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Review Article

Factors influencing response to neoadjuvant chemoradiotherapy in rectal cancer: the role of serum carcinoembryonic antigen and tumor size

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ABSTRACT

Neoadjuvant chemoradiotherapy (NACRT) is a pivotal component in the management of locally advanced rectal cancer (LARC), offering the advantages of tumor downstaging, enhanced resectability, and potential for sphincter preservation. Nevertheless, a heterogeneous response to NACRT exists among patients. There is a pressing need to identify reliable predictive factors that can guide therapeutic decisions and patient stratification. Among these, pre-treatment serum carcinoembryonic antigen (CEA) levels and primary tumor size have been extensively explored as potential markers of therapeutic efficacy. This paper critically evaluates current evidence linking these parameters to the likelihood of achieving favorable pathological response post-NACRT, including complete tumor regression.

Keywords: Rectal carcinoma, Neoadjuvant chemoradiotherapy, Carcinoembryonic antigen, Tumor dimension, Tumor regression, Predictive markers

INTRODUCTION

Rectal cancer comprises a significant subset of colorectal malignancies and represents a considerable global health burden. With rectal tumors accounting for nearly one-third of colorectal cancer cases, locally advanced rectal cancer (LARC)-defined by clinical T3/T4 or node-positive status-demands a multidisciplinary treatment approach. The current standard incorporates neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision (TME), demonstrating notable reductions in local recurrence and increased sphincter preservation rates.[1,2]

Despite uniform protocols, the response to NACRT is highly variable. A subset of patients-approximately 15-30%-achieves pathological complete response (pCR), correlating with improved oncological outcomes and even the potential to defer surgery in select cases.[3,4] On the contrary, some tumors exhibit minimal or no regression. Predicting these responses pre-treatment would substantially improve individualized care. Two accessible and cost-effective clinical parameters that may serve this purpose are serum carcinoembryonic antigen (CEA) levels and tumor size at diagnosis.

CEA is a glycoprotein overexpressed in many gastrointestinal malignancies. It plays a role in cell adhesion and immune modulation and is a validated tumor marker for colorectal cancer.[5] Similarly, tumor size-an index of tumor burden and biological behavior-may impact treatment efficacy by influencing oxygen diffusion, radiation penetration, and stromal resistance.[6] This review aims to elucidate the predictive value of

these parameters based on current literature and clinical insights.

LITERATURE SEARCH

This manuscript reviews relevant clinical studies, meta-analyses, and institutional findings focused on pre-treatment serum CEA and tumor size as predictors of pathological response to NACRT in rectal cancer. Data was extracted from PubMed-indexed English-language human studies conducted between 2000 and 2024. Priority was given to publications that included multivariate analyses, clearly defined pCR or tumor regression grade (TRG), and correlations with survival or recurrence.

BIOLOGICAL BASIS OF TUMOR RESPONSE

Response to NACRT is governed by a combination of genetic, cellular, and microenvironmental determinants. Tumor hypoxia, mutations in tumor suppressor genes like TP53, cellular proliferation rates, and DNA repair mechanisms contribute to resistance or sensitivity to therapy.[7] Smaller tumors, by virtue of enhanced oxygenation and less necrotic core formation, may permit better radiation penetration and drug delivery.[8]

CEA, in contrast, is a marker secreted by colorectal tumor cells into the bloodstream. Elevated pre-treatment CEA levels may reflect greater tumor burden or a biologically aggressive phenotype with an increased propensity for metastasis and chemoresistance. Moreover, CEA can impair apoptosis and interact with immune checkpoints, further reducing therapy efficacy.[9]

SERUM CEA: CLINICAL EVIDENCE AND INTERPRETATION

Multiple retrospective and prospective studies have established serum CEA as a significant predictor of tumor response. A study involving 310 patients by Park and colleagues showed that individuals with pre-treatment CEA levels below 5 ng/mL had a significantly higher pCR rate than those with elevated levels (28.6% vs. 13.9%).[10] CEA <5 ng/mL emerged as an independent prognostic factor in multivariate analysis.

Further support is provided by a comprehensive meta-analysis comprising 17 studies, which concluded that lower pre-NACRT CEA levels were strongly associated with higher pCR rates and longer disease-free intervals.[11] A reduction in serum CEA post-NACRT has also been found to correlate with better histopathological response and improved long-term outcomes.[12]

However, elevated CEA levels may be influenced by benign conditions such as smoking, hepatic disorders, or inflammatory bowel disease. Therefore, while CEA alone lacks specificity, it retains clinical relevance when interpreted alongside imaging and pathological findings.

TUMOR SIZE: IMPACT ON TREATMENT RESPONSE

Tumor size serves as a surrogate for tumor volume and invasiveness. Larger tumors tend to harbor a heterogeneous population of cells, exhibit more hypoxia, and possess a denser stroma-all of which can hinder effective chemoradiation.[13] In a clinical study involving 145 patients, those with tumors smaller than 4 cm demonstrated significantly better pCR rates than those with larger lesions (32% vs. 12%).[14]

A separate investigation by Liu et al involving 228 patients found that tumors measuring less than 3.5 cm were associated with more favorable regression patterns and superior disease-free survival.[15] These findings reinforce the concept that smaller tumors, being more homogeneous and biologically less aggressive, are more amenable to complete regression.

Advanced imaging techniques, particularly MRI, allow for precise measurement of tumor volume, which can be more informative than linear size alone. Studies evaluating tumor volume reduction rates post-NACRT have found them to be more strongly associated with histological tumor regression grades.[16]

INTEGRATION OF CEA AND TUMOR SIZE

When considered in tandem, serum CEA and tumor size provide a robust predictive framework. A prospective study by Huh et al demonstrated that patients with both low CEA (<5 ng/mL) and small tumor size (<3.5 cm) had a significantly higher pCR rate of 42%, compared to just 8% in patients with high CEA and large tumors.[17] This dual-parameter approach has prompted the development of nomograms to stratify patients more accurately.

Yeo et al proposed a predictive model integrating CEA levels, tumor dimensions, and MRI features, achieving a high predictive accuracy for pCR (AUC 0.78).[18] Such tools are expected to support clinical decision-making regarding the feasibility of non-operative management or intensification of neoadjuvant regimens.

CLINICAL RELEVANCE AND FUTURE DIRECTIONS

The implications of accurately predicting NACRT response extend beyond prognostication. Patients with favorable biomarkers may be suitable candidates for "watch-and-wait" approaches, reducing morbidity associated with radical surgery. Conversely, those with less favorable profiles might benefit from escalated strategies such as total neoadjuvant therapy (TNT), incorporation of biologics, or earlier surgical intervention.

Ongoing research seeks to enhance predictive precision by incorporating radiomic data, circulating tumor DNA,

and genomic signatures. Nevertheless, serum CEA and tumor size remain universally available, low-cost, and validated predictors, particularly in resource-limited settings.

CONCLUSION

Pre-treatment serum carcinoembryonic antigen levels and tumor size are reliable and accessible indicators of response to neoadjuvant chemoradiotherapy in rectal adenocarcinoma. Low CEA values (<5 ng/mL) and small tumor dimensions (<3.5-4 cm) are strongly associated with favorable pathological responses, including complete tumor regression. Integration of these parameters into predictive models may refine patient selection, optimize treatment sequencing, and facilitate organ-preserving strategies in the management of rectal cancer.

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