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A Retrospective Cohort Study of Preoperative Carcinoembryonic Antigen and Pathological Stage in Colorectal Cancer Surgery

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Abstract

Background We examined the association of preoperative serum carcinoembryonic antigen with pathological stage and its ability to discriminate advanced disease.

Methods This single-center retrospective cohort included 260 adults undergoing colorectal surgery in Riyadh, Saudi Arabia, from 2021 to 2025. Patients with documented neoadjuvant therapy or prior adjuvant therapy were excluded. The primary outcome was pathological stage III–IV. Logistic regression adjusted for age, sex, and tumor site.

Results Stage III–IV occurred in 51 of 99 patients (51.5%) with carcinoembryonic antigen above 5 ng/mL and 56 of 161 (34.8%) with lower values (adjusted odds ratio, 1.93, 95% confidence interval, 1.14–3.26). The area under the receiver operating characteristic curve was 0.59 (95% confidence interval, 0.52–0.66) for stage III–IV and 0.74 (95% confidence interval, 0.66–0.81) for T3–T4. Higher concentrations were associated with higher adjusted odds of stage III–IV disease (1.21 per doubling, 95% confidence interval, 1.05–1.39). The estimate was less precise after excluding the 28 patients with undocumented neoadjuvant status.

Conclusion Elevated carcinoembryonic antigen was associated with advanced pathological stage. Discrimination for stage III–IV was poor and performance was higher for T3–T4.

Keywords Carcinoembryonic antigen, colorectal cancer, pathological stage, lymph node metastasis, preoperative staging

Introduction

Colorectal cancer is among the most common malignancies and leading causes of cancer-related death worldwide [1]. Pathological stage is the dominant determinant of prognosis and of adjuvant-treatment decisions after curative-intent resection [2,3]. Because definitive pathological stage is known only after surgical resection, preoperative biomarkers that reliably anticipate mural penetration and nodal spread could, in principle, sharpen staging work-up and operative planning.

Carcinoembryonic antigen (CEA) is measured before surgery in most patients with colorectal cancer, principally as a baseline for postoperative surveillance [4,5]. Higher preoperative values have been linked to deeper mural invasion, nodal involvement, and worse survival [5–7], yet reported associations with pathological stage remain inconsistent across clinical series. A recognized source of heterogeneity is neoadjuvant chemotherapy or chemoradiotherapy, which downstages both the primary tumor and regional lymph nodes while altering serum CEA kinetics, thereby decoupling the baseline marker from the final surgical specimen [8,9]. Non-malignant and assay-related false-positive elevations add further clinical noise [10].

Population-based studies have documented variation in colorectal cancer incidence and stage at diagnosis across Saudi Arabia and the Middle East and North Africa [11–15]. Differences in case mix may affect the transportability of stage distributions and predictive values.

We therefore tested the hypothesis that elevated preoperative CEA (>5 ng/mL) is independently associated with advanced pathological stage (III–IV) in patients undergoing surgical resection without neoadjuvant therapy. Secondary objectives were to characterize associations with T category, nodal status, distant metastasis, and microscopic invasion; to assess whether the association is graded across ordered CEA strata; and to quantify the diagnostic discrimination of preoperative CEA, since statistical association alone does not establish individual-level clinical utility.

Patients and Methods

Study design and ethics

This single-center, retrospective cohort study was conducted at Prince Sultan Military Medical City, Riyadh, Saudi Arabia, and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies [16]. The Institutional Review Board of Prince Sultan Military Medical City approved the study protocol (Approval No. E-2914) and waived the requirement for individual informed consent because all clinical data were retrospective and de-identified prior to analysis. The study adhered to the principles of the Declaration of Helsinki.

Participants

Consecutive adults (≥18 years) who underwent surgical resection in the colorectal surgery registry between January 2021 and December 2025 were screened from the institutional surgical registry (n=343). Patients who had received neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy (n=82) were excluded, as were patients with prior adjuvant systemic therapy for an earlier colorectal primary (n=1). All screened patients had a documented preoperative serum CEA value and a recorded pathological stage; no patient required exclusion for missing primary exposure or staging data. The final primary analytic cohort comprised 260 patients (Figure 1). Each record in the analytic cohort was verified to represent a unique patient index resection. Neoadjuvant treatment status was unrecorded for 28 patients clustered in a contiguous block of later registry entries; based on institutional clinical pathways for primary colonic resections, these records were classified as treatment-naïve in the primary analysis, and this assumption was explicitly tested by excluding all 28 records in a prespecified sensitivity analysis.

Data sources and variables

Clinical and pathological data were abstracted from the institutional electronic medical record and the prospective colorectal surgery database. Extracted variables comprised age, sex, American Society of Anesthesiologists (ASA) physical status class, primary tumor site, histological subtype and differentiation, TNM categories and composite pathological stage, total number of regional lymph nodes

retrieved and number of positive nodes, lymphovascular invasion (LVI), perineural invasion (PNI), 30-day postoperative complications, synchronous or metachronous metastatic disease, and documented tumor recurrence. Primary tumor site was classified as colon, rectum/rectosigmoid, or ileocecal/appendiceal/small-bowel primaries managed within the colorectal surgery unit (8 cases, 3.1%, retained in the full registry cohort and excluded in a dedicated colorectal-only sensitivity analysis). Pathological staging followed the American Joint Committee on Cancer / Union for International Cancer Control (AJCC/UICC) TNM classification as reported by institutional gastrointestinal pathologists [17]. Node-positive disease was defined by pathological N category (N1–N2, including N1c tumor deposits).

Exposure and outcomes

The primary exposure was preoperative serum CEA measured in ng/mL (equivalent to μg/L) within 2 weeks prior to index surgical resection, dichotomized a priori at the institutional laboratory upper reference limit of 5.0 ng/mL (elevated >5 ng/mL vs reference ≤5 ng/mL) [10]. Ordered concentration categories (≤5, >5–10, >10–20, and >20 ng/mL) and continuous $\log_2$-transformed CEA (evaluating risk per doubling of serum concentration) were examined secondarily. The primary outcome was advanced pathological stage (stage III–IV vs stage 0–II). Secondary outcomes were locally advanced depth of invasion (T3–T4 vs T0–T2 category), node-positive disease (N1–N2 vs N0), distant metastasis confirmed at surgery (M1), LVI, PNI, number of positive lymph nodes, and total number of lymph nodes retrieved (evaluated as a surgical and pathological specimen-quality control). Exploratory outcomes were overall postoperative complications, documented disease recurrence, and metastatic disease recorded at any time during clinical follow-up. Because standardized longitudinal censoring dates were unavailable in the abstracted dataset, formal time-to-event survival analyses were not performed.

Data quality and missing data handling

All abstracted database fields were audited and standardized prior to statistical modeling. In one record where structured T and N sub-fields were blank, the exact categories were verified directly from the accompanying synoptic pathology text of the same record. ASA physical status was unrecorded in 64 patients (24.6%); T and N categories were unavailable in 3 patients (1.2%), quantitative lymph-node

counts in 2 (0.8%), postoperative complications in 4 (1.5%), and recurrence status in 2 (0.8%). Age, sex, preoperative CEA, composite stage, LVI, PNI, and primary tumor site were 100% complete (N=260). Because the primary exposure, primary outcome, and all prespecified multivariable covariates were complete, and missingness across secondary pathological variables was ≤1.5% (with the exception of ASA class), outcome-specific complete-case analysis was utilized without statistical imputation; ASA class was excluded from the primary multivariable model and evaluated separately in a dedicated sensitivity analysis. Preoperative CEA was markedly right-skewed (Shapiro–Wilk $p<0.001$; range 0.3–2,055 ng/mL); extreme elevations were verified as clinically plausible in advanced disease, retained to prevent spectrum bias, and modeled via categorical stratification and logarithmic transformation. Age followed an approximately normal distribution (Shapiro–Wilk $p=0.94$).

Statistical analysis

Categorical variables were compared using Pearson's χ^2 test without continuity correction, or Fisher's exact test when any expected cell count was <5. Continuous variables were compared using Welch's t-test for normally distributed variables (reported as mean ± standard deviation [SD]) or the two-sided Mann–Whitney U test for skewed distributions (reported as median and interquartile range [IQR]). Crude odds ratios (ORs) with Woolf 95% confidence intervals (CIs) were calculated. Multivariable logistic regression models estimated adjusted ORs controlling for age (continuous), sex, and primary tumor site (rectum/rectosigmoid vs colon/other); there were 107 stage III–IV events, 209 T3–T4 events, and 104 node-positive events. Multivariable regression was not fitted for synchronous M1 disease at surgery due to sparse events (n=5). Dose–response relationships were evaluated via adjusted ORs across ordered CEA categories, the Cochran–Armitage test for linear trend, and adjusted ORs per doubling of continuous CEA ($\log_2$-CEA). Diagnostic discrimination was quantified using the area under the receiver operating characteristic curve (AUC) with 95% CIs derived from 2,000 percentile bootstrap resamples, alongside sensitivity, specificity, positive and negative predictive values (PPV, NPV), and positive likelihood ratios (LR+) at the 5 ng/mL cutoff. Prespecified sensitivity analyses excluded the 8 non-colorectal (appendiceal/small-bowel) primaries (n=252), excluded the 28 patients with unrecorded neoadjuvant

fields (n=232), restricted the cohort strictly to colonic primaries (n=203), adjusted additionally for ASA class III–IV (n=196), and varied the binary CEA threshold (3 ng/mL and 10 ng/mL). Effect modification by tumor site (colon vs rectum) was assessed via the likelihood-ratio interaction test. All hypothesis tests were two-sided with $\alpha=0.05$; secondary and exploratory analyses were not adjusted for multiplicity and are interpreted accordingly. Statistical analyses were performed using Python 3.12 (pandas, SciPy, and scikit-learn libraries), with maximum-likelihood logistic regression fitted by iteratively reweighted least squares.

Results

Cohort and baseline characteristics

Of 343 patients screened in the surgical database, 83 were excluded due to prior neoadjuvant or adjuvant therapy and 260 patients were analyzed (Figure 1). Mean age was 62.9 ± 11.8 years (range 30–93 years), 140 patients (53.8%) were male, and primary tumors arose in the colon in 203 (78.1%), the rectum or rectosigmoid junction in 49 (18.8%), and the appendix or small bowel in 8 (3.1%). Overall median preoperative CEA was 3.2 ng/mL (IQR 1.8–8.2 ng/mL); 99 patients (38.1%) had elevated preoperative CEA (>5 ng/mL; median 12.4 ng/mL, IQR 7.0–23.1) and 161 (61.9%) had normal CEA (≤5 ng/mL; median 1.9 ng/mL, IQR 1.4–2.7). Patients with elevated CEA were slightly older (65.2 ± 12.0 vs 61.5 ± 11.5 years; p=0.014) and more frequently classified as ASA III–IV (48.6% vs 33.3% among the 196 patients with recorded ASA status; p=0.036). Sex distribution, primary tumor site, mucinous or poorly differentiated histology, total lymph-node harvest (median 20.5 vs 20.0 nodes; p=0.982), and the prevalence of LVI or PNI were comparable between groups (Table 1).

Primary outcome advanced pathological stage

Pathological stage III–IV disease was significantly more frequent among patients with elevated preoperative CEA compared with normal CEA (51/99 [51.5%] vs 56/161 [34.8%]; crude OR 1.99, 95% CI 1.20–3.32; p=0.008), and the overall ordinal distribution across stages 0 to IV shifted toward more advanced disease in the elevated-CEA group (Mann–Whitney p<0.001; Figure 2). This association

remained independent after multivariable adjustment for age, sex, and tumor site (adjusted OR 1.93, 95% CI 1.14–3.26; p=0.014; Table 2, Figure 3). Within the same multivariable model, male sex was inversely associated with stage III–IV disease (adjusted OR 0.56, 95% CI 0.34–0.94; p=0.028; stage III–IV prevalence 34.3% in men vs 49.2% in women), whereas age (p=0.868) and rectal/rectosigmoid site (p=0.821) were not (Supplementary Table S1).

Secondary pathological outcomes

Locally advanced mural invasion (T3–T4 category) was present in 92/98 (93.9%) patients with elevated CEA compared with 117/159 (73.6%) with normal CEA (crude OR 5.50, 95% CI 2.24–13.51; adjusted OR 5.55, 95% CI 2.22–13.92; p<0.001). Node-positive disease (N1–N2) occurred in 50/98 (51.0%) versus 54/159 (34.0%) patients, respectively (crude OR 2.03, 95% CI 1.21–3.39; adjusted OR 1.96, 95% CI 1.16–3.33; p=0.013). Granular T and N subcategories were unavailable for 3 patients. The number of metastatic regional lymph nodes was significantly higher in the elevated-CEA group (mean 1.57 ± 2.45 vs 0.91 ± 1.85 positive nodes; median 0 in both groups; Mann–Whitney p=0.003), whereas the total number of examined lymph nodes was virtually identical between groups (mean 23.2 vs 23.3 nodes; p=0.982). Synchronous M1 disease documented at resection (3/99 [3.0%] vs 2/161 [1.2%]; Fisher exact p=0.372), LVI (49.5% vs 48.4%; adjusted OR 1.03, 95% CI 0.62–1.73; p=0.898), and PNI (29.3% vs 24.8%; adjusted OR 1.33, 95% CI 0.75–2.37; p=0.326) did not differ significantly between groups (Table 2).

Dose response and diagnostic discrimination

The prevalence of stage III–IV, T3–T4, and node-positive disease showed positive trends across ordered preoperative CEA strata (Cochran–Armitage trend p=0.008, p<0.001, and p=0.009, respectively) (Table 3, Figure 4A). Compared with patients having CEA ≤5 ng/mL, those with CEA >20 ng/mL exhibited an adjusted OR of 2.77 (95% CI 1.19–6.43; p=0.018) for stage III–IV disease, 9.93 (95% CI 1.28–76.88; p=0.028) for T3–T4 disease, and 2.69 (95% CI 1.14–6.33; p=0.024) for node-positive disease. Modeled continuously on a logarithmic scale, each doubling of serum CEA ($\log_2$-CEA) was associated with 21% higher adjusted odds of stage III–IV disease (adjusted OR 1.21, 95% CI 1.05–1.39; p=0.008). Despite these consistent population-level associations, continuous preoperative CEA discriminated individual

stage III–IV status poorly (AUC 0.59, 95% CI 0.52–0.66; sensitivity 47.7%, specificity 68.6%, PPV 51.5%, NPV 65.2%, LR+ 1.52 at the 5 ng/mL cutoff) and performed similarly for node-positive disease (AUC 0.59, 95% CI 0.51–0.66). Discrimination was substantially better for locally advanced T3–T4 invasion (AUC 0.74, 95% CI 0.66–0.81), where CEA >5 ng/mL yielded a high PPV (93.9%) and specificity (87.5%) but a low NPV (26.4%) in the setting of a high baseline prevalence of T3–T4 tumors across the cohort (81.3%) (Table 4, Figure 4B).

Sensitivity and subgroup analyses

Effect estimates remained directionally consistent across all prespecified sensitivity analyses (Supplementary Table S2). Excluding the 8 appendiceal/small-bowel primaries (restricting strictly to confirmed colorectal adenocarcinoma, n=252) yielded virtually identical results for stage III–IV (adjusted OR 1.89, 95% CI 1.11–3.21; p=0.018), T3–T4 category (adjusted OR 5.74, 95% CI 2.29–14.40; p<0.001), and node-positive disease (adjusted OR 1.87, 95% CI 1.10–3.19; p=0.021). Excluding the 28 patients with unrecorded neoadjuvant fields (n=232) preserved the associations for T3–T4 (adjusted OR 4.78, 95% CI 1.87–12.19; p=0.001) and node-positive disease (adjusted OR 1.79, 95% CI 1.02–3.11; p=0.041) while slightly widening the confidence interval for composite stage III–IV (adjusted OR 1.73, 95% CI 1.00–3.00; p=0.051). Among the 196 patients with documented ASA status, adding ASA III–IV to the multivariable model yielded an adjusted OR of 1.73 (95% CI 0.93–3.23; p=0.082) for stage III–IV and 6.36 (95% CI 2.13–18.99; p<0.001) for T3–T4 disease. In site-stratified analyses, the association with stage III–IV was robust in colonic primaries (n=203; adjusted OR 2.09, 95% CI 1.16–3.74; p=0.013) and attenuated in the smaller treatment-naïve rectal/rectosigmoid subgroup (n=49; OR 1.17, 95% CI 0.35–3.88), without statistically significant interaction (p-interaction=0.40).

Exploratory clinical outcomes

Thirty-day postoperative complications (24.5% vs 22.2%; p=0.666) and documented local or distant recurrence (1/97 [1.0%] vs 7/161 [4.3%]; Fisher exact p=0.265) did not differ significantly between CEA groups, although event counts were low and standardized observation windows were unavailable. Overall metastatic disease recorded at any point in the clinical record (combining synchronous and metachronous

metastases) was twice as frequent among patients with baseline CEA >5 ng/mL (20/98 [20.4%] vs 16/160 [10.0%]; crude OR 2.31, 95% CI 1.13–4.71; p=0.019; Supplementary Table S3).

Discussion

Principal findings

In this surgical cohort, elevated preoperative carcinoembryonic antigen (CEA) was associated with stage III–IV, T3–T4, and node-positive disease after adjustment for age, sex, and tumor site. Discrimination was higher for mural invasion than for composite stage or nodal disease. Exclusion of patients with undocumented neoadjuvant status reduced the precision of the estimate for stage III–IV disease.

Comparison with existing literature

Prior studies have linked CEA to mural depth, nodal involvement, and survival [5–7,18]. Neoadjuvant treatment can affect both CEA and pathological stage [8,9,19]. We excluded patients with documented neoadjuvant treatment and assessed the effect of excluding patients whose treatment status was unrecorded. Estimates for lymphovascular and perineural invasion were imprecise.

More than one-third of patients with normal preoperative CEA had stage III–IV disease, and 48 of 99 with elevated CEA had stage 0–II disease. The positive predictive value of 93.9% for T3–T4 at the 5 ng/mL threshold should be interpreted in the context of the 81.3% prevalence of T3–T4 in the evaluable cohort. Nonmalignant causes of elevated CEA may also contribute to overlap between groups [10].

The inverse association between male sex and stage III–IV was exploratory. The confidence interval for the stage III–IV association included the null in the subset with documented ASA class after additional adjustment. This analysis combined a change in the analytic population with a change in covariate adjustment.

Clinical implications

Preoperative CEA may provide context during multidisciplinary review of conventional staging. Normal values were common among patients with locally advanced or node-positive disease. This study did not

assess incremental discrimination over imaging or whether CEA-guided changes in management improve outcomes.

Strengths and limitations

Strengths of this study include a consecutive surgical registry cohort, 100% completeness of primary exposure, outcome, and core multivariable covariates, rigorous nodal harvest quality control (median 20 nodes retrieved in both groups), comprehensive dose–response and bootstrap ROC discrimination analyses, and extensive sensitivity testing. Several limitations merit consideration. First, the single-center retrospective design is subject to referral and selection biases. Second, residual confounding cannot be excluded: ASA class was unavailable in 24.6% of records, and smoking status, renal or hepatic function, microsatellite instability (MSI) status, and exact assay-to-surgery day intervals were not standardized in the registry. Third, statistical precision was limited for rare endpoints, particularly synchronous M1 disease at resection (n=5), reflecting the clinical reality that most stage IV patients receive upfront systemic therapy rather than primary resection. Fourth, pathological M status was frequently recorded as Mx when intraoperative biopsy of distant sites was not indicated, which may under-ascertain occult stage IV disease. Fifth, neoadjuvant status was unrecorded in 28 registry entries; although excluding them yielded a consistent point estimate (adjusted OR 1.73, p=0.051), prospective documentation is preferable. Finally, the absence of longitudinal censoring dates precluded Kaplan–Meier and Cox proportional-hazards survival modeling.

Conclusion

Elevated preoperative CEA was associated with advanced pathological stage, deeper mural invasion, and nodal involvement in this surgical cohort. Discrimination was limited for stage III–IV and nodal disease and was higher for T3–T4. The incremental value of CEA alongside imaging warrants evaluation.

Statements and Declarations

Ethics Approval and Consent to Participate This study was reviewed and approved by the Institutional Review Board of Prince Sultan Military Medical City, Riyadh, Saudi Arabia (Approval No. E-2914).

Individual informed consent was waived by the Institutional Review Board due to the retrospective design and the use of de-identified clinical records. The study was conducted in full accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments.

Consent for Publication Not applicable. No identifiable individual patient data or images are included in this manuscript.

Data availability The de-identified dataset analyzed during the current study is available from the corresponding author upon reasonable request and subject to institutional approval from Prince Sultan Military Medical City.

Competing Interests The authors declare that they have no competing financial or non-financial interests.

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References

1. Shinji S, Arai T. Recent advances in basic and clinical colorectal cancer research. Cancers (Basel). 2026;18(11):1834. doi:10.3390/cancers18111834.

2. Yumak M, Demir MS. Prognostic factors affecting survival and recurrence in patients undergoing curative surgery for rectal cancer: a 10-year retrospective cohort study from a regional tertiary center in Türkiye. Front Oncol. 2026;15:1679585. doi:10.3389/fonc.2025.1679585.

3. Kataoka K, Kimura K, Imada A, et al. Current and future perspectives of adjuvant therapy for resected colorectal liver metastases. Cancers (Basel). 2026;18(8):1188. doi:10.3390/cancers18081188.

4. Saito G, Sadahiro S, Kamata H, et al. Monitoring of serum carcinoembryonic antigen levels after curative resection of colon cancer: cutoff values determined according to preoperative levels enhance the diagnostic accuracy for recurrence. Oncology. 2017;92(5):276–282. doi:10.1159/000456075.

5. Konishi T, Shimada Y, Hsu M, et al. Association of preoperative and postoperative serum carcinoembryonic antigen and colon cancer outcome. JAMA Oncol. 2018;4(3):309–315. doi:10.1001/jamaoncol.2017.4420.

6. Liu Z, Zhang Y, Niu Y, et al. A systematic review and meta-analysis of diagnostic and prognostic serum biomarkers of colorectal cancer. PLoS One. 2014;9(8):e103910. doi:10.1371/journal.pone.0103910.

7. Pu H, Xie P, Chen Y, et al. Relationship between preoperative and postoperative serum carcinoembryonic antigen and prognosis of patients with stage I–III rectal cancer: a retrospective study of a multicentre cohort of 1022 rectal cancer patients. Cancer Manag Res. 2021;13:2643–2651. doi:10.2147/CMAR.S290416.

8. Castria TB, Lenz G, Valagni G, Kim RD. Role of neoadjuvant therapies in locally advanced colon cancer. Chin Med J (Engl). 2025;138(17):2091–2101. doi:10.1097/CM9.0000000000003756.

9. Liu M, Zhou Q, Lan B, Gan J, Zhang S. Factors influencing pathological complete response following neoadjuvant chemoimmunotherapy in locally advanced microsatellite stable colorectal cancer: a retrospective analysis. Front Med (Lausanne). 2025;12:1587684. doi:10.3389/fmed.2025.1587684.

10. Litvak A, Cercek A, Segal N, et al. False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. J Natl Compr Canc Netw. 2014;12(6):907–913. doi:10.6004/jnccn.2014.0085.

11. Alsadhan N, Pujades-Rodriguez M, Alhurishi SA, et al. Temporal trends in age and stage-specific incidence of colorectal cancer in Saudi Arabia: a registry-based cohort study between 1997 and 2017. Cancer Epidemiol. 2024;93:102699. doi:10.1016/j.canep.2024.102699.

12. Ashi A, Al-Hajeili M, Almaghrabi S, et al. Prevalence of CEA, CA 125, and CA 15-3 serum tumour markers in different regions of Saudi Arabia. Saudi Med J. 2024;45(6):568–575. doi:10.15537/smj.2024.45.6.20230878.

13. Makhlouf NA, Abdel-Gawad M, Mahros AM, et al. Colorectal cancer in Arab world: a systematic review. World J Gastrointest Oncol. 2021;13(11):1791–1798. doi:10.4251/wjgo.v13.i11.1791.

14. Alshamsan B. Colorectal cancer incidence in Saudi Arabia, 2002–2023: age-specific trends and implications for screening and prevention. Prev Med Rep. 2026;66:103505. doi:10.1016/j.pmedr.2026.103505.

15. Znaor A, Eser S, Bendahhou K, et al. Stage at diagnosis of colorectal cancer in the Middle East and Northern Africa: a population-based cancer registry study. Int J Cancer. 2024;155(1):54–60. doi:10.1002/ijc.34895.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X.

17. Brierley JD, Gospodarowicz MK, Wittekind C, eds. TNM Classification of Malignant Tumours. 8th ed. Oxford: Wiley-Blackwell; 2017.

18. Sheng S, Bai X, Wang Y, et al. Effect of elevated CEA levels on the outcome of colorectal cancer patients with different histopathologic types: a SEER population-based study. Biomol Biomed. 2025;25(6):1396–1407. doi:10.17305/bb.2024.11265.

19. Wu S, Gu W. Association of T stage and serum CEA levels in determining survival of rectal cancer. Front Med (Lausanne). 2020;6:270. doi:10.3389/fmed.2019.00270.

Figure Legends

Figure 1. Participant selection from the surgical registry. Of 343 screened patients, 82 were excluded for documented neoadjuvant therapy and one for prior adjuvant therapy. The analysis retained 260 patients, including 28 with undocumented neoadjuvant status.

Figure 2. Distribution of pathological stage (AJCC/UICC 0–IV) stratified by preoperative CEA group. Bar heights represent within-group percentages and numbers above bars denote exact patient counts (Mann–Whitney U test for ordinal stage shift, $p<0.001$).

Figure 3. Forest plot of crude and multivariable-adjusted odds ratios for pathological outcomes comparing elevated (>5 ng/mL) versus normal (≤5 ng/mL) preoperative CEA. *Adjusted models control for age, sex, and primary tumor site (rectum/rectosigmoid vs other). Horizontal error bars denote 95% confidence intervals on a logarithmic scale.

Figure 4. Dose–response and receiver operating characteristic (ROC) discrimination analyses. (A) Prevalence (with 95% confidence intervals) of stage III–IV, T3–T4, and node-positive disease across ordered preoperative CEA categories (some stage III–IV and node-positive estimates overlap). (B) ROC curves for continuous preoperative CEA predicting stage III–IV (AUC 0.59), T3–T4 category (AUC 0.74), and node-positive disease (AUC 0.59).

Table 1. Baseline clinicopathological characteristics by preoperative CEA status

Characteristic	Overall (N=260)	CEA >5 ng/mL (n=99)	CEA ≤5 ng/mL (n=161)	p-value	Statistical Test
Age, years (mean ± SD)	62.9 ± 11.8	65.2 ± 12.0	61.5 ± 11.5	0.014	Welch t-test
Male sex, n (%)	140 (53.8)	48 (48.5)	92 (57.1)	0.174	Pearson χ^2
ASA III–IV, n (%) [n=196 recorded]	76 (38.8)	34 (48.6)	42 (33.3)	0.036	Pearson χ^2
ASA not recorded, n (%)	64 (24.6)	29 (29.3)	35 (21.7)	—	—
Tumor site: colon, n (%)	203 (78.1)	82 (82.8)	121 (75.2)	0.463	Pearson χ^2 (colon vs rectum)
Tumor site: rectum / rectosigmoid, n (%)	49 (18.8)	17 (17.2)	32 (19.9)		
Tumor site: appendix / small bowel, n (%)	8 (3.1)	0 (0.0)	8 (5.0)	—	Excluded in sensitivity
Mucinous component, n (%)	30 (11.5)	12 (12.1)	18 (11.2)	0.818	Pearson χ^2
Poorly differentiated component, n (%)	13 (5.0)	5 (5.1)	8 (5.0)	1.000	Fisher exact
Lymph nodes retrieved (median [IQR])	20.0 [15.2–27.0]	20.5 [15.0–27.8]	20.0 [16.0–27.0]	0.982	Mann–Whitney U
Preoperative CEA, ng/mL (median [IQR])	3.2 [1.8–8.2]	12.4 [7.0–23.1]	1.9 [1.4–2.7]	<0.001	Mann–Whitney U
Lymphovascular invasion, n (%)	127 (48.8)	49 (49.5)	78 (48.4)	0.870	Pearson χ^2
Perineural invasion, n (%)	69 (26.5)	29 (29.3)	40 (24.8)	0.430	Pearson χ^2

Values are presented as n (%), mean ± SD, or median [IQR]. ASA percentages use the 196 patients with recorded ASA status as the denominator. Quantitative lymph-node counts were available for 258 patients. Primary tumor site χ^2 test compares colon versus rectum/rectosigmoid (the 8 appendiceal/small-bowel cases were excluded in a dedicated sensitivity analysis; Supplementary Table S2). Abbreviations: ASA, American Society of Anesthesiologists physical status class; CEA, carcinoembryonic antigen; IQR, interquartile range; SD, standard deviation.

Table 2. Association between elevated preoperative CEA (>5 ng/mL) and pathological outcomes

Pathological Outcome	CEA >5 ng/mL n/N (%)	CEA ≤5 ng/mL n/N (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)*	Adjusted p-value
Advanced stage (III–IV)	51/99 (51.5)	56/161 (34.8)	1.99 (1.20–3.32)	0.008	1.93 (1.14–3.26)	0.014
T3–T4 category	92/98 (93.9)	117/159 (73.6)	5.50 (2.24–13.51)	<0.001	5.55 (2.22–13.92)	<0.001
Node-positive (N1–N2)	50/98 (51.0)	54/159 (34.0)	2.03 (1.21–3.39)	0.007	1.96 (1.16–3.33)	0.013
Distant metastasis (M1) at surgery	3/99 (3.0)	2/161 (1.2)	2.48 (0.41–15.14)	0.372†	Not estimable (5 events)	—
Lymphovascular invasion	49/99 (49.5)	78/161 (48.4)	1.04 (0.63–1.72)	0.870	1.03 (0.62–1.73)	0.898
Perineural invasion	29/99 (29.3)	40/161 (24.8)	1.25 (0.71–2.20)	0.430	1.33 (0.75–2.37)	0.326

*Multivariable logistic regression adjusted for age (continuous), sex, and primary tumor site (rectum/rectosigmoid vs other). Denominators for T3–T4 and node-positive disease exclude 3 patients with unavailable granular T/N categories. †Fisher exact test (expected cell count <5); all other unadjusted comparisons use Pearson χ^2. Positive lymph nodes (n=98 vs 160): mean 1.57 ± 2.45 vs 0.91 ± 1.85 (median 0 in both groups; Mann–Whitney p=0.003). Total lymph nodes retrieved: mean 23.2 vs 23.3 (p=0.982). Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Dose–response analysis: prevalence and adjusted odds ratios across ordered preoperative CEA categories

Outcome	CEA Stratum (ng/mL)	Events / N (%)	Adjusted OR (95% CI)*	p-value	p-trend†
Stage III–IV	≤5.0 (Reference)	56/161 (34.8)	1.00 (Reference)	—	0.008
Stage III–IV	>5.0–10.0	21/42 (50.0)	1.79 (0.89–3.62)	0.103	
Stage III–IV	>10.0–20.0	14/30 (46.7)	1.52 (0.68–3.42)	0.310	
Stage III–IV	>20.0	16/27 (59.3)	2.77 (1.19–6.43)	0.018	
T3–T4 Category	≤5.0 (Reference)	117/159 (73.6)	1.00 (Reference)	—	<0.001
T3–T4 Category	>5.0–10.0	39/42 (92.9)	4.65 (1.33–16.23)	0.016	
T3–T4 Category	>10.0–20.0	28/30 (93.3)	4.72 (1.05–21.19)	0.043	
T3–T4 Category	>20.0	25/26 (96.2)	9.93 (1.28–76.88)	0.028	
Node-Positive (N1–N2)	≤5.0 (Reference)	54/159 (34.0)	1.00 (Reference)	—	0.009
Node-Positive (N1–N2)	>5.0–10.0	21/42 (50.0)	1.86 (0.92–3.77)	0.083	
Node-Positive (N1–N2)	>10.0–20.0	14/30 (46.7)	1.58 (0.70–3.55)	0.273	
Node-Positive (N1–N2)	>20.0	15/26 (57.7)	2.69 (1.14–6.33)	0.024	

*Compared against ≤5.0 ng/mL reference category; multivariable logistic regression adjusted for age, sex, and primary tumor site. †Cochran–Armitage test for linear trend across ordered categories. Continuous $\log_2$-CEA (adjusted OR per doubling of serum CEA concentration for stage III–IV): 1.21 (95% CI 1.05–1.39; p=0.008).

Table 4. Diagnostic discrimination performance of preoperative serum CEA

Pathological Outcome	Continuous CEA AUC (95% CI)*	Sensitivity (>5 ng/mL)	Specificity (>5 ng/mL)	PPV	NPV	LR+
Stage III–IV	0.59 (0.52–0.66)	47.7%	68.6%	51.5%	65.2%	1.52
T3–T4 Category	0.74 (0.66–0.81)	44.0%	87.5%	93.9%	26.4%	3.52
Node-Positive (N1–N2)	0.59 (0.51–0.66)	48.1%	68.6%	51.0%	66.0%	1.53

*Area under the receiver operating characteristic curve (AUC) for continuous preoperative CEA with 95% confidence intervals derived from 2,000 percentile bootstrap resamples. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio (LR+) are evaluated at the conventional 5.0 ng/mL threshold.

Fig1

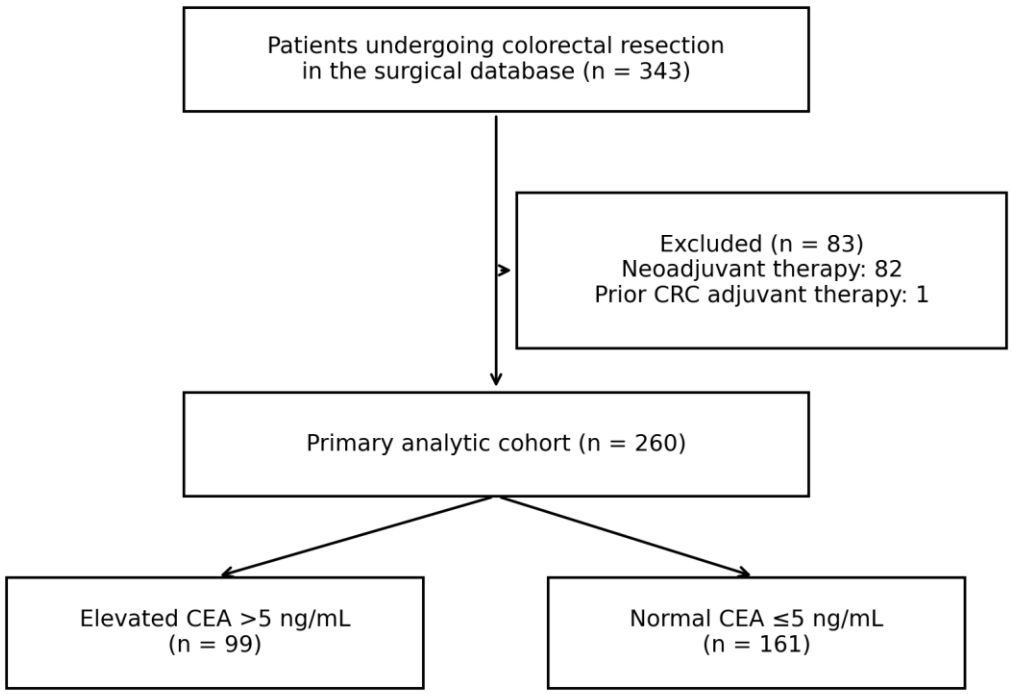


Fig2

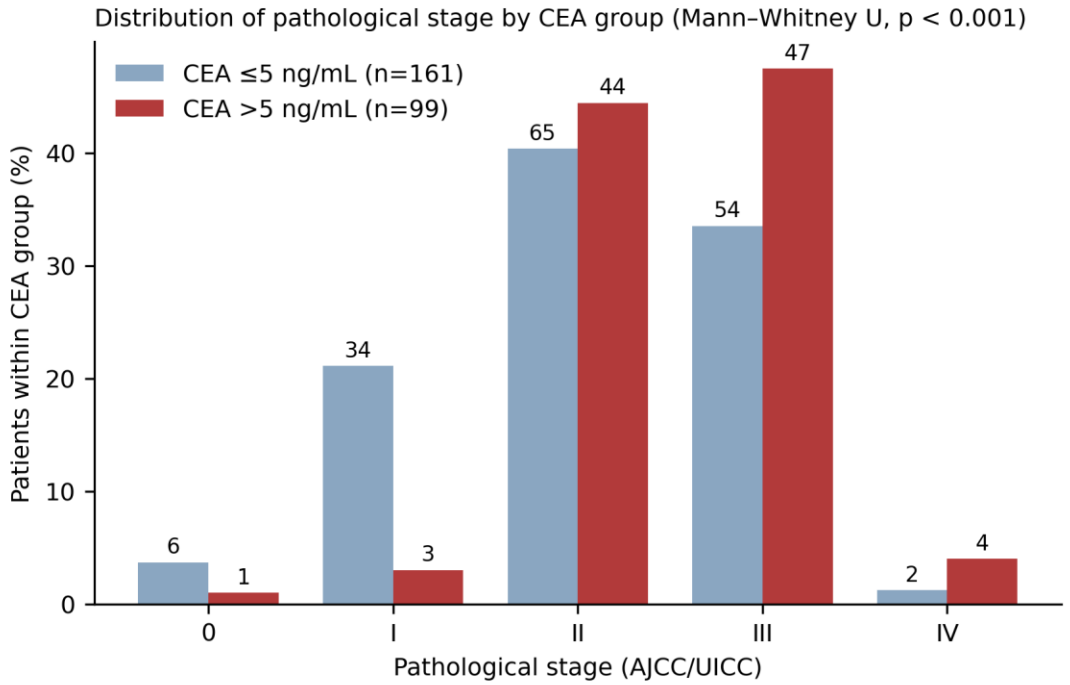

Distribution of pathological stage by CEA group (Mann–Whitney U, p < 0.001)
CEA ≤5 ng/mL (n=161)
CEA >5 ng/mL (n=99)
Patients within CEA group (%)
Pathological stage (AJCC/UICC)
0
I
II
III
IV
6
1
34
3
65
44
54
47
2
4

Fig3

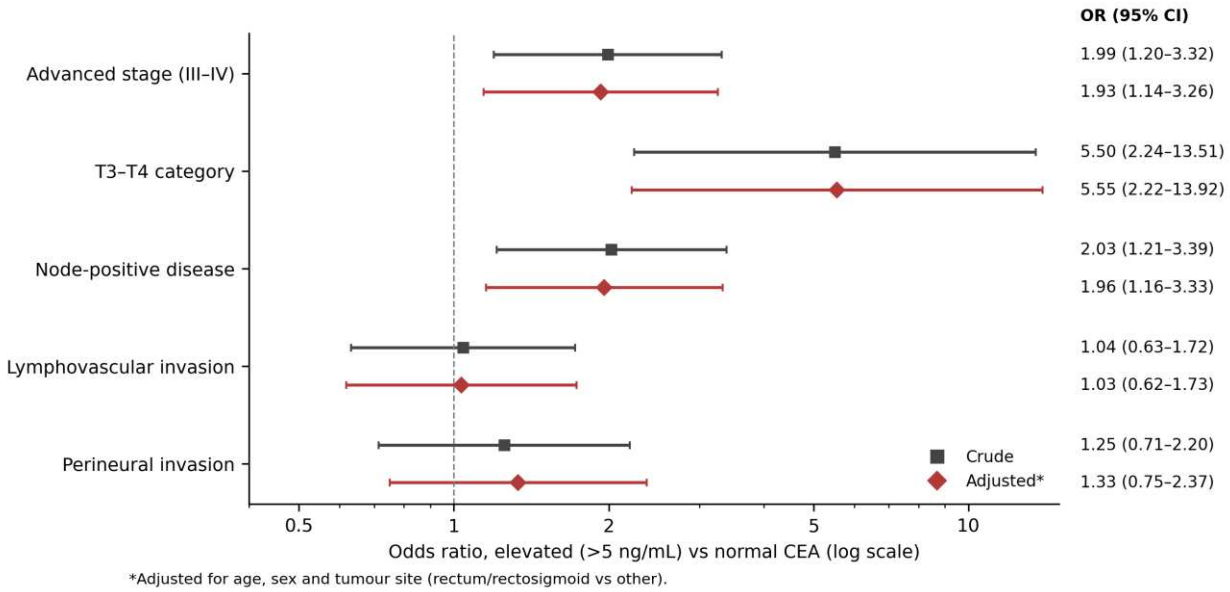
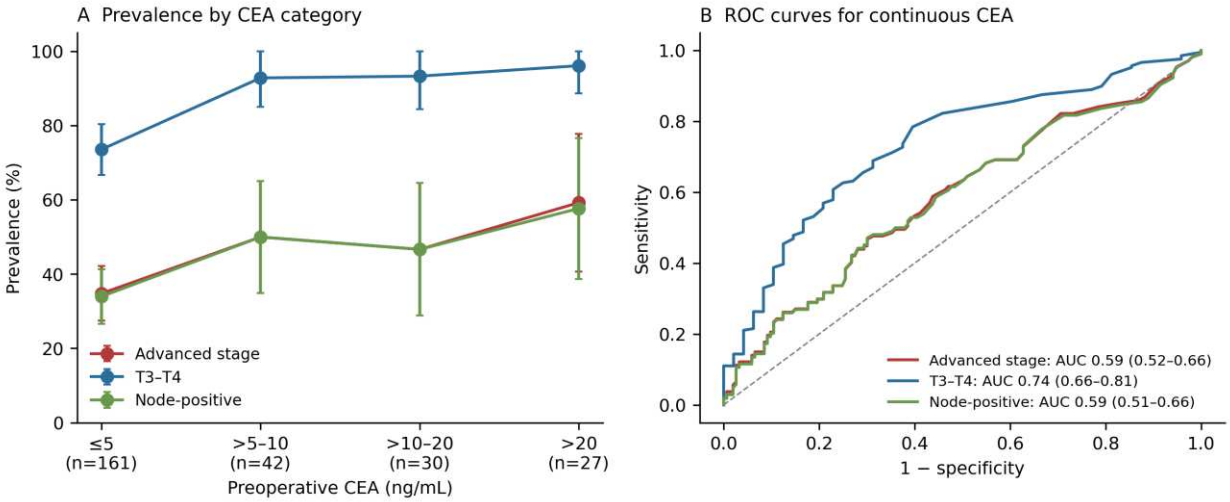

OR (95% CI)
Advanced stage (III–IV)
1.99 (1.20–3.32)
1.93 (1.14–3.26)
T3–T4 category
5.50 (2.24–13.51)
5.55 (2.22–13.92)
Node-positive disease
2.03 (1.21–3.39)
1.96 (1.16–3.33)
Lymphovascular invasion
1.04 (0.63–1.72)
1.03 (0.62–1.73)
Perineural invasion
1.25 (0.71–2.20)
1.33 (0.75–2.37)
Crude
Adjusted*
0.5
1
2
5
10
Odds ratio, elevated (>5 ng/mL) vs normal CEA (log scale)
*Adjusted for age, sex and tumour site (rectum/rectosigmoid vs other).

Fig4


A Prevalence by CEA category
Prevalence (%)
100
80
60
40
20
0
Advanced stage
T3–T4
Node-positive
≤5
(n=161)
>5–10
(n=42)
>10–20
(n=30)
>20
(n=27)
Preoperative CEA (ng/mL)
B ROC curves for continuous CEA
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Advanced stage: AUC 0.59 (0.52–0.66)
T3–T4: AUC 0.74 (0.66–0.81)
Node-positive: AUC 0.59 (0.51–0.66)
0.0
0.2
0.4
0.6
0.8
1.0
1 − specificity