3, whereas three tumors remained at stage 4 (37.5%). On the whole, 32 patients' tumors (29.9%) regressed to stage 0 after CRT. Notably, in 46 tumors (43.0%), the disease stage decreased: 12 (11.2%) showed moderate response, and 34 (31.8%) showed poor response; however, 27 (25.2%) had no response to treatment, and 2 (1.9%) showed tumor progression.

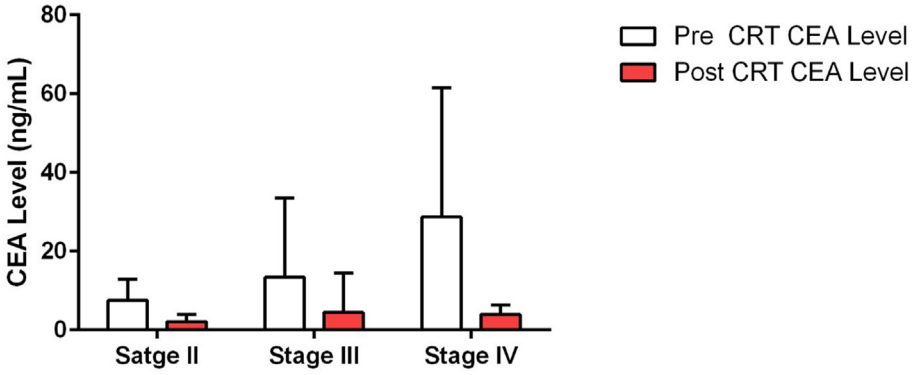

Figure 2: Comparison of plasma levels of carcinoembryonic antigen (CEA) before and after chemoradiotherapy in different tumor stages. Abbreviations: Post-CRT: after chemoradiotherapy; Pre-CRT: before chemoradiotherapy.

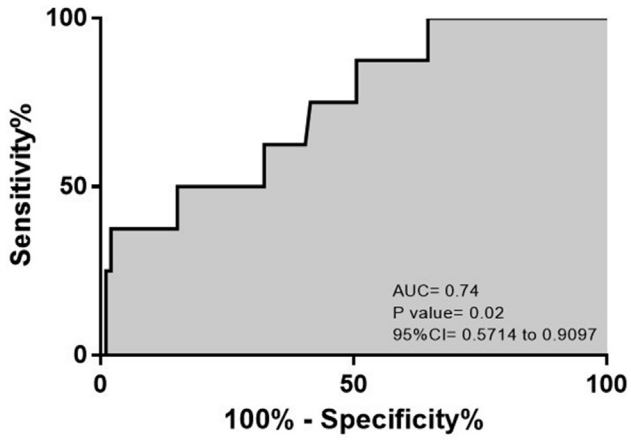

Figure 3: Receiver operating characteristic (ROC) curve analysis for determining the pre-CRT plasma carcinoembryonic antigen (CEA) level cut-off for predicting disease stage.

Relationships among plasma levels of CEA, tumor stage and response to treatment

The treatment effect was classified into complete, moderate, poor, and no response. CRT significantly increased complete response. Correlation analysis revealed that pre-CRT plasma levels of CEA were negatively associated with complete response ($r = -0.22$, $p < 0.05$), whereas post-CRT plasma levels of CEA showed no association ($p > 0.05$). In addition, correlation analysis showed that the pre-CRT tumor stage was negatively correlated with poor, moderate or complete response ($p = 0.03$, $r = -0.19$).

Determining the CEA cut-off for predicting tumor stage or response to CRT

ROC curve analysis indicated that with a pre-CRT CEA cut-off of 12.5 ng/mL, patients could be predicted to have stage 4 tumors (sensitivity = 50%, specificity = 80%, positive predictive value = 2.6, AUC = 0.74, p = 0.02) (Figure 3).

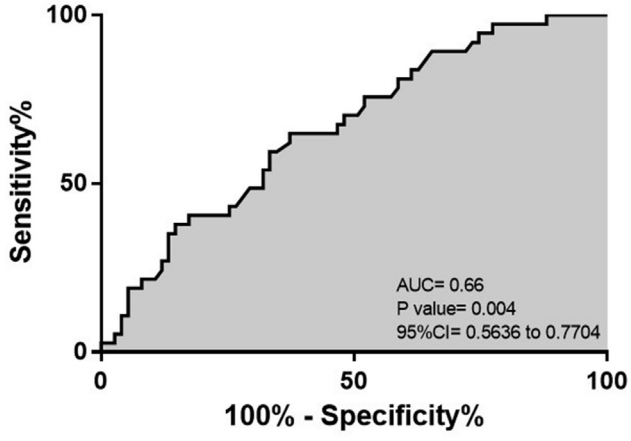

Figure 4: Receiver operating characteristic (ROC) curve analysis for determining the post-CRT plasma carcinoembryonic antigen (CEA) level cut-off for predicting complete or moderate response.

ROC curve analysis was also performed to predict response to CRT. When a post-CRT CEA of 2.6 ng/mL was set as the cut-off, complete response was observed (specificity = 82.6%, sensitivity = 40.5%, positive predictive value = 2.33, AUC = 0.66, p = 0.004) (Figure 4).

Discussion

In this study, we demonstrated that plasma levels of CEA are associated with tumor stage, and chemoradiotherapy is associated with significantly lower plasma levels of CEA and rectal tumor stages. Specifically, this treatment decreased plasma levels of CEA more significantly in higher disease stages (i.e., stages 3 and 4 compared with stage 1 and 2). Importantly, pre-CRT plasma levels of CEA were a predictor of complete response to CRT, whereas post-CRT plasma levels of CEA were not associated with complete response. Moreover, ROC curve analysis indicated that plasma levels of CEA lower than 2.6 ng/mL were predictive of complete response to neoadjuvant CRT. CEA is a glycoprotein widely expressed on the cell membranes in many tissues, such as cancerous cells of the colon and rectum. A portion of this antigen enters the blood circulation and can be detected via radio-immunoassays on plasma samples.[15] CEA has been used as a marker for predicting tumor response to surgery and as a prognostic marker for tumor regression or recurrence. Our results are concordant with those from previous studies indicating that lower pre-CRT plasma levels of CEA, irrespective of other clinical and pathological characteristics, are associated with complete response to neoadjuvant CRT.[15,16] However, some studies similar to ours have shown low sensitivity and specificity of plasma levels of CEA in predicting tumor recurrence after surgery; moreover, inconsistencies exist in whether plasma levels of CEA before and after chemotherapy are associated with pathologic response.[14,17,20] The low sensitivity of plasma CEA levels in predicting response to CRT might be due to other factors, such as tumor grade, location, stage, and patient characteristics, that influence the response to chemoradiotherapy.

In addition, several studies have reported different preclinical CEA level cut-offs for predicting complete pathological response to neoadjuvant chemoradiotherapy. For instance, in a study by Das et al.,[21] a pre-CRT CEA level >2.5 ng/mL has been associated with a lower tumor downstaging rate, whereas in studies by Zeng et al.,[22] Wang et al.,[23] Yang et al.,[24] and Takagawa et al.,[25] the cut-off for predicting complete pathological response has been estimated to be 5, 5, 6, and 10 ng/mL, respectively. Negative post-CRT CEA has been significantly associated with complete pathological response to CRT.[26] In addition, in this study, although we observed no significant association between post-CRT tumor stage or overall response to therapy and post-CRT plasma levels of CEA, through ROC curve analysis, we determined a cut-off for post-CRT plasma levels of CEA. Some studies have determined cut-offs for post-CRT plasma levels of CEA of 2.61 and 2 ng/mL,[24,27–29] values very close to the cut-off identified in this study. Therefore, a decrease in plasma levels of CEA is an important predictor of tumor downstaging and complete pathological response. However, in this study, we did not assess the

association between CEA ratio after CRT and complete response, which might potentially be a more reliable determinant of tumor downstaging than post-CRT plasma levels of CEA.[28,29]

Furthermore, this study showed that pathological stage before CRT is an important determinant of tumor response to CRT. Therefore, the higher the pre-CRT stage, the higher the expected post-CRT stage, although the decrease in tumor stage is greater at higher tumor stages. Furthermore, complete pathological response was negatively associated with pre-CRT tumor stage.

The findings of this study along with other similar studies may aid in predicting complete pathological response and identifying candidates for neoadjuvant chemoradiotherapy, even without the need for surgery. However, this study has several limitations; for instance, we did not consider the role of other determinant factors predicting the response to therapy, such as patient comorbidities; the time elapsed between neoadjuvant chemoradiotherapy and surgery; the pathological characteristics of the tumors, such as tumor differentiation and location; and the predictive value of other markers such as CA19-9. This study design might at least partly explain the discrepancies between the results of this study and similar studies. Furthermore, the definition of complete, moderate, and poor response substantially differs across studies, thus sldo potentially explaining the discrepancies between our study and previous studies.

Conclusion

Neoadjuvant chemoradiotherapy may be effective in inducing complete pathological response in some patients with rectal tumors. Several factors can aid in identifying patients likely to be tumor-free after neoadjuvant chemoradiotherapy, including pre-CRT plasma levels of CEA and tumor stage.

Abbreviations: CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRT, chemoradiotherapy.

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Conflict of interest

The authors do not declare any conflict of interest.

Ethical approval

This study was approved by the institutional ethics committee of *Tehran University of Medical Sciences* under the ethics code *IR. TUMS. REC.1394.1056* on January 11th, 2016, and is compliant with the WMA declaration of Helsinki for medical research including human participants (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).

Consent

Patients included in this study provided informed consent to participate.

Authors contributions

H.A.A., H.Z.M., and R.Z. contributed to the conception and design of this study; H.A.A., R.Z., H.Z.M., and M.T.N. contributed to data collection; H.A.A., R.Z., and H.Z.M. contributed to data analysis and interpretation; R.Z., H.A.A., H.Z.M., K.N., and M.T.N. contributed to writing the manuscript and final revision and approval of the manuscript; H.A.A. and H.Z.M. supervised this project. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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